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Associations between *APOE* polymorphisms and seven diseases with cognitive impairment including Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies in southeast China

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Objective **To explore the effect of *APOE* polymorphisms on patients with cognitive impairments in The Chinese Han population.**

Materials and methods **A total of 1027 cases with Alzheimer's disease (AD), 40 cases with vascular dementia (VaD), 28 cases with behavioral variant frontotemporal dementia (bvFTD), 54 cases with semantic dementia (SD), 44 cases with dementia with Lewy bodies (DLB), 583 cases with mild cognitive impairment (MCI), and 32 cases with vascular cognitive impairment no dementia (VCIND) were recruited consecutively from memory disorders clinics in Huashan Hospital between January 2010 and December 2014. The 1149 cognitively normal controls were recruited from the community epidemiologic investigations. The *APOE* genotypes were determined using the TaqMan assay.**

Results **The distribution of genotype and allele frequencies of *APOE* differed significantly between control and AD or MCI, with *ε4* increasing the risk of AD and MCI in a dose-dependent pattern and *ε2* decreasing the risk of AD, but not the risk of MCI. As for VaD, significant differences in the *APOE* genotype distribution were found compared with the controls. E4/4 increased the risk of VaD and *ε4* increased the risk of VCIND in women. The allele distribution differed between bvFTD and controls, but genotype and allele frequencies of *APOE* did not affect the risk of bvFTD, SD, and DLB.**

Conclusion **In The Chinese Han population, *APOE ε4* increased the risk of AD and MCI in a dose-dependent manner and *ε2* decreased the risk of AD as reported previously. *APOE ε4* might increase risk in VaD and female patients with VCIND, but no effects of *APOE* on bvFTD, DLB, and SD were found. *Psychiatr Genet* 26:124–131**

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Introduction

Dementia is an acquired cognitive impairment syndrome with slow progression. Usually, it starts in mid-adulthood or later and is characterized by dysfunctions and decreases in memory, visual spatial ability, orientation, and calculation as well as alterations in personality, emotion, and behavior. According to the pathogenesis, dementia can be divided into those that are non-degenerative, such as vascular dementia (VaD), and those that are degenerative such as Alzheimer's disease (AD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB). On the basis of an epidemic investigation, in individuals aged older than 65 years, 5.14% had dementia, among whom 62% had AD and 29% had VaD (Jia *et al.*, 2014). The prevalence of other dementias was low, with 0.36% in DLB and 15–22/10000 in FTD (Onyike and Diehl-Schmid, 2013; Vann Jones and O'Brien, 2014).

The pathogenesis of dementia is obscure and it is considered a complicated disease. The genetic aspects have been indicated to play an important role in the development of these diseases (Farlow and Foroud, 2013; Bruni *et al.*, 2014; Loy *et al.*, 2014; Ferencz and Gerritsen, 2015). In many genetic loci related to sporadic dementia, *APOE* is the only one that has been confirmed to be associated with the risk of AD. *APOE*, located in 19q13.2, has three common isoforms termed *ε2*, *ε3*, and *ε4*, which derive six genotypes. Its encoding protein, Apolipoprotein E, consists of 299 amino acids and is a cholesterol carrier involving in lipid transportation and injury repair in the brain. *APOE ε4* increased the risk of AD in a dose-dependent manner, in contrast to *APOE ε2*,

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which plays a protective role (Bertram *et al.*, 2007; Sando *et al.*, 2008; Bonner-Jackson *et al.*, 2012; Wu *et al.*, 2015).

As its genetic effect was so evident in AD, the *APOE* polymorphisms have deservedly been studied in other dementias, such as VaD, FTD, and DLB, but the results have been controversial (Fei and Jianhua, 2013; Berge *et al.*, 2014; Rohn, 2014). A number of studies reported an increased *APOE ε4* frequency in VaD, similar to that found in AD (Treves *et al.*, 1996; Souza *et al.*, 2003), whereas some other findings did not replicate this association (Frank *et al.*, 2002; Huang *et al.*, 2002; Orsitto *et al.*, 2007; Kim *et al.*, 2008). As for FTD, the effect of the *APOE* polymorphisms on the development of the disease was still controversial (Verpillat *et al.*, 2002; Bernardi *et al.*, 2006), so was in DLB (Lovati *et al.*, 2010; Kobayashi *et al.*, 2011; Boot *et al.*, 2013; Berge *et al.*, 2014; Bras *et al.*, 2014). Most of the studies were carried out in White populations and rarely in the Chinese Han population, mostly in VaD (Huang *et al.*, 2002; Liu *et al.*, 2012). Ji *et al.* (2013) found that the *APOE ε4* prevalence of AD and FTD was similar in the Chinese Han population and suggested that the *APOE ε4* allele is a risk factor for both disorders. The effect of *APOE* polymorphisms on DLB and semantic dementia (SD), the subtype of FTD [the other two subtypes were behavioral variant frontotemporal dementia (bvFTD), and progressive nonfluent aphasia (PNFA)] (Neary *et al.*, 1998) has not been investigated in the Chinese Han population as yet.

Here, we carried out a case–control study of five dementias, AD, bvFTD, VaD, SD, and DLB, and two cognitive impairments, mild cognitive impairment (MCI) and vascular cognitive impairment no dementia (VCIND), in Southeast Chinese Han patients to explore whether *APOE* polymorphisms would affect the risks of these conditions. This is the first report of the relationship of *APOE* polymorphisms with the risk of SD/DLB in the Chinese Han population.

Materials and methods

Participants

Two thousand and forty-four patients with cognitive impairment were recruited consecutively from memory disorders clinics in Huashan Hospital between January 2010 and December 2014. Among these, 1027 patients with AD, 40 patients with VaD, 28 patients with bvFTD, 54 patients with SD, 44 patients with DLB, 583 patients with MCI, and 32 patients with VCIND were included in the study. Another 55 patients whose dementia was secondary to an explicit diagnosis of general paresis of insane, Parkinson's disease with dementia, corticobasal degeneration, sequela of brain injury, and PNFA were excluded because of clear causes or small case numbers. The rest of the 159 patients were excluded because of the presence of unspecified dementia. The 1149 cognitively normal controls were recruited from community epidemiologic investigations (Ding *et al.*, 2015).

Table 1 Characteristics of the participants in the patient and control groups

	AD	MCI	VaD	VCIND	bvFTD	SD	DLB	Control
Number	1027	583	40	32	28	54	44	1149
Age at onset (mean ± SD) (range) (years)	68.1 ± 9.54 (37–89)**	67.8 ± 9.04 (25–90)**	67.9 ± 9.11 (38–83)	64.8 ± 7.21 (48–80)**	59.8 ± 12.0 (35–85)**	59.0 ± 8.10 (35–78)**	66.6 ± 9.84 (42–83)	69.4 ± 7.36 (53–93)
Sex (male/female)	452/575	259/324	26/14*	20/12	9/19	26/28	31/13**	530/619
Education level (years)	8.80 ± 4.83**	11.5 ± 3.59	8.72 ± 4.51**	11.0 ± 4.04	9.89 ± 3.97*	8.74 ± 5.03**	9.40 ± 4.35**	11.8 ± 3.89
MMSE score	14.4 ± 6.19**	26.3 ± 2.25**	16.9 ± 5.56**	25.8 ± 2.10**	16.1 ± 8.10**	14.6 ± 8.44**	17.8 ± 8.04**	28.5 ± 2.17

AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.
*$P < 0.05$, **$P < 0.01$. *P* value was derived from the comparison of each patient group and control.

The diagnosis of AD was made according to the diagnostic guidelines for AD of the National Institute of Aging and Alzheimer's Association (Jack *et al.*, 2011). VaD was diagnosed according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et 1'Enseignement en Neurosciences (NINDS-AIREN) (Udaka, 2011). FTLD was diagnosed on the basis of the report of the Work Group on Frontotemporal Dementia and Pick's Disease (McKhann *et al.*, 2001). DLB was diagnosed according to the DLB Consortium criteria (McKeith *et al.*, 2005). MCI was diagnosed according to the criteria established by the International Psychogeriatric Association Expert Conference on MCI (Gauthier *et al.*, 2006). VCIND was diagnosed according to the Vascular Cognitive Impairment Harmonization Standards of the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network (NINDS-CSN) (Hachinski *et al.*, 2006). The enrollment procedures were as reported previously (Guo *et al.*, 2012; Sun *et al.*, 2012). Written consents were obtained from the participants or their legally authorized caregivers. This study was approved by the ethics committee of Huashan Hospital.

Genotyping of APOE

Genomic DNA was extracted from peripheral blood using a Blood Genomic DNA Extraction Kit (Tiangen, Shanghai, China). The *APOE* genotypes were determined using the TaqMan assay according to the method described previously (Koch *et al.*, 2002).

Statistical analysis

Statistical analyses were carried out using SPSS, version 19.0 (SPSS Inc., Chicago, Illinois, USA). Hardy–Weinberg equilibrium tests of *APOE* polymorphisms within the groups were performed using χ^2 analysis. The χ^2-test or the Student *t*-test was used to test for the differences between the patients of each group and control participants in the distribution of sex, age at onset (AAO), education level, and mini-mental state examination scores. The χ^2-test was used to compare the genotypes and allele frequencies between patients groups and control participants. Odds ratio (OR) and the 95% confidence interval (CI) for testing possible associations between patients groups and control group were determined by binary logistic regression analyses; AAO and sex were used as covariates. The potential effects of each genotype on AAO in patients of each group were calculated by one-way analysis of variance and further analysis by post-hoc least significant difference. *P* less than 0.05 was considered significant.

Results

General information

General information of the participants is shown in Table 1. The age of the control participants was

Table 2 Distribution of allele frequencies and genotypes of *APOE* in patients and controls

	APOE genotype [*n* (%)]						*APOE* allele frequency [*n* (%)]			
Group	*ε2/2*	*ε2/3*	*ε2/4*	*ε3/3*	*ε3/4*	*ε4/4*	*ε2*	*ε3*	*ε4*	*ε2+*	*ε4+*
AD ($n=1027$)	2 (0.2)	64 (6.2)	24 (2.3)	527 (51.3)	324 (31.6)	85 (8.3)	92 (4.5)	1443 (70.3)	519 (25.2)	90 (8.8)	433 (42.3)
χ^2 (*P*)			214.1 (2.67×10^{-44})**					237.0 (3.36×10^{-52})**		25.4 (4.74×10^{-7})**	181.1 (2.76×10^{-41})**
MCI ($n=583$)	2 (0.3)	56 (9.6)	16 (2.7)	353 (60.5)	129 (22.1)	27 (4.6)	76 (6.5)	891 (76.4)	199 (17.1)	74 (12.6)	172 (29.5)
χ^2 (*P*)			58.7 (2.22×10^{-11})**					59.1 (1.47×10^{-13})**		3.2 (0.074)	42.5 (7.25×10^{-11})**
VaD ($n=40$)	0 (0)	8 (20.0)	0 (0)	22 (55.0)	6 (15.0)	4 (10.0)	8 (10.0)	58 (72.5)	14 (17.5)	8 (20.0)	10 (25.0)
χ^2 (*P*)			36.7 (6.96×10^{-7})**					8.71 (0.130)		0.48 (0.490)	2.23 (0.135)
VCIND ($n=32$)	0 (0)	4 (12.5)	1 (3.13)	19 (59.4)	8 (25.0)	0 (0)	5 (7.81)	50 (78.1)	9 (14.1)	5 (15.6)	9 (28.1)
χ^2 (*P*)				4.16 (0.527)				2.55 (0.279)		0.002 (0.963)	3.28 (0.70)
bvFTD ($n=28$)	0 (0)	1 (3.6)	0 (0)	19 (67.9)	7 (25.0)	1 (3.6)	1 (1.79)	46 (82.1)	9 (16.1)	1 (3.6)	8 (28.6)
χ^2 (*P*)				8.26 (0.143)				6.61 (0.037)*		3.16 (0.075)	3.10 (0.078)
SD ($n=54$)	1 (1.9)	6 (11.1)	2 (3.7)	36 (66.7)	8 (14.8)	1 (1.9)	10 (9.3)	86 (79.6)	12 (11.1)	9 (16.7)	11 (20.4)
χ^2 (*P*)				3.13 (0.681)				1.17 (0.558)		0.02 (1.000)	0.69 (0.406)
DLB ($n=44$)	0 (0)	3 (6.8)	0 (0)	31 (70.5)	9 (20.5)	1 (2.3)	3 (3.4)	74 (84.1)	11 (12.5)	3 (6.8)	10 (22.7)
χ^2 (*P*)				5.35 (0.374)				4.18 (0.124)		2.67 (0.102)	1.36 (2.43)
Control ($n=1149$)	8 (0.7)	154 (13.4)	21 (1.8)	802 (69.8)	156 (13.6)	8 (0.7)	191 (8.3)	1914 (83.3)	193 (8.4)	183 (15.9)	185 (16.1)

AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.
*$P<0.05$, **$P<0.01$. *P* value was derived from the comparison of each patient group and control.

significantly higher than that of the patients with AAO of AD, MCI, VCIND, bvFTD, and SD. The sex distribution of VaD and DLB was different from that of the controls. The mini-mental state examination score was significantly lower in the patient groups. The distributions of the six common genotypes of *APOE* were under Hardy–Weinberg equilibrium in all patients and control participants (Supplementary Table, Supplemental digital content 1, *http://links.lww.com/PG/A152*).

The *E2* allele reduced the risk and the *ε4* allele increased the risk in a dose-dependent manner in AD and MCI

The distribution of genotype and allele frequencies of *APOE* was compared between each patient and control. The distribution of genotype and allele frequencies of *APOE* differed significantly between control and AD or MCI. There were more *ε4*-carrying patients (*ε2ε4*, *ε3ε4*, *ε4ε4*) in the AD and MCI groups than in the control group (Table 2). Among AD and MCI patients, *ε4* increased AD the risk in a dose-dependent manner. The *E2* allele decreased the risk in AD, but not in MCI. These significances remained after the patients were further stratified by sex (Table 3). We also investigated the effect of *ε2* and *ε4* alleles on the risk of AD and MCI in different ranges of AAO and found that *ε2* played a protective role against AD in patients with AAO of 56–65 and above 76, while MCI with AAO 76–80 (Table 4). The *E4* allele increased the risk of AD in patients with AAO above 56, with the highest OR of 4.894 in 76–80. As for MCI, *ε4* increased the risk in patients with AAO 56–80.

E4/4 increased the risk of VaD and *ε4* increased the risk of VCIND in women

The *APOE ε4/4* genotype increased the risk of VaD, whereas the *ε3/4* genotype, the *ε4* allele, or the *ε2* allele statistically didn't increase the risk. (Table 5). When further stratified by sex, *ε4* was found to increase the risk of VCIND in female patients (Table 3), but neither *ε2* (+) nor *ε4* (+) status affected the risk of VaD and VCIND after stratification by AAO (Table 4). We investigated the AAO of VaD and VCIND according to the dosage of *ε2* and *ε4*, but we found no effect of the allele on AAO (Table 6).

Genotype and allele frequencies of APOE did not affect the risk of bvFTD, SD, and DLB

Only the allele distribution was found to be different between bvFTD patients and controls, with more *ε4* and less *ε2* in bvFTD (Table 2). However, when it was further analyzed by logistic regression, the relationships did not exist (Table 5). The negative results remained after stratification by sex and AAO (Tables 3 and 4).

Moreover, we investigated the AAO according to the dosage of *ε2* and *ε4* in bvFTD, SD, and DLB and found no effect of *ε2* or the *ε4* allele on AAO (Table 6).

Discussion

The results of the relationship between *APOE* and the risk of AD in the current research were identical to those reported in many previous investigations, with *ε4* increasing the risk of AD, lowering the AAO, and *ε2* exerting a 'protective' effect against the risk of AD (Chartier-Harlin *et al.*, 1994; Pastor *et al.*, 2003).

Table 3 Effect of *APOE ε2* and *ε4* haplotype on the risk of AD, MCI, VaD, VCIND, FTD, DLB, and SD stratified by sex

	ε2 +		*ε4* +	
	P	OR (95% CI)	*P*	OR (95% CI)
AD				
Male	1.07×10^{-4}**	0.443 (0.293–0.668)	5.84×10^{-15}**	3.486 (2.548–4.769)
Female	7.91×10^{-4}**	0.507 (0.341–0.754)	2.14×10^{-22}**	4.231 (3.165–5.657)
MCI				
Male	0.092	0.691 (0.449–1.062)	6.80×10^{-4}**	1.870 (1.303–2.683)
Female	0.386	0.838 (0.561–1.250)	8.54×10^{-9}**	2.579 (1.868–3.560)
VaD				
Male	0.671	0.784 (0.254–2.415)	0.489	1.445 (0.509–4.102)
Female	0.324	1.954 (0.516–7.403)	0.086	2.773 (0.867–8.872)
VCIND				
Male	0.200	0.265 (0.035–2.022)	0.650	1.304 (0.414–4.105)
Female	0.367	1.928 (0.464–8.016)	0.013*	5.066 (1.399–18.347)
bvFTD				
Male	0.996	0.000 (0)	0.298	2.471 (0.449–13.598)
Female	0.251	0.301 (0.039–2.345)	0.257	1.904 (0.625–5.802)
DLB				
Male	0.139	0.331 (0.076–1.434)	0.688	1.214 (0.471–3.127)
Female	0.388	0.396 (0.048–3.247)	0.225	2.172 (0.620–7.605)
SD				
Male	0.616	0.698 (0.172–2.842)	0.725	1.249 (0.363–4.302)
Female	0.488	0.614 (0.154–2.438)	0.457	1.509 (0.510–4.466)

AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; OR, odds ratio; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.
*$P<0.05$, **$P<0.01$. *P* value derived from the comparison of each patient group and control.

Table 4 Effect of *APOE ε2* and *ε4* haplotype on the risk of AD, MCI, VaD, VCIND, FTD, DLB, and SD stratified by age at onset

	AAO	AD	*P* value	OR (95% CI)	MCI	*P* value	OR (95% CI)	Control
ε2+	≤55	9 (10.0)	0.069	0.062 (0.003–1.243)	8 (10.8)	0.357	0.197 (0.006–6.242)	1
	56–60	13 (14.4)	0.047*	0.420 (0.179–0.989)	9 (12.1)	0.749	0.862 (0.347–2.141)	15
	61–65	14 (15.6)	0.009**	0.379 (0.183–0.788)	17 (23.0)	0.875	1.050 (0.570–1.936)	64
	66–70	13 (14.4)	0.380	0.697 (0.311–1.561)	17 (23.0)	0.518	1.256 (0.630–2506)	22
	71–75	16 (17.8)	0.058	0.538 (0.284–1.021)	14 (18.9)	0.119	0.588 (0.301–1.147)	36
	76–80	16 (17.8)	0.011*	0.413 (0.209–0.818)	4 (5.4)	0.025*	0.284 (0.094–0.854)	28
	>80	9 (10.0)	0.098	0.477 (0.198–1.147)	5 (6.8)	0.639	0.767 (0.253–2.326)	17
ε4+	≤55	27 (6.2)	0.998		8 (4.7)	0.999		0
	56–60	50 (11.5)	8.15×10^{-4}**	3.656 (1.712–7.810)	15 (8.8)	0.058	2.342 (0.971–5.648)	11
	61–65	77 (17.7)	3.01×10^{-8}**	4.004 (2.451–6.540)	34 (19.9)	1.91×10^{-4}**	2.705 (1.605–4.572)	62
	66–70	72 (16.6)	4.76×10^{-8}**	4.661 (2.682–8.099)	40 (23.4)	8.45×10^{-4}**	2.551 (1.472–4.422)	29
	71–75	81 (18.7)	9.72×10^{-9}**	3.955 (2.472–6.327)	41 (24.0)	0.003**	2.207 (1.315–3.704)	38
	76–80	88 (20.3)	1.06×10^{-9}**	4.894 (2.938–8.152)	24 (14.0)	6.69×10^{-4}**	3.207 (1.639–6.275)	27
	>80	39 (9.0)	8.49×10^{-4}**	3.098 (1.594–6.018)	9 (5.3)	0.525	1.352 (0.534–3.425)	18
		VaD			VCIND			
ε2+	≤65	4 (50.0)	0.354	2.112 (0.435–10.267)	3 (60.0)	0.851	0.870 (0.203–3.732)	80
	>65	4 (50.0)	0.945	0.962 (0.318–2.908)	2 (40.0)	0.412	0.422 (0.054–3.315)	103
ε4+	≤65	2 (20.0)	0.637	1.613 (0.221–11.777)	6 (66.7)	0.081	2.887 (0.877–9.497)	73
	>65	8 (80.0)	0.122	1.978 (0.833–4.697)	3 (33.3)	0.704	1.290 (0.348–4.784)	112
		bvFTD			DLB			
ε2+	≤65	0 (0.0)	0.996	0.000 (0)	2 (66.7)	0.614	0.630 (0.104–3.804)	80
	>65	1 (100.0)	0.987	1.018 (0.120–8.661)	1 (33.3)	0.120	0.201 (0.027–1.519)	103
ε4+	≤65	5 (62.5)	0.358	1.901 (0.483–7.486)	6 (60.0)	0.224	2.507 (0.569–11.044)	73
	>65	3 (37.5)	0.082	3.851 (0.844–17.568)	4 (40.0)	0.883	0.921 (0.306–2.767)	112
		SD						
ε2+	≤65	7 (77.8)	0.205	0.397 (0.095–1.656)				83
	>65	2 (22.2)	0.590	1.563 (0.307–7.947)				103
ε4+	≤65	9 (81.8)	0.337	1.637 (0.598–4.479)				73
	>65	2 (18.2)	0.864	1.150 (0.232–5.701)				112

AAO, age at onset; AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; OR, odds ratio; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.
*$P<0.05$, **$P<0.01$. *P* value derived from the comparison of each patient group and control.

Table 5 Logistic regression of *APOE* genotypes and allele frequencies in patients and controls

	ε2/2	*ε2/3*	*ε2/4*	*ε3/3*	*ε3/4*	*ε4/4*	*ε2+*	*ε4+*
AD								
P	0.169	0.006**	0.286	1.ref	1.14×10^{-22}**	6.74×10^{-14}**	3.67×10^{-7}**	1.26×10^{-35}**
OR	0.330	0.627	1.417		3.326	17.594	0.477	3.866
95% CI	0.068–1.599	0.451–0.872	0.747–2.688		2.552–4.077	8.310–37.250	0.359–0.635	3.125–4.782
MCI								
P	0.432	0.288	0.119	1.ref	1.53×10^{-6}**	4.90×10^{-7}**	0.074	5.86×10^{-11}**
OR	0.534	0.835	1.700		1.927	7.842	0.766	2.227
95% CI	0.112–2.551	0.599–1.164	0.872–3.311		1.475–2.518	3.515–17.496	0.572–1.026	1.753–2.831
VaD								
P	0.999	0.306	0.998	1.ref	0.557	7.96×10^{-7}**	0.868	0.134
OR	0.000	1.601	0.000		1.329	32.492	1.076	1.789
95% CI	0	0.650–3.940	0		0.514–3.440	8.157–129.425	0.457–2.531	0.836–3.832
VCIND								
P	0.999	0.822	0.453	1.ref	0.061	0.999	0.683	0.049*
OR	0.000	0.867	2.235		2.311	0.000	0.799	2.277
95% CI	0	0.248–3.024	0.274–18.237		0.961–5.555	0	0.272–2.346	1.004–5.163
bvFTD								
P	0.999	0.264	0.998	1.ref	0.215	0.134	0.141	0.131
OR	0.000	0.313	0.000		1.872	5.574	0.219	2.036
95% CI	0	0.041–2.407	0		0.695–5.042	0.589–52.265	0.029–1.653	0.808–5.130
SD								
P	0.492	0.110	0.313	1.ref	0.918	0.937	0.391	0.461
OR	2.243	0.326	2.296		1.051	1.128	0.649	1.359
95% CI	0.224–22.458	0.082–1.289	0.456–11.544		0.409–2.698	0.056–22.632	0.241–1.743	0.602–3.071
DLB								
P	0.999	0.269	0.998	1.ref	0.417	0.114	0.112	0.310
OR	0.000	0.504	0.000		1.391	5.736	0.379	1.475
95% CI	0	0.149–1.699	0		0.628–3.082	0.656–50.160	0.115–1.254	0.697–3.124

AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; OR, odds ratio; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.
*$P<0.05$, **$P<0.01$. *P* value was derived from the comparison of each patient group and control.

Table 6 The *APOE ε2* and *ε4* allele dosage effect on age at onset in patients with cognitive impairment

	ε2 (−)		*ε2* (+)		No *ε2*		One *ε2*		Two *ε2*	
VaD, AAO, *n*	68.7 ± 9.45	32	64.4 ± 7.05	8	68.7 ± 9.45	32	64.4 ± 7.05	8	0	0
VCIND, AAO, *n*	65.3 ± 6.43	27	61.8 ± 11.03	5	65.3 ± 6.43	27	61.8 ± 11.03	5	0	0
bvFTD, AAO, *n*	59.2 ± 11.77	27	76.0	1	59.2 ± 11.77	27	76.0	1	0	0
SD, AAO, *n*	59.6 ± 7.36	45	56.0 ± 11.15	9	59.6 ± 7.36	45	55.6 ± 11.86	37	56.0	1
DLB, AAO, *n*	66.6 ± 9.85	41	66.0 ± 9.64	3	66.6 ± 9.85	41	66.0 ± 9.64	3	0	0
	ε4 (−)		*ε4* (+)		No *ε4*		One *ε4*		Two *ε4*	
VaD, AAO, *n*	66.4 ± 9.03	30	72.3 ± 8.22	10	66.4 ± 9.03	30	75.3 ± 9.22	6	67.8 ± 3.86	4
VCIND, AAO, *n*	65.9 ± 7.02	23	61.9 ± 7.29	9	65.9 ± 7.02	23	61.9 ± 7.29	9	0	0
bvFTD, AAO, *n*	59.9 ± 12.8	20	59.8 ± 10.58	8	59.9 ± 12.8	20	58.9 ± 11.10	7	66.0	1
SD, AAO, *n*	58.7 ± 7.98	43	59.9 ± 8.88	11	58.7 ± 7.98	43	60.9 ± 8.70	10	50.0	1
DLB, AAO, *n*	67.8 ± 8.83	34	62.3 ± 11.81	10	67.8 ± 8.83	34	61.7 ± 12.35	9	68.0	1

AAO, age at onset; bvFTD, behavioral variant frontotemporal dementia; DLB, dementia with Lewy bodies; SD, semantic dementia; VaD, vascular dementia; VCIND, vascular cognitive impairment no dementia.

We found that *ε4* increased the risk of MCI in a dose-dependent manner, which was also in accordance with previous reports in both White and Chinese populations (Borenstein *et al.*, 2010; Boyle *et al.*, 2010; Albert *et al.*, 2014; Wang *et al.*, 2014). In contrast, the *APOE ε2* allele appeared to confer cognitive benefits in the White population (Blacker *et al.*, 2007; Bonner-Jackson *et al.*, 2012). Whether *ε2* could decrease the risk of MCI in the Chinese Han population still remains controversial, perhaps because of its considerably lower frequency compared with *ε4*. Borenstein and colleagues investigated 34 MCI patients and 32 controls among Shanghai urban residents, but did not find the 'protective' effect of *ε2*. The population in their study was quite similar to ours, as were the results (Borenstein *et al.*, 2010). Wang *et al.* (2014) tested *APOE* polymorphisms in a Han population and different ethnic minority groups in North China and found the *ε2* allele protective for MCI only in the Han population (OR = 0.48, 95% CI: 0.24–0.96). These differences might be explained by the regional and ethnic diversity.

The protective and risk effects of *APOE* on AD and MCI were found different among varied age ranges and sex distributions, but the results were controversial (Qiu *et al.*, 2004; Corrada *et al.*, 2013; Altmann *et al.*, 2014). Qiu and colleagues found that the *APOE ε4* allele had a stronger risk effect in men than women, and the *ε2* allele conferred a protective effect only in younger-old people (< 85 years) but not in the oldest old (> 85 years). However, other population-based studies showed that *ε4* led to a higher risk of AD in women and *ε2* was not related to prevalent dementia in either sex (Corrada *et al.*, 2013; Altmann *et al.*, 2014). In our results, the *ε4* allele increased the risk of AD and MCI in both men and women, and almost all age ranges older than 56 years. For the *ε2* allele, our data showed its protective effect in both sexes and in the 56–65 and 76–80 AAO range in AD. Interestingly, the *ε2* allele was found to decrease the risk of MCI in the 76–80 AAO range.

In our study, *APOE ε4/4* was found to be a risk factor for VaD and *ε4*-carrying status to be a risk factor in female patients with VCIND. Researches from many groups have verified the relevance of *APOE ε4* and the increased risk of VaD (Souza *et al.*, 2003; Baum *et al.*, 2006; Bharath *et al.*, 2010; Liu *et al.*, 2012) and reported that it also influenced cognitive decline after stroke (Ballard *et al.*, 2004; Wagle *et al.*, 2010). A meta-analysis showed that the pooled OR value in VaD patients in a Chinese population with the *ε4/4* genotype was 3.34 [95% CI (1.89–5.88)] (Liu *et al.*, 2012). Significant risk factors for cognitive impairment after stroke are *APOE ε4*, prestroke cognitive reduction, previous stroke, and neurological impairment (Wagle *et al.*, 2010), but some other researches did not report any links (Huang *et al.*, 2002; Orsitto *et al.*, 2007; Kim *et al.*, 2008). Kim *et al.* (2008) investigated the association of VaD with the *APOE* polymorphisms in Koreans and found no association between *APOE ε4* or the *ε2* allele and the risk of VaD, even after stratification by sex and age. This may be attributed to the complex environmental, compound risk factors of stroke, ethnic backgrounds, and use of different methods among researches (Huang *et al.*, 2005). There is an association between *APOE ε4* and cognitive decline in elderly adults (Packard *et al.*, 2007), so as to *APOE ε4* and hippocampal volume loss (Jak *et al.*, 2007). When stroke occurs, cognitive impairment may manifest as a result of stroke-related structural and functional changes primarily of the hippocampus and reduced cognitive compensatory potential. A recent research found an amino-terminal fragment of apolipoprotein E within neurofibrillary tangles, blood vessels, and reactive astrocytes in the VaD by immunohistochemistry, supporting a role for the proteolytic cleavage of apolipoprotein E in the VaD and supporting the susceptible role of the *APOE* polymorphism in this disease (Rohn *et al.*, 2014).

Whether *APOE* polymorphisms are correlated to FTD remains unclear. Some researches reported that *APOE ε4* increased the risk of FTD (including one study in a Chinese population) (Stevens *et al.*, 1997; Seripa *et al.*, 2011; Fei and Jianhua, 2013), whereas others did not (Geschwind *et al.*, 1998; Verpillat *et al.*, 2002). One meta-analysis, including 364 FTD patients and 2671 controls, found no significant relationship of *ε4* with the risk of FTD, whereas *ε2* was likely to be a risk factor for FTD

(Verpillat *et al.*, 2002). However, *ε2* was reported to be a protective factor for FTD as well (Bernardi *et al.*, 2006). In contrast to the above studies, in our study, we stratified bvFTD and SD of FTD. We did not find a relationship between *APOE* polymorphisms and bvFTD. As for SD, reports related to *APOE* polymorphisms are uncommon. One report described an increased frequency of the *APOE ε4* allele in patients with SD compared with those with bvFTD and PNFA (Short *et al.*, 2002). In our study, no positive results were found. The controversial association between *APOE* polymorphisms and FTD might be attributed to the genetic heterogeneity of FTD.

The *E4* allele has been proven to increase the risk for the development of DLB and decrease its AAO in many studies (Kobayashi *et al.*, 2011; Boot *et al.*, 2013; Berge *et al.*, 2014; Bras *et al.*, 2014). However, the protective effect of the *ε2* allele remains uncertain (Singleton *et al.*, 2002). One study of 156 DLB patients and 519 controls showed that *ε2* reduced the risk for the development of DLB (P=0.004, OR 0.4, 95% CI: 0.3–0.8) and the AAO was delayed by 4 years in *ε2*-carrying patients (Berge *et al.*, 2014). In our study, neither *ε2* (+) nor *ε4* (+) status affected the risk of DLB. The negative results might be attributed to the small sample number and the ethnic background.

This study had a few limitations. The numbers of VaD, VCIND, bvFTD, SD, and DLB groups in our study were small. It is possible that many effects failed to reach significance or even led to false positives. Thus, this should be verified in a much larger sample in the Chinese Han population to better describe the role of *APOE* in the genetic pictures of these diseases in the future.

Conclusion

In this case–control study, we found that *ε4* increased the risk of AD and MCI in a dose-dependent manner and *ε2* decreased the risk of AD in the Chinese Han population. *APOE ε4* might increase the risk in VaD and female patients with VCIND. The relationship between *APOE* and DLB and SD was first reported in the Chinese Han population. Further researches should focus on investigations of other major and minor genes affecting these cognitive impairment diseases, especially bvFTD, DLB, and SD. At the same time, our results should be confirmed in a much larger sample of the Chinese Han population to better describe the role of *APOE* in the genetic pictures of these diseases.

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Conflicts of interest

There are no conflicts of interest.

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