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Early-Onset L-dopa-Responsive Parkinsonism with Pyramidal Signs Due to *ATP13A2, PLA2G6, FBXO7* and *Spatacsin* Mutations

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Abstract

Seven autosomal recessive genes associated with juvenile and young-onset Levodopa-responsive parkinsonism have been identified. Mutations in *PRKN, DJ-1,* and *PINK1* are associated with a rather pure parkinsonian phenotype, and have a more benign course with sustained treatment response and absence of dementia. On the other hand, Kufor-Rakeb syndrome has additional signs, which distinguish it clearly from Parkinson's disease including supranu-clear vertical gaze palsy, myoclonic jerks, pyramidal signs, and cognitive impairment. Neurodegeneration with brain iron accumulation type I (Hallervorden-Spatz syndrome) due to mutations in *PANK2* gene may share similar features with Kufor-Rakeb syndrome. Mutations in three other genes, *PLA2G6* (PARK14), *FBXO7* (PARK15), and Spatacsin (SPG11) also produce clinical similar phenotypes in that they presented with rapidly progressive parkinsonism, initially responsive to Levodopa treatment but later, developed additional features including cognitive decline and loss of Levodopa responsiveness. Here, using homozygosity mapping and sequence analysis in families with complex parkinsonisms, we identified genetic defects in the *ATP13A2* (1 family), *PLA2G6* (1 family) *FBXO7* (2 families), and SPG11 (1 family). The genetic heterogeneity was surprising given their initially common clinical features. On careful review, we found the *FBXO7* cases to have a phenotype more similar to PRKN gene associated parkinsonism. The *ATP13A2* and *PLA2G6* cases were more seriously disabled with additional swallowing problems, dystonic features, severe in some, and usually pyramidal involvement including pyramidal weakness. These data suggest that these four genes account for many cases of Levodopa responsive parkinsonism with pyramidal signs cases formerly categorized clinically as pallido-pyramidal syndrome. 3 2010 Movement Disorder Society

Keywords

parkinsonism; recessive; ATP13A2; PLA2G6; FBXO7; Spatacsin

In 1954, Davison described five cases of juvenile parkinsonism with associated upper motor neuron signs. Post mortem examination revealed lesions in the pallidum, the substantia nigra, the ansa lenticularis, and the corticospinal tract, thus termed pallido-pyramidal disease. Since then some similar cases have been reported, characterized by autosomal recessive inheritance, normal neuroimaging (although usually without T2* assessment), and L-dopa responsiveness.[1–3]

Over the last 10 years numerous autosomal recessive genes causing L-dopa-responsive parkinsonism have been identified.[4–6] Parkin (*PRKN)* gene mutations are associated with hyperreflexia,[7] however, there is only one report of a pallido-pyramidal phenotype.[8] Pyramidal signs are also infrequent in *DJ-1* and *PINK1* mutations.[9] Dopa-responsive dystonia (DRD) can often mimic early-onset parkinsonism (EOPD), sensitive to low L-dopa doses, and carriers of *GTP cyclohydrolase* mutations do usually not develop dyskinesias. Tyrosine hydroxylase,[10] sepiapterin reductase deficiency,[11] and spasticity have been reported in DRD,[12] but these are clinically distinct from pallido-pyramidal disease.

Furthermore, mutations in *ATP13A2*, *PLA2G6, FBXO7,* and *SPG11* have recently been identified in cases similar to Davison's seminal report.[13–16] Here, we summarize the phenotypic and genotypic characteristics of cases with homozygous mutations in these four genes. This case series represent the cases of this syndrome, in which we have mapped the lesions by homozygosity mapping. We restrict our discussion of the literature to findings in cases with homozygous and compound heterozygous changes because only in such circumstances, we can be certain of their pathogenic nature (Table 1).

ATP13A2 (PARK9)

Homozygous and compound heterozygous *ATP13A2* (PARK9) mutations were first described in patients of Jordanian and Chilean ancestries. The main clinical features were juvenile akinetic-rigid parkinsonism, pyramidal weakness, spasticity, and Babinski signs, supranuclear gaze paresis, and cognitive impairment.[13,21,22] On clinical follow-up visual hallucinations, facial-faucial-finger mini myoclonus and oculogyric dystonic spasms were added to the phenotypic spectrum.[23] The Chilean and Japanese kindreds were clinically similar.[13,17] An apparently sporadic Brazilian patient with a single homozygous mutation with disease onset aged 12 was also reported. However, Babinski signs, supranuclear gaze paresis or dementia[18] were absent and the case closely resembled *PRKN* disease. This single case suggests that *ATP13A2* mutations may play a role in EOPD, [24] although it has to be acknowledged that the pathogenicity remains uncertain.

PLA2G6 (PARK 14)

PLA2G6 mutations have been associated with neuro-degenerative disorders with increased basal ganglia iron accumulation, such as infantile neuroaxonal dystrophy (INAD) and neurodegeneration with brain iron accumulation (NBIA-type 2).[25,26] Pathologically, both, INAD and NBIA, show axonal degeneration with spheroid bodies (distended axons) throughout the central nervous system. *PLA2G6* mutations have also been found in patients without spheroids and in classical INAD.[27] INAD presents in infancy and death by age 10 is usual. Typically, NBIA presents between infancy and 30 years of age with faster disease progression in infantile and juvenile onset cases.[19,28] There is clinical heterogeneity as recently L-dopa responsive dystonia-parkinsonism cases with an onset age ranging from 10 to 26, whose main clinical features were severe akinesia and rigidity, generalized dystonia and cognitive impairment, however, with no evidence of brain iron accumulation on neuroimaging were described.[15,19] These latest findings led to a designation of *PLA2G6* as PARK14. However, the fact that identical disease-associated *PLA2G6* mutations may cause

NBIA, INAD, and dystonia-parkinsonism suggests that additional unknown genetic, epigenetic, or nongenetic factors may influence the *PLA2G6*-associated phenotype.[15,19,26]

FBX07 (PARK 15)

A disease-associated variant in *FBXO7* causing p.Arg378Gly has recently been identified in an Iranian kindred which presented with spastic weakness and Babinski signs. Parkinsonism with bradykinesia and rigidity was developed as a late feature in some familial members.[15] Three novel *FBXO7* mutations, c.907+1G>T and p.Thr22Met in the compound heterozygous state and p.Arg498X in homozygous state, were later identified in Dutch and Italian families exhibiting spasticity and Babinski signs, tremor, bradykinesia, and postural instability. Dystonia was also present in the homozygous p.Arg498X mutation carriers. These families expanded the phenotypic spectrum associated with *FBXO7* mutations making it another cause of recessive EOPD (PARK15).[20]

SPATACSIN (SPG11)

Spatacsin (SPG11) is the major mutated gene in autosomal recessive spastic paraplegia with thin corpus callosum (ARHSP-TCC). To date, more than 50 different *SPG11* mutations, including nonsense, spice-site, and frameshift variants, have been reported in familial and idiopathic cases presenting with complicated HSP.[29–31] In addition, an unusual parkinsonism presenting with resting tremor, akinesia and with either weak or no L-dopa response has recently been described in two SPG11 patients from a consanguineous Turkish family. Both showed mental retardation, characteristic of the complex HSP, and bilateral Babinski signs. An ^{123}I-ioflupane SPECT scan revealed dopaminergic denervation in one of the probands. They carried a homozygous frameshift SPG11 mutation (p.His235ArgfsX12).[16]

SUBJECTS AND METHODS

Subjects

Patients from five unrelated consanguineous families with L-dopa-responsive EOPD gave informed consent to this study approved by the local ethics committee. Different cases were clinically examined by the clinicians involved in the patients' care and video footage of all cases was retrospectively reviewed by HH, KPB, and AJL. Clinical details are partly given below and summarized in Table 2. For full information see supplements. We also compare the clinical features of two previously published *PLA2G6* mutation families (Table 2) and the video of Iranian *FBX07* mutation family E. The family trees for families reported here, with the exception of family E where only one proband was available for study, are shown in Figure 1.

Family A (PLA2G6)—This patient was described by Paisan-Ruiz et al.[14] without video documentation.

In summary, onset was at age 26 with progressive cognitive decline, slow movements (video segment 1), clumsiness, progressive imbalance, hand tremor, and slurred speech, followed

by the development of dystonia. There was an excellent L-dopa response. However, after 1 year she developed prominent dyskinesias and improvement declined considerably over the next few years. By age 34 years, she was bed-bound (Video segment 2) and started to have epileptic seizures.

Additional data is also provided now on the previously undescribed cousin, a 36-year-old North Indian female. Her cousin had a foot drag dystonia at age 10. At age 26, she developed arm and leg tremor, followed by infrequent falls from age 29. In view of the findings of ankle clonus and extensor planters on examination a diagnosis of spastic quadriplegia was initially made (Video segment 3). She later developed bradykinesia and extreme rigidity. On examination at age 33, she had a supranuclear vertical gaze palsy, eyelid opening apraxia, a positive glabellar tap sign, and facial hypomimia (Video segment 4). She had developed a pill-rolling tremor, limb bradykinesia, brisk reflexes, and bilateral Babinski signs. She was severely dysarthic with slow tongue movements. L-dopa treatment was beneficial but caused prominent early dyskinesias.

Family B (ATP13A2)—This case was first described in 1995.[32] At age 16 he developed an L-dopa-responsive akinetic rigid syndrome. He developed dyskinesias at high doses and secondary nonresponsiveness to dopaminergic therapy. Over the next 15 years he deteriorated. On examination at age 40 years he was anarthric. He had normal fundi but reduced up- and down-gaze with broken pursuit and slow saccades. There was marked dystonia, brisk reflexes, ankle clonus, and bilateral Babinski signs (Video segment 5).

Brain MRI showed general involutional change involving the cerebral cortex, basal ganglia, and cerebellum with presence of basal ganglia iron on T2* sequences[33]. A sural nerve biopsy performed at age 40 showed acute axonal degeneration, some regeneration, and a very mild chronic inflammatory response with endoneurial and epineurial T-cells. There were numerous cytoplasmic inclusion bodies (1–5 μm in diameter) within the Schwann cells, perineurial and epineurial cells but not in axons. Electron microscopy showed the inclusions to be membrane-bound, irregular, and occasionally folded. Overall they resembled irregular primary lysosomes (Fig. 2).

The proband's cousin was phenotypically very similar. Onset was at age when aged 18 she developed gait difficulty with frequent falls backwards. She developed arm tremor and urine incontinence. Video segment 6 shows her at age 26 years. L-dopa treatment produced significant improvement; however, with the emergence of early drug-induced dyskinesias and the L-dopa effect reduced within 5 years.

Family C (FBX07)—The proband originating from Pakistan from a family with multiple consanguineous loops presented at age 17 years with difficulty opening her eyes, generalized stiffness and bradykinesia. Over 5 years she developed dysarthria, hypophonic speech, frequent respiratory sighs, and urinary problems.

On examination, she had cataracts, prominent apraxia of eye opening, and supranuclear gaze palsy. She had slow saccades with prominent blepharospasm. There was upper and lower

limb rigidity, bradykinesia but no tremor. Reflexes were brisk and the plantars were extensor (Video segment 7).

An L-dopa challenge was strongly positive (UPDRS score 42 pre- and 20 post-treatment). For aggression and mood she later required Olanzapine.

The proband's mother was similarly affected by L-dopa-responsive parkinsonism without tremor and onset at age 24. She had difficulty with upgaze and abnormal respiration with sighs. Aged 40 she had cataracts, was very rigid and slow, incomprehensible speech, cognitive problems, and swallowing difficulties. For details of the proband's aunt and investigational results see supporting information.

Family D (FBX07)—This family with multiple consanguineous loops originated from southeast Turkey. Clinical details and a video of the proband have previously been reported by Hanagasi et al.[34] before the gene was identified. The 26-year-old male proband developed walking difficulties at age 17, followed by L-dopa-responsive limb rigidity and marked bradykinesia. Because L-dopa caused psychosis it had to be withdrawn. See supplements for further clinical details and Ref. 33 for a video. The patient died at age 28.

The patient had four paternal cousins, who were said to have had severe gait difficulty and bradykinesia. Their symptoms had also started before the age of 20, and they had died within a few years in a bedridden state.

Family E (SPG11)—The symptoms of this 27-year-old Asian from a consanguineous family began at age 14 with postural and writing tremor. Aged 17 he developed walking difficulties with imbalance, speech problems, and slowness. His gait became progressively stiff and he complained of leg weakness and falls. Pharmacological treatment (i.e., baclofen, tizanidine, clonazepam) was either ineffective or produced intolerable side-effects. At age 24 (Video segment 8) he presented with mild gynaecomastia, facial hypomimia, laryngeal dystonia, upgaze skew deviation with slowed upward eye movements, hand dystonia and writing tremor, marked spastic paraplegia, bradykinesia, axial rigidity, and imbalance. Reflexes were brisk bilaterally with bilateral ankle clonus. Routine and genetic testing for SCAs 1,2,3,7,17, DRPLA, and SPG4 were normal. An MRI brain scan revealed generalized atrophy with a thin corpus callosum. A DaT-SPECT scan showed decreased bilateral putaminal and caudate uptake. Motor symptoms improved on ropinirole but caused confusion and hallucination.

Family F (PLA2G6)—See Ref. 27 for genetic findings and Video segment 9 for clinical features.

Molecular Analysis

Genome-wide SNP genotyping was carried out using either HumanHap240 or HumanHap317 illumina bead-chips. Homozygosity mapping was performed as previously described[35,36] and using the Homozygosity detector plug-in software within the BeadStudio 3.2 program where a minimum physical size threshold of 1Mb and at least 100 adjacent markers in length were used as limiting parameters (www.illumina.com). Gene screening

analyses for *ATP13A2, PLA2G6, FBXO7,* and *SPG11* were performed by PCR analysis using 10 picomoles of both forward and reverse primers (Supporting information 1) and FastStart Taq DNA polymerase (http://www.roche-applied-science.com). Each purified PCR product was then sequenced with Applied Biosystems BigDye terminator v3.1 sequencing chemistry as per the manufacturer's instructions; the resulting reactions were resolved on an ABI3730 XL genetic analyzer (Applied Biosystems, Foster city, CA) and analyzed by Sequencher 4.8 software (Gene Codes Corporation, Ann Arbor, MI).

RESULTS

All families presented with EOPD that was initially L-dopa responsive. Cognitive and psychiatric features were common in all except the *FBX07* mutation cases where agitation and mood problems occurred only after L-dopa treatment. Supranuclear gaze palsy, severe bulbar signs with speech and swallowing difficulties were present in all families. Pyramidal signs were perhaps most marked in the family E (*SPG11)* and were absent in the Turkish family D (*FBX07*). Dystonia was also present in the PLA2G6 and ATP13A2 families but they were not a significant feature in the *FBX07* mutation families where only one individual had cervical dystonia. MRI brain scans revealed generalized involutional change in most cases. In family E (SPG11), there was a thin corpus callosum in addition to the generalized atrophy. Details of the nerve biopsy in family B are given above in the clinical description.

Comprehensive homozygosity mapping was carried out in nine individuals (eight affected and one unaffected) belonging to four families. No homozygosity mapping was performed in family E as only the proband was available for study. In first instance, we searched for autozygous segments shared among all affected individuals to locate the pathogenic loci,[14] although the proximity of the *FBXO7* gene (5.7 Mb upstream of PLA2G6) to *PLA2G6* on chromosome 22 prevented this analysis alone from distinguishing these loci before gene sequencing (Supporting information 2). Gene sequencing identified the lesion in each family. Similarly, the proximity of the *ATP13A2* gene to the established parkinsonism gene *PINK1* on chromosome 1 meant that homozygosity mapping alone could not delineate the lesion in this family (Supplement 2). In conclusion, Family A carried the previously reported *PLA2G6* mutation (p.Arg741Gln; c.2222G>A), Family B a novel *ATP13A2* mutation (p.Thr367ArgfsX29; c.1103-1104insGA), Families C and D the same *FBXO7* mutation (p.Arg498X; c.1492C>T), and Family E a 2bp SPG11 deletion (c.733_734delAT; p.Met245fsX2) previously reported in families presenting with complicated ARHSP-TCC (Table 1).[29]

DISCUSSION

There are now eight recessive loci, which can lead to EOPD syndromes. These are the classical recessive loci, *PRKN* (PARK2), *PINK1* (PARK6), *DJ-1* (PARK7), the four loci we present examples of here, *ATP13A2* (PARK9), *PLA2G6* (PARK14), *FBX07* (PARK15), and SPG11 and the *PANK2* genes.[16,37] It is important to be able to characterize disease causing mutations and the phenotypic features associated with the mutation in the genes for clinical purposes and, also because observed distinctions may give mechanistic insights.

Loss of function mutations at *PRKN*, *PINK1,* and *DJ-1* nearly always give rise to a pure parkinsonian phenotype which has an early onset, a benign course, sleep benefit and a good and prolonged response to L-dopa. The lifespan of mutation carriers is only marginally reduced and there have been no reports of brain iron accumulation. All three proteins have functions related to mitochondrial biology and *PRKN* mutations are usually not associated with Lewy bodies.[37]

Loss of function mutations in *PLA2G6* and *PANK2* lead to variable and overlapping clinical features of progressive parkinsonism, dystonia, ataxia, and cognitive decline. The endophenotypes range from the aggressive INAD and Hallevorden-Spatz disease with variable brain iron inclusion and death usually before the age of 20 years, through to the patients that present with predominantly EOPD and dystonia and later develop other manifestations. The pathology of these cases is likely to include extensive Lewy bodies as seen in childhood onset neuroaxonal dystrophy,[26] although the neuropathology of adult onset cases with *PLA2G6* mutations has not yet been reported. Over many years there have been reports of Hallervorden-Spatz cases (PKAN/*PANK2*) with extensive Lewy body disease. We suggest that Kufor Rakeb syndrome may also belong to this same class of diseases, as gene products of both *PLA2G6* and *PANK2* impinge on ceramide metabolism. The role of *ATP13A2* as a lysosomal pump fits with this suggestion, although its precise function is not known.[37]

Loss of function mutations in *FBX07* appears to give a phenotype intermediate between the two disease classes. In some cases the phenotype resembles *PRKN* mutation associated phenotype,[33,38] but the disease is generally less benign and has a reduced life expectancy, pyramidal signs and late cognitive problems. This overlap of phenotypes related to *FBX07* and *PRKN* mutations is consistent with the related functions of these two genes and their likely common disease pathway. Like *PRKN*, F-box proteins, such as *FBXO7*, are components of the modular E3 ubiquitin protein ligases.[39]

These findings have allowed us to dissect the pal-lido-pyramidal disease described by Davison[1] into at least five recessive forms of complex parkinsonism with subtle clinical differences. Although there are still typical cases of L-dopa-responsive parkinsonism with pyramidal signs where the genetic cause is yet to be identified these data suggest that these five genes account for many of these cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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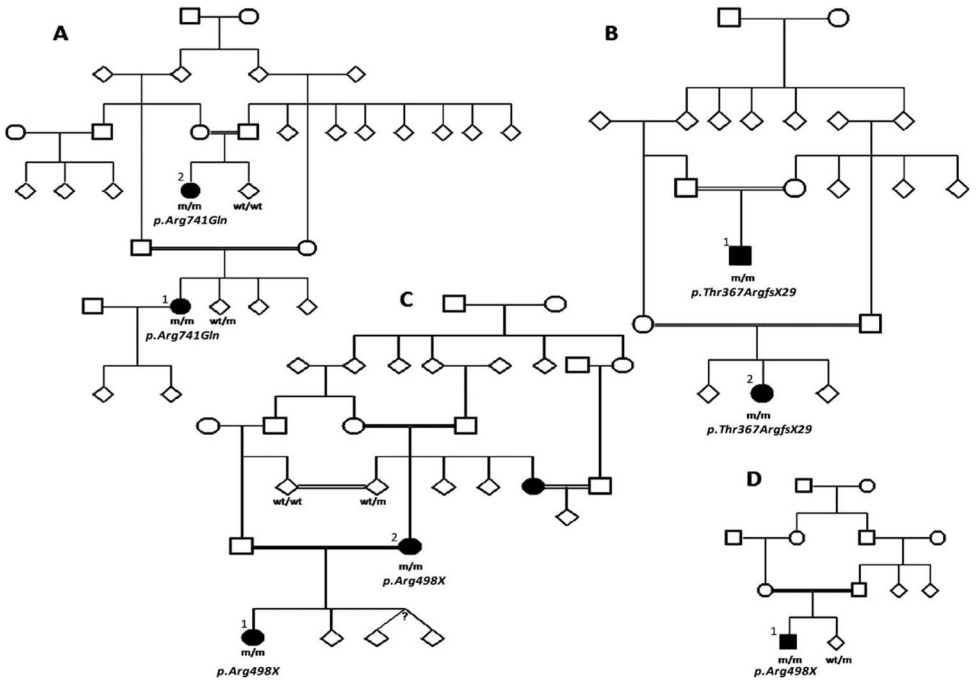

FIG. 1.

Pedigrees of families reported here. Manifesting members are shown in bold. A: *PLA2G6* family, B: *ATP13A2* family, C and D: *FBXO7* families. m/m: homozygous mutation carriers, wt/m: heterozygous mutation carriers, wt/wt: homozygous carriers for the wild type sequence.

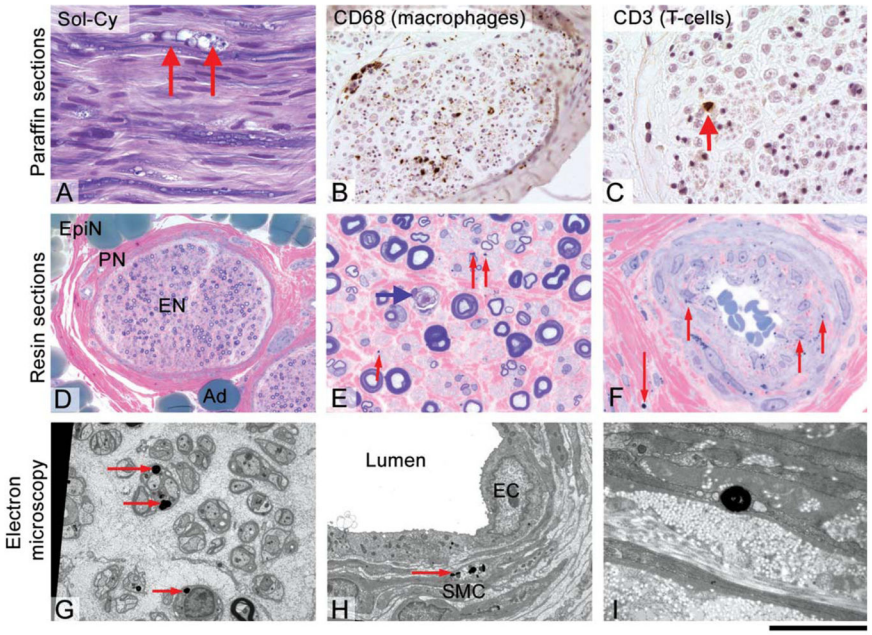

FIG. 2.

Histological and ultrastructural analysis of the sural nerve biopsy of Family B (*ATP13A2*): Paraffin sections (A, B, C) show a reduction of myelinated fibre density with frequent formation of myelin digestion chambers (arrows) (A). Immunohistochemical staining for CD68 on a transverse section shows frequent endoneurial macrophages (B), a characteristic finding in florid axonal neuropathies. Very occasionally, there were endoneurial and scattered epineurial T-cells (CD3 immunohistochemistry; C). Resin semi thin sections (D, E, F) show a mild generalized axon loss, subperineurial, and endoneurial oedema (D) and significant numbers of degenerating axons (E, blue arrow). Strikingly, there are numerous small cytoplasmic inclusion (E, red arrows and F, red arrows). These inclusions were found in the endoneurium, in smooth muscle cells of vessels and in the perineurium. Electron microscopy (G, H, I) confirms the presence of electron dense inclusions of circa 1 μm size, which are always located intracellularly, and are most frequently seen in the cytoplasm of Schwann cells (G, red arrows) and in smooth muscle cells (H, I). Scale bar 40 μm (E, F), 60 μm (A, C), 120 μm (B), 230 μm (D).

TABLE 1

Previously reported and novel autosomal recessive parkinsonism mutations

	cDNA	Protein	References
ATP13A2: PARK9	c.546C>A	p.Phe182Leu	Ref. 17
	c.1103_1104insGA	p.Thr367ArgfsX29	This paper
	c.1306+5G>A	NA	Ref. 13
	c.1510G>C	p.Gly504Arg	Ref. 18
	c.1632_1653dup22	p.Leu552fsX237	Ref. 13
	c.3057delC	p.Gly1019fsX3	Ref. 13
PLA2G6: PARK14	c.109C>T	p.Arg37X	Unpublished data
	c.1078−3C>A	NA	Unpublished data
	c.1715C>T	p.Thr572Ile	Unpublished data
	c.1894C>T	p.Arg632Trp	Ref. 19
	c.2222G>A	p.Arg741Gln	Ref. 14
	c.2239C>T	p.Arg747Trp	Ref. 14
FBXO7: PARK15	c.65C>T	p.Thr22Met	Ref. 20
	c.907+1G>T	NA	Ref. 20
	c.1132C>G	p.Arg378Gly	Ref. 15
	c.1492C>T	p.Arg498X	Ref. 20
SPATACSIN: SPG11	c.704_705delAT	p.His235ArgfsX12	Ref. 16
	c.733_734delAT	p.Met245fsX2	This paper

All ATP13A2, PLA2G6, FBXO7, and Spatacsin mutations identified to date in either recessive parkinsonism or idiopathic Parkinson's disease patients. Only homozygous or compound heterozygous mutations are included because on these have strong evidence for pathogenicity.

NA, Not Applicable.

TABLE 2

Summary of the clinical details of the families reported here (families A–D)

Table	Family A PLA2G6		Family B ATP13A2		Family C FBX07			Family D FBX07	Family E SPG11	Family DP Sina et al.[27] PLA2G6	Family 2 from Paisan-Ruiz et al.[14] PLA2G6
Family/case	1	2	1	2	1	2	3	1	1	Cases 1–3	1
Current age (yr)	35	41	41	44	22	44	22	Died 27	27	23, 25, 31	21
Age of onset (yr)/first symptom	26 Cognitive	29 Falls	16 Psychosis	18 Gait	17 Eyelid dyspraxia	24 Bradykinesia	22 Bradykinesia	17	14	21, 22, 25 Dragging feet	18 Dragging foot
Cognitive decline	++	+++	++	+++	+	+	+	−	+	++	+
Psychiatric features	+	+	++	++	+	++	++	+	(+)	+	+
Extrapyramidal signs	+++	++	++	++	++	++	++	++	++	+++	++
Pyramidal features	+	++	+	++	+	+	+	−	+++	++	++
L-dopa response	++	++	++PT	++PT	+++	++	++	++	++PT*	++	++
L-dopa-induced dyskinesias	++	++	++	++	+	++	++	++	NA	++	+
Dystonia	+++	+++	++	+	−	−	+	−	+	+++	++
Eye movement abnormalities	+	++	++	++	++	+	+	−	+	+	+
Imbalance/impaired postural reflexes	++	++	+	+	+	+	+	+	+	++	+
Dysarthria/dysphonia	+++	+++	++	++	++	++	+++	+++	+	++	+
Swallowing problems	+++/PEG	+++/PEG	++	++	+	++	++	+	−	++	+
Other	Seizures pale blue sclera	Pale blue sclera	Bleph	OA	Bleph cateracts	Cateracts	Cervical dystonia	Nicotine responsive. Dopa induced dystonia and aggression	Nil	Nil	Foot dystonia with hemiparetic gait
MRI brain	Frontal white matter	General atrophy	General/Caudate atrophy	General/Caudate atrophy	Normal	General atrophy	General atrophy	Normal MRI. Beta-CIT SPECT, no uptake	General atrophy, thin corpus callosum	General atrophy	General atrophy

We have previously reported two other families with PLA2G6 mutations and their clinical features are also shown for comparison. +++ = severe, ++ = moderate, + = mild, (+) = related to treatment, − = absent. PEG = Percutaneous endoscopic gastrostomy, Bleph = blepharospasm/clonus, OA = optic atrophy. PT = poorly tolerated:

* treated with ropinerole.