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Genetic variants of PARK genes in Korean patients with early-onset Parkinson's disease

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ABSTRACT

Early-onset Parkinson's disease (EOPD) can be linked to different genetic backgrounds depending on the disease characteristics. In Korean patients with EOPD, however, only 5 PARK genes have been tested. We recruited 70 patients with EOPD from 4 hospitals in Korea, and 12 PARK genes were screened via multigene panel sequencing. Large insertions or deletions were confirmed by multiplex ligation-dependent probe amplification. We found 20 rare variants (2 in *SNCA*, 2 in *PRKN*, 6 in *LRRK2*, 3 in *PINK1*, 1 in *DJ1*, 4 in *FBX07*, 1 in *HTRA2*, and 1 in *EIG4G1*) in 20 subjects regardless of heterogeneity. Two pathogenic variants (*SNCA* in 2 subjects and *DJ1* in one) were from 3 subjects, and 7 likely pathogenic variants (*SNCA*, *LRRK2*, *FBXO7*, and 2 in *PINK1* and *PRKN*) from 7. Akinetic-rigid subtype and dystonia were more common in patients with EOPD with rare variants than in those without rare variants. Multigene panel tests can be effective at identifying genetic variants in patients with EOPD. In addition, we suggest there are different genetic backgrounds in patients with EOPD.

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1. Introduction

Age of onset is an important factor in neurodegenerative diseases that is related to characteristic phenotypes and disease progression (Jang et al., 2016; Koedam et al., 2010; Mehanna et al., 2014). Compared to the patients with typical-onset PD, the patients with early-onset PD (EOPD) had characteristic features, such as a more benign progression, better response to levodopa, and more dyskinesia, have previously been demonstrated (Schrag et al., 1998; Spica et al., 2013; Tang et al., 2016). In addition, previous studies have suggested clinical features associated with genotypes in patients with PD (Koros et al., 2017; Lim and Tan, 2017). Therefore, considering phenotypic discrepancies related to age of onset and genotypes, different genetic backgrounds could be associated with different pathomechanisms, especially in patients with EOPD versus patients with PD with older age of onset (Nalls et al., 2015; Payami et al., 2002).

Various causative genes have been identified in patients with EOPD (Zeng et al., 2018), and diverse detection rates ranging from 3.7% to 16.6% have been reported when these genes were tested in previous studies (Alcalay et al., 2010; Choi et al., 2008; Erer et al., 2016; Guo et al., 2010; Macedo et al., 2009; Mellick et al., 2009). This discrepancy among studies may result from genetic heterogeneity related to ethnicity and geography (Cho et al., 2009). In a previous study of 5 PARK genes (*SNCA*, *PRKN*, *PINK1*, *PARK7*, and

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LRRK2) in 72 patients with EOPD in Korea, 25% had rare variants and 5.6% revealed disease-causing pathogenic variants regardless of heterogeneity (Choi et al., 2008).

Monogenic PD accounts for less than 10% of PD cases (Lesage and Brice, 2009), and susceptibility genes, including *SNCA*, microtubule-associated protein tau, *LRRK2* and glucocerebrosidase (*GBA*), have been validated as significant risk factors for PD (Choi et al., 2012a; Foo et al., 2014; Kim et al., 2010; von Coelln and Shulman, 2016). However, these susceptibility genes also explain a small fraction of the genetic variation in PD. In addition, Spataro et al. suggested that a clear abundance of rare functional variants in PD-related genes is observed in patients with sporadic PD and that these variations may play a role in PD etiology (Spataro et al., 2015). With genome-wide analysis, variants of PD-related genes were reported as risk factors for PD (Chang et al., 2017; Nalls et al., 2014). Therefore, we hypothesized that the numerous rare variants indicate the genetic heterogeneity of EOPD and aimed to investigate rare variants of PD-related genes in Korean patients with EOPD using multigene panel testing.

2. Materials and methods

2.1. Subjects and clinical assessments

The study was approved by the institutional review boards of all involved hospitals, and informed written consent was obtained by all participants. We recruited unrelated patients with EOPD from March 2016 to September 2016 from the Movement Disorders Clinics at 4 hospitals (Gangneung Asan Hospital, Samsung Medical Center, Soonchunhyang University Seoul Hospital, and Chungnam National University Hospital) in South Korea. The ethnicity of all recruited participants was Korean. PD was diagnosed using the Movement Disorders Society Clinical Diagnostic Criteria for Parkinson's Disease (Postuma, 2015), and EOPD was defined as PD with age of onset $\leq$50 years (Choi et al., 2008).

We obtained basic demographic and clinical data, including age, sex, disease duration, and family history. Family history was considered positive if more than 2 patients were reported through the third degree pedigree. Disease severity was evaluated using the United Parkinson's Disease Rating Scale (UPDRS) Part 3 score and the Hoehn and Yahr stage (Hoehn and Yahr, 1998). All enrolled subjects were divided into 3 subgroups based on the primary motor symptoms: akinetic-rigid, tremor-dominant, or mixed subtypes (Kang et al., 2005). In addition, dystonia, which is a characteristic motor symptom for patients with EOPD, was assessed at the clinic in all enrolled subjects. To evaluate premotor symptoms, we evaluated rapid eye movement (REM) sleep behavior disorder (RBD) using the RBD single-question screen (RBD1Q) (Postuma et al., 2012), cognitive function using the Korean version of the Montreal Cognitive Assessment (Lee et al., 2008), and depression using Beck's Depression Inventory (Jo et al., 2007). Constipation and hyposmia were defined based on clinical history. All clinical assessments were performed at drug-naïve status.

We excluded subjects with structural brain lesions on brain magnetic resonance imaging, other known neurodegenerative diseases, psychiatric disorders requiring medication, cognitive decline (Korean Mini–Mental Status Exam score $\leq$20), or musculoskeletal problems mimicking parkinsonism.

2.2. Gene analysis

2.2.1. Gene panel construction

We constructed a multigene panel comprising (1) genes that are reportedly involved in autosomal dominant and recessive Mendelian forms of PD, so called familial PD and (2) genes that are unconfirmed in the Mendelian form. The following 12 genes were selected for the targeted gene sequencing panel: *SNCA* and *LRRK2* for the autosomal dominant form; *PRKN, PINK1, PARK7, ATP13A, FBX07*, and *PLA2G6* for the autosomal recessive form; and *GIGYF2, HTRA2, EIG4G1*, and *UCHL1* for the unconfirmed form (Supplementary Table 1). *VPS35* and *DNAJC6* were not included in the panel due to a lack of clinical and pathological details and will be analyzed separately in another study.

2.3. Multigene panel sequencing

Genomic DNA extracted from peripheral blood leukocytes of patients with EOPD was captured for the SureSelect customized kit (Agilent Technologies, Santa Clara, CA) against the 12 aforementioned PD-related genes. Captured libraries were sequenced with 100-bp paired-end reads using the HiSeq 2500 platform (Illumina, San Diego, CA).

The acquired reads were mapped onto the UCSC hg19 reference genome using Burrows-Wheeler Aligner (v0.7.5a) (Li et al., 2009). Picard (v1.127) (https://broadinstitute.github.io/picard/), SAMTOOLS (v1.2) (Li et al., 2009), and GATK(v3.1-1) (McKenna et al., 2010) were used for deduplicating, sorting, indexing, local realignment, and base recalibration of aligned reads. We calculated depth of coverage and statistics of parameters from the processed BAM files, which are shown in Supplementary Table 2.

2.4. Calling and prioritization of variants

Single-nucleotide variants (SNVs) and insertions/deletions (InDels) were called from the processed reads by Unified Genotyper in GATK. ANNOVAR was used to annotate the variants (Wang et al., 2010). The pathogenicity of SNVs or InDels was evaluated using the SIFT (Ng and Henikoff, 2003), PolyPhen-2 (Adzhubei et al., 2010), GERP++ (Davydov et al., 2010), and PROVEAN prediction tools (Choi et al., 2012b), and splice variants were estimated with the Human Splicing Finder (HSF) (Desmet et al., 2009). We selected exonic and splice variants located in known genes with a rare minor allele frequency ($<$0.01) from the Exome Aggregation Consortium (ExAC) (Table 1; Lek et al., 2016).

Copy number variants (CNVs) were called by an in-house CNV tool that estimates the log2 normalized depth ratio of each targeted

Table 1
Summary of sequencing data analysis: base mapping to target regions

Total reads (N)	13,463,304
Total yield (bp)	1,208,349,409
Average read length (bp)	101
Target regions (bp)	458,428
% Coverage of target regions (more than 1×)	97.45
% Coverage of target regions (more than 10×)	96.62
Mean depth of target regions	1517.5
Number of SNV/InDels	5070319
Number of SNV/InDels in PARK-related genes	94
Number of coding SNV/InDels (more than 3X)	73
Number of rare SNV/InDels (ExAC MAF $<$ 0.01)	28
Number of synonymous SNVs	9
Number of nonsynonymous SNVs	16
Number of SNV/InDels in splice site	1
Number of nonframeshift InDels	2
Number of frameshift InDels	0
Number of CNVs	2

Key: SNV, single nucleotide variant; InDels, insertion and deletion; ExAC, The Exome Aggregation Consortium; MAF, minor allele frequency.

Table 2
Demographic and clinical data of the enrolled patients with EOPD

Variable	Total subjects (n = 70)	With variants (n = 20)	Without variants (n = 50)	*p*-value
Male, n (%)	33 (47.2)	8 (40%)	25 (50%)	0.597
Age of onset, y	44.7 ± 0.6	44.9 ± 5.6	44.6 ± 4.5	0.545
Disease duration				
Subjects with family history of PD, n (%)	4 (5.7)	0 (0)	4 (8)	0.319
Subtypes (AR/TD/mixed), n (%)	35/21/14 (50/30/20)	15/3/2 (75/15/10)	20/11/19 (40/22/38)	0.022*
UPDRS part 3	21.8 ± 1.5	21.8 ± 11.4	21.8 ± 12.6	0.789
Hoehn and Yahr stage	2.0 ± 0.1	2.1 ± 0.7	2.0 ± 0.7	0.565
Dystonia, n (%)	14 (20)	9 (45)	5 (10)	0.002*
Beck's Depression Inventory	13.0 ± 1.1	13.2 ± 8.4	12.9 ± 10.1	0.653
Constipation, n (%)	28 (40)	11 (55)	17 (34)	0.116
REM sleep behavior disorder, n (%)	25 (35.7)	10 (50)	15 (30)	0.167
Hyposmia, n (%)	32 (45.7)	9 (45)	23 (46)	0.116
MoCA-K	24.2 ± 0.7	23.2 ± 4.9	24.5 ± 5.8	0.145

Key: EOPD, early-onset Parkinson's disease; PD, Parkinson's disease; AR, akinetic-rigid subtype; TD, tremor-dominant subtype; UPDRS, unified Parkinson's disease rating scale; REM, rapid eye movement; MoCA-K, Korean version of Montreal Cognitive Assessment.
* *p*-value < 0.05.

region with a pooling method. Finally, we prioritized CNVs containing PD-related genes.

2.5. Sanger sequencing and MLPA

All rare variants were validated by Sanger sequencing. Large deletions and insertions that were suspected by CNV analysis were confirmed by multiplex ligation-dependent probe amplification (MLPA) as described previously (http://ng.neurology.org/content/2/3/e73).

3. Results

3.1. Patient characteristics

We recruited 70 unrelated, drug-naïve, patients with EOPD for this study, and the mean age at onset was 44.7 ± 0.6 years. Demographic and clinical variables of the subjects are shown in Table 2. Of the 70 patients with EOPD, 4 (5.7%) had a family history of PD (Fig. 1). In addition, 11 patients (15.7%) showed dystonia. Regarding premotor symptoms, 40% of enrolled patients had constipation, 35.7% demonstrated RBD, and 45.7% reported hyposmia.

3.2. Multigene panel sequencing

Multigene panel sequencing was performed in all of the enrolled subjects with fully covered PARK-related genes. Following the variant-filtering steps, 19 SNVs/InDels on exons or splice sites from 8 genes were selected as candidate disease-related variants in 20 patients (Table 3). Candidate SNVs or InDels in exon regions were annotated with SIFT, PolyPhen-2, and PROVEAN, as well as GERP++. The MAF (minor allele frequency) of all ethnicities of ExAC was annotated, indicating that most of the variants were novel or extremely rare.

In addition, the splice variant (*PARK7*, NM_001123377.1:c.409+1G>A) was predicted as "site broken," meaning damaged by HSF3 (Table 3). CNVs were calculated using an in-house CNV tool based on the depth-of-coverage ratio around the samples. *SNCA* triplication was detected in 2 patients (Fig. 2), which is a well-known pattern from EOPD (Singleton et al., 2003). All 19 candidate SNVs/InDels and *SNCA* triplications were validated by Sanger sequencing and MLPA, respectively.

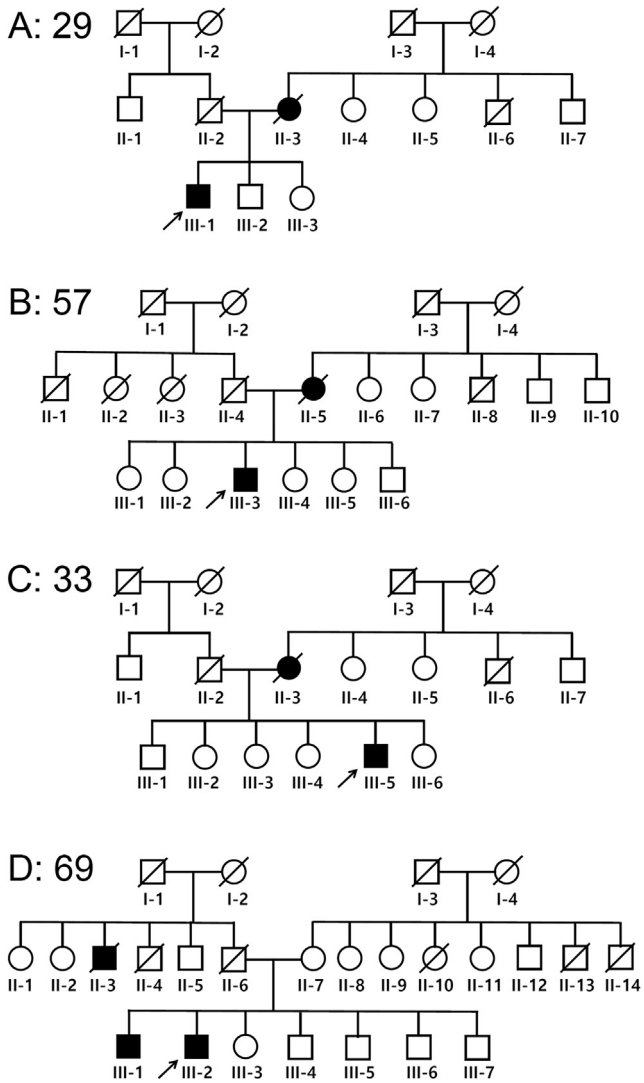

Fig. 1. Pedigree of enrolled patients with EOPD with a family history. Of 70 subjects, 4 had a family history, and no rare PARK gene variants were detected in these 4 subjects. Each number indicates patient's ID.

Table 3
In silico analysis of variants of uncertain significance detected in this study and their frequencies in the ExAC databases

Gene	NM number	cDNA change	Amino acid change	PolyPhen-2	SIFT	GERP++	PROVEAN	HSF3	ExAC						dbSNP
									AFR	AMR	EAS	FIN	NFE	OTH	SAS	
SNCA	NM_000345	Triplication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SNCA	NM_000345	c.171G>T	p.Glu57Asp	0.953	0.01	3.93	−1.98	-	0	0	0	0	0	0	0	-
PRKN	NM_004562	c.814C>A	p.Leu272Ile	0.998	0.36	4.7	−1.63	-	0	0	0.0016	0	0	0	0	rs141366047
PRKN	NM_004562.2	c.941G>A	p.Arg314Gln	0.994	0.1	5.72	−2.72	-	0	0.0002	0	0.0002	0.00001511	0	0	-
PINK1	NM_032409	c.835C>T	p.Arg279Cys	0.987	0.14	5.85	−2.47	-	0.0003	0	0.0005	0	0	0	0.00006056	rs61735932
PINK1	NM_032409.2	c.1024A>C	p.Met342Leu	0.705	0.88	6.04	−0.13	-	0	0	0.0003	0	0	0	0	-
PINK1	NM_032409.2	c.169_170insGCAGGG	p.Arg58_Val59insGlyArg	-	-	-	−0.23	-	0	0	0		0	0	0	-
PARK7	NM_00112d3377.1	c.409+1G>A	-	-	-	5.92	-	Site broken	0	0	0	0	0	0	0	-
LRRK2	NM_198578.3	c.4337C>T	p.Pro1446Leu	1	0.01	5.63	−5.55	-	0	0.00008669	0.0034	0	0	0	0	rs74681492
LRRK2	NM_198578.3	c.922T>A	p.Leu308Met	0.952	0.03	0.395	−0.69	-	0	0	0	0	0	0	0	-
LRRK2	NM_198578.3	c.5740C>A	p.Leu1914Ile	0.326	0.38	5.06	−0.24	-	0	0	0	0	0	0	0	-
LRRK2	NM_198578.3	c.3200G>A	p.Arg1067Gln	0.994	0.2	5.85	−1.78	-	0	0	0.0002	0	0	0	0.0001	rs111341148
LRRK2	NM_198578.3	c.7173C>G	p.His2391Gln	0.003	0.43	0.903	−0.94	-	0	0	0.0011	0	0	0	0	rs199680004
LRRK2	NM_198578.3	c.4106T>C	p.Val1369Ala	0.153	0.05	5.39	−2.07	-	0	0	0	0	0	0	0	-
HTRA2	NM_013247	c.1253A>G	p.Glu418Gly	0.004	1	3.64	5.21	-	0	0	0.0005	0	0	0	0	-
FBXO7	NM_012179	c.155A>G	p.Tyr52Cys	0.006	0.01	3.15	−0.33	-	0	0	0.0055	0	0	0	0.0003	-
FBXO7	NM_012179.3	c.1132C>T	p.Arg378Cys	1	0.01	3.91	−5.15	-	0.0000961	0	0.0005	0	0.00002999	0	0	rs71799110
FBXO7	NM_012179.3	c.803A>G	p.Asn268Ser	0.125	0.49	3.72	−0.73	-	0	0	0.0004	0	0.00001796	0	0.0006	rs188111542
FBXO7	NM_012179.3	c.1065_1066insAAA	p.Leu355_Ser356insLys	-	-	-	−8.54	-	0	0	0	0	0	0	0	-
EIF4G1	NM_004953.4	c.3734C>T	p.Ser1245Phe	0.002	0.77	2.09	−2.38	-	0	0	0.0003	0	0.000015	0	0	-

All demographic and clinical data on the subjects with rare variants are shown in Table 4. Among the detected variants, 6 variants (p.Leu308Met, p.Arg1067Gln, p.Pro1336Leu, p.Val1369Ala, p.Pro1446Leu, p.Leu1914Ile, and p.His2391Gln) in *LRRK2*, 4 variants (p.Tyr52Cys, p.Asn268Ser, p.Leu355_Ser356insLys, and p.Arg378-Cys) in *FBXO7*, and 3 variants (p.Arg58_Val59insGlyArg, p.Arg279-Cys, and p.Met342Leu) in *PINK1* were detected in 13 patients with EOPD. Two patients with EOPD had 2 rare variants (*PARK7* and HTRA2 in 1 patient, and PINK1 and FBXO7 in the other). Two pathogenic variants were detected in 3 patients (4.3%), and *SNCA* triplication was detected in 2 subjects, *PARK7*:c.409+1G>A. In addition, 8 likely pathogenic variants were detected in 8 subjects (11.4%), including p.Glu57Asp in *SNCA* (c.171G>T), p.Leu272Ile and p.Arg314Gln in *PRKN* (c.814C>A and c.941G>A, respectively), p.Arg58_Val59insGlyArg and p.Arg279Cys in *PINK1* (c.169_170insGCAGGG and c.835C>T, respectively), p.Val1369Ala in LRRK2 (c.4106T>C), and p.Leu355_ser356insLys and p.Arg378Cys in *FBXO7* (c.1065_1066insAAA and c.1132C>T, respectively).

3.3. Comparison of clinical data between patients with EOPD with and without PARK gene variants

When we compared the clinical and demographic data of patients with EOPD with and without rare PARK gene variants, patients with EOPD with rare variants had more akinetic-rigid subtype symptoms than those without rare variants (Table 2). In addition, more dystonia was reported in patients with EOPD with rare PARK gene variants than in those without rare variants. For nonmotor symptoms, RBD and constipation were more common in those with rare PARK gene variants than in those without rare variants, but the difference was not significant.

4. Discussion

This is the first study to investigate most PARK genes in patients with EOPD in Korea. In the present study of Korean patients with EOPD, pathogenic and likely pathogenic variants were detected in 3 and 8 patients (4.3% and 11.4%, respectively), and rare PARK gene variants were detected in 20 (28.6%) of the 70 enrolled patients with EOPD. When we compared the clinical characteristics of patients with EOPD with and without rare PARK gene variants, we found that compared to patients without rare variants, patients with rare variants presented more akinetic-rigid symptoms as a main clinical feature even from early disease stages.

Unlike our study, previous studies have assessed 5 or fewer common PARK genes in patients with EOPD or familial PD patients (Choi et al., 2008; Erer et al., 2016; Guo et al., 2010; Macedo et al., 2009; Mellick et al., 2009). When 3 PARK genes (*PRKN, PARK7,* and *PINK1*) were screened in Dutch patients, 3% of patients with EOPD had pathogenic variations (Macedo et al., 2009). Other studies that evaluated 5 PARK genes (*SNCA, PRKN, PINK1, PARK7,* and *LRRK2*) in Australia and Korea detected pathogenic mutations (homozygote or compound heterozygote for autosomal recessive PARK genes, and heterozygote for autosomal dominant PARK genes) in 4.1%–4.2% of patients with EOPD (Choi et al., 2008; Mellick et al., 2009). In the present study, we investigated 8 PARK genes, and 4.3% of patients with EOPD had pathogenic variants. Therefore, based on our results, the number of PARK genes investigated can affect the detection rate, although the rate for genetic PD was still low. Interestingly, the detection rate for pathogenic PARK gene variants differed among the previous studies (Choi et al., 2008; Erer et al., 2016; Macedo et al., 2009; Mellick et al., 2009), and no patients with EOPD had *PRKN* variants in our study. Regional and ethnic differences may account for this discrepancy. In addition, because the youngest age of onset was 31 years in our study and the

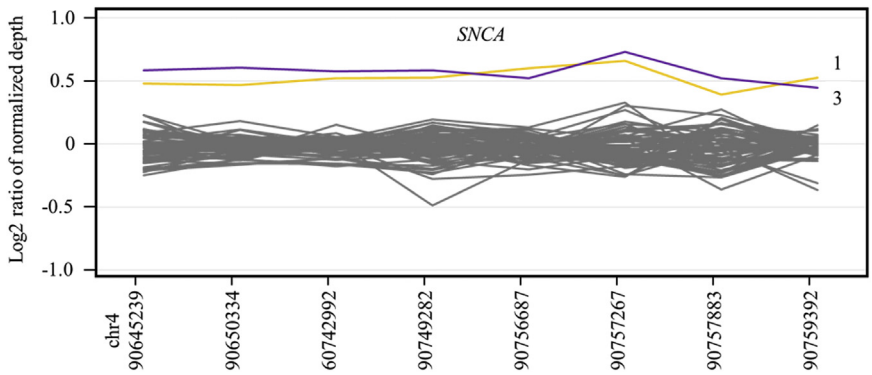

Fig. 2. Copy number variation in the *SNCA* gene. Line plot of copy number variants based on the log2 ratio of normalized depth (y-axis) in 70 patients with EOPD at the *SNCA* genomic position (x-axis). The 2 lines (yellow and purple) represent the entire *SNCA* copy number amplification in patients #1 and #3 compared with the other 68 patients with EOPD with no CNVs in *SNCA* (gray line), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

PRKN variant is associated with juvenile PD, the variable detection rate of *PRKN* variants may also be related to the age of onset among the enrolled patients.

Recently, Mendelian inheritance genes related to monogenic PD showed a clear enrichment of rare variants in sporadic PD, and additional rare variants may contribute to younger age of onset. Because most previous studies did not evaluate rare variants in patients with EOPD, direct comparison with our results is difficult. A recent study that screened 4 PARK genes (*SNCA, Parkin, PINK1,* and *PARK7*) in Turkish patients with EOPD detected pathogenic variants in 3 patients (6%) and likely pathogenic variants in 18 (36%) regardless of homogeneity (Erer et al., 2016). Interestingly, one previous study reported SNCA variants as a cause or genetic risk factor in 25% of patients with EOPD and *PRKN* as the most common genetic cause for EOPD in Korea (Choi et al., 2008). In contrast, our results showed that SNCA is the most common genetic cause and that LRRK2 is the PARK gene with the most common rare variants. Considering these two studies were conducted in Korean EOPD patients, this discrepancy may be due to different recruitment between the two studies, and further studies of larger samples will help identify variants related with EOPD and the exact frequency of causative mutations.

In addition, beyond causative genes, rare variants in PARK gene panels may affect some clinical phenotypes. Regarding parkinsonism, we identified more akinetic-rigid subtypes in patients with EOPD compared with drug-naïve PD patients in Korea (Mun et al., 2016), but more patients with an akinetic-rigid subtype were reported in patients with EOPD, similar to our results (Macedo et al., 2009; Wickremaratchi et al., 2011; Zhou et al., 2013). Therefore, a higher proportion of akinetic-rigid subtypes may be characteristics of EOPD. Moreover, when we compared motor subtypes between patients with EOPD with and without rare PARK gene variants, PARK gene variants were associated with akinetic-rigid subtypes, and this relationship may explain the characteristic motor subtype for EOPD. Similarly, patients with EOPD with rare PARK gene variants had more dystonia, which is another known characteristic motor symptom of EOPD (Wickremaratchi et al., 2011).

For nonmotor symptoms, RBD and constipation were more common in patients with EOPD with rare variants than in those without rare variants, but the difference was not statistically significant. Although one previous study divided patients with PD based on the onset age of 65 years, RBD was more common in patients with PD with a younger age of onset than in those with an older age of onset, although the difference was not statistically significant (Szewczyk-Krolikowski et al., 2014). Constipation was slightly but not significantly more common in patients with EOPD but was significantly more common in those with late-onset PD (Zhou et al., 2013). However, when we recruited drug-naïve PD patients in a previous study, the age of onset was not related to constipation (Park et al., 2018). Furthermore, the prevalence of nonmotor symptoms should be interpreted cautiously, because age may be associated with nonmotor symptoms, and nonmotor symptoms are also common in normal populations.

Interestingly, one previous study suggested a relationship between the number of PARK gene variants and characteristic phenotypes (Macedo et al., 2009). However, only 2 patients had more than 2 rare variants in our study, and the clinical features of these 2 patients differed. Most multiple variants were from *PRKN* in previous studies, and we found only two *Parkin* variants in this study because we recruited relatively older patients with EOPD, not juvenile PD patients. Therefore, further studies including larger samples are warranted to detect the real role of rare PARK gene variants.

The major limitation of this study is that not all PARK genes were included in the gene panel, such as *VPS35*. However, *VPS35* has not been reported in the Korean PD population, and more PARK genes could be investigated with follow-up studies. The small number of enrolled patients with EOPD is another limitation. Consequently, juvenile-onset parkinsonism patients were not enrolled in this study and might have different pathogenic mutations and rare variant frequencies, based on previous studies.

5. Conclusions

In conclusion, we investigated most PARK genes in Korean patients with EOPD. By evaluating more PARK genes, we found more variants in patients with EOPD. Interestingly, we demonstrated that characteristic symptoms are associated with rare variants of PARK genes, and our results provide evidence for the role of rare PARK gene variants in the pathogenesis of PD.

Disclosure

All authors declare no competing interests.

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Table 4
Genetic and clinical information of patients with EOPD genes carrying variants of uncertain significance and known mutations

ID	Gene	cDNA change	Amino acid change	Mutation/VUS	AOO	Sex	FHx	UPDRS part 3	HY	Dystonia	BDI	RBD	Hyposmia	Constipation	MoCA-K
1	*SNCA*	Triplication	-	Pathogenic	44	M	N	29	2	Y	14	N	N	Y	19
2	*SNCA*	c.171G>T	p.Glu57Asp	Likely Pathogenic	48	M	N	10	1	Y	3	N	Y	Y	25
3	*SNCA*	Triplication	-	Pathogenic	45	M	N	37	2	Y	5	N	N	Y	22
8	*LRRK2*	c.4337C>T	p.Pro1446Leu	VUS	48	F	N	12	1	N	2	Y	N	Y	27
13	*LRRK2*	c.922T>A	p.Leu308Met	VUS	50	F	N	25	2	N	1	N	N	N	26
14	*LRRK2*	c.5740C>A	p.Leu1914Ile	VUS	40	M	N	32	2	Y	8	Y	Y	Y	28
18	*LRRK2*	c.7173C>G	p.His2391Gln	VUS	50	F	N	16	2.5	N	26	Y	Y	N	20
19	*LRRK2*	c.4337C>T	p.Pro1446Leu	VUS	48	M	N	8	1.5	N	12	Y	N	N	24
20	*FBXO7*	c.155A>G	p.Tyr52Cys	VUS	50	M	N	31	3	N	14	Y	Y	Y	21
21	*PINK1*	c.169_170insGCAGGG	p.Arg58_Val59insGlyArg	Likely Pathogenic	39	F	N	19	3	N	29	N	Y	Y	15
25	*PRKN*	c.941G>A	p.Arg314Gln	Likely Pathogenic	50	F	N	16	2.5	N	16	Y	Y	Y	11
26	*PARK7*	c.409+1G>A	NA	Pathogenic	47	F	N	10	1.5	N	14	N	N	N	26
	HTRA2	c.1253A>G	p.Glu418Gly	VUS											
39	*PRKN*	c.814C>A	p.Leu272Ile	Likely Pathogenic	32	M	N	22.5	2.5	Y	18	N	N	N	27
40	*LRRK2*	c.3200G>A	p.Arg1067Gln	VUS	48	F	N	36	3	N	16	N	Y	Y	19
55	*EIF4G1*	c.3734C>T	p.Ser1245Phe	VUS	44	F	N	11	1	N	10	N	Y	N	29
62	*PINK1*	c.1024A>C	p.Met342Leu	VUS	45	F	N	43	2	N	29	Y	N	N	27
	FBXO7	c.1065_1066insAAA	p.Leu355_Ser356insLys	Likely Pathogenic											
66	*FBXO7*	c.1132C>T	p.Arg378Cys	Likely Pathogenic	31	F	N	35	3	Y	20	Y	N	N	22
67	*FBXO7*	c.803A>G	p.Asn268Ser	VUS	44	F	N	4	1	N	5	Y	N	Y	28
68	*LRRK2*	c.4106T>C	p.Val1369Ala	Likely Pathogenic	44	F	N	13	2	N	7	N	Y	N	29
70	*PINK1*	c.835C>T	p.Arg279Cys	Likely Pathogenic	50	M	N	27	3	N	16	Y	N	Y	20

Key: EOPD, early-onset Parkinson's disease; AOO, age of onset; UPDRS, unified Parkinson's disease rating scale; HY, Hoehn and Yahr stage; BDI, Beck's Depression Inventory; RBD, rapid eye movement behavior disorder; MoCA-K, Korean version of Montreal Cognitive Assessment.

sponsor had no involvement in the study design; in the collection, analysis, and interpretation of data; and in writing the manuscript. Yuhan Co also had no input into the decision to submit this article for publication. The authors had full access to all the data in the study, and the corresponding author had the final responsibility to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.10.030.

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