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Description of two different phenotypes of FUS-associated Amyotrophic Lateral Sclerosis

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Short Report

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that primarily affects the motor system. A minority of cases are caused by a genetic variant, with *C9orf72, SOD1, TARDBP*, and *FUS* being the most common. Compared with other forms of ALS, *FUS*-associated ALS is relatively aggressive; however, phenotypic heterogeneity has been reported. We will report two cases of *FUS*-associated ALS with a very different clinical presentation. These cases highlight the importance of the different factors influencing the phenotypic presentations of ALS. It is essential to recognise specific genotype-phenotype relationships and environmental factors that could change the clinical course of the disease.

Introduction

Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disease that primarily affects the motor system in the cerebral cortex, brainstem and spinal cord (1). It is a rare disease, with an estimated incidence of 0.7-3 cases per 100,000 individuals and is more common in Europe than in America or Asia (1). ALS can be classified into familial and sporadic ALS, with approximately 10% of the patients having an affected family member. A genetic variant is found in 10-20% sporadic ALS cases and in 50-85% of familial ALS cases (2). More than 40 genes associated with ALS have been identified (3). Low-frequency variants with greater effect are associated with a Mendelian inheritance pattern, incomplete penetrance (<50%), and variable expression (2). Pathogenic genetic variants in *C9orf72, SOD1, TARDBP,* and *FUS* are the most common causes of monogenic ALS (2).

Compared with other forms of ALS, *FUS*-associated ALS is relatively aggressive; however, phenotypic heterogeneity has been reported (4). *FUS* variants are present in 3% of European familial ALS cases, 6-10% of Asian familial ALS cases and 1% of sporadic ALS cases and it is associated with a juvenile onset, typically occurring before 40 years (range 11-80 years; mean age 37 years) (5). The heterogeneity in clinical presentation depends on the specific variant, with truncating frameshift variants associated with earlier onset and faster progression. The earlier the age of presentation is, the shorter the life expectancy, with some cases even experiencing less than a year of life after the first symptoms appear (4). Although cognitive changes are uncommon in *FUS*-associated cases, loss of phonemic fluency, anomia, semantic errors, perseveration, and executive dysfunction, including difficulties with planning and task shifting, have been described (6).

Here, we will discuss the possible causes of two cases of *FUS*-associated ALS with contrasting clinical presentations.

Case 1

Male, 39 years old, left-handed, without family history of ALS or consanguinity, with a history of psoriasis and hypertension, and occasional exposure to tobacco from age 18 to 38. He presented in June 2018 with three months of progressive dysarthria and dysphagia, weight loss of 6 kg in the past 9 months and fatigue and right-hand tremor associated with physical activity during the last 5 years. Examination

showed generalised hyperreflexia, bilateral Hoffmann's reflex, +++/++++ masseteric reflex, persistent glabellar reflex, and marked atrophy of the right first dorsal interosseous muscle and the tongue, with fasciculations. Neurophysiological studies revealed signs of denervation and reinnervation in the bulbar, cervical, thoracic, and lumbar segments, confirming the diagnosis of ALS according to the Gold Coast Criteria (7). Functional tests performed are described in Table 1, and the patient's clinical evolution and therapy are schematized in Figure 1. In the final stage of the disease, cognitive changes in the frontotemporal dementia spectrum were evident, consistent with apathy, irritability, perseveration, logopenia, low cognitive flexibility and difficulties with planning activities. The patient died in his home in February 2021 because of respiratory failure.

Date	Jul-18	Dec-18	Apr-19
6 minutes walk test	Total distance: 526 m; Initial heart rate: 101 bpm; Final heart rate: 121 bpm Modified Borg score: 6/10	Total distance: 554 m; Initial heart rate: 76 bpm; Final heart rate: 202 bpm Modified Borg score: 5/10	Total distance: 420 m; Initial heart rate: 112 bpm; Final heart rate: 152 bpm Modified Borg score: 3/10
30 seconds chair stand test	14 times	16 times	14 times
Five times sit to stand test	10.17 seconds	7.9 seconds	10.3 seconds
Timed up and go test	8.22 seconds	8.63 seconds	10.75 seconds
Single leg stance test	Right: 13.8 seconds; Left: 21.29 seconds	Right 24.41 seconds; Left: 31.13 seconds	-
Box and block test	Right hand: 72 blocks; Left hand: 76 blocks	Right hand: 61 blocks; Left hand: 61 blocks	Right hand: 47 blocks; Left hand: 53 blocks
Hand grip strength	-	Right: 11.3 Kg; Left: 22.6 Kg	Right: 8 Kg; Left: 11.3 Kg
Right manual dynamometry	-	Biceps: 10 Kg; Deltoid: 8.7 Kg; Quadriceps: 15.1 Kg; Tibialis anterior: 7.9 Kg	Biceps: 9.9 Kg; Deltoid: 4.8 Kg; Quadriceps: 12.8 Kg; Tibialis anterior: 6.0 Kg
Left manual dynamometry	-	Biceps: 11.3 Kg; Deltoid: 10.1 Kg; Quadriceps: 16.3 Kg; Tibialis anterior: 6.3 Kg	Biceps: 13.9 Kg; Deltoid: 4.7 Kg; Quadriceps: 16.8 Kg; Tibialis anterior: 5.7 Kg
Forced vital capacity	85%	80%	68%

Table 1: Functional evaluations performed across the disease progression. *m (meters); bpm (beats per minute); Kg (kilograms).*

Next-generation sequencing of 16 genes associated with ALS and hexanucleotide expansion analysis of C9orf72, showed a short deletion in the FUS gene (c.521_523+3delGAGGTG), causing a deletion of a glycine in the G-rich region of the protein (exon 5; p.Gly174del) and changes in splicing (NM_004960.4). This variant was first described in 2009 in three patients with earlier onset ALS (age of onset: 43.3 +/- 6.4 years) (8), and then in a patient from northern England with bulbar onset ALS at age 62 associated with multiple sclerosis (since age 23) (9). Later, another cohort study from Vancouver described this genetic variant present in four patients with sporadic ALS and in 3/678 controls, which suggests an incomplete penetrance (10). This genetic variant has an allelic frequency of 0.0019 in GnomAD exomes, and in silico predictors predict a deleterious effect on protein function due to changes in the amino acid sequence caused by splice-site changes and an increase in nonsense-mediated decay.

Case 2

Female, 77 years old, without family history of ALS or consanguinity, with a history of hypertension and cardiac arrhythmia in treatment with amiodarone, losartan and hydrochlorothiazide. She reported past smoking with 30 pack years calculated (30-45 years old). She had a history of eleven years of muscular weakness in lower limbs with slow progression to upper limbs, requiring support to walk for the last 4 years. Since age 75, she has presented bulbar symptoms given by dysarthria, dysphagia, hypophonia, sialorrhea and dyspnea, with body weight loss of 10 Kg, fasciculations in the face and all limbs, cramps and cervical and lumbar pain. ALSFRS-R was calculated in 18/48 points. She was in treatment with nutritional supplementation, rehabilitation therapies (for the last five years) and riluzole (during the last month).

Physical exam revealed inadequate cough, decreased lung expansibility with hypoventilation in the lower lobes, generalised atrophy, muscular strength of 2/5 in the MRC score in all extremities, generalised hyperreflexia, bilateral neutral plantar response, spastic dysarthria, and tongue fasciculations. Electromyography revealed polyphasic and high-amplitude motor unit action potentials, along with reduced recruitment and fasciculations across cervical, thoracic and lumbar segments. Forced vital capacity was quantified at 67%, with a maximal inspiratory pressure of 65% and a maximal expiratory pressure of 40%, polysomnography showed an Apnea-Hypopnea Index of 10/hour, and a swallowing study established marked dysphagia with laryngeal penetration, but the patient rejected the gastrostomy. She began requiring oxygen supplementation at night.

Four months later, the patient started to require a wheelchair during the day and referred dropped head. Two months later, the patient started to use BiPAP with poor tolerance, for two hours a day. After two and a half years, the dysarthria progressed, and an ALSFRS-R of 17/48 points with a progression index of 0.19 was calculated. One year later, the patient began requiring support with every activity of daily living.

No cognitive changes were noted during the disease progression. In June 2025, after 17 years of ALS symptoms, the patient died with severe weakness and malnutrition.

Next-generation sequencing of 32 genes associated with ALS, showed a missense variant in *FUS* gene: c.188A>G, p.Asn63Ser (NM_004960.4). This genetic variant was first reported in 2009, in a patient with sporadic ALS from a French-Canadian population study (11). A year later, a French study described the variant in a patient with ALS and Frontotemporal Lobar Degeneration (12). More recently, it was described in a 2023 German study of sporadic ALS (13). This genetic variant has also been described in controls, suggesting reduced penetrance (14). GnomAD reports an allelic frequency of 0.000158 and is conserved across Mus musculus, Pan troglodytes, Macaca mulatta, Drosophila melanogaster, and *Xenopus tropicalis*. Also, the 3-nucleotide distance from the splice site could affect splicing.

Discussion

FUS is a DNA and RNA-binding protein highly and ubiquitously expressed and has been identified as an essential component of protein aggregates in ALS and frontotemporal lobe degeneration (4). FUS is predominantly localised in the nucleus and regulates RNA polymerase II activity, alternative splicing, mRNA transport and polyadenylation (15). Transcriptomic diversity related to alternative splicing and alternative polyadenylation is particularly crucial in neurons and explains the relationship with FUS alterations and neurological diseases (15).

Many FUS genetic variants found in ALS patients are classified as of uncertain significance because of a lack of functional studies or their presence in controls (16). Figure 2 shows the FUS domain structure; genetic variants associated with ALS have been identified throughout the entire protein. However, the highest confidence mutations affect the RGG3 or PY NLS domains. Changes in the PY-NLS domain sequence occur in 90% of patients with FUS-associated ALS and alter the protein's nuclear transport, leading to cytoplasmic aggregation (7).

RGG motifs play a crucial role in the nuclear localisation of FUS. Arginine substitutions have been widely studied and are associated with an increased probability of cytoplasmic inclusions, while glycine residues confer greater backbone flexibility due to their smaller size and unique structure. Mislocalization of FUS to the cytoplasm increases the probability of cytoplasmic aggregates and inhibits the translation of many proteins, upregulating non-sense-mediated decay factors (17-18). The N-terminal region is essential for FUS chromatin binding, allowing the protein to regulate gene transcription and alternative splicing (19).

It is interesting that both patients, despite their clinical presentation differences, had a clinical history of hypertension and smoking. A Mendelian randomization study published in 2014 found that increased systolic blood pressure was an independent risk factor for ALS (OR = 1.014, 95% CI 1.003–1.025, P = 0.015) (20). Even though the smoking exposure of the first patient is not as high as in the second patient, a pooled analysis of five prospective cohorts showed a higher risk of ALS in smokers than never smokers (RR= 1.44, 95% CI 1.23–1.68; p<0.0001). The risk of ALS was positively associated with pack-

years smoked, smoke duration (9% increase for each 10 years of smoking; p=0.006) and cigarettes smoked per day (10% increase for 10 cigarettes per day; p<0.001). So, smoking and hypertension could be factors that increase the penetrance of genetic variants associated with ALS (21).

In summary, these case series highlight the importance of the various factors that influence the phenotypic presentation of ALS. Specific genotype-phenotype relationships are necessary to provide a more detailed prognosis. Classifying genetic variants for ALS poses a challenge due to their reduced penetrance and the scarcity of functional studies. Moreover, environmental factors could change the clinical course of the disease and increase the probability of presenting clinical symptoms in a person with a genetic variant associated with ALS.

Declarations

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Informed consent for publication was obtained from the patients or their legal representatives

Data availability statement

The data that support the findings of this study are available from the corresponding author, [PVG], upon reasonable request.

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Author contributions

All authors contributed to the study conception, design, material preparation, data collection and analysis. The first draft of the manuscript was written by Paula V Gaete and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

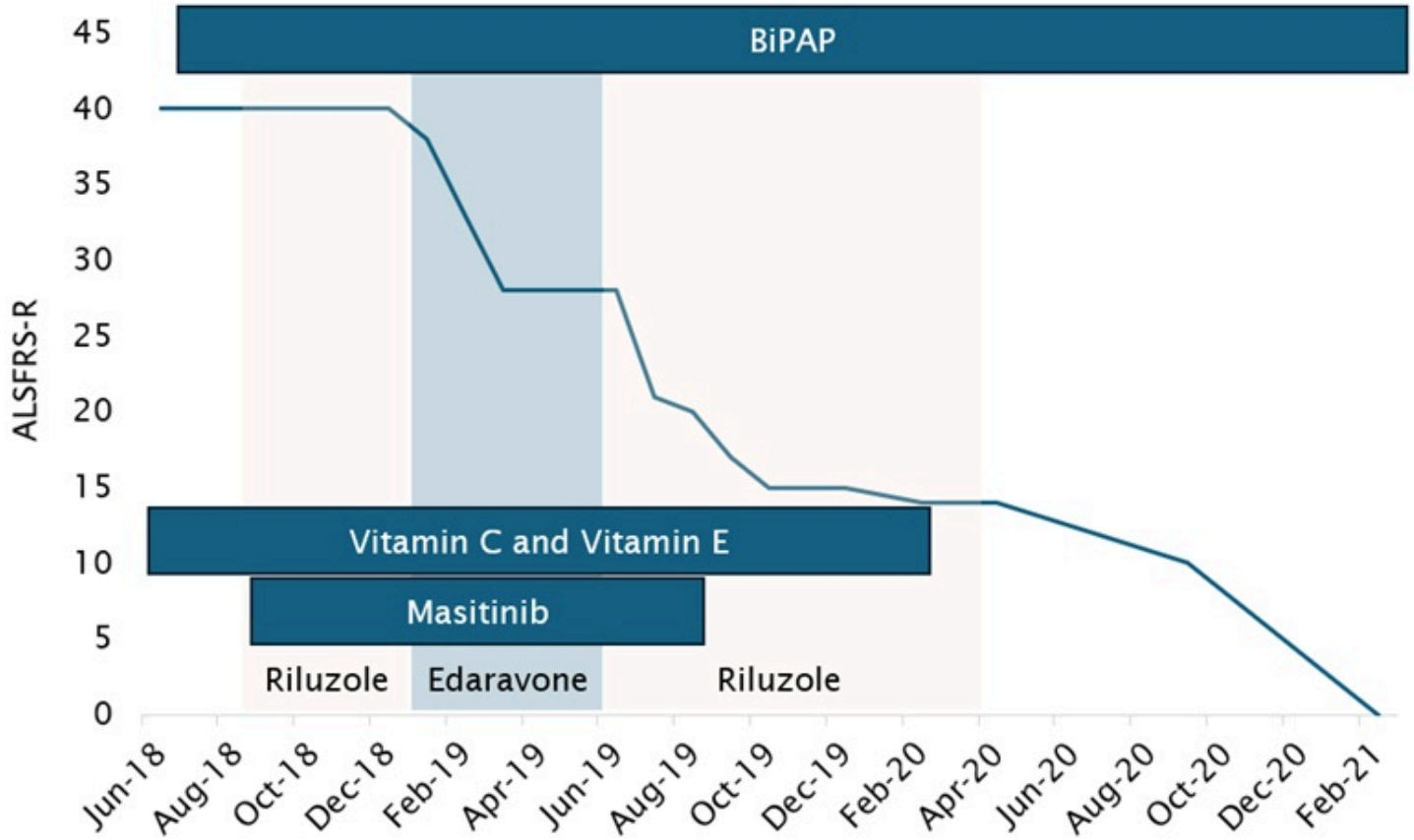


Figure 1

Graphic scheme of disease progression, including ALSFRS-R scores and treatments delivered. Diagnosis of ALS was made in June 2018, the ALSFRS-R score was calculated as 40/48 and the initial progression index was 1.33 for a disease with a six-month progression. The first pulmonary test showed a forced vital capacity of 87%. The patient was in treatment with vitamin C, vitamin E and amitriptyline, and additional therapy with riluzole and masitinib was indicated by the neurologist. Six months later, because of nausea, the riluzole was switched to edaravone, and because of persistent myalgias and fasciculations, pregabalin, lidocaine patches and oral cannabis were added. The patient received physical therapy, occupational therapy, respiratory therapy and speech therapy since his first visit to the Neurology clinic. Seven months later, the progression of the disease began to accelerate, with an ALSFRS-R score of 38/48 in January 2019, associated with a worsening dysarthria and limited movement of hands; to an ALSFRS-R score of 28/48 in March 2019, with evident dysphagia that required changes in dietary consistency and initial limitations to ambulation. In May 2019, the patient started to reduce the duration of physical therapy sessions because of fatigue and pain, and autonomic signs like hyperhidrosis and flushing started to emerge. Botulinic toxin was applied to control sialorrhea, and an ALSFRS-R score of 28/48 was calculated, with a progression index of 2.1. Forced vital capacity was quantified at 68%, so the patient started requiring BiPAP during the day. In July 2019, the patient reported significant pain in the left arm and cervical muscles, weakness in cervical muscles with dropped head and limited ambulation, requiring a motorised wheelchair to mobilise (ALSFRS-R score: 21/48). The last

application of edaravone was applied in June 2019 and riluzole was reinitiated. Masitinib was suspended in September 2019 because of low gastrointestinal tolerability. The patient continued to progress with notable dysphagia, significant dyspnea, orthopnea and marked weakness in all extremities. The patient denied gastrostomy and tracheostomy. In February 2020, the patient reported severe dysarthria and dysphagia, significant dyspnea and orthopnea, generalised severe pain, sarcopenia and insomnia; therefore, morphine and quetiapine were initiated. ALSFRS-R was 14/48. The patient died in his home in February 2021 because of respiratory failure.



Figure 2

FUS domain structure and the genetic variants described in case 1 (c.521_523+3delGAGGTG; p.?) and case 2 (c.188A>G; p.Asn63Ser). FUS domain structure divides the protein into an N-terminal low-complexity region (enriched in the amino acids; glutamine, glycine, serine and tyrosine), three arginine-glycine-glycine motifs (RGG1, RGG2 and RGG3, also known as rich glycine regions), an RNA recognition motif, a zinc finger domain and a nuclear localisation sequence of the PY-consensus type (PY NLS) located in the C-terminal region. The first case described a patient with a genetic variant in *FUS c.521_523+3delGAGGTG,* causing a deletion of a glycine in RGG1 region and changes in splicing, while the second case described a patient with a missense variant in the N-terminal low complexity region of the protein. Figure adapted from: Moens TG, Da Cruz S, Neumann M, Shelkovnikova TA, Shneider NA, Van Den Bosch L. Amyotrophic lateral sclerosis caused by FUS mutations: advances with broad implications. Lancet Neurol 2025;24(2):166-178. RRG: arginine-glycine-glycine motifs. RRM: RNA recognition motif. ZnF : Zinc finger domain. PY-NLS : nuclear localization sequence of the PY-consensus type.