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The *LRRK2* R1628P Variant Plays a Protective Role in Han Chinese Population with Alzheimer's Disease

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Keywords

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SUMMARY

Aims: Alzheimer's disease (AD) and Parkinson's disease (PD) are the most prevalent neurodegenerative disorders that may share some overlapping etiologies. Mutations within leucine-rich repeat kinase 2 (*LRRK2*) have been reported to be responsible for PD, and the location of *LRRK2* is within a linkage peak for sporadic AD (SAD). The aim of this study was to investigate two Asian-specific *LRRK2* variants, R1628P and G2385R, with the association of Han Chinese SAD. **Methods:** Genotyping of R1628P and G2385R was performed by PCR-restriction fragment length polymorphism (RFLP) analysis in 390 patients with SAD and 545 unrelated age- and sex-matched healthy controls. **Results:** The frequency of the C allele within R1628P was more than three times higher in control group (1.7%) than in patients with SAD (0.5%) (OR 0.264; 95% CI, 0.088–0.792, *P* = 0.018). After stratification by the presence of one or two apolipoprotein E *ɛ*4 alleles, the protective effect becomes stronger (*ɛ*44: OR 0.028; 95% CI, 0.003–0.303, *P* = 0.003; *ɛ*4: OR 0.104; 95% CI, 0.013–0.818, *P* = 0.031). However, no difference was found in G2385R variant. **Conclusion:** Our study suggested that R1628P variant within *LRRK2* plays a protective role in Han Chinese population with SAD and such effect has an interaction with the *APOE* genotype.

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The first two authors contributed equally to this work.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and presents with progressive and irreversible memory loss and cognitive decline. The great majority of AD is sporadic (SAD) although early-onset familial AD (EOFAD) can represent up to 5% of the AD cases assessed in memory clinics [1]. The role of genes in the pathogenesis/cause of a proportion (~50%) of EO-FAD is now known to be the result of mutations (at least 230 to date) in three virtually fully penetrant genes—amyloid precursor protein (*APP*), presenilins 1 and 2 (*PS1* and *PS2*, respectively) (http://www.molgen.ua.ac.be/ADMutations). Conversely, to date, no single gene mutation has been found in SAD, and at least in the majority of such cases, gene–environment interactions may play an important role in pathogenesis. To date, the only well-replicated genetic locus for susceptibility to (but not causal for) SAD is the apolipoprotein E (*APOE*) gene, which has three alleles—*e*4,

 ϵ 3, and ϵ 2 [2]. Research continues to identify and confirm other potential susceptibility factors for SAD.

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after AD [3]. Epidemiological studies show that siblings of demented patients with PD (PDD) have an higher risk of developing AD compared with siblings of normal subjects [4], and conversely, it has been shown that first-degree relatives of patients with AD have an increased risk of developing PD [5]. In addition, there was a coexistent Alzheimer pathology in some PD patients with or without dementia [6].

In the current study, we hypothesize a common (or at least overlapping) etiology between SAD and PD with the leucine-rich repeat kinase 2 (*LRRK2*). *LRRK2*, a large gene located on chromosome 12: 40,590,546 –40,763,087, has 51 exons and encodes a multifunctional protein. Mutations within *LRRK2* have been reported to be responsible for both familial and sporadic PD [7,8]. The location of *LRRK2* is within a linkage peak for late-onset SAD [9] and close to the 12q13 risk locus identified in a recent genome-wide association study (GWAS) [10]. Thus, it has been speculated that variants within *LRRK2* may be associated with the risk of developing SAD. Here, we present a case–control study in the Han Chinese population to investigate two Asian-specific *LRRK2* variants, R1628P (rs33949390) and G2385R (rs34778348), with the association of SAD.

Materials and Methods

Ethics Approval

The study protocol was approved by the Ethics Committee of Huashan Hospital.

Subjects

This study included two subject groups: 390 patients with SAD (228 women and 162 men; mean age 69.99 ± 9.907 ; range 47–92) and 545 unrelated age- and sex-matched healthy controls (336 women and 209 men; mean age 68.77 ± 9.192 ; range 47–93). The detailed enrollment procedure as well as inclusion and exclusion criteria for cases and controls was described previously [11]. All participants were of Han Chinese descent, which accounts for approximately 90% of the entire Chinese population. A signed informed consent was obtained from each case (substitute decision maker/guardian) and control.

Genotyping

Genomic DNA was extracted from peripheral blood using a Blood Genomic DNA Extraction Kit (TIANGEN, Beijing, China). Genotyping of R1628P (forward primer: 5'-TTCTGACTACTTTCACT-GAG-3' and reverse primer: 5'-GGAGGTTTACACTAGAAGC-3') and G2385R (forward primer: 5'-TAGCCCTGTTGTGGAAGTG-3' and reverse primer: 5'-TTCAGAGGCAGAAAGGAAG-3') was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. PCR amplification was performed using a GeneAmp PCR system 9600 (Applied Biosystems, Foster City, CA, USA). The PCR products were digested with the restriction enzyme AccI for G2385R and BstUI for R1628P according to the manufacturer's recommendations. Digestion was followed by 2.5% agarose gel electrophoresis. The minor alleles of R1628P were further confirmed by DNA sequencing using an ABI 3730 Automated DNA Sequencer (Applied Biosystems). The APOE genotypes were determined by multiplex amplification refractory mutation system PCR as previously described [12].

Statistical Analysis

The genotypes and allele frequencies in patients with SAD versus controls were compared using the standard chi-square test or the Fisher's exact test, where appropriate. Binary logistic regression analyses were used to estimate odds ratios (ORs) and the 95% confidence interval (CI). Covariates were age, gender, and *APOE* genotype. All statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). The criterion for a significant difference was P < 0.05.

Results

Characteristics of Participants

The general data of the participants are shown in Table 1. No statistically significant differences were observed for age and gender

Table 1	Age,	gender,	and	score	of	MMSE	in	patients	with	AD	and
control											

	Control (n = 545)	AD (n = 390)	Р
Age (years \pm SD)	68.77 ± 9.192	69.99 ± 9.907	0.056
Male/female	209/336	162/228	0.343
MMSE (means \pm SD)	27.81 ± 4.225	14.70 ± 5.835	< 0.0001
APOE ε4 carrier (%)	191 (35.05)	180 (46.15)	0.001
APOE ε4ε4 genotype (%)	7 (0.01)	44 (11.28)	< 0.0001
APOE ϵ 2 carrier (%)	121 (22.2)	31 (7.9)	< 0.0001
APOE ε2ε2 genotype (%)	17 (3.1)	3 (0.8)	0.020

AD, Alzheimer's disease; *APOE*, apolipoprotein E; MMSE, Mini Mental State Examination.



Figure 1 Genotypes of R1628P and G2385R. (**A**) Electrophoresis of BstUldigested R1628P PCR-amplified products on a 2.5% agarose gel. M: marker (D2000); P: PCR product of 419 bp; GG: genotype GG, represented by two fully digested fragments of 263 bp and 156 bp; CG: genotype CG, represented by the undigested PCR product of 419 bp and two smaller fragments of 263 bp and 156 bp. (**B**) Electrophoresis of AccI-digested G2385R PCR-amplified products on a 2.5% agarose gel. M: marker (D2000); GG: genotype GG, represented by an undigested 170-bp fragment; P: PCR product of 170 bp; AG: genotype AG, represented by an undigested PCR product of 170 bp and a shorter fragment of 123 bp, the digested smaller piece of 47 bp cannot be observed. (**C**) DNA sequence chromatogram of R1628P. The upper panel indicates genotype GG, whereas the genotype CG is shown in the bottom one.

Table	2	Genotypes	and	allele	frequencies	of	R1628P	and	G2385R
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R1628P	Control (%)	AD (%)	Р	G2385R	Control (%)	AD (%)	Р
Total	545 (%)	390 (%)		Total	545 (%)	390 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	18 (3.3)	4 (1.0)		AG	22 (4.0)	21 (5.4)	
GG	527 (96.7)	386 (99.0)	0.027	GG	523 (96.0)	369 (94.6)	0.346
C frequency	18 (1.7)	4 (0.5)		A frequency	22 (2.0)	21 (2.7)	
G frequency	1072 (98.3)	776 (99.5)	0.028	G frequency	1068 (98.0)	759 (97.3)	0.351
Male	209 (%)	162 (%)		Male	209 (%)	162 (%)	
CC	0.00	0.00		AA	0 (0.0)	0 (0.0)	
CG	8 (3.8)	1 (0.6)		AG	12 (5.7)	9 (5.6)	
GG	201 (96.2)	161 (99.4)	0.084	GG	197 (94.3)	153 (94.4)	1.000
C frequency	8 (1.9)	1 (0.3)		A frequency	12 (2.9)	9 (2.8)	
G frequency	410 (98.1)	323 (99.7)	0.086	G frequency	406 (97.1)	315 (97.2)	1.000
Female	336 (%)	228 (%)		Female	336 (%)	228 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	10 (3.0)	3 (1.3)		AG	10 (3.0)	12 (5.3)	
GG	326 (97.0)	225 (98.7)	0.259	GG	326 (97.0)	216 (94.7)	0.188
C frequency	10 (1.5)	3 (0.7)		A frequency	10 (1.5)	12 (2.6)	
G frequency	662 (98.5)	453 (99.3)	0.261	G frequency	662 (98.5)	444 (97.4)	0.192
EOAD	193 (%)	134 (%)		EOAD	193 (%)	134 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	6 (3.1)	1 (0.7)		AG	10 (5.2)	7 (5.2)	
GG	187 (96.9)	133 (99.3)	0.247	GG	183 (94.8)	127 (94.8)	1.000
C frequency	6 (1.6)	1 (0.4)		A frequency	10 (2.6)	7 (2.6)	
G frequency	380 (98.4)	267 (99.6)	0.250	G frequency	376 (97.4)	261 (97.4)	1.000
LOAD	352 (%)	256 (%)		LOAD	352 (%)	256 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	12 (3.4)	3 (1.2)		AG	12 (3.4)	14 (5.5)	
GG	340 (96.6)	253 (98.8)	0.111	GG	340 (96.6)	242 (94.5)	0.229
C frequency	12 (1 7)	3 (0.6)		A frequency	12 (1 7)	14 (2 7)	
G frequency	692 (98 3)	509 (99 4)	0 113	G frequency	692 (98.3)	498 (97 3)	0 234
APOF £4 carrier	191 (%)	180 (%)	0.110	APOF £4 carrier	191 (%)	180 (%)	0.201
	0 (0 0)	0 (0 0)		AA	0 (0 0)	0 (0 0)	
CG	10 (5.2)	1 (0.6)		AG	7 (3 7)	10 (5.6)	
GG	181 (94.8)	179 (99 4)	0.011	66	184 (96 3)	170 (94 4)	0.460
C frequency	10 (2.6)	1 (0 3)	0.011		7 (1.8)	10 (2.8)	0.100
G frequency	372 (07 /)	350 (00 7)	0.012	G frequency	375 (08.2)	350 (97.2)	0.466
APOE \$4 noncarriers	354 (%)	210 (%)	0.012	APOE \$4 noncarriers	354 (%)	210 (%)	0.400
	0 (0 0)						
CG	8 (2 3)	3 (1 /)		AG	15 (4 2)	11 (5.2)	
GG	3/6 (07 7)	207 (98.6)	0.754	GG	330 (05.8)	100 (0/ 8)	0 670
C frequency	9 (1 1)	207 (70.0)	0.754		15 (2.1)	11 (2.6)	0.079
G frequency	700 (08 0)	(0.7) /17 (00 3)	0 755	G frequency	603 (07 0)	100 (07 4)	0.682
ABOE and corrier	7 (%)	417 (99.3)	0.755	ABOE and corrier	073 (77.7) 7 (%)	409 (97.4)	0.062
AFUE 844 Carrier	7 (%)	44 (%)			7 (%)	44 (%)	
CC CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	4 (57.1)	1 (2.3)	0.001	AG	0 (0.0)	1 (2.3)	1 000
GG C fraguancy	3 (42.9)	43 (97.7)	0.001	GG A frequency	7 (100.0)	43 (97.7)	1.000
C frequency	4 (28.0)	I (I.I)	0.001	A frequency	0 (0.0)		1 000
G frequency	10 (71.4)	87 (98.9)	0.001	G frequency	14 (100.0)	87 (98.9)	1.000
APOE £44 noncarriers	538 (%)	346 (%)		APUE £44 noncarriers	538 (%)	346 (%)	
	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
	14 (2.6)	3 (0.9)	0.000	AG	22 (4.1)	20 (5.8)	0.010
66	524 (97.4)	343 (99.1)	0.080	66	516 (95.9)	326 (94.2)	0.260
C frequency	14 (1.3)	3 (0.4)		A trequency	22 (2.0)	20 (2.9)	
G frequency	1062 (98.7)	689 (99.6)	0.082	G trequency	1054 (98.0)	6/2 (97.1)	0.266
APOE 2 carrier	121 (%)	31 (%)		APOE 2 carrier	121 (%)	31 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	

R1628P	Control (%)	AD (%)	Р	G2385R	Control (%)	AD (%)	Р
CG	2 (1.7)	0 (0.0)		AG	3 (2.5)	3 (9.7)	
GG	119 (98.3)	31 (100.0)	1.000	GG	118 (97.5)	28 (90.3)	0.100
C frequency	2 (0.8)	0 (0.0)		A frequency	3 (1.2)	3 (4.8)	
G frequency	240 (99.2)	62 (100.0)	1.000	G frequency	239 (98.8)	59 (95.2)	0.102
APOE ϵ 2 noncarriers	424 (%)	359 (%)		APOE £2 noncarriers	424 (%)	359 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	16 (3.8)	4 (1.1)		AG	19 (4.5)	18 (5.0)	
GG	408 (96.2)	355 (98.9)	0.022	GG	405 (95.5)	341 (95.0)	0.738
C frequency	16 (1.9)	4 (0.6)	0.023	A frequency	19 (2.2)	18 (2.5)	
G frequency	832 (98.1)	714 (99.4)		G frequency	829 (97.8)	700 (97.5)	0.741
APOE £22 carrier	17 (%)	3 (%)		APOE £22 carrier	17 (%)	3 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	0 (0.0)	0 (0.0)		AG	0 (0.0)	1 (33.3)	0.150
GG	17 (100.0)	3 (100.0)	_	GG	17 (100.0)	2 (66.7)	
C frequency	0 (0.0)	0 (0.0)		A frequency	0 (0.0)	1 (16.7)	0.150
G frequency	34 (100.0)	6 (100.0)	-	G frequency	34 (100.0)	5 (83.3)	
APOE £22 noncarriers	528 (%)	387 (%)		APOE ϵ 22 noncarriers	528 (%)	387 (%)	
CC	0 (0.0)	0 (0.0)		AA	0 (0.0)	0 (0.0)	
CG	18 (3.4)	4 (1.0)		AG	22 (4.2)	20 (5.2)	0.524
GG	510 (96.6)	383 (99.0)	0.027	GG	506 (95.8)	367 (94.8)	
C frequency	18 (1.7)	4 (0.5)		A frequency	22 (2.1)	20 (2.6)	
G frequency	1038 (98.3)	770 (99.5)	0.028	G frequency	1034 (97.9)	754 (97.4)	0.529

AD, Alzheimer's disease; APOE, apolipoprotein E; EOAD, early-onset AD.

(P > 0.05) between cases and controls. As expected, the Mini Mental State Examination (MMSE) score [13] was significantly lower in patients with SAD than in controls (P < 0.0001). The *APOE* ε 4 allele frequency and the *APOE* ε 44 genotype were significantly different between patients with SAD and control subjects (P < 0.0001), being higher for the SAD group as expected.

Genotype and Allele Frequency Distribution

Polymorphisms of R1628P and G2385R were identified using PCR-RFLP analysis, and the minor alleles of R1628P were further confirmed by DNA sequencing (Figure 1). The allele and genotype distributions of R1628P and G2385R polymorphisms are shown in Table 2, and the corresponding logistic regression analyses are shown in Tables 3 and 4, respectively. To our surprise, the frequency of the C allele within the R1628P variant was more than three times higher in control group (1.7%) than in patients with SAD (0.5%), and this difference was significant (OR 0.264; 95% CI, 0.088–0.792, P = 0.018). After stratifying by the presence of one or two APOE ɛ4 alleles, it was found that in APOE ɛ44 carriers, the C allele frequency in the control group was more than 28 times higher than in the patient group (£44: OR 0.028; 95% CI, 0.003-0.303, P = 0.003; E4: OR 0.104; 95% CI, 0.013-0.818, P = 0.031). In addition, the C allele was totally absent in cases and controls who were carriers of APOE £22. However, we did not observe a difference in the frequencies of the G2385R between the SAD and control group (AA: absent; AG: P = 0.401, OR 1.306, 95% CI 0.700–2.434; allele A: *P* = 0.382, OR 1.315, 95% CI 0.711 –2.431).

Discussion

LRRK2 is a large gene located on chromosome 12 that has 51 exons and encodes a multifunctional protein. Recent studies found *LRRK2* immunopositivity in a subset of neurofibrillary tangles in AD and the parkinsonism–dementia complex of Guam (PDCG) [14]. Although the physical function of *LRRK2* remains unclear, it has been suggested that it may be a cytoplasmic kinase capable of autophosphorylation as well as a GTPase. An interaction with microtubules has also been reported [15–17], suggesting that *LRRK2*-induced neurodegeneration might be partly mediated by the inhibition of microtubule dynamics. Moreover, it is found that *LRRK2* may have an interaction with mitochondria and is involved in pathways that elicit oxidative stress or free radical damage [18].

Despite a plausible role of *LRRK2* dysfunction in neurodegenerative diseases such as PD and AD, most research to date has failed to find an association between *LRRK2* mutations/variants (e.g., G2019S and I2020T, the most common mutations in PD and one Asian-specific variant G2385R) and AD in different ethnic groups including Chinese, Brazilian, Ashkenazi Jewish, Italian, and Norwegian [19–25]. To date, the only exception has been a case–control study in 217 patients with AD and 668 controls in Singapore population [26]. This study identified the association between the

Table 3 Logistic regression analysis of R1628P

R1628P	Control	AD	Р	OR (95% CI)
Total	545 (%)	390 (%)		
CC	0 (0.0)	0 (0.0)		
CG	18 (3.3)	4 (1.0)	0.017	0.261 (0.086-0.788)
GG	527 (96.7)	386 (99.0)		Reference
С	18 (1.7)	4 (0.5)	0.018	0.264 (0.088-0.792)
G	1072 (98.3)	776 (99.5)		Reference
Male	209 (%)	162 (%)		
CC	0 (0.0)	0 (0.0)		
CG	8 (3.8)	1 (0.6)	0.058	0.131 (0.016-1.072)
GG	201 (96.2)	161 (99.4)		Reference
С	8 (1.9)	1 (0.3)	0.061	0.135 (0.017-1.098)
G	410 (98.1)	323 (99.7)		Reference
Female	336 (%)	228 (%)		
CC	0 (0.0)	0 (0.0)		
CG	10 (3.0)	3 (1.3)	0.172	0.396 (0.105-1.496)
GG	326 (97.0)	225 (98.7)		Reference
С	10 (1.5)	3 (0.7)	0.169	0.396 (0.106-1.481)
G	662 (98.5)	453 (99.3)		Reference
EOAD	193 (%)	134 (%)		
CC	0 (0.0)	0 (0.0)		
CG	6 (3.1)	1 (0.7)	0.125	0.184 (0.021-1.600)
GG	187 (96.9)	133 (99.3)		Reference
C	6 (1.6)	1 (0.4)	0.128	0.188 (0.022–1.616)
G	380 (98.4)	267 (99.6)	0.120	Reference
	352 (%)	256 (%)		
CC	0 (0 0)	0 (0 0)		
CG	12 (3.4)	3 (1 2)	0 072	0 306 (0 084–1 112)
GG	340 (96.6)	253 (98.8)	0.072	Reference
C	12 (1 7)	3 (0.6)	0 072	0.307 (0.085–1.109)
G	692 (98 3)	509 (99.4)	0.072	Reference
APOF	191 (%)	180 (%)		Reference
e4 carriers				
CC	0 (0 0)	0 (0 0)		
CG	10 (5.2)	1 (0.6)	0.031	0 102 (0 013-0 810)
GG	181 (94.8)	179 (99 <i>d</i>)	0.051	Reference
C	10 (2.6)	1 (0 3)	0.031	
G	372 (97 4)	359 (99 7)	0.051	Reference
APOF \$4	354 (%)	210 (%)		Reference
noncarriers	334 (%)	210 (%)		
CC	0 (0 0)	0 (0 0)		
CG	8 (2 3)	3 (1 4)	0.475	0.613 (0.160-2.349)
CG GG	0 (2.3) 346 (07 7)	207 (08.6)	0.475	Peference
00 A	9 (1 1)	207 (98.0)	0 473	
A	0 (1.1) 700 (08 0)	3 (0.7)	0.475	0.015 (0.101–2.555) Reference
	700 (98.9)	417 (99.5)		Reference
APUE 844	7 (%)	44 (%)		
Conters	0 (0 0)	0 (0 0)		
CC	0 (0.0)	1 (2.3)	0.002	0.015 (0.001 0.220)
CG	4 (57.1)	1 (2.3)	0.005	0.015 (0.001–0.229)
GG	5 (42.9)	43 (97.7)	0.000	
	4 (28.0)	1 (1.1)	0.003	0.028 (0.003–0.303)
	IU (/1.4)	87 (98.9)		Reierence
APUE 844	538 (%)	346 (%)		
rioncarriers				
	U (U.U)	0 (0.0)	0.070	
CG	14 (2.6)	3 (0.9)	0.079	0.324 (0.092–1.138)
GG	524 (97.4)	343 (99.1)		Reterence

R1628P	Control	AD	Р	OR (95% CI)
С	14 (1.3)	3 (0.4)	0.078	0.324 (0.093–1.135)
G	1062 (98.7)	689 (99.6)		Reference
APOE ε2	121 (%)	31 (%)		
carriers				
CC	0 (0.0)	0 (0.0)		
CG	2 (1.7)	0 (0.0)	0.999	0.000 (0.000)
GG	119 (98.3)	31 (100.0)		Reference
С	2 (0.8)	0 (0.0)	0.999	0.000 (0.000)
G	240 (99.2)	62 (100.0)		Reference
APOE ε2	424 (%)	359 (%)		
noncarriers				
CC	0 (0.0)	0 (0.0)		
CG	16 (3.8)	4 (1.1)	0.027	0.288 (0.095-0.870)
GG	408 (96.2)	355 (98.9)		Reference
С	16 (1.9)	4 (0.6)	0.028	0.291 (0.097-0.876)
G	832 (98.1)	714 (99.4)		Reference
APOE ɛ22	17 (%)	3 (%)		
carriers				
CC	0 (0.0)	0 (0.0)		
CG	0 (0.0)	0 (0.0)	_	_
GG	17 (100.0)	3(100.0)		Reference
С	0 (0.0)	0 (0.0)	_	_
G	34 (100.0)	6 (100.0)		Reference
APOE E22	528 (%)	387 (%)		
noncarriers				
CC	0 (0.0)	0 (0.0)		
CG	18 (3.4)	4 (1.0)	0.028	0.293 (0.098–0.875)
GG	510 (96.6)	383 (99.0)		Reference
С	18 (1.7)	4 (0.5)	0.028	0.296 (0.099–0.878)
G	1038 (98.3)	770 (99.5)		
				Reference

AD, Alzheimer's disease; APOE, apolipoprotein E; EOAD, early-onset AD.

variant R1628P within *LRRK2* and AD (C allele: AD 3.5% vs. control 1.6%, OR 2.3, 95 CI 1.2–4.4, P = 0.018). However, the results we report here are diametrically opposite (C allele: AD 0.5% vs. control 1.7%, OR 0.264, 95 CI 0.088–0.792, P = 0.018). We found the C allele frequency in controls to be more than three times higher than in cases, suggesting that the minor allele C in the R1628P SNP plays a protective role in SAD, especially after stratification for the presence of one or two *APOE* ε 4 alleles. However, these preliminary data need to be further investigated in a larger cohort.

There are several possible explanations for the different findings between the Singapore and Shanghai studies. Firstly, methodological concerns such as ascertainment bias and sample size limitations may influence the results. Here, we used a much larger sample. Our patient group is almost twofold of the Singapore study (390 vs. 217); thus, the result is more convincing. Besides, in our study, we applied very stringent enrollment criteria (patients with any cardinal sign of parkinsonism were excluded from this study) to make sure that our patient group is sufficiently representative. This may explain why the R1628P variant frequency in the controls is comparable (1.7% vs. 1.6%) in both the Shanghai and Singapore studies, while the frequency in patients is very different (0.5% vs. 3.5%). In addition, although epidemiological studies indicated that there may be an overlapping family history between AD and PD, significant association has been reported between APOE 2 allele and sporadic PD [27], in contrast to AD where the *ɛ*2 allele functions as a protective factor. Consistent with this interesting finding, our study revealed a protective effect of the LRRK2 R1628P variant in AD although this is thought to be a risk factor in PD. It remains unclear what the underlying pathologic mechanism might be. We postulate that there must be some complex interactions between the LRRK2 and APOE genes that play an important role in the development of neurodegenerative diseases such as AD and PD. Further research is required to elucidate why the same allele could have a protective role in one neurodegenerative process, but act as a risk factor for another.

In summary, our study indicated a protective effect of the C allele in the *LRRK2* R1628P variant with SAD. This protective effect was more significant among the *APOE e*4 allele carriers. Thus, we propose that there may be an interaction between *APOE*

Table 3 (Continued)

Table 4 Logistic regression analysis of G2385R

	G2385R	Control	AD	Р	OR (95% CI)
AA 0 0 0 0 0 0 0 0 AG 22 14.00 21 6.40 0.40 1.30 0.702-2.84) AG 22 12.00 21 6.27 0.382 1.31 8 reference AG 22 12.00 21 6.27 0.382 1.31 8 reference AG 0.000 0.100 0.100 0.100 AG 1.2 (2) 9 (5.4) 0.81 1 0.896 (2.55-2.202) AG 1.2 (2) 9 (5.4) 0.81 1 0.103 0.25-2.202 AG 1.2 (2.9) 9 (2.8) 0.852 0.811 1.03 0.25-2.202 AG 1.2 (2.9) 9 (2.8) 0.852 0.811 0.30 0.25-2.202 AG 1.2 (2.9) 9 (2.8) 0.82 0.22 (2.57) Reference AG 0.100 0.100 0.100 0.100 Reference AA 0.10.15 1.2 (2.4) 0.12 (2.10,102.2,420) Reference AA 0.10.01 0.10.0 0.10.0 0.10.0 Reference AA 0.10.02 2.0 (2.5 (3.10,102,102,103,103,103,103,103,103,103,103,103,103	Total	545 (%)	390 (%)		
AG 22 (4.0) 21 (5.7) 0.401 Reference A 22 (2.0) 21 (2.7) 0.382 Reference A 22 (2.0) 21 (2.7) 0.382 Reference Male 200 00 162 (3) Reference Reference AA 0 0.0 0 (0.0) Reference Reference AG 10 (2.2) 9 (2.3) 0.852 0.90 (0.380-2.225) GG 406 (97.1) 315 (97.2) 0.852 0.90 (0.380-2.225) G 406 (97.0) 216 (97.7) 1.83 (0.824-4.73) Reference RG 10 (3.0) 12 (2.5) 0.12 1.983 (0.824-4.73) GG 26 (97.0) 216 (94.7) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference Reference AA 0 (0.0) 0 (0.0) Reference Refere	AA	0 (0.0)	0 (0.0)		
GG S23 (96,0) 369 (94,6) Reference A 22 (2,0) 72 (2,7) 0.32 1.51 (0.11-0.34) G 1008 (98,0) 799 (97.3) Reference AA 0.0.0.0 0.0.0. 0.0.0. AA 12 (5.7) 9 (5.6) 0.811 0.99 (0.369-222) GG 197 (94.3) 153 (94.4) Reference Reference A 12 (5.7) 9 (2.8) 0.852 0.919 (0.380-2225) GG 197 (94.3) 153 (94.4) Reference Reference A 12 (5.7) 9 (2.8) 0.127 1.983 (0.24-4.73) Female 336 (8) 22 (2.6) 0.126 1.970 (0.827-4.692) GG 326 (97.0) 12 (6.4) 0.126 1.970 (0.827-4.692) GG 10 (1.5) 12 (2.6) 0.126 1.970 (0.827-4.692) GG 10 (1.5) 12 (2.6) 0.126 1.970 (0.827-4.692) GG 10 (0.1) 12 (0.4) 0.00 0.00 Reference AA	AG	22 (4.0)	21 (5.4)	0.401	1.306 (0.700–2.434)
A 22 (2,0) 21 (2,7) 0.382 1,315 (0.7)1-2.431) G 1068 (98,0) 759 (97.3) Reference Male 209 (3) 162 (3) 162 (3) AA 0.00 0.00 0.811 0.99 (0.36-2.02) GG 12 (2,9) 9 (2,8) 0.82 0.919 (0.369-2.02) G 406 (97.1) 315 (97.7) 8 febrence Female 336 (3) 228 (4) 199 (0.369-2.02) AA 0.00 0.00 193 (30) 12 (2,4) 0.12 AG 10 (3.0) 12 (2,4) 0.12 1.933 (0.824-4.773) Female 336 (3) 12 (2,4) 0.12 1.933 (0.824-4.773) GG 326 (97.0) 216 (47.7) 1.62 (1.97.4) Reference FGDD 193 (3) 134 (43 1.01 1.933 (0.824-4.773) GG 326 (97.0) 21 (2,4) 0.126 1.970 (0.827-2.62) GG 10 (1.0) 7 (2,4) 0.126 1.970 (0.827-2.62) GG 10 (1.0) 7 (2,4) 0.844 1.079 (0.827-2.62) GG 10 (1.0) 7 (2,4) 0.844 1.079 (0.827-2.62) GG 10 (1.0) 7 (2,4) 0.845 1.090 (0.802-2.25) <t< td=""><td>GG</td><td>523 (96.0)</td><td>369 (94.6)</td><td></td><td>Reference</td></t<>	GG	523 (96.0)	369 (94.6)		Reference
G 106 (96.0) 79 (97.3) Reference AA 0.0.0 0.0.0 0.0.0 AG 12 (5.7) 9 (5.6) 0.81 0.996 (0.365-2.02) GG 12 (5.7) 9 (5.6) 0.821 0.919 (0.380-2.225) GG 197 (94.3) 153 (94.4) Reference A 12 (2.9) 9 (2.8) 0.832 0.919 (0.380-22.8) Female 336 (8) 228 (8) - Reference A 0 (0.0) 0.0.0 Reference - AA 0 (0.0) 0.0.0 Reference - GG 662 (98.5) 444 (97.4) 0.804 1.970 (0.827-4.692) GG 10 (5.2) 7 (5.2) 0.844 1.974 Reference E0AO 193 (9.4) 12 (2.6) 0.864 1.970 (0.827-4.692) Reference CG 366 (97.4) 21 (9.7,4) 1.867 1.970 (0.827-4.692) Reference CG 10 (2.6) 7 (5.2) 0.844 1.974 Reference	A	22 (2.0)	21 (2.7)	0.382	1.315 (0.711–2.431)
Male 20 (b) 162 (b) AA 0 (0.0) 0 (0.0) AG 12 (b7) 9 (b.4) Balerance AG 12 (b7) 9 (b.2) 0.851 Balerance AG 12 (b7) 9 (b.2) 0.852 0.19 (b.380-2.225) G 406 (97.1) 315 (97.2) Balerance Balerance Female 338 (k) 222 (b) 0.10 Total 1.983 (b.824-4.773) GG 326 (97.0) 216 (94.7) Balerance 1.973 (b.824-4.773) Balerance AA 0 (b.0) 0.10 1.973 (b.827-4.773) Balerance 1.973 (b.827-4.773) GG 326 (97.0) 216 (97.4) 0.12 1.973 (b.827-4.773) Balerance CA 0 (b.0) 0.153 7.72 0.884 1.979 (b.827-4.273) GG 326 (97.0) 7.52 0.884 1.078 (b.92-2.97) GG 326 (97.4) 261 (97.4) Balerance 1.999 (b.902-2.95) GG 326 (97.4) 7.52 0.884 <	G	1068 (98.0)	759 (97.3)		Reference
AA 0 [0.0] 0 [0.0] AG 12 [5.7] 9 (5.6) 0.811 Reference AG 12 [2.9] 9 (2.8) 0.852 0.919 (0.380-2.22) AG 12 [2.9] 9 (2.8) 0.852 0.919 (0.380-2.22) Fermale 336 (0.1 228 (0.1 Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 10 (0.0) 0 (0.0) Reference Reference AA 10 (0.0) 12 (6.3) 0.127 1.933 (0.827.4 6.92) AG 10 (0.0) 14 (8) Reference Reference AA 10 (0.0) 14 (8) Reference Reference AA 10 (0.2) 7 (5.2) 0.884 1.078 (0.392-2.971) AG 10 (1.5,0) 7 (5.2) 0.884 1.078 (0.392-2.971) AA 0 (0.0) 0 (0.0) Reference A AA 0 (0.0) 0 (0.0) Reference A AA 10 (2.6) 7 (2.6) 0.864 1.575 (0.707-3.504) AG 12 (1.7) 14 (2.7)	Male	209 (%)	162 (%)		
AG 12 (5.7) 9 (5.6) 0.811 0.896 (0.305-5.202) A 12 (2.9) 9 (2.8) 0.852 0.919 (0.380-5.225) G 406 (07.1) 315 (07.2) Reference Fmaile 336 (X) 228 (X) K AA 0 (0.0) 0 (0.0) Reference AG 10 (3.0) 12 (5.3) 0.127 1983 (0.824-4773) GG 326 (7.0) 216 (9.47) Reference A 10 (1.5) 12 (2.6) 0.120 1970 (0.827-462) GG 462 (98.5) 444 (97.4) Reference 1078 (0.392-271) AG 10 (1.5) 12 (2.6) 0.864 1090 (0.402-255) AG 10 (1.5) 72 (2.6) 0.866 1090 (0.402-255) AG 10 (2.6) 72 (2.6) 0.866 1090 (0.402-255) AG 10 (0.0) 72 (2.6) 0.866 1090 (0.402-255) AG 10 (2.6) 72 (2.6) 0.866 1090 (0.402-255) AG 10 (2.7) 12 (3.1) 14 (5.5) 0.266 1557 (0.70-3.506) AG 12 (2.7) 12 (3.4) 14 (5.5) 0.266 1557 (0.70-3.506) AG 12 (2.7) 12 (3.6) 0.260 157 (0.71-6.373	AA	0 (0.0)	0 (0.0)		
GG 172 (2-9) 153 (94.4) Reference A 12 (2-9) 9 (2.8) 0.852 0.919 (0.390-225) G 406 (97.1) 15 (97.2) Reference AA 0 (0.0) 0 (0.0) 1228 (9) Reference AG 10 (0.0) 12 (5.3) 0.127 1.933 (0.824-4.773) GG 326 (97.0) 12 (6.9.7) Reference A 10 (1.5) 12 (2.6) 0.126 1.933 (0.827-4.402) GG 662 (98.5) 444 (97.4) Reference Reference AA 0 (0.0) 0 (0.0) 0.833 1.078 (0.397-2.971) GG GG 138 (94.8) 1.27 (94.8) 0.864 1.079 (0.402-2.955) G.403 (0.97-2.971) GG GG 138 (94.8) 1.27 (97.4) 0.864 1.079 (0.402-2.955) G.404 (0.97.4) Reference AA 10 (2.6) 7 (2.6) 0.864 1.079 (0.402-2.955) G.57 (0.707-3.500) GG 12 (2.4) 14 (5.5) 0.266 1.577 (0.707-3.500) G.57 (0	AG	12 (5.7)	9 (5.6)	0.811	0.896 (0.365–2.202)
A 17 (2.9) 9 (2.8) 0.852 0.919 (0.300-2225) G 336 (2) 228 (3) AA 0 (0.0) 0 (0.0) AA 0 (0.0) 0 (0.0) GG 326 (97.0) 216 (94.7) Reference AG 0 (0.15,0) 12 (2.6) 0.127 1.933 (0.824-4.773) GG 326 (97.0) 216 (94.7) Reference AA 0 (0.15,0) 12 (2.6) 0.126 0.127 1.933 (0.824-4.773) GG 326 (97.0) 216 (94.7) Reference 7.970 (0.827-4.672) Reference AA 0 (0.0,0 0 (0.0) 0 0.00 0 0.00 AG 10 (2.6) 7 (2.6) 0.864 1.078 (0.327-2.971) AG 10 (2.6) 2.61 (9.71) 1.6	GG	197 (94.3)	153 (94.4)		Reference
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Female 336 (n) 228 (n) AA 0 (0,0) 0 (0,0) AG 10 (3,0) 12 (5.3) 0.127 1.983 (0.824-4,773) GG 326 (97,0) 216 (94,7) Reference A 10 (1.5) 12 (2.6) 0.126 1.970 (0.827-4.82) GG 662 (96.5) 444 (97.4) Reference E0AD 193 (n) 134 (n) Reference AA 0 (0,0) 0 (0,0) Reference AG 10 (2.6) 7 (5.7) 0.864 1.090 (0.420-2.95) GG 326 (P7.4) 266 (P7.4) Reference LOAD 352 (R) 256 (R) Reference AA 0 (0,0) 0 (0,0) Reference AA 0 (0,0) 0 (0,0) Reference AA 10 (2.4) 14 (8 (5) 0.266 (1.575 (0.707-3.506) GG 326 (P7.4) 46 (97.4) Reference AA 10 (0,0) 0 (0,0) Reference AA 12 (1.7) 44 (94.5)	G	406 (97.1)	315 (97.2)		Reference
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AG 10 (3.0) 12 (5.3) 0.127 1.983 (0.824-4.723) GG 326 (97.0) 12 (6 (94.7) Reference A 10 (1.5) 12 (2.6) 0.126 1.970 (0.827-4.692) G 662 (98.5) 444 (97.4) Reference CA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AG 10 (2.2) 7 (5.2) 0.884 1.078 (0.392-2.971) GG 336 (97.4) 261 (97.4) Reference CDAD 352 (8) 256 (7) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AA 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.506) AG 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.506) AA 12 (3.4) 14 (5.5) 0.268 1.575 (0.707-3.506) AA 12 (3.4) 14 (5.5) 0.268 1.575 (0.707-3.506) AA 12 (3.4) 14 (5.5) 0.268 1.575 (0.707-3.506) AA 12 (3.4) 14 (5.5) 0.288 1.575 (0.707-3.506) AA 12 (3.4) 180 (9.73) Reference <td< td=""><td>AA</td><td>0 (0.0)</td><td>0 (0.0)</td><td></td><td></td></td<>	AA	0 (0.0)	0 (0.0)		
GG 326 (97.0) 216 (94.7) Reference A 10 (1.5) 12 (2.6) 0.126 1.970 (0.827-4.92) G 660 (98.5) 444 (97.4) Reference EOAD 193 (%) 134 (%) Reference AA 0 (0.0) 0 (0.0) Reference AG 10 (5.2) 7 (5.2) 0.864 1.078 (0.392-2.971) GG 183 (94.8) 127 (94.8) Reference Reference A 10 (2.6) 7 (2.6) 0.866 1.090 (0.402-2.556) G 376 (97.4) 2.61 (97.4) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 660 769.73 105 (5.6) 0.470 Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 670 (98.3) 496 (97.3) Reference 1.575 (0.576-3.971) AFOE (4 carriers 7 (1	AG	10 (3.0)	12 (5.3)	0.127	1.983 (0.824–4.773)
A 10 (1,5) 12 (2,6) 0.126 1.970 (0.827-4.62) G 662 (98,5) 444 (97.4) Reference DAD 193 (2) 134 (2) Reference AA 0 (0.0) 0 (0.0) Reference AG 10 (5.2) 7 (5.2) 0.884 1.073 (0.32-2.575) G 376 (97.4) 256 (7 Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 12 (1.7) 14 (2.7) 0.258 1.575 (0.70-3.506) GG 340 (96.6) 242 (94.5) Reference Reference AA 12 (1.7) 14 (2.7) 0.258 1.575 (0.70-3.506) GG 340 (96.6) 242 (94.5) Reference Reference AA 12 (1.7) 14 (2.7) 0.258 1.575 (0.70-3.506) GG 375 (97.7) 10	GG	326 (97.0)	216 (94.7)		Reference
G 662 98.5 444 97.4 Reference EOAD 193 134 137 134 137 134 137 134 137 134 137 136 137 136 136 137 136 136 137 13	А	10 (1.5)	12 (2.6)	0.126	1.970 (0.827-4.692)
EOAD 193 (k) 134 (k) AA 0 (0.0) 0 (0.0) AG 0 (5.2) 7 (5.2) 0.884 1.078 (0.392-2.971) GG 183 (94.8) 127 (94.8) Reference A 10 (2.6) 7 (2.6) 0.866 1.090 (0.02-2.955) GG 376 (97.4) 26 (197.4) Reference 1.000 (0.02-2.955) AA 0 (0.0) 0 (0.0) Reference 1.000 (0.00) 1.000 (0.0) AG 12 (3.4) 1.44 (5.5) 0.266 1.575 (0.707-3.506) Reference AA 0 (0.0) 0 (0.0) Reference 1.577 (0.716-3.473) Reference APDE de carriers 191 (%) 180 (%) Reference 1.43 (0.534-3.902) APGE de carriers 7 (1.8) 100 (2.8) 0.444 1.467 (0.550-3.911) GG 375 (98.2) 350 (97.2) Reference 1.467 (0.550-3.911) AA 0 (0.0) 0 (0.0) Reference 1.467 (0.550-3.911) GG 375 (98.2) 350 (97.2) Reference <td>G</td> <td>662 (98.5)</td> <td>444 (97.4)</td> <td></td> <td>Reference</td>	G	662 (98.5)	444 (97.4)		Reference
AA 0 0 0 0 0 0 AG 10 15,2 7 15,2 0.864 1.078 (0.392-2.97) GG 18 94.8 17 15,2 0.864 1.078 (0.392-2.97) A 10 (2,6) 7 (2,6) 0.866 1.090 (0.402-2.955) Reference AA 10 (2,0) 7 (2,6) 0.866 1.090 (0.402-2.955) Reference IAA 0 (0,0) 0 (0,0) 0 (0,0) 0 (0,0) Reference Reference AA 0 (0,0) 0 (0,0) 0 (0,0) Reference Reference Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) Reference A 12 (1.7) 14 (2.7) 0.431 (0.534-3.902) Reference Reference A 0 (0.0 0 (0.0 0 (0.0 0 (0.0) 0 (0.0 Reference Refe	EOAD	193 (%)	134 (%)		
AG 10 (5.2) 7 (5.2) 0.884 1.078 (0.392-2.971) GG 183 (94.8) 127 (94.8) Reference A 10 (2.6) 7 (2.6) 0.866 1.090 (0.402-2.955) G 376 (97.4) 261 (97.4) Reference LOAD 352 (%) 256 (%) Reference A 0 (0.0) 0 (0.0) Reference AG 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.506) GG 320 (96.6) 242 (94.5) Reference Reference APOE 44 carriers 191 (%) 180 (%) Reference Reference APOE 44 carriers 191 (%) 180 (%) Reference Reference APOE 44 carriers 19 (%) 0 (0.0) 0 (0.0) Reference Reference APOE 44 carriers 19 (%) 10 (2.8) 0.444 1.467 (0.550-3.911) GG 375 (98.2) 350 (97.2) Reference RA APOE 44 noncarriers 354 (%) 210 (%) Reference APOE 44 noncarr	AA	0 (0.0)	0 (0.0)		
GG 183 94.8) 127 94.8) Reference A 10 12.6) 7 (2.6) 0.866 1.090 0.02-2.953 LOAD 352 1% 256 (%) Reference AA 0 0.00 0 0.00 Reference AA 0 0.00 0.00 Reference Reference AA 12 (1.7) 14 2.7) 0.268 1.575 0.707-3.500 GG 340 (96.6) 242 (94.5) Reference Reference A 12 (1.7) 14 2.7) 0.258 1.575 (0.707-3.500) GG 340 (96.6) 242 (94.5) Reference Reference A 12 (1.7) 14 (2.7) 0.258 1.575 (0.524-3.591) GG 71 (1.8) 10 0.43 1.647 (0.53 1.152 Reference A 1.647 1.513 1.	AG	10 (5.2)	7 (5.2)	0.884	1.078 (0.392-2.971)
A 10 [2,4] 7 [2,6] 0.866 1.090 (0.402-2.955) G 376 (97.4) 261 (97.4) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AG 12 [3,4] 14 [5,5] 0.266 1.575 (0.707-3.506) GG 340 (96.6) 242 (94.5) Reference A 12 [1,7) 14 [2,7) 0.258 1.577 (0.716-3.473) G 662 (98.3) 498 (97.3) Reference APDE #2 carriers 191 (%) 180 (%) Reference A 0 (0.0) 0 (0.0) Reference A 0 (0.0) 0 (0.0) Reference A 7 (1.8) 10 (2.8) 0.444 1.443 (0.534-3.902) GG 78 (8.2) 350 (97.2) Reference Reference A 0 (1.0) 0 (2.8) 0.444 1.447 (0.550-3.911) G 355 (82.2) 350 (97.2) 0.622 1.223 (0.549-2.725) GG <th< td=""><td>GG</td><td>183 (94.8)</td><td>127 (94.8)</td><td></td><td>Reference</td></th<>	GG	183 (94.8)	127 (94.8)		Reference
G 376 (97.4) 261 (97.4) Reference LOAD 352 (8) 256 (8)	А	10 (2.6)	7 (2.6)	0.866	1.090 (0.402-2.955)
LOAD 352 (%) 256 (%) AA 0 (0.0) 0 (0.0) AG 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.506) GG 340 (96.6) 242 (94.5) Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 692 (98.3) 498 (97.3) Reference APOE e4 carriers 191 (%) 180 (%) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AG 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.91) G 375 (98.2) 350 (97.2) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AFOE e4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference AFOE e44 concarriers 7 (%) 44 (%) Reference Reference AFOE e44 concarriers 7 (%)	G	376 (97.4)	261 (97.4)		Reference
AA 0 0 0.0 0 0.0 AG 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.50) GG 340 (96.6) 242 (94.5) Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 692 (98.3) 498 (97.3) Reference APOE 44 carriers 191 (%) 180 (%)	LOAD	352 (%)	256 (%)		
AG 12 (3.4) 14 (5.5) 0.266 1.575 (0.707-3.506) GG 340 (96.6) 242 (94.5) Reference A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 692 (98.3) 498 (97.3) Reference APOE r4 carriers 191 (%) 180 (%) AA 0 (0.0) 0 (0.0) Reference AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534-3.902) GG 184 (96.3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE r4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference Reference Reference Reference Reference Refe	AA	0 (0.0)	0 (0.0)		
GG 340 (%6.6) 242 (94.5) Reference A 1 2 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 692 (98.3) 498 (97.3) Reference APOE r4 carriers 191 (%) 180 (%) AA 0 (0.0) 0 (0.0) 0 (0.0) Reference AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534-3.902) GG 184 (%3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.54-2.697) GG 339 (95.8) 199 (94.8) Reference Reference A 0 (0.0) 1 (1.2) 0.618 1.223 (0.54-2.697) GG 349 (97.9) <td>AG</td> <td>12 (3.4)</td> <td>14 (5.5)</td> <td>0.266</td> <td>1.575 (0.707–3.506)</td>	AG	12 (3.4)	14 (5.5)	0.266	1.575 (0.707–3.506)
A 12 (1.7) 14 (2.7) 0.258 1.577 (0.716-3.473) G 692 (98.3) 498 (97.3) Reference APOE at carriers 19 (%) 180 (%) Reference AA 0 (0.0) 0 (0.0) AG 1.443 (0.534-3.902) AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534-3.902) AG 7 (1.8) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE a4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference A 0 (0.0) 0 (0.0) Reference Reference APOE a4 carriers 7 (%) 44 (%) Reference APOE a4 carriers 7 (%) 44 (%) Reference APOE a4 carriers 7 (%) 44 (%) Reference	GG	340 (96.6)	242 (94.5)		Reference
G 692 (98.3) 498 (97.3) Reference APDE & 4 carriers 191 (%) 180 (%)	А	12 (1.7)	14 (2.7)	0.258	1.577 (0.716–3.473)
APOE 64 carriers 191 (%) 180 (%) AA 0 (0.0) 0 (0.0) AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534–3.902) GG 184 (96.3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550–3.911) G 375 (98.2) 350 (97.2) Reference APOE 64 noncarriers 354 (%) 210 (%)	G	692 (98.3)	498 (97.3)		Reference
AA 0 (0.0) 0 (0.0) AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534-3.902) GG 184 (96.3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE e4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) 0.622 1.223 (0.549-2.725) GG 15 (4.2) 11 (5.2) 0.622 1.223 (0.549-2.725) GG 339 (95.8) 199 (94.8) Reference A 0 (0.0) 0 (0.0) Reference A 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 1 (2.3) 1.000 4.18127 (0.000) GG 14 (100.0) 87 (98.9) Reference Reference APOE e44 noncarriers 538 (%) 346 (%) Reference Reference APOE e44 noncarriers <td< td=""><td>APOE £4 carriers</td><td>191 (%)</td><td>180 (%)</td><td></td><td></td></td<>	APOE £4 carriers	191 (%)	180 (%)		
AG 7 (3.7) 10 (5.6) 0.470 1.443 (0.534-3.902) GG 184 (96.3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE e4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) Reference AG 15 (4.2) 11 (5.2) 0.622 1.223 (0.549-2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.54-2.697) G 693 (97.9) 409 (97.4) Reference Reference APOE e44 carriers 7 (%) 44 (%) Reference Reference AG 0 (0.0) 1 (1.1) 1.000 4.181E7 (0.000) G GG 14 (100.0) 87 (98.9) Reference Reference APOE e44 noncarriers 538 (%) 346 (%) Reference Reference APOE e44 noncarriers	AA	0 (0.0)	0 (0.0)		
GG 184 (96.3) 170 (94.4) Reference A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE # noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) 0.622 1.223 (0.549-2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554-2.697) G 693 (97.9) 409 (97.4) Reference APOE #4 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) GG 14 (100.0) 87 (98.9) Reference APOE #44 noncarriers 538 (%) 346 (%) Reference AA 0 (AG	7 (3.7)	10 (5.6)	0.470	1.443 (0.534–3.902)
A 7 (1.8) 10 (2.8) 0.444 1.467 (0.550-3.911) G 375 (98.2) 350 (97.2) Reference APOE e4 noncarriers 354 (%) 210 (%) Reference AA 0 (0.0) 0 (0.0) 0.622 1.223 (0.549-2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554-2.697) G 693 (97.9) 409 (97.4) Reference APOE e44 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) Reference AG 0 (0.0) 1 (2.3) 1.000 4.18127 (0.000) GG 7 (%) 44 (%) Reference Reference AA 0 (0.0) 1 (1.1) 1.000 6.241127 (0.000) GG 14 (100.0) 87 (98.9) Reference APOE e44 noncarriers 538 (%) 346 (%) AA 0 (0.0) Reference APOE e44 noncarriers 516 (95.9) 326 (94.2) Reference	GG	184 (96.3)	170 (94.4)		Reference
G 375 (98.2) 350 (97.2) Reference APOE e4 noncarriers 354 (%) 210 (%)	А	7 (1.8)	10 (2.8)	0.444	1.467 (0.550–3.911)
APOE &4 noncarriers 354 % 210 % AA 0 (0.0) 0 (0.0) AG 15 (4.2) 11 (5.2) 0.622 1.223 (0.549-2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554-2.697) G 693 (97.9) 409 (97.4) Reference APOE &44 carriers 7 (%) 44 (%) A APOE 0 (0.0) 0 (0.0) 0 (0.0) AReference AA 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) AG 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) AG 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE x44 noncarriers 538 (%) 346 (%) 346 (%) AA 0 (0.0) 0 (0.0) Reference APOE x44 noncarriers 538 (%) 346 (%) Reference AA 0 (0.0) 0 (0.0) Reference A	G	375 (98.2)	350 (97.2)		Reference
AA 0 (0,0) 0 (0,0) AG 15 (4.2) 11 (5.2) 0.622 1.223 (0.549–2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554–2.697) G 693 (97.9) 409 (97.4) Reference APOE £44 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) 0 (0.0) AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) AG 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) AG 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AA 0 (0.0) 0 (0.0) AG 0 (0.0) 0 (0.0) 0 (0.0) Reference Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AE Reference Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AE Reference Reference Reference Reference	APOE £4 noncarriers	354 (%)	210 (%)		
AG 15 (4.2) 11 (5.2) 0.622 1.223 (0.549–2.725) GG 339 (95.8) 199 (94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554–2.697) G 693 (97.9) 409 (97.4) Reference APOE ±44 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) Reference AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) GG 14 (100.0) 87 (98.9) Reference Reference APOE ±44 noncarriers 538 (%) 346 (%) Reference Reference AG 0 (0.0) 0 (0.0) Reference Reference Reference AG 2 (2.1) 20 (5.8) 0.310 1.381 (0.740–2.578) Reference GG 516 (95.9) 326 (94.2) Reference Reference A 2 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558)	AA	0 (0.0)	0 (0.0)		
GG 339 95.8) 199 94.8) Reference A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554–2.697) G 693 (97.9) 409 (97.4) Reference APOE ɛ44 carriers 7 % 44 % Reference AA 0 (0.0) 0 (0.0) Reference Reference AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.00) GG 7 (100.0) 43 (97.7) Reference Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) GG 14 (100.0) 87 (98.9) Reference Reference APOE ɛ44 noncarriers 538 % 346 % Reference Reference<	AG	15 (4.2)	11 (5.2)	0.622	1.223 (0.549–2.725)
A 15 (2.1) 11 (2.6) 0.618 1.223 (0.554–2.697) G 693 (97.9) 409 (97.4) Reference APOE ±44 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) 0 (0.0) Reference AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ±44 noncarriers 538 (%) 346 (%) Reference AQ 0 (0.0) 0 (0.0) 0 (0.0) Reference AA 0 (0.0) 0 (0.0) Reference Reference APOE ±44 noncarriers 538 (%) 346 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference APOE ±44 noncarriers 516 (95.9) 326 (94.2) Reference Reference APOE ±2 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) Reference APOE ±2 carriers 10 (0.0) 0 (GG	339 (95.8)	199 (94.8)		Reference
G 693 (97.9) 409 (97.4) Reference APOE ɛ44 carriers 7 (%) 44 (%) Reference AA 0 (0.0) 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG GG 7 (100.0) 43 (97.7) Reference Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference AA 0 (0.0) 0 (0.0) Reference Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) A	А	15 (2.1)	11 (2.6)	0.618	1.223 (0.554–2.697)
APOE ɛ44 carriers 7 (%) 44 (%) AA 0 (0.0) 0 (0.0) AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AA AA 0 (0.0) 0 (0.0) 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA	G	693 (97.9)	409 (97.4)		Reference
AA 0 (0.0) 0 (0.0) AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AA 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740-2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747-2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA AQ 0 (0.0) 0 (0.0) 0 (0.0)	APOE ε 44 carriers	7 (%)	44 (%)		
AG 0 (0.0) 1 (2.3) 1.000 4.181E7 (0.000) GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%)	AA	0 (0.0)	0 (0.0)		
GG 7 (100.0) 43 (97.7) Reference A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AA 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747-2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA AO (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	AG	0 (0.0)	1 (2.3)	1.000	4.181E7 (0.000)
A 0 (0.0) 1 (1.1) 1.000 6.241E7 (0.000) G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) Reference AA 0 (0.0) 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) A AA 0 (0.0) 0 (0.0) 0 (0.0)	GG	7 (100.0)	43 (97.7)		Reference
G 14 (100.0) 87 (98.9) Reference APOE ɛ44 noncarriers 538 (%) 346 (%) AA 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) A	А	0 (0.0)	1 (1.1)	1.000	6.241E7 (0.000)
APOE ɛ44 noncarriers 538 % 346 % AA 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	G	14 (100.0)	87 (98.9)		Reference
AA 0 (0.0) 0 (0.0) AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) 31 (%)	APOE ε 44 noncarriers	538 (%)	346 (%)		
AG 22 (4.1) 20 (5.8) 0.310 1.381 (0.740–2.578) GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	AA	0 (0.0)	0 (0.0)		
GG 516 (95.9) 326 (94.2) Reference A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	AG	22 (4.1)	20 (5.8)	0.310	1.381 (0.740–2.578)
A 22 (2.0) 20 (2.9) 0.302 1.383 (0.747–2.558) G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	GG	516 (95.9)	326 (94.2)		Reference
G 1054 (98.0) 672 (97.1) Reference APOE ɛ2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	А	22 (2.0)	20 (2.9)	0.302	1.383 (0.747-2.558)
APOE ε2 carriers 121 (%) 31 (%) AA 0 (0.0) 0 (0.0)	G	1054 (98.0)	672 (97.1)		Reference
AA 0 (0.0) 0 (0.0)	APOE £2 carriers	121 (%)	31 (%)		
	AA	0 (0.0)	0 (0.0)		

Table 4 (Continued)

G2385R	Control	AD	Р	OR (95% CI)
AG	3 (2.5)	3 (9.7)	0.323	2.431 (0.418–14.131)
GG	118 (97.5)	28 (90.3)		Reference
A	3 (1.2)	3 (4.8)	0.325	2.350 (0.428–12.898)
G	239 (98.8)	59 (95.2)		Reference
APOE £2 noncarriers	424 (%)	359 (%)		
AA	0 (0.0)	0 (0.0)		
AG	19 (4.5)	18 (5.0)	0.789	1.096 (0.565–2.122)
GG	405 (95.5)	341 (95.0)		Reference
A	19 (2.2)	18 (2.5)	0.759	1.108 (0.576–2.129)
G	829 (97.8)	700 (97.5)		Reference
APOE ɛ22 carriers	17 (%)	3 (%)		
AA	0 (0.0)	0 (0.0)		
AG	0 (0.0)	1 (33.3)	0.999	2.531E18 (0.000)
GG	17 (100.0)	2 (66.7)		Reference
A	0 (0.0)	1 (16.7)	1.000	7.685E9 (0.000)
G	34 (100.0)	5 (83.3)		Reference
APOE ε 22 noncarriers	528 (%)	387 (%)		
AA	0 (0.0)	0 (0.0)		
AG	22 (4.2)	20 (5.2)	0.554	1.207 (0.648–2.249)
GG	506 (95.8)	367 (94.8)		Reference
А	22 (2.1)	20 (2.6)	0.531	1.217 (0.658–2.249)
G	1034 (97.9)	754 (97.4)		Reference

AD, Alzheimer's disease; APOE, apolipoprotein E; EOAD, early-onset AD.

and *LRRK2* in the pathogenesis of neurodegenerative disease. This observation will no doubt provide a new research focus for studying the biological function of *LRRK2*.

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The authors declare no conflict of interest.

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