Genetic Association of Interleukin 33/ST2 Polymorphisms With Behcet’s Uveitis

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Interleukin (IL)33, a member of the IL1 superfamily, functions as a nuclear factor and mediates biological effects by interacting with the ST2 receptor. Recent studies have described IL33 as an emerging pro-inflammatory cytokine in the immune system, and IL33/ST2 gene polymorphisms have been implicated in the pathogenesis of various immune diseases. However, the underlying mechanisms of IL33/ST2 in Behcet’s disease (BD) remain to be defined. Here, we investigated the association between IL33/ST2 gene polymorphisms and BD in 585 BD uveitis (BDU) patients and 834 healthy controls using Agena MassARRAY iPLEX platform. We found that rs3821204 was associated with the development of BDU. Moreover, the frequency of rs2210463 G allele was lower in patients with genital involvement. Association analysis revealed a much greater genetic difference between complete-type and incomplete-type BD groups, including three SNPs (rs7044343, rs1048274, and rs2210463). Our findings suggest that IL33/ST2 gene polymorphisms are involved in the pathogenesis of BDU. Different genetic backgrounds may exist in complete-type and incomplete-type BD patients.

Keywords: Behcet’s disease, Behcet’s uveitis, uveitis, gene polymorphism, single nucleotide polymorphism, interleukin 33, ST2

INTRODUCTION

Behçet’s disease (BD) is a chronic, relapsing, systemic vasculitis involving complex pathologic processes characterized by recurrent episodes of uveitis, oral and genital ulcers, and skin lesions (1). It may also affect the digestive, cardiovascular, and nervous systems and involve joints and large vessels (1). Eye involvement is one of the most serious manifestations of BD with high incidence of disability. It affects about 70% of patients and is characterized by uveitis (BDU) (2). The onset of BD usually occurs in the third or fourth decade of life and is rare in children or individuals over the age of 40 years. The etiology of BD is still unclear, although, an inflammatory response triggered by immune and unknown environmental factors in a genetically susceptible individual has been proposed as its cause. Among all genetic factors, HLA-B51 has been confirmed as the strongest risk factor for BD. However, the presence of HLA-B51 alone is not sufficient to explain all the symptoms of BD patients (3).
Interleukin (IL)33, a member of the IL-1 family, is evolutionarily conserved in mammals and a ligand for the orphan receptor ST2. It is constitutively expressed by tissue barrier cells, such as epithelial and endothelial cells, and various innate immune cells, such as macrophages and dendritic cells. Both enhanced innate immunity and neutrophil hyperactivity with endothelial damage, which are part of BD pathogenesis (4), are related to disrupted IL33 levels. Therefore, we hypothesized that BD may be associated with IL33/ST2 genetic abnormalities.

In the present study, we aimed to establish the role of IL33 and ST2 genes in the risk of developing BDU in a well-characterized Chinese cohort by genotyping and association analysis. We analyzed single nucleotide polymorphisms (SNPs) of IL33 (rs1891385, rs2210463, rs11792633, rs7044343, rs1048274) and ST2 (rs3821204, rs12712142, rs2058660) with respect to BDU pathogenesis and characteristic BDU phenotypes in these patients.

**Materials and Methods**

**Patients**

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. A total of 585 patients with BDU were recruited from the Peking Union Medical College Hospital (PUMCH, 190 patients) and the First Affiliated Hospital of Chongqing Medical University (395 patients) between January 2018 and June 2019. All patients with BD were diagnosed according to the International BD Study Group criteria. Eight hundred and thirty-four healthy controls with no previous history of immune-related diseases were enrolled from the health examination center of PUMCH. All participants were self-reported as Han Chinese and were unrelated.

Of the 585 BD patients included, detailed clinical data for 553 patients was recorded. Based on their clinical characteristics, patients were divided into the following subgroups: complete-type and incomplete-type BD groups (1); severe and non-severe BD groups; early-onset and late-onset BD groups.

In case of complete-type BD, all four main symptoms (ocular lesion, recurrent aphthous ulcers on the oral mucosa, genital ulcers, and skin lesion) appeared during the clinical course. In case of incomplete-type BD, either of the following conditions was met: 1. Three of the four main symptoms, or two main symptoms and two additional symptoms (arthritis without deformity or sclerosis, epididymitis, gastrointestinal lesion represented by ileocecal ulceration, vascular lesions, and central nervous system lesions including and above middle class of severity) appeared during the clinical course; 2. Typical ocular lesions and other main symptoms, or two additional symptoms appeared during the clinical course.

Severe and non-severe BD were classified based on clinical severity score ≥7 or <7 points, respectively. Clinical severity score was determined as previously described (5, 6): 1 point for each of the mild symptoms (oral ulcers, genital ulcers, arthralgia, typical skin lesions such as erythema, nodosum-like lesions, papulopustular lesions, and folliculitis), 2 points for each of the moderate symptoms (arthritis, deep vein thrombosis of the legs, anterior uveitis, gastrointestinal involvement), and 3 points for each of the severe symptoms (posterior/panuveitis, retinal vasculitis, arterial thrombosis, neuro Behcet’s disease, bowel perforation).

In case of early-onset BD, the age of first BD attack was <40 years, while in late-onset BD group, the age of first BD attack was ≥40 years.

**Selection of SNPs**

Considering the vital effects of IL33 and ST2 in immune-mediated diseases, eight SNPs (rs1891385, rs2210463, rs11792633, rs7044343, rs1048274, rs3821204, rs12712142, rs2058660) were designed by the Assay Design Suite (ADS, Agena). After multiplex PCR amplifications, the products were used for locus specific single base extension reactions and the final products were desalted and transferred on to a 384-element SpectroCHIP array. Allele detection was conducted by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). The mass spectrometry data were analyzed using MassArray Typer 4.0 software (Agena).

The current SNP assay method is based on primer extension and offers two levels of specificity. First, a locus-specific PCR reaction takes place, followed by a locus-specific primer extension reaction (iiPLEX assay) in which an oligonucleotide primer anneals immediately upstream of the polymorphic site being genotyped. In the iiPLEX assay, the primer and amplified target DNA are incubated with mass-modified dideoxynucleotide terminators. The primer extension is made according to the sequence of the variant site, and is a single complementary mass-modified base. Through the use of MALDI-TOF mass spectrometry, the mass of the extended primer is determined. The primer’s mass indicates the sequence and, therefore, the alleles present at the polymorphic site of interest (7).

Duplicate samples, negative controls, and blank controls were included on the plates to ensure the accuracy of genotyping.

**Statistical Analysis**

Statistical analyses were performed using PLINK 1.07 software (Shaun Purcell, Boston, MA, USA). The Hardy-Weinberg
equilibrium (HWE) of each SNP was examined by using the Chi-square ($\chi^2$) test in healthy controls. Any SNPs that deviated from the HWE ($P < 0.05$ in the control groups) would be excluded from subsequent analysis. Differences in genotype and allele frequencies between cases and controls, and between different BD subgroups and phenotypes were analyzed using $\chi^2$ test. The odds ratio (OR) and 95% confidence interval (95% CI) of associations were calculated. For multiple comparisons, Pc values (corrected for multiple comparisons by the Bonferroni adjustment test) < 0.05 were deemed to be statistically significant. For genetic model testing (additive, dominant, and recessive model), logistic regression analyses were used.

RESULTS

Patient Characteristics and Sequencing Analysis

The characteristics of the controls and patients with BD are shown in Table 1. The gender distributions in both controls and cases were similar ($p = 0.127$). The median age was 36.0 (31.0–42.0) years and 32.0 (26.0–39.0) years for controls and cases respectively. The success rate for sequencing of each SNP was 99%. The eight SNPs of IL33 and ST2 selected in the present study did not show any deviation from HWE (all $P > 0.05$) in controls, and thus, the data were suitable for further comparisons.

ST2 rs3821204 SNP Was Associated With BD Development

ST2 SNPs rs3821204, rs12712142, and rs2058660 were analyzed in both cases and controls and rs3821204 G allele was found to be associated with BDU development ($X^2 = 7.94$, $P_c = 0.039$; Table 2). Although the frequency of GG genotype of IL33 and ST2 selected in the present study did not show any deviation from HWE (all $P > 0.05$) in controls, and thus, the data were suitable for further comparisons.

| Characteristic | Patients with BDU | Controls |
|----------------|-------------------|----------|
| Male, n (%)    | 484 (82.7%)       | 663 (79.5%)|
| Age (years)    | 32.0 (26.0–39.0)  | 36.0 (31.0–42.0) |
| BD subgroups   |                   |          |
| Complete BD, n | 334               | /        |
| Incomplete BD, n | 219              | /        |
| Severe BD, n   | 132               | /        |
| Un-severe BD, n | 421              | /        |
| Early-onset BD, n | 423            | /        |
| Late-onset BD, n | 130              | /        |
| Phenotypes     |                   |          |
| Uveitis        | 553               | /        |
| Genital ulcer  | 285               | /        |
| Erythema nodosum | 233           | /        |
| Arthritis      | 250               | /        |
| Aphthous ulcer | 545               | /        |

BD, Behcet’s disease; BDU, Behcet’s uveitis.

Five hundred and fifty-three BD patients with detailed clinical data were included in the subgroup and phenotype association analysis.

IL33 SNPs Were Not Associated With BD Development

We then detected IL33 SNPs (rs11792633, rs1048274, rs7044343, rs2210463, and rs1891385) in the study population. Our study showed that neither genotype nor allele frequencies of these five SNPs were statistically significant between patients and healthy controls ($P_c > 0.05$; Table 2). Moreover, logistic regression analysis with three genetic models (i.e., additive, dominant, and recessive) also did not reveal any statistical difference between patient and control groups ($P_c > 0.05$; Table 3).

Correlation of ST2 and IL33 SNPs With the Phenotype Subgroups of BD

Association analyses of ST2 and IL33 SNPs with different BD subgroups and phenotypes were also performed (Tables 4A and 4B). The allele frequencies of IL33 SNPs rs2210463 ($P = 0.0028$, $P_c = 0.022$), rs7044343 ($P = 0.0034$, $P_c = 0.027$), and rs1048274 ($P = 0.0050$, $P_c = 0.040$) were all significantly different between the complete-type and incomplete-type BDU groups. The allele frequency of IL33 SNP rs2210463 ($P = 0.006$, $P_c = 0.048$) was significantly different between patients with and without genital ulcers. No allele frequency differences were found between the early- and late-onset or severe and non-severe BDU groups in any ST2 or IL33 SNP. Moreover, no association was found between erythema nodosum, or arthritis and IL33 or ST2 SNPs.

DISCUSSION

Although the etiopathogenesis of BD remains uncertain, microbial agent triggers, environmental factors, genetic predisposition, and immunological abnormalities have been implicated (8–10). Complex disorders implicating innate and adaptive immunity in humoral and cellular immunity settings are observed in BD. IL33, a member of the IL1 family that potently drives the production of T helper (Th)-2-associated cytokines and promotes responses by cytotoxic NK cells, Th1 cells, and CD8+ T cells (11), has been associated with various immune-related diseases (12, 13). ST2, the receptor of IL33, is highly expressed in many immunocytes (14).

In the present study, we demonstrated significant association between the IL33/ST2 pathway SNP rs3821204 and the development of BDU. The rs3821204 polymorphism occurs in the 3’ untranslated region of ST2, which was found to be functional with the rs3821204 gene mutation by disrupting the binding site of miR-202-3p, resulting in plasma level changes of sST2 (15, 16). sST2 is the soluble form of ST2, which together with the membrane-bound form (ST2L), comprise the two main ST2 existing forms (17). ST2L functions as a transmembrane signaling receptor of IL33, mediating the effect of IL33 on immune-related diseases (12, 13). ST2, the receptor of IL33, is highly expressed in many immunocytes (14).
| SNPs       | Groups     | Allele (%) | OR (95% CI) | \( \chi^2 \) | P   | Genotype (%) | \( \chi^2 \) | P   |
|------------|------------|------------|-------------|--------------|-----|--------------|--------------|-----|
| rs1991385  | BDU        | 318 (27.3) | 846 (72.7)  | 0.991 (0.838,1.172) | 0.012 | 0.914 | CC 41 (7.0) | 236 (40.5) | 305 (52.4) | 0.052 | 0.974 | 1 |
|            | Controls   | 456 (27.5) | 1202 (72.5) |              |     |      | CA 61 (7.4) | 334 (40.3) | 434 (52.4) |     |     |   |
| rs2210463  | BDU        | 474 (40.7) | 999 (60.0)  | 1.032 (0.886,1.202) | 0.164 | 0.686 | 1 GA 98 (16.8) | 278 (47.8) | 206 (35.4) | 1.022 | 0.600 | 1 |
|            | Controls   | 665 (40.0) | 1392 (59.3) |              |     |      | AA 145 (17.4) | 375 (45.1) | 312 (37.5) |     |     |   |
| rs11792633 | BDU        | 537 (45.9) | 633 (54.1)  | 1.118 (0.962,1.299) | 2.103 | 0.147 | 1 CA 125 (21.4) | 287 (49.1) | 173 (29.6) | 2.397 | 0.302 | 1 |
|            | Controls   | 718 (43.1) | 946 (56.9)  |              |     |      | CC 156 (19.7) | 390 (48.9) | 278 (33.4) |     |     |   |
| rs7043434  | BDU        | 574 (49.1) | 596 (50.9)  | 1.121 (0.965,1.302) | 2.226 | 0.136 | 1 TC 140 (23.9) | 294 (50.3) | 151 (25.8) | 3.980 | 0.137 | 1 |
|            | Controls   | 770 (46.2) | 896 (53.8)  |              |     |      | AC 192 (23.0) | 386 (46.3) | 255 (30.6) |     |     |   |
| rs1048274  | BDU        | 588 (50.3) | 580 (49.7)  | 1.136 (0.978,1.320) | 2.779 | 0.096 | 1 GC 148 (25.3) | 292 (50.0) | 144 (24.7) | 4.247 | 0.120 | 0.957 |
|            | Controls   | 780 (47.2) | 874 (52.8)  |              |     |      | GC 198 (23.9) | 384 (46.4) | 245 (29.6) |     |     |   |
| rs2058660  | BDU        | 511 (43.7) | 659 (56.3)  | 0.844 (0.726,0.980) | 4.93 | 0.026 | 1 GA 120 (20.5) | 271 (46.3) | 194 (33.2) | 4.72 | 0.095 | 0.756 |
|            | Controls   | 797 (47.9) | 867 (52.1)  |              |     |      | AA 201 (24.2) | 395 (47.5) | 236 (28.4) |     |     |   |
| rs3821204  | BDU        | 321 (37.9) | 526 (62.1)  | 0.790 (0.670,0.931) | 7.94 | 0.005 | 1 GC 36 (6.2) | 249 (42.6) | 299 (51.2) | 10.12 | 0.006 | 0.051 |
|            | Controls   | 539 (48.0) | 584 (52.0)  |              |     |      | GG 89 (10.7) | 361 (43.4) | 381 (45.8) |     |     |   |
| rs12712142 | BDU        | 358 (44.2) | 452 (55.8)  | 0.826 (0.704,0.970) | 5.48 | 0.019 | 1 GG 54 (9.2) | 250 (42.8) | 280 (47.9) | 6.53 | 0.038 | 0.306 |
|            | Controls   | 580 (53.5) | 504 (46.5)  |              |     |      | AA 112 (13.4) | 356 (42.8) | 364 (43.8) |     |     |   |

BDU, Behcet’s uveitis; OR, odds ratio; CI, confidence interval; \( \chi^2 \), Chi-square test; P, P values adjusted by Bonferroni correction, \( pc = P \times 8 \).
inflammatory processes, while sST2 acts as a decoy receptor that prevents the interaction of ST2L with IL33 (18, 19).

Several studies have reported associations between *IL33* rs7044343 polymorphism and autoimmune diseases, including rheumatoid arthritis, systemic sclerosis, and BD in Turkey (20–22). Previous case-control study revealed a significant association between the rs7044343 TT genotype and Turkish BD patients in the discovery population (22). However, in the present study, rs7044343 SNP was not found to be associated with the development of BD in patients belonging to Chinese Han ethnicity. Ethnic differences may be a reason for this discrepancy, as genetic heterogeneity between races has been reported to be 58% in a previous research (23).

The association of *IL33*/ST2 SNPs with different BD phenotype subgroups were also investigated. No associations were found except for genital ulcer and the BD of the complete-type. As compared with the other phenotype-based subgroups, greater genetic differences were found between the complete-type and incomplete-type BD groups, which indicated that different genetic backgrounds may exist in these groups of BD patients. Although previous studies reported that similar gene mechanisms underlie the pathogenesis of different immune diseases (24, 25), in the present study, rs2058660 [inflammatory bowel disease-associated (26)], rs1891385 [AS-associated (27)], and rs11792633 [systemic sclerosis-associated (28)] SNPs were not associated with either onset or phenotypes of BD. Compared with the classical immune diseases, BD presents more extensive pathological changes in tissues and organs with featured spontaneous exacerbation and remission clinical courses (29), which, together with the genetic findings, indicate that different molecular mechanisms may exist in BD pathology as compared to classical immune diseases.
Our study had several limitations. First, genetic variants may have different effects in diverse ethnicities. In this study, only Chinese Han individuals were recruited, thus, our results may not be generalizable to other ethnicities. Second, all the study subjects were enrolled from two tertiary ophthalmologic centers, therefore, selection bias may exist. Third, the mRNA expressions of BD patients with different SNP genotypes were not analyzed in this study, further studies are needed to validate our findings.

In conclusion, we reported the association of rs3821204, rs2210463, rs7044343, rs1048274 with the development or phenotypes of BDU, and for the first time revealed significant genetic differences between patients with complete-type and incomplete-type BD. Our findings indicate that IL33/ST2 polymorphisms have a close and probable causal association with BDU, and different genetic backgrounds may exist in complete-type and incomplete-type BD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics committee of Peking Union Medical College Hospital. Written informed consent to participate in this study was provided by the participants/participants’ legal guardian/next of kin.

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AUTHOR CONTRIBUTIONS

MP participated in the study design, patient enrollment, data collection and analysis and manuscript drafting. MZ participated in the study design, patient enrollment, data collection and analysis, manuscript drafting, and coordination of experimental work. XL participated in the data interpretation and analysis. PY, CZ, and FG participated in the patient enrollment. MP, YQ, AL, and JX carried out the experimental work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.589639/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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