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Identification of compound heterozygous variants in *OPTN* in an ALS-FTD patient from the CReATe consortium: a case report

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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Abstract

Homozygous loss-of-function mutations in optineurin (*OPTN*) are a rare cause of amyotrophic lateral sclerosis (ALS), whereas heterozygous loss-of-function mutations have been suggested to increase ALS disease risk. We report a patient with ALS and frontotemporal dementia (FTD) from the Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium carrying compound heterozygous loss-of-function variants in *OPTN*. Quantitative real-time mRNA expression analyses revealed a 75–80% reduction in OPTN expression in blood in the *OPTN* carrier as compared to controls, suggesting at least partial nonsense-mediated decay of the mutant transcripts. This case report illustrates the diverse inheritance patterns and variable clinical presentations associated with *OPTN* mutations, and underscores the importance of complete *OPTN* gene screening in patients with ALS and related disorders, especially in the context of clinical genetic testing.

Keywords

Amyotrophic lateral sclerosis; frontotemporal dementia; optineurin; compound heterozygous; mutation

INTRODUCTION

Mutations in the optineurin gene (*OPTN*) were first reported as a rare cause of autosomal recessive amyotrophic lateral sclerosis (ALS) (1). In this study, we report compound heterozygous loss-of-function mutations in *OPTN* in a patient with familial ALS and frontotemporal dementia (FTD) enrolled in the CReATe Consortium.

CASE REPORT

Our patient is a male who first presented with right hand weakness at the age of 58, followed within two months by cognitive (language) symptoms. Left arm weakness developed two months later and he was diagnosed five months after symptom onset with ALS-FTD. His ALS Functional Rating Scale-Revised (ALSFRS-R) at initial assessment was 36 with an estimated progression rate since symptom onset of 1.09 points/month (average to fast). Longitudinal monitoring using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) (2) identified progressive cognitive decline, which initially manifested in an isolated domain (verbal fluency), but after 12 months involved multiple areas (language, and executive functioning, and memory). Full neuropsychological testing confirmed this

impression, with severe impairment (<1st percentile) in language-mediated tasks, (confrontational naming, verbal learning, and sematic/phonemic fluency), and moderate impairments (<5th percentile) in executive function (mental set-shifting, social cognition). Over the ensuing 16 months, ALSFRS-R declined at a rate of 1.67 points/month (fast). He died 21 months after symptoms onset.

The patient's father died without neurological disease at 65 years, while his mother is unaffected at 83. He has one sister who died of ALS at the age of 45, one sibling with multiple sclerosis, and two living siblings without neurological diseases. He has three living and healthy children.

GENETIC AND EXPRESSION ANALYSES

Illumina whole-genome sequencing in our patient identified in *OPTN* one nonsense variant p.Ser262* (NM_001008211.1:c.785C>A) and one frameshift deletion p.Leu430Argfs*16 (NM_001008211.1:c.1289_1290del); both were validated by Sanger sequencing. Mutations in other known familial and recessive ALS genes were excluded(3). PCR amplification using a c.785C>A wild-type or mutant specific primer revealed that these mutations are inherited *in trans* (Figure 1A). Quantitative real-time PCR using RNA isolated from PAXgene Blood RNA kits obtained from the patient and two unrelated controls, showed ~75–80% reduction in *OPTN* expression in our patient compared to controls suggesting that both mutant transcripts undergo (at least partial) nonsense-mediated decay (Figure 1B). cDNA amplification of *OPTN* in a multiplex PCR with an unrelated control gene fragment (*CSF1R*) confirmed the quasi absence of *OPTN* (Figure 1C).

DISCUSSION

We report a patient with novel compound heterozygous loss-of-function mutations in *OPTN* as the probable cause of ALS-FTD. Lack of DNA samples from family members prohibited segregation analysis; however, blood expression studies showed strong reduction in *OPTN* mRNA to ~20% of normal levels. The OPTN protein, encoded by *OPTN*, is a multifunctional ubiquitin-binding adaptor protein known to regulate numerous cellular processes including autophagy, inflammation and necroptosis(4). Homozygous loss-of-function mutations in *OPTN* were first reported in Japanese families with autosomal recessive ALS(1). Heterozygous *OPTN* mutations were subsequently reported as either causative for ALS or as ALS risk factors; however, the exact contribution of these mutations to disease pathogenesis remains uncertain(4–6). The strongest support for an increased ALS risk in individuals heterozygous for loss-of-function variants in *OPTN* is provided by a founder mutation in Moroccan and Ashkenazi Jews (7) and by a recent exome-based genome-wide association study(8). Whether these patients carry undetected second mutations in *OPTN* or mutations in another gene affecting the same functional pathway is not known. Interestingly, we recently reported a patient with FTD and TDP-43 pathology (FTLD-TDP) with heterozygous loss-of-function mutations in *OPTN* and in the gene encoding the TANK Binding Kinase 1 (*TBK1*), an important binding partner of OPTN, supporting a role for *OPTN* in causing disease through an oligogenic mechanism(9).

Compound heterozygous mutations in *OPTN* have previously been reported in a Dutch family with three patients with progressive muscular atrophy without cognitive impairment (10) and in a single case of FTLD-TDP(9). Our findings expand the phenotypic spectrum of compound heterozygous *OPTN* loss-of-function mutations to include ALS-FTD with potentially unknown genetic and environmental factors influencing the ultimate phenotypic presentation in each patient.

Together with the published reports, this new case illustrates that the contribution of *OPTN* mutations to ALS and related disorders is complex. This poses a major challenge for genetic counseling in *OPTN* families, where single heterozygous rare loss-of-function mutations could be considered genetic risk-factors; however, if an additional rare coding variant is located either within *OPTN* or in another gene from the same pathway such as *TBK1*, these mutations could be causative. To identify all possible contributing genetic factors, including partial and full gene deletions, we recommend ALS genetic testing at the exome or genome level, combined with quantitative mRNA analyses, where possible.

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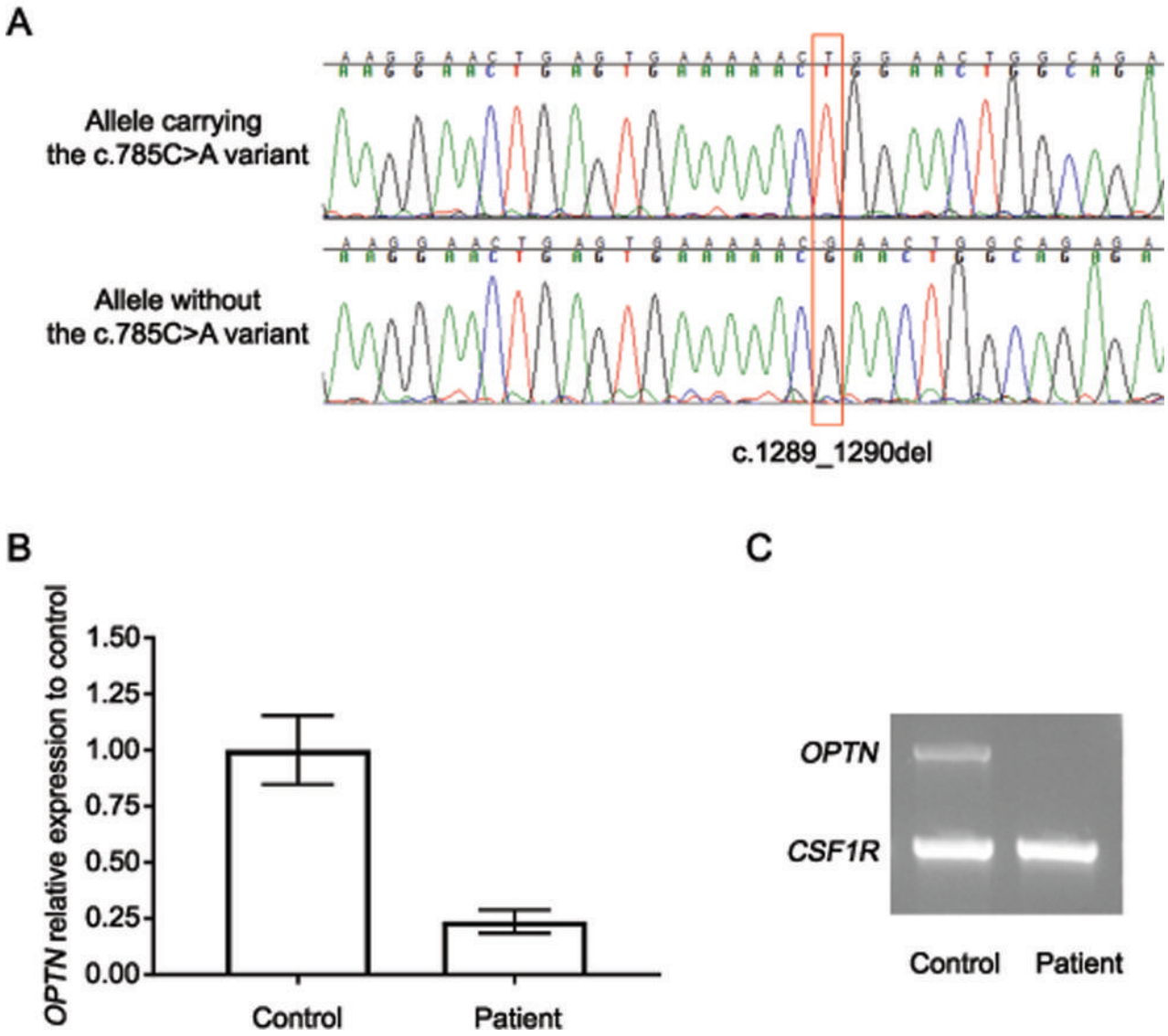

Figure 1: Reduction of *OPTN* mRNA expression in blood.

A) Sanger sequencing was performed using cDNA generated from the *OPTN* patient and sequence traces around the c.1289_1290del mutation (red rectangle) are shown. In the top panel, a primer specific to the mutant allele of the second mutation (c.785C>A) was used, whereas in the bottom panel, a PCR primer only able to amplify the wild-type sequence at c. 785C>A was used. Together these traces show that the two mutations are inherited in *trans*. **B)** Relative expression of *OPTN* mRNA as measured by TaqMan gene expression assay (probe Hs00184221_m1) in the *OPTN* patient and two controls after normalization to the reference gene *RPLPO* (probe Hs00420895_gh) and further normalization to the average expression in controls (100%). Data from three independent experiments (+/− standard deviation) are shown. **C)** Migration profile of the multiplex PCR product from *OPTN* (exons 6–16) and *CSF1R* cDNA is presented for one healthy control and the patient with *OPTN* mutations.