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# *JAK2, STAT3* Gene Polymorphisms in Turkish Patients with Behçet's Disease

## Türk Behçet Hastalarında *JAK2, STAT3* Gen Polimorfizmleri

Darya Farhoomand Aksoy[1], Rahime Aksoy[2], Sevim Gönen[3], Ümit Ölmez[1]

[1]Ankara University Faculty of Medicine, Department of Immunology and Allergy, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
[3]Gazi University Faculty of Medicine, Department of Pediatric Nephrology Ankara, Türkiye

**ABSTRACT**

**Objective:** Behçet's disease (BD) is a chronic, multisystemic inflammatory disorder with an unknown etiology. T cells are crucial in the pathogenesis of BD. Janus kinase-2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) are intracellular signal transduction molecules that increase the risk of developing some autoimmune diseases. By modifying Th1 and Th17 responses, the JAK2 and STAT3 signaling pathways are believed to be effective in BD. This study aimed to determine whether BD in the Turkish population is related to JAK2 and STAT3 polymorphisms.

**Methods:** A case-control study included a total of 197 patients with BD who were referred to the Ankara University Faculty of Medicine and 100 healthy individuals without a history of autoimmune disease or BD in their family or themselves. The genotypes of one single-nucleotide polymorphism (SNPs) (rs10974944) in JAK2 and one SNPs (rs2293152) in the STAT3 gene were analyzed using polymerase chain reaction restriction fragment length polymorphism.

**Results:** The result of this investigation identified that in this disease, there was a significantly increased frequency of the CG genotype of the rs10974944 JAK2 in patients with BD compared with a control group (p=0.031, odds ratio [95% confidence interval: 0.392 (0.163-0.942)]. None of the tested SNPs (rs2293152) of STAT3 were associated with BD.

**Conclusion.** This is the first investigation into JAK2 and STAT3 polymorphisms in Turkish patients with BD. These results suggest that a JAK2 genetic polymorphism may be associated with BD susceptibility.

**Keywords:** Behçet disease, STAT3, JAK2, polymorphism

**ÖZ**

**Amaç:** Behçet hastalığı (BH), etiyolojisi bilinmeyen kronik, multisistemik enflamatuvar bir hastalıktır. BH'nin patogenezinde T hücreler çok önemlidir. Janus kinaz-2 (JAK2) ve sinyal transdüseri ve transkripsiyon 3 aktivatörü (STAT3), hücre içi sinyal iletim molekülleridir ve çeşitli otoimmün hastalıklar için risk faktörü olduğu gösterilmiştir. JAK2 ve STAT3 sinyal yolunun Th1 ve Th17 cevabını değiştirerek BH'ninde etkili olabileceği düşünülmektedir. Bu çalışma, Türk popülasyonunda BH'nin JAK2 ve STAT3 polimorfizmleri ile ilişkili olup olmadığını belirlemeyi amaçlamaktadır.

**Yöntemler:** Olgu-kontrol çalışmasına, Ankara Üniversitesi Tıp Fakültesi'ne başvuran BH olan toplam 197 birey ile ailesinde veya kendisinde otoimmün hastalık veya BH öyküsü olmayan 100 sağlıklı birey dahil edildi. Tek nükleotid polimorfizmi (SNP) ile JAK2 genindeki rs10974944, STAT3 geninde rs2293152 polimorfizmleri, polimeraz zincir reaksiyonu kesim parçası uzunluk polimorfizmi kullanılarak analiz edildi.

**Bulgular:** Bu araştırmanın sonucunda, kontrol grubuyla karşılaştırıldığında, BH'lerde rs10974944 JAK2'nin CG genotipinin sıklığında anlamlı bir artış olduğu belirlendi. [P=0,031, olasılık oranı (%95) güven aralığı] 0,392 (0,163-0,942) STAT3'ün test edilen SNP'lerinin (rs2293152) hiçbiri BD ile ilişkili değildi.

**Sonuç:** BH olan Türk hastalarda JAK2 ve STAT3 polimorfizmlerini araştırdığımız çalışmamız bu alanda yapılan ilk çalışmadır. Bu sonuçlar, JAK2 genetik polimorfizminin BH'ye yatkınlıkla ilişkili olabileceğini düşündürmektedir.

**Anahtar Sözcükler:** Behçet hastalığı, STAT3, JAK2, polimorfizm

**Address for Correspondence/Yazışma Adresi:** Rahime Aksoy PhD, Ankara University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
**E-mail / E posta:** rahimeaksoy77@yahoo.com
**ORCID ID: orcid.org/**0000-0001-8433-3627



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## INTRODUCTION

Turkish dermatologist Dr. Hulusi Behçet, by detecting recurrent aphthae ulcers of the genital and oral mucosa and recurrent ulcers of the eye symptoms, described a triple syndrome that bears his name in 1937 (1). Behçet's disease (BD) is a systemic and chronic inflammatory disease of unknown etiology that triggers proinflammatory activation of the innate and adaptive immune systems (2,3). Although the pathogenesis of BD is unknown, it is believed that the disease is triggered by viral and bacterial agents, and both genetic and environmental factors are important in disease pathogenesis (4). Through genome-wide association studies and subsequent detailed genomic analyses, several susceptibility genes have been discovered, the majority of which are implicated in immunological and inflammatory responses (5). Among them, the HLA-B*51 gene displays the strongest relationship with this disease in a number of ethnic groups, including Turkish, Iranians, Koreans, Arabs, and Greeks (5,6). T cells (Th1 and Th17) play an important role in the pathogenesis of the disease (7,8).

Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) are two critical proteins in the signal transduction pathway that leads to DNA transcription. The human JAK2 and STAT3 genes are located on chromosomes 9p24.1 and 17q21.2, respectively. The JAK2-STAT3 pathway is a signaling target for numerous cytokines that are thought to play important biological roles in immune-mediated diseases (9). This pathway is essential for Th1 cell differentiation and proliferation and is also important for the development of Th17 cells. The importance of Th1 and Th17 cells in immune-mediated diseases such as BD suggests that the JAK2 and STAT3 signaling pathways may also play a role in these diseases (8,10,11). T-cell subsets (Th1 and Th17) were found to be higher in the peripheral blood of patients with BD than in healthy controls, suggesting an important role in the etiopathogenesis of BD (10,11). The role of the JAK/STAT pathway in BD predisposition is still unknown, as there are few and partially contradictory data in the literature (11-14).

In this study, we investigated whether the JAK2 gene rs1097944 and STAT3 gene rs2293152 polymorphisms contributed to the genetic predisposition to the development of BD.

## MATERIALS AND METHODS

### *Patients and Controls*

The study group comprised 197 patients with BD who were referred to the outpatient clinic of the Department of Clinical Immunology and Allergy, Ankara University Faculty of Medicine between 2012 and 2013. Patients with BD and controls were unrelated. All patients were diagnosed according to the 1990 international criteria of the International Study Group for BD (15). The control group comprised 100 healthy adults without a history of autoimmune or BD. The exclusion criteria were age 18 years and the presence of comorbidities. Written informed consent was obtained from all patients, and this research project was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: 08-351-15/2015), in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

### Analysis of the Genetic Polymorphisms of JAK2 and STAT3

Peripheral venous blood samples were collected from the patient and control groups. Genomic DNA was isolated from whole blood using the Norgen Biotek DNA purification kit (Norgen Biotek-Kanada). The extracted DNA was stored at 20 °C until use. Amplification of the target DNA in the JAK2 and STAT3 genes was performed by polymerase chain reaction (PCR) using appropriate primers. Analysis of the JAK2 rs10974944 and STAT3 rs2293152 gene G/C polymorphisms was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR/RFLP) methods. In these SNPs, an 1858 G/C polymorphism with a guanine cytosine change was defined in exons 9 and 17 of the JAK2 and STAT3 genes. PCR was performed using 25 ng genomic DNA, one unit Taq DNA polymerase (Fermentas, Lithuvania), a total of 20 pmol of each primer, and 5 nmol deoksi NTPs under the following conditions: initial denaturation at 95 °C for 5 min followed by 35 cycles of denaturation (94 °C, 50 s), annealing (59 °C, 50 s), extension (72 °C, 50 s), and a final extension at 72 °C for 7 min. The amplified product (10 L) was digested with the specific restriction enzymes AciI (New England Biolabs USA) and MboI (New England Biolabs USA). Digestion results were visualized on 2% agarose gel under UV light. The primers and restriction enzymes used for each SNP are given in Table 1. Moreover The RFLP method was repeated twice to check the reliability of the test.

### *Statistical Analysis*

Statistical calculations were performed using SPSS version 17.0 software (SPSS Inc., IL, USA). Allele and genotype distributions were compared between patients and controls using the chi-square test. A p-value <0.05 was considered significant. Odds ratios (ORs) with 95% confidence intervals (CI) were estimated whenever applicable.

## RESULTS

The BD group (n=197), with 92 (46.7%) males and 105 (53.3%) females. The average age of this group was 38.5±11.5 years. The control group (n=100), with 43 (43%) males and 47 (47%) females and an average age of 36.2±10.4, consisted of healthy volunteers. Allele and genotype frequencies of the samples analyzed for SNPs of JAK2 STAT3 polymorphisms are depicted in Table 2.

**Table 1.** Primers and restriction enzymes used for RFLP analysis

| Gene | SNP | Primers | Tm (°C) | Enzyme |
|---|---|---|---|---|
| JAK2 | rs10974944 | 5'-CAAGGGTCAACTGTAGTACATA-3'<br>5'- CTGCTTGCTAGTGGGTGAAT -3' | 37° | MboI |
| STAT3 | rs2293152 | 5'- TCCCCTGTGATTCAGATCCC -3'<br>5'- CATTCCCACATCTCTGCTCC -3' | 37° | AciI |

RFLP: Restriction fragment length polymorphism.

In 197 Behçet patients, the rs10974944 SNP in the JAK2 gene was analyzed, and the C/C genotype was discovered in 101 patients at a rate of 51.3%, the C/G genotype in 10 patients at a rate of 5.1%, and the G/G genotype in 86 patients at a rate of 43.6%.

Moreover, among 100 healthy controls, the C/C genotype was observed in 47% of 47 individuals, the C/G genotype in 12% of 12 individuals, and the G/G genotype in 41% of 41 individuals. Concerning the distribution of alleles, the frequency of the C allele of JAK2 rs10974944 was found to be 54% with 212 chromosomes, and the frequency of the G allele was found to be 46% with 182 chromosomes when we examined the allele frequencies. However, in the control groups, the C allele was 53% with 106 chromosomes, and the G allele was 42% with 94 chromosomes. No other significant differences were observed in the distribution of GG and CC polymorphisms in JAK2 between patients with BD and controls. Concerning the distribution of allele and genotype, the frequency of the CC genotype of JAK2 rs10974944'nin was significantly higher in patients with BD than in healthy controls [p=0.031, OR (95% CI) 0.392 (0.163-0.942)]. It was noticed that it may indicate an increased risk of predisposition to BD.

Analyzing STAT3 rs2293152 revealed frequencies of the C/C genotype in 58 patients at a rate of 29.4%, frequencies of the C/G genotype in 53 patients at a rate of 26.9%, and the G/G genotype in 86 patients at a rate of 43.7%. The C/C genotype was found in 20% of 20 healthy controls, 35% of 35 healthy controls, and 45% of 45 healthy controls. The frequency of the C allele in the rs2293152 polymorphism in the STAT3 gene was 42.9% with 169 chromosomes, and the prevalence of the G allele was 57.1% with 225 chromosomes. In the control groups, the frequency of c C was 37.5 with 75 chromosomes, and the G allele was 62.5% with 125 chromosomes. There was no significant difference in the distribution of genotypes between patients with BD and controls for STAT3 rs2293152 gene.

## DISCUSSION

This study investigated the association of JAK2 and STAT3 polymorphisms with BD in a Turkish population. Our study identified an association between rs10974944 in JAK2 and BD. The existence of BD in the families of BD patients provides evidence for a genetic component in its etiology. The strongest genetic marker associated with BD is the HLA-B*51 gene on chromosome 6p21, which is positive in Silk Road countries such as Türkiye, Iran, China, and Japan (15). Polymorphisms in molecules that enable the production of cytokines can alter the immune response and create a genetic predisposition to autoimmune diseases. Recent genetic studies have shown associations between BD and interleukin-10 (IL-10), IL23R-IL12RB2, ERAP-1, CCR1-CCR3, KLRC4, and STAT4 genes. These data have demonstrated that genetic factors play an important role in the pathogenesis of BD (2,4,10,15).

Systematic genomic screening has provided evidence of an association with many non-HLA susceptibility loci in the identification of susceptibility genes for BD. Strong linkage disequilibrium is known in the MHC region. However, it remains unclear whether these associations confer susceptibility to BD or whether they are in linkage disequilibrium with HLA-B*51 (16). A study using genomic linkage analysis identified 16 potential loci for BD (1p36, 4p15, 5q12, 5q23, 6p22-24, 6q16, 6q25-26, 7p21, 10q24, 12p12-13, 12q13, 16q12, 16q21-23, 17p13, 20q12-13, Xq26-28), with the strongest linkage reported at loci 12p12-13 and 6p22-24 (17). The human JAK2 and STAT3 genes were located on chromosomes 9p24.1 and 17q21.2, respectively. Although the genes used in our study were not associated with the disease in genomic studies, we believe that they may be associated with the disease in different ethnic groups. Further studies are needed to determine the association between non-HLA susceptibility loci with BD.

The role of the JAK/STAT pathway in the pathogenesis of many autoimmune diseases has received increasing attention in recent years. JAK/STAT polymorphisms have been studied in many inflammatory diseases. Some diseases are associated with them, whereas others are not. The JAK/STAT pathway is also essential for Th1 cell differentiation and proliferation (5,7). Furthermore, it is crucial for the growth of Th17 cells. Both cells (Th1 and Th17) play an important role in immune-mediated diseases such as BD by regulating Th1 and Th17 (5,7,15). Genetic polymorphisms of JAK2 and STAT3 have recently been studied for their association with a variety of autoimmune disorders, including Crohn's disease and ulcerative colitis (4,18).

The STAT3 rs2293152 polymorphism was studied in 595 Caucasian Polish patients with rheumatoid arthritis, and no association with the disease was found (19). According to some research, STAT3 SNPs are significantly associated with diseases such as cancers,

**Table 2.** Association of JAK2 gene (rs10974944) and STAT3 gene (rs2293152) polymorphisms with Behçet's disease

| Gene | SNP | Genotype/allele | BD, (n=197) | Controls (n=100) | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|
| JAK 2 | rs10974944 | GG | 86 (43.7%) | 41 (41%) | **0.662** | 1.115 (0.684-1.816) |
| | | GC | 10 (5.1%) | 12 (12%) | **0.031*** | 0.392 (0.163-0.942) |
| | | CC | 101 (51.3%) | 47 (47%) | **0.487** | 1.186 (0.733-1.921) |
| | | G | 182 (46%) | 94 (42%) | - | |
| | | C | 212 (54%) | 106 (53%) | - | |
| STAT3 | rs2293152 | GG | 86 (43.7%) | 45 (45%) | **0.825** | 0.947 (0.583-1.537) |
| | | GC | 53 (26.9%) | 35 (35%) | **0.149** | 0.684 (0.407-1.147) |
| | | CC | 58 (29.4%) | 20 (20%) | **0.081** | **1.669 (0.936-2.975)** |
| | | G | 225 (57.1%) | 125 (62.5%) | - | |
| | | C | 169 (42.9%) | 75 (37.5%) | - | |

BD: Behçet's disease. SNP: Single-nucleotide polymorphism, OR: Odds ratio, *: P<0.05 statistically significant, CI: Confidence interval.

immunodeficiency, autoimmune disease, viral hepatitis, and multiple sclerosis (15,20). Furthermore, numerous genome-wide association studies have shown that the JAK-STAT pathway is also involved in the pathogenesis of common rheumatologic diseases (21). Polymorphisms in the JAK2 and STAT3 genes in BD have rarely been studied in different populations. The "JAK2 and STAT3 polymorphisms in a Han Chinese Population with BD" study demonstrated the frequency of the GG genotype for rs2293152 in STAT3 gene was significantly higher in patients than in healthy controls [P=0.001, Pc=0.021, (OR)=1.712]. Compared with controls, BD patients more often have the TT genotype at STAT3 rs744166 (p=0.031 Pc=0.651, OR=1.324), and a decrease in the JAK2 rs10119004 GA (p=0.032, Pc=0.672, OR=0.771) genotype was observed (22). Considering this information and the fact that the genetic basis for BD susceptibility is unclear, we investigated whether polymorphisms in the JAK2 and STAT3 genes play a role in the development of BD in the Turkish population.

Our results showed that the frequency of the JAK2 rs10974944 GC genotype was significantly increased in patients with BD, indicating its predisposing role in this disease [p=0.031, odd ratio OR (95% CI) 0.392 (0.163-0.942)]. No significant difference was observed in the distribution of genotypes between patients with BD and controls in STAT3 rs2293152 gene. Importantly, this research is the first to analyze the polymorphisms JAK2 rs10974944 and STAT3 ra2293152 genes in a Turkish population with BD.

STAT3 rs744166 and rs2293152 polymorphisms were compared between BD patients and controls in a study involving 217 BD patients of Spanish Caucasian origin, and no statistically significant difference in genotype analysis for the two polymorphisms was found (rs744166; p=0.80, OR: 1.03, %95 CI: 0.84-1.26: rs2293152; p=0.98, OR: 1.00, %95 CI: 0.82-1.23) (19). Hu et al. (22) discovered in a Chinese Han population that the frequency of the GG genotype for rs2293152 in the STAT3 gene was significantly higher in patients than in healthy controls (p=0.001). In our study, there was no statistically significant difference in the frequency of the GG genotype between patients and healthy controls (p=0.825, OR (95% CI): 0.947 (0.583-1.583). Hu et al.'s (22) research had a higher number of patients than our study. It is possible that the results would be different if there were more patients and control groups in the studies. Geographical differences and ethnicity-specific genetic factors may also contribute to the differences in the results. Similar to other studies investigating the association between gene polymorphisms and BD, our study had some limitations. Other research has used several different SNPs in the JAK2 and STAT3 genes. Furthermore, we believe that further research with more patients and control groups will show that the GC genotype of JAK2 rs10974944 is important in the predisposition of the Turkish population to BD.

## CONCLUSION

Our study is important because it is one of the few studies that investigated JAK2 and STAT3 gene polymorphisms in BD. There is a need to investigate various JAK2 and STAT3 polymorphisms that predispose to BD in the Turkish population. The results of our study will be a pioneer for similar investigations in the future.

### *Ethics*

**Ethics Committee Approval:** This research project was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: 08-351-15/2015).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-Review:** Externally peer-reviewed.

### *Authorship Contributions*

Concept: D.F.A., R.A., S.G., Ü.Ö., Design: D.F.A., R.A., S.G., Ü.Ö., Data Collection or Processing: D.F.A., R.A., S.G., Ü.Ö., Analysis or Interpretation: D.F.A., R.A., S.G., Ü.Ö., Literature Search: D.F.A., R.A., S.G., Ü.Ö., Writing: D.F.A., R.A., S.G., Ü.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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