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Rapidly Progressing and Early-Onset Forms of Amyotrophic Lateral Sclerosis Caused by a Novel *SOD1* Variant in a Lithuanian Family

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Abstract

Objectives

To describe a novel familial variant of superoxide dismutase 1 (SOD1)-associated amyotrophic lateral sclerosis (ALS) in a Lithuanian family, highlighting its variable progression and implications for treatment inclusion criteria.

Methods

This study presents the clinical and genetic findings of a family with the novel *SOD1* variant, including one member diagnosed with early-onset ALS (onset <40 years) and one with a particularly rapidly progressing course of ALS.

Results

The *SOD1* variant NM_000454.5:c.446T>C, NP_000445.1:p.(Val149Ala) was identified in affected family members and 4 asymptomatic members aged 32–56 years. We present detailed disease course of the affected family members obtained during follow-up. Clinically, this variant is associated with variable disease progression, with the time from symptom onset to death ranging from 5 to 77 months.

Discussion

The novel *SOD1* variant p.Val149Ala in this Lithuanian family causes ALS of variable onset and course, including a case of early-onset ALS and one case of rapidly progressing ALS, necessitating recognition by the scientific community and development of tailored therapeutic approaches.

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disease. In 2022, the treatment landscape was revolutionized with the development of tofersen, targeting familial ALS caused by superoxide dismutase 1 (SOD1) gene variants.[1] Despite global prevalence, *SOD1* pathogenic variants show phenotypic diversity across ethnic groups.[2] Comprehensive evaluation of these variants is challenging, particularly in minor populations such as Lithuanians.

Here, we present a novel *SOD1* variant NM_000454.5:c.446T>C, NP_000445.1:p.(Val149Ala), associated with a rapidly progressing form of ALS in a Lithuanian family.

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Methods

Patients Characterization

Clinical data including age at onset, age at diagnosis, time to diagnosis, time to death, and progression milestones were collected and analyzed to assess disease progression. Informed consent forms to disclose were obtained from all living patients or, in the case of deceased patients, from their legal representatives. Genetic risk assessment for family members was informed by pedigree analysis, and presymptomatic testing was offered for adult family members.

Genetic Analysis

A targeted gene panel for neurodegenerative diseases was performed as described[3] in a proband (II:3). Sanger sequencing was performed for segregation analysis.

Results

The clinical course of affected family members is summarized in Table. The p.Val149Ala variant was associated with early onset, rapid progression, and severe clinical outcomes.

The diagnosis of ALS in the family members was made according to the revised El Escorial criteria and met the definition of Probable ALS, laboratory results supported by the time diagnosis was made.[4] We used a combination of clinical, electrophysiologic, and neuroimaging studies to confirm the presence of both upper and lower motor neuron degeneration and to exclude other possible causes of the observed clinical signs. Notably, all affected family members presented with lower motor signs (i.e., muscle wasting, atrophy, fasciculations, and paresis) in their lower limbs. This observation aligns with published literature on the onset of SOD1-ALS.[5]

The targeted gene panel of neurodegenerative diseases revealed heterozygous variant NM_000454.5:c.446T>C, NP_000445.1:p.(Val149Ala) in *SOD1*. This variant segregated in the affected members. It has been identified in 4 asymptomatic members of the family (aged 32–56 years) (Figure). The missense variant replaces valine at codon 149 of SOD1 (p.Val149Ala), which is located in a highly conserved position. Several predictive analysis tools considered this variant to be deleterious (e.g., CADD score 29.2). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the criteria for pathogenicity (PM1, PM2, PP1, PP2, PP3, and PM5) are fulfilled.

Discussion

This study identifies a novel heterozygous variant c.446T>C, p.Val149Ala in the *SOD1* gene within a Lithuanian family, presenting with a variable onset and course, including one case of early onset and one case of rapidly progressing ALS. The variant has not been published in association with ALS phenotype nor has it been listed in public databases (gnomAD) and other sources as ClinVar. However, at the same position, another pathogenic missense variant, c.446T>G, p.Val149Gly, has been reported several times in the literature in various populations (the United States, Turkey, Australia, and Germany).[6-10]

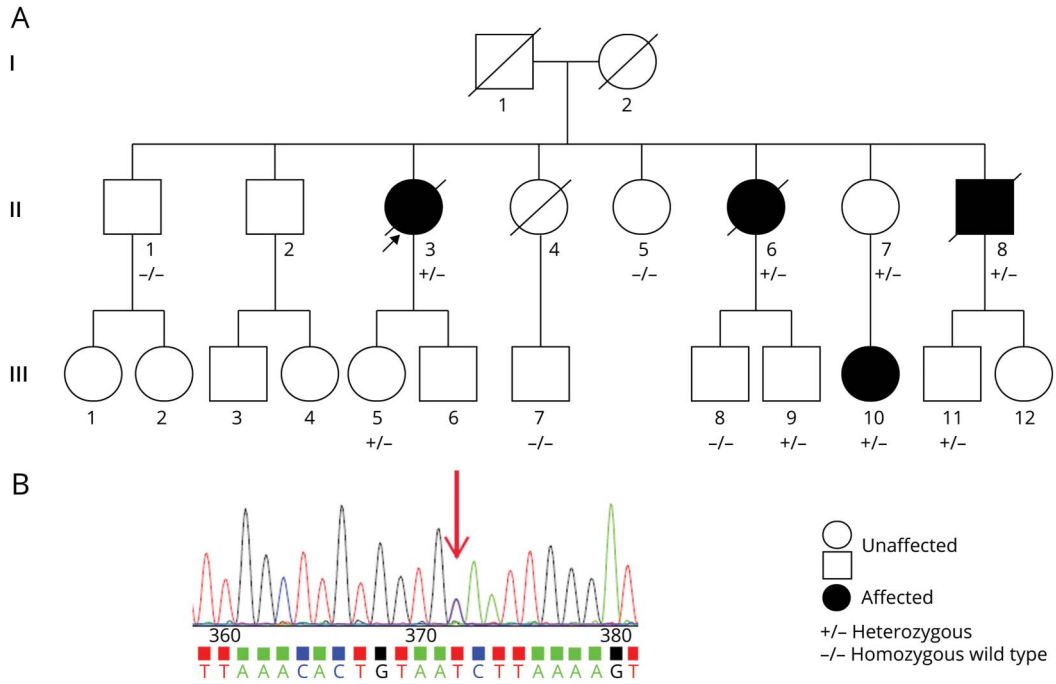
The clinical progression of ALS in the family members carrying the p.Val149Ala variant is notably fast. The time from symptom onset to diagnosis ranged from 2 to 17 months, and the time from symptom onset to death ranged from 5 to 77 months. Such variability, even among individuals with the same mutation within one family, is a known feature of SOD1-ALS.[5] Notably, patient II:8 exhibited an extraordinarily rapid disease course, passing away just 5 months after symptom onset. His death was sudden and

Table Patient Disease Course

Parameter	II:6	II:3	II:8	III:10
Sex	Female	Female	Male	Female
Date of birth	1963	1958	1966	1991
Age at onset (y)	51	61	56	33
Age at diagnosis (y)	52	61	56	33
Time to diagnosis (mo)	17	5	3	2
Time to death (mo)	77	29	5	—
Time to Amb/Supp (mo)	49	14	3	—
Time to NIV/IV (mo)	61	26	—	—
Symptoms at onset	Right leg weakness	Right leg weakness	Right leg weakness	Left leg weakness

Patients are listed by symptom onset chronologically; their numbers correspond to the family pedigree in Figure.
Time to Diagnosis – time in months from symptom onset to diagnosis of probable ALS, laboratory results supported, using the revised El Escorial criteria.[4] Time to Amb/Supp – time in months from symptom onset to becoming nonambulatory or requiring substantial support. Time to NIV/IV – time in months from symptom onset to needing noninvasive ventilation or invasive ventilation intermittently or continuously.

Figure Family Pedigree and Genetic Analysis



(A) Family pedigree indicating affected and unaffected members with the p.Val149Ala variant; (B) Sanger sequencing traces indicating heterozygous c.446T>C, p.(Val149Ala).

occurred before the implementation of either noninvasive or invasive ventilation. In the final weeks of his life, he experienced progressively worsening nightly dyspnea, without fever or other systemic symptoms. The patient was scheduled for admission to an intensive pulmonary unit for long-term treatment with noninvasive pulmonary ventilation because of his recurrent episodes of desaturation while in a supine position. However, he opted not to present at the hospital, citing an improvement in his dyspnea. He subsequently passed away during the night, and an autopsy was not performed. Such rapid progression in a male compared with their female counterparts with the same mutation is consistent with other aggressive *SOD1* variants.[11]

Given the observed variable progression in affected family members and the identification of asymptomatic carriers aged 32–56 years, it is plausible that the p.Val149Ala variant has high but potentially age-dependent penetrance. This means that while most carriers will likely develop ALS symptoms at some point, the age at onset may vary, with some individuals remaining asymptomatic until later in life. It is noteworthy that both patients I:1 and I:2 exhibited no signs of motor neuron disease at the time of their deaths, which occurred at a relatively advanced age. The mother (patient I:1) died at the age of 61 years from an unknown adrenal disease, while the father (patient I:2) died at the age of 71 years from a myocardial infarction. In addition, patient III:10 presented with symptoms early in life and was diagnosed with early-onset ALS (onset <40 years), whereas her mother (patient II:7) remains asymptomatic as of the writing of this article (as ascertained by clinical examination and serum NfL within normal limits).

The p.Val149Ala is in a critical region of the SOD1 dimer interface.[12] This location is vital for the structural integrity and functional activity of the SOD1 enzyme. Disruptions in this region can significantly impair the enzyme's ability to scavenge superoxide radicals, leading to increased oxidative stress and motor neuron death.[13] Structural models suggest that variants at this site destabilize the protein, exacerbating the pathogenic process.[14]

Early identification of the p.Val149Ala variant through genetic testing is crucial for prompt diagnosis and intervention. Genetic testing not only helps predict prognosis but also identifies at-risk family members who may benefit from presymptomatic monitoring and early therapeutic interventions. Tofersen, an antisense oligonucleotide targeting *SOD1* variants, has shown promise in clinical trials and provides a potential therapeutic option for patients with this variant.[1] Including the p.Val149Ala variant in treatment protocols like the ATLAS study could significantly benefit presymptomatic patients.[15]

Conclusion

In conclusion, the novel *SOD1* variant p.Val149Ala is associated with variable disease course and onset with a case of rapidly progressing form of ALS and a case of early-onset (<40 years) ALS in a Lithuanian family. This finding expands

the known spectrum of *SOD1* pathogenic variants and underscores the importance of early genetic diagnosis and tailored therapeutic approaches.

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