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CASE REPORT

Young-Onset Parkinson's Disease with Impulse Control Disorder Due to Novel Variants of F-Box Only Protein 7

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ABSTRACT

F-box only protein 7 (*FBXO7*) is a rare monogenic cause of hereditary Parkinson's disease (PD) with an autosomal recessive mode of inheritance and a broad spectrum of clinical manifestations. Here, we report a *de novo* PD patient with onset at the age of 28 with novel compound heterozygous variants in the *FBXO7* gene (c.1162C>T, p.Gln388X; c.80G>A, p.Arg27His). The clinical features of the patient were problematic impulse control disorder behaviors and pyromania, and pyramidal signs were negative. We describe the novel pathogenic variants of the *FBXO7* gene with detailed clinical pictures to report the expanding genotypes and phenotypes of *FBXO7*-associated parkinsonism.

Key Words Fbxo7 protein; Impulse control disorders; Koreans; Parkinson's disease.

The F-box only protein 7 (*FBXO7*, *PARK15*) gene is a rare monogenic cause of autosomal recessive juvenile Parkinson's disease (PD) originally described as a parkinsonian-pyramidal syndrome. Since genome-wide linkage analysis first revealed a disease-associated variant in the *FBXO7* gene in a consanguineous Iranian family,[1] only seven types of pathogenic variants have been described with a broad spectrum of clinical features.[2] The phenotype associated with the *FBXO7* mutations was reported as early-onset (median age at onset 17 years, ranging from 10 to 52 years) and akinetic-rigidity dominant parkinsonism showing a variable levodopa response with frequent treatment-related complications such as severe dyskinesia and psychosis.[3-5] Apart from pyramidal signs, atypical features have been reported, including mental retardation, eyelid apraxia, supranuclear gaze palsy, and chorea. Recently, rare variants and likely pathogenic variants of the *FBXO7* gene were screened from young-onset PD (YOPD) patients in Korea, but detailed clinical information has not yet been described.[6] In this study, we report a case of YOPD carrying novel compound heterozygous pathogenic variants of *FBXO7* with a genetic analysis of his family members.

CASE REPORT

In 2014, a 28-year-old male complained of left-hand tremor and slow movements. He denied any prodromal symptoms of rapid-eye movement sleep behavior disorder, hyposmia, constipation, or depression. He had no family history of parkinsonism (Figure 1A). In 2015, he was diagnosed with YOPD at another hospital after a year of symptoms, and his initial brain magnetic resonance imaging was unremarkable, while dopamine transporter uptake showed a severe and symmetric decrease (Figure 1B). According to medical records from other hospitals, dopa-

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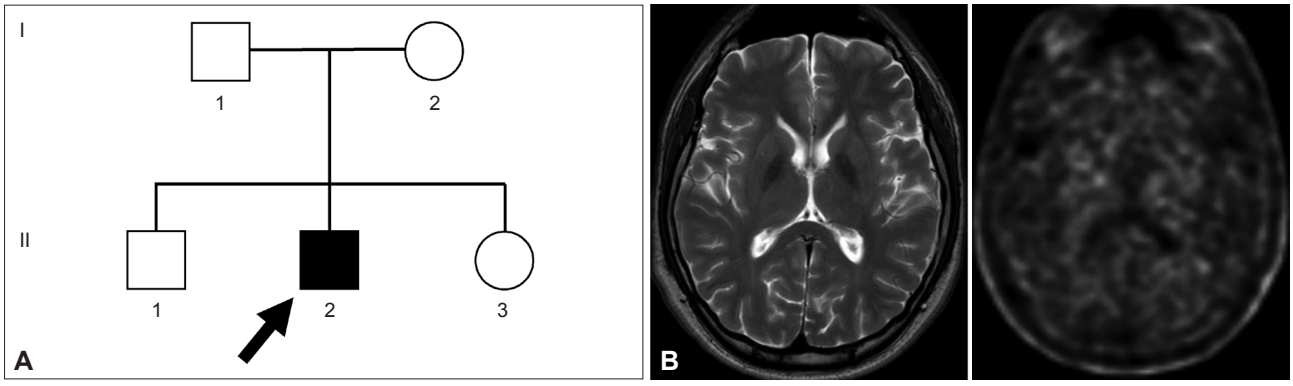

Figure 1. Pedigree and brain imaging of the index case. A: Pedigree of the family. B: Normal brain MRI (left) and ^{18}F-FP-CIT PET (right) showing severe loss of dopamine transporter uptake in the proband. MRI: magnetic resonance imaging, ^{18}F-FP-CIT PET: ^{18}F-*N*-3-Fluoropropyl-2β-carbon ethoxy-3β-4-iodophenyl nortropane positron emission tomography.

minergic medications showed a mild benefit, but he developed delusions and an addiction to mobile games after adding 300 mg of levodopa a day to 1 mg of rasagiline, 0.75 mg of extended-release pramipexole, and 300 mg of amantadine a day. His family members explained that the patient did not show delusions after withdrawal of levodopa. In September 2017, at 31 years of age, he first visited our clinic, and a neurologic examination showed symmetric akinetic-rigid parkinsonism and subjective cognitive impairment (Mini-Mental State Examination score 29 of 30, Frontal Assessment Battery score 16 of 18, 16 years of education). Ocular motor examination showed saccadic hypometria and cogwheel pursuit without gaze limitation. Pyramidal signs were absent, and autonomic dysfunctions were excluded. Although he denied subjectively decreased olfaction, a Brief Smell Identification Test scored 6, which was classified as hyposmia. Although levodopa had been withdrawn due to a provocation of psychosis from the previous hospital, we decided to add levodopa again and gradually increased the dose to alleviate severe off motor symptoms, which limited his activities of daily living. In December 2017, three months after being administered the levodopa, we were informed that he was on trial for arson. He admitted impulsive thinking and behavior such as setting fire to a building or trespassing into a house to set a fire. The problematic impulse control disorder (ICD) behaviors improved after discontinuing the levodopa, adding 25 mg of quetiapine and tapering down the extended-release pramipexole from 0.75 mg to 0.375 mg a day.

In April 2018, we sequenced a 22-gene panel associated with PD (*ATP13A2, ATP1A3, DCTN1, DNAJC13, EIF4G1, FBXO7, GBA, GCH1, GRN, LRRK2, MAPT, PARK2, PARK7, PINK1, PLA2G6, SLC20A2, SNCA, SPG11, SPG15, TAF1, UCHL1, VPS35*) and identified previously unreported compound heterozygous variants of the *FBXO7* gene (NM_012179.3): c.1162C>T (p.Gln388X) and c.80G>A (p.Arg27His). The missense variant (p.Arg27His) was predicted to be disease causing (score: 0.985) by Mutation Taster (http://www.mutationtaster.org) and probably damaging (score: 0.959) by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/). The Combined Annotation-Dependent Depletion (CADD) score of the variant was 23.9. Genetic evaluations of asymptomatic family members showed that each allele was inherited from each parent (Table 1), and the two siblings only carried the missense variant (p.Arg27His). Detailed clinical evaluations confirmed that all monoallelic carriers of the *FBXO7* pathogenic variants were free of neurologic symptoms or signs. Because subject I-1 showed mild parkinsonian signs rating a total Unified Parkinson's Disease Rating Scale motor score of 2 in only the items for bradykinesia, we did not judge his motor signs as clinically significant. According to the American College of Medical Genetics and Genomics (ACMG) Guidelines, we classified the nonsense variant as pathogenic (PVS1, PM5, and PM6) and the missense variant as likely pathogenic: a rare allele frequency, 0.00072% of the population and 0.01% of east Asians,

Table 1. Summarized genetic and clinical features of the patient and asymptomatic family members

	I-1	I-2	II-1	II-2 (proband)	II-3
Sex/age (yr)	M/64	F/63	M/34	M/32	F/25
FBXO7 gene					
c.1162C>T, p.Gln388X	+			+	
c.80G>A, p.Arg27His		+	+	+	+
B-SIT	11	9	10	6	9
Education (yr)	11	11	16	16	16
MMSE	28	25	30	29	30
MoCA	20	25	30	27	30
NMSS	NA	NA	NA	24	NA
UPDRS I	NA	NA	NA	2	NA
UPDRS II	NA	NA	NA	8	NA
UPDRS III	2	0	0	25	0
Hoehn and Yahr	1	0	0	2	0

B-SIT: Brief Smell Identification Test, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, NMSS: Non-Motor Symptoms Scale, UPDRS: Unified Parkinson's Disease Rating Scale.

referenced by The Genome Aggregation Database and located in the ubiquitin-like domain (Ubl), possibly leading to a common pathogenic mechanism of disease (PM2, PM3, PP2, and PP4).

This study was approved by the local Institutional Ethics Committee (IRB No. 1812-106-995), and written informed consent was obtained from the participants.

DISCUSSION

In this study, we report a case of YOPD with novel pathogenic variants in the *FBXO7* gene: a nonsense (c.1162C>T, p.Gln388X) and a missense (c.80G>A, p.Arg27His) variant. The symmetric akinetic-rigid form of parkinsonism was slightly responsive to levodopa, but serious ICD limited medical treatment. Unlike most cases of *FBXO7*-associated parkinsonism, pyramidal signs were absent.

The *FBXO7* gene encodes a member of the F-box protein family, which has a role in the ubiquitin-proteasome system (UPS) and potentially targets key molecules in mitochondrial function.[7] The *FBXO7* protein functions as an adaptor protein in the Skp-Cullin-F-box ubiquitin E3 ligase complex to facilitate ubiquitination and degrade substrates. It can also modulate mitochondrial motility, biogenesis, bioenergetics and mitophagy through interaction with mitochondrial regulators, e.g., glycogen synthase kinase 3β. Impairment of UPS and mitochondrial function could result in the accumulation of misfolded and harmful protein aggregates and the generation of reactive oxygen species, leading to neuronal cell damage, which is a common potential pathogenic mechanism of neurodegenerative disorders.

The *FBXO7* protein has two isoforms: isoform 1 has five functional domains with 522 amino acids, while isoform 2 lacks the N-terminal Ubl domain.[8] Isoform 1 of *FBXO7* is likely to be dominant in humans and evolutionarily preserved. In our case, the missense variant was located in the Ubl region, and three missense mutations and one splicing variant of *FBXO7* have been previously reported to be associated with the same domain.[2] The other truncating mutation is found in the C-terminal proline rich region, in which the most common mutation of *FBXO7*, c.1492C>T, p.R498X, is also located. The role of these two novel variants remains to be demonstrated in further functional studies to understand how they trigger neurodegeneration.

To date, 27 patients with *FBXO7*-related parkinsonism have been listed from 11 families with 7 different types of mutations.[9] Among the cardinal symptoms of PD, the most frequent presenting symptoms and signs were bradykinesia and tremors. One-third of the patients responded well to levodopa medication (n = 6 of 18 reported). Among the atypical symptoms, pyramidal signs were frequent (n = 19 of 26 reported) because the *FBXO7* gene was first identified in a large family with parkinsonian-pyramidal syndrome. Of note, psychiatric symptoms were prominent as complications of dopaminergic treatment, although they have not been thoroughly investigated (n = 11 of 11 reported). Psychiatric features vary in patients with *FBXO7* mutations: visual hallucination, agitation, aggression, manic behavior, disinhibition, episodic crying jags, obsessive compulsive behavior, and ICD (shopping, hypersexuality, and punding) under a mild to moderate dose of levodopa-equivalent daily dose (LEDD) (range 150−500 mg a day).[2,3,5,10] In our case, the patient developed problematic ICD behaviors and pyromania with 775 mg of LEDD. Therefore, the *FBXO7* gene might be included among the differential genetic causes in YOPD patients presenting atypical psychiatric behaviors.

In conclusion, we added a case of *FBXO7*-associated parkinsonism with new pathogenic variants. The salient clinical feature of the case was severe ICD behaviors with a small dose of dopamine agonist and levodopa treatment. In clinical practice, more attention is necessary to monitor the development of medication-induced psychiatric symptoms and to rapidly manage behavioral changes in patients with *FBXO7* mutations.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Dallah Yoo, Beomseok Jeon. Data curation: Dallah Yoo, Ji-Hyun Choi, Jin-Hee Im, Man Jin Kim. Formal analysis: Dallah Yoo, Man Jin Kim, Han-Joon Kim, Sung Sup Park, Beomseok Jeon. Methodology: Dallah Yoo, Han-Joon Kim, Beomseok Jeon. Project administration: Dallah Yoo, Beomseok Jeon. Visualization: Dallah Yoo. Writing—original draft: Dallah Yoo. Writing—review & editing: Dallah Yoo, Ji-Hyun Choi, Jin-Hee Im, Man Jin Kim, Han-Joon Kim, Sung Sup Park, Beomseok Jeon.

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