Research Article

The Association of Chemokine Gene Polymorphisms with VKH and Behcet’s Disease in a Chinese Han Population

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1. Introduction

Uveitis is an intraocular inflammatory disease causing severe visual impairment worldwide [1]. In China, Behcet’s disease (BD) and Vogt-Koyanagi Harada (VKH) disease have the highest incidence in uveitis entities. BD is a chronic, relapsing, multisystemic inflammatory disorder, and its classical clinical characters include oral aphthae, genital ulcers, and recurrent iridocyclitis with hypopyon, which is probably due to an autoimmune response [2]. VKH disease is a multisystem autoimmune disease with a hallmark of diffuse granulomatous uveitis accompanied with poliosis, vitiligo, alopecia, and central nervous system abnormalities [3]. Various genes have been demonstrated to be relevant to different types of uveitis, comprising HLA-B27, HLA-A29, HLA-B51, HLA-DR4, IL-10, STAT4, STAT3, and UBAC2 [4–6] which suggested genetic factors are involved in the occurrence and development of uveitis.

Chemokines are a class of proinflammatory cytokines that are able to attract and activate the migration of circulating leukocytes under both physiological and pathological conditions [7]. According to the related structure and function, four subfamilies of human chemokines are classified: CC chemokines, CXC chemokines, CX3C family, and C family. Previous studies showed that chemokines are involved in various inflammatory and autoimmune diseases [8, 9]. Chemokines also contribute to the pathogenesis of uveitis, and previous researches showed that a higher chemokine production might be responsible for the more severe clinical manifestations in Behcet’s disease [10]. A comparison of Japanese VKH disease patients with controls indicated a dramatic decrease in the chemokine CSF-CCL2/MCP-1 [11]. Genetic variations of chemokine genes have been demonstrated responsible for the induction of chronic inflammation [7]. RANTES (CCL5) is associated with diabetes mellitus type 1 both genetically and functionally [12]. In the onset
and development of childhood Idiopathic Thrombocytopenic Purpura, the polymorphism of SDF-1 (CXCL12) gene may be implicated [13]. Intron 1 of the CXCL9 gene (rs2276686) polymorphism may be closely related to pediatric Crohn’s disease [14]. Among Chinese Han individuals, genetic variations of CXCL12-3’-G801A are involved in the pathogenesis of systemic lupus erythematosus [15]. Only few studies have analyzed the association of uveitis with chemokine gene polymorphisms. In Caucasian patients with HLA-B27 associated acute anterior uveitis, the CCL2-2518G allele was found significantly increased [16] and IL-8 (CXCL8) gene polymorphisms may affect susceptibility to BD in Turkey [17]. However, the association between other chemokine gene polymorphisms with uveitis is largely unknown and has been addressed recently by our group. Earlier we reported that CCL2 polymorphisms were protective for BD [18]. In this study, we expanded the amount of chemokines SNPs and also included VKH disease patients. The results show that none of the other chemokine genes polymorphisms showed an association with BD or VKH disease in the Chinese Han population.

2. Material and Methods

2.1. Study Population. Our study recruited 371 BD and 371 VKH disease patients and 605 healthy individuals which are all from Chinese Han population in the First Affiliated Hospital of Chongqing Medical University from January 2009 to April 2015 (Chongqing, China). According to race (Chinese Han) and geography, patients and the controls were matched. Diagnosis for BD and VKH disease followed the standard of the International Study Group for BD [19] and First International Workshop for VKH disease [20], respectively. The local research ethics committee approved the study and all the recruited individuals signed informed consent before donating blood samples. The Declaration of Helsinki adhered to the tenets.

2.2. Single Nucleotide Polymorphism (SNP) Selection. Screening of target chemokine gene SNPs was according to previously published studies which showed a positive association with other autoimmune and inflammatory diseases. Linkage disequilibrium (LD) data from the Han Chinese Hap Map database were taken into account. Twenty-seven SNPs of twelve genes with a minor allele frequency > 0.05 in Han Chinese were selected. These 27 SNPs in 12 chemokine genes, included 4 SNPs (rs1024610, rs1024611, rs13900, and rs4586) of CCL2 [21, 22], 5 SNPs (rs452179, rs2306630, rs2107538, rs9355610, and rs2280788) of CCL5 [12, 23, 24], 1 SNP (rs854680) of CCL16 [25], 2 SNPs (rs223828 and rs223895) of CCL17 [26–28], 3 SNPs (rs951005, rs2492358, and rs2812378) of CCL21 [29–31], 1 SNP (rs4359426) of CCL22 [32], 2 SNPs (rs2302004 and rs2302005) of CCL24 [33], 3 SNPs (rs2227306, rs2227543, and rs4694178) of CXCL8 [34], 2 SNPs (rs2276686 and rs2869460) of CXCL9 [14, 35], 1 SNP (rs2869462) of CXCL10 [36], 2 SNPs (rs301517 and rs2839693) of CXCL12 [13, 15], and 1 SNP (rs2277680) of CXCL16 [36]. We excluded rs1024611 of CCL2, since a study concerning this gene had been reported previously by our group [18].

2.3. DNA Extraction and Genotyping. Peripheral blood of the three experimental groups including BD and VKH disease patients and the controls was subjected to genomic DNA extraction with the QiAmp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA, USA) and the DNA was stored at −80°C. The Applied Biosystems 7500 Real-Time PCR system was utilized to genotype CCL17/rs223828 (TagMan assay ID: C_30530263_10) by the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). Genotype identification of the other 25 SNPs was conducted with the iPLEX Gold genotyping assay and Sequenom MassARRAY (Sequenom, CA, USA). Sequenom SNP Assay Design software version 3.0 was used to design primers of iPLEX reactions. Primer sequences used were shown in Table 1. The protocol and experimental requirements were performed strictly based on the instructions.

2.4. Statistical Analysis. Hardy-Weinberg equilibrium (HWE) analysis was carried out by the Chi-square ($\chi^2$) test in healthy samples while the genotype frequency was estimated by direct counting. No SNP significantly deviated from HWE ($P > 0.05$). Fisher’s exact test or $\chi^2$ test was applied to evaluate the differences in allele and genotype frequencies of all SNPs between patients and healthy controls using SPSS (version 17.0; 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 ($P_c$)). It was considered to be significant when $P_c < 0.05$. In those genes having more than one SNP we also performed a haplotype analysis. Haplotypes with a frequency of 0.03 or larger were included in the analysis [37, 38]. $P$ values for haplotypes were multiplied with the number of haplotypes in each gene. $P_c < 0.05$ was considered as significant. Gene–gene interaction analysis was performed using MDR software (MDR 3.0.2 obtained from https://sourceforge.net/projects/mdr/).

3. Results

3.1. Clinical Features. The demographics and clinical symptoms of BD and VKH disease and demographics of controls are all shown in Table 2. The healthy cohort is comprised of 321 men and 284 women, who were on average 38.6 ± 11.1 years old. The BD patients consisted of 371 subjects (326 men and 45 women), 33.2 ± 8.4 years old on average. The VKH disease group contained 371 subjects (204 men and 167 women), and the patients were on average 39.8 ± 13.9 years old.

3.2. Chemokine Genotyping Results. Twenty-six SNPs covering 12 chemokine genes (CCL2, CCL5, CCL6, CCL7, CCL12, CCL24, CXCL8, CXCL9, CXCL10, CXCL12, and CXCL16) were genotyped successfully and all SNPs of controls met the Hardy-Weinberg equilibrium. There was no significant difference in allelic and genotypic frequencies for all the 26 SNPs in the patients of BD or VKH...
| Gene | Primers Applied in 1st-PCR | Primers Applied in 2nd-PCR | UEP_SEQ |
|------|---------------------------|---------------------------|---------|
| CCL2 | rs1024610 **ACGTTGGATTTGTTCCATGAC** | rs13900 **ACGTTGGATGCGCGACAG** | CATGGGAAAGGAGATGCAGCTAC |
| | rs4586 **ACGTTGGATGACAGCAGTTC** | | |
| CCL5 | rs425179 **ACGTTGGATGGCTTAAGGCATAATG** | rs2306630 **ACGTTGGATAGCAGGAGG** | AGTGGATAAAGGAGATGCAGCTAC |
| | rs2107530 **ACGTTGGATGTTTTGCTTATCAATC** | rs935610 **ACGTTGGATGACAGGAGG** | AGTGGATAAAGGAGATGCAGCTAC |
| | rs2290788 **ACGTTGGATGACAGGAGG** | | |
| CCL16 | rs854680 **ACGTTGGATGACAGGAGG** | | |
| CCL17 | rs23895 **ACGTTGGATGACAGGAGG** | rs2492358 **ACGTTGGATGACAGGAGG** | |
| | rs2812357 **ACGTTGGATGACAGGAGG** | | |
| CCL21 | rs4359426 **ACGTTGGATGACAGGAGG** | rs2276886 **ACGTTGGATGACAGGAGG** | |
| | rs2869460 **ACGTTGGATGACAGGAGG** | rs2869462 **ACGTTGGATGACAGGAGG** | |
| | rs2839693 **ACGTTGGATGACAGGAGG** | | |
| | rs2869462 **ACGTTGGATGACAGGAGG** | | |
| CXCL8 | rs22237306 **ACGTTGGATGACAGGAGG** | rs2227543 **ACGTTGGATGACAGGAGG** | |
| | rs469178 **ACGTTGGATGACAGGAGG** | | |
| CXCL9 | rs276886 **ACGTTGGATGACAGGAGG** | rs2869460 **ACGTTGGATGACAGGAGG** | |
| | rs2839693 **ACGTTGGATGACAGGAGG** | rs2839693 **ACGTTGGATGACAGGAGG** | |
| | rs2869462 **ACGTTGGATGACAGGAGG** | | |
| CXCL10 | rs22237306 **ACGTTGGATGACAGGAGG** | rs2227543 **ACGTTGGATGACAGGAGG** | |
| | rs469178 **ACGTTGGATGACAGGAGG** | | |
| CXCL11 | rs276886 **ACGTTGGATGACAGGAGG** | rs2869460 **ACGTTGGATGACAGGAGG** | |
| | rs2839693 **ACGTTGGATGACAGGAGG** | rs2839693 **ACGTTGGATGACAGGAGG** | |
| | rs2869462 **ACGTTGGATGACAGGAGG** | | |
| CXCL12 | rs276886 **ACGTTGGATGACAGGAGG** | rs2869460 **ACGTTGGATGACAGGAGG** | |
| | rs2839693 **ACGTTGGATGACAGGAGG** | rs2839693 **ACGTTGGATGACAGGAGG** | |
| | rs2869462 **ACGTTGGATGACAGGAGG** | | |
| CXCL16 | rs276886 **ACGTTGGATGACAGGAGG** | rs2869460 **ACGTTGGATGACAGGAGG** | |
| | rs2839693 **ACGTTGGATGACAGGAGG** | rs2839693 **ACGTTGGATGACAGGAGG** | |
| | rs2869462 **ACGTTGGATGACAGGAGG** | | |

Table 1: Primers applied in the analysis of restriction fragment length polymorphism (RFLP) in the chemokine genes.
were found in the patients of BD. In genotype and C allele (CXCL10/rs2869462 showed an increased frequency of the CC genotype (P = 0.016, OR = 0.72, and 95% CI = 0.552–0.940). In CXCL12/rs1801157, a weak association was detected in the C allele and CC and CT genotype in VKH disease (P = 0.01, OR = 1.327, and 95% CI = 1.069–1.647; P = 0.00118, OR = 1.556, and 95% CI = 1.190–2.033; P = 8.463 × 10^-4, OR = 0.627, and 95% CI = 0.476–0.826). However, after correction for multiple comparisons, all associations described above lost statistical significance.

3.3. Haplotype Analysis. The haplotypes of chemokine genes (CCL2, CCL5, CCL17, CCL21, CCL24, CXCL8, CXCL9, and CXCL12) having more than one SNP were analyzed using the website http://analysis.bio-x.cn/myAnalysis.php. The haplotype TC of the CXCL12 gene including two SNPs (rs1801157 and rs2839693) showed a significant association with VKH (P = 0.008, OR = 0.745, and 95% CI = 0.599–0.927) (Table 5) compared with healthy controls. The other tested haplotypes failed to show an association with either BD or VKH.

3.4. Stratified Analysis according to Gender and Main Clinical Manifestations of BD and VKH Disease. Stratified analyses were conducted to investigate whether the 26 SNPs have an association with gender and the primary clinical features in BD and VKH disease. BD in our population is more often seen in males and we therefore believe that a gender analysis might also be involved in the genetic predisposition to this disease and a previous study showed that chemokine gene SNPs of both CCL2 gene and CCL5 were more prevalent in males than females with BD [39]. To further confirm whether gender could influence genotype and allele frequencies in both diseases we performed the gender stratified study in these two diseases. We chose clinical manifestations with the frequency of approximately 50%. These included the presence of genital ulcers in BD and sunset glow fundus in VKH disease, respectively. Following Bonferroni correction, no association was observed after stratification by gender (Supplemental Tables 3 and 4). Also no significant differences were detected in these SNPs after stratifying VKH with sunset glow fundus or not. Additionally, no significant association was observed when BD was stratified by genital ulcer. MDR analysis was performed to test the gene-gene (epistatic effect) analysis interaction among 26 SNPs of 12 chemokine genes and this analysis showed that no gene-gene interaction existed in these two diseases. (Supplemental Tables 5 and 6).

### Table 2: Clinical features, age, and sex distribution of patients and controls.

| Clinical features       | Total | %  |
|-------------------------|-------|----|
| Patients with BD        | 371   |    |
| Mean age ± SD           | 33.2 ± 8.4 |    |
| Male                    | 326   | 87.9|
| Female                  | 45    | 12.1|
| Uveitis                 | 358   | 96.5|
| Oral ulcer              | 349   | 94  |
| Genital ulcer           | 208   | 56.1|
| Skin lesion             | 272   | 73.3|
| Arthritis               | 53    | 14.3|
| Pathergy reaction       | 8     | 2.2 |
| Patients with VKH disease| 371   |    |
| Mean age ± SD           | 39.8 ± 13.9 |    |
| Male                    | 204   | 55  |
| Female                  | 167   | 45  |
| Sunset glow fundus      | 182   | 49  |
| Headache                | 157   | 42.3|
| Tinnitus                | 146   | 39.4|
| Vitiligo                | 123   | 33.2|
| Alopexia                | 136   | 36.7|
| Gray hair               | 58    | 15.6|
| Controls                | 605   |    |
| Mean age ± SD           | 38.6 ± 11.1 |    |
| Male                    | 321   | 53.1|
| Female                  | 284   | 46.9|

BD = Behcet’s disease, SD = standard deviation; VKH = Vogt-Koyanagi-Harada.
### Table 3: Genotype and allele frequencies of five chemokine genes’ polymorphism in BD and healthy controls.

| Gene | SNP | Total sample | BD n (%) | Controls n (%) | P value | Pc value | OR  | 95% CI       |
|------|-----|--------------|----------|----------------|---------|----------|-----|-------------|
|      |     |              | 368      | 556            |         |          |     |             |
| CCL5 | rs2107538 | CC          | 165 (0.448) | 213 (0.383) | 0.048   | NS       | 1.309 | 1.002–1.710 |
|      |     | CT          | 155 (0.421) | 272 (0.489) | 0.042   | NS       | 0.760 | 0.583–0.991 |
|      |     | TT          | 48 (0.130)  | 71 (0.128)   | 0.903   | NS       | 1.025 | 0.692–1.517 |
|      |     | C           | 485 (0.659) | 698 (0.628)  | 0.170   | NS       | 1.146 | 0.943–1.393 |
|      |     | T           | 251 (0.341) | 414 (0.372)  | 0.873   | NS       | 0.718–1.060 |

| Gene | SNP | Total sample | BD n (%) | Controls n (%) | P value | Pc value | OR  | 95% CI       |
|------|-----|--------------|----------|----------------|---------|----------|-----|-------------|
|      |     |              | 371      | 604            |         |          |     |             |
| CCL7 | rs223828 | CC          | 155 (0.418) | 287 (0.575) | 0.081   | NS       | 0.793 | 0.611–1.029 |
|      |     | CT          | 167 (0.450) | 264 (0.437) | 0.690   | NS       | 1.054 | 0.813–1.368 |
|      |     | TT          | 49 (0.132)  | 53 (0.088)   | 0.028   | NS       | 1.582 | 1.048–2.389 |
|      |     | C           | 477 (0.643) | 838 (0.694)  | 0.020   | NS       | 0.795 | 0.655–0.965 |
|      |     | T           | 265 (0.357) | 370 (0.306)  | 0.879   | NS       | 0.608–1.024 |

### Table 4: Genotype and allele frequencies of three chemokine genes’ polymorphism in VKH and healthy controls.

| Gene | SNP | Total sample | VKH n (%) | Controls n (%) | P value | Pc value | OR  | 95% CI       |
|------|-----|--------------|----------|----------------|---------|----------|-----|-------------|
|      |     |              | 370      | 555            |         |          |     |             |
| CCL5 | rs9355610 | AA          | 97 (0.262)   | 138 (0.249) | 0.644   | NS       | 1.074 | 0.794–1.451 |
|      |     | AG          | 188 (0.508)  | 273 (0.492)  | 0.629   | NS       | 1.067 | 0.820–1.388 |
|      |     | GG          | 85 (0.230)   | 144 (0.259)  | 0.305   | NS       | 0.851 | 0.626–1.158 |
|      |     | A           | 282 (0.516)  | 549 (0.495)  | 0.029   | NS       | 0.805 | 0.662–0.979 |
|      |     | G           | 358 (0.484)  | 561 (0.505)  | 0.761   | NS       | 0.627–0.925 |

| Gene | SNP | Total sample | VKH n (%) | Controls n (%) | P value | Pc value | OR  | 95% CI       |
|------|-----|--------------|----------|----------------|---------|----------|-----|-------------|
|      |     |              | 364      | 552            |         |          |     |             |
| CCL5 | rs9355610 | CC          | 146 (0.401) | 187 (0.339) | 0.055   | NS       | 1.307 | 0.994–1.719 |
|      |     | CT          | 155 (0.426) | 280 (0.507)  | 0.016   | NS       | 0.720 | 0.552–0.940 |
|      |     | TT          | 63 (0.173)  | 85 (0.154)   | 0.442   | NS       | 1.15  | 0.805–1.643 |
|      |     | C           | 447 (0.614) | 654 (0.592)  | 0.355   | NS       | 1.095 | 0.904–1.326 |
|      |     | T           | 281 (0.386) | 450 (0.408)  | 0.914   | NS       | 0.754–1.106 |

| Gene | SNP | Total sample | VKH n (%) | Controls n (%) | P value | Pc value | OR  | 95% CI       |
|------|-----|--------------|----------|----------------|---------|----------|-----|-------------|
|      |     |              | 368      | 547            |         |          |     |             |
| CXCL8 | rs2227543 | CC          | 223 (0.605) | 271 (0.495) | 0.001   | NS       | 1.566 | 1.198–2.048 |
|      |     | CT          | 122 (0.331) | 241 (0.441)  | 9.443 × 10^−4 | NS | 0.637 | 0.478–0.829 |
|      |     | TT          | 23 (0.062)  | 35 (0.064)   | 0.928   | NS       | 0.975 | 0.566–1.679 |
|      |     | C           | 568 (0.771) | 783 (0.716)  | 0.008   | NS       | 1.343 | 1.081–1.668 |
|      |     | T           | 168 (0.228) | 311 (0.284)  | 0.745   | NS       | 0.600–0.925 |
the haplotype TC of the CXCL12 gene including rs1801157 and rs2839693 shows a significant association with VKH.

Behcet's disease, which is considered an autoinflammatory disorder, is characterized by posterior or generalized uveitis with a chronic nature and with recurrent episodes [2]. VKH disease is considered as a multisystem disorder caused by an autoimmune response against melanocyte associated antigens [3]. The attraction of leukocytes to tissues is an important feature of inflammation and is mediated by the local release of chemokines [40]. Genetic variation in the genes encoding these chemokines may affect their function and may be associated with disease predisposition. Several studies have reported investigations concerning the association of a limited number of chemokine genetic variations in patients with different uveitis entities [21, 39, 41], but a large scale analysis on chemokine gene associations with BD or VKH disease has not been reported.

Despite the fact that the 26 SNPs chosen for our study have been proved to be associated with several other immune-mediated diseases, we did not detect any significant association between these SNPs and the two uveitis entities, BD or VKH disease. An exception is the association of the haplotype TC of the CXCL12 gene including rs1801157 and rs2839693 with VKH, which suggests that CXCL12 polymorphisms might be a risk factor contributing to VKH disease in the Chinese population. Our study confirms earlier data presenting the absence of an association between the chemokine genes rs1024610/CCL2 and rs2280788/rs2107538/CCL5 with Behcet's disease or retinal vasculitis in patients from UK [39]. Others showed that the frequency of the T allele of MCP-1 63555 (rs1024610/CCL2) was significantly associated with idiopathic anterior uveitis in Caucasian patients [21], which could not be shown in the uveitis entities we studied. This discrepancy may be due to differences in the uveitis entity studied or due to ethnic effects.

Selection of candidate SNPs is a crucial step for a gene variation study. In our study, 26 SNPs covering 12 chemokine genes (CCL2, CCL5, CCL16, CCL17, CCL21, CCL22, CCL24, CXCL8, CXCL9, CXCL10, CXCL12, and CXCL16) were selected on the basis of earlier association studies in autoimmune diseases, including type 1 diabetes [12], pediatric Crohn's disease [14], and systemic lupus erythematosus [15]. It should be noted that composition and stratification of recruiting population may conclude to different results of an association study. To make sure that our data and results were valid, a series of efforts were made. First of all, the BD patients were diagnosed in strict accordance with the criteria of the International Study Group for BD while the VKH patients were diagnosed in strict accordance with the First International Workshop criteria of VKH disease. Any doubt or uncertainty in patient diagnosis is not allowed. Beyond that, to avoid ethnic bias, BD and VKH disease patients from other ethnic populations other than Chinese Han population were excluded.

Our study has several limitations. We only chose SNPs that have been previously reported to be related to autoimmune and inflammatory diseases, thus other unknown SNPs of chemokine genes with potential association with BD and VKH disease might be excluded. Furthermore, we studied only two common types of uveitis, with all the participants from Chinese Han population. Association of chemokine genes with other types of uveitis or different ethnic populations might also exist and awaits further investigation.

5. Conclusions

A large scale analysis of the role of chemokine genes only shows an association of CCL2 with BD but no effect on predisposition to VKH in Chinese Han population. The haplotype TC of the CXCL12 gene however did show a significant association with VKH compared with healthy controls.

Conflicts of Interest

The authors declare no conflicts of interest.

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