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COQ2 variants in Parkinson's disease and multiple system atrophy

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Abstract

Coenzyme Q2, polyprenyltransferase (*COQ2*) variants have been reported to be associated with multiple system atrophy (MSA). However, the relationship between *COQ2* variants and familial Parkinson's disease (PD) remains unclear. We investigated the frequency of *COQ2* variants and clinical symptoms among familial PD and MSA. We screened *COQ2* using the Sanger method in 123 patients with familial PD, 52 patients with sporadic PD, and 39 patients with clinically diagnosed MSA. Clinical information was collected from medical records for the patients with *COQ2* variants. Allele frequencies of detected rare non-synonymous variants were compared by public database of the Exome Aggregation Consortium (ExAC) and Japanese genetic variation database, using Fisher's exact test. We detected two probands with rare variants in *COQ2*, the p.P157S from Family A, whose patient was clinically diagnosed as having juvenile PD, and the p.H15 N/p.G331S from Family B, whose patients shared common symptoms of PD. Furthermore, in an association study comparing these familial PD and MSA cases with a public variant database, eight non synonymous variants were detected in *COQ2*. Three of these were very rare variants, namely, p.P157S, p.L261Qfs*4, and p.G331S, and one variant, p.G21S, was found to show a significant association with familial PD. *COQ2* variants rarely may associate with the disease onset of familial PD. Our findings contribute to an understanding of *COQ2* variants in neurodegenerative disorders.

Keywords Genetics · *COQ2* · familial Parkinson's disease · multiple system atrophy

Abbreviations

COQ2	Coenzyme Q2
COQ_{10}	Coenzyme Q_{10}
PD	Parkinson's disease
MSA	Multiple system atrophy
MRI	Magnetic resonance imaging

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Introduction

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disorder characterized by Parkinsonian features, cerebellar ataxia, autonomic failure, and corticospinal disorders (Fanciulli and Wenning 2015). Given that multiplex familial cases are rarely reported, MSA was thought to be a non-genetic disorder (Hara et al. 2007). However, MSA reportedly involves parkinsonism more often in first-degree relatives compared with controls (Vidal et al. 2010; Payami et al. 1994; Marder et al. 1996; Elbaz et al. 1999). Thus, the development of symptoms in MSA may involve a genetic component.

Homozygous variants (p.M128V-p.V393A/p.M128V-p.V393A) and compound heterozygous variants (p.R387X/p.V393A) in *coenzyme Q2, polyprenyltransferase* (*COQ2*) (MIM#609825) were discovered in two families with MSA patients (The Multiple-System Atrophy Research Collaboration 2013). Multiple missense *COQ2* variants were also detected in patients with sporadic MSA. *COQ2* is located on chromosome 4q21.23 and encodes para-hydroxybenzoate-polyprenyl transferase (Ashby et al. 1992), variants in which induce ubiquinone deficiency (coenzyme Q_{10} or COQ_{10}) (Quinzii et al. 2006). COQ2 is a catalyzing enzyme in the second step of the reaction sequences in the biosynthesis of COQ_{10}, a fat-soluble substance that functions as an antioxidant, membrane stabilizer, and transporter of electrons from complex I and complex II to complex III in mitochondria. COQ_{10} deficiency results in various types of neurological disorders such as (1) a myopathic form characterized by myoglobinuria and central nervous system-related symptoms of seizures, ataxia, or mental retardation (Ogasahara et al. 1989; Sobreira et al. 1997), (2) infantile encephalopathy (Rotig et al. 2000), and (3) ataxia and cerebellar atrophy similar to MSA (Musumeci et al. 2001).

The genes associated with familial PD, *synuclein alpha* (*SNCA*), *parkin, PTEN-induced putative kinase 1* (*PINK1*), and *DJ-1*, are strongly related to oxidative stress and mitochondrial dysfunction (Henchcliffe and Beal 2008). In addition, based on the pathological findings, both diseases such as PD and MSA also belong to alpha-synucleinopathies (Savica et al. 2018). Thus, we hypothesized that MSA and PD may share a common pathway that induces neurodegeneration. Herein, we analyzed entire exons and exon–intron boundaries in *COQ2* in 123 familial PD, 52 sporadic PD and 39 sporadic MSA cases of Japanese origin. Our results emphasize that *COQ2* variants contribute to the pathogenesis of PD.

Methods

Subjects and methods

This study was approved by the ethics review committee of Juntendo University School of Medicine. All participants gave informed and written consent before participation. The study population consisted of 123 patients with familial PD [mean age at onset: 62.8 ± 12.4 years [± standard deviation (SD)], male:female = 57:66], 52 patients with sporadic PD [mean age at onset: 40.6 ± 8.17 years (± SD), male:female = 19:33], and 39 patients with sporadic MSA [mean age at onset: 56.4 ± 10.2 years (± SD), male:female = 16:23]. The cohort of PD cases was further classified as 70 cases with PD with autosomal dominant inheritance [mean age at onset: 59.7 ± 12.8 years (± SD), male:female = 35:35] and 53 with PD with autosomal recessive inheritance [mean age at onset: 66.9 ± 10.6 years (± SD), male:female = 22:31]. All cases were of Japanese origin. The diagnosis of MSA and PD was established on the basis of clinical criteria (Gilman et al. 2008; Hughes et al. 1992). We defined the mode of inheritance as autosomal dominant in cases with affected family members in at least two consecutive generations, and autosomal recessive in cases with affected siblings only in the same generation. None of the enrolled patients had pathogenic variants, multiplication in the entire exon of *SNCA*, deletions, and multiplications in the entire exons of *parkin* and variants of *PINK1*, variants in exon 31, 41, and 48 of *leucine-rich repeat kinase 2* (*LRRK2*), and no risk variants in *glucocerebrosidase* (GBA).

Sequencing analysis

Genomic DNA was extracted from peripheral blood using QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany). We used primer sets to amplify all coding exons and exon–intron boundaries of *COQ2* and sequenced them with the Sanger method using BigDye Terminators v1.1 Cycle Sequencing Kit and 3130 Genetic Analyzer (Life Technologies, Foster City, CA, USA). PCR and sequence primers were designed using Exonprimer (http://ihg.gsf.de/ihg/ExonPrimer.html). The sequences and PCR and reverse-transcriptase PCR conditions are described in supplementary data. The sequences of the subjects were compared with the *COQ2* reference sequence (NCBI: NM_015697.7). We evaluated the pathogenicity of each variant using Polyphen-2 (Adzhubei et al. 2013), Mutation Taster (Schwarz et al. 2010), Sorting Tolerant From Intolerant (SIFT) (Li et al. 2009), rare exome variant ensemble learner (REVEL) (Ioannidis et al. 2016), and Combined

Annotation Dependent Depletion (CADD) (Kircher et al. 2014). The term 'pathogenic' was defined in a previous report (MacArthur et al. 2014). Evolutionary conservation of the mutated amino acids was evaluated using NCBI Homologene (http://www.ncbi.nlm.nih.gov/homologene/). Protein sequence and functional information were evaluated using UniProt (http://www.uniprot.org/).

Association analysis of *COQ2* variants for familial cases with MSA and PD

To investigate the contribution of rare non-synonymous *COQ2* variants [minor allele frequency (MAF) < 1.0% in public databases] to the pathogenesis of familial PD, we examined and compared the allele frequencies of the *COQ2* variants in the familial PD cases versus the data for the east Asian population from Exome Aggregation Consortium (ExAC) (Lek et al. 2016) and that for the Japanese population from Integrated Japanese Genetic Variation Database (IJGVD) (Nagasaki et al. 2015). For statistical analysis, we performed Fisher's exact test (two-tailed) and calculated the odds ratios and corresponding 95% confidential interval (CI) values to investigate the significant differences between our study samples and public databases. Data were analyzed by SPSS for windows advanced statistics release 6.0 (IBM®, New York, USA).

Results

Variants of *COQ2* in PD and MSA

We detected two rare variants in two familial PD cases: Families A and B. Clinical overviews of each patient are summarized in Table 1. The variants were [c.469C > T, p.P157S] of A-IV-1, and [c.43C > A, p.H15N]/ [c.991G > A, p.G331S] of B-II-1 (Fig. 1). Three variants were heterozygous. With regard to allele frequencies, p.P157S was not seen in ExAC but was rarely observed in IJGVD (MAF 0.04%), with the prediction of protein damages by amino acid changes underlying the prediction of pathogenicity by in silico analysis (Table 2). For Family B, p.H15N was not seen in ExAC but rarely observed in IJGVD (MAF 0.03%) and did not appear as a pathogenic variant in the REVEL and CADD analysis. The p.G331S variant was recorded as SNPs rs758847245, but the frequency was very rare in the absence of gene database of ExAC and IJGVD. We could not asses the segregation study for Family A and B due to their rejection of our proposal. We also detected two truncated variants (p.L261Qfs*4 in Family C with PD and p.K407del in Family D with MSA). In Family C, C-II-4 showed a

Table 1 Clinical overviews of two patients harboring *COQ2* variants

	A-IV-1	B-II-1
COQ2 mutation	p.P157S	p.H15N/p.G331S
Clinical details		
Clinical diagnosis	Juvenile PD	PD
Gender	Female	Male
Age at onset (years)	16	41
Age at examination	64	65
Disease duration	48	24
Neurological findings		
Parkinsonism	+	+
Tremor	−	+
Rigidity	+	+
Akinesia	+	+
Response for levodopa	Good	Good
Dyskinesia	+	+
Orthostatic hypotension	−	NA
Psychosis	Depression	Hallucination
Cognitive functions		
MMSE (/30)	28	NA
HDS-R (/30)	28	29
FAB (/18)	13	NA
Neuroimagings		
Brain MRI	Normal	NA
MIBG myocardial scintigraphy	Normal	NA

PD Parkinson's disease, *MMSE* the Mini-Mental State Examination, *HDS-R* the Revised Hasegawa's Dementia Scale, *FAB* the Frontal Assessment Battery, *MRI* magnetic resonance imaging, *MIBG* Meta-iodobenzylguanidine, *NA* not assessed

frame shift rearrangement of p.L261Qfs*4, which induced exonic skipping of exon 5, which was confirmed by RT-PCR (supplementary Materials and methods). The clinical manifestation of C-II-4 was late-onset supranuclear palsy-parkinsonism. The clinical diagnosis of C-III-2 was confirmed to be PD with hemi-parkinsonism and a good response to levodopa, but C-III-2 did not show variants of p.L261Qfs*4. The clinical diagnosis for C-II-1 was also PD. Family C did not show segregation of p.L261Qfs*4 and shared different symptoms. In Family D, we clinically diagnosed D-II-2 with MSA-cerebellar type (MSA-C). We collected DNA samples from the patient's mother (D-I-2), elder sister (D-II-1), and younger brother (D-II-3), who were all asymptomatic carriers. All three shared p.K407del. The details of the four families (Family A-D) are described in the supplementary information. Thus, we concluded that p.L261Qfs*4 and p.K407del did not directly relate to their phenotype. Overall, the allele frequencies of the putative pathogenic variants were 0.8% (2/246) in familial PD and 0% (0/78) in the MSA case in our cohort. Only p.P157S in Family A and p.G331S in Family B seemed to associate with PD.
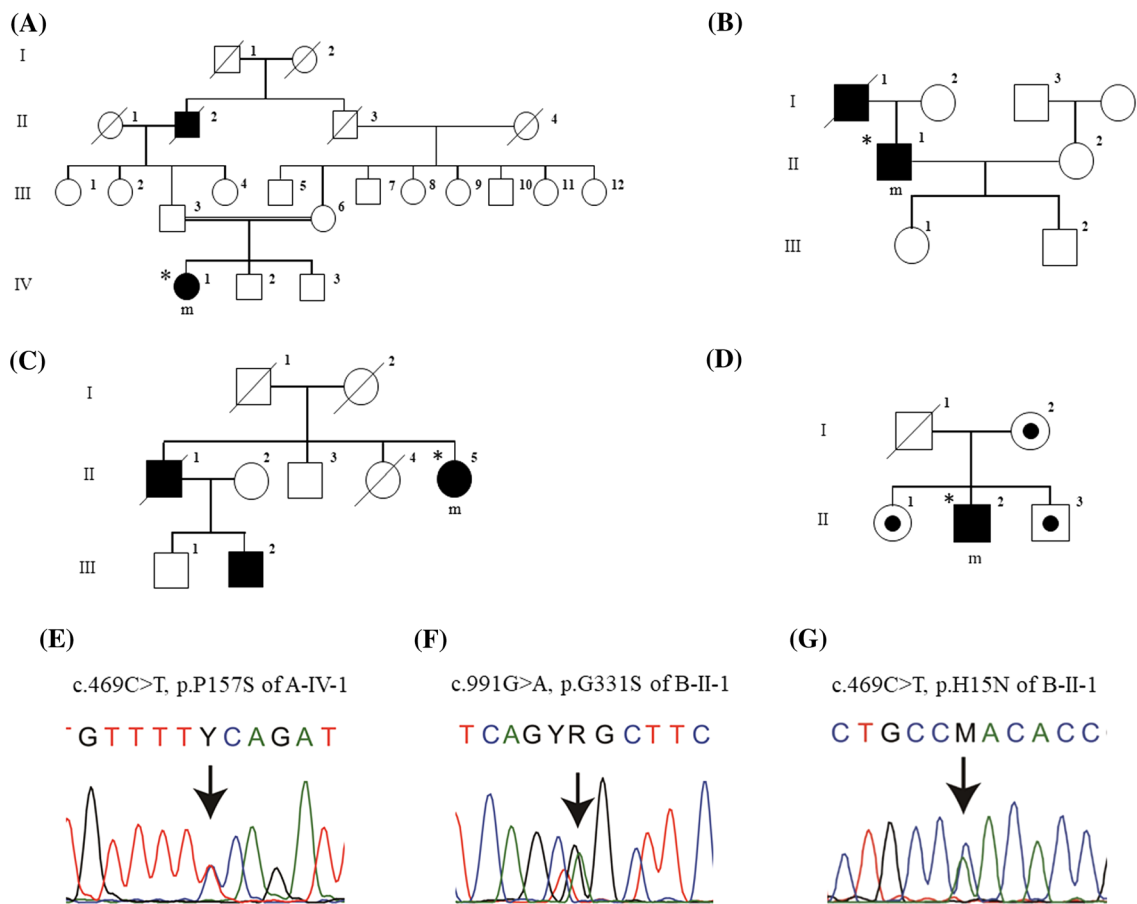
Fig. 1 Family trees of patients harboring *COQ2* variants and the results of direct sequencing of *COQ2* in two PD cases. **a** Family A includes a patient with juvenile Parkinson's disease (PD) (A-IV-1) with p.P157S. A-III-3 and A-III-6 have consanguinity. A-II-2 was diagnosed with PD. **b** Family B includes middle-aged onset and mild symptoms of PD with good response to levodopa, with p.H15N/p. G331S. B-I-1 was diagnosed with PD. **c** C-II-5 was clinically diagnosed as progressive supranuclear palsy-like, harboring exonic skip-ping of exon 5, p.L261Qfs*4. C-II-1 and C-II-2 was clinically diagnosed with PD. C-II-2 did not have p.L261Qfs*4. **d** D-II-2 fulfilled criteria of multiple system atrophy with parkinsonism and dysautonomia, harboring p.K407del. Circle with dot or square with dot indicates asymptomatic carriers. The family C and D did not have segregation of *COQ2* variants. Three heterozygous missense variants in *COQ2*, p.P157S (**e**), p.G331S (**f**) and p.H15N (**g**)

Association analysis of *COQ2* variants between familial PD and MSA versus the public variant database

We identified 11 *COQ2* variants as non-synonymous (p.H15N, p.G21S, p. L25V, p.V66L, p.P157S, p.L261Qfs*4, p.G331S, and p.V393A) or synonymous (p.D298D, p.T317T, and p.S330S) for PD, and five variants as non-synonymous (p.V66L, p.V393A, and p.K407del) or synonymous (p.D298D and p.S330S) for MSA (Table 3). Three other variants, namely, p.L261Qfs*4, p.T317T, and p.G331S, were very rare, with no records in the ExAC and IJGVD. The MAFs of four non-synonymous variants, namely, p.H15N, p.G21S, and p.P157S for familial PD and p.K407del for MSA, were under 1.0% in the public variant database. The p.G21S variant showed different frequencies for familial PD versus ExAc ($p = 0.004$) and versus IJGVD ($p = 0.01$). After Bonferroni correction, p.G21S showed the most significant association with familial PD. In contrast, p.H15N and p.P157S did not show significance in comparison with IJGVD, but their ORs were both 9.66, and the 95% CI did not cross 1 [p.H15N: 95% CI 1.001–93.159; p.P157S: CI 1.002–93.238]. For MSA patients, p.K407del showed different frequencies in MSA versus ExAc ($p = 0.05$) (supplementary Table 1). However, our study of Family D indicated that no segregation of p.K407del. p.V393A was frequently observed in sporadic PD (MAF: 7.7%). The p.V393A, which is previously reported risk variant for MSA (The Multiple-System Atrophy Research Collaboration 2013), variant showed different frequencies in all PD ($n = 175$) versus ExAc ($p = 0.07$) and versus IJGVD ($p = 0.02$). The other five variants for PD did not show statistical significance.

Table 2 Pathogenicity analysis of the identified variants using bioinformatics data

Patients	A-IV-1	B-II-1	
Mutation	p.P157S	p.G331S	p.H15N
rsID	Unknown	rs758847245	Unknown
Position in hg19	8,42,00,202	8,41,88,849	8,42,06,025
Polyphen-2/prediction and confidence			
HumDiv	0.997/probably damaging	0.416/benign	0.462/possibly damaging
HumVar	0.950/probably damaging	0.134/benign	0.223/benign
Mutation Taster	Disease causing	Disease causing	Polymorphism
SIFT	Deleterious	Deleterious	Damaging
REVEL	0.703	0.428	0.049
CADD/Phred (cutoff between 10 and 20)	23.3	22.9	12.9
ExAC (allele frequency, population)	Variant is not found	Variant: chr4:84188849C/T	Variant is not found
Human genetic variation database (allele frequency in Japanese population)	Unknown	Unknown	Unknown
Evolutionary conservation	Yes	Yes	No
Pathogenicity	Yes	Yes	Weak

SIFT Sorting Tolerant From Intolerant, *REVEL* rare exome variant ensemble learner, *CADD* Combined Annotation Dependent Depletion, *ExAC* the Exome Aggregation Consortium

Discussion

We detected two rare variants in *COQ2*, namely p.P157S in Family A and p.G331S in Family B, consisting of patients with juvenile PD and middle-aged onset PD. A-IV-1 with p.P157S manifested as juvenile PD in a woman at 16 years of age, and maintained favorable conditions after 48 years of treatment with levodopa. The patient's parents were consanguineous. Thus, Family A could carry another variant of the bi-allelic variants of another gene. The p.P157S variant observed in this study was similar to the pathogenic variant reported in MSA (The Multiple-System Atrophy Research Collaboration 2013; Sun et al. 2016). The two mutations p.P157S and p.G331S are very rare in the public gene database and whether they are pathogenic mutations or rare variants still remains a controversy. Among other rare variants, we detected three very rare non-synonymous variants—p.P157S, p.L261Qfs*4, and p.G331S—and one variant significantly seen in familial PD: p.G21S. Our study indicates that *COQ2* variants are rarely related to the onset of familial PD. There were no pathogenic variants in patients with MSA.

COQ2 encodes the enzyme in the second step of COQ_{10} biosynthesis (Quinzii et al. 2006). A missense variant in *COQ2* significantly decreases the rate of COQ_{10} synthesis. *COQ2* variant causes primary COQ_{10} deficiency (Quinzii et al. 2006). These deficiencies in COQ_{10} are related to various types of neurological disorders, including myopathy, infantile encephalopathy, and ataxia and cerebellar atrophy (Ogasahara et al. 1989; Rotig et al. 2000; Musumeci et al. 2001). These evidences suggest that *COQ2* variants affect mitochondrial functions more directly and result in various

types of clinical presentations. Indeed, we detected two types of variants from familial PD patients. *COQ2* variants may play a crucial role in neurodegenerative disorders via disturbance of redox reactions in the mitochondrial respiratory chain and oxidative stress. Several types of variants have been known to be related to hereditary PD and mitochondrial impairments, such as missense variants or multiplications in *SNCA*, *parkin*, *PINK1*, *DJ-1*, *HtrA serine peptidase 2 (HTRA2)*, and *F-box protein 7 (FBXO7)* (Henchcliffe and Beal 2008; Burchell et al. 2013; Conedera et al. 2016). These variants induce instability in mitochondrial maintenance, morphological changes, and decreased levels of dopaminergic neurons via increased oxidative stress. *COQ2* variants presumably share a similar pathway and induce the phenotype of PD or parkinsonism.

Regarding the frequency of *COQ2* variants in patients with PD, there are insufficient numbers of reports describing the association between the two. Yang et al. (2015) reported a significantly high frequency of p.V393A in patients with PD in China. However, these did not match our data showing a strong association of PD and p.V393V (Table 3). One report described two variants, p.S347C and p.V393A, in 600 PD cases from a European PD cohort (Sharma et al. 2014). There was no association of p.V393 in a comparison of 500 PD cases and 505 age-matched controls in Taiwan (Lin et al. 2015). Sharma et al. (2014) reported p.P157S in one unaffected person in European controls (0.002, 1/600), with no corresponding record in the ExAC gene database. In the comparative study between familial PD and the gene database for the Japanese population, p.G21S is significantly related to familial PD. The frequency seems to be very rare,

Table 3 Comparative study of allele frequency of *COQ2* variants between Parkinson's disease versus public variant database

Variants		Allele frequency in our PD cases (number of patients) (formula)					Allele frequencies in public gene database					
							ExAC (East Asian)			IJGVD (Japanese population)		
Amino acid	rs number	All patients (175) (x/350)	AD and AR (123) (x/246)	AD (70) (x/140)	AR (53) (x/106)	Negative family history (52) (x/104)	Frequency (alt/ref)	p value (vs. familial PD)	Odds ratio (95% CI) (vs. familial PD)	Frequency (alt/ref)	p value (vs. familial PD)	Odds ratio (95% CI) (vs. familial PD)
p.H15 N	*novel*	0.003	0.004	0.007	0.000	0.000	N.A.	N.A.	N.A.	0.0003 (3/7097)	0.127	9.656 (1.001–93.159)
p.G21S	rs766552045	0.011	0.016	0.014	0.019	0.000	0.001 (2/1586)	0.004	13.107 (2.388–71.978)	0.003 (22/7080)	0.010	5.319 (1.919–15.555)
p.L25 V	rs150145464	0.023	0.024	0.021	0.028	0.019	0.025 (56/2228)	1.000	0.995 (0.424–2.333)	0.011 (79/7019)	0.119	2.221 (0.959–5.145)
p.V66L	rs6818847	0.903	0.923	0.907	0.943	0.856	0.901 (227/25)	0.432	1.316 (0.705–2.456)	0.891 (5811/713)	0.117	1.466 (0.912–2.356)
p.P157S	*novel*	0.003	0.004	0.007	0.000	0.000	N.A.	N.A.	N.A.	0.0004 (3/7103)	0.127	9.664 (1.002–93.238)
p.D298D	rs6535454	0.863	0.878	0.864	0.896	0.827	0.827 (7181/1499)	–	–	0.836 (5944/1160)	–	–
p.L261Qfs*4	*novel**	0.003	0.004	0.007	0.000	0.000	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
p.T317T	rs774220803	0.003	0.000	0.000	0.000	0.010	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
p.S330S	rs1129617	0.12	0.106	0.114	0.094	0.154	0.161 (127/661)	–	–	0.135 (960/6142)	–	–
p.G331S	rs758847245	0.003	0.004	0.007	0.000	0.000	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
p.V393A	rs148156462	0.040	0.033	0.057	0.000	0.058	0.0166 (143/8477)	0.073	1.993 (0.966–4.109)	0.02 (142/6962)	0.166	1.648 (0.799–3.399)

PD Parkinson's disease, *AD* autosomal dominant, *AR* autosomal recessive, *ref* reference, *alt* alteration, *ExAC* the Exome Aggregation Consortium, *IJGVD* Integrative Japanese Genome Variation Database, *CI* confidential interval

but p.G21S may contribute to the disease onset as a relative risk factor.

With regard to *COQ2* variants in MSA, there were no pathogenic variants in our 39 patients. Just one variant, p.K407del, was seemingly related to MSA patients, but the variant did not show segregation in Family D, clinically presenting symptoms as MSA. Several previous studies could not detect pathogenic *COQ2* variants in MSA (Jeon et al. 2014; Sharma et al. 2014; Schottlaender and Houlden 2014). Large population studies also did not support an association between *COQ2* variants and MSA (Sailer et al. 2016; Lin et al. 2015), although our analysis support the association. As our speculation, it may be owing to the regional or racial differences of *COQ2* variants. Because of the small sample size, our study may not have detected significant differences in variants in MSA. Thus, the association of MSA and *COQ2* variants is still debatable. Our study has some limitations. First, the small sample size resulted in statistical weakness. Second, no segregation analysis was conducted for Families A and B. Finally, this was a comparative study that was conducted using data from the public variant database, without age-matched controls.

We reported a genotype–phenotype correlation of *COQ2* variants in PD in the Japanese population. We detected two rare variants, p.P157S and p.G331S, in two familial PD cases and a possible risk variant, p.G21S. Our findings may help the understanding of *COQ2* variants in familial PD.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest relevant to the manuscript.

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