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ORIGINAL ARTICLE

Association of IL-23R and IL-10 variations with Behçet disease: a genetic analysis study

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Abstract

Behçet disease (BD) is an autoimmune and autoinflammatory disease mainly affecting the Silk Road countries. The interindividual severity of BD depends on differences in the polymorphic profiles of the patients. One of the most prominent markers, HLA-B51 positivity, is also observed in 40–60% of patients with BD on the Silk Road. Inflammatory markers such as interleukin 10 (IL-10) and interleukin 23 receptor (IL-23R) are also widely associated with BD etiology. The polymorphisms on these genes may change the susceptibility to BD. In this case-control study, we assessed the associations of IL-10 rs3024498 and IL-23R rs10889677 single-nucleotide polymorphisms (SNPs) with BD susceptibility, if any. Two hundred eighty HLA-B51-positive patients with BD and 300 healthy controls were genotyped for these SNPs using RFLP-PCR. The chi-square test was used for genotyping. We found that IL-23R rs10889677 CC and IL-10 rs3024498 CT genotype frequencies were higher in the BD group than in the control group ($p < 0.0001$ and $p = 0.0293$, respectively). The recessive model (AA + CC vs. AC) and combined genotype (AC + CT) results were also statistically significant ($p < 0.0001$ and $p = 0.0364$, respectively). We conclude that IL-23R rs10889677 and IL-10 rs3024498 SNPs may be associated with the susceptibility to BD.

Keywords Behçet disease · Single-nucleotide polymorphism · Interleukin 10 · Interleukin 23R · Autoimmunity

Introduction

Behçet disease (BD) is a polygenic, chronic, auto-inflammatory, autoimmune disorder that affects numerous body regions and is characterized by recurring oral and vaginal ulcers, skin lesions, and ocular inflammation [1, 2]. According to the International Study Group on BD, the most reliable diagnostic criteria include oral ulceration plus any two of the following: vaginal ulceration, typical skin lesions, typical eye lesions, or pathergy test positivity [3].

Although the underlying pathogenesis of BD is uncertain, it is thought that the fundamental pathophysiologic event is an inflammatory response to environmental variables in a genetically predisposed host, as well as the existence of epigenetic alterations [4–7]. So far, the etiology and pathophysiology of BD have not been determined; nevertheless, immunological abnormalities, environmental problems, and a variety of genetic variables are thought to be risk factors that can enhance susceptibility to BD [8, 9].

HLA-B51's presence seems to be the most accepted condition to integrate genetic components into this disorder [10]. However, the relationship between HLA-B51 and BD is only 20% in the relatives of patients diagnosed, and only 50% of

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individuals with BD are positive for this allele [11]. As the HLA region accounts for a considerable amount of the related genetic risk, identifying other non-HLA risk factors has been challenging.

Strategies to spot such variables are not limited to candidate gene studies but also genome-wide association studies. Candidate genes are characterized according to whether they play any role in disease etiology based on biological and/or immunological evidence [12]. Cytokine and cytokine receptor genes have always attracted the interest of researchers looking for potential genes for autoimmune disorders [12, 13].

Personal differences in the polymorphic cytokine gene inheritance result in genetic variability in the immune responses; thus, cytokine gene polymorphisms may depict or monitor both the duration and the severity of inflammation, hence the progression of various immunologic patterns and conditions, including BD [14–16].

The interleukin 10 (IL-10) gene, with five exons separated by four introns on chromosome 1q31–32, encodes an immunomodulatory cytokine, IL-10 [17], a critical suppressor of cytokines as well as an autoimmune and inflammatory response factor. IL-10 is essential for immunological regulation and the prevention of chronic inflammatory diseases. Other variables, such as genetic variations, contribute to over 75% of the variations in IL-10 expression across individuals [18].

The interleukin 23 (IL-23) is a proinflammatory cytokine that interacts with the IL-23R receptor and promotes the synthesis of IL-17F and IL-17A by Th17 cells, resulting in inflammation. The IL-23 signal transduction pathway is critical in the Th17 cell-mediated immune response and the pathophysiology of autoimmune and inflammatory disorders [19]. Interindividual differences in expression levels of cytokine genes involved in the Th17 response may be driven by variations in cytokine genes, resulting in the pathophysiology of autoimmune disease phenotypes.

We will focus on two single-nucleotide polymorphisms (SNPs), namely, IL-23R rs10889677 and IL-10 rs3024498. Concerning the mRNA stability alteration, as rs10889677 is positioned in the 3′-UTR, the receptor may be overexpressed, leading to T-cell differentiation into the Th17 subpopulation, which may drive elevated production of other cytokines that contribute to inflammation. The rs3024498 is an exonic polymorphism that may change the overall function of the IL-10 cytokine. This study aimed to determine the associations of these two SNPs with BD, if any.

Material and methods

Study subjects

A group of 280 HLA-B51-positive patients with BD (30.1 ± 3.3 years; 132/280 males) diagnosed according to the international classification criteria [20] for BD in the Department of Family Medicine of Biruni University Hospital during the period from January 2021 to September 2021 and a control group including 300 healthy (289 HLA-B51 negative and 11 HLA-B51 positive) individuals (32.9 ± 2.8 years; 138/300 males) participated in the study.

The control group samples were free of any history of autoimmune diseases by clinical examination, questionnaires, or medical history. There was no gender or age bias in the patient and control groups (data not shown).

The presence of any autoimmune disease, smoking, prescription drugs, pregnancy, and alcohol usage was the exclusion criteria for the study samples. The enrolled subjects were of Turkish origin, and informed consent was obtained from all participants in the study.

The procedures applied within the study followed the 1964 Helsinki Declaration ethical standards and the Institutional Ethical Committee of Biruni University (Approval number: 2021/55-16).

Sample preparation

Following the manufacturer's recommendations, the DNA was isolated from the blood retrieved from the patient and control samples using a Blood Genomic DNA Purification Kit (catalog no: DP023-150, Genemark). The quantity and quality of DNA samples were determined, and samples with optical density values between 1.7 and 1.9 were included in the study.

The polymerase chain reaction-restriction fragment length polymorphism [PCR-RFLP] method was applied to explore the IL-10 rs3024498 and IL-23R rs10889677 SNPs.

For IL-10 rs3024498, 5′-GCTTTCAAGAATGAAGTG GTTG-3′ (sense) and 5′-TTAAGCTGTTTCCATAGGGTGA-3′ (antisense) and for IL-23R rs10889677, 5′-CTGTGCTCC TACCATCACCA-3′ (sense) and 5′-TGCTGTTTTTGTGCC TGTATG-3′ (antisense) primer sets were preferred for PCR. The thermal cycler protocol for both PCRs was 96 °C for 2 min, followed by 37 cycles at 95 °C for 20 s, 59 °C for 40 s, 72 °C for 30 s, and an additional 5 min at 72 °C.

One unit of TseI enzyme (catalog no. R0591L, NEB, MA) was used to digest 320 base pairs [bp] of the IL-10 rs3024498 PCR product. The digestion consisted of incubating the PCR product and TseI enzyme mix for 1 h at 65 °C, followed by an electrophoresis run for 25 min at 100 V on 4% agarose gel. Three polymorphic alleles, IL-10 rs3024498 TT [320 bp], IL-10 rs3024498 TC (112 bp + 208 bp + 320 bp), and IL-10 rs3024498 CC (112 bp + 208 bp), were observed.

One unit of MnII enzyme (catalog no. R0163L, NEB, MA) was used to digest the 152-bp-long IL-23R rs10889677 PCR product. The digestion protocol consisted of incubating the PCR product and MnII enzyme mix for 15 min at 37 °C, followed by an electrophoresis run for 30 min at 75 V on 4%

agarose gel. Three polymorphic alleles, IL-23R rs10889677 AA (152-bp), IL-23R rs10889677 AC (70 bp + 82 bp + 152-bp), and IL-23R rs10889677 CC (70 bp + 82 bp) fragments, were observed (Fig.1).

Data processing and statistical analysis

The GraphPad Prism (version 8.2) was used for single-gene-only genotype analysis, whereas Haploview (version 4.2) was used for haplotype analysis. The power of the study was calculated as 80%. The chi-square (χ^2) test was applied for both the Hardy–Weinberg equilibrium of the SNPs and the comparison of genotype-allele frequencies. Odds ratios (OR) and respective 95% confidence intervals (CIs) were used to evaluate the effects of any discrepancies between genotype and allelic distribution. Statistical significance was defined as a two-sided p-value of 0.05.

Results

Distributions of polymorphisms of IL-23R rs10889677 and IL-10 rs3024498 in BD

Two hundred eighty (280) BD patients and 300 control samples were successfully genotyped for IL-23R rs10889677 and IL-10 rs3024498. All alleles were within the range of Hardy–Weinberg equilibrium (HWE) (Data not shown). The allele frequencies and genotype distributions are summarized in Tables 1 and 2.

In the single genotyping study of the IL-23R rs10889677 polymorphism, the overall frequencies of the AA, AC, and CC allele combinations were 51.4, 23.2, and 25.4% in the BD group and 45, 39, and 16% in the control group, respectively. The difference between the frequency of CC genotype was statistically significant between the groups ($p < 0.0001$, OR: 3.343, 95% CI: 1.631–4.316).

The CC genotype of IL-23R rs10889677 has a 2.663-fold risk factor in patients with BD.

Moreover, the recessive model (AA + CC versus AC) was also shown to have an increased risk factor in BD patients ($p < 0.0001$, OR: 2.115, 95% CI: 1.466–3.056). No statistical differences were observed concerning the allele frequencies of IL-23R rs10889677 ($p > 0.05$) (Table 1).

In the single genotyping study of the IL-10 rs3024498 polymorphism, however, the overall frequencies of the CC, CT, and TT allele combinations were 4.6, 12.5, and 82.9% in the BD group and 2.3, 21, and 76.7 in the control group, respectively. The difference between the frequency of the CC genotype was statistically significant between the groups ($p = 0.0293$, OR: 3.343, 95% CI: 1.233–8.492). No statistically significant differences were detected in the case of allele frequencies in the dominant (CC versus CT + TT) and

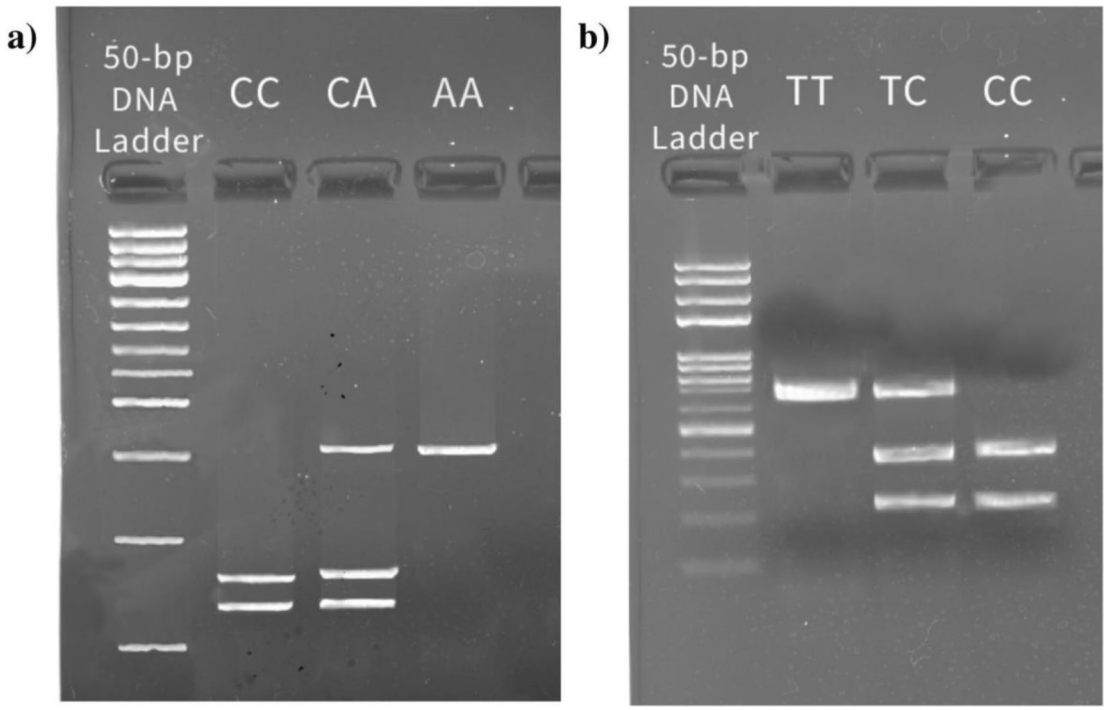

Fig. 1 The RFLP-PCR digestion profiles. **a)** IL-10 rs3024498 polymorphism profiles. Well 1:M50 DNA marker, well 2:rs3024498TT, well 3: rs3024498TC, and well 4: rs3024498CC. **b)** IL-23R rs10889677 polymorphism profiles. Well 1:M50 DNA marker, well 2:rs10889677CC, well 3:rs10889677CA, and well 4:rs10889677AA

recessive (CC + TT versus TT) models of IL-10 rs3024498 ($p > 0.05$) (Table 2).

Combined genotypes of IL-23R rs10889677 and IL-10 rs3024498 SNPs in BD

Table 3 summarizes the combined genotype analysis of IL-23R rs10889677 and IL-10 rs3024498 polymorphisms in BD patients and control samples.

According to the association study among the combined genotypes, AC + CT combined genotype frequency was found to be higher in the BD group than in the AA + CC combined genotype frequency. Thus, AC + CT combined genotype was shown to be a risk factor for BD ($p = 0.0364$) (Table 3).

Discussion

Little is known about the pathophysiology and origin of BD, and it is unclear what factors lead to this complicated etiology. As a general idea, BD is thought to be a multisystem inflammatory and autoimmune disease whose susceptibility

Table 1 Distribution of genotype and allele frequencies of IL-23R rs10889677 polymorphism in BD patients and control subjects

IL-23R rs 10889677	Patient *n* (%)	Control *n* (%)	OR (95% CI)	*p*-value
CC	71 (25.4)	48 (16)	Ref	
AC	65 (23.2)	117 (39)	2.663 (1.631–4.316)	**< 0.0001**
AA	144 (51.4)	135 (45)	1.387 (0.8961–2.130)	0.1401
Dominant AA vs. AC + CC			1.294 (0.9284–1.784)	0.1215
Recessive AA + CC vs. AC			2.115 (1.466–3.056)	**< 0.0001**
C Allele	207 (37)	213 (35.5)	Ref	
A Allele	353 (63)	387 (64.5)	1.065 (0.8386–1.353)	0.6041

Statistically significant values ($p < 0.05$) were shown in bold

Table 2 Distribution of genotype and allele frequencies of IL-10 rs3024498 polymorphism in BD patients and control subjects

IL-10 rs 3024498	Patient *n* (%)	Control *n* (%)	OR (95% CI)	*p*-value
CC	13 (4.6)	7 (2.3)	Ref	
CT	35 (12.5)	63 (21)	3.343 (1.233–8.492)	**0.0293**
TT	232 (82.9)	230 (76.7)	1.841 (0.7008–4.776)	0.2863
Dominant CC vs. CT + TT			2.038 (0.7808–5.306)	0.1951
Recessive CC + TT vs. TT			1.025 (0.7946–1.322)	0.8505
C Allele	61 (10.9)	77 (12.8)	Ref	
T Allele	499 (89.1)	523 (87.2)	0.8303 (0.5802-1.194)	0.3077

Statistically significant values ($p < 0.05$) were shown in bold

Table 3 The combined genetic effects of rs10889677 and rs3024498 SNPs on BD

IL-23R and IL-10 combined genotypes	Patient *n* (%)	Control *n* (%)	OR (%95 Cl)	*p*-value
AA + CC	5 (2)	2 (0.7)	Ref	
AA + CT	17 (6)	25 (8.3)	3.676 (0.6259–19.63)	0.2192
AA + TT	118 (42)	108 (36)	2.288 (0.4765–11.66)	0.4512
AC + CC	7 (2)	5 (1.6)	1.786 (0.2666–11.51)	0.6562
AC + CT	11 (4)	29 (9.8)	6.591(1.053–35.25)	**0.0364**
AC + TT	49 (18)	81 (27)	4.133(0.8266–21.19)	0.1121
CC + CC	3 (1)	0 (0)	0.000 (0.000–5.175)	> 0.999
CC + TT	61 (22)	41 (13.6)	1.680(0.3313–8.730)	0.7015
CC + CT	9 (3)	9 (3)	2.500 (0.4404 -14.62)	0.4065

Statistically significant values ($p < 0.05$) were shown in bold

might depend on variants in distinct immunoregulatory genes due to their influence on cytokine production [21]. This study set out to investigate two cytokine variations, IL-23R rs10889677 and IL-10 rs3024498.

The rs10889677 variation is near the mi-RNA Let-7f binding region; thus, it may control several elements of the IL-23R gene's posttranscriptional regulation [22, 23]. However, the biological significance of this variation on IL-23R production and function is yet unclear. The research conducted by Yalcin et al. in 2014 discovered a meaningful connection between the IL-23R rs10889677 variation and BD in a Turkish population [24]. According to our results, the IL-23R rs10889677CC genotype increases the susceptibility to BD. SNPs in the 3-UTR, such as rs10889677, may promote upregulation of the receptor by strengthening mRNA stability, triggering T-cell differentiation, and leading to increased release of other inflammation-initiating cytokines.

This assumption must be interpreted cautiously because the generalizability of previously published research on this SNP is problematic. SNP rs10889677 is found to have strong associations with several diseases, such as Crohn's disease, ankylosing spondylitis [25], and psoriasis [26], but no associations with rheumatoid arthritis [27], multiple sclerosis [28], rheumatic heart disease [29], and colorectal cancer (CC) [30]. In 2015, Nemati et al. published a paper in which they concluded that rs10889677 leads to decreased risk of CC [31]. These somewhat contradictory results can be attributed to the participation of several components in the etiology of the diseases, such as immunological aberrations, environmental factors, and the population-specific genetic background of the sample groups.

A lack of IL-10 or its aberrant expression can exacerbate the inflammatory response to microbial exposure, resulting in various autoimmune issues. Thus, reduced IL-10 expression elevates pathogens during acute infection and augments the inflammatory response, generating tissue damage and immunopathology, as observed in BD [32, 33]. SNP rs3024498 is reported to be associated with colorectal cancer [34] and motoric cognitive risk syndrome [35]. In this present study, we were also able to show that IL-10 rs3024498 is associated with the susceptibility of BD. Besides, these rs10889677 and rs3024498 combined genotypes were also shown to have associations with BD susceptibility.

Several reasons might account for these inconsistent outcomes. When interpreting disease susceptibility or protection, the findings reported here should support the necessity of genotype and haplotype analysis rather than single-standing SNP analysis. For instance, owing to type II errors, research with a small sample size is always far from a genuine connection. Besides, the SNPs investigated may also have no independent roles in the pathophysiology of BD; instead, they might be relevant to disease expression and progression.

The association with Behçet's disease remains less clear, and more research is needed to establish a definitive link with IL-23R rs10889677 and IL-10 rs3024498 polymorphisms. To the best of our knowledge, this is the first study showing the combined genotype effect of IL-23R rs10889677 and IL-10 rs3024498 polymorphisms on BD. Our findings indicate that variations in both IL-23R rs10889677 and IL-10 rs3024498 appear to play a role in BD susceptibility in the Turkish population. However, there is still much doubt about the association between this polymorphism and BD, which can be clarified with future studies involving larger sample sizes and diverse populations.

Author contributions GY designed and supervised the study; TSa provided the study samples; SS, SBY, and EA performed the experiments; GY, TSo, and TSa performed the data analysis and wrote the paper. All the authors have accepted their responsibility for the entire content of this manuscript and have approved its submission.

Compliance with ethical standards

Ethics approval All authors stated that the protocol for the research project had been approved by the Institutional Ethical Committee of Biruni University (Decision no:2021/55-16).

Conflict of interest The authors declare that they have no conflict of interest.

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