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HOMOZYGOUS OPTN SPLICE-SITE VARIANT IN BULBAR-ONSET AMYOTROPHIC LATERAL SCLEROSIS: A CASE REPORT

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ABSTRACT

ALS caused by changes in the OPTN gene (sometimes called ALS12) is an uncommon genetic form that can present with a range of symptoms, such as bulbar involvement and, in some cases, frontotemporal dementia. The particular splice-site mutation found in this patient appears to be novel, as it has not been documented in existing scientific literature, which makes this case especially noteworthy. Dysfunctional OPTN proteins, resulting from loss-of-function mutations, are linked to motor neuron degeneration by mechanisms like faulty autophagy, increased inflammation in the nervous system, and problems with NF-kB signaling. This report adds to the list of known OPTN mutations associated with ALS and demonstrates the value of advanced genetic testing in patients with early or unusual presentations of motor neuron disease. Sharing newly discovered mutations helps connect genetic changes with clinical outcomes and deepens our understanding of inherited ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder characterized by degeneration of both upper and lower motor neurons. Clinically, patients develop progressive limb weakness, dysarthria, dysphagia, respiratory insufficiency, and ultimately fatal neuromuscular failure. Although most cases are sporadic, approximately 5–10% are familial, with pathogenic variants identified in several genes including SOD1, C9orf72, FUS, TARDBP, and OPTN.

The OPTN gene encodes optineurin, a cytoplasmic adaptor protein involved in multiple cellular pathways such as autophagy, vesicular transport, inflammatory signaling, and maintenance of neuronal integrity. Variants in OPTN are linked to ALS type 12 (ALS12) and may exhibit either autosomal dominant or autosomal recessive inheritance. Loss-of-function mutations, particularly in the homozygous state, are frequently associated with earlier onset and more severe disease manifestations.

We describe a patient with bulbar-onset ALS in whom clinical exome sequencing identified a homozygous splice-site variant in OPTN predicted to disrupt normal RNA splicing.

Case Report

A 41-year-old woman presented with gradually progressive speech and swallowing difficulties. The illness began with slurring of speech, which was followed by worsening dysphagia involving both liquids and solids. Over time, she developed incomplete eye closure and progressive weakness predominantly affecting the right upper limb and lower limb.

There was no history suggestive of sensory involvement, sphincter dysfunction, seizures, cognitive impairment, or toxic exposure. Family history of motor neuron disease was not documented.

Neurological examination revealed severe bulbar involvement with anarthria and dysphagia. Examination of the cranial nerves demonstrated bilateral lower motor neuron facial weakness with facial muscle wasting, jaw drop, exaggerated gag reflex, and a spastic tongue with atrophy. Motor examination showed asymmetric spastic quadriparesis with bilateral extensor plantar responses. Sensory, cerebellar, autonomic, and higher mental function examinations were normal.

Routine laboratory investigations, including hematological and biochemical parameters, were within normal limits. Magnetic resonance imaging of the brain and cervical spine did not reveal any alternative structural etiology. Nerve conduction studies and electromyography demonstrated diffuse motor neuron involvement with active and chronic denervation changes consistent with motor neuron disease.

Considering the relatively young age at onset and the clinical phenotype, genetic analysis was performed. Clinical exome sequencing identified a homozygous splice acceptor variant in the OPTN gene (NM_001008212.2:c.780-2A>C). The variant was classified as likely pathogenic.

This sequence alteration affects the canonical splice acceptor region and is predicted to significantly impair normal mRNA splicing, resulting in abnormal or truncated protein production. The variant was extremely rare in population databases (gnomAD frequency: 0.0001%) and demonstrated a high deleterious splice prediction score (SpliceAI score: 0.99), supporting its pathogenic potential.

The patient was diagnosed with bulbar-onset ALS associated with a homozygous OPTN mutation.

The identified OPTN variant was: OPTN gene, transcript: NM_001008212.2., Variant: c.780-2A>C, Zygosity :Homozygous, Variant type: Splice acceptor variant, Classification: Likely pathogenic, Inheritance pattern: Autosomal recessive.

The variant is predicted to cause abnormal splicing and downstream protein truncation. Loss-of-function OPTN variants have previously been implicated in ALS pathogenesis

DISCUSSION

ALS is genetically heterogeneous, with multiple pathogenic pathways implicated in disease development. While variants in SOD1, C9orf72, FUS, and TARDBP account for a major proportion of familial ALS, increasing recognition of genes

such as OPTN, TBK1, SQSTM1, and UBQLN2 has broadened the molecular understanding of the disease.

Optineurin functions as a ubiquitin-binding adaptor protein involved in selective autophagy, inflammatory regulation, vesicular trafficking, and maintenance of Golgi architecture. Dysfunction of this protein has been associated with impaired autophagic clearance, abnormal intracellular protein accumulation, enhanced neuroinflammation, and progressive motor neuron degeneration.

The association between OPTN mutations and ALS was first reported by Maruyama and colleagues in 2010, who identified homozygous deletions and truncating mutations in patients with recessively inherited ALS. Subsequent studies have demonstrated considerable phenotypic variability associated with OPTN mutations, including differences in age at onset, progression rate, and site of disease onset.

Our patient presented with bulbar-onset ALS, a relatively less frequent phenotype in OPTN-related disease. Previous studies have reported bulbar involvement in a minority of affected individuals. The early age of onset and severe clinical presentation in this patient are consistent with observations that homozygous loss-of-function variants tend to produce more aggressive disease phenotypes.

The c.780-2A>C variant identified in this case affects a highly conserved splice acceptor site and is predicted to markedly alter RNA processing. Although this specific variant has not been extensively described previously, the combination of computational evidence, rarity in population databases, and established pathogenic mechanisms involving loss of optineurin function strongly support its clinical significance.

From a mechanistic perspective, optineurin interacts closely with TANK-binding kinase 1 (TBK1) and participates in pathways regulating autophagy and programmed cell death.

Experimental data suggest that dysregulation of receptor-interacting protein kinase 1 (RIPK1)-mediated necroptosis may contribute to neuronal injury in OPTN-associated ALS, highlighting potential therapeutic targets for future investigation.

This case underscores several important clinical considerations:

1. Genetic evaluation should be considered in younger patients with ALS, even in apparently sporadic cases.
2. OPTN-associated ALS may present with predominant bulbar symptoms.
3. Homozygous splice-site variants can result in severe loss-of-function phenotypes.
4. Molecular confirmation assists in genetic counseling and may have future therapeutic implications.

CONCLUSION

We report a patient with bulbar-onset ALS carrying a homozygous splice acceptor variant in OPTN (NM_001008212.2:c.780-2A>C). This case expands the known mutational and phenotypic spectrum of OPTN-related ALS and reinforces the importance of genetic testing in younger-onset motor neuron disease. Identification of pathogenic variants not only improves diagnostic precision but may also contribute to future genotype-directed therapeutic strategies.

Conflict of Interest: The authors declare no conflict of interest.

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