



## Polygenic determinants of Parkinson's disease in a Chinese population

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### ABSTRACT

It has been reported that some single-nucleotide polymorphisms (SNPs) are associated with the risk of Parkinson's disease (PD), but whether a combination of these SNPs would have a stronger association with PD than any individual SNP is unknown. Sixteen SNPs located in the 8 genes and/or loci (*SNCA*, *LRRK2*, *MAPT*, *GBA*, *HLA-DR*, *BST1*, *PARK16*, and *PARK17*) were analyzed in a Chinese cohort consisting of 1061 well-characterized PD patients and 1066 control subjects from Central South of Mainland China. We found that Rep1, rs356165, and rs11931074 in *SNCA* gene; G2385R in *LRRK2* gene; rs4698412 in *BST1* gene; rs1564282 in *PARK17*; and L444P in *GBA* gene were associated with PD with adjustment of sex and age ( $p < 0.05$ ) in the analysis of 16 variants. PD risk increased when Rep1 and rs11931074, G2385R, rs1564282, rs4698412; rs11931074 and G2385R, rs1564282, rs4698412; G2385R and rs1564282, rs4698412; and rs1564282 and rs4698412 were combined for the association analysis. In addition, PD risk increased cumulatively with the increasing number of variants (odds ratio for carrying 3 variants, 3.494). In summary, we confirmed that Rep1, rs356165, and rs11931074 in *SNCA* gene, G2385R in *LRRK2* gene, rs4698412 in *BST1* gene, rs1564282 in *PARK17*, and L444P in *GBA* gene have an independent and combined significant association with PD. SNPs in these 4 genes have a cumulative effect with PD.

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### 1. Introduction

Parkinson's disease (PD), the second most common progressive neurodegenerative disorder, is characterized by resting tremor, rigidity, bradykinesia, and impaired postural reflexes. The majority of the patients are sporadic cases. Although the etiology of PD remains unclear, approximately 5%–10% of the patients have been found affected by the genetic factors (Dauer and Przedborski, 2003; Samii et al., 2004). Several genes have been identified associating with familial PD. To date, >13 genes have been cloned associating with the monogenic forms of parkinsonism and related disorders (Chartier-Harlin et al., 2011; Lesage and Brice, 2009; Vilariño-Güell et al., 2011; Zimprich et al., 2011). However, these cannot explain the etiology of the vast majority of patients with an apparently sporadic late-onset disease.

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There is an increasing evidence that genetic susceptibility contributes to the etiology of PD. It has been reported that some polymorphisms are associated with the risk of PD, such as Rep1, rs356165, and rs11931074 in *SNCA* gene (Mueller et al., 2005; Satake et al., 2009; Simón-Sánchez et al., 2009; Tan et al., 2010a); G2385R and R1628P in *LRRK2* gene (Ross et al., 2011; Tan et al., 2010a, 2010b); rs242562 and rs2435207 in *MAPT* gene (Skipper et al., 2004; Vandrovicova et al., 2009); and L444P in *GBA* gene (Sidransky et al., 2009; Sun et al., 2010). More recently, genome-wide association studies (GWASs) of complex diseases have identified sequence variants that are consistently associated with the risk of such diseases. Some well-known loci are further confirmed to be linked with the risk of PD, such as *SNCA* and *MAPT*, and some other new loci or polymorphisms were also found to be associated with the risk of PD, such as *PARK16*, *PARK17* (*GAK*), *PARK18* (*HLA-DR*), and *BST1* gene (Edwards et al., 2010; Pankratz et al., 2010; Saad et al., 2011; Satake et al., 2009; Simón-Sánchez et al., 2009; UK Parkinson's Disease Consortium et al., 2011). In *The Lancet*, the International Parkinson Disease Genomic Consortium reported the first meta-analysis of datasets from 5 PD GWASs from the United

States and Europe to identify loci associated with PD (discovery phase). Totally, 11 loci surpassed the threshold for genome-wide significance that included 6 previously identified loci (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK*, and *LRRK2*) (International Parkinson Disease Genomics Consortium et al., 2011).

Because monogenic forms of the disease are rare, a polygenic model has long been suggested to explain the genetic contribution to the pathogenesis of the majority of PD cases. Often, such variants have limited use in the assessment of disease risk in an individual patient because most of them confer a relatively small risk. Whether combinations of individual variants will confer larger more clinically useful associations with increased risk remain to be shown. Until now, there are only a few studies reporting about the gene-gene interaction on susceptibility to PD, such as the interaction of *SNCA* and *MAPT* gene; *SNCA*, *MAPT*, and *GSK3B*; and *FGF20* and *MAOB* (Elbaz et al., 2011; Gao et al., 2008; Trotta et al., 2012; Wider et al., 2011).

There was no systemic evaluation of the independent effects of the 6 known genes or loci (*MAPT*, *SNCA*, *HLA-DRB5*, *BST1*, *GAK*, and *LRRK2*) on the susceptibility to Chinese PD. Whether a combination of single-nucleotide polymorphisms (SNPs) in these genes would have a stronger association with PD than any individual SNPs is unknown. In this study, we investigated whether independent and joint effects of variants in the previously mentioned 8 genes and/or loci will contribute to PD in a Chinese cohort consisting of 1061 well-characterized PD patients and 1066 control subjects from Central South of Mainland China. Because *PARK16* and L444P in *GBA* gene were reported associating with the risk of Asian PD (Satake et al., 2009; Sidransky et al., 2009; Sun et al., 2010), we also analyzed the 2 loci in this study.

## 2. Subjects and methods

### 2.1. Study population

In total, 1061 unrelated sporadic PD patients and 1066 healthy subjects were included in our study. All of them were of Han-Chinese nationality. All these patients were recruited from the outpatient neurology clinics of Xiangya Hospital from October 2003 to November 2010. PD was diagnosed by  $\geq 2$  experienced neurologists according to the UK brain-bank criteria (Hughes et al., 1992). None had a history of neurologic or psychiatric conditions other than PD. Cases with a family history of PD in a first- or second-degree relative were not included. These PD patients came from Hunan, Hubei, Jiangxi, and Chongqi province of China. Six hundred twenty two (58.6%) of the patients were men, and 439 (41.4%) were women. The mean age at disease onset in the patient group was 54.20 (standard deviation, 12.48; range, 16–79) years. Information on family history, demographic characteristics, clinical data, and neurologic examination was completed for each patient. A control group of 1066 healthy Han Chinese individuals from the same geographic areas was obtained, matching for age and sex ( $51.86 \pm 16.53$  years, ranging from 17- to 76-year olds and with a similar male-female ratio) with the PD patients' sample. Individuals with dementia or with a family history of PD in a first- or second-degree relative were excluded, and we also excluded the patients with *Parkin* mutations (Guo et al., 2010). Blood samples were obtained from patients with sporadic PD and controls. Informed consents from all the involved subjects were taken, and the work received approval from the institutional ethics board in Xiangya Hospital.

### 2.2. Genotyping methods

We selected variants that have been reported to be associated with PD in 8 genes or loci—(1) *LRRK2* gene: the R1628P and G2385R

variants residing in the coding region; (2) *GBA* gene: the L444P variant; (3) *MAPT* gene: 2 H1-specific *MAPT* polymorphisms, rs246562 and rs2435207 (these were selected because the complete H1 haplotype associated with PD in Europeans does not occur in Chinese); (4) *SNCA* gene: 2 SNPs, rs356165 and rs11931074, in the 3' untranslated region of the *SNCA* gene, and the CA repeat number within the promoter region (analogous to the Rep1 allele); (5) *PARK16*: rs823156 and rs11240572 in *PARK16* loci; (6) *PARK17* (*GAK*): rs11248051 and rs1564282 in *PARK17* loci; (7) *PARK18* (*HLA-DR*): rs3129882 and rs3117098 in *PARK18* loci; and (8) *BST1* gene: rs4698412 and rs11931532 in *BST1* gene.

Genomic DNA was extracted from peripheral blood leukocytes using the standard protocols. The primers used for polymerase chain reaction (PCR) amplification of 18 SNPs were designed using Primer3 (<http://frodo.wi.mit.edu>) on the Internet. Conditions for amplification are available on request. The PCR products were separated by 6% nondenatured polyacrylamide gels. Each PCR product was purified and directly sequenced on an ABI 3730XL automated sequencer (Applied Biosystems, Inc, Foster City, CA, USA). Alignment and analysis were carried out with DNASTar (DNASTar, Inc, Madison, WI, USA). *SNCA* Rep1 alleles were sized on a high-resolution capillary electrophoresis platform using ABI 3730XL automated sequencer (Applied Biosystems, Inc), and allelic sizes were assessed using GeneScan version 4.0 software (Applied Biosystems, Inc). The Rep1 genotypes were defined according to the length of the PCR product: allele - 2 = 263 bp, allele - 1 = 265 bp, allele 0 = 267 bp, allele 1 = 269 bp, allele 2 = 271 bp, and allele 3 = 273 bp, as defined previously.

### 2.3. Statistical methods

Tests for Hardy-Weinberg equilibrium were performed for each SNP separately among case subjects and control subjects with the use of chi-square test. Pairwise linkage disequilibrium was tested for variants within each of the genes with the use of the program SHEsis (<http://analysis.bio-x.cn/myAnalysis.php>).

Differences in allele frequencies between case subjects and control subjects were tested for each SNP with the use of a logistic regression test. Allelic odds ratios and 95% confidence intervals were estimated on the basis of a multiplicative model. For genotypes, a series of tests assuming an additive, dominant, or recessive genetic model were performed for each of the 16 SNPs with the use of unconditional logistic regression with adjustment for age (age at evaluation for controls and onset for cases) and gender; the model with the lowest *p* value was considered to be the best-fitting genetic model for the respective SNP.

We also put all the SNPs into a logistic regression model to evaluate the association between each SNP and the disease susceptibility. We tested the interaction effect between each 2 SNPs (except for *GBA* L444P) in the additive and multiply model. We also used logistic regression to test for the cumulative effects of 6 SNPs (the statistically significant SNP). Subjects were classified by the total number of risk alleles (*n*) that they possessed (ranging from a minimum of 0 to a maximum of 5). All analyses were performed using SPSS (version 17.0).

## 3. Results

At the beginning, 1061 sporadic PD patients and 1066 healthy subjects were included for genotyping in this study (Supplementary Table 1). Forty-two PD patients and 36 controls samples were excluded from the analysis because DNA samples were not enough for all the 16 SNPs genotyping, and 1019 PD patients and 1030 control samples were fulfilled with all genotyping at 16 SNPs in 8 genes or loci. Demographic characteristics of the samples are shown in Supplementary Table 1.

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