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Apolipoprotein E ε4 Frequency Is Increased among Chinese Patients with Frontotemporal Dementia and Alzheimer's Disease

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Abstract

The relationship between the apolipoprotein E (ApoE) ε4 genotype and an increased risk of developing Alzheimer's disease (AD) has been well established in Caucasians but is less established among other ethnicities. ApoE ε4 has also been associated with several other neurological disorders. Whether ApoE4 ε4 is a risk factor for frontotemporal dementia (FTD) remains controversial. This study examined 432 patients with AD, 62 with FTD, and 381 sex- and age-matched controls. The ApoE ε4 allele frequency was significantly increased among patients in the AD and FTD groups compared with controls. The frequency of the ApoE ε4 allele was 24.86% in late-onset AD ($p < 0.01$), 18.02% in early-onset AD ($p < 0.01$), 16.13% in FTD ($p < 0.01$), and 7.34% in controls. ApoE ε4 prevalence was similar in the FTD and AD groups. The present study suggests that the ApoE ε4 allele is a risk factor for both disorders.

Keywords

Alzheimer's disease; Frontotemporal dementia; Apolipoprotein E

Introduction

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are major causes of dementia in elderly people [1, 2]. AD is the most common source of dementia, affecting more than 35 million people worldwide. After age 65, the incidence of AD doubles every 5 years, with a diagnosis of 1,275 new cases per year per 100,000 persons older than 65 years. AD affects 30–50% of all people aged 85 years or older [3]. FTD is the second most common cause of dementia among patients younger than 65 years [2, 4]. AD presents clinically as a

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progressive cognitive decline that affects memory, mood, and behavior [1]. The disease is characterized by the formation of extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) in specific cortical areas. The accumulation of Aβ plaques and NFTs leads to neuronal loss, white matter degeneration, amyloid angiopathy, inflammation, and oxidative damage [1, 6]. In comparison, FTD is characterized by focal degeneration of the frontal and/or temporal lobes [2]. The onset of FTD symptoms typically occurs during an individual's late 50s or early 60s with changes in personality, social behavior, or language. Eventually, patients with FTD progress to a global dementia [2, 7].

Since the early 1990s, several studies have evaluated the association between the apolipoprotein E (ApoE) ε4 allele and AD in various ethnic groups [8-14]. Although the ε4 allele of the ApoE gene has been established in Caucasians as the most important risk factor of nonmonogenic forms of AD in Caucasians, the influence of ApoE ε4 appears to be weaker among Asian populations [10, 14-17]. In Caucasian, Hispanic, African American, and Japanese populations, ApoE ε4 modulates the age of onset of AD in a dose-dependent manner [9, 11]. It is unclear whether this relationship is preserved in the Chinese population.

ApoE also is a potential risk factor in FTD. Gustafson et al. [18] and Stevens et al. [19] reported higher frequencies of the ε4 allele and the ε4ε4 genotype in FTD. Higher prevalence of the ε4 allele in FTD and primary progressive aphasia has recently been reported by Seripa et al. [20]. However, others have reported no correlation between the ε4 allele and FTD [21-24]. Gustafson et al. [18] and Verpillat et al. [25] reported larger increases in the ε2 allele than the ε4 allele in FTD patients compared with controls. Such findings suggest that the ε2 allele could be a risk factor for FTD.

The above studies examined European or Caucasian participants. The demographics and clinical features of FTD in China have recently been reviewed [26]; however, no study to date has evaluated the correlation between ε2/ε4 and FTD in Chinese patients. The present study aims to investigate the role of ApoE polymorphisms in AD and FTD in a Chinese population. Diagnoses were confirmed using standard international criteria and neuroimaging (computed tomography, CT; magnetic resonance imaging; carbon-11-Pittsburgh compound B-positron emission tomography, PET; fluorodeoxyglucose-PET), and patients were compared with sex-matched healthy Chinese controls.

Materials and Methods

Subjects and Diagnosis

Patients with AD (n = 433) or FTD (n = 62) were recruited randomly at Huanhu Hospital, Tianjin, China, between 2010 and 2012. All subjects underwent extensive examinations and behavioral assessments by trained neurologists. Diagnoses of probable AD were made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Associations [27], and diagnoses of dementia were made according to the DSM-IV criteria [28]. No familial cases of AD were included in this study. To avoid the inclusion of vascular dementia cases, we excluded patients that scored over 2 points on the Hachinski ischemic scale [29]. FTD patients met the following criteria for study inclusion: (a) clinical diagnosis according to

prior clinical consensus criteria for FTD [30, 31] and (b) neuropsychological confirmation of frontal lobe dysfunction. Diagnoses of AD and FTD were based on medical and family histories, age of onset of dementia, neurological examination, and routine blood tests (e.g., biochemistry, vitamin B_{12} levels, hematology, syphilis and HIV serology). All FTD and AD patients displayed characteristic features by magnetic resonance imaging and CT. Carbon-11-Pittsburgh compound B-PET and fluorodeoxyglucose-PET were performed on 29 cases for whom clinical diagnosis was uncertain after multi-disciplinary team conference review. Exclusion criteria were as follows: (a) cerebrovascular disorders, including intracranial mass lesions or hydrocephalus, documented by CT and/or magnetic resonance imaging within the past 12 months; (b) a history of schizophrenia, delusional disorder, or mood disorder with psychotic features or mental retardation according to DSM-IV criteria; (c) abnormalities in syphilis serology, serum folate or vitamin B_{12}, or thyroid hormone levels; (d) a history of traumatic brain injury, Parkinson's or Huntington's disease, and (e) the absence of a knowledgeable subject who could properly report on the patient's behavior. A total of 381 sex-matched elderly controls were selected randomly from the Tianjin community. Controls underwent extensive clinical examination to rule out the following: (a) personal and familial (first-degree relatives) histories of neurological or psychiatric conditions, and (b) organic disease involving the central or peripheral nervous system. ApoE genotypes was determined and data regarding age, sex, education level, and the Mini-Mental State Examination [32] were collected from patients and controls. AD patients were divided into two groups: early-onset AD (EOAD, <65 years at disease onset) and late-onset AD (LOAD, ≥65 years at disease onset). The study included 86 patients with EOAD (mean ± SD, 63.2 ± 5.1 years; range, 42–64 years; male:female ratio, M:F, 37: 49), 346 patients with LOAD (75.3 ± 8.2 years; 65–92 years; M:F, 151: 195), 62 patients with FTD (68.8 ± 6.9 years; 48–79 years; M:F, 26: 36), and 381 healthy controls (71.6 ± 7.5 years; 50–98 years; M:F, 171: 210). The groups did not differ significantly in sex distribution.

ApoE Genotyping

Genomic DNA was extracted from total blood samples, and the ApoE gene was amplified by polymerase chain reaction as described by Wenham et al. [33] with some modifications. Polymerase chain reaction primers were as follows: 5′-TCCAAGGAG-GTGCAGGCGGCGCA-3′ (upstream) and 5′-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3′ (downstream). Each amplification contained 200 ng of genomic DNA, 25 pmol primer, 2.5 μl 10% dimethyl sulfoxide, and 0.5 units Taq DNA polymerase in a final volume of 25 μl. The thermal reactor was programmed as follows: initial denaturation at 94°C for 5 min, 40 cycles at 94°C for 1 min, annealing at 65°C for 1 min, extension at 72°C for 1 min, and final extension at 72°C for 10 min. The amplification product (20 μl) then was digested with 5 units of Cfo1 for at least 3 h at 37°C. Samples were resolved by electrophoresis for 2 h at 200 V on a 12% native polyacrylamide gel. For patient genotyping, gels were stained with 0.5 μg/ml of ethidium bromide, and DNA sizes were determined by imaging under ultraviolet light. We determined all genotypes without knowledge of patient/control status.

Statistical Analysis

Genotype frequencies and ApoE ε4 allele frequencies were calculated for each group and were compared with nondemented controls using a χ^2 test. The level of significance was set at $p < 0.05$. The risks of EOAD, LOAD, and FTD were evaluated for ε4 carriers by calculating the odds ratios (OR) and 95% confidence intervals (CI) between ApoE ε4/ε3 or ε4/ε4 subjects and ApoE ε3/ε3 subjects (table 1).

Ethics

Informed written consent was obtained from all subjects and their relatives. The study was approved by the Huanhu Hospital Ethics Committee.

Results

No significant differences in sex distribution were detected between patient groups and controls. The mean ages of patients with EOAD or FTD were significantly lower than the ages of LOAD patients and controls (table 1). The distribution of ApoE genotypes and corresponding allele frequencies among AD, FTD, and control subjects is shown tables 2 and 3. The frequencies of the ApoE ε4 allele were significantly increased in patients with AD (EOAD and LOAD) and FTD compared with control subjects (LOAD and EOAD, $p < 0.001$; FTD, $p < 0.01$; χ^2 test; table 2). ApoE genotypes did not significantly differ by sex. The frequencies of the ApoE ε2 allele did not significantly differ among the groups. The frequency distribution of the ApoE ε4 allele in FTD patients was statistically similar to that of AD patients ($p = 0.281$, $\chi^2 = 2.536$). The OR of ApoE ε4/ε3 and ε4/ε4 individuals in comparison with ApoE ε3/ε3 individuals regarding diagnoses of EOAD, LOAD, and FTD are summarized in table 4.

Discussion

Our results confirmed higher frequencies of the ApoE ε4 allele in patients with EOAD, LOAD, and FTD compared with controls. To our knowledge, this study is the first to characterize ApoE genotypes in FTD within a Chinese population. Frequencies of ApoE ε2, ε3, and ε4 in elderly healthy controls were similar to previous reports in normal Chinese and Japanese populations [34, 35].

We detected a higher frequency of the ApoE ε4 allele in patients with FTD compared with controls. Several groups have examined the association of FTD with ApoE ε4 status, but their results have been inconsistent. In a Swedish population, Gustafson et al. [18] reported that FTD was associated with an increased frequency of the ε4 allele but not the ApoE ε4/ε4 genotype. In the Netherlands, Stevens et al. [19] found that the ApoE ε4/ε4 genotype was significantly associated with frontal lobe dementia (OR: 4.9; 95% CI: 1.1–20.1). Fabre et al. [36] observed that the ApoE ε4 allele frequency was significantly elevated in the FTD population (52% ε4 carriers) compared to controls (21% carriers). Geschwind et al. [22] identified a trend toward increased ApoE ε4 frequency in FTD compared with controls, but the association was not significant (21 vs. 13%). These inconsistencies suggest that the influence of the ε4 allele on FTD may vary across ethnicities. Our study investigated this association for the first time in a Chinese population. Our results revealed that the ApoE ε4

allele was a significant risk factor for FTD in this group of patients, but males and females were not significantly different.

Our study evaluated a large group of Chinese AD patients and determined that ApoE ε4 allele frequency is the most important risk factor in nonmonogenic forms of AD. This finding is consistent with reports investigating ApoE ε4 in other ethnic groups [12]. Compared to individuals carrying the ε3/ε3 genotype, subjects harboring one or more copies of the ApoE ε4 allele were significantly more likely to present with AD (OR: 4.78; 95% CI: 3.33–6.87). However, the prevalence of ε4 carriers in our study was substantially lower than the 37.08% (95% CI: 31.48–42.82) reported in a meta-analysis of Asian populations [37]. Such differences may be attributed to the inclusion of populations from Iran, Russia, and Turkey under the umbrella term of 'Asian'. The ApoE ε4 carrier prevalence that we observed is consistent with other Chinese and Japanese studies, as recently reviewed in a more recent meta-analysis [10]. In a Chinese population, Wu et al. [38] found the frequency of ApoE ε4 to be 22.3% in a group of AD patients versus 7.5% in controls. In a Japanese population, the distributions of the ApoE ε4 allele in EOAD (31%) and LOAD (27%) groups were similar to the ε4 prevalence observed in our study. We collected data from a very large and well-characterized Chinese population, and our study confirms that the ApoE ε4 allele is an important risk factor for AD. We observed a nonsignificant difference in the frequencies of the ApoE ε2 allele in FTD patients versus controls. Only four ApoE ε2 alleles were identified in our FTD group, and no FTD patients harbored the homozygous ε2/ε2 genotype. Such a low ε2 frequency is not surprising considering the complete absence of the ε2 allele among FTD patients in a previous study [39]. Even in a meta-analysis of 364 FTD patients and 2,671 controls, representation of the ε2 allele did not reach statistical significance [13]. However, when FTD was subtyped into familial and sporadic forms, ε2 was identified as a risk factor for sporadic FTD [18, 25]. Given the low frequency of the ε2 allele and the need to stratify FTD into different subtypes, very large numbers of patients are needed to properly assess the correlation between the ApoE ε2 allele and FTD.

Our observation of a nonsignificant difference in ApoE ε4 prevalence between AD and FTD groups suggests that similar pathogenic pathways involving ApoE may operate in both diseases. Previous studies have reported extensive tau pathology in the brains of AD patients and in patients with certain subtypes of FTD [40]. This pathology consists of abnormally phosphorylated tau protein that accumulates inside neurons [41]. ApoE ε4 facilitates the hyperphosphorylation of tau [42, 43] and correlates with the expression of NFTs [44]. It is hypothesized that NFTs disturb the intracellular transport of molecules in affected neurons, accelerating cell death and precipitating the symptoms of AD and FTD [45].

In addition to tau-related pathology, ApoE ε4 likely contributes to other pathways that account for the stronger association of ApoE ε4 with AD than with FTD. A pathological hallmark of AD is neuritic plaques composed of aggregated Aβ. Numerous studies have found that ApoE ε4 enhances the aggregation [37] and impairs the clearance [46] of Aβ in the brain. This dual role of ApoE ε4 may be a critical determinant of the synaptic loss and memory impairment that characterizes AD [8].

This study is not without limitations. Our cases were not pathology-confirmed; however, all patients were well-characterized by a multidisciplinary team. Following team review, clinical diagnoses remained uncertain for 29 cases, necessitating their evaluation by fluorodeoxyglucose-PET and carbon-11-Pittsburgh compound B-PET. For each of these cases, the primary clinical diagnosis was confirmed by the combined assessments of these two PET analyses. This suggests that clinical assessments of these patients were likely to be highly accurate. Another limitation in the FTD group was associated with the lack of autopsy, which prevented the classification of cases according to the underlying pathology. It is possible that the involvement of ApoE ε4 is distinct in FTLD-tau, FTLD-TDP, FTLD-FUS, and/or FTLD-UPS [2]. Another potential limitation is that our FTD group may underrepresent the behavioral form of FTD. Many patients with the behavioral form of FTD perform flawlessly on simple bedside tests of cognitive function and are considered normal by routine CT brain imaging [1, 40, 41]. Since the diagnosis of the behavioral form of FTD requires a knowledgeable informant with insight into the patient's daily activities, our study ensured that family members of the patients were interviewed alone and in a sensitive manner to identify early and progressive clinical symptoms accurately.

In conclusion, our study demonstrates that the ApoE ε4 allele is associated not only with AD, but also with FTD, in a Chinese population. Our results highlight the utility of ApoE ε4 genotyping to predict the risk for developing FTD and AD, and therefore, to target early preventative measures toward at-risk individuals.

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Table 1

Profiles of AD, FTD, and controls (CTL)

	Patients	M/F	Mean age ± SD, years
AD	432	188/244	72 ± 8.6
EOAD	86	37/49	63.2 ± 5.1
LOAD	346	151/195	75.3 ± 8.2
FTD	62	26/36	68.8 ± 6.9
CTL	361	171/210	71.6 ± 7.5

Table 2

ApoE genotype distributions in EOAD, LOAD, FTD, and controls (CTL)

	2/2	2/3	2/4	3/3	3/4	4/4
AD	0	8	18	235	162	9
EOAD	0	3	5	53	24	1
LOAD	0	5	13	182	138	8
FTD	0	2	2	40	18	0
CTL	1	37	6	288	48	1

Table 3

Frequencies of ApoE alleles in AD, FTD, and controls (CTL)

	ε2	ε3	ε4
AD	26 (3.01%)	640 (74.07%)	198 (22.92%)**
EOAD	8 (4.65%)	133 (77.32%)	31 (18.02%)**
LOAD	18 (2.11%)	507 (73.27%)	167 (24.13%)**
FTD	5 (4.03%)	99 (79.84%)	20 (16.13%)*
CTL	45 (5.91%)	661 (86.75%)	56 (7.34%)

** $p < 0.001$,

* $p < 0.01$ compared with CTL (χ^2 test).

Table 4

Comparison of ApoE ε3/ε4 and ε4/ε4 individuals with ApoE ε3/ε3 individuals with respect to AD and FTD

AD	FTD
4.78 (3.33–6.87)	2.93 (1.55–5.50)

Data are represented as OR (95% CI).