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ORIGINAL ARTICLE

IL-23 Receptor Gene RS1004819, RS7517847, RS11209026 Single Nucleotide Polymorphisms in Turkish Patients with Ulcerative Colitis

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Abstract

Introduction: It was aimed to determine whether IL-23R gene rs1004819, rs751784, and rs11209026 single nucleotide polymorphisms (SNPs) cause susceptibility to ulcerative colitis (UC) or not and to evaluate the relationship between these SNPs and the phenotypic subtypes in Turkish population.

Methods: This case-control study included ninety-eight UC patients (85 males and 13 females) and 41 healthy controls (37 males and 4 females). Clinical and endoscopic features were recorded. Genotyping of the SNPs was analyzed by polymerase chain reaction (PCR) based on direct sequencing.

Results: There was no significant difference between patients with UC and healthy controls regarding the analyzed genotype and allele frequencies (p>0.05). The TG genotype of the IL-23R gene rs7517847 SNP was associated with extensive disease (OR: 3.55; 95% CI: 1.01–12.45). The AA genotype of IL23-R-rs1004819 was more prevalent in patients who never smoked (OR: 4.16; 95% CI: 1.12–15.36), and the GA genotype was related to smoking (OR: 4.46; 95% CI: 1.60–12.48) and left-sided colitis (OR: 2.61; 95% CI: 1.18–5.77). The GG genotype of the IL23-R-rs1004819 SNP was more frequent in patients with UC who had higher scores of clinical activities.

Discussion and Conclusion: Although IL-23R gene rs1004819, rs7517847 and rs11209026 SNPs were not associated with the disease susceptibility, significant associations were reported between the clinical features of UC. Further studies are needed to investigate disease susceptibility to UC in different populations.

Keywords: IL-23 receptor gene; Single nucleotide polymorphisms; Turkish patients; Ulcerative colitis.

Inflammatory bowel diseases (IBDs) are polygenic disorders with a relative risk of 8%-15% for disease onset in each sibling[1,2]. The interleukin-23 receptor (IL-23R) gene locates on the first chromosome (1p31) and it is reported to be associated with susceptibility to various autoimmune diseases[3].

Durer's first declaration of the association of the IL23R gene with IBDs was a milestone in understanding the pathogenesis of IBDs[4]. The IL23R is associated with mucosal integrity and leads to the differentiation of the subsets of Th17 cells that secrete proinflammatory cytokines[5,6].

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A genome-wide association study (GWAS) is used in genetic research to identify specific genetic variations associated with particular diseases. Single Nucleotide Polymorphisms (SNPs) are base pair changes in a specific DNA region occurring in at least 1% of the population. SNPs help understand how genes contribute to disease presentation[7].

Due to different populations studied in GWAS for the IL-23R gene, SNPs revealed inconsistent results. In ulcerative colitis (UC), IL-23R rs1004819, rs7517847, and rs11209026 are the most investigated SNPs of the IL-23R gene[8]. Studies from various countries have shown inconsistent results with these SNPs in UC[8-14]. In this study, we aimed to delineate the associations between these SNPs of the IL-23R gene and disease susceptibility, as well as their influence on the clinical picture of UC patients in the Turkish population.

Materials and Methods

Study Population

The study included ninety-eight patients with ulcerative colitis (UC) (85 males and 13 females) and 41 healthy controls without any chronic diseases (37 males and 4 females) admitted to the inpatient and outpatient services of our gastroenterology department between December 2012 and September 2013 (Table 1). The healthy controls

Table 1. Demographic and Clinical Characteristics of the Study Population

Demographic Features	Patients with UC	Controls	OR(95%CI)
Gender of attainers			
Female (n,%)	13 (13.3)	4 (9.8)	0.71(0.22-2.31)
Male (n,%)	85 (86.7)	37 (90.2)	
			p
Age (mean±SD, years)	32.78±14.89	33±11.97	0.87
Age at diagnosis (years), median	27.86	-	-
Disease duration (years), median	4.86	-	-
CRP (mean±SD, mg/L)	9.20±13.87	3.19±2.33	<0.001
Hb (mean±SD, gr/dL)	13.79±1.87	14.6±1.37	<0.009
Smoking habits (n, %)			
Never smoked	62 (63.28)		
Quitted	13 (13.26)		
Smoker	23 (23.46)		
Extend of UC (n, %)			
Remission	9 (9.18)		
Proctitis	34 (34.7)		
Left sided colitis	42 (42.85)		
Extensive colitis	13 (13.27)		
Mayo Endoscopic Activity Score (n, %)			
0 (Inactive disease)	14 (14.29)		
1 (Mild)	39 (39.80)		
2 (Moderate)	35 (35.71)		
3 (Severe)	10 (10.20)		
Treatments of the patients (n, %)			
No treatment	13 (13.27)		
5-ASA	63 (64.29)		
5-ASA±Steroids±Azothioprin±Anti-TNF alpha	22 (22.44)		
Family history of IBD (n, %)	9 (9.18)		
Mayo Clinical Activity Score (median)	4.16		
Remission (score ≤2) (n, %)	35 (35.72)		
Activation (score >2) (n, %)	63 (64.28)		

SD: Standard deviation; CRP: C-reactive protein; UC: Ulcerative Colitis; IBD: inflammatory bowel disease; Anti-TNF-alpha: Anti-tumor necrosis factor-alpha; 5-ASA: 5-amino salicylic acid.

underwent colonoscopy with indications other than IBDs and no pathology was reported. They also had no family history of IBDs. The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), as reflected in a priori approval by the institution's human research committee. The Local Ethics Committee of our institute (2013-70/17) approved the study, and written informed consent was obtained from all participants. Participants with severe organ failure, malignancies, inflammatory and autoimmune diseases, and gut resection were excluded from the study.

In the UC group, clinical features and medications for UC were recorded. The UC Mayo Scoring system was used to assess clinical activity and was quantified between 0-12. In colonoscopy, the Mayo scoring system is used, and the extent of UC is defined in agreement with the Montreal classification (Table 1).

DNA Extraction and Genotyping

Genotyping of the rs11209026, rs7517847, and rs1004819 regions of the IL23R gene was analyzed by PCR-based direct sequencing. Genomic DNA was isolated from 1 mL of EDTA anticoagulated whole blood using the QIAamp DNA Blood Mini Kit (catalog #: 51106) (QIAGEN, Hilden, Germany) following the manufacturer's instructions. DNA concentrations of the samples were assessed spectrophotometrically. PCR amplification of the related regions of the IL23R gene was performed using the HotStarTaq DNA Polymerase kit (catalog #: 203205) (QIAGEN, Hilden, Germany).

After an initial denaturation at 95°C for 15 minutes, 36 cycles were performed, each consisting of 30 seconds of denaturation at 95°C, 30 seconds of annealing at 60°C, and 30 seconds of extension at 72°C, followed by a final extension of 10 minutes at 72°C. The intensity of the PCR products was checked by gel electrophoresis (Fig. 1). Reagent contamination control was conducted by examining the lane for the "No DNA" blank tube. Then, all successful PCR products were purified using the PureLink® PCR Purification Kit (catalog #: K3100-01) (Invitrogen Life Technologies, USA) according to the manufacturer's instructions. The purified amplicons were submitted for direct sequencing in both directions (forward and reverse) using reagents from the BigDye Terminator v3.1 Cycle Sequencing kit (ABI, Applied Biosystems, USA).

After ethanol precipitation, the subsequent products were run on the ABI-3730 (48 capillaries) automatic sequencer (Applied Biosystems, USA). Bidirectional sequence traces were analyzed with SeqScape® Software v3.0 (Applied Biosystems, USA) and manually reviewed (Fig. 2).

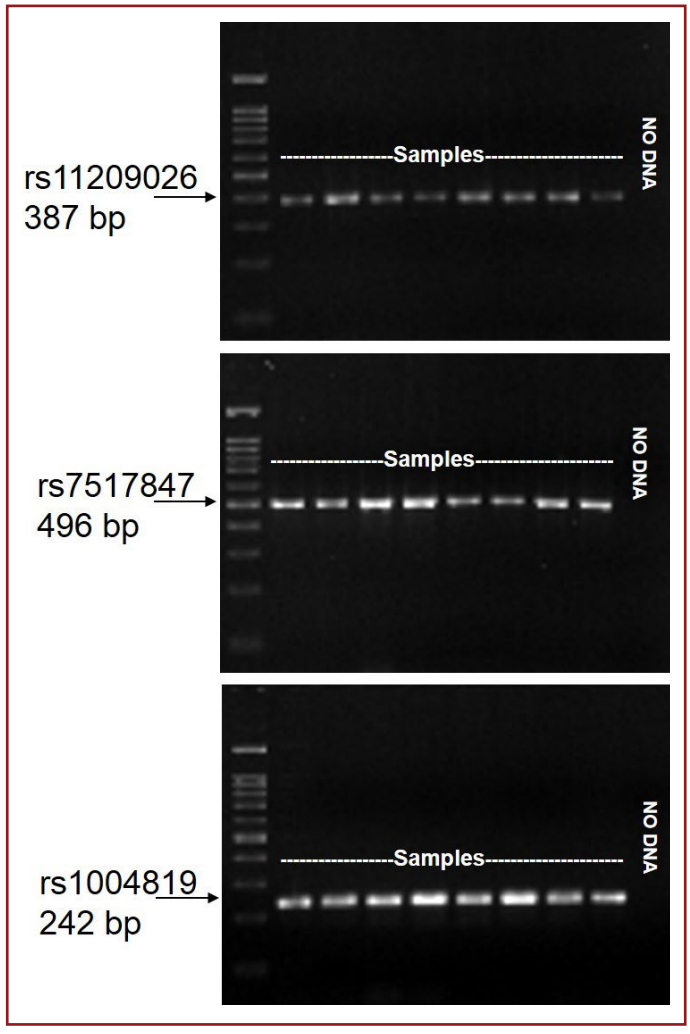

Figure 1. Samples of gel electrophoresis pictures of PCR reactions.

Statistical Analysis

Statistical analysis was conducted using MedicReS E-PICOS AI Smart Biostatistics Software® version 21.3, New York, NY. Data were presented as means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Analyses for differences in demographic and laboratory characteristics were performed using Student's t-test. The odds ratio within its confidence interval was utilized to evaluate the risk of ulcerative colitis and associated clinical features for any genotyping and allele in its observed frequency. The confidence level for statistical significance was set at 95% (α=0.05).

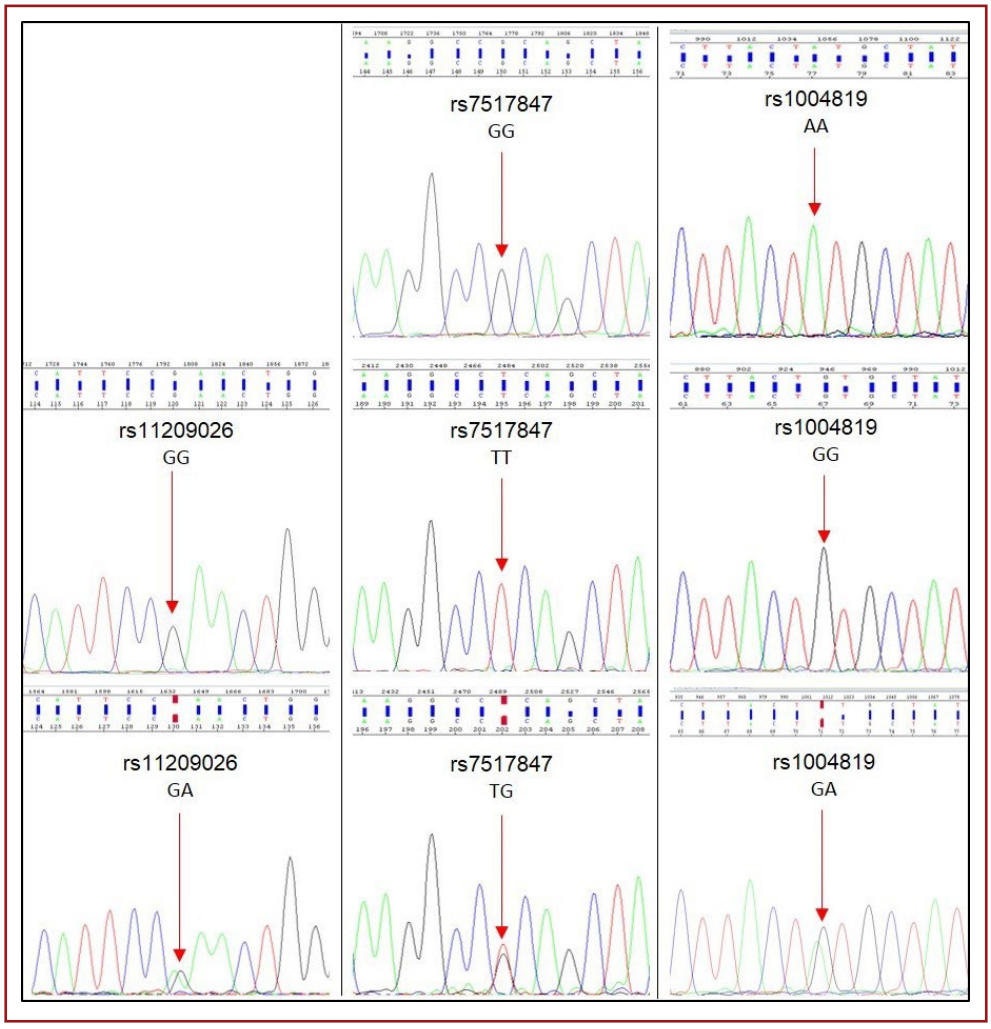

Figure 2. Samples of forward sequencing electropherograms of rs11209026, rs7517847, rs1004819 regions of IL23R gene.

Results

A total of 98 UC patients and 41 healthy controls were included in the study. The mean age and sex distribution in both groups were similar (p=0.87). The demographic and clinical characteristics of the patients and healthy participants are summarized in Table 1. The genotype distribution in UC patients and healthy groups was in Hardy-Weinberg equilibrium. The allele and genotype frequencies of the three SNPs are compared between the groups (Table 2).

In terms of the analyzed allele frequencies and genotypes of the SNPs, no significant association was found between the groups. We also analyzed the influence of IL-23R rs1004819, rs7517847, and rs11209026 SNPs on the clinical picture of UC patients. These three SNPs did not yield any association with the medications for UC. The TG genotype of IL-23R rs7517847 SNP revealed a statistically significant association with a greater extent of UC (OR: 3.55; 95% CI: 1.01-12.45). The AA genotype of IL-23R rs1004819 was more prevalent in patients who never smoked (OR: 4.16; 95% CI: 1.12-15.36), and the GA genotype of this SNP was found in relation to smoking (OR: 4.46; 95% CI: 1.60-12.48) and left-sided colitis (OR: 2.61; 95% CI: 1.18-5.77). The GG genotype of IL-23R rs1004819 SNP was also more frequent in UC patients with higher Mayo clinical activity scores (Table 3).

Discussion

The prevalence of inflammatory bowel diseases (IBDs) is rapidly rising worldwide, and they are responsible for high healthcare costs and social burden. Immunologic, genetic, and environmental factors are not unique for IBDs; presumably, they exert different influences on pathogenesis[1].

Table 2. Genotyping and Allele Frequencies of All Study Population

	Ulcerative Colitis n (%)	Controls n (%)	OR (95%CI)
IL23-R-rs11209026			
Genotypes			
GA	5 (5.1)	2 (4.88)	1.05 (0.20-5.64)
GG	93 (94.9)	39 (95.12)	
Alleles			
G	191 (97.45)	80 (97.56)	0.96 (0.18-5.03)
A	5 (2.55)	2 (2.44)	
IL23-R-rs7517847			
Genotypes			
GG	10 (10.2)	2 (4.88)	2.22 (0.46-10.59)
TG	42 (42.86)	17 (41.46)	1.06 (0.51-2.22)
TT	46 (46.94)	22 (53.66)	0.76 (0.37-1.59)
Alleles			
G	62 (31.63)	21 (25.61)	1.34 (0.75-2.40)
T	134 (68.37)	61 (74.39)	
IL23-R-rs1004819			
Genotypes			
AA	20 (20.41)	8 (19.51)	1.06 (0.42-2.64)
GA	50 (51.02)	21 (51.22)	0.99 (0.48-2.06)
GG	28 (28.57)	12 (29.27)	0.97 (0.43-2.16)
Alleles			
A	90 (45.92)	37 (45.12)	1.03 (0.62-1.73)
G	106 (54.08)	45 (54.88)	

The IL-23R/IL-17 axis is a prominent pathway in the pathogenesis of IBDs, connecting the innate and adaptive immune systems[15,16]. IL-23 plays a key role in the differentiation of T-helper (Th) 17 cells, which secrete proinflammatory cytokines IL-17 and IL-6[1,3].

A genome-wide association study (GWAS) is utilized in genetic research to identify specific genetic variations associated with particular diseases. The method is a case-control study with healthy controls and involves scanning the genomes of many different people to look for genetic markers that can predict the presence of a disease[7].

For UC, GWAS identified more than 20 specific genetic loci[17]. SNPs can be inherited in a Mendelian model and are thought to be associated with the phenotypic specialties of diseases. The human genome likely contains 3-10 million variants of SNPs[18]. Some SNPs are clinically significant variants because they cause changes in protein structures through amino acid alterations[19]. SNPs for specific diseases can exhibit different results depending on the studied ethnicities and countries due to genetic variations.

Table 3. Distribution of IL-23R rs1004819, rs7517847, rs11209026 SNPs Genotype Frequencies According to Clinical Characteristics of UC Patients

Clinical Characteristics	IL23-1-rs11209026		IL23-2-rs7517847			IL23-3-rs1004819		
	GA n (%)	GG n (%)	GG n (%)	TG n (%)	TT n (%)	AA n (%)	GA n (%)	GG n (%)
Disease localization								
Normal	0 (0)	9 (9.68)	2 (20)	3 (7.14)	4 (8.70)	3 (15)	3 (6)	3 (10.71)
Proctitis	4 (80)	29 (31.18)	5 (50)	13 (30.95)	15 (32.61)	8 (40)	13 (26)	12 (42.86)
Left-sided colitis	1 (20)	42 (45.16)	2 (20)	17 (40.48)	24 (52.17)	9 (45)	26 (52)[c]	8 (28.57)
Extensive colitis	0 (0)	13 (13.98)	1 (10)	9 (21.43)[a]	3 (6.52)	0 (0)	8 (16)	5 (17.86)
Mayo Endoscopic Activity Subscore (0-3)								
M.E.A 0	0 (0)	14 (15.05)	2 (20)	6(14.29)	6 (13.04)	4 (20)	5 (10)	5 (17.86)
M.E.A 1	2 (40)	36 (38.71)	5 (50)	17 (40.48)	16 (34.78)	6 (30)	21 (42)	11 (39.29)
M.E.A 2	3 (60)	31 (33.33)	2 (20)	15 (35.71)	17 (36.96)	8 (40)	18 (36)	8 (28.57)
M.E.A 3	0 (0)	12 (12.90)	1 (10)	4 (9.52)	7 (15.22)	2 (10)	6 (12)	4 (14.29)
Mayo Clinical Activity Score (0-12)								
Clinical activation (>2)	1 (20)	34 (36.56)	6 (60)	13 (30.95)	16 (34.78)	7 (35)	14 (28)	14 (50)[e]
Clinical remission (≤ 2)	4 (80)	59 (63.44)	4 (40)	29 (69.05)	30 (65.22)	13 (65)	36 (72)	14 (50)
Smoking Habit								
Never smoked	4 (80)	58 (62.37)	6 (60)	26 (61.90)	30 (65.22)	17 (85)[b]	25 (50)	20 (71.43)
Quitted smoking	1 (20)	12 (12.90)	1 (10)	5 (11.90)	7 (15.22)	3 (15)	8 (16)	2 (7.14)
Smoker	0 (0)	23 (24.73)	3 (30)	11 (26.19)	9 (19.57)	0 (0)	17 (34)[d]	6 (21.43)
Treatment								
No treatment	0 (0)	12 (12.90)	3 (30)	4 (9.52)	5 (10.87)	2 (10)	5 (10)	5 (17.86)
5-ASA	5 (100)	52 (55.91)	6 (60)	23 (54.76)	28 (60.87)	14 (70)	30 (60)	13 (46.43)
5-ASA±Steroids±Azothioprin± Anti-TNF-alpha	0 (0)	29 (31.18)	1 (10)	15 (35.71)	13 (28.26)	4 (20)	15 (30)	10 (35.71)
IBDs in 1st degree relatives	1 (20)	8 (8.6)	0 (0)	3 (7.14)	6 (13.04)	3(15)	4 (8)	2 (7.14)

SNPs: Single nucleotide polymorphisms; UC: Ulcerative colitis; M.E.A: Mayo Endoscopic Activity; 5-ASA: 5-aminosalicylic acid; Anti-TNF-alpha: Anti-tumor necrosis factor-alpha; IBD: Inflammatory bowel disease; [a]: 3.55(1.01-12.45); [b]: 4.16(1.12-15.36); [c]: 2.61(1.18-5.77); [d]: 4.46(1.60-12.48); [e]: 2.81(1.15-6.86).

The IL-23R rs11209026 SNP (p. Arg381Gln) was first identified as a protective polymorphism against Crohn's disease (CD) in a non-Jewish population[4]. Glutamine is essential for intestinal epithelial cells, and its replacement reduces inflammation[4,8]. Studies in some populations confirmed the same result for rs11209026 SNP and CD,[10,20,21] but others did not[12,13,22,23].

For rs11209026, our results are consistent with previous studies[13,14,22]. rs11209026 has been the most investigated SNP in IBDs so far. Systemic meta-analyses about UC and rs11209026A SNP reported the risk in the Caucasian population but not in the Asian population[8,24]. The GA genotype rs11209026 was reported to be protective against IBDs. The allelic frequency of the GA genotype in our study was similar to the Hungarian UC cohort (4.4%)[25].

IL-23R SNP rs11209026 and the polymorphisms of JAK2 and STAT3 genes were studied in Turkish patients with IBDs. The allelic frequency of the adenine base was not statistically different in both groups in our study, as reported in that study[26]. No protective effect of rs11209026 SNP exists against UC in the Turkish population.

We first investigated IL-23R rs7517847 and rs1004819 in the Turkish population. In previous reports, rs7517847 and rs1004819 SNPs were also found in relation to UC susceptibility in Caucasians but not in Asians[8]. Frequencies of alleles and genotypes of rs7517847 and rs1004819 SNPs were not different between the groups in our study, but the TG genotype of rs7517847 displayed a statistically significant association with the greater extent of UC (Table 3).

In the Iranian population, rs7517847 and rs1004819 were studied and no association was found between the patients with UC and the healthy controls. The frequency of the T allele and TG genotype in this study were similar to our results[11]. The presence of blood in the stool and activated bowel movements are two important features of UC[11]. In this study, the homozygous GG genotype of rs7517847 was correlated with the least amount of blood in stool and bowel movements, implying the protective effect of the G allele, but the predisposing effect of the T allele on the presentation of UC.

Our data showed that the TG genotype of rs7517847 correlated with the greater extent of UC, suggesting that extensive localization of UC might increase the possibility of bloody diarrhea. However, the extent of UC does not always reflect severe clinical presentation with bloody diarrhea due to medications. In the Iranian study, endoscopic findings were not reported. Correlating endoscopic localization and presentation with bloody diarrhea, rs7517847 can be proposed as a causative variant of SNP resulting in the acute presentation of UC. Although the study designs were different, protective influences of rs7517847 on UC were identified in Iranian and Hungarian reports[11,25]. Our analyses partly ascertained the relevance because we did not find any relation. Further investigations in different populations should be carried out.

The AA genotype of rs1004819 was in statistically significant association with patients who never smoked, and the GA genotype of this SNP was found in relation to smoking and left-sided colitis. Previous studies did not confirm the IL-23R rs1004819 association with smoking,[10,11] and it may be a unique specialty for Turkish patients with UC. The GG genotype of rs1004819 SNP was also more frequent in UC patients with higher Mayo clinical activity scores. Homozygous expressions of rs1004819 polymorphism in Turkish UC patients may predict UC activation. Nicotine is a protective factor for UC[27]. Both heterozygous expressions of rs1004819 polymorphism and smoking were associated with limited localization. However, it is not clear whether this can be ascribed to the protective influence of nicotine on the mucosa or if heterozygous expression of the polymorphism solely presents with limited localization. The protective influence of nicotine might have been induced by the heterozygous GA genotype of rs1004819 to a wider extent.

Although rs11209026, rs7517847, and rs1004819 SNPs were not susceptible to UC, some genotypes revealed phenotypic associations with UC. The major limitation of this study was the small sample size, especially in the control group. Further studies in larger cohorts are needed in other populations, and our study may be preliminary and a first step in future research.

Main Points

1. IL-23 receptor gene single nucleotide polymorphisms (SNPs) are associated with disease susceptibility in inflammatory bowel diseases (IBDs).
2. Depending on the studied populations and ethnicities, research aiming to develop predictive diagnostic models have resulted in identifying different phenotypic subtypes of the disease associated with these polymorphisms.
3. The most investigated IL-23R gene polymorphisms, rs1004819, rs7517847, and rs11209026, showed no susceptibility to ulcerative colitis in our Turkish population, but rs7517847 was associated with the extent of the disease, and rs1004819 was linked to smoking habits.

4. Further studies in larger sample sized Turkish populations are needed to confirm these results and to explore the relationships between other single nucleotide polymorphisms and inflammatory bowel diseases.

Ethics Committee Approval: The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), as reflected in a priori approval by the institution's human research committee. The Local Ethics Committee of our institute (2013-70/17) approved the study, and written informed consent was obtained from all participants.

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Conflict of Interest: None declared.

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