Genetic Association Study between STK39 and CCDC62/HIP1R and Parkinson’s Disease

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Abstract

Background: The first large-scale meta-analysis of published genome-wide association studies (GWAS) in Parkinson’s disease (PD) identified 5 new genetic loci (ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R). Very recently, a large-scale replication and heterogeneity study also reported that STK39 and CCDC62/HIP1R increased risk of PD in Asian and Caucasian populations. However, their roles still remain unclear in a Han Chinese population from mainland China.

Methods: We examined genetic associations of STK39 rs2102808 and CCDC62/HIP1R rs12817488 with PD susceptibility in a Han Chinese population of 783 PD patients and 725 controls. We also performed further stratified analyses by the age of onset and accomplished in-depth clinical characteristics analyses between the different genotypes for each locus.

Results: No significant differences were observed in the minor allele frequency (MAF) among cases and controls at the two loci (STK39 rs2102808: OR = 1.06, 95% CI = 0.91, 1.23, P = 0.467; CCDC62/HIP1R rs12817488: OR = 0.88, 95% CI = 0.76, 1.01, P = 0.072). Subgroup analyses by the age of onset also showed no significant differences among different subgroups of the two loci. In addition, minor allele carriers cannot be distinguished from non-carriers based on their clinical features at the two loci.

Conclusions: We are unable to demonstrate the association between STK39 and CCDC62/HIP1R and PD susceptibility in a Han Chinese population from mainland China. Additional replication studies in other populations and functional studies are warranted to better validate the role of the two new loci in PD risk.

Introduction

Parkinson’s disease (PD, OMIM #168600) is the second most common adult-onset neurodegenerative disorder involving not only motor impairment but also deficits in behavior, cognition, and daily function [1]. Fewer than 5% of all PD cases can be attributed to genetic mutations in α-synuclein and the other known PD genes [2]. However, the vast majority of PD cases are considered idiopathic, whose specific pathogenesis remains to be elucidated. Understanding the genetic architecture of PD might provide valuable insights into individual risk predictions and gene therapy for PD in the near future.

With the recent developments of high throughput genotyping and genome-wide association studies (GWAS), tremendous progress was made in our understanding of the genetic basis for this complex disorder [3]. Up to now, several GWAS and many candidate gene studies have provided consistent associations with SNCA and MLTPL [4–16], with some evidence for the role of BST1, GAK/DGKQ, and the HLA region in PD susceptibility [7,11–13,16]. The three recent meta-analyses reported eleven new loci: ACMSD, STK39, MCCC1/LAMP3, SYT11, CCDC62/HIP1R, PARK16, STX1B, GGP20, STBD1, GPNMB, and RIT2 [10,17–18]. Hereafter, a large-scale replication and heterogeneity study also reported that STK39 and CCDC62/HIP1R increased risk of PD in Asian and Caucasian populations [19]. In their study, Asian populations include a relatively large sample size from Hong Kong, Singapore, Taiwan, Korea, and Japan [19]. Notably, these studies did not include the Han Chinese population from mainland China.

To provide more evidence into genuine loci contributing to PD across diverse populations, we conducted a case-control study to examine the genetic associations of STK39 (serine/threonine kinase 39, rs2102808) and CCDC62/HIP1R (Coiled-coil domain containing 62/Huntingtin-interacting protein 1-related, rs12817488) among Han Chinese in mainland China. Additional replication studies in other populations and functional studies are warranted to further validate the role of the two new loci in PD risk.

Citation: Li N-N, Tan E-K, Chang X-L, Mao X-Y, Zhang J-H, et al. (2013) Genetic Association Study between STK39 and CCDC62/HIP1R and Parkinson’s Disease. PLoS ONE 8(11): e79211. doi:10.1371/journal.pone.0079211

Editor: Mathias Toft, Oslo University Hospital, Norway

Received April 28, 2013; Accepted September 20, 2013; Published November 27, 2013

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Funding: The study was supported by West China Hospital of Sichuan University, Duke–NUS Graduate Medical School, Singapore Millennium Foundation, and National Medical Research Council. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Materials and Methods

Subjects

The study population included 1508 ethnic Han Chinese subjects comprising 783 sporadic PD patients (448 males, 335 females) and 725 controls (387 males, 338 females), all of whom were recruited from the Department of Neurology of the West China Hospital, Sichuan University. All patients (the mean age at onset 54.19±10.61, range 30–91) met United Kingdom Parkinson’s Disease Society Brain Bank clinical diagnostic criteria for PD as determined by two movement disorder specialists [20], except that patients who had an age at onset younger than 30 years. Sporadic PD was defined as PD without a family history of disease. Healthy control individuals (the mean age 55.26±12.85, range 30–91) of similar race, gender, and age from the same region as the PD patients were included. All subjects were divided into two subgroups according to the age of onset (<50 years of age and ≥50 years of age). The study was approved by the Ethics Committee of Sichuan University. All participants or their legal surrogates signed informed consent. DNA was extracted from venous blood using standard methods.

Genetic Analysis

**STK39** (rs2102808). Genotyping was performed using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry on a MassArray system (Sequenom, San Diego, CA, USA) for **STK39** rs2102808. Approximately 15 ng of genomic DNA was used to genotype each sample. Briefly, locus-specific polymerase chain reaction (PCR) and detection primers for the MALDI-TOF analysis of the **STK39** gene target fragment were designed using the MassArray Assay Design 3.0 software (Sequenom, San Diego, CA, USA). The sample DNAs were amplified by primers flanking the targeted sequence, followed by dephosphorylation and allele-specific primer extension. Eluted extension products were loaded to the dried matrix and finally subjected to MALDI-TOF mass spectrometry. The resultant data were analyzed by the Sequenom MassArray Typer software (Sequenom, San Diego, CA, USA).

**CCDC62/HIP1R** (rs12817488). Genotyping was performed using polymerase chain reaction followed by Restriction Fragment Length Polymorphism (PCR-RFLP) with MspI (Fermentas) for **CCDC62/HIP1R** rs12817488. A 334 bps fragment was amplified by the following primer pair: 5’TCTTGAGGGCTAAG-AGGGG3’ (forward) and 5’TCTTGGGATGTTGAAGTTTGGAGG3’ (reverse). The PCR products were digested overnight with MspI at 37°C and electrophoresed on 2% agarose gel and visualized with ethidium bromide. The rs12817488 variant creates a MspI restriction site which cuts the normal 334 bps PCR products into fragments of 174 bps and 171 bps. The AA genotype gave a single band of 334 bps, the AG genotype two bands of 334 bps+174 bps+171 bps and the GG genotype a mixed band of 174 bps+171 bps. 10% of samples were randomly selected for replication assays, the final results of which were completely concordant with the original results.

Statistical Analysis

We assessed each locus for Hardy-Weinberg equilibrium (HWE) in cases and controls separately with an exact test. Differences between allelic and genotype frequencies in the patients and controls were compared through a Chi-squared test. The two-tailed Student’s-t-test was used to compare the mean age between the different genotypes. A two-tailed P-value ≤0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA) for Windows. For power estimations we used NCSS-PASS software (NCSS, Kaysville, Utah, USA). Odd Ratios (ORs) of **STK39** rs2102808 and **CCDC62/HIP1R** rs12817488 were, respectively, 1.28 and 1.16 in the discovery phase of the original GWAS meta-analysis [10]. Additionally, based on the minor allele frequency (MAF) reported by our own study in Han Chinese controls, estimated power was high for **STK39** (~91%), and modest for **CCDC62/HIP1R** (~55%).

Results

Data on a total of 1508 subjects including 783 cases and 725 controls were used for analysis. None of the single nucleotide polymorphisms (SNPs) departed from HWE in patients and controls. The allele frequencies of each SNP are summarized in Table 1 between cases and controls.

No significant differences were observed in the minor allele frequency among cases and controls at the two loci (rs2102808: OR = 1.06, 95% CI = 0.91, 1.23, P = 0.467; rs12817488: OR = 0.88, 95% CI = 0.76, 1.01, P = 0.072). In **STK39** (rs2102808), subjects with GT+TT genotypes was not significantly different from those with GG genotype (OR = 0.96, 95% CI = 0.78, 1.17, P = 0.657). At the same time, subjects with AG+GG genotypes have no significant differences compared to those with AA genotype at **CCDC62/HIP1R** rs12817488 (OR = 0.89, 95% CI = 0.71, 1.11, P = 0.286). In addition, further stratified analyses according to the age of onset also showed that the associations were not significant among the younger age group and the older age group in **STK39** and **CCDC62/HIP1R** (Table 2).

We also compared the clinical characteristics of PD cases that carried the minor allele with PD Cases who did not carry it (Table 3). However, there was no significant difference in the clinical presentation for gender, age of onset, onset symptoms at **STK39** rs2102808 and **CCDC62/HIP1R** rs12817488.

Discussion

The first large-scale meta-analysis of GWAS in PD identified 5 new PD genetic loci (**ACMSD**, **STK39**, **MCCC1/LAMP3**, **SST11**, and **CCDC62/HIP1R**) [10]. Very recently, a case-control replication study provided support for all these loci in a relatively homogenous Scandinavian population [21]. Moreover, a large replication study [19] and acomprehensive meta-analysis from the PDGene database [22] also investigated the same associations for all 5 loci except **ACMSD** and subgroup analysis by ethnicity also showed similar effect size estimates for **STK39**, **CCDC62/HIP1R**, and **MCCC1/LAMP3** in Asian and Caucasian populations [19]. Besides, the other two intronic SNPs, rs3754775 and rs6740826 in **STK39** showed the strongest evidence of association using an overall MAF threshold of 2% or higher to identify rare genetic

| Table 1. Comparison of Allelic Frequencies between Cases and Controls. |
|------------------------|--------|---------|-----------|-------------|---------|
| Gene                  | SNP    | Cases   | MAF       | Controls   | OR 95%  |
|                       |        |         |           |            | (CI)     | P-value |
| **STK39**             | rs2102808 | 35.12%  | 33.86%    | 1.06       | 0.91, 1.23 | 0.467  |
| **CCDC62/HIP1R**      | rs12817488 | 45.13%  | 48.45%    | 0.88       | 0.76, 1.01 | 0.072  |

doi:10.1371/journal.pone.0079211.t001
variants in a relatively genetically homogeneous Ashkenazi Jewish population (OR = 2.12, 95% CI = 1.24, 3.62, P = 0.005) [8].

In view of the population-specific heterogeneity, we accomplished a case-control study included 1508 subjects to further explore the role of two newly identified genetic variants (STK39 rs2102808 and CCDC62/HIP1R rs12817488) in risk of PD in a Han Chinese population from mainland China. Conversely, we are unable to replicate the association between STK39 rs2102808 and CCDC62/HIP1R rs12817488 and PD susceptibility. Subgroup analyses by age of onset also showed no significant differences among different subgroups of the two loci. In addition, minor allele carriers cannot be distinguished from non-carriers based on their clinical features for gender, age of onset, onset symptoms at the two loci.

Our finding should be interpreted with caution as our modest sample size results in only modest power for some alleles with very small effect sizes. This is especially for CCDC62/HIP1R rs12817488. Future multi-site efforts and meta-analyses will be useful. Genetic heterogeneity across diverse populations may also explain the variances between studies. Our selected SNPs in our cohort might not be genuine functional variants, or the pattern of linkage disequilibrium (LD) might differ so that they are no longer co-ancestral. In the future studies [21].

In conclusion, our study from mainland China demonstrates the role of two newly identified genetic variants (STK39 rs2102808 and CCDC62/HIP1R rs12817488) in risk of PD in a Han Chinese population from mainland China. Conversely, we are unable to replicate the association between STK39 rs2102808 and CCDC62/HIP1R rs12817488 and PD susceptibility. Subgroup analyses by age of onset also showed no significant differences among different subgroups of the two loci. In addition, minor allele carriers cannot be distinguished from non-carriers based on their clinical features for gender, age of onset, onset symptoms at the two loci.

Table 2. Association between the two genetic loci and PD.

| SNP                        | n   | Genotype (%) | OR 95% (CI) | P value |
|----------------------------|-----|--------------|-------------|---------|
| STK39 rs2102808 PD         | 783 | GG 335 (42.8)| 448 (57.2)  | 0.96 (0.78, 1.17) | 0.657 |
| EOPD                      | 262 | 104 (39.7)   | 158 (60.3)  | 0.96 (0.67, 1.39) | 0.851 |
| LOPD                      | 521 | 231 (44.3)   | 290 (55.7)  | 0.95 (0.74, 1.21) | 0.654 |
| Controls                  | 725 | 302 (41.7)   | 423 (58.3)  | 0.96 (0.78, 1.17) | 0.573 |
| Controls <50 yr           | 229 | 89 (38.9)    | 140 (61.1)  | 0.96 (0.67, 1.39) | 0.851 |
| Controls ≥50 yr           | 496 | 213 (42.9)   | 283 (57.1)  | 0.95 (0.74, 1.21) | 0.654 |
| CCDC62/HIP1R rs12817488 PD | 760 | 234 (30.8)   | 526 (69.2)  | 0.89 (0.71, 1.11) | 0.286 |
| EOPD                      | 260 | 78 (30.0)    | 182 (70.0)  | 0.78 (0.52, 1.16) | 0.220 |
| LOPD                      | 500 | 156 (31.2)   | 344 (68.8)  | 0.93 (0.71, 1.23) | 0.622 |
| Controls                  | 708 | 200 (28.2)   | 508 (71.8)  | 0.96 (0.78, 1.17) | 0.573 |
| Controls <50 yr            | 224 | 56 (25.0)    | 168 (75.0)  | 0.96 (0.78, 1.17) | 0.573 |
| Controls ≥50 yr            | 484 | 144 (29.8)   | 340 (70.2)  | 0.96 (0.78, 1.17) | 0.573 |

Table 3. Clinical Characteristics of PD Patients between minor allele carriers and non-carriers.

| Genotype | Pvalue |
|----------|--------|
| STK39 rs2102808 GG | GT+TT |
| General characteristics |
| Gender |
| Male (%) | 190 (56.7) | 258 (57.6) | 0.807 |
| Female (%) | 145 (43.3) | 218 (42.4) |
| Age at onseta |
| Total cohort | 54.75 ± 10.59 | 53.77 ± 10.62 | 0.198 |
| EOPD | 42.47 ± 4.82 | 42.44 ± 4.88 | 0.955 |
| LOPD | 60.28 ± 7.31 | 59.94 ± 7.28 | 0.594 |
| Onset symptoms |
| Resting tremor (%) | 167 (49.9) | 230 (51.3) | 0.589 |
| Bradykinesia-rigidity (%) | 126 (37.6) | 152 (33.9) |
| Mixed symptoms (%) | 16 (4.8) | 21 (4.7) |
| Others (%)b | 26 (7.8) | 45 (10.0) |
| CCDC62/HIP1R rs12817488 AA | AG+GG |
| General characteristics |
| Gender |
| Male (%) | 128 (54.7) | 308 (58.6) | 0.321 |
| Female (%) | 106 (45.3) | 218 (41.4) |
| Age at onseta |
| Total cohort | 54.73 ± 10.70 | 54.12 ± 10.75 | 0.894 |
| EOPD | 42.23 ± 5.10 | 42.53 ± 4.78 | 0.648 |
| LOPD | 60.23 ± 7.1 | 60.25 ± 7.48 | 0.982 |

Onset symptoms

Resting tremor (%) | 112 (47.9) | 270 (51.3) | 0.313 |
Bradykinesia-rigidity (%) | 92 (39.3) | 180 (34.2) |
Mixed symptoms (%) | 7 (3.0) | 28 (5.3) |
Others (%)b | 23 (9.8) | 48 (9.1) |

aData are mean ± SD.

bIncluding pain, weakness, symptoms of autonomic dysfunction and so on.

doi:10.1371/journal.pone.0079211.0003
appear to influence PD risk. Subgroup analyses also showed no significant differences among different subgroups of the two loci. Furthermore, minor allele carriers cannot be distinguished from non-carriers based on their clinical features at the two loci. Additional replication studies in other populations and functional studies are warranted to better validate the role of the two new loci in PD susceptibility.

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