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Original Article

Comparison of IL-23 receptor gene polymorphisms in patients with primary sjögren syndrome, ankylosing spondylitis. and ankylosing spondylitis with sjögren's syndrome

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Abstract: Objectives: The frequency of Interleukin-23 receptor (IL-23R) gene polymorphism was previously studied in Ankylosing spondylitis (AS) and Sjögren syndrome (SS). However, it hasn't been studied in patients AS with SS. Methods: The study included 124 patients with AS, 55 patients with SS and 12 patients with association of AS and SS. Results: It was found that there was an increase in the frequency of rs10889677 gene mutant genotype while a decrease in the frequency of in rs11209032 gene mutant genotype in AS group compared to the healthy controls. In SS group, it was found that there was an increase the frequencies of rs11805303 gene wild genotype and rs2201841 gene wild genotype while a decrease in the frequencies of rs11209032 gene heterozygote genotype and rs10489629 gene mutant genotype when compared to healthy controls. CGCAA haplotype was associated with risk for AS (P=0.0125; RR: 1.32). CGCAG haplotype was associated with protective effect against ankylosing spondylitis (P=0.0042; RR: 0.52). While CTCAA haplotype was found to be protective against SS (P=0.022; RR: 0.46), it was associated with increased risk for association of AS and SS (P=0.0095; RR: 2.79). CTCAG haplotype was associated with protective effect against association of AS and SS (P=0.0151; RR: 0.02). It was observed that TGCGG haplotype increased significantly in SS group compared to the healthy controls and that it was related with increased risk for SS (P=0.032, RR: 2.56). Conclusion: Genotype distribution and genetic diversity vary among ethnic groups. Studies with larger sample size are needed to further clarify this issue.

Keywords: Ankylosing spondylitis, sjögren syndrome, IL-23R gene polymorphism

Introdution

Ankylosing spondylitis (AS) is a chronic, progressive seronegative spondyloarthropathy that primarily involves the axial skeleton and progresses with extra-articular symptoms; in addition, it may also involve peripheral joints [1]. Although etiology hasn't fully understood, genetic and environmental factors play important role in the development of AS. Genetic factors are responsible for 90% of disease susceptibility. HLA-B27 is the best known genetically related factor in AS. However, disease development rate is 5-6% in healthy individuals with HLA-B27 [2]. In genetic studies, contribution of HLA-B27 was estimated to be 30-40% in overall genetic susceptibility to AS. In addition to MHC gene complex, many genetic factors including the interleukin-1 (IL-1) gene complex have been investigated regarding their relationship with AS. The recent studies has focused on the relationship between AS and IL-23R [3]. By previous works, it is possible to identify underlying causes for non-HLA genetic susceptibility in the etiopathogenesis of AS, revealing that ERAP-1, IL-23R, 21q22 and 2p15 gene regions account from disease susceptibility. IL-1 and Th17 regulate cell differentiation and cytokine

release. Both IL-1 and IL-23 gene polymorphisms play role in the AS pathogenesis by contributing to T helper 17 (Th17) cell differentiation [4].

Sjögren syndrome (SS) is a chronic, auto-immune lymphoproliferative disease characterized by mononuclear cell infiltration, which involves exocrine glands, salivary glands and lacrimal glands in particular, and extra glandular involvement could be seen also [5]. There are various studies carried out to clarify the role of genetics in etiopathogenesis, including those focused on interleukin-17 (IL-17) and Th17 cells. In animal studies, it was shown that there was an increase in IL-17 and Th17 cells as well as tissue inflammation and systemic auto-immunity development. These studies showed that systemic autoimmunity developed through IL-23/Th17 in Ro 52 deficiency [6].

The etiopathogenesis of both diseases hasn't been fully elucidated. To explain AS pathogenesis, recent studies have focused on IL-23 and IL-23 receptor gene polymorphism. IL23 is a member of interleukin 12 (IL-12) cytokine family [7]. It plays role on the differentiation of $CD4^+$ T cells to T helper cells producing IL-17 [8]. In various studies, it was shown that IL-23 receptor gene polymorphism is associated with several diseases such as inflammatory bowel disease and psoriasis [9]. In recent years, IL-23 receptor polymorphism has been studied on patients with ankylosing spondylitis and Sjögren syndrome, revealing discrepant results [10]. In the previous studies, it was reported that the association of the diseases with differential immunopathology is increased [11-14]. In our study, we planned to compare IL-23 receptor gene polymorphism among healthy controls and patient groups with ankylosing spondylitis (AS) alone, primary sjögren syndrome (SS) alone, and association of AS and SS, Thus, in both diseases, we aimed to determine whether IL-23R gene polymorphism constitutes genetic susceptibility for development of disease, and to clarify the reasons of increased association of the diseases with different pathogenesis.

Methods

Patients

We reviewed all patients aged ≥18 years who had been followed with the diagnosis of AS and primary SS. In total, 124 patients with AS (65 women, 59 men), 55 patients with primary SS (55 women) and 12 patients with association of AS and SS (5 women, 7 men) who met the inclusion criteria were included to the study. Ninety-six healthy individuals (46 women, 50 men) without known spondyloarthropathy, inflammatory bowel disease or Sjögren syndrome or positive family history were employed as control group. Patients with AS were questioned regarding concurrent Sjögren syndrome. Patients with suspected anamnesis were excluded from the study. Patients with Sjögren syndrome were questioned regarding inflammatory back pain and other characteristics of spondyloarthropathies. Patients with suspected anamnesis were excluded from the study. Patients with the diagnosis of Sjögren syndrome who had family history of spondyloarthropathies were excluded. Demographic and disease-related data of the patients were recorded to a data sheet prepared by the researchers.

The study was approved by Medical Ethics Committee of Pamukkale University, Turkey. All patients and healthy controls were informed about the study, genetic analyses employed and objective of study. All patients and controls gave written informed consent before participation. Venous blood samples were drawn into vacuum tube with 10 cc EDTA. It was stored at -70°C after isolation of DNA which carried out immediately after obtaining blood samples.

Molecular analysis

DNA isolation: 2 ml venous blood was taken into EDTA tubes from the patients and controls. DNA from both groups was isolated by Quick Gene peripheral blood DNA extraction kit (Kurabo, Osaka, JAPAN) and isolation of DNA was performed in Pamukkale University, Medical Genetics Department.

Investigation of polymorphisms associated with IL-23 Gene by restriction fragment length polymorphism (RFLP) method: In this study, we investigated 9 polymorphic regions defined of IL-23R gene (rs11209032, rs10889677, rs11209026, rs2201841, rs11805303, rs7530511, rs10489629, rs7517847 and rs1004819). PCR-RFLP method was used for the determination of the polymorphisms. Forward and reverse primers were designed for all IL-23R polymor-

Table 1. SNP name, forward and reverse primer sequences of each SNPs, restriction enzymes, PCR product size, restricted status of normal genotype of IL-23R polymorphisms

SNPs	Forward Primer	Reverse Primer	Restriction enzyme	PCR Product size (bp)	Restricted status of normal genotype (bp)	Restricted status of heterozygous genotype (bp)	Restricted status of homozygous genotype (bp)
rs11209032	TTGTTACTGGAGTTAAACCTCTTGC	AGGAATAATTGCTGAGATGCAATG	BseMI	265	24+67+174	24+67+174+242	24+242
rs10889677	ATCGTGAATGAGGAGTTGCC	TGTGCCTGTATGTGTGACCA	MnlI	470	61+185+224	61+185+224+285	185+285
rs11209026	AGTCACTCTGTGGCCTAAAGTAAAG	AGATTTTTCTAGTAAACAACTGAAATGA	Hpy188I	350	35+65+250	35+65+250+287	65+287
rs2201841	GGCAAAAGGGAATTGAGAGG	GGCCTATGATTATGCTTTTTCCTG	HpyF3I	420	163+257	25+163+232+257	25+163+232
rs11805303	TCTTCCCAGTCTCCAGTGTG	CCGAACAATTTTTGTTTCCC	MnlI	373	39+136+198	39+136+198+237	136+237
rs7530511	TACCCATCCATTTTAGGTTAAAGAA	GTCTTGAAGTCCTGACCTAAGGTAATC	HphI	614	51+134+429	51+134+185+429	185+429
rs10489629	CCACACCTCGCCAAGACTTT	TATAAGCTTGTTTGATTATGATGTCAGCAA	SspI	348	31+119+198	31+119+150+198	150+198
rs7517847	AAACATTGACATTCCCTTCATAC	GAAATGAGTCACCAATAATCCAC	BseMII	530	29+91+410	29+91+410+501	29+501
rs1004819	GCATTCTAGGACCGTTTTGG	ATCTGGTGGAAATATGTGAAACCTA	TaaI	270	13+71+185	13+71+185+257	13+257

Table 2. Characteristics of the patient and control groups

Parameter	A.S.[1] n=124	A.S+S.S. n=12	S.S.[2] n=55	Control n=96
Age, Years	39.31±10.56	43.75±10.83	49.25±9.7	40.08±10.49
Sex, F/M n (%)	65/59 (52.4/47.6)	5/7 (41.7/58.3)	55 (100)	46/50 (47.9/52.1)
Starting age of the illness, years	33±8.98	34.16±9.11	46.49±9.75	
Duration of the disease	6.24±4.98	9.58±7	2.76±1.72	
BASDAI[3]	4.73±4.83	3.59±0.91		
CRP, mg/dl[4]	0.52±0.64	0.68±0.579		
ESR[5]	17.98±13.68	27.58±18.96		
Uveitis, n (%)	8 (6.5)	1 (8.3)	0 (0)	
Dry eyes, n (%)	34 (27.4)	12 (100)	55 (100)	
Dry mouth, n (%)	10 (8.1)	11 (91.7)	55 (100)	
Schirmer < 5 mm	0 (0)	12 (100)	55 (100)	
Schirmer 5-9 mm	14 (11.3)	0 (0)	0 (0)	

Note: [1]ankylosing spondylitis; [2]sjögren's syndrome; [3]BASDAI: the bath ankylosing spondylitis disease activity index; [4]C-reaktif protein; [5]erytroctes sedimentation rate.

phisms and specific restriction enzymes were used for each polymorphisms. All PCR primers, restriction enzymes for each polymorphic regions, product size and fragments of genotype were listed in **Table 1**. In order to amplify the polymorphic sites of IL-23R, polymerase chain reaction (PCR) method was applied by using each specific primers. Except for rs11209026, the following PCR reaction conditions were performed for other eight polymorphic sites: initial denaturation at 94°C for 2 min followed by 35 cycles of denaturation at 94°C for 20 sec, annealing at 55°C for 10 sec, extension at 72°C for 45 sec and final extension at 72°C for 5 min at PCR machine (Techne, UK). For rs11209026 different from others, 60°C for 10 sec were used at annealing step. Afterwards PCR reaction, 10 µl PCR products were digested with 1 U each specific restriction endonucleases. Allele identification and genotyping were analyzed by using 3% agarose gel electrophoresis (Thermo, USA) stained with ethidium bromide. The statistical analysis was performed by comparing the allele frequencies and the genotypes detected among study and control groups.

Statistical method

In this study, data were analyzed by using Statistical Package for Social Sciences (SPSS) for Windows version 17.0. Descriptive statistics were performed in data analysis. Chi-square test was used to test differences in qualitative variables between the groups. Kruskal-Wallis test was used to compare numerical variables (age, age at disease onset, duration of disease, BASDAİ, sedimentation, CRP) with skewed distribution when comparing 3 or more independent groups. *p* value < 0.05 were considered as statistically significant.

Results

Mean age was 39.31±10.56 years in AS group, 49.25±9.7 years in SS group and 43.75±10.83 years in patients with association of AS and SS, whereas 40.08±10.49 years in the control group. There were no significant differences in the distribution of age and gender among AS group, patients with association of AS and SS and the control group (P>0.05). However, SS group consisted of female patients solely with higher mean age (**Table 2**).

When considering IL-23 receptor gene polymorphism, an increase was observed in the frequency of rs10889677 mutant genotype (AA) while a decrease in the frequency of rs11209032 mutant type (AA) in AS patients compared to the healthy controls (P=0.023 and P < 0.001, respectively; **Table 3**). When allele frequency was evaluated in these genes, it was observed that the frequency of rs10889677 gene minor allele (A allele) was increased in AS group while the frequency of rs11209032 gene minor allele (A allele) was increased in control group (P=0.027 and P < 0.001, respectively; **Table 4**).

When SS group was compared with the healthy controls, an increase was observed in the fre-

Table 3. Distribution of the IL-23R between the groups

IL-23R polymorphism	AS n=124	SS n=55	AS+SS n=12	Control n=96	p1	p2	p3	p4	p5	p6
rs11805303										
CC n (%)	42 (33.9)	44 (80)	5 (41.7)	36 (37.5)	0.323	< 0.001	0.357	< 0.001	0.645	< 0.001
CT n (%)	48 (38.7)	10 (18.2)	3 (25)	42 (43.8)						
TT n (%)	34 (27.4)	1 (1.8)	4 (33.3)	18 (18.8)						
rs10889677										
CC n (%)	43 (34.7)	17 (30.9)	6 (50)	38 (39.6)	0.023	0.353	0.578	0.004	0.557	0.219
CA n (%)	36 (29)	29 (52.7)	3 (25)	39 (40.6)						
AA n (%)	45 (36.3)	9 (16.4)	3 (25)	19 (19.8)						
rs1004819										
GG n (%)	40 (32.3)	16 (29.1)	5 (41.7)	37 (38.5)	0.624	0.503	0.485	0.915	0.395	0.370
GA n (%)	56 (45.2)	26 (47.3)	3 (25)	39 (40.6)						
AA n (%)	28 (22.6)	13 (23.6)	4 (33.3)	20 (20.8)						
rs2201841										
TT n (%)	57 (46)	37 (67.3)	5 (41.7)	40 (41.7)	0.199	0.009	0.934	0.029	0.883	0.251
TC n (%)	33 (26.6)	10 (18.2)	4 (33.3)	36 (37.5)						
CC n (%)	34 (2.4)	8 (14.5)	3 (25)	20 (20.8)						
rs11209032										
GG n (%)	22 (17.7)	1 (1.8)	5 (41.7)	0 (0)	< 0.001	< 0.001	< 0.001	< 0.001	0.049	< 0.001
GA n (%)	74 (59.7)	11 (20)	3 (25)	53 (55.2)						
AA n (%)	28 (22.6)	43 (78.2)	4 (33.3)	43 (44.8)						
rs7530511										
CC n (%)	98 (79)	44 (80)	10 (83.3)	83 (86.5)	0.173	0.516	0.448	0.807	0.080	0.369
CT n (%)	25 (20.2)	10 (18.2)	1 (8.3)	11 (11.5)						
TT n (%)	1 (0.8)	1 (1.8)	1 (8.3)	2 (2.1)						
rs10489629										
AA n (%)	45 (36.3)	18 (32.7)	5 (41.7)	36 (37.5)	0.490	0.003	0.464	0.025	0.207	0.005
AG n (%)	50 (40.3)	32 (58.2)	2 (16.7)	32 (33.3)						
GG n (%)	29 (23.4)	5 (9.1)	5 (41.7)	28 (29.2)						
rs7517847										
TT n (%)	46 (37.1)	25 (45.5)	3 (25)	41 (42.7)	0.068	0.687	0.203	0.192	0.687	0.393
TG n (%)	58 (46.8)	25 (45.5)	7 (58.3)	31 (32.3)						
GG n (%)	20 (16.1)	5 (9.1)	2 (16.7)	24 (25)						
Rs11209026										
GG n (%)	115 (92.8)	48 (87.2)	12 (100)	92 (95.8)	0.335	0.046	0.4712	0.032	0.334	0.462
GA n (%)	9 (7.2)	4 (7.3)	0	4 (4.2)						
AA n (%)	0	3 (5.5)	0	0						

Note: p1 = AS-control; p2 = SS-control; p3 = AS+SS-control; p4 = AS-SS; p5 = AS-AS+SS; p6: SS-AS+SS.

quencies of rs11805303 gene wild genotype, rs1209026 gene heterozygote and mutant genotype and rs2201841 gene wild genotype while a decrease in the frequencies of rs11-209032 gene heterozygote genotype and rs10489629 gene mutant genotype (**Table 3**). Heterozygous rs11209026 genotype was observed in SS group but not in other study groups and controls. When allele frequency was evaluated, a decrease was observed in the frequencies of rs11805303 gene minor allele (T allele) and rs2201841 gene minor allele (C allele) while an increase was observed in the frequencies of rs11209032 gene minor allele (A allele) and rs11209026 gene minor allele (A allele) in patients with SS (**Table 4**).

It was found that rs11209032 gene wild genotype (GG) was increased in patients with association of AS and SS when compared to healthy control group ($P < 0.001$, **Table 2**). When allele frequency was evaluated, it was seen that the

Table 4. Distribution of the IL-23R gene Polymorphism alleles between the groups

IL-23R polymorphism	AS n=124	SS n=55	AS+SS	Control	p1 OR	p2 OR	p3 OR	p4 OR	p5 OR	p6 OR
rs11805303										
C Allele, n (%)	132 (53.2)	98 (89.1)	13 (54.2)	114 (59.4)	0.20	< 0.001	0.66	< 0.001	1	< 0.001
T Allele, n (%)	116 (46.8)	12 (10.9)	11 (45.8)	78 (40.6)	0.77 (0.53-1.14)	5.58 (2.87-10.86)	0.80 (0.34-1.89)	0.13 (0.07-0.26)	0.96 (0.41-2.23)	6.91 (2.53-18.82)
rs10889677										
C allele, n (%)	122 (49.2)	63 (57.3)	15 (62.5)	115 (59.9)	0.027	0.71	1	0.17	0.28	0.82
A allele, n (%)	126 (50.8)	47 (42.7)	9 (37.5)	77 (40.1)	0.64 (0.44-0.94)	0.89 (0.55-1.44)	1.11 (0.46-2.67)	0.72 (0.45-1.13)	0.58 (0.24-1.37)	0.8 (0.32-1.99)
rs1004819										
G allele, n (%)	136 (54.8)	58 (52.7)	13 (54.2)	113 (58.9)	0.438	0.33	0.66	0.73	1	1
A allele, n (%)	112 (45.2)	52 (47.3)	11 (45.8)	79 (41.1)	0.84 (0.58-1.24)	0.78 (0.48-1.25)	0.82 (0.35-1.93)	1.08 (0.69-1.70)	1.02 (0.44-2.38)	0.94 (0.38-2.28)
rs2201841										
T allele, n (%)	147 (59.3)	84 (76.4)	14 (58.3)	116 (60.4)	0.84	0.005	0.82	0.002	1	0.08
C allele, n (%)	101 (40.7)	26 (23.6)	10 (41.7)	76 (39.6)	0.95 (0.64-1.14)	2.11 (1.25-3.58)	0.91 (0.38-2.17)	0.45 (0.27-0.74)	1.04 (0.44-2.43)	2.3 (0.91-5.8)
rs11209032										
G allele, n (%)	118 (47.6)	13 (11.8)	13 (54.2)	53 (27.6)	< 0.001	< 0.001	0.017	< 0.001	0.64	< 0.001
A allele, n (%)	130 (52.4)	97 (88.2)	11 (45.8)	139 (72.4)	2.38 (1.59-3.56)	0.35 (0.18-0.68)	3.09 (1.30-7.34)	6.77 (3.60-12.72)	0.76 (0.33-1.78)	0.11 (0.04-0.3)
rs7530511										
C allele, n (%)	221 (89.1)	98 (89.1)	21 (87.5)	177 (92.2)	0.32	0.40	0.43	1	0.73	0.73
T allele, n (%)	27 (10.9)	12 (10.9)	3 (12.5)	15 (7.8)	2.38 (1.59-3.56)	0.69 (0.31-1.53)	0.59 (0.15-2.22)	1.002 (0.48-2.06)	1.16 (0.32-4.18)	1.16 (0.3-4.5)
rs10489629										
A allele, n (%)	140 (56.5)	68 (61.8)	12 (50)	104 (54.2)	0.69	0.22	0.82	0.35	0.66	0.35
G allele, n (%)	108 (43.5)	42 (38.2)	12 (50)	88 (45.8)	1.09 (0.75-1.60)	1.37 (0.84-2.21)	0.84 (0.36-1.97)	0.80 (0.50-1.26)	1.29 (0.56-2.99)	1.61 (0.66-3.93)
rs7517847										
T allele, n (%)	150 (60.5)	75 (68.2)	13 (54.2)	113 (58.9)	0.76	0.11	0.66	0.19	0.66	0.23
G allele, n (%)	98 (39.5)	35 (31.8)	11 (45.8)	79 (41.1)	1.07 (0.72-1.57)	1.49 (0.91-2.45)	0.82 (0.35-1.93)	0.71 (0.44-1.14)	1.29 (0.55-3.007)	1.81 (0.73-4.44)
rs11209026										
G allele n (%)	239 (94.6)	100 (91)	24 (100)	188 (98.2)	0.342	0.0053	0.475	0.033	0.342	0.053
A allele, n (%)	9 (3.6)	10 (9)	0	4 (1.8)	0.57 (0.17-1.86)	0.21 (0.07-0.70)	1.17 (0.06-22.39)	2.66 (1.05-6.73)	0.51 (0.03-9.11)	4.7 (1.44-15.37)

Note: p1 = AS-control; p2 = SS-control; p3 = AS+SS-control; p4 = AS-SS; p5 = AS-AS+SS; p6 = SS-AS+SS.

Table 5. The IL-23R haplotypes in the study groups

Haplotype	Values	AS	AS+SS	SS
CGCAA	Frequence	0.128 (12.8%)	0.093 (9.3%)	0.056 (5.6%)
	P	0.0125	0.0886	0.1523
	RR	1.32	2.4702	0.407
	95% CI	1.151 to 3.962	0.7438-8.2031	0.1134-1.4610
CGCAG	Frequence	0.063 (6.3%)	0.093 (9.3%)	0.113 (11.3%)
	P	0.0042	0.1047	0.7121
	RR	0.52	0.1790	1.1578
	95% CI	0.1296-0.7082	0.0105-3.0593	0.5515-2.4307
CTCAG	Frequence	0.140 (14%)	0.189 (18.9%)	0.207 (20.7%)
	P	0.071	0.0151	0.825
	RR	0.3223	0.02	1.0492
	95% CI	0.1817-0.5717	0.0105-3.0593	0.5880-1.8721
CTCAA	Frequence	0.155 (15.5%)	0.143 (14.3%)	0.104 (10.4%)
	P	0.0548	0.0095	0.022
	RR	1.7113	2.79	0.46
	95% CI	0.9880-2.9640	1.1882-8.5946	0.1185-0.8600
TGCGG	Frequence	NA	NA	0.012 (1.2%)
	P	NA	NA	0.0302
	RR	NA	NA	2.56
	95% CI	NA	NA	0.6440-246.0047

frequency of minor allele (A allele) was decreased in patients with association of AS and SS ($P < 0.001$, **Table 4**).

When distribution of IL-23R gene polymorphism was evaluated in AS and SS groups, it was found that the frequencies of rs11805303 gene mutant genotype (TT), rs1209026 gene wild genotype (GG) and rs10489629 gene mutant genotype (GG) were increased in AS group while, the frequencies of rs10889677 gene heterozygote genotype (CA) and rs11-209032 gene mutant genotype (AA) were increased in SS group (**Table 3**). When allele frequency was evaluated, it was found that there was no significant difference in the distribution of rs10889677 gene and rs10489629 gene alleles between groups, while the frequency of rs11805303 gene minor allele (T allele) was increased in AS patient group; in addition, the frequencies of rs11209032 gene minor allele (A allele) and rs11209026 gene minor allele (A allele) were increased in SS group (**Table 4**).

When AS group was compared to patients with association of AS and SS regarding distribution of IL-23 gene polymorphism, it was observed that rs11209032 gene wild genotype frequency was increased in patients with association of AS and SS (P=0.049; **Table 3**). When allele frequency was evaluated, distribution of rs11209032 gene minor allele (A allele) was found to be comparable in both groups (**Table 4**).

When SS group and patients with association of AS and SS were compared, the frequencies of rs11805303 gene mutant genotype (TT), rs11209032 gene wilt genotype (GG) and rs10489629 gene mutant genotype (GG) were increased patients with association of AS and SS (**Table 3**). When allele frequency was evaluated, it was observed that the frequency of rs11805303 gene minor allele (T allele) was increased in patients with association of AS and SS while the frequency of rs11209032 gene minor allele (A allele) was increased in SS group (**Table 4**).

Table 5 presents relationships of study groups and IL23R haplotypes. We performed haplotype analysis for alleles (rs1004819, rs7517-847, rs7530511, rs11209026, rs11209032) that could be related to the disease (**Figure 1**). CGCAA haplotype was associated with risk for AS (P=0.0125; RR: 1.32). CGCAG haplotype was associated with protective effect against ankylosing spondylitis (P=0.0042; RR: 0.52). While CTCAA haplotype was found to be protective against SS (P=0,022; RR: 0.46), it was associated with increased risk for association of AS and SS (P=0.0095; RR: 2.79). CTCAG haplotype was associated with protective effect against association of AS and SS (P=0.0151; RR: 0.02). It was observed that TGCGG haplotype increased significantly in SS group compared to the healthy controls and that it was related with increased risk for SS (P=0.032; RR: 2.56).

Discussion

In this study, we evaluated the IL-23R gene polymorphism in two complex autoimmune dis-

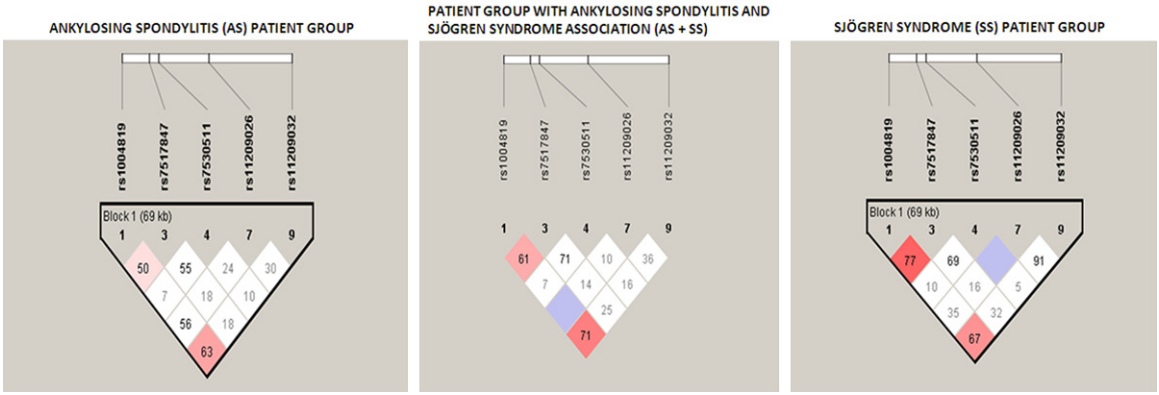

Figure 1. Associated IL-23R haplotypes in study groups.

eases, namely ankylosing spondylitis and Sjögren syndrome, as well as in patients with association of the diseases. The rs11805303, rs10889677, rs1004819, rs2201841, rs11209032, rs7530511, rs10489629, rs7517847 and rs11209026 were evaluated in the present study. In the literature, there are studies on IL23R gene polymorphism in AS patients [15-18]. However, a small number of IL23R gene polymorphisms were evaluated in these studies. There is only one study in which nine IL-23R SNPs were evaluated [19]. Although these studies revealed discrepant results, it was reported that rs10889677, rs1004819, rs2201841 and rs11209032 SNPs are associated with increased risk for AS in general [15-19]. The rs11209026 was considered to be a protective against AS.

In a study, it was reported that there was a relationship between rs1120902, rs10889677 and rs1004819 SNPs and AS [20]. The rs10889677 gene mutant genotype frequency was increased in AS group compared to healthy controls in our study. The biological effect of all these variants on the function and expression of IL-23R is not known yet. However, based on the results of many previous studies, it could be suggested that IL-23R SNPs have an important role in AS development. It is thought that these polymorphisms alter the receptor function. The facts that some SNPs are associated with protection against AS and that some others are associated with increased for AS can be evaluated in the context of alteration in IL-23R function. As similar to these results, increased rs10889677 gene polymorphism was also observed in AS group in our study [20]. This polymorphism may cause T cells to differentiate into Th17 cells by causing receptor overexpression (increasing mRNA stability). Thus, it may increase the release of other cytokines that cause inflammation.

However, in our study, we failed to find an increase in the frequencies of rs1004819 and rs220184 gene polymorphisms which were identified as risk for AS in previous studies. The distribution of rs11209026 gene polymorphism, suggested to be protective against AS, was found to be comparable in AS group and healthy controls (P=0.335). In our study, the frequency of rs11209032 gene polymorphism was decreased in AS group compared to the healthy controls, which is suggested to be associated with increased risk for AS risk.

Ethnic factors have a contribution to the distribution of population. It is known that genetic diversity and genotype distribution vary between different ethnic groups [21]. This may explain discrepancies in our data. However, in previous studies and meta-analyses, it is emphasized that studies should be conducted on sample groups with appropriate size in order to draw accurate conclusions and to assess current status [16, 18, 20, 22]. Nevertheless, it should be kept in mind that different disease mechanisms may appear in different ethnic populations [21]. These data should be interpreted as preliminary data on AS patients in Turkey. Thus, further studies with larger sample size are needed to clarify this issue.

Th17/IL-23 system is important in the development of SS that is an autoimmune disorder characterized by the destruction of acinar tis-

sue in lacrimal and salivary glands [23-25]. However, there is only one study in which IL-23R gene polymorphism was evaluated in SS [19]. In a Hungarian study, no difference was observed in the distribution IL23R gene variant that could suggest a difference in the immunopathology of SS. We observed an increase in the frequencies of rs1180503 gene wild genotype and rs2201841 gene wild genotype while a decrease in the frequencies of rs11209032 gene heterozygote genotype and rs10489629 gene mutant genotype in SS group compared to the healthy controls. These gene polymorphisms could be associated with susceptibility or protection against to SS. However, variations among populations should be taken into consideration. There is a need for studies with larger populations to explain the effect of IL-23R gene polymorphism on SS pathogenesis. Moreover, it is unknown which polymorphism has influence on IL-23R function and how.

Sjögren syndrome may be either primary or secondary. Although the association of SS with autoimmune connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus and scleroderma is well defined, its relationship with spondyloarthropathies is unknown [12, 26, 27]. In the literature, there are studies and case reports on the association of Sjögren syndrome with ankylosing spondylitis and spondyloarthropathies. Gusis et al reported that the rate of association of SS with spondyloarthropathies was 9% while it was reported as 7.6% by Brandit et al [13, 26]. In addition, Kobak et al reported that the rate of association of SS and ankylosing spondylitis as 10% [14]. On the other hand, Difazona et al, reported higher rate of association up to 31.7% [12].

In the literature, there are also studies evaluating sacroiliitis frequency in various rheumatic diseases. However, there is no precise data on frequency of sacroiliitis in SS. In a study from Turkey, the sacroiliitis incidence in SS patients was reported to be as 7%, at a rate similar to general population [28]. These diseases may share a common pathogenesis or may be overlapping syndromes. In addition, molecular similarity theory emerging by infectious agents involved in the pathogenesis of inflammatory joint diseases could also be a factor that may explain the association of these diseases. This issue hasn't been fully understood. It is difficult to suggest whether this association is coincidental, a novel clinical entity or overlapping. Therefore, there is a need for controlled studies with larger populations to clarify the issue.

In this study, we also included the patient group with association of AS and SS to shed light on this issue. We carried out this study by the idea that IL-23 receptor gene polymorphisms may be guiding to explain the association of these diseases. When we assessed IL-23R gene polymorphism in 12 patients with concurrent diagnoses of AS and SS in our clinic, we observed an increase in frequency of rs11209032 gene wild genotype compared to the healthy controls while a decrease in minor allele (allele) frequency. A decrease was observed in the frequency of same gene mutant genotype and minor allele frequency in AS patient group compared to the healthy controls. In SS group, the same gene heterozygote mutant genotype frequency was decreased and minor allele (allele) frequency was increased when compared to healthy controls. When the patients with association of AS and SS were compared with AS patient group, the same gene wild genotype frequency was increased in patients with association of AS and SS while minor allele frequency was increased in AS group. When patients with association of AS and SS were compared with SS patient group, it was seen that the same gene wild genotype frequency was increased in patients with association of AS and SS, while minor allele (A allele) frequency was increased in SS group. These findings arises the idea that IL-23R rs11209032 gene polymorphism plays a role in the pathogenesis of both diseases. However, given the fact that the number of patients with association of AS and SS was smaller and that SS group consisted of female subjects solely, these findings should be interpreted cautiously. Moreover, it is unknown which polymorphism has influence and how. The fact that frequencies of rs11209032 gene mutant, which was evaluated as protective genes for AS and SS, and heterozygote genotype were decreased in patients with association of AS and SS compared to the patients with AS alone, and that the frequency of wild genotype was increased could be interpreted as rs11209032 gene wild genotype is associated with SS development in AS patients. However, further studies are required to clarify this issue.

Also, it should be kept in mind that the genotype distribution and genetic diversity may vary between ethnic groups, and similarly, different disease mechanisms may appear in different ethnic populations.

The data obtained from above-mentioned studies indicate that IL-23/Th17 pathway in ankylosing spondylitis could play a pivotal role in the development of disease as similar to those in inflammatory bowel diseases. As similar to available studies, we also observed that the different SNPs in IL-23R gene either have protective role or increase risk for disease. This can be explained by the fact that the different mutations in the same gene result in different immunological responses accounting from the pathogenesis in IL-23/Th17 pathway. Other causes can be considered as the racial and genetic characteristics.

In haplotype analysis of patient groups in our study, we observed significant findings compared to the healthy control group. We further evaluated these findings in haplotype analysis. CGCAA haplotype was associated with increased risk for AS while CTCAA was associated with increased risk for association of AS and SS. CTCAG haplotype was associated with protective effect against association of AS and SS. CGCAG and CTCAA haplotypes were associated with protective effect against AS and SS, respectively. CTCAG haplotype was associated with protective effect against association of AS and SS. However, TGCGG haplotype was found to be increased in SS group and associated with increased risk for SS.

This is the first study in which IL-23R gene polymorphism was studied in 3 distinct patient groups. The data obtained from this study are important as it indicated that IL-23R gene polymorphisms contributed to pathogenesis in AS, SS and association of AS and SS. As seen in the literature, we observed an increase frequency of in rs10889677 gene mutant genotype while a decrease in frequency of rs11209032 gene mutant genotype in AS group. This could be interpreted as the susceptibility of rs10889677 gene mutant genotype to AS, and as the protective effect of rs11209032 gene mutant genotype against AS. In the literature, there is only one study in which IL-23R gene polymorphism was studied in SS patients, indicating no significant relationship. We observed an increase in frequencies of rs11805303 gene wild genotype and rs2201841 gene wild genotype while a decrease in frequencies of rs11209032 gene heterozygote genotype and rs10489629 gene mutant genotype in SS group when compared to healthy controls. Based on our results, rs11805303 and rs2201841 gene wild genotype was associated to susceptibility to SS while rs11209032 gene heterozygote and rs10489629 gene mutant genotypes were protective gene against SS. It was observed that frequencies of rs11209032 gene mutant and heterozygote genotype frequency, which was evaluated as protective gene for AS and SS, were decreased while wild genotype frequency was increased in patients with association of AS and SS when compared those with AS alone. This result could be interpreted as rs11209032 gene wild genotype is associated with SS development in AS patients. There is a need for controlled studies with larger populations to clarify the issue. Also, the studies in which IL-23R gene polymorphism and IL-23R expression are evaluated together will provide information for predicting the function of the existing gene polymorphism.

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Disclosure of conflict of interest

None.

Authors' contribution

ST: Study planning, organization, data collection, evaluation of results and article writing. AB: Study planning, organization, data collection, evaluation of results, article writing and approval. LE: Molecular analysis of patient and control groups. ET: Molecular analysis of patient and control groups. VC (senior author): Article writing and approval. All authors read and approved the final manuscript.

Abbreviations

AS, ankylosing spondylitis; SS, sjögren syndrome; SNP, single nucleotide polymorphism; IL-23R, Interleukin 23 receptor; IL-1, interleukin 1; IL-17, interleukin 17; Th17, T helper 17; IL-12, interleukin 12; RFLP, restriction fragment le-

ngth polymorphism; PCR, polymerase chain reaction; SPSS, statistical package for social sciences.

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