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RESEARCH ARTICLE

PARK2 gene variants in Korean patients with Parkinson's disease

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Abstract Mutations in *PARK2* are considered a common cause of Parkinson's disease (PD). To assess the frequency of *PARK2* mutations in the Korean population, we screened the *PARK2* gene in 83 Korean PD patients: two young onset (YO, ≤ 49), 32 middle onset (MO, 50–69) and 49 late onset (LO, ≥ 70). Detection of the point mutations was performed by direct sequencing of the *PARK2* exons, and exonic rearrangements were analyzed using multiplex ligation-dependent probe amplification. Five known *PARK2* variants were identified in 53 (63.9 %) of the Korean PD patients: two missense mutations (Y267H and M458L) and three polymorphisms (S167N, L272I and V380L). We also found an increased frequency of *PARK2* variants in PD patients and a lowered PD age at onset (AAO) in those having two variants, suggesting that the genetic variation in *PARK2* gene might be a genetic risk factor of PD in Korean population.

Min-young Park and In won Park have contributed equally to this work.

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Introduction

A *PARK2* mutation was first described in a Japanese family with an autosomal recessive juvenile Parkinson's disease (PD) (Kitada et al. 1998) and 213 different mutations have since been identified throughout *PARK2*, including large deletions or amplifications, small deletions or insertions, as well as missense mutations (The Parkinson Disease Mutation Database, accessed July 2015). Studies have shown *PARK2* mutations in about 40-50 % of early onset FPD, and about 1.3–20 % of SPD patients (Choi et al. 2008; Hedrich et al. 2004; Kann et al. 2002; Mellick et al. 2009; Oczkowska et al. 2013; Sironi et al. 2008), suggesting that PARK2 dysfunction by mutations might be involved in the pathogenesis of both FPD and SPD.

PARK2, an E3 ubiquitin ligase regulates a variety of processes, including receptor trafficking and mitochondrial quality control, via mono- or poly-ubiquitinations of PARK2 substrates (Dawson and Dawson 2014). Several distinct pathomechanisms by PARK2 mutations have been reported. Many missense mutations reduce the enzymatic activity of PARK2, leading to the abnormal accumulation of toxic proteins and neurodegeneration (Corti et al. 2011; Dawson and Dawson 2010; Sul et al. 2013). The mutations in PARK2 gene also change the general physical characteristics of the protein such as stability and/or solubility, promoting aggregate formation and impairing mitochondrial maintenance, collectively resulting in increased cellular toxicity (Gaweda-Walerych and Zekanowski 2013; Hampe et al. 2006; Oczkowska et al. 2013; Sriram et al.

2005). These results suggest that PARK2 mutants might influence the risk of developing PD.

The frequency of *PARK2* mutation has been reported in the 5.5–15.8 % of the Korean population with early onset PD (EOPD) (Choi et al. 2008; Chu et al. 2014; Kim et al. 2012). However, the frequency of *PARK2* mutation has not been examined in Korean PD patients in other age at onset (AAO) groups. Therefore, this is the first analysis of frequency of *PARK2* variants in Korean PD patients with AAO $\geq$ 50 years.

Materials and methods

Subjects

A total of 83 PD patients were included in the study. To analyze the relationship between AAO and variants, we divided patients into three groups based on their AAO of the disease (Mehanna et al. 2014): those younger than 49 years (young onset PD, YOPD), those between 50 and 69 years (middle onset PD, MOPD), and those older than 70 years (late onset PD, LOPD).

Mutation analysis

Genomic DNA was extracted from peripheral blood by standard protocol. The exons 1–12 of the *PARK2* gene were amplified from genomic DNA using intronic primers (Table 1). The reaction mixture for PCR contained 50 ng of genomic DNA and 10 pmol of each primer. The PCR reactions were denatured at 94 °C for 5 min followed by 30 cycles of 94 °C for 45 s, 50–60 °C for 45 s, and 72 °C for 45 s with a final extension of 7 min at 72 °C. The PCR products were purified and sequenced directly using the ABI 3730XL DNA analyzer (Applied Biosystems).

Gene dosage analysis

Exon rearrangements were analyzed with a multiplex ligation-dependent probe amplification (MLPA) assay using commercially available probes (SALSA P051 Parkinson MLPA kits, MRC Holland). Sequence-specific probes enclosed in this kit are against all exons of *PARK2* and *PINK1*, and specific exons of *SNCA* (exons1, 3–6); *PARK7* (DJ-1, exons 1, 3, 5, 7); *TNFRSF9* (exon 3); *ATP13A2* (exon 2, 9); *LPA* (6q26) and two-point mutations (A30P in *SNCA* and G2019S in *LRRK2*). Experimental procedures were conducted for all 83 samples according to the manufacturer protocol. MLPA peaks analysis, normalization, and calculation of dosage ratio were performed with the GeneMarker software (SoftGenetics LLC) with standard parameters of analysis.

Statistical evaluation

The paired *t* test was used to compare mean AAOs among PD patients with no variant, with one variant, and with $\geq$2 variants. Values were expressed as mean $\pm$ SD and $P < 0.05$ was considered statistically significant.

Results

We sequenced all of the 12 exons of the *PARK2* gene from 15 patients selected randomly from our PD samples in order to see a preliminary profile of the *PARK2* gene of our PD patients. Sequence analysis of 15 patients disclosed

Table 1 PCR primers and annealing temperatures

PARK2 exons	Forward primer 5′ → 3′	Reverse primer 5′ → 3′	Amplicon size	Annealing temperature
1	AGGAGGCGTGAGGAGAAACT	GGTCTTCATGAGAACGCTCAG	460	51
2	GTTTGCAGGTCACTGACGAA	TCCAATCTTTCCTGCTTGCT	591	53
3	GCCCCAGTTCAGTGTTGTTT	TAAATATGCACCCGGTGAGG	522	51
4	GGCTGTTGGCAAGAGAGAGA	AAGACAAAGGCGCATAAACG	514	53
5	GGAAAACGAACAGGTTTGGA	GCACAGGTTGGAATTTTGGT	504	51
6	ACTTTGGCACAAGGTCATCC	GCTCGTGTGGCAGAACAATA	399	53
7	CTTAGCAGCTCCGGTCTTTG	CAATTCCTTCATTCCCCAGA	452	53
8	CTAAAGAGGTGCGGTTGGAG	TATGCAGTGCTTGCTTCCTG	537	53
9	AAGCAAGAAATCCCATGCAC	AAGTCTGGCCTAGTGGCTCA	518	53
10	TGAGGGAAGGAAATGTGACC	GGAACTCTCCATGACCTCCA	414	53
11	CCATCCGCCTAGTAGCTGTC	ACACACCAGGCACCTTCAG	400	52
12	TCTAGGCTAGCGTGCTGGTT	TGCAATTTGGCTGTAGTTGG	355	53

three different missense mutations: S167N (exon 4), V380L (exon 10), and M458L (exon 12). We did not detect novel mutations other than the reported variations in exon 4, 10, and 12. Thereafter, we screened sequence variations in these three exons (exon 4, 10 and 12) of other patient samples, based on the above data. In addition, we also screened exon 2 encoding the ubiquitin-like (Ubl) domain, and exon 6 and 7 encoding RING1 domain, because mutations in these domains tend to affect the enzymatic function of PARK2 (Caulfield et al. 2014).

The demographic characteristics of the 83 patients are presented in Table 2 (YOPD, N = 2; MOPD, N = 32; LOPD, N = 49). Five variants identified in this study are S167N (c.500G > A), Y267H (c.799T > C), L272I (c.814C > A), V380L (c.1138G > C), and M458L (c.1372A > C) (Table 3). S167N polymorphism in exon 4 was the commonest variant (allele frequency of 40.4 %) when compared to the other polymorphisms. L272I and V380L alleles were found relatively infrequently (0.6 and 4.2 % of the allele frequencies in the PD patients, respectively).

In order to detect exon dosage changes caused by genomic rearrangements of the known PD genes, we used the SALSA P051-B1 kit. The kit consists of probes for specific exons of *SNCA, PARK7, TNFRSF9, ATP13A2,* and *LPA*, as well as point mutations of *SNCA* A30P and *LRRK2* G2019S. Three out of 83 patients had genomic duplications in the *PARK2* and *PINK1* loci (Fig. 1; Supplementary Table 1) and other major PD gene rearrangements were not detected: two patients had duplication of the *PARK2* gene and one patient had duplication of the *PINK1* gene.

When point mutations and exonic rearrangements were taken together, *PARK2* variants were found in 54 (65 %) of 83 PD patients (Table 4): 23 patients carried compound heterozygous or homozygous variants, and 31 patients carried a single heterozygous variant. One patient with *PINK1* mutation did not have *PARK2* variant.

Discussion

PARK2 is a well-known risk factor for juvenile and early onset occurrence of PD (Kitada et al. 1998). Moreover, the importance of *PARK2* mutations in sporadic PD have also been reported (Foroud et al. 2003; Oczkowska et al. 2013). In the Korean population, *PARK2* mutations were reported in about 5.5–18.5 % of EOPD and FPD (Choi et al. 2008; Chu et al. 2014; Kim et al. 2011, 2012). However, genetic study of late onset PD has not yet been reported. Therefore, this study assessed the frequency of *PARK2* mutation in Korean PD patients, with AAO after 50 years.

We found that S167N polymorphism was the commonest with high frequency (40.4 %) in our study. Studies regarding the allele frequency of S167N vary greatly among populations with different ethnic origins ((Li et al. 2005; Martinez et al. 2010; Mellick et al. 2001; Sakai et al. 2010; Sinha et al. 2005). In the Asian SPD populations (Japanese, Chinese, and Taiwanese), the frequency of S167N polymorphism was 38.6–46.6 % (Supplementary Table 2) and that of Korean SPD in this study also fits in this range. On the other hand, S167N allele was found in only 0.2–2.5 % of a Caucasian population. The frequency of S167N polymorphism was also higher in the Asian EOPD population (around 40 %) than in the Caucasian EOPD population (2.6–12.9 %) (Supplementary Table 3). Taken together, S167N polymorphism may be a susceptibility factor to PD in Asian populations.

The study by Ghione et al.(Ghione et al. 2007) reported that the combination of *PARK2* polymorphisms including S167N (14 % of cases, heterozygous) and environmental

Table 2 Demographics of PD patients with one, with ≥ two variants, and without variant

	Total patients (n = 83)	Patients without variant (n = 28)	Patients with a single variant (n = 32)	Patients with ≥ 2 variants (n = 23)
Gender, M/F (male%)	32/51 (38.6)	11/17 (39.3)	10/22 (31.3)	11/12 (47.8)
AAO, n (%)				
YOPD ≤ 49	2 (100)	1 (50)	–	1 (50)
MOPD 50–69	32 (100)	12 (37.5)	13 (40.6)	7 (21.9)
LOPD ≥ 70	49 (100)	15 (30.6)	19 (38.8)	15 (30.6)
AAO, yr	70.8 ± 10.6	71.4 ± 9.4	71.1 ± 10.7	69.8 ± 12.0
YOPD ≤ 49	40.0 ± 7.1	45	–	35
MOPD 50–69	62.2 ± 6.2	65.5 ± 4.2	60.6 ± 6.9*	59.6 ± 6.1*
LOPD ≥ 70	77.7 ± 5.2	77.9 ± 5.8	78.3 ± 5.5	76.9 ± 4.2

Values are shown as mean ± standard deviation

M male, *F* female, *AAO* age at onset, *PD*, Parkinson's disease, *YOPD* young onset PD, *MOPD* middle onset PD, *LOPD* late onset PD

* $P < 0.05$ compared with no variation group (paired *t*-test)

Table 3 Allele and genotype frequencies of *PARK2* variants in PD patients

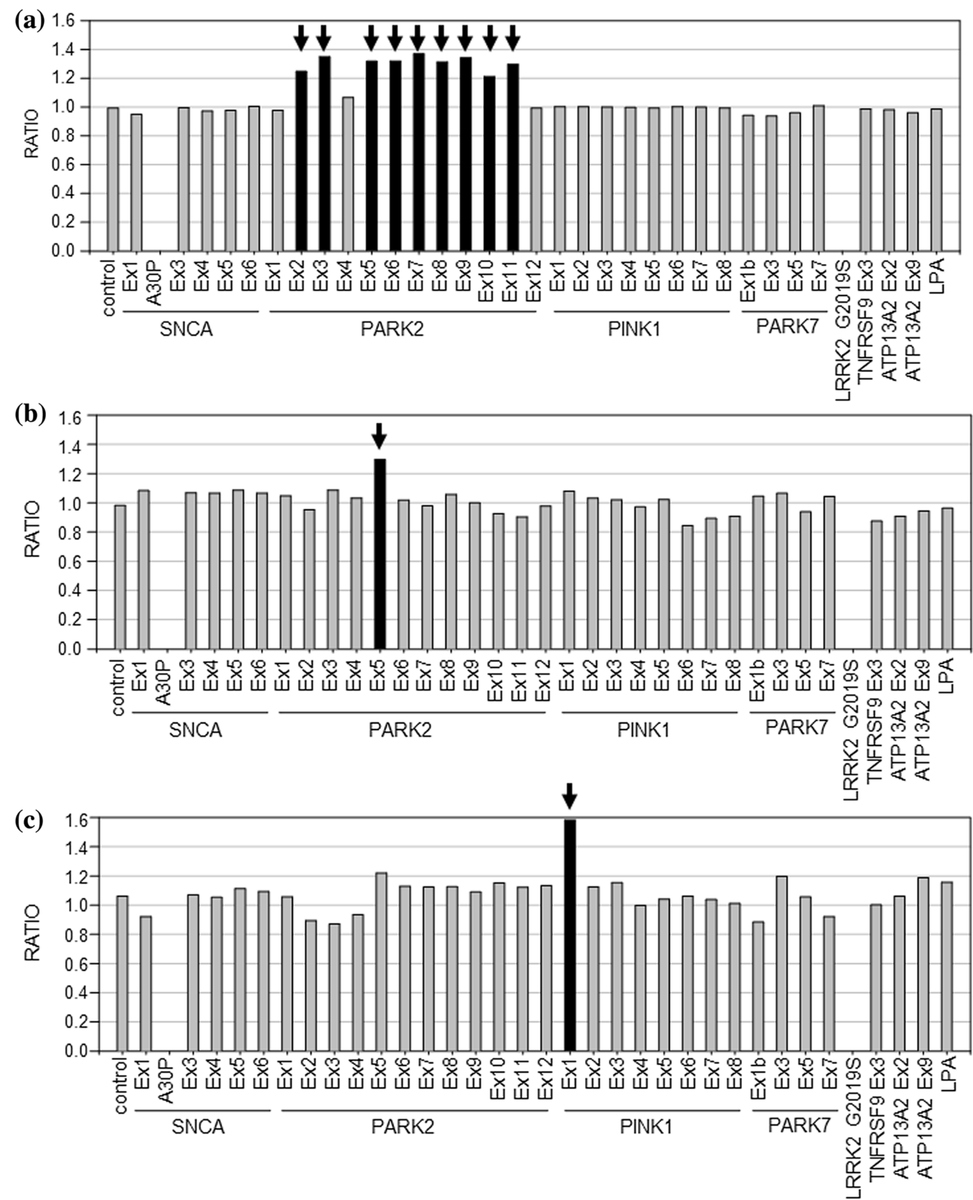
PARK2	Variant allele/genotype	Total PD (n = 83) N (%)	YOPD (n = 2) N (%)	MOPD (n = 32) N (%)	LOPD (n = 49) N (%)
Ex4	S167N (G > A)				
	Allele G	99 (59.6)	2 (50)	40 (62.5)	57 (58.2)
	Allele A	67 (40.4)	2 (50)	24 (37.5)	41 (41.8)
	G/G	32 (38.6)	1 (50)	13 (40.6)	18 (36.7)
	G/A	35 (42.2)	–	14 (43.8)	21 (42.9)
	A/A	16 (19.3)	1 (50)	5 (15.6)	10 (20.4)
	G/A+A/A	51 (61.4)	1 (50)	19 (59.4)	31 (63.3)
Ex7	Y267H (T > C)				
	Allele T	165 (99.4)	4 (100)	64 (100)	97 (99)
	Allele C	1 (0.6)	–	–	1 (1)
	T/T	82 (98.8)	2 (100)	32 (100)	48 (98)
	T/C	1 (1.2)	–	–	1 (2)
	C/C	–	–	–	–
	T/C+C/C	1 (1.2)	–	–	1 (2)
	L272I (C > A)				
	Allele C	165 (99.4)	4 (100)	64 (100)	97 (99)
	Allele A	1 (0.6)	–	–	1 (1)
	C/C	82 (98.8)	2 (100)	32 (100)	48 (98)
	C/A	1 (1.2)	–	–	1 (2)
	A/A	–	–	–	–
	C/A+A/A	1 (1.2)	–	–	1 (2)
Ex10	V380L (G > C)				
	Allele G	159 (95.8)	4 (100)	61 (95.3)	94 (95.9)
	Allele C	7 (4.2)	–	3 (4.7)	4 (4.1)
	G/G	77 (92.8)	2 (100)	29 (90.6)	46 (93.9)
	G/C	5 (6)	–	3 (9.4)	2 (4.1)
	C/C	1 (1.2)	–	–	1 (2)
	G/C+C/C	6 (7.2)	–	3 (9.4)	3 (6.1)
Ex12	M458L (A > C)				
	Allele A	165 (99.4)	4 (100)	63 (98.4)	98 (100)
	Allele C	1 (0.6)	–	1 (1.6)	–
	A/A	82 (98.8)	2 (100)	31 (96.9)	49 (100)
	A/C	1 (1.2)	–	1 (3.1)	–
	C/C	–	–	–	–
	A/C+C/C	1 (1.2)	–	1 (3.1)	–

Ex exon

factors including pesticides, organic solvents, and rural living, strongly affects lowering the AAO of PD. S167N is located in exon 4 encoding the RING0/unique Parkin domain (UPD), a PINK1 interacting domain. PINK1 kinase activates PARK2 via phosphorylation of PARK2 on residue Ser65 (Iguchi et al. 2013; Kondapalli et al. 2012; Okatsu et al. 2012; Seirafi et al. 2015). It would be interesting to know whether S167N polymorphism interferes with the binding of PARK2 to PINK1 when an environmental risk factor is added. It is also probable that S167N polymorphism may promote aggregation or impair mitochondrial homeostasis by environmental and/or other genetic factors. Further functional studies of *PARK2* polymorphisms would be useful for diagnostic and prognostic processes related to PD.

In the Korean LOPD patients, we found *PARK2* exon duplication in only two patients: one had exon 5 duplication and the other had multiple duplications (exon 2, 3,

Fig. 1 MLPA analysis results of three patients with gene dosage alteration



Duplication of *PARK2* exon 2,3,5-11 (**a**), Duplication of *PARK2* exon 5 (**b**), and Duplication of *PINK1* exon 1 (**c**)

5–11) (Fig. 1 and Supplementary Table 1). On the other hand, a larger case study showed duplication of *PARK2* on exons 2–7 in 2,091 PD patients (mean AAO 58.3 ± 12.1 years), and duplication of exon 1, 2, and 3 in 1,686 controls (mean age 66.1 ± 13.1 years) (Kay et al. 2010). Interestingly, only duplication of exon 4 was reported in American, Polish, and French EOPD patients (Ambroziak et al. 2015; Hedrich et al. 2001; Kay et al. 2010; Periquet et al. 2003). Therefore, it seems worthy to further investigate the role of exon 4 of *PARK2* in the pathomechanism of EOPD.

To assess the relevance between variants and AAO, we performed a subgroup analysis (Mehanna et al. 2014): YOPD, MOPD and LOPD (Table 2). In MOPD, the average AAO was lower in patients with ≥2 variants than in patients with one variant, or without variant of statistical significance. We also observed lowered average AAO in LOPD patients with ≥2 variants; however, this was without statistical significance.

In this study, two variants (Y267H and L272I) in exon 7 encoding the RING1 domain were found in LOPD, while two variants (V380L and M458L) in exon 10 and 12 encoding c-terminus, were observed in MOPD (Table 3). RING1 recruits the E2 enzyme, but loss of the RING1 domain does not result in a loss of ligase activity (Chew et al. 2011; Matsuda et al. 2006; Spratt et al. 2013). This suggests that PARK2 is an E2-independent ubiquitin ligase, a RING between RING (RBR) E3 ligase. RING2 in

Table 4 Detected variants in this study

Gene	N	Variants	Exon	Zygosity
PARK2 (n = 54)	15	S167N homo	4	Homoozygous
	29	S167N het	4	Heterozygous
	1	Y267H het	7	Heterozygous
	1	V380L het	10	Heterozygous
	1	S167N het + L272I het	4, 7	Compound heterozygous
	1	S167N homo + V380L het	4, 10	Compound heterozygous
	1	S167N het + V380L homo	4, 10	Compound heterozygous
	2	S167N het + V380L het	4, 10	Compound heterozygous
	1	S167N het + M458L het	4, 12	Compound heterozygous
	1	S167N het + V380L het + Ex5 dup	4, 5, 10	Compound heterozygous
	1	Ex2, 3, 5–11 dup	2, 3, 5-11	Compound heterozygous
PINK1 (n = 1)	1	Ex1 dup	1	Heterozygous

Ex exon, *Dup* duplication, *Homo* homozygous, *Het* heterozygous

the c-terminus of PARK2 is the true catalytic domain, and structural study of RING2 has shown that it is required for E2 recruitment, catalysis, and *trans* autoubiquitination. Consistent with this, AAOs of patients with c-terminal variant (V380L and M458L) were lowered when compared to those of patients with RING1 variant in our study (Table 3). Our data also suggest that the c-terminus of PARK2 might play a more important role than the RING1 region, in PD pathogenesis.

In conclusion, we have for the first time, presented a genetic analysis of the *PARK2* gene in relation to Korean MOPD and LOPD. A high frequency of *PARK2* variants in PD patients was found, suggesting that *PARK2* variants might be a genetic risk factor for PD in Korean populations.

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Compliance with ethical standards

Conflicts of interest The authors have no financial conflicts of interest.

Compliances of bioethical regulation Written informed consent was approved by the Institutional Review Board of Eulji University Hospital. The experimental procedures followed the standard regulation of the Review Board.

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