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Identification of *CHCHD10* variants in Chinese patients with Parkinson's disease

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Conflicts of interest

The authors have no actual or potential conflicts of interest.

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Parkinson's disease (PD) is the second most frequent neurodegenerative age-related disorder which characterized clinically by a variety of motor and non-motor symptoms. The pathogenic mechanisms of PD remains unclear and were caused by the interplay of genetic and environmental factors. So far, over 21 causative genes associated with familial PD have been identified [1,2]. Notably, the genetics findings of PD have also suggested that mitochondrial dysfunction plays a critical role in the pathogenesis of Parkinson's disease (eg, *Parkin*, *PINK1*, *DJ-1*, *LRRK2*, *VPS13C, CHCHD2*) [1,2].

Recently, *CHCHD10*, structurally similar to *CHCHD2*, involved in mitochondrial function and was recently reported as a causative gene for amyotrophic lateral sclerosis/ frontotemporal lobar degeneration (ALS/FTLD) in a large French family by whole-exome sequencing. Soon afterward, several *CHCHD10* mutations were reported to be associated with a broad spectrum of neurodegenerative disorders encompassing ALS, FTD, PD, motor neuron disease and Alzheimer Disease [3,4]. However, the association between *CHCHD10* mutation and PD has not been performed in an Asian population. Here we conducted the genetic analysis of *CHCHD10* in a large cohort of Chinese familial and sporadic PD patients to further investigate the role of *CHCHD10* in PD.

This study studied a cohort of 2487 subjects, comprising 1235 patient with PD and 1252 healthy control individuals matched for age and ethnicity, recruited from the Xiangya Hospital Central South University and State Key Laboratory of Medical Genetics. All participants underwent medical assessments and basic clinical information were collected. This cohort of PD included 192 familial (105 cases exhibited an autosomal-dominant inheritance pattern, and the remaining 87 patients showed autosomal-recessive inheritance) and 1043 sporadic cases. The mean age at onset in patients with PD was 51.92 ± 11.41 years (male = 51.1%). Detailed demographic and clinical characteristics of study participants were showed in the supplementary material. All known PD-related genes were excluded in the previous studies [2]. Written informed consent was given by all cases and our study was approved by the local committee at the Xiangya hospital Central South University ethics committee.

We analyzed the exons and exoneintron boundaries of *CHCHD10* by Sanger sequence. The polymerase chain reaction (PCR) product was sequenced with BigDye terminator v3.1 sequencing chemistry on an ABI 3730xl DNA analyzer (Applied Bio-systems) and analyzed using Chormas DNA sequencing software. SPSS 20.0 software (SPSS Inc, Armonk, NY, USA) were used to perform the statistical analyses. Fisher's exact test was used to test for individual genotypic associations and Hardy-Weinberg assessment. We identified several variations of *CHCHD10* which were showed in the Table 1. A novel missense variant (NM_213720, c.C89T p. Ser30Leu; supplementary material) in exon 2 of *CHCHD10* was identified in a female patient with sporadic PD (Patient M31256). The patient developed

symptoms at the age of 42 years and presented slowly progressive and asymmetric Parkinsonism including tremor, rigidity and bradykinesia. Neurologic examination showed she had hyposmia and mild depression. Brain magnetic resonance imaging (MRI) was unremarkable and other investigations were normal. This Patient responded well to dopaminergic therapies and developed dyskinesia after Levodopa-Benserazide treatment. This p. Ser30Leu carrier had previously been screened negative for mutations in all known PD genes. The p. Ser30Leu substitution changes a conserved amino acid and is predicted to be disease-causing (MutationTaster:http://www.mutationtaster.org/cgi-bin/MutationTaster/MutationTaster69.cgi). The p.Ser30Leu variant was absent in our 1252 health control individuals, Single Nucleotide Polymorphism Database (build 142), 1000 Genome project and ExAC database. In addition, we detected several synonymous variants (c. A48C p.Pro16Pro, c. C72A p.Pro24Pro, c. G294A p. Gln98Gln, c. C312T p.Tyr104Tyr), and the 3′UTR variant c.429 + 34 C > T in PD cases. All those variants were heterozygous except for the c. C72A (p.Pro24Pro) homozygous variant. Analyses of the potential of the 3′UTR c. 429 + 34 C > T variant on miRNA-binding sites were performed using the available online databases miRBase (http://www.mirbase.org/), TargetScan (http://www.targetscan.org/) and PolymiRTS (http://compbio.uthsc.edu/miRSNP/). However, the 3′UTR c.429 + 34 C > T variation does not localize at any binding site of currently known miRNAs and no modifying effect of this variation on the binding sites was found. Although further statistical analysis were performed to define the role of those variants in PD, we did not found statistical differences in genotypic distribution between PD cases and control individuals for these variants in *CHCHD10* gene (Table 1).

For the first time, our finding revealed the clinical manifestations of c.C89T p. Ser30Leu in *CHCHD10* gene in an early onset PD case with no symptoms of muscle weakness, dementia or ALS. It extends the phenotype of *CHCHD10* variants. Further genetic and functional studies are still needed to disclose the role of *CHCHD10* variants in neurodegenerative disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.12.002.

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Table 1

Variants identified in *CHCHD10* in our study.

Chromosomal Position(Hg 19)	rs number	Variant		minor allele frequency (MAF)		1000 Genomes	ExAC	PD vs Control	
		cDNA	Amino acid change	PD (n = 1235)	HC (n = 1252)			OR (95% CI)	*p* value[a]
1 Chr22:24109774	rs179468	c. A48C	p.Pro16Pro	0.304	0.281	0.127	0.179	1.12 (0.95–1.32)	0.191
2 Chr22:24109750	ND	c. C72A	p.Pro24Pro	0.0004	0.0004	ND	ND	1.01 (0.06–16.22)	0.992
3 Chr22: 24109733	ND	c.C89T	p.Ser30Leu	0.0004	0	ND	ND	NA	NA
4 Chr22:24108439	ND	c. G294A	p. Gln98Gln	0.0004	0.0004	ND	ND	1.01 (0.06–16.22)	0.992
5 Chr22:24108412	rs80027270	c.C312T	p.Tyr104Tyr	0.371	0.368	0.226	0.223	1.01 (0.86–1.18)	0.982
6 Chr22:24108160	–	c. 429 + 34 C > T	3 UTR	0.0004	0	ND	ND	NA	NA

Key: PD=Parkinson's disease. HC=Health controls. CI = confidence interval; OR = odds ratio. UTR=Untranslated region. ND=No data were found in database. NA: Not applicable because the genotypes of all of the patients with PD or controls were the major allele.

1000 Genomes: http://browser.1000genomes.org/.

ExAC = The Exome Aggregation Consortium (http://exac.broadinstitute.org).

[a] *p* Value was determined using Fisher's exact test.