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EDITORIAL

ALS: a field in motion

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Amyotrophic lateral sclerosis (ALS) is a multifactorial neurodegenerative disorder driven by complex interactions among genetic, environmental, developmental, and resilience-related factors. The studies in this *Scientific Reports'* Collection highlight major advances across diverse domains that collectively broaden our understanding of ALS pathogenesis. Genetic insights emphasise the need for functional validation, as shown by the non-pathogenic behaviour of the *KIF5A* P986L variant in *Drosophila*. Neuroimaging findings reveal hypothalamic atrophy in primary lateral sclerosis, underscoring widespread extra-motor involvement. Epidemiological analyses propose that early-life exposures may form the initial steps in a multistage pathway to ALS, while geographic correlations between ALS and multiple sclerosis suggest shared environmental determinants. Experimental model innovations demonstrate selective muscle preservation in *SOD1*-G93A mice and introduce electrical impedance myography as a sensitive detection method in zebrafish. Mechanistic work shows that stress influences ALS through PI3K/Akt and focal adhesion pathways, linking environment to cellular vulnerability. Finally, cognitive and brain reserve emerge as important modifiers of disease expression and progression. Together, these studies illustrate ALS as a multisystem, lifespan-spanning disorder shaped by both vulnerability and resilience. Their integration offers a forward-looking framework for advancing biomarker discovery, mechanistic research, and therapeutic development in ALS.

Amyotrophic lateral sclerosis (ALS) remains one of the most complex and devastating neurodegenerative disorders, marked by progressive loss of upper and lower motor neurons and culminating in paralysis and early mortality. Despite decades of investigation, the disease continues to challenge clinicians and scientists alike with its remarkable heterogeneity, multifactorial aetiology, and limited therapeutic options[1,2]. The papers in this Collection span genetics, neuroanatomy, environmental determinants, experimental models and early-detection strategies, bringing together work from four continents (Australia, Europe, North America and Asia), highlighting the global drive to make inroads against this insidious disease (Table 1).

This Collection showcases not only the diversity of ALS research but also the shifting paradigm toward integrative, cross-disciplinary approaches. Together, these studies reinforce ALS as a spectrum of disorders shaped by diverse biological and environmental determinants, while beginning to chart a path toward deeper mechanistic insight and more effective translation.

Genetic complexity and the need for functional validation

Genetic mutations, particularly those in major ALS genes *C9orf72*, *SOD1*, *TARDBP*, and *FUS*, have long served as anchors in ALS research. Yet, with only a fraction of cases attributable to known mutations, questions remain about the pathogenic roles of many rare or newly discovered variants in these and other genes. In this context, the study by Layalle et al.[3] offers essential mechanistic insight into KIF5A, a critical kinesin motor protein implicated in axonal transport. Following the discovery of ALS-associated *KIF5A* mutations[4] and evidence that certain variants induce a toxic gain-of-function that disrupts transport dynamics, which is a key contributor to motor neuron vulnerability in ALS[5], the pathogenicity of individual mutations has become a central question. In *Drosophila* motor neurons, the ALS-associated KIF5A P986L variant does not induce neurodegeneration or disrupt motor function, challenging assumptions about its pathogenicity.

The significance of this finding extends beyond the *KIF5A* gene, highlighting that not all ALS-associated variants are inherently pathogenic and that interpretation should rely on functional validation rather than association alone. Indeed, it illustrates the importance of robust experimental systems for distinguishing benign variants from those that drive disease processes. This principle also applies to risk loci identified through large genome-wide association studies (GWAS), where functional validation has been essential for bridging association signals with disease mechanisms, as exemplified by the *UNC13A* and *SCFD1* risk genes[6–8]. Such

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Article	Key findings	Implications for ALS research
Layalle et al.	The ALS-associated *KIF5A*^{P986L} variant, when expressed in *Drosophila* motoneurons, does not alter NMJ morphology, synaptic transmission, mitochondrial distribution, locomotion or lifespan, and behaves more like a benign/hypomorphic allele than a toxic ALS mutation.	Not all ALS-enriched variants are truly pathogenic; rigorous functional work in tractable models is essential before classifying variants as causal or using them to stratify patients.
Kassubek et al.	CNN-based MRI segmentation shows comparable hypothalamic atrophy in PLS and classical ALS versus controls, despite their very different clinical time-courses, reinforcing shared metabolic/hypothalamic involvement across the MND spectrum.	ALS and PLS likely share core systems-level pathology, with hypothalamic atrophy emerging as a candidate cross-phenotype imaging biomarker linked to energy balance and survival.
Pamphlett et al.	An international case, control questionnaire identifies early-life factors, rural residence, younger parental age, and lower education/years of schooling, as associated with later ALS, consistent with environmental "first steps" within a multistep disease model.	ALS risk may be seeded decades before onset, supporting a multistep framework where early-life environment and social determinants interact with genetics to shape who eventually crosses the disease threshold.
Schilling	Using mortality data (CDC WONDER, WHO), ALS and MS show a correlated geographic distribution after controlling for race, sex, latitude and economic factors, revealing a Simpson's paradox that previously masked this association in pooled data.	ALS and MS may share yet-unresolved environmental or systemic drivers (e.g. latitude-linked factors, toxicants, infections), arguing for cross-disease aetiological work rather than studying each in isolation.
Kawata et al.	In *SOD1*^{G93A} mice, masseter muscle volume, structure, fibre-type composition and myonuclear content are preserved almost to end-stage, with increased satellite cells, whereas limb muscles show pronounced atrophy and remodelling.	Selectively resistant muscles and motor units (like masseter, extraocular, sphincter) harbour intrinsic protective programmes; decoding these may reveal therapeutic mechanisms to stabilise vulnerable NMJs and motor neurons.
Rutkove et al.	An adult-onset *SOD1*^{G93A} zebrafish model exhibits progressive NMJ degeneration, motor neuron loss, muscle atrophy and reduced swimming endurance, and surface electrical impedance myography (EIM) sensitively detects disease-related changes and tracks progression at specific frequencies.	Combining zebrafish genetics with scalable, non-invasive physiological readouts such as EIM offers a rapid, quantitative platform to screen ALS therapeutics and benchmark neuromuscular integrity.
Rasà et al.	Across *SOD1*^{G93A} mice, NSC-34 *SOD1*^{G93A} cells and *TARDBP*-mutant iPSC-derived motor neurons, chronic or acute stress worsens phenotypes and dysregulates PI3K/Akt and focal adhesion pathways (via IL-6, IGF1, collagens), with sex-specific effects on behaviour and gene expression.	Stress biology and lifestyle exposures can modulate ALS trajectories; targeting stress-sensitive signalling hubs (PI3K/Akt, focal adhesion) and reducing chronic stress could be leveraged as disease-modifying strategies in predisposed individuals.

Table 1. Concise overview of each study in the *Scientific Reports*' ALS Collection, summarising its core findings and broader significance for ALS research.

investigations have practical implications for genetic counselling, biomarker development, and the design of targeted therapeutics.

Neuroanatomical signatures: beyond the motor system

ALS is traditionally defined by its motor symptoms, yet mounting evidence suggests the involvement of widespread extra-motor networks. Among these, hypothalamic dysfunction has gained increasing attention[9]. Kassubek et al.[10] apply convolutional neural network-based automatic segmentation to evaluate hypothalamic atrophy in individuals with primary lateral sclerosis (PLS), a pure upper motor neuron disorder on the ALS spectrum. Outcomes reveal prominent hypothalamic atrophy in PLS, echoing observations in classical ALS and reinforcing the concept that metabolic and neuroendocrine dysregulation may contribute to disease mechanisms or symptom expression. Notably, implementing deep learning for neuroanatomical segmentation improved precision in capturing subtle structural changes that may escape conventional volumetric analyses.

This work highlights the hypothalamus as a potential biomarker-rich region and encourages the field to further consider ALS as a multisystem neurodegenerative disease, a framework long recognised in spinal muscular atrophy (SMA)[11]. As phenotypic distinctions between ALS, PLS, and other motor neuron disorders become increasingly nuanced, neuroimaging biomarkers such as those described here may play a key role in earlier diagnosis, patient stratification, and monitoring of disease progression.

Environmental and early-life determinants: reframing ALS pathogenesis

One of the longstanding challenges in ALS research is reconciling the low penetrance of many genetic variants with the relatively stable incidence of disease in the population. Pamphlett and Parkin Kullmann[12] provide a compelling conceptual framework by proposing that early-life events initiate the first steps on the multistep pathway leading to ALS. Their epidemiological analysis supports the idea that prenatal exposures, perinatal complications, or early developmental insults may create latent vulnerabilities which, decades later, interact with additional risk factors to precipitate disease. This multistep model, proposed for ALS more than a decade ago[13], aligns the disease with many cancers and chronic diseases, where cumulative, sequential biological hits eventually cross a threshold into pathology. Crucially, it opens new avenues for preventive strategies. If early-life factors contribute meaningfully to ALS risk, then identifying and mitigating them may reduce susceptibility later in life.

Complementing this developmental perspective, Schilling[14] examines the geographic association between ALS and multiple sclerosis (MS), by identifying regions where both diseases show elevated incidence. This study raises important questions about shared environmental risk factors, including latitude-linked UV exposure, regional toxicants and localised infectious agents.

Together, these papers emphasise that ALS aetiology cannot be fully understood solely through cellular or molecular studies. Geographical, ecological, and life-course perspectives are essential to mapping the complex origins of the disease.

Refining and expanding experimental models

Animal models remain indispensable for ALS research, yet they require continual refinement to accurately capture disease progression and therapeutic responses. In the *SOD1*^{G93A} mouse, Kawata et al.[15] reveal that the

masseter muscle, a key muscle for mastication and one of the strongest human muscles relative to size, remains preserved until the end-stage of disease, in contrast with the profound atrophy affecting limb musculature. Such selective vulnerability/resilience offers valuable insights and is a key feature of ALS[16]. Facial and bulbar motor deficits are clinically significant in ALS, yet the preservation of certain cranial neuromuscular connections may point to differential motor neuron susceptibility and/or distinct protective mechanisms. Mapping these protective pathways could lead to novel therapeutic targets aimed at enhancing motor neuron resilience.

Rutkove et al.[17] used surface electrical impedance myography (EIM) as a non-invasive tool to detect motor deterioration in an adult-onset *SOD1*^{G93A} zebrafish model. Zebrafish offer unique advantages for high-throughput genetic and pharmacological screening due to their rapid development and optical transparency[18]. Demonstrating that EIM can sensitively detect disease-associated physiological changes in this model represents a major step toward standardized, scalable *in vivo* screening tools.

These two papers reinforce a pressing need in ALS research: the development of more nuanced, reliable, and translatable models, while also sharpening our scientific questions so we fully leverage what existing model systems can genuinely reveal[19].

Stress biology as a convergent mechanistic pathway

The interaction between environmental exposures and intrinsic cellular pathways is a growing frontier in ALS research. Rasà et al.[20] provide strong mechanistic evidence that stress exposure influences ALS pathogenesis via PI3K/Akt and focal adhesion pathways, identifying stress-induced dysregulation of survival signalling and cytoskeletal integrity. Using a multisystem approach strengthens the causal link between stress biology and motor neuron vulnerability, and raises important questions about how chronic stressors or systemic inflammation might accelerate disease onset or progression. Notably, the PI3K/Akt pathway sits at the core of cell survival, metabolic regulation and synaptic maintenance, highlighting a potential therapeutic axis.

Their findings dovetail with the early-life vulnerability concept raised by Pamphlett and Parkin Kullmann[12], suggesting that stressors, whether developmental, environmental, or physiological, may converge on shared intracellular pathways, contributing cumulatively to ALS risk.

Cognitive and brain reserve: why the same disease affects people differently

Clinical heterogeneity is a defining feature of ALS[1], and cognitive impairment is common yet variable, complicating care and influencing survival. Temp et al.[21] explore the concept of cognitive and brain reserve, or essentially the idea that certain individuals possess structural or functional neural resources that provide resilience against neurodegenerative damage. Outcomes suggest that both cognitive reserve (shaped by life experiences, education, and intellectual engagement) and brain reserve (reflecting neuroanatomical robustness) modulate clinical presentation and disease progression. Notably, individuals with higher reserve showed slower disease progression and better functional outcomes. These findings echo similar observations in Alzheimer's disease, emphasising that resilience factors are as important as risk factors in shaping disease trajectories[22]. This shift in perspective, toward understanding what protects as much as what harms, may help refine prognostic models and inform personalised therapeutic strategies.

Conclusions

This *Scientific Reports*' ALS Collection captures a field in motion, expanding conceptually, diversifying methodologically, and deepening its appreciation of ALS as a multifactorial disease. Together, these studies demonstrate that ALS cannot be reduced to a single gene, pathway, or environmental agent but must be understood as a dynamic interplay between genetic architecture, developmental history, environmental context, stress biology, and neuroanatomical and cognitive resilience. Integrating these domains, while refining experimental systems and embracing life-course and environmental perspectives, will help move the field toward actionable therapeutic targets and more effective interventions. The path ahead is challenging, but the work in this Collection provides both momentum and direction, reflecting a research community united in tackling one of neuroscience's most formidable mysteries.

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Author contributions

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Declarations

Competing interests

The author declares no competing interests.

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