Apolipoprotein E Gene Polymorphism in a Chinese Population with Vascular Dementia: A Meta-Analysis

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Key Words

Apolipoprotein E • Gene polymorphism • Chinese population • Vascular dementia • Dementia • Meta-analysis

Abstract

Background: Apolipoprotein E (ApoE) gene has been reported to be associated with the development of vascular dementia (VD); however, results from observational studies are conflicting. **Methods:** We surveyed all case-control studies on ApoE gene and VD patients with comprehensive search and review of the references. A meta-analysis was performed to demonstrate the association of ApoE gene with VD by random effects models. The association was assessed by odds ratio (OR) with 95% confidence intervals (CI). **Results:** A total of 18 studies including 935 patients and 1,686 controls were eligible and abstracted. ApoE ϵ 3/4 and ϵ 4/4 genotype, as well as ϵ 4 allele (OR = 1.95, 95% CI: 1.52–2.49; OR = 3.47, 95% CI: 1.85–6.51 and OR = 2.12, 95% CI: 1.64–2.74, respectively) were associated with an increased risk of VD, while ApoE ϵ 3/3 genotype and ϵ 3 allele (OR = 0.65, 95% CI: 0.53–0.79 and OR = 0.65, 95% CI: 0.53–0.80, respectively) trended to protect against VD. There was no significant difference in ApoE ϵ 2 allele frequency, ϵ 2/2, ϵ 2/3 or ϵ 2/4 genotype between VD and controls (OR = 0.85, 95% CI: 0.61–1.17;

OR = 0.89, 95% CI: 0.39–2.01; OR = 0.82, 95% CI: 0.61–1.09 and OR = 1.03, 95% CI: 0.57–1.84, respectively). **Conclusions:** Our results support a genetic association between ApoE polymorphism and VD in the Chinese population.

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Introduction

Dementia is a major public health problem, with over 25 million people affected worldwide and probably over 75 million people at risk during the next 20 years [1]. Vascular dementia (VD) is one of the most prevalent types of dementia that affects the elderly, only second to Alzheimer's disease (AD). Similar to AD, the public health burden of VD threatens to worsen considerably as the world's population ages [2]. Prevalence estimates of VD in developing countries range from 0.6 to 2.1% in those aged over 65 years [3]. In China, a third of the 4.5 million Chinese patients with dementia are predicted to have VD [4]. Due to the increase in VD incidence and the expansion of this disease in developing countries, a large amount of work has been done on identifying susceptibility genes for VD. Several genomic screens have been performed to find genetic linkage to VD. Among various

genes, apolipoprotein E (ApoE), a polymorphic gene mapped at chromosome 19, has recently attracted considerable interest due to its critical role in the lipid metabolism. ApoE is the most important cholesterol-transporting protein and one of the major components of very-low-density lipoproteins [5]. There are three common alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) in exon 4 of the ApoE gene, which generate six genotypes ($\epsilon 2/2$, $\epsilon 2/3$, $\epsilon 2/4$, $\epsilon 3/3$, $\epsilon 3/4$ and $\epsilon 4/4$) and code three major isoforms (E3, wild type with normal function; E2, with reduced affinity for its receptor; E4, with increased affinity for its receptor) [6]. It is supposed that ApoE gene may play a certain role in central nervous system homeostasis [7] and the development of various types of dementia [8]. In the brain, ApoE is critical for the delivery and redistribution of neuronal lipids and recent studies suggest that ApoE is also important for the clearance of toxic, brain-derived species of A β [9]. In multiple pathways affecting neuropathology, ApoE acts directly or in concert with age, head injury, oxidative stress, ischemia, inflammation, and excess amyloid β peptide production to cause neurological disorders, accelerating progression, altering prognosis, or lowering age of onset [10]. Recently, several excellent studies have affirmed that ApoE $\epsilon 4$ is associated with a significantly increased risk of AD [10–12]. Furthermore, there is also growing evidence that polymorphism in the ApoE gene is a major genetic risk factor associated with VD [13–15]. However, it is still unclear whether a relationship exists between ApoE and VD. Additionally, some studies suggested that the ApoE gene was also associated with VD in different ethnic groups [16, 17], but this association has not been consistently replicated [18, 19]. Even regarding the same ethnic groups, the results have been in conflict. To date, there is still controversy about the role of ApoE in the development of VD. Thus, to clarify this inconclusive relationship, we performed a meta-analysis of all available studies to demonstrate the association of ApoE polymorphism with the susceptibility to VD in the Chinese population.

Materials and Methods

Criteria for Considering Studies for this Review

Studies that met all of the following criteria were included: (1) male and female patients of all age groups with clinically definite VD according to DSM criteria or NINDS-AIREN criteria were eligible; (2) case-control or cohort study in Chinese people; (3) healthy persons without dementia as controls; (4) allele frequencies in all cases and the control group in Hardy-Weinberg equilibrium [20]; (5) the distribution of ApoE polymorphism in both

cases and controls is determined; (6) data on ApoE genotype and allele frequency is original. Studies were excluded if the information could not be obtained.

Search Methods for Identification of Studies

We conducted a comprehensive search aimed to obtain all relevant case-controlled studies without language restriction imposed. Eligible studies were identified by searching the electronic literature (PubMed, Embase, China National Knowledge Infrastructure, Chinese Biomedical Database and Wanfang Database) for relevant trials with a time limit of May, 2011. In addition, we performed a manual search of reference lists for original articles. The Mesh search terms used were ApoE, gene polymorphism, Chinese population, vascular dementia, dementia, and case-controlled trial. Terms were exploded whenever possible in each database.

Outcome Measures for this Review

The electronic searches were scrutinized and two independent reviewers obtained full manuscripts of all citations that were likely to meet the predefined selection criteria. Areas of disagreement or uncertainty were resolved by consensus. When multiple articles were published from a single study, we selected the report that contained the most complete and relevant data on the association between ApoE and VD. The extracted data elements included: authors, year of publication, population area, VD diagnostic criteria, ages of patients and controls, number of patients and controls, and genotype information. The presence of heterogeneity between studies was explored with Cochran's Q statistic, which is the weighted sum of squares of the deviations of individual study odds ratios from the Mantel-Haenszel summary odds ratio (OR) [21]. We calculated statistical heterogeneity by an χ^2 test on $N - 1$ degree of freedom with $p < 0.1$ indicating significant heterogeneity [22]. To evaluate the heterogeneity, we also used the I^2 test, taking values in the range of 0–100% [23]. Values of $I^2 < 25$, ≥ 25 , ≤ 50 , and $\geq 50\%$ were considered to represent low, modest, and large heterogeneity, respectively [24]. Due to the detected heterogeneity across studies, we calculated the overall OR and 95% CI by the random effects model. Publication bias was assessed by a funnel plot [25]. To further examine the robustness of the results, we examined the fixed-effects analysis as a sensitivity analysis [26]. The statistical software used for this analysis was Revman 5.1.

Results

Eighty-six studies on the association between ApoE polymorphism and VD were identified in the literature. We excluded 62 studies for the following reasons: reviews or case reports, the publications dealt with other topics, using other diseases as controls, or were not available as full text articles. The primary search identified 24 potentially relevant studies, of which 18 met the selection criteria [17, 27–43]. From the 6 articles excluded, 3 showed duplication of data, and the others did not provide enough data. All eligible studies were considered case-control in

Table 1. Characteristics of all studies included in the meta-analysis

Author	Year	Area	Number		Age, years	
			cases	controls	cases	controls
Zhang et al. [27]	1997	Hubei	37	40	68.8 ± 7.9	66.9 ± 7.5
Zhu et al. [28]	2000	Hubei	49	108	69.9 ± 9.8	70.4 ± 8.8
Zhang et al. [30]	2001	Shanghai	60	200	72.8 ± 7.1	>65
Zhang et al. [29]	2001	Beijing	51	51	67.1 ± 11	65.0 ± 6.6
Huang et al. [31]	2002	Taiwan	70	96	74.7 ± 7.5	72.2 ± 6.9
Lin et al. [32]	2002	Chongqing	58	63	59.1 ± 8.3	59.1 ± 9.5
Xu and Li [33]	2002	Nanjing	47	60	68.9 ± 6.3	63.6 ± 5.5
Lai et al. [34]	2003	Taiwan	30	112	66.2 ± 8.2	71.0 ± 10.6
Lu et al. [35]	2003	Tianjin	65	120	65.6 ± 9.2	63.9 ± 8.0
Su et al. [36]	2003	Shandong	35	40	66.8 ± 5.2	66.2 ± 6.4
Wang and Zhao [37]	2003	Hainan	35	43	56–82	58–79
Zhang et al. [39]	2004	Shandong	26	40	65.5 ± 8.2	63.9 ± 7.3
Lin et al. [38]	2004	Taiwan	40	112	68.7 ± 7.6	71.9 ± 10.8
Feng et al. [40]	2005	Hebei	54	68	67.9 ± 6.2	75.2 ± 7.9
Baum et al. [17]	2006	Hong Kong	144	251	78.0 ± 8.7	78.0 ± 7.4
Yang et al. [41]	2008	Yunnan	10	96	72.1 ± 7.2	74.2 ± 4.7
Li et al. [42]	2009	Guizhou	30	30	70.2 ± 11.6	71.4 ± 10.5
Jiang et al. [43]	2010	Guangxi	85	156	73.9 ± 8.9	71.2 ± 9.3

Table 2. Meta-analysis of ApoE genotypes and the risk of VD in the Chinese population

Genotype	Random effects model OR (95% CI)	Fixed effects model OR (95% CI)	Heterogeneity test p	I ²
ApoE ε2/2	0.89 (0.39, 2.01)	0.79 (0.37, 1.70)	0.90	0%
ApoE ε2/3	0.82 (0.61, 1.09)	0.78 (0.59, 1.03)	0.09	0%
ApoE ε3/3	0.65 (0.53, 0.79)	0.65 (0.55, 0.77)	0.21	20%
ApoE ε2/4	1.03 (0.57, 1.84)	0.97 (0.57, 1.64)	0.81	0%
ApoE ε3/4	1.95 (1.52, 2.49)	1.93 (1.56, 2.39)	0.25	17%
ApoE ε4/4	3.47 (1.85, 6.51)	3.70 (2.06, 6.66)	0.99	0%

design. These studies represented data from 935 VD patients and 1,686 controls in the Chinese population. The main characteristics of these studies are summarized in table 1. Pooling the data of the 18 studies, ApoE allele ε2 frequency was not significantly associated with VD (OR = 0.85, 95% CI: 0.61–1.17, fig. 1), whereas allele ε3 frequency and ε4 frequency were significantly associated with VD (OR = 0.65, 95% CI: 0.53–0.8, fig. 2; OR = 2.12, 95% CI: 1.64–2.74, respectively, fig. 3). The higher frequency of the ε4 allele in VD disease confirmed its role as a risk factor, while ε3 provided weak protection against the development of the disease. Genotypic analysis found

that there was no difference in ApoE ε2/2, ε2/3 or ε2/4 genotype between cases and controls (OR = 0.89, 95% CI: 0.39–2.01; OR = 0.82, 95% CI: 0.61–1.09; OR = 1.03, 95% CI: 0.57–1.84, respectively, table 2). However, our results indicated that ε3/4, ε4/4 and ε3/3 had a strong association with VD (OR = 1.95, 95% CI: 1.52–2.49; OR = 3.47, 95% CI: 1.85–6.51; OR = 0.65, 95% CI: 0.53–0.79, respectively, table 2). Interestingly, ApoE ε3/3 genotype was considerably higher in the controls, while ε3/4 and ε4/4 genotypes were higher in VD patients. This result implies that ε3/4 and ε4/4 genotypes are associated with an increased risk of VD and ε3/3 tends to have a marginally significant protective effect against VD. Besides, we performed a secondary analysis by comparing fixed effect models with random effect models. The results remained the same (tables 2, 3). Publication bias may be acceptably low because funnel plots on the correlation between ApoE ε4 allele and VD for the included studies did not reveal obvious signs of publication bias (fig. 4).

Discussion

Although VD is one of the most common types of dementia, its pathogenesis and etiology are as yet poorly understood. VD is defined as a loss of cognitive function

Fig. 1. Meta-analysis of ApoE $\epsilon 2$ allele and risk of vascular dementia in the Chinese population.

resulting from ischemic, hypoperfusive or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology [44]. Previous findings revealed that ApoE $\epsilon 4$ allele increases the risk of developing atherosclerosis, coronary heart disease, transient ischemic attack or ischemic cerebrovascular disease [7, 45, 46]. Besides, a meta-analysis of 9 case-control studies encompassing 926 patients and 890 control subjects also concluded that possession of ApoE $\epsilon 4$ allele was associated with ischemic cerebrovascular disease [47]. So, ApoE $\epsilon 4$ allele may be associated with VD in which cerebrovascular factors are considered to be of importance in the pathomechanism.

Recently, many researchers reported that the $\epsilon 4$ allele of the ApoE gene increased the risk of various types of dementia, including VD [48]. However, several other retrospective studies found no association. To date, whether or not ApoE $\epsilon 4$ allele leads to a more malignant clinical course remains a matter of debate. McGuinness et al. [49] found that VD patients with ApoE $\epsilon 4$ allele had poorer accuracy on tasks such as choice reaction time and spatial

Table 3. Meta-analysis of ApoE alleles and the risk of VD in the Chinese population

Alleles	Random effects model OR (95% CI)	Fixed effects model OR (95% CI)	Heterogeneity test p	I^2
ApoE $\epsilon 2$	0.85 (0.61, 1.17)	0.82 (0.60, 1.13)	0.99	0%
ApoE $\epsilon 3$	0.65 (0.53, 0.80)	0.66 (0.54, 0.81)	0.80	0%
ApoE $\epsilon 4$	2.12 (1.64, 2.74)	2.12 (1.65, 2.71)	0.59	0%

working memory. Additionally, Davidson et al. [50] also reported that in 89 patients with VD, ApoE $\epsilon 4$ allele frequency was significantly higher than in control subjects ($p < 0.001$) and possession of ApoE $\epsilon 4$ allele increases the risk of VD. These findings provide further support for the association of ApoE in VD and the negative impact of the $\epsilon 4$ allele in VD. In our review, we demonstrated that the ApoE $\epsilon 2/2$, $\epsilon 2/3$ $\epsilon 2/4$ genotype and $\epsilon 2$ allele frequency are nonsignificantly associated with VD. Besides, ApoE $\epsilon 3/4$

Fig. 2. Meta-analysis of ApoE $\epsilon 3$ allele and risk of vascular dementia in the Chinese population.

and $\epsilon 4/4$ genotype as well as $\epsilon 4$ allele are associated with an increased risk of VD, while ApoE $\epsilon 3/3$ genotype and $\epsilon 3$ allele trend to be protective. The results are in accordance with previous studies. Our finding is also in agreement with the results on different ethnic groups [51]. Hence, we could conclude that there is a genetic association between ApoE polymorphism and VD and ApoE $\epsilon 4$ allele is a risk factor for VD. Interestingly, we found that ApoE $\epsilon 3$ allele is protective.

However, there is no consensus in some studies about the relation of ApoE $\epsilon 4$ allele in VD. Kim et al. [52] thought that ApoE $\epsilon 4$ allele did not increase the risk for VD. In their studies they found that neither the ApoE $\epsilon 4$ allele nor the ApoE $\epsilon 2$ allele was more prevalent in VD patients compared with control subjects. Likewise, Pirttila et al. [53] thought that the ApoE gene plays no role in the development of VD. Possible explanations for the lack of agreement of other studies relating to the association of the ApoE $\epsilon 4$ allele and VD might be due to the following reasons: (1) small sample size of patients and low statistical power of individual studies; (2) differences in clinical

diagnosis among individual studies and great clinical heterogeneity of this disorder; (3) naturally occurring polymorphism of the ApoE gene in different human populations; (4) genotyping methods may be a source of heterogeneity. To clarify the role of ApoE in VD, more accurate ethnic definition, unified clinical diagnosis, strict selection of patients, much larger sample size, standard genotyping methods and demographic statistics will be required.

Recently, a complex but consistent effect of ApoE genotype on cognitive performance was observed. ApoE exerts broad and generally adverse effects on a range of neurocognitive functions in cognitively healthy adults [54]. Statistically significant differences were also found between $\epsilon 4$ carriers and noncarriers across multiple domains of cognitive functioning [55]. So, evidence that ApoE $\epsilon 4$ allele could increase the risk of disease may be of great value for the treatment and prevention of VD. Based on the above findings, we could hypothesize that ApoE $\epsilon 4$ may be a potential therapeutic strategy for VD patients.

Fig. 3. Meta-analysis of ApoE $\epsilon 4$ allele and risk of vascular dementia in the Chinese population.

Our meta-analysis had some limitations. Most important of all, the number of patients and controls, although well defined, was relatively small. We surveyed case-control studies related to ApoE gene polymorphism for VD using comprehensive search and review of references; nonetheless, we cannot be certain that all relevant studies have been included. Moreover, we excluded some studies because they did not provide enough data or the allele frequencies were not in Hardy-Weinberg equilibrium. This could have caused a selection and elimination bias. Finally, our analyses did not consider the interaction between genetic and environmental factors, which could have confounded the genetic associations.

Conclusions

Our results support the view that ApoE is of relevance to VD. Significantly, ApoE $\epsilon 4$ allele increased the risk of VD, while ApoE $\epsilon 3$ allele was protective. Our findings

Fig. 4. Funnel plot on the correlation between ApoE $\epsilon 4$ allele and vascular dementia in the Chinese population.

have important implications for genetic epidemiology, and suggest that an improved understanding of the association of ApoE ϵ 4 with VD will be beneficial in the diagnosis and in establishing appropriate therapeutic interventions to prevent the disease.

Disclosure Statement

We have no conflicts of interest with regard to the content of this article.

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