Early-Onset Autosomal-Recessive Parkinsonian-Pyramidal Syndrome

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Abstract-

Genetic factors have been known to contribute to familial Parkinson's disease (PD), one of the most common neurodegenerative disorders. During the past decade, six of eleven causative genes linked to familial forms of PD have been identified to associate with autosomal-recessive young-onset Levodopa-responsive parkinsonism. Among these genes, mutations in Parkin, PINK1 and DJ-1 are associated with a relatively typical parkinsonian phenotype with sustained treatment response to Levodopa. However, mutations in ATP13A2, PLA2G6 and FBXO7 are often associated with rapidly progressive parkinsonism and with additional features including pyramidal signs, cognitive decline and loss of sustained Levodopa responsiveness. Clarifying the phenotypes of each of these autosomal-recessive parkinsonian-pyramidal syndromes and understanding the mechanism of these causative gene products might illuminate the pathogenesis of dopaminergic neuronal degeneration also in the common forms of PD.

Key Words: Parkinson's disease, Parkinsonian-pyramidal syndrome, ATP13A2, PLA2G6, FBXO7.

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INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. The prevalence rate ranged from 56 to 234 per 100,000 worldwide[1], and it was 130.1 per 100,000 in Taiwan[2]. Familial forms of PD were estimated to contribute to 5-10% of all PD cases. In the past decade, a number of PARK locus related disorders have been identified[3,4]. At the present time, 18 loci have been detected so far. Among them, there have been 11 identified causative genes contributing to familial forms of PD in either autosomal dominant or recessive inheritance patterns (Table 1). As compared to the major causative genes for autosomal dominant PD, such as SNCA and LRRK2, in which clinical symptoms are very similar to those of the sporadic form of PD[5], phenotypes of genes contributing to autosomal recessive PD are different, due to young-onset parkinsonism with or without atypical features[3]. Among these recessive genes, mutations in Parkin (PARK2), PINK1 (PARK6) and DJ-1 (PARK7) are associated with a relatively typical parkinsonian phenotype with sustained treatment

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Table 1. Genetic locus and candidate genes of familial PD.

Locus	Chromosome	Gene	Inheritance
PARK 1/4	4q21.3	SNCA	Autosomal dominant
PARK 2	6q25.2-27	Parkin	Autosomal recessive
PARK 3	2p13	Unknwon	Autosomal dominant
PARK 5	4p14	UCHL-1	Autosomal dominant
PARK 6	1p35-p36	PINK1	Autosomal recessive
PARK 7	1p36	DJ1	Autosomal recessive
PARK 8	12q12-q13.1	LRRK2	Autosomal dominant
PARK 9	1p36	ATP13A2	Autosomal recessive
PARK 10	1p32	Unknown	Susceptibility locus
PARK 11	2q36-37	GIGYF2	Autosomal dominant
PARK 12	Xq21-25	Unknown	X-Linked
PARK 13	2p13.1	HTRA2/Omi	Autosomal dominant
PARK 14	22q13.1	PLA2G6	Autosomal recessive
PARK 15	22q11.2-qter	FBXO7	Autosomal recessive
PARK 16	1q32	Unknown	Susceptibility locus
PARK 17	4p16	GAK	Susceptibility locus
PARK 18	6p21.3	HLA-DRA	Susceptibility locus

response to Levodopa. On the other hand, recessive mutations in other PARK genes, including ATPase type 13A2 (ATP13A2, PARK9), phospholipase A2, group VI (PLA2G6, PARK14), F-box only protein 7 (FBXO7, PARK15) can cause juvenile-onset parkinsonism with additional features, such as pyramidal signs, dementia, oculomotor palsy and dystonia.

Since Davison's first report on five young-onset PD cases with presentations of parkinsonism associated with upper motor neuron signs[6], many similar cases are reported. Post mortem examination revealed degeneration in the globus pallidus, the substantia nigra, the ansa lenticularis, and the corticospinal tract, hence termed parkinsonian-pyramidal syndrome. Many gene mutations, including PARK locus genes, such as ATP13A2, PLA2G6, FBXO7, and other neurodegenerative disorders related genes, such as SPG11, PANK2, have recently been identified in cases similar to parkinsonism-pyramidal syndromes. In this review, we summarize the phenotype-genotype correlations in cases with homozygous

Table 2. Clinical phenotypes of currently reported patients carrying either homozygous or compound heterozygous ATP13A2 mutations.

Reference	Ref. 7	Ref. 7	Ref. 7	Ref. 7	Ref. 9	Ref. 9	Ref. 9
Country	Jordanian	Jordanian	Jordanian	Jordanian	Chilean	Chilean	Chilean
Patient code	II-44	II-48	II-49	II-53	II-8	II-9	II-10
Gene mutation	c.1632_1653dup22 (p.552LfsX788)	c.1632_1653dup22 (p.552LfsX788)	c.1632_1653dup22 (p.552LfsX788)	c.1632_1653dup22 (p.552LfsX788)	c.3057delC/ c.1306+5G>A (p.1019GfsX1021/ p.G399_L435del)	c.3057delC/ c.1306+5G>A (p.1019GfsX1021/ p.G399_L435del)	c.3057delC/ c.1306+5G>A (p.1019GfsX1021/ p.G399_L435del)
Age of onset	12	15	13	12	18	17	15
Disease duration	24	19	18	11	27	26	26
Initial symptoms	B,M,R	B,R	M,R	B,R	B,M	B,R	B,M
Levodopa response	+	+	+	+	n/a	Intol.	Intol
peak-dose dyskinesia	-	+	+	+	n/a	n/a	n/a
dystonia	-	+	+	+	n/a	n/a	n/a
increased tone	+	+	+	+	+	+	+
Hyper-reflexia	+	+	+	+	n/a	n/a	n/a
Babinskis sign	+	+	+	+	+	-	+
tremor	-	-	-	-	+	+	+
rigidity	+	+	+	+	+	+	+
bradykinesia	+	+	+	+	+	+	+
slow saccade	+	+	+	+	n/a	-	+
supranuclear palsy	+	+	+	+	+	-	+
visual hallucination	+	+	+	+	+	+	-
Myoclonus	+	+	+	+	+	-	+
Dementia/mental retard	+	-	+	-	n/a	+	+

B: Bradykinesia, M: mental retardation, R: rigidity, G: gait disturbance, Psy: behavioral or psychological, intol. : intolerable. n/a: not available.

or compound heterozygous mutations in these three PARK locus genes associated with parkinsonian-pyramidal syndrome and the possible role of their gene products in neuronal degeneration.

PARK9: ATP13A2

PARK9, previously known as Kufor-Rakeb syndrome, was first described in 1994 in a consanguineous Arab family from the northern highlands of Jordan[7]. The affected five siblings presented with juvenile parkinsonism, pyramidal weakness, dementia and supranuclear gaze palsies during the teenage years[7]. The initial response to levodopa was significant, but response started to decline by six months to four years. After a mean follow up of ten years, there has been a marked narrowing of the levodopa therapeutic window with complication of peak-dose dyskinesias, visual hallucinations and increased spasticity and cognitive decline[8]. In addition, there was emergence of small-amplitude myoclonus over face and upper limbs, naming facial-faucial-finger myoclonus and oculogyric dystonia[8]. The linkage analysis mapped to the chromosome 1p36 and the causative gene, ATP13A2, encoding a predominantly neuronal P-type ATPase, was later identified in another large non-consanguineous Chilean family with similar presentations[9].

Nowadays, ten patients from four families and four isolated individuals were found to have homozygous or compound heterozygous ATP13A2 gene mutations (Table 2)[7-15]. Notably, a proband's brother (patient code NAPO-7 in the Italian family) with homozygous ATP13A2 G877R mutations did not present any symptoms or signs of parkinsonism or pyramidal weakness until examination when he was 31 years old[14]. The mean onset age of parkinsonism in these patients carrying homozygous or compound heterozygous mutations was 14.5±3.3 years old. The initial presentations include unilateral bradykinesia, rigidity and cognitive dysfunction. The most common clinical symptoms included young-onset levodopa responsive parkinsonism (15/15),

Table 2. (Continued)

Reference	Ref. 9	Ref. 10	Ref. 12	Ref. 15	Ref. 14	Ref. 11	Ref. 13
Country	Chilean	Brazilian	Japan	Pakistan	Italian	Afghan	Chinese
Patient code	II-11	BR-3042	A	n/a	NAPO-6	II-3	IIa-IIb
Gene mutation	c.3057delC/ c.1306+5G>A (p.1019GfsX1021/ p.G399_L435del)	c.1510G>C (p.G504R)	c.546C>A (p.F182L)	c.1103-1104insGA (p.T367RfsX29)	c.2629G> A (p.G877R)	c.2742_2743delTT (p.F851CfsX856X)	c.3176T>G/ c.3253delC(p.L1059/ p.L1085WfsX1088)
Age of onset	12	12	22	16	10	10	17
Disease duration	26	10	21	24	30	n/a	1-5
Initial symptoms	M	B	G	B,M,Psy	B,G	B	Psy
Levodopa response	n/a	+	+	+	+	+	+
peak-dose dyskinesia	n/a	+	n/a	+	n/a	+	n/a
dystonia	n/a	n/a	n/a	+	n/a	+	+
increased tone	+	+	+	+	+	+	+
Hyper-reflexia	n/a	+	+	+	+	+	+
Babinskis sign	+	-	+	+	+	-	+
tremor	+	-	+	-	-	+	+
rigidity	+	+	+	+	+	+	+
bradykinesia	+	+	+	+	+	+	+
slow saccade	+	n/a	+	+	+	+	+
supranuclear palsy	+	+	+	+	+	-	+
visual hallucination	-	+	+	-	-	+	-
Myoclonus	+	-	+	+	+	+	+
Dementia/mental retard	+	-	+	+	+	+	+

B: Bradykinesia, M: mental retardation, R: rigidity, G: gait disturbance, Psy: behavioral or psychological, intol. : intolerable. n/a: not available.

Table 3. Clinical phenotypes of currently reported patients carrying either homozygous or compound heterozygous PLA2G6 mutations.

Reference	Ref. 25	Ref. 25	Ref. 25	Ref. 29	Ref. 29	Ref. 28	Ref. 28	Ref. 28	Ref. 26
Country	Indian	Indian	Pakistani	Japanese	Japanese	Iranian	Iranian	Iranian	Chinese
Patient code	Family1 patient1	Family1 patient2	Family2	B1	B2	DP3	DP4	DP5	IV:2:43
Gene mutation	c.2222G>A (pR741Q)	c.2222G>A (pR741Q)	c.2239C>T (p.R747W)	c.1354C>T/ c.1904G>A (p.Q452X/ p.R635Q)	c.1354C>T/ c.1904G>A (p.Q452X/ p.R635Q)	c.1894C>T (p.R632W)	c.1894C>T (p.R633W)	c.1894C>T (p.R634W)	c.991G>T (p.D331Y)
Age of onset	26	10	18	25	30	25	22	21	37
Disease duration	8	16	3	9	8	6	3	2	6
Initial symptoms	B,M,G	G, dystonia	M, G, Psy	G	G	G	G	G	G
Levodopa response	+/-	+	+	+	+	+/-	+/-	+/-	+
peak-dose dyskinesia	+	+	n/a	+	+	+	+	+	+
dystonia	+	+	+	-	-	++	++	++	-
increased tone	+	n/a	+	n/a	n/a	+	+	+	+
Hyperreflexia	+	n/a	+	-	-	+	+	+	-
dysarthria	+	n/a	-	n/a	n/a	+	+	+	n/a
tremor	+	+	-	-	-	+	+	+	+
rigidity	+	n/a	+	+	+	+	+	n/a	+
bradykinesia	+	+	+	+	+	+	+	+	+
impaired postural reflex	+	n/a	+	+	+	+	+	+	+
eye movement abnormality	+	n/a	+	-	-	+	+	+	-
psychiatric features	+	n/a	+	-	+	n/a	+	+	-
Cognitive decline	+	n/a	+	+	+	+	+	+	-
autonomic symptoms	-	n/a	+	-	+	n/a	n/a	-	-

B: Bradykinesia, M: mental retardation, R: rigidity, G: gait disturbance, Psy: behavioral or psychological, n/a: not available.

pyramidal weakness with spasticity or Babinski sign (15/15), supranuclear gaze palsies (13/15) and facial-faucial-finger mini myoclonus (13/15).T2-weighted MRI imaging detected no evidence of brain metals accumulation in these PARK9 patients[14].

Eleven symptomatic heterozygous mutation carriers have been reported[10,13,16], including two from Taiwan[17,18]. The clinical presentations were more restricted to pure levodopa-responsive parkinsonism without addition features of pyramidal weakness, positive Babinski's signs, cognitive decline or myoclonus. The average age of onset of parkinsonism symptoms was 35.5±13.3 year-old, which was much older than patients with homozygous or compound heterozygous mutations (Table 2). Only one patient manifested with supranuclear gaze palsy[16]. The single heterozygous state of recessive gene mutations was hypothesized to have a threshold effect for the development of parkinsonism by possible mechanisms of haplo-insufficiency, dominant negative effect or a new gain of toxic function[19].

ATP13A2 encodes a large, 1,180 amino acid 10-transmembrane protein which is a lysosomal P-type ATPase, whose functions have yet to be fully elucidated[9]. It is suggested to be involved in the transport of several cations from the cytosol to the lysosome[9]. ATP13A2 mutation has been shown to cause the distortion of transmembrane topology of the protein and causes the trans-localization of ATP13A2 from lysosome to accumulate in the endoplasmic reticulum[9]. The degradation of ATP13A2 protein was through an ubiquitin-inde-

Table 4. Clinical phenotypes of currently reported patients carrying either homozygous or compound heterozygous FBXO7 mutations.

Reference	Ref. 32	Ref. 34	Ref. 34	Ref. 34	Ref. 34	Ref. 36	Ref. 36	Ref. 36	Ref. 36
Country	Iranian	Italian	Italian	Dutch	Dutch	Pakistan	Pakistan	Pakistan	Turkish
patient code	50XX	BO-53	BO-56	NIJ-002	NIJ-006	1	2	3	1
Gene mutation	c.1132C>G (p.R378G)	c.1492C>T (p.R498X)	c.1492C>T (p.R498X)	c.65C>T (p.T22M); c.90711G>T	c.65C>T (p.T22M); c.90711G>T	c.1492C>T (p.R498X)	c.1492C>T (p.R498X)	c.1492C>T (p.R498X)	c.1492C>T (p.R498X)
Age of onset	20-30	10	13	18	19	17	24	22	17
Disease duration	5-20	28	16	18	19	5	20	0	10
Symptoms at onset	Equinovarus deformity	Arm tremor, trunk stiffness, G	Hand tremor, B, G	T, anxiety	B, social withdrawal	Eyelid dyspraxia	B	B	n/a
Levodopa response	+	+	+	+	+	+	+	+	+
Dyskinesias	n/a	+	+	+	+	+	+	+	+
Bradykinesia	+	+	+	+	+	+	+	+	+
Rigidity*	+	+	+	+	+	+	+	+	+
Tremor	-	+	+	+	+	-	-	n/a	-
Postural instability	n/a	+	+	+	+	+	+	+	+
Dystonic features	n/a	+	+	-	-	-	-	+	-
Hyperreflexia	+	+	+	+	+	+	+	+	-
Babinski sign	+	+	+	+	+	+	+	+	-
Dementia/cognitive decline	-	-	-	-	-	+	+	+	-
Psychiatric features	-	+	+	+	+	+	+	+	+
Cerebellar signs	-	n/a	n/a	-	-	n/a	n/a	n/a	-
Eye movement abnormality	-	n/a	+	+	+	+	+	+	-
Equinovarus deformity	+	-	+	-	-	n/a	n/a	n/a	n/a

B: Bradykinesia, M: mental retardation, R: rigidity, G: gait disturbance, Psy: behavioral or psychological, n/a: not available.

pendent pathway by the proteasome[9], raising the hypothesis that the mutant ATP13A2 accumulation in the ER may overload the proteasomal degradation pathway and further neuronal dysfunction. Notably, the ATP13A2 protein has recently been identified as a potential modifier of the toxicity induced by a-synuclein in animal models of PD[20]. Loss of ATP13A2 function results in impaired lysosomal function and, consequently, accumulation of SNCA/α-synuclein and neurotoxicity[21]. These findings, together with other recent studies of lysosomal dysfunction in neurodegeneration[22], suggest that strategies to upregulate lysosomal function in neurons represent a promising therapeutic approach for neurodegenerative disorders.

PARK14: PLA2G6

Recessive mutations in PLA2G6 gene can cause a wide spectrum of clinical disorders, including infantile neuroaxonal dystrophy (INAD)[23], neurodegeneration with brain iron accumulation (NBIA)[24], Levodopa-responsive dystonia-parkinsonism syndrome[25], and early-onset PD without complex features[26,27]. The onset age of INAD was between six months and two years of age, associating with severe mental retardation, truncal hypotonia, and progressive spastic tetraparesis. Pathology showed spheroid bodies (axonal swelling) throughout the central and peripheral nervous system[23]. A group of NBIA without PANK2 mutation was caused by PLA2G6 mutation. Patients with NBIA usually had symptoms onset between infancy and 30 years of age

with rapid disease progression[24]. Recent identification of PLA2G6-related Levodopa-responsive dystonia-parkinsonism cases with an onset age ranging from 10 to 26, whose main clinical features were severe akinesia and rigidity, generalized dystonia, pyramidal sign and cognitive impairment, expanded the clinical heterogeneity of PLA2G6 mutations[25]. There is no evidence of brain iron accumulation on neuroimaging in these PLA2G6 related dystonia-parkinsonism cases[25,28]. One recent Chinese cohort has identified the fourth clinical phenotype of PLA2G6 mutation as a pure autosomal-recessive early-onset PD without prominent features of dystonia, pyramidal weakness or dementia[26]. The onset of age of parkinsonism feature was at 37 years old and the response to levodopa was well.

Nowadays, nine patients have been reported to have PLA2G6-related dystonia-parkinsonism. The clinical data were summarized in table 3. The average age of onset of parkinsonism features was 23.7±7.5 years. The presenting symptoms include asymmetric dragging leg, rapid cognitive decline and akinetic-rigidity. In the original patients reported by Paisan-Ruiz, prominent dystonia in the trunk and lower limbs, spasticity, bradykinesia, dysarthria, eye movement abnormality and severe and rapid cognitive decline were noticed[25]. There were no obvious cerebellar signs or atrophy in those patients, which could be distinct from those INAD patients. The initial optimal response to levodopa was not sustained and most of the patients lost their mobility by three years after onset of symptoms. In addition to dystonia, lower limb pyramidal signs were common in these PLA2G6 patients. Cognitive decline was also noted in almost all patients, and some patients also had psychiatric symptoms, including depression and hallucination. Supranuclear gaze palsy was only observed in one patient. One recent report showing three patients with young-onset parkinsonism and cognitive decline to have compound heterozygous mutation of PLA2G6[29]. One patient (Patient A with c.216C>A/c.1904G>A) had iron accumulation in the substantia nigra and striatum on neuroimaging. The other two siblings did not have evidence of brain iron accumulation, but frontotemporal lobar atrophy was noted on head image. Notably, brain pathology in a few patients with PLA2G6 mutations showed widespread Lewy body depositions, particularly in the neocortex, and tau pathology in some cases[30]. These clinical, radiological and pathological features further expand the phenotypes of PLA2G6-related disorders. The fact that identical disease-associated PLA2G6 mutations may cause NBIA, INAD, dystonia-parkinsonism and pure young-onset PD suggests that additional unknown genetic, epigenetic, or nongenetic factors may influence the PLA2G6-associated phenotype.

The PLA2G6 gene encodes a calcium-independent group VI phospholipase A2, which catalyze the hydrolysis of glycerophospholipids with increasing level of free fatty acid lysophospholipid. This phospholipase has been shown to have a role in phospholipid remodeling, arachonic acid release, leukotriene and prostaglandin synthesis, and cellular apoptosis[31]. The mutant PLA2G6 protein carrying disease causing mutation has been shown to cause an approximately 70% reduction in enzyme activity in in vivo assay[26]. However, the exact molecular mechanism that PLA2G6 mutations resulting in neuronal dysfunction remains largely unclear and requires further investigations.

PARK15: FBXO7

A disease-associated variant in FBXO7 gene, p.Arg378Gly, has recently been identified in an Iranian kindred which presented with young-onset PD with pyramidal signs, such as spastic weakness and Babinski signs[32]. Three novel FBXO7 mutations, c.90711G>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[33,34]. These families expanded the phenotypic spectrum associated with FBXO7 mutations making it another cause of young-onset PD with autosomal recessive inheritance (PARK15). Eighteen patients from 5 families have been reported to carry either homozygous or compound heterozygous mutations of FBXO7 gene (Table 4)[32-34]. The average onset age of parkinsonism features was 17.5±4.5 years. The main clinical phenotypes are juvenile-onset parkinsonism and pyramidal signs,

including hyperreflexia and Babinski signs. Rigidity and bradykinesia presented in most of the patients, but resting tremor was not a common feature in these patients with PARK15. Other presenting symptoms include cognitive decline, eyelid apraxia, spuranuclear gaze palsy, slow saccade, gait unsteadiness and early posture imbalance. Levodopa would usually improve clinical symptoms, but levodopa-induced dyskinesia was severe.

Fbxo7 is a member of the F-box-containing protein (FBP) family, characterized by a 40-amino acids domain (the F-box)[35]. Previous studies have revealed that FBPs are often implicated in the ubiquitin-proteasome system and possess diverse functions, including cell cycle progression, synapse formation, plant hormone responses, and the circadian clock[35]. FBXO7 were expressed mainly in cerebral cortex, globus pallidum and the substantia nigra, and with a less extent in the hippocampus and cerebellum[33]. FBXO7 protein has two isoforms. The exact function in the neuron and the pathogenic pathway leading to cell death are still unclear.

SUMMARY

The autosomal-recessive parkinsonian-pyramidal syndromes, including PARK9, PARK14, and PARK15 presented juvenile-onset of PD associated with a complex spectrum of clinical features, which are distinct from typical PD. PARK9 patients often have supranuclear gaze palsy, and some may have facial-faucial-finger mini myoclonus. Patients with PARK14 have early gait disturbance and dystonia. Patients with PARK15 present have prominent spasticity and equinovarus feet deformity was reported to be the initial manifestation. Clarifying the phenotypes of each of these autosomal-recessive parkinsonian-pyramidal syndromes and understanding the mechanism of these causative gene products might illuminate the pathogenesis of dopaminergic neuronal degeneration also in the common forms of PD.

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