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Amyotrophic lateral sclerosis patients with optineurin gene variants: A case series

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Abstract

Background & Objective: Amyotrophic lateral sclerosis (ALS) is an incurable and fatal disease that affects motor neurons, and can be sporadic or familial. Pathogenic variants in the optineurin gene *(OPTN)* have been implicated in the pathogenesis of ALS, type 12 (ALS12). Knowledge of the causative/disease-modifying genes may provide a novel target for gene therapy. *Methods:* We present three patients with ALS who were followed up at our neuromuscular outpatient clinic, and underwent clinical, neurophysiological, neuropsychological, radiological, laboratory, and genetic investigations. We identified variants by analyzing the entire exome and adjacent intronic regions of the causative genes. *Results:* The patients had c.1078_1079del, p.Lys360Valfs*18 and c.1242+1G>A homozygous variants and c.403G>T, p.Glu135* heterozygous variant in *OPTN*, and presented with different clinical features.
Conclusions: Clinicians should be aware of the phenotypes and genetic profiles of patients to gain a better understanding of ALS12 and contribute to the development of new therapies.

Keywords: Amyotrophic lateral sclerosis, optineurin, *OPTN, ALS12*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease caused by the neurodegeneration of motor neurons in the central nervous system. The disease is mostly sporadic and is known to be familial in at least 10% of patients.[1] Pathogenic variants have been reported to be present in up to 15% of patients with "sporadic" disease. Accordingly, this terminology is gradually changing as ALS genetic research advances and genetic testing becomes more widely used in clinical practice.[2,3]

Since the discovery of the superoxide dismutase 1 (*SOD1)* variant in 1993, the number of causative or susceptibility genes has increased considerably.[4] Fused in sarcoma (*FUS*), and transactive response DNA-binding protein (TARDBP) are the two identified ALS genes whose variants are thought to cause a toxic gain of function because their products form cytoplasmic aggregates, a common mechanism in motor neuron disease. The most common known cause of ALS is currently a hexanucleotide repeat expansion in the first intron of chromosome 9 open reading frame 72 *(C9ORF72)*. The size of the repeat is less than 23 in healthy individuals, but can be in the hundreds or thousands in affected individuals.[5] With the advent of whole exome and genome sequencing techniques, the number of ALS genes and mutations, including single nucleotide variations (SNVs), insertions and deletions (INDELs); has increased dramatically in recent years.

In 2010, *OPTN* was first suggested to play a role in the pathogenesis of ALS through autophagy and protein degradation as one of the causes of familial and sporadic ALS, citing autosomal dominant or recessive slowly progressive cases with ALS due to *OPTN* variations occurring in 1-4% of familial cases and in less than 1% of sporadic cases.[6] The study by Pensato *et al.* allowed for the identification of pathogenic or likely pathogenic rare variants. *OPTN* was one of the highest percentages of these, with 1%.[7] In this sense, we will try to interpret the *OPTN* variants and the clinical features of our patients in terms of their pathophysiological contribution.

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Table 1: Selected ALS-related genes investigated in our study

ABCD1, ABHD12, ALS2, ANG, ARHGEF28, C9ORF72, CHCHD10, CHMP2B, CRYM, DAO, DCTN1, ER884, FIG4, FUS, GRN, HNRNPA1, HNRNPA2B1, LUM, MAPT, MATR3, NEFH, NEK1, OPTN, PFN1, PRPH, PSEN1, SETX, SIGMAR1, SOD1, SPART, SPG11, SQSTM1, TAF15, TARDBP, TBK1, TREM2, TUBA4A, UBQLN2, UNC13A, VAPB, VCP, VEGFA.

METHODS

Genomic DNA was extracted from the peripheral blood of patients using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Clinical exome sequencing (CES) was performed using next-generation sequencing (Illumina NextSeq 500) and the Sophia Clinical Exome Solution V2. Forty-two genes associated with ALS (Table 1) were analyzed using the Sophia DDM-V4 platform. To compare variants, the sequencing data were aligned to the human reference genome (hg38). The ClinVar database was screened for known variations, and the novel variants detected in this study were evaluated according to the criteria of the American College of Medical Genetics and Genomics.

RESULTS

Patient 1

A 46-year-old female patient presented with progressive weakness on the right side of her body, which began four years prior. First, her right arm was affected, and then her gait became impaired. During the neurological examination, she exhibited right hemiparesis, marked spasticity, and hyperreflexia in the affected areas. Motor and sensory nerve conduction studies were normal. Needle electromyography (EMG) showed chronic denervation in the right cervical and lumbosacral segments, and genetic analysis revealed a homozygous frameshift variant c.1078_1079del in the *OPTN* (RCV001095475) and a heterozygous missense variant c.122T>C in the *FIG4* (rs121908287) gene (FIG4, phosphoinositide 5-phosphatase) (Figure 1).

Patient 2

A 55-year-old female patient presented with left lower extremity weakness that began seven years ago. During follow-up, she developed weakness in her left upper extremity. Upon examination, left-sided weakness was evident, particularly distally, along with spasticity in the left upper extremity and bilateral lower extremities. Nerve conduction studies revealed mild bilateral carpal tunnel syndrome and were otherwise normal. Needle EMG revealed chronic denervation of the left lumbosacral segment, and the patient's family history revealed that her bedridden brother had been diagnosed with dementia. However, an adequate history of frontotemporal dementia (FTD) could not be obtained. Genetic analysis revealed c.1242+1G>A (rs1206478143) a homozygous pathogenic variant at the splice site of *OPTN* gene (Figure 2).

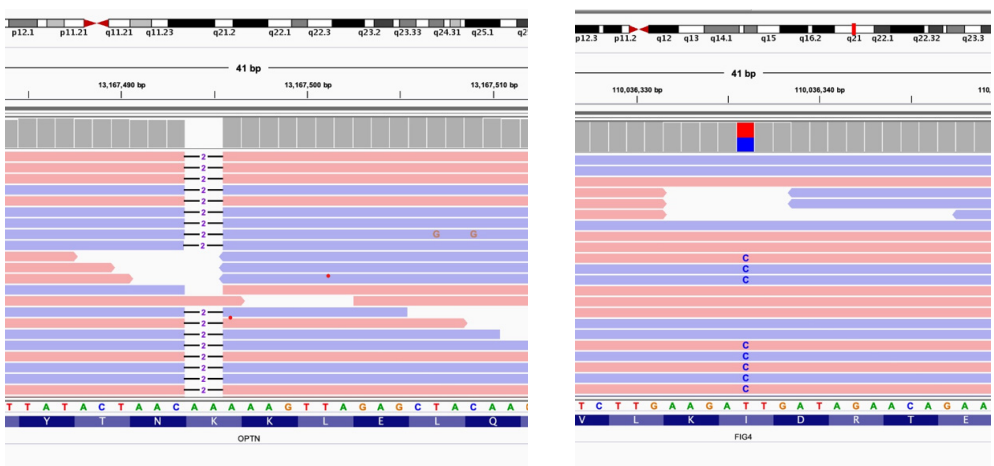

Figure 1. Integrative Genomics Viewer (IGV) visualization of c.1078_1079del, (p.Lys360Valfs*18) variant in the OPTN (left) and c.122T>C, (p.Ile41Thr) variant in the FIG4 (right)

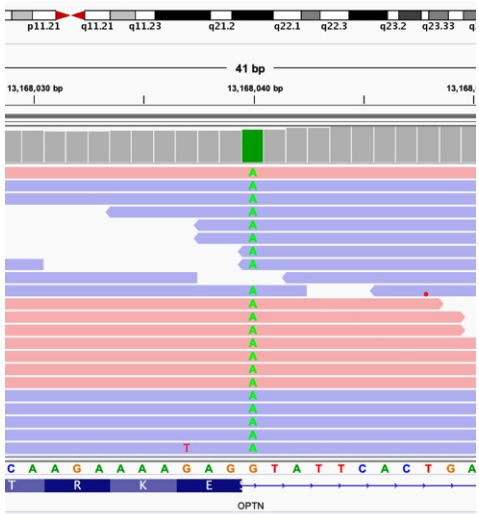

Figure 2 IGV visualization of c.1242+1G>A variant in the OPTN

Patient 3

A 52-year-old male patient experiencing right upper extremity weakness and difficulty speaking was referred to our outpatient clinic. Follow-up examinations revealed left upper extremity weakness and severe dysphagia. Right median and ulnar compound muscle action potential (CMAP) amplitudes were reduced on nerve conduction studies, and needle EMG showed acute and chronic denervation in all four segments. Approximately two years after the onset of symptoms, a percutaneous endoscopic gastrostomy procedure was performed, after which lower extremity weakness developed. Genetic analysis revealed a heterozygous pathogenic c.403G>T (p.Glu135*) (rs140599944) variant in the *OPTN*. In addition, a c.1190T>C, (p.Ile397Thr) (rs755069538) heterozygous variant was found in *TBK1* (tank-binding kinase 1), which is classified as a variant of uncertain significance (VUS). (Figure 3)

Laboratory, cerebrospinal fluid (CSF), or neuroimaging findings were unremarkable in all patients. None of the patients exhibited clinical findings consistent with FTD. No glaucoma was observed during the neuro-ophthalmic examination, except for in Patient 3, for which examination information could not be accessed. Although all patients are known not to be related to their spouses, living in the same village may be significant for homozygous transmission in Patients 1 and 2. Case characteristics and genetic analysis are summarized in Table 2.

DISCUSSION

To date, *OPTN* has been implicated in inflammatory, autoimmune and neurodegenerative diseases, including ALS12.[6] Recent studies have shown that programmed necrosis, also known as necroptosis, and the downstream inflammatory response are involved in the pathophysiological processes of these diseases when *OPTN* is inactivated by variants.[8]

In our series, Patients 1 and 2 exhibited

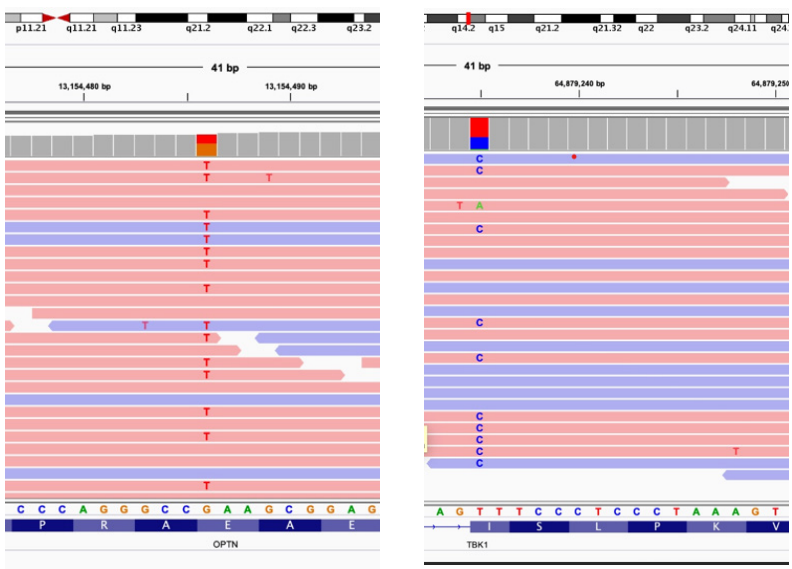

Figure 3. IGV visualization of c.403G>T, (p.Glu135*) variant in the OPTN (Left), c.1190T>C, (p.Ile397Thr) in the TBK1. (Right)

Table 2: Case characteristics and *OPTN* analysis

	Patient 1	**Patient 2**	**Patient 3**
Gender	Female	Female	Male
Age at onset (year)	44	48	48
Duration (month)	41	94	67
Site of onset	Spinal	Spinal	Spinal-Bulbar
Nucleotide change	c.1078_1079del	c.1242+1G>A	c.403G>T
Amino acid change	p.Lys360Valfs18	*Splice Site*	p.Glu135*
Zygosity	Homozygous	Homozygous	Heterozygous
Cognitive decline	No	No	No
Glaucoma	No	No	*NA*
Spasticity	Yes	Yes	No
Respiratory problems	No	No	No
American College of Medical Genetics and Genomics (ACMG)	Pathogenic	Pathogenic	Pathogenic

***NA*: Not-available**

several clinical similarities consistent with previous literature, including slow progression and prominent spasticity.[6] In Patient 1, c.1078_1079del, p.Lys360Valfs*18 is a frameshift variant of *OPTN*, which has been reported to be pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria via a loss-of-function mechanism.[6,9] With the exception of the Greater Middle East (GME) Variome, where the patient's population is located, the allele frequency is exceptionally low across all other databases. (7.3589%) In a case report, two siblings from a consanguineous family with the same variant exhibited different clinical presentations. The index patient rapidly developed progressive clinical features of upper and lower motor dysfunction, apathy and cognitive decline, whereas the brother was diagnosed with FTD without motor neuron dysfunction.[10] However, we did not observe any cognitive decline in our patient. This was confirmed by the neuropsychiatric batteries used during her follow-up. The heterozygous missense variation c.122T>C, p.Ile41Thr, previously reported in ALS patients, was also detected in *FIG4* in the same patient.[11] According to the ACMG criteria, this variant is classified as VUS and is extremely rare in the Genome Aggregation Database (gnomAD: 0.0%), as well as in other databases, including GME Variome. In a Central European cohort study, individuals carrying the *FIG4* variant exhibited longer disease duration, and upper motor neuron predominance was significantly more frequent compared to ALS patients not carrying the *FIG4* variant as seen in *OPTN* variants.[12]

In Patient 2, a homozygous variant c.1242+1G>A in *OPTN* was detected which is classified as pathogenic according to ACMG criteria. This single nucleotide variant (dbSNP: rs1206478143) may disrupt normal splicing, potentially leading to exon skipping or the inclusion of intronic sequences in the mature mRNA. The allele frequency is very low in all databases, including those of the patient's population. (GME Variome) Contributing to the aggregate classification, this variant has previously been reported as pathogenic in two patients, one with familial ALS and the other with limb-onset ALS and slow progression, similar to our patient.[13,14]

The phenotype of Patient 3 expands the clinical features of ALS patients with the *OPTN* variant, which is characterized by rapid deterioration followed by stability. NGS revealed a heterozygous variant c.403G>T, p.Glu135* (rs140599944) in the *OPTN* gene that may be associated with ALS12.[6,15] This sequence change results in a premature translation stop signal p.Glu135* which is expected to result in the absence or degradation of the protein product. Loss-of-function variants in *OPTN* are known to be pathogenic. Patient 3 also had a heterozygous missense variation c.1190T>C, p.Ile397Thr in the *TBK1* gene. According to ACMG criteria, this variation is classified as VUS due to the lack of clear functional and genetic evidence.[16] Optineurin is an important autophagy receptor involved in

a variety of selective autophagy processes where its function is under the regulation of the TBK1 protein. Although pathogenic variants in both *OPTN* and *TBK1* have been associated with neurodegenerative diseases, the mechanistic basis for the specific interaction between optineurin and TBK1 remains unclear.[17] Functional studies are required to suggest that this interaction may explain the phenotypic difference in Patient 3. Another limitation is that we could not perform a segregation analysis, which would have greatly contributed to our study.

Considerable progress has been made in recent years in understanding the pathogenesis of ALS. The complex genetic architecture of ALS is fundamental to our understanding of the disease, and it is becoming increasingly important for patient stratification in clinical trials. Ongoing research efforts, including functional studies to characterize variants of the OPTN protein, are essential for improving our understanding of genotype-phenotype correlations in *OPTN*-associated ALS. This information will be essential for enhancing genetic counseling, predicting disease progression, and potentially tailoring treatment strategies for individuals with specific *OPTN* mutations.

DISCLOSURE

Ethics: Informed consent was obtained from each participant included in the study.

Financial support: None

Conflict of interest: None

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