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Investigation of IL23R, JAK2, and STAT3 gene polymorphisms and gene–gene interactions in Crohn's disease and ulcerative colitis in a Turkish population

BOWEL

Güray Can[1], Ahmet Tezel[2], Hakan Gürkan[3], Hilmi Tozkır[3], Gülbin Ünsal[2], Ali Rıza Soylu[2], Hasan Celalettin Ümit[2]

[1]Department of Gastroenterology, Abant İzzet Baysal University School of Medicine, Bolu, Turkey
[2]Department of Gastroenterology, Trakya University School of Medicine, Edirne, Turkey
[3]Department of Genetics, Trakya University School of Medicine, Edirne, Turkey

ABSTRACT

Background/Aims: Inflammatory bowel diseases are chronic, relapsing, inflammatory conditions. They have a genetic backround resulting in patient susceptibility. The aim of our study is to investigate the involvement of IL23R, JAK2, and STAT3 polymorphisms in inflammatory bowel diseases in a Turkish population.

Materials and Methods: Polymorphisms in IL23R (rs11209026), JAK2 (rs10758669), and STAT3 (rs3816769, rs2293152, rs744166, rs957970, rs8074524) were genotyped in 69 Crohn's disease patients, 157 ulcerative colitis patients, and 89 healthy controls.

Results: The presence of (C) in rs10758669, (T) and (TT) in rs957970, and (TT) in rs744166 were found to increase the susceptibility to Crohn's disease (p=0.049, p=0.016, p=0.010, p=0.035, respectively), while rs2293152 (GC), rs744166 (CT), and rs957970 (CT) provide protection against Crohn's disease (p=0.007, p=0.043, p=0.043, respectively). While rs2293152 (GC) was protective, rs2293152 (CC) increased the susceptibility to ulcerative colitis (p=0.009, p=0.001). All the polymorphisms were associated with age-at-diagnosis, except rs11209026. Furthermore, rs2293152 was associated with an extension in ulcerative colitis, while rs10758669, rs3816769, rs744166, rs2293152, and rs957970 were associated with the subphenotype in Crohn's disease. The presence of rs10758669 (AC) was protective against perianal Crohn's disease (p=0.016). Additionally, rs10758669 and rs2293152 in Crohn's disease and rs8074524, rs3816769, and rs10758669 in ulcerative colitis were associated with the requirement of immunsuppression. Finally, rs8074524 and rs10758669 in Crohn's disease and rs11209026 in ulcerative colitis were associated with disease-related operation.

Conclusion: This is the first study of the single marker association of IL23R, JAK2, and STAT3 polymorphisms with ulcerative colitis and Crohn's disease in a Turkish population. It was demonstrated that these polymorphisms may be effective in the etiology of inflammatory bowel disease in this Turkish population.

Keywords: Crohn's disease, interleukin-23 receptor, janus kinase-2, signal transducer and activator of transcription-3, ulcerative colitis

Original Article

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, repeated inflammatory pathologies of the gastrointestinal system. In the background to the diseases, there is an uncontrolled stereotypic immune response. Though there are similar aspects, they essentially comprise two different diseases: ulcerative colitis (UC), presenting as surficial ulcers limited to the colon, and Crohn's disease (CD), presenting with skip lesions and transmural ulcers that may involve the whole gastrointestinal system. Furthermore, each disease may also cause various pathologies outside the gastrointestinal tract (1,2).

Together with the increase in incidence and prevalence of IBD, recent studies have focused on the etiopathogenesis of IBD. Though there are notable developments in this regard, the etiopathogenesis of IBD remains mysterious. Although the causal factors of IBD not have been clearly revealed yet, it is thought that the complex interaction of environmental, genetic, and immunological factors in

Address for Correspondence: Güray Can E-mail: dr_guraycan@yahoo.com
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genetically-susceptible individuals causes an excessive mucosal immune response against enteric antigens, which consequently contributes to the onset and the progression of IBD (2,3).

Familial aggregation and twin studies have shown that UC and CD have a strong genetic pre-disposition (4). Subsequent genome wide studies have shown that IBD is a polygenic disease incorporating many genes (2). These broad-scale genome studies and selected gene-based relationship studies have revealed possible IBD susceptible genes and chromosomal loci (5,6). Currently, around 100 IBD susceptible genes have been described that may affect all stages of the inflammatory response of the intestinal mucosal immune system, including both innate and adaptive components. While some of these are specifically related to UC or CD, some create a susceptibility to both diseases (7). These genes have functions at different stages of the intestinal immune response, such as microbial identification, leukocyte activation, cytokine regulation, and intestinal epithelial barrier (8). It appears that immune cells, like leukocyte, dendritic cells, and macrophages, and the cytokines responsible for the regulation of these cells play an important role in the etiopathogenesis of IBD. Recently, it was reported that many genes on the IL23/IL23R signal pathway, where interleukin 23 (IL23) and its receptor (IL23R) are found, are also at the loci for susceptibility to UC and CD (5,6,9-13). On the IL23/IL23R signal pathway, there are many molecules that allow the synthesis of proinflammatory cytokines, which move the signal to the nucleus, together with IL23 and IL23R. Janus kinase-2 (JAK2), signal transducer and activators of transcription-3 (STAT3), tyrosine kinase-2 (Tyk2), IL12B, and IL12R are among the components of this pathway, and are responsible for regulation of the innate and adaptive inflammatory response at different levels of intestinal mucosa (14). It is thought that the IL23/IL23R signal pathway may play a central role in the pathogenesis of IBD. Though there are studies showing that IL23R, JAK2, and STAT3 cause susceptibility to UC and CD in different ethnic groups, the results are not consistent (6,13,15-21). The reason for this discrepancy may be that IBD in different ethnic communities may appear through different predominant mechanisms. Furthermore, genetic studies on the pathogenesis of IBD in the Turkish population are very limited. The scale of the contribution of the IL23/IL23R pathway to IBD pathogenesis in Turkish society and whether there is a phenotypic relationship is not known. Therefore, in our study, we aimed to evaluate the relationship of IBD with IL23R, JAK2, and STAT3 gene polymorphisms belonging to the IL23/IL23R pathway in a Turkish population.

MATERIAL AND METHODS

Ethical statement

The study design and procedures were approved by Trakya University Non-Interventional Clinical Studies Ethics Committee (Protocol no: TÜTF-GOKAEK 2013/30, Decision no: 04/07, Date of approval: 02.13.2013). During the study period, the guidelines of the 1975 Helsinki Declaration and national laws were followed. All the patients and healthy subjects gave informed consent.

Study participants and data collection

Patients were included in the study were enrolled from Trakya University School of Medicine, Gastroenterology Department, Inflammatory Bowel Disease Clinic from March 01, 2103 to December 01, 2013. The study included 157 UC patients (63 females, 94 males) and 69 CD patients (33 females, 36 males) above the age of 18 years old who attended regular check-ups at our clinic and who had a diagnosis of IBD according to clinical, endoscopic, radiological, and histopathological criteria. Those with unclassified colitis and those who did not wish to participate were excluded from the study. A control group of 89 healthy volunteers (39 females, 50 males) with no IBD or known chronic inflammatory disease was age and sex-matched to the IBD patient group. The demographic and clinical data of the patients were obtained from the patient records. Phenotyping of patients with UC and CD was completed according to the Montreal classification (22). Information related to the disease phenotypes, medical and surgical requirements related to IBD, appendectomy, hemorrhoidectomy, extraintestinal and intestinal complications, age of diagnosis, family history, and cigarette and alcohol use of the patients was recorded.

Extraction of genomic DNA and genotyping

All the patients and healthy volunteers in the study had 2 mL blood samples taken in K_3EDTA tubes, which was then stored at −80°C. Deoxyribonucleic acid (DNA) extraction from the blood samples was completed using the QIAGEN® QIAamp DNA Mini Kit (cat.no:51304 and 51306, QiagenStraße 1; Hilden, Germany) in accordance with the manufacturer's protocol (23).

For genotyping, the real-time polymerase chain reaction (RT-PCR) method was chosen. The RT-PCR procedure was completed using the PimerDesign®SNPsig Real-Time PCR mutation detection/allelic discrimination Kit (PrimerDesign Ltd.; Southampton, UK) in accordance with the manufacturer's protocol (23). The rs11209026 (G>A, R381Q) of the IL23R gene, rs10758669 (A>C) of the JAK2 gene, and rs3816769 (T>C), rs2293152 (G>C), rs744166 (C>T), rs957970 (C>T), and rs8074524 (C>T) of the STAT3 gene were examined in the obtained genomic DNA (16,17,19-21). The prepared 20 µL PCR solution contained 10 µL PimerDesign®2xPrecision MasterMix, 1 µL Primer/probe mix, 4 µL water not containing ribonuclease and deoxyribonuclease, and 5 µL genomic DNA for each reaction. For each PCR cycle, PCR solutions containing one wild-type and one mutant-type positive control DNA and one negative control with no genomic DNA were prepared to compare with the genomic DNA obtained from the patients. For the prepared solutions to be at optimum levels to distinguish the genotypes, a two-stage cycle, each with denaturation and extension phases of different temperatures and durations, was applied (23). For the passive reference section, the device was

disabled. Thus, fluorogenic data were obtained through channels using *ROX*™ and *VIC*™ stains. Determination of the genotypes was completed using an *ABI StepOnePlus*™ RT-PCR machine. The *ROX*™ channel was coded as a wild-type prop while the *VIC*™ channel was coded as a mutant-type prop. If a signal was obtained from only one channel, it was interpreted as the homozygote genotype of the allele coded by that channel. If signals were obtained from both channels, it was accepted as a heterozygote genotype. The obtained data were separately recorded for each polymorphism.

Statistical consideration

Statistical analysis was carried out using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows software (Version 20.0., IBM Corp.; NY, USA). Analyses of the age and gender distribution of the groups were performed by unpaired Student's t-test, one-way ANOVA, and the Chi-square test, respectively. The Chi-square test was also used to confirm that the frequencies of the allele and genotype in the Hardy-Weinberg equation. The Chi-square test and binary logistic regression were used in the comparison of the frequencies of the alleles and genotypes between the patient and control groups. Fisher's exact test was used under appropriate conditions. For the genotype–phenotype analysis, we used a binary logistic regression test to detect any association between the genotype and different clinical characteristics. Analysis of gene–gene interactions was performed with univariate and multivariate logistic regression tests. All the statistical analyses were evaluated and confirmed by a professional statistician. A p value less than 0.05 was considered to be significant.

RESULTS

A total of 226 IBD patients (157 UC, 69 CD) and 89 healthy volunteers were included in the study. Table 1 summarizes the demographic and clinical characteristics of the patients and healthy volunteers. The allele and genotype frequencies of a total of 7 single nucleotide polymorphisms belonging to three genes were compared between the control and patient groups. In terms of the allele frequencies, there was no significant association found between the UC and control group. The alleles and genotypes that were found to be significantly associated between the patients and controls are shown in Table 2 and Table 3, respectively. In terms of the alleles, there was no significant association with the involvement in the type of UC. The results of the comparison of the allele and genotype frequencies in UC and CD in terms of disease behavior and involvement are shown in Table 4 and Table 5, respectively. It was found that some polymorphisms showed interactions. The results of the gene–gene interactions are given in Table 6. The relationship of the gene polymorphisms with medical treatment and surgery and intestinal and extraintestinal complications is summarized in Table 7.

No associations were established between polymorphisms and other intestinal and extraintestinal complications, such as perforation, fistula, and the involvement of the skin, eye, joint, bile ducts, and kidney. There were also no associations for appendectomy, abdominal operations prior to diagnosis, hemorrhoidectomy, corticosteroid resistance, need for antiTNFa in the first year, alcohol use, and family history.

DISCUSSION

Inflammatory bowel diseases comprise the diseases UC and CD, which present with generally similar gastrointestinal findings. Differences in terms of extraintestinal involvement and the natural progression and treatment response of the disease bring to mind the possibility of effects from the exposure to genetic and environmental factors. Inconsistencies, especially between populations with different ethnic origin, are related mainly to the genetic background. Currently, the primary aims for IBD treatment are to change the natural progression and prevent complications that may develop during the course of the disease. Studies to reveal the genetic factors that play a role in the pathogenesis of IBD may be useful to create targets for the treatment. Recently, there have been important developments made in terms of understanding the pathogenesis of IBD. With the development of genotyping techniques, the results obtained from genome-wide studies have succeeded in defining many susceptibility genes that may affect the pathogenesis of IBD.

In light of recent findings related to the IL23/IL23R pathway playing an important role in the pathogenesis of many chronic inflammatory diseases, the idea that the pathogenesis of UC and CD shares a common mechanism has found support. The IL23/IL23R signal pathway plays a central role at all levels in the innate and adaptive inflammatory response of intestinal mucosa (20). This signal pathway expresses in dendritic cells, macrophages, and T and NK cells intensely. Many important molecules, such as IL23, IL23R, JAK2, Tyk2, and STAT3, found in cell membranes and cytoplasm compose the IL23/IL23R pathway (16,19). The signal pathway activation begins with the binding of IL23 to its own receptor. IL23 is a cytokine with a heterodymeric structure formed of p40 and p19 subunits (24). IL23R is formed from two components: IL-12Rβ1 and IL-23R. The cytoplasmic section of IL-23R binds to JAK2 from the JAK family proteins, while the cytoplasmic section of IL-12Rβ1 binds to Tyk2, again from the JAK family. The STAT protein on this pathway is STAT3 (25,26). Active JAK2 and Tyk2 molecules activate the STAT3 found in cytoplasm by phosphorylation (26). STAT3 transmits the signal from the cytoplasm to the cell nucleus. STAT3 binds to regions related to DNA causing genes to stimulate the synthesis of many proinflammatory cytokines to become active. At the same time, STAT3 directs transcription induction (27). At the end of signal transmission, naive CD4+ T cells transform into Th17 cells, releasing IL17 (28-31). Th17 cells form the front line in the defense system regulating the immune respose through the IL17A, IL17F, and IL22 cytokines they release (31).

Table 1. Demographic and clinical characteristics of all the study participants

Characteristics	UC	CD	Control	p*
Number (n)	157	69	89	-
Age (years) (mean±SD)	44.57±12.9	41.57±13.5	44.79±12.8	0.221
Sex (n) (female/male)	63/94	33/36	39/50	0.308
Age at onset (years) (mean±SD)	37.62±12.23	36.20±13.63		0.440
IBD family history n (%)	32 (20.3)	6 (8.6)		**0.033**
1° relative	20 (12.7)	3 (4.3)		0.059
2° relative	12 (7.6)	3 (4.3)		0.562
Alcohol drinking n (%)	24 (15.3)	18 (26.1)		**0.039**
Smoking n (%)	22 (14.0)	20 (28.9)		**0.009**
pANCA positivity n (%)	58 (56.3)	1 (3.0)		**0.0001**
Extend of UC n (%)				
Proctitis (E1)	20 (12.7)			
Left-sided colitis (E2)	66 (42.0)			
Extensive colitis (E3)	71 (45.2)			
Location of CD n (%)				
Ileal (L1)		19 (27.5)		
Colonic (L2)		7 (10.1)		
Ileocolonic (L3)		43 (62.3)		
Behavior of CD n (%)				
Nonstricturing-nonpenetrating (B1)		39 (56.5)		
Stricturing (B2)		20 (29.0)		
Penetrating (B3)		10 (14.5)		
Perianal involvement (P)		18 (26.1)		
Medications and operations n (%)				
Corticosteroid	72 (45.8)	31 (44.9)		1.000
Azathioprine	17 (10.8)	39 (56.5)		**0.0001**
AntiTNFα	9 (5.7)	16 (23.2)		**0.0003**
Corticosteroid dependence	15 (9.5)	10 (14.5)		0.356
Corticosteroid resistance	13 (8.3)	11 (15.9)		0.102
IBD related surgery	12 (7.6)	29 (42.0)		**0.0001**
Non-IBD abdominal surgery	44 (28.0)	24 (34.8)		0.345
Appendectomy	4 (2.5)	15 (21.7)		**0.0001**
Hemorrhoidectomy	4 (2.5)	9 (13.0)		**0.0036**

IBD: inflammatory bowel disease; antiTNFα: anti tumor necrosis factor alpha; pANCA: perinuclear antineutrophil cytoplasmic antibody; CD: Crohn's disease; UC: ulcerative colitis; SD: standard deviation
*Student's t-test, One-way ANOVA, Chi-squared test and Fisher exact test were used.

Considering the IL23/IL23R pathway intersects with many inflammatory pathways that affect the intestinal immune system, a functional change that can occur in any molecule related to this pathway may increase the risk for the emergence of IBD. However, there are insufficient functional studies in the literature on the components of this pathway, albeit there are many genome-wide and polymorphism studies supporting the association with IBD (19). One of the most important components of the IL23/IL23R pathway, namely IL23R, has been shown to form a predisposition for both UC and CD (6,9,32). In IBD patients, the IL23 serum levels are increased, while in IL23R knockout mice, the IBD symptoms have been observed to regress (24,28). Though

Table 2. Distribution and comparison of the alleles of different SNPs in JAK2, STAT3, and IL23R genes between the patient and control groups

Gene	SNP	Allele	UC n (%)	Control n (%)	p[a]	CD n (%)	Control n (%)	p[a]
IL23R	rs11209026	G	305 (97.1)	172 (96.6)	0.788	138 (100)	172 (96.6)	0.996
		A	9 (2.9)	6 (3.4)		0	6 (3.4)	
JAK2	rs10758669	A	199 (63.4)	115 (64.6)	0.845	74 (53.6)	115 (64.6)	**0.049**[b]
		C	115 (36.6)	63 (35.4)		64 (46.4)	63 (35.4)	
STAT3	rs3816769	T	208 (66.2)	114 (64.0)	0.623	100 (72.5)	114 (64.0)	0.117
		C	106 (33.8)	64 (36.0)		38 (27.5)	64 (36.0)	
	rs2293152	G	152 (48.4)	95 (53.4)	0.303	78 (56.5)	95 (53.4)	0.649
		C	162 (51.6)	83 (46.6)		60 (43.5)	83 (46.6)	
	rs744166	C	111 (35.4)	72 (40.4)	0.286	44 (31.9)	72 (40.4)	0.127
		T	203 (64.6)	106 (59.6)		94 (68.1)	106 (59.6)	
	rs957970	C	101 (32.2)	68 (38.2)	0.199	35 (25.4)	68 (38.2)	**0.016**[c]
		T	213 (67.8)	110 (61.8)		103 (74.6)	110 (61.8)	
	rs8074524	C	245 (78.0)	134 (75.3)	0.505	113 (81.9)	134 (75.3)	0.172[d]
		T	69 (22.0)	44 (24.7)		25 (18.1)	44 (24.7)	
Number of subjects			157 (100)	89 (100)		69 (100)	89 (100)	
Number of alleles			314 (100)	178 (100)		138 (100)	178 (100)	

SNP: single nucleotide polymorphism; CD: Crohn's disease; UC: ulcerative colitis; OR: odd ratio; CI: confidence interval; IL23R: interleukin 23 receptor; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3

[a]Alleles of the patient groups were compared to alleles of the control group using a Chi-square test, Fisher exact test, and logistic regression.

[b]OR: 1.579, 95% CI: 1.002–2.486 (for C allele),

[c]OR: 1.819, 95% CI: 1.116–2.965 (for T allele),

[d]After gender-adjustment, it was found that the rs8074524 (C) allele is associated with CD only in females (p=0.034, OR: 2.49, 95% CI: 1.054–5.872).

studies of UC are limited, there are many polymorphism studies about CD. These have identified that the rs11209026 variant of IL23R is protective against CD (18,32,33). This variant is associated with late onset CD and appears to be protective against CD with ileocolonic involvement (33). A study of a New Zealand population by Ferguson et al. (17) did not show an association with CD. In our study, similar to in the New Zealand population, the IL23R rs11209026 polymorphism alone was not identified to be associated with genotypic and phenotypic presentation or medical and surgical treatment requirements in CD. However, the combination of the IL23R variant with the STAT3 and JAK2 variants increasing the risk of CD was shown to be independently protective against CD. Also, IL23R was shown to increase the protective effect of the STAT3 rs2293152 variant, which is protective against CD. The rs11209026 polymorphism has not been studied much for UC, and furthermore, the results obtained from the studies of different ethnic groups are not compatible with each other. In some populations, it has been identified as a risk factor for UC, while in other popoulations it has been shown to be protective (9). In a German study performed with different variants, a weak association between the rs11209026 variant and UC was reported (34). A study by Duerr et al. (9) found no association in Jewish children, while 7 different variants, including rs11209026, were reported to be associated with UC in non-Jewish UC children. A later broad-series study strongly showed that this variant was protective against CD and increased the risk of UC (12). A study of an Iranian population by Daryani et al. (19) reported that IL23R was not associated with UC. Jürgens et al. (35) investigated the association between IL23R polymorphism and the infliximab response and identified that the response was greater in the risk-forming variant. In our study, similar to studies involving Eastern populations, there was no genotypic or phenotypic association between IL23R polymorphism and UC. However, the combination of the IL23R variant with the STAT3 rs2293152 variant protective against UC independently increased the risk of UC by 7.75-fold. Differently it was shown for the first time that IL23R polymorphism increased the risk of an operation related to IBD in patients with UC. In the Turkish population, though IL23R polymorphism does not affect the etiology alone, the combination with different polymorphisms helps the effect to arise. Gene interactions may reveal possible changes in the functions of synthesized proteins that might occur in IBD. However, the result of gene interactions can only be understood by studies at the molecular level. The reason for the lack of association with IL23R alone may be due to the low number of patients in our study. Studies on larger patient populations may provide more reliable results. Overall, it may be said that, in accordance with the literature, IL23R is a risk factor for UC and is protective against CD in the Turkish population.

JAK2, another important component of the IL23R pathway, is a member of the JAK family and plays a role in some important

Table 3. Distribution and comparison of the genotypes of different SNPs in JAK2, STAT3, and IL23R genes between the patient and control groups

Gene	SNP	Genotype	UC n (%)	Control n (%)	(p)[a]	CD n (%)	Control n (%)	(p)[a]
IL23R	rs11209026	G/G	148 (94.3)	83 (93.3)	0.751	69 (100)	83 (93.3)	0.997
		A/A	0	0	-	0	0	-
		G/A	9 (5.7)	6 (6.7)	0.751	0	6 (6.7)	0.997
JAK2	rs10758669	A/A	67 (42.7)	39 (43.8)	0.894	23 (33.3)	39 (43.8)	0.193
		C/C	25 (15.9)	13 (14.6)	0.856	18 (26.1)	13 (14.6)	0.105
		A/C	65 (41.4)	37 (41.6)	1.000	28 (40.6)	37 (41.6)	1.000
STAT3	rs3816769	T/T	67 (42.7)	36 (40.4)	0.789	38 (55.1)	36 (40.4)	0.078
		C/C	16 (10.2)	11 (12.4)	0.672	7 (10.1)	11 (12.4)	0.802
		T/C	74 (47.1)	42 (47.2)	1.000	24 (34.8)	42 (47.2)	0.144
	rs2293152	G/G	54 (34.4)	25 (28.1)	0.324	29 (42.0)	25 (28.1)	0.090[b]
		C/C	59 (37.6)	19 (21.3)	0.009[c]	20 (29.0)	19 (21.3)	0.352
		G/C	44 (28.0)	45 (50.6)	0.001[d]	20 (29.0)	45 (50.6)	0.007[e]
	rs744166	C/C	18 (11.5)	12 (13.5)	0.687	9 (13.0)	12 (13.5)	1.000
		T/T	64 (40.8)	29 (32.6)	0.220	34 (49.3)	29 (32.6)	0.035[f]
		C/T	75 (47.8)	48 (53.9)	0.426	26 (37.7)	48 (53.9)	0.043[g]
	rs957970	C/C	14 (8.9)	12 (13.5)	0.285	6 (8.7)	12 (13.5)	0.451
		T/T	70 (44.6)	33 (37.1)	0.283	40 (58.0)	33 (37.1)	0.010[h]
		C/T	73 (46.5)	44 (49.4)	0.691	23 (33.3)	44 (49.4)	0.043[i]
	rs8074524	C/C	93 (59.2)	50 (56.2)	0.687	47 (68.1)	50 (56.2)	0.141[j]
		T/T	5 (3.2)	5 (5.6)	0.503	3 (4.3)	5 (5.6)	1.000
		C/T	59 (37.6)	34 (38.2)	1.000	19 (27.5)	34 (38.2)	0.177
Number of subjects			157 (100)	89 (100)		69 (100)	89 (100)	

SNP: single nucleotide polymorphism; CD: Crohn's disease; UC: ulcerative colitis; OR: odd ratio; CI: confidence interval; IL23R: interleukin 23 receptor; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3

[a]Genotypes of the patient groups were compared to genotypes of the control group using a Chi-square test, Fisher exact test, and logistic regression.

[b]After gender-adjustment, it was found that rs2293152 (GG) is associated with CD only in males (p=0.046, OR: 2.53, 95% CI: 1.0058–6.3811).

[c]OR: 2.218, 95% CI: 1.216–4.046. After gender-adjustment, it was found that it is associated with UC only in females (p=0.006, OR: 3.657, 95% CI: 1.405–9.522).

[d]OR: 0.381, 95% CI: 0.221–0.655. After gender-adjustment, it was found that it is associated with UC both in females (p=0.005, OR: 0.301, 95% CI: 0.127–0.714) and in males (p=0.019, OR: 0.433, 95% CI: 0.214–0.875).

[e]OR: 0.399, 95% CI: 0.205–0.776. After gender-adjustment, it was found that it is associated with CD only in females (p=0.033, OR: 0.337, 95% CI: 0.122–0.928).

[f]OR: 2.010, 95% CI: 1.052–3.840,

[g]OR: 0.516, 95% CI: 0.272–0.980,

[h]OR: 2.341, 95% CI: 1.230–4.453,

[i]OR: 0.511, 95% CI: 0.267–0.980,

[j]After gender-adjustment, it was found that rs8074524 (CC) is associated with CD only in females (p=0.033, OR: 2.97, 95% CI: 1.077–8.183).

potential tasks in the pathogenesis of IBD. Together with the different results obtained from studies, the JAK2 rs10758669 variant has been shown to be associated with both UC and CD (6,20). While Ferguson et al. (17) found that JAK2 rs10758669 polymorphism was associated with ileocolonic involvement in CD, they reported that it increased the risk of ileal disease and extraintestinal involvement in stricturing type. Anderson et al. (36) reported that JAK2 was associated with both UC and CD. Prager et al. (37) showed it was only associated with CD. An association with disease phenotype, age at diagnosis, localization, behavior, and medical treatmet was not shown in CD. The most recent meta-analysis reported that, in accordance with previous meta-analyses, the JAK2 rs10758669 variant was associated with both UC and CD (20). However, differences were found between ethnic groups; whereby, while it was associated with both diseases in those of Caucasian descent, it was only associated with UC in those of Asian descent. As only three studies from an Asian population were included in the meta-analysis, there is a need for more studies to confirm the results. The meta-analysis reported that, independent of ethnic groups, it was associated with the age at diagnosis in both pediatric and adult age groups in both diseases (20). In our study, different to the meta-analysis, there was no genotypic or phenotypic association between the JAK2 rs 10758669 variant and UC. Only the (C) allele was identified to increase the risk of a more severe disease progression requiring UC patients to

Table 4. Distrubition and comparison of the allelles in JAK2, STAT3, and IL23R genes between the subphenotypes of Crohn's disease and the ulcerative colitis and control groups

		Control	UC localization n (%)			CD age at diagnosis n (%)			CD localization n (%)			CD behavior n (%)		
	SNP	n (%)	E1	E2	E3	A1	A2	A3	L1	L2	L3	B1	B2	B3
	rs11209026													
IL23R	G	172 (96.6)	39 (97.5)	127 (96.2)	139 (97.9)	0	90 (100)	48 (100)	38 (100)	14 (100)	86 (100)	78 (100)	40 (100)	20 (100)
	A	6 (3.4)	1 (2.5)	5 (3.8)	3 (2.1)	0	0	0	0	0	0	0	0	0
JAK2	A	115 (64.6)	30 (75)	89 (67.4)	80 (56.3)	0	55 (61.1)	19 (39.6)	23 (60.5)	9 (64.3)	42 (48.8)	45 (57.7)	20 (50.0)	9 (45.0)
	C	63 (35.4)	10 (25)	43 (32.6)	62 (43.7)	0	35 (38.9)	29 (60.4)[a]	15 (39.5)	5 (35.7)	44 (51.2)[b]	33 (42.3)	20 (50.0)	11 (55.0)
	rs3816769													
STAT3	T	114 (64.0)	28 (70.0)	85 (64.4)	95 (66.9)	0	60 (66.7)	40 (83.3)[c]	24 (63.2)	11 (78.6)	65 (75.6)	53 (67.9)	33 (82.5)[d]	14 (70.0)
	C	64 (36.0)	12 (30.0)	47 (35.6)	47 (33.1)	0	30 (33.3)	8 (16.7)	14 (36.8)	3 (21.4)	21 (24.4)	25 (32.1)	7 (17.5)	6 (30.0)
	rs2293152													
	G	95 (53.4)	23 (57.5)	66 (50.0)	63 (44.4)	0	52 (57.8)	26 (54.2)	18 (47.4)	8 (57.1)	52 (60.5)	43 (55.1)	20 (50.0)	15 (75.0)
	C	83 (46.6)	17 (42.5)	66 (50.0)	79 (55.6)	0	38 (42.2)	22 (45.8)	20 (52.6)	6 (42.9)	34 (39.5)	35 (44.9)	20 (50.0)	5 (25.0)
	rs744166													
	C	72 (40.4)	11 (27.5)	50 (37.9)	50 (35.2)	0	36 (40.0)	8 (16.7)	12 (31.6)	3 (21.4)	29 (33.7)	26 (33.3)	9 (22.5)	9 (45.0)
	T	106 (59.6)	29 (72.5)	82 (62.1)	92 (64.8)	0	54 (60.0)	40 (83.3)[e]	26 (68.4)	11 (78.6)	57 (66.3)	52 (66.7)	31 (77.5)[f]	11 (55.0)
	rs957970													
	C	68 (38.2)	11 (27.5)	45 (34.1)	45 (31.7)	0	29 (32.2)	6 (12.5)	12 (31.6)	3 (21.4)	20 (23.3)	22 (28.2)	8 (20.0)	5 (25.0)
	T	110 (61.8)	29 (72.5)	87 (65.9)	97 (68.3)	0	61 (67.8)	42 (87.5)[g]	26 (68.4)	11 (78.6)	66 (76.7)[h]	56 (71.8)	32 (80.0)[i]	15 (75.0)
	rs8074524													
	C	134 (75.3)	29 (72.5)	99 (75)	117 (82.4)	0	70 (77.8)	43 (89.6)[j]	32 (84.2)	14 (100)	67 (77.9)	63 (80.8)	34 (85.0)	16 (80.0)
	T	44 (24.7)	11 (27.5)	33 (25)	25 (17.6)	0	20 (22.2)	5 (10.4)	6 (15.8)	0	19 (22.1)	15 (19.2)	6 (15.0)	4 (20.0)

SNP: single nucleotide polymorphism; UC: ulcerative colitis; CD: Crohn's disease; OR: odd ratio; CI: confidence interval; IL23R: interleukin 23 receptor; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3; E1: proctitis; E2: left-sided colitis; E3: extensive colitis; A1: ≤16 years old; A2: 17–40 years old; A3: ≥41 years old; L1: ileal; L2: colonic; L3: ileocolonic; B1: nonstricturing-nonpenetrating; B2: stricturing; B3: penetrating
Chi-squared test, Fisher exact test, and logistic regression were used.
[a]p=0.002, OR: 2.786, 95% CI: 1.447–5.364,
[b]p=0.014, OR: 1.912, 95% CI: 1.134–3.225,
[c]p=0.013, OR: 2.807, 95% CI: 1.238–6.364,
[d]p=0.028, OR: 2.646, 95% CI: 1.107–6.324,
[e]p=0.003, OR: 3.396, 95% CI: 1.502–7.680,
[f]p=0.037, OR: 2.340, 95% CI: 1.051–5.208,
[g]p=0.002, OR: 4.327, 95% CI: 1.747–10.721,
[h]p=0.017, OR: 2.040, 95% CI: 1.137–3.660,
[i]p=0.033, OR: 2.473, 95% CI: 1.076–5.680,
[j]p=0.039, OR: 2.824, 95% CI: 1.053–7.575.

use steroids and azathioprine. For the first time, the association between a JAK2 variant and medical treatment was identified. Generally, our results, while being different to studies in other populations, partially support the results of the study by Prager et al. (37) on a German population. In CD, in accordance with the literature, the JAK2 variant appeared to increase the risk of the disease. In our Turkish population, similar to the New Zealand population, while it increased the risk of ileocolonic involvement, there was no association found with stricturing-ileal and extraintestinal involvement. Compared to the meta-analysis, our results appear to comply mainly with those related to a Caucasian descent. However, while the meta-analysis reported it was associated with both adult and pediatric age groups, in the Turkish population it was found to be associated with only the late onset CD (20). Different results in different populations may be due to differences in the ethnic origin and genetic background. At the same time, differently from the literature, this variant increased steroid and operation requirements in the early period of disease and reduced the anti-TNFa requirements and the risk of perianal involvement in CD. The reduced anti-TNFa requirements and risk of development of perianal involvement in the disease progression may be due to operations undergone in the early period.

The genome-wide studies of another molecule functioning on the IL23R/IL23 pathway, namely STAT3, identified a few gene

Table 5. Distrubition and comparison of the genotypes in JAK2, STAT3, and IL23R genes between the subphenotypes of Crohn's disease and the ulcerative colitis and control groups

	Control	UC localization n (%)			CD age at diagnosis n (%)			CD localization n (%)			CD behavior n (%)		
SNP	**n(%)**	**E1**	**E2**	**E3**	**A1**	**A2**	**A3**	**L1**	**L2**	**L3**	**B1**	**B2**	**B3**
IL23R	rs11209026												
	GG 83 (93.3)	19 (95.0)	61 (92.4)	68 (95.8)	0	45 (100)	24 (100)	19 (100)	7 (100)	43 (100)	39 (100)	20 (100)	10 (100)
	AA 0	0	0	0	0	0	0	0	0	0	0	0	0
	GA 6 (6.7)	1 (5.0)	5 (7.6)	3 (4.2)	0	0	0	0	0	0	0	0	0
JAK2	rs10758669												
	AA 39 (43.8)	11 (55.0)	33 (50.0)	23 (32.4)	0	16 (35.6)	7 (29.2)	8 (42.1)	4 (57.1)	11 (25.6)[a]	16 (41.0)	6 (30.0)	1 (10.0)
	CC 13 (14.6)	1 (5.0)	10 (15.2)	14 (19.7)	0	6 (13.3)	12 (50.0)[b]	4 (21.1)	2 (28.6)	12 (27.9)	10 (25.6)	6 (30.0)	2 (20.0)
	AC 37 (41.6)	8 (40)	23 (34.8)	34 (47.9)	0	23 (51.1)	5 (20.8)	7 (36.8)	1 (14.3)	20 (46.5)	13 (33.3)	8 (40.0)	7 (70.0)
STAT3	rs3816769												
	TT 36 (40.4)	9 (45.0)	28 (42.4)	30 (42.3)	0	20 (44.4)	18 (75.0)[c]	8 (42.1)	5 (71.4)	25 (58.1)	18 (46.2)	15 (75.0)[d]	5 (50.0)
	CC 11 (12.4)	1 (5.0)	9 (13.6)	6 (8.5)	0	5 (11.1)	2 (8.3)	3 (15.8)	1 (14.3)	3 (7.0)	4 (10.3)	2 (10.0)	1 (10.0)
	TC 42 (47.2)	10 (50.0)	29 (43.9)	35 (49.3)	0	20 (44.4)	4 (16.7)[e]	8 (42.1)	1 (14.3)	15 (34.9)	17 (43.6)	3 (15.0)[f]	4 (40.0)
	rs2293152												
	GG 25 (28.1)	8 (40.0)	23 (34.8)	23 (32.4)	0	18 (40.0)	11 (45.8)	6 (31.6)	3 (42.9)	20 (46.5)[g]	16 (41.0)	7 (35.0)	6 (60.0)
	CC 19 (21.3)	5 (25.0)	23 (34.8)	31 (43.7)[h]	0	11 (24.4)	9 (37.5)	7 (36.8)	2 (28.6)	11 (25.6)	12 (30.8)	7 (35.0)	1 (10.0)
	GC 45 (50.6)	7 (35.0)	20 (30.3)[i]	17 (23.9)[j]	0	16 (35.6)	4 (16.7)[k]	6 (31.6)	2 (28.6)	12 (27.9)[l]	11 (28.2)[m]	6 (30.0)	3 (30.0)
	rs744166												
	CC 12 (13.5)	1 (5.0)	9 (13.6)	8 (11.3)	0	7 (15.6)	2 (8.3)	3 (15.8)	1 (14.3)	5 (11.6)	5 (12.8)	2 (10.0)	2 (20.0)
	TT 29 (32.6)	10 (50.0)	25 (37.9)	29 (40.8)	0	16 (35.6)	18 (75.0)[n]	10 (52.6)	5 (71.4)	19 (44.2)	18 (46.2)	13 (65.0)[o]	3 (30.0)
	CT 48 (53.9)	9 (45.0)	32 (48.5)	34 (47.9)	0	22 (48.9)	4 (16.7)[p]	6 (31.6)	1 (14.3)	19 (44.2)	16 (41.0)	5 (25.0)[q]	5 (50.0)
	rs957970												
	CC 12 (13.5)	1 (5.0)	7 (10.6)	6 (8.5)	0	4 (8.9)	2 (8.3)	3 (15.8)	1 (14.3)	2 (4.7)	3 (7.7)	2 (10.0)	1 (10.0)
	TT 33 (37.1)	10 (50.0)	28 (42.4)	32 (45.1)	0	20 (44.4)	20 (83.3)[r]	10 (52.6)	5 (71.4)	25 (58.1)[s]	20 (51.3)	14 (70.0)[t]	6 (60.0)
	CT 44 (49.4)	9 (45.0)	31 (47.0)	33 (46.5)	0	21 (46.7)	2 (8.3)[u]	6 (31.6)	1 (14.3)	16 (37.2)	16 (41.0)	4 (20.0)[w]	3 (30.0)
	rs8074524												
	CC 50 (56.2)	11 (55.0)	36 (54.5)	46 (64.8)	0	28 (62.2)	19 (79.2)[x]	13 (68.4)	7 (100)	27 (62.8)	27 (69.2)	14 (70.0)	6 (60.0)
	TT 5 (5.6)	2 (10.0)	3 (4.5)	0	0	3 (6.7)	0	0	0	3 (7.0)	3 (7.7)	0	0
	CT 34 (38.2)	7 (35.0)	27 (40.9)	25 (35.2)	0	14 (31.1)	5 (20.8)	6 (31.6)	0	13 (30.2)	9 (23.1)	6 (30)	4 (40.0)

SNP: single nucleotide polymorphism; UC: ulcerative colitis; CD: Crohn's disease; OR: odd ratio; CI: confidence interval; IL23R: interleukin 23 receptor; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3; E1: proctitis; E2: left-sided colitis; E3: extensive colitis; A1: ≤16 years old; A2: 17–40 years old; A3: ≥41 years old; L1: ileal; L2: colonic; L3: ileocolonic; B1: nonstricturing-nonpenetrating; B2: stricturing; B3: penetrating
Chi-squared test, Fisher exact test, and logistic regression were used.
[a]p=0.045, OR: 0.441, 95% CI: 0.197–0.984,
[b]p=0.0001, OR: 5.846, 95% CI: 2.166–15.783,
[c]p=0.004, OR: 4.417, 95% CI: 1.599–12.203,
[d]p=0.008, OR: 4.417, 95% CI: 1.474–13.230,
[e]p=0.011, OR: 0.224, 95% CI: 0.071–0.708,
[f]p=0.014, OR: 0.197, 95% CI: 0.054–0.722,
[g]p=0.038, OR: 2.226, 95% CI: 1.044–4.745,
[h]p=0.003, OR: 2.855, 95% CI: 1.431–5–696,
[i]p=0.012, OR: 0.425, 95% CI: 0.218–0.830,
[j]p=0.001, OR: 0.308, 95% CI: 0.155–0.611,
[k]p=0.005, OR: 0.196, 95% CI: 0.062–0.618,
[l]p=0.015, OR: 0.378, 95% CI: 0.173–0.830,
[m]p=0.021, OR: 0.384, 95% CI: 0.171–0.865,
[n]p=0.0005, OR: 6.207, 95% CI: 2.228–17.295,
[o]p=0.010, OR: 3.842, 95% CI: 1.385–10.658,
[p]p=0.003, OR: 0.171, 95% CI: 0.054–0.540,
[q]p=0.024, OR: 0.285, 95% CI: 0.095–0.851,
[r]p=0.0003, OR: 8.485, 95% CI: 2.669–26.971,
[s]p=0.024, OR: 2.357, 95% CI: 1.121–4.955,
[t]p=0.010, OR: 3.960, 95% CI:1.388–11.300,
[u]p=0.002, OR: 0.093, 95% CI:0.021–0.419,
[w]p=0.023, OR: 0.256, 95% CI: 0.079–0.825,
[x]p=0.047, OR: 2.964, 95% CI: 1.016–8.645.

Table 6. The effect of the gene–gene interactions of JAK2, STAT3, and IL23R gene polymorphisms on Crohn's disease and ulcerative colitis

Disease	SNP	p[a]	OR	CI (95%)
UC (genotype)	rs2293152 (GC)/rs11209026 (GA)[b]	0.0001	7.757	2.628–22.896
	rs2293152 (GC)/rs8074524 (TT)[b,c]	0.001	6.269	2.137–18.387
CD (genotype)	rs2293152 (GC)/rs11209026 (GG)[d]	0.003	0.133	0.035–0.504
	rs2293152 (GC)/rs8074524 (TT)[d,e]	0.022	4.578	1.246–16.819
	rs744166 (CT)/rs8074524 (TT)[f,e]	0.004	6.714	1.836–24.546
	rs3816769 (TC)/rs8074524 (TT)[g,e]	0.015	5.009	1.363–18.414
	rs957970 (CT)/rs8074524 (TT)[h,e]	0.001	9.008	2.373–34.195
CD (allele)	rs11209026 (A)/rs10758669 (C)[i]	0.030	0.363	0.146–0.904
	rs11209026 (A)/rs957970 (T)[k,j]	0.005	0.250	0.095–0.662
	rs3816769 (C)/rs957970 (T)[k,j]	0.027	0.359	0.145–0.891

OR: odd ratio; CI: confidence interval; CD: Crohn's disease; UC: ulcerative colitis; SNP: single nucleotide polymophism; IL23R: interleukin 23 receptor; JAK2: janus kinase 2; STAT3: signal transducer and activator of transcription 3

[a]Univariate and multivariate logistic regression were used.

[b]rs2293152 (GC) was associated with UC (p=0.001, OR: 0.381, 95% CI: 0.221-0.655), rs11209026 (GA) was not associated with UC (p=0.751),

[c]rs8074524 (TT) was not associated with UC (p=0.503),

[d]rs2293152 (GC) was associated with CD (p=0.007, OR: 0.399, 95% CI: 0.205-0.776), rs11209026 (GG) was not associated with CD (p=0.997),

[e]rs8074524 (TT) was not associated with CD (p=1.000),

[f]rs744166 (CT) was associated with CD (p=0.043, OR: 0.516, 95% CI: 0.272-0.980),

[g]rs3816769 (TC) was not associated with CD (p=0.144),

[h]rs957970 (CT) was associated with CD (p=0.043, OR: 0.511, 95% CI: 0.267-0.980),

[i]rs11209026 (A) was not associated with CD (p=0.996), rs10758669 (C) was associated with CD (p=0.049, OR:1.579, 95% CI: 1.002-2.486),

[j]rs957970 (T) was associated with CD (p=0.016, OR: 1.819, 95% CI: 1.116-2.965),

[k]rs3816769 (C) was not associated with CD (p=0.117).

locii associated with IBD. In later polymorphism studies, it was shown that some increased the susceptibility for IBD. However, the results of the studies of different populations are insufficient and contradictory (21). For the rs744166 variant of STAT3, Ferguson et al. (17) reported the (G) allele and (GG) genotype were protective against CD. At the same time, it was also identified as protective against colonic and extraintestinal involvement and late onset disease. Studies in a Chinese Han population obtained similar results (38). In contrast, a study of a German population by Franke et al. (13) did not find an association with CD. A meta-analysis evaluating the rs744166 variant of STAT3 reported that the (A) allele was a risk factor for both UC and CD. In the meta-analysis which assessed 7 CD (4244 patients) and 5 UC (10298 patients) studies, it was reported that the (A) allele increased UC and CD susceptibility in those of Caucasian descent more, compared to other ethnic origins (21). In our study, though no genotypic or phenotypic association with UC was identified, the (TT) genotype of the polymorphism appeared to form a risk for CD. At the same time, it was found to form susceptibility for late onset and the stricturing-type disease in CD. The results obtained in our study, though not complying with the literature for UC, showed that rs744166 formed a pre-

Table 7. Association between JAK2, STAT3, and IL23R gene polymorphisms and medical treatment, operations, and intestinal and extraintestinal complications in ulcerative colitis and Crohn's disease

		SNP	p*	OR	CI (95%)
Medical treatment					
UC	Corticosteroid	rs10758669 (C)	0.016	1.765	1.110–2.806
		rs8074524 (T)	0.023	1.870	1.089–3.212
	Corticosteroid in first year	rs3816769 (C)	0.037	1.753	1.035–2.970
		rs3816769 (TC)	0.004	3.533	1.506–8.288
		rs8074524 (T)	0.017	2.018	1.134–3.590
		rs8074524 (CT)	0.011	2.674	1.251–5.712
	Corticosteroid dependence	rs2293152 (C)	0.016	2.829	1.219–6.565
	Azathioprine	rs10758669 (C)	0.016	2.428	1.181–4.990
	Azathioprine	rs8074524 (CC)	0.042	0.108	0.013–0.926
	in first year	rs8074524 (CT)	0.032	10.440	1.222–89.123
CD	Corticosteroid in first year	rs10758669 (AC)	0.041	3.733	1.053–13.242
	Azathioprine	rs2293152 (C)	0.017	0.433	0.217–0.864
		rs2293152 (GG)	0.006	4.257	1.478–12.231
		rs2293152 (GC)	0.021	0.286	0.096–0.852
	AntiTNFα	rs10758669 (C)	0.021	0.363	0.154–0.857
Operation					
UC	IBD related	rs11209026 (A)	0.0001	18.816	4.666–75.873
	operation	rs11209026 (GA)	0.0001	25.179	5.517–114.906
CD	IBD related operation	rs8074524 (CT)	0.028	3.328	1.107–10.003
	Operation in first year	rs10758669 (C)	0.034	2.857	1.081–7.553
Intestinal complications					
CD	Intraabdominal	rs2293152 (C)	0.009	0.134	0.029–0.607
	abscess	rs744166 (T)	0.002	0.182	0.063–0.525
		rs744166 (TT)	0.028	0.102	0.012–0.869
		rs744166 (CC)	0.013	8.800	1.773–43.679
	Obstruction-ileus	rs3816769 (TC)	0.020	0.196	0.050–0.773
	Perianal	rs10758669 (AC)	0.024	0.187	0.043–0.805
Extraintestinal involvement					
UC	Sacroiliitis	rs3816769 (CC)	0.026	4.621	1.199–17.814
	Osteoporosis	rs2293152 (GC)	0.035	0.374	0.150–0.931
CD	Osteoporosis	rs2293152 (GC)	0.010	0.176	0.047–0.662
		rs3816769 (TC)	0.040	3.067	1.053–8.934
Smoking					
UC	Smoking	rs10758669 (C)	0.043	0.462	0.219–0.975
CD	Smoking	rs744166 (T)	0.037	0.441	0.205–0.951
		rs8074524 (CT)	0.039	3.330	1.065–10.409

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; UC: ulcerative colitis; CD: Crohn's disease; AntiTNFα: anti tumor necrosis factor alpha; IBD: inflammatory bowel disease

*Binary logistic regression test was used.

disposition for only CD in our Turkish population. Also, for the first time, the rs744166 polymorphism was revealed to form a risk for stricturing the disease.

Another variant of STAT3 rs2293152 was not found to be associated with UC in a Japanese population, but the (C) allele and (CC) genotype were reported to increase the risk of CD (16). The study of a Chinese Han population found the reverse, with no association identified with CD but an association with UC (38,39). In a Malay population, the (G) allele and (GG) genotype were identified to be protective against CD (40). The studies of rs2293152 in close populations have obtained very different results. In our study, while (CC) formed a risk for UC, (GC) appeared to be protective against UC and CD. Additionally, (CC) formed a risk for extensive involvement in UC and (GG) formed a risk for ileocolonic involvement in CD. This polymorphism appears to be associated with intestinal and extraintestinal complications in both diseases. Furthermore, rs2293152 (GG) forms a risk of a more aggressive disease requiring azathioprine in CD and (C) forms a risk of corticosteroid dependence in UC. Our study obtained different results to other ethnic groups. In our Turkish population, rs2293152 is one of the effective factors in the etiopathogenesis of both UC and CD.

The STAT3 rs3816769 variant was only studied for CD, with the (C) allele and (CC) genotype found to be protective for CD. At the same time, it was reported to be protective against inflammatory-colonic involvement and late-onset disease (17). According to the obtained results, and in accordance with the literature, the rs3816769 (C) allele is protective against CD. Differently, the (T) allele and (TT) genotype increased the risk of late onset and stricturing the disease. The (TC) genotype was protective against obstruction/ileus complications and increased the risk of osteoporosis. In UC, polymorphism carriers had a greater need of corticosteroids in the early period and a sacroiliitis risk. Differences between the studies may be due to differences in genetic background related to ethnic origin and an insufficient number of patients in the study. In our study, the association between rs3816769 in CD and disease complications and treatment requirements was shown for the first time.

Other variants of STAT3, namely rs957970 and rs8074524, were studied in UC and CD in a Japanese population and were not found to be associated with either disease (16). In our Turkish population, rs957970 was found to be associated with only CD. While the (T) allele increased the risk of CD, the (T) allele and (TT) genotype increased the risk of stricturing, ileocolonic involvement, and late onset disease in CD. rs8074524 was generally not associated with IBD, and a direct association with CD was found only in women. Generally, the combination of other variants of STAT3 increased the risk of both CD and UC. It was found that rs8074524 required interaction with other genes to increase penetration. Further it was found that rs8074524 increased the risk of late onset and intestinal resection requirements in CD patients, and the aggressive progression of the disease requiring corticosteroids in the early period and azathioprine requirements in UC. The association with rs957970 and rs8074524 polymorphisms was shown for the first time. However, there may be differences between the genetic risk factors between the genders and these variants appear to affect the clinical progression of the disease and the treatment requirements.

Polymorphism studies generally research the phenotypic association of a single gene. To clearly define the cause–effect relationship of these genetic changes in IBD, there is a need for molecular studies assessing the interactions of different genes with each other, the modifications occurring at the epigenetic level, and protein expression levels and the functional processing of the produced protein. However, studies with different ethnic groups and with larger patient populations may allow more reliable interpretation of the results obtained. IBD is a multifactorial disease with many etiological factors playing a role in its etiopathogenesis. Furthermore, IBD may use different immunogenetic mechanisms in different populations. Currently, when targeted treatment is on the agenda, the success of an administered treatment is directly proportional to revealing the effective mechanisms of that pathogenesis in that population. As a result, the necessity for genetic and molecular studies in different ethnic populations is clear.

In summary, this study showed the association of IL23R, JAK2, and STAT3 gene polymorphsim with UC and CD in a Turkish population for the first time. At the same time, the association of these polymorphisms with subgroups of UC and CD was revealed. The IL23/IL23R signal pathway may be one of the effective factors in the etiology of UC and CD in the population of Trakya. The results obtained for this Turkish population are generally in accordance with the literature, albeit with some differences compared to other populations. The reason for this may be genetic heterogeneity linked to ethnic differences. Studies at the molecular level may reveal the role of these polymorphisms in the pathogenesis of IBD more clearly. Just as showing immunogenetic mechanisms may be helpful in developing treatment modalities for UC and CD, it may be useful as a new DNA-based diagnostic biological marker to determine people at high risk of IBD.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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