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ORIGINAL ARTICLE

Relationship between asthma and IL-17 gene polymorphism in a Turkish population

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Abstract

Background Asthma is a prevalent chronic obstructive disease of the airways.

Aims The aim of our study was to investigate the relationship between asthma and *IL-17F* gene 74488 T > C, *IL-17A* gene -197G > A, and *IL17A* gene -737C > T polymorphisms in Turkish population.

Methods In our study, peripheral blood samples collected from a total of 127 subjects, with 65 in the patient group and 62 in the control group, were analyzed for *IL-17F* gene 74488 T > C, *IL-17A* gene -197G > A, and *IL17A* gene -737C > T polymorphisms using next-generation sequencing.

Results There was no statistically significant relationship between *IL-17A* gene -197G > A and *IL-17A* gene -737C > T polymorphisms and the risk of developing asthma. It was found that the risk of developing asthma was 2.9-fold higher in individuals with a C allele in the *IL-17F* gene 7488 T > C polymorphic site than the individuals with a T allele. It was shown that ATT and GCT haplotype carriers had a greater disease risk compared with the GTT haplotype carriers.

Conclusions In conclusion, IL-17F gene 7488 T > C polymorphism was found to be associated with asthma in the Turkish population. The IL-17 gene should be further investigated as a potential candidate gene in predicting asthma susceptibility and in the treatment of asthma.

Keywords Asthma · *IL-17* · Polymorphism · rs763780 · rs2275913 · rs8193036

Introduction

Asthma is a chronic disease that affects approximately 300 million people worldwide. It affects 1–20% of the population in different countries [1]. According to the World Health Survey (WHS) study, worldwide asthma prevalence is 4.27% and 2.06% in Turkey [2]. Asthma is a multifactorial disease. In addition to environmental exposures, genetic factors have a significant impact on the onset, severity, and treatment of asthma. Polymorphisms in different genes

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have been shown to affect asthma severity and response to therapy [3].

It is known that the expression and secretion of interleukins in patients with asthma have a regulatory effect on the airway and also regulate the therapeutic response [4]. Interleukin-17 is effective in immune and inflammatory response by regulating the expression level of various mediators such as cytokines, chemokines, and transcription factors [4]. IL-17A and IL-17F are found in the airways of patients with asthma, and their expression level correlates with disease severity. These cytokines induce various cytokines, chemokines, and adhesion molecules in bronchial epithelial cells, endothelial cells, fibroblasts, and eosinophils, resulting in airway neutrophilia, airway hyperreactivity, and excessive mucus secretion. Serum IL-17 levels were found to be significantly higher in patients with uncontrolled asthma compared to well-controlled asthma patients and healthy controls [5]. IL-17 is important for protection against extracellular bacteria, fungi, and viruses that infect mucosal cells, but its abnormality or overexpression contributes to a range of pathological outcomes such as asthma, pneumonitis, and pulmonary fibrosis [6]. The genes encoding IL-17A and IL-17F are located in the p12 region of chromosome 6 and are located very close to each other. Both genes are composed of three exons [7–12]. Single-nucleotide polymorphisms (SNPs), the most common type of DNA sequence variation, can exert various effects at the level of gene expression, depending on their location in the genome [13]. It has been stated that IL-17A and IL-17F gene SNPs may be potential risk factors for asthma sensitivity [14].

Materials and methods

Our study was approved by Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Clinical Research Ethics Committee (25.06.2019, decision number 2019/63). This study is a prospective and controlled study conducted in adult patients who are followed up with a diagnosis of asthma. Based on the criteria specified in the Global Initiative for Asthma (GINA) guide [1]. Asthma group: selected among severe asthma cases whose disease could not be controlled despite the necessary asthma control measures, who used the drug at the highest appropriate dose with full compliance and correct technique; 65 patients diagnosed with asthma and 62 volunteers without systemic disease were recruited as the control group. Those with cancer, inflammatory bowel diseases, collagen tissue diseases, psoriasis, autoimmune thyroid diseases, and interstitial lung diseases were excluded from the study. Laboratory studies were carried out at the Intergen Genetics and Rare Diseases Diagnosis Research and Application Center.

In our study, we aimed to investigate the relationship between -197G > A and -737C > T single-nucleotide polymorphisms in the *IL-17A* gene located in the p12 region of the 6th chromosome and 7488 T > C single-nucleotide polymorphism in the *IL-17F* gene with asthma. The human genome 19 (Hg19) coordinates of the three investigated SNPs are given in Table 1. After the informed consent forms were signed by the patient and control groups, 5 ml peripheral blood samples were collected into EDTA tubes. Samples were stored at − 20 °C until the time of analysis. DNA isolation was performed using the HibriGen blood DNA isolation kit (Istanbul, Turkey). Samples with a concentration of 10 ng/µl and above were used, and re-isolation was made from samples with a concentration of less than 10 ng/µl. BIO-RAD T100 Thermal Cycler PCR device was used for PCR. The primers used are given in Table 2. The gel image of the PCR products is given in Fig. 1.

Purified and standardized PCR pools were prepared for next-generation sequencing using the NexteraXT sample preparation kit (Illumina Inc. San Diego, CA, USA). Miseq (Illumina Inc. San Diego, CA, USA) device was used for next-generation sequencing. For the next-generation DNA sequencing device sample preparation, a working template comprising 24 pools was generated. Miseq Reporter (Illumina Inc.) software on the Hg19 version was used for the alignment of the reads. At the end of the alignment, the bam files obtained using IGV (Integrative Genomics Viewer, Broad Institute) software were analyzed. The analysis was performed to cover the region containing 20 base pairs from the exon–intron intersection regions. The minimum depth for the genotyped polymorphisms was determined as 20, and analysis for the regions below 20 was repeated starting

Table 1 Hg19 coordinates of SNP 1, 2, and 3

SNP	Hg19 reference (wild type)	Mutant allele	Hg19 coordinates
SNP 1 *IL-17A* gene -197 G > A **(rs2275913)**	G	A	chr6:52,051,033
SNP 2 *IL-17A* gene -737 C > T**(rs8193036)**	C	T	chr6:52,050,493
SNP 3 *IL-17F* gene 7488 T > C**(rs763780)**	T	C	chr6:52,101,739

Table 2 Primers used in analysis

Primer	Orientation	Sequencing	Genotyping	size (bp)	Sequence (5′-3′)
IL17F-1F	Forward	Exon 1	-	356	GGTCAACCACAACTTAAAGACAGTAAGC
IL17F-1R	Reverse				TTATTTTTTTCTTTTTCTCCACCAGACAG
IL17F-2F	Forward	Exon 2	-	760	AGTTCTCAGTTTGGCACCTTGATACC
IL17F-2R	Reverse				CCGACTTTTCTGTTTCCCATTTATCCTC
IL17F-3F	Forward	Exon 3	SNP3	496	TAGAAAGGTAAGCCACTGCCAGAGG
IL17F-3R	Reverse				TCAGACAGGACTTGTTGCAGAGCAC
IL17A-1F	Forward	Exon 1	SNP1, SNP2	922	CATCATGTCTCCTCTCCTTTCTAGTTCTC
IL17A-1R	Reverse				ATAGTCAGAACCCAGCGTTTCATGC
IL17A-2F	Forward	Exon 2,3	-	1919	GTAGTATAGATTGTCCTGGAACATTGTGTG
IL17A-3R	Reverse				GAAATGAGGCTGTCTTTGAAGGATGAG

SNP1: *IL-17A* gene -197 G > A; SNP2: *IL-17A* gene -737 C > T; SNP3: *IL-17F* gene 7488 T > C

from the PCR step. The coding region and exon–intron intersection regions of *IL-17A* and *IL-17F* genes were analyzed and minor allele frequency (MAF) values were determined by referring to the Ensembl database and Single-Nucleotide Polymorphism Database (dbSNP) for points that differ from the reference sequence. Changes with MAF values greater than 0.01 were considered polymorphism, and those with MAF values less than 0.01 were considered changes with a possibility to cause disease.

Statistical analysis

Analyses were performed using the IBM SPSS 25.0 and R 4.0.4 epitools package. Continuous variables were expressed as mean ± standard deviation. Normal distribution was examined with the Kolmogorov–Smirnov test, and the groups meeting the normal distribution criteria were evaluated with the Student *t* test; those who did not were evaluated with the Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages. The chi-square test was used to examine the Hardy–Weinberg equilibrium for the three SNPs. Genotype and allele frequencies for the patient and control groups are shown, along with odds ratios and 95% confidence intervals. Iterative EM (expectation–maximization) algorithm was used to calculate the expected values in multiple-SNP analyses. All analyses were bilateral and a $p < 0.05$ was considered statistically significant.

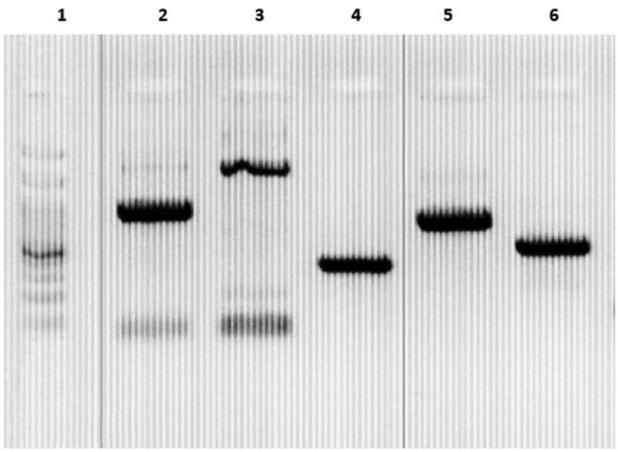

Fig. 1 Gel electrophoresis image of the PCR products of patient no. 8. 1: DNA ladder; 2: IL-17A exon1 (922 bp); 3: IL-17A exon 2–3 (1919 bp); 4: IL-17F exon 1(356 bp); 5: IL-17F exon 2 (760 bp); and 6: IL-17F exon 3 (496 bp) PCR products

Results

The mean age was 43.71 ± 13.22 years in the asthma patient group and 40.74 ± 12.65 years in the control group. Patient group comprised 44 (68%) females and 21 (32%) males whereas the control group comprised 31 (50%) females and 31 (50%) males. There was no difference between the groups in terms of sex regarding the *IL-17A* gene -197G > A, -737C > T, and *IL-17F* gene 7488 T > C polymorphisms (*IL-17A* gene -197G > A polymorphism $p = 0.478$ for genotypes and $p = 0.399$ for alleles, -737C > T polymorphism $p = 0.499$ for genotypes and $p = 0.37$ for alleles, *IL-17F* gene 7488 T > C polymorphism $p = 0.638$ for genotypes and $p = 0.403$ for alleles). Allele and genotype frequency analyses for *IL-17A* gene -197 G > A, *IL-17A* gene -737 C > T, and *IL-17F* gene 7488 T > C polymorphism are shown in Table 3. It was found that the sample genotype frequency distribution was consistent with the Hardy–Weinberg equilibrium ($p > 0.05$).

When age- and gender-adjusted genotype models were analyzed, it was found that there was no statistically significant difference between the groups in terms of disease risk regarding *IL-17A* gene-197G > A and -737C > T polymorphisms (Table 3). It was found that the risk of developing the disease was 2.9-fold higher in individuals with the C allele

Table 3 Allele and genotype distributions of SNP1, SNP2, and SNP3

	Genotype	Patient	Control	OR (95% CI)	*p*-value
SNP1 ***IL-17A*** **gene -197G > A (rs2275913)**	**GG**	32 (49.2%)	30 (48.4%)	Reference	0.351
	GA	22 (33.9%)	27 (43.5%)	0.76 (0.35–1.64)	
	AA	11 (16.9%)	5 (8.1%)	1.86 (0.56–6.146)	
	GG + GA	54 (83.1%)	57 (91.9%)	Reference	0.204
	AA	11 (16.9%)	5 (8.1%)	2.1 (0.67–6.59)	
	G Allel	86 (66.2%)	87 (70.1%)	Reference	0.49
	A Allel	44 (33.8%)	37 (29.9%)	1.20 (0.7–2.04)	
SNP2 IL-17A geni -737C > T (rs8193036)	**CC**	4 (6.2%)	3 (4.8%)	Reference	0.47
	CT	26 (40%)	19 (30.6%)	1.02 (0.20–5.13)	
	TT	35 (53.9%)	40 (64.5%)	0.65 (0.13–3.13)	
	TT	35 (53.9%)	40 (64.5%)	0.64 (0.31–1.30)	0.22
	CC + CT	30 (46.1%)	22 (35.5%)	Reference	
	C Allel	34 (26.2%)	25 (20.1%)	Reference	0.26
	T Allel	96 (73.8%)	99 (79.9%)	0.71 (0.39–1.28)	
SNP3 IL-17F geni 7488 T > C (rs763780)	**TT**	54 (83.1%)	58 (93.5%)	Reference	0.275
	TC	10 (15.4%)	4 (6.5%)	2.80 (0.797–9.87)	
	CC	1 (1.5%)	0 (0%)	0.00 (0.00–0.00)	
	TT + TC	64 (98.5%)	62 (100%)	Reference	-
	CC	1 (1.5%)	0 (0%)	0.00 (0.00–0.00)	
	T Allel	118 (90.7%)	120 (96.8%)	Reference	0.048*
	C Allel	12 (9.3%)	4 (3.2%)	2.9 (0.98–11.19)	

P patient, *C* control, *OR* odds ratio

for *IL-17F* gene 7488 T > C polymorphism than the individuals with the normal T allele, and this change was statistically significant (C vs T, OR = 2.9, 95% CI = 0.98–11.19, $p = 0.048$) (Table 3).

In order to reveal the relationship between the SNPs and disease, the probability of the combination of the alleles in IL-17A gene -197G > A, -737C > T and IL-17F gene 7488 T > C polymorphisms was assessed by using the expectation–maximization algorithm (EM) in multiple-SNP analysis (Table 4). Among the cumulative frequencies, the GTT frequency was found to be the most common, and this haplotype was taken as the reference haplotype (*P*: 44.64%, *C*: 60.55%). It was found that the risk of having the disease was increased in a statistically significant fashion in ATT and GCT haplotype carriers compared with GTT haplotype carriers. When the logistic regression model was adjusted for age and gender, it was shown that the ATT haplotype increased the disease risk 0.39-fold, and the GCT haplotype 0.28-fold ($p = 0.024$, $p = 0.033$, respectively) (Table 5). The global haplotype association *p*-value of 0.016 is a reflection of both the accuracy of our setup for the analysis and of the analysis.

Table 4 Multiple-SNP analysis, haplotype frequency estimation ($n = 127$)

SNP1 rs2275913	SNP2 rs8193036	SNP3 rs763780	Total	Patient	Control	Cumulative frequencies
G	**T**	**T**	0.5198	0.4464	0.6055	0.5198
A	**T**	**T**	0.2175	0.2637	0.1673	0.7372
G	**C**	**T**	0.1118	0.1378	0.0786	0.849
A	**C**	**T**	0.088	0.0599	0.1163	0.937
G	**C**	**C**	0.0274	0.049	0.0067	0.9644
G	**T**	**C**	0.0222	0.0284	0.0108	0.9866
A	**T**	**C**	0.0083	0	0.0148	0.9949
A	**C**	**C**	0.0051	0.0149	-	1

Obtained using two-step iterative EM algorithm

Table 5 Haplotype analysis ($n=127$)

	SNP1 rs2275913	SNP2 rs8193036	SNP3 rs763780	frequency	OR (95% CI)	p
1	**G**	**T**	**T**	0.5243	Referans	––
2	**A**	**T**	**T**	0.2129	0.39 (0.18–0.88)	0.024*
3	**G**	**C**	**T**	0.1078	0.28 (0.09–0.89)	0.033*
4	**A**	**C**	**T**	0.092	1.19 (0.37–3.83)	0.77
rare	**-**	**-**	**-**	0.063	0.20 (0.05–0.73)	0.017*

*Global haplotype association p-value: 0.016

Discussion

Asthma is an important cause of morbidity and mortality [15,16]. IL-17 is one of the key cytokines that play a significant role in the pathogenesis of asthma [17]. *IL-17* gene polymorphisms have been shown to be associated with various autoimmune disorders such as asthma and rheumatoid arthritis, and inflammatory bowel syndrome [18, 19]. In studies performed in different populations, it was reported that *IL-17A* and *IL-17F* single-nucleotide polymorphisms can be potential risk factors for asthma susceptibility [14].

The objects of our analysis, *IL-17A* gene polymorphic sites -737C > T and -197G > A which are localized in 6p12, are found in the promoter region of the gene [20]. SNPs affecting the gene promoter can alter the rate of gene transcription by changing the transcription factor binding site [21]. *IL-17F* gene 7488 T > C polymorphism is found in the coding region of the third exon of the *IL-17F* gene in 6p12 and is a missense variation resulting from the replacement of the 161st amino acid, histidine, by arginine (H161R variant) [22]. *IL-17F* gene 7488 T > C polymorphic site TC heterozygosity, that is, the heterozygous variant of H161R, has been shown to have a protective effect against asthma in the Japanese population ($p=0.0028$) [22]. In line with this study, we also found that both the C allele and CC genotype in the *IL-17F* gene 7488 T > C polymorphic site had low frequency, but in contrast, that *IL-17F* gene 7488 T > C polymorphism increased disease susceptibility.

In the study by Maalmi et al. [21] in the Tunisian asthma population, *IL-17A* gene -197G > A and *IL-17F* gene 7383A > G polymorphisms were found to be associated with asthma in children ($p=0.008$, $p=0.001$, respectively), while no association was found between asthma and IL-17F gene 7488A > G polymorphism. Similar to our study, Maalmi et al.'s [21] study tested all three polymorphisms under the recessive model, as there was a dominance of wild-type alleles in both the cases and the control group compared to the mutant allele. In the study by Bazzi et al. [23] in the Saudi population, IL-17A and IL17F levels were found to be higher in asthma patients and the difference was found statistically significant for IL-17F ($p=0.025$, t-test), but no association was detected between *IL-17F* gene 7488 T > C and asthma.

In line with our study, in a study conducted by Qian et al. [24] in the Chinese population, it was shown that the *IL-17F* gene 7488 T > C polymorphism C allele was significantly associated with asthma ($p=0.0148$). *IL-17F* gene 7488 T > C polymorphic site TC heterozygous genotype was also associated with increased asthma risk (adjusted OR, 1.58; 95% CI, 1.06–2.36; $p=0.0148$). They also demonstrated that this association was prominent in patients with higher IgE levels (≥ 1.85 IU/ml) [24].

The study by Du et al. [25] in the Asian population in 125 asthma patients and 132 healthy subjects demonstrated that *IL-17A* gene -197G > A and -737C > T polymorphisms may be associated with asthma susceptibility and that *IL-17A* gene -197G > A polymorphic site GA heterozygous genotype and *IL-17A* gene -737C > T polymorphic site TT homozygous genotype may contribute to an increased risk of asthma. On the other hand, in our study, *IL-17A* gene -197G > A and -737C > T polymorphisms were not found associated with asthma [25]. In a meta-analysis that included ten studies with a total of 5016 subjects, it was stated that the G allele in the *IL-17A* gene -197G > A polymorphic site is a protective factor against the development of asthma. In the subgroup analysis by age and ethnicity, the G allele in the -197G > A polymorphic site was significantly associated with a reduced risk of asthma in children and Asians [26]. In our study, no relationship was found between the *IL-17A* gene -197G > A polymorphism and the risk of asthma. The *IL-17A* gene -197G > A and -737C > T polymorphisms were evaluated in a meta-analysis involving 2882 asthma patients and 2093 healthy controls from seven case–control studies. In this meta-analysis, *IL-17A* gene -737C > T polymorphism was found to be protective against asthma, while *IL-17A* gene -197G > A polymorphism was not associated with asthma susceptibility, which was consistent with our study [27].

In the study, which included 168 pediatric patients with asthma, 144 bronchiolitis patients, and 205 control subjects, the *IL-17A* gene -197G > A polymorphism was associated with asthma in the genotype frequency test ($p=0.03$). Children with homozygous AA genotype were found to be 2.29

times more likely to have asthma than the others ($p = 0.001$). The A allele in the -197G > A polymorphic site of the *IL-17A* gene has been associated with abnormal lung function and elevated total serum IgE in asthmatics. The distribution of -197G > A polymorphism in patients with bronchiolitis showed a similar trend to that in asthma, with statistically significant differences from controls. Therefore, it has been pointed out that the *IL-17A* gene -197G > A polymorphism can be used to develop markers to assess the risk of asthma in the bronchiolitis population, and may be a potential bridge to connect bacterial colonization and asthma onsets [28].

In our study, eight different haplotypes were detected in the haplotype analysis of the *IL-17A* gene -197G > A and -737C > T, *IL-17F* gene 7488A > G polymorphic sites. GTT haplotype was found to be the most common haplotype, with a frequency of 60% in control samples and 40% in patient samples. Therefore, the GTT haplotype was considered to be the protective haplotype. When GTT haplotype was taken as a reference, ATT and GCT haplotypes, which were the second and third most commonly observed haplotypes, were observed more frequently in the patient group than in the control group, and it was thought that they may cause a predisposition to asthma disease (OR = 0.39, $p = 0.024$ and OR = 0.28, $p = 0.033$, respectively).

Limitations

One of the limitations of our study is the small number of patients. For this reason, we included a variety of studies from the literature with different results. Another limitation is that, because our study was conducted during the COVID-19 pandemic, current pulmonary function tests could not be performed in the patients and the control group. Therefore, a comparison could not be made between the patient and control groups in terms of pulmonary function test parameters.

Conclusion

When all genotypes were examined, it was found that *IL-17A* -197G > A and *IL-17A* -737C > T polymorphisms did not affect the risk of developing asthma in the Turkish population. Individuals carrying the C allele for the *IL-17F* 7488 T > C polymorphism have been shown to have a significantly higher risk of asthma disease. It was found that the risk of having asthma in individuals with the C allele was 2.9 times higher than those with the T allele (OR = 2.9, $p = 0.048$). Our study, in which we investigated the relationship between asthma and *IL-17* gene polymorphisms with the next-generation sequencing technique, is the first report in the Turkish population showing the relationship between asthma and IL-17 gene polymorphisms. Based on the results of our study, it can be concluded that *IL-17F* gene 7488 T > C polymorphism observed in the Turkish population may contribute to the development of asthma.

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Declarations

Ethics approval The study was approved by Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Clinical Research Ethics Committee (25.06.2019, decision number 2019/63).

Consent for publication Consent has been granted by all authors for the publication of this manuscript.

Conflict of interest The authors declare no competing interests.

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