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.

CASE REPORT

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.4 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.

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-
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 (ATP1A2, ATP1A3, DCTN1, DNAJC13, EIF4G1, FBXO7, GBA, GCH1, GRN, LRRK2, MAPT, PARK2, PARK7, PINK1, PLA2G6, SLC20A2, SNCA, SPS11, SPS15, 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.
Novel FBXO7 variants in YOPD with ICD
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Among the cardinal symptoms of PD, the most frequent present- 
were absent.

The FBXO7 gene encodes a member of the F-box protein fam-
ly, 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 ubiquiti-

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.
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and potentially targets key molecules in mitochondrial function.7 
The FBXO7 protein functions as an adaptor protein in the Skp-
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