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Association of Parkinson's Disease GWAS-Linked Loci with Alzheimer's Disease in Han Chinese

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Abstract Alzheimer's disease (AD) and Parkinson's disease (PD) have overlapping pathological mechanisms and genetic background, suggesting it would be meaningful to replicate PD-related genetic variants in AD population to identify new loci of AD. Here, in order to discover potential AD-related loci, we investigated the association between late-onset AD (LOAD) susceptibility and nine single-nucleotide polymorphisms (SNPs) (rs11724635 of **BST1**, rs12637471 of *MCCC1*, rs15553999 of *TMEM229*, rs17649553 of *MAPT*, rs34311866 of *TMEM175-GAK-DGKQ*, rs356182 of *SNCA*, rs6430538 of *ACMSD-TMEM163*, rs76904798 of *LRRK2* and rs823118 of *RAB7L1-NUCKS1*) which were reported to have genome-wide significant associations with PD risk in a recent Genome Wide Association Study performed among white population. We included 2350 samples comprising with 992 sporadic LOAD patients and 1358 gender- and age-matched control subjects who were unrelated northern Han Chinese residents. Finally, among these included genetic variants, only rs76904798 of *LRRK2* was proved to significantly reduce LOAD risk in a multivariate analysis in a dominant model after adjusting for age, sex, and apolipoprotein E (*APOE*) ε4 status (OR = 0.616; 95 % CI 0.446–0.849; Bonferroni corrected $P = 0.027$). In addition, when these data were stratified by *APOE* ε4 status, rs76904798 was still evident among subjects without *APOE* ε4 allele. Our results first time indicated rs76904798 of *LRRK2* is also a common risk genetic variant for LOAD susceptibility in a northern Han Chinese people.

Keywords Alzheimer's disease · Parkinson's disease · Polymorphisms · Susceptibility · Association study

Xi-Chen Zhu and Lei Cao contributed equally to this work.

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Introduction

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is growing in its public health implications. AD is divided into early-onset AD and late-onset AD (LOAD), and both have a genetic component [1]. LOAD is typically defined as onset after 65 years of age, which is widely considered as the proportion of disease vulnerability attribute to heritable genetic factors. Moreover, these susceptibility genetic factors may contribute as much as 80 % to the risk of LOAD [2]. However, to date, apolipoprotein E (*APOE*) gene is the only established susceptibility gene for LOAD, and variations at the *APOE* loci account for only 50 % or less of LOAD risk [3, 4], suggesting more additional risk loci remains to be identified.

AD and Parkinson's disease (PD) are the two most common age-related neurodegenerative disorders. AD is characterized by progressive impairment in memory, judgment, orientation to physical surroundings, and language, and the pathologic features of AD are neuronal loss and the deposition of extracellular plaques containing amyloid β (Aβ) and neurofibrillary tangles (NFT) containing tau [1]. PD manifests as a movement disorder and a distinct form of cognitive impairment with typical pathologic characteristics of the deposition of α-synuclein in multiple brain regions [5]. Although AD and PD are clinically distinct entities, the two diseases appear in a close association in pathological evidence. Aβ, one important hallmark of AD pathology, has been reported present in patients with PD [6–9]. Similarly, PD pathologies have also been reported in some AD cases, for example, pathological evidence indicated Lewy body deposition also exited in AD cases [9, 10]. In addition, AD and PD may also share an overlapping genetic background, such as *APOE* and *MAPT* gene which have been reported linked to the presence of Aβ aggregates [11] and increased tau protein expression [12], and they have been widely accepted as risk genes in AD according to the Alzgene database (http://www.alzgene.org/). Noticeable, genetic variants at the two genes have also been verified to increase PD risk [13, 14]. Taken as a whole, these studies indicated a possible pathological overlap and a potential hereditary association between AD and PD. Hence, it would be meaningful to replicate PD-related genetic variants in AD population to discover more candidate loci which may alter AD risk.

Recently, Nalls and his colleagues performed a large-scale meta-analysis of genome-wide association study (GWAS) with a common set of 7,893,274 variants across 13,708 PD cases and 95,282 controls to identify PD risk loci [15]. Among these genetic variants, nine SNPs (rs11724635 of *BST1*, rs12637471 of *MCCC1*, rs15553999 of *TMEM229*, rs17649553 of *MAPT*, rs34311866 of *TMEM175-GAK-DGKQ*, rs356182 of *SNCA*, rs6430538 of *ACMSD-TMEM163*, rs76904798 of *LRRK2*, and rs823118 of *RAB7L1-NUCKS1*) were included in our study, they achieved a widely accepted genome-wide *P* value threshold of 5×10^{-8} under quality control, and they were never explored in AD genetic studies. Based on the above evidence, the current study was conducted to explore whether these newly identified GWAS-linked PD genetic variants also influenced on LOAD susceptibility.

Methods

Subjects

A total of 2350 samples comprising with 992 sporadic LOAD patients (age at onset, ≥65 years) and 1358 gender- and age-matched control subjects were enrolled. All included LOAD patients and control subjects were unrelated northern Han Chinese residents originally from Shandong province. The LOAD patients were recruited from the Department of Neurology at Qingdao Municipal Hospital and several other hospitals in Shandong province, and all patients were subjected to neuropsychological examination and brain structural neuroimaging. A consensus clinical diagnosis of probable AD must fulfill the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association [16]. And the LOAD patients were defined as sporadic when no member of their first-degree relatives had dementia in their family history. The information (age at onset and family history) of enrolled LOAD patients were obtained from themselves or their caregivers. We included age- and gender-matched healthy control subjects from the Health Examination Center of each collaborating hospital, and these control subjects were confirmed healthy and neurologically normal according to medical history, general examination, laboratory examination, and Mini Mental State Examination (MMSE) (MMSE > 28). The characteristics of the study groups were summarized in Table 1. We obtained informed consents from each subject or a guardian, and this study protocol was approved by the institutional ethics committees of Qingdao Municipal Hospital. The study group described in this study has not been reported before.

SNP Selection and Genotyping

A total of nine SNPs from a GWAS which reported PD-related genetic variants-rs11724635 (*BST1*), rs12637471 (*MCCC1*), rs1555399 (*TMEM229B*), rs17649553 (*MAPT*), rs34311866 (*TMEM175-GAK-DGKQ*), rs356182 (*SNCA*), rs6430538 (*ACMSD-TMEM163*), rs76904798 (*LRRK2*), and rs823118 (*RAB7L1-NUCKS1*) were selected [15]. Based on the widely accepted genome-wide *P* value threshold of 5×10^{-8}, these nine SNPs were proved to link to PD risk in discovery phase (13,728 cases and 95,282 controls), replication phase (5353 cases and 5551 controls) and joint phase (19,081 cases and

Table 1 Characteristics of the study groups

Characteristics	AD ($n = 992$)	Control ($n = 1358$)	P value	OR (95 % CI)
Age (years), mean ± SD			0.189	
Age at examination	79.83 ± 6.69	75.49 ± 6.48		
Age at onset	75.17 ± 6.08			
Gender, *n* (%)			0.067	
Male	408 (41.1)	610 (44.9)		
Female	584 (58.9)	748 (55.1)		
MMSE score, mean ± SD	11.94 ± 6.21	28.49 ± 1.09	<0.001	
APOE ε4 status, *n* (%)			<0.001	
APOE ε4 (+)	284 (28.6)	191 (14.1)		2.451 (1.995–3.011)
APOE ε4 (−)	708 (71.4)	1167 (85.9)		

AD Alzheimer's disease, *APOE* apolipoprotein, *CI* confidence interval, *MMSE* Mini-Mental State Examination, *OR* odds ratio, *SD* standard deviation

100,833 controls) under quality control. Moreover, these SNPs have never been explored in AD population. Two SNPs within the *APOE* gene (rs429358 and rs7412) were also analyzed in this study.

The genotyping methods have been described in our previous literatures [17–21]. Briefly, we isolated genomic DNA from peripheral blood leukocytes with the Wizard Genomic DNA Purification Kit (Promega). Genotyping of rs34311866 (*TMEM175-GAK-DGKQ*), rs356182 (*SNCA*), rs6430538 (*ACMSD-TMEM163*), rs76904798 (*LRRK2*), rs823118 (*RAB7L1-NUCKS1*), rs429358, and rs7412 (*APOE*) were performed by the polymerase chain reaction–ligase detection reaction (PCR–LDR) using the improved multiplex ligase detection reaction (iMLDR) method with technical support from the Shanghai Genesky Biotechnology Company, and the details of the primer sequences used for PCR were shown in Supplementary Table 1. In addition, SNP genotyping of rs11724635 (*BST1*), rs12637471 (*MCCC1*), rs1555399 (*TMEM229B*), and rs17649553 (*MAPT*) was conducted with a custom-by-design 2- × 48-Plex SNPscan™ kit (Genesky Biotechnologies Inc., Shanghai, China) [22]. This kit was made according to a patented SNP genotyping technology by Genesky Biotechnologies Inc., which was based on double ligation and multiplex fluorescent PCR.

Statistical Analysis

We excluded deviations using Hardy–Weinberg equilibrium (HWE) in control subjects by HWE version 1.20 (Columbia University, New York, NY). Univariate analyses of allele and genotype distributions between LOAD patients and control subjects were examined with the χ^2 test or Fisher's exact test. Then, multivariate analyses of the association between SNPs and AD risk were evaluated with the odds ratio (OR) with 95 % confidence intervals (CIs) by logistic regression, adjusting for age of onset (age at examination for control subjects), gender, and *APOE* ε4 status (presence or absence of an ε4 allele). Moreover, the SNPs with minor allele homozygote counts of 14 or more were calculated in three kinds of logistic regression models (dominant, additive, and recessive). When SNPs with minor allele homozygote counts are less than 14 and the number of minor allele homozygotes and heterozygotes are more than 14, only the dominant genetic model could be examined. The interaction of SNPs and *APOE* status was also evaluated by logistic regression. The STPLAN 4.3 software was performed to estimate the statistical power. All statistical analyses were conducted with SPSS 17.0 for Windows. The statistical results were considered significant when the Bonferroni-corrected P value was lower than 0.05 (based on the number of SNPs and logistic regression models analyzed).

Results

Characteristics of the Study Groups

A total of 2350 northern Han Chinese subjects comprising 992 LOAD patients and 1358 controls subjects were included in our study (Table 1). No statistically significant differences found in age (age at onset for LOAD patients and age at examination for control subjects) ($P = 0.189$) or gender ($P = 0.067$). The percentage of *APOE* ε4 carriers was statistically significant between LOAD patients and healthy controls ($P < 0.001$). In addition, MMSE scores were significantly lower in LOAD patients than healthy controls ($P < 0.001$).

Univariate Analysis

From the available data in HapMap database, genotype and allele frequencies of included SNPs (except for rs15553999, rs34311866, and rs76904798 which have no information about CHB genotype data) in our control group were consistent with CHB genotype data (Supplementary Table 2). And

our included SNPs all passed a 95 % call rate threshold, and the details were seen in Supplementary Table 2. The information of included SNPs (chromosome, position, minor allele, alternate allele, HWE value, and minor allele frequency) was summarized in Table 2. The distributions of the included nine SNPs were in HWE for control subjects ($P > 0.05$). As shown in Table 2, most gene locations of these SNPs (rs11724635, rs12637471, rs17649553, rs356182, rs6430538, rs76904798, and rs823118) are intron variant; rs1555399 is in 5′-flanking in *TMEM229B* gene; rs17649553 is in intron1 in *MAPT* gene and rs34311866 is in nonsynon_11 in *TMEM175-GAK-DGKQ*. These included SNPs are not expression quantitative trait loci (eQTLs) according to the eQTL database (http://www.hsph.harvard.edu/liming-liang/software/eqtl/). These SNPs are in linkage disequilibrium with other potentially functional variants according to the results of 1000 Genomes database (http://browser.1000genomes.org/index.html), and they may influence on AD risk with these functional variants.

In total sample, although significant differences were confirmed in allele or genotype of rs12637471, rs356182, rs6430538, and rs76904798 frequencies between LOAD patients and control subjects (Table 3). However, only the distribution of rs356182 allele remains significant after Bonferroni correction (OR = 0.748; 95 % CI 0.661–0.845; Bonferroni corrected $P = 0.000$), suggesting the A allele of rs356182 is the protective allele.

Multivariate Analysis

We revaluated the association of the included SNPs with LOAD risk under three genetic models using logistic regression adjusting for age (age at onset in LOAD patients and age at examination in control subjects), gender, and *APOE* ε4 status to rule out confounding factors in our initial analyses. As Table 4 shows, the minor alleles at rs12637471 and rs6430538 were discovered to alter the risk of developing LOAD under a dominant model (adjusted OR = 1.242, 95 % CI 1.049–1.469, P value 0.012; adjusted OR = 0.289, 95 % CI 0.116–0.721, P value: 0.008); however, these results failed to remain significant after Bonferroni correction. Interesting, the distribution of genotype in rs76904798 significantly reduced LOAD risk in comparison with its wild-type homozygotes under a dominant mode adjusting for age, gender, and *APOE* ε4 status, and the results were still significant even after Bonferroni adjustment (adjusted OR = 0.616, 95 % CI 0.446–0.849, Bonferroni-corrected P value 0.027).

Interactions with APOE Genetics

Afterwards, we stratified the subjects according to *APOE* ε4 status to explore whether *APOE* ε4 affected the connection between the included SNPs and LOAD risk via using logistic regression adjusting for age and gender (Table 5). After stratifying the subjects according to *APOE* ε4 status, a significant association was only observed between the T allele at rs76904798 and LOAD risk under a dominant model in non-*APOE* ε4 carriers (adjusted OR = 0.396, 95 % CI 0.258–0.607, Bonferroni-corrected P value 0.000). In addition, as shown in Table 5, rs76904798 within *LRRK2* gene showed a significant *APOE* interaction in the logistic regression under a dominant model indicating a synergistic effect of *LRRK2* and *APOE* on AD risk.

Discussion

GWAS is a powerful tool for genetic association studies, and independent replication remains the first step in distinguishing true positive from false-positive genetic association findings [23]. Furthermore, since there is a possible pathology overlap

Table 2 Characteristics of included SNPs

SNPs	Chromosome	In or nearest gene(s)	Position	Region	Minor allele	Alternate allele	HWE (P value)	MAF (%)
rs11724635	4	*BST1*	15,737,101	Intron variant	A	C	0.440	37.92
rs12637471	3	*MCCC1*	182,762,437	Intron10	G	A	0.081	32.11
rs1555399	14	*TMEM229B*	67,984,370	5′-flanking	A	T	0.838	46.28
rs17649553	17	*MAPT*	43,994,648	Intron1	T	C	0.946	0.18
rs34311866	4	*TMEM175-GAK-DGKQ*	951,947	onsynon_11	C	T	0.056	12.67
rs356182	4	*SNCA*	90,626,111	Intron variant	A	G	0.727	32.70
rs6430538	2	*ACMSD-TMEM163*	135,539,967	Intron variant	C	T	0.743	0.88
rs76904798	12	*LRRK2*	40,614,434	Intron variant	T	C	0.078	4.57
rs823118	1	*RAB7L1-NUCKS1*	205,723,572	Intron variant	C	T	0.353	46.17

ACMSD-TMEM163 aminocarboxymuconate semialdehyde decarboxylase-transmembrane protein 163, *BST1* bone marrow stromal cell antigen 1, *HWE* Hardy–Weinberg equilibrium, *LRRK2* leucine-rich repeat kinase 2, *MAF* minor allele frequence, *MAPT* microtubule-associated protein tau, *MCCC1* methylcrotonoyl-CoA carboxylase 1, *RAB7L1-NUCKS1* member RAS oncogene family-like 1-nuclear casein kinase and cyclin-dependent kinase substrate 1, *SNCA* synuclein, *SNP* single-nucleotide polymorphism, *TMEM229B* transmembrane protein 229B, *TMEM175-GAK-DGKQ* transmembrane protein175-cyclin G associated kinase-diacylglycerol kinase

Table 3 Distribution of included SNPs in LOAD patients and control subjects

SNP	Allele (1/2)	Power (%)	Allele *n* (%)				Genotype *n* (%)			
			1	2	*P* value	OR (95 % CI)	11	12	22	*P* value
rs11724635	C/A	4.7								
LOAD			1220 (61.49)	764 (38.51)	0.684	1.025 (0.910, 1.155)	372 (37.5)	476 (48.0)	144 (14.5)	0.659
Control			1686 (62.08)	1030 (37.92)			530 (39.0)	626 (46.1)	202 (14.9)	
rs12637471	A/G	18.2								
LOAD			1306 (65.83)	678 (34.17)	0.137	1.098 (0.971, 1.241)	416 (41.9)	474 (47.8)	102 (10.3)	0.011
Control			1844 (67.89)	872 (32.11)			640 (47.1)	564 (41.5)	154 (11.4)	
rs15553999	T/A	5.8								
LOAD			1082 (54.54)	902 (45.46)	0.579	0.968 (0.861, 1.087)	294 (29.6)	494 (49.8)	204 (20.6)	0.856
Control			1459 (53.72)	1257 (46.28)			390 (28.7)	679 (50.0)	289 (21.3)	
rs17649553	C/T	99.9								
LOAD			1982 (99.90)	2 (0.10)	0.465	0.547 (0.106, 2.823)	990 (99.8)	2 (0.2)	0 (0)	0.706*
Control			2711 (99.82)	5 (0.18)			1353 (99.6)	5 (0.4)	0 (0)	
rs34311866	T/C	2.6								
LOAD			1732 (87.30)	252 (12.70)	0.971	1.003 (0.843, 1.194)	750 (75.6)	232 (23.4)	10 (1.0)	0.996
Control			2372 (87.33)	344 (12.67)			1028 (75.7)	316 (23.3)	14 (1.0)	
rs356182	G/A	88.7								
LOAD			1362 (68.65)	622 (31.35)	0.000	0.748 (0.661, 0.845)	456 (46.0)	450 (45.3)	86 (8.7)	0.193
Control			1828 (67.30)	888 (32.70)			618 (45.5)	592 (43.6)	148 (10.9)	
rs6430538	T/C	100								
LOAD			1978 (99.70)	6 (0.30)	0.013	0.340 (0.139, 0.834)	986 (99.4)	6 (0.6)	0 (0)	0.015*
control			2692 (99.12)	24 (0.88)			1334 (98.2)	24 (1.8)	0 (0)	
rs76904798	C/T	33.4								
LOAD			1918 (96.67)	66 (3.33)	0.033	0.719 (0.531, 0.975)	928 (93.5)	62 (6.3)	2 (0.2)	0.01
Control			2592 (95.43)	124 (4.57)			1234 (90.9)	124 (9.1)	0 (0)	
rs823118	T/C	11.4								
LOAD			1037 (52.27)	947 (47.73)	0.289	1.065 (0.948, 1.196)	286 (28.8)	465 (46.9)	241 (24.3)	0.407
Control			1462 (53.83)	1254 (46.17)			402 (29.6)	658 (48.5)	298 (21.9)	

CI confidence interval, *LOAD* late-onset Alzheimer's disease, *OR* odds ratio, *SD* standard deviation, *SNP* single-nucleotide polymorphism

**P* value calculated from Fisher χ^2 test

Table 4 Single-nucleotide polymorphism association with Alzheimer's disease according to different genetic models of inheritance

SNP	Model	*P* value	OR (95 % CI)	*P* value[a]	OR (95 % CI)[a]	P_c value[#]
rs11724635	Dominant	0.452	1.067 (0.901, 1.263)	0.151	1.135 (0.955, 1.348)	>1
	Recessive	0.809	1.029 (0.816, 1.297)	0.719	0.958 (0.757, 1.212)	>1
	Additive	0.685	1.025 (0.910, 1.154)	0.230	1.077 (0.954, 1.216)	>1
rs12637471	Dominant	0.012	1.234 (1.046, 1.456)	0.012	1.242 (1.049, 1.469)	0.324
	Recessive	0.416	1.116 (0.856, 1.454)	0.442	0.900 (0.687, 1.178)	>1
	Additive	0.137	1.098 (0.971, 1.241)	0.128	1.102 (0.972, 1.250)	>1
rs15553999	Dominant	0.628	0.978 (0.894, 1.070)	0.525	0.971 (0.886, 1.064)	>1
	Recessive	0.673	0.958 (0.783, 1.171)	0.518	0.935 (0.761, 1.148)	>1
	Additive	0.578	1.034 (0.920, 1.161)	0.433	0.954 (0.847, 1.074)	>1
rs17649553	Dominant	0.471	0.547 (0.106, 2.823)	0.579	0.628 (0.121, 3.254)	>1
rs34311866	Dominant	0.958	1.005 (0.831, 1.216)	0.948	0.994 (0.818, 1.207)	>1
rs356182	Dominant	0.825	0.982 (0.833, 1.157)	0.540	0.949 (0.802, 1.122)	>1
	Recessive	0.075	0.776 (0.587, 1.026)	0.060	0.761 (0.572, 1.012)	>1
	Additive	0.326	0.939 (0.829, 1.064)	0.184	0.917 (0.807, 1.042)	>1
rs6430538	Dominant	0.018	0.338 (0.138, 0.831)	0.008	0.289 (0.116, 0.721)	0.072
rs76904798	Dominant	0.019	0.686 (0.502, 0.939)	0.003	0.616 (0.446, 0.849)	0.027
rs823118	Dominant	0.685	1.038 (0.867, 1.243)	0.696	1.037 (0.863, 1.246)	>1
	Recessive	0.181	1.141 (0.940, 1.386)	0.253	1.122 (0.921, 1.368)	>1
	Additive	0.299	1.062 (0.948, 1.190)	0.362	1.055 (0.940, 1.185)	>1

The SNPs with minor allele homozygote counts of 14 or more were calculated in three kinds of logistic regression models (dominant, additive, and recessive). When SNPs with minor allele homozygote counts are less than 14 and the number of minor allele homozygotes and heterozygotes are more than 14, only the dominant genetic model could be examined

CI confidence interval, *OR* odds ratio, *SNP* single-nucleotide polymorphism

[#] The P_c values were calculated with Bonferroni correction

[a] Data were calculated by logistic regression, adjusting for age of onset (age at examination for control subject subjects), gender, and apolipoprotein E (*APOE*) ε4 status (presence of one or two APOE ε4 alleles vs the absence of APOE ε4 alleles)

and a potential genetic association between AD and PD, it is important to replicate GWAS-reported PD risk loci in AD population to discover new AD-related genetic variants. In this study, we performed a comprehensive analysis of the association between LOAD risk and nine SNPs which were reported to have close connections with PD risk in a recent GWAS. Our results showed a successful replication of the association of rs76904798 of *LRRK2* with LOAD risk in this independent case–control study. This is the first study to indentify rs76904798 of *LRRK2*, the PD-related locus, also significantly associated with AD susceptibility in a large northern Han Chinese population.

AD and PD are two most common neurodegenerative diseases with a large population of sufferers. Aggregates of insoluble Aβ and NFT consisting of hyperphosphorylated tau protein are classic pathological features of AD [2, 24]. Pathologically, PD is characterized with degeneration of dopamine neurons in the substantia nigra pars compacta and the presence of proteinaceous inclusions immunoreactive for α-synuclein in surviving neurons [25, 26]. Although AD and PD have distinct mechanisms of etiology, different brain regions, and distinct clinical features, they have much overlap in the development of neurodegeneration and share a great similar pathway to induce the occurrence of disease as shown in Fig. 1, including intracellular mechanisms, local tissue environment, systemic environment, and aging [27]. In addition, except for a possible pathological overlap between AD and PD, a growing evidence indicated a potential genetic association also exists in AD and PD. Summarizing and analyzing the numerous pathways which are implicated in PD and AD, many genes have been confirmed to function in both Mendelian and sporadic forms of AD or PD, such as PD-related genes (*MAPT*, *SNCA*, *GBA*, *LRRK2*, *PM20D1*, *GAK*, *MCCC1*, *STK39*, *BST1*, *GPNMB*) [26, 28–35], top 10 genes from the AlzGene database (*APOE*, *BIN1*, *CLU*, *ABCA7*, *CR1*, *PICALM*, *MS4A6A*, *CD33*, *MS4A4E*, *CD2AP*) [36] and a small number of other genes (*APP*, *PSEN1*, *PSEN2*, *DJ1*, *HIP1R*, *PARK2*, *SYT11*, *UCHL*) [37]. Allowing for the overlap of pathology and genetic background between AD and PD, it may be an appropriate method to disclose AD-related genetic factors from the GWAS which explored PD risk loci. In this study, nine SNPs (rs11724635 of *BST1*,

Table 5 Interaction analysis between the SNPs and *APOE* ε4 carrier status

SNP	Model	Absence of *APOE* ε4						Presence of *APOE* ε4						*P* value for *APOE* interaction[b]
		Genotype Case (*n*)/control (*n*)			*P* value[a]	OR (95 %CI)[a]	P_c value[§]	Geneotype Case (*n*)/control (*n*)			*P* value[a]	OR (95 %CI)[a]	P_c value[§]	
		11	12	22				11	12	22				
rs11724635	D	254/430	346/549	108/188	0.664	1.044 (0.859, 1.268)	>1	118/100	130/77	36/14	0.022	1.540 (1.063, 2.230)	0.594	0.061
	R				0.690	1.054 (0.814, 1.365)	>1				0.065	0.544 (0.284, 1.040)	>1	0.475
	A				0.927	1.006 (0.879, 1.152)	>1				0.010	1.454 (1.093, 1.935)	0.270	0.089
rs12637471	D	282/554	350/481	76/132	0.004	1.315 (1.092, 1.582)	0.108	134/86	124/83	26/22	0.559	0.897 (0.624, 1.290)	>1	0.060
	R				0.541	0.920 (0.705, 1.202)	>1				0.299	0.738 (0.416, 1.309)	>1	0.473
	A				0.059	1.139 (0.995, 1.303)	>1				0.374	0.883 (0.670, 1.162)	>1	0.092
rs15553999	D	216/333	348/589	144/245	0.344	0.952 (0.859, 1.054)	>1	78/57	146/90	60/44	0.630	1.052 (0.857, 1.291)	>1	0.420
	R				0.666	0.950 (0.754, 1.198)	>1				0.589	0.885 (0.567, 1.379)	>1	0.756
	A				0.389	0.943 (0.825, 1.078)	>1				0.992	0.999 (0.768, 1.299)	>1	0.738
rs17649553	D	706/1162	2/5	0/0	0.579	0.628 (0.121, 3.254)	>1	284/191	0/0	0/0	–	–	–	0.579
rs34311866	D	534/891	166/266	8/10	0.663	1.050 (0.844, 1.306)	>1	216/137	66/50	2/4	0.287	0.796 (0.522, 1.212)	>1	0.279
rs356182	D	340/537	304/510	64/120	0.389	0.921 (0.763, 1.111)	>1	116/81	146/82	22/28	0.755	1.062 (0.725, 1.546)	>1	0.460
	R				0.395	0.927 (0.633, 1.198)	>1				0.017	0.485 (0.268, 0.878)	0.459	0.089
	A				0.297	0.916 (0.803, 1.069)	>1				0.362	0.877 (0.661, 1.164)	>1	0.779
rs6430538	D	704/1149	4/18	0/0	0.056	0.345 (0.116, 1.025)	0.504	282/185	2/6	0/0	0.053	0.203 (0.040, 1.021)	>1	0.584
rs76904798	D	680/1059	28/108	0/0	0.000	0. 396 (0.258, 0.607)	0.000	248/175	34/16	2/0	0.149	1.579 (0.849, 2.938)	>1	0.000
rs823118	D	200/354	341/560	167/253	0.299	1.116 (0.907, 1.372)	>1	86/48	124/98	74/45	0.270	0.792 (0.522, 1.200)	>1	0.626
	R				0.346	1.113 (0.891, 1.392)	>1				0.497	1.160 (0.755, 1.783)	>1	0.758

Table 5 (continued)

SNP	Model	Absence of *APOE* ε4					Presence of *APOE* ε4					*P* value for *APOE* interaction[b]
		Genotype Case (*n*)/control (*n*)			*P* value[a]	OR (95 %CI)[a]	*P*$_c$ value[§]	Genotype Case (*n*)/control (*n*)			*P* value[a]	OR (95 %CI)[a]	*P*$_c$ value[§]	
		11	12	22				11	12	22				
	A				0.228	1.083 (0.951, 1.234)	>1				0.782	0.965 (0.749, 1.243)	>1	0.923

The SNPs with minor allele homozygote counts of 14 or more were calculated in three kinds of logistic regression models (dominant, additive, and recessive). When SNPs with minor allele homozygote counts are less than 14 and the number of minor allele homozygotes and heterozygotes are more than 14, only the dominant genetic model could be examined

A additive, *APOE* apolipoprotein, *CI* confidence interval, *D* dominant, *OR* odds ratio, *R* recessive, *SNP* single-nucleotide polymorphism

§ The *P*$_c$ values were calculated with Bonferroni correction

[a] Data were calculated by logistic regression, adjusting for age of onset (age at examination for control subject subjects), gender, and apolipoprotein E (*APOE*) ε4 status (presence of one or two APOE ε4 alleles vs the absence of APOE ε4 alleles)

[b] Data were calculated by logistic regression, adjusting for age of onset (age at examination for control subject subjects), gender, apolipoprotein E (*APOE*) ε4 status (presence of one or two APOE ε4 alleles vs the absence of APOE ε4 alleles), and APOE × SNP interaction

rs12637471 of *MCCC1*, rs1555399 of *TMEM229B*, rs17649553 of *MAPT*, rs34311866 of *TMEM175-GAK-DGKQ*, rs356182 of *SNCA*, rs6430538 of *ACMSD-TMEM163*, rs76904798 of *LRRK2*, and rs823118 of *RAB7L1-NUCKS1*) in a recent GWAS which showed close connections with PD risk were enrolled to identify their relationship with AD susceptibility. Finally, our study, for the first time, successfully replicated the association between rs76904798 of *LRRK2* and AD susceptibility in a northern Han Chinese people and indicated a genetic overlap between AD and PD susceptibility at rs76904798 of *LRRK2*.

Mutations in *LRRK2* have been accepted as the most frequent cause of sporadic cases of PD [26, 38–40]. To date, many studies have paid attentions to its role in AD pathology, and *LRRK2* is considered involved in AD-related pathology, such as tau, inflammatory response, oxidative stress, mitochondrial dysfunction, synaptic dysfunction, and autophagy–lysosomal system [26]. Now, *LRRK2* is widely accepted as a potential candidate locus influencing AD risk in recent studies [41–44]. And our results revealed variants at rs76904798 of *LRRK2* would significantly decrease AD risk in comparison with its wild-type homozygotes after analysis in logistic regression adjusting for age, gender, *APOE* ε4 status, and the strong association may result from its potential influence on AD pathology. Furthermore, screening these genetic variants with positive results maybe a promising method to detect and diagnose AD in a northern Han Chinese people, and more experiments in vivo and in vitro are needed to verify these hypotheses. Our results showed rs76904798 of *LRRK2* is a genetic overlap between AD and PD susceptibility, which may come from the influence of *LRRK2* on AD and PD shared mechanism, such as mitochondrial function, oxidative damage, ubiquitin, neurotransmission, and inflammation system (Fig. 1) [26]. In the subgroups stratified by the presence or absence of the *APOE* ε4 allele, our results showed rs76904798 of *LRRK2* alter LOAD susceptibility in *APOE* ε4-negative subjects. In addition, the *P* value for *APOE* interaction showed that the interaction of each SNP and *APOE* genotypes was observed between rs76904798 of *LRRK2* and *APOE*. These results indicated a synergistic effect of *LRRK2* and *APOE* on AD risk. Our study of failing to detect an interaction of *APOE* and other SNPs mainly attributes the age structure of the current study because the effect of *APOE* on AD risk is much stronger in young patient populations [45]. However, previous studies about the *LRRK2* gene in AD have not provided a consistent conclusion. It was negatively associated with AD in Taiwan [46] and southwestern China population [47]; while it was positively associated with AD in a Singaporean population

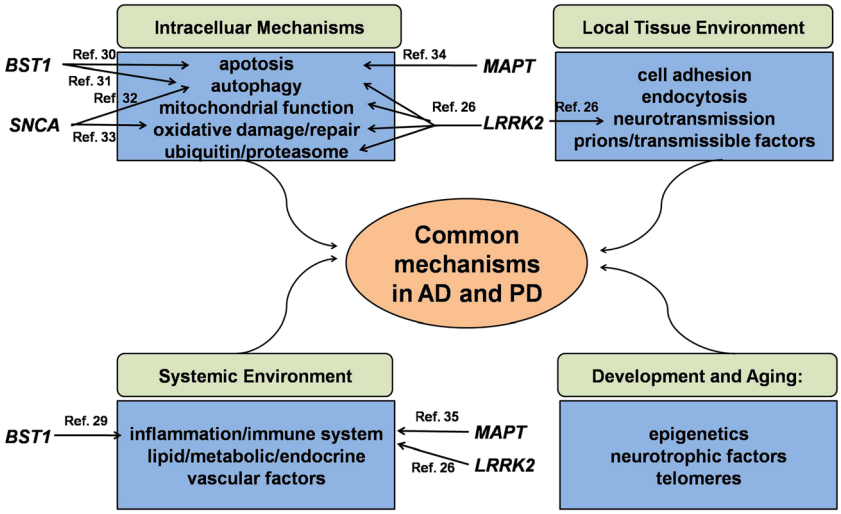

Fig. 1 The potential schematic profile for Alzheimer's disease and Parkinson's disease. Alzheimer's disease (AD) and Parkinson's disease (PD) share a similar pathway to induce the occurrence of disease, including intracellular mechanisms, local tissue environment, systemic environment, and aging

[44] and in our study. This may be caused by the different population structures in these studies, and more studies are needed to be performed to confirm this relation.

Except for the successful replicated SNP, other SNPs were inconsistent with the results of previous mentioned GWAS. Moreover, the reasons of failing to disclose perfect replications may be attributed to several factors. First, as shown in Table 3, many SNPs had a power less than 0.8. This may partly explained by our negative findings. Second, because of gene–gene or gene–environment interactions, the magnitude of the influence of included genetic variants may differ between populations, and our study was performed in the northern Han cohorts who may contain a different allelic heterogeneity compared to white samples. Third, variants at these SNPs did not alter the expression of related protein to impact in LOAD-related pathology so as to alter AD susceptibility. Last, the differences of endogenous genetic background of AD and PD may be the basic and the most important factors of these inconsistent results.

In summary, our study repeated the reported SNPs which were considered to affect PD risk, and we first demonstrated that rs76904798 of *LRRK2* significantly influenced LOAD risk. However, the other genetic variants might not play major roles in the genetic predisposition to LOAD in a northern Han Chinese people. However, these genetic variants have been reported to significantly link to AD; for example, genetic variations at *SNCA* gene have been proved to play a key role in PD pathology [48–50]. A recent study also indicated a close connection between *SNCA* polymorphism and NFT (tau) pathologies which are critical factors in AD pathology [51]. Although our study did not discover significant results, these conclusions need more functional genetic analyses and independent replications across different ethnicities and districts to elucidate the epidemiologic relevance and the potential biochemical mechanisms.

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Compliance with Ethical Standards We obtained informed consents from each subject or a guardian, and this study protocol was approved by the institutional ethics committees of Qingdao Municipal Hospital.

Conflict of Interests The authors declare that they have no competing interests.

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