



No association between genetic variants of the *LRRK2* gene and schizophrenia in Han Chinese



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HIGHLIGHTS

- A two-stage study aimed at identifying association of *LRRK2* with schizophrenia.
- 12 *LRRK2* SNPs were analyzed in Han Chinese with and without schizophrenia.
- Genotype, allele and haplotype frequencies were compared between cases and controls.
- None of the 12 analyzed SNPs showed a positive association with schizophrenia.

ARTICLE INFO

Article history:

Received 23 December 2013

Received in revised form 10 February 2014

Accepted 4 March 2014

Keywords:

Mitochondria

LRRK2

SNP

Schizophrenia

Replication

Han Chinese

ABSTRACT

Mitochondrial dysfunction was widely reported in schizophrenia patients in recent studies. Leucine-rich repeat kinase 2 (*LRRK2*) is a mitochondrial protein, and mutations in the *LRRK2* gene can induce mitochondrial dysfunction. *LRRK2* mutations have been reported to be the most frequent genetic cause of Parkinson's disease (PD). We were interested in whether *LRRK2* variants also play a role in schizophrenia. In this study, we genotyped 12 genetic variants (including 4 tag SNPs and 8 disease-associated variants) in the *LRRK2* gene in a total of 2449 samples composed of two independent Han Chinese schizophrenia case-control cohorts (486 schizophrenia patients and 480 healthy controls from Hunan Province; 624 schizophrenia patients and 859 healthy controls from Shanghai). We compared the genotype, allele and haplotype frequencies of those SNPs between cases and controls. Statistical analyses revealed no association between *LRRK2* variants/haplotypes and schizophrenia in these two schizophrenia case-control cohorts and the combined samples. Our results indicated that the *LRRK2* variants are unlikely to be actively involved in schizophrenia in Han Chinese.

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1. Introduction

Schizophrenia is a severe and prevalent psychiatric disorder [4,26] with a high heritability of approximately 80% and a prevalence of about 1% worldwide [14,33]. The pathogenesis of schizophrenia is complicated and remains controversial. Hitherto,

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a large amount of genetic loci have been reported to confer susceptibility to schizophrenia, but these susceptible loci can only explain a small portion of heritability [7]. Mitochondria are the power plants of eukaryotic cells and are important in modulating neuronal activity [17]. There are increasing lines of evidence implicating the involvement of mitochondria in the pathogenesis of psychiatric disorders [10,31]. Mitochondrial dysfunctions, such as oxidative phosphorylation (OXPHOS) deficiency [2,8,23], abnormal mitochondrial gene expression [13,15,24] and perturbation in mitochondrial network dynamics [27,28], are common in schizophrenia patients and may play a crucial role in disease onset.

The *LRRK2* gene, which encodes a 280 kDa protein, is located on 12q12 and spans 144 kb of genomic region. *LRRK2* is mainly

localized to cytoplasmic structures, such as mitochondrial outer membrane [11], endoplasmic reticulum [36] and Golgi apparatus [11]. The *LRRK2* gene is actively involved in the regulation of mitochondrial dynamics and function [38]. Mutations in the *LRRK2* gene are the most frequent genetic cause of Parkinson's disease (PD) and these mutations play important roles in sporadic PD. Functional characterization showed that these PD related *LRRK2* mutations can induce mitochondrial fragmentation and cytotoxicity [38].

Considering the important role of the *LRRK2* gene in mitochondrial function and the fact that schizophrenia is a neuropsychiatric disease that was reported to be associated with mitochondrial dysfunction, we hypothesized that *LRRK2* genetic variants might confer susceptibility to schizophrenia. In this study, we conducted a comprehensive association study of the *LRRK2* genetic variants with schizophrenia in two independent Han Chinese case-control cohorts. We found no association between the *LRRK2* polymorphisms and schizophrenia, and four PD pathogenic mutations in the *LRRK2* gene were absent in Han Chinese with schizophrenia.

2. Materials and methods

2.1. Subjects

Two cohorts of schizophrenia cases and controls were analyzed in this study. The initial discovery sample was composed of 486 unrelated schizophrenia patients (319 males: mean age \pm SD, 38.3 ± 14.4 years; 167 females: 37.5 ± 19.3 years) and 480 matched healthy controls (323 males: mean age \pm SD, 39.5 ± 15.5 years; 157 females: 41.1 ± 14.3 years) from Hunan Province in South Central China. These case and control samples were previously analyzed for other genetic variants [20,21,40]. The validation sample was composed of 624 unrelated schizophrenia patients (363 males: mean age \pm SD, 33.1 ± 8.7 years; 261 females: 34.2 ± 9.1 years) and 859 matched controls (389 males: mean age \pm SD, 33.0 ± 8.7 years; 470 females: 30.7 ± 7.6 years) from Shanghai urban area with access of health care. The patients from Shanghai were previously reported [34]. The control sample from Shanghai contains 384 individuals reported in our recent study for Alzheimer's disease [3]. All participants were Han Chinese origin. Demographical data, such as age, sex and education year of those participants and peripheral blood were collected. The schizophrenia patients were independently diagnosed by two psychiatrists according to the Diagnostic and Statistical Manual, the Fourth Version (DSM-IV) and had at least a 2-year history of schizophrenia. The control samples were composed of adult individuals who visited the hospital for physical examination and were clinically diagnosed having no psychiatric disorders. The control group was geographically and ethnically matched with the patient group. Written informed consent was obtained from each participant for this study. This study was carried out in compliance to the World Medical Association's Declaration of Helsinki and approved by the institutional review board of Kunming Institute of Zoology.

2.2. SNP selection and genotyping

Genomic DNA of all participants was extracted from peripheral blood using the AxyPrep™ Blood Genomic DNA Miniprep Kit according to the manufacturer's instruction. We retrieved CHB data from the HapMap database (<http://hapmap.ncbi.nlm.nih.gov/>) and defined linkage disequilibrium (LD) block using the Haploview 4.2 [1]. All of the detected 12 SNPs were the same with our previous study [3]. In brief, four tag SNPs (rs732374, rs4473003, rs7298930 and rs7307310) were selected for genotyping depending on the LD information and eight previously reported disease-associated mutations (rs34594498, rs33939927,

rs33949390, rs35801418, rs34637584, rs35870237, rs34778348 and rs3761863) [16,22] were also investigated in this study, following our recent approach for analysis of patients with Alzheimer's disease [3]. Among these disease-associated mutations, rs3761863, rs33949390, rs33939927 and rs35801418 were reported in Caucasian populations; rs34594498, rs34637584 and rs35870237 was reported in both Caucasian and Asian populations; rs34778348 was reported only in Asian population [16,22].

All of the twelve SNPs were genotyped using multiple PCR and the SNaPshot assay following detailed step-by-step procedure described in our previous study [3,37]. In brief, multiplex PCR was performed in a 8 μ L reaction volume containing 20–50 ng genomic DNA, 0.4 mM dNTPs, 0.2–0.5 μ M of each primer, 2.0 mM MgCl₂ and 1.0 U of FastStart Taq DNA Polymerase (Roche Applied Science). The PCR condition is composed of a pre-denaturation cycle at 94 °C for 2 min; 40 amplification cycles of 94 °C for 30 s, 55 °C for 30 s and 72 °C for 1 min. PCR products were cleaned up at 37 °C for 40 min with 1.0 U of shrimp alkaline phosphatase (SAP) and 0.5 U of Exonuclease I (TaKaRa Biotechnology Co. Ltd., Dalian, China), followed by an incubation at 96 °C for 10 min. The single base extension reaction was conducted in a volume of 10 μ L including 4 μ L cleaned up multiplex PCR products, 5 μ L SNaPshot Multiplex Ready Reaction Mix and 0.4–0.8 μ M pooled SNP-specific oligonucleotide primers. Twenty-five cycles of single-base extension reaction were carried out with the following condition per cycle: 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 30 s. Products were purified by SAP (1.0U) 37 °C for 40 min, followed by an inactivation procedure at 75 °C for 20 min. 4 μ L of purified products were mixed with 9 μ L of Hi-Di™ formamide, and analyzed by the ABI PRISM™ 3730xl DNA analyzer (Applied Biosystems). The GeneMarker software was adopted to read the genotyping result [12]. The detailed information for genotyping each variant and primers for SNaPshot assay can be found in our recent study of Alzheimer's disease [3].

2.3. Haplotype inference and statistical analysis

LD plot of the *LRRK2* gene was constructed using Haploview 4.2 program. PHASE2.1.1 software [32] was used for haplotype inference of the 8 common SNPs in the *LRRK2* gene. Deviation from the Hardy–Weinberg equilibrium (HWE) was calculated using the Chi-square test for each SNP. We compared the genotype, allele and haplotype frequencies of the 12 SNPs between case and control samples. Bonferroni corrected *P*-value was adopted for this multiple comparisons. Potential association between certain variants and schizophrenia was estimated using the logistic regression model adjusted by sex and age using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Quanto software [9] was used for power analysis.

3. Results

In total, we analyzed 12 *LRRK2* SNPs in two independent sample sets from South Central China (486 schizophrenia cases and 480 normal individuals) and East China (624 schizophrenia cases and 859 normal individuals), respectively. With false positive rate controlled as 0.05, for minor allele frequency (MAF) from 0.1 to 0.5, the statistical power to detect the odds ratio (OR) value as 1.5 for risk allele was expected to be from 72.9% to 87.8% in our stage 1 samples and 83.4% to 94.6% in the stage 2 samples under the dominant model.

Consistent with our previous analysis for Han Chinese with and without Alzheimer's disease [3], four SNPs (rs33939927, rs35801418, rs34637584 and rs35870237) were not polymorphic in our samples, thus were excluded for further analysis (Table 1). None of the remaining 8 SNPs was deviated from HWE in each of the two control groups (Table 1). The LD structures of the 8

Table 1
Comparison of genotype and allele frequencies of the 12 *LRRK2* SNPs in 486 schizophrenia patients and 480 healthy controls from Hunan Province, and in 624 schizophrenia cases and 859 healthy controls from Shanghai.

SNP ID	Populations	Allele	Number of samples		P-value ^a	Genotype	Number of samples		P-value ^a	Adjusted P-value ^b	HWE P-value ^c
			Case	Control			Case	Control			
			rs732374	Hunan			G/A	658/314			
	Shanghai	G/A	857/387	1179/529	0.936	GG/AG/AA	412/355/87	317/281/64	0.608	0.715	0.880
	Combined	G/A	1515/701	1791/887	0.268	GG/AG/AA	534/447/127	602/587/150	0.206	0.175	0.702
rs34594498	Hunan	C/T	961/11	953/7	0.357	CC/CT/TT	475/11/0	473/7/0	0.355	–	0.872
	Shanghai	C/T	1237/11	1699/19	0.546	CC/CT/TT	613/11/0	840/19/0	0.544	–	0.743
	Combined	C/T	2198/22	2652/26	0.943	CC/CT/TT	1088/22/0	1313/26/0	0.943	–	0.720
rs4473003	Hunan	T/C	630/342	666/294	0.231	TT/CT/CC	200/230/56	236/194/50	0.294	0.273	0.285
	Shanghai	T/C	832/416	875/459	0.481	TT/CT/CC	276/280/68	372/380/107	0.654	0.751	0.515
	Combined	T/C	1462/758	1790/888	0.467	TT/CT/CC	476/510/124	608/574/157	0.311	0.358	0.228
rs33939927 ^d	Hunan	C/T	972/0	960/0	–	CC/CT/TT	486/0/0	480/0/0	–	–	–
	Shanghai	C/T	1248/0	1718/0	–	CC/CT/TT	624/0/0	859/0/0	–	–	–
	Combined	C/T	2220/0	2678/0	–	CC/CT/TT	1110/0/0	1339/0/0	–	–	–
rs33949390	Hunan	G/C	951/21	936/24	0.621	GG/CG/CC	466/19/1	457/22/1	0.874	0.878	0.190
	Shanghai	G/C	1238/10	1707/17	0.594	GG/CG/CC	614/10/0	842/17/0	0.592	–	0.770
	Combined	G/C	2189/31	2637/41	0.697	GG/CG/CC	1080/29/1	1299/39/1	0.896	0.804	0.214
rs35801418 ^d	Hunan	A/G	972/0	960/0	–	AA/AG/GG	486/0/0	480/0/0	–	–	–
	Shanghai	A/G	1248/0	1718/0	–	AA/AG/GG	624/0/0	859/0/0	–	–	–
	Combined	A/G	2220/0	2678/0	–	AA/AG/GG	1110/0/0	1339/0/0	–	–	–
rs7298930	Hunan	A/C	526/446	473/487	0.231	AA/AC/CC	140/246/100	118/237/125	0.091	0.110	0.788
	Shanghai	A/C	694/554	950/768	0.866	AA/AC/CC	191/312/121	265/420/174	0.890	0.923	0.747
	Combined	A/C	1220/1000	1423/1255	0.204	AA/AC/CC	331/558/221	383/657/299	0.340	0.341	0.588
rs34637584 ^d	Hunan	G/A	972/0	960/0	–	GG/AG/AA	486/0/0	480/0/0	–	–	–
	Shanghai	G/A	1248/0	1718/0	–	GG/AG/AA	624/0/0	859/0/0	–	–	–
	Combined	G/A	2220/0	2678/0	–	GG/AG/AA	1110/0/0	1339/0/0	–	–	–
rs35870237 ^d	Hunan	A/G	972/0	960/0	–	AA/AG/GG	486/0/0	480/0/0	–	–	–
	Shanghai	A/G	1248/0	1718/0	–	AA/AG/GG	624/0/0	859/0/0	–	–	–
	Combined	A/G	2220/0	2678/0	–	AA/AG/GG	1110/0/0	1339/0/0	–	–	–
rs7307310	Hunan	C/T	636/336	671/289	0.252	CC/CT/TT	201/234/51	237/197/46	0.294	0.301	0.588
	Shanghai	C/T	837/411	1133/585	0.524	CC/CT/TT	277/283/64	376/381/102	0.620	0.693	0.715
	Combined	C/T	1473/747	1804/874	0.453	CC/CT/TT	478/517/115	613/578/148	0.240	0.274	0.504
rs34778348	Hunan	G/A	944/28	930/30	0.753	GG/AG/AA	458/28/0	451/28/1	0.601	–	0.423
	Shanghai	G/A	1204/44	1661/57	0.758	GG/AG/AA	580/44/0	805/51/3	0.234	–	0.029
	Combined	G/A	2148/72	2591/87	0.991	GG/AG/AA	1038/72/0	1256/79/4	0.160	–	0.025
rs3761863	Hunan	A/G	527/445	490/470	0.162	AA/AG/GG	143/241/202	128/234/118	0.357	0.378	0.591
	Shanghai	A/G	696/552	973/745	0.639	AA/AG/GG	191/314/119	272/429/158	0.892	0.854	0.624
	Combined	A/G	1223/997	1463/1215	0.747	AA/AG/GG	334/555/221	400/663/276	0.911	0.887	0.967

^a P values were calculated by the Fisher's exact test with Bonferroni correction.

^b Binary logistic regression analysis was performed to assess the association of *LRRK2* SNPs with schizophrenia with an adjustment for sex and age. The minor allele frequencies of rs34594498, rs33939927, rs35801418, rs34637584, rs35870237 and rs34778348 were too low and these SNPs were not included in the logistic regression analysis.

^c P values were calculated in the control groups.

^d SNPs rs33939927, rs35801418, rs34637584 and rs35870237 were not polymorphic in both cohorts, thus were not included in the analyses.

SNPs were similar between case and control populations in both cohorts (Fig. 1). We compared the genotype, allele and haplotype frequencies of those 8 SNPs between cases and controls in the two independent cohorts. No significant difference was found for any SNP/haplotype (Tables 1 and 2). Logistic regression analysis revealed that after adjustment for sex and age, there was still no significant association between any SNP and disease in both cohorts. We further pooled these two cohorts together (1110 schizophrenia patients and 1339 healthy controls) for combined analysis, but still observed no significant association between these *LRRK2* variants and schizophrenia.

4. Discussion

LRRK2 is a large multi-domain protein kinase which is important in a variety of cellular functions [18,35]. Mutations in the *LRRK2* gene are the most common cause of familial Parkinson's disease, and also confer genetic susceptibility to Alzheimer's disease, Crohn's disease, cancer [30] and leprosy [39]. Functional characterization showed that PD-related *LRRK2* mutations can influence mitochondrial activities such as mitochondrial fission/fusion [38], mitochondrial depolarization and mitophagy [25]. Since mitochondrial dysfunction is prevalent in neurological diseases, we

speculated that genetic variation in the *LRRK2* gene may confer susceptibility to a wide spectrum of neuropsychiatric diseases including schizophrenia. Note that most of the previous association studies only focused on limited number of *LRRK2* variants, a comprehensive screening is essential for fully evaluating the role of *LRRK2* variants in diseases.

Table 2

Haplotype frequencies of the 8 *LRRK2* SNPs in 486 schizophrenia patients and 480 healthy controls from Hunan Province, and in 624 schizophrenia cases and 859 healthy controls from Shanghai.

Haplotype ^a	Hunan		Shanghai		Combined	
	Case	Control	Case	Control	Case	Control
GCCGATGA	315	267	393	565	708	832
ACTGCCGG	255	285	324	445	579	730
GCTGACCA	144	151	226	297	370	448
GCTGCCGG	99	100	123	176	222	276
ACTGCCAG	27	30	38	54	65	84
GCTGCCGA	30	34	37	53	67	87
Rare haplotypes ^b	102	93	107	128	209	221
P-value	0.365		0.917		0.776	

^a The order of the 8 SNPs for each haplotype: rs732374-rs34594498-rs4473003-rs33949390-rs7298930-rs7307310-rs34778348-rs3761863.

^b Haplotypes with a frequency less than 3% were pooled together.

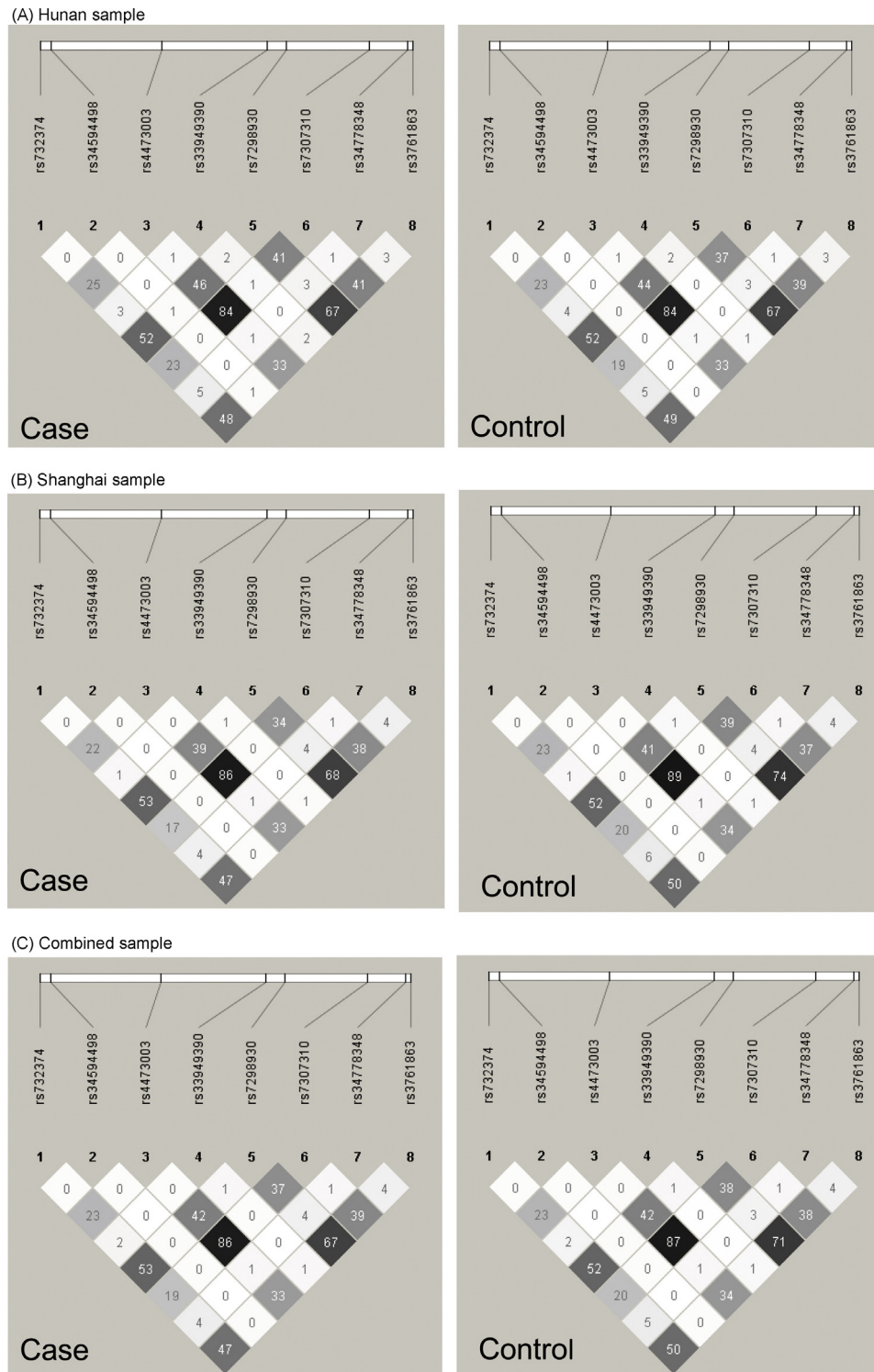


Fig. 1. The linkage disequilibrium (LD) structures of the *LRRK2* gene in schizophrenia patients and healthy controls. The value in each square refers to $r^2 \times 100$. Black squares represent high LD as measured by r^2 , gradually coloring down to white squares of low LD. LD pattern of 8 SNPs in the *LRRK2* gene was reconstructed in schizophrenia patients and controls from Hunan Province (A), Shanghai (B), as well as the combined samples from Hunan Province and Shanghai (C).

In this study, we genotyped 12 *LRRK2* variants (including 8 reported disease-associated mutations and 4 tag SNPs) by using SNaPshot assay in two independent Han Chinese schizophrenia case-control cohorts from South Central China and East China, respectively. These genetic variants are located in the entire *LRRK2* gene region. Analysis for the matrilineal genetic components in the case and control populations showed that our samples were

well-matched and there was no apparent population stratification in our sample (author's unpublished data). Four PD pathogenic mutations [p.R1441C (rs33939927), p.Y1699C (rs35801418), p.G2019S (rs34637584) or p.I2020T (rs35870237)] were not found in any schizophrenia patient or in any normal control, indicating that these mutations were very rare in Han Chinese populations. For the other 8 variants which were polymorphic in our samples,

there was no significant difference between schizophrenia cases and controls in allele, genotype and haplotype frequency distributions. Moreover, adjustment of sex and age had no effect on the result. Our results suggested that the reported pathogenic mutations and common genetic variants in the *LRRK2* gene may not confer susceptibility to schizophrenia in Han Chinese.

There are three limitations in our study. First, although we fully investigated the reported pathogenic mutations and common variants of the *LRRK2* gene through genotyping, we did not sequence this gene to assess the influence of rare variant(s) on schizophrenia. Targeted deep sequencing can help to reveal fundamental characteristics of pathogenic *LRRK2* mutations [29]. Second, schizophrenia is a very complex and heterogeneous disease and variants in the *LRRK2* gene may be associated with certain subtype or symptoms of schizophrenia, or antipsychotic medication. However, it is incapable to get a conclusion in our samples because of the relatively small sample size and insufficient clinical information such as antipsychotic drug treatment, which disabled us to evaluate the influence of antipsychotic drug treatment at the time of testing even though there is a large literature showing that antipsychotic drugs can alter mitochondrial function and mitochondrial gene regulation [5,6]. Similarly, we were unable to control for other relevant clinical factors, such as age onset for first psychosis and length of treatment, to discern their modulation effect on the interaction between *LRRK2* SNPs and schizophrenia. Third, in the validation sample, the average age of female controls was about 3 years younger than that of female patients. Although most of female patients developed disease before age of 30 according to a previous report [19], we could not rule out the possibility for a biased result caused by younger female controls.

In short, we examined 12 genetic variants of the mitochondrial gene *LRRK2* in two independent Han Chinese schizophrenic cohorts, but identified no association between any of the *LRRK2* variants or haplotypes and schizophrenia in these cohorts. Although we genotyped sufficient number of *LRRK2* SNPs, no final conclusion can be drawn from this study because of the single gene approach and the relatively small sample size. Further study of different populations is needed to solidify current finding.

Conflict of interest

The authors declare no conflict of interests.

Acknowledgements

We are grateful to all of the participants in this study. This study was supported by the Strategic Priority Research Program (B) of the Chinese Academy of Sciences (XDB02020000), the Ministry of Science and Technology of China (2011CB910900), and the West Light Foundation of the Chinese Academy of Sciences.

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