Association between polymorphisms of FCRL3, a non-HLA gene, and Behçet’s disease in a Chinese population with ophthalmic manifestations

Ke Li,¹ Min Zhao,¹ Shengping Hou,¹,² Liping Du,¹,² Aize Kijlstra,²,³ Peizeng Yang¹

(Dr. Li and Dr. Zhao contributed equally to this work.)

¹First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China; ²Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, P.R. China; ³Eye Research Institute Maastricht, Department of Ophthalmology, University Hospital Maastricht, Maastricht, the Netherlands

Purpose: Studies have shown a strong association of human leukocyte antigens-B51 (HLA-B51) with Behçet’s disease (BD). However, little is known about the association of non-HLA genes with BD. The polymorphisms of the Fc receptor-like 3 gene (FCRL3), −169C/T, −110A/G, +358C/G, and +1381A/G, have been reported to be associated with several autoimmune diseases. This study was designed to determine whether the polymorphisms of FCRL3 were associated with susceptibility to BD in a Chinese population mainly with ocular involvement.

Methods: A case-control study was performed in 245 Chinese BD patients and 289 controls. Four single nucleotide polymorphisms (SNPs; −169C/T, −110A/G, +358C/G, and +1381A/G) in FCRL3 were detected using polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP). HLA-B51 genotyping was performed by the PCR sequence specific primers method as described previously.

Results: The results showed a significantly higher frequency of the G allele at the −110 site in BD patients compared with that in controls (corrected p=0.044, 75.3% versus 67.5%, χ²=7.72). Haplotype CGCG frequency was significantly higher in patients than in controls (corrected p=0.0096) whereas haplotype TACG frequency was significantly lower in patients compared with controls (corrected p=0.032). There was no relationship between clinical signs and FCRL3 polymorphisms. No significant difference was observed between patients and controls after HLA-B51 stratification concerning the four SNPs.

Conclusions: Our study suggests that the −110 G allele and the haplotype CGCG of FCRL3 are positively associated with BD in a Chinese population and that the haplotype ATCG might be a protective haplotype for BD.

Behçet’s disease (BD) is an idiopathic, multisystem, recurrent chronic inflammatory disease in China. The major clinical manifestations include recurrent oral and genital ulceration, uveitis, and erythema nodosum. Panuveitis was the most common type of uveitis in BD patients in China, although solo anterior uveitis is observed in certain patients [1]. BD exists worldwide and has significant regional differences. It is quite common along the ancient ‘Silk Road’ countries extending from China to the Mediterranean area [2]. Although the precise etiology of BD remains unknown, extensive studies suggest that autoimmunity and genetic factors are involved in its pathogenesis. It has been shown that polymorphisms of several genes such as human leukocyte antigens-B51 (HLA-B51), intercellular adhesion molecule-1 (ICAM-1) [3], and tumor necrosis factor-α (TNF-α) [4] are associated with susceptibility to BD. Among these genes, HLA-B51 is the most strongly associated gene with BD in different ethnic populations [5-8], particularly those from the Middle East to the Far East [9], coinciding with the distribution of BD.

Fc receptor-like genes (FCRLs), also known as FCRL homologs or IRTAs (immunoglobulin superfamily receptor translocation associated genes) [10], and SPAPs (SH2 domain containing phosphatase anchor proteins) cluster on human chromosome 1q21–23 adjacent to the Fc receptor genes [11]. FCRLs have a high structural homology with the classical Fcγ receptor genes (FcγRs) and contain six Ig superfamily members that are known as FCRL1–FCRL6 according to their chromosomal order [12]. Recently, a classical study by Kochi et al. [13] in Japan found that four single nucleotide polymorphisms (SNPs) of FCRL3 (−169C/T, −110A/G, +358C/G, and +1381A/G) were associated with rheumatoid arthritis (RA) and that SNP rs7528684C/T was associated with autoimmune thyroid disease (AITD) and systemic lupus erythematosus (SLE). As various autoimmune disorders may share common pathogenic pathways, genes that have been found to be involved in one autoimmune disease
may also be considered as a candidate associated with other autoimmune diseases. Until now, a FCRL3 polymorphism has yet to be investigated in BD. Therefore, this study was designed to investigate the association of the aforementioned four SNPs of FCRL3 (−169C/T, −110A/G, +358C/G, and +1381A/G) with susceptibility to BD in a Chinese population, mainly with ocular involvement. The result showed a positive association of the −110G allele and the haplotype CGCG and a negative association of the haplotype TACG with BD.

**METHODS**

*Study participants:* Patients and controls were recruited from the Zhongshan Ophthalmic Center of Sun Yat-sen University (Guangzhou, P.R. China) and the First Affiliated Hospital of Chongqing Medical University (Chongqing, P.R. China). The test subjects consisted of 245 Chinese BD patients (aged 28.6±6.0 years) and 289 healthy controls (aged 34.2±10.0 years). All control subjects were matched ethnically and geographically with the patients.

The diagnosis of Behçet’s disease followed the criteria of the International Study Group for Behçet’s disease [14]. The clinical characteristics of the patients are presented in Table 1. All subjects gave their written informed consent for this study, and the study protocol was approved by the local institutional ethics committee.

**Single nucleotide polymorphisms and genotyping:** DNA was prepared by proteinase K digestion and salt extraction from peripheral blood of patients and controls and stored at −70 °C until use. The four SNPs in FCRL3, namely −169C/T (rs7528684 or fcrl3_3), −110G/A (rs11264799 or fcrl3_4), +358 C/G (rs945635 or fcrl3_5), and +1381A/G (rs3761959 or fcrl3_6), were genotyped by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

Genotyping of the −110A/G SNP was performed according to the method as described previously [15]. The primers of the three remaining sites were designed using Primer Premier 5.0 software (Premier Biosoft International, Palo Alto, CA). The details of the primers and enzymes used for PCR-RFLP genotyping are presented in Table 2.

**RESULTS**

Four SNPs in FCRL3 were determined in 245 BD patients and 289 healthy controls. The results showed that all the cases and controls were in HWE. We analyzed LD with these four SNPs and haplotype analysis with Haploview software, and the four SNPs of FCRL3 are not in high LD (D*=46–87; r^2=0.10–0.74; Figure 1). The frequency of the G allele at the −110 site was

| Clinical features | Patients (n=245) |
|------------------|-----------------|
| Male             | 204             | 83.3 |
| Female           | 41              | 16.7 |
| Uveitis          | 235             | 95.9 |
| Hypopyon         | 53              | 21.6 |
| Oral ulcer       | 226             | 92.2 |
| Skin lesions     | 120             | 49   |
| Genital ulcer    | 95              | 38.8 |
| Positive pathergy| 81              | 33.1 |
| Arthritis        | 60              | 24.5 |

N=number of patients.

PCR was performed in 15 μl volumes containing 7.5 μl Premix Taq (Ex Taq Version; TaKaRa Biotechnology Co. Ltd, Dalian, China), 0.5 μl primers (10 μmol/l), and 0.1 μg of genomic DNA. The PCR products were then digested by the proper restriction enzymes and separated by electrophoresis on 2~3% agarose gels and stained with GoldView™ (SBS Genetech, Beijing, China). The images were recorded digitally. HLA-B51 genotyping was performed by the PCR-sequence specific primers (PCR-SSP) method as described previously [16].

**Statistical analysis:** Statistical analysis was performed with the SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL). Hardy–Weinberg equilibrium (HWE) was tested by the χ^2 test. We evaluated the frequency of genotypes and alleles in this study using the χ^2 test or Fisher’s exact test. The haplotype frequency and linkage disequilibrium (LD) of the SNPs were estimated with the Haploview 3.2 program [17]. A haplotype frequency less than 0.03 was not studied further. All the data were corrected by Bonferroni correction.

**Table 1. Clinical characteristics of patients with BD.**

![Figure 1. Location and pair-wise linkage disequilibrium values of four FCRL3 SNPs in a Chinese population. These four SNPs span 1 kb of the FCRL3 region. Values of the pair-wise D’ (multiply by 100) are shown in one block.](image)
significantly higher in patients (75.3%) than in controls (67.5%; corrected p=0.044, \(\chi^2=7.72\); Table 3). The −110 GG genotype was also found to be increased in patients (p=0.007), but this significance was lost after Bonferroni correction (corrected p=0.084). The frequency of the −169C→T:−110A:+358C:+1381G haplotype was significantly higher in patients compared with controls (13.3% versus 7.0%, respectively; \(p=6.0\times10^{-4}\), corrected p=0.0096, \(\chi^2=11.70\); Table 4). The frequency of haplotype −169T:−110A:+358C:+1381G was significantly lower in patients than that in controls (3.0% versus 7.0%, respectively; \(p=0.002\), corrected p=0.032, \(\chi^2=9.27\); Table 4). No significant difference in the remaining three SNPs tested was observed between BD patients and controls in the distribution of other alleles and genotypes.

Table 2. Details of the primers and enzymes used for PCR-RFLP genotyping.

| SNPs         | dbSNP ID | Forward primer | Reverse primer | Tm (°C) | Restriction enzyme |
|--------------|----------|----------------|----------------|---------|-------------------|
| −169C→T(fcrl3_3) | rs7528684 | GAAAATAATACA   | GGCCTTTAAA    | 56.9    | BsmFI             |
| −110A→G(fcrl3_4) | rs11264799 | AATTGACAGTTA   | AACCCTGGTTAC  | 56.9    | PleI              |
| +358C→G(fcrl3_5) | rs945635  | CTCAATCCCGGT   | CTATAACAAAC   | 60.3    | HaeIII            |
| +1381A→G(fcrl3_6) | rs3761959 | TCTAGCTTTTCA   | TGATAGCAGACTA | 60.3    | MspI              |

Tm=melting temperature

Table 3. Frequency of alleles and genotypes of four FCRL3 SNPS in BD patients and controls.

| SNPs         | Genotype/ allele | BD (%) | Controls (%) | \(\chi^2\) | p     | Corrected p | OR (95% CI) |
|--------------|-----------------|--------|--------------|------------|-------|-------------|-------------|
| −169 C→T    | CC              | 69 (28.3) | 86 (29.8) | 1.95   | 0.38  | NS          | 1.1 (0.8–1.3) |
|             | CT              | 121 (49.6) | 127 (43.9) |         |       |             |             |
|             | TT              | 54 (22.1)  | 76 (26.3)  |         |       |             |             |
|             | C               | 259 (53.3) | 299 (51.7) | 0.26   | 0.61  | NS          | 0.9 (0.7–1.2) |
|             | T               | 227 (46.7) | 279 (48.3) |         |       |             |             |
| −110 A→G    | AA              | 17 (7.1)  | 46 (16.0)  | 10.03  | 0.007 | NS          |             |
|             | AG              | 85 (35.3) | 95 (33.0)  |         |       |             |             |
|             | GG              | 139 (57.7) | 147 (51.0) |         |       |             |             |
|             | A               | 119 (24.7) | 187 (32.5) | 7.72   | 0.0055| 0.044       | 0.7 (0.5–0.9) |
|             | G               | 363 (75.3) | 389 (67.5) |         |       |             | 1.5 (1.1–1.9) |
| 358 C→G     | CC              | 81 (33.2) | 97 (33.6)  | 1.12   | 0.57  | NS          |             |
|             | CG              | 122 (50.0) | 134 (46.4) |         |       |             |             |
|             | GG              | 41 (16.8)  | 58 (20.1)  |         |       |             |             |
|             | C               | 283 (58.0) | 328 (56.7) | 0.17   | 0.68  | NS          | 1.1(0.8–1.4) |
|             | G               | 205 (42.0) | 250 (43.3) |         |       |             | 0.9(0.7–1.2) |
| 1381 A→G    | AA              | 40 (16.4)  | 54 (18.8)  | 0.5    | 0.78  | NS          |             |
|             | AG              | 122 (50.0) | 140 (48.6) |         |       |             |             |
|             | GG              | 82 (33.6)  | 94 (32.6)  |         |       |             |             |
|             | A               | 203 (58.4) | 248 (56.9) | 0.23   | 0.63  | NS          | 0.9 (0.7–1.2) |
|             | G               | 285 (41.6) | 328 (43.1) |         |       |             | 1.1 (0.8–1.4) |

BD= Behçet’s disease; OR=odds ratio; 95% CI=95% confidence interval; NS=not significant.
we further analyzed the relationship between the SNPs and various clinical parameters such as uveitis, hypopyon, oral or genital ulcers, multiform skin lesions, and arthritis. No significant difference was noted between any of the mentioned clinical characteristics and the investigated SNPs. Of the 245 patients, 204 (83.3%) were men and 41 (16.7%) were women. No significant difference was found in the four SNPs between male and female patients.

Since the BD patients showed different clinical features, we further analyzed the relationship between the SNPs and various clinical parameters such as uveitis, hypopyon, oral or genital ulcers, multiform skin lesions, and arthritis. No significant difference was noted between any of the mentioned clinical characteristics and the investigated SNPs. Of the 245 patients, 204 (83.3%) were men and 41 (16.7%) were women. No significant difference was found in the four SNPs between male and female patients.

As HLA-B51 has been shown to be strongly associated with BD, we also investigated its frequency in patients and controls. The result showed that 99 (40.4%) patients were HLA-B51 positive as compared to 28 (9.7%) of the controls, a significant difference. HLA-B51 stratification analysis showed a significant difference for the −110 A/G allele, the AA genotype, and the haplotype CGCG and TACG. The difference, however, lost its significance when the Bonferroni correction was applied (Table 5).

**DISCUSSION**

In this study, we analyzed the association of four FCRL3 SNPs with BD in a Chinese population. The results showed that the −110G allele was significantly increased in the BD patients. The frequency of the haplotype CGCG was also found to be significantly increased in these patients whereas a significantly decreased frequency of haplotype TACG was noted. These results suggest that polymorphisms of FCRL3 are associated with the susceptibility to BD in a Chinese population.

BD is one of the most common uveitis entities in China [1]. Its distribution along the old ‘Silk Road’ and the clustering of the disease in families suggest that genetic factors may play a role in the pathogenesis of this disease. HLA-B51 has been shown to be strongly associated with BD in different ethnic populations. Little is known about the association of non-HLA genes with BD, although polymorphisms of several genes have been investigated in this disease [3,4]. In this study, we focused on the association of four FCRL3 SNPs with BD mainly because of the role this gene may play in the pathogenesis of autoimmunity and its association with other autoimmune diseases. FCRL has been shown to have a high structural homology with the classical FcγR, which are expressed mainly on the surface of a variety of immune cells. Moreover, previous studies showed that polymorphisms of FCγR were associated with a variety of autoimmune diseases [18,19]. FCRL has been found to be expressed predominantly on B cells and has also been detected at low levels in CD4+ and CD8+ T cells [13]. FCRL3 may play a role in the differentiation of B cells into autoreactive cells and has been presumed to function through modulating signal transduction via activation/inactivation of signaling tyrosine protein kinases [20]. Furthermore, the −169C/T SNP of FCRL3 has been shown to influence the level of FCRL3 expression on B cells through altering the binding affinity of the nuclear factor-kappa-B (NF-xB) [13], an important immunoregulatory factor, according to recent studies in both murine models and humans with diverse forms of autoimmunity [21]. It is not clear whether the −110 SNP has any functional role. The association of this SNP with BD as disclosed in our study appears to suggest a possible involvement of FCRL3 in the development of BD.

Our study showed a significantly higher frequency of the G allele at the −110 site in BD patients, which is consistent with that observed in patients with autoimmune Addison’s disease (AAD) in a UK population [15]. This identical polymorphism between BD and AAD seemed to show a susceptibility that both have in common. Interestingly, two studies by Japanese investigators showed a decreased frequency of the G allele in the −110 site in RA and autoimmune pancreatitis [13,22]. Furthermore, a study reported by Simmonds et al. [23] showed that three of the four SNPs studied here (the −110 SNP was the exception) were associated with Graves’ disease.

With regard to the haplotype analysis, we found two haplotypes, CGCG and TACG, that were associated with BD. The former was found to be significantly higher in BD patients while the latter was lower in BD patients. The findings suggest that the FCRL3 −110G allele may be linked with susceptibility to BD, and those people with the haplotype CGCG are more prone to BD than those without this haplotype. On the contrary, the haplotype ATCG might be a protective haplotype to BD. Our results were different from those found in AAD [15] and SLE [24]. In the study of AAD, seven alleles and haplotypes were investigated, the haplotype TGGGAAA

| Haplotypes | BD | Controls | χ² | Fisher's p | Corrected p | OR |
|-----------|-----|----------|----|------------|-------------|----|
| TGGG      | 180 (47.0) | 210.5 (36.4) | 0.033 | 0.86 | NS | 1.1 (0.9–1.5) |
| CAGG      | 90.0 (18.2) | 116.0 (20.1) | 0.57 | 0.45 | NS | 1.0 (0.8–1.4) |
| CGGA      | 84.2 (17.2) | 106.9 (18.5) | 0.28 | 0.6 | NS | 0.8 (0.6–1.1) |
| CGCG      | 64.9 (13.3) | 40.6 (7.0) | 11.7 | 0.0006 | 0.0096 | 2.4 (1.6–3.7) |
| TACG      | 14.5 (3.0) | 41.3 (7.0) | 9.27 | 0.002 | 0.032 | 0.3 (0.1–0.6) |

BD=Behçet’s disease; OR=odds ratio; NS=not significant.
was found to be significantly increased among AAD patients compared to the controls. In the study of SLE, the frequency of haplotype CGA was found to be significantly higher among SLE patients compared to the controls.

As BD shows a variety of manifestations clinically and the aforementioned result revealed an association of the polymorphisms of FCRL3 with this disease, it is reasonable to test whether certain clinical features are linked to this polymorphism. Unexpectedly, none of the clinical features including uveitis, hypopyon, oral ulcer or genital ulcer, multiform skin lesions, and arthritis were found to be associated with the identified susceptible allele at the −110 site. Similarly, there was no association between any of the investigated clinical features and the haplotypes. These results are generally consistent with those in a previous study performed in our laboratory recently searching for an association between SUMO4 polymorphisms and BD. This study found no association between haplotype AGAT, which was already found to be significantly lower in BD patients, and any of the clinical characteristics in BD patients [25]. However, it is worthwhile to point out that there was a bias in the recruited BD patients in our current study. All the patients enrolled in this study came from ophthalmic centers, and the results merely revealed the association of the FCRL3 polymorphisms with BD patients, mainly with ocular involvement. The association of FCRL3 polymorphisms with BD in the whole population with this disease should be studied on the patients from dermatology and rheumatology centers.

Previous studies have showed that the association of FCRL3 with diseases could be more striking after stratification with some parameters [26,27]. Genetic susceptibility to BD is well documented for HLA-B51. We therefore analyzed the association of the −110 SNP and the remaining three SNPs with BD based on the HLA-B51 antigen stratification. Unfortunately, we did not find any association of these SNPs and haplotypes with BD after stratification for

| SNPs   | Genotype/allele | BD n=146 (%) | Controls n=261 (%) | Χ² | p | Corrected | OR (95% CI) |
|--------|-----------------|--------------|--------------------|----|---|------------|-------------|
| −169 C→T | CC              | 45 (30.8)    | 77 (29.5)          | 0.22 | 0.9 | NS         | 1.1 (0.8–1.4) |
|        | CT              | 67 (45.9)    | 118 (45.2)         |     |    |            |              |
|        | TT              | 34 (23.3)    | 66 (25.3)          |     |    |            |              |
|        | C               | 159 (54.1)   | 272 (52.1)         | 0.29 | 0.59 | NS         |              |
|        | T               | 135 (45.9)   | 250 (47.9)         |     |    |            |              |
| −110 A→G | AA              | 10 (6.9)     | 45 (16.5)          | 7.73 | 0.02 | NS         |              |
|        | AG              | 56 (38.6)    | 86 (33.1)          |     |    |            |              |
|        | GG              | 79 (54.5)    | 131 (50.4)         |     |    |            |              |
|        | A               | 76 (26.0)    | 172 (33.1)         | 4.38 | 0.04 | NS         | 0.7 (0.5–1.0) |
|        | G               | 216 (74.0)   | 348 (66.9)         |     |    |            | 1.4 (1.0–1.9) |
| +358 C→G | CC              | 47 (32.2)    | 85 (32.6)          | 0.24 | 0.89 | NS         |              |
|        | CG              | 73 (50.0)    | 125 (47.9)         |     |    |            |              |
|        | GG              | 26 (17.8)    | 51 (19.5)          |     |    |            |              |
|        | C               | 168 (57.1)   | 295 (56.5)         | 0.03 | 0.86 | NS         | 1.0 (0.8–1.4) |
|        | G               | 126 (42.9)   | 227 (43.5)         |     |    |            | 1.0 (0.7–1.3) |
| +1381 A→G | AA              | 26 (17.8)    | 49 (18.8)          | 0.5  | 0.78 | NS         |              |
|        | AG              | 72 (49.3)    | 127 (48.8)         |     |    |            |              |
|        | GG              | 48 (32.9)    | 84 (32.3)          |     |    |            |              |
|        | A               | 125 (42.5)   | 225 (43.3)         | 0.043 | 0.84 | NS         | 1.0 (0.7–1.3) |
|        | G               | 169 (57.5)   | 295 (56.7)         |     |    |            | 1.0 (0.8–1.4) |

BD = Behçet’s disease; OR=odds ratio; 95% CI=95% confidence interval; NS= not significant.
HLA-B51. This could be due to the insufficient sample size. Our sample size for the −110 SNP (28 HLA-B51 positive normal controls and 99 HLA-B51 positive BD patients) can only reach a 26% power value to detect a 2.0 odds ratio (OR) value at the 5% significance level. As there is a substantial difference in clinical manifestations between male and female BD patients, a stratification analysis according to sex was also performed in our study. Similarly, there was also no association following sex stratification in these patients. The small size of the sample for the female BD patients may be insufficient for this analysis. Therefore, a larger patient population is needed to clarify the association of FCRL3 with Behcet's disease in different HLA and sex status.

In conclusion, our study revealed that the −110G allele and haplotype CGCG are positively associated and haplotype TACG is negatively associated with the susceptibility to BD. These results may provide clues for the development of an adequate and effective therapy [28]. A pharmacogenomic relationship has been studied in open-angle glaucoma between β1-adrenergic receptor with betaxolol, between prostaglandin F2α receptor and the latanoprost, and between glucocorticoid receptor and intraocular pressure [29]. It is important to test whether the polymorphisms revealed by our study are associated with the sensitivity of certain medicines in the treatment of BD. As a multi-systemic autoimmune disease, BD may share mechanisms in common with other autoimmune diseases. Therefore, the predisposing gene for BD may also be involved in other autoimmune diseases in a similar way. It is necessary to clarify whether the discovered polymorphisms of FCRL3 are associated with other autoimmune diseases. Furthermore, studies are needed to investigate whether the observed associations with BD are also present in other ethnic populations.

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