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Association Between Monocyte Chemotactic Protein 1 Variants and Age-Related Macular Degeneration Onset Among Chinese People

Authors' Contribution:
Study Design A
Data Collection B
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Data Interpretation D
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Background: We assessed the potential association between monocyte chemotactic protein 1 (MCP-1) variants (rs1024611 and rs3760396) and age-related macular degeneration (AMD) susceptibility among Chinese Han people.

Material/Methods: Our research included 129 AMD patients and 131 healthy controls. Genotyping for MCP-1 variants was performed in the 2 groups, and genotype and allele distributions were checked between groups by χ^2 analysis. Odds ratio (OR) and 95% confidence interval (CI) reflected the potential association between MCP-1 variants and AMD risk. The linkage disequilibrium of polymorphisms was detected using Haploview.

Results: Significant differences in rs1024611 genotype distributions were detected between the 2 groups, and homozygous carriers with GG genotype had higher AMD incidence (P<0.05, OR=2.650, 95% CI=1.127–6.231). The rs1024611 G allele frequency was significantly higher in AMD patients, suggesting that the G allele promotes AMD onset (P<0.05, OR=1.447, 95% CI=1.013–2.068). Strong linkage disequilibrium was found between rs1024611 and rs3760396, and haplotype $A_{rs1024611}$–$C_{rs3760396}$ was significantly associated with decreased risk of AMD (P=0.001, OR=0.502, 95% CI=0.335–0.752).

Conclusions: MCP-1 rs1024611 variant appears to contribute to risk of AMD in the Chinese Han population, and the interaction of MCP-1 polymorphisms may also influence individual susceptibility to AMD.

MeSH Keywords: Amplified Fragment Length Polymorphism Analysis • Macular Degeneration • Receptors, CCR2

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Background

Age-related macular degeneration (AMD) is a progressive and chronic disease of the retina, and is an important cause of irreparable visual loss among older people worldwide [1]. AMD occurs in people aged 55 years and older in developed countries [2]. AMD is categorized into dry and neovascular subtypes [3], and neovascular AMD is the main causes of AMD-related vision loss. AMD is a complicated illness, and various lifestyle risk factors appear to affect its onset and development, such as nutrition, diet, smoking, and obesity [4,5]. Without effective treatment, neovascular AMD leads to severe visual impairment, with an average loss of 4 lines of visual acuity within 2 years of disease onset [6]. A major study found projected that 196 million people will have AMD by the year 2020, reaching 288 million by 2040 [7]. The pathogenesis of AMD is still incompletely understood, but it has been proved to be influenced by both environmental and genetic factors [8].

Monocyte chemotactic protein 1 (MCP-1), or chemokine (C-C motif) ligand 2 (CCL2), belongs to the CC chemokine subfamily. It has important influences on host defence, and can involve monocytes and macrophages in acute and chronic phases of inflammation [9]. Previous studies have revealed that higher expression of MCP-1 is present in patients with several inflammatory disease, including neuropsychiatric syndromes such as systemic lupus erythematosus [10], rheumatoid arthritis (RA) [11], and osteoarthritis [12]. The encoding gene, *MCP-1*, seats at chromosome 17, and several genetic mutations are recognized.

Previous evidence reveals functional abnormalities of the innate immune system take part in AMD via altering inflammatory homeostasis in the eyes [13]; we therefore speculated that MCP-1 is involved in AMD initiation. Furthermore, a major study found a significantly higher concentrations of MCP-1 in AMD patients, which further confirms our hypothesis [14]. Single-nucleotide polymorphism (SNP) in *MCP-1* can change the expression and structure of its coding protein, thus influencing individual susceptibility to AMD. Rs1024611 seats on positions -2518 in *MCP-1* 5'-flnking region with the allele mutation of A to G, and affects *MCP-1* transcription activity [15]. Rs3760396 is confirmed as a deleterious mutation in the Chinese Han population, and has been reported to be correlated with lung cancer [16]. However, their genetic association with AMD risk in the Chinese Han population has been unclear.

In the present study, we detected a strong association between *MCP-1* SNPs and AMD risk among Chinese Han people, and we also assessed the linkage disequilibrium of rs1024611 and rs3760396 polymorphisms.

Material and Methods

Subjects

A total of 129 individuals with AMD in at least 1 eye were enrolled as the case group. All cases were diagnosed and confirmed through ophthalmoscope examination, color fundus photography, fluorescein and indocyanine green angiography, and optical coherence tomography, and all were admitted to the Affiliated Hospital of Qingdao University. Inclusion criteria for AMD patients were: >50 years old and diagnosed with dry AMD by 2 ophthalmologists [17]. Exclusion criteria were: high myopia (spherical equivalent>6.00 diopters); macular atrophy due to other causes such as trauma, inflammation, and vascular illness; other neovascularized maculopathies like angioid steaks, retinal angiomatous, and proliferation; and polypoidal choroidal vasculopathy. The control group consisted of 131 age- and sex-matched healthy persons who were attending routine health examinations. The controls received visual acuity measurements, slit-lamp biomicroscopy, ophthalmoscope examination, and color fundus photography. The controls were age 50 years or older, without any macular pathology or early AMD such as drusen, RPE changes, retinal diseases, and glaucoma, or other diseases influencing study results, such as cancer and inflammatory diseases, and they had no AMD family history. All participants were Chinese Han people, without blood relation.

Sample collection

A 5-ml peripheral vein blood sample was obtained from each participant, anticoagulated by 0.5% EDTA (pH 8.0), and then stored at –20°C. Total genomic DNA was separated using the TaKaRa Genome DNA Extraction Kit (Dalian Biological Engineering Co., China), and stored at 20°C for later use.

Determination of polymorphisms

MCP-1 gene 2 polymorphisms rs1024611 and rs3760396 were genotyped in 129 AMD cases and 131 healthy controls. Sequences for the 2 polymorphisms were directly amplified via polymerase chain reaction (PCR). The primer sequences for the 2 variants were designed using Primer Premier 5.0, and synthesized in Shanghai Sangon biotech Co. (Table 1). The PCR cycling conditions were set as follows: an initial denaturation step of 95°C for 7 min, tracked by 35 cycles of 95°C degeneration for 1 min, annealing at different temperatures for 1 min (57°C for rs1024611 and 52°C for rs3760396), and extension at 72°C for 1 min, and a final extension at 72°C for 10 min.

The PCR products of rs1024611 were diagnosed by the restriction enzyme PvuII for 4 h at 37°C, and the diagnosed products were then analyzed through agarose gel electrophoresis

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Table 1. Primer sequences for *MCP-1* gene polymorphisms rs1024611 and rs3760396.

SNP		Primer sequences
rs1024611	Sense	5'-CCGAGATGTTCCCAGCACAG- 3'
	Reverse	5'-CTGCTTTGCTTGTGCCTCTT- 3'
rs3760396	Sense	5' -GCAACAGCCTCCTAACTC-3'
	Reverse	5'-AATAGCCTGCTCAAGGTC-3'

Table 2. The baseline demographics of AMD and healthy controls.

Characteristics		Case, n=129	Control, n=131	P
Age (year)	The range	52–88	51–84	0.124
	Mean value	70.89±8.96	69.24±8.40	
Gender (%)	Male	63 (48.84)	70 (53.44)	0.458
	Female	66 (51.16)	61 (46.56)	
Smoking (%)	Yes	45 (34.88)	38 (29.01)	0.310
	No	84 (65.12)	93 (70.99)	
Drinking (%)	Yes	41 (31.78)	32 (24.43)	0.187
	No	88 (68.22)	99 (75.57)	
Hypertension (%)	Yes	62 (48.06)	35 (26.72)	<0.001
	No	67 (51.94)	96 (73.28)	

AMD – age-related macular degeneration.

and visualized under UV light. Samples producing a 929bp band were typed as AA genotype, samples producing 2 bands of 707bp and 222bp were typed as GG genotype, and samples producing 3 bands of 929, 707, and 222bp were typed as AG genotype. The rs3760396 PCR products were genotyped by direct sequencing. Following amplification, the PCR products of rs3760396 were purified with a purification kit, and sequenced by automated DNA sequencing with an Applied Biosystems 3730×l automated sequencer (Applied Biosystems, Foster City, CA, USA). The sequence analysis was performed using Vector NTI software.

Statistical analysis

All data analyses were performed using PASW statistics 18.0 statistical software. All genotype and allele frequencies for our variables of interest were determined through direct counting. Hardy-Weinberg equilibrium (HWE) for each polymorphism was evaluated by chi-square test to assess the quality of the genotype in the control group. Chi-square analysis was performed to compare the differences in genotype and allele distributions between groups. Potential associations between *MCP-1* 2 polymorphisms and AMD risk were assessed by calculating odds ratio (OR) and 95% confidence interval (CI). The linkage disequilibrium of *MCP-1* 2 polymorphisms was tested by Haploview software. Significance was set at a *P* value of<0.05.

Results

The baseline characteristics of study subjects in the case and control groups

In this study, a total of 129 AMD patients and 131 healthy controls were included. The case group consisted of 63 males and 66 females and their age range was 52–88 years old, with a mean age of 70.89±8.96. In the control group, the male/female ratio was 70/61 and the average age was 69.24±8.40, with the range of 51–84 years old. There was no significant difference in distribution of age and sex between the 2 groups (*P*>0.05). We also found that smoking and drinking were also not risk factors for AMD in this population (*P*>0.05). There was significantly more hypertension in the case group than in the control group (*P*=0.001) and it was a risk factor for AMD. The data ae listed in Table 2.

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Table 3. Genotype and allele distributions of MCP-1 gene polymorphisms rs1024611 and rs3760396 in case and control group.

Genotype/allele	Case n=129 (%)	Control n=131 (%)	χ^2	P	OR (95% CI)
rs1024611					
AA	10 (7.75)	21 (16.03)	–	–	1
GA	66 (51.16)	68 (51.91)	2.927	0.087	2.038 (0.893–4.654)
GG	53 (41.09)	42 (32.06)	5.177	0.023	2.650 (1.127–6.231)
A	86 (33.33)	110 (41.98)	–	–	1
G	172 (66.67)	152 (58.02)	4.143	0.042	1.447 (1.013–2.068)
rs3760396					
CC	101 (78.29)	112 (85.50)	–	–	1
GC	25 (19.38)	18 (13.74)	1.646	0.200	1.540 (0.794–2.988)
GG	3 (2.33)	1 (0.76)	1.197	0.274	3.327 (0.341–32.495)
C	227 (87.98)	242 (92.37)	–	–	1
G	31 (12.02)	20 (7.63)	2.822	0.093	1.652 (0.915–2.983)

Table 4. Haplotype analysis of *MCP-1* rs1024611 and rs3760396 polymorphisms in AMD occurrence.

rs1024611–rs3760396	Haplotype (%)		P	OR (95% CI)
	Case, 2n=258	Control, 2n=262		
G–C	175 (67.83)	152 (58.02)	–	Ref.
A–C	52 (20.16)	90 (34.35)	0.001	0.502 (0.335–0.752)
A–G	31 (12.01)	20 (7.63)	0.332	1.346 (0.737–2.460)

HWE test

Genotype and allele distributions for *MCP-1* variants rs1024611 and rs3760396 in cases and controls are summarized in Table 3. Chi-square testing showed that genotype distributions were all in HWE in cases and controls (P>0.05). The results demonstrated that our study groups were from the same Mendelian population and had good representativeness.

Distribution of genotypes and alleles of *MCP-1* gene polymorphisms

As shown in Table 3, AA genotype frequency of rs1024611 was decreased in AMD patients compared with the controls, and its GG genotype frequency in AMD patients was significantly higher than in controls (7.75% *vs.* 16.03%, 41.09% *vs.* 32.06%, P=0.023), indicating that GG genotype of rs1024611 was remarkably correlated with the risk of AMD occurrence (OR=2.650, 95% CI=1.127–6.231). Additionally, G allele frequency was also significantly higher in cases compared with controls (66.67% *vs.* 58.02%), with a P value of 0.042, and it also conferred increased risk of AMD (OR=1.447, 95% CI=1.013–2.068). All results suggested the obvious connection for *MCP-1* rs1024611 polymorphism with AMD incidence risk among Chinese Han people.

The genotypes of rs3760396 polymorphism had a distribution of 78.29%, 19.38%, 2.33% for CC, GC, and GG genotypes in AMD cases, and 85.50%, 13.74%, and 0.76% in healthy controls, respectively. The C and G allele frequencies were 87.98% and 12.0% in cases and 92.37% and 7.63% in controls, respectively. But no remarkable dissimilarity emerged in genotype or allele distributions between 2 groups (P>0.05). We speculated that *MCP-1* rs3760396 polymorphism did not have a significant influence on AMD origination.

Linkage disequilibrium and haplotypes analyses of *MCP-1* polymorphisms

We analyzed the linkage disequilibrium of *MCP-1* rs1024611 and rs3760396 polymorphisms, and the results showed a strong linkage disequilibrium between them. Three haplotypes were detected: $G_{rs1024611}$–$C_{rs3760396}$, $A_{rs1024611}$–$C_{rs3760396,}$ and $A_{rs1024611}$–$G_{rs3760396,}$ and their frequencies were 67.83%, 20.16%, 12.01% in AMD patients and 58.02%, 34.35%, 7.63% in the controls, respectively. $A_{rs1024611}$–$C_{rs3760396}$ haplotype was significantly less common in AMD patients (P=0.001) compared with the controls, suggesting that it is a protective factor against AMD (OR=0.502, 95% CI=0.335–0.752). The data are shown in Table 4.

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Discussion

With the increasing aging population, the prevalence of AMD is also increasing in developing countries. AMD has become the major cause of irreversible blindness in the elderly, and is identified as a significant public health problem that imposes increasing social and economic burdens. Evidence suggests AMD progression is caused by a complex interplay of genetic and environmental factors [13]. Significant evidence exists indicating inflammation-associated molecules (cytokines and chemokines), immune cells (macrophages), and complement proteins all take part in AMD initiation and progression [18]. A number of AMD susceptibility genes have been identified, such as cytokine genes (e.g., tumor necrosis factor (*TNF*) gene, interloukin-10 (*IL-10*) gene); the toll-like receptor 3 (*TLR3*) gene; and various other genes regulating complement, high-density lipoprotein, extracellular matrix, and angiogenic pathways [18–20].

Many factors reportedly affect AMD occurrence, including aging, smoking, family history, sunlight exposure, oxidative stress, hypertension, and inflammation [13,21–24]. A series of studies have confirmed that the complement cascade and immune mechanism-mediated inflammatory reaction are critical factors in the onset and development of AMD [25,26]. AMD is now regarded as a persistent, low-grade, chronic, inflammatory disease.

MCP-1 is an important inflammatory factor, and exerts important influences on immunity-related diseases. MCP-1 is secreted by multiple cell types, including mononuclear cells, macrophages, endothelial cells, and smooth muscle cells, and it functions mainly by promoting the mononuclear migration circulating in blood and differentiating into macrophages [27]. Jonas et al. measured the concentration of cytokines in the aqueous humor of eyes with exudative AMD, and detected dramatically higher concentrations of MCP-1, which supports the pivotal effects of MCP-1 on AMD progression [14]. Rs1024611 seats on positions -2518 in *MCP-1* 5'-flnking region with the allele mutation of A to G, and can affect MCP-1 transcription activity [15]; it is reportedly linked to myocardial infarction (MI) and diabetic retinopathy (DR) [28,29]. Moreover, Sun et al. demonstrated that rs1024611 polymorphism is significantly correlated with MCP-1 expression [30]. However, few studies have been performed to explore the genetic association between *MCP-1* gene polymorphisms and AMD susceptibility in the Chinese Han population.

Our research assessed the potential association of the *MCP-1* gene rs1024611 and rs3760396 variants with AMD among Chinese Han people. A strong association was found between *MCP-1* gene rs1024611 variant and AMD susceptibility. We noted that the rs1024611 GG genotype and the G allele increased individual susceptibility to AMD. This result was consistent with previous studies. Sharma reported that GG genotype and G allele of *MCP-1* rs1024611 variant are significantly correlated with increased risk of AMD in Indians [31]. However, Bonyadi found that CCL2–2518 (rs1024611) was not significantly association with AMD in Iranians [32]. This may derive from genotype distribution differences of rs1024611 in various ethnic populations. Reportedly, rs3760396 is a risk factor for lung cancer in a subtype-specific manner among Chinese Han people [31]. However, in the present study, no substantial link emerged between rs3760396 variant and AMD susceptibility. In addition, a strong linkage disequilibrium was found between rs1024611 and rs3760396 polymorphisms, and haplotype $A_{rs1024611}$–$C_{rs3760396}$ significantly decreased the individual susceptibility to AMD in this study population. It was worth noting that G allele in rs1024611 was still found in more than 50% of subjects in the control group. Combined with the results of haplotype analysis, we speculated that the single-polymorphism locus might not result in significant changes in gene function. Interactions between genetic factors and environmental factors might also be involved in the pathogenesis of AMD. Further investigations are required to address the issue.

Our study has certain limitations. Firstly, the relatively small sample size reduced the statistical power of our results. Second, only a single Han population was included, which might have biased our results. Third, the molecular mechanisms underlying the association of rs1024611 polymorphism with AMD risk were not explored in our study, nor did we assess whether rs1024611 confers risk of AMD through altering MCP-1 expression or structure. We also did not study the interaction of gene polymorphisms and environmental factors. Thus, further studies with larger sample sizes and multiple ethnic groups are required to verify our findings.

Conclusions

In conclusion, *MCP-1* rs1024611 polymorphism appears to contribute to the risk of AMD among Chinese Han people, but rs3760396 does not. In addition, the interaction of rs1024611 and rs3760396 may influence individual susceptibility to AMD.

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