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ORIGINAL ARTICLE

Association of the Polygenic Risk Score with the Incidence Risk of Parkinson's Disease and Cerebrospinal Fluid α-Synuclein in a Chinese Cohort

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Abstract

Parkinson's disease (PD) is attributed to interactions among genes and environmental and lifestyle factors, but the genetic architecture of PD is complex and not completely understood. To evaluate whether the genetic profile modifies PD development and cerebrospinal fluid (CSF) pathological biomarkers, we enrolled 418 PD patients and 426 age- and sex-matched normal controls. Forty-six single nucleotide polymorphisms (SNPs) that were reported to be significantly associated with PD in large-scale genome-wide association studies (GWASs) were genotyped and analysed. The alleles associated with PD were used to build polygenic risk score (PRS) models to represent polygenic risk. The Cox proportional hazards model and receiver operating characteristic (ROC) analyses were used to evaluate the prediction value of the PRS for PD risk and age at onset. The CSF α-synuclein levels were measured in a subgroup of control subjects ($n = 262$), and its relationship with the PRS was analysed. We found that some SNPs identified from other populations had significant correlations with PD in our Chinese cohort. The PRS we built had prediction value for PD risk and age at onset. The CSF α-synuclein level had no correlation with the PRS in normal subjects.

Keywords Parkinson's disease · Single nucleotide polymorphisms · Polygenic risk score · CSF biomarker · α-Synuclein

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by a variety of symptoms, including postural instability, rigidity and resting tremor (Dias et al. 2013; Kalia and Lang 2015). PD is suggested to be attributed to interactions among genes and environmental and lifestyle factors (Li and Le 2017; Kalinderi et al. 2016), but the genetic architecture of PD is complex and is not completely understood. A series of genome-wide association studies (GWASs) on PD have identified a large number of single nucleotide polymorphisms (SNPs) with hypothesised or known relationships with PD (Nalls et al. 2014; Redensek et al. 2017; Satake et al. 2009). However, none of them could completely explain all of the symptoms or the specific pathogenesis of PD (Keller et al. 2013; Lorraine and Kalia 2015; Nalls et al. 2011). The recent development of polygenic risk score (PRS) has attracted much attention because the score can capture the

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comprehensive effects of multiple genetic loci and has been suggested as a promising approach to classify the genetic risk of PD (Escott-Price et al. 2015).

Previous studies have proven the value of the PRS model for PD risk prediction, and the age at onset has also been found to correlate with the PRS (Escott-Price et al. 2015; Hall et al. 2013; Ibanez et al. 2017). Because disease-risk genetic loci vary according to ethnicity, PRS must be established for different ethnicities. In the present, we have built our own PRS models, and we propose that if an individual's PRS is related to their disease liability, then individuals having the highest PRS may be considered the most likely to develop PD, even at a younger age. Because no GWAS data on PD were available for the Chinese population before the start of our study, we investigated PD-related SNPs identified in other populations and built several PRS models to determine the contribution of the polygenic profile to the incidence risk of PD and the age at onset of the disease in a Chinese cohort.

α-Synuclein is a major component of Lewy bodies (Shulman et al. 2011), which are the core molecules involved in PD pathogenesis. Cerebrospinal fluid (CSF) α-synuclein has been proposed as a potential biomarker to distinguish PD (Liguori et al. 2019), but the biomarkers are not sufficient for use as a diagnostic tool (Gao et al. 2014; Spillantini et al. 1997). The SNCA gene, which encodes the α-synuclein protein, was the first gene to be associated with autosomal dominant parkinsonism (Polymeropoulos 1997), but the functional consequences of the mutations have not been characterized (Ibanez et al. 2017). We analysed the relationship between the PRS (especially that built upon the SNCA gene) and CSF α-synuclein to explore the impact of genetic risk on PD pathologies.

Methods

Subjects

A total of 418 PD patients and 426 age- and sex-matched normal controls were consecutively recruited from Chongqing Daping Hospital from January 2015 to November 2018. The exclusion criteria were (1) a family history of PD; (2) concomitant neurological disorders; (3) severe cardiac, pulmonary, hepatic and renal diseases; and (4) long-term smoking or drinking. This study was approved by the Institutional Review Board of Daping Hospital, and all subjects and their caregivers provided informed consent.

Clinical Assessments and Diagnosis of PD

The clinical assessment and diagnosis of PD were performed following a previously used protocol (Bu et al. 2015). Briefly, demographic characteristics were collected, including age (age at onset for the PD patients and age at inclusion for the control subjects), sex, education level and comorbidity conditions, including diabetes, hypertension, dyslipidaemia, coronary artery disease and history of stroke. All subjects underwent clinical assessments, including medical history, a physical examination and laboratory and neuropsychological tests.

PD was diagnosed according to the criteria of the UK PD Society Brain Bank (Meara et al. 1999). Each PD patient was assessed with the Hoehn and Yahr staging scale (H&Y) and Unified Parkinson's Disease Rating Scale (UPDRS) (Hughes et al. 1992; LeWitt et al. 2019).

SNP Selection

The SNPs reported in a large-scale meta-GWAS of PD in Europe (Nalls et al. 2014), a large-scale GWAS in Japan (Satake et al. 2009) and a review from 2017 that summarized 13 GWASs and their meta-analyses (Redensek et al. 2017) were initially included in the selection process. The alleles were excluded if (1) the minor allele frequency (MAF) of the SNPs in the Chinese population was less than 0.05 (http://asia.ensembl.org/) or (2) the SNPs had been verified not to be associated with the PD risk in Chinese cohorts (Chang et al. 2011, 2015; Chen et al. 2016; Guo et al. 2015; Li et al. 2013; Liu et al. 2013, 2015; Lou et al. 2019; Wang et al. 2016; Wu et al. 2018; Yan et al. 2011; Zhou et al. 2014; Zou et al. 2018). Detailed data for the selection and exclusion processes are provided in Supplementary Table 1. Finally, a total of 46 SNPs in 20 candidate genes were selected in this study.

Genotyping

Genotyping was conducted following a previously described method (Zeng et al. 2015). Briefly, genomic DNA was extracted from venous blood leukocytes using the Wizard genomic DNA purification kit (Promega, Madison, WI, USA). Genotyping of the 46 SNPs was carried out with a multiplex polymerase chain reaction-ligase detection reaction (PCR-LDR) method. For each SNP, the alleles were distinguished by different fluorescent labels of allele-specific oligonucleotide probe pairs. Different SNPs were distinguished by different extended lengths at the 3′ end. All SNPs in the study had an overall call rate that was greater than 95%.

CSF Sampling and Analysis

A subgroup of the control group ($n = 262$, aged from 50 to 93 years) underwent CSF sampling and analysis. These subjects had urinary system diseases, and the CSF samples were collected during lumber anaesthesia before surgery for their diseases. Specifically, CSF samples free from any blood contamination were collected in polypropylene tubes by lumbar

Table 1 Characteristics of the cases/controls

Characteristics	PD ($n = 418$)	Controls ($n = 426$)	P value
Age, mean (SD), year	65.65 (10.48)	66.65 (9.13)	0.14
Female, n (%)	197 (47.13)	193 (45.31)	0.60
Education level, mean (SD), year	8.32 (3.90)	10.25 (2.71)	< 0.001
Unified Parkinson's Disease Rating Scale, mean (SD)	36.68 (19.80)	NA	NA
Hoehn & Yahr scale, mean (SD)	2.18 (2.42)	NA	NA
Diabetes (%)	12.75	13.19	0.85
Hypertension (%)	34.00	38.37	0.19
Dyslipidaemia (%)	14.25	11.99	0.34
Coronary artery disease (%)	27.50	18.23	0.002
Stroke history (%)	8.75	7.19	0.85

PD, Parkinson's disease; *MMSE*, Mini-Mental State Examination; *ADL*, Activities of Daily Living Scale; *NA*, not applicable

puncture, centrifuged at 1800×g at 4 °C for 10 min within 1 h, and stored frozen at − 80 °C until analysis.

The α-synuclein levels were measured with a commercially available ELISA kit (BioLegend, Covance, USA) (Kang et al. 2013). All measurements were performed in one round of analysis with one batch of reagents by an experienced laboratory technician who was blinded to the clinical information.

Statistical Analyses

Differences between groups were assessed by the two-sample independent t test, Mann-Whitney U test, chi-square test, Fisher's exact test or analysis of variance (ANOVA) according to the characteristics of the data. The data are expressed as the mean ± standard deviation (SD) for numerical variables or as the count (%) for categorical variables. All hypothesis testing was two-sided, and statistical significance was defined as $P < 0.05$. All statistical computations were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) or PLINK version 1.09 (Massachusetts, USA), and all figures were created using GraphPad Prism 6.01 (GraphPad Software, Inc., San Diego, CA).

Single SNP Analyses The allele and genotype distributions of the SNPs between the PD patients and control subjects were analysed using chi-square statistics. Odds ratios (OR) (calculated relative to the common genotype) and 95% confidence intervals (CIs) were corrected for age and sex using logistic regression models.

Computation of Polygenic Risk Scores The SNPs associated with PD ($P < 0.05$) in our cohort were selected to generate the PRS model (model 1). For each subject, the PRS was

Table 2 Allele distributions of the significant SNPs

SNP	Neighbouring gene	Risk allele	Risk allele frequency		OR (95% CI)	P value
			PD	controls		
rs4698412	BST1	A	0.4239	0.3553	1.34 (1.10–1.63)	0.004307
rs4538475	BST1	A	0.5036	0.446	1.26 (1.04–1.53)	0.01923
rs11060180	CCDC62	G	0.1739	0.2183	0.75 (0.59–0.96)	0.02327
rs199498	MAPT	T	0.4652	0.5164	0.81 (0.67–0.99)	0.0363
rs6532194	SNCA	C	0.3639	0.4846	0.61 (0.50–0.74)	5.87×10^{-7}
rs11931074	SNCA	G	0.3789	0.4894	0.64 (0.52–0.77)	4.84×10^{-6}
rs3857059	SNCA	A	0.3777	0.4847	0.65 (0.53–0.78)	9.57×10^{-6}
rs356220	SNCA	C	0.3777	0.4812	0.65 (0.54–0.79)	1.86×10^{-5}
rs356165	SNCA	G	0.3789	0.4824	0.65 (0.54–0.79)	1.87×10^{-5}
rs356219	SNCA	A	0.3777	0.48	0.66 (0.54–0.80)	2.31×10^{-5}
rs356182	SNCA	A	0.247	0.3357	0.65 (0.53–0.80)	7.2×10^{-5}
rs2736990	SNCA	A	0.3297	0.4214	0.68 (0.55–0.82)	0.000108
rs894278	SNCA	G	0.4281	0.3803	1.22 (1.00–1.48)	0.0472

SNP, single nucleotide polymorphism; *OR*, odds ratio; *CI*, confidence interval; *PD*, Parkinson's disease; the ORs and 95% CIs were adjusted for age and sex

Table 3 The discriminative performance of the PRSs for the cases/controls

PRS models	*P* thresholds of SNPs	Logistic regression		ROC curve analyses		
		OR (95% CI)	*P* value	AUC (95% CI)	Sensitivity	Specificity
Model 1	< 0.05	1.24 (1.14–1.34)	< 0.001	0.61 (0.57–0.65)	0.78	0.42
Model 2	< 0.01	1.24 (1.14–1.35)	< 0.001	0.60 (0.56–0.64)	0.78	0.38
Model 3	SNCA only	1.21 (1.12–1.31)	< 0.001	0.59 (0.55–0.62)	0.61	0.53

PRS, polygenic risk score; *SNP*, single nucleotide polymorphism; *ROC*, receiver operating characteristic curve; *AUC*, area under the curve; the associations of the PRSs with the PD risk were tested with a logistic regression model adjusted for age, sex and comorbidities; the discriminative ability of each PRS model for the cases/controls status was tested with ROC curve analysis

calculated by summing the risk allele counts of the SNPs weighted by the natural logarithms of their respective ORs (calculated based on the present study). To build a more rigorous PRS model, only SNPs with a *P* value threshold of 0.01 in the logistic regression analysis were included in model 2. Because SNCA (the encoding gene of α-synuclein) is a critical gene for PD, model 3 was also generated with all selected SNPs located in SNCA loci.

The associations of the PRSs with the PD risk were tested with a logistic regression model including age, sex, education level and comorbidities as covariates. To compare the discriminative ability of the PRSs for cases/controls and biomarker abnormality, receiver operating characteristic (ROC) analysis was performed by plotting the true positive rate against the false positive rate. The area under the curve (AUC), sensitivity and specificity with 95% CIs were calculated. Moreover, the subjects were partitioned into tertiles (with PRS cutoffs at 33.33% and 66.67%); the association of the PRS with the age at onset and the cumulative incidence rate of PD were reflected through a Cox proportional hazards model. Relationships between the PRS and the CSF α-synuclein levels were assessed in a subgroup of control subjects; the Spearman or Pearson correlation coefficient (chosen based on the data distribution) was used to assess the correlations.

Results

Characteristics of the Study Subjects and SNP Distributions

The characteristics of the subjects are shown in Table 1. No significant differences were noted in age ($P = 0.14$), sex ($P = 0.60$) or the incidence rates of diabetes, hypertension, dyslipidaemia and stroke between the PD patients and controls. The PD patients had a higher proportion of coronary artery diseases ($P = 0.002$) and a lower average education level ($P < 0.001$).

Thirteen of the 46 SNPs were significantly associated with the PD risk ($P < 0.05$, Table 2), including two SNPs (rs4698412 and rs4538475) on the BST1 gene, one SNP (rs11060180) on the CCDC62 gene, one SNP (rs199498) on the MAPT gene and nine SNPs (rs6532194, rs11931074, rs3857059, rs356220, rs356165, rs356219, rs356182, rs2736990 and rs894278) on the SNCA gene. The directions of the OR values for these SNPs were consistent with those reported in the GWASs. Only the SNPs on SNCA (except for rs894278) remained significant after Bonferroni correction ($P < 0.001$). Information on the included SNPs (neighbouring genes, chromosomes, minor alleles, Hardy-Weinberg equilibrium values and positions) and their allele and genotype frequencies are summarized in Supplementary Tables 2, 3 and 4.

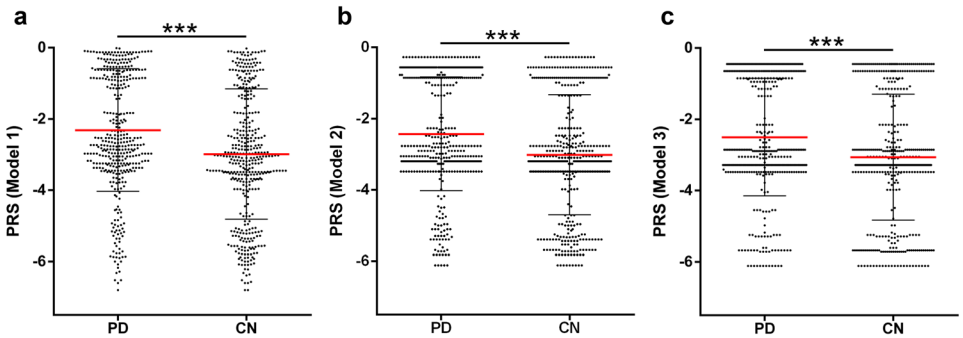

Fig. 1 Comparison of PRSs between the PD patients and controls. **a** PRS was built with 13 SNPs with $P < 0.05$. **b** PRS was built with 9 SNPs with $P < 0.01$. **c** PRS was built with all SNPs of the SNCA gene. PRS, polygenic risk score; PD, Parkinson's disease; CN, control

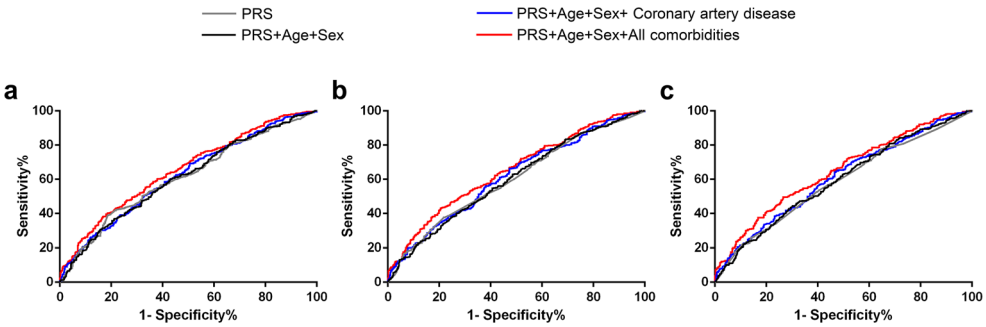

Fig. 2 Discriminative ability of different PRS models for PD. (a) PRS was built with 13 SNPs with $P < 0.05$. (b) PRS was built with 9 SNPs with $P < 0.01$. (c) PRS was built with all SNPs of the SNCA gene; PRS, polygenic risk score; PD, Parkinson's disease; ROC, receiver operating characteristic curve; AUC, area under the curve

Discriminative Performance of PRSs for the Cases/Controls

Three PRS models were developed (Table 3). As expected, the average PRSs in the PD patients were significantly higher than those in the controls based on all of the PRS models (Mann-Whitney test, $P < 0.001$, Fig. 1). Logistic regression analyses with adjustment for age, sex, education level and comorbidities showed a positive relationship between the PD risk and PRSs (OR > 1). We compared the discriminative ability of each PRS model for the case/control status with ROC curve analyses (Table 3). Model 1 had a sensitivity of 0.78 and a specificity of 0.42 (AUC = 0.61). Model 2 had a sensitivity of 0.78 and a specificity of 0.38 (AUC = 0.60). No significant difference was detected between the two models. The sensitivity of model 3 (0.61) based on the SNCA gene alone was lower than that of the other models, but the specificity (0.53) was higher. The discriminative abilities of these models were improved when age, sex and comorbidities were taken into account (Fig. 2).

Predictive Ability of the PRSs for the PD Incidence Rate and Age at Onset

The modulating effects of the PRSs on the development of PD were evaluated using a Cox proportional hazards model (Fig. 3). The PRS from model 1 was chosen for the analysis. The subjects were classified into three risk groups based on the PRS tertiles. The log-rank test revealed that a higher PRS was significantly associated with a younger age at onset (high PRS vs. low PRS, OR = 1.54, 95% CI 1.23–1.99; intermediate PRS vs. low PRS, OR = 1.57, 95% CI 1.25–2.05). For example, for a cohort with a high PRS, the expected age at development of PD in half of the subjects is approximately 71 years (dotted line parallel with the *x*-axis, Fig. 3), which is earlier than that of subjects with a low PRS (the expected age for developing PD in half of the subjects is approximately 77 years). Moreover, the cumulative incidence rates in the high-PRS group were higher than those in the low-PRS group. For example, among two groups of 70-year-old subjects (with high and low PRS), the percentage of PD patients in the high-PRS group was higher than that in the low-PRS group (48% vs. 30%, dotted line parallel with the *y*-axis, Fig. 3).

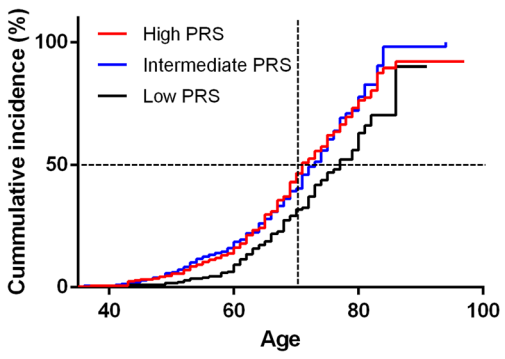

Fig. 3 Cumulative incidence rates of PD in three genetic risk groups. The subjects were partitioned into tertiles (low PRS vs. intermediate PRS vs. high PRS, with PRS cutoffs at 33.33% and 66.67%); PRS, polygenic risk score; PD, Parkinson's disease

Correlations between the PRSs and CSF α-Synuclein Levels

The correlations between the PRSs and CSF α-synuclein levels were analysed in the control group ($n = 262$), and no significant relationships were found (model 1: $P = 0.80$, Spearman $\rho = -0.016$; model 2: $P = 0.77$, Spearman $\rho = -0.018$; model 3: $P = 0.64$, Spearman $\rho = -0.029$) (Fig. 4). The general linear regression adjusted for age, sex, education level and comorbidities also showed no significant relationship between the PRSs and CSF α-synuclein levels (model 1, $\beta = 0.07$, $P = 0.37$; model 2, $\beta = 0.08$, $P = 0.29$; model 3, $\beta = 0.09$, $P = 0.25$).

Discussion

In this study, we explored the effect of genes on PD development and the pathological process by screening and integrating PD-associated SNPs identified from large GWASs and building polygenic risk models. Only 13 of the 46 SNPs identified in other populations had significant correlations with PD, and the PRSs based on these 13 SNPs were associated with the PD risk and age at onset in our Chinese cohort.

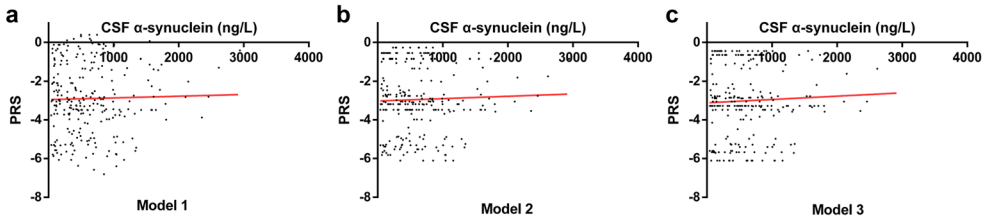

Fig. 4 Correlations between PRSs and CSF α-synuclein levels. Scatterplots of **a** PRS model 1, **b** PRS model 2, and **c** PRS model 3 with the CSF α-synuclein levels. CSF, cerebrospinal fluid; Spearman's correlation coefficients (ρ) were used to assess the correlations

Three PRS models containing different numbers or categories of SNPs were built for case/control discrimination. We found no improvement in the discriminative abilities when more SNPs were included in the PRS model. Thus, considering the high expense of genotype sequencing, a PRS model based on fewer SNPs (SNPs with a *P* threshold of 0.01 in our study) would be more accessible. The PRS model built upon the SNCA allele had relatively higher specificity and lower sensitivity in discriminating cases/controls, which suggested that PD was a disease that could be attributed to multiple genetic profiles instead of a single gene.

The discriminative performances of our PRS models were improved when age, sex and comorbidities were taken into consideration, which meant that PD was a complex disease attributed to various factors instead of heredity alone (Lorraine and Kalia 2015). Although the predictive power and accuracy of these PRS models are still insufficient for application in clinical work, we believe that further studies including more accurate genetic information and more environmental or lifestyle risk factors will provide more accurate prediction of PD.

We used a Cox regression survival model for the age at onset analysis because it provided more power than a simple linear regression model. Consistent with previous findings (Escott-Price et al. 2015; Hall et al. 2013; Ibanez et al. 2017), individuals with a high genetic risk (high-PRS) were more likely to develop PD, and the time of incidence was earlier than that in individuals with a low genetic risk (low-PRS), which suggested that the incidence risk of PD and the age at onset were modified by the polygenic profile. From a clinical perspective, our PRS models may serve as a predictor for identifying individuals at risk for developing PD at a given age and provide potential PD patients with access to early diagnosis and treatment. Of course, additional studies should be performed to strengthen the predictive power of PRS models. From a scientific research perspective, since the PD risk was closely related to the genetic architecture, further studies are required to progress from evidence of a polygenic contribution to exploration of the deep mechanisms by which the genetic profile contributes to PD.

We found that all selected SNPs on the SNCA gene had strong correlations with PD in our Chinese cohort. We noted that these SNPs were also highly associated with PD in other ethnicities. These results suggest that the SNCA gene may play a critical role in PD development. To the best of our knowledge, only one study had examined the relationship between the PRS of PD and CSF biomarkers which suggested no association between the PRSs and the CSF α-synuclein levels (Ibanez et al. 2017). Our study also suggested that the PRSs were not associated with the CSF α-synuclein levels. These findings suggest that the risk SNPs for the SNCA gene probably influence the function but not the expression level of α-synuclein. Considering that SNCA is one of the most important susceptibility genes of PD and the gene encoding the α-synuclein protein (Polymeropoulos 1997), the roles of these SNPs in SNCA in the development of PD deserve investigation in future studies.

The present study has several limitations. First, the case/control approach assumes that normal controls do not develop PD and considers the disease process to be a dichotomous variable; errors may exist because some controls may be in the preclinical stage of PD, and follow-up research is needed to fully address this problem. Second, the correlation between genes and PD was based on the PRS model, which was effective but could not represent the whole genetic profile of PD. Third, the PRSs are based on SNPs identified in other ethnicities. Because risk loci of PD may differ among different ethnicities, a PRS model built upon SNPs identified in the Chinese population would provide a more accurate prediction of the genetic risk of PD in Chinese subjects. Fourth, the correlation analyses between CSF α-synuclein and PRS were limited to non-PD subjects in the present study. The correlation needs to be further studied by including PD patients in the future.

Conclusions

In the present study, some SNPs identified from other populations had significant correlations with PD and its age at onset in our Chinese cohort. The genetic risk profiles of PD appear to vary among populations. Thus, specific PRS models should be constructed for the Chinese population with its own genetic risk loci.

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Data Availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

This study was approved by the Institutional Review Board of Daping Hospital, and all subjects and their caregivers provided informed consent.

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

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