Associations between polymorphisms of IL-17F and IL-17A genes with disease activity and clinical outcome of Ankylosing Spondylitis

Erkol İnal E[1], Görükmez O[2], Eroğlu S[3], Özemri Sağ[4], Solak Ö[3], Görükmez Ö[4], Yakut T[4]

ACTA REUMATOL PORT. 2016;41:232-239

ABSTRACT

Aims: In this study, we aimed to investigate the associations between the 7383A/G and 7488A/G polymorphisms of the interleukin (IL)-17F gene and the G197A polymorphism of the IL-17A gene with disease activity and clinical outcomes in Turkish patients with ankylosing spondylitis (AS).

Methods: The study included 101 AS patients and 106 healthy controls. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, in addition to scores of the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index and Bath Ankylosing Spondylitis Functional Index (BASFI) of the patients, were recorded. The frequencies of genotypes 7383A/G and 7488A/G of the IL-17F and G197A of IL-17A genes and alleles were compared between the patients and healthy controls.

Results: There were significant differences in the allele frequencies and genotype distribution of IL-17F 7488A/G. There were also significant differences in the CRP levels and BASFI scores of patients due to the genotype distribution of the IL-17F 7488A/G polymorphism (p= 0.029, 0.045, respectively).

Conclusions: This study suggests that the IL-17F 7488A/G polymorphism may be associated with susceptibility to AS, disease activity and functional status in Turkish patients. Further studies with larger numbers of AS patients, with a long-term follow-up, are needed to elucidate the observed relations.

Keywords: Ankylosing spondylitis; 7383 A/G; 7488 A/G; G197A; IL-17 gene

1. Department of Physical Medicine and Rehabilitation/Süleyman Demirel University, Faculty of Medicine
2. Department of Medical Genetics/Bursa ğevket Yılmaz Education and Research Hospital
3. Department of Physical Medicine and Rehabilitation/Afyon Kocatepe University, Faculty of Medicine
4. Department of Medical Genetics/Uludağ University, Faculty of Medicine

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the axial skeleton[1,2]. The precise aetiology is unknown, but several studies have pointed to a genetic link with the presence of human leucocyte antigen (HLA)-B27[3], endoplasmic reticulum amino peptidase 1[4], interleukin (IL)-10[5], IL-12B[6], the IL-1 receptor antagonist[7,8], IL-23 receptor genes[9-13], HLA-B60 and HLA-DR[14]. Genome-wide linkage screens have suggested various additional genetic markers located on different chromosomes[15-17].

Studies have confirmed the roles of interleukins, such as IL-6, 8, 17 and 23, in the pathogenesis of AS[3,14,18]. A study of serum IL-17 levels in Chinese AS patients reported higher levels of IL-17 in patients compared to healthy controls[18]. IL-17A, which was the first discovered member of the IL-17 family in 1993, has been targeted in the treatment of AS[19,20]. Five other cytokines of this family (IL-17B–IL-17F), which are responsible for the pathogenic activity of T Helper (TH) 17 cells, have been discovered[21]. *IL-17A* and *IL-17F* genes encode IL-17A and IL-17F, respectively. These genes were reported to be involved in the expression of various cytokines, chemokines and adhesion molecules, which have roles in several chronic inflammatory diseases[22]. The highest overall amino acid sequence identity (approximately 50%) was found between *IL-17A* and *IL-17F* genes among the IL-17 family. Both genes

are located on chromosome 6p12[23].

Polymorphisms of *IL-17A G197A* and *IL-17F 7488A/G* have been reported to be associated with the susceptibility to ulcerative colitis[23], and the *IL-17F* gene was reported to be associated with chronic inflammatory diseases, including rheumatoid arthritis[24], Behcet's disease[25], asthma[22,26] and inflammatory bowel diseases[23,27]. However the impact of *IL-17* gene polymorphisms (*7383A/G* and *7488A/G* linked to *IL-17F* and *G197A* linked to *IL-17A*) on the course of AS and the role of these polymorphisms in the susceptibility to the disease have not been studied. Therefore, we aimed to investigate the associations between the *7383A/G* and *7488A/G* polymorphisms of the *IL-17F* gene and the *G197A* polymorphism of the *IL-17A* gene with disease activity and clinical outcomes in Turkish patients with AS.

PATIENTS AND METHODS

STUDY POPULATION

One hundred and one AS patients and one hundred and six healthy controls from the Departments of Physical Medicine and Rehabilitation of Süleyman Demirel University and Kocatepe University Education and Research Hospitals were included in this study. Informed consent was obtained from all the participants. The study was approved by the ethics committee of Süleyman Demirel University Medical School. All patients were diagnosed with AS according to The Modified New York criteria. This criterion consists of two parts as clinical and radiological. Clinical criteria include 3 items as 1- Low back pain ≥ 3 months, improved by exercise and not relieved by rest, 2-Limitation of lumbar spine in sagittal and frontal planes, and 3- Limitation of chest expansion (relative to normal values corrected for age and sex). Radiological criteria consist of two items as bilateral grade 2-4 sacroiliitis or unilateral 3-4 sacroiliitis. A patient must have bilateral grade 2-4 or unilateral grade 3-4 sacroiliitis and any of the clinical criteria to be diagnosed as AS[28]. Patients who had rheumatoid arthritis or other inflammatory or genetic diseases were excluded from the study.

The age and gender of all of the participants, disease and medication duration, articular involvement type (only axial or both axial and peripheral articular), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were recorded. The ESR was measured by a spectrophotometric assay (Alifax Test - 1 THL, 950 nm, Italy). CRP was determined with the turbidimetric method (TOSHIBA ACCUTE/TBA--40FR, Tokyo, Japan). ESR ranges normally 2–8 mm/h for men and 2–20 mm/h for women and CRP ranges between 0 and 3 mg/dl.

Disease activity was assessed with The Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[29], and functional status was measured with the Turkish version Bath Ankylosing Spondylitis Functional Index (BASFI)[30]. The BASDAI and BASFI are self-administered questionnaires and higher scores indicate higher activity and more severe impairment of the disease[29,30].

The clinical status was evaluated with the Bath Ankylosing Spondylitis Metrology Index (BASMI). Higher scores indicate greater disease involvement[2]. The pain severity was measured on a 0–10 cm Visual Analog Scale.

The distribution of the genotypes and the allele frequencies of the *7383A/G* and *7488A/G* polymorphisms of the *IL-17F* gene and *G197A* polymorphism of the *IL-17A* gene were compared between the patients and healthy controls. The patients were divided into three groups according to the genotypes of *7383A/G* and *7488A/G* of *IL-17F* gene and *G197A* of *IL-17A* gene as having AA, AG or GG genotype.

DNA COLLECTION AND GENOTYPING

Blood samples of the patients and healthy controls were collected in ethylenediaminetetraacetate tubes. DNA isolation was performed according to the procedures of the DNA isolation kit used (Gentra Puregene Blood Kit, Qiagen), and the samples were stored at -20° C until polymerase chain reaction (PCR).

The *IL-17F* gene polymorphisms *7383A/G* and *7488A/G* and *IL-17A* gene polymorphism *G197A* were determined using the PCR-restriction fragment length polymorphism method. For the *IL-17F* gene polymorphisms *7383A/G* and *7488A/G*, forward 5' GTGTAGGAACTTGGGCTGCATCAAT 3' and reverse 5' AGCTGGGAATGCAAACAAAC 3' primers were used[23]. For the *IL-17A* gene polymorphism *G197A*, forward 5' AACAAGTAAGAATGAAAAGAGGACATGGT 3' and reverse 5' CCCCCAATGAGGTCATAGAAGAATC 3' primers were used[31].

The PCR was performed as follows: After the first denaturation for 5 min at 94° C, denaturation continued for 1 min at 94° C, which was continued with 35 cycles of annealing for 1 min at 58° C, followed by extension for 1 min at 72° C and a final extension for 10

min at 72° C. Four hundred and seventy base pairs (bps) amplification products were digested with AvaII (New England Biolabs, USA) for the *IL-17F* gene *7383A/G* polymorphism and with NlaIII (New England Biolabs, USA) for the *IL-17F* gene *7488A/G* polymorphism at 37° C, and they were separated by size on agarose gel. AvaII digestion of the PCR product yielded 470 bps for allele A and 75 and 395 bps for allele G. NlaII digestion of the PCR product yielded 52, 130 and 288 bps for allele A and 418 bps for allele G 52[10]. One hundred and two bps amplification products were digested with EcoNI (New England Biolabs, USA) for the *IL-17A G197A* polymorphism at 37° C, and they were separated by size on agarose gel. EcoNI digestion of the PCR product yielded 102 bps for allele A and 68 and 34 bps for allele G[23].

STATISTICAL ANALYSES

Data were analysed using the Statistical Package for Social Sciences (SPSS) software, version 15.0 for Windows (SPSS Inc., Chicago, IL). For the presentation of continuous quantitative variables, mean and standard deviation were used. Frequencies and percentages were used for categorical data. To determine whether the allele frequencies were stable within patients and controls, X^2 analysis of the Hardy–Weinberg equilibrium for the genotypes was conducted. For parametric variables, a one-way ANOVA test was used. For non-parametric variables, the Kruskal–Wallis test was used for comparisons between the groups (AA, GG and AG). Bonferroni correction was used for multiple correction analysis on the data that were statistically significant. A value of $p<0.033$ was accepted as significant in the post hoc analyses. For evaluation of categorical variables, a chi-square (X^2) test was performed and Fisher's exact test, if required. Between-group comparisons of the genotype distribution and allele frequency were performed on the X^2 test. Multivariate linear regression analysis was performed to predict the effect of the *IL-17F* gene *7488A/G* polymorphism on the BASFI scores and CRP. A logistic regression analysis was conducted to detect the relationships between the susceptibility to AS and non-AA genotypes of the *IL-17F 7488A/G* polymorphism. PASS software was used for the power

TABLE I. GENOTYPE DISTRIBUTIONS AND ALLELE FREQUENCIES OF IL-17F AND IL-17A POLYMORPHISMS BETWEEN IN PATIENTS WITH ANKYLOSING SPONDYLITIS AND HEALTHY CONTROLS

		Patients (n=101)	Controls (n=106)	p
IL-17F 7383A/G		Genotypes (%)		
	AA	88 (87.1%)	84 (79.2%)	0.130
	AG	10 (9.9%)	20 (18.9%)	0.067
	GG	3 (3.0%)	2 (1.9%)	0.612
		Alleles (%)		
	A	186 (92.1%)	188 (88.7%)	0.158
	G	16 (7.9%)	24 (11.3%)	
IL-17F 7488A/G		Genotypes (%)		
	AA	77 (76.2%)	94 (88.7%)	0.018
	AG	20 (19.8%)	10 (9.4%)	0.034
	GG	4 (4%)	2 (1.9%)	0.374
		Alleles (%)		
	A	174 (86.1%)	198 (98.0%)	0.011
	G	28 (13.9%)	14 (2.0%)	
IL-17A G197A		Genotypes		
	AA	11 (10.9%)	10 (9.4%)	0.729
	AG	51 (50.5%)	46 (43.4%)	0.306
	GG	39 (39.8%)	50 (47.2%)	0.214
		Alleles (%)		
	A	73 (36.1%)	66 (31.1%)	0.140
	G	129 (63.9%)	146 (68.9%)	

Abbreviation; IL: Interleukin

TABLE IIA. DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN RELATION TO IL-17F 7383A/G GENOTYPES

	AA (n=88)	AG (n=10)	GG (n=3)	p
Age (years)	41.9±12.0	41.6±9.9	40.3±5.1	0.971
ESR (mm/h)	22.0±17.5	35.1±10.4	19.3±7.2	0.124
CRP (mg/dl)	9.5±14.9	31.3±50.3	1.4±1.6	0.163
Duration of disease (months)	86.1±84.4	63.7±78.4	61.7±57.5	0.568
Duration of medication (months)	74.5±70.1	62.1±79.1	61.0±58.5	0.754
BASFI	2.4±2.1	1.3±1.3	3.9±3.0	0.125
BASMI	2.3±2.4	2.0±2.1	2.0±1.0	0.918
BASDAI	2.6±1.8	3.2±1.6	3.7±0.8	0.355
Pain (VAS)	3.7±2.5	3.8±1.8	5.7±2.5	0.347

Abbreviations; IL: Interleukin, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: Visual Analog Scale

TABLE IIB. DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN RELATION TO IL-17F 7488A/G GENOTYPES

	AA (n=77)	AG (n=20)	GG (n=4)	p
Age (years)	42.7±11.7	38.6±10.8	42.0±12.8	0.366
ESR (mm/h)	22.3±20.2	28.9±17.5	13.0±5.7	0.228
CRP (mg/dl)	10.7±23.0	15.6±17.1	3.5±5.9	0.029
Duration of disease (months)	86.3±89.2	79.4±60.9	42.3±44.0	0.500
Duration of medication (months)	74.4±73.7	73.2±62.5	42.3±44.1	0.632
BASFI	2.3±2.1	1.9±1.6	4.8±2.7	0.045
BASMI	2.2±2.3	2.4±2.4	3.5±1.9	0.307
BASDAI	2.7±1.9	2.9±1.5	2.2±1.3	0.726
Pain (VAS)	3.6±2.5	4.4±2.2	3.8±2.8	0.333

Abbreviations; IL: Interleukin, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: Visual Analog Scale

TABLE IIC. DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN RELATION TO IL-17A G197A

	AA (n=11)	AG (n=51)	GG (n=39)	p
Age (years)	47.5±10.4	41.6±13.2	40.6±9.2	0.223
ESR (mm/h)	28.8±21.4	25.9±21.7	18.2±14.6	0.108
CRP (mg/dl)	18.7±40.5	12.7±21.6	7.6±12.2	0.669
Duration of disease (months)	46.0±39.7	95.6±99.7	77.4±63.0	0.305
Duration of medication (months)	44.7±40.5	77.5±79.4	74.7±63.9	0.382
BASFI	1.8±1.7	2.5±2.1	2.3±2.3	0.554
BASMI	1.6±1.4	2.5±2.4	2.1±2.4	0.512
BASDAI	2.4±1.7	2.8±2.0	2.7±1.6	0.785
Pain (VAS)	3.0±1.9	4.0±2.7	3.5±2.1	0.488

Abbreviations; IL: Interleukin, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: Visual Analog Scale

analysis. A value of $p<0.05$ was accepted as significant in all the statistical analyses.

RESULTS

One hundred and one consecutive patients who were admitted to outpatient clinics of the Physical Medicine and Rehabilitation Department of Süleyman Demirel University and Afyon Kocatepe University hospitals and one hundred and six sex, age and ethnicity matched healthy controls participated in this study. The mean age of the patients was 41.9±11.6 years and the mean age of the healthy controls was 41.4±11.6 years (p=0.794). Thirty-two (31.7%) of the patients and 47 (44.3%) of the healthy controls were female (p=0.061). Forty-eight (47.5%) of the patients had only axial involvement, and 53 (52.5%) patients had both axial and peripheral involvement.

The allele frequencies in the AS patients and controls did not confirm to Hardy–Weinberg equilibrium for the three polymorphisms ($p>0.05$). There were no significant differences in the genotype distribution and allele frequencies of *IL-17F 7383 A/G* and *IL-17A G197A* between the patients and healthy controls ($p>0.05$). However, there was a significant difference in the allele frequencies and genotype distribution of the *IL-17F 7488 A/G* polymorphism in the patients compared to those of the healthy controls (Table I).

With regard to the clinical and laboratory findings, there was no significant difference between the patients and the healthy controls due to the genotype distribution of the *IL-17F 7383A/G* and *IL-17A G197A* polymorphisms. We found a significant difference in the CRP levels and BASFI scores due to the genotype distribution of the *IL-17F 7488A/G* polymorphism (p=0.029, 0.045, respectively) (Tables IIA, IIB and IIC). The AS patients with the AG genotype of *IL-17F 7488A/G* polymorphism had significantly higher levels of CRP compared to those of the patients with the GG genotype (p=0.021). The AS patients with the GG genotype had significantly higher BASFI scores than those of patients with the AG genotype of *IL-17F 7488A/G* polymorphism (p=0.033). The power of the study for the statistically significant data was found to be 0.99 and 0.99, respectively.

Multivariate linear regression analysis was performed to predict the effect of the genotypes with the *IL-17F 7488A/G* polymorphism on the BASFI scores and CRP. When age, gender and the *IL-17F 7488A/G* polymorphism were taken as independent variables, genotypes with the IL-17F 7488A/G polymorphism showed no significant relationship with BASFI scores and CRP (p=0.843, =-0.021; p=0.483, =0.072, respectively). In the logistic regression analysis of a sex- and age-adjusted model, having a genotype other than AA (AG or GG genotypes) of the *IL-17F 7488A/G* polymorphism increased the risk of AS development approximately 3-fold (p=0.022, OR, 95% CI=2.504, 1.140–5.500). Patients with AG genotype were found to have an increased risk of AS development (p=0.042, OR, 95% CI=2.354, 1.033–5.363).

DISCUSSION

In the present study, we investigated the role of the *IL-17F* gene polymorphisms at positions *IL-17F 7383A/G* and *IL-17F 7488A/G* and the *IL-17A* gene polymorphisms at position *G197A* in AS susceptibility and severity for the first time according to the best of our knowledge. We have two main results. Firstly, there was no significant difference in the distribution of the genotypes and the frequencies of alleles of the *IL-17F 7383A/G* and *IL-17A G197A* polymorphisms, whereas the frequencies of the genotypes and alleles of the *IL-17F 7488A/G* polymorphism were significantly different in the patients compared to those of the healthy controls. Namely, individuals who had the AG genotype and a G allele at the site of the *IL-17F 7488A/G* polymorphism were susceptible to the development of AS, whereas those with the AA genotype at the same loci seemed not to be prone to develop AS. Secondly, the BASFI scores and CRP levels of the AS patients with the *IL-17F 7488A/G* genotypes were significantly different. However, these differences disappeared in linear regression analyses.

IL-23 is a key pro-inflammatory cytokine in the immune system and plays a central role in the differentiation of native CD4± T cells into IL-17-producing TH cells[32]. Research has suggested that TH 17 cells, which produce IL-17, are responsible for various types of tissue damage, including damage to joints[33]. The key role of IL-17 and TH 17 cells in tissue inflammation, autoimmunity and host defence has led investigators to focus on these molecules[34,35]. Several authors have reported a relation between disease susceptibility and the severity of AS with the *IL-23R* polymorphism[9-11]. In contrast, other authors found no association between the *IL-23R* gene polymorphisms and the development

of AS and suggested that attention should be focused on other genes which take part in relation with IL-23[32-36]. Therefore, we hypothesized that there may be an association between the development of AS and the *7383A/G* and *7488A/G* polymorphisms of the *IL-17F* gene and the *G197A* polymorphism of the *IL-17A* gene. Finally, we found that the frequencies of AG genotype and G allele of the *IL-17F 7488A/G* polymorphism were significantly higher in the patients with AS compared to those of healthy controls.

Chronic inflammation is a hallmark of the pathogenesis of *Helicobacter pylori*-induced gastric cancer. Similar to this study, another study of a relatively larger patient and a healthy control population found that the *7488A/G* polymorphism of the *IL-17F* gene was involved in the susceptibility to gastric cancer but that the *IL-17A G197A* polymorphism did not play a role[31]. The *7488A/G* polymorphism of the *17F* gene was reported to be associated with the severity of rheumatoid arthritis[24]. In our study, we found no significant association between either the *IL-17F 7383A/G* or the *IL-17A G197A* polymorphisms and AS disease susceptibility and severity. Another report found no association between the genotypes and allele distribution of the *IL-17F 7488A/G* and *IL-17F 7383A/G* polymorphisms and the susceptibility to osteoarthritis in patients with osteoarthritis compared to healthy controls[37]. Consistent with this finding, no relations were found between Crohn's Disease[27], gastric cancer[38], Behcet's disease[25,39] and asthma[40] and the genotype distribution and allele frequencies of the *IL-17F 7488A/G* polymorphism.

In the present study, the occurrence of the G allele and AG genotype at the *IL-17F 7488A/G* polymorphism site was related to the development of AS, and genotypes other than AA (AG or GG) found to increase the risk of AS development approximately 3-fold. A previous study also reported that the *IL-17F 7488A/G* polymorphism was associated with gastric cancer[31]. In the present study, having the AA genotype of *IL-17F 7488A/G* appeared to have possible preventive effects against AS. In a study of the *IL-17F 7383A/G* polymorphism, Jang et al. found a higher frequency of the heterozygote genotype in Korean patients with Behcet's disease and a higher susceptibility to the disease[25]. The same study found that the GG genotype was more dominant in controls and had a protective role in preventing the development of Behcet's disease. In addition, the authors reported significant differences in the distribution of A/G alleles in patients with Behcet's disease compared to controls and that having the G allele protected individuals against the development of the disease[25]. On the other hand, the G allele and GA or GG genotypes at the *IL-17 F 7488A/G* gene site[31] and at *IL-17A G197A* gene loci[38] were associated with an increased risk of gastric cancer when compared to healthy controls. Having the G allele or GG genotype of the *IL-17A G197A* polymorphism was related to disease susceptibility in Norwegian rheumatoid arthritis patients[41]. Moreover, the frequency of the A allele of *IL-17A G197A* was significantly correlated with the development of ulcerative colitis in a Japanese population[23]. The susceptibility to various diseases seemed to be associated with different *IL-17* gene polymorphisms. These discrepancies may be due to the different pathogenesis of the diseases, as well as the various ethnicities and environmental exposures.

We also found significant differences in the CRP levels and BASFI scores according to the distribution of the *IL-17F 7488A/G* polymorphism genotypes. Although the differences disappeared in the regression analyses, having the GG genotype seemed to be associated with higher BASFI scores and therefore worse functional status. Patients with the AG genotype may be prone to higher levels of CRP, suggesting that this polymorphism might be associated with greater disease activity in AS. Consistent with this finding, an earlier study reported a relationship between the *IL-17F 7488A/G* polymorphism and disease activity and CRP levels in patients with rheumatoid arthritis compared to healthy controls[24]. In the latter study, having the AG genotype of the *IL-17F 7488A/G* polymorphism increased the severity of rheumatoid arthritis, similar to the present study of AS patients. The authors suggested that the *IL-17F* His161Arg substitution may directly regulate the expression of IL-17F, which plays an important role in T-cell-triggered inflammation[24]. These results indicate that various genotypes of the *IL-17* gene polymorphism can influence the severity of several diseases, perhaps, by affecting the expression of IL-17. However, the treatment modalities may also have influenced ESR and CRP[1]. This should be taken into account when interpreting the present results.

Based on the findings of the present study, we conclude that there is no relationship between the distributions of the alleles and genotypes of the *IL-17A G197A* polymorphism and susceptibility to AS. Previous studies reported the same results in patients with Behcet's disease[39] and *H. pylori*-induced gastric cancer[31]. Contrarily, previous studies found a significant association between the *IL-17 G197A* polymorphism and sus-

ceptibility to rheumatoid arthritis[41], ulcerative colitis[23], Behcet's disease[25] and gastric cancer[38] was reported.

There are several limitations of our study. The first is the small patient population, which was from two tertiary hospitals attended by a specific population of patients. This might have also affected the patient selection. The second is the cross-sectional design which limits our abilities to draw a direct relationship between these three polymorphisms and AS.

CONCLUSIONS

To the best of our knowledge this is the first study investigating the relationships between *IL-17* polymorphisms and AS. We conclude that the *IL-17F 7488A/G* polymorphism may be associated with AS susceptibility, disease severity and functional status in Turkish patients. Nevertheless, the results observed herein need to be supported in future studies. These results also support the idea that similar gene loci may be responsible for the susceptibility to certain diseases, consistent with the findings of previous studies.

CORRESPONDENCE TO
Erkol İnal E
Süleyman Demirel University, Faculty of Medicine,
Department of Physical Medicine and Rehabilitation, Cunur
Isparta, Turkey
E-mail: esraerkol@hotmail.com

REFERENCES

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet Rev 2007; 369: 1379-1390.
2. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garret SL, Calin A. Defining spinal mobility in Ankylosing Spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994; 21: 2281-2285.
3. Zambrano-Zaragoza JF, Agraz-Cibrian JM, González-Reyes C, Durán-Avelar Mde J, Vibanco-Pérez N. Ankylosing spondylitis: from cells to genes. Int J Inflam 2013; 2013: 501653.
4. Davidson SI, Wu X, Liu Y, et al. Association of ERAP1, but not IL23R, with ankylosing spondylitis in a Han Chinese population. Arthritis Rheum 2009; 60: 3263-3268.
5. Lv C, Wang Y, Wang J, Zhang H, Xu H, Zhang D. Association of Interleukin-10 gene polymorphisms with ankylosing spondylitis. Clin Invest Med 2011; 34: E370.
6. Wong RH, Wei JC, Huang CH, et al. Association of IL-12B genetic polymorphism with the susceptibility and disease severity of ankylosing spondylitis. J Rheumatol 2012; 39: 135-140.
7. Jin GX, Duan JZ, Guo WL, Li L, Cui SQ, Wang H. Association between IL-1RN gene polymorphisms and susceptibility to ankylosing spondylitis: a large Human Genome Epidemiology review and meta-analysis. Genet Mol Res 2013; 12: 1720-1730.
8. McGarry F, Neilly J, Anderson N, Sturrock R, Field M. A polymorphism within the interleukin 1 receptor antagonist (IL-1Ra) gene is associated with ankylosing spondylitis. Rheumatology (Oxford) 2001; 40: 1359-1364.
9. Brionez TF, Reveille JD. The contribution of genes outside the major histocompatibility complex to susceptibility to ankylosing spondylitis. Curr Opin Rheumatol 2008; 20: 384-391.
10. Duan Z, Pan F, Zeng Z, et al. Interleukin-23 receptor genetic polymorphisms and ankylosing spondylitis susceptibility: a meta-analysis. Rheumatol Int 2012; 32: 1209-1214.
11. Lee YH, Choi SJ, Ji JD, Song GG. Associations between interleukin-23R polymorphisms and ankylosing spondylitis susceptibility: a meta-analysis. Inflamm Res 2012; 61: 143-149.
12. Dong H, Li Q, Zhang Y, Tan W, Jiang Z. IL23R gene confers susceptibility to ankylosing spondylitis concomitant with uveitis in a Han Chinese population. PLoS One 2013; 8: e67505.
13. Pimentel-Santos FM, Ligeiro D, Matos M, et al. Association of IL23R and ERAP1 genes with ankylosing spondylitis in a Portuguese population. Clin Exp Rheumatol 2009; 27: 800-806.
14. Rudwaleit M, Höhler T. Cytokine gene polymorphisms relevant for the spondyloarthropathies. Curr Opin Rheumatol 2001; 13: 250-254.
15. Zhang G, Luo J, Bruckel J, et al. Genetic studies in familial ankylosing spondylitis susceptibility. Arthritis Rheum 2004; 50: 2246-2254.
16. Australo-Anglo-American Spondyloarthritis Consortium (TASC), Reveille JD, Sims AM, Danoy P, et al. Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet 2010; 42: 123-127.
17. Laval SH, Timms A, Edwards S, et al. Whole-genome screening in ankylosing spondylitis:evidence of non-MHC genetic-susceptibility loci. Am J Hum Genet 2001; 68: 918-926.
18. Chen WS, Chang YS, Lin KC, et al. Association of serum interleukin-17 and interleukin-23 levels with disease activity in Chinese patients with ankylosing spondylitis. J Chin Med Assoc 2012; 75: 303-308.
19. Rouvier E, Luciani MF, Mattéi MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J Immunol 1993; 150: 5445-5456.
20. Baeten D, Baraliakos X, Braun J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013; 382: 1705-1713.
21. Paradowska A, Ma li iski W, Grzybowska-Kowalczyk A, Łacki J. The function of interleukin 17 in the pathogenesis of rheumatoid arthritis. Arch Immunol Ther Exp (Warsz) 2007; 55:329--334.
22. Hizawa N, Kawaguchi M, Huang SK, Nishimura M. Role of interleukin-17F in chronic inflammatory and allergic lung disease. Clin Exp Allergy 2006; 36: 1109-1114.
23 Arisawa T, Tahara T, Shibata T, et al. The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis. J Clin Immunol 2008; 28: 44--49.
24. Paradowska-Gorycka A, Wojtecka-Lukasik E, Trefler J, Wojciechowska B, Lacki JK, Maslinski S. Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA). Scand J Immunol 2010; 72: 134--141.
25. Jang WC, Nam YH, Ahn YC, et al. Interleukin-17F gene polymorphisms in Korean patients with Behcet's disease. Rheumatol Int 2008; 29: 173-178.

26. Kawaguchi M, Takahashi D, Hizawa N, et al. IL-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity. J Allergy Clin Immunol 2006; 117: 795-801.
27. Seiderer J, Elben I, Diegelmann J, et al. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. Inflamm Bowel Dis 2008; 14: 437-445.
28. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27 :361-368.
29. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: reliability and validity. Rheumatol Int 2005; 25: 280-284.
30. Karatepe AG, Akkoc Y, Akar S, Kirazli Y, Akkoc N. The Turkish version of the Bath Ankylosing Spondylitis and Dougados Functional indices: reliability and validity. Rheumatol Int 2005; 25: 612-618.
31. Wu X, Zeng Z, Chen B, et al. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. Int J Cancer 2010; 127: 86-92.
32. Murphy CA, Langrish CL, Chen Y, et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 2003; 198: 1951-1957.
33. Steinman L. A brief history of T (H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. Nat Med 2007; 13: 139-145.
34. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov 2012; 11: 763-776.
35. Song IH, Poddubnyy D. New treatment targets in ankylosing spondylitis and other spondyloarthritides. Curr Opin Rheumatol 2011; 23: 346-351.
36. Chen C, Zhang X, Li J, Wang Y. Associations of IL-23R polymorphisms with ankylosing spondylitis in East Asian population: a new case-control study and a meta-analysis. Int J Immunogenet 2012; 39: 126-130.
37. Southam L, Heath O, Chapman K, Loughlin J. Association analysis of the interleukin 17 genes IL17A and IL17F as potential osteoarthritis susceptibility loci. Ann Rheum Dis 2006; 65: 556--557.
38. Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. Hum Immunol 2009; 70: 547-551.
39. Shu Q, Yang P, Hou S, et al. Interleukin-17 gene polymorphism is associated with Vogt-Koyanagi-Harada syndrome but not with Behçet's disease in a Chinese Han population. Hum Immunol 2010; 71: 988-991.
40. Ramsey CD, Lazarus R, Camargo CA Jr, Weiss ST, Celedón JC. Polymorphisms in the interleukin 17F gene (IL17F) and asthma. Genes Immun 2005; 6: 236-241.
41. Nordang GB, Viken MK, Hollis-Moffatt JE, et al. Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology (Oxford). 2009; 48: 367-370.