Published in final edited form as:

Parkinsonism Relat Disord. 2020 November ; 80: 142–147. doi:10.1016/j.parkreldis.2020.09.035.

Novel compound heterozygous *FBXO7* mutations in a family with early onset Parkinson's disease

Oswaldo Lorenzo-Betancor^{#a,b}, Yi-Han Lin^{#a,b}, Ali Samii^{a,b}, Suman Jayadev^b, Hojoong M. Kim^{a,b}, Katelan Longfellow^{a,b,2}, B. Jane Distad^b, Dora Yearout^a, Ignacio F. Mata^{a,b,3}, Cyrus P. Zabetian^{a,b,*}

^aVeterans Affairs Puget Sound Health Care System, Seattle, WA, USA

^bDepartment of Neurology, University of Washington School of Medicine, Seattle, WA, USA

[#] These authors contributed equally to this work.

Abstract

Background: Mutations in the *F-box protein 7 (FBXO7)* gene result in autosomal recessive parkinsonism. This usually manifests as early-onset parkinsonian-pyramidal syndrome but patients exhibit high phenotypic variability. Here we describe the findings of a Yemeni family with two novel *FBXO7* mutations.

Methods: Clinical data and DNA were available for three siblings with early-onset parkinsonism together with their parents and three unaffected siblings. A targeted next generation sequencing panel was used to screen the proband for mutations in 14 genes known to cause a parkinsonian disorder. In addition, *SNCA*, *PARK2*, *PINK1*, and *PARK7* were screened for copy number variants.

Results: The proband carried two novel compound heterozygous *FBXO7* mutations: a missense mutation in exon 1 (p.G39R; c.115G > A) and a frameshift mutation in exon 5 (p.L280fs; c.838del). The mutations segregated with disease in the family with the exception of a potentially pre-symptomatic individual whose age was below the age of onset in two of their three affected siblings. P.G39R occurred at a highly conserved amino acid residue and both mutations were predicted to be deleterious in silico. In contrast to most reported families, the phenotype in this pedigree was consistent with clinically typical Parkinson's disease (PD) with a lack of pyramidal signs and good response to dopaminergic therapy.

Conclusions: Our study expands the phenotype associated with *FBXO7* to include early-onset PD and broadens the list of causative mutations. These data suggest that *FBXO7* should be

* Corresponding author. Geriatric Research, Education, and Clinical Center, VA Puget Sound Healthcare System, 1660 S. Columbian Way, Seattle, WA, 98108, USA. zabetian@uw.edu (C.P. Zabetian).

²Present affiliation: Franciscan Neurology Associates at St. Joseph, Tacoma, WA, USA.

³Present affiliation: Lerner Research Institute, Genomic Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA.

Declaration of competing interest

The authors report no conflict of interest related to this work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.parkreldis.2020.09.035>.

included in clinical genetic testing panels for PD, particularly in patients with early onset or a recessive inheritance pattern.

Keywords

FBXO7; Genetics; Mutation; Parkinson's disease; Parkinsonism

1. Introduction

In 2008 mutations in the *F-Box Protein 7 (FBXO7)* gene were reported to cause a rare autosomal recessive condition known as parkinsonian-pyramidal syndrome (PPS; PARK15; OMIM 260300) in an Iranian pedigree [1]. Individuals with PPS typically present in the 2nd to 3rd decade with levodopa-responsive parkinsonism and pyramidal signs such as increased deep tendon reflexes, extensor plantar responses, pyramidal weakness, and spasticity. Other features sometimes present include cognitive impairment, upward gaze palsy, dysarthria, dysphagia, and dystonia [2–6]. Over time, the spectrum of disease phenotypes associated with *FBXO7* has broadened. Of the nine families reported to date, six had PPS [1,3–7] but three lacked pyramidal findings altogether [2,4,8]. Two of the families without pyramidal signs displayed early-onset, atypical parkinsonism [2,4] and one had features consistent with Parkinson's disease (PD) with onset of symptoms in the 5th to 6th decade [8].

In the present study we describe a Yemeni family with early onset, recessive parkinsonism but without pyramidal features. Affected members of the family share two novel compound heterozygous *FBXO7* mutations. We compare the phenotype of this pedigree with that reported for other families with *FBXO7*-related parkinsonism.

2. Methods

2.1. Study participants

The family was enrolled in the Parkinson's Genetic Research Study (PaGeR) at the University of Washington and VA Puget Sound Health Care System in Seattle. The study was approved by the Institutional Review Board at both sites and all participants provided written informed consent.

Each individual underwent a full neurological examination performed by a movement disorder specialist and had a blood sample drawn for DNA extraction.

2.2. Targeted sequencing and analysis of copy number variation

Genomic DNA was extracted from peripheral blood or saliva using standard methods. The proband was screened using a targeted next generation sequencing panel which included 14 genes related to disorders in which parkinsonism is a central feature: *ATP13A2*, *DNAJC13*, *EIF4G1*, *FBXO7*, *GBA*, *LRRK2*, *PARK2*, *PARK7*, *PINK1*, *PLA2G6*, *RAB39B*, *SNCA*, *VPS35*, and *SYNJ1*. In addition, *SNCA*, *PARK2*, *PINK1*, and *PARK7* were screened for copy number variation using multiplex ligation-dependent probe amplification (MLPA; MRC-Holland, Amsterdam, Netherlands) as previously described [9]. Candidate variants identified in the panel were assessed for co-segregation with disease by Sanger sequencing

in all available family members. Additional details about the sequencing methods and data processing steps employed in the study are provided in the Supplementary Materials.

3. Results

3.1. Demographics

The family is of Yemeni origin and all of the members who were enrolled immigrated to the US. The proband's parents are not, to their knowledge, related and were born in different villages in Yemen.

3.2. Clinical findings

3.2.1. Individual A01 (proband)—The proband developed unilateral stiffness at age 21 which later became bilateral and progressively worsened such that it severely interfered with her activities of daily living (ADLs). She first presented to a neurologist at age 26 and on examination had bilateral resting tremor in her lower extremities as well as postural and action tremor in her hands. She had moderate to severe bradykinesia and rigidity that were worse on the left. She displayed symmetric normoactive deep tendon reflexes with no clonus, and the Hoffman and Babinski reflexes were absent. During ambulation she had stooped posture, decreased bilateral arm swing with arms held flexed at her side, and took several small steps while turning. Cognition could not be formally assessed because of a language barrier. While she required assistance with ADLs, information collected from her family suggested that this was predominantly due to motor impairment rather than cognitive decline. She had a normal brain MRI. Serum copper and ceruloplasmin, and 24-h urine copper levels were normal. A levodopa trial was initiated with substantial improvement in motor symptoms. However, levodopa was soon discontinued due to aggressive behaviors. She was later started on low-dose ropinirole and rasagiline with a good clinical response. By age 30, her rigidity and bradykinesia had worsened and she had developed marked dystonia. Although she continued to have a good response to ropinirole, higher doses of the medication were not tolerated because of recurrent behavioral aggression. She never displayed medication-induced dyskinesia. Her dystonia was managed with muscle relaxants and periodic botulinum toxin injection.

3.2.2. Individual A02—This individual's symptom onset was at 27 years of age, after her second pregnancy. She reported progressive stiffness, tremor, and gait impairment that eventually began to interfere with her ADLs. She was first assessed by a neurologist at age 30 and on examination had a bilateral action tremor but no resting tremor, and left greater than right moderate to severe bradykinesia and rigidity. She displayed normoactive and symmetric deep tendon reflexes with no clonus, and the Babinski reflex was absent. She ambulated with no arm swing bilaterally and took multiple steps when turning. Cognition was not formally assessed because of a language barrier. A brain MRI was unremarkable and serum copper level was normal. She was later started on levodopa which resulted in a robust improvement in motor symptoms. At subsequent visits her family raised concern that some cognitive decline might have occurred. However, the individual reported that she was able to keep up with schoolwork without difficulty. The treating neurologists suspected that the family's concern might primarily be the result of problems with motor speech control in

the off state rather than true deficits in cognition. Signs of motor parkinsonism progressively worsened and by age 33 she had substantial off-time dystonia. She continued to have an excellent response to levodopa but developed significant motor fluctuations and peak-dose dyskinesia.

3.2.3. Individual A05—This individual first complained of neck tension and forward tilting of his neck at age 30. Within months this was followed by progressive difficulty with handwriting and slowness when performing fine motor tasks. Within a year he developed right-sided tremor that started in his arms and later progressed to his legs, as well as a shuffling gait. At age 32 he was diagnosed with early-onset Parkinson's disease (PD) by a community movement disorder specialist and offered a levodopa trial but declined, choosing instead to pursue alternative treatments. At age 33 he underwent a research examination and was found to have a slight bilateral postural and action tremor but no resting tremor. He had moderate axial rigidity and mild bilateral appendicular rigidity. He had right greater than left mild to moderate bradykinesia. His total MDS-UPDRS III score was 47. He had normal eye movements, normal deep tendon reflexes, an unremarkable gait, and the Babinski reflex was absent. He denied any cognitive changes and his Montreal Cognitive Assessment score was 27/30.

3.2.4. Individual Z02—This individual, the father of the proband, suffered a right brain stroke at age 54 with a residual mild left hemiparesis. Pertinent past medical history included poorly controlled diabetes mellitus type 2 (diagnosed in his late 40s) and congestive heart failure. At age 72 he underwent a research examination and was found to have mild weakness of the left lower face and left upper and lower extremities. Tone was slightly increased at the left elbow, wrist, knee, and ankle. Tone and strength were normal elsewhere. No tremor was observed. Deep tendon reflexes were slightly hyperactive throughout the left upper and lower extremities, normoactive in the right upper extremity and knee, and absent at the right ankle. The Babinski reflex was absent bilaterally. Sensation to light touch and temperature were diminished in the lower extremities in a symmetric, distal-to-proximal gradient consistent with peripheral polyneuropathy. His MDS-UPDRS III score was 18 with all points likely attributable to his prior stroke. Information collected from this individual and his family indicated that his motor deficits had been stable for many years and there were no concerns about cognitive decline.

3.2.5. Individuals Z01, A03, A04, and A08—These individuals were examined by a study neurologist and found to have a normal neurologic examination with MDS-UPDRS III scores of 0 in all instances. There were no concerns of cognitive decline.

3.3. Genetic findings

Analysis of the targeted sequencing panel from the proband revealed two novel mutations in the *FBXO7* gene: a missense mutation in exon 1 (p.G39R; c.115G > A) within the ubiquitin-like domain and a frameshift mutation in exon 5 (p.L280fs; c.838del) within the FP domain (Fig. 1; variants are annotated according to transcript ID number ENST00000266087.7). Neither mutation was present in the Genome Aggregation Database (<https://gnomad.broadinstitute.org>). P.G39R was predicted to be deleterious in silico as evidenced by

a Combined Annotation Dependent Depletion (CADD) score of 26.8. No plausible pathogenic variants meeting our pre-defined criteria (Supplementary Material) were discovered in any other genes on the panel and no copy number variants were observed in *SNCA*, *PARK2*, *PINK1*, or *PARK7* by MLPA. Sanger sequencing of *FBXO7* exons 1 and 5 in the remainder of the family showed that the two mutations occurred in trans to one another and that all three affected members of the pedigree (A01, A02, A05) were compound heterozygotes (Fig. 1). In addition, individual A08 carried both mutations but had an entirely normal neurologic examination. However, the age of this individual at the assessment was less than the age of onset of two of the three affected members of the family.

4. Discussion

In the present paper we describe a Yemeni family in which two novel *FBXO7* mutations segregate with early-onset levodopa responsive parkinsonism in an autosomal recessive pattern. The one exception is a potentially pre-symptomatic individual (A08; Fig. 1) whose age at the last assessment was below the age of onset in two of their three affected siblings. Unlike most of the previous families described with *FBXO7*-related parkinsonism, in our family clear pyramidal signs were lacking and the phenotype was consistent with PD rather than PPS. *FBXO7* mutations have only been reported to cause typical PD in one other family in which age at onset ranged from 41 to 52 [8]. Our family is unique in that while the phenotype is PD, the onset of symptoms occurred between 21 and 30 which is much closer to the age at onset observed in pedigrees with PPS.

A total of seven causative *FBXO7* mutations (four missense, two nonsense, and one splice site) have been reported in the literature, but only one (R498X) has been observed in more than one family. The ancestral origin of the families has varied (e.g. Iran, Turkey, Italy, Netherlands, China) with no preponderance in any single population. The PPS phenotype is the most common but other clinical findings vary across families (Table 1). Associated findings include dystonia [4–6], dysarthria [2–5,7,8], dysphagia [2,4,7], vertical gaze limitation or palsy [4,6,7] and oculogyric crises [4,5]. Many patients had some degree of cognitive impairment [2–6] and psychiatric problems reported include hallucinations/psychosis [2,4,7,8], severe depression [8], and impulse control disorder [5,6].

Mitophagy, the selective autophagy of mitochondria, is an important quality control mechanism that eliminates damaged mitochondria and impairment of this process has been implicated in the pathogenesis of PD [10]. Proteins encoded by two well-studied PD genes, *PINK1* (a mitochondrial kinase), and *Parkin* (an E3 ubiquitin ligase), act in a common pathway to control turnover of mitochondria. *FBXO7*, through its N-terminal ubiquitin-like domain, interacts directly with *Parkin* and recruits it to damaged mitochondria thus promoting mitophagy [11]. A previously reported *FBXO7* missense mutation (p.T22M) in the ubiquitin-like domain has been shown to severely reduce *FBXO7* binding to *Parkin* and inhibit *Parkin* recruitment [11]. One of the two new mutations we observed (p.G39R) occurs nearby in a highly conserved residue within the ubiquitin-like domain (Fig. 1) and thus might disrupt *FBXO7* function through a similar mechanism. The other new mutation we identified (p.L280fs) occurs near the midpoint of the protein and results in a frameshift that affects the functionally important FP, F-box, and proline-rich (Pro-rich) domains. The Pro-

rich domain is critical for maintaining protein stability; an affected individual homozygous for a nonsense mutation (p.R498X) in this region displayed normal mRNA levels but FBXO7 protein was undetectable [12]. More recent evidence suggests that FBXO7 plays important roles in cellular homeostasis independent of Parkin-mediated mitophagy and thus *FBXO7* mutations might influence PD pathogenesis through multiple molecular pathways [13].

In summary, this study expands the phenotype associated with *FBXO7* to include early-onset PD and extends the list of causative mutations. Our data suggest that *FBXO7* should be considered when performing genetic testing for patients with clinically typical PD, particularly those with early onset or with a recessive pattern of inheritance. Further studies will be needed to better understand genotype-phenotype correlation and the distribution of *FBXO7* mutations in PD populations across the world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We sincerely thank all of the individuals who participated in this study.

Funding

This work was funded by a grant from the Department of Veterans Affairs (I01 CX001702) and a gift from the Dolsen Foundation. Dr. Lin and Dr. Longfellow were supported by the Veterans Affairs Advanced Fellowship Program in Parkinson's Disease.

References

- [1]. Shojaaee S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi GA, Fakhrai-Rad H, Ronaghi M, Elahi E, Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays, *Am. J. Hum. Genet* 82 (6) (2008) 1375–1384. [PubMed: 18513678]
- [2]. Yalcin-Cakmakli G, Olgiati S, Quadri M, Breedveld GJ, Cortelli P, Bonifati V, Elibol B, A new Turkish family with homozygous FBXO7 truncating mutation and juvenile atypical parkinsonism, *Park. Relat. Disord* 20 (11) (2014) 1248–1252.
- [3]. Wei L, Ding L, Li H, Lin Y, Dai Y, Xu X, Dong Q, Lin Y, Long L, Juvenile-onset parkinsonism with pyramidal signs due to compound heterozygous mutations in the F-Box only protein 7 gene, *Park. Relat. Disord* 47 (2018) 76–79.
- [4]. Paisan-Ruiz C, Guevara R, Federoff M, Hanagasi H, Sina F, Elahi E, Schneider SA, Schwingenschuh P, Bajaj N, Emre M, Singleton AB, Hardy J, Bhatia KP, Brandner S, Lees AJ, Houlden H, Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations, *Mov. Disord* 25 (12) (2010) 1791–1800. [PubMed: 20669327]
- [5]. Gunduz A, Eken AG, Bilgic B, Hanagasi HA, Bilguvar K, Gunel M, Basak AN, Ertan S, FBXO7-R498X mutation: phenotypic variability from chorea to early onset parkinsonism within a family, *Park. Relat. Disord* 20 (11) (2014) 1253–1256.
- [6]. Conedera S, Apaydin H, Li Y, Yoshino H, Ikeda A, Matsushima T, Funayama M, Nishioka K, Hattori N, FBXO7 mutations in Parkinson's disease and multiple system atrophy, *Neurobiol. Aging* 40 (2016) 192 e1–192 e5.
- [7]. Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia Guedes L, Szczerbinska A, Zhao T, Dubbel-Hulsman LO, Wouters CH, de Graaff E, Oyen WJ, Simons EJ, Breedveld GJ,

- Oostra BA, Horstink MW, Bonifati V, FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome, *Neurology* 72 (3) (2009) 240–245. [PubMed: 19038853]
- [8]. Lohmann E, Coquel AS, Honore A, Gurvit H, Hanagasi H, Emre M, Leutenegger AL, Drouet V, Sahbatou M, Guven G, Erginel-Unaltuna N, Deleuze JF, Lesage S, Brice A, A new F-box protein 7 gene mutation causing typical Parkinson's disease, *Mov. Disord* 30 (8) (2015) 1130–1133. [PubMed: 26010069]
- [9]. Cornejo-Olivas MR, Torres L, Mata IF, Mazzetti P, Rivas D, Cosentino C, Inca-Martinez M, Cuba JM, Zabetian CP, Leverenz JB, A Peruvian family with a novel PARK2 mutation: clinical and pathological characteristics, *Park. Relat. Disord* 21 (5) (2015) 444–448.
- [10]. Ashrafi G, Schwarz TL, The pathways of mitophagy for quality control and clearance of mitochondria, *Cell Death Differ.* 20 (1) (2013) 31–42. [PubMed: 22743996]
- [11]. Burchell VS, Nelson DE, Sanchez-Martinez A, Delgado-Camprubi M, Ivatt RM, Pogson JH, Randle SJ, Wray S, Lewis PA, Houlden H, Abramov AY, Hardy J, Wood NW, Whitworth AJ, Laman H, Plun-Favreau H, The Parkinson's disease-linked proteins Fbxo7 and Parkin interact to mediate mitophagy, *Nat. Neurosci* 16 (9) (2013) 1257–1265. [PubMed: 23933751]
- [12]. Zhao T, De Graaff E, Breedveld GJ, Loda A, Severijnen LA, Wouters CH, Verheijen FW, Dekker MC, Montagna P, Willemsen R, Oostra BA, Bonifati V, Loss of nuclear activity of the FBXO7 protein in patients with parkinsonian-pyramidal syndrome (PARK15), *PloS One* 6 (2) (2011), e16983. [PubMed: 21347293]
- [13]. Randle SJ, Laman H, Structure and function of fbxo7/PARK15 in Parkinson's disease, *Curr. Protein Pept. Sci* 18 (7) (2017) 715–724. [PubMed: 26965690]

Fig. 1.

A. Simplified pedigree. Arrowhead = proband; AAO = age at onset; NA = not available; WT = wild type allele. Age is age at the last assessment. To disguise the identity of unaffected individuals in the youngest generation, sex is not shown (diamond shapes), position in the pedigree is not in birth order, and ages are only provided as a range. **B.** Summary of mutations in relation to FBXO7 protein domains. Previously described mutations (upper) and the compound mutations found in the present family (lower) are mapped to the known FBXO7 protein domains. Ub-like = ubiquitin-like; CDK = cyclin dependent domain (CDK6 interaction); FP = Fbxo7/PI31 domain (important for dimerization and interaction with PSMF1 –proteasome inhibitor subunit 1- protein); PINK1 = PTEN-induced kinase 1; Pro-rich = proline-rich domain. **C.** Amino acid sequence alignment of the FBXO7 protein

generated with Jalview showing that glycine at position 39 (red arrow) is highly conserved across vertebrate species. The conservation histogram reflects conservation of the physico-chemical properties for each alignment column; absolutely conserved residues (score 11) are indicated by a yellow asterisk. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1

Clinical characteristics of families with FBXO7-related parkinsonism.

	Shojaee et al., 2008	Di Fonzo et al., 2009	Paisan-Ruiz et al., 2010	Yalcin-Cakmakli et al., 2014	Gunduz et al., 2014	Lohmann et al., 2015	Conedera et al., 2016	Wei et al., 2017	Present study
Number of families	1	2	2	1	1	1	1	1	1
Number of affected individuals	10	2	3	2	2	2	1	1	3
Allele	R378G	R498X	T22 M	R498X	R498X	L34R	R498X	N51S	G39R
Allele	R378G	R498X	c.1144+1G > T	R498X	R498X	L34R	R498X	E470X	L280fs
Country of origin	Iran	Italy	Netherlands	Turkey	Turkey	Turkey	Turkey	China	Yemen
Parental consanguinity	+	-	+	+	+	+	-	-	-
Sex	8 M/2F	1F/1 M	3F	1F/1 M	1 M/1F	1F/1 M	1F	1 M	F
Age at onset	3rd decade	10/13	17/24/22	10/14	12/15	52/41	17	16	21
Age at last assessment	NA	NA	22/44/22	14/21	14/17	62/52	NA	32	30
Initial symptom ^a	Spasticity	Tremor, writing difficulty, trunk stiffness (1)/Tremor, bradykinesia, unsteadiness (1)	Eyelid dyspraxia (1)/Bradykinesia (2)	Bradykinesia, gait imbalance, falls	Chorea, tics, apathy (1)/Tremor, bradykinesia, tics (1)	Hand tremor, leg cramps (1)/Panic attacks (1)	Akinesia, abulia, resting tremor	Left hand postural and action tremor	Asymmetric stiffness
Resting tremor	-	+	-	-(1)/+(1)	-(1)/+(1)	+(1)/NA (1)	+	+	-
Rigidity	+(3)/-(7)	+	+	+	+	+	+	+	+
Bradykinesia ^a	+(3)/-(7)	+	+	+	+	+	+	+	+
Postural instability ^a	NA	+	+	+	+	-(1)/+(1)	+	-	+
Pyramidal signs ^a	+	+	+	-	+	-	+	+	-

	Shojaee et al., 2008	Di Fonzo et al., 2009	Paisan-Ruiz et al., 2010	Yalcin-Cakmakli et al., 2014	Gunduz et al., 2014	Lohmann et al., 2015	Conedera et al., 2016	Wei et al., 2017	Present study
Cognitive impairment ^a	-	-	+	+	+	-	+	+	±
Levodopa response ^a	+ (1)/No trial (2)/NA (7) ^b	+	+	+	+ (1)/No trial (1) ^c	+	+	+	+
Motor fluctuations ^a	NA	+	NA	NA	NA	NA	+	-	+
Dyskinesias ^a	NA	+	+	+	NA	NA	-	-	+
DRT-induced psychotic manifestations	NA	Agitation (1)/Behavioral disturbance (1)	Disinhibition, visual hallucinations (1)/Disinhibition, violent conduct (1)	Psychosis and agitation	Psychosis, agitation, irritability, aggression (1)/Agitation, punting, impulsive behavior (1)	Hallucinations (1)/None (1)	ICD, aggressive behavior, disinhibition	Manic behavior	Aggressive behavior
Brain MRI ^a	Normal (3)/NA (7)	Unremarkable	Normal (1)/Diffuse atrophy (2)	Normal	Mild cerebral atrophy (1)/Normal (1)	Mild cortical atrophy (1)/Normal (1)	Diffuse cerebral and brainstem atrophy	Mild diffuse atrophy	Normal
Presynaptic dopaminergic deficit (DAT-SPECT)	NA	NA	Present (1)	NA	NA	NA	NA	NA	NA
Other findings	Equinovarus deformity	Dysarthria, dysphagia, urinary and fecal incontinence, slow saccades, reduced upgaze	Dysarthria, dysphagia, cataracts, eyeopening apraxia, blepharospasm, upgaze palsy, cervical dystonia	Marked improvement with nicotine, nicotine induced oculogyric crisis and retrocollis	Dysarthria, dysphagia, tongue protrusions, myoclonic jerks	Dysarthria, choreic dystonia, oculogyric crisis, cervical dystonia, tics	OCD, downgaze limitation, bilateral equinovarus, dystonia	Dysarthria, RBD	Dystonia

DRT = dopamine replacement therapy; NA = not available; RBD = REM sleep behavior disorder; ICD = impulsive control disorder; OCD = obsessive-compulsive disorder.

^aThe number of individuals in each pedigree with this finding is in parentheses; if no count is provided, the finding was either present (+) or absent (-) in all affected individuals.

^bOnly 3 of the 10 affected individuals had parkinsonism and were offered a trial of levodopa; 1 had a robust response and 2 declined treatment.

^cThere was no levodopa trial, but the individual had a partial response to pramipexole.