



# 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*, rs77351827/*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  $\geq 65$  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:  $62.34 \pm 9.150$  years, 300/227) and (healthy controls:  $47.75 \pm 10.856$  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.

**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.

## 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  $\geq 50$  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*, rs61169879/*BRIP1*, rs666463/*DNAH17*, rs75859381/*RPS12*, rs76116224/*KCNS3*, 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*, *MCC1*, 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

**TABLE 1** | Assessment of the relationship level of 12 novel loci with PD in the Chinese Han population.

SNPs/candidate gene	HWE ( $p$ -value)	Association test	PD	Control	$p$	OR (95%CI)	$p^a$	OR (95%CI) <sup>a</sup>
rs10748818/ <i>GBF1</i>	0.73	Genotypic (GG/GA/AA)	78/259/190	54/194/187	-	-		
		Dominant [(GG + GA)/AA]	337/190	248/187	0.028*	0.748(0.576–0.970)	0.275	0.834(0.601–1.155)
		Recessive [GG/(GA + AA)]	78/449	54/381	0.285	1.226(0.844–1.780)	0.857	1.030(0.745–1.424)
		Alleles(G/A)	415/639	302/508	<b>0.035*</b>	<b>1.221(1.014–1.472)</b>		
rs11950533/ <i>C5orf24</i>	0.99	Genotypic (CC/CA/AA)	259/218/50	209/186/40	-	-		
		Dominant [(CC + CA)/AA]	477/50	395/40	0.877	1.035(0.669–1.602)	0.857	1.030 (0.745–1.424)
		Recessive [CC/(CA + AA)]	259/268	209/226	0.734	1.045(0.811–1.347)	0.416	0.875(0.634–1.208)
		Alleles(C/A)	736/318	604/266	0.848	1.019(0.839–1.239)		
rs34025766/ <i>LCORL</i>	0.85	Genotypic (TT/AT/AA)	423/96/8	336/94/5	-	-		
		Dominant [(TT + AT)/AA]	519/8	430/5	0.622	0.754(0.245–2.323)	0.438	1.716(0.439–6.710)
		Recessive [TT/(AT + AA)]	423/104	336/99	0.253	1.198(0.879–1.634)	0.683	0.922(0.625–1.361)
		Alleles(T/A)	942/112	766/104	0.358	1.142(0.860–1.516)		
rs55961674/ <i>KPNA1</i>	0.95	Genotypic (CC/CT/TT)	416/103/8	333/96/6	-	-		
		Dominant [(CC+CT)/TT]	519/8	429/6	0.858	0.907(0.312–2.635)	0.900	1.087(0.295–4.004)
		Recessive [CC/(CT+TT)]	416/111	333/102	0.375	1.148(0.846–1.557)	0.797	0.951(0.646–1.399)
		Alleles(C/T)	935/119	762/108	0.447	1.114(0.844–1.470)		
rs61169879/ <i>BRIP1</i>	0.77	Genotypic (CC/CT/TT)	97/271/159	84/222/129	-	-		
		Dominant [(CC + CT)/TT]	368/159	306/129	0.862	0.976(0.739–1.288)	0.792	0.953(0.669–1.359)
		Recessive [CC/(CT + TT)]	97/430	84/351	0.721	0.943(0.681–1.304)	0.457	1.168(0.775–1.761)
		Alleles(C/T)	465/589	390/480	0.755	0.972(0.811–1.164)		
rs666463/ <i>DNAH17</i>	0.81	Genotypic (AA/AT/TT)	498/29/0	409/26/0	-	-		
		Dominant [(AA + AT)/TT]	527/0	435/0	-	-	-	-
		Recessive [AA/(AT + TT)]	498/29	409/26	0.753	1.092(0.633–1.883)	0.337	1.421(0.693–2.912)
		Alleles(A/T)	1025/29	844/26	0.756	1.089(0.636–1.863)		
rs75859381/ <i>RPS12</i>	0.60	Genotypic (TT/CT/CC)	467/59/1	395/40/0	-	-		
		Dominant [(TT + CT)/CC]	526/1	435/0	-	-	1.000	-
		Recessive [TT/(CT+CC)]	467/60	395/40	0.268	0.788(0.517–1.202)	0.939	0.980(0.578–1.660)
		Alleles(T/C)	993/61	830/40	0.244	0.785(0.521–1.181)		
rs76116224/ <i>KCNS3</i>	0.99	Genotypic (AA/AT/TT)	523/4/0	429/6/0	-	-		
		Dominant [(AA+AT)/TT]	527/0	435/0	-	-	-	-
		Recessive [AA/(AT + TT)]	523/4	429/6	0.532 <sup>b</sup>	0.541(0.149–1.957)	0.955	0.953(0.180–5.050)
		Alleles(A/T)	1,050/4	864/6	0.533 <sup>b</sup>	1.823(0.513–6.480)		
rs76949143/ <i>GS1-124K5-11</i>	0.24	Genotypic (TT/AT/AA)	385/135/7	333/90/12	-	-		
		Dominant [(TT + AT)/AA]	520/7	423/12	0.113	2.107(0.822–5.400)	0.438	0.624(0.189–2.054)
		Recessive [TT/(AT + AA)]	385/142	333/102	0.215	0.830(0.619–1.114)	0.688	1.080(0.740–1.576)
		Alleles(T/A)	905/149	756/114	0.511	0.916(0.705–1.191)		
rs77351827/ <i>CRLS1</i>	1.00	Genotypic (CC)	527	435	-	-		
		-	-	-	-	-	-	-
		-	-	-	-	-	-	-
		Alleles(C)	1,054	870	-	-		
rs7938782/ <i>RNF141</i>	0.36	Genotypic (AA/GA/GG)	373/143/11	303/115/17	-	-		
		Dominant [(AA + GA)/GG]	516/11	418/17	0.095	1.908(0.884–4.117)	0.120	0.469(0.181–1.217)
		Recessive [AA/(GA + GG)]	373/154	303/132	0.705	1.055(0.799–1.393)	0.951	1.011(0.710–1.440)
		Alleles(A/G)	889/165	721/149	0.341	0.889(0.697–1.133)		
rs850738/ <i>FAM171A2</i>	0.68	Genotypic (AA/GA/GG)	184/248/95	144/220/71	-	-		
		Dominant [(AA + GA)/GG]	432/95	364/71	0.486	0.887(0.633–1.243)	0.186	1.337(0.869–2.056)
		Recessive [AA/(GA + GG)]	184/343	144/291	0.555	1.084(0.829–1.418)	0.775	1.051(0.748–1.477)
		Alleles(A/G)	616/438	508/362	0.981	1.002(0.835–1.202)		

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

<sup>a</sup>Adjusted age and sex by logistic regression.

<sup>b</sup>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.

SNPs (candidate gene)	Genotype, allele	Age onset < 50 years				Age onset ≥ 50 years				Male				Female			
		PD	Control	$p_1$	OR (95%CI) <sub>1</sub>	PD	Control	$p_2$	OR (95%CI) <sub>2</sub>	PD	Control	$p_3$	OR (95%CI) <sub>3</sub>	PD	Control	$p_4$	OR (95%CI) <sub>4</sub>
rs10748818 ( <i>GBF1</i> )	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	104			80	83		
	G	30	169	0.766	0.931 (0.579–1.495)	385	133	0.117	1.219(0.952– 1.562)	234	161	0.080	1.251(0.973– 1.608)	181	141	0.222	1.190(0.900– 1.572)
rs11950533 ( <i>C5orf24</i> )	A	62	325			577	243			366	315			273	253		
	CC	24	119	<b>0.034*</b>		235	90	0.783		146	108	0.704		113	101	0.954	
	CA	17	103			201	83			123	106			95	80		
	AA	5	25			45	15			31	24			19	16		
rs34025766 ( <i>LCORL</i> )	C	65	341	0.757	1.080 (0.663–1.759)	671	263	0.944	0.991(0.764– 1.285)	415	322	0.594	1.073(0.828– 1.390)	321	282	0.781	0.959(0.712– 1.291)
	A	27	153			291	113			185	154			133	112		
	TT	38	188	-		385	148	0.418		240	190	-		183	146	-	
	AT	8	55			88	39			55	46			41	48		
rs55961674 ( <i>KPNA1</i> )	AA	0	4			8	1			5	2			3	3		
	T	84	431	0.274	1.535 (0.709–3.321)	858	335	0.961	1.010(0.689– 1.481)	535	426	0.862	0.966(0.654– 1.427)	407	340	0.133	1.375(0.907– 2.086)
	A	8	63			104	41			65	50			47	54		
	CC	36	190	-		380	143	0.568		239	185	-		177	148	-	
rs61169879 ( <i>BRIP1</i> )	CT	8	55			95	41			57	49			46	47		
	TT	2	2			6	4			4	4			4	2		
	C	80	435	0.767	0.904 (0.465–1.758)	855	327	0.328	1.197(0.834– 1.718)	535	419	0.558	1.120(0.767– 1.634)	400	343	0.643	1.101(0.732– 1.658)
	T	12	59			107	49			65	57			54	51		
rs666463 ( <i>DNAH17</i> )	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	0.920(0.587– 1.440)	425	165	0.922	1.012(0.796– 1.287)	257	208	0.776	0.965(0.757– 1.231)	208	182	0.912	0.985(0.751– 1.291)
rs75859381	T	52	269			537	211			343	268			246	212		
	AA	42	229	0.978 <sup>a</sup>		456	180	0.613		284	222	0.499		214	187	0.768	
	AT	4	18			25	8			16	16			13	10		
	-	-	-			-	-			-	-			-	-		
rs75859381	A	88	476	0.978 <sup>a</sup>	0.832(0.275– 2.517)	937	368	0.617	0.815(0.364– 1.823)	584	460	0.505	1.270(0.628– 2.566)	441	384	0.771	0.883(0.383– 2.037)
	T	4	18			25	8			16	16			13	10		

(Continued)

TABLE 2 | Continued

SNPs (candidate gene)	Genotype, allele	Age onset < 50 years				Age onset ≥ 50 years				Male				Female			
		PD	Control	p <sub>1</sub>	OR (95%CI) <sub>1</sub>	PD	Control	p <sub>2</sub>	OR (95%CI) <sub>2</sub>	PD	Control	p <sub>3</sub>	OR (95%CI) <sub>3</sub>	PD	Control	p <sub>4</sub>	OR (95%CI) <sub>4</sub>
(RPS12)	CT	5	21			54	19			33	19			26	21		
	CC	0	0			1	0			0	0			1	0		
	T	87	473	0.818 <sup>a</sup>	0.773(0.284– 2.104)	906	357	0.583	0.861(0.504– 1.470)	567	457	0.252	0.714(0.401– 1.273)	426	373	0.602	0.857(0.478– 1.534)
rs76116224 (KCNS3)	C	5	21			56	19			33	19			28	21		
	AA	45	242	1.000 <sup>b</sup>		478	187	1.000 <sup>a</sup>		296	236	0.899 <sup>a</sup>		227	193	0.098 <sup>a</sup>	
rs76949143 (GS1- 124K5-11)	AT	1	5			3	1			4	2			0	4		
	-	-	-			-	-			-	-			-	-		
	A	91	489	1.000 <sup>b</sup>	0.930(0.107– 8.057)	959	375	1.000 <sup>a</sup>	0.571(0.153– 2.133)	596	474	0.899 <sup>a</sup>	0.629(0.115– 3.447)	454	390	0.099 <sup>a</sup>	0.462(0.430– 0.497)
rs77351827 (CRLS1)	TT	1	5			3	1	<b>0.042*</b>		4	2			0	4		
	AT	7	51			128	39			78	48	0.241		57	42		
	AA	1	5			6	7			5	6			2	6		
rs7938782 (RNF141)	A	9	61			140	53			88	60			61	54		
	CC	46	247	-		481	188	-		300	238	-		227	197	-	
rs850738 (FAM171A2)	C	92	494	-		962	376	-		600	476	-		454	394	-	
	AA	33	176	0.969		340	127	0.085		210	162	0.327		163	141	0.693	
	GA	12	64			131	51			84	66			59	49		
rs850738 (FAM171A2)	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 (FAM171A2)	AA	15	74	0.843		169	70	0.300		102	82	0.345		82	62	0.587	
	GA	24	127			224	93			140	121			108	99		
	GG	7	46			88	25			58	35			37	36		
rs850738 (FAM171A2)	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.

<sup>a</sup>Continuous correction for Chi-square test when at least one cell has an expected value of less than 5.

<sup>b</sup>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.

*GS1-124K5-11* is the RAB guanine nucleotide exchange factor 1 pseudogene. The related functional gene of *GS1-124K5-11* 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 *GS1-124K5-11* 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/*GS1-124K5-11*, 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 *GS1-124K5-11* 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. JY: 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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