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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 (ε2/ε3 versus ε2/ε4 versus ε3/ε3=22.85% versus 7.62% versus 56.95%) and controls (ε2/ε3 versus ε2/ε4 versus ε3/ε3=17.27% versus 2.72% versus 66.87%; $p<0.001$). Univariate analysis showed that the *APOE* ε3/ε3 genotype [OR, 0.393 (95% CI, 0.237–0.653); $p<0.001$] and ε3/ε4 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* ε3/ε3 and ε3/ε4 genotypes played a protective role against cerebral infarction in Chinese men, but not women. Additionally, the ε2/ε4 genotype may be a potential risk factor in men, whereas ε3/ε4 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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1691 4 — 27

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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 (ε2, ε3, and ε4) [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 ε2, ε3, and ε4, respectively. Different combinations of these three alleles generate six genotypes (ε2/ε2, ε3/ε3, ε2/ε3, ε3/ε4, ε2/ε4, and ε4/ε4) [13,14]. Although the frequency of these alleles/genotypes varies among different populations, *APOE* ε3/ε3 is the most common genotype, and ε3 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 with noncerebral 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. 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,

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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 participants	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	1.714±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.

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 ε3/ε3 was the most common type in both groups (56.95% of patients and 66.87% of controls), followed by genotype ε2/ε3 (22.85% of patients and 17.27% of controls), and ε3/ε4 (10.82% of patients and 12.01% of controls). Allele ε3 was the most common allele (patients: 73.79% of patients and 81.85% of controls), followed by allele ε2 (15.67% of patients and 10.43% of controls) and allele ε4 (10.54% of patients and 8.06% of controls).

Comparison between carriers and non-carriers in terms of genotype ε3/ε3 indicated that its frequency was significantly higher in the control group compared to the patient group (p<0.001, OR 0.656, 95% CI 0.526–0.817 in males and p=0.008, OR 0.654, 95% CI 0.477–0.896 in females). A statistically significant variance in genotype ε2/ε4 was also determined to be statistically significant (p < 0.001, OR 3.042, 95% CI 1.798–5.148 in males and p=0.007, OR 2.775, 95% CI 1.293–5.956 in females). The variance in genotype ε2/ε3 between male patients and the control group was also statistically significant (p=0.009, OR 1.426, 95% CI 1.096–1.855), but not in females. The correlation of various *APOE* genotypes to serum lipid concentrations is presented in Table 3.

Univariate logistic analysis showed that age (p<0.001, OR 1.022, 95% CI 1.016–1.027 in males and p<0.001, OR 1.031, 95% CI 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 1.634, 95% CI 1.385–1.927 in males and p=0.023, OR 1.675, 95% CI 1.074–2.613 in females) were determined to be significant risk factors 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 1.111, 95% CI 1.052–1.172) were significant risk factors for cerebral infarction in males, but not in females, whereas high-density lipoprotein levels (p=0.008, OR 0.698, 95% CI 0.536–0.908) were a favorable factor for cerebral infarction in males, but not in females. The favorable factors for cerebral infarction that were associated with the *APOE* ε3/ε3 and ε3/ε4 genotypes were statistically significant in males (p<0.001, OR 0.393, 95% CI 0.237–0.653 and p<0.001, OR 0.376, 95% CI 0.221–0.637, respectively).

Discussion

In the Chinese population, the predominant genotype is ε3/ε3, whereas the most common allele is ε3 [18,23–26]. In the present investigation, genotype ε3/ε3 accounted for 62.48% of the genotypes observed in the Chinese population, followed by ε2/ε3 (19.74%), ε3/ε4 (11.48%), ε2/ε4 (4.88%), ε4/ε4 (0.98%),

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

Genotype	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	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%)	
ε2/ε3	–	142/138	–	–	–	–	P=0.009 (OR 1.426, 95% CI 1.096–1.855)
ε2/ε4	–	–	47/21	–	–	–	<0.001 (OR 3.042, 95% CI 1.798–5.148)
ε3/ε3	–	–	–	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%)	
ε2/ε4	–	–	22/10	–	–	–	P=0.007 (OR 2.775, 95% CI 1.293–5.956)
ε3/ε3	–	–	–	175/247	–	–	P=0.008 (OR 0.654, 95% CI 0.477–0.896)
Alleles	ε2	ε3	ε4				
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%)				

and ε2/ε2 (0.44%). Our results also confirmed the findings of previous research studies.

In the present study, the ε2/ε4 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 ε3/ε3 genotype had a lower prevalence in patients than controls, thereby suggesting its potential protective role. In the male group, participants with the ε3/ε3 genotype had lower levels of serum total cholesterol and low density lipoprotein. In the female group, participants with the ε3/ε3 genotype had lower levels of serum triglyceride, total cholesterol, and low density

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Table 3. Association of *APOE* genotypes with serum lipid concentrations of Chinese patients with cerebral infarction.

	APOE	TG, mmol/L	TC, mmol/L	HDL, mmol/L	LDL, mmol/L
Males	ε2/ε3				
	Cases	1.838±1.711	4.633±1.146	1.138±0.412	2.905±0.905
	Controls	1.793±3.040	4.289±1.906	1.144±0.776	2.500±1.139
	P values	0.881	0.068	0.935	<0.001
	ε2/ε4				
	Cases	2.105±1.179	4.972±1.098	1.016±0.215	3.286±0.872
	Controls	1.179±0.609	4.091±1.699	0.980±0.433	2.589±1.397
	P values	0.001	0.013	0.650	0.015
	ε3/ε3				
	Cases	1.589±1.203	4.905±1.200	1.158±0.324	3.002±0.951
	Controls	1.477±1.855	4.321±1.562	1.135±0.576	2.467±0.995
	P values	0.323	<0.001	0.498	<0.001
Females	ε2/ε4				
	Cases	1.781±0.950	4.942±1.095	1.209±0.266	3.134±0.916
	Controls	2.119±1.610	5.658±1.107	1.331±0.328	3.260±0.494
	P values	0.462	0.098	0.273	0.687
	ε3/ε3				
	Cases	1.696±1.182	5.273±1.309	1.262±0.302	3.142±0.995
	Controls	1.450±1.180	4.648±1.391	1.187±0.352	2.665±1.044
	P values	0.035	<0.001	0.024	<0.001

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			

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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.

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.

References:

1. Brott T, Adams HP, Olinger CP et al: Measurements of acute cerebral infarction: A clinical examination scale. Stroke, 1989; 20: 864–70
2. Fletcher AP, Alkjaersig N, Lewis M et al: A pilot study of urokinase therapy in cerebral infarction. Stroke, 1976; 7: 135–42
3. Hofmeijer J, Kappelle LJ, Algra A et al., HAMLET Investigators: Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): A multicentre, open, randomised trial. Lancet Neurol, 2009; 8: 326–33
4. Mao N, Zhang L, Guo HW, Neurology DO: [Study on the types and risk factors of cerebral infarction recurrence after anti platelet drugs two grade prevention of patients with cerebral infarction.] Chinese Journal of Medicinal Guide, 2017 [in Chinese]
5. Walcott BP, Kuklina EV, Nahed BV et al: Craniectomy for malignant cerebral infarction: prevalence and outcomes in US hospitals. PLoS One, 2011; 6: e29193
6. Howard G, Wagenknecht LE, Cai J et al: Cigarette smoking and other risk factors for silent cerebral infarction in the general population. Stroke, 1998; 29: 913–17
7. Lund HL, Holme I, Hjermann I, Tonstad S: Risk-factor profile for the incidence of subarachnoid and intracerebral haemorrhage, cerebral infarction, and unspecified stroke during 21 years' follow-up in men. Scand J Public Health, 2006; 34: 589–97
8. Mahley RW: Apolipoprotein E: Cholesterol transport protein with expanding role in cell biology. Science, 1988; 240: 622–30
9. Siest G, Pillot T, Régis-Bailly A et al: Apolipoprotein E: An important gene and protein to follow in laboratory medicine. Clin Chem, 1995; 41: 1068–86
10. Kantarci OH, Hebrink DD, Achenbach SJ et al: Association of APOE polymorphisms with disease severity in MS is limited to women. Neurology, 2004; 62: 811–14
11. Martin ER, Lai EH, Gilbert JR et al: Slotterbeck BD.SNPing away at complex diseases: Analysis of single-nucleotide polymorphisms around APOE in Alzheimer disease. Am J Hum Genet, 2000; 67: 383–94
12. Kumar A, Misra S, Kumar P et al: Relationship of apolipoprotein (APOE) ε4 gene polymorphism with the risk of ischemic stroke: A hospital based case-control study. Meta Gene, 2017; 12: 154–58
13. Svobodová H, Kucera F, Stulc T et al: Apolipoprotein E gene polymorphism in the Mongolian population. Folia Biologica, 2007; 53: 138–42
14. Yousuf FA, Iqbal MP: Review: Apolipoprotein E (Apo E) gene polymorphism and coronary heart disease in Asian populations. Pak J Pharm Sci, 2015; 28: 1439–44
15. Tanyanyiwa DM, Marais AD, Byrnes P, Jones S: The influence of ApoE genotype on the lipid profile and lipoproteins during normal pregnancy in a Southern African population. Afr Health Sci, 2016; 16(3): 853–59
16. Mongeargilés JA, Gasparinibereng uer R, Gutierrezagulló M et al: Influence of APOE genotype on Alzheimer's disease CSF biomarkers in a Spanish population. Biomed Res Int, 2016; 2016: 1390620
17. Jairani P, Aswathy P, Gopala S et al: Interaction with the MAPT H1H1 genotype increases dementia risk in APOE epsilon 4 carriers in a population of Southern India. Dement Geriatr Cogn Disord, 2016; 42: 255–64
18. Yin R, Pan S, Wu J et al: Apolipoprotein E gene polymorphism and serum lipid levels in the Guangxi Hei Yi Zhuang and Han populations. Exp Biol Med, 2008; 233: 409–18
19. Al-Dabbagh NM, Al-Dohayan N, Arfin M, Tariq M: Apolipoprotein E polymorphisms and primary glaucoma in Saudis. Mol Vis, 2009; 15: 912–19

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20. Achourirassas A, Ali NB, Cherif A et al: Association between ACE polymorphism, cognitive phenotype and APOE E4 allele in a Tunisian population with Alzheimer disease. J Neural Transm (Vienna), 2016; 123(3): 317–21
21. Clark D, Skrobot OA, Adebiyi I et al: Apolipoprotein-E gene variants associated with cardiovascular risk factors in antipsychotic recipients. Eur Psychiatry, 2009; 24: 456–63
22. Karahan Z, Uğurlu M, Uçaman B et al: Relation between Apolipoprotein E gene polymorphism and severity of coronary artery disease in acute myocardial infarction. Cardiol Res Pract, 2015; 2015: 363458
23. Kao JT, Tsai KS, Chang CJ, Huang PC: The effects of apolipoprotein E polymorphism on the distribution of lipids and lipoproteins in the Chinese population. Atherosclerosis, 1995; 114: 55–59
24. Li GP, Wang JY, Yan SK et al: Genetic effect of two polymorphisms in the apolipoprotein A5 gene and apolipoprotein C3 gene on serum lipids and lipoproteins levels in a Chinese population. Clin Genet, 2004; 65: 470–76
25. Liu H, Mao P, Xie C et al: Apolipoprotein E polymorphism and the risk of intracranial aneurysms in a Chinese population. BMC Neurology, 2016; 16: 14
26. Han S, Xu Y, Gao M et al: Serum apolipoprotein E concentration and polymorphism influence serum lipid levels in Chinese Shandong Han population. Medicine, 2016; 95: e5639
27. Hendrikse J. Cerebral infarction. 2017

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