Analysis of genetic polymorphisms for age-related macular degeneration (AMD) in Chinese Tujia ethnic minority group

Shengchun Liu¹,², Mingxing Wu¹, Bianwen Zhang¹, Xiaojing Xiong¹, Hao Wang¹ and Xiyuan Zhou¹*

Abstract

Background: Age-related macular degeneration (AMD) can cause vision loss or blindness in elderly. The associations between single nucleotide polymorphism (SNP) and AMD in Chinese Tujia ethnic minority group are still unclear.

Methods: A total of 2122 Tujia volunteers were recruited and 197 of them were diagnosed with AMD (either dry or wet type). Then the blood specimens of these 197 AMD patients and 404 controls from the remaining 1925 normal Tujia volunteers were collected to detect the frequencies of 39 chosen SNPs. The Bonferroni method was used to correct the *P* values from the Fisher’s exact test.

Results: The mean age of the 197 AMD patients (113 males and 84 females) was 68.4197 years old. No significant differences in allelic and genotypic frequencies were found for all the 39 SNPs between the patients and controls. However, weak correlations between 10 SNPs (CFH rs1329428 TT genotype, CFH rs3753394 CC genotype and T allele, CFH rs1410996 AA genotype, CFH rs800292 AA genotype, CFH rs800292 A allele, VEGF rs833061 TT genotype and C allele, VEGF rs2010963 CG genotype, VEGFR2 rs1531289 TT genotype, ARMS2 rs10490924 TT genotype, KCTD10 rs238104 GC genotype, rs1531289 T allele and ARMS2 rs10490924 T allele) and AMD were shown.

Conclusions: The effects of 39 SNPs have found no associations with the morbidity of AMD in Chinese Tujia ethnic minority group.

Keywords: Age-related macular degeneration, Single nucleotide polymorphism, Chinese Tujia ethnic minority group

Background

Age-related macular degeneration (AMD) is the main cause of blindness and vision loss in old people in developed countries [1]. The formation of deposits, inflammation and ultimately neurodegeneration in the macula are typical features of the disease. In general, AMD can be divided into two subtypes: the non-exudative (dry or atrophic) subtype and the exudative (wet or neovascular) subtype [2]. The development of the disease is a complex interplay of age, environmental, genetic, metabolic and many other factors [3].

Epidemiological and gene-mapping studies supported that the genetic factors played important roles in the pathogenesis of AMD [4, 5]. A genome-wide study reported 52 independently AMD associated variants by analyzing more than 15,000 patients and controls. The results also showed that rare variants could directly affect causal genes [6]. In addition, other researchers found that the loci 3p13 and 10q26 had a relationship with the complex basis of the AMD by analyzing 70 families and these genes were involved in immune response, inflammation and retina homeostasis [7]. Genome-wide association study had also been used to clarify the possible relationships between SNPs and outcomes of anti-vascular endothelial growth factor (VEGF) treatment for exudative AMD and the results showed that the age-related maculopathy susceptibility 2 (ARMS2/HTRA1) polymorphism rs10490924 might be a good marker to predict the effect of ranibizumab treatment [8].

* Correspondence: zhouxiyuan2002@163.com
1 Department of Ophthalmology, the Second Affiliated Hospital of Chongqing Medical University, NO.74, Linjiang Road, Yuzhong District, Chongqing 400010, China
Full list of author information is available at the end of the article

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The Chinese Tujia ethnic minority group mainly live on the mountains in the middle of China. Due to the relative isolation of mountain, this ethnic minority group may have its own specific genome. The genetic analysis of Y chromosome in Chinese Tujia ethnic minority group demonstrated that the 17 Y-STR loci were highly polymorphic [9]. Previous studies conducted by Chinese epidemiologists reported that gene variants in CFH, ARMS2 and HTRA1 were related to an increased risk of AMD in a northern Chinese population, which was partially consistent with the results of the western world [10, 11]. However, the epidemiology analysis of AMD in Chinese Tujia ethnic minority group and its potential pathogenic mechanism had not been reported.

In this study, we calculated the morbidity of AMD in 2122 Tujia volunteers. Then we analyzed the frequencies of 39 AMD-associated SNPs in 197 AMD patients and 404 normal controls. Our goal was to identify the possible pathogenic SNPs of AMD in Chinese Tujia ethnic minority group.

Methods

Patients and data collection

Our study recruited 2122 individuals who belonged to Chinese Tujia ethnic minority group in the Second Affiliated Hospital of Chongqing Medical University from January 2009 to December 2016 (Chongqing, China). Diagnosis and grading for AMD followed the standard of clinical age-related maculopathy staging (CARMs) system and maculopathy could be classified into five grades. Grade 1: no drusen or 10 small drusen without pigment abnormalities. Grade 2: approximately 10 small drusen or 15 intermediate drusen. Grade 3: approximately 15 intermediate drusen or any large drusen. Grade 4: geographic atrophy with involvement of the macular center. Grade 5: exudative AMD. Volunteers with Grade 2 or above AMD (either unilateral eye or bilateral eyes) were recruited as the patients group [12]. The ethics committee of the Second Affiliated Hospital of Chongqing Medical University approved the study and the medical records and blood samples were obtained from volunteers with written informed consents.

Single nucleotide polymorphism (SNP) selection

Target genes and SNPs were chosen according to previously published studies [13–26]. As a result, 39 SNPs of 16 genes were selected and included 8 SNPs (rs1061170, rs800292, rs3753394, rs1410996, rs1329428, rs6677604, rs380390, rs10737680) of complement factor I(CFI), 2 SNPs (rs3732379, rs3732378) of C-X3-C motif chemokine receptor 1(CX3CR1), 4 SNPs (rs943080, rs3025039, rs833061, rs2010963) of VEGF, 4 SNPs (rs9554322, rs7337610, rs9582036, rs9499322) of vascular endothelial growth factor receptor (VEGFR), 1 SNP (rs1531289) of VEGFR2, 1 SNP (rs6987702) of tribbles pseudokinase 1(TRIB1), 2 SNPs (rs1800775, rs3764261) of cholesteryl ester transfer protein(CETP), 1 SNP (rs2338104) of potassium channel tetramerization domain containing 10(KCTD10), 2 SNPs (rs10033900, rs11728699, rs7439493, rs4698775) of complement factor H(CFH), 1 SNP (rs1883025) of ATP binding cassette subfamily A member 1(ABCA1), 1 SNP (rs11728699, rs7439493, rs4698775) of complement factor I(CFI), 2 SNPs (rs3732379, rs3732378) of C-X3-C motif chemokine receptor 1(CX3CR1), 4 SNPs (rs943080, rs3025039, rs833061, rs2010963) of VEGF, 4 SNPs (rs9554322, rs7337610, rs9582036, rs9499322) of vascular endothelial growth factor receptor (VEGFR), 1 SNP (rs1531289) of VEGFR2, 1 SNP (rs6987702) of tribbles pseudokinase 1(TRIB1), 2 SNPs (rs1800775, rs3764261) of cholesteryl ester transfer protein(CETP), 1 SNP (rs2338104) of potassium channel tetramerization domain containing 10(KCTD10), 1 SNP (rs8017304) of RAD51 paralog B (RAD51B) and 1 SNP (rs1883025) of ATP binding cassette subfamily A member 1(ABCA1).

DNA extraction and genotyping

Peripheral blood of AMD patients and the controls were subjected to genomic DNA extraction by using the QIAmp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA, USA) and the DNAs were stored at −80°C. Genotype identifications of the 39 SNPs were conducted with the iPLEX Gold genotyping assay and Sequenom Mass ARRAY (Sequenom, CA, USA). Sequenom SNP Assay Design software (version 3.0) was used to design the primers of iPLEX reactions [27]. Primer sequences used were shown in Additional file 1: Table S1.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) analysis was carried out in normal controls and no SNPs significantly deviated from HWE (P>0.05). Fisher’s exact test was applied to evaluate the differences in allele and genotype frequencies of all SNPs between patients and healthy controls by using SPSS (version 19.0; SPSS Inc., Chicago, IL). The Bonferroni method was conducted to perform correction for multiple comparisons whereby the P value was multiplied with the number of comparisons (P corrected (Pc)) [27]. It was considered to be significant when Pc was less than 0.05.

Results

A total of 2122 volunteers aged from 50 to 90 years old were recruited to our study. The fundus examination was used to diagnose and divided the volunteers into five grades according to the clinical age-related maculopathy staging (CARMs) system. The representative images of grade 2 to 5 AMD were shown in Fig. 1. Among the 2122 volunteers, we found that 197 cases (113 males and 84 females) could be diagnosed as AMD and the mean age was 68.4±6 years. We found AM (Table 1). Moreover, only 404 normal volunteers (245 males and 159 females, mean age was 63.5±4 normal volu) accepted the SNPs examinations and we assigned them to the normal control group.

Next, the blood specimens from AMD cases and controls were collected to detect the genome sequences. We
chose 39 SNPs covering 16 genes to figure out if these SNPs could be pathogenic factors for AMD in Chinese Tujia ethnic minority group. As a result, we found that all 39 SNPs of controls met the Hardy-Weinberg equilibrium. No significant differences in both allelic and genotypic frequencies were found for all the 39 SNPs between the patient and control groups according to the $P_c$ values (Additional file 2: Table S2). However, the $P$ values showed weak correlations between 10 SNPs of 5 genes and AMD (Table 2). Compared with the AMD patients, the frequencies of the CFH rs1329428 TT genotype ($P=0.023$, OR = 1.649 and 95% CI = 1.069–2.543), CFH rs3753394 CC genotype ($P=0.006$, OR = 1.738 and 95% CI = 1.164–2.594) and T allele ($P=0.029$, OR = 1.307 and 95% CI = 1.027–1.664), CFH rs1410996 AA genotype ($P=0.008$, OR = 1.814 and 95% CI = 1.164–2.826) and CFH rs800292 AA genotype ($P=0.009$, OR = 1.787 and 95% CI = 1.154–2.769) were decreased in the controls. On the contrary, the frequency of the CFH rs800292 A allele ($P=0.011$, OR = 0.730 and 95% CI = 0.571–0.932) was increased in the controls. Moreover, the frequencies of the VEGF rs833061 TT genotype ($P=0.020$, OR = 1.511 and 95% CI = 1.067–2.138) and C allele ($P=0.021$, OR = 1.390 and 95% CI = 1.051–1.837), VEGF rs2010963 CG genotype ($P=0.032$, OR = 1.462 and 95% CI = 1.033–2.071), VEGFR2 rs1531289 TT genotype ($P=0.040$, OR = 2.025 and 95% CI = 1.020–4.022), ARMS2 rs10490924 TT genotype ($P=0.002$, OR = 1.928 and 95% CI = 1.280–2.904) and KCTD10 rs238104 GC genotype ($P=0.019$, OR = 1.505 and 95% CI = 1.068–2.120) were decreased and the frequencies of VEGFR2 rs1531289 T allele ($P=0.012$, OR = 0.690 and 95% CI = 0.516–0.924) and ARMS2 rs10490924 T allele ($P=0.037$, OR = 0.687 and 95% CI = 0.482–0.978) were increased in the controls comparing with the AMD patients.

**Discussion**

In present study, we compared the frequencies of 39 SNPs of 16 genes between 193 AMD patients and 404 controls from Chinese Tujia ethnic minority group. It had reported that ARMS2 and CFH variants were associated with neovascular AMD in the Thai, Korean and Chinese Han population [28–30] and no previous studies focused on the associations between SNPs and AMD in Tujia ethnic minority group. Therefore, we designed this research to identify the potential associations. Finally, our results showed that no significant differences for these 39 SNPs were found between the two groups. However, the $P$ value suggested that the AMD had weak correlations with CFH SNPs, VEGF family SNPs and ARMS2 SNP.

The major candidate genes for AMD pathogenesis were CFH and ARMS2 [31, 32]. Previous study reported gene variants in CFH and ARMS2 were related to increased risks of AMD in Chinese Han population [33].
| Genes | SNPs | Total sample | Case | Control | HWE | P | Pc | OR | 95%CI |
|-------|------|--------------|------|---------|-----|---|----|----|------|
| CFH   | rs1329428 | 197 404 |      |         |     |   |    |    |      |
|       | CC    | 59 136 | 0.175 | 0.361 | NS  | 0.842 | 0.583–1.217 |
|       | CT    | 94 208 | 0.386 | 0.860 | NS  | 0.612–1.209 |
|       | TT    | 44 60 | 0.023 | 0.164 | NS  | 1.069–2.543 |
|       | C     | 212 480 |      |         |     |   |    |    |      |
|       | T     | 182 328 | 0.065 | 0.796 | NS  | 0.624–1.015 |
| CFH   | rs3753394 | 197 404 |      |         |     |   |    |    |      |
|       | CC    | 55 74 | 0.416 | 0.006 | NS  | 1.738 | 1.164–2.594 |
|       | CT    | 89 208 | 0.163 | 0.784 | NS  | 0.558–1.104 |
|       | TT    | 53 124 | 0.357 | 0.837 | NS  | 0.573–1.223 |
|       | C     | 199 356 |      |         |     |   |    |    |      |
|       | T     | 195 456 | 0.029 | 1.307 | NS  | 1.027–1.664 |
| CFH   | rs1410996 | 190 386 |      |         |     |   |    |    |      |
|       | GG    | 60 137 | 0.128 | 0.469 | NS  | 0.873 | 0.603–1.262 |
|       | GA    | 87 204 | 0.194 | 0.795 | NS  | 0.562–1.125 |
|       | AA    | 43 55 | 0.008 | 1.814 | NS  | 1.164–2.826 |
|       | G     | 207 478 |      |         |     |   |    |    |      |
|       | A     | 173 319 | 0.056 | 0.786 | NS  | 0.614–1.006 |
| CFH   | rs800292 | 193 402 |      |         |     |   |    |    |      |
|       | GG    | 54 140 | 0.190 | 0.095 | NS  | 0.727 | 0.500–1.058 |
|       | GA    | 95 205 | 0.686 | 0.932 | NS  | 0.661–1.313 |
|       | AA    | 44 57 | 0.009 | 1.787 | NS  | 1.154–2.769 |
|       | G     | 203 485 |      |         |     |   |    |    |      |
|       | A     | 183 319 | 0.011 | 0.730 | NS  | 0.571–0.932 |
| VEGF  | rs833061 | 192 403 |      |         |     |   |    |    |      |
|       | TT    | 113 196 | 0.881 | 0.020 | NS  | 1.511 | 1.067–2.138 |
|       | TC    | 67 171 | 0.079 | 0.727 | NS  | 0.509–1.039 |
|       | CC    | 12 36 | 0.261 | 0.680 | NS  | 0.345–1.338 |
|       | T     | 293 563 |      |         |     |   |    |    |      |
|       | C     | 91 243 | 0.021 | 1.390 | NS  | 1.051–1.837 |
| VEGF  | rs2010963 | 189 396 |      |         |     |   |    |    |      |
|       | CC    | 27 64 | 0.089 | 0.558 | NS  | 0.865 | 0.531–1.408 |
|       | CG    | 99 170 | 0.032 | 1.462 | NS  | 1.033–2.071 |
|       | GG    | 63 162 | 0.078 | 0.722 | NS  | 0.502–1.038 |
|       | C     | 153 298 |      |         |     |   |    |    |      |
|       | G     | 225 494 | 0.349 | 1.127 | NS  | 0.877–1.448 |
| VEGFR2 | rs1531289 | 197 404 |      |         |     |   |    |    |      |
|       | CC    | 118 275 | 0.181 | 0.048 | NS  | 0.701 | 0.492–0.998 |
|       | CT    | 62 111 | 0.310 | 1.212 | NS  | 0.836–1.758 |
|       | TT    | 17 18 | 0.040 | 2.025 | NS  | 1.020–4.022 |
|       | C     | 298 661 |      |         |     |   |    |    |      |
|       | T     | 96 147 | 0.012 | 0.690 | NS  | 0.516–0.924 |
| ARMS2 | rs10490924 | 197 404 |      |         |     |   |    |    |      |
|       | GG    | 57 137 | 0.625 | 0.213 | NS  | 0.791 | 0.546–1.145 |
However, our results showed negative correlation, which might be caused by the racial and sample size differences. Furthermore, VEGF gene played an important role in regulating angiogenesis and permeability [34]. The SNPs of VEGF were related to the formation of choroidal neovascularization in exudative AMD. Therefore, anti-VEGF agents had been widely used to treat the exudative AMD. The alleles in CFH, ARMS2, and VEGFA were associated with genetic anticipation and inadequate response to the anti-VEGF agents in AMD patients [35]. The relationship between the delayed functional and limited response to the injection of bevacizumab and the CFH gene polymorphism T1277C was also identified [36]. In our study, no associations were found between the SNPs of VEGF family genes and the morbidity of AMD. However, a stratified analysis had not been carried out and the relationships between SNPs of VEGF family genes and morbidity of exudative AMD were still unclear. In addition, the SNPs of VEGF family genes might affect the AMD by impacting the drug responses in Chinese Tujia ethnic minority group.

Our study had several limitations. We only chose SNPs that have been previously reported and no new SNPs were found. A genome-wide study should be carried out to find more pathogenic SNPs. Furthermore, the stratified analysis of different ages, genders or AMD types should also be used to deeply investigate the associations between the SNPs and the AMD morbidity in Chinese Tujia ethnic minority group. Last, we only recruited a very small sample size of patients in our study and the representativeness of our findings was limited. In the future, we would collect more patients to perform the SNP detections.

Conclusions
In sum, the chosen 39 SNPs had no associations with the morbidity of AMD in Chinese Tujia ethnic minority group.

Additional files

Additional file 1: Table S1. Primer sequences we used to detect the 39 SNPs were listed in the table. (XLSX 11 kb)

Additional file 2: Table S2. The distributions of allelic and genotypic frequencies for 39 SNPs were listed in the table. The details of HWE, \( P \) value, \( P_{\text{correct}} \) value, OR and 95% CI were also shown. (XLS 102 kb)

Abbreviations
AMD: Age-related macular degeneration; CARMS: Clinical age-related maculopathy staging; HWE: Hardy-Weinberg equilibrium; SNP: Single nucleotide polymorphism

Acknowledgements
Not applicable.

Funding
This study was supported by Epidemiological investigation of Han and Tujia AMD in Southwest China and study of related gene polymorphisms(cstc2015shmszx120058). The funding body was mainly used in the specimens collection and data analysis.

Availability of data and materials
The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors’ contributions
XZ made substantial contributions to conception and designed the whole research; Acquisition of data and analysis and interpretation of data were mainly performed by SL, MW, BZ, XX and HW. All authors agreed to be

| Genes     | SNPs | Case | Control | HWE    | \( P \) | \( P_{\text{correct}} \) | OR    | 95% CI     |
|-----------|------|------|---------|--------|--------|---------------------|-------|------------|
| GT        | 86   | 200  | 0.169   | NS     | 0.786  | 0.558–1.108        |
| TT        | 54   | 66   | 0.002   | NS     | 1.928  | 1.280–2.904        |
| G         | 200  | 474  |         |        |        |                     |
| T         | 194  | 332  | 0.008   | NS     | 0.722  | 0.567–0.920        |
| Total sample | 197 | 403  |         |        |        |                     |
| GG        | 19   | 44   | 0.673   | NS     | 0.633  | 0.871              |
| GC        | 110  | 184  | 0.019   | NS     | 1.505  | 1.068–2.120        |
| CC        | 68   | 175  | 0.037   | NS     | 0.687  | 0.482–0.978        |
| G         | 148  | 272  |         |        |        |                     |
| C         | 246  | 534  | 0.193   | NS     | 1.181  | 0.919–1.518        |
| Total sample | 193 | 402  |         |        |        |                     |
| AA        | 3    | 0    | 0.573   | NS     | 0.034  |                     |
| AG        | 12   | 22   | 0.714   | NS     | 1.145  | 0.554–2.365        |
| GG        | 178  | 380  | 0.277   | NS     | 0.687  | 0.348–1.356        |
| A         | 18   | 22   |         |        |        |                     |
| G         | 368  | 782  | 0.084   | NS     | 1.739  | 0.921–3.281        |
accountable for all aspects of the work. The final version of the manuscript were approved all authors.

Ethics approval and consent to participate
The ethics committee of the Second Affiliated Hospital of Chongqing Medical University approved the study and the medical records and blood samples were obtained from volunteers with written informed consents.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
1Department of Ophthalmology, the Second Affiliated Hospital of Chongqing Medical University, NO.74, Linjiang Road, Yuzhong District, Chongqing 400010, China. 2Chongqing Key Laboratory of Ophthalmology, Chongqing Medical University, NO.74, Linjiang Road, Yuzhong District, Chongqing 400010, China.

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