Observational Study

Medicine®

OPEN

Correlation of gene polymorphisms of CD36 and ApoE with susceptibility of Alzheimer disease

A case–control study

Li Zhou, PhD[a], Hai-Yan Li, PhD[b], Ji-Hui Wang, PhD[b], Zhe-Zhi Deng, PhD[b], Yi-Long Shan, PhD[b], Sha Tan, PhD[b], Yi-Hua Shi, MM[a], Ming-Xing Zhang, MM[a], San-Xin Liu, MM[b], Bing-Jun Zhang, MM[b], Ming-Fan Hong, PhD[c,*], Zheng-Qi Lu, PhD, MD[b,*], Xu-Ming Huang, BM[a,*]

Abstract

This research was aimed to explore correlation of gene polymorphisms of CD36 and ApoE with susceptibility of Alzheimer disease (AD).

This study was a case–control study. Two hundred eleven AD hospitalized patients were selected as the AD group and 241 subjects were selected as the control group. PCR-RFLP was used to detect three loci (rs7755, rs3211956, and rs10499859) of *CD36* gene and ApoE genotype. Chi-square test and univariate nonconditional logistic regression analysis were used to calculate the odds ratio (OR) and 95% confidence interval (95% CI). The haplotypes were constructed using SHEsis online software and the correlation between haplotypes and AD was analyzed. Meanwhile, differences of 3 alleles of ApoE and 6 genotypes (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4) were compared between AD and control groups.

The frequencies of rs7755 genotype ($\chi^2 = 10.780$, $P = .005$) and allele ($\chi^2 = 10.549$, $P = .001$) were statistically different between 2 groups. The genotype frequency of rs3211956 was statistically different between AD and control groups ($\chi^2 = 10.119$, $P = .006$). For the rs7755 locus, GG genotype (OR: 2.013, 95% CI: 1.098–3.699) was an independent risk factor for AD compared with AA genotype. In the dominant model, the risk to develop AD in AG/GG genotype was 1.686 times higher than AA genotype. For the rs3211956 locus, compared with TT genotype, GT genotype (OR: 0.536, 95% CI: 0.340–0.846) was a protective factor for AD after adjusting various physiological and biochemical factors. In the dominant model, the risk of GT/GG genotype to develop AD was reduced by 41.6%. For ApoE gene, the distribution differences of E2/E3 ($\chi^2 = 9.216$, $P = .002$), E3/E4 ($\chi^2 = 7.728$, $P = .005$), and E4/E4 had statistical significance between the 2 groups. The frequencies of allele E2 ($\chi^2 = 9.359$, $P = .002$) and E4 ($\chi^2 = 13.995$, $P < .001$) were statistically significant between AD and control groups.

The rs7755 and rs3211956 loci polymorphisms of *CD36* gene and genotype E2/E3, E3/E4, E4/E4 of *ApoE* gene, and E2 and E4 alleles were statistically related with AD.

Abbreviations: AD = Alzheimer disease, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, HWE = Hardy–Weinberg equilibrium, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, PCR-RFLP = polymerase chain reaction - restriction fragment length polymorphism analysis, TC = total cholesterol, TG = triglycerides.

Keywords: AD, ApoE, CD36, polymorphism

1. Introduction

Alzheimer disease (AD) is a chronic progressive neurodegenerative disorder with an unknown etiology. It endangers human health and is the fourth leading cause of death after cardiovascular disease, cancer, and acquired immune deficiency syndrome.[1,2] Onset of AD is insidious in clinic, and often accompanies by impaired handling daily-life and mental behavior, hypomnesia, and other cognitive dysfunction.[3] At present, the total number of AD patients in the world are nearly 30 million, while patients in China are close to 10 million. As the aggravating population aging phenomenon in China, the number of AD patients in our country will become 3 times of the total AD patients in other regions of the world, will seriously threaten the social stability and family happiness, and bring heavy burden to society.[4]

Studies on susceptibility genes of AD are of great significance for the diagnosis and prevention of AD.[5,6] Known susceptibility genes of AD included *APP*, *PS1*, *PS2*, and *ApoE*, and it was also found that some susceptibility genes were associated with AD in recent years, such as *SORLA*, *TFAM*, and *CR*. These genes have important clinical value in assisting diagnosis and early detection

Editor: Marco Onofrj.

The authors declare that they have no conflict of interest.

[a] Department of Rehabilitative Medicine, The First Affiliated Hospital/School of Clinical Medicine of Guangdong, Pharmaceutical University, [b] Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, [c] Department of Neurology, Rehabilitative Medicine, The First Affiliated Hospital/School of Clinical Medicine of Guangdong, Pharmaceutical University, Guangzhou, China.

[*] Correspondence: Ming-Fan Hong, The First Affiliated Hospital/School of Clinal Medicine of Guangdong, Pharmaceutical University, No 19, NongLinXia Road, Guangzhou 510080, Guangdong Province, China (e-mail: MingFanHong@hainan.net); Zheng-Qi Lu, The Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Tianhe District, Guangzhou 510630, Guangdong Province, China (e-mail: ZhengQiLu@hainan.net), Xu-Ming Huang, The First Affiliated Hospital/School of Clinical Medicine of Guangdong, Pharmaceutical University, No 19, NongLinXia Road, Guangzhou 510080, Guangdong Province, China (e-mail: huangxmfahgd@163.com).

Medicine (2018) 97:38(e12470)

Received: 5 February 2018 / Accepted: 25 August 2018

http://dx.doi.org/10.1097/MD.0000000000012470

of AD. CD36 is a major member of the scavenger receptor and is a multifunctional beta scavenger receptor. Gene encoding *CD36* is located on human chromosome 7.[7]*CD36* gene is associated with fatty acid metabolism and serum cholesterol regulation.[8–10] Meanwhile, *CD36* gene polymorphism is associated with susceptibility to diseases, such as type 2 diabetes mellitus, coronary heart disease, and atherosclerosis.[11–15] Many of the risk factors for these diseases are also the influencing factors of AD. At present, the study on single nucleotide polymorphisms (SNPs) of *CD36* gene and susceptibility to AD has not been reported. Therefore, by analyzing the correlation between SNPs of *CD36* gene and susceptibility to AD, this study was to explore the impact of *CD36* gene on the pathogenesis of AD. *ApoE* gene is one of known AD susceptibility genes, and the correlation between ApoE genotypes and AD was also conducted, which provided further scientific reference for scientific research and clinic.

2. Materials and methods

2.1. Subjects

Patients with AD diagnosed by the elderly psychiatrist who were hospitalized at The First Affiliated Hospital/School of Clinal Medicine of Guangdong were collected from October 2015 to February 2017. Patients with acute stroke, cancer, severe lung, liver, kidney disease, and mental illness, and patients with incomplete clinical case data collection and unsuccessful SNP genotyping were excluded. This study enrolled 452 subjects, including 211 patients with AD and 241 healthy control subjects. Subjects in control group were subject who received health examination in certain community in the region. All patients included in the present study provided written informed consent before their inclusion. The study was approved by the Ethics Committee of The First Affiliated Hospital/School of Clinical Medicine of Guangdong.

2.2. Clinical data collection

2.2.1. Demographic information. Standardized questionnaires were conducted by trained researchers for face-to-face interrogation or measurement, and the questionnaire included name, gender, age, height, weight, smoking and drinking status, and cognitive function assessment.

Subject blood indicators were collected: fasting blood samples of all subjects were drawn in the early morning and sent to the hospital clinical laboratory for blood indicators test. Fasting blood glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using enzymatic test. Blood samples were preserved from the subjects: EDTA tubes were used to draw 4 to 5 mL of the peripheral blood (for genomic DNA extraction), and then samples were numbered and stored at −80°C.

2.3. Diagnostic criteria

2.3.1. Diagnostic criteria for dementia. The diagnosis of dementia was based on the DSM-IV modification criteria. All patients who were diagnosed with dementia were further scanned with skull computed tomography (CT) or magnetic resonance imaging (MRI). Dementia of AD was diagnosed on the basis of the criteria established by the NINCDS-ADRDA.

2.4. SNP typing of CD36 and ApoE genes

The CD36 chromosomal location and gene sequence were searched in the human genome NCBI database. In the SNP database of HapMap phase 2, the information of SNP loci, *CD36* gene of Han population in Beijing, China, and genotyping data of all SNP loci in CD36 extension region were found. Further Haploview software was used to import data; 3 tag SNP loci were selected by comprehensive literatures, namely rs7755, rs3211956, rs10499859.

DNA was extracted according to AxyPrep-96 blood genomic DNA kit instructions. Polymerase chain reaction - restriction fragment length polymorphism analysis (PCR-RFLP) was used to detect the genotypes of three SNP loci of CD36 and genotype of ApoE-specific sequence. The data were collected and corrected by GENESCAN (TM) 672 software (Applied Biosystems, Nieuwekerk/Ijssel, the Netherlands), and then Genemapper software was applied to data analysis and genotyping.

2.5. Statistical analysis

The results were analyzed using IBM SPSS 21.0 software (IBM Chicago, IL). The baseline clinical characteristics were compared in this study. Chi-square test was used for categorical variables. Continuity variables were expressed as mean ± standard deviation, and independent-sample *t* test was used for comparison of differences between 2 groups. The population representativeness of the samples was tested using the Hardy–Weinberg equilibrium (HWE) test, and the genotype, allele frequency, and coincidence degree between groups were compared using the Chi-square test. According to the characteristics of the data, Chi-square test, univariate and multivariate nonconditional logistic regression analysis were used to calculate the odds ratio (OR) and its 95% confidence intervals (95% CIs), and compare relative risk degree of dominant, recessive and additive model in polymorphic loci to induce AD. Linkage disequilibrium analysis and haplotype construction were performed by SHEsis online software (http://analysis.bio-x.cn/myAnalysis.php). Bilateral hypothesis test was used, and test level was $\alpha = 0.05$.

3. Results

3.1. Clinical characteristics of AD and control groups

In this study, mean ages of 211 subjects with AD and 241 subjects in control group were 69.14 ± 4.18 years old and 67.86 ± 5.29 years old. Compared with control group, the mean age ($P < .05$) and fasting blood glucose level ($P = 0.011 < .05$) were higher in the AD group. Hypertension systolic blood pressure (SBP) and hypotension diastolic blood pressure (DBP) levels in the AD group were higher than the control group. Meanwhile, plasma HDL-C level in AD groups was lower than control group. There were no significant differences in gender, smoking, alcohol consumption, body mass index, and levels of TG, TC, and LDL-C between 2 groups ($P > .05$) (Table 1).

3.1.1. HWE test. Chi-square test was used to analyze AD and control groups to determine whether they conformed to the HWE. $P > .05$ indicated that the samples conformed to the HWE and they had the population representativeness. The HWE test was performed on SNP loci of AD and control groups in this study. All study groups conformed to HWE and had population representativeness ($P > .05$) as summarized in Table 2.

Table 1

Comparison of clinical characteristics between AD and control groups.

Groups		Sample size	Mean value	Standard deviation	t/χ^2	P
Age	AD group	211	69.140	4.177	2.876	.004
	Control group	241	67.858	5.291		
FBG	AD group	211	5.209	0.951	2.540	.011
	Control group	241	4.978	0.978		
BMI	AD group	211	23.087	2.848	1.519	.129
	Control group	241	22.648	3.245		
SBP	AD group	211	137.437	15.425	9.274	.000
	Control group	241	123.587	16.192		
DBP	AD group	211	82.210	10.144	3.777	.000
	Control group	241	78.800	9.047		
TG	AD group	211	1.198	0.268	0.752	.452
	Control group	241	1.179	0.271		
TC	AD group	211	4.653	1.083	−1.538	.125
	Control group	241	4.806	1.026		
LDL-C	AD group	211	2.738	0.677	1.509	.132
	Control group	241	2.636	0.742		
HDL-C	AD group	211	1.153	0.267	−2.314	.021
	Control group	241	1.215	0.301		
Gender (male/female)	AD group		113/98		0.190	.663
	Control group		134/107			
Smoking (Yes/No)	AD group		46/165		0.146	.702
	Control group		49/192			
Drinking (Yes/No)	AD group		22/189		0.162	.697
	Control group		28/213			

AD = Alzheimer disease.

3.2. Distribution of genotype and allele frequencies of CD36 SNP loci

The distribution of genotype and allele frequencies of CD36 SNP loci in AD and control groups are summarized in Table 3. The genotype frequencies of AA, AG, and GG in Rs7755 were 20.9%, 51.2%, and 28.0% in AD group and 33.6%, 47.3%, and 19.1% in control group, respectively. The allele frequencies of A and G were 46.4% and 53.6% in the AD group and 57.3% and 42.7% in the control group, respectively ($\chi^2=10.780$, $P=.005$), and distribution was statistically significant ($\chi^2=10.549$, $P=.001$). The genotype frequency of rs3211956 was significantly different between AD and control groups ($\chi^2=10.119$, $P=.006$); however, allele T and G showed no significant difference between the 2 groups ($P>.05$). Genotype and allele frequencies of rs10499859 in AD and control groups showed no statistically significant difference.

3.3. Distribution of genotype and allele frequencies of ApoE

The distribution frequencies of the 6 genotypes and alleles of *ApoE* gene in AD and control groups are summarized in Table 4. The genotype frequencies of E2/E2, E2/E4, and E3/E3 were not significantly different between AD and control groups. The distribution frequencies of E2/E3 ($\chi^2=9.216$, $P=.002$), E3/E4 ($\chi^2=7.728$, $P=.005$), and E4/E4 ($\chi^2=4.918$, $P=.027$) were statistically different between the 2 groups. The allele frequencies of E2 ($\chi^2=9.359$, $P=.002$) and E4 ($\chi^2=13.995$, $P<.001$) were statistically different between AD and control groups; however, allele E3 showed no significant difference between 2 groups ($P>.05$).

Table 2

HWE test of SNP loci in AD and control groups.

	AD group		Control group	
	χ^2	P	χ^2	P
Rs7755	0.176	.675	0.271	.602
Rs3211956	3.694	.055	3.678	.055
Rs10499859	0.407	.524	0.495	.482

Table 3

Distribution of genotype and allele frequencies of SNP loci.

SNPs		AD group	Control group	χ^2	P
Rs7755	Genotype			10.780	.005
	AA	44 (0.209)	81 (0.336)		
	AG	108 (0.512)	114 (0.473)		
	GG	59 (0.280)	46 (0.191)		
	Alleles			10.549	.001
	A	196 (0.464)	276 (0.573)		
	G	226 (0.536)	206 (0.427)		
Rs3211956	Genotype			10.119	.006
	GG	18 (0.085)	15 (0.062)		
	GT	68 (0.322)	113 (0.469)		
	TT	125 (0.592)	113 (0.469)		
	Alleles			2.859	.091
	G	104 (0.246)	143 (0.297)		
	T	318 (0.754)	339 (0.703)		
Rs10499859	Genotype			1.981	.371
	AA	93 (0.441)	112 (0.465)		
	AG	91 (0.431)	108 (0.448)		
	GG	27 (0.128)	21 (0.087)		
	Alleles			0.863	.300
	A	277 (0.656)	332 (0.689)		
	G	145 (0.344)	150 (0.311)		

AD = Alzheimer disease.

Table 4

Distribution of genotype and allele frequencies of ApoE.

Genotype	AD group	Control group	χ^2	*P*
E2/E2	1 (0.47)	5 (2.07)	2.201	.138
E2/E3	14 (6.64)	38 (15.77)	9.216	.002
E2/E4	11 (5.21)	10 (4.15)	0.287	.592
E3/E3	97 (45.97)	125 (51.88)	1.565	.211
E3/E4	78 (36.97)	60 (24.9)	7.728	.005
E4/E4	10 (4.74)	3 (1.24)	4.918	.027
E2	27 (6.4)	58 (12.03)	9.359	.002
E3	286 (67.77)	348 (72.20)	2.105	.147
E4	109 (25.83)	76 (15.77)	13.995	.000

AD = Alzheimer disease.

3.4. Logistic regression analysis of correlation between CD36 SNP loci and AD

Genotype and allele frequencies of SNP loci rs7755 and rs3211956 were significantly different between AD and control groups. And single factor analysis results were indicated that there was a significant difference in age, FBG, BMI, SBP, DBP, HDL-C between AD group and control group (all $P < .05$). Therefore, the 2 loci and the physiological and biochemical factors were included in the logistic regression equation for further analysis.

Univariate logistic regression showed that as for rs7755 locus, compared with AA genotype, the AG genotype (OR: 1.744, 95% CI: 1.110–2.740) and GG genotype (OR: 2.361, 95% CI: 1.387–4.021) could increase the risk of AD. In the recessive model, the risk of AD in GG genotype was 1.645 times of the AG/GG genotype. The risk of AD was 1.921 times higher in the AG/GG genotype in the dominant genetic model. After adjusting for physiological and biochemical factors, including age, FBG, BMI, SBP, DBP, and HDLC, compared with AA genotype, the risk of AG genotype to develop AD was not statistically significant, GG genotype (OR: 2.013, 95% CI: 1.098–3.699) was still an independent risk factor for AD. In the dominant model, risk of AG/GG genotype to develop AD was 1.686 times of AA genotype. In the recessive model, risk of GG genotype to develop AD was not statistically significant.

For the rs3211956 locus, compared with TT genotype, the GT genotype (OR: 0.544, 95% CI: 0.367–0.807) reduced the risk of AD, and there was no statistical correlation between the GG genotype and the risk of AD. In the recessive model, there was no statistical correlation between the GG genotype and the risk of AD. In the dominant model, risk of GT/GG genotype to develop AD was reduced by 39.3%. After adjustment for age, FBG, BMI, SBP, DBP, and HDLC compared with TT genotype, GT genotype (OR: 0.536, 95% CI: 0.340–0.846) was still a protective factor in AD. In the dominant model, risk of AG/GG genotype to develop AD was reduced by 41.6%, while, in the recessive model, the risk of GG genotype to develop AD was not statistically significant. The results are summarized in Table 5.

3.5. Correlation between haplotypes of CD36 gene and pathogenesis of AD

The distribution differences of haplotypes were analyzed in AD and control groups, and results indicated that haplotypes AGA (OR = 0.454, 95% CI: 0.273 ~ 0.755, $P = .002$) and ATA (OR = 0.61, 95% CI: 0.456–0.816, $P = .001$) were protective factors for AD. Haplotype GTA (OR = 2.136, 95% CI: 1.520–3.0000, $P < .001$) was risk factor for AD. Details are summarized in Table 6.

4. Discussion

AD is an insidious and progressive neurodegenerative disease with age correlation. A study showed that incidence of AD was on the rise with age between 65 and 85 years,[3] and seriously affected the quality of life of the elderly. Our results showed that age difference between AD and control groups showed statistical significance, and age of AD group was higher than that of control

Table 5

Logistic regression analysis of the correlation between CD36 SNP loci and AD.

SNPs	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
rs7755				
AA	Reference		Reference	
AG	1.744 (1.110–2.740)	.016	1.550 (0.928–2.590)	.094
GG	2.361 (1.387–4.021)	.002	2.013 (1.098–3.699)	.024
Dominant	1.921 (1.255–2.943)	.003	1.686 (1.039–2.734)	.034
Recessive	1.645 (1.060–2.555)	.027	1.516 (0.915–2.512)	.106
Rs3211956				
TT	reference		reference	
GT	0.544 (0.367–0.807)	.002	0.536 (0.340–0.846)	.007
GG	1.085 (0.522–2.253)	.827	0.909 (0.396–2.088)	.822
Dominant	0.607 (0.418–0.882)	.009	0.584 (0.379–0.902)	.015
Recessive	1.405 (0.690–2.863)	.349	1.195 (0.533–2.679)	.665

CI = confidence interval, OR = odds ratio.

* Adjusting the physiological and biochemical factors, including age, FBG, BMI, SBP, DBP, HDLC [According to univariate analysis, there was a significant deviation ($P < .05$)].

Table 6

Correlation between haplotypes of *CD36* gene and pathogenesis of AD.

Haplotype*	AD group (n = 211)	Control group (n = 241)	χ^2	OR (95% CI)	P
AGA*,†	22.83 (0.054)	53.92 (0.112)	9.663	0.454 [0.273∼0.755]	.002
AGG*	17.27 (0.041)	11.53 (0.024)	2.109	1.741 [0.817∼3.712]	.146
ATA*,†	102.08 (0.242)	165.57 (0.343)	11.144	0.61 [0.456∼0.816]	.001
ATG*	53.82 (0.128)	44.98 (0.093)	2.704	1.42 [0.934∼2.160]	.100
GGA*	45.42 (0.108)	46.62 (0.097)	0.293	1.126 [0.732∼1.734]	.589
GGG*	18.47 (0.044)	30.92 (0.064)	1.809	0.668 [0.370∼1.207]	.179
GTA*,†	106.66 (0.253)	65.89 (0.137)	19.625	2.136 [1.520∼3.002]	.000
GTG*	55.44 (0.131)	62.57 (0.130)	0.005	1.014 [0.688∼1.494]	.944

AD = Alzheimer disease, CI = confidence interval, OR = odds ratio.

* The haplotypes were sequenced according to the sequence of rs7755, rs3211956, and rs10499859 genotypes.

† Haplotype was significantly related with AD ($P < .05$).

group, indicating that age was an influencing factor of AD's pathogenesis.

At the same time, this study found that some metabolic-related factors in AD group were different from control group. Fasting blood glucose, hypertension SBP, and hypotension DBP levels in AD group were higher than the control group, while plasma HDL-C level was lower than the control group. A study had shown[16] that the incidence of dementia in patients with diabetes mellitus was significantly higher than nondiabetic patients. Another study on long-term follow-up of normal elderly in community showed that blood glucose was elevated, and especially 2-hour postmeal blood glucose was elevated, which increased onset risk of AD.[17]

The long-term use of antihypertensive agents in elderly hypertensive patients could significantly reduce the incidence of AD.[18] Hyperlipidemia may be an important factor in the development of AD.[19] The study found that serum TC level was significantly related with the incidence of AD and mild cognitive impairment.[20] These findings were similar to our results, indicating that there were certain degree correlations between metabolic factors and occurrence and development of AD.

Genetic factors of AD have been confirmed both at home and abroad, some of these genetic factors are susceptible genes of AD, and some are susceptible genes of atherosclerosis or coronary heart disease. Many susceptible genes for AD now have been proven. The recent foreign studies had shown that SNP of rs3211892 locus of *CD36* gene was related with susceptibility to onset of AD. CD36 may affect the development and progression of AD in 3 aspects. In the central nervous system, CD36 is involved in angiogenesis, oxidation, and inflammatory processes.[21] At the same time, *CD36* gene polymorphism is also a susceptible gene for atherosclerosis and cardiovascular and cerebrovascular diseases, so the correlation between CD36 and AD should be paid attention. However, its correlation with AD in China has not been reported; the genetic factors of Chinese and western populations have the same points and have different points,[22–24] so to explore the correlation between the domestic CD36 SNP and the occurrence and development of AD may be of great significance.

In this study, by analyzing correlation between the three SNP loci of *CD36* gene and the onset of AD, results showed that the genotypes and allele frequencies of SNP rs7755 and rs3211956 of *CD36* gene were statistical differences between AD and control groups. As for the rs7755 locus, compared with AA genotype, GG genotype (OR: 2.013, 95% CI: 1.098–3.699) was still an independent risk factor for AD after adjusting for various physiological and biochemical factors. In the dominant model, the risk of AG/GG genotype to develop AD was 1.686 times of AA genotype. As for the rs3211956 locus, the GT genotype (OR: 0.544, 95% CI: 0.367–0.807) reduced the risk to develop AD compared with TT genotype. After adjusting for various physiological and biochemical factors, compared with TT genotype, GT genotype (OR: 0.536, 95% CI: 0.340–0.846) was still a protective factor in AD. In the dominant model, the risk of GT/GG genotype to develop AD was reduced by 41.6%. However, genotype and allele frequencies of rs10499859 were no significant difference between 2 groups. Although these 3 loci had not yet been confirmed to correlate with the occurrence and development of AD, they had been confirmed to correlate with coronary heart disease and atherosclerosis. Therefore, we speculated that SNPs of *CD36* gene was also related with susceptibility to AD.

ApoE as susceptibility gene of AD had been confirmed in a number of studies both at home and abroad.[25–27] This study also confirmed the susceptibility of *ApoE* gene polymorphisms to AD and found that distribution differences of E2/E3, E3/E4, E4/E4 were statistically significant between 2 groups. The frequencies of alleles E2 and E4 were statistically different between AD and control groups. It was shown that E4 was a risk factor for AD, and E2 was a protective factor of AD. ApoE genotyping diagnosis was of great significance for early AD: first of all, early diagnosis of AD was possible, which was different from the main features of conventional diagnosis, and measures was taken early to delay the onset of dementia or reduce the number of cases.

Due to the limitation of manpower and material resources, a few loci were selected in this study. Meanwhile, this study was a case–control study with a small number of cases. In the future, large-scale molecular genetic epidemiological studies should be carried out in community population, which was more meaningful to control onset of AD. In conclusion, this study found SNP loci of *CD36* gene that showed statistically significant correlation with susceptibility to AD, providing reference basis for clinical and scientific research.

Author contributions

Conceptualization: Xu-Ming Huang.
Data curation: Li Zhou, Xu-Ming Huang.
Formal analysis: Li Zhou.
Investigation: Li Zhou, Hai-Yan Li, San-Xin Liu.
Methodology: Hai-Yan Li, Ji-Hui Wang, Yi-Hua Shi.
Resources: Ji-Hui Wang, Zhe-Zhi Deng, Ming-Xin Zhang.
Software: Yi-Long Shan, Sha Tan.
Supervision: Bing-Jun Zhang.
Validation: Ming-Fan Hong, Zheng-Qi Lu.
Visualization: Xu-Ming Huang.

Writing – original draft: Ming-Fan Hong, Zheng-Qi Lu, Xu-Ming Huang.
Writing – review & editing: Ming-Fan Hong, Zheng-Qi Lu, Xu-Ming Huang.

References

[1] Parker GR, Cathcart HM, Huang R, et al. Apolipoprotein gene E4 allele promoter polymorphisms as risk factors for Alzheimer's disease. Psychiatr Genet 2005;15:271–5.
[2] Wang GD, Lai DJ, Burau KD, et al. Potential gains in life expectancy from reducing heart disease, cancer, Alzheimer's disease, kidney disease or HIV/AIDS as major causes of death in the USA. Public Health 2013;127:348–56.
[3] Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol 2011;7:137.
[4] Liu S, Li C, Shi Z, et al. Caregiver burden and prevalence of depression, anxiety and sleep disturbances in Alzheimer's disease caregivers in China. J Clin Nurs 2017;26:1291–300.
[5] Bartley M, O'Neill D. Early Alzheimer's disease. N Engl J Med 2010;363:80–2.
[6] Querfurth HW, Laferla FM. Alzheimer's disease. N Engl J Med 2010;362:329.
[7] Armesilla AL, Vega MA. Structural organization of the gene for human CD36 glycoprotein. J Biol Chem 1994;269:18985–91.
[8] Nergizunal R, Rademakers T, Cosemans JM, et al. CD36 as a multiple-ligand signaling receptor in atherothrombosis. Cardiovasc Hematol Agents Med Chem 2011;9:42–55.
[9] Silverstein RL. Type 2 scavenger receptor CD36 in platelet activation: the role of hyperlipemia and oxidative stress. Clin Lipidol 2009;4:767.
[10] Febbraio M, Hajjar DP, Silverstein RL. CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. J Clin Invest 2001;108:785–91.
[11] Collotteixeira S, Martin J, Mcdermottroe C, et al. CD36 and macrophages in atherosclerosis. Cardiovasc Res 2007;75:468–77.
[12] Silverstein RL, Li W, Park YM, et al. Mechanisms of cell signaling by the scavenger receptor CD36: implications in atherosclerosis and thrombosis. Trans Am Clin Climatol AssocV 121 2010;206–20.
[13] Yun YM, Song EY, Song SH, et al. CD36 polymorphism and its relationship with body mass index and coronary artery disease in a Korean population. Clin Chem Lab Med 2007;45:1277–82.
[14] Banerjee M, Gautam S, Saxena M, et al. Association of gene variants rs1761667 (G > A) and rs1527483 (C > T) with Type 2 diabetes in North Indian population. Int J Diabetes Mellitus 2010;2:179–83.
[15] Gautam S, Banerjee M. The macrophage Ox-LDL receptor, CD36 and its association with type II diabetes mellitus. Mol Genet Metab 2011; 102:389–98.
[16] Xiong YY, Zhao QH, Guo QH, et al. Prevalence of dementia in diabetics: A community-based case-control study. Peoples Military Surgeon 2011; S1:32–5.
[17] Ohara T. [Glucose tolerance status and risk of dementia in the community: the Hisayama study]. Neurology 2013;115:90–7.
[18] Kume K, Hanyu H, Sakurai H, et al. Effects of telmisartan on cognition and regional cerebral blood flow in hypertensive patients with Alzheimer's disease. Geriatr Gerontol Int 2012;12:207–14.
[19] Kivipelto DM, Laakso MP, Tuomilehto J, et al. Hypertension and hypercholesterolaemia as risk factors for Alzheimer's disease. CNS Drugs 2002;16:435–44.
[20] Shepardson NE, Shankar GM, Selkoe DJ, et al. Cholesterol and statins in Alzheimer's disease. Arch Neurol 2011; 68: 1239–1244.
[21] Šerý O, Janoutová J, Ewerlingová L, et al. CD36 gene polymorphism is associated with Alzheimer's disease. Biochimie 2017;135:46–53.
[22] Kane RA, Kane RL. Effect of genetic testing for risk of Alzheimer's disease. N Engl J Med 2009;361:298–9.
[23] Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med 2009;361:245–54.
[24] Farrer LA. Intercontinental epidemiology of Alzheimer disease: a global approach to bad gene hunting. JAMA 2001;285:796–8.
[25] Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.
[26] Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994; 7:180–184.
[27] Hawkes CA, Gentleman SM, Nicoll JA, et al. Prenatal high-fat diet alters the cerebrovasculature and clearance of (-amyloid in adult offspring. J Pathol 2015;235:619–31.