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ORIGINAL ARTICLE

Association of rs11209032 and rs1004819 Polymorphisms in Interleukin-23 Receptor Gene With Ankylosing Spondylitis

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ABSTRACT

Objectives: This study aims to investigate the distribution of human leukocyte antigen B27 (HLA-B27) alleles (+/-) and interleukin-23 receptor (IL-23R) gene rs11209032 and rs1004819 polymorphisms among ankylosing spondylitis (AS) patients in a Turkish cohort.

Patients and methods: The study sample comprised 106 AS patients (89 males, 18 females; mean age 38.9±10 years; range 19 to 65 years) and 82 healthy controls (70 males, 12 females; mean age 32.15±7.07 years; range 19 to 51 years). Distribution of HLA-B27 alleles (+)/(-) in AS patients were observed by reverse hybridization technique. Genotyping of IL-23R rs11209032 and rs1004819 polymorphisms of AS patients and healthy controls were performed by real time polymerase chain reaction.

Results: Of the AS patients, 69 (65.1%) were HLA-B27 positive. Distribution of rs11209032 genotype frequencies in AS group were 31.1% for GG, 50.9% for GA, and 17.9% for AA; while in control group, it was 34.1% for GG, 53.7% for GA, and 12.2% for AA. Distribution of rs1004819 genotype frequencies in AS group were 30.2% for CC, 52.8% for CT, and 17.0% for TT; while in control group, it was 42.7% for CC, 46.3% for CT, and 11.0% for TT. There was no significant difference between AS patients and controls in terms of genotype frequencies of IL-23R gene rs11209032 and rs1004819 polymorphisms.

Conclusion: No association was found between AS and IL23R rs11209032 and rs1004819 polymorphisms in this Turkish AS cohort.

Keywords: Ankylosing spondylitis; human leukocyte antigen B27; interleukin-23 receptor gene; polymorphism.

Ankylosing spondylitis (AS) is the prototype of a group of inflammatory diseases which share epidemiological, clinical, anatomopathological, radiological, and immunogenetic features.[1] The age- and sex-adjusted prevalence was estimated to be 0.49% for AS[2] in Turkey, and the prevalence of the disease is between 0.1 and 1.4% worldwide.[3] The exact pathogenesis of AS, the common form of spondyloarthritis, remains unknown. Human leucocyte antigen B27 (HLA-B27) has the most important role in etiopathogenesis of AS, and contributes to 20% to 30% of the genetic risk. HLA-B27 is positive in 90% to 95% of Caucasian AS patients.[4,5] AS occurs in up to 75% of monozygotic twins compared to 27% in HLA-B27 positive dizygotic twins, indicating that there is a substantial non-major histocompatibility complex (MHC) genetic component underlying the disease.[4] The interleukin-23 receptor (IL-23R) gene, which is located on chromosome 1p31, is considered to have a role in molecular basis of AS pathogenesis.[6] IL-23 gene, a member of the hematopoietin receptor family, is formed by two cytokine receptor domains and encodes IL-23R.[7] IL-23R and its ligand IL-23 are key components of the immunoregulatory pathway. Recent studies have shown that some single nucleotide polymorphisms (SNPs) of the IL-23R gene are strongly associated with several autoimmune diseases, such as Crohn's disease, AS, and Behçet's

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disease.[8] Because of the similarities between AS and these diseases in clinical and immunological aspects, near-term scientific studies focused on the relationship between gene polymorphisms of IL-23 and AS. Burton et al.[9] genotyped 14,436 SNP in AS patients and reported presence of an association between IL-23R polymorphisms and AS. Among these SNPs, rs11209032 is localized at intergenic region and does not encode an amino acid. Besides, this SNP is thought to be associated with the shearing of messenger ribonucleic acid or have a function in the interaction of IL-23R and its adjacent gene IL-12RB2 by an unknown mechanism.[10] Qian et al.[11] reported that the rs1004819 SNP is localized in intron and may exert its influence by regulating differential splicing of IL-23R messenger ribonucleic acid. Both polymorphisms may affect the splicing process of IL-23R messenger ribonucleic acid which may explain the relationship between these SNPs and AS. To our knowledge, the IL-23R gene polymorphism has not been studied in Turkish AS cohort yet.

In this study, we aimed to investigate the distribution of HLA-B27 alleles (+/-) and IL-23R gene rs11209032 and rs1004819 polymorphisms among AS patients in a Turkish cohort.

PATIENTS AND METHODS

The study was conducted in Afyon Kocatepe University Faculty of Medicine between January 2013 and January 2014. The study sample comprised 106 AS patients (89 males, 18 females; mean age 38.9±10 years; range 19 to 65 years) diagnosed according to 1990 New York criteria and 82 healthy controls (70 males, 12 females; mean age 32.15±7.07 years; range 19 to 51 years). Patients were carefully screened, and those with a history of inflammatory disease other than AS and malignity were excluded. All participants provided written informed consent and the study was performed under a protocol approved by the local Medical Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. About 2 mL aliquots of peripheral blood samples were collected from the participants and stored in ethylenediaminetetraacetic acid-coated vacutainers. Genomic deoxyribonucleic acid (DNA) was extracted from a 200 µL peripheral blood sample by using a High Pure Template Preparation kit (Roche Diagnostics, Mannheim, Germany). Then, DNA amount and DNA purity were quantified for each DNA sample by Nanodrop ND-1000 spectrophotometer V 3.7 (NanoDrop Technologies Inc., Wilmington, DE, USA). DNA samples were stored at -20 °C until they were analyzed. Distribution of HLA-B27 alleles (+/-) in AS patients were performed by reverse hybridization technique using HLA-B27 StripAssay® (ViennaLab Diagnostics GmbH, Vienna, Austria). Genotyping of IL-23R rs11209032 and rs1004819 polymorphisms of AS patients and healthy controls were performed by real time polymerase chain reaction on a LightCycler® 480 real-time polymerase chain reaction system (Roche Diagnostics, Vienna, Austria) using LightCycler® FastStart DNA Master HybProbe (Roche Diagnostics, Mannheim, Germany), LightSNIP IL-23R rs11209032 and IL-23R rs1004819 Reagent Mix (Tib Molbiol, Berlin, Germany).

Statistical analysis

Statistical analysis was performed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) software program. In patients and controls, allele and genotypic frequencies related to IL-23R gene rs11209032 and rs1004819 polymorphisms were compared using Chi-square test. Comparison of HLA-B27 allele (+/-) distribution and rs11209032 and rs1004819 frequencies among AS patients with or without a family history of AS was made using chi-square test.

RESULTS

Sixty-nine AS patients (65.1%) were found positive and 37 (34.9%) were found negative in terms of HLA-B27 alleles. Distribution of rs11209032 genotype frequencies in AS group were 31.1% for GG, 50.9% for GA, and 17.9% for AA; while in control group, it was 34.1% for GG, 53.7% for GA, and 12.2% for AA. Distribution of rs1004819 genotype frequencies in AS group were 30.2% for CC, 52.8% for CT, and 17.0% for TT; while in control group, it was 42.7% for CC, 46.3% for CT, and 11.0% for TT. Of the patients with AS, 31.9% had a family history of AS, while 68.1%

had no family history of AS. In patients with a family history of AS, the HLA-B27 positivity increased to 78.3%; while in AS patients with a negative family history of AS, the frequency of HLA-B27 positivity was 61.2%. However, the difference did not reach a statistically significant value (p>0.05).

Genotype and allele frequencies of AS patient and control groups in terms of IL-23R gene rs11209032 and rs1004819 polymorphisms are shown in Table 1. There was no significant difference in genotype and allele frequencies of both polymorphisms between AS patient and control groups (p>0.05). Genotype distribution of rs11209032 and rs1004819 polymorphisms with regards to the family history of AS are shown in Table 2. The differences between AS patients with or without a family history of AS were not statistically significant (p>0.05). A comparison of the genotype frequencies of rs11209032 and rs1004819 polymorphisms in HLA-B27 positive and negative AS patients revealed no significant difference (p>0.05) (Table 3).

DISCUSSION

The primary goal of the current study was to investigate the association between rs11209032 and rs1004819 polymorphisms in IL-23R gene and AS in Turkish population. Secondly, we assessed HLA-B27 allele frequency in AS patients. The major findings were as follows: *(i)* No significant association was found between these polymorphisms and AS in this patient cohort. *(ii)* HLA-B27 allele frequency was low compared to Caucasians. *(iii)* Distribution of genotype frequencies of rs11209032 and rs1004819 polymorphisms in AS patients were similar between HLA-B27 positive and negative groups. To the best of our knowledge, this study is the first investigating IL-23R gene polymorphisms in Turkish population.

Ankylosing spondylitis, the prototypic sero-negative arthropathy, is known to be highly heritable, with >90% of the risk of developing the disease determined genetically.[12,13] Genetic factors have been strongly implicated in its etiology.[4] Despite the prominence of HLA-B27 in genetic susceptibility of AS, its contribution to overall genetic predisposition is only between 16% to 40%. Furthermore, since the genetic contribution of the entire MHC region in AS is at most 50%, genetic factors residing outside the MHC region account for a substantial portion of the overall genetic effect in AS.[14,15] Timms et al.[16] demonstrated suggestive linkage of AS

Table 1. Genotype and allele frequencies of interleukin-23 receptor rs11209032 and rs1004819 polymorphisms in patients with ankylosing spondylitis and controls

	AS group (n= 106)			Control group (n=82)			
	n	%	*p*	n	%	*p*	*p*
rs11209032							
Genotypes							
GG	33	31.1		28	34.1		0.555
GA	54	50.9		44	53.7		
AA	19	17.9		10	12.2		
GA+AA	73	68.9	0.703	54	65.9	0.248	0.663
Alleles	**212**			**164**			
G	120	56.6		100	60.98		0.393
A	92	43.4		64	39.02		
rs1004819							
Genotypes							
CC	32	30.2		35	42.7		0.167
CT	56	52.8		38	46.3		
TT	18	17.0		9	11.0		
CT+TT	74	69.8	0.437	47	57.3	0.782	0.092
Alleles	**212**			**164**			
C	120	56.6		108	65.9		0.068
T	92	43.4		56	34.1		

AS: Ankylosing spondylitis; Genotypic frequencies of interleukin-23 receptor rs11209032 and rs1004819 polymorphisms between ankylosing spondylitis patients with and without a family history of ankylosing spondylitis.

Table 2. Genotypic frequencies of interleukin-23 receptor rs11209032 and rs1004819 polymorphisms between ankylosing spondylitis patients with and without a family history of ankylosing spondylitis

	Family history (+) (n=40)		Family history (-) (n=66)		
	n	%	n	%	*p*
rs11209032					
Genotypes					
GG	15	37.5	21	31.8	
GA	20	50.0	29	43.9	0.338
AA	5	12.5	16	24.2	
rs1004819					
Genotypes					
CC	14	35.0	22	33.3	
CT	21	52.5	33	50.0	0.845
TT	5	12.5	11	16.7	

Table 3. Distribution of genotype frequencies of interleukin-23 receptor rs11209032 and rs1004819 polymorphisms in ankylosing spondylitis patients according to human leukocyte antigen B27 positivity

	HLA-B27 (+) (n=67)		HLA-B27 (-) (n=35)		
	n	%	n	%	*p*
rs11209032					
Genotypes					
GG	21	31.3	10	28.6	
GA	34	50.7	18	51.4	0.945
AA	12	17.9	7	20.0	
rs1004819					
Genotypes					
CC	22	32.8	10	28.6	
CT	35	52.2	19	54.3	0.894
TT	10	14.9	6	17.1	

HLA-B27: Human leucocyte antigen B27.

to chromosome 2q13, a region containing the IL-1 family gene cluster, and IL-23R gene on chromosome 1q as strong candidates for involvement in the disease.

Human leucocyte antigen-B27 is a MHC class I molecule that is encoded on chromosome 6p.[17] There is a wide range of variation in the frequency of HLA-B27 allele and the distribution of its subtypes across populations which has a significant impact on the prevalence of AS in different racial/ethnic groups.[18] Roberts et al.[19] reported that HLA-B27 allele was positive in 164 (93.2%) of 176 AS patients in a New Zealand population. In two different studies held in Chinese population, Yi et al.[20] reported a percentage of 93.3% of HLA-B27 positivity in 360 AS patients, while Xiong et al.[21] reported a percentage of 90.7% in 350 AS patients. On the other hand, in the study conducted in India with a smaller sample size (n=40), Sharma et al.[22] found a very low frequency of HLA-B27 allele positivity (30%) in AS patients. Similar to our findings, the HLA-B27 allele frequency in AS patients were found as 62.5% in Serbia, 69% in Qatar, and 71.7% in Iran populations.[23-25]

The studies carried out in Turkey shows a HLA-B27 allele positivity ranging from 70% to 74.5%, which is consistent with the findings of the current study.[26-28] Furthermore, we investigated the frequency of HLA-B27 after dividing AS patients according to presence of family history of AS and detected no significant difference among AS patients with or without a family history of AS in terms of HLA-B27 allele distribution.

Interleukin-23 plays a key role in both natural and acquired immune system. IL-23 molecule is secreted in peripheral tissues (such as skin, gastrointestinal tract and lung) from activated dendritic cells and macrophages in response to environmental hazardous signals.[29,30] It is suggested that IL-23 pathway may have important implications in the pathogenesis of chronic inflammatory diseases.[10] The studies concerning IL-23R gene polymorphisms, conducted on different populations, revealed a strong association with inflammatory bowel disease and psoriasis.[31-33] In contrast, no association was found between IL-23R gene polymorphisms with rheumatoid arthritis and systemic lupus erythematosus.[34,35] Because of the similarities between the clinical and immunological aspects of inflammatory bowel disease and AS, scientific studies investigating the impact of genetic factors on AS development focused on the relationship between AS and IL-23R gene polymorphism.[10] Previous studies have conflicting results since there is no consensus whether IL-23R gene polymorphism has a protective effect against or constitutes a risk factor for AS.[9,36-38]

Dong et al.,[39] studied three SNPs (rs7517847, rs11209032, and rs17375018) in 291 AS patients and 312 healthy controls. Consistent with our findings, they reported no significant difference between two groups in terms of

genotype and allele frequencies. However, Wang et al.[10] reported that the differences in the genotypes of rs11209032 and the differences in the genotypes and allele frequencies of rs6677188 between cases and controls were significant. Pimentel-Santos et al.[40] studied eight SNPs including rs11209032, and they reported no significant association between rs11209032 and AS. However, in the meta-analysis conducted by Karaderi et al.[41] including a United Kingdom patient cohort, four of the eight SNPs showed significant associations with AS (rs11209032 had the highest association), when cases with inflammatory bowel disease and/or psoriasis were excluded. However, it was stated that these polymorphisms could contribute to either increased or decreased susceptibility to AS. Likewise, in the meta-analysis by Duan et al.[42] including 11 studies conducted in 13 different populations, it was concluded that the rs11209032 and rs1004819 polymorphisms had associations with increased susceptibility to AS, while rs1343151, rs10489629, and rs11209026 polymorphisms had a protective effect against AS, based on ethnicity.[42] Furthermore, Lee et al.[43] reported that although rs11209032 and rs1004819 polymorphisms have associations with AS in European populations, such associations were not found in Asian populations. Consequently, we were unable to find any association between IL-23R gene rs11209032 and rs1004819 polymorphisms and AS in this study group.

In conclusion, this study revealed no association between rs11209032 and rs1004819 polymorphisms of IL-23R gene and AS in Turkish patients. The previous literature has divergent results in different populations. The reason for the discrepancy may be due to the ethnic differences, regional differences, and limited working group. Beside, AS is a complicated disease and pathogenesis of the disease may vary among patients. However, further studies are necessary to validate or replicate the association between AS and IL-23R polymorphisms in other ethnic population samples.

Declaration of conflicting interests

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