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A novel *OPTN* variant causing PSP-CBS-like phenotype in familial amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis is a fatal neurodegenerative disease which is familial in nearly 10% of affected patients [1]. Most familial ALS (FALS) are caused by mutations in *C9orf72, SOD1, TARDBP* and *FUS* genes [1]. Mutations of *OPTN* gene is a rare cause of FALS with heterogeneous clinical associations such as frontotemporal dementia (FTD), primary open angle glaucoma, and Paget's disease of the bone [1,2]. We describe two siblings with a novel OPTN mutation and atypical parkinsonian phenotype.

Patient 1: The proband-1 (III-1) is a 52 year old lady with progressively worsening slowness of activities, speech disturbance, and stiffness with abnormal posturing of the right forearm and hand. On clinical examination, she had hypomimia, spastic dysarthria, slow vertical and horizontal saccadic eye movements, nuchal rigidity, increased tone of the right upper and lower limb with presence of dystonia, asymmetric bradykinesia, stimulus sensitive myoclonus, limb-kinetic and ideomotor apraxia of the right upper limb. Deep tendon reflexes were brisk with extensor plantar response and exaggerated pectoral, trapezius jerk and palmomental reflexes. Over the next two years, she developed recurrent backward falls, dysphagia, dysarthria, emotional lability, and urinary incontinence. On examination, she had vertical gaze restriction corrected by the vestibulo-ocular reflex (VOR) and slow saccadic movements, increased tone of the axial and appendicular musculature and fixed dystonia of the right upper limb. She also developed generalized wasting of muscles, however, there were no fasciculations (supplementary video- 1). She was cognitively normal (Montreal Cognitive Assessment score (MoCA): 26.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.11.003.

Patient 2: Proband-2 (III-2) is 48 years and had similar symptoms and had upgaze restriction with preserved VOR, overactivity of frontalis, axial rigidity, exaggerated deep tendon reflexes, spasticity, muscle weakness and atrophy without fasciculations, asymmetric dystonia, bradykinesia, and ideomotor apraxia affecting the distal right upper limb (supplementary video-2). He was cognitively normal (MoCA: 29).

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Investigations and differential diagnosis: The routine blood and CSF assessments, ophthalmic and metabolic screening were normal in both patients. Based on the clinical features, a differential diagnosis of autosomal recessive tauopathy with possible corticobasal variant of progressive supranuclear palsy (poss. PSP-CBS) was initially considered. However, the MRI scans of both probands did not reveal any characteristic neuroimaging findings of PSP (supplementary Figure-1). The asymmetric onset of pyramidal pattern of weakness, hyperreflexia, wasting, and bulbar symptoms also pointed towards motor neuron disorder. Needle EMG performed revealed a neurogenic pattern of involvement in both patients. Patient 1 and Patient 2 satisfied the El Escorial world federation of neurology criteria for definite ALS and probable ALS, respectively. This led us to revise the diagnosis to familial ALS-Parkinsonism complex.

We performed clinical exome sequencing to identify the underlying genetic variation in the two affected siblings and 1 unaffected member of family (Figure-1a). Other siblings did not give consent for genetic analysis. DNA was extracted from the blood sample and targeted gene capture using a customised capture kit was performed. The DNA libraries were sequenced on the Illumina sequencing platform and aligned to the human reference genome (GRCh37/hg19). A pathogenic, homozygous, nonsense variation (c.1195G > T, p.Glu399Ter, Figure-1b) was identified in the exon 12 of the *OPTN* gene (ENST00000378748) that results in premature truncation of the protein product (CADD score = 38). This variant is not reported from ethnically matched controls (n = 6028) and publically available databases.

Mutation in *OPTN* gene are implicated only in a small proportion (< 1%) of ALS and has heterogeneous clinical phenotypes [1,2]. To the best of our knowledge, a phenotype with features of PSP-CBS and ALS in relation to *OPTN* mutation has never been reported [2–4]. Other known phenotypes of *OPTN* related FALS such as FTD, glaucoma, and Paget's disease were absent in both siblings at the time of presentation. This case-report expands the phenotypic manifestations of *OPTN* mutation to include a PSP-CBS like presentation. However, an important shortcoming is the lack of genetic data of the unaffected siblings to unequivocally demonstrate segregation with the phenotype.

The *OPTN* gene is an autophagy regulator and may have profound effect on disorders associated with protein accumulation when mutated. *OPTN* mutations are known to disrupt the normal interaction between optineurin and associated proteins such as ubiquitin and TBK1 leading to an aggregation of different degenerative proteins such as TDP-43 and tau. Furthermore, *OPTN* also interacts with PINK1-Parkin,

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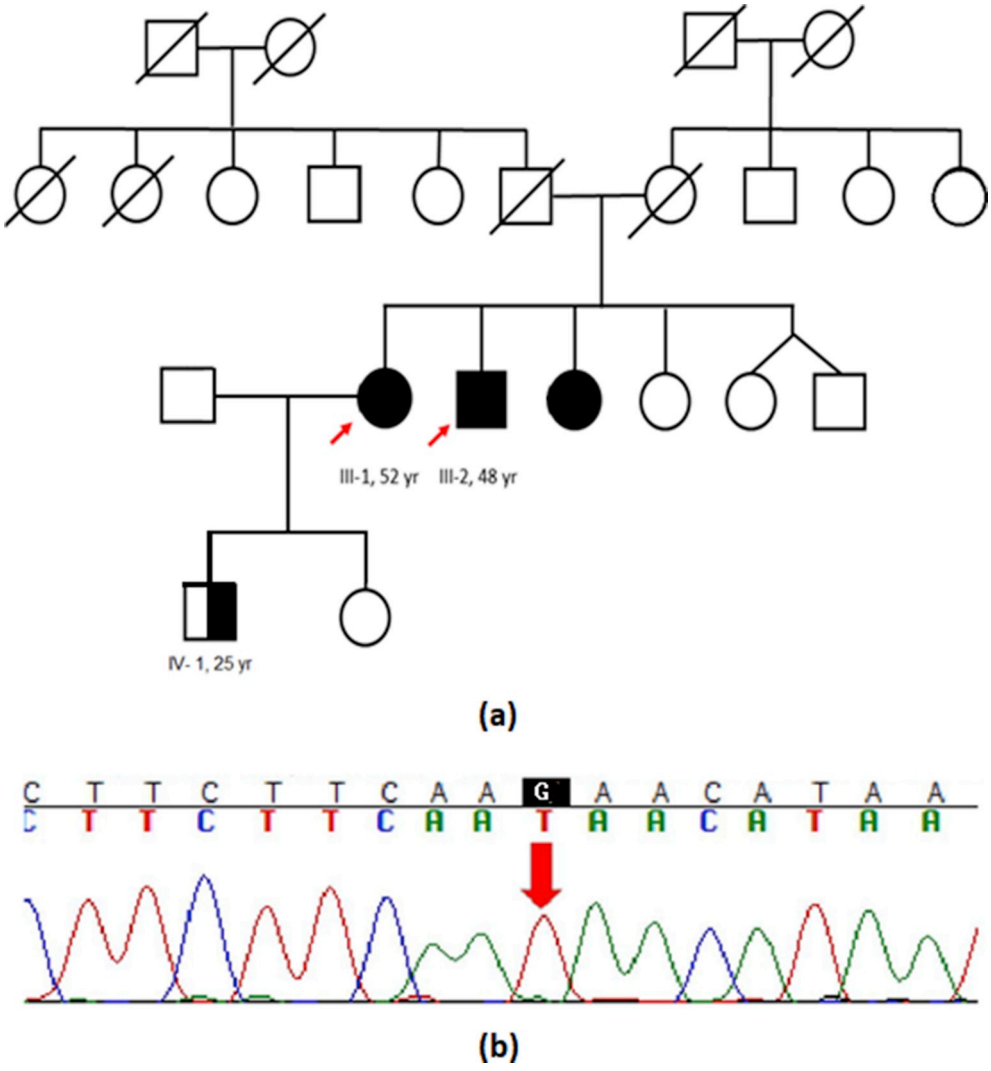

Figure-1. The genealogical tree and sequence chromatograms of the patients.
(a) The genealogic tree of the family. Square = male; circle = female; diagonal blackline = deceased; black filled symbol = affected; empty symbol = clinically healthy relative; red arrow = proband. Numbers show age at time of the study or age at death.
(b) Sequence chromatogram and alignment to the reference sequence showing the variation c.1195G > T in exon 12 of the OPTN gene. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

which can modulate alpha-synuclein deposition. Hence, *OPTN* has a critical regulatory role in disorders with tau, TDP43 and alpha-synuclein pathology and may lead to variable clinical presentations [4,5]. To conclude, *OPTN* related FALS may have diverse clinical phenotypes and calls for meticulous clinical examination and a high index of suspicion.

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Declaration of competing interest

The authors report no financial interests or conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.11.003.

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