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, Yi-Long Shan, PhD\^b, Sha Tan, PhD\^b, Yi-Hua Shi, MM\^b, Ming-Xing Zhang, MM\^b, San-Xin Liu, MM\^b, Bing-Jun Zhang, MM\^b, Ming-Fan Hong, PhD\^c, Zheng-Qi Lu, PhD, MD\^d, Xu-Ming Huang, BM\^e

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 (χ² = 10.780, P = .005) and allele (χ² = 10.549, P = .001) were statistically different between 2 groups. The genotype frequency of rs3211956 was statistically different between AD and control groups (χ² = 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/E2 (χ² = 9.216, P = .002), E3/E4 (χ² = 7.728, P = .006), and E4/E4 had statistical significance between the 2 groups. The frequencies of allele E2 (χ² = 9.359, P = .002) and E4 (χ² = 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
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 7.17 CD36 gene is associated with fatty acid metabolism and serum cholesterol regulation.18-19 Meanwhile, CD36 gene polymorphism is associated with susceptibility to diseases, such as type 2 diabetes mellitus, coronary heart disease, and atherosclerosis.11-13 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 Clnal 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 Haplovie software was used to import data; 3 tag SNP loci were selected by comprehensive literatures, namely rs7755, rs3211956, rs10499859. DNA was extracted according to AsyPrep-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/Bassel, 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 α = 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.
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 1

| Groups                          | Sample size | Mean value | Standard deviation | $V_x^2$ | $P$    |
|--------------------------------|-------------|------------|--------------------|---------|--------|
| 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  | .104   |
|                                | 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    |                    |         | .702   |        |
| 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.*

### Table 3

| SNPs      | Genotype | AD group | Control group | $\chi^2$ | $P$    |
|-----------|----------|----------|---------------|----------|--------|
| Rs7755    | AA       | 44 (0.209)| 81 (0.336)   | 10.780   | .005   |
|           | AG       | 108 (0.512)| 114 (0.473) |          |        |
|           | GG       | 59 (0.280)| 46 (0.191)   |          |        |
|           | Alleles  |          | 10.549       | .001     |        |
| Rs3211956 | A        | 196 (0.464)| 276 (0.573) | 10.119   | .006   |
|           | G        | 226 (0.536)| 206 (0.427) |          |        |
| Rs10499859| GG       | 18 (0.085)| 15 (0.062)   | 2.859    | .091   |
|           | 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) |          |        |

*AD = Alzheimer disease.*

### Table 2

| HWE test of SNP loci in AD and control groups. | AD group | Control group |
|-----------------------------------------------|----------|---------------|
| $\chi^2$ | $P$    | $\chi^2$ | $P$    |
|---------|--------|---------|--------|
| Rs7755  | 0.176  | .675    | 0.271  | .602   |
| Rs3211956| 3.694  | .055    | 3.678  | .055   |
| Rs10499859| 0.407  | .524    | 0.406  | .482   |

*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, and HDLC between AD group and control group (all \( P < 0.05 \)). 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 AA genotype, compared with GG genotype. In the recessive model, risk of 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: 0.544, 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, \( P=0.002 \)) and ATA (OR=0.61, 95% CI: 0.456–0.816, \( P=0.001 \)) were protective factors for AD. Haplotype GTA (OR=2.136, 95% CI: 1.520–3.0000, \( P<0.001 \)) 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 4

| Genotype | AD group | Control group | \( \chi^2 \) | \( P \) |
|----------|----------|---------------|-------------|--------|
| 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       | 19 (8.64)| 27 (11.03)    | 9.359       | .002   |
| E3       | 296 (67.77)| 348 (72.29)  | 2.105       | .147   |
| E4       | 10 (2.25)| 76 (15.77)    | 13.995      | .000   |

**AD** = Alzheimer disease.

### Table 5

| SNPs     | Crude OR (95% CI) | \( P \) | Adjusted OR* (95% CI) | \( P \) |
|----------|------------------|-------|-----------------------|-------|
| rs7755   | \( r^2 \)        |       |                       |       |
| AA       | Reference        | .016  | 1.550 (0.928–2.590)   | .094  |
| AG       | 1.744 (1.110–2.740) | .002  | 2.013 (1.098–3.699)   | .024  |
| Dominant | 1.60 (1.56–2.555) | .003  | 1.56 (1.00–3.42)      | .034  |
| Recessive| 1.56 (1.060–2.555)| .027  | 1.56 (1.00–3.86)      | .106  |
| rs3211956| \( r^2 \)        |       |                       |       |
| TT       | Reference        | .002  | 0.536 (0.340–0.864)   | .007  |
| Dominant | 0.607 (0.418–0.882)| .009  | 0.584 (0.379–0.902)   | .015  |
| Recessive| 1.405 (0.690–2.803)| .349  | 1.195 (0.533–2.679)   | .665  |

\( \text{Adjusted OR} = \frac{\text{Adjusted} \times \text{Crude} \times \text{Reference}}{\text{Adjusted} \times \text{Adjusted} \times \text{Reference}} \)

* Adjusting the physiological and biochemical factors, including age, FBG, BMI, SBP, DBP, and HDLC [According to univariate analysis, there was a significant deviation (\( P < 0.05 \)].
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, inflammation, 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; so the correlation between CD36 and AD should be paid attention.

| Haplotype | AD group (n=211) | Control group (n=241) | $\chi^2$ | 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)   | 11.55 (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)   | 43.98 (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 (0.157)        | 19.625  | 2.136 [1.520–3.002] | .000 |
| GTG       | 55.44 (0.131)   | 62.97 (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).

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.

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