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CASE REPORT

Nearly Abolished Dopamine Transporter Uptake in a Patient With a Novel *FBXO7* Mutation

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ABSTRACT

Mutations in the F-box only protein 7 (*FBXO7*) gene are the cause of autosomal recessive parkinsonian-pyramidal syndrome. Herein, we report a patient with a novel *FBXO7* mutation with a unique clinical presentation. A 43-year-old male visited our hospital with complaints of progressing gait disturbance since a generalized tonic clonic seizure. There were no past neurological symptoms or familial disorders. Neurological examination revealed bradykinesia, masked face, stooped posture, parkinsonian gait, and postural instability. The bilateral uptake by dopamine transporters was nearly abolished, as determined by N-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET). Next-generation sequencing revealed a heterozygous c.1066_1069delTCTG (p.Ser356ArgfsTer56) frameshift variant and a heterozygous c.80G>A (p.Arg27His) missense variant of the *FBXO7* gene. The patient's specific clinical features, medication-refractory parkinsonism and seizures further broaden the spectrum of *FBXO7* mutations. The nearly abolished dopamine transporter uptake identified by ^{18}F-FP-CIT PET is frequently found in patients with *FBXO7* mutations, which is different from the usual rostrocaudal gradient that is observed in patients with Parkinson's disease.

Keywords Dopamine transporter; *FBXO7* mutation; Genetic parkinsonism; PET.

Mutations in the F-box only protein 7 (*FBXO7*) gene are the cause of autosomal recessive parkinsonian-pyramidal syndrome (PARK15, OMIM 260300). These gene mutations were first reported in 2008, and only 35 cases in 17 families have been reported.[1] Clinically, medication-responsive young-onset parkinsonism with pyramidal signs is predominant, and various clinical symptoms, such as dystonia, chorea, perioral myoclonus, slow saccade, upgaze palsy, cognitive decline, and hallucination, have been reported (Supplementary Table 1 in the online-only Data Supplement).

Herein, we report a patient with a novel *FBXO7* mutation with a unique clinical presentation. We summarize the updated clinical characteristics of the mutation and discuss the nearly complete loss of dopamine transporter uptake, identified by a functional neuroimaging, in *FBXO7* mutations.

CASE REPORT

A 43-year-old male patient presented with a gait disturbance that had progressed for 10 months before the first visit. The patient grew up without any problems after having 5 to 6 afebrile seizure events before 2 years of age. He had exotropia, which developed in childhood. After graduating from university, he completed his Korean military duty service without any problems. Ten months before the visit to our hospital, he experienced a generalized tonic clonic seizure for approximately 20 minutes. Due to this seizure, he was sent to the emergency room of an-

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other hospital and was admitted for treatment of status epilepticus. Electroencephalography (EEG) did not show any abnormal findings, but he was prescribed levetiracetam 1,000 mg and lacosamide 50 mg two times per day. After discharge, the patient started to show abnormal behaviors such as stubborn personality, reduced communication, and new hobbies, such as fishing, which he had not done before. He also showed gait disturbance. At the next outpatient visit to that hospital, he was suspected to have parkinsonism and started anti-parkinsonian medications. The treatments were not effective, and he came to our outpatient clinic. The patient had a brother and sister who were normal. The parents said that the patient was normal before this seizure event but developed the problems since then. He had mild constipation but did not have other autonomic dysfunctions, hyposmia or rapid eye movement sleep behavior disorder.

Neurological examination revealed that the patient had exotropia, bradykinesia, masked face, stooped posture, parkinsonian gait, and postural instability (Supplementary Video 1 in the online-only Data Supplement). There was no rigidity or resting tremor, and the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III score was 14 points. The patient had no pyramidal signs or dystonia. The cognitive function test showed mild cognitive decline with a Mini-Mental Status Exam (MMSE) score of 28, a Montreal Cognitive Assessment score of 21, and a Clinical Dementia Rating (CDR) of 0.5 (sum-of-box 1.5). In brain magnetic resonance imaging (MRI), bilateral hypointensities in both globus palliduses were found in the susceptibility weighted imaging (SWI) sequence (Figure 1A and B). The bilateral dopamine transporter uptake was nearly eliminated, as determined by an N-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET) scan (Figure 1C). EEG and laboratory tests, including screening for Wilson disease, were normal.

Next-generation sequencing was performed on 340 target

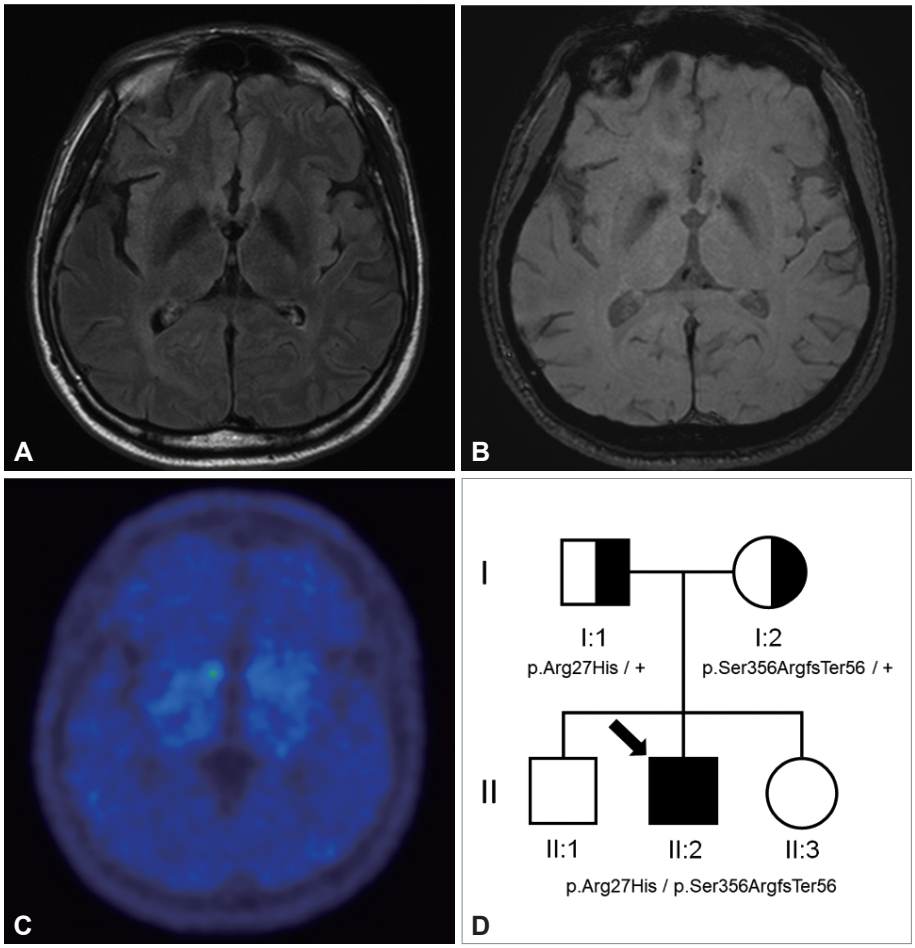

Figure 1. Neuroimaging findings and pedigree of the index patient. A: FLAIR sequence of the brain MRI showing no abnormal findings. B: Bilateral hypointensities were found in both pallidum in the SWI sequence. C: ^{18}F-FP-CIT PET shows the loss of dopamine transporters in the whole striatum. D: The pedigree shows that the *FBXO7* frameshift and missense variants were inherited in trans. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging; ^{18}F-FP-CIT, N-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane; PET, positron emission tomography; FBXO7, F-box only protein 7.

genes to identify the genetic cause of his young-onset parkinsonism. These genes included *ATP13A2, CHMP2B, COQ2, C9orf72, DCTN1, DNAJC6, EIF4G1, GBA, GIGYF2, GRN, HTRA2, LRRK2, MAPT, PARK2, PARK7, PDE8E, PDGFB, PINK1, PLA2G6, POLG, SLC6A3, SLC20A2, SLC30A10, SMPD1, SNCA, SOD1 SPG11, TH, UCHL1, VPS35,* and *FBXO7*. A heterozygous c.1066_1069delTCTG (p.Ser356ArgfsTer56) frameshift variant and a heterozygous c.80G>A (p.Arg27His) missense variant of the *FBXO7* gene were found. Segregation analysis showed that the *FBXO7* p.Ser356ArgfsTer56 frameshift variant and the p.Arg27His missense variant were inherited from the mother and father, respectively (Figure 1D). p.Ser356ArgfsTer56 was not reported in the Asian population, and it was identified as a pathogenic variant as PM2 and PM3 in PVS1 according to the American College of Medical Genetics and Genomics guidelines. The p.Arg27His missense variant was reported previously in a Korean patient with *FBXO7* mutations.[2] The minor allele frequency in the Asian population was 0.009% (gnomAD East Asian). It was predicted to be tolerated by SIFT and probably damaging by Polyphen-2 in in silico analyses. The p.Arg27His missense variant was classified as likely pathogenic (PS1, PM2, and PM3). These compound heterozygous variants are thought to be the genetic cause of the condition in this patient.

The patient received levodopa 150 mg three times a day, pramipexole extended release form 0.75 mg and amantadine 100 mg two times a day, but there was no improvement in his symptoms. However, he showed complications such as aggressive behavior, somnolence, and impulse control disorder to gaming and shopping. Therefore, we could not increase the doses of antiparkinsonian medications. One year later, the patient's gait abnormality had worsened, and his cognitive function deteriorated, making him more stubborn and forgetful. In the follow-up cognitive function test, there was marked dysfunction in visuospatial function, memory, and frontal/executive function on the Seoul Neuropsychological Screening Battery with MMSE 29, CDR 0.5 (sum-of-box 4.5).

DISCUSSION

The patient was diagnosed with young-onset parkinsonism with a p.Ser356ArgfsTer56 novel frameshift and a p.Arg27His missense variant in the *FBXO7* gene. Interestingly, the nearly complete loss of dopamine transporter uptake that was identified by ^{18}F-FP-CIT PET in this case has been reported in previous case reports, and all but one of these cases harbored a *FBXO7* mutation.[2-5] The only case with normal uptake showed divergent clinical characteristics, such as infantile onset, epilepsy, cerebellar degeneration, spastic paraplegia and parkinsonism.[5] This phenotypic heterogeneity might be based on differences in gene expression and brain dysfunction, which explains the normal dopamine transporter uptake.

In patients with Parkinson's disease (PD), the signals of dopamine receptor uptake are maintained to some extent in the striatum, such as the anterior portion of the putamen and caudate, regardless of the severity of symptoms.[6] This rostrocaudal gradient pattern is also found in genetic parkinsonism caused by *LRRK2, SNCA, GBA, VPS35,* and *ATP1A3* mutations.[7] In contrast, patients with *PINK1* and *DCTN1* mutations or spinocerebellar ataxia types 2 and 3 may show a homogeneously decreased pattern similar to our case.[7,8] This pattern suggests a more widespread dopaminergic denervation and different pathophysiologic progress in patients with these genetic mutations.[9] Therefore, the loss of dopamine uptake in this case is a characteristic finding of *FBXO7* mutations and several other genetic causes of parkinsonism, which is different from the usual rostrocaudal gradient that is observed in patients with idiopathic PD.

This patient also had unique clinical characteristics that are different from those of previous reports. 1) There was a seizure event at the onset of symptoms. 2) There was a poor medication effect. 3) Brain MRI showed globus pallidus hypointensity on SWI.

Seizures have only been reported in one case thus far.[5] FBXO7 protein is distributed widely in the frontal, temporal, and occipital cerebral cortex, hippocampus, globus pallidus, substantia nigra, and cerebellar cortex of the brain.[10] This topographic distribution can explain seizures with the severe loss of function of the *FBXO7* gene. However, further studies are needed to determine its association with and pathophysiological role in seizures.

In previous studies, the levodopa response was reported in all cases (Supplementary Table 1 in the online-only Data Supplement), except one in a low-dose trial of 100 mg/day.[5] In that case, there were hypointensities in the globus pallidus in the gradient recall echo sequence, which is similar to the present case. These results suggest that severe cases of *FBXO7* mutations present with clinical findings of neurodegeneration with brain iron accumulation (NBIA) spectrum disorder, and levodopa unresponsiveness might result from postsynaptic dysfunction.

In conclusion, this case was a patient with parkinsonism with a unique course due to a novel *FBXO7* mutation. The patient's specific clinical features, medication-refractory parkinsonism and seizures further broadened the spectrum of *FBXO7* mutations. The pallidal hypointensity suggests that the disease exists in the form of an NBIA-related disorder. Finally, the nearly abolished dopamine transporter uptake that was identified by ^{18}F-FP-CIT PET is frequently found in patients with *FBXO7* mutations, and this is different from the usual rostrocaudal gradient that is observed in patients with PD.

Ethics Statement

Informed consent was obtained from the patient for using his case and video for publication purpose.

Supplementary Video Legends

Video 1. The patient shows stooped posture, slightly shuffling gait, masked face, and bilateral hand hypokinesia that were not responsive to levodopa treatment.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22006.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Chaewon Shin. Data curation: Eun Young Kim, Chaewon Shin. Formal analysis: all authors. Funding acquisition: Chaewon Shin. Investigation: Chaewon Shin. Methodology: Eun Young Kim, Chaewon Shin. Project administration: Chaewon Shin. Resources: Seon Young Kim, Youngduk Seo, Chaewon Shin. Software: Chaewon Shin. Supervision: Chaewon Shin. Validation: Eun Young Kim, Chaewon Shin. Visualization: Eun Young Kim, Youngduk Seo, Chaewon Shin. Writing—original draft: Eun Young Kim, Chaewon Shin. Writing—review & editing: all authors.

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Supplementary Table 1. Summary of previous reports with *FBXO7* mutation

	Shojaee et al.[1]	Di Fonzo et al.[2]		Paisan-Ruiz et al.[3]		Yalcin-Cakmakli et al.[4]	Gunduz et al.[5]	Lohmann et al.[6]	Conedera et al.[7]	Wei et al.[8]	Jin et al.[9]	Lorenzo-Betancor et al.[10]	Yoo et al.[11]	Correa-Vela M[12]	Wang et al.[13]	This study	Total	Frequency (%)
Reported year	2008	2009		2010		2014	2014	2015	2016	2018	2020	2020	2020	2020	2021	2022		
Family no.	1	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	18	
No. of cases	10	2	2	3	1	2	2	2	1	1	2	3	1	1	2	1	36	
Zygosity	Homozygote	Homozygote	Compound heterozygote	Homozygote	Homozygote	Homozygote	Homozygote	Homozygote	Homozygote	Compound heterozygote	Compound heterozygote	Compound heterozygote	Compound heterozygote	Homozygote	Compound heterozygote	Compound heterozygote		
Mutation																		
Mutation 1	R378G	R498X	IVS7+1G/T	R498X	R498X	R498X	R498X	L34R	R498X	N51S	W134X	G39R	Q388X	S123X	R345P	S356RfsTer56		
Mutation 2	R378G	R498X	T22M	R498X	R498X	R498X	R498X	L34R	R498X	E470X	IVS5-1G>A	L280fs	R27H	S123X	R345P	R27H		
Country of origin	Iran	Italy	Netherlands	Pakistan	Turkey	Turkey	Turkey	Turkey	Turkey	China	China	Yemen	Korea	Morocco	China	Korea		
Clinical findings																		
Sex	F 2, M 8	F, M	F, M	F 3, M 1		F, M	F, M	F, M	F	M	M 2	F 2, M	M	F	F, M	M		
AAO		10, 13	18, 19	17, 24, 22	17	14, 10	13, 17	52, 41	17	16	6 mo, 6 mo	21, 27, 30	28	2	30, 31	42		
Parkinsonism																		
Rigidity	3	2	2	3	1	2	2	2	1	1	2	3	0	1	2	1	28	77.8
Bradykinesia	3	2	2	3	1	2	2	2	1	1	NA	3	1	1	2	1	27	79.4
Rest tremor	0	2	1	0	0	1	1	2	1	1	NA	1	1	NA	1	0	12	36.4
Postural instability	3	2	2	3	1	2	2	2	1	0	NA	2	0	NA	2	1	23	69.7
Dystonia	NA	2	0	1	0	0	1	0	0	0	NA	2	0	NA	1	0	7	30.4
Pyramidal signs																		
Babinski signs	10	2	2	3	0	0	1	NA	0	1	NA	0	0	NA	1	0	20	64.5
Spasticity	10	2	0	NA	NA	0	NA	NA	NA	NA	2	0	0	NA	2	0	16	69.6
Hyperactive DTR	10	2	2	3	0	0	1	0	0	1	NA	0	0	NA	1	0	20	60.6
Cognitive decline	0	0	0	3	0	2	1	0	1	1	2	2	0	1	1	1	15	41.7
Other signs		Dysarthria, dysphagia, slow saccades, urinary/fecal incontinence, reduced upgaze	Slow saccades, dysphagia, reduced upgaze	Apraxia of eye opening, supranuclear gaze palsy, slow saccades, swallowing difficulty		Periporal myoclonus, tongue protrusion, psychosis	Chorea, tic, tachphemia, ICD	pRBD, hallucination	Slow saccades				Saccadic hypometria, cogwheel pursuit, hyposmia	Acute ataxia, kinetic tremor, upgaze limitation, absence epilepsy, paraplegia, dysphagia, optic neuropathy		Seizure, abnormal behavior		
Treatment																		
Levodopa response	Responsive 1/ no trial 2/NA 7	2	2	3	1	2	2	2	1	1	NA	Responsive 2/ no trial 1	1	0	2	0	19	88.0
Motor fluctuation	NA	2	2	NA	0	NA	NA	NA	1	0	NA	1	NA	NA	NA	0	6	31.6
Dyskinesia	NA	2	2	3	1	2	NA	NA	0	0	NA	1	NA	NA	NA	0	11	57.9
Complications	NA	Behavioral disturbances 2	Behavioral disturbances 2	Mood disorder 1	Pyschosis, agitation	Psychosis, agitation, ICD	ICD	Hallucination	ICD, aggression, disinhibition	Manic behavior	NA	Aggressive behavior	Delusion, ICD		Gastrointestinal symptoms	Aggressive behavior, ICD, somnolence		
Imaging																		
MRI	Normal	Normal	Normal	General atrophy 2	Normal				Temporal atrophy	Mild general atrophy	Normal	Normal	Normal	Iron accumulation both pallidum	Moderate hippocampal and extensive cortical atrophy	Normal		
PET/SPECT			CIT SPECT no uptake		CIT PET no uptake									CIT PET no uptake	DaTSCAN normal	CIT PET no uptake	4	

NA, not available; AAO, age at onset; DTR, deep tendon reflex; pRBD, probable rapid eye movement sleep disorder; ICD, impulse control disorder; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; CIT, N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane.

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