

ASSOCIATION OF APOLIPOPROTEIN E ALLELE 4 WITH ALZHEIMER'S DISEASE IN CHINESE POPULATION

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SUMMARY

Several studies have shown similar distribution of the apolipoprotein E polymorphism in different population despite differences in their genetic background and environmental factors. Significant association of the apoE ϵ 4 allele with familial and sporadic Alzheimer disease was also reported in Caucasians. In the current study, we investigated the polymorphism of apoE in 120 Chinese subjects with sporadic Alzheimer's disease (AD), 50 with multi-infarct dementia (MID) and 180 normal controls. Furthermore, we explored the association between apoE ϵ 4 allele and AD and MID in Chinese patients. The frequencies of the three apoE alleles detected were as follows: AD— ϵ 2=0.046, ϵ 3=0.663, ϵ 4=0.292; MID— ϵ 2=0.12, ϵ 3=0.71, ϵ 4=0.17; normal controls— ϵ 2=0.072, ϵ 3=0.822, ϵ 4=0.106. Association analysis suggested that the apoE ϵ 4 allele was significantly associated with AD (RR=3.49, $p<0.005$), but no association was found between apoE polymorphism and MID or normal controls. These results are consistent with previous reports on other populations, suggesting that the influence of apoE ϵ 4 in Chinese AD might be important too.

Key words: Alzheimer's disease, apolipoproteins, allele, Chinese

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by β amyloid deposits in parenchymal senile plaques and cerebral blood vessel walls as well as neurofibrillary tangles (NFT) within neurons in the cerebral cortex and hippocampus. Patients with AD experience gradually decreasing attention span, and alterations in mood, often coupled with frustration and agitation. As the disease progresses patients ultimately cannot care for their simplest needs and become bedridden and totally dependent on caregivers.

Apolipoprotein E (apoE) is a polymorphic protein that plays an important role in the metabolism of cholesterol and triglycerides. There are three major isoforms of apoE protein: E2, E3 and E4. These isoforms are encoded by three codominant alleles of apoE gene: ϵ 2, ϵ 3 and ϵ 4.

Strittmatter et al (1993) described a significant association between familial and sporadic AD and the apoE allele ϵ 4. Later, this association of AD and apoE ϵ 4 were confirmed in a number of independent studies (Mayeux, 1993; Noguchi et al, 1993; Poirier et al, 1993).

In this study, we have identified some Chinese AD samples to explore the association of AD and apoE polymorphism. Apart from the normal controls, some cases of multi-infarctive dementia (MID) have also been recruited.

METHODS

PATIENT POPULATION

All the subjects were recruited from the wards and outpatient department of the Shanghai Mental Health Centre. There were 120 Chinese patients with sporadic AD (male 50, female 70, mean age 77.68 ± 7.62 years), 50 MID patients (male 36, female 14, mean age 70.66 ± 7.89 years) and 180 elderly normal control subject (male 91, female 89, mean age 62.38 ± 12.21 years) without any confirmed neuropsychiatric diseases were included in the study. Clinical diagnosis of AD and MID were made according to diagnostic criteria of DSM-IV and the NACHINSHI scale was used. In order to aid the diagnosis, CT scan of the brain was carried out and history of hypertension, apoplexy, hyperlipidaemia and diabetes was taken. Depression was excluded by clinical assessment.

APOLIPOPROTEIN E GENOTYPING

Genomic DNA was extracted from peripheral leukocytes and apoE genotyping was performed as described by Jiang et al (1996).

STATISTICAL ANALYSIS

Allele frequencies of the AD, MID and normal control groups were estimated by counting alleles and calculating sample proportions. Z statistic was calculated for comparing allele frequency between two proportions. Association analysis was performed by the method of Woolf (1955).

RESULTS

FREQUENCY OF apoE ALLELES

apoE typing was performed in 120 sporadic AD cases, 50 MID patients and 180 age-matched controls. Table 1 shows different apoE genotype and allele distribution in patients and controls. In all cases and controls, apoE ε3 was the most common, followed by the ε4 and ε2 alleles. Compared with controls, the ε4 allele frequency was markedly increased (29.17% versus 10.56%, $P < 0.05$) while the ε3 allele frequency was markedly decreased (66.25% versus 82.22%, $P < 0.05$) in AD cases. There was no significant difference in ε4 frequency between MID and controls. No significant difference was found in ε2 allele frequency.

ASSOCIATION WITH apoE ε4 ALLELE

Statistical analysis revealed a significant association between AD and apoE ε4 allele (RR=3.49, $P < 0.005$) (see Table 2) but there was no association between MID and apoE ε4 alleles (see Table 3). These results suggest that the ε4 allele should be exclusively associated with AD.

DISCUSSION

In this study, we recruited 120 AD and 50 MID patients and 180 normal elderly controls in a Chinese population in Shanghai. apoE genotyping was performed and the frequency of each allele was calculated according to well-established methods. The distribution of apoE allele frequency in Chinese normal elderly controls was similar to most of the data reported in various populations around the world: apoE ε3 was the most common allele, followed by apoE ε4 is the less common one and apoE ε2 was the most scarce one. In normal Chinese elderly controls, the frequency of apoE ε4 (0.106) was less than that in Caucasians (0.16) while the frequency of apoE ε3 was higher (0.822 vs 0.76).

Between MID and normal controls, no difference was found in the distribution of apoE allele frequency. However, a significant difference existed in the distribution of apoE allele frequency between AD and normal controls. The frequency of apoE ε4 was significant higher in AD (29.17% vs. 0.56%). Compared with that in Caucasians AD patients, the frequency of apoE ε4 is relatively lower in Chinese AD, but it is similar in normal controls drawn from the two populations (Guo et al, 1996).

We analyzed the association between AD and each of the apoE ε4 alleles. A significant association of apoE ε4 with AD was detected, the relative risk (RR) value was 3.49. This result is similar to the findings reported in the literature (Van Duijn et al, 1994).

Association analysis did not reveal any association between MID and apoE allele. This accorded with the finding by Jiang et al (1996).

In conclusion, an association of apoE ε4 allele with AD in Chinese population was confirmed by the present study.

Table 1. Distribution of apoE genotypes and alleles in AD, MID patients and controls(%)

ApoE genotype	ADa	MIDb	Controls
E4/4	8 (0.085)	1 (0.001)	2 (0.029)
E4/3	46 (0.387)	13 (0.174)	32 (0.241)
E4/2	8 (0.027)	2 (0.002)	2 (0.041)
E3/2	3 (0.061)	8 (0.119)	22 (0.171)
E2/2	0 (0.002)	1 (0.005)	1 (0.014)
E3/3	55 (0.439)	25 (0.676)	121 (0.504)
ε4	70 (0.292)	17 (0.17)	38 (0.106)
ε3	159 (0.663)	71 (0.71)	296 (0.822)
ε2	11 (0.046)	12 (0.12)	26 (0.072)

a: apoE polymorphism in AD was significantly different from MID ($P < 0.05$) and controls ($P < 0.05$).

b: apoE polymorphism in MID cases was similar to that of controls. The allele frequencies are in Hardy-Weinberg equilibrium.

Table 2. Association between AD & apoE ε4 allele

	AD	Control	Total
with ε4 allele	70	38	108
without ε4 allele	170	322	512
Total	240	360	600

Table 3. Association between MID & apoE ε4 allele

	MID	Control	Total
with ε4 allele	17	38	55
without ε4 allele	83	322	405
Total	100	360	460

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