RESEARCH ARTICLE OPEN ACCESS

Genetic Variants Associated With Neurodegenerative Disorders in Patients With Amyotrophic Lateral Sclerosis and Phenotypic Variability

Maurizio Grassano,[1,*] Emanuele Koumantakis,[2,*] Francesca F. Palumbo,[1] Maura Brunetti,[1] Giovanni De Marco,[1,3] Ilaria Merulla,[1,3] Claudia Paolantonio,[1] Barbara Iazzolino,[1] Marcella Testa,[1] Umberto Manera,[1,3] Antonio Canosa,[1,3] Rosario Vasta,[1] Giuseppe Fuda,[1] Paolina Salamone,[1] Giulia Marchese,[1] Federico Casale,[1] Salvatore Gallone,[3] Gabriele Mora,[1] Cristina Moglia,[1,3] Andrea Calvo,[1,3,†] and Adriano Chiò[1,3,4,†]

Correspondence
Dr. Grassano
maurizio.grassano@unito.it

Neurology® 2025;105:e214180. doi:10.1212/WNL.0000000000214180

Abstract

Background and Objectives

The genetic contribution to clinical heterogeneity in amyotrophic lateral sclerosis (ALS) remains poorly understood, particularly regarding the role of genes associated with other neurodegenerative disorders. This study aimed to determine whether rare variants in neurodegeneration-associated genes influence ALS risk and clinical phenotype.

Methods

This case-control study included patients with ALS without pathogenic variants in major ALS genes from the population-based Piemonte and Valle d'Aosta Register for ALS and matched controls. High-impact rare variants (minor allele frequency <0.01% or novel) in 151 genes associated with neurodegenerative disorders were identified through whole-genome sequencing. Main outcomes included ALS risk, motor phenotype, cognitive status, and survival. Findings were replicated in the Project MinE dataset (6,596 ALS cases, 2,454 controls).

Results

The study population consisted of 791 ALS patients (median age 67.9 years; 46.3% women) and 747 matched controls. One hundred twenty-seven ALS cases (16.1%) carried at least one rare variant in neurodegeneration-associated genes compared with 91 (12.2%) controls (odds ratio [OR] 1.37; 95% CI 1.04–1.80; $p = 0.027$). In particular, novel variants in Parkinson disease–associated genes (OR 3.62; 95% CI 1.33–9.80; $p = 0.01$) and hereditary neuropathy genes (OR 3.30; 95% CI 1.55–7.03; $p = 0.002$) conferred a 3-fold increased risk. These findings were independently replicated in the Project MinE dataset (OR 1.43; 95% CI 1.30–1.57; $p < 0.001$). Stratified analysis also confirmed the enrichment of rare variants in Parkinson disease and hereditary neuropathy-associated genes. Variant carriers were more likely to present with the flail arm phenotype (OR 2.05; 95% CI 1.05–3.98; $p = 0.03$) and showed increased risk of frontotemporal dementia (OR 1.85; 95% CI 1.04–3.21; $p = 0.03$) and shorter survival (hazard ratio 1.99; 95% CI 1.26–3.14; $p = 0.003$).

Discussion

Rare variants in genes associated with other neurodegenerative disorders influence both ALS susceptibility and clinical features, highlighting genetic pleiotropy across neurodegenerative diseases. Our findings support a model in which ALS arises from a complex and heterogeneous genetic landscape involving multiple variants, often shared with other neurodegenerative

MORE ONLINE

Supplementary Material

*These authors contributed equally to this work as co-first authors.

†These authors contributed equally to this work as co-last authors.

[1]"Rita Levi Montalcini" Department of Neuroscience, University of Turin, Italy; [2]Department of Public Health and Pediatrics, University of Turin, Italy; [3]Neurologia 1U, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; and [4]Institute of Cognitive Sciences and Technologies, National Council of Research, Rome, Italy.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

Glossary

ALS = amyotrophic lateral sclerosis; **ALSbi** = ALS with behavioral impairment; **ALScbi** = ALS with cognitive-behavioral impairment; **ALSci** = ALS with cognitive impairment; **ALS-CN** = ALS with normal cognition; **ALS-FTD** = ALS with frontotemporal dementia; **ALSFRS-R** = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; **OR** = odds ratio; **PARALS** = Piemonte and Valle d'Aosta Register for ALS.

conditions, that shape disease expression. Although these findings suggest potential future expansion of genetic screening beyond classical ALS genes, such variants should be interpreted cautiously in clinical practice pending further functional validation.

Introduction

Substantial genetic overlap exists between neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). Variants in genes primarily associated with one neurodegenerative disorder can influence risk and presentation of others. The *C9orf72* repeat expansion and *TARDBP* mutations cause frontotemporal dementia and contribute to parkinsonism.[1,2] Similarly, variants in *KIF5A*[3] and *SPTLC1*[4] have been implicated across multiple neurodegenerative conditions.

As whole-genome and whole-exome sequencing become more common in ALS clinical practice, variants in genes previously associated with other neurodegenerative disorders are increasingly detected. However, whether these variants contribute to clinical presentation in ALS or should be considered in genetic counseling remains unknown.

This study aimed to characterize rare variants in genes associated with various neurodegenerative disorders among patients with ALS and to determine whether these variants contribute to ALS risk or modify disease presentation, potentially explaining phenotypic variability.

Methods

Study Population

The study cohort consisted of 1,324 patients with ALS from the population-based Piemonte and Valle d'Aosta Register for ALS (PARALS)[5] and 744 healthy controls of matched ancestry. To minimize misdiagnosis risks, particularly of ALS cases that could be confounded for other neurodegenerative disorders, we included only patients with definite or probable/laboratory-supported ALS according to El Escorial criteria.[6] Patients were also excluded if they carried a pathogenic variant in a known ALS-associated gene. Detailed selection criteria and cohort characteristics are provided in the Supplementary Materials.

Clinical Measures

Participants were classified into established motor phenotype based on the region of onset, the propagation of motor symptoms, and the degree of upper and lower motor neuron dysfunction[7]: classic ALS phenotype (mixed upper and lower motor neuron signs in the upper or lower limbs), bulbar phenotype (dysarthria and/or dysphagia as initial symptoms and no spinal involvement for the first 6 months after symptoms onset), flail arm syndrome (progressive weakness in upper limbs confined to the flail limbs for at least 12 months after symptom onset), flail leg syndrome (progressive distal onset of weakness and wasting in the lower limbs with minimal upper limb involvement), pyramidal variant (clinical manifestations dominated by upper motor neuron signs), and respiratory onset (initial respiratory symptoms with only mild spinal or bulbar signs in the first 6 months after onset). Clinical data, including survival, were retrieved from the epidemiologic register data. At the time of diagnosis, patients also underwent a standardized neuropsychological assessment, including a comprehensive battery of cognitive and behavioral tests. Based on these evaluations, patients were classified according to the Consensus Criteria for frontotemporal cognitive and behavioral syndromes in ALS[8] into 5 categories: ALS with normal cognition (ALS-CN), ALS with cognitive impairment (ALSci), ALS with behavioral impairment (ALSbi), ALS with cognitive-behavioral impairment (ALScbi), and ALS with frontotemporal dementia (ALS-FTD). Complete assessment protocols are described in the Supplementary Materials.

Whole-Genome Sequencing and Variant Filtering

Whole-genome sequencing analysis and screening for the C9orf72 intronic expansion was performed on all participants.[9,10] We defined high-impact variants as ultra-rare (minor allele frequency <0.1% in Genome Aggregation Database) or novel variants with either loss-of-function consequences or missense variants with Combined Annotation-Dependent Depletion score >20. We analyzed 145 genes associated with neurodegenerative disorders based on Ensembl annotations (eTable 1). Sequencing procedures, quality control, and variant filtering criteria are detailed in the eMethods.

Statistical Analysis

We examined differences in variant burden between cases and controls using logistic regression, adjusted for sex, site of

onset, 5 ancestry-defining principal components, and total genetic load. To test whether ALS cases carrying rare variants in non-ALS neurodegeneration-associated genes have different phenotypic features, we fitted multiple regression models. Linear regression models were used to evaluate associations with continuous clinical measures, including age at disease onset, diagnostic delay, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score at diagnosis, and ALSFRS-R rate of decline. For categorical phenotypes, logistic regression models were fitted with mutational burden (presence of rare variants) as the outcome variable. For motor phenotype analysis, classic ALS served as the reference category, with bulbar onset, flail arm syndrome, flail leg syndrome, pyramidal variant, and respiratory onset included as predictor variables in a single multinomial model. For cognitive phenotype analysis, patients were dichotomized into 2 groups: those with frontotemporal dementia (ALS-FTD) vs those without full dementia, which included patients with normal cognition (ALS-CN) and those with intermediate cognitive-behavioral impairment (ALSci, ALSbi, and ALScbi combined). All models were adjusted for sex and age at onset as covariates. Survival was analyzed using Kaplan-Meier curves with long-rank tests and Cox regression models adjusted for sex and age at onset. Complete statistical methods are available in the Supplementary Material.

We performed separate analyses grouping variants by their associated neurodegenerative disease category: Alzheimer disease and related dementia, Parkinson disease and related movement disorders, hereditary spastic paresis, hereditary neuropathies, and spinal muscular atrophies. The identified genes and their associated phenotypes are shown in eMethods.

All statistical tests were 2-sided, and statistical significance was set at 0.05. Analyses were performed using R version 4.3.0.

Replication Analysis

For replication, we analyzed summary data from Project MinE (6,596 ALS cases and 2,454 controls) using identical filtering criteria for variants in the same neurodegeneration-associated genes identified in our discovery cohort. Associations were assessed using Fisher exact tests to estimate odds ratios (ORs), 95% CIs, and p values. Because only aggregated data were available, adjustments for population stratification or polygenic load could not be performed in the replication cohort.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino (protocol number 0038876). All participants provided written informed consent before enrollment.

Data Availability

Individual-level whole-genome sequencing data from the PARALS cohort are available on the dbGaP web portal (accession number phs001963.3). Clinical data are available on reasonable request from qualified researchers. Project MinE data are accessible at databrowser.projectmine.com.

Results

Study Cohort Description

After excluding 284 cases with variants in established ALS genes and 206 cases that did not meet the criteria for a definite or probable/laboratory-supported diagnosis, a total of 791 ALS individuals were included in the final study cohort. Among the 791 ALS patients analyzed, 425 (53.7%) were male, with median age at diagnosis of 67.9 years. Motor phenotypes included: bulbar (32.2%), classic (31.4%), flail arm (6.3%), flail leg (18.7%), pyramidal (9.6%), and respiratory (1.8%). Five hundred fifty-seven patients (70.4%) underwent neuropsychological testing: cognitive and behavioral impairment was observed in 31.4% of them, while an additional 14.2% presented a full blown FTD (eTable 2).

Disease Risk

Overall, 127 of 791 (16.1%) ALS patients carried at least one rare variant compared with 91 of 744 (12.2%) controls (eTable 3). Logistic regression analysis confirmed that the presence of rare variants moderately increased ALS risk (OR 1.37; 95% CI 1.04–1.80; $p = 0.027$), with a stronger association detected for novel variants (OR 1.75; 95% CI 1.22–2.52; $p = 0.003$) (Figure 1, eTable 4A).

Genetic Overlap Between ALS and Other Neurodegenerative Disorders

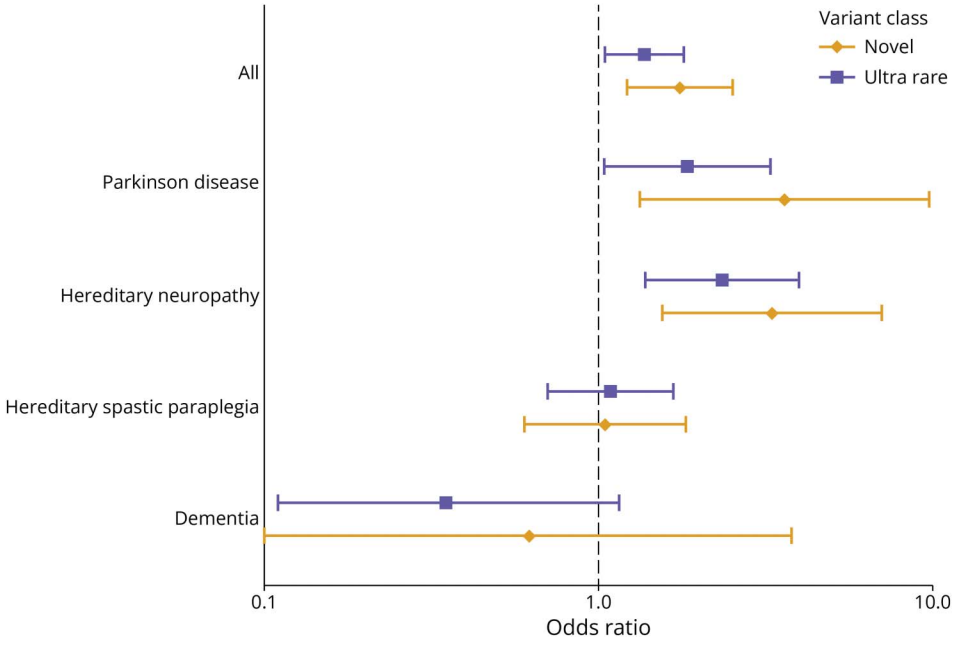
When grouping genes by their associated neurodegenerative diseases, novel variants in Parkinson disease–associated genes increased ALS risk more than 3-fold (OR 3.62; 95% CI 1.33–9.80; $p = 0.01$). Similar increases were seen with novel variants in hereditary neuropathy genes (OR 3.30; 95% CI 1.55–7.03; $p = 0.002$) (Figure 1, eTable 4B).

Disease Phenotype and Progression

The flail arm phenotype showed significant enrichment of variants in neurodegeneration-associated genes (OR 2.05; 95% CI 1.05–3.98; $p = 0.03$) (eTable 5A), particularly in Parkinson disease–associated genes (OR 3.52; 95% CI 1.29–9.63; $p = 0.01$). No other motor or cognitive phenotype demonstrated significant enrichment in rare variants (eTable 5B). The presence of a neurodegeneration-related variant did not significantly influence age at disease onset (mean difference 0.07 years; 95% CI −0.11 to 0.25; $p = 0.41$).

Similarly, no significant differences were observed in time from onset to diagnosis (mean difference −1.10 months; 95% CI −3.07 to 0.88; $p = 0.28$) or ALSFRS-R score at diagnosis (mean difference −0.21 points; 95% CI −1.32 to 0.89; $p = 0.71$). The ALSFRS-R progression rate at diagnosis was slightly higher in variant carriers compared with noncarriers,

Figure 1 Forest Plot Summarizing Univariate Logistic Regressions' Results Evaluating the Association Between Carrying At Least 1 Rare Variant in the Different Gene Subgroups and ALS Risk in the PARALS Cohort



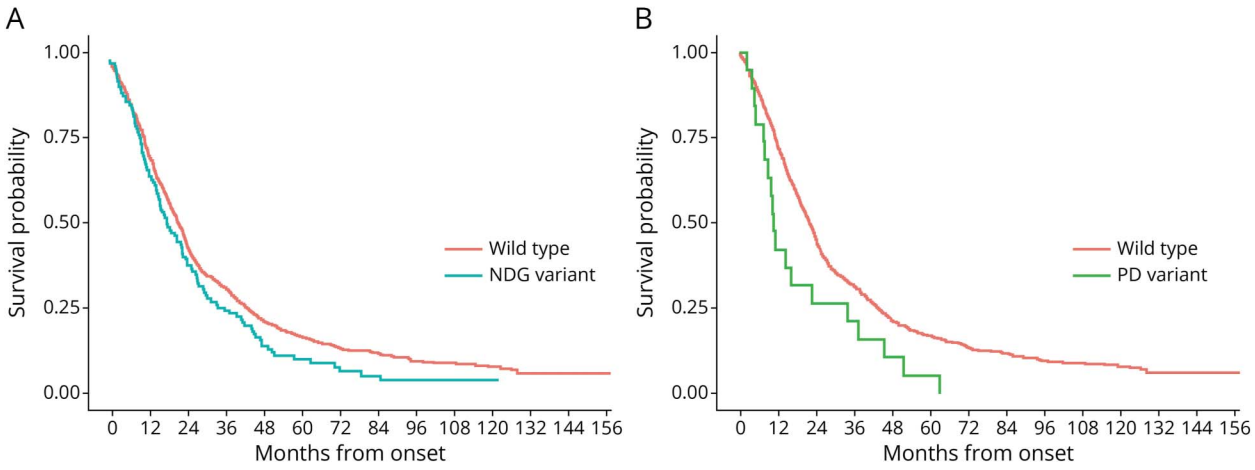
Analyses were performed considering only novel mutations (yellow) and both novel and non-novel mutations (purple). ALS = amyotrophic lateral sclerosis; PARALS = Piemonte and Valle d'Aosta Register for ALS.

but this difference was not statistically significant (mean difference 0.29 points per month; 95% CI −0.05 to 0.62; p = 0.09). A more aggressive disease course was observed in carriers of novel variants, especially in Parkinson disease–associated genes, that showed significantly shorter survival (hazard ratio 1.99; 95% CI 1.26–3.14; p = 0.003) (Figure 2, eTables 6 and 7). Among the 557 patients who underwent neuropsychological testing, variant carriers also showed increased risk of frontotemporal dementia (OR 1.85; 95% CI 1.04–3.21; p = 0.03) (eTable 6).

Replication Analysis

The findings from the PARALS cohort were independently replicated in the Project MinE dataset, comprising 6,596 ALS patients and 2,454 controls. Overall, variant burden across neurodegeneration-related genes was significantly enriched in ALS patients for rare (OR 1.43; 95% CI 1.30–1.57; $p = 1.41 \times 10^{-11}$) and novel variants (OR 1.40; 95% CI 1.27–1.55; $p = 1.32 \times 10^{-10}$). Stratified analysis confirmed the enrichment of novel variants in Parkinson disease–associated genes (OR 1.39; 95% CI 1.14–1.70; p = 0.001) and hereditary

Figure 2 Survival Kaplan-Meier Curves After Stratification by Carriage of a Novel Mutation in NDG-Associated Genes (A), or in PD-Associated Genes (B)



The log-rank test's p value (p) is reported. NDG = Neurodegeneration; PD = Parkinson disease.

neuropathy genes (OR 1.45; 95% CI 1.22–1.73; $p = 1.56 \times 10^{-5}$), in line with results from the primary cohort. Ultra-rare variant burden in these gene groups also replicated significantly (Figure 3, eTable 8).

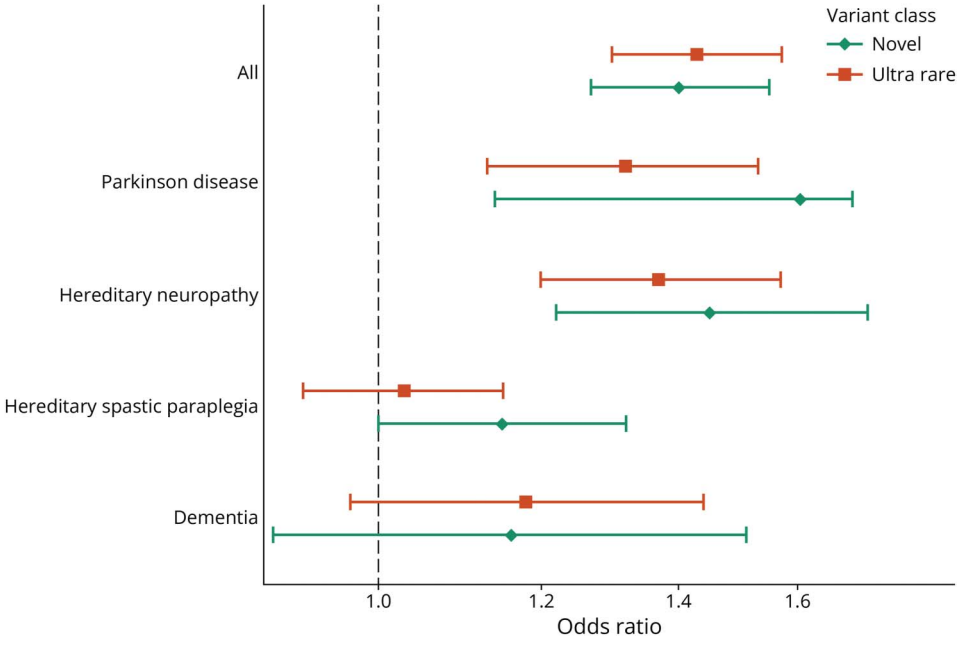
Discussion

This study demonstrates that rare variants in genes associated with other neurodegenerative disorders increase ALS risk in 2 independent cohorts of European ancestry, supporting the significant role these genetic variations play in ALS pathogenesis.[11] These variants may account for a portion of the missing heritability in ALS that has not been explained by common risk variants or by known ALS-related genes. Our data support a complex genetic disease model with contributions from many disease-causing or disease-modifying gene variants which encompass not only known ALS genes but also other genes from the neurodegenerative disease spectrum. Moreover, rare variants also influence disease progression, suggesting that they are not incidental but contribute to ALS pathogenesis and progression.

These findings extend evidence for shared genetic architecture across neurodegenerative disorders, particularly between ALS and Parkinson disease[12,13] and genetic neuropathies. While approximately one-third of patients with ALS exhibit extrapyramidal signs,[14] the association between Parkinson disease–related variants and the flail arm phenotype—characterized by predominant lower motor neuron symptoms distinct from parkinsonian features—demonstrates genuine pleiotropic effects rather than variant enrichment in cases with mixed phenotypes.[15] Similarly, while hereditary motor neuropathies are known ALS mimics[16] and may also present with upper motor neuron features, we observed that neuropathy-associated variants are enriched in patients with typical ALS presentations and not just in those with distal limb-onset forms. Importantly, our analysis was restricted to patients with a definite or probable ALS diagnosis, reducing the likelihood that these overlaps reflect clinical misdiagnosis or disease mimics (eTable 9). This finding strengthens evidence for shared pathogenic mechanisms across neurodegenerative disorders with distinct clinical presentations.[17,18] Our results also suggest that specific ALS phenotypes may have distinct genetic backgrounds, indicating that different molecular mechanisms may underlie various patterns of motor neuron degeneration. Notably, the association of Parkinson disease–associated gene variants with both the flail-arm phenotype—typically associated with longer survival—and a more aggressive disease highlights how genetic profiling may uncover biologically meaningful ALS subtypes that are not fully captured by traditional phenotype-based definitions.

In our large Italian cohort, approximately 1 in 6 individuals with sporadic ALS without known ALS-related variants carried at least one rare variant in genes linked to other neurodegenerative disorders (eTable 10). This observation should not be considered a definitive estimate, as the frequency of identified variants will likely vary according to population ancestry, gene sets analyzed, and criteria used for variant filtering. Nevertheless, our findings have important clinical implications. Our results indicate that rare variants in neurodegeneration-associated genes contribute significantly to the genetic landscape of ALS and are likely involved in its

Figure 3 Forest Plot Summarizing Univariate Logistic Regressions' Results Evaluating the Association Between Carrying At Least 1 Rare Variant in the Different Gene Subgroups and ALS Risk in the Replication Cohort From Project MinE



Analyses were performed considering only novel mutations (green) and both novel and non-novel mutations (orange). ALS = amyotrophic lateral sclerosis.

pathogenesis. However, it is important to note that the aggregate effect size is relatively small. As such, causality should not be attributed to individual variants at this stage, particularly in a clinical context. The precise mechanistic role—whether they act primarily as modest risk factors or whether a subset represents high-impact, pleiotropic variants—remains to be determined. This distinction is crucial for clinical interpretation and application. While our data support the potential future expansion of genetic screening panels to include neurodegeneration-associated genes beyond classical ALS genes, we emphasize that these variants should be interpreted cautiously in clinical practice. Additional functional studies and larger, diverse cohorts are needed to determine their pathogenicity and clinical relevance for patients and family members. Notably, the observed association of these variants with shorter survival and frontotemporal dementia may still help clinicians anticipate disease progression and develop tailored management strategies.

A key limitation of this study is the inability to disentangle the individual effects of rare variants. It is possible that certain variants increase ALS risk, while others may influence disease progression or phenotype. By analyzing variants in aggregate, we may obscure opposing or modifying effects. Moreover, population-specific associations cannot be excluded. Nonetheless, replication of our findings in the large, independent Project MinE cohort supports their robustness and encourages further investigation in diverse populations.

Our findings contribute to a growing body of evidence suggesting that neurodegenerative disorders arise within a highly complex and variable genetic landscape. As with other ageing-associated conditions, ALS likely emerges from the interplay of multiple genetic risk variants, some of which are shared across the neurodegenerative disease spectrum. This broader genetic context may not only shape individual susceptibility but also influence clinical expression, progression, and response to therapies.

In conclusion, our study reveals that rare variants in neurodegeneration-associated genes influence both ALS susceptibility and clinical features, further highlighting genetic pleiotropy across neurodegenerative disorders and potentially explaining some of the clinical heterogeneity observed in ALS.

Author Contributions

M. Grassano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. E. Koumantakis: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. F.F. Palumbo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Brunetti: major role in the acquisition of data. G. De Marco: major role in the acquisition of data. I. Merulla: major role in the acquisition of data. C. Paolantonio: major role in the acquisition of data. B. Iazzolino: major role in the acquisition of data. M. Testa: major role in the acquisition of data. U. Manera: major role in the acquisition of data. A. Canosa: major role in the acquisition of data. R. Vasta: major role in the acquisition of data. G. Fuda: major role in the acquisition of data. P. Salamone: major role in the acquisition of data. G. Marchese: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Casale: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. S. Gallone: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Mora: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Moglia: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Calvo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Chiò: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This work was supported by the Italian Ministry of Health (Ministero della Salute, Ricerca Sanitaria Finalizzata, grant RF-2016-02362405); the Progetti di Rilevante Interesse Nazionale Program of the Ministry of Education, University and Research (grant 2017SNW5MB); the European Commission's Health Seventh Framework Program (FP7/2007-2013 under grant agreement 259867); and the Joint Program Neurodegenerative Disease Research (JPND) (Strength, ALS-Care and Brain-Mend projects), granted by Italian Ministry of Education, University, and Research. This work was also supported in part by the American Academy of Neurology (grant number 3142), the ALS Association, and the American Brain Foundation. This study was performed under the Department of Excellence grant of the Italian Ministry of Education, University, and Research to the "Rita Levi Montalcini" Department of Neuroscience, University of Torino, Italy.

Disclosure

M. Grassano has received a research grant from the American Academy of Neurology, the ALS Association, and the American Brain Foundation. A. Calvo has received a research grant from Cytokinetics. A. Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, Cytokinetics, Lilly, Ferrer, Zambon Biotech, and Amylyx Pharmaceuticals; and has received a research grant from Biogen. All other authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® May 23, 2025. Accepted in final form August 7, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Brian C. Callaghan, MD, MS, FAAN.

References

1. Cooper-Knock J, Shaw PJ, Kirby J. The widening spectrum of C9ORF72-related disease; genotype/phenotype correlations and potential modifiers of clinical phenotype. *Acta Neuropathol*. 2014;127(3):333-345. doi:10.1007/s00401-014-1251-9
2. Quadri M, Cossu G, Saddi V, et al. Broadening the phenotype of TARDBP mutations: the TARDBP Ala382Thr mutation and Parkinson's disease in Sardinia. *Neurogenetics*. 2011;12(3):203-209. doi:10.1007/s10048-011-0288-3
3. Nicolas A, Kenna KP, Renton AE, et al. Genome-wide analyses identify KIF5A as a novel ALS gene. *Neuron*. 2018;97(6):1267-1288. doi:10.1016/j.neuron.2018.02.027
4. Johnson JO, Chia R, Miller DE, et al. Association of variants in the *SPTLC1* gene with juvenile amyotrophic lateral sclerosis. *JAMA Neurol*. 2021;78(10):1236-1248. doi:10.1001/jamaneurol.2021.2598
5. Chiò A, Mora G, Moglia C, et al. Secular trends of amyotrophic lateral sclerosis: the Piemonte and Valle d'Aosta Register. *JAMA Neurol*. 2017;74(9):1097-1104. doi:10.1001/jamaneurol.2017.1387
6. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1(5):293-299. doi:10.1080/146608200300079536
7. Chiò A, Calvo A, Moglia C, Mazzini L, Mora G, PARALS study group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry*. 2011;82(7):740-746.
8. Strong MJ, Abrahams S, Goldstein LH, et al. Amyotrophic lateral sclerosis: frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(3-4):153-174. doi:10.1080/21678421.2016.1267768
9. Grassano M, Calvo A, Moglia C, et al. Mutational analysis of known ALS genes in an Italian population-based cohort. *Neurology*. 2021;96(4):e600-e609. doi:10.1212/WNL.0000000000011209
10. Grassano M, Calvo A, Moglia C, et al. Systematic evaluation of genetic mutations in ALS: a population-based study. *J Neurol Neurosurg Psychiatry*. 2022;93(11):1190-1193. doi:10.1136/jnnp-2022-328931
11. Krüger S, Battke F, Sprecher A, et al. Rare variants in neurodegeneration associated genes revealed by targeted panel sequencing in a German ALS cohort. *Front Mol Neurosci*. 2016;9:92. doi:10.3389/fnmol.2016.00092
12. Wainberg M, Andrews SJ, Tripathy SJ. Shared genetic risk loci between Alzheimer's disease and related dementias, Parkinson's disease, and amyotrophic lateral sclerosis. *Alzheimers Res Ther*. 2023;15(1):113. doi:10.1186/s13195-023-01244-3
13. Olsen CG, Busk ØL, Holla ØL, et al. Genetic overlap between ALS and other neurodegenerative or neuromuscular disorders. *Amyotroph Lateral Scler Frontotemporal Degener*. 2024;25(1-2):177-187. doi:10.1080/21678421.2023.2270705
14. Calvo A, Chiò A, Pagani M, et al. Parkinsonian traits in amyotrophic lateral sclerosis (ALS): a prospective population-based study. *J Neurol*. 2019;266(7):1633-1642. doi:10.1007/s00415-019-09305-0
15. Lualdi M, Casale F, Rizzone MG, et al. Shared and unique disease pathways in amyotrophic lateral sclerosis and Parkinson's disease unveiled in peripheral blood mononuclear cells. *ACS Chem Neurosci*. 2023;14(23):4240-4251. doi:10.1021/acschemneuro.3c00629
16. Kwan J, Vullaganti M. Amyotrophic lateral sclerosis mimics. *Muscle Nerve*. 2022;66(3):240-252. doi:10.1002/mus.27567
17. Wightman DP, Savage JE, Tissink E, Romero C, Jansen IE, Posthuma D. The genetic overlap between Alzheimer's disease, amyotrophic lateral sclerosis, Lewy body dementia, and Parkinson's disease. *Neurobiol Aging*. 2023;127:99-112. doi:10.1016/j.neurobiolaging.2023.03.004
18. Koretsky MJ, Alvarado C, Makarious MB, et al. Genetic risk factor clustering within and across neurodegenerative diseases. *Brain*. 2023;146(11):4486-4494. doi:10.1093/brain/awad161