CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Homozygous *SOD1* Variation L144S Produces a Severe Form of Amyotrophic Lateral Sclerosis in an Iranian Family

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Neurol Genet 2022;8:e645. doi:10.1212/NXG.0000000000000645

Abstract

Objectives

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by degeneration of motor neurons determining progressive muscular atrophy, weakness, and death from respiratory failure.

Methods

Here, we report clinical and molecular findings of a novel Iranian family affected with a severe form of early-onset familial ALS.

Results

Three siblings born to consanguineous parents developed a form of ALS characterized by early-onset lower limb involvement and a fast progression, proving fatal at age 16 years for 1 of them. Molecular analysis of the *SOD1* gene revealed the homozygous substitution c.434T>C in exon 5 resulting in the amino acid change p.Leu144Ser (L144S), previously reported as a dominant variant. Both parents were heterozygous carriers. The probands' mother recently developed a late-onset ALS with predominant upper motor neuron involvement.

Discussion

This report adds p.L144S to the short list of homozygous *SOD1* variants and suggests that the development of an earlier-onset and/or faster disease progression can occur when 2 mutated alleles are present.

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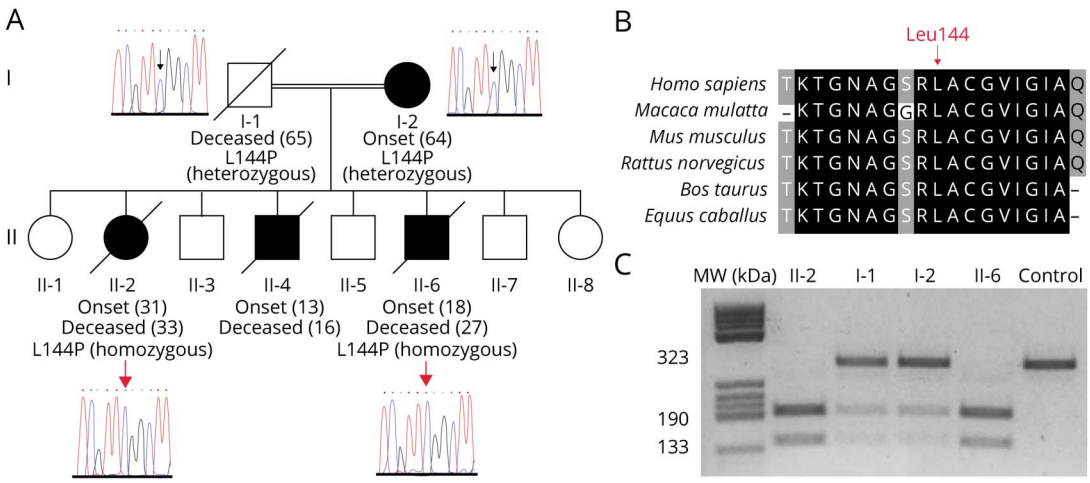
Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Figure Pedigree of the Iranian Family Described in the Text



(A) Electropherograms shown the homozygous c.434T>C *SOD1* variant in two affected siblings (black symbols II-2 and II-6), whereas their consanguineous parents (I-1 and I-2) are heterozygous carriers. Black symbols indicate affected patients. Age at symptom onset, age at death, and *SOD1* genotype for patients who underwent genetic testing are indicated. (B) Partial SOD1 protein sequence alignment among different species. Affected residue is a well-conserved amino acid (leucine 144). (C) PCR-RFLP analysis of c.434T>C variant in members of the family whose DNA was available. XmnI endonuclease cuts mutated molecules producing two bands of 190 and 133 bp, whereas wild-type amplicons remain uncut.

More than 200 variants in the *SOD1* gene, encoding a copper-zinc superoxide dismutase, have been found in patients with familial amyotrophic lateral sclerosis (fALS) and patients with sporadic ALS (sALS) (alsod.iop.kcl.ac.uk/Als/index.aspx), and most of them are dominantly inherited.[1,2]

Only 6 *SOD1* variants (L84F, N86S, D90A, L117V, L126S, and G27delGGACCA) have been so far reported as homozygous changes in patients with fALS, but a recessive inheritance was demonstrated only for few of them. In this regard, the D90A mutation is known to exhibit a pathogenetic behavior according both dominant and recessive modes of inheritance.[2,3]

Here, we disclosed the c.434T>C (p.L144S) *SOD1* variant in an Iranian family presenting a severe early-onset form of ALS. The mutation was previously reported in heterozygosis in patients with fALS and sALS, sharing lower limb onset, a relative benign course, and long survival time. Notably, the affected individuals in our pedigree displayed c.434T>C in homozygous state, whereas their mother, heterozygous carrier of the mutation, developed ALS symptoms at a later age.

Case Report

The probands (patients II-2 and II-6) are 2 Iranian siblings born from consanguineous parents (Figure, A). A third affected member (II-4 in pedigree) was the first child to develop symptoms of ALS at age 13 years and died at age 16 years after a rapid disease progression. Proband II-2 clinical manifestations started at age 31 years (after the delivery of the second child) with paresthesia of her toes and progressed rapidly with painful weakness of upper and lower extremities in 1 year, followed by dysarthria and dysphagia, and leading to death at age 33 years.

Patient II-6 presented at age 18 years with gait disturbance due to lower limb weakness and progressed within 9 years with upper limb weakness, dysphagia, and respiratory failure requiring tracheostomy. He died at age 27 years. Several years later, at age 64 years, the probands' mother started developing a proximal, hypertonic, and asymmetric weakness, predominant in lower limbs, causing difficulty in rising from the sitting position and climbing stairs, followed by ataxia and lower limb numbness. EMG-NCV and MEP showed signs suggestive of ALS with prevalent upper motor neuron (UMN) involvement. She is currently 65 years of age. The father died at age 65 years from causes unrelated to ALS. Written informed consent was obtained from all participants in the study.

Molecular analysis of the *SOD1* gene in patients II-3 and II-7 revealed the homozygous substitution c.434T>C in exon 5 resulting in the amino acid change p.Leu144Ser. Both parents were heterozygous carriers (Figure, A). DNA from patient II-5 and from unaffected siblings was not available for molecular testing. Leucine at position 144 is highly conserved across species (Figure, B) and takes part in an active loop comprising the SOD1 active center. The variant was confirmed by PCR-RFLP analysis (Figure, C).

Discussion

The L144S SOD1 variant has been initially described in 2 fALS relatives presenting an early onset (mean = 42.5 years) and an unusual prolonged survival (9 and 13 years).[4] A mutational screening performed on 60 ALS Iranian patients identified *SOD1* mutations in 11.7% of the cohort, and the heterozygous L144S mutation was found in 2 siblings and in an sALS case. All of them displayed initial lower limb involvement, early disease onset (28 and 27 years in fALS and 45 years in sALS) and extended survival (still alive after an average of 10 years).[5]

Early age at onset and a slow progression with extended survival were also observed in 3 Brazilian and in 8 Polish patients with ALS carrying this variant.[6,7] L144S is the second most frequent SOD1 variant among patients with ALS in Poland and has been proposed to derive from a founder allele.[7] A change in the same codon (p.L144F) also displayed incomplete penetrance, lower limb onset, and variable progression, supporting the importance of the conserved codon 144.

In this report L144S occurs in homozygous state in 2 affected siblings of an Iranian family presenting early-onset and fast progressive ALS. The more severe phenotype observed in the probands could be explained by the presence of 2 mutated alleles. The probands' mother, who carried the variant in heterozygous state, had a later disease onset with predominant UMN involvement. This finding rules out a recessive disease inheritance in this pedigree. Because the probands' father died at age 65 years, it could be supposed that he was a presymptomatic carrier. However, incomplete penetrance cannot be excluded.

The L144S variant has been previously identified in 4 asymptomatic individuals (2 of them younger than 45 years),[7] suggesting incomplete penetrance. On the other hand, we can speculate on the existence of genetic modifiers, partially protecting the heterozygous carriers and slowing disease onset in the parents.

In conclusion, we described a familial form of ALS due to L144S SOD1 variant presenting both in heterozygous and homozygous fashion in the affected members. The older age at onset and the disease phenotype in the heterozygous patient resemble the previous reported cases, whereas the occurrence of the L144S variant in homozygous state results in a more severe and fast progressive disease.

This report may add a piece of knowledge in the comprehension of *SOD1*-related ALS pathogenesis, and it is also relevant for therapeutics development with *SOD1* antisense strategy approaching to clinical use.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Acknowledgment

Gratitude has to be expressed to the patient for participating in this research. The authors thank "Associazione Amici del Centro Dino Ferrari" for its support. GPC and SC are members of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD).

Study Funding

This study received support by grant CP 20/2018 (Care4-NeuroRare) from Fondazione Regionale per la Ricerca Biomedica (FRRB) to SC and by Italian Ministry Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico Ricerca Corrente 2020 to GC.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures..

Publication History

Received by *Neurology: Genetics* July 15, 2021. Accepted in final form October 15, 2021.

Appendix Authors

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Roberto Del Bo, BS	Neuroscience Section, Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Italy	Analysis or interpretation of data
Megi Meneri, MD, PhD	University of Milan, Italy; Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Major role in the acquisition of data
Giacomo Pietro Comi, MD	Neuroscience Section, Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Neuromuscular and Rare Diseases Unit, Department of Neuroscience, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Stefania Corti, MD, PhD	Neuroscience Section, Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Dario Ronchi, PhD	Neuroscience Section, Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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