Analysis of 12 GWAS-Linked Loci With Parkinson’s Disease in the Chinese Han Population

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A recent large-scale European-originated genome-wide association study identified 38 novel independent risk signals in 37 loci for Parkinson’s disease (PD). However, whether these new loci are associated with PD in Asian populations remains elusive. The present study aimed to explore the relationship between the 12 most relevant loci with larger absolute values for these new risk loci and PD in the Chinese Han population. We performed a case-control study including 527 PD patients and 435 healthy controls. In the allele model, it was found that rs10748818/GBF1 was associated with PD in the Chinese Han population \(p = 0.035, \) odds ratio (OR) 1.221, 95% confidence interval (CI) 1.014–1.472. After further age-stratified analysis, rs11950533/C5orf24 and rs76949143/GS1-124K5·11 were shown related to early-onset PD \(p = 0.034\) and late-onset PD \(p = 0.042\) in genotype model, respectively. In contrast, no significant association with PD was found in the remaining nine loci (rs34025766/LCORL, rs55961674/KPNA1, rs61169879/BRIP1, rs666463/DNAH17, rs75859381/RPS12, rs76116224/KCNS3, rs77551827/CRLS1, rs7938782/RNF141, and rs850738/FAM171A2) either in allele or genotype frequencies. Our study revealed that the variants of rs10748818/GBF1 were associated with PD in the allele model; after age-stratified analysis, rs11950533/C5orf24 and rs76949143/GS1-124K5·11 were associated with early-onset PD and late-onset PD in the Chinese Han population, respectively.

Keywords: Parkinson's disease, single nucleotide polymorphisms, Chinese population, GBF1, C5orf24, GS1-124K5·11

INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disorder next to Alzheimer’s disease, with a prevalence of 1.7% in the Chinese Han population aged ≥ 65 years (1). The majority of PD cases are sporadic with elusive etiology. Varying factors contribute to the development of PD, including environmental and genetic factors. Mounting evidence has revealed that the latter may provide significant clues to causes of PD (2).
Genome-wide association study (GWAS)-related loci, such as single nucleotide polymorphisms (SNPs) in SNCA, GBA, and LRRK2, are reported to be associated with PD (3). Pooling 17 datasets from PD GWAS available from European ancestry samples, a recent large-scale meta-analysis identified 38 novel independent risk signals in 37 loci for PD (4). However, whether these new loci are associated with PD in Asian populations remains elusive. Referring to the regression coefficient in the results of this meta-analysis, we selected the 12 most relevant loci with larger absolute values for exploration (The detailed information of 38 SNPs was shown in Supplementary Table 2). Consequently, a study including 527 PD patients and 435 healthy controls was performed to investigate the association between the 12 new loci and PD in the Chinese Han population.

MATERIALS AND METHODS

Subjects

A total of 962 subjects of Han Chinese ethnicity were enrolled in the study, including 527 sporadic PD patients and 435 controls. The mean age and sex ratio (male/female) of the two groups were (PD patients: 62.34 ± 9.150 years, 300/227) and (healthy controls: 47.75 ± 10.856 years, 238/197), respectively. To minimize the effect of the familial PD, all patients recruited are sporadic cases. And the young-onset patients were excluded. The cases were defined using the United Kingdom Parkinson’s Disease Society Brain Bank criteria. All subjects participating in the study signed written informed consent. This study was approved by the Ethics Committee of First Affiliated Hospital of Zhengzhou University.

Genotyping and Data Analysis

Genomic DNA was extracted from peripheral blood collected from the patients and controls using the Blood Genome Extraction Kit (BioTeke Co, Beijing, China). SNPs were genotyped using improved multiple ligase detection reaction (iMLDR) technology (Geneskybiotech, Shanghai, China). All relevant specific polymerase chain reaction (PCR) primers and ligation primers were listed in Supplementary Table 1.

Statistical analysis was performed using IBM SPSS Statistics 26.0. The age difference was assessed using the t test. The Hardy-Weinberg equilibrium in genotype-frequency of controls was assessed using the $\chi^2$ test. Logistic regression analysis was used to calculate the risk analysis of each SNP in dominant, recessive models after adjusting for age and gender. Chi-squared tests were adopted to compare differences of sex ratio, genotype frequency, and allele frequency after age and gender-stratified analysis. Multiple tests were performed using the Bonferroni correction method. A 2-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Frequencies of all 12 variants in the cases and controls met with Hardy-Weinberg equilibrium ($p > 0.05$, Table 1). In the allele model, the result showed that the rs10748818/GBF1 variant exhibited significant difference between PD patients and the controls [$p = 0.035$, odds ratio (OR) 1.221, 95% confidence interval (CI) 1.014–1.472, Table 1]. A higher level of G allele was observed in the patients compared with the controls. In dominant and recessive models, rs10748818/GBF1 was not associated with PD after sex and age adjustment via logistic regression [$p = 0.275$, (OR) 0.834, (CI) 0.601–1.155, Table 1]. In addition, age-stratified analysis showed rs11950533/C5orf24 (genotype model: $p = 0.034$, Table 2) and rs76949143/GS1-124K5-11 (genotype model: $p = 0.042$, Table 2) were associated with early-onset PD (age < 50 years) and late-onset PD (age ≥ 50 years), respectively.

In contrast, no statistical difference in genotype or allele frequency was detected between PD patients and the controls in the remaining nine loci (rs34025766/LCORL, rs55961674/KPNA1, rs6169879/BRIP1, rs666463/DNAH17, rs75859381/RPS12, rs76116224/KCNN3, rs77351827/CRLS1, rs7938782/RNF141, and rs850738/FAM171A2, Tables 1, 2), neither between groups of the same sex or the same age. All detailed information on the relationship level of 12 loci with PD is shown in Tables 1, 2.

DISCUSSION

Given the effects of ethnic heterogeneity, our present study investigated the 12 new identified PD-associated variants in a Han Chinese population. We demonstrated that rs10748818/GBF1 exhibited a difference between PD patients and the controls in the allele mode. After age-stratified analysis, rs11950533/C5orf24 and rs76949143/GS1-124K5-11 were associated with early-onset PD and late-onset PD, respectively. To the best of our knowledge, our study is the first to show the association of SNPs in GBF1, C5orf24, and GS1-124K5-11 genes. No statistical difference in genotype or allele frequency was detected between PD patients and the controls in the remaining nine loci. Our study, however, failed to replicate the association of the reported SNPs with PD by Nalls et al. in the European population, which may partially be due to the genetic heterogeneity caused by ethnic and geographical differences (detailed 38 loci information of the GWAS results by Nalls et al. are shown in Supplementary Table 2). Additionally, the interaction between environmental and genetic factors may influence gene expression.

The first Han Chinese GWAS by Foo JN analyzed a total of 22,729 subjects (5,125 PD cases and 17,604 controls) from Singapore, Hong Kong, Malaysia, Korea, mainland China, and Taiwan and replicated associations at SNCA, LRRK2, MCCCI, and 14 other European PD loci but did not identify Asian-specific loci with large effects on PD risk (5). A two-stage meta-analysis of GWAS identified 17 new loci, which were associated with the risk of PD in the European population (26,000 PD patients and 403,000 healthy controls). However, the following study did not find any association between the five most commonly

**Abbreviations:** PD, parkinson’s disease; OR, odds ratio; CI, 95% confidence interval; GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; PTSD, post-traumatic stress disorder; HWE, Hardy-Weinberg equilibrium; RABGEF1, RAB guanine nucleotide exchange factor 1.
| SNPs/candidate gene | HWE (p-value) | Association test | PD | Control | p | OR (95%CI) | p* | OR (95%CI)* |
|---------------------|--------------|------------------|----|---------|---|------------|----|-------------|
| rs10748818/GBF1     | 0.73         | Genotypic (GG/GA/AA)  | 78/259/190 | 54/194/187 | - | -         |    | -           |
| rs11950533/C5orf24  | 0.99         | Dominant [GG + GA/AA] | 337/190 | 248/187 | 0.028* | 0.748(0.576–0.970) | 0.275 | 0.834(0.601–1.155) |
| rs34025766/LCORL    | 0.85         | Recessive [GG/AA + AA] | 78/449 | 54/381 | 0.285 | 1.226(0.844–1.780) | 0.857 | 1.03(0.745–1.424) |
| rs55961674/KPNA1    | 0.95         | Alleles(G/A) | 415/639 | 302/508 | 0.035* | 1.221(1.014–1.472) |    | -           |
| rs61169879/BRIP1    | 0.77         | Dominant [GG + GA/AA] | 259/218/50 | 209/186/40 | - | -         |    | -           |
| rs686463/DVASH1     | 0.81         | Recessive [GG/AA + AA] | 223/104 | 336/99 | 0.253 | 1.198(0.879–1.634) | 0.683 | 0.922(0.625–1.361) |
| rs75859381/RPS12    | 0.60         | Alleles(T/A) | 942/112 | 766/104 | 0.358 | 1.142(0.860–1.516) |    | -           |
| rs76116224/KCNS3    | 0.99         | Dominant [AA + AT/TT] | 993/61 | 830/40 | 0.244 | 0.785(0.521–1.181) |    | -           |
| rs76949143/GS1-124KS1| 0.24        | Recessive [AA/AT + TT] | 523/4 | 429/6 | 0.532* | 0.541(0.149–1.957) | 0.955 | 0.953(0.180–5.050) |
| rs77351827/CRILS1   | 1.00         | Alleles(A/T) | 1,050/4 | 864/6 | 0.533* | 1.823(1.513–6.480) |    | -           |
| rs7938782/RNF141    | 0.36         | Dominant [AA + GA/GG] | 373/143/11 | 303/115/17 | - | -         |    | -           |
| rs850738/FAM171A2   | 0.68         | Recessive [AA/AG + GA/GG] | 373/154 | 303/132 | 0.705 | 1.055(0.799–1.393) | 0.951 | 1.011(0.710–1.440) |

* A two-tailed p < 0.05 was considered significant.
* Adjusted age and sex by logistic regression.
* Continuous correction for Chi-square test when at least one cell has an expected value of <5.

PD, Parkinson’s disease; SNPs, single nucleotide polymorphisms; HWE, Hardy-Weinberg equilibrium; CI, confidence interval; OR, odds ratio. The bold means the P value < 0.05.
### TABLE 2: Age-stratified analysis and sex-stratified analysis of 12 loci.

| Genotype (candidate gene) | SNPs | Age onset < 50 years | Age onset ≥ 50 years | Male | Female |
|---------------------------|------|----------------------|----------------------|------|--------|
|                           |      | PD Control p1 OR (95%CI) | PD Control p2 OR (95%CI) | PD Control p3 OR (95%CI) | PD Control p4 OR (95%CI) |
| rs10748818 (GBF1)         |      |                      |                      |      |        |
| GG                        | 7    | 28 0.370             | 71 26 0.132          | 44 27 0.126 | 34 27 0.524 |
| GA                        | 16   | 113                  | 243 81               | 146 107 | 131 87 |
| AA                        | 23   | 106                  | 167 81               | 110 114 | 80 83 |
| G                         | 30   | 169 0.766            | 385 133 0.117        | 234 161 0.080 | 230 141 0.222 |
| A                         | 62   | 325                  | 577 243              | 366 315 | 273 253 |
| rs11950533 (C5orf24)      |      |                      |                      |      |        |
| CC                        | 24   | 119 0.034*           | 235 90 0.783         | 148 108 0.704 | 113 101 0.954 |
| CA                        | 17   | 103                  | 201 83               | 123 106 | 95 80 |
| AA                        | 5    | 25                   | 45 15                | 31 24  | 19 18 |
| C                         | 65   | 341 0.757            | 671 263 0.944        | 415 322 0.594 | 321 282 0.781 |
| A                         | 27   | 153                  | 291 113              | 185 154 | 133 112 |
| rs34025766 (LCORL)        |      |                      |                      |      |        |
| TT                        | 38   | 188                  | 385 148 0.418        | 240 190 | 183 146 |
| AT                        | 8    | 55                   | 88 39                | 55 46  | 41 48 |
| AA                        | 0    | 4                    | 8 1                  | 5 2   | 3 3 |
| T                         | 84   | 431 0.274            | 858 335 0.961        | 535 426 0.862 | 407 340 0.133 |
| A                         | 8    | 63                   | 104 41               | 65 50  | 47 54 |
| rs55961674 (KPNA1)        |      |                      |                      |      |        |
| CT                        | 8    | 55                   | 95 41                | 57 49  | 46 47 |
| TT                        | 2    | 2                    | 6 4                  | 4 4   | 4 2 |
| C                         | 80   | 435 0.767            | 855 327 0.328        | 535 419 0.558 | 400 343 0.643 |
| A                         | 12   | 59                   | 107 49               | 65 57  | 54 51 |
| rs61169879 (BRIP1)        |      |                      |                      |      |        |
| CC                        | 9    | 45 0.673             | 88 39 0.439          | 55 40 0.544 | 42 44 0.351 |
| CT                        | 22   | 135                  | 249 87               | 147 128 | 124 94 |
| TT                        | 15   | 67                   | 144 62               | 98 70  | 61 59 |
| C                         | 40   | 225 0.714            | 425 165 0.922        | 257 208 0.776 | 208 182 0.912 |
| A                         | 52   | 269                  | 537 211              | 343 268 | 246 212 |
| rs666463 (DNAH17)         |      |                      |                      |      |        |
| AA                        | 42   | 229 0.978*           | 456 180 0.613        | 284 222 0.499 | 214 187 0.768 |
| AT                        | 4    | 18                   | 25 8                 | 16 16  | 13 10 |
| T                         | 4    | 18                   | 25 8                 | 16 16  | 13 10 |
| rs75859381 (TT)           |      |                      |                      |      |        |
### TABLE 2 | Continued

| Genotype, allele | Age onset < 50 years | Age onset ≥ 50 years | Male | Female |
|------------------|----------------------|----------------------|------|--------|
|                  | PD                  | Control              | p\textsubscript{1} | OR (95%CI)\textsubscript{1} | PD                  | Control              | p\textsubscript{2} | OR (95%CI)\textsubscript{2} | PD                  | Control              | p\textsubscript{3} | OR (95%CI)\textsubscript{3} | PD                  | Control              | p\textsubscript{4} | OR (95%CI)\textsubscript{4} |
| (RPS12)          | CT                  | 5                    | 21               | 54                  | 19               | 33                  | 19               | 26                  | 21               | 426                  | 373               | 0.602               | 0.857              | 0.478               | 1.534               |
|                  | CC                  | 0                    | 0                | 1                   | 0                | 0                   | 0                | 1                   | 0                | 906                  | 357               | 0.583               | 0.861              | 1.470               | 1.040               |
|                  | T                   | 87                   | 473              | 0.818\textsuperscript{a} | 0.773(0.284--2.104) | 507               | 457              | 0.252               | 0.714(0.401--1.273) | 426                  | 373               | 0.602               | 0.857              | 0.478               | 1.534               |
|                  | C                   | 5                    | 21               | 56                  | 19               | 33                  | 19               | 28                  | 21               | 959                  | 375               | 1.000\textsuperscript{a} | 0.930(0.107--8.067) | 596                  | 474               | 0.899\textsuperscript{a} | 0.629(0.115--3.447) |
|                  | rs76116224          | AA                   | 45               | 242                | 1.000\textsuperscript{a} | 296               | 236              | 0.899\textsuperscript{a} | 0.571(0.153--2.133) | 227                  | 193               | 0.098\textsuperscript{a} | 0.462(0.430--0.497) |
|                  | (KCNS3)             | AT                   | 1                | 5                  | 3                | 1                   | 4                | 2                   | 0                | 4                    |
|                  | A                   | 91                   | 489              | 1.000\textsuperscript{a} | 0.930(0.107--8.067) | 596               | 474              | 0.899\textsuperscript{a} | 0.629(0.115--3.447) | 454                  | 390               | 0.099\textsuperscript{a} | 0.462(0.430--0.497) |
|                  | T                   | 1                    | 5                | 3                  | 1                   | 4                | 2                   | 0                | 4                   |
|                  | rs76949143          | TT                   | 38               | 191                | -                  | 347               | 142              | 0.042\textsuperscript{a} | 217                  | 184               | 0.241               |
|                  | (GS1-124K5-11)      | AT                   | 7                | 51                 | 128               | 39               | 78                | 48               | 57                |
|                  | AA                  | 1                    | 5                | 6                  | 7                   | 5                  | 6                   | 2                | 6                   |
|                  | A                   | 9                    | 61               | 140                | 53                 | 88                | 60                | 61               | 54                |
|                  | rs77351827          | CC                   | 46               | 247                | -                  | 481               | 188              | -                  | -                  | 300                  | 238               | -                  |
|                  | (CRLL5)             | C                   | 92               | 494                | -                  | 962               | 376              | -                  | -                  | 600                  | 476               | -                  | 454               | 394               |
|                  | rs7938782           | AA                  | 33               | 176                | 0.969              | 340               | 127              | 0.085              | 0.629(0.115--3.447) | 163                  | 141               | 0.693               |
|                  | (RNF141)            | GA                  | 12               | 64                 | 131               | 51                | 84                | 66                | 59                | 49                |
|                  | GG                  | 1                    | 7                 | 10                 | 10                 | 6                 | 10                | 5                 | 7                 |
|                  | A                   | 78                   | 416              | 0.890              | 1.045(0.563--1.938) | 811               | 305              | 0.159              | 1.250(0.916--1.707) | 504                  | 390               | 0.433              | 0.880(0.638--1.212) | 385                  | 331               | 0.751               | 1.062(0.732--1.540) |
|                  | G                   | 14                   | 78               | 151                | 71                 | 96                | 86                | 69               | 63                |
|                  | rs850738            | AA                  | 15               | 74                 | 0.843              | 169               | 70               | 0.300              | 1.021              | 82                  | 345               | 0.82               | 0.587              |
|                  | (FAM171A2)          | GA                  | 24               | 127                | 224               | 93                | 140               | 121              | 108               | 99                |
|                  | GG                  | 7                    | 46               | 88                 | 25                 | 58                | 35                | 37               | 36                |
|                  | A                   | 54                   | 275              | 0.591              | 1.132(0.721--1.777) | 562               | 233              | 0.235              | 0.862(0.675--1.101) | 344                  | 285               | 0.401              | 0.901(0.705--1.150) | 272                  | 223               | 0.329               | 1.146(0.872--1.507) |
|                  | G                   | 38                   | 219              | 400                | 143               | 256               | 191              | 182              | 171              |

\*A two-tailed p < 0.05 was considered significant.

\textsuperscript{a}Continuous correction for Chi-square test when at least one cell has an expected value of less than 5.

\textsuperscript{b}Adjusted by Fisher’s exact test when at least one cell has an expected value of <1.

PD, Parkinson’s disease; SNPs, single nucleotide polymorphisms; CI, confidence interval; OR, odds ratio. The bold means the P value < 0.05.
identified candidate variants in the European population with PD in the Chinese population (506 PD patients, 496 MSA patients, and 894 age- and sex-matched healthy controls) (6). Recently, we reported that rs34043159 of IL1R2 and rs4073221 of SATB1 were associated with PD in Chinese Han people (492 PD patients and 524 healthy controls). Further subgroup analysis showed that both rs34043159 of IL1R2 and rs4073221 of SATB1 were associated with late-onset PD. rs34043159 of IL1R2 was associated with PD in female patients, while rs4073221 of SATB1 was associated with PD in both male and female patients (7). The two loci were suggested to be involved in the pathogenesis of PD. But there are still more genetic factors to be identified. Here, we identified another three loci, which were associated with the increased risk of PD.

GBF1, also named ARF1GEF, encodes a member of the Sec7 domain family, which is a guanine nucleotide exchange factor and activates small GTPases of the Arf family. It is involved in regulating the recruitment of proteins to membranes and has been reported to play an essential role in the regulation of the spatial organization and function of mitochondria in a microtubule-dependent manner (8). Numerous studies have implicated that mitochondrial and apoptosis dysfunction are both strongly linked with PD pathogenesis (9). GBF1 localizes at the early Golgi (10) and also links to lipid droplet metabolism (11), plasma membrane signaling, and organelle transport along microtubules with its substrate Arf1. Furthermore, it is involved in the regulation of Golgi fragmentation and is essential for Golgi disassembly and subsequent mitosis entry (12). The fragmentation of the Golgi apparatus is an essential process in the development of apoptosis, which may be related to PD susceptibility. These studies indicated the association of GBF1 with PD.

The C5orf24 is chromosome 5 open reading frame 24, and it has been shown that its DNA methylation level is related to negative affect scores in drug addicts (13). A study identified C5orf24 was upregulated in patients with posttraumatic stress disorder (PTSD) and high intrusion symptoms at baseline and downregulated in participants following treatment (14). However, further investigations are needed to explore the roles of C5orf24 genes played in pathophysiologic pathways of PD.

GSI-124K5-11 is the RAB guanine nucleotide exchange factor 1 pseudogene. The related functional gene of GSI-124K5-11 is RAB guanine nucleotide exchange factor 1 (RABGEF1), which is the upstream factor of the endosomal Rab GTPase cascade. Mutations in Parkin are the second-most-common known cause of PD, and Parkin plays a critical role in mitophagy through ubiquitination of mitochondria. RABGEF1 is recruited to damaged mitochondria via ubiquitin binding downstream of Parkin in mammalian cultured cells and promotes autophagy of damaged mitochondria (15). Overexpression of A53T-Alpha-Synuclein upregulated the expression of RABGEF1 in the mouse midbrain/brainstem (16). However, the role of GSI-124K5-11 in the pathogenesis of PD needs to be further explored.

There are several limitations in the current study, such as the relatively small sample size. Noteworthy, the molecular mechanisms between rs10748818/GBF1, rs11950533/C5orf24, rs76949143/GSI-124K5-11, and PD are still unclear, so more functional experiments should be designed to explore the pathogenesis.

In conclusion, our study demonstrated that the variants of GBF1, C5orf24, and GSI-124K5-11 are associated with PD in the Han Chinese population. It remains to be determined whether geographic or environmental factors are involved in the genetic consequences of these loci. Further genetic analysis and function studies are needed to understand the role of these variants in the pathogenesis of PD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of First Affiliated Hospital of Zhengzhou University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LF: data curation, formal analysis, and writing—original draft. CS: resources and funding acquisition. XH and HZ: formal analysis. CM: conceptualization and funding acquisition. YX: funding acquisition and supervision. ZZ: methodology. YF: data curation. HL, SZ, and ZH: writing—review & editing. YJ: supervision. All authors: contributed to the study's conception and design.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.623913/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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