# PACTALS 2025

12th MND Australia Care Forum

Theme:
Towards Precision in ALS/MND Treatments and Care

# ABSTRACT BOOK

**7 - 9 September 2025**
Melbourne Convention and Exhibition Centre, Australia

Organised by:

mnd Australia

PACTALS
Pan-Asian Consortium for Treatment and Research in ALS

# Table of Contents

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-B001*

# GEOMETRIC DEEP LEARNING FOR PREDICTING ALS DIAGNOSES

Thomas B Shaw[1,2,3†*], Akshit Beniwal[1*], Robert D Henderson[3,4], Matthew C Kiernan[5,6], Shyuan T Ngo[3,7], Frederik J Steyn[3,8], Sicong Tu[5,9], Markus Barth[1,2,10], Fernanda L Ribeiro[1,11]

[1] School of Electrical Engineering and Computer Science, The University of Queensland, St Lucia, QLD, Australia
[2] Centre for Advanced Imaging, AIBN, The University of Queensland, St Lucia, QLD, Australia
[3] Department of Neurology, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
[4]UQ Centre for Clinical Research, Herston Queensland, Australia
[5]Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia
[6]Neuroscience Research Australia, Randwick, NSW, Australia
[7]Australian Institute for Bioengineering and Nanotechnology, UQ, QLD, Australia
[8]School of Biomedical Sciences, The University of Queensland, St Lucia, QLD, Australia
[9]South Eastern Sydney Local Health District, Randwick, NSW, Australia
[10]ARC Training Centre for Innovation in Biomedical Imaging and Technology (CIBIT), Centre for Advanced Imaging, The University of Queensland, QLD, Australia
[11] Justus-Liebig University Giessen

†Corresponding Author
*These authors contributed equally to this work

## INTRODUCTION:

Geometric Deep Learning (GDL) is a rapidly evolving field extending deep learning to non-Euclidean data like graphs and meshes(1). The unique geometric brain features (i.e., structural shape/topology) of people with ALS has potential to provide disease biomarkers using a single MRI scan. In this study we aim to classify ALS patients and controls by leveraging geometric brain features using GDL.

## METHODS:

The dataset comprised 701 MRI scans: 184 with a confirmed diagnosis(2) of ALS and 517 age-matched controls, aggregated from multiple Australian MND clinics and sites associated with the Asia-Pacific MND Imaging Initiative. We focused on regions of interest (ROIs) including motor and somatosensory cortices, and white matter bundles including the corpus callosum. A modified GDL network(3) was used to predict a diagnosis of ALS, and follow-up analyses were conducted to explore the geometric changes that defined the diagnosis (shape deformations). Model performance was assessed using k-fold cross-validation, and on independent unseen data.

## RESULTS:

Our final model achieved 86% accuracy (validation) and 67.3% (independent test set) in predicting ALS/controls, and validation and test recalls of 85% and 76.6%, respectively. Incorporating multiple brain regions into our model improved performance, indicating that ALS is defined by more widespread structural changes. An ablation study on the model architecture highlighted the importance of combining specific ROIs, with the geometry of the corpus callosum being of particular importance for diagnostic differentiation.

## CONCLUSION:

Our work can identify subtle structural brain changes in ALS and can be used for assisting clinicians in diagnostic accuracy. Our results show that ALS-specific topological shifts in the brain can reveal diagnostic biomarkers that are not visible to the naked eye, thereby supporting an earlier diagnosis and facilitating recruitment into clinical trials. Involvement of the corpus callosum confirms that white matter pathways are key components of disease progression and pathogenesis.

**REFERENCES:**

1. M. Bronstein, J. Bruna, Y. LeCun, A. Szlam, P. Vandergheynst, Geometric deep learning: going beyond Euclidean data. **34**, 18–42 (2017).

2. S. Vucic, *et al.*, Gold Coast diagnostic criteria: Implications for ALS diagnosis and clinical trial enrollment. *Muscle Nerve* **64**, 532–537 (2021).

3. Y. Feng, Y. Feng, H. You, X. Zhao, Y. Gao, MeshNet: Mesh Neural Network for 3D Shape Representation. [Preprint] (2018). Available at: http://arxiv.org/abs/1811.11424 [Accessed 16 March 2025].

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-B002*

# A BLOOD-BASED BIOMARKER TO MONITOR AUTOPHAGY DYSFUNCTION IN ALS

[1]Perera, N; [2]Nijagal, B; [1]Tomas, D; [1]Cuic, B; [1]Luikinga, S, [1]Turner, BJ

[1]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC 3052, Australia,
[2]Metabolomics Australia, Bio21 Institute, The University of Melbourne, Parkville VIC 3010, Australia

## INTRODUCTION:

Autophagy, the recycling of cytoplasmic waste, is essential for cellular health and metabolism. Autophagy dysfunction is linked to ALS pathology. However, the development of autophagy-targeted therapies has been stalled by the lack of methods to measure human autophagy. We aimed to address this by identifying a blood-based biomarker to distinguish normal from impaired autophagy.

## METHODS:

We hypothesized that autophagy impairment will result in metabolite changes detectable in blood. Global deletion of the essential autophagy gene *Atg7* was induced in adult transgenic mice (Atg7fl/flxCAG-Cre) using tamoxifen. After one month of autophagy deletion, tissue and serum were collected. Western blotting was used to validate autophagy deletion and mass spectrometry was used for metabolomic analyses to detect lipid and polar metabolite (sugars, amino acids) species. Next, mass spectrometry was also used to conduct a plasma metabolomic analysis in a cohort of ALS patients (n=103) and healthy controls (n=30). Finally, the autophagy deletion metabolomic signature from mice was compared to the metabolomic signature of ALS patients to identify overlapping metabolites.

## RESULTS:

A 50% reduction in Atg7 protein and a 2-fold rise in p62 protein in the central nervous system confirmed the significant reduction of the autophagy pathway arising from autophagy deletion in Atg7fl/flxCAG-Cre mice. Principal component analysis (PCA plots) revealed control and autophagy-deficient mice clustering into separate groups indicating autophagy deletion gives rise to a unique metabolite signature. From volcano plots, 11 polar metabolites and 20 lipids were identified as significantly changing with autophagy deletion in mice (fold changes ≥1.5). Remarkably, 13 lipids and 10 polar metabolites were consistently altered in both autophagy-deficient mice and ALS patients, forming an ALS autophagy metabolomic signature.

## CONCLUSION:

Our results underscore the critical role of autophagy dysfunction in ALS. With further validation and refinement, this autophagy biomarker could fill a critical gap in pre-clinical and clinical practices by offering a measurable endpoint for autophagy interventions—ultimately improving prediction, diagnosis, and treatments for autophagy impacted diseases such as ALS.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-B003*

# THE BIOMECHANICS OF WALKING WITH MND: A JOINT-LEVEL PERSPECTIVE ON THE LOWER LIMB

[*1]James L. Williamson, [*2]Cory J. Holdom, [1]Georgia O'Reilly, [3,4]Robert D. Henderson, [1]Sally Neville, [2,4]Shyuan T. Ngo, and [*1,4]Frederik J. Steyn, [*1]Taylor J. M. Dick

*Equal contribution
[1]School of Biomedical Sciences, The University of Queensland, Building 64, St Lucia, QLD, 4072, Australia, [2]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Building 75, St Lucia, QLD, 4072, Australia, [3]Centre for Clinical Research, The University of Queensland, Building 71, Herston, QLD, 4029, Australia, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Ned Hanlon Building, Herston, QLD, 4029, Australia.

## INTRODUCTION:

Assessments of gait in people living with MND (plwMND) have primarily focused on gross measures of walking performance [1], which provide limited mechanistic insight into functional capacity or decline. Comprehensive gait measures that characterise the body's motions and forces reveal distinct *movement signatures* that could serve as novel movement markers for the development of clinical outcome measures and intervention.

## METHODS:

We completed a biomechanics assessment in 9 plwMND and 9 Controls (HREC #2022/HE001787). Participants walked at their preferred speed on an instrumented treadmill (FIT5, Bertec Inc.) that measured ground reaction forces. Simultaneously, participant movements were measured using a 3D motion capture system (Miqus, Qualisys AB). Digital twins [2] of each participant were created to examine lower limb mechanics and energetics of their movement patterns.

## RESULTS:

PlwMND walked at slower speeds (0.62±0.40 vs 1.17±0.14ms$^{-1}$), with shorter step lengths (0.39±0.19 vs 0.64±0.06m), and reduced step frequencies (41.1±18.4 vs 55.3±5.04 steps min$^{-1}$) compared to controls (all: $p<0.03$). Peak ankle plantar flexion, knee flexion and hip extension joint angles were all lower in plwMND, compared to Controls (all:$p\leq0.036$). On average, plwMND walked with a 72% reduction in peak ankle propulsive power and a 67% reduction in positive ankle work, compared to controls (both: $p<0.001$). Despite an increased contribution of the hip to lower limb total positive work, alterations in knee and hip mechanics were limited in plwMND. Rather than a redistribution of work across the lower limb, plwMND may rely on their more proximal joints owing to a reduced capacity of the ankle to produce positive work and power.

## CONCLUSION:

Unique biomechanical changes occur in gait of plwMND, with the ankle as a locus of lower limb deficits. The identification of ankle-based *movement signatures* may inform the development of technologies that monitor disease progression (*e.g.,* actigraphy), or improve mobility (*e.g.,* ankle exoskeletons) in plwMND.

## REFERENCES:

1. Hausdorff et al, *J Appl Physiol.* **88(6)**:2045-2053, 2000.
2. Delp et al., *IEEE. Trans. Biomed. Eng.* **54**:1940–1950, 2007.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-DS/S001*

# INTRAMUSCULAR NERVE BUNDLES REFLECT TDP-43 PATHOLOGY IN MEDULLA AND SPINAL CORD OF ALS PATIENTS

[1]Kurashige, Takashi; [1]Murao T; [1]Kanaya Y; [1]Dodo Y; [1]Sugiura T; [2]Kuraika K; [1]Ohshita T

[1]Department of Neurology, NHO Kure Medical Center and Chugoku Cancer Center, Aoyamacho 3-1, Kure, Japan, [2]Department of Diagnostic Pathology, NHO Kure Medical Center and Chugoku Cancer Center, Aoyamacho 3-1, Kure, Japan.

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) shows progressive muscle weakness and atrophy caused by neuronal death associate with TAR DNA-binding protein 43 (TDP-43). We previously reported that axonal TDP-43 accumulations in intramuscular nerve bundles preceded clinical fulfillment of the Gold Coast criteria[1]. However, the relationship between axonal pTDP-43 accumulations and TDP-43 pathology in central nervous system is not clear. Here, we aimed to clarify this association by comparing intramuscular nerve bundles with brainstem and spinal cord.

## METHODS:

The post-mortem study included 11 sporadic ALS patients with TDP-43 pathology (ALS- TDP) and 12 patients with non-ALS disease. Brainstem, spinal cord, and skeletal muscles (tongue, diaphragm, biceps brachii, and iliopsoas) were evaluated by histochemistry and immunohistochemical analysis.

## RESULTS:

All 11 ALS patients exhibited axonal phosphorylated TDP-43 (pTDP-43)-positive accumulations in intramuscular nerve bundles; 12 non-ALS patients did not. In the tongue and CNXII, pTDP-43-positive nerve bundles (61.2 ± 14.8 %) negatively correlated with remaining neurons (20.0 ± 5.5 / section) ($p=0.0217$, $r=-0.6787$). Iliopsoas muscle and L2 anterior horn also showed that the percentage of pTDP-43- positive nerve bundles (57.0 ± 18.2 %) correlated with remaining neurons (23.5 ± 7.9 / section) ($p=0.0479$, $r=-0.6065$). In the diaphragm and C4 anterior horn, the percentage of pTDP-43-positive nerve bundles (68.4 ± 10.6%) was not correlated with remaining neurons (18.6 ± 5.8 / section), which was less than a half of C4 anterior horn neurons in control participants (39.3 ± 4.4 / section). Biceps brachii muscle and C6 anterior horn did not show any correlations between pTDP-43-positive nerve bundles and remaining neurons.

## CONCLUSION:

The percentage of intramuscular nerve bundles with axonal pTDP-43 accumulations might reflect the severity of motor neuron loss in ALS- TDP patients.

## REFERENCES:

1. Kurashige. et al., TDP-43 accumulation within intramuscular nerve bundles of patients with amyotrophic lateral sclerosis. JAMA Neurology 2022;79(7):693-701.

Basic Science

*BS-O-DS/S002*

# POPULATION-WIDE DRUG SCREENING WITH SPORADIC ALS PATIENT-DERIVED MOTOR NEURONS

1Qian, E; 1Lim, K; 1Trần,-Lê BC; 1Dharmadasa, T; 2Kiernan, MC; 3Talbot, K; 1Turner, BJ; 1Bye, CR.

1The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia. 2Neuroscience Research Australia; University of New South Wales, Sydney, Australia; 3Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

## INTRODUCTION:

Despite over 150 drugs reaching clinical trial for Amyotrophic lateral sclerosis (ALS), little progress has been made in identifying effective treatments for patients. A major roadblock in ALS drug development has been the failure of drugs tested in monogenic animal models of the disease to translate into clinically effective drugs for the predominant sporadic form of the disease.

## METHODS:

To develop an alternative drug discovery pathway for ALS, we built an iPSC library from over 100 patients and successfully established a sporadic ALS model and drug screening pipeline. In a first-of-its-kind screen, we re-assessed the effect of 107 drugs that have previously undergone evaluation in Phase 1-3 clinical trials for ALS using motor neurons from 16 sporadic ALS patients.

## RESULTS:

Strikingly, 95% of the drugs tested did not rescue sporadic patient-derived motor neuron health, results that are consistent with the clinical trial outcomes for the drugs. Only 3 drugs showed significant efficacy, including riluzole. Motor neurons from different patients exhibited highly divergent responses, providing strong stratification of responding and non-responding patients. Combinatorial testing of the 3 effective therapies identified a drug combination with 6.5x higher efficacy than the current standard of care, and importantly efficacy across all patients.

## CONCLUSION:

This study suggests patient-derived motor neurons provide a clinically translatable model of sporadic ALS, and highlight strong heterogeneity in drug responses between patients. The ability to model the efficacy of drugs both at an individual and population level in the sporadic ALS population in an important achievement for ALS drug discovery, and may provide the foundation for precision medicine in the future.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-G001*

# GENETICS LED DRUG REPURPOSING CANDIDATES FOR AMYOTROPHIC LATERAL SCLEROSIS

[1,2,3]Gerring, Zachary, [1,4]Bhalala, Oneil, [1,2]Fearnley, Liam, [3]Oikari, Lotta, White, Anthony[3], [3]Derks, Eske, [1,4]Watson, Rosie, Yassi, Nawaf[1,4], Bahlo, Melanie[1,2], Reay, William[5]

[1]Population Health and Immunity Division, Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, 3052, Australia, [2]The Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, 3052, Australia, [3]QIMR Berghofer Medical Research Institute, Herston, Queensland, 4006, Australia, [4]Department of Medical Biology, University of Melbourne, Parkville, Victoria, 3052, Australia, [5]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, 7000, Australia

## INTRODUCTION:

Given the increasing bottlenecks in drug discovery pipelines, repurposing existing drugs for ALS may represent a path to expedite translation and improve disease outcomes. However, ALS is a heterogeneous disease for which the aetiology remains poorly characterised, complicating efforts to effectively repurpose drugs. We propose that the polygenic architecture of ALS genetic liability, which ranges from ultra-rare, high-impact variation to common frequency loci of small-individual effect, could be leveraged to prioritise drug repurposing candidates which are more generalisable to the ALS clinical population[1].

## METHODS:

We utilised common and rare frequency ALS genetic risk in a novel approach to uncover therapeutic classes that may be prospective repurposing opportunities in ALS. These data were sourced from the largest ALS to-date genome-wide (common variant) and exome- wide (rare variant) association study[2]. An integrative gene-ranking pipeline was developed across different common and rare-variant methods which were then tested for enrichment amongst group of targets in related therapeutic categories. Targets of top therapeutic categories were also examined for dysregulation using publicly available transcriptomic data from ALS stem-cell derived motor neurons.

## RESULTS:

Common variant-led enrichment analyses revealed MAP kinase signalling related downregulation through BRAF inhibitors as a prospective target for repurposing, as well providing some additional support for previous genetic evidence supporting repurposing antihypertensive compounds[3]. Rare variant-led approaches prioritised B-vitamin related candidates, such as cobalamin and niacin. Clinical characterisation of these putative repurposing opportunities revealed genetic support to existing biology for which related compounds are actively proceeding through ALS clinical studies[4]. Moreover, leveraging transcriptomic data from ALS derived cell lines carrying a selection of pathogenic variants in genes that cause familial forms of ALS (*C9orf72*, *SOD1*, *FUS*, and *TARDBP*) suggested that the action of BRAF inhibitors may be of particular relevance to *C9orf72* hexanucleotide repeat expansion carriers, whilst the signal for B-vitamin signalling related targets was strongest in *SOD1* carriers.

## CONCLUSION:

We demonstrate the importance of considering the therapeutic actionability of both common and rare-variant mediated risk for ALS given the immense biological heterogeneity of this disorder. Future preclinical and clinical studies are now warranted to further characterise the tractability of these prioritised compounds.

**REFERENCES:**

1. Reay WR, Cairns MJ. Advancing the use of genome-wide association studies for drug repurposing. *Nat Rev Genet*. 2021;22(10):658-671. doi:10.1038/s41576-021-00387-z

2. van Rheenen W, et al. Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. *Nat Genet*. 2021;53(12):1636-1648. doi:10.1038/s41588-021-00973-1

3. Pain O, et al. Harnessing transcriptomic signals for amyotrophic lateral sclerosis to identify novel drugs and enhance risk prediction. *Heliyon*. 2024;10(15):e35342. doi:10.1016/j.heliyon.2024.e35342

4. Oki R, et al. Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early- Stage Amyotrophic Lateral Sclerosis: A Randomized Clinical Trial. *JAMA Neurol*. 2022;79(6):575-583. doi:10.1001/jamaneurol.2022.0901

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-O-G002*

# INVESTIGATING THE RPSA-MOBP RISK LOCUS IN ALS: AN INTEGRATIVE GENOMIC AND FUNCTIONAL APPROACH

Garton, Fleur[1]; Giacomotto, Jean[2, 3], Stringer, Brett[2]; Wong, Cheong[1]; Ziser, Laura[1]; Thompson, Mike J. [4]; Li, Ang[1,5]; Cheng, Fei-Fei[1]; Wray, Naomi[1,3,5]; Henders, Anjali[1]; McRae, Allan[1];

[1]Institute for Molecular bioscience, University of Queensland, Brisbane, 4072, QLD Australia [2]Griffith Institute for Drug Discovery (GRIDD), Griffith University, Brisbane, 4122, QLD Australia, [3] Queensland Brain Institute, University of Queensland, Brisbane, 4072, QLD Australia [4]Department of Computer Science, University of California Los Angeles, LA, CA, USA, [4]Oxford Big Data Institute, University of Oxford, Oxford, UK

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterised by motor neuron deterioration. Genetic factors play a significant role in all cases, with 15 genome-wide significant risk loci identified to date. Follow-up of these loci is a powerful strategy for research translation, as drug targets supported by genetic evidence are more likely to succeed in clinical development.

## METHODS:

Here, we focus on the *RPSA-MOBP* locus on chromosome 3 (rs631312, OR = 1.08 ± 0.23, p = 3.3 × $10^{-12}$). We employ integrative *in silico* analyses to prioritise candidate genes, combining multiple 'omics-based approaches, including Functional Mapping and Annotation (FUMA), Polygenic Priority Scoring (PoPS), Transcriptome-Wide Association across/within tissues (TWAS), gene- based expression analysis (mBAT-combo), chromatin interaction mapping (H-MAGMA), and Mendelian Randomisation (SMR) with GWAS data ($N_{cases}$ = 29,612, $N_{controls}$ = 122,656).

## RESULTS:

Both *RPSA* and *MOBP* were prioritised as candidate genes. *RPSA*, highly conserved in zebrafish (88% homology) was selected for functional modelling. The *rpsa*-ko zebrafish (CRISPR/Cas9) had significant motor neuron defects, resembling TDP43-deficient models and spinal muscular atrophy (SMA) with profound motility impairment and early death.

## CONCLUSION:

This study identifies RPSA as a critical gene for motor neuron health, with implications for ALS pathogenesis. The RPSA/MOBP locus is also associated with other neurodegenerative diseases including Frontotemporal dementia/FTD, Corticobasal degeneration/CBD and Progressive Supranuclear Palsy/PSP, highlighting its potential as a therapeutic target for multiple conditions.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-O-MP001*

# MULTI-REGION BRAIN TRANSCRIPTOMIC ANALYSIS OF AMYOTROPHIC LATERAL SCLEROSIS REVEALS WIDESPREAD AND TDP-43-ASSOCIATED RNA ALTERATIONS

[1]Grima, N; [1]Smith AN; [2]Shepherd CE; [1]Henden L; [3]Zaw T; [3]Carroll L; [1]Rowe DB; [2,4,5]Kiernan MC; [1]Blair IP; [1]Williams KL

[1]Macquarie University Motor Neuron Disease Research Centre, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109 Australia. [2] Neuroscience Research Australia, Randwick, NSW 2031, Australia. [3]Australian Proteome Research Facility, Macquarie University, Sydney, NSW 2109, Australia. [4]Brain and Mind Centre, The University of Sydney, Sydney, NSW 2050, Australia. [5]Department of Neurology, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia.

## INTRODUCTION:

ALS is characterised by the progressive loss of motor neurons in the motor cortex and spinal cord. While there is growing evidence that ALS pathological changes are not confined to these motor regions, there are limited studies that directly compare the molecular alterations between motor and non-motor regions.

## METHODS:

We generated a 165-sample brain transcriptome dataset derived from 22 sporadic ALS cases with pTDP-43 pathological staging and 11 non-neurological controls. RNA-seq was performed on five post-mortem brain regions that are differentially impacted by pTDP-43 inclusion pathology: motor cortex (pathology always present), prefrontal cortex and hippocampus (pathology sometimes present), and occipital cortex and cerebellum (pathology rarely present). Differential gene expression, transcript usage, predicted cell-type proportion and alternative splicing analyses were performed, comparing ALS-specific changes between brain regions.

## RESULTS:

Significant gene expression changes were observed in ALS cases relative to controls for all five brain regions, with the cerebellum demonstrating the largest number of differentially expressed genes. Gene expression changes and corresponding enriched pathways, were largely concordant across brain regions, suggesting that ALS-linked mechanisms including inflammation, mitochondrial dysfunction and oxidative stress, are also dysregulated in non-motor brain regions. Extensive variation in RNA splicing was identified in the ALS brain, with 26-41% of alternatively spliced genes unique to a given brain region. Cryptic splicing events, previously reported to be associated with TDP-43 loss-of-function, were also detected in ALS cases across all five brain regions. Finally, a unique gene expression profile was specifically detected in the cerebellum of ALS cases with the greatest regional burden of pTDP-43 pathology (stage 4).

## CONCLUSION:

Together our findings highlighted widespread transcriptome alterations in ALS post-mortem brain and suggested that, despite the absence of pTDP-43 inclusion pathology in the cerebellum, changes in the cerebellum may occur in response to regional spread of pTDP-43 pathology elsewhere in the brain.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP002*

# RECAPITULATING DISEASE PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) *IN VIVO*

[1]**Chau–Bao Tran–Le** ,[1]Valeria Rytova, [1]Doris Tomas, [1]Brittany Cuic, [1]Elizabeth Quian, [1]Katherine Lim, [1]Azin Amin, [1]Mouna Haidar, [1]Bradley Turner, [1]Chris Bye

[1] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia.

## INTRODUCTION:

ALS clinical symptoms begin focally before spreading to involve more regions. The spread of clinical symptoms is mirrored by TDP-43 pathology in the motor neurons of these regions. Limited inoculation studies *in vivo* have demonstrated pathogenic TDP-43 can spread from region to region over time, leading to the hypothesis that protein transmission may contribute to disease progression in ALS. However, existing models of protein transmission rely on inoculation with high levels of mutant proteins, leading to a rapid transmission that does not accurately reflect ALS progression in patients.

To address this gap, we sought to develop an *in vivo* model that recapitulates disease transmission without inoculation using pathogenic protein.

## METHODS:

Human iPSC-derived spinal cord cells from a healthy donor and a familial ALS patient with mutant TDP-43 were transplanted into the striatum of host mice. Transgenic TDP-43$^{Q331K}$ mice, which overexpress human mutant TDP-43, were used as the disease host to create a disease-relevant environment.

## RESULTS:

Transplantation resulted in a high number of human cells surviving in mouse brains at 3, 6 and 9 months. At 9 months post-transplantation, human motor neurons from a healthy donor in disease host mice exhibited a significant reduction in nuclear TDP-43 intensity, along with the presence of phosphorylated TDP-43 puncta in the cytoplasm. In contrast, transplanted cells from a mutant TDP-43 donor exhibited increased cytoplasmic TDP-43 intensity at 6 months.

## CONCLUSION:

Our data suggests that prolonged exposure of motor neurons to an ALS disease environment result in TDP-43 pathology, and that cells from ALS patients have a greater susceptibility to TDP-43 mis-localisation. The model provides a potential early-stage model of disease and evidence that TDP-43 transmission can occur in human cells in the absence of inoculation.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP003*

# RANOLAZINE RESCUE MITOCHONDRIAL FUNCTION AND DYNAMICS IN ALS PATIENT IPSC-LOWER MOTOR NEURONS

[1,2]Jiang, Leanne; [3]Gill, MK; [1]Howe, SL; [4]Dunlop, F; [1]Tracey, TJ; [4]Russell, A; [3]Steyn, FJ; [1]Ngo, ST

[1]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, Australia, [2]Perron Institute for Neurological and Translational Sciences, University of Western Australia, Perth, Australia, [3]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia, [4]School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia

## INTRODUCTION:

Mitochondria play a crucial role in cellular metabolism and fuel utilisation. Mitochondria are highly dynamic and maintain healthy networks by undergoing constant fission and fusion events. Aberrations in mitochondrial dynamics have been identified in *in vitro* and *in vivo* models of ALS[1]. To date, no study has investigated mitochondrial dynamics in the soma of ALS patient-derived motor neurons. Our objective was to track mitochondrial dynamics in the soma of ALS induced pluripotent stem cell- derived lower motor neurons (iPSC-LMNs) at baseline. We also aimed to investigate the therapeutic effects of a metabolic modulator, ranolazine on mitochondrial dynamics of these iPSC-LMNs.

## METHODS:

We generated iPSC-LMNs from control (n=5) and ALS (n=5: sporadic, sporadic/FTD, *C9orf72*, $SOD1^{D77Y}$, CRISPR-$TARDBP^{A382T}$) lines. We assessed motor neuron survival, TDP-43 mislocalisation, mitochondrial membrane potential, live-cell mitochondrial dynamics, nuclear encoded mitochondrial gene expression, and conducted proteomics on insoluble TDP-43 bound lysates. Subsequently, mitochondrial dynamics was assessed following treatment with Ranolazine (0.1µM, 1µM, and 10µM).

## RESULTS:

At baseline, all ALS iPSC-LMNs exhibit a motor neuron disease like phenotype, with motor neuron death ($p<0.0001$) and TDP-43 mislocalisation ($p<0.01$). Live-cell mitochondrial dynamics imaging revealed mitochondrial network fragmentation in the soma of ALS iPSC-LMNs, where mitochondria have fewer branches ($p<0.01$) and undergo more fission events ($p<0.01$). Gene array data highlight a significant decrease in the expression of complex I and V across all ALS lines ($p<0.01$). Proteomics data indicate that >1000 proteins are identified in ALS iPSC-LMNs that are not observed in control iPSC-LMNs. Ranolazine treatment at 0.1uM rescued mitochondrial dynamics showing an improvement in fusion events ($p<0.005$).

## CONCLUSION:

Our findings suggest that increased mitochondrial fission is a common feature in the soma of ALS derived iPSC-LMNs, and that Ranolozine can rescue mitochondrial dynamics. Further assessments of genomic and proteomic profiles will elucidate the mechanisms of action to improve ALS readouts.

## REFERENCES:

1. Wang P, Deng J, Dong J, Liu J, Bigio EH, Mesulam M, et al. TDP-43 induces mitochondrial damage and activates the mitochondrial unfolded protein response. PLoS genetics. 2019;15(5):e1007947.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP004*

# NOVEL GABA-MODULATING SMALL MOLECULES ARE PROTECTIVE IN CELLULAR, ZEBRAFISH AND TWO MOUSE MODELS OF ALS

[1]Cyril Jones Jagaraj; [1]Sina Shadfar; [1]Prachi Mehta; [1]Julie Hunter; [1]Sonam Parakh; 1Julie D Atkin

[1]MND Research Centre, Macquarie University, Sydney, Australia.

## INTRODUCTION:

Hyper-excitability in the motor cortex is implicated as a major disease mechanism in ALS. It is present early in pathology, well before motor neuron (MN) loss and symptom onset, implying it is a highly effective therapeutic target because it acts upstream in pathophysiology. Hyperexcitability results from either more excitatory and/or less inhibitory signalling. Whilst much previous research in ALS has focussed on the former, MN function is strongly regulated by inhibitory gamma- aminobutyric acid (GABA)-ergic interneurons. GABA, the major CNS inhibitory neurotransmitter, binds to $GABA_A$ receptors ($GABA_A$ R) - ligand-gated chloride (Cl-) channels. Defects in GABA signalling are increasingly described in ALS patients and early in mouse models, where they correlate with disease progression[1]. Interestingly, riluzole also modulates $GABA_A$ signalling as well as its well-known glutamatergic actions. Together these data imply that GABA-ergic signalling is important, but neglected, as a therapeutic target in ALS. Hence, we predict that GABA-based therapeutics will be highly effective in preventing hyperexcitability and thus neurodegeneration in ALS.

**AIM:** To examine if a novel class of compounds are protective in cellular, zebrafish and two mouse models of ALS.

## METHODS:

*Neuronal cells* expressing ALS-variants TDP-43, SOD1 or FUS; inclusion formation, mislocalisation to the cytoplasm, and apoptosis.
*Zebrafish* expressing ALS-cyclin F–movement impairment using a Zebrabox tracking system
*Mouse models* Intraperitoneal administration of compound (or saline vehicle litter/gender matched controls) 3x /week (50 mg/kg) to both *$SOD1^{G93A}$* and *NEFH-hTDP-43ΔNLS (ΔNLS)* mice, and non-transgenic controls was performed in pre-symptomatic mice. Rotarod, grip strength, neurological score and body weight were examined

## RESULTS:

Using an unbiased screening approach we identified novel $GABA_A$ receptor-binding compounds that were protective in cellular and zebrafish models of ALS. We synthesised 150 novel compounds via medicinal chemistry and screening assays in cellular and zebrafish models were used to perform structure-activity relationships, to guide further synthesis. The best lead compound, ML4-10, was protective against multiple cellular phenotypes in neuronal cells; inclusions formed by mutant SOD1, TDP-43 and FUS, TDP-43 mis-localisation, and apoptosis in cells, and *in vitro* against oxidative stress. Hence ML4-10 clears TDP-43 pathology, the major pathological ALS hallmark. We then performed ligand binding assays to identify the target of ML4-10 and found that it binds to inhibitory $GABA_A$ receptors. Ml4-10 was also protective against motor impairment in a zebrafish ALS model ($CCNF^{S521G}$). It was then tested in two mouse models: *$SOD1^{G93A}$* and *NEFH-hTDP-43ΔNLS*. ML4-10 prevented motor neuron loss, delayed disease onset, improved rotarod performance and grip strength, or prevented body weight loss in these models.

Basic Science
*BS-O-MP005*

# DEVELOPING A PEPTIDE TREATMENT STRATEGY FOR ALLEVIATING GGGGCC-INDUCED C9ALS/FTD NEURODEGENERATION

[1]Chan, Ho Yin Edwin; [1] Chen Huizhen; [1]Leong Lok I Maggie; [1]Ngo Chi Kei Jacky

[1]School of Life Sciences, The Chinese University of Hong Kong, Room 509B Mong Man Wai Building, Hong Kong, China

## INTRODUCTION:

The GGGGCC repeat expansion within the first intron of chromosome 9 open reading frame 72 (*C9orf72*) gene has been identified as the most common genetic cause of familiar ALS and FTD cases. This group of patients is commonly referred to as C9ALS/FTD patients. The expanded GGGGCC sequence is bidirectionally transcribed into GC-rich repetitive RNAs. Both the sense GGGGCC and antisense CCCCGG RNA form RNA foci, which sequester RNA binding proteins, including transcriptional regulatory protein YY1. This study investigated the use of a YY1 protein fragment, $YY1^{19}$, as a peptide-based therapeutic for C9ALS/FTD.

## METHODS:

To evaluate $YY1^{19}$'s binding affinity for GGGGCC RNA, fluorescence polarization (FP) assays were performed. The biological activity of $YY1^{19}$ was assessed using the CytoTox96® Non-Radioactive Cytotoxicity Assay, which quantifies cell death by measuring lactate dehydrogenase (LDH) release, a marker of apoptosis. The inhibitory activity of YY119 peptide is strongly influenced by its structural conformation. To identify the critical pharmacophores responsible for its function, we conducted a comprehensive structure-activity relationship (SAR) study by synthesizing nineteen alanine-substituted variants of YY119. Each variant contained a single alanine substitution at a distinct amino acid position. A *Drosophila* model of C9ALS/FTD was used to evaluate the effect of $YY1^{19}$ in vivo.

## RESULTS:

Results demonstrated a binding affinity (Kd) of 106 ± 22.64 mM for $YY1^{19}$, supporting its potential for targeted interactions with GGGGCC RNA. Treatment of SK-N-MC cells expressing pAG3-$(GGGGCC)_{66}$ with varying concentrations of $YY1^{19}$ resulted in significantly enhanced potency, with an $IC_{50}$ value of 114.8 ± 38.38 nM, demonstrating high efficacy in inhibiting GGGGCC RNA-induced cell death.

Retinal degeneration was observed in flies expressing expanded $(GGGGCC)_{36}$ under the gmr-GAL4 driver. Administration of $YY1^{19}$ provided significant neuroprotection, highlighting its therapeutic potential for neurodegenerative diseases associated with GGGGCC RNA expansions.

Building upon these insights, we implemented a peptide engineering strategy to optimize $YY1^{19}$ for enhanced binding and functional activity. A promising variant, $YY1^{19x}$, exhibited a significantly improved binding affinity for GGGGCC RNA. FP assays confirmed a >70- fold increase in affinity compared to the original $YY1^{19}$ peptide. This enhancement highlights the potential of engineered peptides in targeting RNA repeats involved in neurodegenerative diseases, offering a more potent therapeutic strategy for conditions such as C9ALS/FTD.

## CONCLUSION:

We identified a fragment in YY1 called $YY1^{19}$, which is a peptide derived from the YY1 protein. The $YY1^{19}$ peptide shows high RNA- binding affinity towards GGGGCC RNAs. We further performed peptide engineering on YY119, and identified a variant, $YY1^{19x}$, which exhibits an ~70-fold improvement in GGGGCC RNA binding.

## REFERENCE:

1. Chen et al. (2023) Mutant GGGGCC RNA prevents YY1 from binding to Fuzzy promoter which stimulate Wnt/b-catenin pathway in C9ALS/FTD. Nat. Commun. **14**(1):8420

Basic Science
*BS-O-MP006*

# EXPLORING THE CELL BIOLOGY OF GENE-ENVIRONMENT INTERACTIONS IN ALS USING HUMAN IPSCS

[1]Thorne, Bryony; [1]Talbot J; [1]Bindoff A; [1]Phipps A; [1]Atkinson R; [1]King A; [1]Perry S; [1]Cook A

[1]Wicking Dementia Research and Education Centre, University of Tasmania, 17 Liverpool St, Hobart, Australia

## INTRODUCTION:

The development of ALS is described as a multistep process in which different genetic and environmental factors interact and contribute to disease progression (1, 2). High penetrance mutations in ALS-associated genes account for several steps in this process, however, it remains unclear how these gene variants interact with environmental exposures to increase disease risk. Our objective is to determine whether specific gene variants confer increased vulnerability to degeneration when exposed to organophosphate and organochlorine pesticides as exemplar environmental exposures associated with ALS.

## METHODS:

Neural stem cells (NSCs) and cortical neurons were generated from human induced pluripotent stem cell (iPSC) lines carrying ALS-associated TARDBP Q331K and FUS R216C gene variants alongside isogenic controls (3). Following exposure to pesticides for 72 hours, we measured cell viability, subcellular TDP-43 and FUS localisation, and neuronal activity by multielectrode array. Multi-parameter 'cell painting' was performed to quantify organelle-specific changes.

## RESULTS:

Exposure to organophosphate and organochlorine compounds resulted in a significant concentration-dependent decrease in cell viability. Sublethal concentrations of these compounds induced changes to TDP-43 and FUS staining intensity and subcellular localisation, with differences specific to TARDBP Q331K and FUS R216C cells identified. This was accompanied by morphological changes to organelles and subcellular features including mitochondria, nucleoli, and the cytoskeleton.

## CONCLUSION:

Organophosphate and organochlorine pesticides influence cellular processes implicated in ALS pathogenesis and TARDBP Q331K and FUS R216C gene variants may increase vulnerability to these compounds. We are testing these associations using iPSC models with other ALS-associated variants in these genes; this may be important for understanding the multistep process of ALS pathogenesis.

## REFERENCES:

1. Al-Chalabi A, Calvo A, Chio A et al. The Lancet. 2014; 13: 1108-1113
2. Zufiria M, Gil-Bea F, Fernandez-Torron R. Progress in Neurobiology. 2016;142: 104-129
3. Pantazis C, Yang A, Lara E et al. Cell Stem Cell. 2022; 29: 1685-1702

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP007*

# DIVERGENT NEURONAL EXCITABILITY PROFILES ON A SINGLE-CELL AND SYNAPTIC NETWORK LEVEL IN IPSC-DERIVED MOTOR NEURONS FROM SALS PATIENTS

[1,2]Do-Ha D; [1,2]Issac A; [1]Maksour S; [1,2]McAlary L; [1,2]Ooi L

[1]School of Science, and Molecular Horizons, University of Wollongong, NSW, Australia, [2]ARC Centre of Exellence in Quantum Biotechnology, Australia.

**INTRODUCTION**:
An early clinical observation in ALS patients is hyperexcitability of motor neurons in the cortex and spinal cord, prior to hypoexcitability and deterioration of motor neuron function[1]. The mechanisms that underlie the alterations in electrical signalling of ALS motor neurons throughout disease progression are not yet fully understood. Here, we characterised the electrical signature on a single-cell and network level of induced pluripotent stem cell (iPSC)-derived motor neurons from sALS patients and healthy control donors.

**METHODS**:
We generated iPSC-derived motor neurons from 6 sALS patients and 5 healthy control donors, including a pair of monozygotic twins discordant for sALS. Whole-cell patch clamping was used to assess the electrophysiological properties of single motor neurons from sALS patients and healthy control donors. Moreover we used microelectrode arrays (MEAs) to measure neuronal network activity in iPSC- derived motor neuron cultures. Following electrophysiological characterisation, immunocytochemistry was performed to quantify synapsin-1, a pre-synaptic marker, in motor neuron cultures from sALS patients and healthy control donors.

**RESULTS**:
We found that iPSC-derived motor neurons from the sALS patients exhibited an increase in repetitively firing and $Na^+$ currents, compared to those from healthy control donors, consistent with increased intrinsic neuronal excitability. However, when examining the network activity of sALS motor neuron cultures using microelectrode arrays (MEAs), we measured a 40% reduction in the mean firing rate and 20% reduction in burst duration in sALS motor neuron cultures, suggesting reduced synaptic activity on a network level. Moreover synchronous firing, an indicator of the strength of synaptic connections, was also reduced in sALS motor neuron cultures. Consistent with the functional output, quantification of pre- synaptic marker synapsin-1 showed a significant reduction in axonal synapsin-1 puncta in sALS motor neuron cultures compared to healthy control cultures ($P<0.0001$).

**CONCLUSION**:
Our findings suggest that intrinsic hyperexcitability does not correlate with increased synaptic network activity *in vitro.* These data highlight an important distinction in the interplay between intrinsic excitability and synaptic activity in ALS.

**REFERENCES**:
1. Do-Ha et al., 2018, 'Impairments in Motor Neurons, Interneurons and Astrocytes Contribute to Hyperexcitability in ALS: Underlying Mechanisms and Paths to Therapy', *Molecular neurobiology*, vol. 55, no. 2, pp. 1410–1418.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP008*

# *C9ORF72* PATIENT-DERIVED SPINAL CORD ORGANOIDS REVEAL KEY ALS PHENOTYPES

*Li Jun Loh[1], Joel Mason[1], Yifan Wang[2], Yupei You[3], Heejung Shim[2], Forough Habibollahi[4], Brett Kagan[4], Bradley Turner[1]*, Samantha Barton[1]**

1. Florey Institute of Neuroscience and Mental Health, Melbourne VIC
2. School of Mathematics and Statistics/Melbourne Integrative Genomics, University of Melbourne VIC
3. Walter and Eliza Hall Institute, Melbourne VIC
4. Cortical Labs, Melbourne VIC

## INTRODUCTION:

ALS patient induced pluripotent stem cell (iPSC)-derived motor neurons provide an important disease model but lack the complexity of the human CNS. We aimed to generate spinal cord organoids from ALS patient-derived iPSC harbouring *C9orf72* expansion mutations, and CRISPR-Cas9 gene-edited isogenic controls, that faithfully recapitulate the complexities of the CNS for the interrogation of ALS disease pathways and the identification of effective therapeutic strategies.

## METHODS:

Spinal cord organoids were generated using iPSCs from three independent ALS patients harbouring *C9ORF72* mutations and their respective isogenic controls. Organoids were caudalised and ventralised to the spinal cord pMN domain (methodology manuscript in preparation). To assess cell populations and pathology, immunocytochemical and RNAScope analyses were performed. MNs in the organoids were labelled using a HB9::GFP lentivirus and their axonal length tracked over time. Organoids underwent electrophysiological recordings over time using a multi-electrode array (MEA) system. Organoids also underwent single cell RNA sequencing to identify mutation dependent gene expression changes.

## RESULTS:

We established and phenotyped spinal cord organoids with enhanced *HOX10* expression, consistent with lumbar specification. Immunocytochemical analysis revealed diverse cell populations (MN, interneurons, astrocytes and oligodendrocytes). RNAScope revealed the presence of RNA foci. MEA profiling of organoids is ongoing; preliminary studies revealed increased spikes and bursting events in *C9ORF72* patient- derived organoids, compared to isogenic counterparts, suggesting a hyperexcitable phenotype in our organoids. MN from *C9ORF72* patients revealed shorter neurite lengths, compared to isogenic counterparts (n=3 independent differentiations of all lines, *$p<0.05$). Single cell RNA sequencing data analyses are ongoing, revealing new insights into the molecular pathways underlying ALS phenotypes.

## CONCLUSION:

We have pioneered a novel organoid model of ALS which recapitulates mature and functional spinal cord architecture. *C9ORF72* patient-derived spinal cord organoids revealed neurodegenerative and excitability phenotypes consistent with ALS, reinforcing the potential of spinal cord organoids for disease modelling and drug screening.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-MP009*

# RNA-BINDING REGULATION OF TDP-43 AGGREGATION IN MOTOR NEURON DISEASE

Bademosi AT[1], Chye YJ[1], Ellis S[1], Kellet E[1], Meunier FA[1,2], Walker AK[1,3]

[1] Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia, 4072
[2] School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia, 4072
[3] Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, 2006

**INTRODUCTION**:
The hallmark of neurodegenerative diseases such as motor neuron disease (MND) is the abnormal accumulation of proteins associated with their altered function. How, why, and when these proteins begin to aggregate has not been fully elucidated. In up to 97% of all MND cases, TAR DNA-binding protein-43 (TDP- 43) is a key protein that is mislocalised from its native nuclear presence into cytoplasmic inclusions. The precise mechanism that drives the aggregation of TDP-43 in MND is unknown, however identifying the changes in the dynamics of the protein within the nucleus could shed light on how the different mutations contribute to its altered function in MND.

**METHODS**:
To unravel the underlying mechanism of protein aggregation in MND (1), we applied nanoscale single-molecule imaging (2-3) to identify the changes in the dynamics of TDP-43 caused by well characterised pathogenic-causing mutations, cellular stressors, and RNA interaction. Single molecule tracking of mEOS3 tagged proteins, enabled the characterisation of proteins dynamics at nanoscale.

**RESULTS**:
We observe that different MND-linked mutations uniquely inhibit the mobility of TDP-43, and oxidative stressors such as arsenite also immobilise TDP-43 molecules within inclusions. Furthermore, our data indicates that post-translational modifications in TDP-43 such as acetylation similarly restricts its dynamics within the nucleus and the overexpression of GU-rich RNA that preferentially binds to TDP-43 releases it from confinement within these inclusions.

**CONCLUSION**:
Together, our data suggests that the confinement of normal protein dynamics is indicative of its function. For example, the immobilisation of TDP-43 is a key step in the formation of toxic aggregates in disease which RNA-interaction might be key to preventing.

**REFERENCES**:
1. Keating SS, Bademosi AT, San Gil R, Walker AK. Aggregation-prone TDP-43 sequesters and drives pathological transitions of free nuclear TDP-43. 2023. *Cell Mol Life Sci*.

2. Bademosi AT, et al., EndophilinA-dependent coupling between activity-induced calcium influx and synaptic autophagy is disrupted by a Parkinson-risk mutation. 2023. *Neuron*.

Basic Science
*BS-O-O001*

# NOVEL REDOX REGULATED GENE THERAPY PROTECTIVE IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

**[1]Parakh S;** [1]Shadfar S; [1]Hunter J; [1]Mumtaz N, [1]Prachi M, [1]Atkin JD

[1]Motor Neuron Disease (MND) Research Centre, Macquarie Medical School (MMS), Macquarie University, Sydney, Australia

## INTRODUCTION:

Gene therapy has been transformed by the advent of adeno-associated virus (AAV) vectors, which offer structural simplicity and a strong safety profile [1]. Redox dysregulation— an imbalance in oxidation and reduction reactions leading to oxidative stress—has emerged as a key pathological feature of sporadic ALS [2]. We have demonstrated that restoring redox homeostasis using nucleoredoxin (NRX), a novel nucleocytoplasmic redox regulator confers neuroprotection in MND models, both in vitro and in vivo. Specifically, NRX-AAV9-mediated gene therapy significantly improved MND phenotype in the ΔNLS-TDP-43 mouse model [3], (provisional patent filed) which recapitulates the cytoplasmic mislocalization of TDP-43, a hallmark of most ALS cases.

## METHODS:

AAV9 PHP.B.NRX-GFP was transduce into the brain and spinal cord of ΔNLS TDP-43 mice via lateral tail vein injection for expression in motor neurons. A similar construct encoding GFP only was used as a negative control. Injections were performed into mice, 1 week before mutant human TDP-43 ΔNLS expression was induced by removal of Dox, hence prior to the onset of symptoms/pathology to ensure widespread expression in neurons. Analysis of motor phenotype, neurological score and survival was examined.

## RESULTS:

NRX expression improved several cellular dysfunctions induced by TDP-43 such as inclusion formation, cytoplasmic mislocalisation, nuclear morphology defects, DNA damage and apoptosis in neuronal cells. Importantly, delivering NRX by AAV9-based vector by intravenous (i.v.) administration significantly improved motor impairment - muscle strength, motor function, ALS-TDI neurological score, disease onset, motor neuron counts and survival.

Importantly, overexpression of NRX did not induce toxicity in wildtype or ΔNLS-TDP-43 mice, implying it is an ideal gene therapy candidate.

## CONCLUSION:

NRX is a novel nucleocytoplasmic protein that regulates redox homeostasis in both nuclear and cytoplasmic compartments implicated in TDP-43 pathology. Our findings provide compelling evidence that NRX gene therapy is protective in the ΔNLS-TDP-43 mouse model, making it a promising candidate for mitigating MND disease phenotypes.

## REFERENCES:

1. Phase, I., II Phase IIPhase II, and I. I. I. Phase III. "The clinical landscape for AAV gene therapies." nature reviews| Drug DIScoVery 20 (2021): 173.

2. Jagaraj, Cyril Jones, Sonam Parakh, and Julie D. Atkin. "Emerging evidence highlighting the importance of redox dysregulation in the pathogenesis of amyotrophic lateral sclerosis (ALS)." Frontiers in cellular neuroscience 14 (2021): 581950.

3. Walker, Adam K., et al. "Functional recovery in new mouse models of ALS/FTLD after clearance of pathological cytoplasmic TDP-43." Acta neuropathologica 130 (2015): 643-660

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-O-O002*

# ASSESSING INTRINSIC OLIGODENDROCYTE DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

[1,2]Beau, Francois-Xavier; [1]Mason J; [1]Andres A; [3]Gonsalvez D; [1]Turner B; [3]Barton S

[1]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia.
[2]Department of Anatomy and Physiology, The University of Melbourne, Melbourne, Australia
[3]Department of Anatomy and Developmental Biology, Monash University, Melbourne, Australia

## INTRODUCTION:

Oligodendrocytes (OLs) facilitate myelination and are critically important for motor neuron health and function. OL loss and myelin disruptions have been identified in *SOD1*-ALS rodent models, and reduced myelination correlates with TDP-43 aggregation in human tissue, but mechanisms underpinning OL involvement in ALS remain to be investigated.

## AIMS & HYPOTHESIS:

This study aims to characterize OL function in ALS and determine whether OLs are intrinsically dysfunctional.
We hypothesize that patient-derived iPSC OLs will exhibit myelination anomalies in ALS, independent of neuronal influence.

## METHODS:

ALS patient-derived iPSCs (*SOD1*: n=2, *C9orf72*: n=3), alongside their respective CRISPR-Cas9 generated isogenic controls, were differentiated into either OPCs[1] or spinal cord- patterned myelinating organoids[2]. In organoids, Myelin Basic Protein (MBP) immunolabelling was used to assess myelin sheath number and length per OL to characterize myelinating capacity.
To assess intrinsic OL dysfunction, OPCs were transplanted into myelin-deficient immunodeficient *Shiverer* mice (n=2-3 iPSC differentiation to OPCs, and n=3-6 mice per differentiation for each iPSC line), where human OLs myelinate healthy mouse axons. This chimeric model isolates possible OL dysfunction from neuronal influence. The same myelin analyses were conducted.

## RESULTS:

In organoids, OLs from ALS patients formed longer but fewer myelin sheaths in two *C9orf72* lines compared to isogenic controls ($p<0.05$ for both), whereas *SOD1* OLs showed shorter but more abundant sheaths ($p<0.05$).
Chimeric mice demonstrated robust integration of human iPSC-derived OLs (human nuclei+Sox10+) and extensive myelination (MBP+) in the corpus callosum. ALS patient oligodendrocytes produced longer sheaths in one *C9orf72* line compared to its isogenic control when myelinating mouse neurons ($p<0.05$), but no differences were seen in the *SOD1* lines.

## CONCLUSION:

OLs exhibit disease-specific dysfunction in ALS, with analyses of chimeric mice suggesting cell-autonomous defects. These findings suggest OLs could be potential therapeutic targets in ALS.

## REFERENCES:

[1]Barton, S. K., Magnani, D., James, O. G., Livesey, M. R., Selvaraj, B. T., James, O. T., Perkins, E. M., Gregory, J. M., Cleary, E., Ausems, C. R. M., Carter, R. N. C., Vasistha, N. A., Zhao, C., Burr, K., Story, D., Cardinali, A., Morton, N. M., Hardingham, G. E., Wyllie, D. J. A., & Chandran, S. (2021). Transactive response DNA-binding protein-43 proteinopathy in oligodendrocytes revealed using an induced pluripotent stem cell model. *Brain Communications*, 3(4), fcab255.

[2]James, O. G., Selvaraj, B. T., Magnani, D., Burr, K., Connick, P., Barton, S. K., Vasistha, N. A., Hampton, D. W., Story, D., Smigiel, R., Ploski, R., Brophy, P. J., Ffrench-Constant, C., Lyons,
D. A., & Chandran, S. (2021). iPSC-derived myelinoids to study myelin biology of humans. *Developmental Cell, 57*(1), 146.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-AT001*

# iMOVE-MND: IMPROVING MOBILITY VIA EXOSKELETONS IN PEOPLE LIVING WITH MND

[1]James L. Williamson, [1,2]Dina Wickremeratne, [3]Zachary F. Lerner, [4, 5]Robert D. Henderson, [2,4]Shyuan T. Ngo, [1,4]Frederik J. Steyn, [1]Taylor J. M. Dick

[1]School of Biomedical Sciences, The University of Queensland, Building 64, St Lucia, QLD, 4072, Australia, [2]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Building 75, St Lucia, QLD, 4072, Australia, [3]Department of Mechanical Engineering and Orthopedic Surgery, Northern Arizona University, Building 69, Flagstaff, AZ, 86011, United States, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Ned Hanlon Building, Herston, QLD, 4029, Australia, [5]Centre for Clinical Research, The University of Queensland, Building 71, Herston, QLD, 4029, Australia.

**INTRODUCTION**:

Current approaches to improving gait in MND involve the prescription of assistive devices like ankle-foot orthoses. These devices often restrict users to a "one-size-fits-all" approach [1]. Wearable assistive technologies that adapt to the user and environment, in real time, may offer individualized support. Advances in robotics have enabled the design of lightweight, portable, and personalized wearable devices [2] aimed at enhancing lower-limb function. Here we evaluate (i) the short-term influence of, and (ii) user perceptions and attitudes towards, portable robotic ankle exoskeletons as mobility aids in MND.

**METHODS**:

Ten people living with MND (plwMND) (7M, 3F, 60±10 years, 85.8±19.7 kg) participated in this study (HREC 2024/HE000042). Participants walked with and without robotic ankle exoskeleton assistance (SPARK, Biomotum Inc.) at fast-preferred speeds, both overground and on an instrumented treadmill (FIT5, Bertec Inc.). Overground walking environments included variable terrains (*e.g.,* ramps and stairs) to establish real-world feasibility. Lab-based treadmill walking was accompanied with a gait analysis, where participant biomechanics were measured using force plates and motion capture (Miqus, Qualisys AB). Perceptions and attitudes towards ankle exoskeletons were assessed via a survey and semi-structured interview.

**RESULTS**:

Preliminary results indicate ankle exoskeletons increased preferred walking speeds in plwMND by 0.13±0.03 $ms^{-1}$ compared to a shoe-only (shod) condition ($p<0.001$). Simultaneously, peak vertical ground reaction forces of plwMND increased by an average of 5.5%, with assistance, compared to shod ($p=0.010$). When asked to rate their satisfaction with real-world device performance, 90% of participants were either 'very satisfied' or 'satisfied'. When asked if they would wear the device in their daily life, 80% of participants responded with either 'definitely yes' or 'probably yes'. All participants who traversed stairs with the device (N=7), reported feeling comfortable during assisted stair ascent and descent.

**CONCLUSION**:

Robotic ankle exoskeletons may improve walking performance in plwMND, with potential to improve independence and quality of life.

**REFERENCES**:

1. Majmudar et al., *Muscle & Nerve*. **50(1)**:4-13, 2014.
2. Conner et al., *IEEE Open J Eng Med Biol*, **2**:320-323, 2021.

Basic Science
*BS-P-B001*

# EPIGENETIC REGULATION IN MOTOR NEURONE DISEASE: INSIGHTS FROM GENE EXPRESSION AND NEXT-GENERATION SEQUENCING

Millar, Doug; Melki, JR

MiND Biosciences, Randwick, NSW, 2031

**INTRODUCTION**:
Motor Neurone Disease (MND) is a debilitating neurodegenerative disorder characterised by progressive motor neurone dysfunction, muscle weakness, and respiratory failure. The majority of MND cases occur sporadically, with only ~10% attributed to known genetic mutations. Recent evidence indicates that epigenetic mechanisms, including DNA methylation, histone modifications, and RNA modifications, may play a critical role in disease initiation and progression (1,2). These processes can alter gene expression without modifying the underlying DNA sequence. In this study, we aimed to investigate the expression patterns of key epigenetic regulators in MND motor neurones to gain insights into potential disease mechanisms and identify novel diagnostic targets.

**METHODS**:
We studied motor neurons obtained from patients diagnosed with MND and those from healthy individuals. Initially we investigated the expression patterns of key genes involved in epigenetic regulation using standard real-time mRNA quantification. We have also employed Next-generation sequencing (NGS) to characterise genome-wide DNA and RNA epigenetic profiles. Custom bioinformatic pipelines were then used to identify significantly altered epigenetic marks and correlate them with changes in gene expression and disease progression.

**RESULTS**:
Preliminary analyses revealed large differences (up to 70-fold) in the expression of some key genes involved in the epigenetic regulation of DNA and RNA. Subsequent analysis also found substantial differences in epigenetic patterns between MND and control motor neurones, with certain regions exhibiting modifications correlating with reduced expression of neuroprotective genes.

**CONCLUSION**:
Our results offer valuable insights into the epigenetic landscape of MND and underscore the potential for epigenetic biomarkers as novel diagnostic tools. Further research may clarify how these epigenetic changes influence disease progression and pave the way for targeted interventions aiming to restore normal gene expression and improve patient outcomes.

**REFERENCES**:
1. Younesian S, Yousefi AM, Momeny M, Ghaffari SH, Bashash D. The DNA Methylation in Neurological Diseases. Cells. 2022 Oct 31;11(21):3439. doi: 10.3390/cells11213439. PMID: 36359835; PMCID: PMC9657829.

2. Junya L, Lijuan X, Xin Z, Kai L, Mingyan L, Ke D. Role of N6-methyladenosine modification in central nervous system diseases and related therapeutic agents. Biomedicine & Pharmacotherapy. 2023 162, 114583. Doi: 10.1016/j.biopha.2023.114583

PACTALS 2025
pactalscongress.com
MND Australia Care Forum
Theme: From Discovery to Delivery

Basic Science

*BS-P-B002*

# MONITORING NEURODEGENERATION WITHIN CORE MOTOR PATHWAYS IN AMYOTROPHIC LATERAL SCLEROSIS USING DIFFUSION MRI

[1,2]Hannes Almgren, [4]Colin J. Mahoney, [1,3]William Huynh, [1]Arkiev D'Souza, [1]Sienna Berte, [1,2]Jinglei Lv, [1,5]Chenyu Wang, [6]Matthew C Kiernan, [1,2*]Fernando Calamante, [1,3*]Sicong Tu

[1] Brain & Mind Centre, The University of Sydney, Sydney, Australia, [2] School of Biomedical Engineering, Faculty of Engineering, The University of Sydney, Sydney, Australia, [3] Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia, [4] Department of Neurology, Liverpool Hospital, NSW, Australia, [5] Sydney Neuroimaging Analysis Centre, Sydney, Australia, [6] Neuroscience Research Australia; Scientia Professor of Neuroscience, University of NSW, Sydney, Australia. *Equal contribution.

**INTRODUCTION**:
Diffusion MRI is sensitive to white matter changes in amyotrophic lateral sclerosis (ALS). The current study aimed to establish disease profiles across core motor pathways, and their relevance to clinical progression in ALS.

**METHODS**:
Sixty-five participants (ALS=47; Control=18) were recruited for the study. White matter integrity of motor, somatosensory, and premotor subdivisions within the corticospinal tract and corpus callosum were quantified by fibre density, fibre-bundle cross-section, structural connectivity, and fractional anisotropy. Analyses focused on identifying diffusion metrics and tract profiles sensitive to ALS pathology, and their association with clinical progression.

**RESULTS**:
Reduced fibre density of the motor subdivision of the corpus callosum (CC) and corticospinal tract (CST) demonstrated best performance in classifying ALS from controls (area-under- curve: CCmotor=0.81, CSTmotor=0.76). Significant reductions in fibre density (CCmotor: $p<0.001$; CSTmotor: $p=0.016$), and structural connectivity (CCmotor:$p=0.008$; CSTsomatosensory: $p=0.012$) indicated presence of ALS pathology. Reduced fibre density & cross-section significantly correlated with severity of functional motor impairment (ALSFRS-R; CCmotor: $r=0.52$, $p=0.019$; CSTmotor: $r=0.59$, $p=0.016$). The largest effect sizes were generally found for motor and somatosensory subdivisions across both major white matter bundles.

**CONCLUSION:**
Current findings suggest that ALS does not uniformly impact the corticospinal tract and corpus callosum. There is a preferential disease profile of neurodegeneration mainly impacting primary motor fibres. Microstructural white matter abnormality indicated presence of ALS pathology while macrostructural white matter abnormality was associated with functional motor impairment. Quantification of white matter abnormality in corticospinal tract and callosal subdivisions holds translational potential as an imaging biomarker for neurodegeneration in ALS.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-B003*

# MOTOR UNIT TRACKING USING HIGH-DENSITY SURFACE ELECTROMYOGRAPHY IN PEOPLE DIAGNOSED WITH MOTOR NEURON DISEASE

[1]Bayer PA; [2]Del Vecchio A; [1]Thomas HJ; [3]Perju-Dumbrava L; [1]Ferri A

[1]Institute for Health and Sport, Victoria University, Footscray, Australia, [2]Department of Artificial Intelligence in Biomedical Engineering, Friedrich-Alexander-University, Erlangen, Germany, [3]Calvary Health Care Bethlehem, Caulfield South, Australia.

**INTRODUCTION**:
High-density surface electromyography (HDsEMG) is a novel tool that can identify and longitudinally track motor unit (MU) characteristics in healthy individuals. A hallmark symptom of motor neuron disease (MND) is the progressive degeneration of MUs. Therefore, we aimed to evaluate if HDsEMG can also be used to track individual MUs in people diagnosed with MND, and therefore to follow the disease progression. This case report presents the characteristics of longitudinally tracked MUs of the tibialis anterior of an individual with MND, who was participating in an exercise training program.

**METHODS**:
A 44-year-old male with spinal onset MND who was 4 months post diagnosis at time of enrolment, performed isometric ramp contractions at 35%, 50% and 70% of maximal voluntary force of the ankle dorsi-flexors every four weeks for 16 weeks. HDsEMG recordings from the tibialis anterior were obtained using a 64-electrode grid. MU tracking was performed through correlation analysis of the MU action potentials. Changes in MU discharge rate and peak-to-peak value after 16 weeks were assessed.

**RESULTS**:
The average number of identified MUs across all force levels was 14 at baseline and decreased to 10 after 16 weeks. For each force level, four MUs were tracked across 16 weeks. Correlation values of tracked MUs ranged from 0.80 to 0.95. After 16 weeks, the discharge rate of all MUs (except one) increased, with an average of 5.3±7 pulses per second. MU action potential peak-to-peak values increased in average by 30.6% in 7 MUs (0.06±0.05mV) and decreased by 31.5% in 5 MUs (0.09±0.10mV).

**CONCLUSION**:
In early stages of disease when some MUs are still functional, HDsEMG along with decomposition and correlation analysis, is a suitable tool for tracking individual MUs over time. These methods could be valuable for monitoring MND progression, studying MU remodeling, and evaluating effects of interventions.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-B004*

# INVESTIGATING DNA DAMAGE IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): UNVEILING PROSPECTIVE ALS BIOMARKERS

[1]Shashi Gautam, [1]Sayanthooran Saravanabavan, [1]Edwin Lim, [1,2]Julie D Atkin

[1]Macquarie Medical School, Macquarie University Centre for MND Research, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia, [2]La Trobe Institute for Molecular Science, La Trobe University, Bundoora, VIC, Australia.

**INTRODUCTION**:
DNA damage and genomic instability are emerging as critical factors in ALS pathogenesis. Circular RNAs (circRNAs), which result from back-splicing of the transcript have shown to contribute to genomic instability [1]. ALS associated proteins TDP43, FUS are involved in circRNA biogenesis and therefore their dysregulation could potentially trigger genomic instability in motor neurons. DNA Ligase III (LIGIII) is crucial for DNA repair [2]. LIGIII deficiency therefore leads to increased sensitivity to oxidative stress. My project aims to identify DNA repair related biomarkers in ALS by examining repair protein expressions in serum and differentially expressed circRNA in ALS to evaluate their impact on DNA repair in ALS.

**METHODS**:
CircRNAs with potential TDP43, FUS binding sites were selected for expression analysis via qRT-PCR in cells expressing TDP43/FUS with loss of nuclear localization signal(ΔNLS). DNA damage stimuli were used to induce double-strand or single-strand DNA breaks. Serum samples from healthy and ALS patients were obtained. Western blotting was performed on pooled serum samples to detect DNA repair proteins.

**RESULTS**:
Preliminary results revealed that circRNA associated with a DNA repair gene, Tumor Protein p53 Binding Protein 1 (*circTP53BP1*) was found to increase with etoposide treatment and was dysregulated in cells expressing TDP43ΔNLS. In patient serum, the expression of LIGIII was significantly decreased in ALS patients as compared to the healthy controls.

**CONCLUSION**:
We identify *circTP53B1* to be dysregulated in cells expressing TDP43ΔNLS, and that serum expression of LIGIII is dysregulated in ALS patients, therefore indicating potential DNA damage related ALS biomarker candidates.

**REFERENCES**:
1. Zhou Tet.al., Emerging roles of circular RNAs in regulating the hallmarks of thyroid cancer. 2024; Cancer Gene Ther. Pg507-516.
2. Paes Dias M et.al., Loss of nuclear DNA ligase III reverts PARP inhibitor resistance in BRCA1/53BP1 double-deficient cells by exposing ssDNA gaps. 2021; Mol Cell. Pg4692- 4708.

Basic Science
*BS-P-B005*

# DOWNREGULATION OF MIR-423-3P EXACERBATES STRESS GRANULE PATHOLOGY IN CELL MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

Shiffali Khurana[1,2], Vanshika Ahuja[1], Bandana Kumari Sahu[1], Sagar Verma[1,$], Mandaville Gourie-Devi[3,4**], Nirmal Kumar Ganguly[1], Uma Dhawan[2**], Vibha Taneja[1*]

[1]*Department of Biotechnology and Research, Sir Ganga Ram Hospital, Delhi, India*
[2]*Department of Biomedical Science, Bhaskaracharya College of Applied Sciences, University of Delhi, India*
[3]*Department of Neurophysiology, Sir Ganga Ram Hospital, Delhi, India*
[4]*Department of Neurology, Sir Ganga Ram Hospital, Delhi, India*
[$]*Current affiliation:*
*Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden*

**BACKGROUND AND AIMS:**
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by selective loss of motor neurons and pathological accumulation of stress granules (SGs), dynamic ribonucleoprotein aggregates formed under cellular stress. This study aimed to investigate the role of exosomal miRNAs in SOD1-based cell model of ALS.

**METHODS:**
We performed exosomal miRNA sequencing from conditioned media of motor neuronal cells expressing wild-type and ALS-associated mutants, L84F and G85R. For identification of target genes of significantly dysregulated miRNAs, multimiR was exploited. Pathway enrichment of predicted target genes was performed using EnrichR, with pathways considered significant at $P < 0.05$. Additionally, we validated the expression levels of key dysregulated miRNAs in serum-derived exosomes of sporadic ALS (sALS) patients. To explore the functional implications of miRNA dysregulation, we tested whether miRNA mimics could rescue miRNA levels and modulate the expression of key target genes.

**RESULTS:**
Twenty-eight differentially expressed miRNAs were commonly regulated by both L84F and G85R SOD1 mutants. Among them, miR-423-3p was significantly downregulated in exosomes derived from mutant SOD1. Target prediction and functional enrichment analyses revealed that miR-423-3p regulates genes involved in SG dynamics, unfolded protein response, BDNF-TrkB and mTORC1 signaling, and ATF6/PERK-mediated gene expression. Downregulation of miR-423-3p led to increased expression of target genes, PABPC1, DDX1, EIF4EBP1 and ATF6 as confirmed by luciferase reporter assays, qRT-PCR and western blotting. Further, miR-423-3p was significantly downregulated in sALS patients (n = 35) as compared to healthy individuals (n = 35) ($P < 0.0001$). Moreover, higher levels of miR-423-3p were associated with males ($P = 0.039$) and a positive correlation was observed between miR-423-3p expression and age at onset ($P = 0.018$).

**CONCLUSIONS:**
Our findings suggest that miR-423-3p could serve as a potential biomarker for ALS. Targeting miR-423-3p or its downstream effectors may offer a novel therapeutic strategy for mitigating SG-associated neurotoxicity in ALS.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-B006*

# MACHINE LEARNING TO UNCOVER UNIQUE LIPID BIOMARKERS FOR MND

[1,2]Luikinga SJ, [1]Tharoonphansak C, [3]Narayana V, [4]Eisner A, [1]Lin V, [1]Tomas D, [1]Cuic B, [1]Turner BJ

[1] Motor neuron disease laboratory, The Florey Institute of Neuroscience and Mental Health, Parkville, Melbourne, Australia, [2]Australian Institute for Bioengineering and Nanotechnology, St Lucia, Brisbane, Australia, [3]Metabolomics Australia, Parkville, Melbourne Australia, [4]University of Melbourne, Parkville, Melbourne, Australia.

## INTRODUCTION:

Increasing evidence suggests that altered metabolism is a major feature shared between most people living with MND (plwMND). Several studies have reported hypermetabolism in plwMND, independent of their genetic status [1-3], and it is now widely viewed that metabolic alterations likely contribute to worse prognosis[4]. Several lipidomic studies have provided new insights into the extent of metabolic and lipid dysregulation in MND. Evaluation of blood and postmortem samples obtained from plwMND, as well as muscle and spinal cord samples from preclinical mouse models of MND have shown significant lipid alterations, closely linked to energy metabolism and neuronal health. We recently discovered extensive lipid dysregulation in the spinal cord and skeletal muscle of the TDP-$43^{Q331K}$ mouse model of MND [5]. We therefore hypothesized that circulating lipids could be a useful biomarker in MND.

## METHODS:

We collected blood samples from three preclinical mouse models of MND: $SOD1^{G93A}$, $C9ORF72^{500}$, and TDP-$43^{Q331K}$. We performed targeted lipidomic analysis on plasma from pre-symptomatic, transgenic mice compared to their wildtype littermates. We utilised this mouse lipidomic profile as a discovery dataset, which we then validated in a human dataset comprising plasma lipidomic profiles from plwMND, non-neurodegenerative disease controls, and Parkinson's disease (PD) patients. Due to the heterogeneity of MND, we iteratively evaluated potential lipid biomarkers, using combinations of 3 lipids from distinct subclasses. Machine learning and bioinformatic tools were implemented to minimize false positives and to increase the sensitivity of our dataset.

## RESULTS:

A total of 160 lipids across the mouse dataset were significantly altered, resulting in a total of 438,480 combinations to be tested in the human lipid dataset. Filtering was done with AUC cutoff of 0.7 and odds ratio based on the group analysis (i.e. MND vs control, MND vs PD and PD vs control). For example, if lipid A has an odds ratio of 1.02, it means a 1 unit increase in A is associated with 1.02 times higher odds of the sample having MND. This filtering reduced the total number of remaining combinations to 717. Exclusion of combinations that performed well in control vs PD led to a reduction in the total number of combinations to 159. Final filtering based on a positive correlation with disease outcome (higher odds of an individual having MND) resulted in 18 remaining combinations of lipids in our final dataset of MND specific biomarkers.

## CONCLUSION:

We have identified a blood lipid profile which appears to be specific and unique to MND. Further validation in a larger cohort of plwMND, asymptomatic gene carriers and controls, is ongoing.

## REFERENCES:

1. Desport, J.C., et al., Neurodegener Dis, 2005. 2(3-4): p. 202-7.
2. Bouteloup, C., et al., J Neurol, 2009. 256(8): p. 1236-42.
3. Funalot, B., et al., Amyotroph Lateral Scler, 2009. 10(2): p. 113-7.
4. Steyn, F.J., et al., J Neurol Neurosurg Psychiatry, 2018. 89(10): p. 1016-1023.
5. Luikinga, S., et al., bioRxiv, 2022: p. 2022.08.30.505901.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-B007*

# TONGUE MUSCLE ABNORMALITIES AND SURVIVAL OUTCOMES IN MND

Thomas B Shaw[1,2,3]* Patrick Aiken[4] Jeryn Chang[5] Fernanda L Ribeiro[1] Xiangyun Zhu[1,6,7] Robert D Henderson[3,7] Matthew C Kiernan[8,9] Pamela A McCombe[3] Shyuan T Ngo[3,10] Shana T Taubert[7] Frederik J Steyn[3,5] Sicong Tu[11,12] Markus Barth[1,2,10] Brooke-Mai Whelan[4]†

1. School of Electrical Engineering and Computer Science, The University of Queensland, St Lucia, QLD, Australia
2. Centre for Advanced Imaging, The University of Queensland, St Lucia, QLD, Australia
3. Department of Neurology, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
4. School of Health and Rehabilitation Sciences, The University of Queensland, St Lucia, QLD, Australia
5. School of Biomedical Sciences, The University of Queensland, St Lucia, QLD, Australia
6. School of Medicine and Dentistry, Griffith University, Gold Coast, QLD, Australia
7. Queensland Health, Queensland, Australia
8. Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia
9. Neuroscience Research Australia, Randwick, NSW, Australia
10. Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, QLD, Australia
11. South Eastern Sydney Local Health District, Randwick, NSW, Australia
12. ARC Training Centre for Innovation in Biomedical Imaging and Technology (CIBIT), Centre for Advanced Imaging, The University of Queensland, St Lucia, QLD, Australia

*Corresponding Author
†Senior Author

## INTRODUCTION:

MND impacts muscles involved in speech and swallowing, including the tongue. We have shown that tongue musculature is sensitive to change in bulbar presentations of MND[1]. However, no studies have assessed internal tongue musculature *in vivo* and their impact on speech in MND. We used MRI to assess morphological changes in key tongue muscles among patients with MND and controls and collected and analysed speech samples to evaluate the relationship between muscle degeneration and speech function.

## METHODS:

MRI data were collected over 8 years from MND (n=96), and control (n=105) participants from datasets across Australia. Superior and inferior longitudinal, genioglossus, and transverse/vertical muscle volumes were extracted using in-house AI tools. A subset of participants provided speech samples for analysis of diadochokinetic articulation rate to be compared with tongue volume. Case-control comparisons and within-case analyses were conducted, examining muscle volumes against disease severity and progression. Survival analyses were conducted with Cox proportional hazards models.

## RESULTS:

We report significant deviations in muscle volumes in MND patients versus controls. A substantial effect of diagnosis on individual tongue muscle volumes was found, and an effect of bulbar presentation on volumes over disease progression. ALSFRS-R bulbar sub-score has little predictive value for volume decrease. Survival probabilities significantly differed across volume clusters determined by K-means clustering. Decreased volumes of genioglossus and transverse/vertical muscles were associated with worse survival outcomes. Additionally, inferior longitudinal and transverse/vertical muscle volume were significantly correlated ($p<0.05$) with articulation rate and average syllable duration.

## CONCLUSION:

The present study developed MR techniques as *in vivo* biomarkers for MND, combined with speech pathology metrics. Findings have established relationships between muscle atrophy and patient survival. Lower articulation rates are associated with reduced tongue volume and its connection to tongue atrophy suggests articulation rate may serve as a simple, non- invasive marker of bulbar dysfunction.

**Words:299**

**REFERENCES**:

[1] T. B. Shaw *et al.*, "Segmentation of the Human Tongue Musculature Using MRI: Field Guide and Validation in Motor Neuron Disease," Dec. 13, 2024, *medRxiv*. doi: 10.1101/2024.12.12.24318964.

Basic Science

*BS-P-B008*

# THE AUSTRALIAN SPORADIC ALS TRANSCRIPTOMIC RESOURCE: INSIGHTS INTO DISEASE PROGRESSION AND SPLICING FROM LONG- AND SHORT-READ RNA SEQUENCING

Wai Cheong[1], Laura Ziser[1], Lachlan Sparke[1], Robert Henderson[2], Leanne Wallace[1], Naomi Wray[1,3], Anjali Henders[1], Pamela McCombe[4], Allan McRae[1], Fleur Garton[1]

1. Institute for Molecular Bioscience - University of Queensland
2. Royal Brisbane and Women's Hospital, Queensland
3. The Big Data Institute - University of Oxford
4. Centre for Clinical Research - University of Queensland

**INTRODUCTION**:

Amyotrophic lateral sclerosis (ALS) is a fatal disease that progressively impairs the nervous system and motor function. The disease exhibits significant heterogeneity, driven by a complex interplay of genetic and environmental factors, making it challenging to pinpoint its underlying mechanisms.

To address this, we have generated a comprehensive blood transcriptomic data from a large human cohort (NALS=121, Ncontrols=58) as a resource for the Sporadic ALS Australia Systems Genomics Consortium. Initial differential expression (DE) analyses support blood as a relevant proxy for disease, with pathway enrichment overlapping DE findings in ALS iPSC derived-motor neurons (e.g. p53 pathway).

**METHODS**:

Here, we expand on this by investigating disease progression and splicing, performing longitudinal analyses on N=41 cases and long- read RNAseq (NALS=8, Ncontrols=8) analyses. RNA was extracted from PAXgene tubes and libraries prepared using the Illumina Stranded Total RNA RiboZero Plus or Iso-Seq® Express 2.0 Kit. Sequencing was performed on the DNBSEQ-T7 (~50M reads, PE150bp) and the PacBio Revio (~10M reads per sample). Longitudinal analysis was conducted using the R package "varianceParition" with sex as a covariate. Gene expression changes associated with disease progression (ALSFRS-R) were modelled using regression analysis.

**RESULTS**:

While no individual transcript met FDR significance, pathway enrichment analysis of the top 100 genes identified enriched pathways including regulation of RNA splicing (GO:0043484), Apoptosis (WP254), and regulation of tumour necrosis factor-mediated signalling pathway (GO:0010803).

For splicing analyses we conducted discovery and validation studies, identifying 73 significant splicing clusters. Notably, two were found in RSRP1, a gene involved in spliceosomal complex assembly and apoptosis.

**CONCLUSION**:

The dataset represents the most comprehensive ALS blood transcriptomic resource to date and provides novel insight into disease mechanisms. Ongoing integration with ALS tissue data and genetic risk loci aims to further elucidate pathways for potential therapeutic targeting.

**REFERENCES**:

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-CM001*

# THE NOTORIOUS SUSPECTED ALS: TO BE OR NOT TO BE?

[1]Merkulov YA; [2]Plieva EL; [2]Lezina DS; [3]Pyatkov AA; [2]Merkulova DM

[1]Institute of General Pathology and Pathophysiology, 8 Baltiyskaya St., Moscow, Russia, [2]BM Guekht Neurology Center, Central Clinical Hospital «RZD-Medicine», 2 Budayskaya St., Moscow, Russia, [3]Sechenov First Moscow State Medical University, 11-1 Rossolimo St., Moscow, Russia

**INTRODUCTION**:
Amyotrophic lateral sclerosis (ALS) is a terminal neurodegenerative disorder with typical cases involving lesions of both upper and lower motor neurons (UMN, LMN). While relevant Russian guidelines are under legalization, international revisions to the diagnostic criteria of ALS from the initial El Escorial to the Awaji have been challenged by the controversial inclusion and elimination of the Suspected clinical disease category. The currently trending Gold Coast proposal is to acknowledge progressive LMN dysfunction in at least two body regions without signs of UMN involvement as ALS.

**CASE REPORT**:
A 44-year-old male was referred for motor neuron disease evaluation with complaints of weakness mostly in his legs progressing over 6 months to frequent stumbling and falling and muscle twitching. The patient didn't relate the onset of symptoms to anything and denied contact with toxic, illicit, or medical substances. His systematic evaluation was negative for malignancy or infection. His preceding MRI work-up had insignificant findings, and his lab results were within reference values, except for the elevated serum creatine kinase. He was diagnosed with unspecified neuromuscular pathology by a geneticist, with spinal muscular atrophy and Pompe disease excluded. Electromyographic (EMG) examination was negative in identifying neuromuscular blocking and inconclusive in nerve conduction velocity assessment. However, the motor unit potentials (MUPs) were found to be significantly increased in amplitude and duration, with numerous fibrillations (fibs) and fasciculation potentials (FPs) in all of the studied muscles. On admission, there were no signs of cranial nerve and pseudobulbar involvement. His arm muscles had 5/5 strength and sufficient bulk. He could stand on his toes, somewhat worse on his heels, and elements of the steppage gait were seen. He rose from a squat with the help of his hands, but no Gowers' maneuver or scapular winging was present. His arm tendon reflexes were borderline brisk, and knee reflexes were preserved despite thigh muscle hypotrophy, but no spasticity or pathologic reflexes were detected. Generalized fasciculations, spontaneous and evoked by a reflex hammer, were clinically apparent. There were no sensory, pelvic, or coordination impairments. Repeated EMG confirmed chronic neurogenic changes with polyphasic MUPs increased in duration by 67%, 78%, 52%, and 23% in the quadriceps, tibialis anterior, deltoid, and mentalis muscle respectively, with matching amplitudes up to 5572 µV max. Simultaneously the profuse and widespread fibs and FPs defined the ongoing denervation. The MRI images were reevaluated as nonspecific, and the upper limit of normal corticolumbar conduction time was identified by transcranial magnetic stimulation. Thus, idiopathic steady progression of LMN signs in several body regions of this patient led to the diagnosis of ALS, its lumbosacral form as per the domestic classification, and timely initiation of treatment with riluzole (RLZ).

**CONCLUSION**:
As illustrated above, LMN-based ALS appears to be the case, and future research is crucial to confirm or deny this logic regarding the justification of early RLZ trials in such patients.

**REFERENCES**:
1. Zavalishin IA (Ed.) Amyotrophic lateral sclerosis. Guidelines for doctors. Moscow: Eurasia+; 2007, 447 p.
2. Shefner JM, Al-Chalabi A, Baker MR, et al. A proposal for new diagnostic criteria for ALS. Clin Neurophysiol 2020;131:1975–1978.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-CT&P001*

# THE CHALLENGES OF RUNNING ALS INVESTIGATOR-INITIATED TRIALS AND OPPORTUNITIES TO IMPROVE

[1]Ramsey, Eleanor; [1]Timmins, Hannah C; [1]Mazumder, Srestha; [1]Talbot, Dayna-Lee; [1]Murphy, Paris M; [1]Ashhurst, Jasmine F; [1,2]Kiernan, Matthew C.

[1] Neuroscience Research Australia, 139 Barker St, Randwick, Australia, [2]University of New South Wales, Sydney, Australia

**INTRODUCTION**:
Treatment for ALS in Australia is limited to Riluzole and Edaravone. Given the limited ALS treatment options available it is highly beneficial for people diagnosed with ALS to have the opportunity to participate in a clinical trial. This is an overview of the challenges faced by ALS clinical trial units in Australia to facilitate ALS clinical trials, in particular investigator-initiated trials.

**METHODS:**
The progress of three investigator-initiated, mult-icentre, randomised, controlled trials of repurposed drugs carried out in Australia was reviewed, the challenges encountered and the areas for potential improvement. Clinical trial units across Australia specialising in ALS were surveyed to identify the barriers to running clinical trials in ALS at their site and opportunities to improve.

**RESULTS**:
The progress of three investigator-initiated, multi-centre, randomised, placebo-controlled trials of repurposed drugs carried out in Australia was reviewed, the challenges encountered and the areas for potential improvement. Clinical trial units across Australia specialising in ALS were surveyed to identify the barriers to running clinical trials in ALS at their site and opportunities to improve.

**CONCLUSION**:
As Australia is currently a desirable destination for initiating clinical trials and ALS awareness in the community is high, we are in a position to leverage this to make novel improvements that would allow for ALS investigator-initiated trials to start up faster, run cost efficiently and give Australian ALS patients access to more drug trial opportunities. Possible solutions identified include developing an Australian platform study protocol, creating an ALS placebo dataset from historical studies, establishing novel long- standing clinical trial contracts for both sites and suppliers using the national ALS Clinical Trial Network and funding study coordinator positions rather than study visits.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-E001*

# LIPID-LOWERING DRUGS AND AMYOTROPHIC LATERAL SCLEROSIS: A MENDELIAN RANDOMIZATION STUDY

[1]Kailin Xia, [2]Ninghao Huang, [1]Yajun Wang, [1]Gan Zhang, [1]Lu Tang, [1]Linjing Zhang, [2]Tao Huang, [1]Dongsheng Fan

[1]Department of Neurology, Peking University Third Hospital, 49 North Garden Road, Beijing, China
[2]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, 38 Xueyuan Road, Beijing, China;

**INTRODUCTION**:
There has been growing evidence of abnormal lipid metabolism in amyotrophic lateral sclerosis (ALS), even in the presymptomatic stage. Some epidemiological studies indicate that premorbid higher levels of circulating lipids were associated with the risk of ALS, implying a potential effect of modifying lipids on ALS[1,2]. However, the effect of lipids lowering drugs on ALS remains elusive. Therefore, we performed a drug target MR to study whether lowering lipids and ALS are genetically associated.

**METHODS**:
We obtained the largest European-based GWASs data for TG, HDL-C, LDL-C, ApoA1, ApoB, and ALS. Drug target MR were adopted to test the effect of LDL-C-lowering targets (ACLY, HMGCR, PCSK9, and NPC1L1) on ALS[3].

**RESULTS**:
We first verified all the lipid fractions of concern increased the risk of ALS at significant or nominal levels except TG.
Using 2 SNPs in the region of the ACLY gene and 55 SNPs in the region of the PCSK9 gene, we found that the risk of ALS was lowered by 90.1% (IVW-ACLY: OR=0.099, 95% CI 0.012-0.854, P=0.035) and 13.5% (IVW-PCSK9: OR=0.865, 95% CI 0.774-0.966, P=0.010), respectively, with a genetically predicted SD decrease in LDL. In contrast, the results using 25 SNPs in the region of the HMGCR gene and 14 SNPs in the region of NPC1L1 suggested the effect of reduced LDL driven by these genes on ALS was null (IVW-HMGCR: OR=0.971, 95% CI 0.820-1.149, P=0.728; NPC1L1: OR=0.997, 95% CI 0.663-1.499, P=0.989). Considering that different lipid-lowering drugs are commonly used together in clinical; we evaluated the efficacy of combining ACLY and PCSK9 inhibitors. The results showed that it has a protective effect on ALS risk and is more effective than using PCSK9 inhibitors alone (IVW: OR=0.859, 95% CI 0.769-0.960, P=0.007).

**CONCLUSION**:
Our MR analysis supported the hypothesis that the use of ACLY or PCSK9 inhibitors or combining them may improve disease outcome, revealing the potential benefits of population- wide targeted lipid-lowering strategies in ALS prevention; this also makes correlating the genetic profile of a patient to a specific lipid- lowering goal possible.

**REFERENCES**:
1. Mariosa D, et al. Blood biomarkers of carbohydrate, lipid, and apolipoprotein metabolisms and risk of amyotrophic lateral sclerosis: A more than 20-year follow-up of the swedish amoris cohort. Ann Neurol. 2017;81:718-728
2. Seelen M, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. Journal of Neurology. 2014;261:1949-1956
3. Xiao W, et al. Effects of genetically proxied lipid-lowering drugs on acute myocardial infarction: A drug-target mendelian randomization study. Lipids Health Dis. 2024;23:163

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-E002*

# RELATIONSHIP BETWEEN PRIOR EXPOSURE TO ARTHROPOD VIRUSES AND AMYOTROPIC LATERAL SCLEROSIS IN MALAYSIAN PATIENTS

[1,2]Zulhairy-Liong, NA; [1]Lee CLL; [1]Tan MP; [1]Capelle DP; [1,2]Edgar S; [1]Soo CI; [2]Ahmad-Annuar A; [1]Shahrizaila N; [3]Sam IC

[1]Department of Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia, [2]Department of Biomedical Science, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia, [3]Department of Medical Microbiology, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.

**INTRODUCTION**:
Emerging evidence suggests genetic and environmental factors including exposure to neurotropic viruses might cumulatively trigger the onset of ALS. In Malaysia, arthropod-borne viruses such as dengue (DENV), Zika (ZIKV) and chikungunya (CHIKV) are endemic pathogens, but the link with neurodegeneration has yet to be explored. This study aims to assess the association between past exposure to DENV, ZIKV and CHIKV with ALS through a case-control study.

**METHODS**:
A total of 103 Malaysian ALS patients (onset: 32-78 years) diagnosed according to revised El-Escorial criteria were recruited from University Malaya Medical Centre (UMMC), and samples from 206 age- and sex-matched, non-ALS controls (age: 30-80 years) were collected from UMMC and AGELESS cohort. IgG seropositivity against DENV and CHIKV were measured by anti-DENV and anti-CHIKV indirect ELISA IgG respectively (Euroimmun, Germany), while IgG seropositivity against ZIKV was tested using sandwich-type NuGen ZIKV IgG Capture ELISA (InBios International, USA). Chi-squared test and logistic regression were used to compare the seropositivity between groups.

**RESULTS**:
Significantly higher IgG seropositivity against CHIKV was found in ALS patients (20.4% vs 9.2% in controls) and multivariate analysis has shown that past exposure to CHIKV was significantly associated with ALS (OR=2.97; 95% CI:1.49, 5.95; $p$=0.002). Conversely, more DENV seropositives were found in controls (88.4%) than ALS patients (76.9%), indicating a negative link (OR=0.35; 95% CI:0.18, 0.67; $p$=0.002). No difference was observed in seropositivity against ZIKV between patients and controls (3.8% in patients, 5.1% in controls; OR=0.91; 95% CI:0.26,3.14; $p$=0.875).

**CONCLUSION**:
This is the first study providing evidence of a significant association between past CHIKV exposure and ALS, and a negative association with exposure to DENV. These preliminary findings warrant a further study of the possible role of these infections in a larger cohort of ALS patients and controls, especially in other CHIKV and DENV-endemic regions.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-G001*

# STRATEGIC ALS AUSTRALIA SYSTEMS GENOMICS CONSORTIUM: SALSA-SGC

**Anjali K Henders[1],** Laura Ziser[1], Fleur Garton[1], Allan McRae[1], Shyuan T. Ngo[1], Matthew Kiernan[2], Nigel Laing[3], Susan Mathers[4], Merrilee Needham[5], Dominic Rowe[6], David Schultz[7], Steve Vucic[8], Pamela McCombe[9], Robert Henderson[9,] Ian P Blair[6], Naomi R Wray[1], and the SALSA-System Genomics Consortium.

[1]The University of Queensland, Queensland; [2]The University of New South Wales, New South Wales; [3]Harry Perkins Institute, Western Australia; [4]Calvary Health Care Bethlehem, Victoria; [5]Fiona Stanley Hospital, Western Australia; [6]Macquarie University, New South Wales; [7]Flinders Medical Centre, South Australia; [8]The University of Sydney, New South Wales; [9]Royal Brisbane and Women's Hospital, Queensland;

## INTRODUCTION:

The **Strategic ALS Australia – Systems Genomics Consortium (SALSA)** was established in 2015 to provide dedicated infrastructure to support longitudinal collection of clinical data and biological samples from individuals with ALS in Australia. The aim to use collaborative system genomics approaches will accelerate understanding of risk factors and pathways underlying the aetiology of the disease. Additional data via linkage to the National MindAUS registry has also been established.

## METHODS:

Harmonised data has been collected to include longitudinal sociodemographic, clinical and biological samples every three months from diagnosis, together with environmental and lifestyle risk factor data. Using bead-array technology, genome-wide SNP data has been generated for all cases.

## RESULTS:

At census (Dec 2024) the cohort consisted of **1393 cases and 350 controls** recruited across seven clinical sites (5 states) in Australia between 2015 and 2024. Consistent with international registry data, within cases, 64.5% are male and 35.3% are female, with approximately 9% self-reporting having a first degree relative with an ALS/FTD diagnosis. Approximately 59% have a primary diagnosis of Classic ALS with onset of symptoms most common in lumbar (32%) and cervical (28%) regions.

Included in the SALSA protocol is routine genetic screening and has identified individuals carrying known pathogenic variants in *C9orf72* (6.7%) and *SOD1* (1.1%). Screening of an *UNC13A* variant supports recruitment into the MAGNET Clinical trial and to date 20 individuals have been identified as carrying the *C/C* genotype of the rs12608932 SNP (18.5% of total patients screened).

Generating genome-wide SNP data enables generation of polygenic risk scores (PRS), for complex traits and biomarkers. Here we present an ALS PRS predictor developed using the latest GWAS from Project Mine and demonstrate a significant difference between cases and controls for **both** familial and sporadic cases. We have also calculated PRS scores for > 100 complex traits and biomarkers and present distributions for those known to have an association with an ALS diagnosis.

## CONCLUSION:

SALSA-SGC continues to provide a centralised resource and support to ALS / MND research in Australia. The dedicated website (http://salsasgc.org) includes an online data explorer to enable data mine clinical and genetic phenotypes in real-time.

## REFERENCES:

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-G002*

# INTEGRATED MULTI-OMICS ANALYSIS IDENTIFIES NOVEL RISK LOCI FOR AMYOTROPHIC LATERAL SCLEROSIS IN THE CHINESE POPULATION

[1]Ji, He; [1]Dongsheng, Fan

[1]Neurolgy department, Peking University Third Hospital, Beijing, China

**INTRODUCTION**:

Epigenetic processes are influenced by both environmental factors and genetic components, which serve as mediators in the relationships between genetic risk, environmental exposure, and disease of ALS. DNA methylation, the most well-characterized and extensively studied epigenetic variation, has significant potential for elucidating the pathogenic mechanisms of sALS. DNA methylation levels can be modulated by pharmacological treatments, lifestyle changes, and rehabilitation programs; these options provide potential strategies to delay or prevent disease onset and progression. Therefore, identifying and validating sALS- specific methylation markers as potential therapeutic targets is crucial for advancing sALS treatment strategies.

**METHODS**:

In this study, we profiled epigenome-wide DNA methylation and SNP array data in 687 blood-derived DNA samples (480 sALS cases, 207 controls) collected from patients at the Department of Neurology at Peking University Third Hospital (PUTH-ALS cohort). This is the largest multi-omic study of its kind in the Han Chinese population. We used the Illumina Human Methylation 450 Bead Chip to identify DNA methylation patterns associated with ALS. The methylation samples were obtained from a much larger multi-omic study that included 1,234 sALS cases and 2,850 controls[3]. Consequently, our study was able to utilize both genomic and epigenomic resources, providing insights into the pathogenesis of sALS from the perspective of gene-environment interactions. We investigated the possible biological significance of our findings in sALS pathogenesis by examining functional information for corresponding annotated genes and by utilizing other available multi-omics data, such as ALS postmortem expression profiles (NYGC-ALS) and ALS European GWAS summary statistics (EU-ALS).

**RESULTS**:

Here, we analyzed epigenome-wide DNA methylation patterns in peripheral blood cells from 480 patients with sporadic ALS (sALS) and 207 controls of Han Chinese ancestry (Peking University Third Hospital ALS cohort, PUTH-ALS) using an Illumina Infinium Human Methylation450 Bead Chip. After rigorous quality control, we identified several differentially methylated positions (DMPs), 12 of which were high-confidence hypermethylated biomarkers in the PUTH-ALS cases: cg26515084 (*ANKLE2*), cg14338936 (*SSH2*), cg14642222, cg14746032 (*TNFRSF21*), cg16209303 (*CDC42BPB*), cg14187266 (*ADAMTS9*), cg27325861 (*LOC100130581*), cg25801052 (*ARID5A*), cg00743991 (*PTPRN*), cg08296288 (*ELAVL3*), cg16125874 (*CLEC14A*), cg15421321 (*JAG2*). Reduced corresponding gene expression was observed in the New York Genomic Center ALS cohort's postmortem brain tissue expression profile. We also identified a 34-loci signature that can assess sALS risk based on abnormal methylation patterns (AUC = 0.915). This risk assessment has the potential to aid in early clinical diagnosis of sALS.

**CONCLUSION**:

Our study provides strong evidence that DNA methylation plays an important role in sALS pathogenesis, and the observed DNA methylation aberrations may serve as valuable references for identifying diagnostic biomarkers.

Basic Science

*BS-P-G003*

# MUTATION IN NEK1 CAUSES CILIARY DYSFUNCTION AS A NOVEL PATHOGENETIC MECHANISM IN ALS

[1]Min-Young Noh; [2]Seoung-il Oh;[1]Sugyeong Ahn; [1]Mi-Hyeon Kang; [3]Sun Joo Cha; [3]Minyeop Nahm; [1]Seung Hyun Kim*

[1] Department of Neurology, College of Medicine, Hanyang University, Seoul, Republic of Korea

[2] Department of Neurology, Kyung Hee University Medical Center, Seoul, Republic of Korea

[3] Dementia Research Group, Korea Brain Research Institute, Daegu, Republic of Korea

**INTRODUCTION**:

Neuronal primary cilia, vital for signaling and cell-cycle regulation, have been implicated in maintaining neuronal identity. While a link between primary ciliary defects and neurodegenerative diseases is emerging, the precise pathological mechanisms remain unclear.

**METHODS**:

We studied the genetic contribution of *NEK1* to ALS pathogenesis by analyzing the exome sequences of 920 Korean patients with ALS. To understand the disease contribution of *NEK1* variants in ALS, we performed a series of functional studies using patient fibroblasts, focusing on primary cilia and microtubule- related phenotypes. These findings were also validated in iPSC-derived motor neurons (iPSC- MNs).

**RESULTS**:

*NIMA-related kinase 1* (*NEK1*), a gene encoding a serine/threonine kinase involved in cell cycle regulation, has been identified as a risk gene for amyotrophic lateral sclerosis (ALS). Here, we report that mutations in *NEK1* cause primary ciliary abnormality, cell cycle re- entry, and disrupted tubulin acetylation in ALS. We analyzed the whole-exome sequences of 920 Korean patients with sporadic ALS and identified 16 *NEK1* variants in 23 patients. We found that two novel variants, p.E853Rfs*9 and p.M1?, reduced *NEK1* expression, resulting in loss-of-function (LOF), and one synonymous splicing variant (p.Q132=) exhibited an aberrant isoform lacking exon 5. All three *NEK1* variants exhibited abnormal primary ciliary structure, impaired sonic hedgehog signaling, and altered cell-cycle progression. Furthermore, the ALS- linked variants induced intracellular calcium overload followed by AurA-HDAC6 activation, resulting in ciliary disassembly. These defects were restored by treatment with the intracellular Ca2+ chelator, BAPTA. We also found that *NEK1* variants cause decreased -tubulin acetylation, mitochondrial alteration, and impaired DNA damage response (DDR). Notably, drug treatment to inhibit HDAC6 restored the *NEK1*-dependent deficits in patient fibroblasts. We confirmed that data found in patient fibroblasts were reproduced in the iPSC- MNs model.

**CONCLUSION**:

Our results suggest that *NEK1* contributes to ALS pathogenesis through the LOF mechanism, and HDAC6 inhibition provides an attractive therapeutic strategy for *NEK1* variants associated with ALS treatment.

**REFERENCES**:

1. Ma R et al. Primary cilia and ciliary signaling pathways in aging and age-related brain disorders. Neurobiol Dis 2022;163:105607.

2. Kenna KP et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. Nat Genet 2016;48(9):1037-42.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-G004*

# COMPREHENSIVE GENETIC TESTING EXPANDS THE NUMBER OF CLINICALLY-RELEVANT MUTATIONS IN ALS GENES IN A MULTI-ETHNIC MALAYSIAN COHORT

[1,2]Zulhairy-Liong, NA; [1,2]Edgar S; [3,4]Ellis M; [1]Capelle DP; [3,4,5]Kennerson ML; [1]Shahrizaila N; [2]Ahmad-Annuar A

[1]Department of Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia, [2]Department of Biomedical Science, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia, [3]Northcott Neuroscience Laboratory, ANZAC Research Institute, Sydney Local Health District, Concord, NSW, Australia, [4]Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [5]Molecular Medicine Laboratory, Concord Hospital, Concord, NSW, Australia.

## INTRODUCTION:

While extensive genetic studies have been conducted in Western and East-Asian countries, little is known about ALS genetic background in Southeast Asia. This study aimed to expand genetic analysis of Malaysian ALS patients who were negative for mutations in the two most common ALS genes (*SOD1*, *C9orf72*).

## METHODS:

A total of 202 ALS patients, diagnosed based on revised El-Escorial-Awaji criteria, were recruited from University Malaya Medical Centre for genetic screening. Of these, 6/202(3%) patients harbored *SOD1* mutations, and 3/165(1.8%) had *C9orf72* repeat expansion. Of the remaining patients, 113 (38.9% Malay, 35.4% Chinese, 19.5% Indian, 6.2% others; onset 19-79 years) underwent whole genome/exome sequencing to screen for single nucleotide polymorphisms and small insertion/deletions in 42 ALS-associated genes. Candidate variants were prioritized based on MAF ≤1% in East Asian populations, CADD score ≥15, classified as pathogenic, likely pathogenic or variants of uncertain significance (VUS) according to the ACMG guidelines, and found in ≤1% of 132 healthy controls from Singapore Sequencing Malay/Indian Project databases [1, 2].

## RESULTS:

In 38.9% (44/113) of our patients, at least one pathogenic, likely pathogenic or VUS was identified. Eleven patients (9.7%) harbored two or more variants. One pathogenic *FIG4* variant (p.K657Sfs*2) and 7 likely pathogenic variants in *FUS* (p.R485Pfs*32; onset 19 years), *TARDBP* (p.I383del; onset 45 years), *DCTN1* (c.279+1G>A), *GRN* (c.599-1G>C), *NEK1*(p.I633Nfs*28), *SPAST* (p.E449G) were found in 7 cases (6.2%), all apparently sporadic. Additionally, 36 patients (31.9%) carried ≥1 VUS in 22/42 genes. No significant differences were observed in gender, ethnicity, age of onset, or disease duration between patients carrying multiple, one or no variant.

## CONCLUSION:

In addition to mutations in *SOD1* and *C9orf72*, 6.2% of patients carried clinically-relevant variants in other ALS-associated genes and were classified as genetically solved, indicating the importance of comprehensive genetic screening irrespective of age of onset, family history or ethnicity.

## REFERENCES:

1. Wong, et al. (2014). Insights into the genetic structure and diversity of 38 South Asian Indians from deep whole-genome sequencing. PLoS Genet, 10(5), e1004377. https://doi.org/10.1371/journal.pgen.1004377
2. Wong, et al. (2013). Deep whole-genome sequencing of 100 southeast Asian Malays. Am J Hum Genet, 92(1), 52-66. https://doi.org/10.1016/j.ajhg.2012.12.005

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-G005*

# A GENOME-WIDE ASSOCIATION STUDY IDENTIFIES *ADAM25-GPM6A* LOCUS ASSOCIATED WITH AGE AT ONSET IN JAPANESE PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

[1]Nakamura Ryoichi; [1]Tohnai G; [1]Atsuta N; [2]Matsuda Y; [3,4]Morimoto S; [2]Ito D; [2]Katsuno M; [5]Izumi Y; [6]Morita M; [7]Iwata I; [7]Yabe I; [8]Nakazato T; [8]Hattori N; [9]Hirayama T; [9]Kano O; [10]Tamura A; [11]Suzuki N; [11]Aoki M; [12]Shibuya K; [12]Kuwabara S; [13]Oda M; [14]Hashimoto R; [14]Aiba I; [15]Ishihara T; [15]Onodera O; [16]Yamashita T; [16]Ishiura H; [17]Bokuda K; [17]Shimizu T; [18]Ikeda Y; [19]Hasegawa K; [20]Tanaka F; [21]Yokota T; [22]Kanai K; [23]Noto Y; [5]Kaji R; [1]Niwa J; [1]Doyu M; [1]Okada Y; [3,4]Okano H; [2]Nakatochi M; [1]Sobue G; on behalf of the Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS) study group

[1]Aichi Medical University, Nagakute, Japan; [2]Nagoya University, Nagoya, Japan; [3]Keio University, Kawasaki, Japan; [4]Tokyo Metropolitan Institute for Geriatrics and Gerontology,Tokyo, Japan; [5]Tokushima University, Tokushima, Japan; [6]Jichi Medical University, Shimotsuke, Japan; [7]Hokkaido University, Sapporo, Japan; [8]Juntendo University, Tokyo, Japan; [9]Toho University, Tokyo, Japan; [10]Mie University, Tsu, Japan; [11]Tohoku University, Sendai, Japan; [12]Chiba University, Chiba, Japan; [13]Vihara Hananosato Hospital, Miyoshi, Japan; [14]NHO Higashinagoya National Hospital, Nagoya, Japan; [15]Niigata University, Niigata, Japan; [16]Okayama University, Okayama, Japan; [17]Tokyo Metropolitan Neurological Hospital, Tokyo, Japan; [18]Gunma University, Maebashi, Japan; [19]NHO Sagamihara National Hospital, Sagamihara, Japan; [20]Yokohama City University, Yokohama, Japan; [21]Tokyo Medical and Dental University, Tokyo, Japan; [22]Fukushima Medical University, Fukushima, Japan; [23]Kyoto Prefectural University, Kyoto, Japan

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) exhibits a wide range of clinical variability, including differences in age at onset (AAO), site of onset, and survival time. AAO is a key prognostic factor influencing disease progression and survival. In Japanese patients with ALS, AAO ranges from 20 to 80 years, with a median AAO of 62.1 years. This variability may be driven by multiple factors, including genetic factors. This study aims to identify the genetic factors influencing AAO in Japanese patients with ALS.

## METHODS:

We analyzed genotype data from 1,808 Japanese ALS patients, imputing 6,963,364 variants. A genome-wide association study (GWAS) was conducted, using the BOLT-LMM algorithm, adjusting for sex, onset site, and the first two principal components. Genome-wide significant variants were examined in a replication cohort of 207 Japanese patients with ALS. Additionally, we assessed mRNA expression in induced pluripotent stem cell (iPSC)-derived motor neurons.

## RESULTS:

In the discovery phase, *ADAM25-GPM6A* locus at 4q34.2 reached genome-wide significance ($p < 5 \times 10^{-8}$) for AAO of ALS. The lead SNP, rs113161727 (minor A allele) was associated with a younger AAO ($p = 4.60 \times 10^{-8}$, $\beta = -4.27$, SE = 0.78). This finding was validated in the replication cohort ($p = 6.81 \times 10^{-3}$, $\beta = -5.10$, SE = 1.87) and confirmed by meta-analysis ($p = 1.08 \times 10^{-9}$, $\beta = -4.40$, SE = 0.72). Among 65 ALS patients with pathogenic *SOD1* variants, those with rs113161727 had an AAO 10.2 years younger than those without it ($p = 0.002$). The SNP was associated with increased *GPM6A* expression in iPSC-derived motor neurons, suggesting that *GPM6A* is an AAO modifier.

## CONCLUSION:

We identified a novel AAO-associated locus in ALS, implicating *GPM6A* as a genetic modifier. This finding highlights genetic diversity in ALS and informs future precision medicine approaches.

## REFERENCES:

1. Yokoi D, et al. Age of onset differentially influences the progression of regional dysfunction in sporadic amyotrophic lateral sclerosis. *J Neurol.* 2016;263:1129–36.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-G006*

# GLYCOLYSIS INHIBITION DOWNREGULATES DNA REPAIR PATHWAYS IN NEURONS

Thais Sobanski [1], Derek J. Richard[2], Frederik J. Steyn[3], Shyuan T Ngo[1]

[1] The Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Saint Lucia, Queensland, Australia.
[2] Cancer and Ageing Research Program, Centre for Genomics and Personalised Health, Queensland Universit of Technology, Brisbane, QLD, Australia.
[3] School of Biomedical Sciences, University of Queensland, Saint Lucia, Queensland, Australia.

## INTRODUCTION:

Metabolic pathways provide cells with the nucleic acids and energy required to repair DNA [2]. Both metabolic and DNA repair dysfunction are considered hallmarks of several neurodegenerative diseases, including ALS. In recent years, it has been shown that crosstalk exists between glycolysis and DNA repair processes, and that proteins previously known to regulate cell metabolism seem to also modulate DNA repair activity [2-3]. The most deleterious form of DNA lesion is the DNA double- strand break (DSB), which if not repaired efficiently can lead to genomic instability [3]. There are two main pathways of DNA DSB repair: Non-Homologous End-Joining (NHEJ) and Homologous Recombination (HR). Because neurons do not divide, they are unable to rely on HR, making them more susceptible to DNA damage [2,3]. Whether glycolysis directly regulates DNA repair activity in neurons remains unknown.

## METHODS:

Glycolysis was inhibited using 2DG (2-Deoxy-D-glucose) or GNE-140 (Lactate dehydrogenase inhibitor) in differentiated SH-SY5Y cells. To identify how glycolysis inhibition affects DNA repair, we performed global transcriptome analysis with Clariom S Assays and quantitative mass spectrometry on cells treated with 2DG. Immunofluorescence was used to determine the kinetics of γ-H2AX (DNA damage marker). DNA repair protein levels and gene expression was quantified by western blot and qPCR, respectively. For experiments, a minimum of n=3 biological replicates were performed. Statistical significance was evaluated using Student's t-test or one-way ANOVA.

## RESULTS:

In addition to the expected decrease in glycolysis pathways, we observed a significant downregulation of key DNA repair genes and proteins in 2DG treated cells. Inhibition of glycolysis by 2DG decreased the mRNA and protein expression levels of key DNA repair kinases ATM and PRKDC (DNA-PK).

As these two proteins are essential for the downstream initiation of the HR and NHEJ DSB repair pathways, it is possible that downregulation of these two effector kinases, by 2DG treatment, could impair the recognition and repair of DSBs. Inhibition of glycolysis also led to a higher number of γ-H2AX foci (marker of DNA Damage), when compared to control cells, both before and after DNA damage. These findings suggest that in 2DG treated cells, DSBs may accumulate even in the absence of exogenous damage, and that the cells are repaired more slowly.

## CONCLUSION:

In SH-SY5Y neurons, inhibition of glycolysis appears to result in an increased susceptibility to DNA damage due to the downregulation of key DNA repair kinases. Our data provides initial insights into the mechanisms by which metabolic deprivation in ALS makes neurons more susceptible to DNA damage.

## REFERENCES:

1. Vandoorne T, Bock KD, Bosch LVD (2018) Energy metabolism in ALS: an underappreciated opportunity? 135:489–509. https://doi.org/10.1007/s00401-018-1835-x
2. Cucchi D, Gibson A, Martin SA (2021) Full article: The emerging relationship between metabolism and DNA repair. 20:943–959. https://doi.org/10.1080/15384101.2021.1912889
3. Gioia U, Francia S, Cabrini M, et al (2019) Pharmacological boost of DNA damage response and repair by enhanced biogenesis of DNA damage response RNAs.https://doi.org/10.1038/s41598019-42892-6

Basic Science
*BS-P-MP001*

# INTERROGATING THE ANATOMICAL ORIGINS OF AMYOTROPHIC LATERAL SCLEROSIS

[1,2]Viden, Aida; [1,2]Bye, Christopher; [1,2]Turner, Bradley J; [1,2]Haidar, Mouna

[1]Florey Institute of Neuroscience and Mental Health, 30 Royal Parade, Parkville, VIC, 3052, Australia, [2]University of Melbourne, Parkville, VIC, 3010, Australia.

**INTRODUCTION**:
Amyotrophic lateral sclerosis (ALS) is characterised by the degeneration of upper motor neurons (UMNs) within the brain and downstream lower motor neurons (LMNs) within the brainstem and spinal cord. While both populations are affected, the site of disease initiation in ALS remains unknown. Our study aims to interrogate the neuroanatomical origin of neurodegeneration in ALS.

**METHODS**:
We crossed floxed mutant $SOD1^{G37R}$ transgenic ALS mice with Uchl1- and HB9-Cre reporter mice to achieve UMN- or LMN-specific mutant SOD1 deletion, respectively. We aimed to assess (i) disease onset via weight loss, rotarod and grip strength, (ii) survival, and (iii) UMN, LMN and neuromuscular junction (NMJ) pathologies at a symptom onset (T1) and end stage (T2) timepoint.

**RESULTS**:
Mice lacking mutant SOD1 within Uchl1-expressing UMNs (*Uchl1-SOD1*) displayed a significant delay in symptom onset, reduced motor deficits and extension in survival by 4.5 months relative to SOD1 control mice (*SOD1*). We additionally observed an attenuation of LMN loss at T1, and a preservation of NMJ innervation at T2. Strikingly, mice lacking SOD1 within HB9-expressing LMNs (*HB9- SOD1*) displayed only minimal motor deficits, an extension in survival of over 9 months, with no apparent LMN or NMJ pathologies at both T1 and T2 timepoints relative to *SOD1* mice.

**CONCLUSION:**
Our findings demonstrate that UMN pathology may contribute to downstream LMN loss, and preservation of LMN integrity is vital to halt ALS disease progression. Collectively, this study is the first to assess the dual interdependence of UMN and LMN pathologies in ALS, providing valuable insights for future therapeutic targeting strategies.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-MP002*

# *IN VIVO* AXONAL TRANSPORT OF MITOCHONDRIA AND SIGNALLING ENDOSOMES IS IMPAIRED IN FAST α-MOTOR NEURONS IN MND MICE

Tosolini, Andrew P. [1, 2, 3]; Ngo , Shyuan T. [2]; Schiavo, Giampietro [3, 4]

[1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, St Lucia, Australia
[2]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, Australia
[3]Department of Neuromuscular Diseases and UCL Queen Square Motor Neuron Disease Centre, Queen Square Institute of Neurology, University College London, United Kingdom
[4]UK Dementia Research Institute, University College London, United Kingdom

**INTRODUCTION**:

Axonal transport ensures the long-range delivery of essential cargoes between proximal and distal neuronal compartments and is critical for neuronal function and survival. Signalling endosomes propagate neuromuscular signalling events to the soma via retrograde transport. To regulate axonal bioenergetics and neuronal homeostasis, mitochondria frequently reposition throughout motor axons to respond to fluctuating local energy demands. Regardless of the MND- causing gene mutation, evidence from various cellular and mouse MND models highlight impairments in axonal transport. Indeed, $SOD1^{G93A}$ and $TDP\text{-}43^{M337V}$ mice display pre- symptomatic transport perturbations, suggesting that such impairments are an early contributor to MND. Additionally, in several MND mouse models, there is selective vulnerability of motor neurons, where fast α-motor neurons are more vulnerable than slow α-motor neurons, which are more resistant to disease. This work aims to determine if axonal transport deficits are specific to an organelle and/or α-motor neuron subtype in MND mice.

**METHODS**:

*In vivo* signalling endosome transport in $SOD1^{G93A}$ and TDP43rNLS mice was visualised in fast/slow α-motor axons by injecting a fluorescently-labelled atoxic fragment of tetanus neurotoxin into tibialis anterior or soleus muscles, respectively. *In vivo* mitochondrial axonal transport was assessed in $SOD1^{G93A}$:Mito.CFP mice, which express cyan fluorescent protein (CFP) in neuronal mitochondria. Intravital imaging of sciatic nerves from live, anaesthetised mice was performed to assess organelle axonal transport dynamics *in vivo*, and the time-lapse microscopy videos were assessed using TrackMate (FIJI).

**RESULTS**:

Axonal transport of signalling endosomes was selectively perturbed in fast, but not slow, α- motor neurons. Moreover, mitochondrial transport was also perturbed in fast α-motor neurons.

**CONCLUSION:**

We provide evidence that the bidirectional transport of multiple intracellular organelles is selectively impaired in fast, but not slow, α- motor neurons in multiple MND mouse models. Altered axonal transport dynamics of endosomes and mitochondria, may in part, underpin the selective vulnerability of motor neuron subtypes.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-MP003*

# DISCOVERING CORE MECHANISMS OF ALS USING PHENOTYPIC SCREENING

**Anthony Basilone[1],** Christian Makhoul[1], Kaylene J. Simpson[2], Michael P. Menden[1], Danny M. Hatters[1]

[1]Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, Victoria, Australia.

[2]Victorian Centre for Functional Genomics, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia.

## INTRODUCTION:

Amyotrophic Lateral Sclerosis (ALS) is predicted to involve defects in various cellular mechanisms, including protein homeostasis, RNA metabolism, vesicular transport, and mitochondrial functioning amongst others. It remains unclear as to what the sequence of events are that drive disease at the molecular level and how these pathways are connected to those events.

## METHODS:

To gain more insight into this biology, we applied a creative machine learning approach and high throughput knock-down involving familial ALS genes. Knockdown was undertaken using a siRNA screen in neuronal-like SH-SY5Y cells, targeting the 43 ALS genes, along with 202 other genes indirectly related to ALS and 324 randomly selected control genes (which are not expected to be involved in ALS). The premise is that the knockdown phenotypes will connect in a way that reflects the normal function of the genes. To uncover unknown functions, we performed an agnostic phenotype screen to assess the effects of altering a wide variety of molecular functions – specifically markers of nucleic acids, cell shape, and cytoskeleton.

## RESULTS:

Machine learning identified 127 phenotypic features in the cells, creating signatures defined as Z-scores against a mock siRNA control. The analysis highlighted hotspots where ALS genes were statistically enriched together phenotypically (11 groups out of 55 groups in total), which reassuringly supported the experiment's rationale in grouping genes expected to be functionally connected. This included anticipated functions (e.g., macroautophagy) and, importantly, others not so clearly understood to be associated with ALS (which will be discussed).

## CONCLUSION:

This work lays the foundation for further exploratory research regarding the ALS genes. The screen can be built upon by moving to a more robust CRISPR knockout model and expanding the phenotypic readouts to include other relevant markers such as stress granules and TDP-43 localisation patterns.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-MP004*

# INVESTIGATING THE ROLE OF ASTROCYTE AUTOPHAGY IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

[1]Dushana Alagiyawanna, [1]Doris Tomas, [1]Brittany Cuic, [1]Bradley Turner, [1]Nirma Perera

[1]Department of Anatomy and Physiology, The Florey Institute of Neuroscience and Mental Health, 30 Royal Parade Parkville, Melbourne, Australia

## INTRODUCTION:

Autophagy is an indispensable cellular mechanism which recycles and eliminates harmful protein aggregates, a pathological hallmark of ALS. Motor neuronal autophagy has been explored extensively in order to delay motor neuron degeneration by clearing toxic protein aggregates. However, glia additionally display ALS protein aggregates, with glial autophagy being significantly under-explored. Astrocytes make up one of the largest glial cell populations in the central nervous system and are crucial for supporting neuronal health.

Therefore, the investigation of astrocytic autophagy is vital to understand alternative pathways which contribute to disease progression and aid therapeutic development. This study investigated the role of astrocyte autophagy on ALS disease progression.

## METHODS:

The impact of astrocytic autophagy deletion was first investigated in a pilot study using healthy mice. Tamoxifen-inducible Cre-lox recombination was used to disrupt the essential autophagy gene, Atg7, from astrocytes in a temporal and spatially controlled manner. This occurred at postnatal 90 days of age to avoid developmental consequences. Subsequently, the impact of astrocyte autophagy deletion in ALS $SOD1^{G93A}$ mouse weight, motor function, and survival were investigated. Tissue was analysed via immunohistochemistry to observe the effects of astrocyte autophagy deletion on motor neuron survival and western blot to validate Atg7 deletion.

## RESULTS:

Immunohistochemical analysis demonstrated that Atg7 is significantly reduced in astrocytes, highlighting successful autophagy disruption. Furthermore, p62 is a surrogate inverse marker of autophagy rate and was significantly elevated in astrocytes, further confirming astrocyte- specific autophagy disruption.

Furthermore, western blot analysis demonstrated a significant increase in p62 in the brain, further demonstrating autophagy disruption in this mouse model.

## CONCLUSION:

We have validated the successful deletion of astrocyte-specific autophagy in healthy mice. Behaviour tests are currently ongoing to assess the impact of astrocytic autophagy deletion in $SOD1^{G93A}$ mice.

## REFERENCES:

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-MP005*

# NOVEL STRATEGIES TO PREVENT DNA DAMAGE AND ENHANCE DNA REPAIR IN AMYOTROPHIC LATERAL SCLEROSIS

Fabiha Farzana[1], Sina Shadfar[1], Cyril Jones Jagaraj[1], Prachi Mehta[1], Julie D. Atkin[1,2]

[1]Motor Neuron Disease Research Centre, Macquarie Medical School, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia.
[2]Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Melbourne, VIC 3086, Australia.

## INTRODUCTION:

DNA damage is increasingly implicated in neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS). ALS is a severely debilitating condition affecting both upper and lower motor neurons. Approximately 15% of ALS cases are familial with known genetic mutations in over 40 proteins, including TDP-43 and C9orf72. The aetiology of ALS is complex, with many cellular mechanisms implicated in pathology, including DNA damage. DNA undergoes continuous attack from many sources and cells normally preserve genomic integrity by the 'DNA damage response'. Neurons are particularly vulnerable to DNA damage due to their post-mitotic nature. Double stranded breaks (DSBs) are the most deleterious type of damage which are repaired by Non-Homologous End Joining (NHEJ) repair in neurons (Farg et al., 2017a; Walker et al., 2017; Konopka et al., 2020). There are few effective treatments for ALS, and currently no therapeutic approaches to enhance DNA repair and thus inhibit DNA damage in ALS are available. We previously showed that a novel chaperone from the thioredoxin family, which also possesses redox activity - protein disulphide isomerase (PDI) – is protective in ALS including DNA damage (Parakh et al., 2020, Shadfar et al., 2025). However, the mechanisms remain poorly defined. Two PDI mutants have been previously described in ALS patients, but these also remain poorly characterised (Gonzalez-Perez et al., 2015). The aim is to examine whether PDI functions in DNA repair, thus preventing DNA damage, in ALS.

## METHODS:

Using cellular models, PDI-WT, a redox- inactive mutant, and two ALS mutants – PDID292N and PDIR300H were examined against DNA damage induced by ALS mutant proteins, TDP-43(Q331K), TDP43(A315T) and C9orf72 associated dipeptide repeat proteins (PolyGA50, PolyGR50, PolyPR50) using western blotting and immunocytochemistry. Also, peptides mimicking the redox activity of PDI were administered to a mouse model - TDP-43ΔNLS – to determine if they were protective against DNA damage induced by TDP-43.

## RESULTS:

We show here that overexpression of PDI prevents DNA damage induced by ALS mutant TDP43(Q331K), TDP-43(A315T) in neuronal cell lines, by analysing widely used DSB markers: phosphorylated H2AX (gamma- H2AX), 53BP1 DNA damage foci, using immunocytochemistry. The PDI-WT was the most protective against DNA damage. We also show that overexpression of PDI prevents DNA damage induced by ALS mutant C9orf72 PolyGA50, and PolyPR50. The redox-inactive mutant was also protective against DNA damage induced by PolyGA50 demonstrating that the redox activity is not required for this function. However, the ALS-associated mutants were not protective against DNA damage induced by PolyGA50, demonstrating that in ALS, this protective function is lost. However, the PDI-R300H protein retained some protective activity against DNA damage induced by PolyPR50 whereas the redox-inactive mutant and the PDI-D292N were not protective. The DNA repair activity of PDI was confirmed by the protective activity of the peptides in cell culture. Moreover, the PDI peptides were protective in an ALS mice model (TDP43-ΔNLS), assessed by several markers confirming that PDI is protective against DNA damage in ALS in vivo.

**CONCLUSION**:

These results suggest that PDI functions in NHEJ DNA repair, which is protective against DNA damage induced in ALS. The PDI peptides also inhibited DNA damage in ALS in vivo. This study therefore identifies a novel therapeutic strategy to enhance DNA repair and thus inhibit DNA damage in ALS and possibly other diseases characterised by DNA damage.

**REFERENCES**:

1. Gonzalez-Perez, Paloma et al. "Identification of rare protein disulfide isomerase gene variants in amyotrophic lateral sclerosis patients." *Gene* vol. 566,2 (2015): 158-65. doi:10.1016/j.gene.2015.04.035
2. Farg, Manal A et al. "The DNA damage response (DDR) is induced by the C9orf72 repeat expansion in amyotrophic lateral sclerosis." *Human molecular genetics* vol. 26,15 (2017): 2882-2896. doi:10.1093/hmg/ddx170
3. Parakh, Sonam et al. "The Redox Activity of Protein Disulfide Isomerase Inhibits ALS Phenotypes in Cellular and Zebrafish Models." *iScience* vol. 23,5 (2020): 101097. doi:10.1016/j.isci.2020.101097
4. Konopka, Anna et al. "Impaired NHEJ repair in amyotrophic lateral sclerosis is associated with TDP-43 mutations." *Molecular neurodegeneration* vol. 15,1 51. 9 Sep. 2020, doi:10.1186/s13024-020-00386-4
5. Walker, Callum et al. "C9orf72 expansion disrupts ATM-mediated chromosomal break repair." *Nature neuroscience* vol. 20,9 (2017): 1225-1235. doi:10.1038/nn.4604
6. Shadfar, Sina et al. "The Redox Activity of Protein Disulphide Isomerase Functions in Non-Homologous End-Joining Repair to Prevent DNA Damage." *Aging cell*, e70079. 15 May. 2025, doi:10.1111/acel.70079

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-MP006*

# ENHANCING SKELETAL MUSCLE REGENERATION IN ALS VIA INTRAMUSCULAR ALLOSTERIC ACTIVATION OF THE P2X7 RECEPTOR

*Cassandra Margotta[1], P. Fabbrizio[1], S. Caravita[1], A. Passoni[2], A. Lanno[2], A. M. Siciliano[2], N. Innocenti[3], C. Nastasi[4], A. Tosolini[5], F. J Steyn[6], E. Davoli[2], E. Biasini[3], S. T Ngo[5] and G. Nardo[1]*

*[1]Research Center for ALS, Department of Neuroscience, Mario Negri Institute for Pharmacological Research IRCCS, Milan, Italy.*
*[2]Mass Spectrometry Centre for Health and Environment, Mario Negri Institute for Pharmacological Research IRCCS, Milan, Italy.*
*[3]Department of Cellular, Computational and Integrative Biology, University of Trento, Trento, Italy,*
*[4]Laboratory of Cancer Pharmacology, Department of Oncology, Mario Negri Institute for Pharmacological Research IRCCS, Milan, Italy.*
*[5]The Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane QLD, Australia.*
*[6]School of Biomedical Sciences, the University of Queensland, Brisbane, QLD, Australia.*

## INTRODUCTION:

Amyotrophic Lateral Sclerosis (ALS) is a fatal motor neuron disorder characterised by early skeletal muscle failure and irreversible atrophy at the periphery. We recently found that the intramuscular activation of the P2X7 purinergic receptor improved motor performance in ALS mice by enhancing satellite cells and the muscle pro-regenerative activity of infiltrating macrophages (**1**).

Here, we translated this evidence into a therapeutic strategy by investigating the disease-modifying effects of enhancing the P2X7 pathway in the skeletal muscle of ALS mouse models using a highly selective P2X7 positive allosteric modulator, the ginsenoside compound K (CK) (**2**).

## METHODS:

Fast-progressing (PrP-FUS) and slow-progressing (SOD1G93A) ALS mouse models were utilised alongside *ex vivo* immunohistochemical, biochemical, and biomolecular analyses, as well as *in vitro* approaches on immortalised and primary cells, to assess the therapeutic potential of CK.

## RESULTS:

Data showed that CK stimulates, via the P2X7 pathway, the proliferation and differentiation of muscle satellite cells isolated from ALS mice. Additionally, CK polarised primary macrophage cells towards an M2 anti-inflammatory phenotype, which is crucial for effective muscle regeneration (**3**).

In parallel, a targeted pharmacokinetic and pharmacodynamics study was conducted to determine the optimal CK dose regimen. These data allowed us to obtain *in vivo* evidence in fast (PrP-FUS) and slow (SOD1G93A) transgenic mice. Intramuscular treatment with CK increased muscle mass, which correlated with macrophage immunomodulation and more mature muscle fibres in ALS mice undergoing muscle atrophy.

## CONCLUSIONS:

Our data provided the first evidence to show that selective activation of the P2X7 pathway with CK exerts positive effects on skeletal muscle regeneration in ALS mice. Ongoing behavioural monitoring will systematically assess the effectiveness of this therapeutic strategy in promoting muscle regeneration. This approach has the potential to be utilised independently or in combination with CNS- targeted drugs to enhance the efficacy of future clinical treatments for ALS.

## REFERENCES:

1. Fabbrizio et al., Cell Mol Life Sci. 2021;79(1):7
2. Sharma et al., Biomolecules. 2020;10(7):1028
3. Tidball JG. Nat Rev Immunol. 2017;17(3):165

**ABSTRACT TOPIC**: Molecular Pathogenesis

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-MP007*

# VISUALIZING THE DYNAMICS OF THE PROTEIN INTERACTION NETWORK OF FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS

[1]Hanieh Beyrampour-Basmenj; [1]Christian Makhoul; [1]Danny M. Hatters

1 Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, Victoria, Australia.

**INTRODUCTION**:
Although most Amyotrophic Lateral Sclerosis (ALS) cases are sporadic, the identification of mutations in specific genes has provided important insights into how the disease develops. To date, mutations in at least 43 genes have been associated with ALS, with the most common being *SOD1, FUS, C9orf72*, and *TARDBP* (TDP-43). Central to ALS pathology is the TDP-43 protein, which forms abnormal cytoplasmic aggregates in nearly all ALS cases, regardless of the specific genetic mutation involved. We hypothesize that cellular models of ALS will show specific losses and gains in protein-protein interactions within the TDP-43- centered network, highlighting key mechanisms involved in disease onset.

**METHODS**:
To investigate this hypothesis, we developed a high-throughput microplate array platform utilizing the NanoBiT split-luciferase assay, a dynamic and sensitive technique suitable for studying subtle changes in protein-protein interactions. By comparing these interactions between control and ALS cellular models, we aim to uncover the molecular mechanisms driving early ALS pathogenesis.

**RESULTS**:
We will describe our work in progress by assaying a wide range of protein-protein interactions among the 43 ALS genes. This includes interactions between TDP-43 and key ALS-related proteins, including HNRNPA1 and SQSTM1. Future experiments will investigate whether known ALS-linked mutations (such as those in TDP-43, e.g., M337V, A315T, and Q331K) alter these interactions and thus impact the network.

**CONCLUSION**:
This study examines protein-protein interactions within the TDP-43 network, emphasizing ALS-associated genes to identify critical molecular changes involved in ALS pathogenesis.

**REFERENCES**:
1. Freibaum BD, et al. Global analysis of TDP-43 interacting proteins. J Proteome Res. 2010;9(2):1104-20.
2. Feneberg E, Gordon D, et al. ALS-linked TDP-43 mutation disrupts protein interactions in motor neuron oxidative stress response. Neurobiol Dis. 2020;144:105050.

Basic Science
*BS-P-MP008*

# MITOCHONDRIAL RESPIRATION IN SKELETAL MUSCLE OF HUMANS WITH MOTOR NEURON DISEASE: A PILOT STUDY

Hannah J Thomas[1], Navabeh Zare[1], Patricia Bayer[1], Dale Taylor[1], James Broatch[1], Itamar Levinger[1], Andrew Garaham[1], David Bishop[1], Alessandra Ferri[1]

[1]Institute for Health and Sport, Victoria University, Melbourne, Victoria, Australia

**INTRODUCTION**: The causes of motor neuron death in motor neuron disease (MND) are still unknown, however, evidence suggests that mitochondrial dysfunction may be involved in the pathogenesis of MND. Mitochondrial abnormalities have been shown to precede disease onset in SOD1 mouse models (Hervias et al *Muscle Nerve* 2006). However, muscle mitochondrial function in humans with MND has not been adequately explored. We tested the hypothesis that mitochondrial respiration in individuals with MND is compromised compared to healthy individuals, and the reduced mitochondrial respiration is linked to reduced cardiorespiratory fitness in individuals with MND.

**METHODS**: High-resolution mitochondrial respirometry was performed on skeletal muscle biopsies taken from the vastus lateralis of participants with MND (N=3, F: 33%, Age: 61±15 years, BMI: 29.2±5.4, time since MND onset: 28±8 months, ALSFRS-R: 35±9), and sex matched, middle-aged adults (N=8, F:37.5%, Age: 58±7 years, BMI: 27.2±3.6). Participants also underwent a maximal cardiorespiratory exercise test ($\dot{V}O_2$peak).

**RESULTS**: Compared to healthy adults, individuals with MND presented with lower Complex I leak (MND: 8.66±1.83 pmol O2/s/mg, Healthy: 18.66±5.00 pmol O2/s/mg; P<0.01), Complex I peak (MND: 23.20±5.18 pmol O2/s/mg, Healthy: 61.24±14.07 pmol O2/s/mg; P<0.01), Complex I+II peak (MND: 33.98±11.00 pmol O2/s/mg, Healthy: 73.19±14.99 pmol O2/s/mg; P<0.01), and Complex I+II capacity (MND: 39.48±12.90 pmol O2/s/mg, Healthy: 79.77±15.66 pmol O2/s/mg; P<0.01). With the small sample size, there was no significant difference between groups in $\dot{V}O_2$peak (MND: 19.39±9.91 mL/kg/min, Healthy: 24.23±5.65; P=0.32), age (P=0.58), or BMI (P=0.48).

**CONCLUSION**: Results suggest Individuals with MND may have decreased mitochondrial respiration when compared to sex matched, healthy, middle-aged adults despite being of similar age, BMI, and fitness. Continuation of this research with a larger number of individuals with MND may confirm these results and elucidate whether mitochondrial impairments may be involved in the pathogenesis of MND and could be targeted to improve muscle function.

Basic Science
*BS-P-MP009*

# HIGH THROUGHPUT COMPOUND SCREENING UNRAVELS PATHOGENESIS OF C9ORF72-ALS/FTD

Keiko Imamura[1,2,3,4], Makoto Furusawa[2], Keisuke Shibata[2], Haruhisa Inoue[1,2,3,4]

1. Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan
2. Takeda-CiRA (T-CiRA) Joint Program, Fujisawa, Japan.
3. iPSC-Based Drug Discovery and Development Team, RIKEN BioResource Research Center (BRC), Kyoto, Japan
4. Medical-Risk Avoidance Based On iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Kyoto, Japan

## BACKGROUND

Repeat expansions in C9ORF72 are a common genetic cause of amyotrophic lateral sclerosis. Neuropathological hallmarks unique to C9ORF72-ALS/FTD include accumulation of repeat RNA and dipeptide repeat proteins resulting from unconventional translation of repeat RNA.

## METHODS

Motor neurons were generated from ALS patient iPS cells (iPSCs) with C9ORF72 repeat expansion. A high-throughput screening was conducted to identify compounds that reduce RNA foci, thereby indicating accumulation of RNA repeats, as well as compounds that reduce accumulation of dipeptide repeat proteins using iPSC-derived patient motor neurons. The selected compounds were evaluated using neural organoids generated from ALS patient iPSCs.

## RESULTS

A high-throughput screening of approximately 75,000 compounds was performed, and 426 compounds were extracted to reduce RNA foci. Furthermore, 161 compounds were selected to exhibit concentration-dependent efficacy with low cytotoxicity. Among them, we identified 18 compounds for inhibiting the accumulation of dipeptide repeat proteins. We generated neural organoids from patient iPSCs, and molecular profiling of identified compounds on ALS pathogenesis was acquired by single cell RNA-seq analysis.

## CONCLUSIONS

We have identified potential targets for inhibiting the accumulation of repeat RNAs and dipeptide repeat proteins in C9ORF72 -ALS/FTD by compound screening. This may have the potential to enable an understanding of the pathogenesis of repeat expansion diseases and the development of therapeutics.

Basic Science
*BS-P-MP010*

# DECIPHERING THE MECHANISMS OF C9ORF72 REPEAT EXPANSION IN MOTOR NEURON DISEASE: DIPEPTIDE REPEAT PROTEIN PRODUCTION, STALLING, AND CYTOTOXICITY

[1]Castillo, Kevin; [1]Hatters, Danny;[2]Furic, Luc

[1]Department of Biochemistry and Pharmacology and Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Melbourne, 3052 Victoria, Australia, [2] Translational Prostate Cancer Research Laboratory, Peter MacCallum Cancer Centre, Melbourne, 3052 Victoria, Australia, [3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, 3052 Victoria, Australia.

## INTRODUCTION

The most common familial cause of MND is the presence of a GGGGCC hexanucleotide repeat expansions in Intron 1 of the C9ORF72 gene that can range from 30 to thousands. These expansions lead to abnormal bidirectional transcription and incorrect gene splicing, resulting in various disease-related mechanisms that are not fully understood. One of these mechanisms of toxicity involves the production of dipeptide repeats (DPRs) from the hexanucleotide sequence through a non- canonical translation termed Repeat Associated Non-AUG (RAN) translation. Due to the highly unusual structure and the lack of clarity of the RAN translation mechanism of the repeat expansion, we aim to explore the mechanisms governing DPR production, stalling, and toxicity in the context of a more native-like C9ORF72 gene sequence.

## METHODS:

To achieve this, we have created a C9ORF72 minigene casette stripped back to contain the minimum elements required to drive ran translation. This includes exon 1a and the intron 1, which is adjacent 5' to the repeat sequence. We made versions with a short wild-type like repeat lengths (2 repeats) and disease-linked lengths (81 repeats). Both short and long repeats produced ran-translated products, when the cassettes were placed upstream a gfp reporter. To determine what endogenous proteins are bound to the minigene, we used proximity labeling involving a novel assay we developed that can target small epitope tags. This approach was expected to identify proteins on newly translated peptides.

## RESULTS:

The approach found that in the Gly-Ala frame, there were limited interactors to the RAN products. However, in the Gly-Arg frame, we detected many proteins involved in translation, nucleolar function, RNA metabolism, and mitochondria.

## CONCLUSION:

These findings support other studies pointing to the Arg-rich DPRs being most toxic and interfering with translation.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-MP011*

# CELL FUSION: A NOVEL THERAPEUTIC STRATEGY TO INHIBIT CELL DEATH AND ALLEVIATE NEURODEGENERATION IN ALS

[1]Do-Yeon Lee, PhD, [1]Jung-Joon Sung, MD, PhD*

[1]Department of Neurology, Seoul National University Hospital, Seoul 03080, South Korea.

## INTRODUCTION:

Most current approved medications for neurodegenerative diseases (ND) focus only to alleviate symptoms or -disease progression but failed to fundamentally inhibit neuronal cell death. Initial cell therapeutic mechanism in ND are believed to replacing dyingneurons with healthy cells being differentiated on their own after transplantation but currently accepted as supporting dying cells with changing the microenvironment, such as anti-inflammation, secretion of growth factors, and elimination of toxic substances, which are considered to have inherent limited efficacy by having shown many failures in the clinical trials. Therefore, a novel therapeutic approach focused on inhibiting cell death is required. We initiated our investigation with the fundamental question of whether cell fusion could prevent cell death and evaluated the efficacy and safety of the novel cell therapeutic approach based on cell fusion through both in vitro and in vivo studies. Cell fusion may provide a more promising strategy for neurological disorders since although cell therapy is essential that transplanted cells must differentiated into neuronal cells and connected with recipient neurons for proper function and cell fusion can use existing recipient cellular types and connection. ALS is a progressive, fatal disease that leads to the deterioration of motor neurons and severe muscle atrophy. The mechanisms and progression of ALS remain unclear, and no effective treatments are available. We hypothesized that cell fusion may exert therapeutic effects by fundamentally inhibiting apoptosis and neuronal cell death, thereby mitigating the progression of ALS, a typical incurable neurodegenerative disorder.

## METHODS:

We generated fusogenic human umbilical cord mesenchymal stem cells (fhUC-MSCs) and verified the occurrence of cell fusion. To evaluate whether cell fusion mitigates apoptosis, cellular damage was induced, followed by the selective fusion of apoptotic cells to confirm the resulting effect. The therapeutic potential of cell fusion was further evaluated through experiments conducted in an SOD1 G93A mouse, a representative of ALS model.

## RESULTS:

We found that after fusion with neurons, there was no alteration in neuronal function, and the neurons consistently generated stable electrical signals. To evaluate whether cell fusion mitigates apoptosis, cellular damage was induced, followed by the selective fusion of apoptotic cells to confirm the resulting effect. Additionally, motor neurons expressing mutant superoxide dismutase 1 (SOD1) G93A were subjected to fusion. We observed evidence of cell fusion and demonstrated an inverse correlation between cell fusion and both apoptosis and organelle damage. Furthermore, we provide evidence of changes in CNS inflammation and apoptosis, as well as in vivo cell fusion within the spinal cord of SOD1 G93A mice following intraspinal injection of fhUC- MSCs. fhUC-MSCs significantly reduced glial- induced neuroinflammation and apoptosis, while increasing motor neurons numbers. We demonstrated that fhUC-MSCs prevented neuronal cell death, significantly delayed disease onset, slowed motor deterioration, and prolonged survival compared to hUC-MSCs alone in SOD1 G93A mice.

## CONCLUSION:

This study suggests that cell fusion provide a novel perspective on neuroregeneration, potentially leading to innovative strategies for ALS and other neurodegenerative diseases.

## REFERENCES:

1. Lamptey, R. N. L. et al. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. Int J Mol Sci 23 (2022).
2. Temple, S. Advancing cell therapy for neurodegenerative diseases. Cell Stem Cell 30, 512- 529 (2023).
3. Sullivan, S. & Eggan, K. The potential of cell fusion for human therapy. Stem Cell Rev 2, 341-349 (2006).
4. Kiernan, M. C. et al. Amyotrophic lateral sclerosis. Lancet 377, 942-955 (2011).
5. Singh, T. et al. Neuronal mitochondrial dysfunction in sporadic amyotrophic lateral sclerosis is developmentally regulated. Sci Rep 11, 18916 (2021).
6. Lee, D. Y., Kwon, Y. N., Lee, K., Kim, S. J. & Sung, J. J. Dual effects of TGF-beta inhibitor in ALS - inhibit contracture and neurodegeneration. J Neurochem 168, 2495-2514 (2024).

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-MP012*

# INVESTIGATING SPINAL CORD MOTOR CIRCUITRY VULNERABILITY AND DEGENERATION IN THE TDP-43$^{Q331K}$ MOUSE MODEL OF ALS

[1]Matthews, Lyzette; [1]Johnstone, Oliver; [2]Crane, James; [1]King, Anna; [1]Perry, Sharn

[1]Wicking Dementia Research and Education Centre, University of Tasmania, 17 Liverpool Street, Hobart, Australia.
[2]School of Medicine, University of Tasmania, 17 Liverpool Street, Hobart, Australia.

## INTRODUCTION:

Motor circuit degeneration is commonly studied in SOD1 mouse models, but these lack the TDP- 43 pathology present in 97% of ALS cases (1). Therefore, investigating motor circuit degeneration in TDP-43 models is crucial. In SOD1 mice, spinal interneuron loss precedes motor neuron loss (2), attributing to the onset of early phenotypic symptoms. However, the role of TDP-43 pathology in spinal interneuron vulnerability and degeneration remains unclear.

We aim to examine the vulnerability and degeneration of spinal interneuron populations in the TDP-43$^{Q331K}$ mouse model at 10, 16 and 40 weeks of age.

## METHODS:

The TDP-43$^{Q331K}$ mouse line was crossed with Chrna2-Cre mice to create four experimental groups. Mice were monitored for weight and neurological decline, undergoing motor tests such as grip strength and DigiGait at 10 and 16 weeks. Spinal cord tissue was analyzed for motor neuron and spinal interneuron loss, with preliminary focus on Renshaw cells and motor neurons.

## RESULTS:

Preliminary investigations showed no significant differences in ChAT+ motor neuron counts in lumbar regions 1-3 and 4-6 weeks between Chrna2-Cre/TDP-43$^{Q331K}$ groups at 10 weeks. However, at 16 weeks, ChAT+ motor neurons were significantly reduced in lumbar regions 4-6 in both TDP-43$^{Q331K}$ groups compared to controls. No changes in CB/GPHN+ Renshaw cells were observed.

At 40 weeks, TDP-43$^{Q331K}$ mice exhibited significant motor neuron loss in both thoracic and lumbar regions, with lumbar loss coinciding with an increase in ventral horn CB/GPHN+ Renshaw cells.

## CONCLUSION:

This ongoing work will characterize spinal inhibitory and excitatory interneurons in the TDP-43$^{Q331K}$ mouse model throughout disease.

## REFERENCES:

1. Suk TR, Rousseaux MWC. The role of TDP-43 mislocalization in amyotrophic lateral sclerosis. Mol Neurodegener. 2020;15(1):45.
2. Wootz H, Fitzsimons-Kantamneni E, Larhammar M, Rotterman TM, Enjin A, Patra K, et al. Alterations in the motor neuron-renshaw cell circuit in the Sod1(G93A) mouse model. J Comp Neurol. 2013;521(7):1449-69.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science

*BS-P-MP013*

# MURINE ARYLAMINE N-ACETYLTRANSFERASE 2 AS A MODULATOR OF SKELETAL MUSCLE RESPONSES IN MND: IMPLICATIONS FOR DISEASE PROGRESSION AND MYOGENESIS

[1]Melinder K. Gill; [2]Stephanie L. Howe; [1]Neville Butcher; [2,3]Shyuan Ngo; [1]Rodney F. Minchin; [1,3]Frederik Steyn

[1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia
[2]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia
[3]Royal Brisbane and Women's Hospital, Herston, Brisbane, Australia

## INTRODUCTION:

Skeletal muscle dysfunction occurs early in MND and likely contributes to disease onset and progression. Improved understanding of factors that impact skeletal muscle will facilitate the development of therapeutics that can preserve muscle health and function in MND. Here, we investigate the role of murine arylamine N-acetyltransferase 2 (mNat2), an enzyme known for its role in mitochondrial function[1], as a modulator of muscle responses to disease.

## METHODS:

We assessed the expression and activity of mNat2 in muscle (gastrocnemius and tibialis anterior) of $SOD1^{G93A}$ mice, and the effect of germline deletion of mNat2 on disease onset and progression. Next, we determined the role of mNat2 on the differentiation of murine C2C12 myoblasts using siRNA knockdown. Bulk RNA-sequencing datasets were generated from *in vivo* and *in vitro* experiments to explore underlying molecular mechanisms.

## RESULTS:

*In vivo* mNat2 expression and activity in gastrocnemius and tibialis anterior muscle of $SOD1^{G93A}$ mice increased three-fold at disease onser, and remained elevated throughout disease ($p<0.001$). Germline deletion of mNat2 in $SOD1^{G93A}$ mice resulted in an earlier and steeper decline in disease phenotype and faster loss of body weight ($p<0.001$). *In vitro*, mNat2 activity and expression increased during differentiation of C2C12 muscle cells ($p<0.001$). siRNA-knockdown of mNat2 in C2C12 myoblasts resulted in impaired myogenesis, and aberrations in the cytoskeleton matrix. Bulk RNA-sequencing datasets indicate that mNat2 knockdown leads to dysregulation in myogenic regulation, cell cycle, and cytoskeleton maintenance.

## CONCLUSION:

An early and persistent increase in mNat2 activity may facilitate a critical muscle response at disease onset in the $SOD1^{G93A}$ mouse. Consequently, germline loss of mNat2 contributes to earlier and more rapid progression of motor dysfunction. siRNA-mNat2 attenuated C2C12 differentiation, likely due to dysregulation of myogenesis. Findings suggest a potential role for mNat2 in modulating the response of skeletal muscle to MND.

## REFERENCES:

1. Choudhury C, Gill MK, McAleese CE, et al. The Arylamine N-Acetyltransferases as Therapeutic Targets in Metabolic Diseases Associated with Mitochondrial Dysfunction. Pharmacological Reviews 2024;76:300-320.

Basic Science
*BS-P-MP014*

# WILL REDUCING ABNORMAL CORTICAL ACTIVITY IN MND HAVE A THERAPEUTIC EFFECT?

Mouna Haidar, Aida Viden, Christin Daniel, Bradley Turner

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with no effective treatment. In ALS, cortical hyperexcitability is a consistent and early feature arising from the overactivity of upper motor neurons (UMNs) in the primary motor cortex and leads to excitoxicity and subsequent loss of spinal motor neurons. Therefore, targeting cortical hyperexcitability known to occur early in ALS may present as an effective treatment. The *primary aim* of this project is to assess the therapeutic effect of an inhibitory chemogenetic or DREADD (Designer Receptor Activated by Designer Drugs) targeted specifically to overactive UMNs in ALS mice harbouring human mutations in the superoxide dismutase-1 gene ($SOD1^{G93A}$).

We stereotaxically injected the inhibitory hM4Di DREADD into Layer V of the primary motor cortex in $SOD1^{G93A}$ mice and treated with clozapine-N-oxide (CNO) or saline. We performed whole cell patch clamp experiments to record UMNs in presymptomatic $SOD1^{G93A}$ mice expressing hM4Di in UMNs and observed a dose dependent reduction in the firing frequency of a hM4Di-expressing UMN following bath application of CNO, relative to pre-CNO treatment with control aCSF. Importantly, we demonstrate we can inhibit hyperactive UMNs in $SOD1^{G93A}$ mutant mice and provide feasibility for our inhibitory chemogenetic approach. $SOD1^{G93A}$ mice expressing hM4Di in UMNs treated with CNO revealed a significant improvement in motor coordination on a Rotarod, while no difference was detected in Grip Strength, relative to saline treated controls. We observed a trend for delayed symptom onset and extended survival, relative to saline treated controls. We are now processing tissue for histological and biochemical analysis for ALS-like neuropathological changes, including (i) upper and lower motor neuron counts, (ii) UMN dendritic morphology, (iii) axonal pathology, (iv) muscle denervation, (v) neuroinflammation and (vi) protein misfolding and mislocalisation. These data may provide support for targeting cortical hyperexcitability as a promising therapeutic modality for ALS patients.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-MP015*

# LRP4 OVEREXPRESSION IN MUSCLE HELPS STABILIZE NEUROMUSCULAR SYNAPSES IN SOD1G83A ALS MODEL MICE

[1]Noakes· PG; [1]Agrawal, U; [1]Vincent Chen V; [2]Chand K; [3]Ngo ST; [4,5]Mei L; [5]Xiong W-C; [1]Lavidis NA

[1] School of Biomedical Sciences, The University of Queensland, St Lucia, Qld Australia.

[2]Perinatal Research Center, Centre for Clinical Research, The University of Queensland, St Lucia, Qld Australia.

[3]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, Qld Australia.

[4]Chinese Institute for Medical Research Beijing, China.

[5]Department of Neurosciences, School of Medicine Case Western University, OH, USA,

**INTRODUCTION**:
Amyotrophic lateral sclerosis (**ALS**) is a progressive neurodegenerative disorder characterized by the loss of motor neurons and neuromuscular junctions (**NMJs**), leading to muscle atrophy and paralysis. The Low-Density Lipoprotein Receptor-Related Protein 4 (**LRP4**) plays a critical role in NMJ formation and maintenance through its interaction with Muscle-Specific Kinase (**MuSK**). This study investigated the effects of overexpressing LRP4 in the muscles of SOD1G93A ALS model mice.

**METHODS**:
To study the consequence of overexpression of LRP4 in skeletal muscle in SOD1G93A mice, we crossed Human Skeletal Actin (HSA)-LRP4 heterozygous females with heterozygote male SOD1G93A mice. This crossing generated control (wild type, [WT, +/+]), LRP4/+, SODG93A/+, and SODG931-HSA-LRP4 double transgenic mice. At selected ages of ALS-like phenotypes, hindlimb muscles were assessed for muscle innervation status. Muscle innervation status was assessed using antibodies to components of the motor nerve terminal, and fluorescently labeled alpha bungarotoxin to label post-synaptic acetylcholine receptors (AChRs). NMJ morph a FIJI image software plugin developed by Jones and Gillingwater[1] was used to quantify NMJ morphology and the overlap of pre-synaptic nerve terminals to apposed post-synapticAChRs. This overlap was used as measure of muscle innervation/denervation status.

**RESULTS:**
We assessed NMJ morphology, innervation status, and muscle function at pre-symptomatic (P30), onset (P60), mid-stage (P120), and end- stage (P150-175) mice. So far, our results show that LRP4 overexpression in skeletal muscle preserved muscle innervation, particularly at the later stages of disease. At the onset and mid- stage, SOD1G93A/HSA-LRP4 mice exhibited a less NMJ denervation compared to SOD1G93A mice. By the end stage, SOD1G93A/HSA-LRP4 mice retained significantly more innervated NMJs and had fewer denervated NMJs ($p <$ 0.05; $n$=4; 80 NMJs/$n$/muscle) compared to SOD1G93A mice, suggesting that LRP4 overexpression may help preserve NMJ integrity. Importantly, the overexpression of LRP4 in muscle of HSA-LRP4 mice did not result in any negative effects on NMJ morphology or muscle function, indicating that LRP4 overexpression is well-tolerated in healthy muscle.

**CONCLUSION:**
Enhancing LRP4 expression could be a viable therapeutic strategy to delay NMJ degeneration in ALS. Current studies are underway to explore combinatory approaches targeting LRP4 in combination with other potential effector proteins from the neural-agrin motor nerve to muscle signaling pathway, such as Dok-7 to further enhance NMJ preservation and improve muscle strength in ALS models.

**REFERENCES:**
**1.** Minty et al, aNMJ-morph: a simple macro for rapid analysis of neuromuscular junction morphology.. doi: 10.1098/rsos.200128.

Basic Science
*BS-P-MP016*

# CAN WE HARNESS HYPOTHERMIA TO TREAT MOTOR NEURON DISEASE?

[1]Atkinson, Rachel; [1]Cook, Anthony; [1]King, Anna

[1]Wicking Dementia Research and Education Centre, University of Tasmania, 17 Liverpool Street, Hobart, Australia

## INTRODUCTION:

When our core body temperature is cooled, our cells activate protective processes regulated by a family of proteins known as cold shock proteins, which prevent damage to our nervous system. These pathways are activated in mammals that hibernate in winter and in humans during therapeutic cooling following stroke and spinal cord injuries. Amyotrophic lateral sclerosis (ALS) is a complex, multifactorial disease, and over 90% of cases are sporadic with no known genetic cause. There has been limited success in halting or reversing the disease when targeting specific disease mechanisms individually, highlighting the need for treatment strategies spanning multiple disease pathways. Strikingly, the myriad of pathways protected in cold stress and those adversely affected in ALS show considerable overlap. This project investigates whether cold stress could be harnessed as a treatment strategy for ALS.

## METHODS:

Firstly, we will determine whether there are underlying alterations to cold shock proteins in ALS by examining our banks of MND-related tissue, cell, and blood samples, and publicly available MND proteomic and transcriptomic datasets. We will then determine whether manipulation of the cold stress response can provide protection to the nervous system in animal (mSOD1 G93A mice) and cellular models (patient iPSC lines) of ALS, using drugs targeting temperature regulation centers within the brain (A1 receptor agonist drug, N6-cyclohexyladenosine, CHA) or anti-sense oligonucleotide (ASO) -based drugs that directly act upon cold shock proteins.

## RESULTS:

Our initial studies in wildtype mice demonstrate that CHA can induce and maintain a hypothermic state between 26°C and 30°C for a minimum of 2 hours, followed by recovery and normal behaviour of mice. These initial data will now allow us to proceed with further studies in mSOD1 mice.

## CONCLUSION:

If these interventions improve ALS-related phenotypes, there is real potential to advance new treatment options for the majority of ALS cases with sporadic aetiology. This project aims to investigate the potential of this alternative treatment strategy for ALS by harnessing the protective effects of cold stress.

Basic Science
*BS-P-MP017*

# IDENTIFYING THE DISRUPTED PATHWAY OF INSULIN-LIKE GROWTH FACTOR-1-MEDIATED SIGNALLING IN MOUSE NEUROBLASTOMA CELLS EXPRESSING FUS MUTATION

Yousun (Sunny) An, Katherine Robinson, Angela Laird Neurodegeneration Treatment Team, Motor Neuron Disease Research Centre, Macquarie University

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder associated with mutations in specific genes, including FUS (Fused in Sarcoma), SOD1 (superoxide dismutase 1), and TDP-43. In this study, we identify the disrupted pathways of insulin-like growth factor 1 (IGF-1) signalling in neuronal cells expressing the mutant FUS relevant to ALS. To experimentally investigate the pathogenic mechanisms involved, we established in vitro cellular models using the mouse neuroblastoma cell line N2a, by expressing EGFP- human FUS wild-type ($hFUS^{WT}$) or the familial ALS-associated mutant $FUS^{R521G}$.

Our findings reveal significant alterations in IGF-1-mediated pathways in hFUS-expressing N2a cells under both serum presence and absence in the culture medium. The $hFUS^{R521G}$ mutation led to diminished Akt activation during serum starvation, resulting in the upregulation of oxidative stress defence molecules, such as catalase, in N2a cells. IGF-1 is a critical component of serum that is essential for maintaining cell growth and survival, and its deficiency has been linked to various neurodegenerative diseases, including ALS. Numerous studies suggest that external IGF-1 delivery may serve as a potential therapeutic approach for treating neurological disorders; however, the mechanism of action of IGF-1 remains poorly understood. To test the hypothesis that the IGF-1/Akt/FoxO signalling pathway is a key mechanism contributing to the altered phenotypes in $hFUS^{R521G}$ N2a cells, we assessed the subcellular localisation of FoxO using immunofluorescence and biochemical fractionation assays. Our results indicate that nuclear FoxO accumulated within the nucleus of $hFUS^{R521G}$ cells; however, external stimulation with IGF-1 facilitated the export of FoxO to the cytoplasm. Notably, there was no significant difference in the localisation of FoxO in N2a cells expressing $hFUS^{WT}$ and non-transfected wild-type cells. We further examined the effect of IGF-1 on the expression levels of catalase through western blot analysis. Our data confirmed that the upregulation of catalase in $hFUS^{R521G}$ cells was restored to control levels following external IGF-1 administration. To determine whether FoxO activity influenced the expression of antioxidant genes, such as *CAT*, *TXN*, and *SOD1*, in the identified genotypes of hFUS N2a cells, we utilised the FoxO inhibitor AS1842856 to prevent FoxO transcriptional activity. The enhanced catalase expression levels as the mRNA, in $hFUS^{R521G}$ cells, were reversed by AS1842856, while expression levels in non-transfected wild-type or $hFUS^{WT}$ N2a cells remained unchanged.

In conclusion, these findings provide an understanding of the altered signalling pathway in N2a cells expressing $hFUS^{R521G}$ and support further investigations into the therapeutic potential of IGF-1 for neuroprotection in ALS.

Basic Science
*BS-P-N001*

# PROFILING MITOCHONDRIAL-DERIVED VESICLES TO INFORM THERAPEUTIC STRATEGIES FOR IMMUNE-MEDIATED NEURODEGENERATION IN MND

[1]Hansen, Aggie; [1,2]Vella, Laura; [1,2]Turner, Bradley
[1]Florey Institute of Neuroscience and Mental Health, Parkville VIC 3052, Australia
[2]Florey Department of Neuroscience and Mental Health, University of Melbourne, Parkville VIC 3052, Australia

## INTRODUCTION:

Pathological aggregation of TDP-43 protein is a common hallmark of MND. TDP-43-induced mitochondrial damage has been suggested to result in the release of immunogenic molecules such as fragmented mitochondrial DNA (mtDNA). Such molecules can activate the innate immune pathways, such as the cGAS/STING pathway, contributing to pathological neuroinflammation. Here, it is hypothesised that these immunogenic molecules are packaged into mitochondrial-derived vesicles (MDVs) and exported from the cell, contributing to disease propagation. This project aims to investigate if these MDVs contain these immunogenic substances hence if extracellular MDV cargo can inform MND-related neuroinflammation.

## METHODS:

The project will use a dox-inducible TDP-43 overexpression SH-SY5Y neuroblastoma cell model to purify and analyse mitochondrial-derived extracellular vesicles. These extracellular vesicles will be isolated from the culturing media of TDP-43 empty vector and over-expression wild-type TDP-43 using an ultracentrifugation and density gradient isolation protocol. These vesicles will undergo western- blot analysis to investigate and compare the mitochondrial protein cargo across the cell lines. Following this, healthy SH-SY5Y cells will be incubated with these extracellular vesicles to assess the role of MDVs in active disease propagation. Changes in cellular disease state will be analysed using western-blotting, qPCR and ELISA analysis for cGAS/STING- associated secondary messengers.

## RESULTS:

The isolation of extracellular vesicles from the dox-inducible TDP-43 overexpression SH- SY5Y neuroblastoma cell model via ultracentrifugation has been optimized and validated. Currently, the difference in mtDNA cargo in the TDP-43 wild-type overexpression cells is being analysed and compared across treated and treatment control cells to elucidate any changes in cargo following TDP-43 overexpression as well as potentially identify the mitochondrial-derived vesicle population that can undergo further purification via density gradient separation.

## CONCLUSION:

By profiling the mitochondrial-derived protein cargo of extracellular vesicles purified from this cell model of TDP-43 proteinopathy, we hope to elucidate the contribution of this extracellular vesicle function in immune-mediated neurodegeneration in MND.

Basic Science
*BS-P-N002*

# EXPRESSION OF FATTY ACID BINDING PROTEIN 4 AND POTASSIUM CHANNEL KV1.3 IN MICROGLIA ISOLATED FROM SOD1$^{G93A}$ MOUSE BRAIN AND SPINAL CORD

Amelia Miklavec[1], Liam Koehn[1] and Joseph A Nicolazzo[2]
[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia.
[2] Centre for Drug Candidate Optimisation, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia.

## INTRODUCTION:

Excessive inflammation in amyotrophic lateral sclerosis (ALS) is mediated by chronically activated microglia (1). Fatty acid binding protein 4 (FABP4) and potassium channel Kv1.3 are upregulated in other inflammatory conditions (2, 3). Therefore, this study investigated the expression of FABP4 and Kv1.3 in SOD1$^{G93A}$ transgenic mouse brains and spinal cords.

## METHODS:

Brain and spinal cord tissue were collected from symptomatic P120 male and female SOD1$^{G93A}$ mice. Western blotting measured FABP4 abundance in SOD1$^{G93A}$ homogenates compared to wild-type (WT). Magnetic-activated cell sorting was used to isolate microglia from brain and spinal cord tissue, and purity confirmed via fluorescence-activated cell sorting. qPCR was performed to measure FABP4 and Kv1.3 mRNA in microglia.

## RESULTS:

The average purity of isolated microglia was 90%. No significant differences were observed in FABP4 expression between SOD1$^{G93A}$ and WT mice in brain or spinal cord homogenates or isolated microglia across male and female cohorts. Kv1.3 expression remained unchanged except for a significant 142% upregulation in spinal cord microglia isolated from male SOD1$^{G93A}$ mice compared to WT.

## CONCLUSION:

These findings suggest that FABP4 is not upregulated in ALS-associated microglia, while Kv1.3 expression shows tissue- and sex-specific changes, underscoring the importance of these factors in neuroinflammation and may inform therapeutic strategies targeting microglial activation.

## REFERENCES:

1. Barreto-Núñez R, Béland LC, Boutej H, Picher-Martel V, Dupré N, Barbeito L, et al. Chronically activated microglia in ALS gradually lose their immune functions and develop unconventional proteome. Glia. 2024;72(7):1319-39.
2. Makowski L, Hotamisligil GS, Tuncman G, Görgün CZ, Fazio S, Parker RA, et al. Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. Nature. 2007;447(7147):959-65.
3. Rus H, Pardo CA, Hu L, Darrah E, Cudrici C, Niculescu T, et al. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proceedings of the National Academy of Sciences. 2005;102(31):11094-9.

Basic Science
*BS-P-N003*

# A PATHOGENIC ROLE OF C5AR2 ACTIVATION IN AMYOTROPHIC LATERAL SCLEROSIS

John D. Lee[1], Jenny N. Fung[1], Alana Julianisya[1], Austin Read[1], and Trent M. Woodruff[1]
[1] School of Biomedical Sciences, the University of Queensland, QLD, Australia

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron degeneration, leading to paralysis and respiratory failure. Increasing evidence implicates neuroinflammation as a key driver of ALS progression. We have previously demonstrated that complement C5a-C5aR1 signaling contributes to motor neuron degeneration in ALS; however, the role of the second C5a receptor, C5aR2, remains unclear. In this study, we investigated the pathogenic role of C5aR2 by crossing $SOD1^{G93A}$ mice with C5aR2 deficient ($C5aR2^{-/-}$) mice to generate $SOD1^{G93A}$ x $C5aR2^{-/-}$ mice. Disease progression was assessed through survival analysis, motor function tests, and histological examination of neuroinflammatory markers. $SOD1^{G93A}$ x $C5aR2^{-/-}$ mice exhibited significantly extended survival and improved motor function compared to $SOD1^{G93A}$ controls. These functional improvements were associated with reduced neuroinflammation, including decreased microglia activation in the spinal cord. To further investigate the role of C5aR2 in neuroinflammation, we assessed cytokine responses in primary microglia isolated from WT and $C5aR2^{-/-}$ mice following stimulation with lipopolysaccharide and TDP-43 aggregates (ALS-associated pathology). Microglia from $C5aR2^{-/-}$ mice exhibited significantly reduced secretion of TNFα and IL-6, indicating a diminished pro- inflammatory response. Together, these findings identify C5aR2 as a pathogenic mediator in ALS, promoting neuroinflammation and disease progression. Targeting C5aR2 signaling may represent a novel therapeutic strategy for ALS by mitigating complement-driven inflammation.

Basic Science
*BS-P-O001*

# FLUID DYNAMICS PROMOTE THE INDUCTION OF SPINAL CORD ORGANOIDS FOR TRANSPLANTATION

Suong Ngoc Anh Dang[1,2], Keiko Imamura[1,2,3], Haruhisa Inoue[1,2,3]

[1]iPSC-Based Drug Discovery and Development Team, RIKEN BioResource Research Center (BRC), Kyoto, Japan
[2]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan
[3]Medical-Risk Avoidance Based On iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Kyoto, Japan

## BACKGROUND

Amyotrophic lateral sclerosis (ALS) is an intractable disease caused by a progressive loss of motor neurons in spinal cords and motor cortex. Cellular therapy has been expected as ALS treatment, including the transplantation of stem cell-derived neural progenitors and glia to support the damaged motor neurons. However, several difficulties such as the optimization of cells for transplantation need to be overcome. In addition, the importance of interneurons has recently been demonstrated in ALS.

## METHODS

We generated spinal cord organoids using a bioreactor with vertical mixing.

## RESULTS

We developed a system to generate spinal cord organoids with an enriched number of motor neurons, interneurons, and glia by vertical mixing. Lesion-specific and cell-type enriched organoids were generated by fluid dynamic approach followed by confirmation with single-cell RNA-seq analysis, immunohistochemistry, and transplantation to mice.

## CONCLUSIONS

This technology using fluid dynamics may lead to an opportunity for the development of practical materials for transplantation strategies.

Basic Science
*BS-P-O002*

# DEVELOPING A MICROFLUIDIC MODEL OF THE CORTICOMOTOR SYSTEM

Kathryn Maskell, Yiing yap, Jyoti Chuckowree, Tracey Dickson, Catherine Blizzard
Menzies Institute for medical Research, Tasmania, Australia.

## INTRODUCTION:

ALS selectively affects the corticomotor system, but we are yet to understand where pathology begins or how it leads to degeneration of cells within this circuit. To investigate how specific cell populations within the corticospinal tract propagate and eventually succumb to disease pathology, we have designed an *in vitro* model that recapitulates key features of the corticomotor system.

## METHODS:

We created a novel microfluidic culture device with three interconnected and fluidically isolated chambers to house cortical neurons, spinal cord neurons, and muscle cells. The chambers are divided by innovative 'axon diode' microchannels, where one-way axon growth is encouraged by the 'axon entry' side being wider than the 'axon exit' side. Primary murine cortical and spinal cord neurons, along with C2C12 myoblasts, are plated into the respective chambers and cultured for up to 21 days.

## RESULTS:

Primary cortical and spinal cord neurons grow to relative maturity in our model, with axons growing through the axon diodes 5 days post-culture. Neurons in the middle chamber grew most of their axons through the ‘axon entry’ into the muscle chamber, rather than backwards into the cortical chamber, validating our design. We have verified synapse formation via quantification of pre- and post- synaptic puncta (synaptophysin and PSD-95, respectively) on spinal neuron dendrites, as well as NMJ-like connections between spinal neurons and differentiated myoblasts. In addition, we can maintain fluidic isolation between chambers for over 2 hours, offering the opportunity to apply cell-type specific therapeutics or experimental manipulations.

## CONCLUSION:

We have designed a novel microfluidic model and an associated culture protocol that captures key aspects of the corticomotor system. Future studies will leverage this model by introducing ALS associated pathologies to the circuit in a cell-type specific manner, enabling the evaluation of how pathology spreads, and where drugs need to be administered to halt disease progression.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-O003*

# THE IMPACT OF RESCUING SCHWANN CELLS ON LOWER MOTOR NEURON FUNCTION IN ALS

Katherine Lewis[1], Georgina Craig[2], Robin McAllen[1], Andrew Tosolini[3,4] David Gonsalvez[5], Bradley Turner[1] & Samantha Barton[1]

1. The Florey Institute, The University of Melbourne, Melbourne VIC
2. Li Ka Shing Knowledge Institute, Unity Health, St Michael's Hospital, Toronto, Canada
3. School of Biomedical Sciences, The University of Queensland, Brisbane QLD
4. Australian Institute of Biotechnology and Nanotechnology, Brisbane, QLD
5. Department of Anatomy and Developmental Biology, Monash University, Melbourne VIC

## INTRODUCTION:

While ALS is characterised by the degeneration of motor neurons, it has been well established that the surrounding glia play a role in its pathology and neurodegeneration. Schwann cells, the myelinating cells of the peripheral nervous system, have been shown to exhibit ALS pathology including cytoplasmic TDP-43 aggregates[1,2]. We aimed to characterise the intrinsic contributions of Schwann cells to ALS by crossing the *TDP-43$^{Q331K}$* mouse with a P0-cre mouse, to excise the pathological human transgene from Schwann cells alone.

## METHODS:

We assessed behavioural changes (hind-limb grip strength and Rotarod walking test from 2-10 mo), compound muscle action potential (CMAP) electrophysiology along the sciatic nerve and in the gastrocnemius muscle (10 mo), sciatic nerve conduction velocity (10 mo), and histological analysis of sciatic nerve myelin density using Spectral Confocal Reflectance (SCoRe) Microscopy (10 mo) in *TDP-43$^{Q331K}$* (TDP), wildtype (WT), and *P0-Cre/TDP-43$^{Q331K}$* (P0-cre/TDP) mice.

## RESULTS:

There was no significant genotype effect between WT (n=28), TDP (n=27), and P0-cre/TDP (n=28) mice in the hind-limb grip strength test. In the Rotarod test, both TDP (n=27) and P0-cre/TDP (n=28) mice performed progressively worse than the WT ($p<0.05$; n=28). Electrophysiology revealed decreased CMAP amplitude ($p<0.05$) and reduced conduction velocity ($p<0.05$) in TDP (n=7) and P0- cre/TDP (n=7) mice compared to WT (n=6), suggesting no apparent rescue. SCoRe revealed increased myelin density in TDP mice ($p<0.05$; n=4 female; 7 male) compared to WT (n=3 female; 7 male) and P0-cre/TDP mice (n=5 male), suggesting a rescue in P0-cre/TDP mice. Analyses of the Nodes of Ranvier, neuromuscular junction, electron microscopy, and axon transport, are underway to uncover the extent of Schwann cell involvement in ALS.

## CONCLUSION:

These data suggest that Schwann cells may play an intrinsic role in ALS, particularly regarding peripheral myelin health, but their rescue may not be sufficient to ameliorate motor neuron degeneration in ALS.

## REFERENCES:

1. Nakamura-Shindo, K., Sakai, K., Shimizu, A., Ishida, C., & Yamada, M. (2020). Accumulation of phosphorylated TDP-43 in the cytoplasm of Schwann cells in a case of sporadic amyotrophic lateral sclerosis. *Neuropathology*, *40*(6), 606-610.

2. Riva, N., Gentile, F., Cerri, F., Gallia, F., Podini, P., Dina, G., ... & Quattrini, A. (2022). Phosphorylated TDP-43 aggregates in peripheral motor nerves of patients with amyotrophic lateral sclerosis. *Brain*, *145*(1), 276-284.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Basic Science
*BS-P-O004*

# SARM1 INHIBITION LIMITS AXONAL DEGENERATION INDUCED BY KAINIC ACID-INDUCED EXCITOTOXICITY

[1]Leng Cheng, Jan; [1]Thorne, B; [1]Talbot J; [1]Atkinson R; [1]Perry S; [1]King A; [1]Cook A
[1]Wicking Dementia Research and Education Centre, University of Tasmania, 17 Liverpool St, Hobart, Australia

## INTRODUCTION:

Axon degeneration is a common feature of neurodegenerative conditions, including amyotrophic lateral sclerosis (ALS). A key player in axon degeneration is the SARM1 protein. Deletion of SARM1 was shown to potently protect axons from pro-degenerative insults, such as axon severing, and in models of chemotherapy-induced peripheral neuropathy [1,2]. Our objective was to determine if SARM1 inhibition would also protect axons against excitotoxicity-induced degeneration.

## METHODS:

We used CRISPR/Cas gene editing of human induced pluripotent stem cells (iPSC) to introduce a point mutation in the SARM1 gene ($SARM1^{K193R}$) that has a dominant-negative action on endogenous SARM1 [3]. We also used a small molecule inhibitor of SARM1, DSRM-3716. Using these models, we quantified axon degeneration following kainic acid exposure of MAP2- and Tau-expressing 3D neurospheres. Axon degeneration was quantified using an optimized semi-automated CellProfiler-based image analysis pipeline.

## RESULTS:

We observed a statistically significant protective effect against KA-induced axon degeneration in $SARM1^{K193R}$ expressing neuronal cultures compared to isogenic neuronal cultures. However, SARM1 inhibition did not protect iPSC-derived neuronal cultures against organophosphate-induced axonal degeneration in this model. The protective effects of SARM1 inhibition against KA were specific to axons, as dendrites were not protected. Use of the SARM1 inhibitor, DSRM-3716, trended towards a protective effect against KA-induced axon degeneration with SARM1 inhibition compared to controls but did not reach statistical significance.

## CONCLUSION:

SARM1 limits KA-induced axon degeneration in iPSC-derived neuronal cultures. However, further optimization of our models is required, and it appears that SARM1 inhibition is insufficient in arresting neurodegeneration in all contexts, such as organophosphate exposure. We are also extending this work to identify novel approaches to inhibiting SARM1.

## REFERENCES:

1. McGuinness et al., (2024). The Neuroscientist, 30(4), 473–492.
2. Bosanac et al., (2021). Brain, 144(10), 3226–3238.
3. Geisler et al., (2019). The Journal of Experimental Medicine; 216(2), 294–303.

Basic Science
*BS-P-O005*

# VISUALIZATION OF DYSREGULATED PROTEINS INVOLVED IN MOTOR NEURON DISEASE USING ELECTRON CRYOTOMOGRAPHY

Alemu Gebrie Chekol, Debnath Ghosal, Arcot Anil Kumar Manasi, Danny M. Hatters

Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Victoria 3052, Australia.

One of the leading genetic causes of motor neuron disease is the expansion of GGGGCC hexanucleotide repeats in intron 1 of the C9ORF72 gene. The hexanucleotide repeat expansion can contain hundreds or thousands of repeats. Through repeat-associated non-AUG translation, five dipeptide repeat proteins (DPRs) are produced from six reading frames of both sense and antisense repeat-containing transcripts. Two of these contain arginine, which are highly toxic in cellular and animal models . Our team and others previously found the arg-rich DPRs readily cluster together and with other cellular proteins, and can stall ribosomes. Here we describe the progress to date of our project to visualize the structures of the DPR protein complexes in cells using electron cryotomography. The poster will describe our progress in expressing the DPRs in cell culture, purifying DPR-stalled ribosomal complexes and ion milling of the material.

Basic Science
*BS-P-O006*

# DEVELOPMENT OF ANTISENSE OLIGONUCLEOTIDES TO RESTORE AXONAL HEALTH IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

Jessica Mantegna[1,2], Steve Wilton[2,3], Bradley Turner[1,4], Anthony Akkari[1,2,3,5], Frances Theunissen[1,2,3, 5]

[1]School of Health Science, The University of Notre Dame Australia, Fremantle, WA, Australia
[2]Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia
[3]Precision Medicine Centre, Murdoch University, Murdoch, WA, Australia
[4]Florey Institute of Neuroscience and Mental Health, Melbourne
[5]Black Swan Biotech, Perth, WA, Australia

Presentation type: Poster Category: Other

Sterile alpha and Toll/interleukin-1 receptor motif-containing 1 (SARM1) is a pro-degenerative protein responsible for programmed axon degeneration following injury, in response to toxins or other insults. Hyperactivity of SARM1 has been seen in amyotrophic lateral sclerosis (ALS), resulting from rare genetic variants leading to SARM1 gain of function. Deletion of *SARM1* has been shown to reduce motor axon degeneration and neuromuscular denervation in a TDP-43 mouse model of ALS. Moreover, modulation of SARM1 via a RNase H1 antisense oligonucleotides (ASOs) has been shown to delay programmed axon degeneration in dopaminergic neurons, protecting against morphological changes and mitochondrial dysfunction, providing strong evidence that modulating SARM1 has therapeutic potential in neurodegenerative disease contexts. This project will develop ASOs using phosphorodiamidate morpholino oligomer (PMO) chemistry to promote exon skipping or intron retention leading to nonsense mediated decay of SARM1 mRNA and subsequent reduction of SARM1 protein. To assess ASO candidates for SARM1 exon skipping, 26 designs— using negatively charged 2′-*O*-methyl chemistry for initial screening—targeting exons 2, 4, 7 and 8 were delivered into the neuroblastoma cell line SH-SY5Y using Lipofectamine RNAiMAX at concentrations of 100 nM and 50 nM. 24 hours post-transfection, the cells were harvested, and RNA extracted to assess exon skipping potential via RT-PCR and gel electrophoresis. Results of initial screening demonstrated the potential capability of 8 ASOs: 4 targeting exon 4, 1 targeting exon 7, and 3 targeting exon 8 with Sanger sequencing confirming the skipping of each target exon. These sequences will be micro-walked 5bp up and downstream of the initial sequence to determine the strongest splice site to induce exon skipping. These results highlight a promising first step in developing an ASO therapy with high selectivity that that has the potential to modulate SARM1 activity and may protect against programmed axon degeneration in sporadic ALS.

Basic Science
*BS-P-O007*

# SELETIVE MODULATION OF VOLTAGE-GATED SODIUM CHANNELS ON MOTOR NEURONS AS A THERAPEUTIC STRATEGY FOR AMYOTROPHIC LATERAL SCLEROSIS

Jessica AI Muller[1], Refik Kanjhan[1], Van Tran[1], Charan Kotapati[1], Mark Bellingham[2], Jean Giacomotto[3] and Fernanda C Cardoso[1]
[1]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia [2]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia [3]Griffith Institute for Drug Discovery, Griffith University, Brisbane, Australia

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease for which efficient treatments are unavailable. Clinical investigations have pinpointed aberrant motor neuron hyperexcitability mediated by ion channels as a pivotal pathological mechanism in ALS. Riluzole, the standard treatment, mitigates hyperexcitability through non-selective inhibition of ion channels, including voltage- gated sodium (NaV) channels in the central nervous system (CNS).

In the CNS, the sodium channels subtypes NaV1.2 and NaV1.6 stand out as potential targets for pharmacological intervention in ALS. Although there are no endogenous ligands modulating NaV channels, venomous animals harbour a rich repository of peptides that modulate NaV channels. Venom-derived peptides function as invaluable pharmacological probes in disease contexts and hold great therapeutic potential

In this work, we performed structure–activity relationship investigations on venom- derived peptides to understand their potency and selectivity for NaV1.2 and/or NaV1.6. We applied rational design, chemical synthesis and automated electrophysiology to optimize the pharmacology of venom-derived peptides on these NaV subtypes. Select optimized analogues were further evaluated using manual electrophysiology on mouse motor cortex to investigate their efficacy in inhibiting NaV channel subtypes to counteract hyperexcitability in ALS $SOD1^{G93A}$ mouse model.

Using this approach, we identified 5 analogues showing interesting potency and selectivity towards NaV1.2 and/or NaV1.6. *In vivo* evaluations using a zebrafish model of motor neurodegeneration demonstrated that the venom peptide here named PROPETx and the optimized analogue OPT6 effectively prevented motor function loss and increased survival. These results highlight the potential of selective NaV channel inhibition in halting motor neuron degeneration. We hope our research will deliver novel drug candidates to treat ALS via selective inhibition of NaV channel subtypes.

Basic Science
*BS-P-O008*

# REBALANCING EXCITABILITY WITH GENE THERAPY

Joshua R Curson[1], Ebony S. Bax[1], Petra L. Sedlak[1], Li Xu[1], Pankaj Sah [1, 3], Margreet C. Ridder[1, 2]

1. The Queensland Brain Institute, The University of Queensland, St Lucia 4072, Australia
2. The School of Biomedical Sciences, The University of Queensland, St Lucia 4072, Australia
3. Joint Center for Neuroscience and Neural Engineering, and Department of Biology, Southern University of Science and Technology, Shenzhen, Guangdong Province, P. R. China, 518055

Neuronal hyperexcitability is a clinical feature of ALS. The ability to control the excitability of defined neuronal populations, using light- and drug-activated receptors is rapidly advancing our understanding of brain function. We believe this same technology can be adapted to rebalance excitability in ALS where multiple signalling pathways converge to ultimately induce excitotoxic cell death. The main pharmacological treatment that has been found to slightly delay the course of ALS, riluzole, acts by reducing neuron excitability. Our gene therapy approach to reduce neuronal excitability uses a hyperexcitability-counteracting silencing receptor (HyCSR) that is optimised for human clinical use and is potentiated by ivermectin, a safe TGA-approved drug that reaches the brain via oral delivery. Our current study aims to determine the safety and efficacy of rebalancing excitability in spinal cord motor neurons of a preclinical ALS mouse model using our IVM-activated HyCSR gene therapy.

Basic Science
*BS-P-O0009*

# DEVELOPING A CNS-PENETRATING ANTISENSE THERAPY APPROACH FOR SOD1-MEDIATED ALS

[1,2]Pitteri, Matteo; [1]Shabanpoor F; [1]Turner BJ
[1]The Florey Institute of Neuroscience & Mental Health, The University of Melbourne, Australia,
[2]Department of Anatomy & Physiology, The University of Melbourne, Australia.

## INTRODUCTION:

Antisense oligonucleotides (ASOs) are gaining momentum as the genetic therapy of choice for correcting disease-causing mutations in ALS. However, a major limitation of ASOs is their poor penetration across cell membranes and their inability to overcome the blood-brain barrier (BBB).[1,2] As such, ASOs must be delivered intrathecally for targets in the central nervous system (CNS), which is invasive, technically challenging, and indeed may underlie the limited efficacy of Tofersen – an ASO targeting *SOD1*.[3] While Tofersen was shown to be safe and exhibits clear target engagement, the functional benefits it provides are modest. Thus, our work aims to develop a novel ASO therapy for SOD1- ALS that offers greater clinical efficacy by overcoming the BBB via systemic delivery.

## METHODS:

We have designed and screened ASOs in human neuronal cells and transgenic SOD1-G93A mice using the latest generation of backbone chemistries, including locked nucleic acid (LNA) and phosphorodiamidate morpholino oligo (PMO) modifications. Additionally, we have synthesised and conjugated a range of BBB- penetrating peptides (BPPs) to the most potent ASOs to enhance their cell/BBB-permeability and enable systemic administration.

## RESULTS:

Our ASOs exhibit more potent SOD1 knockdown compared to Tofersen when delivered via intracerebroventricular injection into SOD1-G93A mice. Our *in vitro* assays demonstrate that BPP-ASO conjugates reduce SOD1 levels up to threefold more than their unconjugated counterparts. This is the first report of successful conjugation of BPPs to ASOs of LNA chemistry, enhancing their activity in *SOD1* patient-derived iPSC motor neurons. Furthermore, by incorporating a Cyanine-7 fluorescent tag into the synthesis of our BPPs, we have identified optimal BPP-ASO combinations based on their penetration into a human BBB organoid model.

## CONCLUSION:

By leveraging this BPP technology to enhance the CNS bioavailability of our superior ASOs, we endeavour to define a lead BPP-ASO conjugate for potential clinical studies.

## REFERENCES:

1. Pardridge WM. *Front Aging Neurosci*. 2020;11:373.
2. Dowdy SF, et al. *Nucleic Acid Ther.* 2022;32(5):361-368.
3. Miller TM, et al. *N Engl J Med.* 2022;387:1099-110.

Basic Science
*BS-P-O010*

# INVESTIGATING TDP-43 MODULATION AND THERAPEUTIC POTENTIAL OF A MORPHOLINO ANTISENSE OLIGONUCLEOTIDE TARGETING *TARDBP* IN A HUMANISED ALS MOUSE MODEL

Taoro-González, Lucas[1]; Muñoz de Bustillo-Alfaro, Ramón A.[1]; Mejzini, Rita[2,3,4]; Loren Flynn, Lezanne Ooi[6], Dzung Do-Ha[6], Chloe Sligar[6], Adam Walker [8], Bradley Turner[7], Francess Theunissen Akkari, Patrick A. [2,3,4,5]; Acevedo-Arozena, Abraham[1]

1. U. Hospital of the Canary Islands; ITB-ULL, FIISC and CIBERNED (Spain).
2. Personalized Medicine Centre, Murdoch U. (Australia).
3. The Perron Institute for Neurological and Translational Science, (Australia).
4. Department of Neurology, Duke U. (USA).
5. The U. of Western Australia (Australia).
6. School of Science, Molecular Horizons, University of Wollongong
7. Florey Institute of Neuroscience and Mental Health, Melbourne
8. University of Sydney

The pathological hallmark of most sporadic ALS cases is the simultaneous nuclear clearance and cytoplasmic accumulation of TDP-43, resulting in both the loss of its nuclear functions, including splicing regulation, and its toxic mislocalisation to the cytoplasm. However, the precise mechanisms by which TDP-43 dysregulation drives motor neuron degeneration remain poorly understood.

To explore this neurodegenerative process, we have developed a potent morpholino antisense oligonucleotide (PMO) therapeutic candidate designed to selectively modulate TARDBP/TDP-43 expression. Here, we present compelling preliminary findings on TARDBP modulation and its effects in sALS iPSC-derived neuronal models. Additionally, we introduce the first in vivo investigations of TARDBP-PMO administration in our genomically humanised TARDBP mouse models. These models feature a fully human TARDBP gene, replacing the endogenous murine Tardbp locus— including all exons and introns—and encompass both a wild-type (WT) human allele and a mutant allele carrying the human M337V mutation.

Using this unique humanised system, we aim to model in vivo human TDP-43 modulation while evaluating different ASO treatment strategies. By establishing optimised dosing regimens that modulate TARDBP regulation, we will assess the feasibility of this therapeutic approach in vivo.

Clinical

*C-O-B001*

# DIAGNOSTIC VALUE OF THRESHOLD TRACKING TRANSCRANIAL MAGNETIC STIMULATION PARADIGMS IN AMYOTROPHIC LATERAL SCLEROSIS

Aicee Dawn Calma[1,2], Nathan Pavey[1,2], Cláudia Santos Silva[1,3,4], Mehdi A.J. van den Bos[1], Con Yiannikas[2], Michelle A. Farrar[6,7], Matthew C Kiernan[8,9], Parvathi Menon[1,2], Steve Vucic[1,2]

1. Brain and Nerve Research Centre, Concord Clinical School, University of Sydney, Concord Hospital, Sydney, Australia.
2. Department of Neurology, Concord Repatriation General Hospital, Sydney, Australia
3. Department of Neurosciences and Mental Health, Unidade Local de Saúde de Santa Maria, Lisbon, Portugal
4. Faculdade de Medicina-Instituto de Medicina Molecular, Centro de Estudos Egas Moniz, Universidade de Lisboa, Lisbon, Portugal.
5. Discipline of Paediatrics and Child Health, School of Clinical Medicine, UNSW Medicine and Health, The University of New South Wales, Sydney, Australia.
6. Neuroscience Research Australia, Sydney, Australia.
7. Scientia Professor of Neuroscience, University of NSW; and Department of Neurology, SouthEastern Sydney Local Health District, Sydney, Australia.

**OBJECTIVE:**

Threshold tracking transcranial magnetic stimulation (TMS) is a valuable diagnostic tool in providing insight into cortical excitability in amyotrophic lateral sclerosis (ALS). Recently, various tracking paradigms have been proposed, but their relative diagnostic performance remains unclear. This study aimed to evaluate and compare the diagnostic utility of serial ascending and parallel threshold tracking TMS paradigms in ALS.

**METHODS:**

Threshold tracking TMS was performed on 90 prospectively recruited individuals with suspected ALS. Short interval intracortical inhibition (SICI) was recorded using both serial ascending and parallel paradigms across interstimulus intervals (ISI) of 1–7 ms. The primary outcome was the ability of each paradigm to differentiate ALS from ALS-mimicking disorders, assessed using receiver operating characteristic (ROC) analysis with the DeLong method.

**RESULTS:**

Reduced SICI effectively distinguished ALS from mimics across both paradigms, confirming the diagnostic relevance of cortical inhibition measures. However, the serial ascending paradigm demonstrated significantly better diagnostic accuracy, with a higher mean area under the curve (AUC) for SICI (1–7 ms) (0.81, 95% CI 0.72–0.91) compared to the parallel paradigm (0.72, 95% CI 0.61–0.83, p=0.0065). This superiority was particularly evident at ISI 1–5 ms and remained consistent regardless of site of disease onset, degree of functional impairment, or lower motor neuron involvement. Notably, in ALS patients with relatively few upper motor neuron signs, both paradigms exhibited comparable diagnostic performance.

**CONCLUSION:**

Threshold tracking TMS reliably differentiates ALS from mimic disorders, with the serial ascending paradigm providing superior diagnostic accuracy. Given its enhanced performance, the serial ascending threshold tracking TMS paradigm should be considered the preferred diagnostic tool for ALS in both clinical and research settings.

Clinical

*C-O-B002*

# MULTI-OMICS PROFILING REVEALS METABOLIC REPROGRAMMING AND THERMOGENESIS IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS

[1]Linjing,Zhang; [1]Dongsheng Fan

[1]Department of Neurology, Peking University Third Hospital, Garden Road code 49, Haidian District, Beijing 100191, China

## INTRODUCTION:

To elucidate metabolic perturbations in amyotrophic lateral sclerosis (ALS) and identify diagnostic biomarkers for early-stage disease detection.

## METHODS:

Untargeted metabolomics and quantitative lipidomics were integrated to characterize recurrently dysregulated pathways across discovery (Cohort 1: 36 ALS patients vs. 32 age-/sex-matched healthy controls) and validation (Cohort 2: 68 ALS patients vs. 46 age-/sex-matched healthy controls) cohorts. Plasma samples were collected after overnight fasting. Analyses were adjusted for BMI, with significance thresholds set at |fold change (FC)| >2 and false discovery rate (FDR) <0.05. Machine learning-based recursive feature elimination was employed to construct biomarker panels, validated for diagnostic accuracy in Cohort 2.

## RESULTS:

In Cohort 1, untargeted metabolomics identified 223 significantly altered metabolites. KEGG pathway analysis revealed prominent upregulation of galactose metabolism, oxidative phosphorylation, and folate biosynthesis, alongside downregulation of caffeine metabolism, terpenoid/steroid biosynthesis, TCA cycle, and glucagon signaling pathway. Quantitative lipidomics identified 75 dysregulated lipids, with strikingly 68 metabolites enriched in thermogenesis pathways, including downregulated medium/long-chain acylcarnitines and upregulated triglycerides. Pathways such as fat digestion/absorption, glycerolipid metabolism, cholesterol metabolism, and insulin resistance were significantly upregulated. Machine learning-derived biomarker panels demonstrated robust diagnostic performance: the metabolomic panel (1,3-dimethyluric acid, isoleucine-glycine, C12-OH-carnitine, ph-C14- carnitine) achieved an AUC of 0.97, while the lipidomic panel (C10:0-, C18:2-, C8:1-2OH-, and C18:1-carnitines) yielded an AUC of 0.99 in Cohort 2.

## CONCLUSION:

This study reveals a metabolic shift from glucose to fatty acid utilization in ALS, coupled with impaired thermogenesis pathways, suggesting potential dysfunction in brown adipose tissue regulation. These findings highlight novel diagnostic biomarkers and underscore the need to investigate metabolic dysregulation as a mechanistic and therapeutic target in ALS.

## REFERENCES:

1 Goutman SA, Guo K, Savelieff MG, Patterson A, Sakowski SA, Habra H, Karnovsky A, Hur J, Feldman EL. Metabolomics identifies shared lipid pathways in independent amyotrophic lateral sclerosis cohorts. Brain. 2022 Dec 19;145(12):4425-4439. doi: 10.1093/brain/awac025. PMID: 35088843; PMCID: PMC9762943.

2 Guo K, Figueroa-Romero C, Noureldein MH, Murdock BJ, Savelieff MG, Hur J, Goutman SA, Feldman EL. Gut microbiome correlates with plasma lipids in amyotrophic lateral sclerosis. Brain. 2024 Feb 1;147(2):665-679. doi: 10.1093/brain/awad306. PMID: 37721161; PMCID: PMC10834248.

3 Guo K, Savelieff MG, Jang DG, Teener SJ, Zhao L, Hur J, Goutman SA, Feldman EL. Longitudinal Metabolomics in Amyotrophic Lateral Sclerosis Implicates Impaired Lipid Metabolism. Ann Neurol. 2025 Feb 20. doi: 10.1002/ana.27208. Epub ahead of print. PMID: 39976286.

Clinical

*C-O-B003*

# PLASMA MISFOLDED SOD1 IN AMYOTROPHIC LATERAL SCLEROSIS

[1]Tsai, Li-Kai; [1]Kuo, Yih-Chih; [2]Ting, Chen-Hung; [2]Chang, Hsiang-Yu; [2]Wang, I-Fan

[1]Department of Neurology, National Taiwan University Hospital, Chung-Shan South Road, Taipei City, Taiwan.

[2]Garage Brain Science, Central Taiwan Innovation Campus, Ministry of Economic Affairs, Nantou City, Taiwan

## INTRODUCTION:

1. The plasma misfolded superoxide dismutase 1 (mSOD1) level is elevated in patients with *SOD1* gene mutation and some patients with sporadic amyotrophic lateral sclerosis (ALS).
2. Although plasma mSOD1 is a potential biomarker for ALS diagnosis, the characteristics of plasma mSOD1 are still unclear, regarding plasma-central nervous system (CNS) correlation, temporal changes, abnormal rate in sporadic ALS, and features of patients with elevated plasma mSOD1.
3. This study aims to characterize plasma mSOD1 using an ALS mouse model and ALS patients with and without *SOD1* gene mutation.

## METHODS:

1. We investigated an ALS mouse model with human *SOD1/G93A* transgenes, 4 ALS patients with *SOD1* gene mutation, and 142 patients with sporadic ALS.
2. Plasma mSOD1 levels were measured using biotinylated isoxazole (b-isox) chemical precipitation, followed by enzyme-linked immunosorbent assay analysis.
3. The plasma mSOD1 levels were correlated with the mSOD1 levels in brain and spinal cord of ALS mice and in cerebrospinal fluid (CSF) of ALS patients.
4. The temporal changes of mSOD1 were analyzed in plasma of ALS mice and patients and brain and spinal cord of ALS mice.
5. The clinical features were compared between sporadic ALS patients with and without elevation of plasma mSOD1 levels.
6. The Revised ALS Functional Rating Scale (ALSFRS-R) was used to represent disease severity.

## RESULTS:

1. The plasma levels of mSOD1 were elevated in ALS mice with *SOD1/G93A* transgenes, but not in wild-type mice or a mouse model of spinal muscular atrophy.
2. The levels of mSOD1 were well correlated between plasma and CNS tissues.
3. The plasma mSOD1 levels increased along with the disease progression but further reduced at the end-stage disease, at which there are only small amount of residual motor neuron (full of mSOD1) in the spinal cord.
4. Patients with *SOD1* gene mutations had elevated levels of mSOD1 in plasma and CSF.
5. Tofersen (an antisense oligonucleotide) treatment in one patient with *SOD1* gene mutation reduced the levels of mSOD1 both in plasma and CSF.
6. About one fifth of patients with sporadic ALS showed elevated levels of plasma mSOD1.
7. The levels of mSOD1 were well correlated between plasma and CSF in patients with sporadic ALS.
8. The lower the ALSFRS-R, the lower the percentage of sporadic ALS patients having elevated levels of plasma mSOD1; the concept is similar to the results in end-stage ALS mice mentioned above.
9. The clinical features were comparable between sporadic ALS patients with and without elevated levels of mSOD1, regarding onset pattern, duration, severity, and aggressiveness of disease.

## CONCLUSION:

1. The levels of mSOD1 are correlated between plasma and CNS tissues or CSF.
2. About one fifth of sporadic ALS patients had elevated levels of plasma mSOD1 and there is no obvious difference in clinical features between those with and without elevated plasma mSOD1 levels.

## REFERENCE:

1. Lai et al. Increase of HCN current in SOD1-associated amyotrophic lateral sclerosis. Brain. 2024;147:4240-4253.

Clinical

*C-O-B004*

# PLASMA PDGFR BETA LEVELS: A POTENTIAL INDICATOR OF DISEASE DURATION IN ALS

Lu Tang; Gan Zhang; Lu Chen; Xiaolu Liu; Dongsheng Fan

Department of Neurology, Peking University Third Hospital, Beijing, China

## INTRODUCTION:

Blood-brain barrier (BBB) breakdown has been implicated in the pathology of several neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). Soluble platelet-derived growth factor receptor beta (PDGFRβ) has emerged as a potential indicator of BBB integrity. However, the relationship between plasma PDGFRβ levels, ALS pathology, and ALS patients' progression remains unclear.

## METHODS:

A total of 72 participants were included in this study, comprising 48 patients with ALS and 24 healthy controls. BBB function was assessed by measuring plasma PDGFRβ levels using enzyme-linked immunosorbent assay (Raybiotech). Neurodegenerative pathology was evaluated using plasma neurofilament light chain (NFL) levels measured by Simoa technology. Given that BBB dysfunction is primarily driven by to inflammatory factors, we analyzed inflammatory cell counts from blood routine tests in ALS patients.

## RESULTS:

The plasma PDGFR level was not associated with plasma NFL level or the age of the subjects at sampling. There was no statistical difference in plasma PDGFR levels among patients with different disease progression rates (DPR) and different plasma NFL levels. However, in ALS patients with disease duration of less than 2 years, the mean plasma PDGFR level was significantly higher than that of patients with disease duration exceeding 2 years ($2594.7 \pm 824.34$ vs. $1827.5 \pm 999.52$ pg/mL, $p = 0.026$). The plasma NFL levels of patients with disease duration of less than 2 years or more than 2 years were both significantly higher than those of healthy controls (both $p<0.01$). Further analysis revealed that the neutrophil count was significantly higher in patients with a disease duration of less than 2 years than in those with a disease duration exceeding 2 years ($(4.47 \pm 1.37) \times 10^6$/mL vs. $(3.58 \pm 1.00) \times 10^6$/mL, $p =0.027$).

## CONCLUSION:

The plasma PDGFRβ levels in ALS patients with different disease durations are distinct, which may reflect the varying blood-brain barrier function at different stages of the disease and may also be associated with the neutrophil counts at these stages.

## REFERENCES:

1. Wang et al., Dynamic changes of CSF sPDGFRβ duringageing and AD progression and associations with CSF ATN biomarkers. Mol Neurodegener, 2022 Jan 15;17(1):9.

2. Kort et al., Normal cerebrospinal fluid concentrations of PDGFRβ in patients with cerebral amyloid angiopathy and Alzheimer's disease. Alzheimers Dement. 2022 Oct;18(10):1788-1796.

Clinical

*C-O-CM001*

# ENHANCING THE LIVED EXPERIENCE OF PEOPLE WITH AMYOTROPHIC LATERAL SCLEROSIS: BEST PRACTICE LEARNINGS FROM PATIENT ADVISORY GROUPS IN THE ASIA-PACIFIC REGION

[1]Sellati R; [1]Ali T; [1]Harari O; [1]Levy O

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

## INTRODUCTION:

Research investigating the journey of people with amyotrophic lateral sclerosis (ALS) has demonstrated that they face many challenges and barriers, including delays in diagnosis and challenges with access to specialists, genetic testing, and treatments. Patient Advocacy Groups (PAGs) are developing initiatives to help address these challenges. This study sought to identify and map innovative engagement models employed by PAGs to enhance patient care. Results from the Asia-Pacific region (APAC) are presented here.

## REPORT:

Literature reviews identified PAGs and their resources developed for people impacted by ALS. Resources were evaluated across five themes: adopting technology, community engagement, fostering partnerships, advocacy & policy influence, and education & awareness. Of the resources identified, a number were developed by PAGs from APAC, demonstrating their commitment to improving the patient experience. Taiwan's Motor Neuron Disease Association (MNDA) was noteworthy for efforts in adopting technology. In collaboration with the National Taipei University of Technology, a small, low-cost device was developed enabling people with ALS to answer yes/no questions through motor imagination. The device addresses a high unmet need, particularly in people with late-stage ALS who have difficulties communicating. The Korean ALS Association (KALSA) was notable for community engagement through their development of multiple community-driven resources. Their website's "Information Board" provides ALS-related updates and resources so that members can stay engaged with the ALS community. The Beijing Oriental Rain ALS Care Center (ORACC) has a focus on education & awareness. To help improve caregiver education and prevent health complications, ORACC conducted training for people with ALS, and their families/caregivers, providing advice on psychological, nutritional, and communicative support.

## CONCLUSION:

PAGs from APAC, such as MNDA, KALSA, and ORACC, have developed resources that adopt new technology, engage the community, and increase education and awareness. These initiatives can enhance the experience of people with ALS and their caregivers.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Clinical

*C-O-CN&I001*

# ASSOCIATION BETWEEN CLINICAL FEATURES AND ASTROGLIOSIS AS VISUALISED BY $^{18}$F-THK5351 PET IN MOTOR NEURON DISEASE

[1] Higashihara M; [2]Ishibashi K; [3]Hatanaka Y; [1]Kurihara M; [1]Komori Y; [1]Takahashi K; [1]Funakawa K; [4]Matsubara T; [1]Ihara R; [3]Sonoo M; [5]Kato T; [6]Murayama S; [7]Tokumaru AM; [2]Ishii K; [1]Iwata A

[1]Department of Neurology, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Itabashi-ku, Tokyo, JAPAN, [2]Research team for Neuroimaging, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Itabashi-ku, Tokyo, JAPAN, [3]Department of Neurology, Teikyo University, Itabashi-ku, Tokyo, JAPAN, [4]Department of Neurology, Tokushima University, Tokushima city, Tokushima, JAPAN, [5]Department of Rehabilitation, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Itabashi-ku, Tokyo, JAPAN, [6]Brain bank for Aging research, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Itabashi-ku, Tokyo, JAPAN, [7]Department of Radiology, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Itabashi-ku, Tokyo, JAPAN.

## INTRODUCTION:

The PET radioligand $^{18}$F-THK5351 binds to monoamine oxidase B, which is expressed on astrocytes, and therefore $^{18}$F-THK5351 PET can be used to visualise astrogliosis. The aim of this study is to investigate the clinical utility of $^{18}$F-THK5351 PET in MND.

## METHODS:

We recruited patients with MND fulfilling the Gold Coast criteria or PLS consensus diagnostic criteria. The $^{18}$F-THK 5351 PET study was conducted along with neurological and neuropsychological assessment using the Edinburgh cognitive and behavioural screen Japanese version (ECAS-J).

## RESULTS:

A total of 41 patients (age 70.6±8.7 years) were enrolled. The site of onset was 14 bulbar, 11 upper limb (UL) and 14 lower limbs (LL). $^{18}$F-THK5351 uptake in the primary motor cortex (PMC) was positive in 26 patients (63.4%), who had a higher upper motor neuron score (10.2 vs 2.4, $p<0.001$) than the negative uptake group. When the localisation of uptake in the PMC was examined, approximately half of the patients with bulbar or LL-onset showed a diffuse uptake. The remainder exhibited localised uptake in the lateral part of the PMC in patients with bulbar-onset and in the medial part in patients with LL-onset disease, corresponding to the facial and LL areas of the cortical homunculus, respectively. Patients with UL- onset disease showed localised uptake in the precentral knob or lateral part of the PMC. Interestingly, the percentage of PMC uptake was lower in the UL-onset group (27.3%) than in the LL-onset (85.7%, $p<0.01$) or bulbar-onset group (71.4%, $p<0.05$). Furthermore, 15 patients showed an increased uptake in the extra-motor cortex (EMC) with lower total ECAS scores (84.2 vs 100, $p<0.01$) and ALS- specific scores (62.9 vs 77.3, $p<0.01$), suggesting an association between cognitive impairment and astrogliosis in the EMC.

## CONCLUSION:

$^{18}$F-THK 5351 PET successfully visualised astrogliosis in the PMC and EMC, which correlated with various clinical features of MND.

## REFERENCES:

1. Shefner JM. et al., Clin Neurophysiol. 89(5):979-986, 2021
2. Turner M, et al., J Neurol Neurosurg Psychiatry. 91:373–377, 2019
3. Higashihara M, et al., Clin Nucl Med. 6(12):e582-e583, 2021
4. Abrahams S, et al, Amyotroph Lateral Scler Frontotemporal Degener. 15:9-14, 2014
5. Watanabe Y, et al., Amyotroph Lateral Scler Frontotemporal Degener. 22(1-2):66-72, 2021

Clinical
*C-O-CN&I002*

# LONGITUDINAL ASSESSMENT OF CORTICAL MOTOR FUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

Dayna-Lee Talbot[1], Dhayalen Krishnan[1,2], Jasmine F. Ashhurst[1,2], Susanna B. Park[3], Steve Vucic[4], Hannah C. Timmins[1], Matthew C. Kiernan[1,2,5]

**Affiliations:**

1. *Neuroscience Research Australia, Sydney, Australia.*
2. *Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia.*
3. *School of Medical Sciences, University of Sydney, Australia*
4. *Brain and Nerve Centre, Concord Hospital, Sydney, Australia.*
5. *University of New South Wales, Sydney, Australia*

**BACKGROUND**:
Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive and fatal neurodegenerative disease of the motor neurons. While the exact aetiology of ALS is yet to be determined, mounting evidence suggests that cortical hyperexcitability plays a role in the disease pathophysiology. Short interval intracortical inhibition (SICI) remains the most sensitive parameter for assessing cortical motor function in ALS. While an initial SICI value has been utilised to support a diagnosis of ALS, less is known about the change in cortical excitability as the disease progresses.

**METHODS:**
Motor cortex function was prospectively assessed in ALS patients, through serial paired- pulse threshold-tracking transcranial magnetic stimulation assessment over >12 months. Motor evoked potentials were recorded from the abductor pollicis brevis. Demographic information and clinical variables were analysed.

**RESULTS:**
A cohort of 52 ALS patients (69.2% limb-onset) underwent longitudinal assessment of cortical motor function. Mean ALSFRS-R score at baseline was 39.5±1.0 denoting relatively mild clinical deficits at study commencement. Cortical motor dysfunction was evident at baseline, with reduction in averaged SICI when compared to healthy controls ($p=0.004$). In terms of disease trajectory, ALS patients experienced a significant progressive decline in averaged SICI, after 6 months ($p<0.001$). The decline in averaged SICI did not differ significantly between bulbar and limb phenotypes *(n.s).* The progressive change in averaged SICI was more robust in the dominant hemisphere, with the proportion of ALS patients who demonstrated a clinically abnormal averaged SICI value (<5.5%) increasing from 42.6% to 92.6%.

**Conclusion:**
ALS patients demonstrate progressive abnormalities in the motor cortex, evident through longitudinal assessment. While SICI represents a diagnostic biomarker, the progressive decline in SICI observed in the present series suggests a potential role in monitoring disease progression as well as the efficacy of therapeutic intervention.

Clinical

*C-O-CT&P001*

# PRIMEC AS A PROMISING ORAL THERAPY FOR ALS: PHASE 2B STUDY RESULTS AND BIOMARKER FINDINGS, AND THE UPCOMING PHASE 3 STUDY (PARAGON)

**Shefner JM**[1], Drory VE[2], Chio A[3], Lunetta C[4], Shoesmith C[5], Zimri S[6], Russek-Blum N[6], Shtossel D[6], Kerem N[6], van Eijk RPA[7], Shapira G[8], Shomron N[8], Tracik F[6], Rosenfeld J[9] & Cudkowicz ME[10]

[1]Barrow Neurological Institute, Phoenix, AZ, USA; [2]Neuromuscular Diseases Unit, Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [3]University of Turin, Turin, Italy; [4]Istituti Clinici Scientifici Maugeri IRCCS, Department of Neurorehabilitation, Institute of Milan, Italy; [5]Department of Clinical Neurological Sciences, Division of Neurology, London Health Sciences Centre, London, ON, Canada; [6]NeuroSense Therapeutics, Ltd, Herzliya, Israel; [7]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [8]Faculty of Medical and Health Science, Tel Aviv University, Tel Aviv, Israel; [9]Department of Neurology, Loma Linda University School of Medicine & [10] Mass General Brigham Neuroscience Institute, Healey & AMG Center for ALS, Department of Neurology, MGH, Harvard Medical School, Boston, MA, USA

## INTRODUCTION:

PrimeC, an oral combination of two well-characterized drugs in optimized doses, targets neuroinflammation, iron metabolism, and RNA regulation. We report the results of a randomized, placebo-controlled, double-blind (DB) Phase 2b trial (PARADIGM; NCT05357950) evaluating PrimeC over 6 months of DB followed by 12 months of open label.

## METHODS:

Sixty-eight participants with ALS (PALS) were randomized (2:1) to receive PrimeC or placebo for 6 months, with a 12-month open-label extension (OLE). Outcomes included safety, ALSFRS-R, vital capacity, and survival. Multiple biomarker assessments included NfL, NDE TDP-43, PGJ2, microRNA profiles, serum ferritin, and transferrin.

## RESULTS:

PrimeC demonstrated a favorable safety and tolerability profile over 18 months. Participants originally randomized to PrimeC experienced a progression rate 29.2% less than original placebo participants.at 6 months (2.23 points; 95% CI [-0.606, 5.069]; p=0.12) and by 32.8% at 18 months (7.92 points; 95% CI [1.318, 5.038]; p=0.007). The bulbar domain showed the greatest difference (mean: 3.18 points; p=0.001).

Those randomized to PrimeC showed reduced ferritin (p=0.05) and a trend towards increased transferrin (p=0.13). In the placebo group, Ferritin levels correlated with faster ALSFRS-R decline (Spearman's rho=-0.5, p=0.021), but not in the PrimeC arm (Spearman's rho=0.05, p=0.761).

Over 100 microRNA species were differentially expressed. PrimeC significantly downregulated hsa- miR-199a-5p, a novel biomarker linked to ALS progression. Further biomarker findings will be discussed.

## CONCLUSION:

The favorable safety profile, positive changes on clinical outcomes, and changes in markers of target engagement support further exploration in a Phase 3 trial. PARAGON ALS is a double blind, placebo controlled, 48-week trial that will enroll approximately 300 to 500 PALS. Primary outcome will be assess the joint effect on ALSFRS-R and overall survival at 48 weeks; multiple functional and biomarker outcomes will also be collected. The trial is scheduled to begin internationally in the 3rd quarter of 2025.

Clinical

*C-O-CT&P002*

# PHASE 1 OPEN-LABEL EXTENSION STUDY OF AN MTOR INHIBITOR IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Susan Mathers[1, 2], Dominic Rowe[3], Philip White[4], Melanie Quintana[4], John Clark[5] and Michael Thurn[5].
[1]Calvary Health Care Bethlehem, Caulfield South, VIC 3162, Australia
[2]School of Clinical Sciences, Monash University, Clayton, VIC 3800, Australia
[3]Centre for MND Research, Faculty of Medicine and Health Research, Macquarie University, Sydney, NSW 2109, Australia
[4]Berry Consultants, Austin, Texas, 78746, USA
[5]Neurizon Therapeutics Ltd, South Melbourne, VIC 3205, Australia

## INTRODUCTION:

A key pathological feature of amyotrophic lateral sclerosis (ALS) is the formation of cytoplasmic protein aggregates. The induction of autophagy in diseased cells is viewed as a possible therapeutic approach to clear the toxic build-up of intracellular pathological proteins associated with the clinical manifestations of ALS. Inhibition of the mammalian target of rapamycin (mTOR) pathway has been shown to induce autophagy, clear protein aggregates and provide benefits in mouse models of ALS. NUZ-001 (Monepantel) is a potent oral small molecule inhibitor of mTOR that is being developed for a range of neurodegenerative conditions and has been shown in preclinical studies to prevent the aggregation of TAR DNA-binding protein 43 (TDP-43), a key pathological feature of ALS. Here, we investigate the long-term safety, tolerability, and efficacy of orally administered NUZ-001 in up to 12 evaluable subjects with ALS who previously completed the Phase 1 MON-2021- 001 Study

## METHODS:

The Phase 1 open-label extension study was a multicenter study of NUZ-001 administered orally for a duration of 12 months to up to 12 evaluable subjects with ALS. The following were assessed during the study: long-term safety and tolerability, efficacy (ALS Functional Rating Scale–Revised, ALSSQOL-R Quality of Life Questionnaire, Edinburgh Cognitive and Behavioural ALS Screen [ECAS], seated Slow Vital Capacity [SVC]), and biomarker measures (plasma and CSF neurofilament/light chain [NfL] and urinary $p75^{ECD}$ levels).

## RESULTS:

Once daily oral administration of NUZ-001 at a dose of 10 mg/kg in 10 eligible patients with ALS over a 12-month period was well-tolerated and did not result in any dose-limiting toxicities.

## CONCLUSION:

Preliminary assessments of NUZ-001's therapeutic effect on survival and function (ALSFRS-R and Vital Capacity) indicate promise when compared to historical control patients from the PRO-ACT database with similar baseline characteristics. Encouraging functional data will also be presented supporting progression of NUZ-001 into a larger Phase 2/3 clinical study.

Clinical

*C-O-CT&P003*

# CLINICAL TRIAL OF BOSUTINIB FOR AMYOTROPHIC LATERAL SCLEROSIS: IDREAM STUDY

○Haruhisa Inoue[1], Keiko Imamura[1], Naohiro Egawa[2], Takashi Ayaki[2], Makiko Nagai[3], Kazutoshi Nishiyama[3], Yasuhiro Watanabe[4], Takenobu Murakami[4], Ritsuko Hanajima[4], Hiroshi Kataoka[5], Takao Kiriyama[5], Hitoki Nanaura[5], Kazuma Sugie[5], Takehisa Hirayama[6], Osamu Kano[6], Masahiro Nakamori[7], Hirofumi Maruyama[7], Shotaro Haji[8], Koji Fujita[8], Naoki Atsuta[9], Naoto Takahashi[10], Satoshi Morita[11], Gen Sobue[9], Ryosuke Takahashi[3], Yuishin Izumi[8]

1. Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan
2. Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
3. Department of Neurology, Kitasato University School of Medicine, Sagamihara, Japan
4. Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan
5. Department of Neurology, Nara Medical University School of Medicine, Kashihara, Japan
6. Department of Neurology, Toho University Faculty of Medicine, Tokyo, Japan
7. Department of Clinical Neuroscience and Therapeutics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
8. Department of Neurology, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan
9. Department of Neurology, Aichi Medical University, Nagakute, Japan
10. Department of Hematology, Nephrology, and Rheumatology, Akita University Graduate School of Medicine, Akita, Japan
11. Department of Biomedical Statistics and Bioinformatics, Kyoto University, Kyoto, Japan

**INTRODUCTION:**

Bosutinib is a selective inhibitor of the Src/c-Abl tyrosine kinase approved for the treatment of chronic myelogenous leukemia (CML), which was identified through induced pluripotent cell (iPSC)-based drug repurposing as a molecularly targeted therapeutic candidate for ALS. This clinical trial evaluated the efficacy and safety of bosutinib in ALS patients for up to 24 weeks.

**METHODS:**

In this open-label, multicenter phase 2 clinical trial, patients with ALS received bosutinib for up to 24 weeks. Patients were randomly assigned to a 200-mg once-daily (QD) group or a 300-mg QD group of bosutinib. Primary endpoints were the change from baseline to week 24 in the total ALS Functional Rating Scale-Revised (ALSFRS-R) in each dose group, as well as safety. Secondary endpoints were the change from baseline to week 24 in ALSFRS-R in the combined dose group. Efficacy was assessed with the total ALSFRS-R compared to the placebo arm or edaravone arm in edaravone Study MCI186- 19 and with ALS registry data from JaCALS.

**RESULTS**:

A total of 33 participants were enrolled; 26 received either 200 mg or 300 mg of bosutinib daily. The mean change from baseline in the ALSFRS-R score at week 24 showed a numerically smaller reduction in both the 200 mg and 300 mg dose group compared to that in the placebo group in Study MCI186-19. The study achieved 1 of 2 secondary endpoints for efficacy assessment. In an exploratory evaluation, comparison with the data of ALS patient registry (JaCALS) supported the clinical activity of bosutinib. No new safety signals were identified in ALS participants.

**CONCLUSION:**

This is a Phase 2 open-label clinical trial. No new safety concerns were identified in the 24-week bosutinib treatment of patients with ALS. Three out of four efficacy endpoints were met in the efficacy analysis.

Clinical
*C-O-MP001*

# GLIAL CELL-TYPE SPECIFIC IMMUNE AND METABOLIC SHIFTS ACROSS THE MND-BVFTD SPECTRUM

[1]Jeryn Chang, [2]Stephanie Howe; [3]Zherui Xiong; [3]Quan Nguyen; [2]Shyuan Ngo; [1]Frederik Steyn
[1]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Australia
[2]Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Australia
[3]Queensland Institute of Medical Research, Herston, Queensland, Australia

## INTRODUCTION:

Central nervous system (CNS) glial cells provide critical support for immunity and neuronal health. Dysfunction of glial cells are well documented across the MND-bvFTD disease spectrum,[1,2] however the impact of glia in non-motor areas of the CNS, like the hypothalamus, remains unknown.

## METHODS:

Eight hypothalamic (MND=3, bvFTD=3, bvFTD-MND=2) and six lumbar spinal cord (MND=3, bvFTD-MND=3) donor tissues were sourced from the Sydney Brain Bank. Tissues were formalin-fixed paraffin embedded and processed using the Chromium Next GEM (10x Genomics) FLEX single-cell protocol. After preprocessing, hypothalamic cell types were predicted using the Human Hypomap as the reference dataset[3] and spinal cord cell types were manually annotated using known marker genes. Gene ontology enrichment analysis between diseases were conducted using PANTHER v19. Terms with FDR-adjusted p- values less than 0.05 were considered significant.

## RESULTS:

Gene ontology enrichment analysis shows contrasting enriched pathways between lumbar spinal cord and hypothalamic glia. In spinal cord astrocytes, tau (pFDR<0.01) and amyloid- beta (pFDR=0.03) protein binding were downregulated in bvFTD-MND compared to MND; while responses to unfolded protein (pFDR<0.01) and topologically-incorrect protein (pFDR<0.01) were downregulated in MND compared to bvFTD-MND. Interestingly, CNS myelin formation (pFDR<0.01) and myelin assembly (pFDR=0.04) were positively regulated in MND spinal cord oligodendrocytes.

No significant terms were identified for spinal cord microglia.

Significant terms were identified for hypothalamic microglia, but not astrocytes and oligodendrocytes. Terms for fatty acid elongation (pFDR<0.01) and lipid biosynthetic process (pFDR<0.01) were upregulated in MND microglia. Immune terms like toll-like receptor 7 signaling (pFDR<0.01) and lymphocyte aggregation (pFDR<0.01) were upregulated in bvFTD and bvFTD-MND microglia.

## CONCLUSION:

Results show contrasting roles of glia across the MND-bvFTD spectrum in hypothalamic and spinal cord tissues. Differences in enriched terms indicate disease-specific immune and metabolic shifts in the hypothalamus and supports a focus towards the proliferation of disease-associated microglia in the MND-bvFTD spectrum.

## REFERENCES:

1. Philips T, Rothstein JD. Glial cells in amyotrophic lateral sclerosis. *Exp Neurol*. Dec 2014;262 Pt B:111-20. doi:10.1016/j.expneurol.2014.05.015
2. Hartnell IJ, Blum D, Nicoll JAR, Dorothee G, Boche D. Glial cells and adaptive immunity in frontotemporal dementia with tau pathology. *Brain*. Apr 12 2021;144(3):724-745. doi:10.1093/brain/awaa457
3. Tadross JA, Steuernagel L, Dowsett GKC, et al. A comprehensive spatio-cellular map of the human hypothalamus. *Nature*. 2025/02/05 2025;doi:10.1038/s41586-024-08504-8

Clinical

*C-O-NM001*

# EVALUATING THE IMPACT OF WEIGHT LOSS AND ACCURACY OF PREDICTIVE ENERGY EQUATIONS IN AUSTRALIANS WITH AMYOTROPHIC LATERAL SCLEROSIS

[1, 2]Sewell-Green, Amber; [1]Capstick R; [2,3]Matthews-Rensch KL; [4]Henderson R; [4,5]Ngo ST; [1,4]Steyn FJ
[1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia, [2]Dietetics and Foodservices, Royal Brisbane and Women's Hospital, Australia, [3]Queensland Centre for Mental Health Research, The Park Centre for Mental Health Treatment, Research and Education, Wacol, Australia, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Australia, [5]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia.

## INTRODUCTION:

Weight loss, lower BMI and malnutrition are associated with worse prognosis in ALS[1,2]. This study evaluated the impact of negative energy balance on prognosis and survival in people living with ALS (plwALS), and the suitability of current energy equations to guide weight management support in an Australian cohort.

## METHODS:

This prospective case-control study was conducted from March 2016 to October 2024; 170 patients with probable or definite ALS had body composition (BodPod, Cosmed), metabolism (REE; QuarkRMR, Cosmed), functional capacity (ALS- Functional Rating Scale-Revised) and disease progression assessed. Baseline measures were compared to data from 173 non-neurodegenerative disease controls. Participants with ALS were then categorised based on Global Leadership Initiative on Malnutrition (GLIM)[3] weight loss criteria; stable (≤0%), minor loss (0- 5%) or major loss (>5%). Changes in body composition, progression, and survival were compared across these groups. Eighty-two plwALS provided 3-Day-Food- Diaries at baseline to calculate energy intake (Xyris FoodWorks10). Daily estimated energy requirements (EER), calculated from 13 equations used in ALS, were compared to daily estimated energy intake (EEI) and accuracy to predict weight status.

## RESULTS:

Initial weight loss (>5%) was associated with greater loss of weight and fat free mass over time ($p=0.01$), faster functional decline (ALSFRS-R scores, $p=0.01$) and increased risk of earlier death (32.9±14.0 vs 57.6±33.0 months, $p<0.001$). No EER equation performed well; however, equations incorporating body composition and ALS-validated activity levels predicted weight status more accurately (32% vs 17%). Adjusting for higher ideal body weight improved accuracy to predict major weight loss (60%; range 0-60%).

## CONCLUSION:

Weight loss, suggesting insufficient calorie intake, is associated with worse prognosis in an Australian ALS cohort. Current equations for predicting weight status have limited accuracy. Incorporating disease specific activity, injury factors and altered metabolic demands into energy equations may help prevent malnutrition and promote weight maintenance in plwALS.

## REFERENCES

1. Marin B, Desport J-C, Kajeu P, Jésus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of ALS patients. BMJ Publishing Group; 2010.p. 628.
2. Shimizu T, Nakayama Y, Matsuda C, Haraguchi M, Bokuda K, Ishikawa- Takata K, et al. Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study. J Neurol. 2019;266(6):1412-20.
3. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9.

Clinical
*C-O-RM001*

# ASSOCIATION OF DEEP LEARNING-BASED CHEST CT-DERIVED RESPIRATORY PARAMETERS WITH DISEASE PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS

[1]Seok-Jin Choi; [1]Jong-Su Kim; [1]Jung-Joon Sung; [2]Kyu Sung Choi
[1]Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea
[1]Department of Radiology, Seoul National University Hospital, Seoul, Republic of Korea

## INTRODUCTION:

Forced vital capacity (FVC) is a standard measure of respiratory function in amyotrophic lateral sclerosis (ALS) but has some limitations, particularly for patients with bulbar impairment. This study aimed to investigate the prognostic value of deep learning-based chest computed tomography (CT)-derived respiratory parameters in ALS progression and survival.

## METHODS:

This retrospective study included ALS patients diagnosed between January 2010 and July 2023 who underwent chest CT at a single tertiary hospital. Deep learning-based software measured lung and respiratory muscle volume, normalized for height as lung volume index (LVI) and respiratory muscle index (RMI). Logistic regression assessed the parameter changes across King's clinical stages. Tracheostomy-free survival was evaluated using Cox regression and time-dependent receiver operating characteristic (ROC) analyses. Measured FVC was predicted by a Gaussian process regressor (GPR) model with lung volume, respiratory muscle volume, age, and sex.

## RESULTS:

The study included 261 subjects (mean age 65.2 ± 11.9 years; 59.8% male). Both the LVI and RMI declined according to King's stage ($p < 0.001$ for both). High LVI and RMI groups showed better survival (all $p < 0.001$). After adjusting for covariates, both LVI (hazard ratio [HR] 0.998, 95% confidence interval [CI] 0.996–1.000, $p = 0.021$) and RMI (HR 0.992, 95% CI 0.988–0.996, $p < 0.001$) were identified as independent prognostic factors for survival. In subgroup with bulbar impairment, both LVI (HR 0.998, 95% CI 0.996–1.000; $p = 0.029$) and RMI (HR 0.991, 95% CI 0.987–0.996; $p < 0.001$) were independent prognostic factors, while FVC was not. Time-dependent ROC showed no significant differences between LVI, RMI, and FVC for survival prediction. The GPR model estimated FVC with approximately 9% error.

## CONCLUSION:

Chest CT-derived metrics, LVI and RMI, reliably reflect ALS progression, enable FVC prediction, and support assessment in patients with limited respiratory function testing.

## REFERENCES:

1. Choi SJ et al., The 43rd Annual Meeting of the Korean Neurological Association, 2024.

Clinical
*C-O-O001*

# AMPLIFYING THE LIVED EXPERIENCE OF MND VOICE IN AUSTRALIA

[1]Labra J; Camden P; Malpress K; [2]Yap MY; Sklavenitis L; Simpson J.
[1]MND Australia, 20 Bradley St, Woden, Australian Capital Territory, Australia, [2]FightMND, PO Box 3073 Burnley North, Victoria, Australia.

## INTRODUCTION:

The value and importance of engaging people with lived experience (PLEx) in activities related to their condition; and recognising them as equal partners in healthcare and research collaborations, are well-established.[1-6]

Historically, MND PLEx representation in Australia was inconsistent, lacking national cohesion and resulting in varying outcomes. There was a clear need for more structured pathways to connect professionals with PLEx, ensuring more meaningful and impactful engagement.

## METHODS:

A Steering Committee with equal representation from MND Australia (MNDA) and PLEx was established. The initial concept of a small 'PLEx advisory group' evolved into a larger, inclusive 'network', co-designed with key MND community stakeholders.

## RESULTS:

The National MND Lived Experience Network (LEN) was launched in June 2024 to facilitate bidirectional engagement between PLEx and professionals, on topics related to care, advocacy, and research. This innovative design sets it apart from other MND lived experience models, which typically focus only on research.

Within the first six months, 143 PLEx registered with the LEN across Australia. Members include: living with MND (35%), former carers (42%), current carers (17%) and gene carriers (6%).

Since September 2024, a variety of professional groups have submitted >30 engagement requests, with 46% of members participating in one or more activities. This has resulted in >185 instances of lived experience voices being heard, believed to be (anecdotally) a significant increase.

Program evaluation is positive, indicating:

- strengthened PLEx/ professional relationships
- increased PLEx empowerment
- valued PLEx input in professional activities
- a shift in MNDA (ie. peak body) processes to enhance lived experience representation in core business.

## CONCLUSION:

The Australian LEN showcases an innovative model that fosters bidirectional engagement between professionals and PLEx at a national level. Early outcomes suggest the model is making a positive impact, amplifying the lived experience of MND voices across Australia.

## REFERENCES:

1. Musson LS, McDermott CJ & Hobson EV (2019) Exploring patient and public involvement in motor neuron disease research. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 20:7-8, 511-520, DOI: 10.1080/21678421.2019.1643373
2. Snowball et al. Engagement of people with lived experience of dementia advisory group and cross-cutting program: reflections on the first year. *Research Involvement and Engagement* (2022) 8:28 https://doi.org/10.1186/s40900-022-00359-5
3. Wiles LK, Kay D, Luker JA, Worley A, Austin J, Ball A, et al. (2022) Consumer engagement in health care policy, research and services: A systematic review and meta-analysis of methods and effects. PLoS ONE 17(1): e0261808. https://doi.org/10.1371/journal.pone.0261808
4. Consumer and community engagement: A review of the literature (2012). Published by the Centre for Clinical Governance Research, Australian Institute of Health Innovation, Faculty of Medicine, University of NSW and the Agency for Clinical Innovation, NSW.

5. Statement on Consumer and Community involvement in Health and Medical Research, National Health and Medical Research Council (2016), Consumers Health Forum of Australia. https://www.nhmrc.gov.au/about-us/publications/statement-consumer-and-community-involvement-health-and-medical-research Cited 13.2.2025
6. International Alliance of ALS/ MND – Fundamental Rights for People Living with ALS/ MND (January 2024). https://www.als-mnd.org/wp-content/uploads/2024/04/Fundamental-rights-for-people-living-with-ALS-MND-FINAL.pdf Cited: 13.2.2025

Clinical

*C-P-AT001*

# GLOBAL ACCESS TO VOICE PRESERVATION IN ALS/MND POPULATIONS: A PILOT PROJECT

[1]Chudge Jarnail, [1]Mabe Jessica, [1]Simon Julia, [1]de Majo Martina, [1]Cummings Cathy

[1] International Alliance of ALS/MND Association, Francis Crick House, 6 Summerhouse Road, Moulton Park, Northampton NN3 6BJ. UK.

## INTRODUCTION:

Voice is integral to a person's self-identity and communication is fundamental for social relationships. Dysarthria is among the most common symptoms of Amyotrophic Lateral Sclerosis (ALS)/ Motor Neuron Disease (ALS/MND) for people living with the disease (PALS). It is characterized by difficulty in articulation and intelligibility of speech. Voice Preservation (VP) technologies involve recording samples of a person's speech to preserve their natural voice from which a synthetic voice can be created with the aim of enhancing quality of life. Voice banking, however, has high costs and is available in relatively few languages resulting in limited access. The International Alliance of ALS/MND Associations led a pilot project in Colombia, working with PALS and their caregivers to understand how to deliver a communication solution that is accessible, affordable, and capable of replication across the Global South.

## METHODS:

Through a collaboration between the National University Hospital (HUN), the Colombian Association of Amyotrophic Lateral Sclerosis (ACELA), and the Alliance, the project has delivered a pilot involving 12 PALS. Engaging a Speech Language Therapist, the process involved user selection, clinical assessment to establish a baseline, introduction to voice banking and subsequent creation of synthetic voices. Devices were provided to each participant to enable assessment of their synthetic voices through augmentative alternative communication.

## RESULTS:

The project developed a range of artefacts to be shared with the global community ranging from introductory materials through to step-by-step guides on using communication devices. The initial feedback from the participants is overwhelmingly positive. A key finding has been the importance of providing awareness and training in the use of the technology and ensuring an equitable value exchange between the technology provider and the community to establish a sustainable framework.

## CONCLUSION:

We aim to apply the learnings and insights from this pilot to other low- and middle-income countries.

Clinical

*C-P-AT002*

# ASSISTIVE TECHNOLOGY FOR PEOPLE WITH MOTOR NEURON DISEASE IN NEW ZEALAND, A QUESTIONNAIRE STUDY OF USE, CHALLENGES AND PERSPECTIVES

[1,2]Gauld, N; [2]Hikaka, J; [3]Buchanan, S; [4]Faletau, J; [5]Cleland, J. 6Buetow, S.

[1]Motor Neurone Disease New Zealand, 14 Erson St, Royal Oak, Auckland, New Zealand, [2]DSchool of Pharmacy, The University of Auckland, Park Rd, Grafton, Auckland, New Zealand; [3]University of Otago, Leith St, Dunedin. New Zealand; [4]Pacific Public Health Directorate, National Public Health Service, Te Whatu Ora, Claude Rd, Greenlane, Auckland, New Zealand; [5]Te Whatu Ora Bay of Plenty, Cameron Rd, Tauranga, New Zealand; [6]Department of General Practice and Primary Health Care, University of Auckland, Park Rd, Grafton, Auckland, New Zealand.

## INTRODUCTION:

Assistive technology is used in motor neuron disease (MND) to aid breathing, communication and daily living, aiding quality of life. There has been little research to date about access to, use of and perspectives about assistive technology for people with MND (pwMND) in New Zealand.

Aim: To ascertain usage of assistive technology including non-invasive ventilation, communication aids and mobility aids by pwMND in New Zealand and how this varies by location. To describe challenges to access and reasons for non-use of these items by people who may benefit from it.

## METHODS:

PwMND were invited to complete a three-part survey (informed by literature and co-designed with those with lived experience). Surveys could be completed online (Qualtrics), on paper or by telephone interview. PwMND were recruited through Motor Neurone Disease New Zealand, the MND Patient Registry, social media and word of mouth. Descriptive statistics were used.

## RESULTS:

The survey is still in the field stage with the deadline of 16 April and 47 online responses (12% of the estimated MND population in NZ) received within the first 5 days.

Results will be available by 1 May. These will include number of participants and their demographics; proportion completing the survey online, on paper or by telephone.

For non-invasive ventilation, power wheelchairs and other mobility devices, and communication devices the following will be reported: proportion using and challenges with the equipment including challenges with access. Access will be analysed by location (urban versus rural), age and progression rate.

## CONCLUSION:

The final results and conclusion will be reported in early May.

Clinical

*C-P-B001*

# SERUM GFAP AS A SURVIVAL PREDICTOR IN ADVANCED ALS: A MULTICENTER ANALYSIS

[1]Hee-Jae Jung, [2]Woo-Seung Jeong, [3]Minsung Kang, [1]Eun-Jae Lee, [1]Young-Min Lim, [3]Jin-Sung Park, [1]Hyunjin Kim
[1] Department of Neurology, Asan medical center, University of Ulsan, College of Medicine, Seoul, Republic of Korea,
[2] University of Ulsan, College of Medicine, Seoul, Republic of Korea,
[3]Department of Neurology, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease, underscoring the need for reliable biomarkers to predict its progression and prognosis.[1] While serum neurofilament light chain (NfL) is widely recognized as an ALS biomarker,[2] its limited specificity necessitates the identification of additional biomarkers. This study investigates the potential of serum glial fibrillary acidic protein (GFAP) and brain-derived neurotrophic factor (BDNF) as complementary biomarkers for ALS.

## METHODS:

Serum levels of NfL, GFAP, and BDNF were quantified using ultrasensitive single-molecule array (SIMOA) assays in two independent ALS cohorts from Asan Medical Center (AMC, n=65) and Kyungpook National University Chilgok Hospital (KNUH, n=53), along with 15 healthy controls. The diagnostic performance of each biomarker was assessed using receiver operating characteristic (ROC) curve analysis. Correlations between biomarker levels, ALS Functional Rating Scale-Revised (ALSFRS-R) scores, and disease progression rates were examined. Survival analysis was conducted using Cox regression and Kaplan-Meier methods.

## RESULTS:

Serum levels of NfL, GFAP, and BDNF distinguished ALS patients from controls, with area under the ROC curve (AUC) values of 0.969, 0.613, and 0.875, respectively. NfL and GFAP levels increased significantly with advancing King's stage (NfL: $\tau$=0.226, p=0.011; GFAP: $\tau$=0.160, p=0.023). Baseline serum NfL correlated with disease progression rate (r=0.309, p=0.001), whereas GFAP and BDNF did not. Notably, GFAP emerged as an independent predictor of survival, with patients in the highest GFAP quartile exhibiting a mortality hazard ratio of 7.473 (95% CI: 2.238–24.957, p=0.001) in advanced-stage ALS (King's stage 3–4).

## CONCLUSION:

Serum GFAP may serve as a prognostic biomarker for survival in advanced ALS, while serum NfL reflects disease progression rate. These findings highlight the potential utility of combining multiple biomarkers to enhance prognostication and clinical management of ALS.

## REFERENCES:

McMackin R, Bede P, Ingre C, Malaspina A, Hardiman O. Biomarkers in amyotrophic lateral sclerosis: current status and future prospects. Nature Reviews Neurology 2023;19:754-768.

Lu C-H, Macdonald-Wallis C, Gray E, et al. Neurofilament light chain. Neurology 2015;84:2247-2257.

Clinical

*C-P-B002*

# TELOMERE LENGTH AND BIOLOGICAL AGE IN ALS: EVIDENCE FOR ACCELERATED AGING?

Sane Hemangi*[2,4]; Gokulchandran Nandini[1]; Kulkarni Pooja[2]; Sharma Priyanka[3]; George Vinnit[2]; Sharma Alok[1,4]

1. Department of Medical Services, NeuroGen Brain and Spine Institute, Plot No.: 19, Sector-40, Seawoods, Navi Mumbai – 400706, India
2. Department of Research and Development, NeuroGen Brain and Spine Institute, Plot No.: 19, Sector-40, Seawoods, Navi Mumbai – 400706, India
3. Department of Neurorehabilitation, NeuroGen Brain and Spine Institute, Plot No.: 19, Sector-40, Seawoods, Navi Mumbai – 400706, India
4. Asha Ek Hope Foundation for MND/ALS, India

## INTRODUCTION:

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder with a short lifespan of average of 3 to 5 years. Telomeres, protective caps of chromosomes, shorten with age and serve as aging biomarkers [1]. Genetic studies suggest that increased telomere length was associated with lower risk of ALS [2]. This study aims to assess biological age through telomere length, in relation to the chronological age, thereby evaluating aging in ALS patients.

## METHODS:

This cross-sectional observational study includes a total of 20 participants (7 males, 13 females) aged between 32 to 70 years with clinical definite or probable ALS diagnosed as per El Escorial criteria. Patients with muscular atrophy due to other causes, primary lateral sclerosis, progressive bulbar palsy or chronic inflammatory neuropathies were excluded. A genetic test measured the telomere length which provided the biological age for each patient. The difference between the chronological and biological age was calculated for each patient. Also, mean chronological and biological age was estimated for the whole group.

## RESULTS:

The sample included 20 ALS patients of which 7 were males and 13 were females. All patients showed higher biological age than their chronological age. The chronological age range was 32 to 70 years, and the biological age range was 40 to 82 years. The mean chronological age was 51.70 ± 10 years, and the mean biological age was 62.85 ± 10.4 years. The mean telomere length was 6.8 ± 1.3 kbp. Difference between the mean chronological and biological age was 11.15 years.

## CONCLUSION:

The study suggests that ALS patients have much higher biological age than their chronological age due to short telomere length. Telomere shortening may play a key role, highlighting the need for further research on aging in ALS patients.

## REFERENCES:

1. Rossiello, F., Jurk, D., Passos, J.F. et al. Telomere dysfunction in ageing and age-related diseases. Nat Cell Biol 24, 135–147 (2022). https://doi.org/10.1038/s41556-022-00842-x
2. Zhang, R., Ban, H., Li, J., et al. (2021). Leukocyte telomere length and amyotroperal sclerosis: A Mendelian randomization study. Orphanet hic latJournal of Rare Diseases, 16, 142. https://doi.org/10.1186/s13023-021- 02135-2

Clinical

*C-P-B003*

# CXCR4 EXPRESSION IN CD4+T CELLS: POTENTIAL BIOMARKERS FOR ALS PROGRESSION

[1]Ke, Shupei; [1]Xu, Chunzuan; [1]Lu, Yingqian; [1]Liu, Changyun; [1]Zou, Zhangyu; [1]Chen, Sheng

[1] Department of Neurology, Union Hospital, Fujian Medical University, No.29 Xinquan Road, Gulou District, Fuzhou, Fujian Province, China

## INTRODUCTION:

ALS (Amyotrophic Lateral Sclerosis) is a neurodegenerative disease involving spinal cord cells, brainstem nuclei, and pyramidal tracts, causing upper and lower motor neuron damage. Patients typically die within 3-5 years post-diagnosis [1]. Neuroinflammation is a key hallmark and therapeutic target in ALS [2]. ALS patients have persistent peripheral inflammation that may worsen neurodegeneration [3]. CD4+ T cells are critical. We hypothesize that CXCR4 expression in CD4+ T cells links to their phenotypic shift and ALS progression. We measured CXCR4 changes in peripheral CD4+ T cell subsets using flow cytometry.

## METHODS:

This study recruited 130 participants, including 90 ALS patients and 40 healthy controls, from Union Hospital of Fujian Medical University between December 2023 and February 2025. ALS diagnosis was based on the revised El Escorial criteria. The study was approved by the Ethics Committee, and written informed consent was obtained. Peripheral blood samples were analyzed using flow cytometry with a BD FACSCelestaTM cytometer and FlowJo VX software. Statistical analyses were performed using Mann-Whitney tests, and software including GraphPad Prism version 8 and R version 4.2.2.

## RESULTS:

In our study, we observed that CXCR4 is highly expressed in peripheral CD4+ T cells from ALS patients. To further investigate this phenomenon, we measured the expression of CXCR4 in peripheral CD4+ T cells from both ALS patients and healthy controls (HCs). The results showed that, compared with the healthy control group, the proportion of CD4+ CXCR4+ T cells was significantly increased in the ALS cohort ($P < 0.001$). More importantly, we found a significant increase in the proportion of CXCR4+ population within the central memory T cell (Tcm) subset in the ALS group ($P<0.001$).

We evaluated the diagnostic potential of CD4+ CXCR4+ T cells and CXCR4+ Tcm cells using ROC analysis. The results showed that CD4+ CXCR4+ T cells have moderate diagnostic capability(AUC=0.7607,CI=0.67-0.85,$P<0.001$), while CXCR4+ Tcm cells exhibit higher accuracy ( AUC=0.9004, CI:0.82-0.97, $P<0.001$).

Both markers may serve as potential biomarkers for ALS, with CXCR4+ Tcm cells showing particularly high diagnostic value.

## CONCLUSION:

While the pathogenesis of ALS is multifactorial, our study has revealed a significant increase in the proportion of CD4+ CXCR4+ T cells and CXCR4+ Tcm cells in ALS patients, which may be closely related to disease progression. Notably, the high diagnostic accuracy of CXCR4+ Tcm cells (AUC=0.9004) suggests their potential as a biomarker for ALS. However, this finding is only preliminary, and further validations in larger cohorts will be needed to explore their role in the pathogenesis of ALS. Nonetheless, targeting CXCR4 or modulating the activity of these T cells may offer new therapeutic insights for slowing ALS progression.

## REFERENCES:

[1] S. A. Goutman et al., “Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis,” Lancet Neurol., vol. 21, no. 5, pp. 480–493, May 2022.

[2] K. G. Hooten et al., “Protective and Toxic Neuroinflammation in Amyotrophic Lateral Sclerosis,” Neurotherapeutics, vol. 12, no. 2, pp. 364–375, Apr. 2015.

[3] C. Cui et al., “Correlation between leukocyte phenotypes and prognosis of amyotrophic lateral sclerosis,” eLife, vol. 11, p. e74065, Mar. 2022.

Clinical
*C-P-B004*

# SPHINGOSINE-1-PHOSPHATE AS A PREDICTOR OF NEUROLOGICAL DETERIORATION IN SPINAL BULBAR MUSCULAR ATROPHY

Park Jinsung
Kyungpook National University Chilgok Hospital

**BACKGROUND AND OBJECTIVES**:

Spinal and bulbar muscular atrophy (SBMA) is a genetic motor neuron disease that show slowly progressive muscular weakness and atrophy, caused by increased CAG repeats in the exon 1 of the androgen receptor gene. There are clinical markers that are used to predict neurological deterioration but the lack of quantitative biomarkers limits the sensitive evaluation. This study aimed to identify potential biomarkers associated with SBMA progression.

**METHODS**:

Plasma samples from 21 SBMA patients were collected at baseline and 3-4 years post- diagnosis, were employed to untargeted and targeted metabolomics using liquid chromatography-mass spectrometry. The levels of identified metabolites were further analyzed in relation to the rate of disease progression, which was defined by changes in ALSFRS-R scores during the follow-up period.

**RESULTS:**

Plasma S1P concentrations emerged as a promising marker for diagnosing and monitoring SBMA progression, as identified through targeted and untargeted metabolomics. Plasma S1P levels showed a significant decrease over the follow-up period in the fast progression group, defined by ALSFRS-R changes greater than -3 points. Additionally, follow-up S1P concentrations showed positive correlations with ALSFRS-R that showed negative correlation with serum creatine kinase levels.

**CONCLUSION:**

Plasma S1P showed a promising diagnostic marker for SBMA. Despite the inherent variability in S1P levels requiring careful interpretation, it might be a novel marker reflecting neurological progression. More studies are needed to understand the underlying patho-mechanism of S1P and its regulation in SBMA, to strengthen the validity of these findings.

Clinical

*C-P-B005*

# USE OF ELECTRONIC NOSE TECHNOLOGY IN DIAGNOSIS AND PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS / MOTOR NEURONE DISEASE

Principal Investigators:
Robert Nona. PhD Candidate UQCCR – Robert.nona@uqconnect.edu.au
Prof Pamela McCombe UQCCR, Neurologist The Royal Brisbane & Women's Hospital, Queensland

Co-Investigators
A/Prof Robert Henderson Neurologist, RBWH
Dr David Fielding – Head of Respiratory Medicine, RBWH Prof Xue Li – School of IT & Engineering, UQ
Dr Tony Chen – Faculty of Sciences, Engineering and IT, University of Adelaide

## INTRODUCTION:

Metabolic biomarkers have been widely studied in amyotrophic lateral sclerosis (ALS) (1). Exhaled volatile organic compounds (VOCs), can be detected using the electronic nose (e-Nose) device, and associated with many diseases (1, 2) . There has been one small case-control e-Nose study showing a difference in ALS (3). At this stage, the usefulness and importance of this finding is unknown. We will therefore perform a larger case-control study VOCs in ALS patients in RBWH.

## METHODS:

ALS subjects from the RBWH MND Clinic. Health controls. Exclusions: malignancy, exacerbation of COPD, poorly controlled diabetes, and hyper/hypothyroidism. The Cyranose e-Nose device standardised operating procedures were used, including collection and analysis of 1 litre exhaled air. The PC-ENose software, performs principal component analysis (PCA): ALS vs controls. ALS cohort analysis: sex, region of onset, disease type and family history ALS. Qualitative analysis of VOC smell printing was used show metabolic categories of VOCs related to sensors: ALS vs controls.

## PRELIMINARY RESULTS:

To date (21st February 2025), 34 valid e-Nose samples have been collected – 18 ALS (8 male) and 16 control (9 male) subjects. PCA shows a significant difference in Euclidean distance between ALS and controls ($p = 0.0356$). Further PCA in the ALS cohort: there was no significant difference by sex, region of onset, disease type, and family history. Smell print shows higher sensor 5 resistance in ALS, which would be consistent with higher lipid metabolism vs controls (4)

## DISCUSSION:

There is good preliminary data to suggest e-Nose is a valid, non-invasive, metabolic biomarker in ALS. Further subject data will continue to be gathered support, with an aim for serial measurements, to help support the e-Nose as a diagnostic and prognostic biomarker in ALS.

## REFERENCES:

1. Steyn FJ *et al.* Hypermetabolism in ALS is associated with a greater functional decline and shorter survival. Neurodegeneration. 2018; 89: 1016-1023
2. Farraia MV *et al.* The electronic nose technology in clinical diagnosis: A systematic review. Porto Biomed J. 2019;4(4):e42-e
3. Fielding D *et al*. Volatile organic compound breath testing detects in-situ squamous cell carcinoma of bronchial and laryngeal regions and shows distinct profiles of each tumour. J Breath Res. 2020;14(4):046013.
4. Dragonieri S, Quaranta VN, Carratu P, Ranieri T, Marra L, D'Alba G, et al. An electronic nose may sniff out amyotrophic lateral sclerosis. Respir Physiol Neurobiol. 2016;232:22-5.
5. Doty AC *et al.* Assessment of the Portable C-320 Electronic Nose for Discrimination of Nine Insectivorous Bat Specials – Implications for Monitoring White-nose Syndrome. Biosensors. 2020; 10 (12): 1-26.

Clinical

*C-P-B006*

# SERUM TRANSTHYRETIN IN ALS: INSIGHTS FROM A CROSS-SECTIONAL AND LONGITUDINAL STUDY

[1,2,3]Zhang, Yixuan*; [1,2,3]Huang, Xin*; [1,2,3]Zhu, Dengge; [1,2,3]Chen, Lu; [1,2,3]He, Ji#; [1,2,3]Fan, Dongsheng#

[1]Department of Neurology, Peking University Third Hospital, Beijing, China,

[2]Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China,

[3]Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China

## INTRODUCTION:

Transthyretin (TTR) is known to promote neurite outgrowth[1] and axonal transport[2], while also exerting neuroprotective effects in Alzheimer's disease (AD) by inhibiting amyloid-beta (Aβ) aggregation[3] and facilitating its clearance[4]. Emerging evidence suggests that TTR may also play a protective role in TDP-43 proteinopathies[5]. This study aims to investigate serum TTR levels in amyotrophic lateral sclerosis (ALS) patients and explore its associations with clinical characteristics and prognosis.

## METHODS:

We enrolled 611 ALS patients diagnosed as possible, probable, or definite ALS at Peking University Third Hospital from 2018 to 2024, along with 346 controls, including individuals with peripheral neuropathy (n=100), central nervous system (CNS) infections (n=29), CNS autoimmune diseases (n=86), cerebrovascular diseases (n=62), Parkinson's syndrome (n=50), and AD (n=19). Serum TTR levels were quantified using immunoturbidimetry, and serum neurofilament light chain (NFL) levels were measured via digital single-molecule immunoassay. Clinical data, including sex, age, disease duration, ALS Functional Rating Scale-Revised (ALSFRS-R) scores, King's Clinical Staging System (KCSS) stages, cerebrospinal fluid (CSF) protein levels, and the CSF/serum albumin ratio (Qalb), were collected for analysis.

## RESULTS:

(1) Serum TTR levels were significantly elevated in ALS patients compared to controls, with males exhibiting higher levels than females ($p<0.0001$). (2) Patients with flail arm syndrome, flail leg syndrome, or monomelic atrophy—characterized by slower disease progression—had significantly lower TTR levels than those with classical ALS ($p=0.011$). Correlation analyses showed significant associations between TTR levels and age ($p=0.015$) as well as BMI ($p=0.000$). After adjusting for BMI, partial correlation analysis revealed positive correlations between TTR and NFL ($p=0.004$), ALSFRS-R scores ($p=0.038$), Qalb ($p=0.023$), and CSF protein levels ($p=0.027$). In patients within two years of disease onset, TTR was negatively correlated with disease progression rate (ΔFS) ($p=0.043$). Notably, in patients younger than 45 years, TTR exhibited the strongest positive correlation with NFL ($R^2=0.149$, $p=0.0028$). TTR levels were also significantly associated with absolute neutrophil count ($p=0.019$), absolute lymphocyte count ($p=0.0079$), and erythrocyte sedimentation rate (ESR) ($p<0.0001$). (3) Kaplan–Meier survival analysis demonstrated that, within two years of disease onset, younger patients (<45 years) with higher TTR levels exhibited significantly shorter survival times ($p=0.017$).

## CONCLUSION:

Serum TTR levels in ALS exhibit dynamic changes associated with disease progression. While TTR is positively correlated with markers of neurodegeneration, its early-stage relationship with disease progression suggests a potential compensatory or stress-related response. However, this response appears insufficient to alter disease trajectory. Further research is needed to clarify the role of TTR in ALS pathophysiology.

**REFERENCES:**

1. Fleming, C.E., M.J. Saraiva, and M.M. Sousa, Transthyretin enhances nerve regeneration. J Neurochem, 2007. 103(2): p. 831-9.
2. Eira, J., et al., Transthyretin Promotes Axon Growth via Regulation of Microtubule Dynamics and Tubulin Acetylation. Front Cell Dev Biol, 2021. 9: p. 747699.
3. Du, J., et al., Identification of beta-amyloid-binding sites on transthyretin. Protein Eng Des Sel, 2012. 25(7): p. 337-45.
4. Yang, D.T., et al., Transthyretin as both a sensor and a scavenger of β-amyloid oligomers. Biochemistry, 2013. 52(17): p. 2849-61.
5. Chu, Y.P., et al., Transthyretin attenuates TDP-43 proteinopathy by autophagy activation via ATF4 in FTLD-TDP. Brain, 2023. 146(5): p. 2089-2106.

Clinical

*C-P-CM001*

# THE EXPERIENCE OF SUFFERING IN ALS: A CASE REPORT

[1]Ang CM, [5]Rasyid M, [5]Krishnan P, [1]Zainuddin S, [1]Lam CL, [4]Pek EW, [3]Soo CI, [2]Shahrizaila N, [1]Capelle D
[1] Palliative Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[2] Neurology Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[3] Respiratory Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[4] Rehabilitation Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[5] Hospis Malaysia, Cheras, Kuala Lumpur, Malaysia

## INTRODUCTION:

Suffering is a complex, multidimensional experience for people living with Amyotrophic Lateral Sclerosis (PLWALS), encompassing psychological, physiological, social, and spiritual distress when they have exhausted their coping resources for perceived loss. While multidisciplinary clinics have been shown to improve quality of life, less attention has been given to the specific details of their suffering. Here, we report the experience of a patient with ALS who exhibited a range of psychological and emotional distress in her journey.

## CASE DISCUSSION:

A 42-year-old mother, diagnosed ALS at the peak of her career. She was initially in denial, challenging the diagnosis in the hopes of a misdiagnosis. Over six months, she experienced a rapid deterioration with ALS Functional Rating Scale (ALSFRS) dropping from 42 to 15. She lost strength, ability to swallow safely and speech gradually incomprehensible. Denial was replaced by fear and anxiety of what was to come, necessitating admission to the palliative unit. Her hope was rekindled upon learning about artificial feeding and ventilation, and whilst non-invasive ventilation helped alleviate symptoms, a feeding tube was not tolerated.

There was despair in experiencing constant breathlessness as well as losing the ability to enjoy the simple pleasures such as eating, further enhancing her suffering. Psychological and spiritual support, including cognitive behavioural therapy, antidepressants, and spiritual interventions, were provided. After three weeks, she was able to overcome her anxiety and gained confidence to return home with support from her family and community hospice.

## CONCLUSION:

Whilst the loss of functional abilities in PLWALS is clearly apparent, their suffering is often overlooked resulting in considerable distress. Addressing the psychological and existential aspects of suffering through personalised, compassionate care is crucial. Interventions aimed at transforming the psychological processes of suffering from an early stage of diagnosis may provide a more sustained effect in reducing the suffering of PLWALS.

## REFERENCES:

Tan SB, et al. BMJ Supportive & Palliative Care 2016;0:1–6. doi:10.1136/bmjspcare-2015-001064

Cassell, Eric J. *The Nature of Suffering and the Goals of Medicine.* Originally published in *The New England Journal of Medicine*, Vol. 306, No. 11, March 18, 1982, pp. 639-645.

Clinical

*C-P-CM002*

# SURVEY OF CONSTIPATION IN AUSTRALIANS WITH MND USING THE LIVED EXPERIENCE NETWORK

[1]Werth, Barry; [1]Fisher, Murray.

[1]Susan Wakil School of Nursing and Midwifery, Faculty of Medicine and Health, University of Sydney, Sydney, Australia.

## INTRODUCTION:

Constipation is one of the most common symptoms encountered by people with MND.[1,2,3] However, there has been little research conducted on constipation in MND.[2] Constipation not only causes pain but is also associated with anxiety and depression in people with MND, affecting quality of life (QoL).[2] Improved management of constipation will increase QoL. The aim of this study is to assess the prevalence and treatment of constipation in Australians with MND as well as its impact on QoL.

## METHODS:

An on-line survey of Lived Experience Network (LEN) members will be conducted using a short questionnaire consisting of 12 questions regarding Rome criteria for functional constipation, oral and other treatments used for constipation, and impact of constipation on QoL. The LEN members to be surveyed comprise active and past carers as well as people living with MND.

## RESULTS:

Based on the few international studies previously conducted, it is expected that approximately 50% of Australians with MND will report being troubled with constipation. This poster will report the results of this preliminary national survey.

## CONCLUSION:

This survey of LEN members will provide preliminary data regarding constipation in MND in a quick, efficient manner, prior to conducting an in-depth longitudinal study of constipation in people with MND using data collected by the 15 Australian clinics in the MiNDAUS registry.

## REFERENCES:

1. Lau FS, Brennan FP, Gardiner MD. Multidisciplinary management of motor neurone disease. Aust J Gen Pract 2018;47(9):593–6.
2. Niu T, Zhou X, Li X et al. Development and validation of a dynamic risk prediction system for constipation in patients with amyotrophic lateral sclerosis. Front Neurol 2022;13:1060715.
3. Dharmadasa T, Henderson RD, Talman PS, et al. Motor neurone disease: progress and challenges. Med J Aust 2017;206(8):357–62.

Clinical

*C-P-CM003*

# BEYOND TRADITIONAL BULBAR FUNCTION MEASURES: AUTOMATED SPEECH ANALYSIS AND PATIENT EXPERIENCE OF COMMUNICATION CHANGE AS INTEGRATED CLINICAL MARKERS IN ALS

Brooke-Mai Whelan [1], Elaine Kearney [1,7], Adam P. Vogel [2], Robert Henderson [3,4], Shana Taubert [4], Patrick Aiken[1], Anthony Angwin[1], Rebecca Packer[1], Adriana Penman[1], David Copland [1,5], Salma Charania[6]

1. School of Health and Rehabilitation Sciences, The University of Queensland
2. Speech Pathology, The University of Melbourne and Redenlab, Melbourne
3. University of Queensland Centre for Clinical Research, Faculty of Medicine The University of Queensland
4. Metro North Hospital and Health Service
5. Queensland Aphasia Research Centre
6. School of Health, Medical and Applied Sciences, Central Queensland University
7. Metro South Hospital and Health Service

**INTRODUCTION:**
Current clinical assessment methods in ALS, such as the ALSFRS-R, lack sensitivity to subtle speech changes and fail to capture the complex relationship between dysarthria progression and its psychosocial impact. While this limitation is recognized, few studies have explored how acoustic analysis combined with patient- reported outcomes could provide a more comprehensive understanding of dysarthria progression in ALS over time.

**METHODS:**
This longitudinal study investigated a cohort of ALS participants using a novel integrated assessment framework. Participants underwent bi-monthly assessments over an 8-month period via a telehealth platform with audio capture functionality. The protocol analysed three complementary data streams: automated acoustic parameters from connected speech, patient-reported measures of communication experience, and standard clinical assessment indices (i.e., speech subscore of ALSFRS-R).This multidimensional approach aimed to address the limitations of conventional scalar measures and capture the nuanced relationship between objective speech deterioration and patient reported experience of communicative functioning and dysarthria burden.

**RESULTS:**
Preliminary analysis suggests that integrating automated acoustic biomarkers with patient-reported outcomes reveals patterns of change not captured by traditional assessment scales. Specific speech parameters and dysarthria-related functional and psychosocial metrics demonstrated sensitivity to change before conventional clinical measures detected decline.

**CONCLUSION:**
This study challenges the conventional single-domain approach to bulbar assessment in ALS by demonstrating the value of combining automated speech analysis with patient-reported experiences of dysarthria. The high-frequency longitudinal monitoring approach enabled detection of subtle speech changes that preceded observable clinical decline. It also provides valuable data on disease and clinical outcome assessment stability. This novel approach has implications for both clinical trials and routine monitoring, offering a more comprehensive, sensitive, and telehealth-compatible method for tracking speech changes in ALS.

Clinical
*C-P-CM004*

# WITHDRAWAL OF NON-INVASIVE ASSISTED VENTILATION IN PATIENTS WITH MOTOR NEURONE DISEASE

[1] Dr Corey Lau, [2]Tanya Munn

[1] Royal Prince Alfred Hospital, Sydney Local Health District
[2]Concord Centre for Palliative Care, SLHD

## INTRODUCTION:

The use of non-invasive assisted ventilation (NIV) improves quality of life and survival in selected patients with respiratory failure from Motor Neurone Disease (MND). A small percentage of these patients who are ventilator-dependent later request to have NIV withdrawn, because the burdens outweigh the benefits for them. However, there are currently no uniform guidelines for safe and effective withdrawal of assisted ventilation.

## REPORT:

We report three Case Studies of NIV withdrawal in patients with MND in our Palliative Care Unit. All three patients were commenced on a Syringe Driver with morphine, midazolam and levomepromazine in preparation of the NIV withdrawal. Stat doses of morphine and midazolam were given prior to the commencement of weaning of the NIV, which was managed by the Respiratory Clinical Nurse Consultant. Extra prn doses were also available should the patient exhibit any signs of distress during the process. All three patients died peacefully within an hour of commencement of NIV withdrawal (19-58minutes).

## CONCLUSION:

NIV withdrawal in patients with MND can be safely and effectively carried out. Communication and support of the patient's family are also important parts of the process. However, current practices vary, and uniform Practice Guidelines would be invaluable.

Clinical

*C-P-CM005*

# AN EVALUATION OF THE ALSSQOL-SF IN THE MALAYSIAN CONTEXT THROUGH COGNITIVE INTERVIEWING

Wafa Sabirin[1], Fazlina Ahmad[2], Saiful Adni Abd Latif[2], Sheriza Izwa Zainuddin[1], Chee-Loong Lam[1], Chun-Ian Soo[1], Kee-Huat Chuah[1], Sakinah Sabirin[1], Nortina Shahrizaila[1], David Paul Capelle[1]

[1]Department of Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
[2]Department of Biomedical Science, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
Correspondence: David Paul Capelle, E-Mail: david.capelle@um.edu.my

## BACKGROUND

The optimization of quality of life (QOL) is an important goal of care for people living with ALS (PALS) in the absence of curative treatment. The ALSSQOL-SF has been developed and validated to measure QOL across the biopsychosocial and spiritual domains in the specific context of ALS. It has been translated and validated in several languages, however its applicability in the context of the multicultural, multiethnic Malaysian population has not yet been investigated.

## METHODS

The QOL of 21 patients was measured using either the original English version or a translation into the Malay language. PALS were instructed to share their thoughts while completing the instrument in the manner of a "think aloud" process as commonly used in cognitive interviewing (CI) methodology. We evaluated how participants interpreted the questions and chose their answers.
Interviews were transcribed and thematically analysed.

## RESULTS

The quantitative survey responses were comparable to those from previous validation studies, scoring lowest (worst) in the domain of "physical symptoms" and highest (best) in the domain of "interaction with people and environment". Language and cultural factors affected the interpretation and responses to questionnaire items. Items related to spirituality posed some difficulties in interpretation and the topic of intimacy was perceived of variable relevance.

## CONCLUSION

This study highlights the relevance of cultural and language-related factors in measuring QOL based on a questionnaire initially developed in a different (European/North American) context. Cultural factors affect experiences of suffering in ALS and this needs to be considered when considering the suitability of a QOL instrument across different cultures. Additionally, domains of QOL are often differentially weighted, in particular the importance of intimacy.
The process of completing a questionnaire can be burdensome and uncomfortable when it involves confronting the emotional distress of progressive disease. On the other hand, it can be perceived as beneficial if it serves to direct care in order to reflect individual preferences.

Clinical

*C-P-CM006*

# EFFECT OF A BRIEF MINDFULNESS INTERVENTION ON THE EMOTION AND QUALITY OF LIFE OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

[1]Xin Huang[†],[1]Guanghao Hou[†], [2]Hui Li, [1]Tielun Yin, [1]Hong Liu, [1]Yanjing Yang, [1]Linna Bai,[1]Wenxia Ban, [1]Jiaying Zhang, [1]Ruixue Zhang, [1,3,4#]Dongsheng Fan, [1,3,4#]Shan Ye

1. Department of Neurology, Peking University Third Hospital, Beijing, China.
2. Department of Psychiatry, Peking University Sixth Hospital, Beijing, China.
3. Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China.
4. Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China.

## INTRODUCTION:

Amyotrophic lateral sclerosis(ALS) is a rapidly progressive neurodegenerative disorder without effective treatments[1]. 25%-41% of ALS patients experienced neuropsychiatric disorders[2-4]. In addition, it has been observed in clinical practice that patients with ALS often experience a storm phase of mental breakdown at the time of disease diagnosis. To help patients get through this period, we designed a brief mindfulness intervention program for individuals who have recently been diagnosed with ALS. This study aims to investigate the impact of the brief mindfulness intervention on emotional well-being and QOL.

## METHODS:

This prospective intervention study enrolled patients who had newly been diagnosed with ALS at Peking University Third Hospital. Participants were instructed to engage in a daily 20-minute audio-guided mindfulness training program for two weeks, including breathing awareness, body scan, and meditation. The effectiveness of the interventions was evaluated using several scales including PHQ-9, HAMD-17, HAMA, CPSS, ALSAQ40, ESS, PSQI, and ZBI. The scores before and after the intervention were compared by SPSS.

## RESULTS:

Ninety-one patients (aged 54.15(10.10) years, 52 males [56.5%]) were finally enrolled in the analysis. ALSAQ40 scores(t=2.84, P=0.006*) and ESS(Z=2.09, P=0.036*) significantly decreased following a 2-week mindfulness intervention compared to baseline. Depression levels, as measured by PHQ-9 and HAMD-17, were significantly reduced in ALS patients diagnosed with depression. Additionally, stress levels, QOL, and caregiver burden were significantly improved in other ALS patients. Improvements in QOL were associated with the duration of diagnostic delay.

## CONCLUSION:

Our study indicated that a brief mindfulness intervention lasting two weeks could significantly reduce negative emotions, such as depression and stress, while also improving the QOL for ALS patients. Brief mindfulness interventions are promising as a component of the integrated treatment regimen for ALS.

## REFERENCES:

1. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, Sobue G. Amyotrophic lateral sclerosis. Lancet. 2022 Oct 15;400(10360):1363-1380. doi: 10.1016/S0140-6736(22)01272-7. Epub 2022 Sep 15. PMID: 36116464; PMCID: PMC10089700.
2. Heidari ME, Nadali J, Parouhan A, Azarafraz M, Tabatabai SM, Irvani SSN, Eskandari F, Gharebaghi A. Prevalence of depression among amyotrophic lateral sclerosis (ALS) patients: A systematic review and meta-analysis. J Affect Disord. 2021 May 15;287:182-190.
3. Beswick E, Park E, Wong C, Mehta AR, Dakin R, Chandran S, Newton J, Carson A, Abrahams S, Pal S. A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis. J Neurol. 2021 Dec;268(12):4510-4521.
4. Jellinger KA. Understanding depression with amyotrophic lateral sclerosis: a short assessment of facts and perceptions. J Neural Transm (Vienna). 2024 Feb;131(2):107-115.

Clinical

*C-P-CM007*

# TDP-43 PROTEINOPATHIES AS A DISEASE SPECTRUM: LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY

[1]Ashhurst, Jasmine F, [1]Kiernan, Matthew C

[1]Neuroscience Research Australia, Margarete Ainsworth Building, 139 Barker St, Randwick, Australia.

## INTRODUCTION:

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a TDP-43 proteinopathy of the elderly, typically seen in patients older than 80 years of age. At present, a definitive diagnosis of LATE is made based on neuropathological changes at autopsy. Neuropathological changes of LATE are characterised by the anatomical distribution of TDP-43 in the amygdala +/- hippocampus +/- middle frontal gyrus. LATE is commonly associated with cognitive impairment, typically 'dementia of the Alzheimer's type'.

TDP-43 is a protein encoded by the TARDBP gene. Mutations in the gene encoding TARDBP are causative for Amyotrophic Lateral Sclerosis (ALS) in <5% of familial cases of ALS. However, TDP-43 pathology is found at autopsy in >90% of patients diagnosed with ALS.

## REPORT:

In this case series, we discuss the cases of two patients previously diagnosed with and treated for ALS, who were subsequently diagnosed with LATE following post-mortem studies. Both patients died in their mid to late 70's (76, 79), following a preceding history of relatively slowly progressive limb weakness for 7-12 years. Patient one's disease had a pattern of upper limb weakness more so than lower limb weakness, as well as dysarthria and dysphagia requiring PEG feeding. Patient two's disease was limited to unilateral limb weakness, thought initially to be due to Primary Lateral Sclerosis or Mills' variant ALS. Cognitive impairment was not a major feature in either of these patient's clinical courses.

## CONCLUSION:

Unifying phenotypic features of an ALS-presentation of LATE include limb-onset disease, slower disease progression compared to typical ALS, without prominent cognitive features. Recognition of LATE and its mimics is of increasing relevance, particularly in an aging population, with potential interventions directed against TDP-43.

Clinical

*C-P-CM008*

# PARANEOPLASTIC AMYOTROPHIC LATERAL SCLEROSIS ASSOCIATED WITH ANTI- SOX1 ANTIBODIES

[1]Ashhurst, Jasmine F, [2]Granot, Ron, [1]Kiernan, Matthew C.

[1]Neuroscience Research Australia, Margarete Ainsworth Building, 139 Barker St, Randwick, Australia.
[2]East Neurology, 403/251 Oxford St, Bondi Junction, Australia.

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that is universally fatal. Anti-Sry-like high mobility group box (SOX) 1 antibodies are strongly associated with cancer, in particular non- small cell lung cancer (NSCLC). Anti-SOX1 antibodies have been associated with a number of neurological conditions, most commonly Lambert-Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration.

## REPORT:

The present case describes an 83 year old male who presented with a 6 month history of progressive dysarthria, dysphagia, dyspnoea and weight loss. Neurological examination revealed a wasted and weak tongue, with fasciculations present. He was dysarthric and limb examination revealed globally brisk reflexes, with spread of reflexes noted in the lower limbs.

Anti-SOX1 antibodies were positive in the serum, though not detected in cerebrospinal fluid. Structural imaging of the chest, abdomen and pelvis did not reveal malignancy. Electromyography confirmed widespread complex fasciculations, leading to a diagnosis of bulbar-onset ALS.

## CONCLUSION:

Paraneoplastic ALS is an uncommon presentation, and this case appears to be the second presentation of anti- SOX1 associated ALS described.

Clinical

*C-P-CM009*

# ELEVATED PYRIDOXINE DUE TO VITAMIN SUPPLEMENTATION WORSENED FASCICULATIONS IN MND

[1]Ashhurst, Jasmine F, [1]Thompson, Alexandra, [1]Kiernan, Matthew C.

[1]Neuroscience Research Australia, Margarete Ainsworth Building, 139 Barker St, Randwick, Australia.

## INTRODUCTION:

The most common neurological side effect from pyridoxine is peripheral neuropathy. Rare cases of pyridoxine toxicity have described fasciculations. It has been postulated that the fasciculations represented a transient state of peripheral nerve hyperexcitability, which was supported by electromyographic findings of numerous fasciculation potentials of normal morphology, in an otherwise healthy patient. The fasciculations abated with cessation of vitamin B6 supplementation (1).

## REPORT:

Our case features a 51 year old male with a 12 month history of progressive spasticity and mild fasciculations in all limbs. Following extensive investigation, he was ultimately diagnosed with motor neuron disease (MND). He was prescribed vitamin B6 by a naturopath, after which time the patient and his family noted a marked increase in the extent and persistence of fasciculations. Pyridoxine serology revealed a supratherapeutic level of 726nmol/L (reference 35-110), at which time he ceased taking the B6 vitamin supplements. Over the following fortnight, the patient and his family described a dramatic reduction in his observed fasciculations

## CONCLUSION:

The present case represents a further instance of pyridoxine neurotoxicity manifesting as transient peripheral nerve hyperexcitability in the context of MND. That the marked exacerbation of fasciculations proved largely reversible with withdrawal of pyridoxine supplementation further suggests the utility of checking pyridoxine levels in the context of clinical presentations associated with peripheral nerve hyperexcitability syndromes.

## REFERENCES:

1. Krishnan D, Kiernan MC. Neurotoxic risks from over-the-counter vitamin supplements. Med J Aust. 2023 Apr 17;218(7):304-306.

Clinical

*C-P-CM010*

# THE DEVELOPMENT OF A SYSTEMICALLY DELIVERABLE ANTISENSE THERAPY FOR THE TREATMENT OF MOTOR NEURON DISEASES

[1]McCarthy, Louise; [2]Turner Bradley; [2]Shabanpoor, Fazel

[1]Department of Anatomy and Physiology, University of Melbourne, 30 Royal Parade, Parkville, Australia, [2]Motor Neuron Disease, Florey Institute, 30 Royal Parade, Parkville, Australia.

## INTRODUCTION:

Antisense oligonucleotides (ASOs) are emerging therapies for motor neuron diseases and are currently approved for the treatment of familial amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). The blood-brain barrier significantly limits the ability of naked ASOs to reach their target sequences in the central nervous system (CNS), necessitating regular invasive intrathecal injections. To overcome this challenge, chemical modifications to ASO backbones and conjugated peptide delivery vehicles are being explored for systemic administration. This study aimed to optimise peptides that we have previously developed and shown to efficiently deliver conjugated ASOs into the CNS via an intramuscular route. These peptides leverage retrograde axonal transport to reach their target pre-mRNA in the nuclei of lower motor neurons.

## METHODS:

The FDA-approved ASO Spinraza® was used as a model cargo to assess the delivery efficiency and nuclear uptake of peptide-ASO conjugates targeting survival motor neuron-2 (SMN2) mRNA. Conjugates were synthesised using alkyne-azide click chemistry, purified via high-performance liquid chromatography, and characterised by matrix- assisted laser desorption/ionisation time-of-flight mass spectrometry.

The *in vitro* uptake and activity of peptide-ASO conjugates were evaluated in SMA patient-derived fibroblasts using quantitative polymerase chain reaction.

## RESULTS:

*In vitro* activity assays demonstrated significant upregulation of full- length SMN2 mRNA compared to untreated controls.

## CONCLUSION:

We have further optimised our lead retrograde transporter peptides. Our results demonstrated significantly higher levels of SMN2 upregulation, which, together with previous *in vivo* studies, suggest that our optimised peptides enhance ASO delivery into the CNS following intramuscular injection. This approach offers a safer and more efficient alternative to the current intrathecal delivery method.

Clinical

*C-P-CM011*

# SHORT-TERM SAFETY AND EFFICACY OF INTRAVENOUS EDARAVONE IN MOTOR NEURON DISEASE: A CASE SERIES

[1]Mohd Noh, Mimi Nashra; [2]Tan JK; [3]Rathika Rajah; [2]Remli, Rabani

[1]Department of Medicine, Hospital Al-Sultan Abdullah Universiti Teknologi MARA (UiTM) Puncak Alam, Selangor, Malaysia, [2]Department of Medicine, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia, [3]Department of Medicine, Hospital Canselor Tuanku Muhriz, National University of Malaysia, Kuala Lumpur, Malaysia.

## INTRODUCTION:

Edaravone, a neuroprotective agent with oxygen radical scavenging properties, has been explored in amyotrophic lateral sclerosis (ALS). While clinical trials suggest benefits in selected ALS patients, its role in progressive bulbar palsy (PBP) remains unclear. Bulbar-onset ALS and PBP progress rapidly, leading to early dysphagia and respiratory decline.

## METHODS:

We present three cases of MND, including two with PBP, receiving IV edaravone alongside riluzole.

## RESULTS:

### Case 1:

A 56-year-old woman with limb onset ALS (ALSFRS-R: 28) started riluzole in July 2024. By October (ALSFRS-R: 26), IV edaravone was initiated. After five cycles, she reported fatigue (ALSFRS-R: 18), reflecting ongoing disease progression.

### Case 2:

A 67-year-old man with one year history of progressive speech difficulty and bulbar palsy was diagnosed with PBP. Despite riluzole, he required PEG and BiPAP. His ALSFRS-R was 37 at edaravone initiation via peripherally inserted central catheter, complicated by recurrent catheter-related infections. After seven cycles, ALSFRS-R remained between 33-37, with no meaningful improvement in bulbar function.

### Case 3:

A 67-year-old man with six months history of dysarthria and dysphagia was diagnosed with PBP in November 2024 (ALSFRS-R: 40). He tolerated three edaravone cycles via chemoport without complications. ALSFRS-R remained stable, and swallowing function did not deteriorate.

## CONCLUSION:

Short-term edaravone therapy showed variable responses, with no clear benefit in bulbar-onset cases. Infusion-related complications included fatigue and catheter infections. Findings highlight the need for alternative administration routes and individualized treatment approaches, warranting further research into edaravone's role in bulbar-predominant MND.

Clinical

*C-P-CM012*

# NECK FLEXION WEAKNESS PREDICTS RESPIRATORY DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

Nathan Pavey[1], Alyssa Tieppo, Andrew Hannaford[1], Parvathi Menon[1], Matthew Silsby, Steve Vucic[1]

1. Brain and Nerve Research Centre, Concord Clinical School, University of Sydney, Concord Hospital, Sydney NSW Australia.

**INTRODUCTION:**

Neck flexion weakness is often observed in amyotrophic lateral sclerosis (ALS) with advancing disease along with declining respiratory function. Medical Research Council (MRC) scoring and hand-held dynamometry (HHD) may serve as a potential surrogate marker for respiratory dysfunction.

**METHODS:**

Sixty-two ALS patients were prospectively recruited at Brain and Nerve Research Centre. Neck flexion strength using both MRC scoring and HHD, alongside standard respiratory function testing with spirometry, Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), In addition disease onset site and duration with ALSFRS-R was recorded.

**RESULTS:**

Neck flexion weakness (MRC $\leq$4) was present in 27% of patients and was associated with significantly reduced FVC (70.0±7.2% vs 86.8±2.4% predicted, P=0.038). HHD measurements demonstrated significant correlation with both FVC (R=0.487, P<0.001) and FEV1 (R=0.465, P<0.001). The association was most prominent with bulbar onset disease ($R^2$=0.673, P=0.002). Notably, neck flexion weakness was a significant predictor of FVC $\leq$50% predicted ($Chi^2$=7.68, P=0.006), a threshold indicating need for ventilatory support.

**CONCLUSION:**

Neck flexion weakness, particularly when quantified by HHD, serves as a reliable surrogate marker for respiratory dysfunction in ALS patients. This simple bedside assessment could alert the treating clinician of the impending need for ventilatory support. This enhances the clinical assessment in resource-limited settings or in patients with bulbar dysfunction who struggle with formal spirometry.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Clinical

*C-P-CM013*

# THE NECESSITY TO RAISE AWARENESS OF ACCESSIBILITY FEATURES AND IMPROVE SUPPORT SYSTEMS AMONG PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AND THEIR CAREGIVERS

Takehisa Hirayama[1], Junpei Nagasawa[1], Mari Shibukawa[1], Harumi Morioka[1], Tatsuhiro Yokoyama[1], Hiroshi Tsuda[1], Kota Bokuda[2], Mieko Ogino[3], Hiroyuki Takao[4], Mitsuya Morita[5], Yoshiaki Takahashi[6], Ryoichi Nakamura[7], Naoki Atsuta[7], Makoto Urushitani[8], Koji Yamanaka[9], Yuishin Izumi[10], Osamu Kano[1]

[1] Department of Neurology, Toho University Faculty of Medicine,[2] Department of Neurology, Tokyo Metropolitan Neurological Hospital,[3] Department of Neurology, Office of Medical Education, International University of Health and Welfare, School of Medicine,[4] Department of Neurosurgery, Jikei University School of Medicine,[5] Division of Neurology, Department of Internal Medicine, Jichi Medical University,[6] Yui Life Communication Laboratory,[7] Department of Neurology, Aichi Medical University School of Medicine,[8] Department of Neurology, Shiga University of Medical Science,[9] Department of Neuroscience and Pathobiology, Research Institute of Environmental Medicine, Nagoya University,[10] Department of Neurology, Tokushima University Graduate School of Biomedical Sciences

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive degeneration of motor neurons. As ALS progresses, patients experience declining limb weakness, and impaired speech, making it increasingly difficult to perform daily activities. Consequently, assistive technology plays a crucial role in helping patients with ALS maintain their daily routines [1]. Although digital assistive technologies have improved significantly, challenges remain in ensuring accessibility for individuals with disabilities [2]. However, research on awareness of the accessibility features of digital devices in patients with motor disabilities remains limited. Therefore, we aimed to assess the awareness and needs related to accessibility functions in digital devices among patients with ALS.

## METHODS:

We conducted a nationwide webinar in October 2023 titled "ALS Café. At the conclusion of the webinar, we administered a survey via Google Forms (Google, Menlo Park, CA, USA) to gather data on accessibility features. Additionally, we distributed a self-report questionnaire to patients with ALS and their caregivers, including family members, to assess their awareness and use of accessibility features.

## RESULTS:

A total of 55 people participated in the survey, including 31 patients with ALS and 24 caregivers. The average age of respondents was 57.1 ± 10.1 years, and the mean ALSFRS-R score was 26.6 ± 14.1. Ninety-five percent of respondents owned an ICT device, such as a smartphone, personal computer (PC), tablet, or smart speaker. The percentage of respondents aware of ICT device accessibility features was 69.6%. Awareness was lower among older respondents: 28.6% of those under 70 were unaware of accessibility features, while 50% of those over 70 were unaware. The most frequently used accessibility features included browsing assistance (32.1%), followed by voice operation (30.4%), mouse or touch pen operation (26.8%), synthesized voice reading (23.2%), gaze input operation (19.6 %), and switch operation (14.3%). Regarding government services, 85% of respondents were unaware of IT support centers for persons with disabilities. When asked who provided support for using ICT devices, the most common response was self-support (49.1%), followed by physical therapists (27.1%), family members (27.1%), and nurses (9.1%). Among the 27 participants who reported having no support, 66.7% had an ALSFRS-R score of > 30 points.

## CONCLUSION:

Although many patients with ALS use ICT devices, awareness of accessibility features remains insufficient. Early education and proactive support regarding ICT accessibility features are necessary, particularly for older patients with ALS.

## REFERENCES:

1. Leigh PN, et al. The management of motor neurone disease. J Neurol Neurosurg Psychiatry. 2003;74(suppl 4):iv32-47. 2. Botelho FHF. Accessibility to digital technology: virtual barriers, real opportunities. Assist Technol. 2021;33(sup1):27-34

Clinical

*C-P-CM014*

# CARE AUGMENTATION BY LOCATION -LINKED MESSAGING (CALL-ME) A PILOT RANDOMISED CONTROL TRIAL OF CARE AUGMENTATION BY LOCATION-LINKED MESSAGING IN AMYOTROPHIC LATERAL SCLEROSIS WITH RESPIRATORY IMPAIRMENT

[1,3]Chiwera T; [1,2]Muzafar I; [1]Tuck R; [1]Saidu K; [1,3]Al-Chalabi A

[1]Department of Neurology, Motor Nerve Clinic, King's College Hospital London, Denmark Hill, London, United Kingdom,

[2] Guy's, King's College, and St Thomas' Hospital (GKT) School of Medical Education, King's College London, London, United Kingdom,

[3]Department of Basic and Clinical Neuroscience, King's College London, Maurice Wohl Clinical Neuroscience Institute, London, United Kingdom,

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease which may cause type 2 respiratory failure, resulting from respiratory muscle weakness and paralysis. Inappropriate administration of high-flow oxygen in this population is a risk when an unplanned hospital attendance occurs due to respiratory symptoms, and may result in oxygen- induced hypercapnia, causing significant morbidity and mortality. Additionally, increasing breathlessness in ALS may be indicative of a progression towards the end of life. A potential solution is to notify the ALS team when a patient attends an emergency department to enable appropriate oxygen administration.

## METHODS:

This was a single-centre (King's College Hospital, London, UK) phase IIa randomised controlled 12-month pilot study, using a smartphone to alert the local ALS team if a patient was in the emergency department for more than 15 minutes. Correct functioning of the alert system was tested by the study team. There were 20 ALS patients with King's Stage 3 or 4 ALS, randomised 1:1 to either standard care or a smartphone app.

## RESULTS:

During the study, no member of the active intervention arm was admitted to the King's emergency department. 6 out of 20 participants died within 12 months of randomisation. One participant in the intervention arm had a prolonged inpatient stay without their smartphone. One participant faced technological issues with their device. Five of 10 participants provided compliance data: two carried the phone every day, one 1-2 times per week, and two never.

## CONCLUSION:

While the study was unable to establish efficacy due to a lack of emergency department attendance, it has provided valuable information on feasibility and patient acceptability. This study also highlights the need for early warning systems that require minimal patient input to facilitate effective, timely and appropriate intervention by the clinical team.

## REFERENCES:

1. Mamede de Carvalho et al., Diaphragmatic neurophysiology and respiratory markers in ALS. *Front Neurol*. 2019 Feb 21;10; Pg143.

2. Spinelli et al., Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. *Intensive Care Med*. 2020 Feb 3;46(4); Pg606– 618.

3. Washington et al., Engaging specialist palliative care in the management of amyotrophic lateral sclerosis: A patient, family, and provider-based approach. *J Palliative Care*. 2020 Feb 17;37(2); Pg170–176.

Clinical

*C-P-CM015*

# A CASE OF PROBABLE MMN TO ALS PROGRESSION: UNFORTUNATE MISDIAGNOSIS OR INCOMPREHENSIBLE OVERLAP?

[1]Merkulov YA; [2]Fedorova AN; [2]Lezina DS; [2]Gamburg AM; [2]Merkulova DM

[1]Institute of General Pathology and Pathophysiology, 8 Baltiyskaya St., Moscow, Russia, [2]BM Guekht Neurology Center, Central Clinical Hospital «RZD-Medicine», 2 Budayskaya St., Moscow, Russia

## INTRODUCTION:

Multifocal motor neuropathy (MMN) is a rare, treatable immune-mediated neuromuscular disorder the pathophysiology of which is not yet understood. By mimicking symptoms of fatal amyotrophic lateral sclerosis (ALS), it has been posing thrilling challenges to clinicians for over 40 years. To the best of the authors' knowledge, there are no published case reports of MMN to ALS transformation.

## REPORT:

A Caucasian male patient, aged 50, presented at our clinic with complaints of proximal arm weakness, preceded by painful cramps in the legs, which he linked to a prior COVID-19 infection. Neurologic examination revealed mild asymmetric deltoid muscle (DM) weakness, minimal involvement of proximal and good equal distal leg strength, 2+ tendon reflexes, and normal sensation. He had no upper motor neuron signs, no bulbar involvement, no fasciculations, and no muscle hypotrophy. Electrodiagnostics (EDX) showed prominent fibrillations in the DMs, but not in the vastus lateralis (VLM) and mentalis muscles (MM). Motor unit potentials (MUPs) were prolonged in the DMs and VLMs, with a corresponding fivefold increase in amplitude. MM's MUPs were unremarkable. The patient refused further evaluation and then lost contact for a year. Upon returning he exhibited a 10+ kg weight loss, asymmetric yet diffuse proximal muscle weakness with atrophy and fasciculations, absent other than ankle reflexes and low muscle tone. No pseudo-/bulbar or sensory dysfunction was present. He had been diagnosed with ALS elsewhere, though no gene mutations associated with ALS or type 4 spinal muscular atrophy were detected. Oncological screening was negative. EDX indicated substantial patchy denervation and reinnervation with deteriorated DMs, intact MM, and bilateral median nerve "probable" motor conduction blocks (CBs), with other nerves unaffected. Abnormal titers of anti-sulfatide antibodies (ABs) were also noted. Therefore, a re-diagnosis of MMN was made, followed by a high-dose 2 g/kg intravenous immunoglobulin (IVIg) treatment, which led to an increase in muscle strength and regression of spontaneous fasciculations within days. The temporal relief was objectivized, and CBs and ABs were no longer present. However, the subsequent IVIg cycle didn't halt the progression of his disabling flaccid tetraparesis, and the patient was shifted to the second line cyclophosphamide (CTX) IV therapy, starting at 200 mg/d, followed by the intermittent protocol by Pestronk et al. After 6 mos and 17 g of CTX he had no adverse reactions and his condition stabilized, although displayed multidirectional trends. By consensus, the medical board recommended rituximab (RTX) as the third line of treatment. However, by the fifth infusion (375 $mg/M^2$) due to ongoing debilitating disease progression, the patient gave up hope. He was transferred to another institution, and passed away from ALS within the following year. Although not documented, he was administered riluzole (RLZ), but no miracle happened.

## CONCLUSION:

As expressed in the title of this case, it calls for further research on substances like RLZ to extend beyond the scope of ALS and confront the frustrating reality faced by such patients.

## REFERENCES:

1. Joint Task Force of the EFNS and the PNS guideline on management of multifocal motor neuropathy - first revision. J Peripher Nerv Syst. 2010;15:295-301.

2. https://neuromuscular.wustl.edu/antibody/ctxrx2.html

Clinical
*C-P-CM016*

# DEVELOPING THE AUSTRALIAN MOTOR NEURONE DISEASE GUIDELINE: A COLLABORATIVE, EVIDENCE-BASED APPROACH USING GRADE METHODOLOGY

Zachary Munn[1], Cindy Stern[1], Danielle Pollock[1], Timothy Barker[1], Steve Vucic[2] for the Australian MND Guideline Development Group
[1]Health Evidence Synthesis, Research, and Impact (HESRI), University of Adelaide, Australia

[2]Brain and Nerve Research Centre, Concord Clinical School, The University of Sydney, Sydney, Australia

## INTRODUCTION:

Motor Neurone Disease (MND) is a progressive neurodegenerative condition with no cure, requiring multidisciplinary, evidence-based care. Currently, there is no nationally endorsed **Australian MND guideline** to standardise care and improve outcomes. This project aims to develop a **comprehensive, evidence-based guideline** for MND, ensuring alignment with international best practices while incorporating perspectives from clinicians, researchers, policymakers, and individuals with lived experience.

## METHODS:

The guideline is being developed with the MND community following the **GRADE (**Grading of Recommendations, Assessment, Development, and Evaluation) approach and in line with the **National Health and Medical Research Council** guidelines for guidelines. A scoping review was conducted to identify existing guidelines and research gaps to inform prioritisation of the guideline topics and scope. This process involved **multistakeholder engagement**, including a **Guideline Development Panel (GDP)** and advisory groups representing clinicians, researchers, policymakers, and people with lived experience. A **systematic process for outcome selection and prioritisation** is being implemented, informed by recent advancements in guideline methodology, and systematic reviews being conducted for each prioritised question to underpin evidence-based recommendations.

## RESULTS:

The **guideline scope** has been determined through stakeholder consultation, identifying **priority clinical questions** covering multidisciplinary management, symptom control, assistive technologies, palliative care, and service delivery. An **outcome prioritisation framework** has been co-developed, incorporating perspectives from all stakeholder groups. Preliminary evidence synthesis has commenced, with recommendations being formulated based on the best available evidence.

## CONCLUSION:

The **Australian MND Guideline** represents a major step forward in standardising care for people living with MND in Australia. By combining **rigorous evidence synthesis, broad stakeholder engagement, and an inclusive approach to lived experience**, the guideline aims to improve **clinical practice, patient outcomes, and health system efficiencies**. The final recommendations will be launched in **late 2025**, with strategies for implementation and monitoring to support uptake.

Clinical

*C-P-CN&I001*

# IDENTIFICATION OF SENSORY INVOLVEMENT IN SPINAL BULBAR MUSCULAR ATROPHY (SBMA): NEUROPHYSIOLOGICAL AND FUNCTIONAL EVIDENCE OF SENSORY DYSFUNCTION

[1]Lin, Cindy (Shin-Yi); [2]Park SB; [1]Tu S; [2]Li T; [3]Carroll A; [4]Henderson R; [5]Silsby M; [6]Vucic S, [7]Kiernan MC

[1]Central Clinical School, Faculty of Medicine and Health, Brain and Mind Centre, The University of Sydney, Australia

[2]School of Medical Sciences, Faculty of Medicine and Health, Brain and Mind Centre, The University of Sydney, Australia

[3]Department of Neurology and Neurophysiology, St Vincent's Hospital, Sydney, Australia

[4]Department of Neurology, Royal Brisbane & Women's Hospital (RBWH), Queensland, Australia

[5]Department of Neurology, Westmead Hospital, Sydney, Australia

[6]Brain and Nerve Research Centre, Concord Clinical School, The University of Sydney, New South Wales, Australia

[7]Neuroscience Research Australia (NeuRa), UNSW, Sydney, Australia

## INTRODUCTION:

Spinal bulbar muscular atrophy (SBMA) is a rare X-linked neurodegenerative disorder characterized by muscle weakness and sensory deficits. This study aims to elucidate the sensory involvement in both central and peripheral nervous systems in SBMA in contrast to patients with amyotrophic lateral sclerosis (ALS) and healthy controls (HC), employing comprehensive assessments of peripheral nerve excitability, evaluations of sensory functions, and multimodal magnetic resonance imaging (MRI).

## METHODS:

The study recruited 44 subjects (14SBMA, 20ALS, 10HC). SBMA patients completed questionnaires, underwent clinical neurophysiological evaluations including Total Neuropathy Score (TNSc), Von Frey monofilament, and Grating Orientation Task (GOT). Functional status was evaluated with the ALS Functional Rating Scale-Revised and Grooved Pegboard test. Median motor and sensory nerve excitability was measured with the TRONDNF protocol1. Longitudinal nerve excitability was measured in a subset of SBMA (interval of 5.5±2.1 years). All SBMA received structural and diffusion-weighted MRI.

## RESULTS:

SBMA patients showed significantly worse peripheral neuropathy (TNSc: 9.2±3.7 vs 1.1±1.2, $P<0.001$), impaired tactile spatial acuity with GOT thresholds (7.1±2.9mm vs 3.3±2.7mm, $P<0.001$), reduced hand dexterity with pegboard times (99.5±24.1s vs 72.9±22.1s, $P<0.001$) and reported greater sensory disturbance on patient questionnaires (8.6±2.8 vs 6.5±1.0, $P<0.05$) compared to HC. There were markedly reduced sensory nerve action potentials (SNAPs) compared to both ALS and HC (10.9±8.3μV vs. 35.3±15.9μV and 35.5±17.3μV, $p<0.001$). Distinctive alterations in sensory excitability parameters were observed in SBMA compared to HC, including threshold electrotonus, accommodation half- time, and resting I/V slope (all $p<0.05$). Combination of sensory excitability alterations indicate a relatively depolarized resting membrane potential in SBMA patients. Longitudinal paired nerve excitability analysis revealed progressive sensory axon dysfunction while motor excitability remained stable, suggesting sensory deficits can progress independently to motor symptoms. Neuroimaging analyses revealed a significant positive correlation between white matter integrity involving corticospinal pathways, extending into adjacent frontal and temporal lobe tracts, with peak SNAPs ($P_{FWE}<0.05$).

## CONCLUSION:

These findings demonstrated the significant sensory involvement in SBMA and highlight the potential utility of sensory excitability testing as a clinical marker for distinguishing SBMA from ALS and monitoring disease progression.

## REFERENCES:

1. Kiernan, Matthew C., et al. "Measurement of axonal excitability: Consensus guidelines." Clinical Neurophysiology 131.1 (2020): 308-323.

Clinical

*C-P-CN&I002*

# SLEEP PARAMETER DURING REM SLEEP PERIOD PREDICT RESPIRATORY FAILURE IN AMYOTROPHIC LATERAL SCLEROSIS

Seung-Ah Lee[1], Jee Hyun Kim[1], Suk-won Ahn[2], Yoon-Ho Hong[3], Jung-Joon Sung[3], Jee-Eun Kim[4]*

[1]Department of Neurology, Ewha Womans University College of Medicine, Seoul, Korea [2] Department of Neurology, Chung Ang University, College of Medicine, Seoul, Korea [3]Department of Neurology, Seoul National University, College of Medicine, Seoul, Korea [4] Department of Neurology, Seoul Medical Center, Seoul, Korea

**BACKGROUND & OBJECTIVE:**

Bulbar muscle weakness and associated dysphagia/respiratory failure is utmost important clinical issue in amyotrophic lateral sclerosis because it closely related to patient's quality of life and survival. Early application of noninvasive ventilation and gastrostomy improves prognosis. However, deciding the timing of noninvasive ventilation and gastrostomy is not so easy that clinical symptoms and simple perioximetry cannot detect earlier respiratory muscle weakness. Also, many ALS patient has bulbar muscle weakness that barrier to perform exact bedside pulmonary function test (even including sniff nasal inspiratory pressure). This study aims to evaluate utility of sleep parameter during rapid eye movement (REM) sleep as possible biomarkers for respiratory and bulbar muscle weakness in ALS.

**METHODS**:

We retrospectively reviewed polysomnography (PSG), with hypercapnia also assessed using at least one of the following: end-tidal carbon dioxide (ETCO2) or transcutaneous CO2 monitors. All patients met the revised El Escorial criteria for probable or definite ALS at the time sleep studies were performed. REM sleep parameter (REM duration, presence of REM associated OSA and REM predominant OSA, REM associated hypercapnia) was analyzed. REM-predominant OSA was defined as a REM-apnea-hypopnea-index (AHI) /non-REM (NREM) AHI ≥ 2. Severity of dysphagia was categorized by swallowing category of the ALS severity scale and functional dysphagia scale based on videofluoroscopic studies. Disease duration, ALS severity scale and its progression rate, Respiratory category of the ALS severity scale, blood gas analysis, pulmonary function test, Pittsburgh Sleep Quality index, NIV/gastrostomy application was reviewed.

**RESULTS:**

Total 11 ALS (6 males) were included and 3 had bulbar-onset ALS. The median age of patient was 63 years old [interquartile range (IQR), 59-71 years old] and the median disease duration was 20 months [IQR, 12-21.5]. Most of ALS patients showed low sleep efficiency, high arousal rates (mainly with respiratory problems), and all had AHI>5. Six ALS patients (54.5%) showed hypercapnia and 66.7% of these cases were REM-related. Among patients with moderate or severe dysphagia, noninvasive ventilation use within 3 months of PSG, or death during the follow up period, 66.7%, 55.6% and 50%, respectively, had REM-related sleep issues.

**CONCLUSION:**

Along with frequent sleep complaints, various degrees of impairment to sleep microstructure and architecture were observed in ALS. Sleep parameters during REM period as REM duration, presence of REM associated OSA and REM predominant OSA, REM associated hypercapnia can be a possible biomarker for earlier detection of bulbar and respiratory muscle failure.

Clinical

*C-P-CN&I003*

# FUNCTIONAL AND MICROSTRUCTURAL CHANGES IN APPETITE-CONTROL BRAIN REGIONS IN PATIENTS LIVING WITH MND

[1]Jeryn, Chang; [2,3]Jinglei, Lv; [4,5,6]Pamela, A McCombe; [4,5,6]Robert, D Henderson; [7]Diana, Lucia; [8]Christine, C Guo; [9]Saskia, Bollmann; [10]Kelly, Garner; [4,5,6,7]Shyuan, T Ngo; [1,4,5,6]Frederik, J Steyn ;[4,9,11]Thomas, B Shaw

[1]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Australia

[2]School of Biomedical Engineering, Faculty of Engineering, The University of Sydney, Australia

[3]Brain and Mind Centre, The University of Sydney, Australia

[4]Department of Neurology, Royal Brisbane and Women's Hospital, Australia

[5]UQ Centre for Clinical Research, The University of Queensland, Australia

[6]Wesley Medical Research, The Wesley Hospital, Australia

[7]Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Australia

[8]ActiGraph, LLC, Pensacola, FL, USA

[9]School of Information Technology and Electrical Engineering, The University of Queensland, Australia

[10]School of Psychology, University of New South Wales, Australia

[11]Centre for Advanced Imaging AIBN, The University of Queensland, Australia

## INTRODUCTION:

The loss of appetite in people living with MND (plwMND) contributes to weight loss[1,2], which is associated with faster disease progression and earlier death[3]. Central appetite mechanisms that contribute to loss of appetite in MND are poorly understood. We sought to investigate differences in functional and diffusion MRI- based metrics in plwMND in relation to appetite.

## METHODS:

Forty-two plwMND and twenty-four non-neurodegenerative disease control participants underwent functional imaging at fast, and following a liquid meal. During imaging, food and non-food visual stimuli were presented.

Functional signals were extracted in a voxel- wise general linear model and contrast estimates were extracted. Participants subsequently underwent multishell diffusion imaging. Images were processed using constrained spherical deconvolution to estimate fibre orientation distributions and fixel metrics.

## RESULTS:

Reduced activation and reduced fibre cross-section are seen in non-motor areas that are involved in emotional regulation and reward. Comparing differences in activations between fasted and satiated states when viewing images of high calorie foods, plwMND have reduced activations in the right temporal pole (pFWE=0.043). Appetite scores are associated with reduced activations of the right cerebellar nuclei (pFWE=0.005) in plwMND when shown images of food during a fasted state.

Investigations were then expanded to related tracts. We observed significant decreases in fibre density and cross-section in the internal capsule region of the nigrostriatal and temporopontine pathways (pFWE<0.05). Furthermore, the fornix crus was associated with appetite scores in controls (pFWE<0.05) but not in plwMND.

## CONCLUSION:

Results show widespread functional changes and white matter degeneration throughout emotion and reward pathways in plwMND. We observed no significant structural differences in people plwMND relative to measures of appetite, yet strong functional changes suggest a link between psychosocial, emotional, and secondary factors influencing appetite loss in plwMND. Results add to an evolving understanding of the impact of disease on non- motor areas of the brain.

**REFERENCES:**

1. Shojaie A, Al Khleifat A, Sarraf P, Al-Chalabi A. Analysis of non-motor symptoms in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. May 2024;25(3-4):237-241. doi:10.1080/21678421.2023.2280618

2 Sarmet M, Kabani A, Maragakis NJ, Mehta AK. Appetite and quality of life in amyotrophic lateral sclerosis: A scoping review. Muscle Nerve. Dec 2022;66(6):653-660. doi:10.1002/mus.27694

3. Ngo ST, van Eijk RPA, Chachay V, et al. Loss of appetite is associated with a loss of weight and fat mass in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. Nov 2019;20(7-8):497-505. doi:10.1080/21678421.2019.1621346

Clinical
*C-P-CN&I004*

# PROPOSED PROTOCOL FOR FASCICULATION DETECTION BY MUSCLE ULTRASOUND IN AMYOTROPHIC LATERAL SCLEROSIS

Mingsheng Liu, Liying Cui
Peking Union Medical College Hospital

**OBJECTIVE:**

To provide a feasible protocol for detecting fasciculation by MUS in clinical practice and investigate potential diagnostic value of fasciculation among ALS patients.

**METHODS:**

The study comprised 149 ALS patients and 54 non-ALS patients, all underwent MUS on selected muscle groups in bulbar, cervical, thoracic and lumbosacral regions. The intensity of fasciculation was divided into five grades based on firing frequency and number in the involved muscle groups. The fasciculation diagnostic score was defined according to the diagnostic indicators with high specificity for ALS.

**RESULTS:**

The detection rate of fasciculation were highest in the lumbosacral (970/1622, 59.81%) and cervical (841/1516, 55.47%) muscle groups, followed by the thoracic muscles (148/548, 34.31%), and the bulbar muscle groups (102/652, 15.64%) among ALS patiens ($p<0.05$). The detection of fasciculation in bulbar and thoracic muscle groups and detection of high-grade fasciculation in cervical and lumbosacral muscle groups were highly specific among ALS patients. For fasciculation diagnostic score, ROC analysis showed that the area under curve (AUC) was 0.961 (95%CI 0.927-0.996). The optimal cut-off value was 1 point with 95.77% of sensitivity and 88.89% of specificity.

**CONCLUSIONS:**

Fasciculation was most often detected in lumbosacral and cervical muscle groups, followed by thoracic muscle groups, and least common in bulbar muscle groups. The detection of fasciculation in bulbar and thoracic muscle groups and detection of high-grade fasciculation in cervical and lumbosacral muscle groups have high specificity for the diagnosis of ALS, which should be the main targets during MUS examination. A total of 13 muscle groups were recommended for routine fasciculation detection for each patient. Fasciculation by MUS examination could become a timesaving and easily-operated indicator for ALS diagnosis.

Clinical

*C-P-CN&I005*

# VARIANCE AND RELIABILITY OF METHODS FOR MEASURING THE CORTICAL SILENT PERIOD IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

[1,2]Kuroiwa R; [2]Shibuya K; [1,2]Nara T; [1]Morita M; [1]Murata A; [2]Kuwabara S

[1]Department of Rehabilitation Medicine, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.
[2]Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.

## INTRODUCTION:

Cortical silent period (CSP) may serve as a pathogenic biomarker of amyotrophic lateral sclerosis (ALS).[1] Variation in CSP measurement methods has hindered reproducibility and comparison between studies.[2] This study investigated the variance and reliability of different methods for measuring CSP in patients with ALS.

## METHODS:

CSP was measured using single-pulse transcranial magnetic stimulation in 25 patients with ALS (9 men, 16women; mean age 69.8 years old), and recorded from the abductor pollicis brevis. The stimulus intensity was set at 150% of the resting motor threshold. The CSP onset was manually determined as the stimulus onset, MEP onset, or MEP offset. The coefficient of variation (CV) and intraclass correlation coefficient (ICC) of each data set were calculated.

## RESULTS:

Stimulus onset, MEP onset, and MEP offset had CSP means of 175.9 ms,133.6 ms and 97.4 ms, respectively, with CVs of 0.09, 0.11, and 0.15, with ICCs of 0.87, 0.86, and 0.84.

## CONCLUSION:

The variance and reliability of CSP measurements differed depending on the definition of CSP onset. While all methods showed high reliability, the MEP offset-based measurement exhibited the greatest variability. These findings highlight the importance of standardized CSP measurement protocols to enhance reproducibility and comparability in ALS study.

## REFERENCES:

1. Siciliano G, et al. J Neurol Sci. 1999 Oct 31;169(1-2):93-7.
2. Hupfeld KE et al., J Neurosci Methods. 2020 Dec 1;346:108950.

Clinical

*C-P-CN&I006*

# AMYOTROPHIC LATERAL SCLEROSIS: ULTRASONOGRAPHIC ASSESSMENT OF TONGUE AND VAGUS NERVE AND CORRELATION WITH SPEECH

Seena Vengalil[1], Arjun Chandrashekar[1], Yamini BK[2], Karthik Kulanthaivelu[3], Keerthipriya MS[1], Saraswati Nashi[1], Deepak Menon[1], Atchayaram Nalini[1]

1. Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India-560029
2. Department of Speech Pathology and Audiology, National Institute of Mental Health and Neurosciences, Bangalore, India-560029
3. Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neurosciences, Bangalore, India-560029

**INTRODUCTION:**

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative condition. Ultrasound is useful in detecting tongue fasciculation, tongue thickness (TT)and vagus nerve (VN) atrophy. We conducted this study to estimate the TT, VN cross-sectional area (CSA) and speech changes in ALS patients and to correlate TT and VN changes with speech.

**METHOD:**

60 patients with definite/probable ALS and 60 controls (30 age,sex matched)were included. Clinical, demographic features, ALSFRS-R were collected. TT and VN CSA were measured using 3.5MHz and 17 MHz probes in Philips EPIQ 7G ultrasound machine. Accoustic and temporal parameters of speech were analysed using Computerized Speech Lab (CSL, Pentax).

**RESULTS:**

The mean age of the cases and the controls were 50.2 ± 11.9 and 51.7 ± 10.1 years. M:F in ALS and controls were 20:16 and 32:28. Mean ALSFRS-R -33.2. Bulbar onset-14, bulbar involvement at presentation-25. The mean TT in ALS and controls were 25.02 ± 4.8 and 28.96 ± 2.4 mm respectively ($p<0.001$). Bulbar onset ALS had lower mean TT than limb onset (22 vs 25.5 $p<0.01$). Mean CSA of right and left VN showed significant difference in ALS (1.8 ± 0.57 $mm^2$, 1.7 ± 0.57 $mm^2$) compared to controls (2.44 ± 0.30, 2.46 ± 0.30, $P<0.001$). Patients with bulbar onset had lower VN CSA than limb onset, though non- significant. Jitter% of vowels, burst duration, voice onset time for consonants [k], [t] were increased in bulbar ALS Fricative sound [ʃ]LF level and Diadochokinetic rate for the [ka] sequence showed positive correlation with TT while Voice Onset Time (VoT) had significant negative correlation. Few speech parameters correlated with vagus CSA.

**CONCLUSION:**

TT and VN CSA were reduced significantly in ALS compared to controls and even those with limb onset had lower TT and VN CSA. TT and VN CSA correlated with few speech parameters.

Clinical

*C-P-CN&I007*

# ENLARGED PERIVASCULAR SPACES (EPVS) IN AMYOTROPHIC LATERAL SCLEROSIS AND ITS CLINICAL IMPLICATIONS

[1,2]Hsueh SJ, [2]Chao CC

[1]Department of Neurology, National Taiwan University Hospital Bei-Hu Branch, 37 Neijiang St, Taipei, Taiwan
[2] Department of Neurology, National Taiwan University Hospital, 7 Zhongshan S. Rd, Taipei, Taiwan

## INTRODUCTION:

The CNS perivascular space system had been proposed to involve in the development of neurodegenerative disorders. [1,2,3] The presence of enlarged perivascular spaces (ePVS) had been considered to be a sign of perivascular space dysfunction, which could lead to accumulation of toxic metabolites and abnormal proteins, similar to some proposed mechanisms of ALS[4]. In this study, we quantified the severity of ePVS using an established score, and analyzed its relationship with clinical presentations and structural parameters in ALS.

## METHODS:

We enrolled sporadic ALS patients who fulfilled the criteria for definite or probable ALS according to the Awaji Criteria. We recorded the disease onset age, disease duration, along with the clinical pattern, including global functional deficits and upper/lower motor neuron involvements. From the images of the patients, we quantified 1) ePVS of the centrum semiovale, basal ganglia, and brainstem, graded according to the classification proposed by Potter et al[5], 2) white matter tract DTI parameters, and 3) volume of cortical and subcortical gray matter structures involved in motor function. The ePVS was then correlated with these clinical and structural markers.

## RESULTS:

55 patients (33 male, 61.38±10.95 years old) and 37 controls were enrolled for analysis. There was no significant difference in regional and total ePVS grades between patients and controls. The basal ganglia regional ePVS grade is significantly correlated with the patients' muscle strength (p=0.021), while the centrum semiovale regional ePVS grade is correlated to the volume of middle (P=0.009) and superior frontal (P=0.004) gyrus. The global ePVS burden is correlated with the patients' disease progression characterized by changes of ALSFRS-R score (p=0.037). No significant correlation was identified between either regional or global ePVS and upper or lower motor neuron involvements.

## CONCLUSION:

Development of ePVS may contribute to the clinical presentation, cerebral structural changes, and disease progression in ALS patients.

## REFERENCES:

1. Wardlaw JM et al. Nat Rev Neurol. 2020;16(3):137-153.
2. Jeong SH et al. Neurology. 2022 Oct; 99(16):e1791-e1802. doi: 10.1212/WNL.0000000000200989.
3. Wood KH et al. Mov Disord. 2024 Sep;39(9):1504-1513. doi: 10.1002/mds.29908.
4. Eisen A et al, Prog Neurobiol. 2024; 234:102571. doi: 10.1016/j.pneurobio.2024.102571.
5. Potter GM et al. Cerebrovasc Dis. 2015 Jan; 39(4): 224–231. doi: 10.1159/000375153

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Clinical

*C-P-CN&I008*

# DIFFERENT PATTERNS OF FASCICULATION IN SPINAL AND BULBAR MUSCULAR ATROPHY AND AMYOTROPHIC LATERAL SCLEROSIS: A MUSCLE ULTRASONOGRAPHIC STUDY

[1,2]Nara T; [2]Shibuya K; [3]Ikeda S; [1,2]Kuroiwa R; [2]Otani R; [2]Ogushi M; [2]Suichi T; [4,5]Shiko Y; [5]Takahashi K; [2]Misawa S; [1]Murata A; [2]Kuwabara S

[1]Department of Rehabilitation Medicine, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.
[2]Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.
[3]Department of Laboratory Medicine, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.
[4]Department of Biostatistics, Graduate School of Medicine, Saitama Medical University, 38 Morohongou, Irumagun, Japan.
[5]Biostatistics section, Clinical Research Center, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba, Japan.

## INTRODUCTION:

While the usefulness of muscle ultrasonography for detection of fasciculations in amyotrophic lateral sclerosis (ALS) has been highlighted, distributions and characteristics of fasciculations in spinal and bulbar muscular atrophy (SBMA) have not been fully elucidated. This study aimed to elucidate distributions and characteristics of fasciculations in SBMA, and to compare the results of those in ALS.

## METHODS:

In 24 SBMA and 16 ALS patients, muscle ultrasonography was systematically performed in the tongue, upper limb muscles (biceps brachii, triceps brachii, first dorsal interosseous [FDI], abductor pollicis brevis and abductor digiti minimi), trunk muscles (Th10 paraspinals and rectus abdominis) and lower limb muscles (vastus lateralis, biceps femoris, tibialis anterior and gastrocnemius). We assessed the presence of fasciculations, and the fasciculation intensity (scored from 0 to 3) for each muscle.

## RESULTS:

All SBMA and ALS patients showed fasciculations at least in two muscles. In SBMA patients, fasciculations were most frequently found in the tongue (100%), FDI (93%) and tibialis anterior (80%), whereas less frequently present in the proximal limb and trunk muscles, irrespective of age, disease duration and CAG repeat numbers. By contrast, in ALS patients, fasciculations were more diffusely distributed including the proximal limb and trunk muscles. When fasciculations were present, the intensity was higher in ALS patients, except for the tongue.

## CONCLUSION:

Both diseases exhibit extensive fasciculations, although their patterns differ. While fasciculations in ALS are generally intense, those in SBMA are more widespread, involving the tongue and distal limb muscles. These findings suggest distinct pathophysiological mechanisms underlying motor neuron death in SBMA and ALS.

Clinical

*C-P-CN&I009*

# THE ROLE OF THE PERIPHERAL IMMUNE SYSTEM IN MEDIATING AXONAL DYSFUNCTION IN EARLY-STAGE AMYOTROPHIC LATERAL SCLEROSIS: AN AGE- AND SEX-BASED ANALYSIS

[1]Wang Zhuoya, [1]Cao Wen, [1]Chen Lu, [1]Zhang Shuo, [1]Tang Lu, [1]Cui Wenjuan, [1]Kong Mingjun, [1]Yu Ling. [1]Fan Dongsheng, [1]Zheng Wei

[1] Department of Neurology, Peking University Third Hospital, Beijing, China.

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive loss of motor neurons (MNs), with axonal dysfunction playing a critical role in the early stages [5, 6]. However, the molecular mechanisms underlying this dysfunction remain unclear. In recent years, an increasing number of studies have found that peripheral immune dysregulation plays a key role in ALS pathogenesis [1-4]. This study aims to investigate the correlation between peripheral immune dysregulation and axonal dysfunction in ALS.

## METHODS:

This cohort study, conducted from January 2018 to May 2024, included 372 sporadic ALS patients within the first 12 months of disease onset. Peripheral immune markers (including total leukocytes, lymphocytes, monocytes, neutrophils, basophils, eosinophils, and platelets) and their derived metrics—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII)—were analyzed for their correlation with the relative score of the compound muscle action potential (CMAP) using multiple linear regression. Analyses were stratified by age, sex, and body mass index to identify demographic-specific immune mechanisms. Mediation analysis was conducted to assess the extent to which peripheral immunity mediated axonal dysfunction.

## RESULTS:

After adjusting for covariates, multivariate analysis revealed that higher counts of total leukocytes ($P$ = 0.005), neutrophils ($P$ = 0.036), and neutrophil-related metrics, including NLR ($P$ = 0.036) and SII ($P$ = 0.020), were significantly associated with higher CMAP relative scores, an indicator of axonal dysfunction in lower MNs (LMNs) in ALS patients. The strength of these associations varied by age and sex. Mediation analyses showed that axonal dysfunction of LMNs accounted for 57.4% of the association with leukocytes, 53.9% with neutrophils, 53.3% with NLR, and 47.0% with SII.

## CONCLUSION:

In the early stages of ALS, peripheral immune dysregulation contributes to disease progression by mediating peripheral nerve damage, with these effects varying by age and sex. Understandingthese immune-axonal interactions may offer insights into disease mechanisms and inform immunotherapeutic strategies.

## REFERENCES:

1. Cao W, Cao Z, Tian Y, Zhang L, Wang W, Tang L, Xu C, Fan D (2023) Neutrophils Are Associated with Higher Risk of Incident Amyotrophic Lateral Sclerosis in a BMI- and Age-Dependent Manner. Ann Neurol 94:942-954

2. Murdock BJ, Goutman SA, Boss J, Kim S, Feldman EL (2021) Amyotrophic Lateral Sclerosis Survival Associates With Neutrophils in a Sex-specific Manner. Neurol Neuroimmunol Neuroinflamm 8

3. Murdock BJ, Zhao B, Pawlowski KD, Famie JP, Piecuch CE, Webber-Davis IF, Teener SJ, Feldman EL, Zhao L, Goutman SA (2024) Peripheral Immune Profiles Predict ALS Progression in an Age- and Sex-Dependent Manner. Neurol Neuroimmunol Neuroinflamm 11:e200241

4. Murdock BJ, Zhou T, Kashlan SR, Little RJ, Goutman SA, Feldman EL (2017) Correlation of Peripheral Immunity With Rapid Amyotrophic Lateral Sclerosis Progression. JAMA Neurol 74:1446- 1454

5. Yu H, Chen L, Zhang S, He J, Fan D (2021) Early Axonal Dysfunction of the Peripheral Nervous System Influences Disease Progression of ALS: Evidence From Clinical Neuroelectrophysiology. Front Neurol 12:574919

6. Zhang L, Ji T, Wu C, Zhang S, Tang L, Zhang N, Liu X, Fan D (2022) Serum Neurofilament Light Chain Levels May Be a Marker of Lower Motor Neuron Damage in Amyotrophic Lateral Sclerosis. Front Neurol 13:833507

Clinical

*C-P-CN&I010*

# VOXEL-MIRRORED HOMOTOPIC CONNECTIVITY IN UPPER MOTOR NEURON-DOMINANT AMYOTROPHIC LATERAL SCLEROSIS IS ASSOCIATED WITH DIFFERENT SPREAD DIRECTIONS

Jieying Wu[1,5], Yingsheng Xu[1], Tielun Yin[1], Nan Zhang[1], Jianqiao Ge[4], Dongsheng Fan[1,2,3*], Shan Ye[1,2,3*]

[1] Department of Neurology, Peking University Third Hospital, Beijing, China

[2] Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China

[3] Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China

[4] Center for MRI Research, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China

[5] Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China

[*] Contribute equally as a co-corresponding author.

## ABSTRACT

### INTRODUCTION:

By adopting the method of voxel- mirrored homotopic connectivity (VMHC), the correlation of the synchrony of spontaneous neural functional activities between symmetrical regions is determined to be mediated by the corpus callosum (CC). This study investigates whether there are abnormalities in homotopic functional connectivity (FC) across different spread directions in individuals with upper motor neuron-dominant (UMN-D) amyotrophic lateral sclerosis (ALS).

### METHODS:

The UMN-D ALS patients are categorized into two groups based on the direction of symptom spread—horizontal spread (group H) and vertical spread (group V). Indices of interhemispheric functional and structural changes are derived via analyses of VMHC and probabilistic fiber tracking.

### RESULTS:

The grey matter VMHC analysis shows that intergroup differences in the superior frontal gyrus (SFG) are greater in group H than in V and HC. According to CC-based VMHC analysis, group H exhibits a major advantage compared to group V.

### CONCLUSION:

In UMN-D ALS, the results of VMHC analysis vary with different spread directions. In group H, homotopic FC significantly increased, possibly associated with early bilateral limb involvement and subsequent compensatory increases in SFG. Changes in homotopic FC are not correlated with structural lesions or clinical scores of the CC, suggesting that alterations in homotopic FC may be bidirectional rather than unidirectional.

### KEYWORDS:

Upper motor neuron-dominant amyotrophic lateral sclerosis, Resting-state functional magnetic resonance imaging, Voxel-mirrored homotopic connectivity, Diffusion tensor imaging, Spread directions, Contralateral co-movement test.

Clinical
*C-P-CN&I011*

# UNVEILING STRUCTURAL DAMAGE OF THE CORPUS CALLOSUM IN AMYOTROPHIC LATERAL SCLEROSIS THROUGH DIFFUSION TENSOR IMAGING AND SPREAD DIRECTION PERSPECTIVES

Jieying Wu, MD[1,4], Yingsheng Xu, MD[1], Tielun Yin, MS[1], Nan Zhang, BSc[1], Dongsheng Fan, PhD[1,2,3]*, Shan Ye, MD[1,2,3]*

[1] Department of Neurology, Peking University Third Hospital, Beijing, China
[2] Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China
[3] Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China
[4] Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China
* Contribute equally as a co-corresponding author.

## ABSTRACT

### INTRODUCTION:
Damage to the corpus callosum (CC) in amyotrophic lateral sclerosis (ALS) patients has been confirmed via electrophysiological, neuroimaging, and autopsy studies. Additionally, the CC is hypothesized to serve as a pathway for the spread of pathological information. This study aimed to investigate whether the CC plays a mediating role in the symptomatic spread of ALS.

### METHODS:
In this observational study, diffusion tensor imaging (DTI) data were acquired from 45 individuals with the upper motor neuron-dominant (UMN-D) phenotype of ALS. The UMN-D ALS patients were categorized into two groups based on the direction of symptom spread, including 25 patients with horizontal spread (group H) and 20 patients with vertical spread (group V). Diffusivity indices were derived through whole-brain analysis and probabilistic fiber tracking.

### RESULTS:
According to the voxel-based analysis and tract-based spatial statistics, differences in axial diffusivity (AD) in the CC were observed between disease subgroups, with patients in group H showing higher AD values than those in group V. Fiber tracking analysis revealed persistent differences in the AD indices of CC-primary motor cortex (PMC) fibers between the two disease subgroups.

### CONCLUSION:
In UMN-D ALS patients, the direction of symptom spread may be related to the degree of CC involvement. The AD metric may be a more specific indicator of CC damage.

### KEYWORDS:
Upper motor neuron-dominant amyotrophic lateral sclerosis, Corpus callosum, Horizontal spread, Vertical spread, Axial diffusivity

Clinical
*C-P-CN&I012*

# THE CONTRALATERAL CO-MOVEMENT TEST IN A CHINESE POPULATION WITH AMYOTROPHIC LATERAL SCLEROSIS

Jieying Wu[a,b], Can Sun[a], Yingsheng Xu[a], Dongsheng Fan[a,c,d,*], Shan Ye[a,c,d,*]
[a] *Department of Neurology, Peking University Third Hospital, Beijing 100191, China*
[b] *Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, 100053, China*
[c] *Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing 100191, China*
[d] *Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing 100091, China*
* *Contributed equally as a co-corresponding author.*

## ABSTRACT

**INTRODUCTION:**
Mirror movements are often overlooked in amyotrophic lateral sclerosis (ALS) patients. Although the contralateral co-movement (COMO) test can be used to evaluate mirror movements in ALS patients, it lacks a systematic evaluation. The aim of this study was to validate the effectiveness of the Chinese version of the COMO test in a Chinese ALS population.

**METHODS:**
We prospectively enrolled 173 ALS patients as the disease group and 28 healthy individuals as controls. All participants were evaluated via the Chinese version of the COMO test. Univariate analysis and multiple linear regression were used to compare differences between groups. Subgroup analysis of the COMO scores was performed on the basis of different disease characteristics.

**RESULTS:**
The COMO score in the ALS group was significantly greater (5.00% [1.67-10.00]) than that in the healthy control group (1.67% [0.00-3.33]). After adjusting for confounders, this difference remained significant. Multivariate linear analysis suggested that the upper motor neuron (UMN) score independently predicted the COMO score ($P$<0.001). The COMO score was not affected by different onset regions or lateralizations. Propensity score matching revealed no significant difference in COMO scores between uninvolved limb segments and the corresponding limb segments in other patients. The Cronbach α of the Chinese COMO test was 0.621.

**CONCLUSION:**
The Chinese COMO test can serve as a potential tool for assessing mirror movements in Chinese ALS patients. The UMN score is a factor influencing the COMO score. The COMO test can provide objective evidence for ALS characteristics and the severity of UMN damage.

**KEYWORDS:**
Amyotrophic lateral sclerosis; Contralateral Co-Movement test; Mirror movement; Chinese version

Clinical

*C-P-CN&I013*

# CORNEAL CONFOCAL MICROSCOPY CHANGES PREDICT DISEASE PROGRESSION OF ALS

[1]Zou, Zhangyu; [1]Wen, Yunqin; [1]Chen, Sheng; [1]Liu, Changyun
[1]Department of Neurology, Fujian Medical University Union Hospital, No. 29, Xinquan Road, Fuzhou, China

## INTRODUCTION:

The present study endeavors to quantitatively analyze corneal nerve fibers via corneal confocal microscope (CCM), appraise small fiber neuropathy in amyotrophic lateral sclerosis (ALS) patients, probe its association with sensory abnormalities, skin sympathetic response (SSR), and heart rate variability (HRV), and assess its clinical utility in gauging the disease progression of ALS.

## METHODS:

Fifty-four ALS patients and twenty-six healthy controls were included. All participants underwent a CCM examination. Four high-definition images from different quadrants for each side eye were randomly selected as pictures of the corneal sub-epithelial nerve. Accmetrics automated software was used to analyze corneal nerve fiber parameters.

## RESULTS:

Corneal nerve fiber density (CNFD) and corneal nerve fiber length (CNFL) were significantly lower, while nerve fiber tortuosity (NFT) was significantly higher in the ALS group than those in the control group ($P<0.05$).

ALS patients with subjective sensory abnormalities had significantly lower CNFD, corneal nerve branch density (CNBD) and CNFL compared to those without subjective sensory abnormalities ($P<0.05$). When using CNFD to identify ALS patients with subjective sensory abnormalities, the area under the curve (AUC) was 0.769 (95% CI 0.616-0.923).

Multivariate regression analysis revealed that CNBD/CNFD and serum neurofilament light chain (NfL) were independent predictors of rapid disease progression of ALS. We constructed a nomogram model based on the aforementioned predictor factors, which possesses good predictive performance.

## CONCLUSION:

Our study substantiates the presence of small fiber neuropathy in ALS patients. CCM parameters, particularly CNFD, might potentially serve as biomarkers for identifying ALS with sensory impairment. Moreover, the study uncovers that serum NfL and CNBD/CNFD are independent predictors of rapid disease progression in ALS.

## REFERENCES:

1. Fu et al., Small fiber neuropathy for assessment of disease severity in amyotrophic lateral sclerosis: corneal confocal microscopy findings. Orphanet J Rare Dis, 2022;17(1): 7.
2. Ferrari et al., Corneal confocal microscopy reveals trigeminal small sensory fiber neuropathy in amyotrophic lateral sclerosis. Front Aging Neurosci, 2014;6: 278.
3. Wang et al., Corneal confocal microscopy detects small-fiber neuropathy in patients with amyotrophic lateral sclerosis. Zhonghua Nei Ke Za Zhi, 2022;61(1): 77-81.

Clinical

*C-P-CT&P001*

# QRL-101 – PHASE 1 STUDIES EVALUATING SAFETY AND PHARMACODYNAMICS OF A KCNQ2/3 MODULATOR IN HEALTHY VOLUNTEERS & NEXT STEPS FOR DEVELOPMENT IN ALS

Angela Genge[1], Thomas S Bowman[1], Hannah Kaneb[1], Samantha Rubino[1], Taylor Gray [1], Sharon Lu[1], Amit Jain[1], Guzide Adhikari[1], Sandy Hinckley[1], Daniel Elbaum[1], Emma Bowden[1]
[1]QurAlis, Cambridge Massachusetts, United States

## INTRODUCTION

In people living with ALS, evidence of increased cellular excitability in peripheral and central motor neurons has been observed through advanced neurophysiological, imaging, and biochemical techniques; hyperexcitability has also been associated with decreased longevity [1,2,3]. Preclinical studies in models of ALS indicate QRL-101, a potent, selective KCNQ2/3 channel positive allosteric modulator, may be effective in reducing motor system hyperexcitability. Phase 1 studies with QRL-101 utilizing electrophysiological markers were conducted to validate target engagement and evaluate the suitability of this motor neuron excitability modulator for continued development in the ALS patient population.

## METHODS

Phase 1 studies supporting early development of QRL-101 have been completed in healthy volunteers: QRL-101-01 (single ascending dose), QRL-101-03 (multiple ascending dose), and QRL-101-05 (PK-PD). Study QRL-101-04 to evaluate PK-PD in ALS patients is also underway.

## RESULTS

QRL-101 was found to be generally safe and well tolerated. As of 28 November 2024, no serious adverse events have been reported. The dose levels assessed resulted in exposure levels that exceed those anticipated to be required for target engagement. The electrophysiology endpoints utilized allowed assessment of the potential PK-PD relationship for QRL-101.

## CONCLUSIONS

Results of these studies support initiation of a Phase 2 POC study in ALS, planned for the near future. A safe and tolerable dose range has been determined.

Reducing motor system hyperexcitability is a potential therapeutic strategy in ALS. Electrophysiology endpoint results support continued use of these measures as markers of target engagement. These studies have used an operational framework of fit-for-purpose, exploratory electrophysiology endpoints. These endpoints may be scalable to other, larger, multi-center, global clinical trials. Findings from these studies will be used to advance the development of QRL-101 in ALS and other neurodegenerative diseases.

## REFERENCES

1. Shibuya K, Otani R, Suzuki YI, Kuwabara S, Kiernan MC. Neuronal Hyperexcitability and Free Radical Toxicity in Amyotrophic Lateral Sclerosis: Established and Future Targets. *Pharmaceuticals (Basel).* 2022 Mar 31;15(4):433. doi: 10.3390/ph15040433.
2. Wainger BJ, Kiskinis E, Mellin C, et al. Intrinsic membrane hyperexcitability of ALS patient-derived motor neurons. *Cell Rep.* 2014;7(1): 1-11.doi:10.1016/j.celrep.2014.03.019.
3. Kanai K, Shibuya K, Sato Y, Misawa S, Nasu S, Sekiguchi Y, Mitsuma S, Isose S, Fujimaki Y, Ohmori S, Koga S, Kuwabara S. Motor axonal excitability properties are strong predictors for survival in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2012 Jul;83(7):734-8. doi: 10.1136/jnnp-2011-301782.

Clinical

*C-P-CT&P002*

# PACTALS CLINICAL TRIAL READINESS – A SURVEY ON THE CURRENT STATE OF PLAY IN MEMBER COUNTRIES

[1]Fung WY, [2]Agustini S, [3]Nalini A, [4]Ohnmar O, [5]Fan DS, [6]Hoang NTT, [7]Hu CJ, [8]Kano O, [9]Kulkantrakorn K, [10]Ng K, [11]Prado M, [12]Remli R, [13]Son BG, [14]Sung JJ, [15]Vucic S, [16]Ngo S, [17]Talman P, [18]Kiernan M, [13]Kim SH, [19]Sobue G, [20]Shahrizaila N on behalf of PACTALS

[1]PACTALS, [2]Department of Neurology, Mayapada Hospital, Indonesia, [3]National Institute of Mental Health and Neuro Science, [4]Yangon General Hospital, [5]Peking University Third Hospital, [6]Department of Neurology, Military Hospital 175, [7]Taipei Medical University, [8]Toho University, [9]Thammasat University, [10]National University Hospital, Singapore, [11]College of Medicine, University of the Philippines Manila, [12]Universiti Kebangsaan Malaysia, [13]Hanyang University Hospital, [14]Seoul National University Hospital, [15]University of Sydney, [16]University of Queensland, [17]Deakin University, [18]Neuroscience Research Australia, [19]Aichi Medical University, [20]Universiti Malaya

## INTRODUCTION:

The Pan-Asian Consortium for Treatment and Research in ALS (PACTALS) was established to provide a platform for effective collaborations in achieving similar standards of care, treatment and research in the region. The current study aims to identify the clinical trial readiness of PACTALS member countries.

## METHODS:

28 representatives from 13 member countries were invited to participate in an online survey to determine their existing research capabilities focusing on the establishment of ALS disease registers.

## RESULTS:

Responses were received from 17/28 (61%) with at least one response from every PACTALS member country. 10/13 countries (77%) had an ALS patient registry, 40% national (Australia, China, Philippines, Japan) and 60% institutional registries. The top two challenges in establishing a disease registry were limitations in technical infrastructure and trained personnel. Data quality and consistency, along with funding constraints were identified as the top challenges in maintaining a registry. All respondents were keen to collaborate, particularly in studies on disease management and disease stratification as well as participation in clinical trials. However, there were limitations in data sharing capabilities. The top barriers identified were local data protection laws and limited technical infrastructure for secure data transfer, with 35% also highlighting political or institutional resistance.

## CONCLUSION:

There are variations in the clinical-trial readiness and availability of disease registers amongst the PACTALS member countries. Mentorship programmes and inclusive collaborative research are some of the measures that might help overcome the barriers in achieving equity in ALS care and research in the Asia-Pacific region.

## REFERENCES:

1. Shahrizaila, N. et al., Amyotrophic lateral sclerosis and motor neuron syndromes in Asia. Journal of Neurology, Neurosurgery & Psychiatry 87.8 (2016) 821-830

Clinical

*C-P-CT&P003*

# CLINICAL TRIAL INVOLVEMENT AS A POTENTIAL SURVIVAL MODIFIER IN MOTOR NEURONE DISEASE

Hannah C. Timmins1, Srestha Mazumder1, Dayna-Lee Talbot1, Paris M. Murphy1, Jasmine F. Ashhurst1, Eleanor Ramsey1, Matthew C. Kiernan 1

1. Neuroscience Research Australia, Sydney, Australia.
2. University of New South Wales, Sydney, Australia..

## INTRODUCTION:

Due to the complex pathophysiology of motor neurone diseases (MND), effective treatment strategies likely require the use of novel compounds working synergistically[1]. Clinical trials are critical in the translation of novel therapies into clinical care practice; however, they may also form an integral part of immediate care plans. Given the dearth of therapeutic options and potential benefits, this study aimed to evaluate if participation in clinical trials improves survival outcomes.

## METHODS:

A total of 63 patients (Age: 64.7± 1.4) with a diagnosis of MND (Limb onset: 66.7%) were included in the analysis. Diagnosis was established using the Gold Coast criteria, with confirmation occurring 11.5 ± 1.1 months after symptom onset. Mean survival from symptom onset was compared between those enrolled in a clinical trial and those who did not participate using Kaplan–Meier Survival Analysis. Fisher's exact test and independent samples t- tests were used to examine factors effecting clinical trial enrolment. Results are presented as mean ± standard error.

## RESULTS:

The mean survival for the cohort was 36.5±2.1 months. Patients enrolled in clinical trials had a significantly longer survival duration (39.7±3.1 months) compared to those who did not participate (32.3±2.5months, ($\chi^2$ (1) = 4.141, p = 0.042). Those who took part in clinical trials did not differ significantly in site of onset or age from those who did not participate.

## CONCLUSION:

Patients enrolled in trials demonstrated prolonged survival compared to those who did not participate. Given the limited therapeutic options for MND, clinical trial involvement may play a role in improving patient outcomes and should be considered as part of comprehensive disease management strategies.

## REFERENCES:

1. Kiernan MC et al., Improving clinical trial outcomes in amyotrophic lateral sclerosis. Nature reviews Neurology. 2021

Clinical

*C-P-CT&P004*

# TETRAMETHYLPYRAZINE NITRONE IN AMYOTROPHIC LATERAL SCLEROSIS: A RANDOMIZED CLINICAL TRIAL

Xiaolu Liu, MD[1,2,3]; Huifang Shang, MD[4]; Qianqian Wei, MD[4]; Xiaoli Yao, MD, PhD[5]; Ling Lian, MD[5]; Jingxia Dang, MD[6]; Rui Jia, MD[6]; Zhiying Wu, MD, PhD[7]; Hongfu Li, MD, PhD[7]; Qi Niu, MD[8]; Xi Cheng, MD[8]; Zhangyu Zou, MD, PhD[9]; Sheng Chen, MD, PhD[9]; Min Zhang, MD, PhD[10]; Yang Liu, MD, PhD[10]; Yaling Liu, MD[11]; Qi Liu, MD[11]; Xusheng Huang, MD, PhD[12]; Hongfen Wang, MD[12]; Honglin Feng, MD[13]; Shuyu Wang, MD[13]; Dongsheng Fan, MD, PhD[1,2,3]

[1] Department of Neurology, Peking University Third Hospital, Beijing, China;

[2] Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China;

[3] Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China;

[4] Department of Neurology, West China Hospital, Sichuan University, Sichuan, China;

[5] Department of Neurology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;

[6] Department of Neurology, The First Affiliated Hospital of Xi'an Jiaotong University, Xian, China;

[7] Department of Neurology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China;

[8] Department of Neurology, Jiangsu Province Hospital, Nanjing, China;

[9] Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, China;

[10] Department of Neurology, Tongji Hospital, Tongji Medical College of HUST, Wuhan, China;

[11] Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang, China;

[12] Department of Neurology, Chinese PLA General Hospital, Beijing, China;

[13] Department of Neurology, The First Affiliated Hospital of Harbin Medical University, Harbin, China;

**INTRODUCTION:**

Despite the approval of four medicines by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis (ALS), there remains notable unmet clinical demand. Tetramethylpyrazine nitrone (TBN), a multifunctional neuroprotective agent, has exhibited promising results in ameliorating motor dysfunction and enhancing cognition in preclinical models of various neurodegenerative diseases, including ALS. The objective of this study was to evaluate the safety and efficacy of orally administered TBN in patients with ALS.

**METHODS:**

The phase 2 study is a multi-center, randomized, double-blind and placebo-controlled trial conducted at 11 hospitals in China. Patients were diagnosed with definite or probable ALS based on the revised El Escorial criteria. Eligible patients were aged 45-70 years with an ALS onset for no more than 2 years, achieved scores of at least 2 on each item of the Revised ALS Functional Rating Scale (ALSFRS-R) score, and had a forced vital capacity (FVC) of at least 80%. Additionally, eligible patients also experienced a decrease of 1-4 points in the ALSFRS-R score during a 3-month screening period. Those who met all the criteria were then randomly assigned 1:1:1 to a low-dose TBN group, high-dose TBN group, or placebo group. The primary efficacy endpoint was the change in ALSFRS-R score from the baseline to 180 days. The secondary endpoints included the change in FVC, grip strength, ALS Assessment Questionnaire-40 (ALSAQ-40) results, and the proportion of endpoint events during the 180 days. Both the primary and secondary endpoints were analyzed in the full analysis set (FAS). Safety evaluations were performed on all patients who received at least one dose of the study drug and underwent at least one assessment after baseline. This study has been registered with the Chinese Clinical Trial Registration Center (ChiCTR2000039689).

**RESULTS**:

A total of 155 patients (mean [SD] age, 55.0 [6.5] years; 115 men [74.2%]) were randomized (51 [32.9%] to the low-dose tetramethylpyrazine nitrone group, 52 [33.6%] to the highdose tetramethylpyrazine nitrone group, and 52 [33.6%] to the placebo group). No significant differences were observed in ALSFRS-R score changes between low-dose tetramethylpyrazine nitrone (least squares [LS] mean difference, −0.89 points; 95% CI −3.25 to 1.48 points) and high-dose tetramethylpyrazine nitrone (LS mean difference, −0.20 points; 95% CI −2.48 to 2.07 points) compared with placebo. High-dose tetramethylpyrazine nitrone showed a significantly slower decline in grip strength at day 180 (LS mean difference, 2.46 kg; 95% CI, 0.15-4.76 kg). In a subgroup of patients younger than 65 years with slower disease progression, tetramethylpyrazine nitrone significantly attenuated the decline in grip strength (LS mean difference, 3.63 kg; 95% CI, 0.84-6.41 kg), bulbar scores (LS mean difference, 0.66 points; 95% CI, 0.03-1.29 points), and respiratory scores (LS mean difference, 0.54 points; 95% CI, 0.03-1.06 points). Adverse events were mostly mild or moderate, with no severe treatment-related adverse events or deaths.

**CONCLUSION:**

This randomized clinical trial demonstrates that tetramethylpyrazine nitrone is safe and well-tolerated in patients with ALS. There was no difference in the primary end point across the low-dose, high-dose, and placebo groups, with significant benefits in a subgroup of younger patients with slower disease progression.

**REFERENCES:**

1. Lin J, Wang Q, Zhou S, Xu S, Yao K. Tetramethylpyrazine: a review on its mechanisms and functions. Biomed Pharmacother. 2022;150:113005

Clinical

*C-P-CT&P005*

# TASKFORCE-LED GLOBAL EFFORT: OPTIMIZING ALS/MND CLINICAL TRIAL ENDPOINTS

[1]de Majo Martina, [2]Van Damme Philip, [3]Dave Kuldip, [4]van Eijk Ruben, [5]Sheean Bec, [6]Fournier Christina Nicole, [1]Kaya Alper, [1]Robinson Michael, [1]Ocampo Felipe, [7]Genge Angela, [1]Green Phil, [1]Cummings Cathy

[1] International Alliance of ALS/MND Association, Francis Crick House, 6 Summerhouse Road, Moulton Park, Northampton NN3 6BJ. UK. 2Experimental Neurology and Leuven Institute for Neurodegenerative Disorders (LIND), University of Leuven, Leuven, Belgium. 3 The ALS Association, Arlington, VA, USA. 4 Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands. 5 FightMND, Melbourne, Australia. 6Department of Neurology, Emory University, Atlanta, GA, USA.7Clinical Research and ALS Clinic, Montreal Neurological Institute and Hospital, Montreal, Canada.

## INTRODUCTION:

The International Alliance of ALS/MND associations is a global network of amyotrophic lateral sclerosis (ALS) and Motor Neuron Disease (MND) associations informed by people living with ALS (PALS) and their caregivers (CALS). In ALS/MND most clinical trials testing new therapies generated negative results, and most available treatments only marginally slow disease progression(1). Recommendations to improve ALS/MND trial protocols have been proposed by expert panels and regulatory agencies, including the adoption of more accurate endpoints(2). Today, there is no consensus for which set of outcome measures should be used in ALS/MND trials(3).

## METHODS:

The Alliance is driving a global multi-stakeholders taskforce to facilitate discussion on outcome measures for ALS/MND trials. ALS/MND clinical trials ran in the last 5 years were reviewed and a 13-question survey was conducted to collect direct input from sponsors on their current and preferred selection of endpoints.

## RESULTS:

We sent our survey to 35 industry sponsors that were either running or planning to run an ALS/MND trial, receiving 18 responses. We found that, excluding safety and tolerability measures, the ALS functional rating scale (ALSFRS) and the combined assessed function survival (CAFS) score were the most used primary endpoints respectively in literature and across survey responses. For secondary and exploratory measures, slow vital capacity (SVC) and Neurofilament Light Chain (NfL), respectively, were the most popular among industry respondents. When asked to rank the endpoints according to their importance, respondents chose ALSFRS and survival as the most relevant secondary endpoints and biomarkers as the most important exploratory measures. Most respondents declared that they wished they could use NfL as their primary endpoint but were unable to because of regulatory requirements and insufficient validation.

## CONCLUSION:

Excluding safety and tolerability, the most used primary endpoints in our sample are ALSFRS and survival primarily because of their acceptance by regulators.

## REFERENCES:

1.Petrov, et al., Front Aging Neurosci (2017).
2.Longinetti, & Fang, Current Opinion in Neurology (2019).
3.Zahir, F. et al. Quality of Life Research (2023).

Clinical

*C-P-CT&P006*

# EVALUATION OF NUN-004, A NOVEL ENGINEERED EPHRIN ANTAGONIST, IN HEALTHY VOLUNTEERS AND PATIENTS WITH ALS: A PHASE I/IB, OPEN-LABEL, ESCALATING DOSE AND EXTENDED ACCESS STUDY

Michael Gerometta[1] · Robert D. Henderson[2] · Richard Friend[3]· Leanne T. Cooper[1] · Jing Zhao[1] · Andrew W. Boyd[4] · Perry F. Bartlett[1]

[1] Queensland Brain Institute, University of Queensland, St Lucia, Brisbane, QLD 4072, Australia

[2] UQ Centre for Clinical Research, Royal Brisbane and Women's Hospital Campus, Herston, QLD 4029, Australia

[3] Nucleus Network, Clive Berghofer Cancer Research Centre, Herston, QLD 4006, Australia

[4] School of Medicine, University of Queensland, St Lucia, Brisbane, QLD 4072, Australia

## ABSTRACT

### INTRODUCTION:

Erythropoietin-producing hepatocellular carcinoma A4 (EphA4) is implicated in the pathophysiology of amyotrophic lateral sclerosis (ALS). EphA4 fusion protein (EphA4-Fc) inhibits EphA4 function *in vivo* but is too short-lived for prolonged therapy. NUN-004 (mEphA4-Fc) is a modified EphA4-Fc engineered for an extended half-life and has completed a first-in-human phase I/Ib study. The objective was to assess the safety, tolerability, pharmacokinetics, immunogenicity and efficacy of NUN-004 in healthy volunteers and patients with ALS.

### REPORT:

In this open-label study, Part 1 enrolled 20 healthy volunteers in five single ascending dose cohorts (1, 3, 10, 20 and 30 mg/kg), followed by Part 2, which enrolled eight patients with ALS in two multiple ascending dose cohorts (cycle 1: 15 and 30 mg/kg) who could continue into an extended access phase (cycles 2 – 6: 15 mg/kg) for a total of 6 months' treatment. All participants received intravenous NUN-004; multiple dosing was administered weekly in 28-day cycles. Primary endpoints included safety assessments, single- and multiple-dose pharmacokinetics, and anti-drug antibodies. Efficacy assessments were Amyotrophic Lateral Sclerosis Function Rating Score Revised (ALSFRS-R) and forced vital capacity.

NUN-004 was well tolerated, with no serious adverse events or discontinuations. NUN-004 exposure generally increased with dose. Single-dose half-life was 111.7 (± 22.8) h in healthy volunteers ($n$ = 20) and 74.4 (± 19.4) h in patients ($n$ = 6). Steady state was observed in patients by day 8. No antibody response was observed.

ALSFRS-R showed a slight improvement (+0.09 points/month) to cycle 4 and a slight decline (−0.35 points/month) over the whole study. Forced vital capacity trends were consistent with ALSFRS-R.

### CONCLUSION:

This study supports the safety, tolerability and extended half-life of NUN-004, and provides preliminary evidence for its ability to ameliorate disease progression in an ALS cohort.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Clinical

*C-P-CT&P007*

# THE IMPACT OF DIAGNOSTIC DELAYS ON CLINICAL TRIAL ELIGIBLITY IN AMYOTROPHIC LATERAL SCLEROSIS

Paris M. Murphy[1], Hannah C. Timmins[1], Srestha Mazumder[1], Dayna-Lee Talbot[1], Jasmine F. Ashhurst[1], Eleanor Ramsey[1], Matthew C. Kiernan[1,2]

[1]Neuroscience Research Australia, Sydney, Australia, [2]University of New South Wales, Sydney, Australia

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive and terminal neurodegenerative disorder with limited treatment options, highlighting the critical need for clinical trials to identify effective therapeutics. However, clinical trials rely on stringent eligibility criteria to ensure the selection of appropriate candidates. Unfortunately, diagnostic delays can pose significant barriers to patient inclusion, often resulting in patients surpassing the clinical thresholds for trial participation. Consequently, the aim of this study was to quantify the proportion of patients deemed ineligible for clinical trials upon reaching specialised clinics.

## METHODS:

Data was sourced from ALS patients at their initial appointment at a specialised MND clinic, from 2023 to 2024, via the MiNDAUS national registry. Following a comprehensive review of recent clinical trials conducted in Australia, patients were assessed on their ability to meet common eligibility criteria, including a progression rate of ≥0.5, respiratory vital capacity of ≥60%, symptom duration of ≤24 months and the absence of the end point criteria of non-invasive ventilation (NIV) or percutaneous endoscopic gastrostomy (PEG).

## RESULTS:

Data was collected from 47 ALS patients (Age: 61.6 ± 11.4 years, Male: 76.6%) who were diagnosed 12.5 ± 10 months after initial symptoms. Disease onset was categorised into lumbar (55.3%), cervical (23.4%) and bulbar (21.3%). The mean ALSFRS was 36.2 ± 6.8, indicating mild to moderate impairment. A total of 42.5% of patients were ineligible for clinical trials, 25.5% due progression rate, 14.6% from inadequate respiratory vital capacity, 19.1% from prolonged symptom duration and 12.7% from reaching end points.

## CONCLUSION:

A substantial proportion of patients were deemed ineligible for clinical trials, underscoring the critical need for improvements in early diagnosis to enhance access to clinical trials. By addressing these barriers, we may increase the potential for patients to benefit from emerging therapies and improve the overall success of clinical research in ALS.

Clinical

*C-P-CT&P008*

# INVESTIGATION OF THE EFFECT OF TOFERSEN IN A JAPANESE FAMILIAL ALS PATIENT WITH SOD1 MUTATION

[1,2]Nagano S; [1]Nagashima N; [1]Fujioka T; [1]Kihara K; [1]Ogawa K; [1]Okuno T; [1]Mochizuki H

[1]Department of Neurology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka, Japan, [2]Department of Neuro-developmental and -degenerative Disease Research, United Graduate School of Child Development, Osaka University, 2-2 Yamadaoka, Suita, Osaka, Japan.

## INTRODUCTION:

There is no established curative treatment for amyotrophic lateral sclerosis (ALS). Familial ALS accounts for approximately 5-10% of all ALS cases, and more than 30 different causative genes have been reported. In April 2023, Tofersen, an antisense oligonucleotide against SOD1, was approved in the United States for the treatment of familial ALS with SOD1 mutations (SOD1-ALS). We examined the course of an SOD1-ALS patient treated with Tofersen at our hospital, in comparison with the natural history of other SOD1-ALS patients.

## METHODS:

Muscle strength and daily functioning were evaluated with a hand-held dynamometer (HHD) and the ALS Functional Rating Scale- Revised (ALSFRS-R) in an SOD1-ALS patient (39 years old at onset, male) who received intrathecal Tofersen injection since April 2020. The clinical course was also compared with two other SOD1-ALS patients with the same mutation (L127S) who had not received Tofersen (Case 1: male, 69 years old at onset; Case 2: male, 61 years old at onset).

## RESULTS:

In the patient who received Tofersen, there was improvement in ALSFRS-R from the start of treatment, and no significant worsening in HHD. On the other hand, in Case 1 patient who did not receive Tofersen, upper limb muscle weakness appeared 4 years after onset, and the patient died of respiratory failure 6 years after onset. In Case 2 patient of untreated ALS, bulbar symptoms appeared 3 years after onset, upper limb muscle weakness appeared 4 years later, respiratory muscle paralysis appeared 10 years later, and the patient died 12 years after onset. These results suggest that while muscle weakness progresses in SOD1-ALS as well as sporadic ALS in 4 to 5 years after onset, the progression is clearly delayed in the Tofersen-treated case.

## CONCLUSION:

Tofersen may contribute to the inhibition of progression of SOD1-ALS. Further studies are needed.

## REFERENCES:

1. Miller et al., Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med 387, 1099-1110, 2022.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

Clinical
*C-P-CT&P009*

# FINAL RESULTS FROM THE PHASE 3 VALOR TRIAL AND OPEN-LABEL EXTENSION EVALUATING EFFICACY AND SAFETY OF TOFERSEN IN ADULTS WITH SOD1-ALS

[1]Miller, TM; [2,3]Sobue G; [4]Cudkowicz ME; [5,6]Shaw PJ; [7]Genge A; [8]Graham D; [8]Sun P; [9]McNeill M; [8]Malek S; [8]Inra J; [8]Garafalo S; [8]Fradette S, on behalf of the VALOR and OLE Working Group

[1]Department of Neurology, Neuromuscular Medicine, Washington University School of Medicine, Saint Louis, MO, USA; [2]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Aichi Medical University, Aichi, Japan; [4]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [5]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK; [6]National Institute for Health and Care Research (NIHR) Sheffield Biomedical Research Centre and NIHR Clinical Research Facility, University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [7]Department of Neurology and Neurosurgery, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada; [8]Biogen, Cambridge, MA, USA; [9]Biogen, Maidenhead, UK.

## INTRODUCTION:

Tofersen, the first approved therapy for *SOD1*-ALS, was evaluated in the Phase 3, randomized, double-blind, placebo-controlled VALOR trial over 28 weeks. At trial conclusion, participants could enroll in an OLE study.

## METHODS:

Integrated analyses of VALOR and the OLE were prospectively planned for comparison of early-start versus placebo/delayed-start tofersen (~6 months later). Key efficacy endpoints included measures of axonal injury and neurodegeneration (neurofilament light chain [NfL]), function and strength (ALSFRS-R, SVC, HHD), survival (event-free survival [EFS] and overall survival), and quality of life (QoL). The OLE completed in August 2024, ~5.5 years after VALOR began.

## RESULTS:

VALOR enrolled 108 participants (tofersen 100 mg, n=72; placebo, n=36). 95/108 (88%) participants transitioned to the OLE. At OLE completion, participants had the opportunity for ≥3.5 years follow-up from the start of VALOR (median opportunity for follow-up: 4.8 years). 46/108 participants completed the OLE (early-start, 34/72 [47%]; placebo/delayed-start, 12/36 [33%]). Tofersen led to sustained NfL reductions over time, consistent with slowing of neurodegeneration. Over 148 weeks, early- vs placebo/delayed-start tofersen led to lower declines in clinical function, respiratory and strength, and QoL. A subset of participants in each group (10.7-17.3% vs. 21-27.3%) exhibited improvement in function and strength, with a higher proportion in the early start group.

Early-start tofersen was also associated with a lower risk of death or permanent ventilation compared to the placebo/delayed-start group. In the faster-progressing subgroup (defined by median plasma NfL level at baseline), EFS was extended ~3.4 years with early- vs. placebo/delayed-start group (Cox hazard ratio: 0·47 [95% CI: 0.186, 1.183]). Most AEs were

consistent with ALS disease progression or known side effects of lumbar puncture. Nine participants (8.7%) had a total of 10 serious neurologic AEs. No new safety concerns were identified.

## CONCLUSION:

Final data from VALOR/OLE highlight the long-term effects of tofersen in adults with *SOD1*-ALS.

Clinical

*C-P-CT&P010*

# FIRST-IN-HUMAN STUDY DESIGN TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ASCENDING DOSES OF ALN-SOD IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AND SOD1 VARIANTS

[1] Lee, Yi-Chung; [2]Levy, Oren; [2]Pham, Ly; [2]Miller, Jutta; [3]Sostelly, Alexandre; [2]Banerjee, Poulabi; [2]Tong, Zhentao; [2]Rosario, Maria; [2]Mahmood, Adnan; [2]Harari, Olivier

[1]Taipei Veterans General Hospital, Taipei City, Taiwan, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, [3]Alnylam Pharmaceuticals, Cambridge, MA, USA.

## INTRODUCTION:

Mutations in the superoxide dismutase 1 (*SOD1*) gene account for 15–30% of familial and 1–2% of sporadic amyotrophic lateral sclerosis (ALS) cases. ALN-SOD is an investigational, intrathecally administered, RNA interference therapeutic that targets SOD1 mRNA, utilizing a novel platform that results in robust and prolonged knockdown of targeted transcripts. Here we describe the design of a first-in-human (FIH) trial to evaluate ALN-SOD in participants with SOD1-ALS.

## REPORT:

The phase 1 study (NCT06351592) will consist of a ~2-year treatment period (incorporating a 4-week placebo-controlled phase and 96-week open-label phase), and a 24-week safety follow-up period. Participants will be assigned to one of three ascending dose cohorts, with an optional fourth cohort to explore an additional dosing regimen. The first 3–6 participants in each cohort will enter into a 4-week double- blind, placebo-controlled crossover phase; participants will receive ALN-SOD on Day 1 and placebo on Day 29, or vice-versa. Once participants have been followed for ≥12 weeks, review of emerging data will determine dose escalation. Within-patient dose escalation will be permitted in Cohort 1 if there is inadequate cerebrospinal fluid (CSF) SOD1 knockdown. Once a dose level clears safety review, a cohort may be further expanded up to 15 participants. All participants will continue into the open-label phase of the treatment period, during which they will receive repeated dosing of ALN-SOD for 96 weeks. The interval between multiple dosing will be adapted based on emerging SOD1 data and applied to subsequently enrolled participants.

The frequency of lumbar punctures for CSF sampling will taper over time, going from approximately every 4 weeks for the first few months, to approximately every 12 weeks during the second year of treatment.

## CONCLUSION:

Findings from this FIH study will guide the selection of ALN-SOD dosing regimens for assessment in the subsequent clinical development program.

## ORIGINAL PRESENTATION:

Motor Neurone Disease Association (MNDA) 35th International Symposium 2024; poster presentation #CLT-07.

Clinical
*C-P-DS/S001*

# PROGNOSTIC FACTORS IN PATIENTS WITH MOTOR NEURON DISEASE: A SINGLE CENTRE STUDY

Mei Lian Goh[1], Su Rong Fam[1], Si Yan Leo[1], Carlyne Li[3], Ian Xu[4], Mavis Ang[2], Josiah Chai[2]

1. Department of Nursing, National Neuroscience Institute, Singapore.
2. Department of Neurology, National Neuroscience Institute, Singapore.
3. Lee Kong Chian School of Medicine, National Technological University, Singapore.
4. Duke-NUS Medical School, Singapore.

## BACKGROUND

Motor Neuron Disease (MND) is a progressive neurodegenerative disorder with variable clinical phenotypes and survival. Identifying prognostic factors is crucial for patient management and clinical decision-making. This study aims to investigate prognostic factors associated with survival in MND patients.

## METHODOLOGY

A retrospective review was conducted on deceased MND patients at the National Neuroscience Institute (NNI) from 2018 to 2024. Data on demographics, clinical features, time to various clinical milestones, progression rate, mobility status, ventilatory and nutritional support, as well as treatment were analyzed. To identify prognostic factors, patients were stratified into 3 groups based on survival duration (symptom onset to death): short $< 3$ years, normal $3 - 5$ years and long $> 5$ years.

## RESULTS

Of the 31 deceased MND patients, 71.0% were male and 29.0% were female. The mean and median age at presentation were 56.7 and 57.9 years respectively (range from 37.9 to 74.7). Limb onset MND contributed to 80.7% of patients, whereas bulbar onset contributed to 19.3%. The median duration (in months) from symptom onset to diagnosis and various clinical milestones were: Diagnosis – 12; Wheelchair Bound - 30; Non-invasive ventilation (NIV)- 39; Percutaneous Endoscopic Gastrostomy(PEG) - 30; Tracheostomy - 20 ; Bedbound- 43; and Death - 45.

Thirteen (42%) patients are in the normal survival group, whereas 9 (29%) each are found in the short and long survival groups. Subgroup analysis showed statistically significant association between diagnosis delay and time to wheelchair to survival duration. Shorter diagnosis delay was associated with short survival duration. Conversely, longer diagnosis delay (>12 months) was associated with a longer survival. No patients with time to wheelchair >24 months died within 3 years.

## CONCLUSION

Time to diagnosis and time to wheelchair are important prognostic factors in MND patients. Longer diagnostic delay and later onset of wheelchair use are associated with improved survival.

Clinical

*C-P-DS/S002*

# ALS WITH AND WITHOUT UPPER MOTOR NEURON SIGNS: A COMPARATIVE STUDY SUPPORTING THE GOLD COAST CRITERIA

[1†]Hee-Jae Jung, [2†]E-nae Cheong, [1,3]Jungmin So, [2]Yangsean Choi, [1]Eun-Jae Lee, [1]Hyunjin Kim, [1]Young-Min Lim
[1] Department of Neurology, Asan medical center, University of Ulsan, College of Medicine, Seoul, Republic of Korea
[2]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[3] Department of Neurology, Korea University Ansan Hospital, Ansan, Republic of Korea
[†] These authors contributed equally to this work.

## INTRODUCTION:

The Gold Coast criteria enable the diagnosis of amyotrophic lateral sclerosis (ALS) even in the absence of upper motor neuron (UMN) signs, which were previously required.[1, 2] However, it remains unclear whether ALS patients with UMN signs (ALSwUMN) and those without (ALSwoUMN) exhibit similar clinical characteristics and prognosis.

## METHODS:

We enrolled ALS patients diagnosed according to the Gold Coast criteria and classified them into ALSwUMN and ALSwoUMN groups. Clinical data, motor evoked potentials (MEP), serum biomarkers (neurofilament light chain, glial fibrillary acidic protein, and brain-derived neurotrophic factor), and imaging parameters (motor band sign, cortical thickness, and white matter volume) were assessed. Survival analysis was conducted using the Kaplan-Meier method.

## RESULTS:

A total of 51 ALSwUMN and 20 ALSwoUMN patients were included. The two groups exhibited largely comparable clinical and laboratory characteristics. Abnormal MEP findings were more frequent in ALSwUMN than in ALSwoUMN (94.0% vs. 63.2%, $p = 0.017$). The motor band sign scores did not differ significantly. Both groups demonstrated cortical thinning in the precentral and entorhinal regions compared to healthy controls. However, ALSwUMN patients exhibited additional thinning in the lateral orbitofrontal, insular, and temporal pole regions, whereas ALSwoUMN patients showed additional thinning in the pars opercularis. Regarding white matter volume, both groups had reductions in the thalamus, cerebellum, and amygdala. Additionally, ALSwUMN patients exhibited reduced white matter volume in the brainstem. No significant difference in survival was observed between the two groups.

## CONCLUSION:

Although ALSwUMN patients exhibited greater electrophysiological UMN involvement and some variations in cortical thickness and white matter volume, their overall characteristics and prognosis were not significantly different from those of ALSwoUMN patients. These findings support the Gold Coast criteria, which recognize ALSwoUMN as a valid ALS phenotype.

## REFERENCES:

1. Shefner JM, Al-Chalabi A, Baker MR, et al. A proposal for new diagnostic criteria for ALS. Clinical Neurophysiology 2020;131:1975-1978.
2. Turner MR. Diagnosing ALS: the Gold Coast criteria and the role of EMG. Practical Neurology 2022;22:176-178.

Clinical

*C-P-DS/S003*

# MONOCLONAL GAMMOPATHY IN AMYOTROPHIC LATERAL SCLEROSIS: NO IMPACT ON CLINICAL PROGRESSION AND IMMUNOTHERAPY OUTCOMES

Hyunkee Kim[a,b], Ji-Eun Uhm[c], Jinseok Park[a,b], Young sung Kim [a,b], Wonjae Sung [a,b], Sanggon Lee[d], Seung Hyun Kim[a,b] , Ki-Wook Oh[a,b]

[a]*Department of Neurology, Hanyang University College of Medicine, Seoul, Republic of Korea.*
[b]*Cell Therapy Centre, Hanyang University Hospital, Seoul, Republic of Korea*
[c]*Division of Hematology-Oncology, Department of Internal Medicine, Hanyang University College of Medicine, Hanyang University Seoul Hospital, Seoul 04763, Korea*
[d]*Department of Neurology, Chung-Ang University Gwangmyeong Hospital, 110 Deokan-ro, Gwangmyeong 14353, Korea*

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) remains a progressive and fatal disorder with limited treatment options. Monoclonal gammopathy has been reported at a higher prevalence in ALS patients, raising questions about its clinical significance.

## METHODS:

This retrospective study analyzed 2,400 ALS patients at Hanyang University Hospital (2005–2023). Among them, 25 patients with monoclonal gammopathy were identified and compared to ALS patients without it. Clinical characteristics, disease progression rates (ΔFS), and electrophysiological features were analyzed. Immunoglobulin subtypes were examined, and treatment outcomes were evaluated in 9 patients who received immunotherapy.

## RESULTS:

ALS patients with monoclonal gammopathy were older (p=0.009) and predominantly male (p=0.0084). The IgM subtype was associated with slower disease progression (p=0.011) compared to IgA and IgG, though survival was not significantly different. Nerve conduction studies revealed predominantly axonal patterns with no demyelination. Immunotherapy had no significant effect on ΔFS or survival (p=0.91), and disease trajectories remained unchanged before and after treatment.

## CONCLUSION:

Monoclonal gammopathy in ALS patients do not impact disease progression or polyneuropathy risk. While the IgM subtype was linked to a slower decline, it did not confer a therapeutic advantage. Immunotherapy did not alter clinical outcomes. These findings suggest that monoclonal gammopathy may be an incidental finding in ALS and does not warrant targeted treatment.

## REFERENCES:

1. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron D. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. Dec 2000;1(5):293-9. doi:10.1080/146608200300079536
2. Gordon PH, Rowland LP, Younger DS, et al. Lymphoproliferative disorders and motor neuron disease: an update. *Neurology*. Jun 1997;48(6):1671-8. doi:10.1212/wnl.48.6.1671
3. Younger DS, Rowland LP, Latov N, et al. Motor neuron disease and amyotrophic lateral sclerosis: relation of high CSF protein content to paraproteinemia and clinical syndromes. *Neurology*. Apr 1990;40(4):595-9. doi:10.1212/wnl.40.4.595
4. Nobile-Orazio E, Carpo M, Meucci N. Are there immunologically treatable motor neuron diseases? *Amyotroph Lateral Scler Other Motor Neuron Disord*. Mar 2001;2 Suppl 1:S23-30.
5. Patten BM. Neuropathy and motor neuron syndromes associated with plasma cell disease. *Acta Neurol Scand*. Jul 1984;70(1):47-61. doi:10.1111/j.1600-0404.1984.tb00802.x
6. Younger DS, Rowland LP, Latov N, et al. Lymphoma, motor neuron diseases, and amyotrophic lateral sclerosis. *Ann Neurol*. Jan 1991;29(1):78-86. doi:10.1002/ana.410290114

Clinical

*C-P-DS/S004*

# OVERVIEW OF ADULT SPINAL MUSCULAR ATROPHY (SMA) PATIENTS IN A TERTIARY NEUROSCIENCE CENTRE IN SINGAPORE

Si Yan Leo[1], Su Rong Fam[1], Mei Lian Goh[1], Rachel Yzelman[2], Hui Xin Huang[3], Xing Tong Yong[4], Mavis Ang[5], Josiah Chai[5]

1. Department of Nursing, National Neuroscience Institute, Singapore.
2. Department of Physiotherapy, Tan Tock Seng Hospital, Singapore.
3. Department of Occupational Therapist, Tan Tock Seng Hospital, Singapore
4. Department of Speech Therapist, Tan Tock Seng Hospital, Singapore
5. Department of Neurology, National Neuroscience Institute, Singapore

**BACKGROUND:**

SMA is rare in Singapore, with limited data on adult patients. This study aims to provide an overview of adult SMA patients seen at the National Neuroscience Institute (NNI).

**METHODOLOGY:**

Retrospective review was conducted on SMA patients seen in NNI since October 2024. Data on demographics, clinical features, mobility, ventilatory and nutritional support were analysed. For those receiving Risdiplam, Motor Function Measure (MFM)-32, Revised Upper Limb Measure (RULM), 6 Minute Walk Test (6MWT), Voice Handicap Index (VHI)-10, Eating Assessment Tool (EAT)-10, and quality of life (EQ-5D) assessment were included.

**RESULTS:**

We identified 17 adult SMA patients, 12 (70%) were female, and median age 38 years (25-56); 53% were SMA Type 3 and 47 % were Type 2. In SMA type 2, all eight were wheelchair bound. In SMA type 3, five were still walking and 4 were wheelchair bound.

SMA Type 2 had following baseline mean scores: MFM-32 total score - 11%; RULM – 22; EAT10 – 15; VHI10 - 9.5; EQ-5D – 55. Respiratory function measured in 1 patient showed peak cough flow (PCF) 150 L/min and Forced Vital Capacity (FVC) 1.18 Litres.

SMA Type 3 had following baseline mean scores: MFM-32 total score- 42%; RULM – 30; EAT10 - 2.5; VHI10 - 8.5; EQ-5D 74; PCF 145 L/min and FVC 2.8 Litres.

Non-invasive ventilation and cough assist device were used by 5 (29%) and 6 (35%) SMA Type 2 respectively, compared to only 1(5.8%) SMA type 3 using both devices.

Nine (53%) patients (4 SMA Type 2 and 5 SMA Type 3) were on Risdiplam, with improvement in swallowing function, speech and quality of life shown by 3 months of treatment.

**CONCLUSION:**

SMA Type 2 and Type 3 show different baseline in motor, bulbar and respiratory function. Risdiplam treatment demonstrates potential in improving bulbar function and quality of life.

Clinical

*C-P-DS/S005*

# TARGET ALS GLOBAL RESEARCH INITIATIVE (AGRI)

Amy Easton[1], Laura Dugom[1], Judith Chavira[2], Lizzi Neylon[10], Kaycie Opiyo[3] ,Michael Weiss[3], Arleen Matos[4] ,Senda Ajroud-Driss[4], Jingqi Zhu[5] ,James Berry[5], Huy Tran[6] ,Bjorn Oskarsson[6], Nathan Budden[7] ,Cindy Ly[7], Gilbert Gutierrez[8] ,John Ravits[8], Benjamin Hoover[9] , Sarah Griffen[9] ,Matthew Harms[9],Neil Shneider[9], Whitney Dailey[10],Shafeeq Ladha[10], Cassandra Holmes[11],Nicholas Streicher[11], Brent Harris[11], Sarah Berth[12], Frances Aponte[13], Brenda Deliz[13] ,Valerie Wojna[13], Manuela Quiroga Carillo[14] ,Martha Peña[14], Marc Gotkine[15], NortinaShahrizaila[16], Vishnu V Venugopalan[17], Nalini Atchayaram[18], Seok-Jin Choi[19], Jeannine Heckman[20], Marcondes C Franca [21] Manish Raisinghani[1], Robert Bowser[2, 10]

1. Target ALS, New York, New York, USA.
2. Department of Translational Neuroscience, Barrow Neurological Institute, Phoenix, AZ, USA.
3. Department of Neurology, University of Washington, WA, USA.
4. Department of Neurology, Northwestern University, Chicago, IL, USA.
5. Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
6. Department of Neurology, Mayo Clinic Jacksonville, Jacksonville, FL, USA.
7. Department of Neurology, Washington University St. Louis, St. Louis, MO. USA.
8. Department of Neurosciences, University of California, San Diego, San Diego, CA, USA.
9. Department of Neurology, Columbia University Medical Center, New York NY, USA.
10. Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA.
11. Department of Neurology and Pathology, Georgetown University, Washington, DC, USA. 12 Baylor
12. College of Medicine, Waco, TX, USA.
13. University of Puerto Rico, San Juan, Puerto Rico.
14. Instituto Roosevelt, Bogotá, Colombia.
15. Hebrew University, Jerusalem, Israel.
16. University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia
17. All India Institute of Medical Sciences (AIIMS), New Delhi, India
18. National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India
19. Seoul National University Hospital, Seoul, South Korea
20. University of Cape Town, South Africa
21. University of Campinas, Campinas, Brazil

## BACKGROUND:

ALS is a devastating disease of motor neuron degeneration for which the cause is still largely unknown. Target ALS has launched the first global research initiative to identify new genetic and environmental factors impacting disease risk and progression in ALS patients. The initiative encompasses two observational studies: 1) a Global Natural History Study where patients may participate in an in-clinic study for a comprehensive longitudinal clinical characterization of disease progression and 2) an in-community study that enables a one-time study visit to collect environmental, clinical, and genetic data from patients not able to come into clinic. State-of-the-art multi-omic datasets and digital health data are generated from the study and available for mining alongside the clinical and demographic data. Collectively, a rich dataset from at least 6000 patients and 1200 healthy controls will be generated over the next 5 years. Our global research initiative will leverage insights from clinical and genetic variation in patients across ancestral backgrounds to yield a better understanding of the disease.

**METHODS:**

The Natural History Study is a multi-site international study conducted around the world with newest sites just on-boarding in India, Brazil, South Korea, Malaysia, and South Africa. Longitudinal clinical assessments and cognitive measures occur every 4 months in the clinic, along with collection of blood (plasma, serum), urine, and cerebrospinal fluid (CSF). At-home measures of speech and motor function using Aural Analytics or Modality AI platforms and respiratory function using the ZEPHYRx platform are also collected in a subset of study participants. Environmental and occupational history data are collected by questionnaire. ALS participants are followed for up to 20 months and healthy controls are seen at the clinic twice (time 0 and 12 months). Short read (Illumina) and long read (PacBio) sequencing is conducted on blood samples from patients enrolled in the Natural History Study. Proteomics analysis using TMT LC-MS and Neurofilament light analyses (Immunoassay) are generated in collaboration with University of Gottenberg. In- community outreach events have been held in Los Angeles, CA and Phoenix, AZ. Patient- centered events provide educational materials and resources, translated into Spanish, and collect a blood sample by phlebotomy. Blood is shipped to Psomagen (Washington D.C., US) for long read sequencing. The data are uploaded the Target ALS Data Engine in real-time for investigators in industry and academia to mine. The Data Engine is a cloud-based federated technology platform that facilitates metadata analyses with other clinical studies. The protocols are conducted in accordance with ethical standards, including IRB/ IEC approval, adhering to GCP guidelines, and ensuring informed consent is collected from all participants.

**RESULTS:**

To date, 192 participants (82 HC, 99 ALS) have been enrolled in the Global Natural History Study. 24% of ALS participants are known genetic mutation carriers. 86 % of our participants are white, of European descent. Increased enrollment at our international sites is rapidly enriching the diversity of the samples and data we are collecting. Preliminary analysis of ALS-FRS-R scores and digital health data shows disease progression over time in this cohort. Sequencing data, proteomics, Neurofilament light and all metadata from the study can be found in the Target ALS Data Engine. More than 290 investigators already have access to the Data Engine and have been actively working to develop new therapeutics and biomarkers for ALS. The longitudinal biofluid biorepository currently holds 18,000 biofluid vials that can be requested for research. Free access to these samples has reduced a significant barrier to identifying diagnostic and disease biomarkers critical for clinical use. In-community outreach events launched in December 2024 have been successful in educating and enabling patients of diverse races and ethnicities to participate in research. Long read sequencing and associated metadata from 300 patients is anticipated by the end of 2025.

**CONCLUSION:**

AGRI is the first truly global research initiative on ALS. Data from the study is already informing the heterogeneous nature of disease and has allowed for development of novel biomarkers that can predict and track disease progression. We anticipate novel insights from ALS populations outside of the USA will help further our understanding of disease and provide the framework to enable future clinical studies in diverse parts of the world.

Clinical

*C-P-DS/S006*

# MiNDAUS REGISTRY:A PATIENT DATA PLATFORM SUPPORTING MOTOR NEURONE DISEASE CLINICAL CARE, POLICY DEVELOPMENT AND RESEARCH

Steve Vucic[1], Matthew Kiernan[1,2], Susan Mathers[3], Laura Perju-Dumbrava[3], David Schultz[4], Antony Winkel[5], Robert Henderson[6], Merrilee Needham[7], Jessie Chen[8], Lauren Giles[9], Tom Jenkins[10], Dev Nathani[7], Matthew Bellgard[12,13], Samar Aoun[7], Anne Hogden[14], Keith Malpress[14], Geoffrey Thomas[14], Gethin Thomas[14], Clare Sullivan[14], Catherine Hansen[15], Katrina Sangster[16], Lura Ziser[19] Arabelle Douglas[3,18], Paul Talman[16,18]

1. University of Sydney, NSW
2. Neuroscience Research Australia, NSW
3. Calvary Health Care Bethlehem, VIC
4. Flinders Medical Centre, SA
5. Sunshine Coast University Hospital, NSW
6. Royal Brisbane and Women's Hospital, QLD
7. University of Western Australia, WA
8. Launceston General Hospital, TAS
9. Flinders Medical Centre, SA
10. Northern Health, VIC
11. St John of God, WA
12. University of East London, UK
13. Queensland University of Technology, QLD
14. University of New South Wales, NSW
15. MND Australia, ACT
16. Deakin University, VIC
17. MND Australia, ACT
18. Barwon Health, VIC
19. University of Queensland, QLD

Motor neurone disease (MND)/Amyotrophic lateral sclerosis (ALS) impacts over 2700 Australians at any given time. Rare disease patient data has the potential to underpin public health and clinical research, informing health service design and delivery. Its purposeful application provides the ability for prompter diagnosis and patient-centred therapeutic interventions, in addition to supporting new and innovative research anddevelopment. Rare disease data platforms can promote and disseminate knowledge, inform clinical practice and care, identify and recruit clinical trial participants enabling seamless integration of all aspects of care.

The Australian MiNDAUS Partnership has established a person-centred, custom- designed, national MND resource linking patient and clinical data. The MiNDAUS Registry is built upon an open-source digital health platform. It includes the capacity for patients and their carers to record and report personal information and preferences, disease progression and needs in real time, which can be shared with their networks, health professionals and research groups.

The MiNDAUS Registry was launched in 2022, includes 15 MND clinic sites across Australia with 871 registrations (708 living, 165 deceased). Data collected facilitates reporting of, clinical phenotype, survival, serial ALSFRS-R, forced vital capacity/body weight, time to diagnosis and key disease milestones/interventions. The MiNDAUS Registry aims to empower those living with MND to better self-manage and be supported by timely and personalized services. The Platform aims to use data in real- time for clinical management, enrolment in clinical trials, and inform health service delivery and evidence-based policy development.

Clinical

*C-P-DS/S007*

# DETECTION OF CONDUCTION BLOCK MAY HELP DIFFERENTIATING MULTIFOCAL MOTOR NEUROPATHY FROM EARLY-STAGE UPPER-LIMB ONSET AMYOTROPHIC LATERAL SCLEROSIS

[1]Shih-Yu, Fang; [1,2,3]Yi-Chung Lee

[1]Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan, [2]Department of Neurology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan, [3]Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

## INTRODUCTION:

Multifocal motor neuropathy (MMN) is an uncommon neurological condition associated with pure motor symptoms and predilection for upper limb involvement. Differentiation with early-staged amyotrophic lateral sclerosis (ALS), which is crucial because of its treatability with timely usage of intravenous immunoglobulin (IVIG), currently relies on clinical progression, electrophysiological criteria, and detection of anti-GM1 IgM antibodies. Our study aimed to investigate the clinical and biomarkers features of patients with the two diseases.

## METHODS:

We compared the clinical presentations, results of serum and cerebrospinal fluid analysis, and nerve conduction study (NCS) between eight patients diagnosed with definite, probable, or possible MMN, and 153 patients of ALS. Of these, 53 patients with distal-upper-limb onset form ALS were further separated for subgroup comparison, whose initial presentation may mimic MMN. For the interpretation of NCS results, conduction block was defined by the consensus provided by European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS) in 2010.[1]

## RESULTS:

Compared to ALS group, patients of MMN had younger age at onset (43.1±10.5 and 57.5±12.5 respectively, p=0.002) and shorter delay from symptoms onset to diagnosis (37.0±31.4 and 17.8±17.5, p=0.065), though the later was not statistically significant. None of them presented with upper motor neuro signs in neurological examination, and atrophy of weak muscle less happened (37.5% and 78.6%, p=0.023). MMN patients have lower creatine kinase (CK) level (105.9±63.5 and 271.9±229.8, p<0.001) and higher IgM level (151.9±53.6 and 98.7±51.1, p=0.010), but there was no difference in the CSF protein, IgG, albumin, and IgG index. In the aspect of NCS, the conduction block was more frequently found in MMN patients (75% and 17.9%, p=0.001), by both the criteria of definite and probable conduction blocks. All the above differences were also observed in the comparison between patients with MMN and distal-upper-limb onset form ALS. Among the patients of MMN, six of eight were diagnosed with definite or probable MMN based on the existence of conduction block, and the rest of two had possible MMN due to responsiveness to IVIG treatment. However, none of them underwent tests for anti-GM1 IgM antibody. To be noticed, the conduction blocks were more common between the stimulations over a long segment of limbs, like forearm and Erb's point in median or ulnar nerves, raising the need for multiple stimulation points during NCS.

## CONCLUSION:

Our study provided a valid real-world data on the difference between the patients of MMN and ALS. Thorough evaluations of conduction block in NCS and response to IVIG treatment can adequately help distinguish MMN from ALS in the early stage of disease even without anti- GM1 IgM antibody tested.

## REFERENCES:

1. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. *J Peripher Nerv Syst*. 2010;15(4):295-301.

Clinical

*C-P-DS/S008*

# MetALS: A STUDY TO INVESTIGATE THE ROLE OF METABOLIC PARAMETERS AND BODY COMPOSITION ON DISEASE PHENOTYPE AND PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

[1]Chiwera Theresa; [2]Ngo S; [1]Al-Chalabi A

[1]Department of Basic and Clinical Neuroscience, King's College London, Maurice Wohl Clinical Neuroscience Institute, London, United Kingdom,

[2]Department of Biomedical Sciences, Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, Australia.

## INTRODUCTION:

Hypermetabolism (an increase in resting energy metabolism) has been observed in both familial and sporadic ALS patients, and resting energy expenditure moreover seems to increase with proximity to death. The aim of the project is to delineate in detail the changes in metabolism that occur in individuals with ALS, on a macroscopic and molecular scale.

## METHODS:

We propose to examine the genetic and environmental correlates of any changes, identify links between these factors and endophenotype, clinical phenotypes, symptoms and disease progression. This is a cross-sectional case-control study and longitudinal observational cohort study. The study is designed in 2 parts, each with its own primary hypothesis:

*Part A*: People with ALS are more likely to be hypermetabolic than controls

*Part B:* ALS patients who are hypermetabolic will progress faster than those who are normometabolic

Part A participants opting from repeated visits will have a single study visit, whereas patients enrolled in both parts will attend 4-6 months follow ups longitudinally.

We will investigate determinants of this increased energy expenditure and whether metabolic factors are causal in the development of ALS using Mendelian randomization. To ensure the most robust results possible are obtained, validated equipment and techniques will be used to probe the impact of ALS patients' body composition and energy balance on disease progression and survival (BodPod and QUARK RMR/Q-NRG). Validated clinical questionnaires; blood samples to measure biomarkers linked to metabolic state; detailed phenotypic clinical information will be collected in addition to anthropometric measures. This information will allow us to explore the underlying associations in much greater depth.

## RESULTS:

The study has all local hospital R&I approvals. Ethical approval for amendment submitted and we anticipate recruitment of participants and data collection will commence soon. Initial results will be presented at PACTALS meeting.

## CONCLUSION:

This is a new and rapidly moving field, and we aim to develop tools that can be used in clinical settings to assess metabolism and body composition for our patients, to inform decisions about nutritional support and allow tailoring of future treatments.

## REFERENCES:

1. Al-Chalabi et al., Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. The Lancet. Neurology 2014;13: Pg1108–13.
2. Steyn et al., Hypermetabolism in ALS is associated with greater functional decline and shorter survival. Journal of neurology, neurosurgery, and psychiatry 2018:
3. Blond et al., A new indirect calorimeter is accurate and reliable for measuring basal energy expenditure, thermic effect of food and substrate oxidation in obese and healthy subjects. European eJournal of Clinical Nutrition and Metabolism 2011;6: e7-e15.

Clinical

*C-P-DS/S009*

# THE CLINICAL AND PARACLINICAL CHARACTERISTICS OF SPINAL AND BULBAR MUSCULAR ATROPHY AT THE UNIVERSITY MEDICAL CENTER OF HO CHI MINH CITY, VIETNAM

**Author's Name**: Vu Thi Thuy
**Affiliation**: Department of Neurology, University Medical Center of Ho Chi Minh City, 215 Hong Bang Street, Ward 11, District 5, Ho Chi Minh City, Vietnam.
**Contact Information**: Email: thuy.vt1@umc.edu.vn | Phone: +84914809690

## INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA) is a rare inherited disease affecting the lower motor neurons, caused by a genetic mutation in the Androgen Receptor gene on the X chromosome. Diagnosis of this disease in Vietnam is limited due to the lack of genetic testing and the possibility of misdiagnosis.

## REPORT

We retrospectively collected patients admitted to our neurology department or visited our neurology clinic at the University Medical Center of Ho Chi Minh City with confirmed SBMA diagnoses between 2022 and 2024. We identified 27 patients suspected of having SBMA, with 13 patients confirmed to have a CAG repeat expansion (45-59 repeats) in the AR gene. Of the 13 patients, 61.5% had symptom onset between 30 and 39 years, the median and interquartile range (IQR) age was 32(29-38) years. The median and IQR time from onset to diagnosis was 8(3.5-10) years. All patients had difficulty walking at the time of diagnosis, 69.2% presented with postural tremor. 77.8% had gynecomastia on ultrasound. 11 of the 13 patients underwent creatine kinase (CK) testing, all patients had elevated serum CK levels, the median and IQR value was 2327(892- 3597) U/L. The percentage of patients with sensory nerve action potential amplitude abnormalities was high (91%), while abnormalities in compound muscle action potential amplitude were less frequent (51.5%). The needle electromyography examination showed neurogenic changes in all patients, including chronic reinnervation changes (100%) and denervation phenomena in 81.8%.

## CONCLUSION

Our abstract highlights the characteristics of SBMA. Patients with SBMA usually experience symptom onset in the third decade of life, presenting with postural tremors, difficulty walking, gynecomastia, and elevated CK levels. Sensory conduction abnormalities are more common than motor conduction abnormalities, needle electromyography shows chronic neurogenic changes. We hope to raise awareness of the disease so that patients can receive an appropriate diagnosis earlier.

Clinical

*C-P-DS/S010*

# CLUSTERING OF LONGITUDINAL AMYOTROPHIC LATERAL SCLEROSIS FUNCTIONAL RATING SCALE-REVISED (ALSFRS-R) SCORES IN KOREAN ALS POPULATION

[1]Yong Sung Kim, [1]Hyunkee Kim, [1]Wonjae Sung, [1]Jinseok Park; [2]Bugyeong Son; [3]Kyong Jin Shin; [1]Ki-Wook Oh, [1]Seung Hyun Kim

[1]Department of Neurology, Hanyang University Hospital, College of Medicine, Hanyang University, Seoul, Republic of Korea,

[2]Cell Therapy Center, Department of Neurology, Hanyang University Seoul Hospital, Seoul, Republic of Korea,

[3]Department of Neurology, Haeundae-Paik Hospital, Inje University, Republic of Korea.

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease marked by diverse clinical phenotypes and varying rates of functional decline, which complicate accurate prognostication and personalized management.[1,2] While previous studies have mainly focused on survival analysis in Western populations, there is limited research examining the actual clinical progression of ALS, particularly in Asian cohorts.[3-6] This study aims to investigate the clinical progression of Korean patients with ALS and conduct cluster analysis based on the progression patterns.

## METHODS:

We conducted a study involving 796 ALS patients from Hanyang University Hospital between 2005 and 2023, each having at least five ALSFRS-R measurements over a three-year period. Longitudinal ALSFRS-R scores were analyzed using a mixture of Gaussian processes (MoGP), identifying 21 clusters with diverse progression trajectories, encompassing both linear and non-linear patterns. To address the challenges associated with heterogeneous trajectories, Principal Component Analysis (PCA) and k-means clustering were employed to classify patients into four distinct clusters based on their progression patterns.

## RESULTS:

The mixture of Gaussian processes (MoGP) analysis identified 21 clusters with various progression trajectories, revealing significant heterogeneity in ALS clinical progression. The trajectories included linear, sigmoid, concave, and convex patterns, indicating differing rates of functional decline. Due to the small patient numbers per cluster, further clustering was performed using ALSFRS-R scores from 1 to 36 months post-onset. This secondary analysis yielded 4 clusters: slow, sigmoid, intermediate, and fast. The intermediate cluster showed rapid early progression followed by deceleration, while the sigmoid cluster had slow initial progression that later accelerated. These distinct progression patterns were consistent with known ALS phenotypes, highlighting the heterogeneity of ALS progression, especially with the intermediate cluster's unique characteristics, such as a higher prevalence of lower limb onset and rapid early decline.

## CONCLUSION:

This study identified significant heterogeneity in ALS progression among Korean patients, revealing diverse patterns including linear, sigmoid, concave, and convex trajectories. The clustering analysis further categorized patients into four clusters (slow, sigmoid, intermediate, and fast) based on their progression rates. The distinct patterns and characteristics, particularly the unique intermediate cluster, underscore the complexity and variability of ALS progression, emphasizing the need for tailored prognostication and management strategies.

## REFERENCES:

1. Feldman EL, Goutman SA, Petri S, et al. Amyotrophic lateral sclerosis. The Lancet 2022;400(10360):1363-1380. DOI: 10.1016/S0140-6736(22)01272-7.
2. Goutman SA, Hardiman O, Al-Chalabi A, et al. Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis. The Lancet Neurology 2022;21(5):480-493.
3. Westeneng H-J, Debray TP, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. The Lancet Neurology 2018;17(5):423-433.

Clinical
*C-P-E001*

# ALS VARIANTS OF ALS IN KOREAN POPULATION

Hyunkee Kim[a,b], Byung Woo Choi[a], Hye sun Lee[c], Jinseok Park[a,b], Young sung Kim [a,b], Wonjae Sung [a,b], Seung Hyun Kim[a,b] , Ki-Wook Oh[a,b]
[a]*Department of Neurology, Hanyang University College of Medicine, Seoul, Republic of Korea.*
[b]*Cell Therapy Centre, Hanyang University Hospital, Seoul, Republic of Koreac*
[a]*Department of Neurology, Asan Medical center, Seoul, Republic of Korea*

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder with limited therapeutic options and a complex diagnostic process. Recent studies suggest distinct clinical and genetic characteristics among ALS patients carrying superoxide dismutase 1 (SOD1) gene variants. However, data from Korean populations remain limited. This preliminary study investigates clinical features and genetic profiles of SOD1 variants in Korean ALS patients diagnosed between 2005 and December 2023.

## METHODS:

This retrospective analysis enrolled ALS patients diagnosed between January 2005 and December 2023 who underwent genetic testing including SOD1 gene sequencing. Patients lacking SOD1 genetic analysis or missing key clinical data (age of onset, ALSFRS-R score) were excluded. Clinical features, disease severity (ALSFRS-R), progression rates (initial delta FS), and diagnostic delay were collected and compared between patients with SOD1 variants and non-genetic ALS controls. Identified SOD1 variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

## RESULTS:

Out of the enrolled cohort, 58 patients had SOD1 variants. Compared with controls, SOD1 patients presented with significantly younger onset (mean age 44.33 ± 16.25 vs. 57.12 ± 11.27 years, $p<0.0001$). Initial ALSFRS-R scores were significantly lower in the SOD1 group (35.38 ± 10.74 vs. 38.47 ± 6.49, $p<0.0001$), and initial delta FS was higher, indicating faster progression (1.07 ± 0.95 vs. 0.82 ± 0.8, $p=0.033$). Genetic analysis identified 23 unique SOD1 variants, predominantly p.Phe21Cys (17.24%) and p.Gly86Ser (15.52%), most classified as pathogenic or likely pathogenic per ACMG criteria. No significant differences were observed in diagnostic delay.

## CONCLUSION:

Korean ALS patients with SOD1 gene variants exhibit earlier onset, faster clinical progression, and a high prevalence of familial ALS compared to non-genetic ALS patients. These results emphasize the importance of genetic counseling, early diagnosis, and potential targeted management strategies in this subgroup.

## REFERENCES:

Martinelli I, Ghezzi A, Zucchi E, et al. Predictors for progression in amyotrophic lateral sclerosis associated to SOD1 mutation: insight from two population-based registries. J Neurol. 2023;270:6081-6092. doi:10.1007/s00415-023-11963-0.

Ruffo P, Perrone B, Conforti FL. SOD-1 Variants in Amyotrophic Lateral Sclerosis: Systematic Re-Evaluation According to ACMG- AMP Guidelines. Genes. 2022;13(3):537. doi:10.3390/genes13030537.

Berdyński M, Miszta P, Safranow K, et al. SOD1 mutations associated with amyotrophic lateral sclerosis analysis of variant severity. Sci Rep. 2022;12:103. doi:10.1038/s41598-021-03891-8.

Clinical

*C-P-E002*

# FROM ENVIRONMENT TO SYMPTOMS: MAPPING PREMORBID RISK FACTORS ONTO AMYOTROPHIC LATERAL SCLEROSIS CLINICAL FEATURES IN A LARGE PATIENT-REPORTED DATABASE IN CHINA

[1]Xinyu Li; [2]Qianrui Chen; [3]Dongsheng Fan, [3]Lu Chen
[1]Peking University Health Science Center, Peking University, Beijing, China
[2] School of Health Humanities, Peking University, Beijing, China
[3]Department of neurology, Peking University Third Hospital, Beijing, China

## ABSTRACT

### OBJECTIVE:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with multifactorial causes, including genetic and environmental factors. This study aims to explore the pre-onset factors influencing ALS onset and progression among the Chinese population, leveraging the world's largest patient-reported ALS database.

### METHODS:

Data from 1421 ALS patients were collected through the AskHelpU platform, including detailed information on occupational exposure, lifestyle habits, dietary patterns, and medical history. Statistical analyses were conducted using SPSS to identify associations between these factors and clinical characteristics such as age at onset and disease progression rate.

### RESULTS:

The study identified significant associations between pre-onset factors and the clinical characteristics of ALS in Chinese patients. High-fat diets ($p = 0.017$, $r = -0.063$), emotional setbacks ($p = 0.005$, $r = -0.075$), and high stress levels ($p < 0.001$, $r = -0.179$) were associated with earlier onset, whereas higher vitamin intake delayed onset ($p = 0.007$, $r = 0.071$). Exposure to pesticides was linked to delayed onset ($p = 0.007$, $r = 0.071$), while smoking correlated with bulbar onset impairments ($p = 0.025$). Pre-existing conditions, such as hypertension ($p < 0.001$, $r = 0.157$) and thyroid disease ($p = 0.003$, $r = 0.078$), were associated with delayed onset, highlighting the multifactorial etiology of ALS. Patients with occupations involving physical labor, such as agriculture, showed faster ALS progression ($p < 0.001$, $r = 0.128$), while those in education exhibited slower progression ($p = 0.009$, $r = -0.090$).

### CONCLUSION:

This study comprehensively examined the effects of environmental, occupational, lifestyle, and medical factors on ALS onset and progression, leveraging China's first patient- reported ALS database. It provides novel insights into the regional variations in ALS etiology, emphasizing the multifactorial nature of the disease.

Clinical

*C-P-E003*

# CURRENT BURDEN OF MOTOR NEURON DISEASES IN CHINA AND PREDICTION OF FUTURE TRENDS

[1,2,3]Zhao, Chen; [4,5]Gào, Xīn; [4,5]Liu, Zhike; [1,2,3]Fan, Dongsheng

[1]Department of Neurology, Peking University Third Hospital, Beijing, China
[2]Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China
[3]Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China
[4]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China
[5]Key Laboratory of Epidemiology of Major Diseases, Peking University, Ministry of Education, Beijing, China

## INTRODUCTION:

Motor neuron diseases (MND) are a group of neurodegenerative disorders caused by the degeneration of upper and lower motor neurons[1]. Amyotrophic lateral sclerosis (ALS) is the most common subtype of MND and is characterized by high mortality and severe disability[2]. This study aimed to comprehensively assess the epidemiological burden of MND in China utilizing the Global Burden of Disease (GBD) 2021 database and project its trends from 2022 to 2045, thereby offering evidence-based insights for MND prevention policies.

## METHODS:

Using data from the GBD 2021 study, the disease burden of MND was assessed through metrics including deaths, prevalence, disability- adjusted life years (DALYs), and their corresponding age-standardized rates[3]. The descriptive analysis reported point estimates and 95% uncertainty intervals (UI) for MND burden indicators in 2021 across the total population, genders, and age groups. Correlation analysis used scatter plots and generalized additive models to evaluate the relationship between the socio-demographic index (SDI) and the MND burden. Disease burden trends were forecasted to 2045 using the Nordpred model, based on age-period-cohort analysis. All data processing, analysis, and visualization were performed using R (version 4.3.3).

## RESULTS:

In 2021, the age-standardized DALYs, mortality, and prevalence rates of MND in China were reported as 7.67 (95% UI: 4.88– 10.06) per 100,000, 0.18 (95% UI: 0.11–0.25) per 100,000, and 2.30 (95% UI: 1.84–2.80) per 100,000, respectively. From 1990 to 2021, DALYs, deaths, and prevalence increased by 40%, 126%, and 30%, respectively. Significant age- and sex-related disparities were observed, with higher burdens among older populations and males. Globally, the MND disease burden exhibited an "inverse L-shaped" relationship with SDI levels. Countries with a higher SDI level demonstrated a higher disease burden. A similar trend was observed in East Asia countries. Projections suggest that MND prevalence in China will peak in 2034 before declining slightly, while DALYs and deaths are expected to rise steadily, increasing by 54% and 90%, respectively, by 2045.

## CONCLUSION:

The burden of MND in China has increased significantly over the past three decades and is projected to continue rising in the next two decades. This study provides crucial data on the epidemiology of MND in China. It holds significant implications for developing MND management policies aimed at mitigating its health and economic impacts.

**FUNDINGS:**
Beijing Natural Science Foundation (Grant No. 7254447); The Postdoctoral Fellowship Program of China Postdoctoral Science Foundation (Grant No. GZC20240064)

**REFERENCES:**

1. Foster LA, Salajegheh MK. Motor Neuron Disease: Pathophysiology, Diagnosis, and Management. The American journal of medicine 2019; 132(1): 32-7.
2. Feldman EL, Goutman SA, Petri S, et al. Amyotrophic lateral sclerosis. Lancet 2022; 400(10360): 1363-80.
3. Collaborators GBD 2021. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990- 2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024; 403(10440): 2133-61.

Clinical

*C-P-G001*

# CLINICAL IMPLICATIONS OF VARIANTS OF UNCERTAIN SIGNIFICANCE IDENTIFIED BY MULTI-GENE PANEL IN KOREAN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

[1, 2]Jin-Ah Kim; [1, 3]Jung-Joon Sung; [1, 4]Yoon-Ho Hong

[1]Department of Translational Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

[2]Genomic Medicine Institute, Medical Research Center, Seoul National University, Seoul, Republic of Korea

[3]Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea

[4]Department of Neurology, Seoul National University Seoul Metropolitan Government Boramae Medical Center, 20 Boramaero-5-Gil, Seoul, Republic of Korea

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) involves complex genetic contributions, leading to an increase in genetic screening in clinical practice. Consequently, the detection of variants of uncertain significance (VUS) has also risen, yet significant challenges remain in interpreting their clinical relevance and providing effective counseling. This study aimed to conduct an in-depth genetic analysis of Korean ALS patients by utilizing multi-gene panel testing, focusing on assessing the clinical relevance of VUS and evaluating the impact of expanding gene panel on clinically actionable variants.

## METHODS:

We retrospectively analyzed genetic testing data from ALS patients between January 2018 and December 2023. Methodology evolved from targeted next-generation sequencing panels of 26 genes (2018-2021) to an expanded panel of 44 genes (2022-2023). Variants were classified according to the ACMG guidelines, and VUS were classified into high (VH) or low (VL) probability of pathogenicity based on the 28 ACMG criteria. Clinically actionable variants were defined as pathogenic, likely pathogenic (P/LP), or VH variants.

## RESULTS:

In a total of 379 patients, 16 P/LP variants and 135 VUS were identified. While the detection rate of P/LP variants was consistent between the two panels at approximately 4%, VUS were identified twice as high with the 44-gene panel compared to the 26-gene panel (22.7% vs. 46.4%). Further analysis of VUS revealed that VH variants, as well as clinically actionable variants, were most prevalent in patients with onset before the age of 40 years, with their proportions decreasing progressively with age ($P = 0.011$), whereas VL variants showed no such an age-related trend. The gene panel expansion had little impact on detecting clinically actionable variants in patients with onset age under 40 years (30% vs. 32%), but significantly increased the detection rate in those over 40 years (14% vs. 22%, $P = 0.035$). Twenty-seven patients (7.1%) were identified as oligogenic carriers, with the majority (88.9%) identified only with the expanded gene panel.

## CONCLUSION:

Our results underscore the significant role of genetic factors in younger individuals with ALS, and also highlight the utility of expanded multi-gene panel for improving the detection of clinically actionable variants and oligogenic carriers particularly in older-onset patients.

## REFERENCES:

1. Goutman et al. Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis. Lancet Neurol 2022;21:465-479.
2. Mehta PR et al. The impact of age on genetic testing decisions in amyotrophic lateral sclerosis. Brain 2022;145:4440-4447.
3. Shepheard SR et al. Value of systematic genetic screening of patients with amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2021;92:510-518.
4. Iacoangeli A et al. Oligogenic structure of amyotrophic lateral sclerosis has genetic testing, counselling and therapeutic implications J Neurol Neurosurg Psychiatry 2025;13:jnnp-2024-335364.

Clinical
*C-P-G002*

# *TARDBP* VARIANTS IN TAIWANESE ALS PATIENTS: GENETIC SPECTRUM, CLINICAL FEATURES, AND FOUNDER EFFECTS

[1,2,3] Kang-Yang Jih, [1,2]Shih-Yu Fang, [1,2]Yi-Chung Lee,
[1]Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Department of Neurology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan
[3]Department of Physiology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan.

## INTRODUCTION:

*TARDBP* is one of the most commonly implicated genes in amyotrophic lateral sclerosis (ALS). It encodes TAR DNA-binding protein 43 (TDP-43), a protein critical to ALS pathology, whose pathogenic variants disrupt its nuclear-cytoplasmic translocation, leading to aggregation. This study aimed to investigate the role of *TARDBP* variants in a Taiwanese ALS cohort.

## METHODS:

We analyzed the coding regions of *TARDBP* using Sanger sequencing in 650 unrelated ALS patients recruited between 2000 and 2024. The cohort included 388 men and 262 women, with an average age of onset of 56 ± 13 years.
Approximately 20% presented with bulbar-onset ALS. Haplotype analysis was conducted using single nucleotide polymorphism and short tandem repeat markers flanking *TARDBP*.

## RESULTS:

Pathogenic *TARDBP* variants were identified in 17 probands and 11 of their relatives, with an average age of onset of 49.1 ± 10.3 years, 32% of whom had bulbar-onset disease. Six probands carried the p.M337V variant, five had p.S375G, two had p.N378D, and one each carried p.G348C, p.G348V, p.G376D, or p.I383V.
Haplotype analysis suggested a common founder for the p.S375G variant and most families with p.M337V. Asymptomatic carriers were also identified, suggesting incomplete penetrance.

## CONCLUSION:

Our study revealed that pathogenic *TARDBP* variants are a significant genetic contributor to ALS in Taiwan, associated with earlier disease onset but reduced penetrance. The recurrent M337V and p.S375G variants likely reflect a founder effect.

## REFERENCES:

1. B.R. Brooks, Natural history of ALS: symptoms, strength, pulmonary function, and disability, Neurology 47(4 Suppl 2) (1996) S71-81; discussion S81-2.
2. J.M. Gregory, D. Fagegaltier, H. Phatnani, M.B. Harms, Genetics of amyotrophic lateral sclerosis, Current Genetic Medicine Reports 8 (2020) 121-131.
3. M. Grassano, A. Calvo, C. Moglia, L. Sbaiz, M. Brunetti, M. Barberis, F. Casale, U. Manera, R. Vasta, A. Canosa, S. D'Alfonso, L. Corrado, L. Mazzini, C. Dalgard, R. Karra, R. Chia, B. Traynor, A. Chio, Systematic evaluation of genetic mutations in ALS: a population-based study, J Neurol Neurosurg Psychiatry 93(11) (2022) 1190-3.

Clinical

*C-P-G003*

# SOD1: MUTATION SPECTRUM, GENOTYPE-PHENOTYPE CORRELATIONS AND DISEASE OUTCOME IN AN INDIAN ALS COHORT

[1]Muddasu Keerthipriya, [1]Ananthapadmanabha Kotambail, [2]Gautham Arunachal, [3]Priya Treesa Thomas, [1]Saraswati Nashi, [1]Seena Vengalil, [1]Nalini A

[1]Department of Neurology, National Institute of Mental Health and Neurosciences, Street Hosur Road, Bengaluru, India.

[2]Department of Human Genetics, National Institute of Mental Health and Neurosciences, Street Hosur Road, Bengaluru, India.

[3]Department of Psychiatric Social work, National Institute of Mental Health and Neurosciences, Street Hosur Road, Bengaluru, India.

## INTRODUCTION:

SOD1 gene mutation was first identified in 1993 as a cause of familial ALS (FALS). Since then, over 40 genes have been associated with ALS, shedding light on its molecular mechanisms. SOD1 mutations account for 10-20% of familial ALS cases and 1-2% of sporadic cases. This study represents India's first report on the SOD1 gene mutation spectrum in ALS patients.

## METHODS:

Retrospective analysis was conducted on ALS patients evaluated between 2017 and 2023 who underwent Next-Generation Sequencing and tested positive for SOD1 mutations. In 2024 and 2025, telephonic follow-up calls were made to assess patient outcomes. The study was performed at a quaternary care referral center for ALS in India.

## RESULTS:

A total of 26 ALS patients (16 men) from different families were identified with pathogenic or likely pathogenic SOD1 mutations. Median age at onset (AAO) was 46.5 years (range: 16-65), with a median disease duration of 13.5 months (range: 2-84). No significant difference was observed between familial and sporadic ALS cases. Majority of patients (23/26, 88.5%) had limb onset ALS, with 17(73.9%) presenting lower extremity weakness. Bulbar onset ALS was seen in 3(11.5%) patients. 13(50%) patients showed LMN predominant phenotype. The median survival was 36 months. 19 different SOD1 variants, including 5 novel mutations, were identified. Most mutations (24/26) were missense mutations, with one in-frame deletion and one in-frame-insertion, 5/26 were homozygous mutations. Among the five patients with homozygous mutations, AAO was significantly lower compared to heterozygous patients (27 vs. 52 years, p=0.039). However, survival duration, though shorter in homozygous group (32.4 vs. 62.7 months), was not significantly different from heterozygous group.

## CONCLUSION:

This study provides important insights into SOD1 mutations in Indian ALS patients, identifying new genetic variants and disease progression patterns. The findings emphasize the importance of genetic screening for ALS and could help guide future research and targeted therapies.

## REFERENCES:

1. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng HX, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993 Mar 4;362(6415):59-62. doi: 10.1038/362059a0. Erratum in: Nature. 1993 Jul 22;364(6435):362. doi: 10.1038/364362c0. PMID: 8446170.
2. Nijs M, Van Damme P. The genetics of amyotrophic lateral sclerosis. Curr Opin Neurol. 2024 Oct 1;37(5):560-569. doi: 10.1097/WCO.0000000000001294. Epub 2024 Aug 22. PMID: 38967083; PMCID: PMC11377058.
3. Domi T, Schito P, Sferruzza G, Russo T, Pozzi L, Agosta F, Carrera P, Riva N, Filippi M, Quattrini A, Falzone YM. Unveiling the SOD1-mediated ALS phenotype: insights from a comprehensive meta-analysis. J Neurol. 2024 Mar;271(3):1342-1354. doi: 10.1007/s00415-023-12074-6. Epub 2023 Nov 6. PMID: 37930481.
4. Chen LX, Xu HF, Wang PS, Yang XX, Wu ZY, Li HF. SOD1 Mutation Spectrum and Natural History of ALS Patients in a 15-Year Cohort in Southeastern China. Front Genet. 2021 Oct 14;12:746060. doi: 10.3389/fgene.2021.746060. PMID: 34721532; PMCID: PMC8551486

Clinical

*C-P-G004*

# FUNCTIONAL VERIFICATION AND CLINICAL PHENOTYPES OF AMYOTROPHIC LATERAL SCLEROSIS WITH NOVEL MUTATIONS OF VAPB GENE

[1]Qi, Yixin; [1]Chen, Jianmin; [1]Chen, Sheng; [1]Lu, Yingqian;[1]Liu, Changyun; [1*]Zou Zhangyu [1]Department of Neurology, Fujian Medical University Union Hospital, No. 29, Xinquan Road, Fuzhou, China

## INTRODUCTION:

Vesicle-associated membrane protein- Associated Protein B (VAPB) is a pathogenic gene associated with Amyotrophic Lateral Sclerosis (ALS). VAPB mutations account for a significant proportion (up to 43.6%) of familial ALS cases in Portuguese/Brazilian populations, yet reports of VAPB mutations in ALS patients of other ethnicities remain scarce. This study aimed to screen the VAPB gene in a large cohort of Chinese ALS patients and analyze genotype-clinical phenotype correlations.

## METHODS:

Whole-genomic DNA was extracted from 275 sporadic ALS (sALS) patients and 15 familial ALS (fALS) pedigrees. All exons of the VAPB gene were sequenced, followed by Sanger sequencing for mutation validation. Pathogenicity of identified mutations was assessed according to ACMG guidelines, and functional validations of the mutations were performed at the protein level.

## RESULTS:

In a cohort of 275 sporadic amyotrophic lateral sclerosis (ALS) patients, we identified three novel VAPB missense variants: c.38A>C (p.Gln13Pro), c.511G>A (p.Glu171Lys), and c.659T>G (p.Leu220Arg), alongside the known pathogenic mutation c.166C>T (p.Pro56Ser). Clinically, patients harboring the novel variants exhibited distinct phenotypic profiles: spinal-onset ALS was observed in carriers of p. Glu171Lys and p.Leu220Arg, while bulbar-onset ALS characterized the p.Gln13Pro case. Electromyography revealed widespread neurogenic damage in all patients, consistent with classic ALS progression. Notably, disease progression was rapid across all three cases, with significantly shorter survival times in p.Q13P and p.L220R carriers— 21 months and 32 months, respectively. Pathogenicity prediction using SIFT, Polyphen-2, and VarCards suggested all Four mutations are likely deleterious, with p.E171K exhibiting the highest damaging score. Further functional validation via immunofluorescence revealed that p.Q13P and p.E171K mutations form small insoluble cytoplasmic inclusions in HEK293 cells, while p.P56S generates medium-to-large aggregates. These aggregates triggered activation of the unfolded protein response (UPR) pathway and ubiquitinated puncta formation, ultimately activating the endoplasmic reticulum (ER)-associated apoptotic pathway

## CONCLUSION:

In this study, three novel exonic missense mutations in the VAPB gene and one previously known pathogenic mutation were identified among 275 sporadic amyotrophic lateral sclerosis (SALS) patients. All four mutation carriers exhibited classic ALS phenotypes with rapid disease progression. Functional validation revealed that p.P56S, p.Q13P and p.E171K mutations formed insoluble cytoplasmic inclusions in cells. These aggregates likely triggered activation of the unfolded protein response (UPR) pathway and ubiquitinated puncta formation, thereby exacerbating endoplasmic reticulum (ER) stress. This amplified ER stress ultimately activated the ER-associated apoptotic pathway, inducing cell apoptosis.

## REFERENCES:

1. Chadi, Gerson et al. Genetic analysis of patients with familial and sporadic amyotrophic lateral sclerosis in a Brazilian Research Center. Amyotrophic lateral sclerosis & frontotemporal degeneration vol. 18,3-4 (2017): 249-255.
2. Aliaga, Leonardo et al. Amyotrophic lateral sclerosis-related VAPB P56S mutation differentially affects the function and survival of corticospinal and spinal motor neurons. Human molecular genetics vol. 22,21 (2013): 4293-305.
3. Chen, Xi et al. "High Glucose Inhibits Neural Stem Cell Differentiation Through Oxidative Stress and Endoplasmic Reticulum Stress." Stem cells and development vol. 27,11 (2018): 745-755.

Clinical
*C-P-G005*

# GENETIC SPECTRUM OF KOREAN PATEITNS WITH AMYOTROPHIC LATERAL SCLEROSIS

Young-Eun Kim[a], Wonjae Sung[b], Jong Eun Park[c], Ki-Wook Oh[b,d], Jinseok Park[b,d], Seung Hyun Kim[b,d]
[a]Department of Laboratory Medicine, Hanyang University College of Medicine, Seoul, Korea [b]Department of Neurology, Hanyang University College of Medicine, Seoul, Korea
[c]Departments of Laboratory Medicine, Hanyang University Medical Center, Guri Hospital, Guri, Korea

[d]Cell Therapy Center, Hanyang University Hospital, Seoul, Korea

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by progressive loss of cortical, bulbar, and spinal motor neurons. To date, more than 30 genes linked to ALS have been identified, accounting for about 70% of familial ALS (fALS) and approximately 15% of sporadic ALS (sALS). In this study, we aimed to decipher the genetic spectrum of ALS in Korea.

## METHODS:

From January 2015 to Dec 2024, a total of 1,573 patients with clinical suspicion of ALS or lower motor neuron syndrome (LMNS) were analyzed by whole exome sequencing (WES). We screened variants in genes that have previously been reported causative or related to ALS. In addition, we compared the genetic spectrum of 22 major genes (*SOD1, FUS, ANXA11, C9orf72, SETX, SPG11, ALS2, GRN,, TBK1, SQSTM1, OPTN, MAPT, TARDBP, UBQLN2, VABP, DCTN1, CCNF, CHCHD10, MATR3, PRN1, TUBA4A*, and *VCP)* in the Korean ALS population with those from other ethnicities.

## RESULTS:

The frequency of pathogenic variants (PV) or likely pathogenic variants (LPV) in Korean sALS was 3.2% (51/1573) that was comparable to those in Japanese but lower than those in Chinese and Caucasian. Among Korean sALS, 24.5% (385/1247) carried more than one variant of uncertain significance (VUS) in the major ALS genes. As many as 1.4% (n=22) of Korean sALS had PV/LPV in *SOD1* followed by *SPG11* (n=7), *ANXA11*, *NEK1*, *TARDBP* (n=3), *ALS2*, *DCTN1, FUS,* and *VCP* (n=2). One patient carried exon2-4 deletion in *OPTN* gene. There were apparent differences of genetic spectrum between Korean and Caucasian ALS patients mainly due to the frequency of hexanucleotide expansion in *C9orf72* gene.

## CONCLUSION:

The genetic spectrum in Korean patients with ALS was different from those in other ethnicities. We suggest these findings better define genetic features of Korean ALS patients.

Clinical

*C-P-N001*

# IMMUNE CHECKPOINT CHANGES CORRELATE WITH THE PROGRESSION AND PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

[1]Chen, Sheng; [1]Xu, Chunzuan; [1]Liu, Changyun; [1]Lu, Yingqian; [1]Zou, Zhangyu
[1]Department of Neurology, Fujian Medical University Union Hospital, 29# Xinquan Road, Fuzhou, China

## INTRODUCTION:

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive motor neuron loss. While immune system dysfunction plays a critical role in ALS pathogenesis, the role of immune checkpoints remains poorly understood. Previous studies identified elevated programmed death-1 (PD-1) levels in ALS patients[1], but the broader landscape of immune checkpoint alterations and their clinical significance remain unexplored. This study aims to investigate the expression of immune checkpoints in ALS patients and evaluate their potential as biomarkers for diagnosis, prognosis, and therapy.

## METHODS:

Seventy-two participants, including 46 ALS patients and 26 healthy controls, were recruited for flow cytometry experiments to measure PD-1 levels in CD4+ T cells and their subsets. Another 63 participants (44 ALS patients and 19 with ALS mimic syndromes) were included for serum immune checkpoint measurement experiments using Luminex technology. The study also utilized a single-molecule array to screen the neurofilament light chain (NFL) in serum. The demographic characteristics, disease duration, site of onset, and ALS Functional Rating Scale-Revised (ALSFRS-R) scores were recorded. The expression of PD-1 in T cells and its subsets was analyzed using flow cytometry, and the levels of 14 serum immune checkpoint molecules were measured.

## RESULTS:

1. Flow Cytometry:
- ALS patients exhibited significantly higher PD-1 expression in CD4+T cells ($p = 0.008$) and Th9 ($p = 0.009$) and Th17 subsets ($p = 0.034$).
- High PD-1-expressing CD4+T cells correlated with worse prognosis ($p = 0.016$).

2. Luminex Assay:
- Serum levels of 10 immune checkpoint molecules (including sPD-1, sBTLA, sIDO, sTIM-3, sCTLA-4/CD152, sCD80, sGITR, sCD137, sCD27, and sCD28) were significantly elevated in ALS patients compared to mimics ($p < 0.05$).
- Young ALS patients showed higher levels of sPD-1, sBTLA, and sTIM-3 compared to young mimics ($p < 0.05$).

3. Correlations:
- sPD-1, sPD-L1, sBTLA, sTIM-3, sCD80, sGITR, sHVEM, and sCD137 levels negatively correlated with ALSFRS-R scores.
- sPD-1, sPD-L1, sPD-L2, sBTLA, sCTLA-4, and NFL levels positively correlated.
- No significant differences in checkpoint levels were observed between rapid and slow-progressing ALS groups.

## CONCLUSION:

This study identifies aberrant immune checkpoint expression in ALS, with both membrane-bound and soluble PD-1 levels linked to disease progression and prognosis. High PD-1-expressing CD4+T cells may represent exhausted T cells contributing to neuroinflammation. Serum immune checkpoint profiles, particularly sPD-1 and sBTLA, show promise as biomarkers for ALS severity and monitoring. Further multicenter studies are needed to validate these findings and explore targeted immunotherapies.

## REFERENCES:

1. Beers DR, Zhao W, Thonhoff JR, et al. Serum programmed cell death proteins in amyotrophic lateral sclerosis. Brain, Behavior, & Immunity - Health. 2021;12:100209.

Clinical

*C-P-N002*

# IMMUNE CELLS AND PROTEINS RELEVANT TO DISEASE PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS

[1]Fujita K; [2]Itou T; [2]Okuzono Y; [2]Warude D; [2]Shuuichi M;
[1]Mihara Y; [1]Matsui N; [3]Morino H; [2]Kikukawa Y; [1]Izumi Y
[1]Department of Neurology, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, [2]Oncology Drug Discovery Unit Japan, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited., Fujisawa, Japan, [3]Department of Medical Genetics, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

## INTRODUCTION:

The immune system has garnered attention due to its association with disease progression in amyotrophic lateral sclerosis (ALS). However, the role of peripheral immune cells in this context remains controversial. Here, we aimed to comprehensively profile immune cells and proteins concerning the rate of disease progression in patients with ALS.

## METHODS:

We enrolled 23 patients with non-rapid ALS (ΔALSFRSR/month < 1), 7 patients with rapid ALS (ΔALSFRS-R/month > 1), and 10 healthy controls. Patients with ALS had disease duration of 10.4 ± 6.4 months and a mean ALSFRS-R score of 39.9 ± 5.2. We conducted single-cell RNA-sequencing of peripheral blood mononuclear cells and serum proteomics through a proximity extension assay combined with next-generation sequencing.

## RESULTS:

The single-cell analysis revealed an increased prevalence of Th17 compared to regulatory T cells and a higher frequency of effector CD8 T cells relative to naïve CD8 T cells in rapidly progressive ALS. The proteomics revealed several inflammation proteins that were associated with rapid disease progression. Of these, interleukin-17A correlated with the frequency of Th17, while killer cell lectin-like receptor D1 (CD94) correlated with the frequency of effector CD8 T cells.

## CONCLUSION:

We revealed relationships between rapid progression and increase in Th17 and effector CD8 T cells, and relevant proteins such as interleukin-17A and killer cell lectin-like receptor D1 (CD94) in the blood in ALS patients, suggesting these cell types together relate to disease progression in ALS.

## REFERENCES:

1. Itou T, Fujita K, Okuzono Y, Warude D, Miyakawa S, Mihara Y, Matsui N, Morino H, Kikukawa Y, Izumi Y. Th17 and effector CD8 T cells relate to disease progression in amyotrophic lateral sclerosis: a case control study. J Neuroinflammation 2024;21(1):331.

Clinical

*C-P-NM001*

# THE IMPACT OF BLOOD LIPID CLASSES ON RISK OF DEVELOPING AMYOTROPHIC LATERAL SCLEROSIS: A SYSTEMATIC REVIEW AND GRADE ANALYSIS

[1,2]Sewell-Green, Amber; [3]Kuiper M; [3]Beelen A; [1, 4]Steyn FJ; [4,5]Ngo ST; [2,6]Matthews-Rensch KL
[1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia, [2]Department of Dietetics and Foodservices, Royal Brisbane and Women's Hospital, Australia, [3]Department of Rehabilitation, Physical Therapy Science and Sports, University Medical Centre Utrecht, Utrecht, the Netherlands, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Australia, [5]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia, [6]Queensland Centre for Mental Health Research, The Park Centre for Mental Health Treatment, Research and Education, Wacol, Australia

## INTRODUCTION:

Amyotrophic Lateral Sclerosis (ALS) is associated with altered lipid metabolism (1, 2). This systematic review evaluated the impact of blood lipid classes on risk of developing ALS.

## METHODS:

A systematic search following PRISMA guidelines was conducted across six databases (PubMed, Embase, CINAHL, Scopus, Cochrane Library and Web of Science), in March 2024. MeSH terms "Amyotrophic Lateral Sclerosis" AND "Lipids" and related variants were applied. Studies were included if they reported on adult clinical studies and statistical risk of developing ALS. Standard mean difference and 95% confidence intervals (SMD[95%CI]) in baseline lipid levels were generated and descriptive statistics applied, categorising findings into reduced, no effect, or increased risk of developing ALS. GRADE criteria assessed the quality of evidence.

## RESULTS:

Searches identified 6,454 papers, yielding eight eligible studies (n=7 sterol lipids, n=1 fatty acids). There were no significant differences between ALS-cases and controls in baseline levels for five sterol lipids; total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or LDL/HDL ratio ($I^2$= 67.7%-97.6%). After removing one high-bias study, results for risk o f developing ALS were heterogeneous, with no effect on risk for TG (n=4/5), TC (n=3/6), LDL-C (n=3/6), or LDL/HDL (n=2/4). HDL-C had inconsistent results (no effect, reduced risk and increased risk of onset n=2/6 each), while remaining studies suggested higher blood sterols reduced disease risk. The study of fatty- acids indicated increased disease risk with higher arachidonic acid, and reduced risk with higher alpha-linoleic acid levels. GRADE of evidence was low for sterol lipids, and very low for fatty acids.

## CONCLUSION:

Observational studies examining the impact of blood sterol lipid levels on ALS risk are inconsistent and of low evidence. Further research using standardised methodologies and more precise technologies, such as Lipidomics screenings, are needed to clarify the role of lipids as clinical biomarkers in ALS.

## REFERENCES:

1. van Mantgem MJ, van Rheenen W, Hackeng AV, van Es MA, Veldink JH, van den Berg LH, et al. Association Between Serum Lipids and Survival in Patients With Amyotrophic Lateral Sclerosis A Meta- analysis and Population-Based Study. Neurology. 2023;100(10):E1062-E71.
2. Area-Gomez E, Larrea D, Yun T, Xu Y, Hupf J, Zandkarimi F, et al. Lipidomics study of plasma from patients suggest that ALS and PLS are part of a continuum of motor neuron disorders. Scientific reports. 2021;11(1):13562-.

Clinical

*C-P-RM001*

# UPTAKE OF RESPIRATORY SUPPORTS THROUGH COMMUNITY BASED RESPIRATORY CARE IN INDIVIDUALS WITH MOTOR NEURONE DISEASE (MND)

[1]Travlos, J. Vivienne

[1]Clinical Services, MotorNeurone Disease Association of Western Australia, 1/184 Raleigh Str, Carlisle 6101, Perth, Australia

## INTRODUCTION:

Individuals with Motor Neurone Disease (MND) live with bulbar and respiratory muscle weakness that impacts their ability to chew, swallow, breathe deeply and cough. Loss of these functions places them at high risk of cardiorespiratory compromise, including hypoventilation, aspiration, respiratory failure and death.

Timely provision and uptake of respiratory supports (such as breathing exercises, use of non-invasive ventilators [NIV], salivary management, lung volume recruitment [LVR] and mechanical in-ex sufflator [MIE] cough assistance devices) can minimise the impact of these sequalae[1], improve quality of life and enhance survival[2]. Respiratory supports can be implemented at home by community based respiratory physiotherapists in consultation with their multidisciplinary team (MDT) through individualised Respiratory Care Plans (RCP).

## METHODS:

Retrospective review of outcomes in individuals supported through MNDAWA between May 2021 – Dec 2024 offered home RCPs, including uptake of NIV and respiratory adjuncts, time to need for MIE, hospital avoidance and end of life comfort/distress.

## FINDINGS:

161 of 254 individuals with MND supported through MNDAWA were offered RCPs. Successful uptake was facilitated of NIV in 40.5%, LVR in 23% and MIE in 32%. An estimated 86 hospital admissions were avoided.

Timely implementation of RCP's supported by community based respiratory therapists within an MDT may optimize respiratory function and can minimise respiratory distress in individuals with MND.

## REFERENCES:

1. Sheers, N. L., O'Sullivan, R., Howard, M. E., & Berlowitz, D. J. (2023). The role of lung volume recruitment therapy in neuromuscular disease: a narrative review. *Frontiers in Rehabilitation Sciences, 4*. doi:10.3389/fresc.2023.1164628
2. Ackrivo J, Hsu JY, Hansen-Flaschen J, Elman L, Kawut SM. Noninvasive ven□la□on use is associated with beter survival in amyotrophic lateral sclerosis. *Ann. Am. Thorac*. 2021;18(3):486-494.

Clinical

*C-P-RM002*

# THE COMBINATION OF IPV AND MI-E FOR THE CARE OF AIRWAY CLEARANCE

[1]Ogino, Mieko; [2]Taira A; [1]Ogino A; [1] Tominaga N

[1]Department of Neurology, International University of Health and Welfare, Ichikawa hospital, Ichikawa, Chiba, Japan,
[2]Department of Neurology, International University of Health and Welfare, Narita hospital, Narita, Chiba, Japan

## INTRODUCTION:

Advanced-stage ALS patients with symptoms of bulbar paralysis have difficulty in expectorating due to dysphagia and respiratory muscles weakness, which can lead to repeated respiratory infections and atelectasis. Effective expectorant care is necessary to prevent this.

## METHODS:

Among the patients admitted between August 2020 and March 2021, 6 ALS patients with mechanical insuffication-exsuffication: MI-E alone (group A) and 5 ALS patients with intrapulmonary percussive ventilator: IPV (group B) were retrospectively studied using chest CT.

## RESULTS:

In group A, five out of six cases remained unchanged or worsened, while in group B, three out of five cases improved. Only one patient in group B deteriorated, who was not introduced to NPPV according to her decision.

## CONCLUSION:

The combination of two procedures, MI-E and IPV, as expectorant care may be effective. Although a randomized controlled trial is difficult from an ethical point of view, a prospective study with a larger number of patients is needed.

Clinical

*C-P-O001*

# DOXYCYCLINE INHIBITS MMP-9 AND INACTIVATES MICROGLIA TO PRESERVE PERINEURONAL NETS IN THE SOD1$^{G93A}$ ALS MICE

[1]Cheung, Sang Won; [2]Ridder, Margreet; [1]Bellingham, Mark C, and; [1,2]Noakes, Peter G.
[1]School of Biomedical Science, The University of Queensland, St Lucia, Australia, [2]Queensland Brain Institute, The University of Queensland, St Lucia, Australia.

## INTRODUCTION:

Perineuronal nets (PNNs) are an extracellular matrix structure that encases excitable neurons. PNNs play a role in neuroprotection against oxidative stress. Oxidative stress within motor neurons can trigger neuronal death, which has been implicated in amyotrophic lateral sclerosis (ALS). We investigated PNN breakdown and the contributing cellular factors in the SOD1$^{G93A}$ transgenic ALS mouse model. Compared with wild-type controls, we observed PNN breakdown around α-motor neurons in the ventral horn of between onset and mid-stage disease SOD1G93A mice. This breakdown was observed with increased microglia expressing matrix metallopeptidase-9 (MMP-9), an endopeptidase degrading PNNs. Microglia also engulfed PNN components in the SOD1$^{G93A}$ mouse. Following PNN breakdown, α-motoneurons of onset SOD1$^{G93A}$ mice showed increased expression of 3-nitrotyrosine, a marker for protein oxidation, which could render them vulnerable to death (1).

## METHODS:

To test whether MMP-9 expressing glia were degrading PNNs and rendering α-motor neurons vulnerable to oxidative stress, we administered doxycycline (625mg/kg), a potent MMP-9 inhibitor and microglial inactivator, via feed in WT and presymptomatic SOD1$^{G93A}$ mice (P30) until early mid-stage (P100) and end-stage (P140). Immunofluorescence and confocal microscopy were used to detect and measure proteins of interest, and MMP-9 zymography was used to measure MMP-9 protein activity. In addition, body weight and hindlimb grip strength were measured between P30 and P140.

## RESULTS:

Doxycycline administration significantly reduced microglial activation as assessed through morphology and number in the ventral horn of P100 SOD1$^{G93A}$ mice and decreased PNN breakdown. Doxycycline administration reduced the amount of PNNs phagocytosed by microglia and reduced overall MMP-9 activity in the early mid-stage SOD1$^{G93A}$ mice. In addition, a small increase in hindlimb grip- strength was observed in doxycycline treated SOD1$^{G93A}$ mice compared to vehicle treated SOD1$^{G93A}$ mice between onset and early mid- stage disease.

## CONCLUSION:

These results suggest that MMP-9 and activated microglia degrade PNNs around α-motor neurons, resulting in their eventual death in ALS disease, and doxycycline may slow this pathology.

## REFERENCES:

1. Cheung SW, Bhavnani E, Simmons DG, Bellingham MC, Noakes PG. Perineuronal nets are phagocytosed by MMP-9 expressing microglia and astrocytes in the SOD1$^{G93A}$ ALS mouse model. Neuropathol Appl Neurobiol. 2024:e12982. doi: 10.1111/nan.12982. PMID: 38742276.

Clinical

*C-P-O002*

# EVALUATION OF LONG-TERM PROGNOSIS OF EDARAVONE IN ALS PATIENTS: A REAL-WORLD COMPARATIVE STUDY USING SUNRISE JAPAN AND JACALS REGISTRY DATA

[1]Gen Sobue; [2] Naoki Atsuta; [3] Kaoru Ishizaki; [3] Rie Ueba; [3] Risa Ueki; [3] Takafumi Hashimoto; [3] Satoshi Yuki

[1] Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Japan, [2] Department of Neurology, Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Japan, [3] Mitsubishi Tanabe Pharma Corporation, 1-1-1 Marunouchi Chiyoda-ku, Tokyo, Japan.

## INTRODUCTION:

Edaravone was approved in June 2015 in Japan as a drug to slow the progression of functional impairment in amyotrophic lateral sclerosis (ALS). The Clinical trials have confirmed its effect on slowing functional decline as assessed by the ALS Functional Rating Scale-Revised (ALSFRS-R), and its long-term effects, including on survival, have not been verified. The Edaravone Post-Marketing Survey (PMS), named SUNRISE Japan, aims to examine the safety, effectiveness, and long-term prognosis of edaravone in ALS patients under real-world conditions[1]. Therefore, we investigated the long-term prognosis of edaravone using data from SUNRISE Japan, with the Japanese Consortium for Amyotrophic Lateral Sclerosis Research (JaCALS) disease registry data serving as a control.

## METHODS:

The edaravone group used the analysis dataset from SUNRISE Japan. The control group consisted of patients from the JaCALS registry, and comparisons were made between propensity score-matched population. The primary endpoint was defined as the time from baseline to the earlier occurrence of either death or permanent initiation of mechanical ventilation, and comparisons were made using the Log- Rank test. Additionally, comparisons were conducted within patient populations comparable to those in the clinical trial
MCI186-19.

## RESULTS:

The analysis is currently being conducted according to the statistical analysis plan. Detailed results will be reported at the conference.

## CONCLUSION:

This investigation, which examines the long- term prognostic impact of edaravone under real- world conditions using existing registry data from JaCALS, may provide a valuable reference for studies on other neurodegenerative diseases.

## REFERENCES:

1. Real-world safety of the novel, free radical scavenger edaravone for amyotrophic lateral sclerosis patients: Data from the post-marketing surveillance SUNRISE Japan. Neurol Clin Neurosci. 2021; 9: 223–229.

Clinical

*C-P-O003*

# THE ALL-ENCOMPASSING NATURE OF CARE IN MND

[1]Neville, Sally; [2]Ngo, Shyuan; [1]Steyn, Frederik; [3]Packer, Rebecca

[1]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Brisbane Queensland Australia.

[2]Austrailan Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane Queensland Australia.

[3] School of Health and Rehabilitation Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Brisbane Queensland Australia.

## INTRODUCTION:

The provision of care for people living with MND (plwMND) largely rests with informal caregivers generally family members (1-2). Time burdens and the impacts on carers physical, emotional, social wellbeing and quality of life are high and ever increasing as their loved one progresses (3-4). Here we investigate the perspectives of Australian carers to gain a greater understanding of the experiences of informal caregivers to elucidate the broader landscape of MND care in Australia, and to identify areas of priority and need.

## METHODS:

In-depth semi-structure interviews were conducted with 13 caregivers of plwMND to determine the burdens and challenges associated with caring for someone living with MND. Carers were selected using a purposeful sampling strategy including family, professional and former carers from across four Australian states. Interviews were conducted via the Zoom platform and were analysed qualitatively using content analysis as outlined by Graneheim and Lundman 2004 (5).

## RESULTS:

Four themes were developed as being important to people caring for plwMND. These themes – 1) transversing the MND landscape, 2) constantness of care, 3) carer wellbeing and 4) social interactions - were intrinsically linked to each other, suggesting that it is difficult to view any aspect of MND care in isolation. Rather care is a highly complex and all-encompassing set of circumstances that required constant integration, vigilance and problem solving. The “transversing the MND landscape” theme related to the external MND service landscape and how carers interact with health, support and financial support services. “Constantness of care” relates to the home environment and the physical tasks and routines that MND care requires. “Carer wellbeing” relates to the impact MND care has on the carers physical and mental wellbeing. “Social interactions” outlines carers relationships and social experiences at a family, friend and broader community level.

## CONCLUSION:

Caring for someone with MND is a complex and all-encompassing task in which no aspect of care, support or service provision should be viewed in isolation but rather as piece of a larger picture.

## REFERENCES:

1. Ng L, Kee K, Amatya B, Khan F. Patient/carer perceptions of disability in motor neurone disease and carer coping. International journal of therapy and rehabilitation. 2011;18(10):568-78.

2. Galvin M, Carney S, Corr B, Mays I, Pender N, Hardiman O. Needs of informal caregivers across the caregiving course in amyotrophic lateral sclerosis: a qualitative analysis. BMJ Open. 2018;8(1):e018721-e.

3. Chiò A, Gauthier A, Vignola A, Calvo A, Ghiglione P, Cavallo E, et al. Caregiver time use in ALS. Neurology. 2006;67(5):902-4.

4. Conroy É, Kennedy P, Heverin M, Hardiman O, Galvin M. Care, burden and self-described positive aspects of caring in amyotrophic lateral sclerosis: an exploratory, longitudinal, mixed-methods study. BMJ Open. 2023;13(1):e064254-e.

5. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105-12.

Clinical

*C-P-O004*

# CHARACTERISTICS OF FLEXIBLE ENDOSCOPIC EVALUATION OF SWALLOWING (FEES) DURING INTAKE OF SOLIDS IN PERSONS WITH AMYOTROPHIC LATERAL SCLEROSIS (PALS)

[1]Belur YK; [1]Thuvassery P; [1]Valiyapeediyyekkal A; [2]Vengalil S; [2]Masaraddi HN; [2]Keerthipriya M; [3]Thomas TP; [2]Atchayaram N

[1]Department of Speech Pathology and Audiology, NIMHANS, Bengaluru-560029, India

[2]Department of Neurology, NIMHANS, Bengaluru-560029, India

[3]Department of Psychiatric Social Work, NIMHANS, Bengaluru-560029, India

## INTRODUCTION

Dysphagia is inevitable in persons with amyotrophic lateral sclerosis(pALS) and timely referral for dysphagia evaluation leads to better management (Perry et al. 2021) in early stages too. The aim of this study was to describe the characteristics of flexible endoscopic evaluation of swallowing (FEES) during intake of solids in pALS.

## METHODS:

pALS(n=10)[El Escorial criteria; males(n=4) and females(n=6)] with mean age 53.4 years(SD±10.66, range:40-72 years) were the participants. 30%(n=3) had bulbar onset and 70%(n=7) had spinal onset ALS. Mean onset duration of ALS was 12.2 months(SD±5.47). All participants had normal or early eating problems according to ALS Functional Rating Scale–Revised[Swallowing score:4 or 3 respectively]. FEES was carried out using basic Langmore FEES protocol during intake of solids. Three standardized scales were used. New Zealand Secretion Scale(NZSS) was used to rate section management. Penetration Aspiration Scale(PAS) and Yale Pharyngeal Residue Severity Rating Scale(YPRSRS) were used to analyse swallowing safety and efficiency for solids.

## RESULTS:

In general, on FEES, velopharyngeal competence and vocal cord movements were decreased in 70 %(n=7) of pALS. On NZSS, secretion management was normal(NZSS=0) for 70% (n=7) of pALS and abnormal (NZSS=3) for all bulbar onset pALS(n=3). On PAS, all had a safe swallow(PAS 1-2) during intake of solids but swallowing duration was greater than 55 seconds

On YPRSRS, none of the pALS had residue at pyriform sinus(grade I) but 60%(n=6) had trace or mild residue(grade II and III) at vallecular area. In latter, cyclic ingestion was utilized post intake of solids for clearance of vallecular residue by 50%(n=3) of these pALS.

## CONCLUSION:

This study, with normal or early eating problems in pALS, emphasizes safe swallow of solids with increased meal duration. Presence of vallecular residue suggests possible reduction in tongue pressure (Pizzorni et al, 2020) and highlights necessity to use safe swallow strategies from early stage of dysphagia.

## REFERENCES:

1. Perry, B. J., Nelson, J., Wong, J. B., & Kent, D. M. (2021). The cumulative incidence of dysphagia and dysphagia-free survival in persons diagnosed with amyotrophic lateral sclerosis. *Muscle & nerve*, *64*(1), 83-86.
2. Pizzorni, N., Ginocchio, D., Bianchi, F., Feroldi, S., Vedrodyova, M., Mora, G., & Schindler, A. (2020). Association between maximum tongue pressure and swallowing safety and efficacy in amyotrophic lateral sclerosis. *Neurogastroenterology & Motility*, *32*(8), e13859.

Clinical

*C-P-O005*

# LEVEL OF KNOWLEDGE ON AMYOTROPHIC LATERAL SCLEROSIS AMONG NURSING STUDENTS IN SELECTED COLLEGES IN THE PHILIPPINES

[1]Durante, Cherry Ann; [2]San Juan, Estrella

[1]Department of Nursing, Philippine Women's University, Manila, Philippines [2]Department of Nursing, University of Perpetual Help – Dr Jose G Tamayo Medical University, Laguna, Philippines.

## INTRODUCTION:

ALS can affect individuals differently based on various factors, including genetics, environment, and healthcare access. The level of knowledge about ALS among nursing students would directly impact their ability to provide care and accurate health teaching to patients suffering from the disease.

## METHODS:

This study utilized a cross-sectional research design that employed an 18-item self-administered questionnaire that were distributed in February to March 2023. 190 nursing students from four colleges were recruited to be part of the study.

## RESULTS:

Most participants were female (62%) and on their 3rd year of study (49%). Results showed that more than half (51.58%) of the students had low knowledge about ALS, while 40% had average level of knowledge. About 68% had poor knowledge about the definition of the disease, while 97.89% failed to identify the risk factors. 35% were not able to recognize manifestations; while 22% were not able to detect possible complications. One out of four lacked knowledge on treatment. Almost 90% were not able to identify how to diagnose the disease. Chi-square tests for association were run and it was found out that year level was associated with knowledge level and the association was statistically significant ($chi2 = 69.77$; $p\text{-value}<0.0001$).

## CONCLUSION:

Because of the results of this study, the researchers conclude that there is a low level of knowledge about ALS among the nursing students in the 4 participating universities. There is a need to enhance the level of instruction about amyotrophic lateral sclerosis, to equip the student nurses with knowledge and skill to treat future ALS patients.

## REFERENCES:

1. Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., … & Zoing, M. C. (2011). Amyotrophic lateral sclerosis. The Lancet, 377(9769), 942-955.
2. Renton, A. E., Chio, A., & Traynor, B. J. (2014). State of play in amyotrophic lateral sclerosis genetics. Nature Neuroscience, 17(1), 17-23.
3. Wijesekera, L. C., & Leigh, P. N. (2009). Amyotrophic lateral sclerosis. Orphanet Journal of Rare Diseases, 4(1), 1-22.

Clinical

*C-P-O006*

# DYSARTHRIA AND ASSOCIATED IMPACTS ACROSS INDIVIDUALS WITH MOTOR NEURON DISEASE (MND): A MULTIPLE CASE REPORT STUDY

[1, 2]Charania, Salma; [1]Packer R; [1]Scarinci N; [3,4]Cornwell PL; [1]Rumbach A

[1]School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, Australia, [2]School of Health, Medical and Applied Sciences, Central Queensland University, Rockhampton, Australia, [3]School of Health Sciences and Social Work, Griffith University, Gold Coast, Australia, [4]The Hopkins Centre, Division of Rehabilitation, Metro South Health and Griffith University, Brisbane, Australia

## INTRODUCTION:

The limited amount of research regarding the heterogenous nature of dysarthria associated with MND and the impacts on daily activities and psychosocial wellbeing restricts the ability of speech-language pathologists to provide evidence-based management. Therefore, the aim of the study was to describe the heterogeneity of dysarthria presentation and progression, and its associated impacts on daily activities and psychosocial wellbeing across individuals with MND over a 12-month period.

## METHODS:

A longitudinal multiple case study design was used. Six individuals with MND were assessed at 5 timepoints (i.e., baseline, 3-months, 6- months, 9-months, 12-months) using perceptual clinician-rated assessments (French Dysarthria Assessment [2nd Ed][1], Mayo Clinic Dysarthria Rating Scale[2,3], Amyotrophic Lateral Sclerosis – Severity Scale [Speech Subsystem])[4] and patient self-reported measures (Amyotrophic Lateral Sclerosis Functioning Rating Scale – Revised[5], Communication Effectiveness Index – Modified[6,7], Dysarthria Impact Profile (and Depression, Anxiety, Stress Scale [Short Form])[8]. Case reports were prepared following the CARE guidelines[9].

## RESULTS:

Variability in dysarthria presentation and progression was observed across cases. Bulbar-onset MND cases presented with mild dysarthria at timepoint 1 which rapidly deteriorated to a severe mixed dysarthria by the end of the study. Spinal-onset MND cases did not present with dysarthria until the 6-month timepoint. Degree of impairment (e.g., dysarthria presence, type, and/or severity) does not necessarily translate to the degree of activity limitation (e.g., reduced speech intelligibility) and/or participation restriction (e.g., communication effectiveness). Factors beyond dysarthria (e.g., hearing impairment, fine motor skills, and mobility) contributed to the heterogenous decline in communication effectiveness. All cases experienced mild/moderate or moderate impact to their psychosocial wellbeing at each timepoint.

## CONCLUSION:

The heterogenous presentation and progression of MND dysarthria, along with its multifaceted impact on daily activities and psychosocial wellbeing, support the need for of patient- centered and holistic speech pathology management. This includes engagement of interdisciplinary care for communication difficulties experienced by individuals with MND.

## REFERENCES:

1. Enderby PM, Palmer R. FDA-2: Frenchay dysarthria assessment: examiner's manual. Pro-ed; 2008.
2. Darley FL, Aronson AE, Brown JR. Clusters of deviant speech dimensions in the dysarthrias. J Speech Hear Res. 1969;12(3):462-96.
3. Duffy JR. Motor speech disorders: Substrates, differential diagnosis, and management. Elsevier Health Sciences; 2012.
4. Hillel AD, Miller RM, Yorkston K, McDonald E, Norris FH, Konikow N. Amyotrophic lateral sclerosis severity scale. Neuroepidemiology. 1989;8(3):142-50.
5. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS- R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999;169(1-2):13-21.

6. Ball LJ, Beukelman DR, Pattee GL. Communication effectiveness of individuals with amyotrophic lateral sclerosis. J Commun Disord. 2004;37(3):197-215.
7. Lomas J, Pickard L, Bester S, Elbard H, Finlayson A, Zoghaib C. The communicative effectiveness index: development and psychometric evaluation of a functional communication measure for adult aphasia. J Speech Hear Disord. 1989;54(1):113-24.
8. Henry, J.D. and Crawford, J.R., 2005. The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British journal of clinical psychology*, *44*(2), pp.227-239.
9. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med. 2013 Sep;2(5):38-43

MNDA CARE FORUM
*M-O-I&NH001*

# AMPLIFYING THE LIVED EXPERIENCE OF MND VOICE IN AUSTRALIA

[1]Labra J; Camden P; Malpress K; [2]Yap MY; Sklavenitis L; Simpson J.
[1]MND Australia, 20 Bradley St, Woden, Australian Capital Territory, Australia, [2]FightMND, PO Box 3073 Burnley North, Victoria, Australia.

## INTRODUCTION:

The value and importance of engaging people with lived experience (PLEx) in activities related to their condition; and recognising them as equal partners in healthcare and research collaborations, are well-established.[1-6]

Historically, MND PLEx representation in Australia was inconsistent, lacking national cohesion and resulting in varying outcomes. There was a clear need for more structured pathways to connect professionals with PLEx, ensuring more meaningful and impactful engagement.

## METHODS:

A Steering Committee with equal representation from MND Australia (MNDA) and PLEx was established. The initial concept of a small 'PLEx advisory group' evolved into a larger, inclusive 'network', co-designed with key MND community stakeholders.

## RESULTS:

The National MND Lived Experience Network (LEN) was launched in June 2024 to facilitate bidirectional engagement between PLEx and professionals, on topics related to care, advocacy, and research. This innovative design sets it apart from other MND lived experience models, which typically focus only on research.

Within the first six months, 143 PLEx registered with the LEN across Australia. Members include: living with MND (35%), former carers (42%), current carers (17%) and gene carriers (6%).

Since September 2024, a variety of professional groups have submitted >30 engagement requests, with 46% of members participating in one or more activities. This has resulted in >185 instances of lived experience voices being heard, believed to be (anecdotally) a significant increase.

Program evaluation is positive, indicating:

- strengthened PLEx/ professional relationships
- increased PLEx empowerment
- valued PLEx input in professional activities
- a shift in MNDA (ie. peak body) processes to enhance lived experience representation in core business.

## CONCLUSION:

The Australian LEN showcases an innovative model that fosters bidirectional engagement between professionals and PLEx at a national level. Early outcomes suggest the model is making a positive impact, amplifying the lived experience of MND voices across Australia.

## REFERENCES:

1. Musson LS, McDermott CJ & Hobson EV
2. (2019) Exploring patient and public involvement in motor neuron disease research. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 20:7- 8, 511-520, DOI: 10.1080/21678421.2019.1643373
3. Snowball et al. Engagement of people with lived experience of dementia advisory group and cross- cutting program: reflections on the first year. *Research Involvement and Engagement* (2022) 8:28 https://doi.org/10.1186/s40900-022-00359-5
4. Wiles LK, Kay D, Luker JA, Worley A, Austin J, Ball A, et al. (2022) Consumer engagement in health care policy, research and services: A systematic review and meta-analysis of methods and effects. PLoS ONE 17(1): e0261808.https://doi.org/10.1371/journal.pone.0261808
5. Consumer and community engagement: A review of the literature (2012). Published by the Centre for Clinical Governance Research, Australian Institute of Health Innovation, Faculty of Medicine, University of NSW and the Agency for Clinical Innovation, NSW.
6. Statement on Consumer and Community involvement in Health and Medical Research, National Health and Medical Research Council (2016), Consumers Health Forum of Australia.https://www.nhmrc.gov.au/about-us/publications/statement-consumer-and-community-involvement-health-and-medical-research Cited 13.2.2025
7. International Alliance of ALS/ MND – Fundamental Rights for People Living with ALS/ MND (January 2024). https://www.als-mnd.org/wp-content/uploads/2024/04/Fundamental-rights-for- people-living-with-ALS-MND-FINAL.pdf Cited: 13.2.2025

MNDA CARE FORUM

*M-O-I&NH002*

# DEVELOPING A MOTOR NEURON DISEASE MASSIVE OPEN ONLINE COURSE (MND MOOC) TO INCREASE GLOBAL KNOWLEDGE, UNDERSTANDING AND AWARENESS OF MND

Perry Sharn; Atkinson RA; Phipps A; Handley E; Vickers J

Wicking Dementia Research and Education Centre, University of Tasmania, 17 Liverpool Street, Hobart 7000, Tasmania, Australia.

## INTRODUCTION:

The Wicking Dementia Research and Education Centre (WDREC), has previously developed successful Massive Open Online Courses (MOOC)s on dementia and traumatic brain injury. These free, open access courses, designed to appeal to diverse adult learners, have reached over 700,000 people globally, and have significantly increased global dementia knowledge and awareness (1) and contributed to the translation of dementia knowledge into risk reduction behaviour (2). The Dementia MOOCs have been integrated and embedded within university health courses including medicine, nursing and paramedicine, extending the educational reach and broader community impact of this dementia education. There is considerable potential to use a MOOC to increase global MND knowledge and awareness. As such, the WDREC is developing an MND MOOC that will bring together information on all aspects of MND, from neuroscience principles to care approaches, to create an educational MND resource to increase the knowledge and understanding of MND globally.

## METHODS:

This educational platform will be designed in collaboration with Australian MND groups, people with MND, their families and care teams, and national and international MND researchers, to deliver an accessible, multidisciplinary course targeting a broad range of learners within the MND community. The MND MOOC will be designed to be applicable to participants from diverse educational, professional and personal backgrounds, from members of the wider community interested in MND, to health care professionals wanting to increase their understanding of the disease.

## RESULTS:

Centred around four modules; Who gets MND?, MND and the Body?, Diagnosing MND and Living with MND, the MND MOOC will combine personal interviews, animations, and video clips to support a diverse learner base. Module 1 explores MND epidemiology and risk factors; module 2 describes the disease processes underlying MND, module 3 explores the diagnosis and medical management of MND; and Module 4 explores person-centred care and living with MND.

## CONCLUSION:

The MND MOOC will be developed as an educational resource to increase global knowledge and awareness of MND. Accessibility and relevance to the end-user are key driving strategies for the design and learning approach. MOOC-based approaches are important for improving health literacy across neurological conditions.

## REFERENCES:

1. Eccleston, C., Doherty, K., Bindoff, A. et al. Building dementia knowledge globally through the Understanding Dementia Massive Open Online Course (MOOC). npj Sci. Learn. 2019; **4**(3):https://doi.org/10.1038/s41539-019-0042-4
2. Farrow M, Fair H, Klekociuk SZ, Vickers JC. Educating the masses to address a global public health priority: The Preventing Dementia Massive Open Online Course (MOOC). PLoS One. 2022;17(5):e0267205.

MNDA CARE FORUM

*M-O-I&NH003*

# CONTINUING THE GAME IN SPITE OF THE BEAST: MAKING GAMING ACCESSIBLE TO PEOPLE WITH MND

[1]Edwards, Alicia

[1]MND Queensland, 1/89 Factory Road, Oxley Queensland Australia.

## INTRODUCTION:

Motor Neurone Disease (MND), often called "The Beast," relentlessly strips individuals of their physical abilities, profoundly impacting their independence and daily lives. While medical care and functional support are priorities, maintaining social connections, hobbies, and interests is equally critical for well- being. Gaming, a rapidly growing pastime in Australia—where 81% of people play video games—offers cognitive stimulation, stress relief, and social engagement. The GameOn With MND Project was launched to help people with MND continue gaming despite physical challenges, exploring ways to improve accessibility and preserve this meaningful activity as a source of enjoyment, connection, and autonomy.

## METHODS:

A survey was distributed to people living with MND with an interest in gaming. Focus groups were held to further explore concepts identified in the survey with participants including people living with MND and allied health professionals. Additionally, accessible controllers were trialled and gaming accessibility features explored.

## RESULTS:

The GameOn Project gathered insights from individuals living with MND and their carers through surveys and focus groups, revealing significant barriers to continued gaming. 23 people living with MND who are interested in gaming responded to the survey. 43% had to reduce or stop playing due to physical decline, fatigue, and loss of dexterity. Pressing buttons (33%), difficulty holding controllers (24%), and maintaining posture (19%) were the most cited physical challenges. Additionally, 70% reported that mental and physical fatigue limited their ability to game for extended periods.

Beyond the physical barriers, psychological impacts were profound. Many participants described increased frustration, loss of independence, and diminished enjoyment due to their declining abilities. Communication barriers (57%) further isolated players, reducing their ability to engage in multiplayer experiences. Some expressed feelings of grief as they lost access to a previously enjoyable and social activity. Despite these challenges, awareness of adaptive gaming solutions was low, with most participants unaware of available assistive technologies. The findings highlight a need for better accessibility solutions and support to help people with MND maintain engagement in gaming and mitigate the associated emotional distress.

## CONCLUSION:

The GameOn Project highlights the barriers people with MND face in gaming while creating resources to support them, health professionals, and game developers. By increasing awareness and improving accessibility, these resources aim to preserve autonomy, joy, and social connection, ensuring gaming remains an inclusive and meaningful activity for people with MND.

## REFERENCES:

1. Tan et al., International Society for Stem Cell Research (ISSCR) 7th Annual Meeting 2009; Pg226.

MNDA CARE FORUM
*M-O-I&NH004*

# OCCUPATIONAL THERAPY MEETS McGYVER – SOLVING FUNCTIONAL CHALLENGES WITH CREATIVITY AND INNOVATION

Sarah Solomon – Senior Occupational Therapist
Calvary HealthCare Bethlehem

**INNOVATIONS & NEW HORIZONS**

## INTRODUCTION:

People living with Motor Neurone Disease (MND) have never fit into a standard pathway of providing Occupational Therapy (OT) input or solving functional challenges due to the vast and varied functional impairments that can occur. Best practice for OT includes providing advice on required Assistive Technology (AT) with consideration of individual situations, goals and understanding what is important to them.

However, what if 'standard' commercially available AT doesn't exist to assist to help address the challenge identified and there is no time to wait for suppliers to 'invent' a solution?

## REPORT:

I will discuss and showcase creative solutions to address unique functional impairments that couldn't be solved with off-the-shelf AT. The focus will be on the implementation of bespoke ideas and customised solutions that have been created for various individuals living with MND to ensure they could independently complete tasks that were important to them.

The solutions discussed will include ideas for controlling an electric lift recliner chair, hands-free cigarette smoking, scratching an itch, controlling an electric toothbrush and donning and doffing a pair of glasses. Solutions have been co-designed with clients and created using 3D printing, thermoplastic, Men's Shed resources, TADVIC and assistance from friends and families. The exploration of the psychological benefits of client lead design and processes will also be discussed.

## CONCLUSION/RESULTS:

Feedback from clients is that this inventive and holistic OT input ensures the unique challenges are not put in the 'too hard basket' and left unsolved. They report it has also led to renewed connections with family and friends over projects. I hope this will inspire OT's not to let the funding models we work within squash our core OT creative abilities and ensure people can do what is most important to them; whatever that may be.

MNDA CARE FORUM

*M-O-IPIC&S001*

# INTERNATIONAL NETWORK FOR ALS RESEARCH AND CARE (INARC)

**Juliette Foucher**[1,2,3], Tommy M Bunte[3,4,5], Vanessa Bertone[3,6], Mathias Couillard[3,6], Corey Straub [6, 7]

**Affiliations:**

1) Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
2) Department of Neurology, ME Neurology, Karolinska University Hospital, Stockholm, Sweden
3) International Network for ALS Research and Care, INARC, Canada
4) Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
5) Treatment Research Initiative to Cure ALS, TRICALS, the Netherlands
6) Genge Partners Inc., Montreal, Canada
7) Quralis inc. Cambridge, United Stated of America

## OBJECTIVE:

The International Network for Amyotrophic Lateral Sclerosis (ALS) Research and Care (INARC) was founded in 2022 and registered as a non-for profit in 2024. INARC's main goals are to offer a platform dedicated to staff members for ALS clinics and research teams who are not physicians. By nurturing experience and expertise exchanges to improve problem solving skills, the ultimate goal is to increase the standard ALS care and research. We aim to describe the genesis of INARC, its membership, provide a preview of the 2025 meeting and goals for the upcoming launch of INARC Regional Boards into Asia-Pacific (APAC) and North America.

## METHODOLOGY:

A questionnaire was sent to all attendees ahead of INARC meetings, with the request to fill out one questionnaire per team and/or site. Google Form was used to support the questionnaire. The following themes were targeted: team/site set-up, palliative care and end of life in ALS, and clinical trials, and spiritual care. Data was then extracted in excel format for analysis.

## RESULTS:

Over the past three years an increase in attendees was seen from 20 attendees in 2022 to 56 in 2025. Attendees represented the following countries: Canada, Ireland, Belgium, the UK, Germany, Denmark, Sweden, the Netherlands, Spain, Italy, Slovenia, Switzerland, and Norway. 85% of the sites reported publicly funded palliative services, and 80% of the sites considered palliative care physicians as needed in ALS research teams. The majority of sites (55%) had a dedicated staff member to support spiritual needs of patients under different titles, with only one site having a dedicated spiritual care counselor. The majority of sites (52.6%) had staff members dedicated solely to research or care, with only 47.4% of sites having professionals active in both research and care.

## DISCUSSION AND CONCLUSION:

These meetings highlighted differences between sites, with one example being task repartition within teams. In larger sites, we found task-dedicated and specialized personnel, when smaller sites request more multi-tasking from their staff members (both in care and research). In both contexts, clear communication came up as the key for a successful care and research continuum, with the benefit of saving time on both ends. The meetings reported here focused on European sites. As ALS is not limited to the European continent only, but needs between sites and regions may vary, INARC will establish different Regional Boards to reflect the global ALS community.

MNDA CARE FORUM

*M-O-TLIEBC001*

# 'INVEST' IN YOUR VOICE: HOW A NOVEL CO-DESIGNED VOICE BANKING SERVICE SUPPORTS PEOPLE WITH MND

[1]Krikheli, Lillian; [2]Jackson, Nicholas
[1]Discipline of Speech Pathology, La Trobe University, Melbourne, Australia. [2]Speech Pathology, Calvary Health Care Bethlehem, Melbourne, Australia.

## INTRODUCTION:

This project aimed to enhance the uptake and completion of voice banking for people with Motor Neurone Disease (plwMND) in a specialist service through the development of a co-designed framework. Created collaboratively with plwMND and speech pathologists, the framework aimed to address existing barriers in service delivery and improve voice banking timeliness and uptake. Previous service evaluations in the literature, have highlighted inconsistencies in voice banking referral and completion rates, even within dedicated services, underscoring the need for structured and person-centred approaches.

## METHODS:

A mixed-methods approach was employed. Quantitative data were collected via a retrospective database review measuring changes in voice banking completion rates, uptake rates, and the time taken from diagnosis to recording. Qualitative data were gathered through a survey capturing the experiences and perspectives of plwMND participating in the new voice banking clinic model. Descriptive statistics and thematic analysis were used for data interpretation.

## RESULTS:

Following the 2023 implementation of the co-designed framework, clinic referrals for voice banking increased significantly. The mean number of days between voice banking being offered and completion decreased by 88.01% (from 159 to 19 days). Additionally, the median time from diagnosis to voice banking completion reduced by 72.73% (from 462 to 126 days). These results suggest the new framework markedly improved service efficiency and timeliness.

## CONCLUSION:

The early introduction of voice banking, supported by a co-designed framework, can significantly improve service outcomes for plwMND. Timely referrals at diagnosis and active patient involvement are critical for ensuring individuals with MND can successfully preserve their voices.

## REFERENCES:

Jackson, N., Krikheli, L., & Jackson, N. (2023, Dec). *'Invest' in your voice: How a novel co-designed voice banking service supports people with MND.* Presented at the 2023 International ALS/MND Allied Professionals Forum, Basel, Switzerland.

MNDA CARE FORUM
*M-O-TLIEBC002*

# DEVELOPING THE AUSTRALIAN MOTOR NEURONE DISEASE GUIDELINE: A COLLABORATIVE, EVIDENCE-BASED APPROACH USING GRADE METHODOLOGY

Zachary Munn[1], Cindy Stern[1], Danielle Pollock[1], Timothy Barker[1], Steve Vucic[2] for the Australian MND Guideline Development Group

[1]Health Evidence Synthesis, Research, and Impact (HESRI), University of Adelaide, Australia
[2]Brain and Nerve Research Centre, Concord Clinical School, The University of Sydney, Sydney, Australia

## INTRODUCTION:

Motor Neurone Disease (MND) is a progressive neurodegenerative condition with no cure, requiring multidisciplinary, evidence-based care. Currently, there is no nationally endorsed **Australian MND guideline** to standardise care and improve outcomes. This project aims to develop a **comprehensive, evidence-based guideline** for MND, ensuring alignment with international best practices while incorporating perspectives from clinicians, researchers, policymakers, and individuals with lived experience.

## METHODS:

The guideline is being developed with the MND community following the **GRADE (**Grading of Recommendations, Assessment, Development, and Evaluation) approach and in line with the **National Health and Medical Research Council** guidelines for guidelines. A scoping review was conducted to identify existing guidelines and research gaps to inform prioritisation of the guideline topics and scope. This process involved **multistakeholder engagement**, including a **Guideline Development Panel (GDP)** and advisory groups representing clinicians, researchers, policymakers, and people with lived experience. A **systematic process for outcome selection and prioritisation** is being implemented, informed by recent advancements in guideline methodology, and systematic reviews being conducted for each prioritised question to underpin evidence-based recommendations.

## RESULTS:

The **guideline scope** has been determined through stakeholder consultation, identifying **priority clinical questions** covering multidisciplinary management, symptom control, assistive technologies, palliative care, and service delivery. An **outcome prioritisation framework** has been co-developed, incorporating perspectives from all stakeholder groups. Preliminary evidence synthesis has commenced, with recommendations being formulated based on the best available evidence.

## CONCLUSION:

The **Australian MND Guideline** represents a major step forward in standardising care for people living with MND in Australia. By combining **rigorous evidence synthesis, broad stakeholder engagement, and an inclusive approach to lived experience**, the guideline aims to improve **clinical practice, patient outcomes, and health system efficiencies**. The final recommendations will be launched in **late 2025**, with strategies for implementation and monitoring to support uptake.

MNDA CARE FORUM
*M-O-TLIEBC003*

# EXPLORING THE NARRATIVE BEHIND THE NUMBERS: USING DATA TO IMPROVE CARE AND SUPPORT FOR THOSE LIVING WITH MOTOR NEURONE DISEASE (MND)

[1]Tull, Victoria
[1]Access & Education, MND Victoria, 265-267 Canterbury Rd, Canterbury VIC 3126, Australia

## INTRODUCTION:

MND Victoria currently supports over 600 individuals diagnosed with MND living in Victoria, Tasmania and the NSW border. Anecdotally, demand for MND Victoria Support Services has increased in recent years, highlighting the need for a data review to identify emerging trends, to inform client advocacy and better support clients' current and future needs.

## REPORT:

Data analysis focused on client records from the past six years, beginning in 2019, which aligns with MND Victoria's adoption of a new Customer Relationship Management (CRM) system (Salesforce). The number of clients supported has grown significantly, from 499 clients in Dec 2019 to 639 in Dec 2024; an increase of nearly 30%.

Reviewing illness duration for clients who died between 2019 and 2024 revealed a median average length of illness of 1.13 years, alarmingly less than half the 2.5-year average life expectancy noted in the broader literature[1].

Another key finding was the median average age of diagnosis; 70 years, at the upper limit of the commonly reported diagnostic age range of 50-70 years[1].

Contributing factors may include delayed diagnosis, a higher proportion of rapidly progressive MND subtypes, age-related comorbidities, sample size (n=1219), or data input accuracy.

## CONCLUSION:

Whilst further investigations are warranted, findings may point to a broader, concerning trend of shorter life expectancy, post-diagnosis. The marked client increase supports advocacy for additional staffing to meet client and carer needs.

Given the ageing population and time since the last national MND analysis (2015), these findings highlight the need for comparison with national and international data. A shorter life expectancy would impact many aspects of care, including staffing, timing and intensity of supports, demands on MND Clinics, and earlier access to palliative care.

## REFERENCES:

[1]Deloitte Access Economics 2015: Economic analysis of motor neurone disease in Australia, report for Motor Neurone Disease Australia, Deloitte Access Economics, Canberra, November.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

MNDA CARE FORUM

*M-O-TLIEBC004*

# EXPLORING THE UPTAKE OF NON-INVASIVE VENTILATION BY PEOPLE WITH MOTOR NEURONE DISEASE IN AUSTRALIA: A QUALITATIVE STUDY

Marnie Graco*,[1,2] Kylie Russo*,[1,2,3] Nicole Grivell,[1,2,4] Kate Carey,[1,2] Charissa Zaga, [1,2] Krisha Saravanan,[1] Nicole L Sheers, [1,2] David J Berlowitz[1,2]

1. Institute for Breathing and Sleep, Austin Health, Heidelberg, Vic, Australia; 2. Department of Physiotherapy, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Vic, Australia; 3. Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Qld, Australia; 4. FHMRI Sleep Health, Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia

## INTRODUCTION:

Motor neurone disease (MND) remains an incurable condition, with treatment primarily focusing on symptom management and enhancing quality of life. Non-invasive ventilation (NIV) improves overall wellbeing and extends survival in people with MND (pwMND) however, its uptake is low in Australia.[1] We have demonstrated that NIV uptake is inequitable; related to where people live and their gender. The aim of this study was to explore factors that influence the uptake of NIV from the perspectives of pwMND, their caregivers, and healthcare professionals (HCPs) who provide care to pwMND.

## METHODS:

Semi-structured interviews with pwMND, their caregivers, and HCPs. Interviews and data analysis were informed by the COM-B (Capability, Opportunity, Motivation = Behaviour) framework and the Theoretical Domains Framework (TDF). All interviews were recorded, transcribed. Data analysis was initially guided by Framework Analysis followed by an indicative analysis to identify factors influencing NIV uptake at different stages of the patient journey.

## RESULTS:

Eight pwMND, four caregivers, and 27 HCPs (nine neurologists, eight respiratory physicians, five nurses, three physiotherapists, one palliative care physician, and one MND advisor) were interviewed. A total of 29 key influencing factors were identified, characterised according to the primary target of any future intervention.

Of the 12 factors referring to people with lived experience of MND (pwMND or caregiver), six related to peoples' motivations to try NIV (e.g emotional responses, conscious decisions). Nine factors referred to HCPs, primarily related to skills, knowledge, professional roles, and beliefs about NIV. All eight factors referring to the health system related to inconsistent and inadequate NIV service delivery models.

## CONCLUSION:

This research has identified many important factors influencing the uptake of NIV among pwMND. Targeted interventions that address these factors will be developed to increase NIV uptake, reduce health care inequity, and ultimately, to optimise quality of life for those affected.

## REFERENCES:

1. Talman P, Duong T, Vucic S, Mathers S, Venkatesh S, Henderson R, Rowe D, Schultz D, Edis R, Needham M, Macdonnell R. Identification and outcomes of clinical phenotypes in amyotrophic lateral sclerosis/motor neuron disease: Australian National Motor Neuron Disease observational cohort. BMJ open. 2016 Sep 1;6(9):e012054.

MNDA CARE FORUM

*M-O-TLIEBC005*

# TRIAL AND TRIUMPHS IN COMMUNITY BASED RESPIRATORY CARE FOR ADULTS WITH MOTOR NEURONE DISEASE (MND): WEST AUSTRALIAN EXPERIENCE

[1]Travlos, J. Vivienne

[1]Clinical Services, MotorNeurone Disease Association of Western Australia, 1/184 Raleigh Str, Carlisle 6101, Perth, Australia

## INTRODUCTION:

Individuals with Motor Neurone Disease (MND) live with bulbar and respiratory muscle weakness that impacts their ability to chew, swallow, breathe deeply and cough. Loss of these functions places them at high risk of cardiorespiratory compromise, including hypoventilation, aspiration, respiratory failure and death.

Timely provision and uptake of respiratory supports (such as breathing exercises, use of non-invasive ventilators, salivary management, lung volume recruitment and cough assistance devices) can minimise the impact of these sequalae and improve quality of life. Type of respiratory adjuncts may change from manual to mechanical with disease progression[1].

This study aimed to explore the experiences of individuals with MND along their disease course of uptake and utility of respiratory supports prescribed at home by a respiratory physiotherapist within a multidisciplinary team (MDT).

## METHODS:

Qualitative case studies of eight individuals with various MND types (bulbar onset, ALS & PLS) receiving clinical care from the MND Association of WA by a respiratory physiotherapist.

## FINDINGS:

Barriers to uptake of respiratory supports include denial, fear, variations in clinical review, equipment and service funding through state health and federal disability services. Facilitators include individual motivation, carer support and direct channels of communication amongst clinicians.

## CONCLUSION:

Proactive implementation of respiratory supports and uptake into daily routine may reduce anxiety and improve perceived control in this rapidly degenerative neuromuscular disease.

## REFERENCES:

1. Sheers, N. L., O'Sullivan, R., Howard, M. E., & Berlowitz, D. J. (2023). The role of lung volume recruitment therapy in neuromuscular disease: a narrative review. *Frontiers in Rehabilitation Sciences, 4*. doi:10.3389/fresc.2023.1164628

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

MNDA CARE FORUM

*M-O-TLIEBC006*

# BRIDGING HEALTH EQUITY GAPS FOR AUSTRALIANS WITH MND: CO-DESIGNING SOLUTIONS WITH THE MND COMMUNITY

[1]Hutchinson, K., [2]Labra, J., [3]Dyson, N., [3]Cullen, M., [4]Graco, M., [5]Giles, L., [6]Winkel, A, [7]Aoun, S., [8]Francis, R., [9]Johnson, K., [10]Travlos, V., and [1] Hogden, A.

[1] School for Population Health, University of NSW, Room 317, Level 3, Samuels Building, Sydney, New South Wales, Australia [2] MND Australia, 20 Bradley Street, Australian Capital Territory, Australia, [3] National Lived Experience Network, MND Australia, 20 Bradley Street, Australian Capital Territory, Australia, [4]Institute for Breathing and Sleep, Austin Health,145 Studley Road, Melbourne, Victoria, Australia, [5]Department of Neuroscience, Launceston General Hospital, 280 Charles Street, Launceston, Tasmania, Australia, [6]Department of Neurosciences, Sunshine Coast Health, 6 Doherty St, Birtinya, Queensland, Australia, [7]Perron Institute, Ground RR Block QE II Medical Centre Ralph & Patricia Sarich Neuroscience Building, 8 Verdun St, Nedlands Western Australia, Australia,[8]College Nursing Health Sciences, Flinders University and Caring Futures Institute, Sturt Road, Bedford Park, Adelaide, South Australia, Australia, [9]MND Victoria, 256 Canterbury Road, Canterbury, Victoria, Australia, [10]Clinical Services, Motor Neurone Disease Association of Western Australia, U1/184 Raleigh St, Carlisle, Perth, Western Australia, Australia

## INTRODUCTION:

Optimal care for people living with MND (plwMND) is achieved through access to specialised multidisciplinary clinics (1-3). Coordinated inter-professional and integrated specialised MND care can extend survival, improve quality of life, reduce hospital admissions and slow functional decline (4). However, there is inequitable access to and funding for MND care across Australia. This study aims to bridge health inequities that limit or exclude access to specialist care for all Australians living with MND through co-designed solutions with stakeholders across Australia.

## METHODS:

This study will undertake national consultations through focus groups with the MND community and diverse stakeholders (plwMND, their family carers, healthcare, and support service providers) across metropolitan, regional, rural, and remote areas of Australia. Using service mapping methodology, we will map specialist and local services to gain a national picture of current access to care. Thematic analysis will then identify barriers, enablers, and context-specific concerns related to access to MND care, informing the co-design of solutions to overcome these challenges. A stakeholder advisory group will guide, advise, and monitor all aspects of the study.

## RESULTS:

We will present preliminary results from the focus groups, highlighting the barriers and enablers to access MND care across Australia, along with context and population-specific challenges. A comprehensive national service map will include clinic locations, staffing composition, funding, governance, referral and care pathways, use of telehealth and access to research. Region-specific information relevant to accessing local and/or specialist care will also be integrated into the service map, including cross-border and geographical location issues, technological infrastructure, and the availability of the care workforce.

## CONCLUSION:

This national care research study will identify context- and population-specific issues accessing care across Australia and will inform national consultations to co-design solutions. The service will map the specialist MND healthcare services in Australia and how they operate. This study will provide evidence for national advocacy and policy initiatives, service design, clinical practice, and care guidelines for the MND community.

## REFERENCES:

1. National Institute for Clinical Excellence. Motor neurone disease: assessment and management: National Institute of Clinical Excellence; 2019 https://www.nice.org.uk/guidance/ng42.
2. Shoesmith C, Abrahao A, Benstead T, Chum M, Dupre N, Izenberg A, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. Canadian Medical Association Journal. 2020;192(46):E1453.
3. MND New Zealand. New Zealand Best Practice Recommendations for the Care of People with Motor Neurone Disease 1 November 2022: MND New Zealand 2022 https://mnd.org.nz/research/bpr/.
4. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. Journal of Neurology, Neurosurgery and Psychiatry. 2015;86(5):496-501.

MNDA CARE FORUM
*M-O-TLIEBC007*

# DYSPHAGIA IN NEURODEGENERATIVE DISEASES: IMPLICATIONS FOR SWALLOWING, DRY MOUTH, AND ORAL HEALTH

By Dr Victoria Tamara Perchyonok, Oral Health therapist with Adult Scope, Special Needs Oral Care, Clinical Lecturer, The University of Melbourne.

**ABSTRACT:**

Dysphagia, or difficulty swallowing, is a prevalent and often debilitating condition in individuals with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). The progressive loss of neuromuscular control impacts swallowing function, leading to significant risks including malnutrition, dehydration, and aspiration pneumonia. These challenges are further compounded by associated conditions such as xerostomia (dry mouth) and compromised oral hygiene, which can exacerbate discomfort, increase the risk of dental decay, and negatively impact overall health.

This presentation explores the critical intersection of dysphagia and oral health, emphasizing the need for a multidisciplinary approach in managing oral care for individuals with neurodegenerative diseases. Effective oral health management strategies, including the use of minimally invasive (MI) fluoride varnish, silver diamine fluoride (SDF), and glass ionomer cement (GIC), play a crucial role in preventing dental disease and maintaining comfort. Additionally, a structured oral care protocol tailored to patients with dysphagia can significantly reduce the risk of aspiration pneumonia and other complications.

A key component of improving oral health outcomes in this vulnerable population is the **education and training of caregivers and healthcare staff**. Implementing structured oral health education programs for those providing daily care ensures consistent, high-quality preventative measures and enhances patient quality of life. This presentation will highlight the importance of integrating oral health education into the care framework, providing insights into best practices and the latest evidence-based approaches for maintaining oral hygiene in individuals with neurodegenerative conditions.

By combining preventative dental interventions with comprehensive caregiver education, we can significantly improve both **oral and systemic health outcomes** for individuals with neurodegenerative diseases. This session will offer practical recommendations for integrating these strategies into daily care, bridging the gap between oral health and overall well-being in neurodegenerative disease management.

MNDA CARE FORUM

*M-O-TLIEBC008*

# ENHANCING MND CARE: EVALUATING THE EFFECTIVENESS OF IN-PERSON MND UPSKILL WORKSHOPS

[1]Warraich ST; [1]Jewel S; [1]Gibbs A; [1]Opie G; [1]Collins A

[1]Motor Neurone Disease NSW, Building 4 Gladesville Hospital, Victoria Road, Gladesville, NSW, Australia

## INTRODUCTION:

MND is a complex and progressive neurological condition requiring multifaceted support. A recurring challenge for people living with MND (plwMND) is accessing care from knowledgeable and experienced workforce, particularly for those in regional and rural settings (1). To improve access to a knowledgeable support network, MND NSW developed and delivered MND Upskill education workshops across 22 locations in NSW, ACT and NT. The project aimed to increase understanding of MND, raise support needs awareness, improve confidence and practical skills so that plwMND have access to a skilled support network.

## METHODS:

MND Upskill workshops integrated knowledge and insights from multiple disciplines to impart a comprehensive understanding of the disease. The workshops covered research informed content on variants of MND, causes, genetics, treatment options, clinical trials, evidence-based symptoms and their management strategies, and highlighted the role of multidisciplinary care team. In addition, the workshops provided networking opportunities, and an overview of available assistive technologies, along with practical applications of some of these technologies. To date, 40 MND Upskill workshops have been delivered: 23 for health and community care professionals and 17 for plwMND and Carers, tailored to their respective needs. These sessions engaged 486 participants (349 health and community care professionals and 137 people plwMND and Carers).

## RESULTS:

Post-workshop survey feedback was received from 90% of the participants (439 attendees). Of those, 98% stated an increased understanding of MND, 95% indicated improved support needs awareness, 95% reported raised confidence in supporting plwMND and 98% expressed willingness to recommend MND Upskill. A follow-up survey is currently being conducted to assess how well the content has been retained and applied, and to identify areas where more information or support is needed.

## CONCLUSION:

As evident from post-workshop survey results, the MND Upskill project made a significant positive impact by building a more empowered support network. MND NSW will share insights into what attendees valued and outline the next steps towards building a more knowledgeable and supportive care system for plwMND, with potential for national expansion.

## REFERENCE:

1. Velaga VC et al., Palliative and End-of-life care for people living with Motor Neurone Disease: ongoing challenges and necessity for shifting directions. Brain Sci. 2023, 13, 920.

MNDA CARE FORUM
*M-O-TLIEBC009*

# MEETING THE ASSISTIVE TECHNOLOGY NEEDS OF PEOPLE WITH MND – NSW AND VIC COLLABORATIVE MODEL

Alicia Gibb – MND NSW FlexEquip (Equipment Service) Manager
Amy Schneider – MND Victoria Equipment Service Team Leader
Jo Whitehouse – MND Victoria General Manager Support Services

## INTRODUCTION:

Motor Neurone Disease (MND) presents as a progressive, debilitating condition with changing functional needs over time, requiring frequent adjustments to AT to enhance quality of life and ensure safety of people living with MND and their carers.

The NSW and Victoria MND Equipment services hire/loan bundle approach to the provision of assistive technology (AT) offers a timely, streamlined, person-centred method to support all individuals living with MND.

## OBJECTIVE:

- To highlight the significant benefits of accessing specialized AT services tailored to the changing needs of large cohort of people living with MND
- Demonstrate the collaborative approach across MND NSW and MND Victoria equipment services in providing critical support through the provision of high quality assistive technology, significantly improving functional independence and overall well-being for individuals living with MND.
- To demonstrate the cost effectiveness and high level of AT provision to people with MND through quantitative analysis of the MND NSW and Victorian equipment services
- To highlight the transition between AT items throughout the MND progression and improved quality of life and care outcomes of people throughout that progression

## OUTCOMES/RECOMMENDATIONS:

This project demonstrates the collaboration and expansion of the MND NSW and Victoria equipment services over a three-year period to meet the complex needs of people with MND. In 2024, MND NSW and MND Victoria provided 7,589 AT items valued at $10,532,497 to 946 clients, underscoring the scale and importance of these services.

Quantitative analysis demonstrates that an extensive equipment loan service offering AT to people with MND is significantly more cost effective than purchase of AT items to meet the changing needs of people with MND.

Qualitative reviews through case study presentations illustrate the process of accessing and changing AT throughout disease progression, demonstrating both the challenges and successes of the service delivery model.

This collaborative approach not only enhances patient care but also emphasizes the necessity of timely, accessible AT solutions as a cost effective option for those with progressive neurological conditions.

MNDA CARE FORUM
*M-O-W&C001*

# TIPS AND TRICKS ON WELLBEING AND COMMUNICATION TO NOT JUST SURVIVE BUT THRIVE WITH MND

Sklavenitis, Leanne
122 Hoskins Street Sandgate 4017, Brisbane, Australia

## INTRODUCTION:

As a lived experience of MND for eight years, Leanne Sklavenitis knows the impact MND has on wellbeing and communication. Leanne's purpose is to inspire, motivate and educate the MND community from all perspectives. Despite having lost her ability to walk unaided, has lost arm strength and her voice, she continues to lead as normal a life as possible. In a constantly changing environment, Leanne will share many tips, tricks and take home strategies for the benefit of all allied health professionals and MND clients. These include strategies on physical and emotional wellbeing, and many communication ideas on the use of eye gaze to thrive and be heard in the community.

## METHODS:

With the use of AI technology, this presentation will wow and inspire you. Leanne draws on her 35 plus years as a personal trainer and leader in the fitness industry. Leanne lives and breathes MND every day and her ideas stem from trying everything herself over the years. Leanne is a member of the International Alliance of MND/ALS and has presented internationally, most recently in Montreal, Canada in December 2024 to a standing ovation.

## RESULTS:

This presentation will provide many take home tips for allied health professionals to use with their clients, as well as people with lived experience no matter what stage they are at, that can be put into practice immediately.

## CONCLUSION:

The ideas shared on wellbeing and communication will benefit all allied health services, professionals and people with lived experience all around the world.

## REFERENCES:

Sklavenitis, Leanne, 2017-2025 lived experience
https://leannesklavenitis.com/

MNDA CARE FORUM

*M-O-W&C002*

# EXPLORING PREFERENCES FOR MANAGEMENT OF COGNITIVE AND BEHAVIOURAL CHANGES IN MOTOR NEURONE DISEASE

[1,2]Francis, Rebecca; [3]Attrill, S; [1,2]Doeltgen, S

[1]Speech Pathology, College of Nursing and Health Sciences, Flinders University, Adelaide, Australia. [2]Caring Futures Institute, Flinders University, Adelaide, Australia. [3]Adelaide University, Adelaide, Australia.

## INTRODUCTION:

Cognitive and behavioural changes in MND occur in up to 50% of people with MND (pwMND) [1] and are associated with poorer outcomes and reduced quality of life [2]. However, currently it is unclear how pwMND and carers would prefer to learn about and manage cognitive and behavioural changes. We explored how pwMND and carers experience cognitive and behavioural changes and how they would prefer to learn about, recognise and manage this symptom.

## METHODS:

Qualitative design consisting of semi-structured interviews with pwMND and carers. Responses were analysed deductively using the Theoretical Domains Framework [3], then inductively themed using thematic analysis [4].

## RESULTS:

Participants (n=24) were from Australia (n=14), the UK (n=9) and Kenya (n=1). There were twelve pwMND (M=11, F=1) and twelve carers (M=3, F=9). Analyses revealed six themes: i. What I have experienced, ii. What I have experienced related to my care, iii. How this affects me, iv. If I had known, it might have been different, v. What I do to manage and vi. I want care that is relational, individualised, informative and empowering.

## CONCLUSION:

All participants reported they were not aware that cognitive and behavioural changes were associated with MND, however, half of the pwMND described experiencing changes to their cognition and behaviour. Both pwMND and carers described wanting to learn about cognitive and behavioural changes and believed this would have been helpful in understanding the disease. However, preferences on how and when these conversations would optimally occur varied.

Most participants described a preference for regular open discussions with their health care professionals, with regular opportunities to receive general information that was responsive to their current and individual needs. Further research, which is co-constructed with pwMND and carers, is needed to determine best approaches to discussing cognitive and behavioural changes in MND with families.

## REFERENCES:

1. Strong, M.J., et al., Amyotrophic lateral sclerosis-frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2017. 18(3-4): p. 153-174.

2. Radakovic, R., et al., Quality of life, cognitive and behavioural impairment in people with motor neuron disease: a systematic review. *Quality of Life Research*, 2024. 33(6): p. 1469-1480.

3. Atkins, L., et al., A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation Science*, 2017. 12: p. 1-18.

4. Braun, V. and V. Clarke, Using thematic analysis in psychology. *Qualitative Research in Psychology*, 2006. 3(2): p. 77-101.

PACTALS 2025
MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

MNDA CARE FORUM
*M-O-W&C003*

# THE ALL-ENCOMPASSING NATURE OF CARE IN MND

[1]Neville, Sally; [2]Ngo, Shyuan; [1]Steyn, Frederik; [3]Packer, Rebecca

[1]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Brisbane Queensland Australia.
[2]Austrailan Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane Queensland Australia.
[3] School of Health and Rehabilitation Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland, Brisbane Queensland Australia.

## INTRODUCTION:

The provision of care for people living with MND (plwMND) largely rests with informal caregivers generally family members (1-2). Time burdens and the impacts on carers physical, emotional, social wellbeing and quality of life are high and ever increasing as their loved one progresses (3-4). Here we investigate the perspectives of Australian carers to gain a greater understanding of the experiences of informal caregivers to elucidate the broader landscape of MND care in Australia, and to identify areas of priority and need.

## METHODS:

In-depth semi-structure interviews were conducted with 13 caregivers of plwMND to determine the burdens and challenges associated with caring for someone living with MND. Carers were selected using a purposeful sampling strategy including family, professional and former carers from across four Australian states. Interviews were conducted via the Zoom platform and were analysed qualitatively using content analysis as outlined by Graneheim and Lundman 2004 (5).

## RESULTS:

Four themes were developed as being important to people caring for plwMND. These themes – 1) transversing the MND landscape, 2) constantness of care, 3) carer wellbeing and 4) social interactions - were intrinsically linked to each other, suggesting that it is difficult to view any aspect of MND care in isolation. Rather care is a highly complex and all-encompassing set of circumstances that required constant integration, vigilance and problem solving. The “transversing the MND landscape” theme related to the external MND service landscape and how carers interact with health, support and financial support services. “Constantness of care” relates to the home environment and the physical tasks and routines that MND care requires. “Carer wellbeing” relates to the impact MND care has on the carers physical and mental wellbeing. “Social interactions” outlines carers relationships and social experiences at a family, friend and broader community level.

## CONCLUSION:

Caring for someone with MND is a complex and all-encompassing task in which no aspect of care, support or service provision should be viewed in isolation but rather as piece of a larger picture.

## REFERENCES:

1. Ng L, Kee K, Amatya B, Khan F. Patient/carer perceptions of disability in motor neurone disease and carer coping. International journal of therapy and rehabilitation. 2011;18(10):568-78.
2. Galvin M, Carney S, Corr B, Mays I, Pender N, Hardiman O. Needs of informal caregivers across the caregiving course in amyotrophic lateral sclerosis: a qualitative analysis. BMJ Open. 2018;8(1):e018721-e.
3. Chiò A, Gauthier A, Vignola A, Calvo A, Ghiglione P, Cavallo E, et al. Caregiver time use in ALS. Neurology. 2006;67(5):902-4.
4. Conroy É, Kennedy P, Heverin M, Hardiman O, Galvin M. Care, burden and self-described positive aspects of caring in amyotrophic lateral sclerosis: an exploratory, longitudinal, mixed-methods study. BMJ Open. 2023;13(1):e064254-e.
5. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105-12.

MNDA CARE FORUM
*M-O-W&C004*

# SLEEP FOR PEOPLE WITH MOTOR NEURON DISEASE AND THEIR FAMILIES IN NEW ZEALAND, A QUESTIONNAIRE STUDY

[1,2]Gauld, N; [2]Hikaka, J; [3]Buchanan, S; [4]Faletau, J; [5]Cleland, J. [6]Rutherford, S; [7]Buetow, S.

[1]Motor Neurone Disease New Zealand, 14 Erson St, Royal Oak, Auckland, New Zealand, [2]DSchool of Pharmacy, The University of Auckland, Park Rd, Grafton, Auckland, New Zealand; [3]University of Otago, Leith St, Dunedin. New Zealand; [4]Pacific Public Health Directorate, National Public Health Service, Te Whatu Ora, Claude Rd, Greenlane, Auckland, New Zealand; [5]Te Whatu Ora Bay of Plenty, Cameron Rd, Tauranga, New Zealand; 6Centre for Person Centred Research, Auckland University of Technology, Auckland, New Zealand; [7]Department of General Practice and Primary Health Care, University of Auckland, Park Rd, Grafton, Auckland, New Zealand.

## INTRODUCTION:

Little research has been carried out about what affects sleep in motor neuron disease (MND).

Aim: To ascertain sleep concerns for people with MND (pwMND), family and those bereaved in New Zealand (NZ).

## METHODS:

PwMND were invited to complete a three-part survey (informed by literature and co-designed with those with lived experience). Similarly, family carers of pwMND and those bereaved in the last two years completed a shorter survey. Surveys could be completed online (Qualtrics), on paper or (for pwMND only) by telephone interview. Participants were recruited through Motor Neurone Disease New Zealand, the MND Patient Registry, social media and word of mouth. Descriptive statistics were used.

## RESULTS:

The survey is still in the field until 16 April. To date 121, 65 and 30 responses have been received from pwMND, family of pwMND and bereaved family, respectively. The pwMND respondents represent 30% of the estimated 400 pwMND in NZ.

Of pwMND surveys to date, 41% reported sleep troubles affecting their activities the next day, on average 5.2 nights per week. This compared with 59% of family carers on average 4.2 nights per week, and 50% of bereaved on average 5.3 nights per week.

Many family of pwMND reported worse sleep since the person got MND (61%) but 43% of bereaved reported improvement in sleep since bereavement.

MND affected sleep of 79% of pwMND in some way. Most common reasons were: muscle cramps (35%), worries about family (31%), worries about the future (25%), pain other than cramps (21%), breathing equipment (16%), and worries about money because of MND (15%). MND-related concerns affecting sleep for family carers will be reported, as will factors associated with poor sleep.

## CONCLUSION:

Sleep is significantly affected by MND for pwMND and family carers. The final results and conclusion will be reported in early May.

MNDA CARE FORUM
*M-O-I&NH001*

# INNOVATIONS IN MND CARE: AN AFFORDABLE STRATEGY MONITORING WEIGHT AT HOME

[1]Sheehy TP; [2]Young CM

[1]Department of Physiotherapy, Calvary Health Care Bethlehem, 476 Kooyong Rd, Melbourne, Australia
[2]Department of Nutrition and Dietetics, Calvary Health Care Bethlehem, 476 Kooyong Rd, Melbourne, Australia

## INTRODUCTION

Weight loss is often associated with people living with MND and may lead to a more rapid progression[1]. Regular monitoring of weight can often be complicated as MND progresses and mobility deteriorates. Those who cannot stand on a regular scale or who cannot easily attend a service with a wheelchair or hoist scale, will often miss out on the benefits of regular weight monitoring or are forced to purchase weighing devices for home that are prohibitively expensive.

## METHODS:

This poster details the setup of an affordable strategy to monitor the weight of people living with MND who are using a hoist at home.

## RESULTS:

N/A

## CONCLUSION:

This poster demonstrates that clinicians should think outside the box, whilst ensuring it is appropriate and safe. With the inequality of disability funding between NDIS and Aged Care, this strategy will assist in monitoring weight at very little cost to people living with MND in Victoria.

## REFERENCES:

National Institute for Healthcare and Excellence (NICE), "Motor neurone disease: assessment and management," NICE, United Kingdom, 2020. https://www.nice.org.uk/guidance/ng42/resources/motor-neurone-disease-assessment- and-management-1837449470149

MNDA CARE FORUM
*M-O-I&NH002*

# INNOVATIONS IN MND CARE: ACHIEVING QUALITY OF LIFE GOALS FOR VENTILATED INDIVIDUALS THROUGH ACCESS TO HYDROTHERAPY A CASE STUDY

[1]Sheehy TP; [1]Parker KF

[1]Department of Physiotherapy, Calvary Health Care Bethlehem, 476 Kooyong Rd, Melbourne, Australia

## INTRODUCTION:

Hydrotherapy is a modality for people living with Motor Neurone Disease (MND) to exercise and remain physically active[1]. Hydrotherapy provides both physical and psychological benefits for people living with MND[2]. Although hydrotherapy has been shown to be safe for individuals that are ventilated via a tracheostomy in other conditions[3,4], there is no literature of this in MND.

## METHODS:

This case report details the successful involvement of a 46 year old ventilator-dependent person via tracheostomy with MND in accessing a warm water pool. This poster outlines the careful preparation and individualised approach required to ensure the person's safety and comfort, highlighting the importance of personalised care plans and team
collaboration in achieving positive outcomes for complex, ventilator-dependent individuals.

## RESULTS:

The person, who had long-term mechanical ventilation needs and minimal voluntary muscle activity due to advanced MND, was able to safely access a warm water pool to achieve his goal of floating. This was facilitated by the coordinated efforts of a multidisciplinary care team including physiotherapists, an allied health assistant, nursing staff, a disability support worker and family. Key considerations in the process, including goal setting, risk assessment and management, individual monitoring, tracheostomy and ventilator management, and communication between team members, are also discussed.

## CONCLUSION:

This case study underscores the value of interdisciplinary teamwork, innovation and a can-do attitude in exploring care options to achieve the goals of people with severe respiratory dependence and advanced neuromuscular disease.

## REFERENCES:

1. Lau FS, Brennan FP, Gardiner MD. Multidisciplinary management of motor neurone disease. Aust J Gen Pract. 2018 Sep;47(9):593-597. doi: 10.31128/AJGP-02-18-4495. PMID: 30244551.
2. Motor Neurone Disease Association. Physiotherapy and exercise with MND. April 2023. https://www.mndassociation.org/sites/default/files/2023-04/6A%20Physiotherapy.pdf. (accessed on 4th April 2025)
3. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009 May 30;373(9678):1874-82. doi: 10.1016/S0140-6736(09)60658-9. Epub 2009 May 14. PMID: 19446324; PMCID: PMC9906655.
4. Wegner S, Thomas P, James C. Hydrotherapy for the long-term ventilated patient: A case study and implications for practice. Aust Crit Care. 2017 Nov;30(6):328-331. doi: 10.1016/j.aucc.2017.01.001. Epub 2017 Feb 7. PMID: 28187904.

MNDA CARE FORUM
*M-O-I&NH003*

# THE ROLE OF THE MND PALLIATIVE CARE CLINICIAN IN MND EDUCATION IN VICTORIA

Turton Jane. MND Palliative Care Clinician- Southern Metro Region Palliative Care Consortium, Main St Mornington, Vic, Australia
Mitchell Samantha. Team Leader, MND Advisor/Support Coordinator, MND Victoria, Canterbury Rd, Surrey Hills, Vic, Australia Barbeler Carol. MND Palliative Care Clinician- Gippsland Palliative Care Consortium, 412 Landsborough St, Warragul, Vic, Australia

## INTRODUCTION:

Each of the eight health regions of Victoria have funding for the role of Motor Neurone Disease (MND) Palliative Care Clinician. The funding is provided by the Victorian Government and facilitated by MND Victoria, who also provide ongoing education for the incumbent in the role.

The MND Palliative Care Clinician is a health professional. Currently there are seven MND Palliative Care Clinicians, all but two are registered nurses. All have extensive and advanced knowledge of MND.

The purpose of the MND Palliative Care Clinician (formerly MND Shared Care Worker) is to ensure that the palliative care workforce and aged care facility staff have access to the knowledge and skills needed to support people in their care who are living with Motor Neurone Disease. This process is done via the development of collaborative links with the service providers in the community, or in Residential Aged Care Facilities (RACF).

The position of MND Palliative Care Clinician in each region works slightly differently; this has happened in response to the community and RACF's needs within each region.

Some of the MND Palliative Care Clinicians have more client-based face to face contact, whereas others support RACF's and Community Palliative Care Services and other health professionals.

## METHODS:

- Education in facilities in response to new resident/ education to care agencies.
- Education is given for complex situations or challenges.
- Debriefing sessions to community care staff or facility staff, post the passing of the person with MND.
- Education sessions and support online
- Webinars and podcasts.
- Program of Experience in Motor Neurone Disease (PEM)- an immersive experience each year for two days at Calvary Kooyong Precinct – Statewide Progressive Neurological Disease Service (Offered through Southern Metro Region Palliative Care Consortium (SMRPCC)).
- Top Up Funding (TUF) provided to people with MND who have been on community palliative care programs for 90 days - application via MND Palliative Care Clinicians

## RESULTS:

Currently there are 541 people living with MND who are registered with MND Victoria, each person is eligible for support in their care from the MND Palliative Care Clinician

Education has been provided online and face to face to NDIS carers, Home Care Package Providers, RACF's, and community palliative care providers. The staff being Registered Nurses, Enrolled Nurses, Personal Care Workers, Disability Support Workers, and Allied Health staff
Online free education to providers across Victoria and interstate.

**CONCLUSION:**

The role of the MND Palliative Care Clinician is a vital connection between the person living with MND and the care provider.

Through the work of the MND Palliative Care Clinician, carers and service providers are educated, supported and empowered to provide exemplary care, enhancing the overall quality of life of the family and person living with MND.

**REFERENCE:**

SMRPCC website MND Victoria Website
Palliative Care Victoria Website

MNDA CARE FORUM
*M-O-I&NH004*

# LUNCHTIME SESSIONS- FREE ONLINE MND EDUCATION FOR ALL

Turton Jane
MND Palliative Care Clinician- Southern Metro Region Palliative Care Consortium. Main Street Mornington, Victoria, Australia

INTRODUCTION:
The Southern Metro Region Palliative Care Consortium (SMRPCC) has collaborated with the 160 Residential Aged Care Facilities in its region for many years.

The ongoing fear of COVID outbreaks in Aged Care Facilities has resulted in a reluctance of Facilities to allow face-to-face education sessions for their staff. As a response, we tried a new concept of a series of online sessions, that were free and easy to access. Three of the seven sessions were on Motor Neurone Disease (MND).

The first series demonstrated an increasing interest with more than 50 people registering for some sessions with an attendance rate of 30%.

Evaluations indicated high satisfaction with the program. When we repeated the series, we found that there were many participants from outside the region with participants from a wide distribution of Victorian aged care nurses, but also participants from interstate.

**METHODS:**
Initially, seven sessions were planned. Four sessions specifically on Palliative Care, three on various aspects of MND including MND Overview, MND symptom Management and PEG Management in MND

Advertising for the sessions has been through SMRPCC Newsletter and email updates, and through Palliative Care Victoria Newsletters,

**RESULTS**:
Listening to participants feedback the initial three sessions relating to MND have been increased to five sessions. We now provide regular sessions on MND Respiratory Management and MND Managing Pain and Discomfort.

Now, up to 90 people register for each session. The program is currently running continuously and has had more than 1000 participants in the financial year 23/24. Because of its reach, all consortia in Victoria, under the name of the Victorian Palliative Care Network and are sharing the load and facilitating the program together

**CONCLUSION:**
Online Free education on MND and Palliative Care has been well received.

Listening to participant feedback has increased the number of MND and Palliative Care topics being offered.

Numbers of participants have dramatically increased, and participants report they are from all states in Australia

**REFERENCES:**
SMRPCC website

MNDA CARE FORUM

*M-O-TLIEBC001*

# THE IMPACT OF BLOOD LIPID CLASSES ON RISK OF DEVELOPING AMYOTROPHIC LATERAL SCLEROSIS: A SYSTEMATIC REVIEW AND GRADE ANALYSIS

[1,2]Sewell-Green, Amber; [3]Kuiper M; [3]Beelen A; [1, 4]Steyn FJ; [4,5]Ngo ST; [2,6]Matthews-Rensch KL [1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia, [2]Department of Dietetics and Foodservices, Royal Brisbane and Women's Hospital, Australia, [3]Department of Rehabilitation, Physical Therapy Science and Sports, University Medical Centre Utrecht, Utrecht, the Netherlands, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Australia, [5]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia, [6]Queensland Centre for Mental Health Research, The Park Centre for Mental Health Treatment, Research and Education, Wacol, Australia

## INTRODUCTION:

Amyotrophic Lateral Sclerosis (ALS) is associated with altered lipid metabolism (1, 2). This systematic review evaluated the impact of blood lipid classes on risk of developing ALS.

## METHODS:

A systematic search following PRISMA guidelines was conducted across six databases (PubMed, Embase, CINAHL, Scopus, Cochrane Library and Web of Science), in March 2024. MeSH terms "Amyotrophic Lateral Sclerosis" AND "Lipids" and related variants were applied. Studies were included if they reported on adult clinical studies and statistical risk of developing ALS. Standard mean difference and 95% confidence intervals (SMD[95%CI]) in baseline lipid levels were generated and descriptive statistics applied, categorising findings into reduced, no effect, or increased risk of developing ALS. GRADE criteria assessed the quality of evidence.

## RESULTS:

Searches identified 6,454 papers, yielding eight eligible studies (n=7 sterol lipids, n=1 fatty acids). There were no significant differences between ALS-cases and controls in baseline levels for five sterol lipids; total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or LDL/HDL ratio ($I^2$= 67.7%-97.6%). After removing one high-bias study, results for risk of developing ALS were heterogeneous, with no effect on risk for TG (n=4/5), TC (n=3/6), LDL-C (n=3/6), or LDL/HDL (n=2/4). HDL-C had inconsistent results (no effect, reduced risk and increased risk of onset n=2/6 each), while remaining studies suggested higher blood sterols increased disease risk. The study of fatty-acids indicated increased disease risk with higher arachidonic acid, and reduced risk with higher alpha-linoleic acid levels. GRADE of evidence was low for sterol lipids, and very low for fatty acids.

## CONCLUSION:

Observational studies examining the impact of blood sterol lipid levels on ALS risk are inconsistent and of low evidence. Further research using standardised methodologies and more precise technologies, such as Lipidomics screenings, are needed to clarify the role of lipids as clinical biomarkers in ALS.

## REFERENCES:

1. van Mantgem MJ, van Rheenen W, Hackeng AV, van Es MA, Veldink JH, van den Berg LH, et al. Association Between Serum Lipids and Survival in Patients With Amyotrophic Lateral Sclerosis A Meta-analysis and Population-Based Study. Neurology. 2023;100(10):E1062-E71.
2. Area-Gomez E, Larrea D, Yun T, Xu Y, Hupf J, Zandkarimi F, et al. Lipidomics study of plasma from patients suggest that ALS and PLS are part of a continuum of motor neuron disorders. Scientific reports. 2021;11(1):13562-.

PACTALS 2025
12th MND Australia Care Forum
Theme: From Discovery to Delivery
pactalscongress.com

MNDA CARE FORUM

*M-O-TLIEBC002*

# EVALUATING THE IMPACT OF WEIGHT LOSS AND ACCURACY OF PREDICTIVE ENERGY EQUATIONS IN AUSTRALIANS WITH AMYOTROPHIC LATERAL SCLEROSIS

[1, 2]Sewell-Green, Amber; [1]Capstick R; [2,3]Matthews-Rensch KL; [4]Henderson R; [4,5]Ngo ST; [1,4]Steyn FJ
[1]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia, [2]Dietetics and Foodservices, Royal Brisbane and Women's Hospital, Australia, [3]Queensland Centre for Mental Health Research, The Park Centre for Mental Health Treatment, Research and Education, Wacol, Australia, [4]Department of Neurology, Royal Brisbane and Women's Hospital, Australia, [5]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia.

## INTRODUCTION:

Weight loss, lower BMI and malnutrition are associated with worse prognosis in ALS[1,2]. This study evaluated the impact of negative energy balance on prognosis and survival in people living with ALS (plwALS), and the suitability of current energy equations to guide weight management support in an Australian cohort.

## METHODS:

This prospective case-control study was conducted from March 2016 to October 2024; 170 patients with probable or definite ALS had body composition (BodPod, Cosmed), metabolism (REE; QuarkRMR, Cosmed), functional capacity (ALS- Functional Rating Scale-Revised) and disease progression assessed. Baseline measures were compared to data from 173 non-neurodegenerative disease controls. Participants with ALS were then categorised based on Global Leadership Initiative on Malnutrition (GLIM)[3] weight loss criteria; stable (≤0%), minor loss (0-5%) or major loss (>5%). Changes in body composition, progression, and survival were compared across these groups. Eighty-two plwALS provided 3-Day-Food- Diaries at baseline to calculate energy intake (Xyris FoodWorks10). Daily estimated energy requirements (EER), calculated from 13 equations used in ALS, were compared to daily estimated energy intake (EEI) and accuracy to predict weight status.

## RESULTS:

Initial weight loss (>5%) was associated with greater loss of weight and fat free mass over time (p=0.01), faster functional decline (ALSFRS-R scores, p=0.01) and increased risk of earlier death (32.9±14.0 vs 57.6±33.0 months, p<0.001). No EER equation performed well; however, equations incorporating body composition and ALS-validated activity levels predicted weight status more accurately (32% vs 17%). Adjusting for higher ideal body weight improved accuracy to predict major weight loss (60%; range 0-60%).

## CONCLUSION:

Weight loss, suggesting insufficient calorie intake, is associated with worse prognosis in an Australian ALS cohort. Current equations for predicting weight status have limited accuracy. Incorporating disease specific activity, injury factors and altered metabolic demands into energy equations may help prevent malnutrition and promote weight maintenance in plwALS.

## REFERENCES

1. Marin B, Desport J-C, Kajeu P, Jésus P, Nicolaud B, Nicol M, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of ALS patients. BMJ Publishing Group; 2010. p. 628.
2. Shimizu T, Nakayama Y, Matsuda C, Haraguchi M, Bokuda K, Ishikawa- Takata K, et al. Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study. J Neurol. 2019;266(6):1412-20.
3. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9.

MNDA CARE FORUM
*M-O-TLIEBC003*

# SURVEY OF CONSTIPATION IN AUSTRALIANS WITH MND USING THE LIVED EXPERIENCE NETWORK

[1]Werth, Barry; [1]Fisher, Murray.
[1]Susan Wakil School of Nursing and Midwifery, Faculty of Medicine and Health, University of Sydney, Sydney, Australia.

## INTRODUCTION:

Constipation is one of the most common symptoms encountered by people with MND.[1,2,3] However, there has been little research conducted on constipation in MND.[2] Constipation not only causes pain but is also associated with anxiety and depression in people with MND, affecting quality of life (QoL).[2] Improved management of constipation will increase QoL. The aim of this study is to assess the prevalence and treatment of constipation in Australians with MND as well as its impact on QoL.

## METHODS:

An on-line survey of Lived Experience Network (LEN) members will be conducted using a short questionnaire consisting of 12 questions regarding Rome criteria for functional constipation, oral and other treatments used for constipation, and impact of constipation on QoL. The LEN members to be surveyed comprise active and past carers as well as people living with MND.

## RESULTS:

Based on the few international studies previously conducted, it is expected that approximately 50% of Australians with MND will report being troubled with constipation. This poster will report the results of this preliminary national survey.

## CONCLUSION:

This survey of LEN members will provide preliminary data regarding constipation in MND in a quick, efficient manner, prior to conducting an in-depth longitudinal study of constipation in people with MND using data collected by the 15 Australian clinics in the MiNDAUS registry.

## REFERENCES:

1. Lau FS, Brennan FP, Gardiner MD. Multidisciplinary management of motor neurone disease. Aust J Gen Pract 2018;47(9):593–6.
2. Niu T, Zhou X, Li X et al. Development and validation of a dynamic risk prediction system for constipation in patients with amyotrophic lateral sclerosis. Front Neurol 2022;13:1060715.
3. Dharmadasa T, Henderson RD, Talman PS, et al. Motor neurone disease: progress and challenges. Med J Aust 2017;206(8):357–62.

MNDA CARE FORUM
*M-O-TLIEBC004*

# PRIORITISING THE FACTORS INFLUENCING NON-INVASIVE VENTILATION UPTAKE BY PEOPLE WITH MOTOR NEURONE DISEASE: A MODIFIED DELPHI STUDY

[1,2,3]Russo K; [1,2]Carey K; [1,2,4]Grivell N; [1,2]Berlowitz, DJ; [1,2]Graco, M; the NIV in MND stakeholder advisory group

[1] Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia, [2]Department of Physiotherapy, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia, [3]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Qld, Australia, [4] FHMRI Sleep Health, Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia

**INTRODUCTION:**
Non-invasive ventilation (NIV) increases quality of life and life expectancy in people with motor neurone disease (MND). Increasing access and acceptance of NIV is key. This study aimed to compile a list of factors influencing NIV uptake in MND and to establish consensus on their importance and feasibility.

**METHODS:**
A three-stage modified Delphi study with an expert panel of 19 healthcare professionals, advocates, researchers, and people with lived experience of MND in Australia. Three rounds of web-based voting were conducted. Rounds 1 and 2 were completed by 19 panelists during a two-day in-person/online workshop. Round 3 was completed remotely by 18 panelists. Influencing factors were discussed, rated, and ranked according to their importance and how feasible they were to address in a future co-design project.

**RESULTS**:
Thirty NIV uptake influencing factors were identified and refined by the group. Consensus on level of importance was reached for 22 (73%) factors (14=High importance; 6=Moderate; 2=Low) and feasibility on 19 (63%) factors (3=High feasibility; 4=Moderate; 12=Low). The top five influencing factors based on importance were: (1) Significant variation in the composition of MND multidisciplinary teams and their models of care across Australia (Moderate-high feasibility), (2) Provision of timely and consistent information about NIV (High feasibility), (3) Person with MND well connected and supported by MND community (Moderate- high feasibility), (4) Inequitable funding models to access NIV equipment (Low feasibility), and (5) Clinicians' skill in presenting NIV information that is tailored to the patient's goals and responsive to their current physical, emotional and mental state (Moderate feasibility).

**CONCLUSION:**
This study generated a list of NIV influencing factors ranked according to their importance. Along with the feasibility rankings, these findings are informing a co-design project, with the MND community, to develop, test, and implement interventions that target these important influences on NIV uptake.

MNDA CARE FORUM

*M-O-TLIEBC005*

# FROM TEAM TO MODEL: EMBEDDING TRUE MULTIDISCIPLINARY CARE FOR PEOPLE LIVING WITH MND IN THE COMMUNITY

Dan Charny[1], Alicia Edwards[1]
[1]MND Queensland, Oxley, QLD, Australia

## INTRODUCTION

Motor Neurone Disease (MND) brings complex, progressive challenges that demand a coordinated and holistic approach to care. At MND Queensland, a team of allied health professionals supports people with MND (PwMND) through community-based care. While the team has long operated collaboratively, we recognised the need to move from parallel practice toward a true multidisciplinary model—one that mirrors the integrated care of hospital-based multidisciplinary clinics (MDCs) and brings it into the community[1].

## METHODS

MND Queensland currently employs a team of nine allied health professionals with a shared commitment to real-time collaboration, joint appointments, and proactive problem-solving. A standardised multidisciplinary assessment was introduced at initial visits to ensure early identification of needs beyond the presenting discipline. The organisation also expects that initial visits are conducted in a team setting in all but exceptional circumstances. This model supports role clarity, reduces duplication, and aligns with best-practice guidelines for MND care[2, 3].

## RESULTS

The transition has led to stronger interdisciplinary relationships and more coordinated care. Staff report increased satisfaction, citing greater opportunities for collaboration, shared learning, and on-the-spot problem-solving. The new model also reduces the number of separate appointments for clients. While client feedback has been profession-specific to date, it consistently reflects high satisfaction with care and deep appreciation for staff expertise and responsiveness.

## CONCLUSION

Embedding a multidisciplinary model of care within the community context can extend the benefits of MDCs beyond the hospital setting[4]. This approach enhances care quality, supports team cohesion, and has the potential to reduce service fragmentation and client burden. Ongoing reflection and adaptation will ensure the model continues to meet the evolving needs of PwMND and their families.

## REFERENCES

1. Hardiman O. Multidisciplinary care in ALS: measuring the immeasurable. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2015; 16(Supp 1):S5.
2. Patient experience in adult NHS service: improving the experience of care for people using adult NHS services. [CG138] 17 June 2021. https://www.nice.org.uk/guidance/cg138
3. Motor neurone disease: assessment and management. [NG42] 23 July 2019. https://www.nice.org.uk/guidance/ng42
4. Galvin M, Ryan P, Maguire S, Heverin M, Madden C, Vajda A, et al. 2017. The path to specialist multidisciplinary care in amyotrophic lateral sclerosis: A population-based study of consultations, interventions and costs. PLoS ONE 12(6): e0179796. https://doi.org/10.1371/journal.pone.0179796

MNDA CARE FORUM
*M-O-TLIEBC006*

# DEVELOPMENT OF A SPECIALTY-DRIVEN HOME PALLIATIVE CARE SERVICE IN MOTOR NEURONE DISEASE

Krishnan P[1], Capelle D[2], Hamzah E[1] , Shahrizaila N[3]
[1]Hospis Malaysia, Kuala Lumpur, Malaysia, [2]Palliative Department, Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia, [3]Neurology Department, Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia.

## INTRODUCTION:

Community palliative care (CPC) services in Malaysia remain isolated, with limited integration into the broader healthcare system (1) . Despite the need for early palliative care involvement, many patients are referred late in their disease trajectories, reducing the potential benefits (2). In response to these challenges, this article aims to describe a change within a CPC service in Malaysia, shifting towards a specialty-driven approach tailored for patients with motor neurone disease (MND) (3). This change seeks to address existing gaps in care by offering more timely and specialized support for people suffering from MND.

## METHODS:

A memorandum of understanding (MoU) was established in 2022 between Hospis Malaysia (HM), an interdisciplinary team providing home palliative care service in Kuala Lumpur and the neurology department at University Malaya Medical Centre (UMMC), a teaching hospital running a multidisciplinary team (MDT) clinic for MND, with the objectives to integrate CPC into patient's care pathways and facilitate exchange of skills and knowledge. Key components included visiting position for both teams, joint assessments of palliative needs and monthly MDT case discussions.

## RESULTS:

Before the MoU, referrals to HM averaged 5 per year but increased to 23 cases in 2022 and 25 in 2023. In total, 43 patients were cared for in 2023, with 14 deaths by year-end. 2023 mortality data indicated 63% were referred within 2 years of diagnosis, and length of care for 64% of patients was 4-6 months. This is significantly longer compared to those with other neurodegenerative diseases as well as organ failures and cancer, where an average of 50% received care for less than a month from the time of referral. Home was the preferred place of care and death for 92% of patients, with 77% achieving home death. 50% required out of hours support with only 15% requiring emergency home visits.

## CONCLUSION:

This collaboration fostered trust between teams, patients, and caregivers leading to early CPC involvement with promising outcomes. The MoU has been renewed for another 5 years, with plans to study patient and caregiver outcomes to further strengthen the collaboration.

## REFERENCE:

1. Segarmurthy MV, Lim RB, Yeat CL, et al. Mapping Palliative Care Availability and Accessibility: A First Step to Eradicating Access Deserts in the Low- and Middle-Income Settings. *J Palliat Care.* 2024;39(4):255-263. doi:10.1177/08258597231214485

2. Oliver DJ, Borasio GD, Caraceni A, De Visser M, Grisold W, Lorenzl S, et al. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. European Journal of Neurology. 2016;23(1):30-8.

3. Hogden A, Foley G, Henderson R, James N, Aoun S. Amyotrophic lateral sclerosis: improving care with a multidisciplinary approach. Journal of Multidisciplinary Healthcare 2017;Volume 10:205–15.

MNDA CARE FORUM
*M-O-IPIC&S001*

# AN EVALUATION OF THE ALSSQOL-SF IN THE MALAYSIAN CONTEXT THROUGH COGNITIVE INTERVIEWING

Wafa Sabirin[1], Fazlina Ahmad[2], Saiful Adni Abd Latif[2], Sheriza Izwa Zainuddin[1], Chee-Loong Lam[1], Chun-Ian Soo[1], Kee-Huat Chuah[1], Sakinah Sabirin[1], Nortina Shahrizaila[1], David Paul Capelle[1]

[1]Department of Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
[2]Department of Biomedical Science, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.
Correspondence: David Paul Capelle, E-Mail: david.capelle@um.edu.my

## BACKGROUND

The optimization of quality of life (QOL) is an important goal of care for people living with ALS (PALS) in the absence of curative treatment. The ALSSQOL-SF has been developed and validated to measure QOL across the biopsychosocial and spiritual domains in the specific context of ALS. It has been translated and validated in several languages, however its applicability in the context of the multicultural, multiethnic Malaysian population has not yet been investigated.

## METHODS

The QOL of 21 patients was measured using either the original English version or a translation into the Malay language. PALS were instructed to share their thoughts while completing the instrument in the manner of a "think aloud" process as commonly used in cognitive interviewing (CI) methodology. We evaluated how participants interpreted the questions and chose their answers.
Interviews were transcribed and thematically analysed.

## RESULTS

The quantitative survey responses were comparable to those from previous validation studies, scoring lowest (worst) in the domain of "physical symptoms" and highest (best) in the domain of "interaction with people and environment". Language and cultural factors affected the interpretation and responses to questionnaire items. Items related to spirituality posed some difficulties in interpretation and the topic of intimacy was perceived of variable relevance.

## CONCLUSION

This study highlights the relevance of cultural and language-related factors in measuring QOL based on a questionnaire initially developed in a different (European/North American) context. Cultural factors affect experiences of suffering in ALS and this needs to be considered when considering the suitability of a QOL instrument across different cultures. Additionally, domains of QOL are often differentially weighted, in particular the importance of intimacy.
The process of completing a questionnaire can be burdensome and uncomfortable when it involves confronting the emotional distress of progressive disease. On the other hand, it can be perceived as beneficial if it serves to direct care in order to reflect individual preferences.

MNDA CARE FORUM

*M-O-W&C001*

# THE EXPERIENCE OF SUFFERING IN ALS: A CASE REPORT

[1]Ang CM, [5]Rasyid M, [5]Krishnan P, [1]Zainuddin S, [1]Lam CL, [4]Pek EW, [3]Soo CI, [2]Shahrizaila N, [1]Capelle D

[1] Palliative Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[2] Neurology Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[3] Respiratory Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[4] Rehabilitation Department, Universiti Malaya Medical Centre, Lembah Pantai, Kuala Lumpur, Malaysia,
[5] Hospis Malaysia, Cheras, Kuala Lumpur, Malaysia

## INTRODUCTION:

Suffering is a complex, multidimensional experience for people living with Amyotrophic Lateral Sclerosis (PLWALS), encompassing psychological, physiological, social, and spiritual distress when they have exhausted their coping resources for perceived loss. While multidisciplinary clinics have been shown to improve quality of life, less attention has been given to the specific details of their suffering. Here, we report the experience of a patient with ALS who exhibited a range of psychological and emotional distress in her journey.

## CASE DISCUSSION:

A 42-year-old mother, diagnosed ALS at the peak of her career. She was initially in denial, challenging the diagnosis in the hopes of a misdiagnosis. Over six months, she experienced a rapid deterioration with ALS Functional Rating Scale (ALSFRS) dropping from 42 to 15. She lost strength, ability to swallow safely and speech gradually incomprehensible. Denial was replaced by fear and anxiety of what was to come, necessitating admission to the palliative unit. Her hope was rekindled upon learning about artificial feeding and ventilation, and whilst non-invasive ventilation helped alleviate symptoms, a feeding tube was not tolerated.

There was despair in experiencing constant breathlessness as well as losing the ability to enjoy the simple pleasures such as eating, further enhancing her suffering. Psychological and spiritual support, including cognitive behavioural therapy, antidepressants, and spiritual interventions, were provided. After three weeks, she was able to overcome her anxiety and gained confidence to return home with support from her family and community hospice.

## CONCLUSION:

Whilst the loss of functional abilities in PLWALS is clearly apparent, their suffering is often overlooked resulting in considerable distress. Addressing the psychological and existential aspects of suffering through personalised, compassionate care is crucial. Interventions aimed at transforming the psychological processes of suffering from an early stage of diagnosis may provide a more sustained effect in reducing the suffering of PLWALS.

## REFERENCES:

1. Tan SB, et al. BMJ Supportive & Palliative Care 2016;0:1–6. doi:10.1136/bmjspcare-2015-001064
2. Cassell, Eric J. *The Nature of Suffering and the Goals of Medicine.* Originally published in *The New England Journal of Medicine*, Vol. 306, No. 11, March 18, 1982, pp. 639-645.

MNDA CARE FORUM
*M-O-W&C002*

# EMOTIONAL ADJUSTMENT AND MND: THE BENEFITS OF AN IN-HOUSE COUNSELLING PROGRAM FOR PEOPLE WITH MND AND THEIR FAMILIES

[1]Bradhurst, B; [1]Whitehouse, J; [1]Hamilton, K; [1]Crask, E

[1] MND Victoria, 265-267 Canterbury Road, Canterbury, Vic, Australia

## INTRODUCTION:

People living with Motor Neurone Disease (MND) and their families experience ongoing, multiple losses requiring continual emotional adjustment. With no known cure, the emotional impacts of the disease are significant. Multidisciplinary and community-based services provide best practice person-centred care for people living with MND in Victoria, however, a recent survey[1] found that MND- specific grief support was lacking, particularly in regional areas.

## METHODS:

To assess the feasibility and acceptability of an in-house counselling program for people living with MND and their families, a counselling program was trialed from January to December 2024. The pilot program offered flexibly responsive emotional adjustment support to people living with MND and their families from the time of diagnosis to bereavement, via phone, telehealth, and in-person sessions. The program was promoted using in-house newsletters, flyers, and word of mouth. The service was evaluated at 12 months using an anonymous online survey of clients, family members, and staff.

## RESULTS:

An overwhelming majority of respondents found the service helpful in addressing their issues and strongly recommended the service to others. All respondents endorsed that they were satisfied with the service and perceived the counsellor as skilled and effective. Identified improvements included enhancements to the counselling room and improved promotion of the service.

## CONCLUSION:

Survey results and other feedback has demonstrated the feasibility and acceptability of an in-house counselling service for providing emotional adjustment support to people with lived experience of MND. The program will continue to be evaluated to inform ongoing refinement and possible broader implementation of the program.

## REFERENCES:

MND Victoria (2023) *Grief and Bereavement Project*. Internal Report. Unpublished.

MNDA CARE FORUM

*M-O-W&C003*

# DESCRIPTIVE ANALYSIS OF PATIENTS WITH MOTOR NEURONE DISEASE WHO UNDERWENT VOLUNTARY ASSISTED DYING IN WESTERN AUSTRALIA

[1]Nathani, Dev

[1]Perron Institute for Neurological and Translational Science, Ground Floor, RR Block, QE II Medical Centre, Ralph & Patricia Sarich Neuroscience Building, 8 Verdun St, Nedlands, WA 6009

**INTRODUCTION:**

Some patients with motor neurone disease (MND) have undergone voluntary assisted dying (VAD) since it legalised in Western Australia in July 2021. An analysis was undertaken to better understand the characteristics of such patients.

**METHODS:**

Medical records of patients in the author's motor neuron disease clinic were reviewed to identify patients who underwent VAD. Extracted information included patient demographics and various disease characteristics documented within 3 months of the 2 following timepoints: timepoint-1 (T1) was date of VAD first request, timepoint-2 (T2) was date of using the VAD substance.

**RESULTS:**

As of February 2025, 22 patients were identified. 14(64%) were male. Onset was bulbar in 5(23%), respiratory in 1(5%), upper limb in 9(41%) and lower limb in 7(32%). 4(18%) lived alone, 15(68%) with their partner, 3(14%) with their child. Median age was 63 years at symptom onset. Median ALS-FRS decline rate was 1.2 points/month. At T1, the median ALS- FRS was 20.5, 5/18 had no mobility aid, 5/18 needed a walking aid, 8/18 were wheelchair-bound, 11/18 were recommended NIV (4 refused), 10/18 were recommended a PEG (5 refused), and 5/18 had a communication aid. The median time between T1 to T2 was 56 days. At T2, the median ALS-FRS was 18, 5/22 had no mobility aid, 3/22 needed a walking aid, 14/22 were wheelchair-bound, 14/21 were recommended NIV (6 refused), 17/22 were recommended a PEG (9 refused), and 10/21 had a communication aid. Patient characteristics at T2 compared with T1, included lower ALS-FRS (18 vs 20.5), increased wheelchair dependence (64% vs 44%), recommendation for NIV (67% versus 61%), recommendation for PEG (77% vs 56%), and use of communication aid (48% vs 28%).

**CONCLUSION:**

Most patients have significant functional impairment with high frequency of wheelchair dependence, and need for NIV or PEG by the time they use the VAD substance.

MNDA CARE FORUM
*M-O-W&C004*

# DIRECTING CARE TOWARDS THE CARER: EMPOWERING CARERS TO SUPPORT LOVED ONES WITH MOTOR NEURONE DISEASE (MND)

[1]O'Connor M; [2]Whitehouse J; [3]Tull V

[1,2,3] Support Services, MND Victoria, 265-267 Canterbury Rd, Canterbury VIC 3126, Australia

## INTRODUCTION:

In late 2023, MND Victoria received a grant from FightMND to develop a series of five educational videos to support carers of individuals with motor neurone disease (MND). Recognizing a significant gap in resources available to carers, particularly in navigating common care challenges, MND Victoria initiated the Carers Can Project. Launched in November 2024, the project aimed to provide carers and individuals living with MND with initial strategies to manage care challenges while awaiting specialist support. The videos were designed to be applicable across the early stages of MND and offer timely, accessible and practical advice.

## REPORT:

Guided by feedback from a reference group consisting of MND Victoria staff and carers (past and present), five key topics were selected for the videos: managing comfort in bed, self- care, communication changes, eating difficulties, and fatigue. Six experienced health professionals contributed to the videos, alongside staff and carers, ensuring a personal, relatable approach to care. Each video was accompanied by an educational booklet summarizing key points. The videos were made available on MND Victoria's YouTube channel and website, with outreach to the broader MND community through emails, newsletters, and social media.

## CONCLUSION:

The Carers Can Project successfully produced five educational videos, empowering carers with practical strategies to implement while awaiting healthcare support. Released in late November 2024, the videos have garnered 866 views on the project webpage and 618 views on YouTube. The 'Taking Care of the Carer' video emerged as the most popular, with 208 views (33.7%), signaling strong interest in carer wellbeing. Preliminary analytics suggest a continued demand for resources focused on supporting carers, highlighting a valuable area for future development.

# PACTALS 2025

12th MND Australia Care Forum

Theme:
Towards Precision in ALS/MND Treatments and Care

**7 - 9 September 2025**
Melbourne Convention and Exhibition Centre, Australia

Organised by:

mnd Australia

PACTALS
Pan-Asian Consortium for Treatment and Research in ALS

Visit our website
for more information

pactalscongress.com