Association of APOE Gene Polymorphisms with Cerebral Infarction in the Chinese Population

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Background: Apolipoprotein E (ApoE) is a multifunctional protein that plays an important role in lipoprotein metabolism. However, the relationship between APOE gene polymorphisms and cerebral infarction in the Chinese population remains unclear. Therefore, we studied the role of APOE gene polymorphisms in patients with cerebral infarction in a Chinese population.

Material/Methods: This study involved 906 patients with cerebral infarction and 1,141 individuals without cerebral infarction who served as controls. APOE genotypes were identified in all participants who participated in the study. Factors influencing cerebral infarction were also analyzed.

Results: Statistically significant variances in the distribution and frequencies of the APOE genotypes in the patients were observed (2/2/3 versus 2/2/4 versus 3/3/3=22.85% versus 7.62% versus 56.95%) and controls (2/2/3 versus 2/2/4 versus 3/3/3=17.27% versus 7.22% versus 66.87%; p<0.001). Univariate analysis showed that the APOE e3/e3 genotype [OR, 0.393 (95% CI, 0.237–0.653); p<0.001] and e3/e4 genotype [OR, 0.376 (95% CI 0.221–0.637); p<0.001] played a protective role against cerebral infarction in Chinese men.

Conclusions: Statistically significant variances in the distribution and frequencies of the APOE genotypes of the patients and controls were observed. The study demonstrated that the APOE e3/e3 and e3/e4 genotypes played a protective role against cerebral infarction in Chinese men, but not women. Additionally, the e2/e4 genotype may be a potential risk factor in men, whereas e3/e4 genotype may play a potential protective role against this disease in women.

MeSH Keywords: Apolipoproteins E • Cerebral Infarction • China • Polymorphism, Genetic

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Background

Cerebral infarction (or ischemic stroke) is due to localized brain tissue necrosis or cerebral ischemia caused by cerebral blood disorders, resulting from a blockage in the blood vessels that supply blood to the brain [1–3]. Cerebral infarction has emerged as a global disease, with increasing incidence and prevalence in different parts of the world [4,5]. The risk factors of cerebral infarction include gender, age, dyslipidemia, hypertension, diabetes, tobacco smoking, and alcohol abuse [6,7]. Preventing cerebral infarctions plays an important role in reducing its morbidity and mortality rate.

Apolipoprotein E (ApoE) is a multifunctional protein that plays an important role in lipoprotein metabolism. The human apolipoprotein E (APOE gene; OMIM 107741) is located on chromosome 19q13.32 [8,9]. The three major isoforms of human apolipoprotein E [E2 (OMIM 107741.0001), E3 (OMIM 107741.0015), and E4 (OMIM 107741.0016)], as identified by isoelectric focusing, are encoded by three alleles (e2, e3, and e4) [10–12]. These three alleles encode different isoforms with various structures and functions, including receptor binding capacity and lipid metabolism based on the presence of either a C or T nucleotide at codons 112 (A) and 158 (B). ApoE2 (Cys112, Cys158), ApoE3 (Cys112, Arg158), and ApoE4 (Arg112, Arg158) are encoded by e2, e3, and e4, respectively. Different combinations of these three alleles generate six genotypes (e2/e2, e3/e3, e2/e3, e2/e4, e3/e4, and e4/e4) [13,14]. Although the frequency of these alleles/genotypes varies among different populations, APOE e3/e3 is the most common genotype, and e3 is the most predominant allele in most populations [15–20]. Several studies have demonstrated the association of APOE polymorphisms with cardiovascular disease, sea-blue histiocytic disease, lipoprotein glomerulopathy, and Alzheimer disease II [21,22]. In the present study, we examined the APOE allele/genotype frequencies in patients with cerebral infarction and matched controls.

Material and Methods

Participants

This study included 2,047 participants, which consisted of 906 patients [males: females=601: 305 (or 1.97: 1)] with cerebral infarction and 1,141 individuals without cerebral infarction [males: females=774: 367 (or 2.11: 1)] as healthy controls. Participants visited Meizhou People’s Hospital, located in Guangdong Province, China between February 2016 and April 2017; ages ranged from 13 to 98 years. The study protocol was approved by the Ethics Committee of Meizhou People’s Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University. Written informed consent was obtained from all participants prior to enrollment in the study.

Plasma lipid measurements

Approximately 3 mL of blood was collected from each study participant and the plasma was separated and stored at –80°C until analysis. Plasma levels of triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) were measured.

DNA extraction and genotyping

Blood samples were collected from the study participants and stored in 2-mL vacuum tubes containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA was extracted from each blood sample by using a QIAamp DNA Blood Mini Kit (Qiagen, Germany) following the manufacturer’s instructions, and DNA concentration was quantified by using a NanoDrop 2000™ spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA). PCR was performed according to the following protocol: 50°C for two minutes, pre-denaturation at 95°C for 15 minutes, followed by 45 cycles at 94°C for 30 seconds and 65°C for 45 seconds. The amplified products were detected by using an APOE Gene typing Detection kit (gene-chip assay) (Sinochips Bioscience Co., Ltd., Zhuhai, Guangdong, China).

Statistical analysis

SPSS statistical software version 19.0 was used for data analysis. The data were expressed as the mean ±SD. Regression analysis was used assess the interactions between APOE genotypes and various factors. The chi-square test and ANOVA were used to analyze the association between specific APOE genotypes and clinical characteristics. A value of p<0.05 was considered statistically significant.

Results

A total of 906 Chinese patients, consisting of 601 men (66.34%) and 305 women (33.66%), and 1,141 controls, comprising 774 men (67.84%) and 367 women (32.16%), were recruited into the study. The patients’ mean age was 67.54±12 years, whereas the mean age of the control participants was 62.88±15.10 years. Most of the study participants were from Southern China, including seven areas of Meizhou City, Guangdong Province and some regions of Jiangxi Province. The characteristics of the patient and control groups are presented in Table 1. The comparison between the patients and the controls indicated statistically significant variances in the clinical parameters of cerebral infarction, which included age, hypertension, hypercholesterolemia, triglycerides, total cholesterol, low density lipoprotein,
apolipoprotein A1, and apolipoprotein B, except for high-density lipoprotein and smoking.

The distribution and frequencies of the APOE genotypes and alleles in the patient and control groups are summarized in Table 2. Genotype e3/e3 was the most common type in both groups (56.95% of patients and 66.87% of controls), followed by genotype e2/e3 (22.85% of patients and 17.27% of controls), and e3/e4 (10.82% of patients and 12.01% of controls). Allele e3 was the most common allele (patients: 73.79% of patients and 81.85% of controls), followed by allele e2 (15.67% of patients and 10.43% of controls) and allele e4 (10.54% of patients and 8.06% of controls).

Comparison between carriers and non-carriers in terms of genotype e3/e3 indicated that its frequency was significantly higher in the control group compared to the patient group (p<0.001, OR 1.111, 95% CI 1.052–1.172) for cerebral infarction in male and female patients (Table 4). Additionally, diabetes mellitus (p=0.005, OR 1.267, 95% CI 1.073–1.496) and triglyceride levels (p<0.001, OR 1.017–1.045 in females), hypertension (p<0.001, OR 4.447, 95% CI 3.887–5.088 in males and p<0.001, OR 3.899, 95% CI 2.738–5.554 in females), hypercholesterolemia (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 3.188, 95% CI 2.048–4.964 in females), low density lipoprotein (p<0.001, OR 2.093, 95% CI 1.725–2.539 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), ApoA1/ApoB (p<0.001, OR 2.733, 95% CI 2.270–3.290 in males and p<0.001, OR 2.439, 95% CI 1.638–3.631 in females), and age (p=0.007, OR 1.074–2.613 in females) were determined to be significant risk factors for cerebral infarction in males and females (Table 4).

### Discussion

In the Chinese population, the predominant genotype is e3/e3, whereas the most common allele is e3 [18,23–26]. In the present investigation, genotype e3/e3 accounted for 62.48% of the genotypes observed in the Chinese population, followed by e2/e3 (19.74%), e3/e4 (11.48%), e2/e4 (4.88%), e4/e4 (0.98%).

### Table 1. Clinical characteristics of Chinese male and female nonstroke controls and patients with cerebral infarction.

|                      | Males                  | Females                |
|----------------------|------------------------|------------------------|
|                      | Patients               | Controls               | p Values | Patients               | Controls               | p Values |
| Number of patients   | 601                    | 774                    |          | 305                    | 367                    |          |
| Age, years           | 66.23±12.12            | 62.14±15.28            | <0.001   | 70.11±11.35            | 64.04±15.34            | <0.001   |
| HTN                  | 399 (66.39)            | 210 (27.13)            | <0.001   | 210 (68.85)            | 119 (32.42)            | <0.001   |
| H/C                  | 195 (32.45)            | 87 (11.24)             | <0.001   | 111 (36.39)            | 54 (14.71)             | <0.001   |
| TG, mmol/L           | 1.71±1.439             | 1.498±2.012            | 0.026    | 1.770±1.223            | 1.522±1.331            | 0.013    |
| TC, mmol/L           | 4.856±1.195            | 4.335±1.607            | <0.001   | 5.242±1.300            | 4.729±1.546            | <0.001   |
| LDL, mmol/L          | 3.009±0.935            | 2.491±1.041            | <0.001   | 3.176±0.963            | 2.724±1.182            | <0.001   |
| Apo-A1, g/L          | 1.008±0.213            | 0.911±0.303            | <0.001   | 1.063±0.258            | 0.974±0.305            | <0.001   |
| Apo-B, g/L           | 0.975±0.284            | 0.833±0.300            | <0.001   | 1.031±0.301            | 0.919±0.369            | <0.001   |
| Apo-A1/Apo-B         | 1.113±0.391            | 1.222±0.587            | <0.001   | 1.110±0.413            | 1.183±0.525            | 0.047    |

Values for age expressed as the mean ±SD. Numbers in parentheses are percentages. HTN – hypertension; H/C – hypercholesterolemia; TG – triglycerides; TC – total cholesterol; LDL – low-density lipoprotein; Apo-A1 – apolipoprotein A1; Apo-B – apolipoprotein B.
and $e_2/e_2$ (0.44%). Our results also confirmed the findings of previous research studies.

In the present study, the $e_2/e_4$ genotype was found to have a higher prevalence in male and female patients, and was thus considered as a risk factor for cerebral infarction. The $e_3/e_3$ genotype had a lower prevalence in patients than controls, thereby suggesting its potential protective role. In the male group, participants with the $e_3/e_3$ genotype had lower levels of serum total cholesterol and low density lipoprotein. In the female group, participants with the $e_3/e_3$ genotype had lower levels of serum triglyceride, total cholesterol, and low density lipoprotein.

### Table 2. Genotypes and allele distribution in Chinese case and control groups.

| Genotype | $e_2/e_2$ | $e_2/e_3$ | $e_2/e_4$ | $e_3/e_3$ | $e_3/e_4$ | $e_4/e_4$ | $p$ values |
|----------|-----------|-----------|-----------|-----------|-----------|-----------|------------|
| **Total** |           |           |           |           |           |           |            |
| Cases    | 4 (0.44%) | 207 (22.85%) | 69 (7.62%) | 516 (56.95%) | 98 (10.82%) | 12 (1.32%) | < 0.001 |
| Controls | 5 (0.43%) | 197 (17.27%) | 31 (2.72%) | 763 (66.87%) | 137 (12.01%) | 8 (0.70%) |            |
| **Males** |           |           |           |           |           |           |            |
| Cases    | 2 (0.33%) | 142 (23.63%) | 47 (7.82%) | 341 (56.74%) | 61 (10.15%) | 8 (1.33%) | < 0.001 |
| Controls | 1 (0.13%) | 138 (17.83%) | 21 (2.71%) | 516 (66.67%) | 92 (11.89%) | 6 (0.77%) |            |
| $e_2/e_3$ | –         | 142/138   | –         | –         | –         | –         | (OR 1.426, 95% CI 1.096–1.855) |
| $e_2/e_4$ | –         | –         | 47/21     | –         | –         | –         | < 0.001 (OR 3.042, 95% CI 1.798–5.148) |
| $e_3/e_3$ | –         | –         | –         | 341/516   | –         | –         | < 0.001 (OR 0.656, 95% CI 0.526–0.817) |
| **Females** |           |           |           |           |           |           |            |
| Cases    | 2 (0.66%) | 65 (21.31%) | 22 (7.21%) | 175 (57.38%) | 37 (12.13%) | 4 (1.31%) | 0.018 |
| Controls | 4 (1.09%) | 59 (16.08%) | 10 (2.72%) | 247 (67.30%) | 45 (12.26%) | 2 (0.54%) |            |
| $e_2/e_4$ | –         | –         | 22/10     | –         | –         | –         | (OR 2.775, 95% CI 1.293–5.956) |
| $e_3/e_3$ | –         | –         | –         | 175/247   | –         | –         | (OR 0.654, 95% CI 0.477–0.896) |
| **Alleles** | $e_2$     | $e_3$     | $e_4$     |           |           |           |            |
| **Total** |           |           |           |           |           |           |            |
| Cases    | 284 (15.67%) | 1,337 (73.79%) | 191 (10.54%) |           |           |           | < 0.001 |
| Controls | 238 (10.43%) | 1,860 (81.51%) | 184 (8.06%) |           |           |           |            |
| **Males** |           |           |           |           |           |           |            |
| Cases    | 193 (16.06%) | 885 (73.63%) | 124 (10.32%) |           |           |           | < 0.001 |
| Controls | 161 (10.40%) | 1,262 (81.52%) | 125 (8.07%) |           |           |           |            |
| **Females** |           |           |           |           |           |           |            |
| Cases    | 91 (14.92%) | 452 (74.10%) | 67 (10.98%) |           |           |           | P=0.005 |
| Controls | 77 (10.49%) | 598 (81.47%) | 59 (8.04%) |           |           |           |            |
Table 3. Association of APOE genotypes with serum lipid concentrations of Chinese patients with cerebral infarction.

| Variable | Males | | | | | Females | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | APOE | TG, mmol/L | TC, mmol/L | HDL, mmol/L | LDL, mmol/L | APOE | TG, mmol/L | TC, mmol/L | HDL, mmol/L | LDL, mmol/L |
| | e2/e3 | | | | | e2/e4 | | | | |
| Cases | 1.838±1.711 | 4.63±1.146 | 1.138±0.412 | 2.905±0.905 | 2.105±1.179 | 4.972±1.098 | 1.016±0.215 | 3.286±0.872 |
| Controls | 1.793±0.404 | 4.289±1.906 | 1.144±0.776 | 2.500±1.139 | 1.179±0.609 | 4.091±1.699 | 0.980±0.433 | 2.647±0.995 |
| P values | 0.881 | 0.068 | 0.935 | <0.001 | 0.001 | 0.13 | 0.65 | 0.015 |
| | e3/e3 | | | | | e3/e4 | | | | |
| Cases | 1.589±1.203 | 4.905±1.200 | 1.158±0.324 | 3.002±0.951 | 1.58±1.802 | 5.273±1.309 | 1.262±0.302 | 3.142±0.999 |
| Controls | 1.477±1.855 | 4.321±1.562 | 1.135±0.576 | 2.467±0.995 | 2.119±1.610 | 5.658±1.107 | 1.331±0.328 | 3.260±0.494 |
| P values | 0.323 | <0.001 | 0.498 | <0.001 | 0.462 | 0.098 | 0.273 | 0.687 |
| | e3/e3 | | | | | e3/e4 | | | | |
| Cases | 1.589±1.203 | 4.905±1.200 | 1.158±0.324 | 3.002±0.951 | 1.58±1.802 | 5.273±1.309 | 1.262±0.302 | 3.142±0.999 |
| Controls | 1.477±1.855 | 4.321±1.562 | 1.135±0.576 | 2.467±0.995 | 2.119±1.610 | 5.658±1.107 | 1.331±0.328 | 3.260±0.494 |
| P values | 0.323 | <0.001 | 0.498 | <0.001 | 0.462 | 0.098 | 0.273 | 0.687 |

Table 4. Logistic regression analysis of factors that influence Chinese patients with cerebral infarction.

| Variable | Males | | | | | Females | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | OR | 95% CI | p Values | OR | 95% CI | p Values |
| Age | 1.022 | 1.016–1.027 | <0.001 | 1.031 | 1.017–1.045 | <0.001 |
| HTN | 4.447 | 3.887–5.088 | <0.001 | 3.899 | 2.738–5.554 | <0.001 |
| H/C | 2.733 | 2.270–3.290 | <0.001 | 3.188 | 2.048–4.964 | <0.001 |
| DM | 1.267 | 1.073–1.496 | 0.005 | | | |
| TG | 1.111 | 1.052–1.172 | <0.001 | | | |
| TC | 0.672 | 0.567–0.797 | <0.001 | 0.662 | 0.466–0.830 | <0.001 |
| HDL | 0.698 | 0.536–0.908 | 0.008 | | | |
| LDL | 2.093 | 1.725–2.539 | <0.001 | 2.439 | 1.638–3.631 | <0.001 |
| Apo-A1/Apo-B | 1.634 | 1.385–1.927 | <0.001 | 1.675 | 1.074–2.613 | 0.023 |
| APOE | | | | | | | | | |
| e3/e3 | 0.393 | 0.237–0.653 | <0.001 | | | |
| e3/e4 | 0.376 | 0.221–0.637 | <0.001 | | | |
lipoprotein. These findings suggest that the ε3/ε3 genotype is a protective factor of cerebral infarction. Univariate logistic analysis demonstrated that the APOE ε3/ε3 and ε3/ε4 genotypes play a protective role in cerebral infarction in Chinese men, but not in women.

Additionally, statistically significant variances in the distribution and frequencies of the ε2/ε3 and ε2/ε4 genotypes in men and ε2/ε4 genotype in women between patients and controls were observed. However, univariate logistic analysis indicated that these genotypes had no association with cerebral infarction. This may be because our sample size was not large enough. The prevalence of risk factors in this non-cerebral infarction group was high, particularly that of total cholesterol. This form of selection could explain why logistic analysis showed that total cholesterol is not a risk factor for cerebral infarction. Future studies involving a higher number of study participants, including patients and healthy control subjects, can solve this problem. And further studies with a large sample size are necessary to confirm our findings.

Cerebral infarction is result of complex interactions involving various environmental and genetic factors [27]. APOE polymorphisms seem to be very good candidates in studying the interplay between genetic and acquired risk factors. Future large-scale studies involving patients that will elucidate the pathophysiological pathways of cerebral infarction may lead to new insights and treatments for this particular cardiovascular disorder.

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Conclusions

Statistically significant variances in the distribution and frequencies of APOE genotypes were observed between the patients with cerebral infarction and control participants. The present study demonstrated that the APOE ε3/ε3 and ε3/ε4 genotypes play a protective role for cerebral infarction in Chinese men, but not in women. Additionally, the ε2/ε4 genotype may be a potential risk factor for cerebral infarction in men, whereas the ε3/ε4 genotype potentially plays a protective role against this disease in women. However, our findings needed further validation in Chinese population in other provinces.

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Conflicts of interest

None.
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