



LRP10 Mutations May Correlate with Sporadic Parkinson's Disease in China

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Abstract

LDL receptor-related protein (LRP) 10 was recently identified as a Parkinson's disease gene through genome-wide linkage and sequencing analysis, but its role in Parkinson's disease in various populations is still unclear. The aim of this study was to determine the frequency and spectrum of LRP10 mutations in a cohort of Parkinson's disease patients from mainland China. All LRP10 exons and their flanking intron regions were screened by direct sequencing in 567 unrelated Parkinson's disease patients and 600 unrelated controls. We detected 29 exonic or splicing variants in 79 patients with Parkinson's disease. Five variants (c.A181C:p.I61L, c.C652T:p.Q218X, c.C833T:p.T278I, c.T1592G:p.I531S, c.T1697C:p.L566P) were predicted to be disease-causing or damaging by multiple *in silico* tools. Our study provides genetic evidence that LRP10 defects may correlate with sporadic Parkinson's disease.

Keywords LDL receptor-related protein 10 · LRP10 · Parkinson's disease · Genetic variants

Introduction

Parkinson's disease (PD), whose prevalence and incidence increase with age, is the second most frequently occurring neurodegenerative disorder after Alzheimer's disease [1]. PD is predicted to cause increasing economic and social burden as the global population ages [1–3]. This condition

involves progressively debilitating motor symptoms such as resting tremor, bradykinesia, rigidity, and postural instability [4]. The pathological hallmarks of Parkinson's disease are loss of nigrostriatal dopaminergic neurons, with intracellular inclusions containing α -synuclein protein (i.e., Lewy bodies and Lewy neurites) in surviving neurons [5].

Genetic risk factors have been described for PD; pedigree and genome-wide association studies have established links with mutations in SNCA, DJ-1, GBA, LRRK2, CHCHD2, and other genes [6, 7]. However, many open questions remain about the etiology of PD.

Recently, a genome-wide linkage and sequencing study provided evidence for a role of the LRP10 gene in α -synucleinopathies [8]. Furthermore, that study reported that brains of Caucasian patients with different LRP10 variants contained abundant α -synuclein aggregation in the form of brainstem and cortical Lewy bodies and Lewy neurites. The role of LRP10 protein in α -synucleinopathies remains controversial, and its frequency and expression in non-White ethnicities are poorly understood [9–13].

Therefore in this work, we sequenced the entire LRP10 coding region, exon-intron boundaries, as well as untranslated and flanking regions in order to clarify the potential role of LRP10 in Han Chinese patients with sporadic PD.

Quanzhen Zhao, Pingping Ning and Xinglong Yang contributed equally to this work.

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Materials and Methods

Study Subjects

The study protocol was approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu, China). Written informed consent from the participants/their parents/legally authorized representative of participants was obtained. PD was diagnosed based on MDS Clinical Diagnostic Criteria [14]. A total of 567 Han Chinese patients (289 men and 278 women) diagnosed with PD were recruited from among inpatients at the Department of Neurology of West China Hospital, Sichuan University, in southwest China. Patients had a mean age of 62.9 (SD, 10.7; range, 24–95). As controls, 600 unrelated healthy Han Chinese subjects without a history of neurodegenerative disease were recruited.

DNA Sequencing and Statistical Analysis

Genomic DNA was collected from peripheral blood leukocytes using a standard phenol-chloroform procedure. All seven exons of LRP10 (NM_014045) were PCR-amplified as previously reported [15]. PCR products were directly sequenced using a targeted approach using an ABI3730 automated DNA sequencing system (BGI, Shenzhen, China).

LRP10 was analyzed by direct nucleotide sequencing (Shanghai Genesky Bio-Tech, Shanghai, China), and variants were identified using Complete Genomic Analysis Tools (version 2.2.0.26; www.completegenomics.com/analysis-tools/cgatools). The detected mutations were validated as known or novel by comparison with direct sequencing of controls and with sequences in the ExAC (<http://exac.broadinstitute.org/>) and 1000 Genomes Project databases (<http://www.1000genomes.org/>). The potential function of genetic variants was predicted using the following in silico tools: MutationTaster (<http://www.mutationtaster.org/>), SIFT (<http://sift.jcvi.org/>), Polymorphism Phenotyping version 2 (http://genetics.bwh.harvard.edu/pph/pph_help_text.html), Cadd_Raw (<http://cadd.gs.washington.edu/>), and Dann (<http://bioinformatics.oxfordjournals.org/content/31/5/761>). The frequencies of allele and genotype were determined by direct counting of LRP10 alleles. Minor allele frequencies were compared using the chi-squared test in SPSS 21.0 (IBM, Chicago, USA).

Results

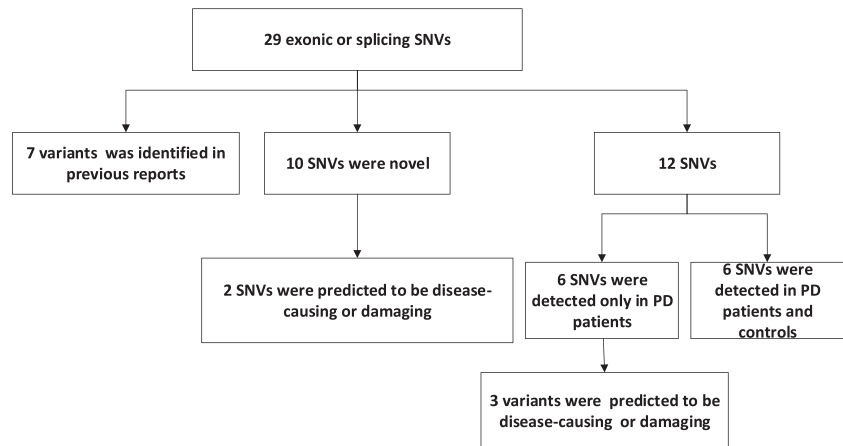
A total of 29 exonic or splicing single-nucleotide variants (SNVs) were detected in 79 patients with PD (Supplement

Table 1 Clinical features of Han Chinese patients carrying five potentially pathogenic LRP10 variants

Feature	Patient				
	Case 1	Case 2	Case 3	Case 4	Case 5
Nucleotide change	c.A181C:p.I61L	c.C652T:p.Q218X	c.C833T:p.T278I	c.T1592G:p.I531S	c.T1697C:p.L566P
Minor allele frequency	-	-	-	-	-
Sex	Female	Male	Female	Male	Female
Family history	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>
Age, year	54	62	70	64	60
Age at disease onset, year	51	55	65	61	57
Response to levodopa	+	+	+	+	+
Initial area of involvement	Left upper limb	Left lower limb	Right upper limb	Left upper limb	Left lower limb
Initial symptom	Bradykinesia	Tremor	Tremor	Bradykinesia	Bradykinesia
Cognitive dysfunction	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>
Olfactory dysfunction	<i>Y</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>
RBDSQ	5	1	4	1	1
HAMD	21	2	25	1	6
HAMA	25	2	16	2	4
UPDRS-III	49	11	48	8	41
H-Y	3	1.5	3	1	3
RLS	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>

Abbreviations: *N*, no; *Y*, yes; *RBDSQ*, REM Sleep Behavior Disorder Screening questionnaire; *HAMD*, Hamilton Depression Scale; *HAMA*, Hamilton Anxiety Scale; *UPDRS-III*, Unified Parkinson's Disease Rating Scale-III; *H-Y*, Hoehn-Yahr; *RLS*, restless legs syndrome

Fig. 1 Flow chart of the analysis of 29 LRP10 single-nucleotide variants (SNVs)

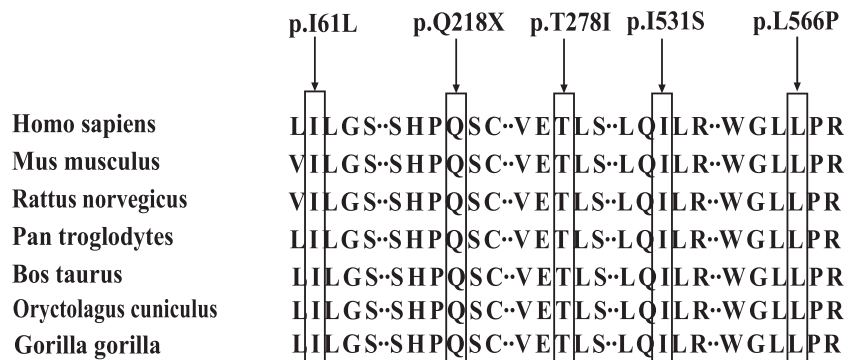


1), all of whom were heterozygous for the variants. Seven variants were identified in the previous reports [9, 13, 16], although in these studies the allele frequencies did not differ between PD patients and controls. Of the 29 variants identified in the present study, 10 were novel. Two of the novel variants (p.T278I, p.I531S) were predicted to be disease-causing or damaging by the five in silico tools mentioned above.

Minor allele frequencies of the other 12 variants were smaller than 0.05 in the ExAC and 1000 Genomes Project databases. Six of 12 variants were detected only in PD patients but not in healthy controls, and three (p.I61L, p.Q218X, p.L566P) were predicted to be disease-causing or damaging. Interestingly, variant c.T1697C(p.L566P), identified in our study, and variant c.C1696 > T(p.L566F), previously identified [13], were predicted to alter the same residue in the LRP10 protein sequence. The other six variants were detected in controls, and their frequencies were similar between cases and controls.

The clinical features of patients carrying the two novel variants and three known variant are listed in Table 1, and the flow chart for analyzing the 29 SNVs is shown in Fig. 1 and Supplement 1. All five mutated residues are highly conserved among species (Fig. 2).

Fig. 2 Alignment of partial LRP10 protein sequences from various species, showing conservation of the mutations p.I61L, p.Q218X, p.T278I, p.I531S, and p.L566P



Discussion

In the present study, we sequenced the LRP10 gene in 567 Han Chinese PD patients and identified five rare, potentially pathogenic exonic variants. LRP10 mutations were previously recognized as a potential cause of PD, Parkinson's disease dementia, and dementia with Lewy bodies in different populations [8]. Two previous studies in Chinese populations similarly reported evidence for a role of LRP10 in patients with sporadic or familial PD, and identified three potentially pathogenic variants independently (Fig. 3) [13, 16]. However, other work based on the International Parkinson's Disease Genomics Consortium database that includes 2835 individuals with PD and 5343 healthy individuals, mainly of northern European ancestry, did not identify LRP10 as a disease-causing gene in PD or dementia with Lewy bodies [10]. Similarly, studies on dementia with Lewy bodies and multiple system atrophy found no association between LRP10 and synucleinopathies [9, 11, 12]. These differences may be explained by ethnic variations among the study populations.

Interestingly, we found five rare, potentially pathogenic exonic variants in five PD patients by in silico analysis.

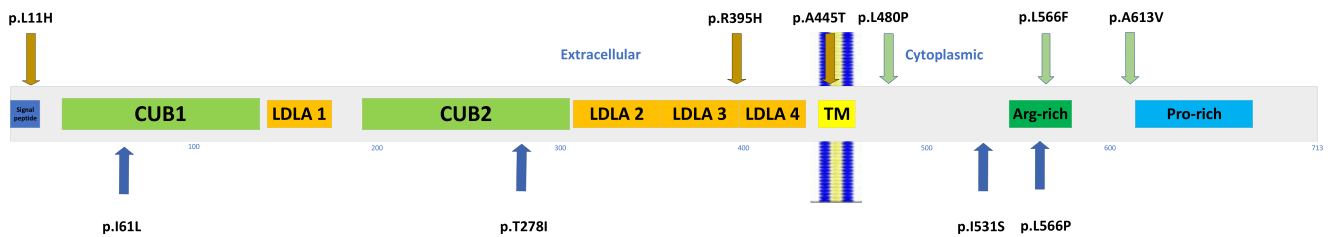


Fig. 3 LRP10 protein structure showing the different domains and repeats. Blue arrows indicate the positions of the coding variants identified in the present study. (The splicing variant c.C652T:

p.Q218X, 496 is not shown). Brown arrows indicate the positions of the coding variants identified in Chen et al [16]. Light green arrows indicate the positions of the coding variants identified in Shi et al [13]

Clinical manifestations of all five patients carrying these variants included all typical Parkinson's symptoms, similar to a previous study in another Chinese population [13, 16]. In the present study, the age at PD onset was over 50 years, and all patients showed good response to treatment with levodopa (> 30%). All five PD patients lacked a family history of PD, which may indicate that the variants are de novo mutations. However, incomplete penetrance or non-pathogenic variants cannot be completely ruled out. Since parental samples are not available, it is difficult to clarify the origins of the mutations.

LRP10 is a member of the low-density lipoprotein receptor family, although little is known about its function. Previous studies have shown that LRP10 is localized in vesicular structures closely associated with proteins implicated in trafficking between the trans-Golgi network and endosomes, including vacuolar protein sorting-associated protein 35 (VPS35) [8]. VPS35 has been associated with autosomal dominant PD through its ability to enhance mitochondrial fragmentation [17, 18]. Some studies suggested that LRP10 may play a role in the canonical Wnt/ β -catenin signaling pathway, which regulates mitochondria morphology and function [19, 20]. Mitochondrial dysfunction appears to play an important role in the pathogenesis of PD [21, 22]. Collectively, these results may support a role for LRP10 in the pathogenesis of PD.

Our research has some limitations. Firstly, although we applied the MDS criteria, the diagnosis of these patients was not confirmed by pathology. Secondly, the number of patients recruited in our study was not large, and we could not include an adequate number of patients with familial PD. Thirdly, the potential function of genetic variants was only predicted by *in silico* tools. Finally, we were unable to obtain blood samples from parents of the patients with the five mutations. Analysis of such samples might help clarify the origins of the mutations, such as incomplete penetrance. Further studies, such as *in vitro* experiments, are needed in order to clarify whether these variants are functionally important.

Despite these limitations, our results suggest that LRP10 may play a role in sporadic Parkinson's disease in Han Chinese patients. These findings should be verified and extended in larger samples, preferably from different ethnic groups, and analyzed in conjunction with familial pedigree

data. Such work may help to elucidate how LRP10 contributes to the pathogenesis of neurodegenerative diseases.

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Authors' Contributions YMX(Yanming Xu), QZZ, PPN, and XLY participated in conceiving and designing the study, analyzing and interpreting the data, as well as drafting and reviewing the manuscript. CHS and YMX(Yuming Xu) collected, analyzed, provided relevant information of the patients and controls in another Chinese population, and participated in reviewing the manuscript. QYS participated in collecting the data and reviewing the manuscript. HYH, DX and YLC participated in collecting clinical data and helped review the manuscript. All authors read and approved the final version of the manuscript.

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Data Availability The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethical Approval The protocol of this study was approved by the Ethics Committee of West China Hospital of Sichuan University (Chengdu, China), and the study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its amendments.

Consent to Participate On admission, each participant signed written informed consent for their data to be analyzed and published anonymously for research purposes.

Consent to publication On admission, each participant signed written informed consent for their data to be analyzed and published anonymously for research purposes.

Code Availability The software applications used and/or analyzed in this study are available from the corresponding author on reasonable request.

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