Oligogenic basis of sporadic ALS
The example of SOD1 p.Ala90Val mutation

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Abstract

Objective
To characterize the clinical and neuropathologic features of patients with amyotrophic lateral sclerosis (ALS) with the superoxide dismutase 1 (SOD1) p.Ala90Val mutation, as well as the mutation frequency and the role of oligogenic mechanisms in disease penetrance.

Methods
An index patient with autopsy-proven ALS was discovered to have the SOD1 p.Ala90Val mutation, which was screened in 2 Finnish ALS cohorts (n = 453). Additional contributing variants were analyzed from whole-genome or whole-exome sequencing data.

Results
Seven screened patients (1.5%) were found to carry the SOD1 heterozygous mutation. Allele-sharing analysis suggested a common founder haplotype. Common clinical features included limb-onset, long disease course, and sensory symptoms. No TDP43 pathology was observed. All cases were apparently sporadic, and pedigree analysis demonstrated that the mutation has reduced penetrance. Analysis of other contributing genes revealed a unique set of additional variants in each patient. These included previously described rare ANG and SPG11 mutations. One patient was compound heterozygous for SOD1 p.Ala90Val and p.Asp91Ala.

Conclusions
Our data suggest that the penetrance of SOD1 p.Ala90Val is modulated by other genes and indicates highly individual oligogenic basis of apparently sporadic ALS. Additional genetic variants likely contributing to disease penetrance were very heterogeneous, even among Finnish patients carrying the SOD1 founder mutation.

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Superoxide dismutase 1 (SOD1) mutations are the second most common cause of familial amyotrophic lateral sclerosis (ALS) explaining approximately 12%–20% of familial and 1%–2% of sporadic ALS.\(^1\) Usually, SOD1 mutations have an autosomal dominant pattern of inheritance.\(^1\)

SOD1 mutation c.269C>T, p.Ala90Val (previously called A89V) has been described in 3 family members with ALS with variable age at onset, incomplete penetrance, and sensory neuropathy\(^2\) and in 4 additional individuals with ALS.\(^3\)–\(^5\) The ethnicity of the patients was not reported.

We identified the SOD1 p.Ala90Val mutation through whole-exome sequencing (WES) in our neuropathologically examined index patient with ALS and investigated its frequency and additional genetic burden in 2 Finnish ALS cohorts.

Methods

The index patient was autopsied because of a clinically atypical motor neuron disease. DNA was extracted from his liver tissue, and a heterozygous SOD1 p.Ala90Val mutation was found in WES performed at the Institute for Molecular Medicine Finland (FIMM, Helsinki, Finland). This mutation was screened in 2 ALS cohorts. The Helsinki cohort (n = 300), collected 1995–2014, was subjected to whole-genome sequencing (WGS) at Broad Institute, Boston, MA. The Turku cohort (n = 153) consisted of samples sent to the TYKS Laboratory of Medical Genetics between 2007 and 2016 for SOD1 sequencing with the diagnosis of definitive or probable ALS or phenotype consistent with motor neuron disease in the referral. WES was performed at FIMM to the p.Ala90Val mutation–positive samples of the Turku cohort. Sequencing details are shown in e-Methods. All p.Ala90Val-positive samples were screened for the C9orf72 repeat expansion using the previously described method.\(^6\)

To identify additional coding or splicing variants in the p.Ala90Val-positive samples, we analyzed other neurodegenerative disease and SOD1 pathway genes from their WES/WGS data (e-methods and table e-1, links.lww.com/NXG/A152).

Neuropathologic analysis was performed following the standard protocol. Clinical information was examined from medical records.

Standard protocol approvals, registrations, and patient consents

We obtained approval for the use of patient tissue samples was obtained from the National Supervisory Authority for Welfare and Health (Valvira).

Results

Genetic analyses

The SOD1 mutation NM_000454.4 c.269C>T, p.Ala90Val found in the index patient was analyzed in the Helsinki and Turku cohorts (n = 453). Seven additional heterozygous cases were found (1.5%). This mutation is in the gnomAD database\(^7\) in 1/8,367 Finnish samples (heterozygote) but absent in all other populations (95,693 samples) after removing neurologic patients. There is a statistically significant difference in the carrier frequency of the p.Ala90Val between the Finnish patients with ALS (7/453, excluding index) and the Finnish gnomAD population (1/8,367) (p = 6.9 × 10\(^{-9}\), Fisher exact test).

Although the patients were not known to be related, allelesharing analysis of the samples indicates a common haplotype of at least 379,7 kb (Chr21:32723906-33103636) with 8 rare single nucleotide polymorphism markers, implying a common ancestor (table e-2, links.lww.com/NXG/A152).

None of the patients had a family history of ALS, and altogether 6 unaffected carriers (aged 50–87 years) of p.Ala90Val were identified in the families of P6 and P8 (figure e-1, links.lww.com/NXG/A152). Analysis of other neurodegeneration implicated genes (n = 1,115) revealed that all patients had additional potentially contributing variants (table and table e-3, links.lww.com/NXG/A152). Each patient had a unique profile of other variants, the number of possibly or probably contributing variants varied between 4 and 14 per patient. Seven of the 8 patients had at least 1 variant that we considered "probably pathogenic" (table and table e-3, links.lww.com/NXG/A152). Three patients had mutations previously described in ALS: P6, a heterozygous ANG mutation; P7, a heterozygous SPEG11 mutation; and P8 was compound heterozygous for SOD1 p.Ala90Val and p.Asp91Ala confirmed by family member testing (figure e-1, links.lww.com/NXG/A152). Four other patients had probably pathogenic variants in genes previously associated with motor neuron disease or peripheral neuropathy: P1 in ARHGEF28, P3 in UNC13A, P4 in ARHGEF10, and P5 in ADGRB2/BAI2. P2 was the only one who did not have any probably pathogenic

Data availability statement

The data set is available upon reasonable request from the corresponding author.

Glossary

ALS = amyotrophic lateral sclerosis; IHC = immunohistochemistry; SOD1 = superoxide dismutase 1; WES = whole-exome sequencing; WGS = whole-genome sequencing.

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### Table Clinical features and selected genetic findings of patients 1–8

<table>
<thead>
<tr>
<th>Patient</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (y)</td>
<td>40</td>
<td>51</td>
<td>70</td>
<td>47</td>
<td>43</td>
<td>32</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>14</td>
<td>7</td>
<td>7</td>
<td>18</td>
<td>25\textsuperscript{a}</td>
<td>6\textsuperscript{a}</td>
<td>15\textsuperscript{a}</td>
<td>7</td>
</tr>
<tr>
<td>Site of onset</td>
<td>Lower limb</td>
<td>Limb\textsuperscript{b}</td>
<td>Upper limb</td>
<td>Lower limb</td>
<td>Lower limb</td>
<td>Lower limb</td>
<td>Lower limb</td>
<td>Lower limb</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td>Cramps, difficulties with balance, and diminished control of legs</td>
<td>NA</td>
<td>Weakness of limbs, predominantly right upper limb</td>
<td>Difficulty walking, stumbling, and problems with balance</td>
<td>Muscle twitches</td>
<td>Distal lower limb weakness</td>
<td>Pain and later weakness in the lower limbs</td>
<td>Distal lower limb weakness</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Initial EMG</td>
<td>Sensorimotor polyneuropathy</td>
<td>NA</td>
<td>Motor axon damage, suggestive of motor neuron disease</td>
<td>Consistent with motor neuron disease</td>
<td>Consistent with motor neuron disease</td>
<td>Compatible with motor neuron disease</td>
<td>Compatible with motor neuron disease</td>
<td>Compatible with motor neuron disease</td>
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<tr>
<td>Sensory neuropathy in EMG</td>
<td>Yes\textsuperscript{c}</td>
<td>NA</td>
<td>No</td>
<td>Yes\textsuperscript{d}</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Cognitive symptoms</td>
<td>No</td>
<td>NA</td>
<td>Yes\textsuperscript{d}</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cerebral infarct in MRI</td>
<td>No</td>
<td>NA</td>
<td>Yes\textsuperscript{d}</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>Creatine kinase</td>
<td>Elevated</td>
<td>NA</td>
<td>Normal</td>
<td>Elevated</td>
<td>Slightly elevated</td>
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<td>Cause of death</td>
<td>ALS</td>
<td>Suspected myocardial infarction</td>
<td>ALS</td>
<td>Respiratory failure</td>
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<td>Family history of ALS</td>
<td>No</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>C9orf72</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Intermediate allele (23 repeats)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: ALS = amyotrophic lateral sclerosis; NA: information not available; WES = whole-exome sequencing; WGS = whole-genome sequencing.

\textsuperscript{a} The patient is alive.

\textsuperscript{b} More detailed information about the site of onset is not available.

\textsuperscript{c} The amplitude of antidromic sensory potentials of patient P1 at age 40 years: median nerve 4.8 mV (normal value ≥20 mV), ulnar nerve 3.6 mV (normal value ≥17 mV), and sural nerve 5.8 mV (normal value ≥6 mV), and of patient P4 at age 53 years: ulnar nerve 4.9 mV and sural nerve 8.7 mV, the median nerve had no response in the study. The EMG studies were performed using the standard protocol.

\textsuperscript{d} In addition to small old infarcts in the left occipital lobe and right posterior frontal area, there was a mild expansion in the cortical liquor spaces and mild atrophy in the hippocampi, changes in the pons area and in the periventricular white matter that were interpreted as degenerative. This patient also had cognitive symptoms, and a neuropsychological assessment at age 76 years revealed predominantly frontal lobe problems that were not at the level of dementia.

\textsuperscript{e} The patient had variants in 3 SOD1 pathway genes: FBXW8, NOB1, and ALOX15.

\textsuperscript{f} Mutation has been previously reported in patients with ALS; the references are in the supplemental material (e-references, links.lww.com/NXG/A152).

\textsuperscript{g} Deletions in exons 7 and 8 of the SMN1 and SMN2 genes were investigated by the PCR-restriction fragment length polymorphism method. Comprehensive list and information of genetic variants are in table e-3, links.lww.com/NXG/A152.
variants according to our interpretation; she had nevertheless variants in 3 SOD1 pathway genes: FBXW8, NOB1, and ALOX15 (table e-3, links.lww.com/NXG/A152). None of the patients had a C9orf72 repeat expansion, but P6 had 23 hexanucleotide repeats in C9orf72 (the significance of which is presently unclear).

Clinical features
The patients’ clinical features are summarized in the table. The age at onset was variable (32–70 years). All had a limb-onset disease, with typical presenting symptoms including fasciculations, weakness, and difficulties with walking and balance. The initial EMG and nerve conduction study of P1 (index) revealed sensorimotor polyneuropathy; later, he had stocking-like sensory abnormalities in both feet, and both soles showed hyperesthesia in addition to the motor symptoms. The initial EMG of P4 was consistent with motor neuron disease, and a later EMG revealed additional distal sensory polyneuropathy. P7 had reduced vibration sense in his feet, and P5 had paresthesia in her hands. All patients had a long disease course, 7–25+ years; 3 of the patients were still alive at the time of this study.

Neuropathologic features
The index patient’s brain weighed 1527 g and appeared macroscopically normal. The anterior roots of the spinal cord were atrophic. Microscopically, the anterior horns showed significant loss of neurons (figure, C).

The axon density was markedly lowered in the anterior roots compared with the dorsal roots (figure, A–B).

There was mild neurodegeneration in the hypoglossal nucleus at the level of the medulla oblongata (figure, D). Immunohistochemistry (IHC) showed no TDP43-positive inclusions in the anterior horns, cortical areas, or in the hypoglossal nucleus. No hyaline conglomerate inclusions, reported to be specific for some SOD1 mutations, were detected on neurofilament (SMI32) IHC. Tau, and beta amyloid stainings were negative. P62 staining showed only a few positive neurites, but no intraneuronal inclusions. The muscle samples showed very strong group atrophy and fairly abundant reinnervation (figure, E–F). The cause of death was concluded to be motor neuron disease.

Figure Neuropathologic findings of the autopsied patient (index)

(A) Plastic-embedded sections from the dorsal spinal root show normal density of axons, whereas (B) severe loss of both myelinated and unmyelinated axons is seen in the anterior spinal roots (toluidine blue ×600 magnification). (C) There is severe neuronal loss in the anterior spinal columns, and the remaining neurons appear chromatolytic (hematoxylin and eosin [HE]-stained section from the lumbar spinal cord, ×400 magnification). (D) The hypoglossal nucleus was mildly degenerated (HE-stained section from the medulla oblongata, ×400 magnification. (E) Muscle biopsy taken from the vastus lateralis showed atrophic small groups (arrow) and overrepresentation of type 2 fibers, suggesting abundant reinnervation (double immunohistochemistry for myosin, ×200 magnification). (F) Higher magnification shows that both type 1 (brown) and type 2 (red) fibers (arrows) are atrophic (×400 magnification).
Discussion

In this study, 1.5% of the patients with ALS carried the SOD1 mutation p.Ala90Val, making it a major mutation in Finnish patients with ALS based on its frequency, although it had previously been described in only 7 patients.2–4 In the Helsinki cohort, it is the third most common currently known ALS mutation after C9orf72 repeat expansion and SOD1 p.Asp91Ala (unpublished data). There is a clear enrichment of p.Ala90Val in the Finnish population.

There were 6 unaffected family members who were confirmed to carry the p.Ala90Val mutation illustrating the proposed reduced penetrance and oligogenic mechanisms in ALS.4 The SOD1 p.Ala90Val probably plays a dominating role in our patients despite the additional rare variant burden because (1) the clinical features were similar in all patients thus far reported2 and (2) the neuropathology of the index patient was consistent with SOD1-related ALS.5 The p.Ala90Val mutation has been shown to cause a conformational change on the SOD1 protein,10 and SOD1 enzymatic activity has been shown to be reduced in the CSF of a patient with the mutation.5 In silico analysis with MutationTaster (mutatontaster.org/), PolyPhen-2 (genetics.bwh.harvard.edu/pph2/), and SIFT (provean.jcvi.org/index.php) predicts p.Ala90Val to be deleterious.

We cannot exclude the role of environmental factors in disease penetrance with total confidence. However, 3 of the 8 patients had mutations previously described in ALS, and 4 additional patients had probably pathogenic rare variants in genes previously implicated in motor neuron disease or peripheral neuropathy. Our data represent an illustrative example of a mutation whose penetrance appears to require additional genetic factors. It also demonstrates the genetic heterogeneity of sporadic ALS: despite sharing a founder mutation, the spectrum of other variants was very heterogeneous; each patient had a unique set of variants. The small sample size and varying sequencing methodology preclude powerful analyses of the discovered variants on clinical features. At present, it is not possible to make firm conclusions on the pathogenic role of the potentially contributing variants in individual patients, although in the p.Asp91Ala compound heterozygous P8, the disease-causing effect is clear. The allele frequency of many variants (table e-3, links.lww.com/NXG/A152) suggests predisposing or disease-modifying rather than disease-causing effects.

Acknowledgment

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Disclosure

Disclosures available: Neurology.org/NG.

Publication history

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<table>
<thead>
<tr>
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<th>Location</th>
<th>Role</th>
<th>Contribution</th>
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</thead>
<tbody>
<tr>
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Appendix (continued)

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<tbody>
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