FILSLAN
Filière de Santé Maladies Rares Sclérose Latérale Amyotrophique et Maladies du Neurone Moteur

ARSLA
Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone

JR12
ALS and MND research meeting

12TH ALS AND MND RESEARCH MEETING

October 7 and 8, 2026

ICM, Paris

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Advancing ALS and Motor Neurone Disease Research Together

Twelve editions, hundreds of scientific contributions, countless discussions and encounters: year after year, the FILSLAN and ARSLA Research Days bring together a community united by a shared ambition to better understand amyotrophic lateral sclerosis and other motor neurone diseases, and to translate scientific progress into meaningful advances for patients.

This 12th edition once again reflects the vitality and diversity of our community. The programme includes four keynote lectures, one round table, 26 oral presentations and 20 posters, spanning the full spectrum of research from fundamental molecular mechanisms and pathophysiology to biomarkers, neuroimaging, epidemiology and therapeutic development.

Several major and timely themes will shape this year's discussions: dysregulation of translation initiation in ALS and FTD, peripheral TDP-43 pathology, the role of clinical and biological markers in prevention trials, and the contribution of neuroimaging to understanding disease heterogeneity and progression. The round table devoted to genome-exposome interactions will broaden this perspective by exploring how genetic susceptibility, environmental exposures and their complex interplay may influence ALS risk.

These Research Days are also designed to foster collaboration. The presentation of FILSLAN-supported projects, the ARSLA session and awards, and the prominent contribution of early-career researchers illustrate our shared commitment to nurturing emerging talent and developing innovative, multidisciplinary and international research projects.

The strength of this meeting lies above all in its collective spirit. I would therefore like to warmly thank all the speakers, moderators, researchers, healthcare professionals, partners and organisers who have contributed to this programme.

May these two days provide an opportunity not only to share knowledge, but also to generate new ideas and collaborations capable of accelerating progress for people living with ALS and motor neurone diseases.

Professor Philippe Couratier
Coordinator, FILSLAN

Wednesday 7 October 2026

9:30 - 9:45	Opening - Philippe COURATIER (FILSLAN), Valérie GOUTINES (ARSLA) and Edor KABASHI (ARSLA)
9:45-11:45	**SESSION 1: PATHOPHYSIOLOGY OF MOTOR NEURONE DISEASES** Moderators: Séverine BOILLÉE and Pascal LEBLANC
9:45	• **Conference: Translation initiation dysregulation: a master driver in ALS/FTD** **Franck MARTIN** IBMC, Architecture et Réactivité de l'ARN, UPR 9002, Strasbourg
	• 6 oral communications (6 x 15 minutes)
10:15	OC 1.1 - Charlotte GAVARD *Institute for Neurosciences of Montpellier, Inserm UMR 1298, Montpellier*
10:30	OC 1.2 - Véronique MARCHAND-PAUVERT *Sorbonne Université, CNRS, Inserm, LIB, Paris*
10:45	OC 1.3 - Gani OUEDRAOGO *Aix Marseille Univ, CNRS, CRMBM, Marseille*
11:00	OC 1.4 - Aline HAETTY *Institute for Neurosciences of Montpellier*
11:15	OC 1.5 - Farah AL HAJJ *Inserm UMR_S 1329, STEP, CRBS, Strasbourg*
11:30	OC 1.6 - Chloé SUBECZ *Laboratoire Chimie Physique et Chimie du Vivant, CNRS UMR 8228, ENS, Paris*
11:45-12:00	Break (15 minutes)
12:00-12:30	**FILSLAN PROJECT AWARD** (3 x 10 minutes) • ALS-Gut and its POP sub-cohort: gut microbiota, pollutant exposure and disease progression in a French nationwide ALS cohort, Gaëlle BRUNETEAU • Clinical and genetic characteristics of ALS in Latin America: a prospective, multicenter study in Ecuador, Uruguay and Argentina, Daniells ERAZO • Where Are We with the premodiALS Study, and What Is Planned Next? Laura TZEPLAEFF
12:30-14:00	Lunch buffet / First poster session
14:00-15:15	**ARSLA SESSION** Moderators: Pierre-François PRADAT and Cédric RAOUL
	• Brief introduction, Valérie GOUTINES
	• 4 oral communications (4 x 15 minutes)
	OC A.1 - Guillaume CARON *Université Paris Cité, CNRS, Saints-Pères Paris Institute for the Neurosciences, Paris*
	OC A.2 - Christophe CARREAU *CIRB Collège de France, CNRS UMR7241, INSERM U1050, PSL University, Paris*
	OC A.3 - Giuseppina GIGLIA-MARI *Institute NeuroMyoGene, Lyon*
	OC A.4 - Lara MIGLIACCIO *Paris Brain Institute*
	• ARSLA calls: a new category to propel transnational projects toward the Institut Charcot, Pierre-François PRADAT and Cédric RAOUL
15:15-15:30	Bringing clinical perspectives to the bench, Lenny POMMEROLLE
15:30-16:00	Break (30 minutes)
16:00-18:00	**SESSION 2: BIOMARKERS AND THERAPIES IN MOTOR NEURONE DISEASES** Moderators: Hélène BLASCO and Gaëlle BRUNETEAU
16:00	• **Conference: Beyond the brain and the spinal cord : peripheral TDP-43 pathology in ALS** **Philippe CODRON** ALS reference center, Department of Neurology, Neurobiology and Neuropathology, Department of Pathology, University Hospital of Angers. Inserm U1083-CNRS 6015, SFR ICAT, Health Innovation and Artificial Intelligence Department
	• 6 oral communications (6 x 15 minutes)
16:30	OC 2.1 - Giorgia QUERIN *Pitié-Salpêtrière Hospital, ALS reference center, Paris*
16:45	OC 2.2 - Laura TZEPLAEFF *Rechts der Isar Hospital of the Technical University Munich*
17:00	OC 2.3 - Lingyi ZHANG *INSERM, STEP–CRBS, UMR-S1329, Strasbourg*
17:15	OC 2.4 - Emmanuelle GENIN *INSERM U1081, CNRS UMR 7284, IRCAN, Nice*
17:30	OC 2.5 - Jelena SCEKIC-ZAHIROVIC *German Center for Neurodegenerative Diseases (DZNE), Ulm*
17:45	OC 2.6 - Nicolas BOISSART *Neurocentre Magendie-INSERM U1215, Bordeaux*
From 19:00	ARSLA Awards Evening (on registration)

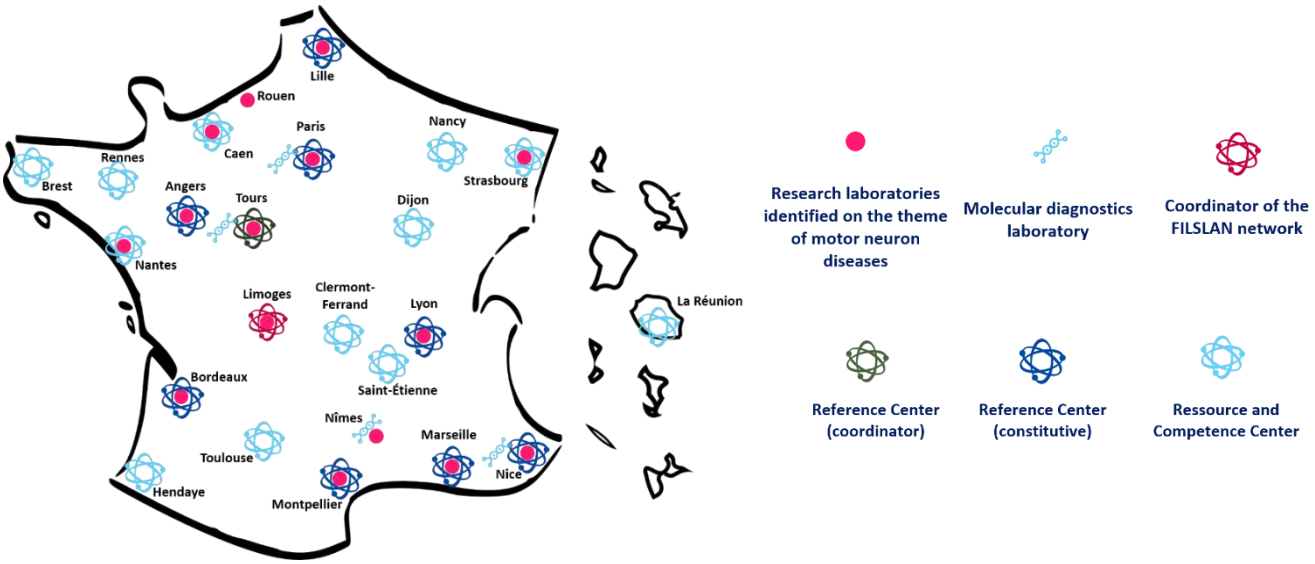
Thursday 8 October 2026

8:45-9:00	Welcome
9:00-11:00	**SESSION 3: MOLECULAR MECHANISMS OF MOTOR NEURONE DISEASES** Moderators: Stéphanie MILLECAMPS and Caroline ROUAUX
9:00	• **Conference: Prevention trials for ALS and FTD: the role of clinical and biological markers** **Michael BENATAR** Professor of Neurology, University of Miami
9:30 9:45 10:00 10:15 10:30 10:45	• 6 oral communications (6 x 15 minutes) OC 3.1 - Florence ROUSSEL *Institut Polytechnique de Paris, CNRS UMR 7654, Palaiseau* OC 3.2 - Philippe GOSSET *Institute of Psychiatry, Psychology and Neuroscience, King's College London* OC 3.3 - Nour HALABI *Imagine Institute, Unité 1163, Paris* OC 3.4 - Shiyang HE *Institut NeuroMyoGène, (INMG-PGNM), UMR5261, INSERMU1315, Lyon* OC 3.5 - Helena MOTALN *Department of Biotechnology Jožef Stefan Institute, Ljubljana* OC 3.6 - Hoang Hung CAI *SABNP, Inserm 1204, , Paris-Saclay University*
11:00-11:15	Break (15 minutes)
11:15-12:15	**CONFERENCE: Neuroimaging in ALS: Understanding Disease Heterogeneity and Progression** Moderator: Philippe COURATIER **Federica AGOSTA** Associate Professor of Neurology at Vita-Salute San Raffaele University (UniSR), Milan
12:15-13:45	Lunch buffet / Second poster session
13:45-14:00	Announcement of ARSLA awards / Research support actions ARSLA scientific committee jury: Pascal BRANCHEREAU, Florence ESSELIN, Gwendal LE MASSON, Caroline ROUAUX
14:00-16:00	**ROUND TABLE: GENOME–EXPOSOME INTERACTIONS** Moderator: Philippe COURATIER and Giancarlo LOGROSCINO
14:00	• **Global epidemiology of ALS** **Giancarlo LOGROSCINO** Center for Neurodegenerative Diseases and Aging Brain - University of Bari/Pia Fond. Card. G. Panico
14:25	• **The exposome and ALS** **Robert BAROUKI** INSERM Institute of Public Health
14:50	• **ALS risk factors - familial design and synergistic effects** **Fang FANG** Institute of Environmental Medicine, Karolinska Institutet
15:15	Discussions
16:00-16:15	Closing / General conclusion

FILSLAN

FILSLAN is the national network for rare diseases dedicated to Amyotrophic Lateral Sclerosis and motor neurone diseases. The network was created in 2014 by the Ministry of Social Affairs and Health as part of PNMR 2 and under the responsability of DGOS. Since January 2021, Professor Philippe COURATIER is the national coordinator of the FILSLAN network which is located at the Limoges University Hospital. Today, 22 ALS Centers have been labeled.

FILSLAN network



The FILSLAN team

Aurélie THEILLAUMAS (BNDMR and TPE), Daniells Andréa ERAZO (research), Philippe COURATIER (national coordinator), Julie CATTEAU (project manager) and Coline AUPART (communication, event, training)

ACT4ALS-MND

National Network for Clinical Research in Amyotrophic Lateral Sclerosis- Motor Neurone Diseases

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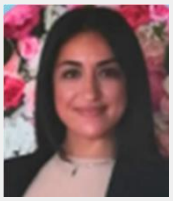

Alizé CHALANÇON
project manager

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FILSLAN website

ARSLA

Founded in 1985, ARSLA is the French National Association for ALS Research. ARSLA is committed to discovering treatments and a cure for ALS, and to serving and empowering people affected by the disease.

The association offers a range of services to support patients and their families. For example, it provides, free of charge, equipment that improves quality of life, such as communication devices that allow people with ALS to communicate despite their limitations.

ARSLA, together with Institut Imagine, is the driving force behind Institut Charcot, an institute dedicated to accelerating concrete solutions for people living with ALS through translational research and the federation of different actors (researchers, clinicians, patients' associations, and institutions), placing patients and caregivers at the heart of the research process.

Only donations make this support possible and speed up ALS research. Your donation today can help find a cure. www.arsla.org.

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Calls

Since 2006, ARSLA has invested over € 13 million to support more than 250 research projects. This support is done across three categories of calls:

- **Academic projects**: fundamental research, genetics, molecular/cellular biology, e-health/information technology, new evaluation criteria, and epidemiology/natural history.
- **Young researcher projects**: research carried out as part of a 4th-year PhD thesis on ALS.
- **Proof-of-concept projects**: projects with concrete applications for patients, using translational approaches, that require one year of maturation before they can be considered for Institut Charcot's translational pipeline and accelerated toward clinical development and application.

Donate and change the future of ALS !

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Effik is a French pharmaceutical company, a subsidiary of the Italfarmaco Group, that operates in more than twenty countries. With strong local roots and a global vision, Effik applies its expertise in two areas: Neurology and Women's Health. In each of these areas, Effik develops solutions to meet the needs of patients and healthcare professionals, whilst meeting the highest standards of quality, safety and regulatory compliance. Neurology is a key focus area, centred on amyotrophic lateral sclerosis (ALS). Effik's involvement is part of a commitment to partnership with clinicians, researchers and patient organisations. The fact that Effik will be taking part in the ALS and Motor Neuron Disease Research Days in 2026, for the 10th consecutive year, demonstrates its commitment to research and patients.

BRONZE

Biogen is a leading biotechnology company that pioneers innovative science to deliver new medicines to transform patients' lives and to create value for shareholders and our communities.

We apply deep understanding of human biology and leverage different modalities to advance first-in-class treatments or therapies that deliver superior outcomes. Our approach is to take bold risks, balanced with return on investment to deliver long-term growth.

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SESSION 1: PATHOPHYSIOLOGY OF MOTOR NEURONE DISEASES

Moderators: Séverine BOILLÉE and Pascal LEBLANC

- Conference: TRANSLATION INITIATION DYSREGULATION: A MASTER DRIVER IN ALS/FTD

Franck MARTIN

Institut de Biologie Moléculaire et Cellulaire, Architecture et Réactivité de l'ARN, UPR 9002 du CNRS, 2 allée Konrad Roentgen, F-67084 Strasbourg, Université de Strasbourg

Translation initiation, which consists in the assembly of the ribosome on the start codon, is the rate-limiting step that defines the translational landscape of the cell to produce its proper proteome. Therefore, translation initiation is a highly regulated process that can be further modulated by several *cis*-acting elements such as the 5'UTRs, the presence of uORFs, the start codon context or the presence of secondary structures in the vicinity of the start codon. In neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), the translation initiation process is dysregulated and this defect is a major driver that triggers the pathology. In our laboratory, we decipher the molecular mechanisms of translation on specific *C9ORF72* transcripts that are critical for these neurodegenerative diseases.

- Presentations selected from abstracts submitted

OC 1.1 - CONTRIBUTION OF NEUTROPHILS TO AMYOTROPHIC LATERAL SCLEROSIS PATHOGENESIS

Gavard C (1), Ritacco C (1,3), Galliere A (1), Issa Y (1), Brugioti V (1), De La Cruz E (1,2), Esselin F (1,2), Vincent T (1), Raoul C. (1,2)

(1) Institute for Neurosciences of Montpellier, Inserm UMR 1298, University of Montpellier, France. (2) ALS Reference Centre, University of Montpellier, CHU Montpellier, Montpellier, France. (3) Hematology laboratory, GIGA Institute, University of Liège, Belgium.

Purpose : Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motoneuron loss, leading to paralysis and respiratory failure. Increasing evidence highlights a major immune imbalance in ALS patients. [1] Among these alterations, an elevated neutrophil-to-lymphocyte ratio is associated with faster disease progression and reduced patient survival. [2] Neutrophils, the most abundant circulating leukocytes, play a central role in inflammatory responses. However, under dysregulated immune conditions, some of their functions, including the formation of neutrophil extracellular traps (NETs), may become detrimental to surrounding tissues. [3] This study aims to clarify the role of neutrophils and NETs in ALS progression.
Methods : Here, we investigate the role of neutrophils in ALS progression, focusing on their recruitment, activation, and impact on motoneurons using both murine models and patient-derived data. To address this, we combined flow cytometry, imaging, in vitro live-cell analysis, and in vivo behavioral experiments.
Results : ALS patients and $SOD1^{G93A}$ mice exhibited an increased neutrophil-to-lymphocyte ratio together with a higher proportion of circulating neutrophils. In $SOD1^{G93A}$ mice, we observed an early infiltration of neutrophils into the spinal cord. Neutrophils isolated from symptomatic ALS mice displayed an enhanced capacity to generate NETs in vitro. Importantly, NET-associated mechanisms promoted motoneuron death in vitro.
Conclusion : Our findings identify neutrophils and NETs as active contributors to ALS pathogenesis and motoneuron degeneration. Targeting neutrophil-driven inflammation may therefore represent a promising therapeutic strategy to slow disease progression in ALS.

Reference :

1. Wang, H., Liu, Y.-T., Ren, Y.-L., Guo, X.-Y. & Wang, Y. Association of peripheral immune activation with amyotrophic lateral sclerosis and Parkinson's disease: A systematic review and meta-analysis. J. Neuroimmunol. 388, 578290 (2024).
2. Leone, M. A. et al. Neutrophils-to-Lymphocyte Ratio Is Associated with Progression and Overall Survival in Amyotrophic Lateral Sclerosis. Biomedicines 10, 354 (2022).
3. Chou, M.-L. et al. Blood-brain crosstalk: the roles of neutrophils, platelets, and neutrophil extracellular traps in neuropathologies. Trends Neurosci. 46, 764–779 (2023).

Keywords : amyotrophic lateral sclerosis, neuroimmunity, neutrophils.
Acknowledgements/funding : Fondation Radala and Association pour la recherche sur la SLA (ARSLA).
Emails : charlotte.gavard@inserm.fr ; cedric.raoul@inserm.fr

OC 1.2 - PROPRIOCEPTIVE DYSFUNCTION AND SPINAL-CORTICAL NETWORK DISORGANIZATION IN ALS

Preuilh A (1), Lackmy-Vallée A (1), Sangari S (1,2), Querin G (1,3), Pradat PF (1,3), Marchand-Pauvert V (1)

(1) Sorbonne Université, CNRS, Inserm, Laboratoire d'Imagerie Biomédicale, LIB, Paris (France); (2) Shirley Ryan AbilityLab, Northwestern University, Chicago (USA); (3) AP-HP, Centre Référent SLA, Hôpital Pitié-Salpêtrière, Paris (France)

Amyotrophic lateral sclerosis (ALS) is increasingly viewed as a multisystem network disorder in which motor neuron degeneration is accompanied by impaired sensorimotor integration. We propose that proprioceptive dysfunction, particularly affecting muscle spindle-related pathways, may contribute to spinal and cortical network disorganization in ALS.

Using non-invasive electrophysiological paradigms in ALS patients, we showed that spinal interneuron circuits driven by group Ia/II muscle spindle afferents display early loss of inhibition and progressive enhancement of excitatory propriospinal transmission. By contrast, Ib tendon-organ and cutaneous pathways were relatively preserved at group level, but became altered when disease stage was considered. These findings support an afferent- and stage-dependent hierarchy of spinal dysfunction, progressing from early disinhibition to maladaptive excitation [1].

In a complementary fMRI study, focal muscle-tendon vibration targeting hand muscle spindles revealed impaired kinesthetic perception in ALS despite the absence of overt sensory deficits. Compared with controls, patients showed reduced activation in prefrontal and cerebellar regions during proprioceptive stimulation, and these activations correlated with hand motor disability and cognitive impairment [2].

Together, these findings indicate that ALS-related motor impairment extends beyond motor output. Altered spindle-derived proprioceptive input may deprive spinal interneuron circuits and cortical sensorimotor networks of appropriately calibrated feedback, promoting compensatory reorganization that may become maladaptive during disease progression. Proprioceptive dysfunction should therefore be considered not only as a sensory manifestation of ALS, but also as a potential contributor to motor network instability and neurodegenerative progression.

References: [1] Sangari S, Lackmy-Vallée A, Peyre I, et al. Afferent-driven modulation of spinal interneuron circuits across disease stages in amyotrophic lateral sclerosis. Neurobiology of Disease. 2026;219:107270. [2] Preuilh A, Lackmy-Vallée A, Béranger B, et al. Impaired kinesthesia and cerebral integration during tendon vibration in amyotrophic lateral sclerosis. Clinical Neurophysiology. 2026;187:2111864.

Keywords: amyotrophic lateral sclerosis; proprioception; spinal interneurons

Acknowledgements/funding: ARSLA 2013, FTL 2015, AFM-Téléthon 2015, ANR 2022. Conflict of interest: none declared.

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ARSLA funding

OC 1.3 - SODIUM HOMEOSTASIS AND TISSUE MICROSTRUCTURE ALTERATIONS IN AMYOTROPHIC LATERAL SCLEROSIS – AN ULTRA-HIGH-FIELD 7T BRAIN MRI STUDY

Ouedraogo G (1, 2), Appukuttan S (1,3), Dary H (1), Nagel AM (4), Gilson M (3), Guye M (1), Ranjeva JP (1), Verschueren A (2), Attarian S (2), Grapperon AM (1,2), Zaaraoui W (1)

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Context: Reliable imaging biomarkers for amyotrophic lateral sclerosis (ALS) remain lacking. Ultra-high-field 7T MRI enables more sensitive assessment of cortical grey matter (GM), deep grey nuclei, and white matter (WM) tracts. In this study, we used multimodal 7T MRI to investigate regional alterations in tissue microstructure and sodium homeostasis in patients with ALS.

Methods: A cohort of 20 ALS patients and 20 healthy controls (HCs) underwent a 7T MRI protocol including diffusion, sodium, and T1-weighted imaging. Quantitative metrics included diffusion-derived fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), sodium-derived total sodium concentration (TSC), short and long sodium T2 relaxometry ($T2_s$ and $T2_l$), sodium signal fraction (f_{Na}) [1,2], and regional volume. Regional metrics were extracted from Desikan–Killiany cortical parcels, anatomically segmented subcortical GM structures, and JHU WM tracts. Regional volumes were normalized to whole-brain volume. Group comparisons were performed between ALS patients and HCs using uncorrected exploratory statistical testing ($p<0.005$).

Results: Increased TSC was observed in the motor cortex (bilateral precentral gyri, $p<0.0005$, and right paracentral gyrus) and motor tracts (superior corona radiata, internal capsule and cerebral peduncles). TSC was also increased in the right thalamus, caudate, extra-motor frontal (superior, middle-, orbito-frontal, pars opercularis) and cingulate regions ($p<0.0005$–0.005). Reduced f_{Na} and increased $T2_l$ were found in extra-motor frontal regions. Diffusion showed AD changes in motor regions (decrease in the corticospinal tract, increase in the precentral), increased AD, MD and RD in paracentral and cingulate regions, increased RD in the corpus callosum and decreased FA in the left caudate ($p<0.001$). At the selected threshold, atrophy was restricted to one internal capsule region.

Conclusion: Multimodal 7T MRI revealed alterations in sodium homeostasis and tissue microstructure in motor, cognitive, and associative regions involved in ALS, with limited atrophy, supporting its potential as an early biomarker.

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Keywords: 7T MRI, ALS, Sodium MRI, Diffusion MRI

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OC 1.4 - DEEP CEREBELLAR NUCLEI CIRCUITRY IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motoneuron degeneration. While motor cortex and spinal cord pathology are central, emerging human neuroimaging studies reveal early cerebellar connectivity deficits in ALS patients[1], suggesting a broader circuit involvement. Notably, V1 interneurons, critical inhibitory regulators of motoneurons, degenerate before motoneuron loss, implicating non-cell-autonomous mechanisms. Recent anatomical work has identified direct projections from the deep cerebellar nuclei (DCN) to spinal V1[2] interneurons, positioning the cerebellum as a potential direct modulator of spinal motor circuits. However, the role of DCN connectivity and function in ALS remains unknown. Using the ALS SOD1^{G93A} mouse model, our data reveal early synaptic dysregulation in DCN neurons before ALS symptom onset, as early as P21. Furthermore, these synaptic alterations coincide with a significant decline in fine motor skills, as assessed by the single-pellet reaching task at P40. We hypothesize that early cerebellar circuit dysfunction contributes to ALS pathophysiology by disrupting DCN inhibitory synapse formation and organization. Elucidating these mechanisms may uncover novel insights into cerebellar involvement in ALS and reveal new therapeutic targets for mitigating disease progression.

Keywords : deep cerebellar nuclei, circuitry, ALS

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OC 1.5 - CHALLENGING THE ADULT-ONSET PARADIGM: NEURODEVELOPMENTAL AND IMMUNE CONTRIBUTIONS TO ALS

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ALS is defined as an adult-onset neurodegenerative disease (NDD). However, accumulating evidence suggests that at least a subset of NDD cases including ALS might take their roots in neurodevelopment [1]. A serendipitous observation made in our lab in 2016 on the Sod1^{G86R} mouse model of ALS supports this suggestion. At that time, our Sod1^{G86R} colony was exposed to a gastrointestinal nematode infection and treated with ivermectin (IVM): while mice that were adult at the time of the event developed the expected ALS-like symptoms, younger animals instead remained healthy and fertile for months. This unexpected finding led to two alternative hypotheses: (1) developmental administration of IVM *per se* abolished ALS onset, or (2) early-life activation of the innate immune system - induced by helminth infection - conferred long-term neuroprotection. To test the first hypothesis, Sod1^{G86R} mice were administered different IVM doses during different developmental time windows. The approach failed to recapitulate neuroprotection, and the first hypothesis was ruled out. The second hypothesis is being tested, by treating early postnatal animals with IL-25, IL-33, and NeuromedinU (NMU), typically induced by helminth infection and responsible for the activation of the type-2 immune pathway [2] . In accordance with this hypothesis, early postnatal *SOD1^{G93A}* spinal extracts display reduced IL-33/ST2 signaling.
In parallel, to test for neurodevelopmental defects in mouse models of ALS, motor behaviour and neuronal function were assessed during early postnatal development. Our data revealed that Sod1^{G86R} pups display reduced growth and transient delay in sensorimotor and locomotor development, while preliminary voltage-clamp recordings in newborn *SOD1^{G93A}* motoneurons highlight increased synaptic activity, suggesting early network hyperexcitability. Ongoing studies are examining how these changes evolve during the first postnatal week.
Overall, the project aims at challenging our current understanding of ALS, and identifying the early-life pathways that shape lifelong central nervous system resilience or susceptibility.

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Keywords: Neurodevelopment; ALS; Innate Immunity
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OC 1.6 - ARTIFICIAL STABLE CELL MODEL FOR TDP-43 AGGREGATION: STUDY OF THE DYNAMICS AND CONSEQUENCES OF TDP-43 AGGREGATION

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TDP-43 mislocalization and aggregation are common features of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). However, the mechanisms underlying the transition of nuclear TDP-43 to cytoplasmic aggregates, and their contribution to disease pathogenesis, remain poorly understood. To address this gap, we recently developed a system that enables inducible cytoplasmic accumulation and aggregation of TDP-43 through forced liquid–liquid phase separation using a multivalent protein scaffold [1]. Upon induction, TDP-43 accumulates into a spectrum of cytoplasmic assemblies, ranging from submicrometric condensates to larger insoluble aggregate-like structures that display hallmarks of proteinopathy [1]. We now have extended this system using inducible cell lines to establish a putative link between aggregation, RNA splicing defects and progressive cytotoxicity. To characterize the temporal dynamics and consequences of TDP-43 aggregation, we monitored cell proliferation, viability, pathological biomarkers, and RNA integrity over a period of 1 to 14 days following induction. Together, these findings establish a physiologically relevant cellular model for investigating the mechanisms underlying pathological TDP-43 aggregation and its downstream effects, while also providing a robust platform for the screening and evaluation of TDP-43-targeted therapeutic strategies.

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Keywords: TDP-43, aggregation, cell model
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FILSLAN PROJECT AWARD

- ALS-GUT AND ITS POP SUB-COHORT: GUT MICROBIOTA, POLLUTANT EXPOSURE AND DISEASE PROGRESSION IN A FRENCH NATIONWIDE ALS COHORT

Gaëlle BRUNETEAU

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive death of motor neurons. The gut microbiota, a key player in the gut-brain axis, may modulate the pathophysiology of ALS, but human data are sparse and contradictory. Humans are widely exposed to environmental and dietary chemical contaminants, which may disturb the gut microbiota and thereby contribute to chronic diseases, including neurodegenerative diseases. Among them, persistent organic pollutants (POPs) are highly stable and widespread in soil, water and food, making interaction with the gut microbiota inevitable.

The ALS-Gut study aims to characterize the gut microbiota quantitatively and qualitatively in a large cohort of French ALS patients (n=300) and to explore the link between gut microbiota signatures and the phenotype and progression of ALS. The national cohort "Le French Gut" will provide ALS-Gut with a reference map of gut microbiota in 100,000 volunteers, from which 900 controls matched for age, sex and BMI will be selected. In a sub-cohort of 100 ALS-Gut participants, blood POPs levels will be measured at baseline, making it possible to explore for the first time the links between POPs exposure, gut microbiota changes, and ALS phenotype and progression.

The ALS-Gut study is funded by FilSLAN (French healthcare network for ALS and other rare motor neuron diseases) and ARSLA (French non-profit organization for ALS research) and sponsored by AP-HP (Assistance Publique-Hôpitaux de Paris). The POP sub-cohort is supported by additional funding from ARSLA.

- CLINICAL AND GENETIC CHARACTERISTICS OF ALS IN LATIN AMERICA: A PROSPECTIVE, MULTICENTER STUDY IN ECUADOR, URUGUAY AND ARGENTINA

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Background: Amyotrophic lateral sclerosis (ALS) varies in its clinical presentation and genetic characteristics across populations. Although a younger age at onset has been reported in Latin America, genetic data from the region remain limited. We aim to investigate the clinical and genetic characteristics of ALS across three Latin American countries with differing ancestral backgrounds.

Methods: This multicentre observational study includes patients with ALS in Ecuador, Uruguay and Argentina, known to have a different ancestral origin background. Clinical, nutritional and cognitive data are collected alongside blood samples for *C9orf72* repeat expansion testing and next-generation sequencing of an ALS gene panel. Genome-wide genotyping is planned to investigate genetic risk variants and ancestry. The study will also establish a biological collection of ALS cases and controls without neurodegenerative disease in Uruguay and Argentina.

Results: Recruitment and follow-up for the Ecuadorian pilot cohort have been completed. Among 66 patients, the sex ratio was 0.8, median age at symptom onset was 54 (IQR: 44.0- 66.0) years and median age at diagnosis was 56 (IQR: 46.0- 67.0) years. Familial ALS was reported in 7% of patients, and 80% had spinal onset. The mean ALS-specific cognitive score was 64 (±20.8) points, and the mean total score was 87.9 (±24.7) points. Genetic testing identified a *C9orf72* repeat expansion in 1/66 of patients and variants in *SOD1*, *SPG7* and *SPTLC1* in 1/66 each. Whole-genome sequencing has also been completed for these patients, and genomic analyses are currently ongoing. Recruitment of patients and controls is beginning in Uruguay and Argentina.

Conclusion: The Ecuadorian pilot cohort provides initial clinical and genetic data on ALS in a Latin American population, including a younger age of onset. Planned genome-wide analyses and recruitment across three countries will enable investigation of how genetic variation and ancestry relate to ALS risk and clinical presentation.

- WHERE ARE WE WITH THE PREMODIALS STUDY, AND WHAT IS PLANNED NEXT?

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Background: premodiALS is a multicenter longitudinal study investigating individuals at risk of developing ALS (1). Funded through the JPND Call 2021 (BMBF 01ED2204A), it is currently still actively recruiting participants.

Objectives: The study aims to identify early molecular and clinical changes before symptom onset by following participants annually using a multimodal approach, with the ultimate goal of discovering biomarkers and therapeutic targets for early intervention.

Methods: premodiALS is recruiting presymptomatic gene mutation carriers (PGMCs) at genetic risk for ALS, alongside symptomatic patients (early ALS or ALS mimics) and unaffected controls across 15 recruitment centers in Germany, France, Switzerland, Slovakia, Türkiye, Israel, and the Czech Republic. Additional recruitment centers and countries are expected to join premodiALS during 2026. Participants are assessed annually, with the current ethics approval allowing one baseline visit and four follow-up visits. At each visit, participants undergo a comprehensive clinical assessment and provide biological samples, including serum, plasma, urine, tear fluid, and cerebrospinal fluid (CSF)

Results: Recruitment started in early 2022, and 280 participants are currently enrolled as of Jully 2026. To date, targeted proteomic analyses have identified proteins commonly altered in both ALS patients and PGMC in blood, including neurofilaments (NEFH: $P<0.010$), MAPT ($P<0.050$), and others. In urine, a faster increase of $p75^{ECD}$ over one year has been observed in ALS (FC=1.26) and PGMC (FC=1.21) individuals compared to controls ($P<0.010$). Lipidomic analyses have also revealed consistent alterations over time in presymptomatic individuals, particularly within the triglyceride family (FDR<0.1). Smell test analyses showed impaired olfactory function in ALS patients at baseline and at 1-year follow-up ($P < 0.05$). Presymptomatic individuals also showed numerically lower olfactory function compared with controls, although not significant ($P = 0.079$ at baseline; $P = 0.051$ at 1-year follow-up). Further ongoing analyses include extended proteomic, metabolomic, and miRNA profiling, as well as behavioral, cognitive, and neurological assessments. In addition, a questionnaire based on the EARLY-ALS questionnaire (2), has been implemented to identify prodromal symptoms, healthcare utilization patterns, comorbidities, lifestyle factors, and weight changes preceding symptom onset.

Discussion: Altogether, premodiALS aims to better characterize the clinico-molecular signature of ALS in the presymptomatic phase. Identifying these early features may facilitate earlier diagnosis and enable timely enrollment in clinical trials. Recruitment is ongoing, and we actively encourage further collaboration, as joining forces and expanding the cohort will strengthen statistical power.

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ARSLA SESSION

Moderators: Pierre-François PRADAT and Cédric RAOUL

OC A1 - MODULATING MOTONEURONS EXCITABILITY TO DELAY ALS

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Motor units, which consist of a motoneuron (MN) and the muscle fibers it innervates, are specialized for different types of movement, such as slow (S) for posture, fast-fatigue-resistant (FR) for repeated contractions or fast-fatigable (FF) for few powerful and short contractions. These MN subtypes display specific electrophysiological properties that are largely determined by the expression of distinct ion channels. Among these properties, bistability refers to the ability of a MN to sustain firing after a transient excitatory input. This phenomenon results from the coordinated activation of ion channels, allowing MN to maintain activity without continuous synaptic excitation. However, there are conflicting results regarding the type of MN that are bistable. Indeed, it was shown in adult cats in vivo that bistable MN are rather small, whereas it was shown in juvenile mice in vitro that bistable MN are rather large. In amyotrophic lateral sclerosis, motor units exhibit differences in vulnerability. FF motor units degenerate first, followed by FR, whereas S remain relatively preserved until late stage of the disease. Therefore, we aimed to determine the type of motor units that are bistable and whether there is a link between MN bistability and vulnerability. Our recent in vivo intracellular recordings in adult wild-type and SOD1(G93A) mice demonstrate that bistable MN consistently exhibit delayed firing, counter-clockwise hysteresis, and are predominantly associated with slow and small FR motor units. Moreover, all identified bistable MN do not express the cellular marker MMP9 (MMP9- is associated with disease resistance), whereas most non-bistable MN are MMP9+ (disease vulnerable), further supporting a link between bistability and resistance to degeneration. These findings suggest that selective MN vulnerability may arise, at least in part, from intrinsic electrophysiological properties. The next experiments will determine whether bistability directly contributes to neuroprotection or simply represents a hallmark of resistant MN.

Keywords: in vivo intracellular recordings, motoneuron, bistability

Funding: This work was funded by ARN and ARSLA.

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OC A2 - NEW INSIGHTS INTO ALS PATHOPHYSIOLOGY: IS SPINAL CORD AGING LINKED TO IMPAIRED EN1 TRANSFER?

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Aging is the major risk factor for amyotrophic lateral sclerosis (ALS), yet the mechanisms linking aging to motoneuron vulnerability remain poorly understood. The ENGRAILED1 (EN1) transcription factor is expressed in oculomotor neurons (OMNs), which are resistant to degeneration in ALS, while spinal motoneurons (spMNs) do not express EN1. SpMNs instead receive EN1 protein secreted by V1 interneurons that is specifically internalized by spMNs thanks to the presence of EN1 binding sites in the extracellular matrix (ECM) at their surface. This uptake of EN1 seems pivotal to their survival, as spMNs deprived of exogenous EN1 undergo retrograde degeneration [1]. In the En1 heterozygote (*En1-Het*) mouse, recombinant EN1 protein injected intrathecally specifically targets spMNs and saves them from retrograde degeneration [1]. We hypothesized that *En1* hypomorphism can impact MN survival and that age- and disease-related ECM remodeling impairs EN1 transfer to spMNs, thereby contributing to neurodegeneration. Indeed, we find that while 50% of spMNs are lost, OMN numbers are unchanged at 7 months in *En1-Het* mice. However, for spMNs in these mice, we observed a decrease in the levels of Aggrecan, an ECM protein that surrounds spMNs [2], suggesting a feedback loop between EN1 and ECM levels and accelerated spinal cord aging. In parallel, lumbar spinal cord sections from ALS patients were analyzed for EN1 and Aggrecan levels in spMNs. Preliminary results revealed reduced EN1 and Aggrecan immunoreactivity in ALS spMNs. Thus, ALS patients and *En1*-Het mice display convergent alterations of EN1 signaling and ECM integrity. These findings support a model in which aging- or disease-induced ECM remodeling limits EN1 transfer to spMNs, contributing to neuronal vulnerability.

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OC A3 - SMN-DEPENDENT REGULATION OF BASE EXCISION REPAIR FOLLOWING OXIDATIVE DNA DAMAGE IN SPINAL MUSCULAR ATROPHY

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Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by deficiency of the Survival Motor Neuron (SMN) protein. Oxidative stress is increasingly recognized as a contributor to neurodegeneration, yet the molecular mechanisms linking SMN deficiency to oxidative vulnerability remain poorly understood. Oxidative DNA lesions, including 8-oxo-guanine (8-oxoG), are primarily repaired by the Base Excision Repair (BER) pathway initiated by the DNA glycosylase OGG1.

Here, we identify SMN as a previously unrecognized regulator of BER following oxidative DNA damage. Using SMN-depleted cellular models, we show that SMN-deficient cells display marked hypersensitivity to acute and chronic oxidative stress, similarly to OGG1-deficient cells. SMN depletion leads to persistent accumulation of 8-oxoG after stress exposure, indicating defective lesion repair. This phenotype is not due to altered OGG1 protein expression, but to impaired recruitment of BER factors to damaged chromatin. Indeed, SMN is required for efficient chromatin association of OGG1 and XRCC1 following oxidative damage. Proximity ligation assays further show that SMN localizes in close proximity to both 8-oxoG lesions and OGG1 after damage, supporting a direct role at oxidative repair sites. In addition, SMN physically interacts with OGG1, and this interaction is dynamically remodeled upon oxidative stress. GST pull-down analyses reveal constitutive binding of OGG1 to the SMN N-terminal domain and damage-induced binding to the SMN C-terminal domain, while the Tudor domain appears dispensable.

Importantly, this work also opened a translational perspective. SMN-deficient cells are highly sensitive to chronic oxidative stress, and this vulnerability can be reduced by antioxidant treatment, suggesting that antioxidant-based strategies may help counteract oxidative damage in SMA cells and complement existing SMN-restoring therapies.

Together, these findings establish a mechanistic and translational link between SMN deficiency, defective oxidative DNA repair, genome instability and cellular vulnerability in SMA.

Key word: SMN, oxidative damage, antioxidants

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OC A4 - STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN GENETIC FRONTOTEMPORAL LOBAR DEGENERATION

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Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) exist on a clinicopathological continuum, driven largely by shared genetic mechanisms. Mutations in the *C9orf72* gene represent the most common genetic cause of both conditions, frequently manifesting as FTD, ALS, or a combined FTD-ALS phenotype. A major clinical challenge remains the inability to predict individual disease trajectories or the onset of motor neuron dysfunction prior to clinical manifestation.

This research investigated pre-symptomatic neuroimaging markers across major genetic FTD cohorts (*C9orf72*, *GRN*, and *MAPT*), with a primary focus on identifying early biomarkers associated with ALS pathogenesis. Structural gray matter analyses revealed widespread, early cortical and subcortical atrophy in asymptomatic *C9orf72* expansion carriers long before clinical onset. These alterations selectively affected networks mediating behavior, language, and motor control, mirroring the multifaceted clinical spectrum of the *C9orf72* mutation and its strong link to ALS. The most atrophic regions were able to discriminate mutation carriers from non-carriers, demonstrate a longitudinal progression predictive of clinical evolution, and correlate with global clinical scales. Subsequent functional connectomics analyses demonstrated early disruptions in inter-regional network communication specifically within *C9orf72* carriers. This dysfunction appears driven primarily by primary neuronal damage, characterized by gray matter pathology and loss of structural-functional coupling. Notably, posterior brain networks, particularly visual processing regions, exhibited preserved or heightened functional connectivity, suggesting an active pathophysiological compensatory mechanism to preserve global network integrity during the latent phase.

These early structural and functional signatures offer potential non-invasive biomarkers for disease onset and clinical progression toward an ALS phenotype. Identifying these pre-manifest alterations provides critical therapeutic windows for disease-modifying interventions before irreversible neurodegeneration occurs.

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PLACE OF CLINICAL EXPOSURE IN BIOMEDICAL RESEARCH TRAINING: A NATIONAL SURVEY OF RESEARCH PROFESSIONALS

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Introduction: Biomedical researchers frequently work on human diseases without direct contact with patients. Most scientists are rarely, if ever, exposed to the clinical setting during their training and subsequent careers. Following a clinical observation placement in ALS center, we sought to assess the current level of patient exposure among biomedical research professionals and their perception of the potential value of clinical immersion during research training.
Methods: An anonymous online survey was distributed nationally to individuals involved in biomedical research, including students, PhD candidates, postdoctoral fellows, engineers, technicians and researchers from academic and non-academic institutions. Questions addressed current exposure to patients, perceived impact of clinical immersion on research activities, and attitudes toward the integration of clinical observation placements into research training.
Results: A total of 135 respondents completed the survey. Direct clinical exposure to patients was reported by 25% of participants, whereas 44% reported indirect exposure only (through conferences or testimonials for instance) and 38% reported no exposure. Despite this limited direct contact, 76% considered that clinical immersion could moderately or strongly modify their understanding of disease and/or influence the way they conduct research. Regarding training, 70% supported the integration of optional clinical observation placements and 25% supported mandatory placements. The main barriers identified were ethical and confidentiality concerns, lack of time, and administrative constraints rather than lack of interest. Among respondents working on motor neuron diseases (n=15), all reported previous exposure to patients or patient testimonials, although this exposure remained predominantly indirect (14 on 15).
Conclusion: Biomedical researchers report limited direct exposure to patients but express strong interest in clinical immersion experiences. These findings support the development of initiatives aimed at strengthening interactions between researchers, clinicians and patients during research training.

Keywords: Clinical immersion; Biomedical research; Research training
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SESSION 2: BIOMARKERS AND THERAPIES IN MOTOR NEURONE DISEASES

Moderators: Hélène BLASCO and Gaëlle BRUNETEAU

- **Conference: BEYOND THE BRAIN AND THE SPINAL CORD : PERIPHERAL TDP-43 PATHOLOGY IN ALS**

Philippe CODRON

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive degeneration of upper and lower motor neurons. Cytoplasmic accumulation of phosphorylated TAR DNA-binding protein 43 (pTDP-43) is the pathological hallmark of most ALS cases. While ALS has traditionally been viewed as a disease confined to the brain, spinal cord and motor nerves, recent studies have reported pTDP-43 pathology in multiple other tissues, such as skeletal and cardiac muscle, skin, minor salivary glands and the gastrointestinal tract, collectively referred to as peripheral pathology. This communication will review the current evidence for peripheral pTDP-43 pathology in patients with ALS and discuss how these findings may reshape current concepts of disease pathogenesis. While their biological significance is yet to be determined, these observations may provide new opportunities for pathology-based biomarkers and therapeutic monitoring.

- Presentations selected from abstracts submitted

OC 2.1 - SPINAL CORD ATROPHY ACROSS CLINICAL PHENOTYPES AND STAGES IN AMYOTROPHIC LATERAL SCLEROSIS: RESULTS FROM A LARGE MULTICENTER MAGNETIC RESONANCE IMAGING COHORT

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Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of upper and lower motor neurons, leading to marked clinical heterogeneity. While spinal cord (SC) involvement is a hallmark of the disease, its spatial distribution and clinical relevance remain incompletely understood.

Objectives

To characterize the spatial distribution of SC atrophy in ALS using cervical and thoracic MRI coverage, and determine its association with clinical phenotype, disease stage, progression rate, and survival in a large multicenter French cohort.

Material and methods

We conducted MRI analysis of 179 patients with ALS and 62 healthy controls (HCs) from the French multicenter PULSE cohort (NCT NCT0288587). Harmonized SC MRI acquisitions were performed across expert centers. SC cross-sectional area (CSA) was quantified from cervical to thoracic vertebral levels using standardized automated processing via the Spinal Cord Toolbox software. Clinical, functional, genetic, respiratory, and survival data were prospectively collected. Associations between CSA and disease phenotype, site of onset, King's College clinical stage, disease aggressiveness, and survival were evaluated using correlation analyses and multivariate Cox regression models.

Results

Compared with HC, patients showed significant SC atrophy predominantly involving cervical segments and extending into the upper thoracic cord. Spinal-onset patients exhibited more extensive atrophy than bulbar-onset patients, and lower-limb-onset cases demonstrated broader thoracic involvement than upper-limb-onset cases. Increasing King's College stage was associated with progressive rostrocaudal extension of atrophy. Patients with slower progression displayed more pronounced atrophy, likely reflecting longer disease duration. Importantly, upper cervical CSA was independently associated with survival after adjustment for established clinical predictors.

Conclusion

In one of the largest multicenter SC MRI studies in ALS to date, SC atrophy emerges as a robust imaging feature. Its spatial extent reflects disease phenotype and stage, and upper cervical involvement independently predicts survival, supporting its potential role as a biomarker for patient stratification in clinical trials.

Keywords: spinal cord MRI, ALS, phenotype prediction, surrogate biomarker

Acknowledgments

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OC 2.2 - LONGITUDINAL CHANGES IN URINARY P75^{ECD} LEVELS IN PRESYMPTOMATIC AND EARLY ALS – A PREMODIALS STUDY

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Objectives: Urinary biomarkers provide a minimally invasive approach for monitoring ALS, with p75ECD emerging as a strong candidate. Urinary p75ECD is elevated in ALS, correlates with ALSFRS-R decline, and is associated with reduced survival, supporting its role as a marker of disease severity and progression [1,2]. Here, we investigate p75ECD in pre-symptomatic ALS as a potential early prognostic indicator.

Materials and methods: PremodiALS is a prospective observational study enrolling pre-symptomatic gene mutation carriers (PGMC), early symptomatic ALS patients or ALS mimics, and unaffected controls. Urinary p75ECD was measured by sandwich ELISA at baseline and 1-year follow-up. Group differences were analyzed using generalized linear models (Gamma distribution) with Tukey post hoc tests. Longitudinal changes were assessed using mixed-effects models with random intercepts. Analyses were adjusted for sex, age, and center. Correlations between urinary p75^{ECD} and clinical measures (ALSFRS-R, NEFL, motor signs) were evaluated.

Results: This analysis included 187 participants at baseline (47 controls, 53 PGMC, 68 ALS, 20 mimics) and 110 at one-year follow-up (37 controls, 35 PGMC, 29 ALS, 8 mimics). ALS participants had significantly higher urinary p75^{ECD} levels than controls at baseline ($P=0.005$) and follow-up ($P<0.001$). Longitudinally, p75ECD increased significantly in ALS participants ($P<0.001$) and in PGMC ($P=0.003$), particularly in C9ORF72 ($P<0.001$) and SOD1 ($P<0.001$) PGMC. No significant change was observed in controls or mimics. Urinary p75ECD negatively correlated with ALSFRS-R ($P=0.012$), positively correlated with plasma ($P=0.018$) and CSF ($P=0.016$) NEFL, and increased in parallel with upper and lower motor neuron signs.

Conclusion: Consistent with previous reports, urinary p75^{ECD} is elevated in ALS and correlates with ALSFRS-R scores. Notably, although longitudinal increases have been described in ALS, we show a similar increase in PGMC, particularly in *C9ORF72* and *SOD1* carriers. These findings suggest that urinary p75^{ECD} is part of an evolving molecular signature in PGMC preceding phenoconversion.

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Keywords: pre-symptomatic, fluid biomarker, study recruitment

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OC 2.3 - HYPOTHALAMIC MECHANISMS OF HIGH-CALORIE INTERVENTION IN ALS

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Amyotrophic lateral sclerosis (ALS) is a lethal motor neuron disease, characterized by gradual dysfunction of muscles and eventual paralysis, lacking effective therapy. Metabolic alterations are observed in ALS patients and ALS mouse models prior to the onset of motor symptoms, linked to dysregulated neuropeptides and atrophy of hypothalamus. Recently, melanin concentrating hormone (MCH) was proved to be involved in metabolic abnormalities in ALS [1]. High-fat diet (HFD) compensates weight loss and prolong survival in ALS mice and in fast-progressors patients but the underlying mechanisms are largely unknown [2]. This study aims to illustrate a clearer ALS-associated hypothalamic gene profile and clarify the effects of HFD on energy metabolism in two ALS transgenic mouse models with distinct phenotypes ($FUS^{\Delta NLS/+}$ and $SOD1^{G86R}$) at pre-symptomatic and symptomatic stage. Single-cell RNA sequencing of hypothalamus was conducted in these ALS mutant mice and their non-mutant littermates (control mice). Our preliminary results show that at pre-symptomatic stage, $FUS^{\Delta NLS/+}$ mice showed less differentially expressed genes (DEGs) among the major cell types in hypothalamus than $SOD1^{G86R}$ mice, further analysis is ongoing. After HFD intervention, peripheral tissues (liver, epididymal or periovarian WAT, tibialis anterior muscle) were also collected and RNA sequenced. Body mass, locomotion, energy expenditure, and respiratory exchange ratio were measured by indirect calorimetry. Circadian patterns of these parameters were assessed. Ambulatory activity was altered in symptomatic stage $FUS^{\Delta NLS/+}$ mice compared to control mice, but this defect was compensated by HFD. These results hint that hypothalamic transcriptomic changes in ALS are shown before motor symptoms appear, and that HFD may affect the metabolism in ALS through multiple pathways.

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Keywords: Hypothalamus, Transcriptomics, High-fat diet.

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OC 2.4 - DEVELOPMENT OF A FUNCTIONAL THREE-DIMENSIONAL HUMAN NEUROMUSCULAR JUNCTION MODEL TO STUDY EARLY DEGENERATIVE MECHANISMS IN *CHCHD10*-ASSOCIATED ALS

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Neuromuscular junction (NMJ) degeneration is among the earliest pathological events observed in amyotrophic lateral sclerosis (ALS), supporting the "dying-back" hypothesis whereby pathology initiates at the synapse and subsequently progresses retrogradely toward motor neuron cell bodies. However, the mechanisms linking ALS-associated genetic alterations to NMJ destabilization remain poorly understood.

Mutations in the *CHCHD10* gene, encoding a mitochondrial protein involved in inner membrane organization, cause familial forms of ALS and ALS/frontotemporal dementia (ALS-FTD) syndromes [1, 2]. Our previous studies have demonstrated early mitochondrial dysfunction and NMJ abnormalities in the *Chchd10^S59L/+* mouse model, highlighting a central role for the motor unit in disease initiation and progression [3].

To investigate these mechanisms in a human-relevant context, we are developing a 3D iPSC-derived NMJ model. Motor neurons and skeletal muscle cells differentiated from induced pluripotent stem cells (iPSCs) obtained from patients carrying the *CHCHD10^S59L* variant and from healthy controls are co-cultured in microfluidic devices designed to reconstruct functional human motor units. This platform reproduces the spatial organization of neuronal and muscular compartments, promotes directed motor axon growth, and enables the formation of mature NMJ-like structures. Importantly, these engineered NMJs exhibit spontaneous and evoked muscle contraction, demonstrating functional synaptic connectivity.

Using this model, we have identified structural, functional, and mitochondrial alterations associated with the *CHCHD10* variant at the human NMJ. Ongoing crossed co-culture experiments combining control and mutant motor neurons and muscle cells will dissect the respective contributions of each compartment to NMJ degeneration and identify the primary site of pathological initiation.

This model represents a novel translational platform to unravel early mechanisms of motor unit dysfunction and identify the cellular origins of NMJ failure in *CHCHD10*-associated diseases. It will also provide a valuable tool for evaluating therapeutic strategies aimed at restoring mitochondrial homeostasis and preserving neuromuscular junction integrity.

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Keywords: Neuromuscular junction, mitochondria, human motor units

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OC 2.5 - EARLY CAUDOPUTAMEN ATROPHY IN *Fus*$^{\Delta NLS/+}$ MICE IS ASSOCIATED WITH STRIATAL NEUROINFLAMMATION AND BEHAVIOURAL DEFICIT

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Amyotrophic lateral sclerosis (ALS) is traditionally considered to be a disease affecting upper and lower motor neurons, but increasing evidence indicates broader vulnerability of cortical and subcortical circuits [1]. Neuroimaging studies in patients point to the additional involvement of the caudate and putamen, particularly in cases with cognitive and behavioural impairment (ALSci/bi) or frontotemporal dementia (ALS/FTD) [2]. We investigated large-scale patterns of brain atrophy in the *Fus*$^{\Delta NLS/+}$ mouse model of ALS/FTD [3] using high-resolution *ex vivo* magnetic resonance imaging, proteomic profiling, and behavioural analysis across disease stages. Volumetric analysis of over 600 brain structures revealed early and progressive atrophy of the dorsal striatum (caudoputamen) preceding the appearance of the atrophy of motor cortex. The lack of volumetric changes upon white-matter segmentation demonstrated that caudoputamen shrinkage was driven by grey-matter atrophy, a finding histologically confirmed by decreased neuronal density in the mutant mice. Structural findings were supported by proteomic analysis, which revealed early activation of complement pathways, innate immune responses, and extracellular matrix remodelling in early-stage striatal samples, and adaptive-immunity inflammatory signalling and apoptotic pathways at later-stage. The identified inflammatory pathways were corroborated by *in situ* transcriptomics showing altered expression of key genes within the caudoputamen. These structural and molecular findings aligned with the selective functional abnormalities in striatum-dependent behavioural tasks displayed by the *Fus*$^{\Delta NLS/+}$ mice, with delayed procedural learning despite preserved cognitive flexibility. Together, these findings identify the caudoputamen as an early site of vulnerability in the FUS-associated ALS/FTD model, linking structural degeneration, inflammatory molecular programs, and behavioural alterations. Our results reveal a previously underappreciated striatal axis of neurodegeneration that may contribute to the emergence of behavioural symptoms within the ALS/FTD spectrum. These observations are consistent with neuroimaging findings of prominent caudate atrophy in sporadic-FTD patients with pathologically confirmed FUS proteinopathy, thereby supporting the translational relevance of the *Fus*$^{\Delta NLS/+}$ model.

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Keywords: ALS/FTD, caudoputamen, atrophy, behavioural deficit

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OC 2.6 - THERAPEUTIC POTENTIAL OF THE X PROTEIN OF ORTHOBORNAVIRUS BORNAENSE TYPE 1 EXPRESSED IN ASTROCYTES OF A TRANSGENIC MICE MODELS OF AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis is characterized by a progressive motoneuron loss, in which mitochondrial dysfunction and astrocyte-mediated non-cell-autonomous mechanisms, contribute to disease onset and progression. The X protein of the Orthobornavirus Bornaense type 1 enhances mitochondrial fusion [1], and when selectively expressed in neurons, improves motoneuron survival and motor performance in $SOD1^{G93A}$ mice [2]. Its genetically modified form, X_{A4} protein, with enhanced mitochondrial targeting, further improves survival. Here, we aim to expand these protective effects to glial mitochondria and investigate the impact of astrocyte-specific expression of X or X_{A4} proteins in $SOD1^{G93A}$ mice.

AAV10 vector, encoding X or X_{A4} proteins under an astrocyte-specific promoter was used. Viral constructs or PBS control were injected intracerebroventricularly into $SOD1^{G93A}$ mice at P0. Protein expression was assessed at P40 and P90 by immunohistochemistry. Disease progression was monitored longitudinally through motor performance using several motor tests and by body weight measurements. Motoneuron survival was also evaluated by immunohistochemistry at P90 whereas the lifespan of mice was determined.

X and X_{A4} expression were confirmed to be largely restricted to astrocytes. Treated mice exhibited slower weight loss with delayed disease onset. They also performed better on the rotarod and during the swimming test. However, no significant changes were observed in the inverted grid and grip tests. Finally, X and X_{A4}-protein-treated SOD1 mice exhibited reduced motoneuron degeneration at P90, while X protein treatment also conferred a modest but significant survival benefit.

Astrocyte-specific expression of X and X_{A4} proteins improve disease outcomes in $SOD1^{G93A}$ mice including delayed disease onset, improved motor performance and reduced motoneuron degeneration. In addition, X protein confers a modest extension of survival. These findings support the therapeutic potential of this protein and suggest that its beneficial effects on disease progression may involve modulation of astrocyte reactivity.

Keywords: Mitochondria, X protein, Astrocytes

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ARSLA funding

SESSION 3: MOLECULAR MECHANISMS OF MOTOR NEURONE DISEASES

Moderators: Caroline ROUAUX and Stéphanie MILLECAMPS

Conference: PREVENTION TRIALS FOR ALS AND FTD: THE ROLE OF CLINICAL AND BIOLOGICAL MARKERS

Michael BENATAR

Professor of Neurology, University of Miami

The idea that it might be possible to prevent some forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) has finally come of age. Indeed, the first ALS prevention trial (ATLAS) is already underway in which unaffected carriers of highly penetrant *SOD1* mutations associated with rapidly progressive ALS are randomized to receive an SOD1 antisense oligonucleotide (ASO) based on a rise in plasma neurofilament light chain (NfL). The design of ATLAS was predicated upon key insights gleaned from the study of pre-symptomatic ALS through the longstanding *Pre-fALS* study. As the field prepares for future disease prevention trials in other genetic forms of disease, it is clear that there are many gaps in our knowledge. Principal among these is identifying of new clinical markers and biomarkers that might be used to predict phenoconversion to ALS or FTD. In turn, a combination of these markers might be used as eligibility criteria for future prevention trials. Selection and refinement of outcome measures such as phenoconversion across an array of phenotypes, is another key challenge. This presentation will focus on emerging evidence for the existing of prodromal clinical syndromes and novel biomarkers and their relevance to future prevention trials.

- Presentations selected from abstracts submitted

OC 3.1- DYSREGULATED PrP^{C}-PDK1 SIGNALING SENSITIZES MOTOR NEURONS TO INFLAMMATION AND DRIVES ALS PROGRESSION

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Amyotrophic lateral sclerosis (ALS) is the most common motor neuron degenerative disease in adults. ALS is associated with the selective loss of motor neurons in the spinal cord, brainstem, and cortex, which causes progressive paralysis and death by respiratory failure. ALS is a proteinopathy associated with the misfolding and dysfunction of several proteins. Among these proteins, Cu/Zn Superoxide Dismutase 1 (SOD1), an intracellular enzyme implicated in antioxidant processes, was incriminated in ALS. The toxicity of pathological SOD1 relies on a toxic gain-of-function notably due to formation of intracellular aggregate inclusions of SOD1. Nevertheless, the secretion and accumulation of pathological SOD1 in the surrounding milieu of motor neurons raises the unexplored possibility that abnormal SOD1 triggers neurotoxicity through binding to membrane receptors and alteration of their signaling activity. Exploiting different cell models, we show that plasma membrane cellular prion protein (PrP^{C}) is a neuronal receptor for misfolded hSOD1^{G93A}. hSOD1^{G93A} interaction with PrP^{C} corrupts PrP^{C} signaling function, leading to 3-phosphoinositide-dependent kinase 1 (PDK1) overactivation and downstream under-shedding of TNFα receptors (TNFRs) by ADAM10/17 α-secretases. Cell surface accumulation of TNFR renders ALS neurons hyper-vulnerable to TNFα inflammation. Intraperitoneal injection of a PDK1 inhibitor in Tg-hSOD1^{G93A} ALS mice rescues the ADAM-mediated TNFR shedding, protects spinal cord motor neurons from neurodegeneration, improves motor performance, and extends survival. The clinical relevance of this neurodegenerative mechanism is underscored by reduced levels of shed TNFRs in the cerebrospinal fluid of a broad cohort of ALS individuals, across both genetic and sporadic forms of diseases. Our findings identify the PrP^{C}/PDK1/ADAM/TNFR signaling pathway linking extracellular ALS-linked proteins to inflammatory-driven neurodegeneration, defines shed TNFR as a mechanistic biomarker of ALS progression, and places PDK1 as a novel therapeutic target to mitigate ALS.

Keywords: Amyotrophic Lateral Sclerosis, PDK1, therapeutic target

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OC 3.2- SIGMA-1 RECEPTOR STIMULATION RESCUES ALS/FTD MUTANT TDP43-INDUCED DISRUPTION OF THE VAPB-PTPIP51 ER-MITOCHONDRIA TETHERING PROTEINS VIA INHIBITION OF GSK3β

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Background: Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are clinically related neurodegenerative diseases. These pathologies are characterized by the presence of TAR DNA-binding protein 43 (TDP-43) accumulations and familial cases of ALS/FTD by mutation of the TDP-43 encoding gene. In addition, a wide range of physiological functions are altered in ALS/FTD, including many of which are regulated by signaling between the endoplasmic reticulum (ER) and mitochondria. This signaling involves close physical contacts between the two organelles that are mediated by the VAPB-PTPIP51 ER-mitochondria "tethering" proteins. Several studies have shown that mutant genes which cause familial ALS/FTD disrupt the VAPB-PTPIP51 tethers and that this involves activation of GSK3β. Loss of Sigma-1 receptor function is also seen in ALS/FTD and there is evidence that Sigma-1 receptor agonists can repair damaged ER-mitochondria signaling. However, the underlying mechanisms are not properly understood. **METHODS:** We have tested the reference Sigma-1 receptor agonist PRE-084 and ANAVEX2-73, a further Sigma-1 receptor agonist which is in clinical trials for Alzheimer's disease, in *in vitro* models (neuronal cell line SH-SY5Y and primary culture of rat cortical neurons) to assess its effect on the VAPB-PTPIP51 complex. **RESULTS:** Here, we show that PRE-084 stimulates VAPB-PTPIP51 binding and rescues ALS/FTD mutant TDP43 induced disruption to the VAPB-PTPIP51 interaction and linked ER-mitochondria Ca^{2+} delivery. We also show that these effects involve inhibition of GSK3β. Finally, we show that ANAVEX2-73, also stimulates VAPB-PTPIP51 binding via inhibition of GSK3β. **CONCLUSION:** Together, our findings provide novel insights into the mechanisms by which drugs that stimulate the Sigma-1 receptor, influence defective ER-mitochondria signaling in ALS/FTD.

Keywords: Amyotrophic lateral sclerosis, VAPB, PTPIP51
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OC 3.3 - FUS ORCHESTRATES METABOLIC HOMEOSTASIS IN ALS HIGHLIGHTING CLINICALLY RELEVANT THERAPEUTIC STRATEGIES

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Mutations in the Fused in Sarcoma (FUS) gene cause a juvenile-onset form of amyotrophic lateral sclerosis (FUS-ALS) characterised by rapid, severe motor neuron degeneration. Although ALS is increasingly recognised as having a systemic metabolic component, how FUS dysfunction alters metabolism remains poorly defined. We hypothesised that FUS maintains metabolic homeostasis through PPAR-α signalling and mitochondrial fatty acid oxidation (FAO), and that restoring this pathway improves motor outcomes. In our study, we combined a *fus*$^{-/-}$ zebrafish knockout with FUS patient-derived fibroblasts (p.Gly504fs*12) and matched controls, two models that capture key pathological features of ALS. In zebrafish, locomotor function was measured with the touch-evoked escape response (TEER) assay, and PPAR-α was restored by hPPAR-α plasmid injection or with fenofibrate treatment; *fus*$^{-/-}$ larvae were further characterised by immunohistochemistry, RNA-sequencing and metabolomics. Patient-derived fibroblasts were analysed by RNA-sequencing, untargeted metabolomics, immunofluorescence, western blot, live-cell mitochondrial imaging (MitoTracker, TMRM), targeted FAO flux and RT-qPCR. *fus*$^{-/-}$ larvae showed a disorganised mitochondrial network, and transcriptomic analysis revealed altered metabolic pathways and reduced PPAR-α signalling, with a predicted FUS–PPAR-α interactome. Restoring PPAR-α rescued these locomotor deficits by plasmid injection (hPPAR-α) which improved swimming distance and velocity, and fenofibrate treatment improved swimming distance in *fus*$^{-/-}$ larvae. The juvenile FUS patient fibroblasts recapitulated this phenotype, showing cytoplasmic FUS mislocalisation, fragmented mitochondria, reduced PPAR-α, lower mitochondrial mass and membrane potential, and impaired FAO with depleted carnitine-shuttle and CPT1-dependent acylcarnitines. Overall, these findings indicate that FUS regulates metabolic homeostasis through PPAR-α signalling and mitochondrial fatty acid oxidation, and that disruption of this axis drives disease. PPAR-α activation and fenofibrate therefore represent promising therapeutic strategies for FUS-associated ALS.

Key words: FUS-ALS; mitochondrial dysfunction; lipid metabolism

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OC 3.4 - CHARACTERIZATION OF PATHOLOGICAL TROPISM OF TDP-43 VARIANTS

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Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disorder driven by progressive motor neuron (MNs) degeneration, resulting in muscle paralysis and leading to death typically within 1-5 years after symptom onset. A key protein in ALS is TDP-43, encoded by the *TARDBP* gene, whose pathological inclusions are observed over 95% of ALS patients. While most ALS cases are sporadic, approximatively 10% are familial. More than 50 ALS-pathogenic *TARDBP* variants have been reported, primarily within the prion-like domain (PLD).

We identified a new missense G376V-TDP-43 variant within the TDP-43 PLD in two French families. This variant is associated with a distal myopathy (DM) rather than ALS. Muscle biopsies revealed degenerative myopathy changes including rimmed vacuoles, sarcomere disruption, and myofibrillar disorganization. In cell-based models, G376V-TDP-43 enhanced cytoplasmic TDP-43 condensate formation, promoted aggregation, and altered phase separation properties. Consistently, G376V-TDP-43 promoted cytoplasmic condensates in patient-derived myoblasts and triggered cryptic exons inclusions in patient muscle tissue. Importantly, no neurogenic alteration was detected.

Strikingly, the G376D-TDP-43 substitution at the same residue position was previously linked to rapidly progressive ALS. This highlights that different amino-acid changes at the same residue can lead to markedly opposing clinical outcomes: a non-lethal myopathy versus a fatal ALS.

Our project, aims to determine whether G376V-TDP-43 drives muscle-specific pathogenicity tropism, leading only to myopathy or whether modifiers present in these families mitigate its pathological potential, resulting in a milder phenotype. To address this, we generated CRISPR-Cas9 engineered iPSCs carrying G376V- or G376D-TDP-43, and are exploring the functional consequences in iPSC-derived MNs. In parallel, we engineered patient-derived iPSCs with the G376V-TDP-43 mutation corrected and substituted by the ALS-associated G376D-TDP-43 variant, to assess the influence of genetic background of the DM-families on the behavior of an ALS-driving mutation.

We will present our initial findings and future strategies to explore this genotype–phenotype divergence.

Reference: [1]. Zibold A, et al. The new missense G376V-TDP-43 variant induces late-onset distal myopathy but not amyotrophic lateral sclerosis. Brain. 2024 May 3;147(5):1768-1783.

Keywords: TDP-43, variants, pathogenicity tropism.

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OC 3.5 - PHOSPHORYLATED FUS$^{P\text{-}Y526}$ IN ALS PATHOLOGY

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Fused in Sarcoma (FUS) is a predominantly nuclear DNA/RNA-binding protein that forms abnormal cytoplasmic inclusions in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). In ALS, such inclusions are primarily associated with mutant FUS. Phosphorylation at Tyr526 has been shown to inhibit nuclear import of FUS. The aim of our study was therefore to determine the extent of Tyr526 phosphorylation of FUS and to assess its potential contribution to the formation of mutant FUS inclusions both *in vitro* and in human tissue. Double immunofluorescence labelling was performed with HEK293T cells transfected to express ALS-associated FUS mutations, in patient-derived lymphoblasts, and in post-mortem human brain and spinal cord tissue from ALS patients and controls. Images were acquired using a laser scanning confocal microscope. Cells and neurons with clearly visible nuclei were selected and the nuclear-to-cytoplasmic ratio of phospho-Tyr526 FUS, total FUS, and phosphorylated (active) Abl were quantified using Image J. For each condition and tissue type, over 300 cells and at least 100 neurons were analyzed. Phosphorylation of FUS at Tyr526 by Src-family kinases was associated with altered nucleocytoplasmic distribution and increased aggregation of FUS in cellular models. Distinct patterns of phospho-Tyr526 FUS co-localization were observed within intracellular FUS-positive aggregates. In post-mortem frontal cortex tissue, as well as in motor cortex tissue, neurons from ALS patients showed increased cytoplasmic phospho-Tyr526 FUS localization compared with controls. The burden of phospho-Tyr526 FUS-positive aggregates was even more pronounced in spinal cord neurons. The observed overlap between c-Abl kinase activity and phosphor-Tyr526 FUS distribution in cortical neurons suggests that c-Abl may contribute to cytoplasmic mislocalization and aggregation of FUS in ALS. These findings support a role for phosphorylation-dependent mechanisms in FUS pathology that may influence disease progression.

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Keywords:

FUS phosphorylation, nucleocytoplasmic shuttling, ALS-associated FUS mutations

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OC 3.6 - DISEASE-RELATED ARGININE RESIDUES PREVENT FUS SPATIAL SEPARATION IN COMPARTMENTS OF HETEROGENEOUS RNA-BINDING PROTEIN COMPOSITION

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Amyotrophic lateral sclerosis (ALS) is a major neurodegenerative disease associated with DNA/RNA processes in cells. Accordingly, mutations in Fused in Sarcoma (FUS) – a DNA/RNA-binding protein with essential functions in RNA metabolism and DNA repair, represent one of the most common genetic causes of familial ALS. In addition, the presence of FUS cytoplasmic inclusions has been reported in the neurons of affected patients. Notably, FUS harbors a single RNA Recognition Motif (RRM), allowing its binding to nascent mRNA in the nucleus. Another characteristic of FUS is that many pathological mutations lie within the Nuclear Localization Signal (NLS) domain of the protein, which contributes to its nuclear import. Our research focuses on characterizing the functional role of the NLS domain and whether it contributes to mediating the protein-protein interaction with other RNA-binding proteins, independently of its role in nuclear import. By using Microtubule bench, a cellular approach combined with High Content Screening, we demonstrated that NLS-arginine residues regulate the interactions of FUS with other RNA-binding proteins in cytoplasmic condensates and prevent its phase separation in mRNA-rich compartments. Because FUS heterotypic interactions mostly take place in an mRNA-rich environment, we also used the Microtubule bench to show the role of FUS RRM in the interaction with other nuclear RNA-binding proteins. Understanding these molecular interactions can be useful to better delineate the functions of FUS and potentially develop therapeutic strategies to maintain FUS in a functional/structurally stable state.

Reference :

Valenti, D. *et al.* RNA-binding protein diversity and NLS arginines regulate FUS mixing in mRNA-rich compartments. *Cell Reports* **45**, 117430 (2026).

CONFERENCE: NEUROIMAGING IN ALS: UNDERSTANDING DISEASE HETEROGENEITY AND PROGRESSION

Moderator: Philippe COURATIER

Federica AGOSTA

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Amyotrophic lateral sclerosis (ALS) varies widely in its clinical presentation and rate of progression. Neuroimaging offers a way to investigate the brain changes underlying this variability. This talk will examine how structural and functional MRI reveal patterns of motor and extra-motor involvement, and how longitudinal imaging can help characterize disease progression. It will also discuss the potential of imaging biomarkers to improve patient stratification and support clinical trials, alongside the challenges that remain before they can be used routinely in clinical practice.

ROUND TABLE: GENOME–EXPOSOME INTERACTIONS

Moderator: Philippe COURATIER and Giancarlo LOGROSCINO

(3 * 25 minutes and 45 minutes of discussion)

- Global epidemiology of ALS

Giancarlo LOGROSCINO

Center for Neurodegenerative Diseases and Aging Brain - University of Bari/Pia Fond. Card. G. Panico

- The exposome and ALS

Robert BAROUKI

INSERM Institute of Public Health

- ALS risk factors - familial design and synergistic effects

Fang FANG

Institute of Environmental Medicine, Karolinska Institutet

P1 - FUNCTIONAL ANALYSIS OF NEW MOLECULAR MARKERS OF MOTONEURONS VULNERABLE TO AMYOTROPHIC LATERAL SCLEROSIS

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Modification of the electrical properties of motoneurons is a key contributor to the progression of amyotrophic lateral sclerosis (ALS) disease. Experimental studies have revealed a differential vulnerability of motoneurons in ALS, with the low -excitability fast fatigable (FF) motoneurons being the most vulnerable and the first to degenerate, while high- excitable slow (S) motoneurons exhibit the greatest resistance. These findings support the hypothesis that the high functional demand on FF motoneurons underlies their increased vulnerability.

To broaden our understanding of the role of neuronal excitability in selective degeneration and to improve the functional characterization of motoneuron subtypes, we performed single-cell transcriptomic analysis using the patch-seq method on FF and S motoneurons, identified through patch-clamp electrophysiology [1] [2].

We analyzed the expression of voltage-gated ion channels in RNA samples from FF and S motoneurons. We found that *Cacna2d3*, a gene coding for the $Ca_V\alpha2\delta3$ regulatory subunit of high voltage-gated calcium channels, was significantly upregulated in FF motoneurons. Due to its elevated expression in ALS vulnerable motoneurons, we are currently investigating its role in both motoneuron physiology and under ALS pathological condition.

In *Cacna2d3*$^{-/-}$ deficient motoneurons, we observed a drastic change in the subcellular localization of the P/Q type calcium channel $Ca_V2.1$, the main calcium channel involved in motoneuron neurotransmission, suggesting a regulatory role of $Ca_V\alpha2\delta3$. Consistently, motor behavioral studies show that Cacna2d3$^{-/-}$ mice display enhanced endurance, yet show increased sensitivity to physical exhaustion.

This project aims to define the molecular basis of electrophysiological features underlying motoneuron vulnerability in ALS. We will evaluate the impact of $Ca_V\alpha2\delta3$ loss on neurotransmission and firing properties through spinal cord electrophysiological recordings in wildtype and *Cacna2d3*$^{-/-}$ mice. We will also evaluate its impact on ALS onset and progression by analyzing behavioral and histopathological changes in *SOD1*^{G93A} mice with a Cacna2d3-deletion.

References:

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Keywords: Motoneuron vulnerability, Calcium channel, Electrical activity

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P2 - PARASPECKLE IMPAIRMENT IN ALS MUSCLE CONTRIBUTES TO ALTERED MUSCLE HOMEOSTASIS

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by degeneration of motor neurons and progressive paralysis. Muscles also undergo cellular alterations, such as imbalances in RNA and protein metabolism and mitochondrial homeostasis [1].

Paraspeckles, a nuclear membraneless organelle, regulate these pathways through nuclear RNA and proteins sequestration. NEAT1_2, a long non-coding RNA acts as a scaffold to form paraspeckles by interacting with RNA binding proteins such as FUS and SFPQ that can be mutated in ALS [2]. Paraspeckles accumulate in the motor neurons of ALS patients [3] but their status in ALS muscle is not known. Therefore, we aim to explore their status and their role in the ALS muscle.

In primary myotube cultures from sporadic ALS patients, we show alterations of paraspeckle number and size independently from NEAT1_2 expression, suggesting paraspeckle malformation. Moreover, paraspeckles lost their stress sensing function in ALS myotubes. By depleting paraspeckles in control myotubes, we uncovered that paraspeckles are involved in the regulation of major muscular pathways such as muscular contraction, oxidative phosphorylation and thermogenesis. Therefore, paraspeckle alteration could be involved in muscle impairment in ALS. We are currently investigating whether genes that were differentially expressed after paraspeckle depletion in control muscle cells, are dysregulated in ALS myotubes and whether paraspeckles contribute to their dysregulation.

Altogether, our findings identify paraspeckles as contributor to ALS pathophysiology. The observed alterations suggest that paraspeckle dysfunction may actively participate in muscle impairment rather than merely reflecting disease progression.

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Keywords : Paraspeckle, ALS Muscle, NEAT1-2

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P3 - SAFETY, FEASIBILITY, PRELIMINARY EFFECTS, AND LIVED EXPERIENCE OF ATALANTE EXOSKELETON-ASSISTED GAIT TRAINING IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: In ALS, progressive lower-limb weakness and fatigability compromise gait and autonomy, while limiting the feasibility of conventional walking practice [1,2,3]. Lower-limb exoskeletons may enable supervised, task-specific gait training, but evidence in ALS remains scarce. This study evaluated the safety, feasibility and preliminary effects of an Atalante exoskeleton-assisted gait training program, together with patients' lived experience.

Methods: In a prospective monocentric ABA pilot study, 10 ambulant patients with ALS underwent three consecutive 6-week phases over 18 weeks: baseline (usual care), intervention (Atalante exoskeleton-assisted gait training added to usual care; 18 sessions, three sessions/week), and withdrawal (usual care). Clinical outcomes and exoskeleton-specific patient-reported outcomes were repeatedly assessed every 3 weeks and analyzed using linear mixed-effects models. Post-training semi-structured interviews were audio-recorded, transcribed verbatim and analyzed using inductive qualitative content analysis.

Results: No serious adverse events occurred, and one mild adverse event was certainly related to the intervention. No outcome showed significant phase-specific slopes or slope contrasts, although several measures showed trends compatible with attenuated decline during the intervention phase and a return toward a less favorable trajectory after withdrawal. Exoskeleton-specific patient-reported outcomes indicated high intrinsic motivation and acceptability, with high ratings for usefulness for standing, perceived safety, participation, and installation/uninstallation. Perceived gait-training efficacy was positive. Interviews revealed positive expectations and experiences, with high expectation fulfilment. Participants reported improved upright posture, stability, smoother gait, reduced stiffness, and reduced fear of falling, although some effects were short-lived. Most characterized the intervention positively and would have continued training if available.

Conclusions: Atalante exoskeleton-assisted gait training was safe, feasible, and acceptable in ALS. Although no significant phase-specific effects were demonstrated, patient reported outcomes and qualitative findings suggest that the intervention was meaningful and perceived as beneficial.

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Keywords: ALS, Atalante exoskeleton, exoskeleton-assisted gait training.

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P4 - *CREB3*^{R119G} DRIVES NEURONAL RESILIENCE IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by the loss of glutamatergic corticospinal neurons (CSN) and cholinergic neurons (MN). It results in muscular weakness, fasciculations and atrophy that eventually lead to respiratory failure. It is mostly sporadic in 90% of cases, but genetics is expected to highly contribute to disease onset and progression. Indeed, genome-wide association studies (GWAS) identified a few genetic disease modifiers, mostly associated with a negative outcome, and demonstrated that ALS is primarily a disease of excitatory glutamatergic neurons.

Using comparative cross-species single-cell transcriptomics from mouse models and human ALS patients, we formerly showed that disease-vulnerable neuronal populations undergo ER stress and altered mRNA translation. Importantly, we identified the transcription factor CREB3 (*cAMP-responsive element-binding protein* 3) and its regulatory network as a resilience marker of neuronal dysfunction in ALS. Through genetic and epidemiologic analyses, we further identified the rare variant *CREB3*^{R119G} (*rs11538707*) as a new disease modifier in ALS that decreases both the risk of developing ALS and the progression rate of ALS patients [1]. Our project now aims at determining the mechanisms of neuronal resilience activated by *CREB3*^{R119G}. To this end, we started characterizing the molecular signature of induced pluripotent stem cells (iPSC) and iPSC-derived motor neurons (iPSC-MN) harboring a homozygous insertion of the R119G variant. We sought to combine multi-omics approaches (RNAseq, CUT&TAG, mass spectrometry) to identify the molecular pathways selectively activated by the variant proteins, in presence and absence of disease-relevant cellular stressors, and tie the latter to TDP-43 function.

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Keywords: ALS, CREB3, iPSC-MN.

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P5 - AGING AND ALS-ASSOCIATED MUTATIONS INFLUENCE STRESS GRANULE DYNAMICS IN *C. ELEGANS*

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The formation of stress granules (SGs) is a conserved process through which proteins and mRNA reversibly assemble into cytoplasmic biomolecular condensates. They are formed in response to translational arrest induced by various stresses, such as heat shock, oxidative stress, or hypoxia, and rapidly disassemble upon stress relief to facilitate translational recovery [1]. However, aging or mutations can disrupt SG dynamics properties, from liquid-like to more aggregated states [2]. This transition may contribute to the formation of protein aggregates characteristic of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Characterized by the degeneration of motor neurons in the central nervous system, ALS is associated with mutations in RNA-binding proteins (RBPs) such as FUS and TDP-43 [3]. These proteins are physiologically localized to SGs and their mutations alter SG dynamics and promote their transition into solid-like states. This process has been proposed as a contributing factor in the formation of neurodegenerative protein aggregates. Here, we investigate how aging and ALS-associated mutations affect SG dynamics in vivo. Using confocal imaging of transgenic *Caenorhabditis elegans* expressing SG markers, we identified distinct age-dependent trajectories of SG dynamics in germline and somatic tissues, revealing tissue-specific alterations of SG behavior during aging. We further examine how ALS-associated mutations influence SG assembly, disassembly, and age-dependent changes in SG properties.

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Keywords: Stress granules, protein aggregation, ALS

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P6 - DIAGNOSTIC PERFORMANCE OF SERUM NEUROFILAMENT LIGHT CHAIN IN PATIENTS REFERRED FOR SUSPECTED AMYOTROPHIC LATERAL SCLEROSIS: A REAL-WORLD MONOCENTRIC COHORT

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Introduction: The diagnosis of amyotrophic lateral sclerosis (ALS) remains challenging, particularly at early disease stages. Serum neurofilament light chain (sNfL) is increasingly used as a biomarker of axonal degeneration, but its diagnostic value and limitations in real-world diagnostic settings remain incompletely characterized [1-3].
Methods: We performed a retrospective, single-centre observational study using data extracted from the French National Rare Disease Registry (BNDMR) at Toulouse University Hospital. Consecutive adults who underwent sNfL measurement for suspected ALS between June 2023 and December 2025 were included. Final diagnoses were established after review of clinical follow-up. The primary objective was to evaluate the diagnostic performance of sNfL for distinguishing ALS from alternative diagnoses. Secondary analyses focused on ALS patients with normal sNfL and non-ALS patients with elevated sNfL.
Results: A total of 348 patients were included: 260 with confirmed ALS and 88 with an alternative diagnosis. Mean sNfL concentration was 167 ng/L (median 122 ng/L) in ALS patients compared with 63 ng/L (median 26 ng/L) in non-ALS patients. Using the local laboratory upper reference limit of 30 ng/L, only 9/260 ALS patients (3.5%) had normal sNfL concentrations, whereas 66/260 (25.4%) had concentrations exceeding 200 ng/L. Conversely, 35/88 non-ALS patients (39.8%) had elevated sNfL levels, including 13/88 (14.8%) with concentrations >100 ng/L. Diagnostic performance was good, with an area under the ROC curve of 0.847.
Conclusion: In this real-world cohort of patients referred for suspected ALS, sNfL showed good diagnostic performance and high sensitivity for ALS. However, elevated sNfL was frequent among ALS mimics, including markedly increased levels in some cases, highlighting that sNfL lacks absolute specificity and must be interpreted within the clinical context. Characterization of these discordant cases may improve interpretation of sNfL results and help define the optimal role of this biomarker in the diagnostic work-up of patients with suspected ALS.
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Keywords: amyotrophic lateral sclerosis – neurofilament light chain - diagnosis
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P7 - PERSONALIZED WHOLE-BRAIN MODELLING OF AMYOTROPHIC LATERAL SCLEROSIS REVEALS INDIVIDUAL CORTICAL EXCITABILITY PROFILES

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Keywords: Whole-brain modeling, Cortical excitability, patient stratification

Acknowledgements: This work was supported by ARSLA through the VirtuALS project, which aims to develop patient-specific digital twins based on digital biomarkers for individual ALS phenotype characterization.

Purpose:

Amyotrophic lateral sclerosis (ALS) is increasingly recognized as a multisystem disorder involving altered cortical excitability and brain connectivity. EEG can reveal changes in brain rhythms, but these changes may arise from different mechanisms: degeneration of structural connections, altered excitation-inhibition balance within cortical regions, or both. This study aimed to use personalized whole-brain computational modelling to investigate whether resting-state EEG abnormalities in ALS are better explained by patient-specific brain connectivity, altered excitation and inhibition in motor versus non-motor cortices, or a combination of these mechanisms.

Methods:

We analysed participants from the SOMALS study [1], a multimodal ALS cohort including EEG recordings at rest in 26 ALS patients and 26 healthy controls. For the first step of the VirtuALS project, the whole-brain activity was simulated in each participant using a mechanistic model that includes subject-specific individual structural connectivity derived from diffusion MRI. Using simulation-based inference [2], we inferred model parameters that correspond to global coupling between cortical regions, and region-grouped excitatory and inhibitory gains for left motor, right motor and non-motor regions of interest.

Results: Model parameter distributions were successfully estimated for each subject from resting-state EEG. Preliminary results showed inter-individual variability including within the ALS group, suggesting that resting-state EEG abnormalities may reflect heterogeneous combinations of structural connectivity and cortical excitability changes. Ongoing group-level analyses will determine whether these individualized parameter distributions reveal ALS-specific alterations.

Conclusion

This work provides a proof of concept for using personalized, neurobiologically grounded whole-brain models to interpret EEG abnormalities in ALS, and proposes a mechanistic explanation for altered excitation-inhibition balance in patients. Such model-derived parameters could provide new digital biomarkers for patient stratification and for studying motor versus non-motor involvement. To our knowledge, this is the first study to use a personalized whole-brain modeling framework to investigate excitation-inhibition alterations in ALS.

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P8 - EXPLORING THE LINK BETWEEN RNA-BINDING OF TDP-43 AND ITS AGGREGATION

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TDP-43 is a nuclear RNA-binding protein found in cytoplasmic inclusions of neurons in two major neurodegenerative diseases, ALS and FTLD [1]. So far, there is no efficient drug for curing these diseases. Recently, we demonstrated that tandem RNA recognition motifs (RRM) of TDP-43 bind to its RNA target in a cooperative manner through intermolecular interactions [2]. This cooperative binding of TDP- 43 to mRNA is critical to maintain the solubility of TDP- 43 in the nucleus and the miscibility of TDP- 43 in cytoplasmic stress granules [2]. More recently, we successfully developed an automated detection pipeline to assess TDP-43 self-assembly combined to functional screen in living cells. We showed that the post-translational modifications affect nuclear TDP-43 localization and consequently its functions. Currently, we explore the structural effect of a pathological mutation on residues belonging to RRM domains. This fundamental knowledge will pave the way to elucidate the mechanism of TDP-43 proteinopathy and to design small molecules interfering with TDP-43 aggregation.

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RNA-binding protein, TDP-43, RNA

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P9 - EXPRESSION OF A CRYPTIC EXON EMBEDDED IN INTRON 6 OF *Fus* GENE IN A SPINAL MUSCULAR ATROPHY MOUSE MODEL

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Infantile spinal muscular atrophy (SMA) is a group of neurodegenerative diseases characterized by motor neuron degeneration, muscle atrophy, and progressive muscular weakness. In most cases, SMA is caused by mutations in the Survival Motor Neuron 1 (SMN1) gene leading to a shortage in the ubiquitous protein SMN. The copy gene SMN2 modulates the SMA phenotype by the production of a reduced amount of SMN protein. Three innovative disease-modifying therapies, namely nusinersen, onasemnogene abeparvovec-xioi (Zolgensma), and risdiplam (Evrysdi), remarkably improve patient outcomes but achieve no definite cure and the long-term effects remain unknown. These observations prompted renewed efforts to better understand disease mechanisms and develop combinatorial treatments to improve the SMN-dependent treatments of those patients who need it. Beyond the loss of motor neurons, the reduction of SMN protein in all cells of the body causes multiorgan and metabolic defects in SMA patients and mouse models. SMN protein interacts with FUS and TDP-43, two proteins encoded by genes associated with amyotrophic lateral sclerosis (ALS). The observation that mutations of *FUS* induce significant dysfunctions in metabolic pathways also altered in SMA interrogates about *FUS* gene expression in SMA. First, we explore the autoregulatory mechanism involving the retention of introns 6 and 7, and no significant differences were detected between control and SMA mouse models. Interestingly, RNA sequencing analysis of the spinal cords from an SMA mouse model at post-natal day 11 (P11) treated with flunarizine or its diluent uncovered a "cryptic" exon embedded in intron 6 whose utilization might produce altered *Fus* mRNA transcripts. Moreover, ongoing RT-PCR studies will confirm our preliminary results of a sex-dependent expression of this exon upon drug treatment. These findings further highlight the functional link between genes whose mutations are associated with SMA and ALS diseases.

Keywords: SMA, FUS, cryptic exon, flunarizine

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P10 - SPEECH-BASED ACOUSTIC MARKERS IN SPINAL AND BULBAR MUSCULAR ATROPHY

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Objective:

Spinal and bulbar muscular atrophy (SBMA) is a rare lower motor neuron disease in which dysarthria remains poorly characterized. Because SBMA may be misdiagnosed as amyotrophic lateral sclerosis (ALS), identifying disease-specific speech markers is clinically relevant. This study aimed to characterize acoustic speech features associated with SBMA.

Methods:

Speech recordings from 18 dysarthric men with genetically confirmed SBMA and 34 age- and sex-matched healthy controls were analysed. Acoustic analyses focused on three speech dimensions: voice height, speech rate during reading of a sentence containing multiple tongue-tip consonants, and diadochokinetic (DDK) rate for syllables engaging different articulators (lips, tip of the tongue, back of the tongue). Group comparisons were performed using parametric or non-parametric statistics as appropriate. DDK performance was further examined using mixed-effects models including place of articulation and group.

Results:

Compared with controls, SBMA patients exhibited higher voice height, with substantial inter-individual variability, and slower speech rate during reading. Maximum syllable repetition rates involving the lips and anterior tongue were preserved. In contrast, tasks engaging posterior tongue movements were selectively impaired. This pattern differs from the more generalized speech slowing typically reported in ALS.

Conclusions:

SBMA dysarthria is associated with distinct acoustic features, including elevated voice height, reduced reading rate, and selective slowing of posterior tongue movements. This pattern contrasts with the more generalized speech impairment typically observed in ALS. The presence of elevated voice pitch—an atypical finding in flaccid dysarthria—suggests mechanisms extending beyond lower motor neuron dysfunction and warrants further investigation. Overall, acoustic speech measures may provide clinically relevant, non-invasive markers to support differential diagnosis, disease monitoring, and outcome assessment in SBMA.

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Keywords: Spinal and Bulbar Muscular Atrophy, flaccid dysarthria, acoustic markers

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P11 - *NOP56* GGCCTG REPEAT EXPANSION IS ABSENT IN AMYOTROPHIC LATERAL SCLEROSIS FRENCH CASES

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Repeat expansion disorders predominantly cause spinocerebellar degenerations. Spinocerebellar degenerations are a spectrum of hereditary neurodegenerative disorders encompassing the molecular and clinical continuum from motor neuron disease to cerebellar disease. Cerebellar ataxia form SCA36 is caused by *NOP56* GGCCTG large repeat expansions, reminiscent of the *C9ORF72* hexanucleotide GGGGCC expansions, the most frequent genetic cause of Amyotrophic Lateral Sclerosis (ALS). In addition, first and second motor neuron signs are frequent in SCA36 [1], raising the question of possible forms without cerebellar ataxia corresponding to ALS presentation.
The screening of 400 ALS cases including 100 neuropathological cases and 300 familial index cases (with no variant in any ALS-related gene) did not identify any *NOP56* expansion. This result was consistent with previous studies in Italy, China and South Africa [2]. A sequence-specific RNA-mediated toxicity was associated to selective neuronal vulnerability differing in *NOP56* and *C9ORF72* expansions [3]. Moreover we observed that motor signs in SCA36 are always in association with cerebellar ataxia in French cases. The research of new repeat expansions causing ALS deserves to be further explored.

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Keywords: repeat expansion, disease cause, genetics

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P12 - AN UNDER-APPRECIATED ROLE FOR LACTATE METABOLISM IN AMYOTROPHIC LATERAL SCLEROSIS: LESSONS FROM SPORTS MEDICINE

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Key words: lactate, exercise, denervation

Lipid and glucose metabolism are critically modified in amyotrophic lateral sclerosis (ALS), yet lactate is the key modulator of the balance between glucose and lipid metabolism, while being an essential fuel for motor neurons and neuromuscular junctions (NMJs). Lipid metabolism, and weight loss associated with hypermetabolism, is increased at disease initiation in patients, $SOD1^{G86R}$ mice and $TDP\text{-}43^{Q331K}$ mice, whereas low circulating lactate and high muscle glycogen is a major goal of endurance athletes, to drive lipid metabolism and to spare muscle glycogen [1]. Lactate production varies between different athletic events with VLamax (the maximum rate of lactate production via anaerobic glycolysis) changing between ~0.9 mmol/l/s in 100m sprint, ~0.5 mmol/l/s in middle distance, ~0.3 mmol/l/s in marathon, changing fuel preference from glucose to lipid, as lactate (via lactoyl CoA and then malonyl CoA) inhibits carnitine palmitoyl transferase 1, the rate limiting lipid transporter. Lactate is also a highly regulated signalling molecule, acting on GPCRs (e.g. HCAR1), direct lactylation of multiple targets, controlled by multiple shuttles and transporters [2]. Increased lactate production and metabolism have revolutionised sports science, athletic training and ameliorated absolute human performance (https://inscyd.com). However, lactate metabolism is understudied in ALS, despite lactate metabolism being highly compromised by preferential denervation of fast twitch muscle producing lactate, at the beginning of the disease, reviewed in [1]. The critical factors, Ra (rate of lactate production) and Rd (lactate metabolism) are unknown in ALS, but can be optimized using simple techniques which may be applied to patients at the beginning of denervation. Thus, it is not known whether abnormal lactate metabolism is derivative or causative of spreading denervation. Potential means of restoring lactate at the beginning of denervation are feasible in patients [2] and will be presented for discussion.

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P13 - SIGMA-1 RECEPTOR AS A THERAPEUTIC TARGET IN ZEBRAFISH MODELS OF CHARCOT-MARIE-TOOTH TYPE 2A DISEASE

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Charcot-Marie-Tooth type 2A (CMT2A) is one of the most frequent and severe forms of CMT. It leads to serious sensori-motor deficits, and some patients also show optic atrophy or hearing loss [1,2]. CMT2A is caused by mutations in *MFN2,* which encodes Mitofusin-2 (MFN2), a mitochondrial outer membrane GTPase regulating mitochondrial dynamics. Unfortunately, no treatment is available. In order to better understand the altered signaling pathways and to test novel therapeutic strategies, we developed zebrafish models overexpressing two of the most prevalent dominant mutations: $MFN2^{R94Q}$ and $MFN2^{R364W}$, which differentially impact zebrafish physiology. We analyzed multiple parameters, including locomotion, motor neuron length, visual acuity, and mitochondrial integrity. We found that $MFN2^{R94Q}$ and $MFN2^{R364W}$ zebrafish had locomotor deficits. Then, since Sigma-1 Receptor (S1R) – a chaperone protein involved in multiple cell survival mechanisms – is an ideal target in several nervous system diseases [3], we evaluated the effect of the reference agonists, PRE-084 and a novel agonist developed by SITERA Pharmaceuticals (Drug 1). Treatment with both agonists rescued the locomotor alteration. Similar results were obtained in zebrafish overexpressing S1R. These deficits were associated with a reduction in motoneuron axonal length, which was also rescued by the two compounds. The visual acuity assessment also indicates a visual impairment that improved with Drug 1. Then, we found a decrease in basal and maximal mitochondrial respiration in $MFN2^{R94Q}$-expressing larvae compared to controls. These parameters tend to be rescued by both agonists. To highlight pathways affected by the mutations and the treatments effect, an unbiased transcriptome analysis has been performed. Data analysis is ongoing. In conclusion, these relevant zebrafish models improved our understanding of the physiopathological mechanisms underlying CMT2A and allowed the validation of S1R as a promising therapeutic target in CMT2A.

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Keywords: CMT2A, Mitofsin-2, zebrafish

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P14 - ALS-GUT: METAGENOMIC CHARACTERIZATION OF THE INTESTINAL MICROBIOTA IN ALS PATIENTS AND ASSOCIATION WITH CLINICAL PHENOTYPES

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Background

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease affecting upper and lower motor neurons, leading to severe disability and death, typically within 3–5 years [1,2]. Increasing evidence suggests that the gut microbiota may play a role in neuroinflammatory and metabolic pathways involved in neurodegeneration [3,4]. However, robust human data characterizing gut microbial alterations in ALS and their clinical relevance remain limited and inconsistent.

Objectives

The primary objective of this study is to characterize the gut microbiota in a large French cohort of ALS patients using metagenomic sequencing. Secondary objectives include investigating associations between microbiota features and clinical phenotype, disease severity, and progression, and therapeutic management.

Methods

ALS-Gut is a prospective French multicenter observational study. Three hundred patients with ALS will be recruited across 18 expert ALS centers in collaboration with the French Gut initiative Clinical data including ALS Functional Rating Scale–Revised (ALSFRS-R), respiratory function, nutritional status, disease duration, and treatments will be systematically recorded. Stool samples will be collected and processed using standardized procedures. Gut microbiota composition and functional potential will be analyzed using shotgun metagenomic sequencing. Bioinformatic analyses will assess taxonomic diversity, microbial community structure, and functional pathways. Associations between microbiota profiles and clinical variables will be explored using multivariable statistical models.

Discussion

The ALS-GUT study will, for the first time, enable, to characterize quantitatively and qualitatively the gut microbiota in a large of French patients with ALS disease and to identify changes associated with the disease compared to healthy subjects.

It will also lead to determining potential associations between observed alterations of the microbiota and the clinical phenotype of ALS, its progression profile, and its therapeutic management, including nutritional and respiratory aspects.

This study will open new avenues for innovative therapeutic strategies aiming to modulate gut microbiota, in order to limit the progression of motor dysfunction.

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KeyWords:

1. Amyotrophic Lateral Sclerosis (ALS)
2. Gut Microbiota
3. Metagenomics

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P15 - OMICS INVESTIGATION OF NEURODEVELOPMENT IN MOUSE MODELS OF AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting motor neurons of the motor cortex (MC) and spinal cord (SC), leading to rapidly progressing paralysis and death within two to five years. With reported pediatric and juvenile cases, genetic or epidemiologic link with neurodevelopmental diseases such as autism and schizophrenia, and the neurodevelopmental roles of several ALS-related genes, a putative neurodevelopmental origin of ALS is merging, along with boarder neurodegenerative conditions [1]. In particular *FUS* mutations cause juvenile ALS in humans, perinatal lethality in $Fus^{\Delta NLS/\Delta NLS}$ homozygous mice, and brain development defects in $Fus^{\Delta NLS/+}$ heterozygous mice [2]. Homozygous truncating mutation of *SOD1* leads to paediatric ALS in humans, and the $Sod1^{G93A}$ mouse model leads to perinatal excitability alterations in upper and lower motor neurons [3]. Together, these observations motivate a broader, unbiased investigation of early molecular alterations across genetically distinct ALS models.

My PhD project hypothesize that, at least a subclass of genetic ALS cases might arise from infraclinical neurodevelopmental impairments, which might be efficiently compensated by the developing central nervous system, until compensatory mechanisms weaken with age. My project aims at characterizing the molecular landscapes of the developing motor cortex and spinal cord, at birth, in the genetically and phenotypically complementary $Sod1^{G86R}$ and $Fus^{\Delta NLS/+}$ mouse models of ALS, using transcriptomic (snRNA-seq) and proteomic (LC-MS) investigations. This integrative approach aims to identify initially impaired neurodevelopmental pathways, that might be either common or specific to $Sod1^{G86R}$ or $Fus^{\Delta NLS/+}$ mouse models of ALS.

Altogether, this project may not only inform on developmental ALS-related molecular alterations and novel therapeutic targets, but may also contribute to shifting the perspective of the origin of ALS.

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Key words: Neurodevelopment, Transcriptomics, Proteomics

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P16 - EFFECTS OF FUS MUTATIONS ON TFIIH INTERACTION, NUCLEOLAR HOMEOSTASIS, AND THE CELLULAR RESPONSE TO GENOTOXIC STRESS

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FUS (Fused in Sarcoma) is an RNA-binding protein involved in multiple nuclear processes, including gene expression regulation, stress responses, and genome maintenance. Mutations in FUS are responsible for a subset of familial amyotrophic lateral sclerosis (ALS) cases and lead to altered subcellular localization and cellular dysfunction. Beyond its canonical roles, FUS has been implicated in liquid-liquid phase separation (LLPS).

Here, we identify a physical and functional relationship between FUS and the TFIIH complex, a key factor in RNAPII transcription and DNA repair. We show that FUS interacts with TFIIH under basal conditions and that this interaction is enhanced following UV-induced genotoxic stress. Upon UV irradiation, both proteins accumulate at the nucleolar periphery, suggesting a coordinated response associated with nucleolar reorganization after DNA damage.

Functional analyses using TFIIH mutants affecting XPB and TTDA subunits reveal that nucleolar retention of FUS is independent of a fully functional TFIIH complex. Conversely, depletion of FUS does not prevent TFIIH relocalization to the nucleolar periphery, indicating that their recruitment to this compartment occurs independently.

Despite this, FUS depletion leads to significant functional alterations, including reduced basal RNAPII transcription, impaired recovery of RNAPI transcription after UV irradiation, and decreased DNA repair capacity. However, DNA repair remains partial compared to nucleotide excision repair-deficient XPC cells, suggesting a modulatory role for FUS in this pathway.

Together, these results support a model in which FUS is not required for TFIIH recruitment at nucleolar periphery after UV but is essential for optimal transcriptional and DNA repair responses following genotoxic stress. We further investigate ALS-associated FUS mutants, including variants affecting the low-complexity domain (PLD) and nuclear localization signal (NLS), to determine how disease-linked alterations impact TFIIH interaction and nuclear stress responses.

This work provides new insight into how FUS dysfunction may contribute to ALS pathophysiology by altering transcriptional homeostasis and DNA damage response mechanisms.

Keywords: Amyotrophic lateral sclerosis (ALS) / FUS / DNA damage response

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P17- DRUMS: A Treatable Mimic of Flail-Arm ALS

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Introduction: Progressive upper-limb motor syndromes resembling flail-arm amyotrophic lateral sclerosis (ALS) have been reported in association with spinal longitudinal extradural cerebrospinal fluid collections (SLECs), but heterogeneous terminology has limited recognition of this potentially treatable condition [1–3].

Methods: We retrospectively included all consecutive patients evaluated at our tertiary neuromuscular center between May 2014 and June 2026 with lower motor neuron involvement of one or both upper limbs and a SLEC on spinal MRI. Clinical, electrophysiologic, neuroradiologic, diagnostic, treatment, and outcome data were reviewed. Imaging was centrally reassessed by a neuroradiologist blinded to clinical and electrophysiologic findings.

Results: Seven men were included. Median age at motor symptom onset was 57 years and median diagnostic delay was 40 months. Weakness predominantly involved C5–C6 myotomes in 5 patients and C7–C8 in 2 and was asymmetric in 4. All patients had upper-limb amyotrophy without objective sensory loss, lower-limb weakness, bulbar or respiratory involvement, or definite pyramidal signs. EMG demonstrated chronic multimyotomal cervical neurogenic changes in all patients and active denervation in 4. No extracervical neurogenic abnormalities were found in the 6 patients assessed. ALS was the initial diagnosis in 2 patients. Three spinal MRIs were initially reported as normal despite retrospectively visible SLECs; in another patient, the SLEC was not linked to the motor syndrome for nearly 7 years. A dural defect was localized in 6 patients. Among 3 patients who underwent closure, complete motor recovery was observed in 1 and stabilization with disappearance of active denervation in 1.

Conclusion: We propose the term duropathy-related upper-limb motor syndrome (DRUMS) to facilitate recognition of this underrecognized, potentially treatable mimic of flail-arm ALS.

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Keywords: ALS mimic – duropathy - brachial amyotrophy

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P18 - EXPLORING THE LINK BETWEEN NUP50 DEFICIENCY AND TDP-43 DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease defined by the progressive loss of motor neurons and, in the vast majority of cases, by the nuclear depletion and cytoplasmic accumulation of the RNA-binding protein TDP-43 [1]. Recently, loss-of-function variants in the nucleoporin NUP50, a component of the nuclear pore complex implicated in importin-dependent nuclear import, have been associated with an increased risk of ALS [2]. Because TDP-43 relies on the same import machinery as it shuttles between the nucleus and cytoplasm, we investigated whether reduced NUP50 expression is associated with alterations in TDP-43 localization and function in neuronal cell models.

NUP50 was depleted in immortalized neuronal cell lines using gene-silencing approaches. TDP-43 loss of function was assessed through complementary splicing-based readouts [3], while its subcellular distribution was examined by fluorescence microscopy. Similar analyses were subsequently performed in human iPSC-derived motor neurons. Preliminary results suggest that NUP50 depletion may be associated with features reminiscent of TDP-43 dysfunction, including altered RNA processing and a progressive, time-dependent redistribution of TDP-43 toward the cytoplasm, occasionally accompanied by the appearance of aggregates at the nuclear periphery.

Taken together, these preliminary observations raise the possibility that reduced NUP50 expression may contribute to alterations in TDP-43 homeostasis, potentially linking nucleocytoplasmic transport defects to ALS-associated pathology. However, these findings remain preliminary and are currently being further investigated. Ongoing analyses in human iPSC-derived motor neurons using immunofluorescence and RNA sequencing are being performed to assess whether similar molecular alterations can be detected in a more physiologically relevant model.

Keywords: amyotrophic lateral sclerosis, NUP50, TDP-43

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P19 - ANALYSIS OF STRESS RESPONSE IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENT IPSC-DERIVED MOTOR NEURONS TO CHARACTERIZE THE PATHOGENIC IMPACT OF THE p.CYS218TYR TIA1 VARIANT

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Keywords:
ALS genetics, iPSC motor neurons, Stress granules

Abstract (297 / 300 words)
Several pathogenic mechanisms have been proposed for Amyotrophic Lateral Sclerosis (ALS) motor neuron (MN) degeneration. One of them is RNA metabolism dysregulation based on the identification of mutations in genes encoding mRNA binding proteins, such as TDP-43 (TAR DNA-Binding Protein), FUS (FUsed in Sarcoma) and TIA1 (T-Cell-Restricted Intracellular Antigen-1), which regulate the expression level and/or splicing processes of multiple cellular targets. TIA1 is also the main component of stress granules (SGs), which are transiently formed to protect mRNA during cellular stress, supporting the hypothesis that impaired stress responses may contribute to ALS disease processes [1]. We aimed to characterise the impact of the RNA recognition motif-linked p.C218Y TIA1 variant, identified in a patient with early ALS onset, in iPSC-derived MNs differentiated for 35 days according to a protocol established to generate ALS vulnerable MNs [2]. Various heat shock conditions were applied, and SG induction/clearance were compared by immunofluorescence at different time points in MNs expressing mutant TIA1, the corresponding CRISPR/Cas9-corrected line and MNs from healthy controls. Our preliminary results suggest altered SG dynamics in mutant TIA1 MNs consecutive to defects in SG formation with preserved SG clearance. These observations differ from previous ones for Prion-like domain-linked TIA1 variants, which rather resulted in SG clearance delay using another cellular model [1]. Moreover, we did not observe any abnormal accumulation/deposit/aggregation of TIA1, TDP-43 or p62 autophagic marker in these patient MNs even after stress insult. RNA sequencing analysis are ongoing and will allow to decipher the stress response pathways.

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P20- EXOME SEQUENCING IN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS WITH NEGATIVE ROUTINE GENETIC TESTING

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons, leading to paralysis and death. The genetic contribution to ALS has become increasingly evident, with numerous causal genes and risk factors identified over the last decade [1–3].

Objectives: To investigate the genetic basis of ALS cases and to assess the contribution of whole-exome sequencing (WES) to the molecular diagnosis of the disease.

Methods: This retrospective monocentric study was conducted at the ALS Reference Medical Biology Laboratory of Tours University Hospital. Patients diagnosed with ALS and presenting no pathogenic variant (classe 4 or 5, ACMG) after routine targeted panel analysis (39 ALS genes) were included. Whole-exome sequencing (WES), covering the coding regions of approximately 22,000 genes, was performed retrospectively. Bioinformatic analyses were carried out using an in-house exome analysis pipeline recently developed at Tours University Hospital and the DIAGHO genomic variant interpretation platform developed by the HUGO (Hôpitaux Universitaires du Grand Ouest) network. Identified variants were classified according to current recommendations, and functional enrichment analyses were performed on rare variants predicted to be deleterious.

Results: Candidate disease-associated variants were identified in 7 patients. Functional enrichment analysis of rare and predicted deleterious variants confirmed the relevance of variants previously identified through conventional approaches and highlighted additional candidate variants. At the cohort level, enrichment analysis revealed two major biological pathways associated with ALS susceptibility: protein post-translational modification and DNA repair mechanisms.

Conclusions and Perspectives: These findings support the integration of WES into the genetic analysis of unresolved ALS cases and and provide novel candidate genes and generate novel pathophysiological hypotheses. Beyond its application in ALS, exome sequencing may contribute to improving the classification of motor neuron disorders and other neurodegenerative diseases, ultimately supporting more personalized patient management.

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Keywords: Amyotrophic lateral sclerosis; Whole-exome sequencing; Genetic variants

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