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Interleukin-18 (-607 C/A and -656 G/T) Gene Promoter Polymorphism in Asthma Patients

Astım Hastalarında İnterlökin-18 Gen Promotör (-607 C/A ve -656 G/T) Polimorfizmleri

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ABSTRACT

Aim: Asthma is a chronic inflammatory disease characterized by variable airway obstruction and influenced by genetic and environmental factors. Interleukin-18 (IL-18), a cytokine essential for both innate and adaptive immunity, is encoded by a gene located on chromosome 11q22.2-q22.3. This study aimed to investigate the association between asthma and IL-18 gene promoter polymorphisms -607 C/A and -656 G/T in the Turkish population.
Material and Methods: Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were utilized to examine genotypes in 100 asthma patients (53 males, 47 females) and 101 healthy controls (50 males, 51 females). Genotypic frequencies in both polymorphic regions were compared between groups.
Results: In the -607 region, genotype distributions were CC 49 (49.0%), CA 46 (46.0%), and AA 5 (5.0 %) in asthma patients, while controls showed CC 64 (63.4%), CA 34 (33.7%), and AA 3 (2.9%). The CC genotype was significantly lower in patients, with a borderline significant reduction in C allele frequency (p=0.054). In the -656 region, distributions in patients were GG 49 (49.0%), GT 37 (37.0%), and TT 14 (14.0%), compared to GG 55 (54.5%), GT 41 (40.6%), and TT 5 (4.9%) in controls. Although GG and GT genotypes exhibited no significant differences, the TT genotype was notably higher in patients (p=0.040).
Conclusion: The IL-18 -607 CC genotype may have a protective effect against asthma, whereas the -656 TT genotype increases risk. These outcomes underline the significance of IL-18 promoter polymorphisms in asthma development and potential use in genetic risk evaluation.
Keywords: Asthma; interleukin-18; rs1946518 C/A polymorphism; rs1946519 G/T polymorphism.

ÖZ

Amaç: Astım, değişken hava yolu tıkanıklığı ile karakterize kronik bir inflamatuar hastalıktır ve genetik ve çevresel faktörlerden etkilenir. Hem doğuştan gelen hem de edinilmiş bağışıklıkta önemli rol oynayan bir sitokin olan interlökin-18 (IL-18), 11q22.2-q22.3 kromozom bölgesinde yer alan bir gen tarafından kodlanır. Bu çalışmanın amacı, Türk popülasyonunda astım ile IL-18 geni promotor polimorfizmleri -607 C/A ve -656 G/T arasındaki ilişkinin araştırılmasıdır.
Gereç ve Yöntemler: 100 astım hastası (53 erkek, 47 kadın) ve 101 sağlıklı kontrolde (50 erkek, 51 kadın) genotiplerin incelenmesinde polimeraz zincir reaksiyonu (PCR) ve restriksiyon fragman uzunluk polimorfizmi (RFLP) kullanıldı. Her iki polimorfik bölgedeki genotip frekansları gruplar arasında karşılaştırıldı.
Bulgular: -607 bölgesinde astım hastalarında genotip dağılımları CC 49 (%49,0), CA 46 (%46,0) ve AA 5 (%5,0) iken, kontrollerde CC 64 (%63,4), CA 34 (%33,7), ve AA 3 (%2,9) görüldü. CC genotipi hastalarda önemli derecede daha düşüktü ve C allel frekansında sınırda anlamlı bir azalma vardı (p=0,054). -656 bölgesinde, hastalardaki genotip dağılımları GG 49 (%49,0), GT 37 (%37,0) ve TT 14 (%14,0) iken, kontrol grubunda GG 55 (%54,5), GT 41 (%40,6) ve TT 5 (%4,9) idi. GG ve GT genotipleri bakımından önemli bir fark bulunmazken, TT genotipi hastalarda belirgin şekilde daha yüksekti (p=0,040).
Sonuç: IL-18 -607 CC genotipinin astıma karşı koruyucu bir rolü bulunurken, -656 TT genotipi hastalık riskini artırıyor olarak görünmektedir. Bu sonuçlar, IL-18 promotor polimorfizmlerinin astım gelişimindeki önemini ve genetik risk değerlendirmesinde potansiyel kullanımını vurgulamaktadır.
Anahtar kelimeler: Astım; interlökin-18; rs1946518 C/A polimorfizmi; rs1946519 G/T polimorfizmi.

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INTRODUCTION

Asthma is a multifactorial chronic respiratory disease characterized by variable airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. It is frequently associated with atopy and elevated serum immunoglobulin E (IgE) levels (1). Allergic asthma presents a major public health concern, affecting a considerable portion of the global population, with its prevalence steadily increasing in recent decades, partly due to rising air pollution and urbanization (2). Genetic and environmental factors jointly contribute to asthma as a multifactorial disease (3). Asthma arises from a complex interplay between host-related and environmental factors. Risk factors include personal aspects such as genetics, gender, and obesity, as well as environmental triggers like allergens, air pollution, infections, and smoke exposure. These environmental exposures, especially in genetically predisposed individuals, are pivotal in initiating and perpetuating the inflammatory responses characteristic of allergic asthma (4).

Asthma's hallmark is chronic airway inflammation, involving diverse inflammatory cells and mediators, leading to distinct pathological changes (5). Asthma progression typically involves three stages: chronic inflammation, bronchial hyperresponsiveness, and airflow obstruction (6). These changes are mediated by the activation and infiltration of immune cells such as mast cells, eosinophils, and T-helper (Th2) lymphocytes (7), which coordinate the secretion of cytokines like interleukin (IL)-4, IL-5, IL-9, and IL-13 (8,9).

Among the cytokines involved in asthma pathogenesis, IL-18 has gained increasing attention due to its regulatory roles in both innate and adaptive immunity. IL-18, a cytokine vital for Th1 cell differentiation and inflammation, is encoded by a gene on chromosome 11q22.2-q22.3, with six exons and five introns (10-12). As part of the IL-1 cytokine family, IL-18, also recognized as the interferon (IFN)-γ inducing factor, modulates both innate and acquired immunity (13-15). Recent investigations emphasize its role in autoimmune, inflammatory, and infectious diseases, including asthma. For instance, Wu et al. (16) identified associations between IL-18 polymorphisms, particularly -607 C/A and -137 G/C, and allergic rhinitis and asthma. Similarly, Pawlik et al. (17) connected the -137 G allele in the IL-18 promoter region to severe asthma.

While classical allergic diseases are mediated by IgE, emerging data suggest that other cellular mechanisms, governed by cytokines like IL-18, play critical roles (18). IL-18 gene polymorphisms influence cytokine expression and inflammatory responses, thereby affecting asthma susceptibility.

Considering these findings, growing evidence supports a regulatory role for IL-18 in asthma development through multiple immune pathways. It has been clearly demonstrated that IL-18 has a dichotomous role in the pathogenesis of asthma by the induction of both Th1 and Th2 immune responses. Initial studies had indicated that IL-18, particularly in conjunction with IL-12, might attenuate allergic inflammation by suppressing IgE production and airway hyperreactivity, but later studies found that IL-18 could also enhance the production of Th2 cytokines, underscoring the complex and context-dependent nature of this molecule in the pathogenesis of allergic asthma (10). Therefore, investigating IL-18 promoter polymorphisms may provide insights into its regulatory influence on disease susceptibility.

This study aimed to assess the relationship between asthma and IL-18 promoter polymorphisms -607 (rs1946518) C/A and -656 (rs1946519) G/T in a Turkish cohort.

MATERIAL AND METHODS

Study Design and Groups

This case-control study analyzed blood samples from asthma patients and healthy individuals. The independent variables in this study were the IL-18 gene promoter polymorphisms, while the dependent variable was asthma status. The study included 100 asthma patients and 101 healthy controls, all recruited from Balikesir University Faculty of Medicine, Department of Chest Diseases. Asthma patients were diagnosed based on the Global Initiative for Asthma (GINA) criteria. Individuals were excluded if they had any autoimmune disorder, chronic systemic disease (such as cardiovascular, hepatic, renal, or neurological conditions), malignancy, or a history of regular medication use unrelated to asthma. Additionally, patients who had experienced an asthma exacerbation within the past two months or were receiving oral corticosteroids or immunosuppressive therapy were not included. The control group consisted of age-matched individuals who presented to the outpatient clinic for routine check-ups. These individuals had no history of asthma or other chronic diseases, were not on regular medication, and had no known autoimmune, neurological, or malignant conditions. The power calculation was performed using G*3 Power version 3.1.9.7 (19). Based on previous studies examining associations between IL-18 promoter polymorphisms and inflammatory diseases, a moderate effect size (Cohen’s w = 0.3) was assumed for chi-square tests of independence. Using this estimate, with a significance level of $\alpha = 0.05$ and power $(1-\beta) = 0.80$, a minimum of 124 individuals (62 asthma patients and 62 controls) were required to detect significant differences in genotype distribution across two groups in a 2×3 comparison design. Given the analysis of two rare IL-18 promoter variants (-607 C/A and -656 G/T) and to ensure adequate statistical power, we included a total of 201 (101 asthma patients and 100 controls) participants (20-23).

DNA Extraction

Genomic DNA was isolated from peripheral blood samples using the PureLink Genomic DNA Mini Kit (Invitrogen, Cat. No. K182000, USA) according to the manufacturer’s instructions.

Polymerase Chain Reaction (PCR)

The -607 (rs1946518) A/C and -656 (rs1946519) G/T polymorphisms are located in the promoter region of the IL-18 gene (24, Figure 1).

To analyze these regions, specific primers were designed using RestrictionMapper (www.restrictionmapper.org), NCBI (www.ncbi.nlm.nih.gov), and Integrated DNA Technologies (www.idtdna.com). Primers for -607 region were 5'-GTCCTGAA...TTATAAAG-3' (Forward) and 5'-CTATTCCT...TGATAGCA-3' (Reverse). Primers for -656 region were 5'-CCGGCAAG...CTGTTGCAG-3' (Forward) and 5'-CTATTCCT...GACTGACC-3' (Reverse).

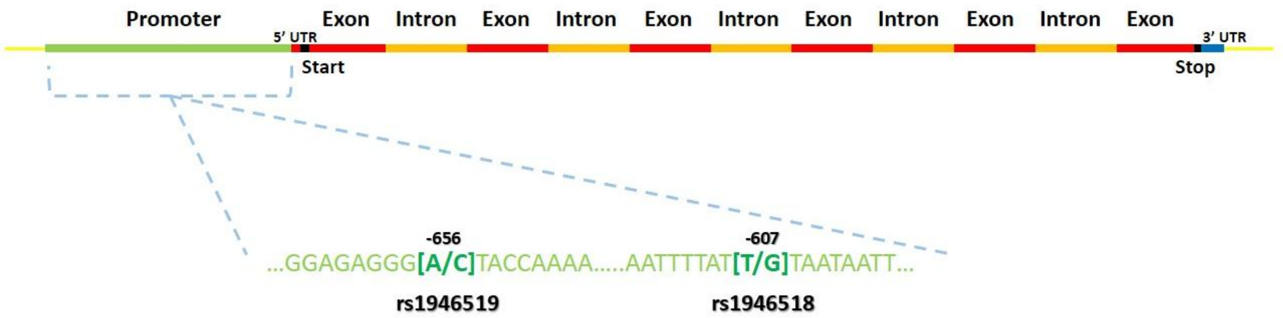

Figure 1. The location of the -607 (rs1946518) and -656 (rs1946519) polymorphisms in the IL-18 gene promoter region (24)

The PCR reaction mixture for the -607 region consisted of 32.5 µl sterile distilled water, 1 µl dNTP mix (Thermo Scientific, Cat. No. R0192, USA), 5 µl 10X reaction buffer (Thermo Scientific, Cat. No. B34, USA), 4 µl $MgCl_2$ (25 mM; Thermo Scientific, Cat. No. R0971, USA), 1 µl forward primer (100 pmol/µl), 1 µl reverse primer (100 pmol/µl), 5 µl template DNA (~100 ng), and 0.5 µl Taq DNA Polymerase (5 U/µl; Thermo Scientific, Cat. No. EP0402, USA). For the -656 region, the reaction mix included 33.7 µl sterile distilled water, 1 µl dNTP mix, 5 µl 10X reaction buffer, 3 µl $MgCl_2$ (25 mM), 1 µl forward primer (100 pmol/µl), 1 µl reverse primer (100 pmol/µl), 5 µl template DNA, and 0.3 µl Taq DNA Polymerase (5 U/µl). The PCR cycling protocol included an initial denaturation at 94 °C for 5 minutes, followed by 35 cycles of denaturation at 94 °C for 1 minute, annealing at 60.5 °C for the -607 region and 52.5 °C for the -656 region (1 minute each), and extension at 72 °C for 1 minute. A final extension step was performed at 72 °C for 10 minutes. PCR results were visualized using 1.5% agarose gel electrophoresis.

Restriction Fragment Length Polymorphism (RFLP)

PCR products were digested with restriction enzymes Tru1I (10 U/µl; Thermo Scientific, Cat. No. ER0981, USA) and MwoI (10 U/µl; Thermo Scientific, Cat. No. ER1731, USA). For the -607 C/A polymorphism, a 30 µl digestion reaction was prepared using 10 µl PCR product, 2 µl 10X Buffer R (Thermo Scientific, Cat. No. BR5, USA), 1 µl Tru1I (10 U/µl), and 18 µl nuclease-free water. Incubation occurred overnight at 65 °C, followed by inactivation at 80°C for 20 minutes. For the -656 G/T polymorphism, the 30 µl reaction mixture included 10 µl PCR product, 2 µl 10X FastDigest Green Buffer (Thermo Scientific, Cat. No. B72, USA), 1 µl MwoI FastDigest enzyme (10 U/µl), and 17 µl nuclease-free water. The digestion was carried out at 37 °C for 25 minutes, followed by enzyme inactivation at 65 °C for 5 minutes. The digestion products were separated on a 3% agarose gel stained with a suitable nucleic acid dye and visualized under UV light using a 100 bp DNA ladder (Thermo Scientific, Cat. No. 15628019, USA) as molecular size marker.

Statistical Analysis

All statistical analyses were performed using NCSS 2007 software (Kaysville, Utah, USA). Descriptive statistics were presented as mean±standard deviation for continuous variables, and as number and percentage for categorical variables. The normality of data distributions was assessed using the Shapiro-Wilk test, and the homogeneity of variances was evaluated with Levene's test. Comparisons of continuous variables between groups were conducted using the independent samples t-test. Categorical variables were compared using the Pearson chi-square or Fisher's exact test. Hardy-Weinberg equilibrium (HWE) was tested separately in patients and controls for both -607 C/A and -656 G/T polymorphisms. All statistical tests were two-tailed, and a p-value less than 0.05 was considered statistically significant.

Ethical Considerations

Approval was obtained from the Ethics Committee at Balıkesir University (no: 2017/139, date: 29.11.2017). The study adhered to the Declaration of Helsinki principles, with informed consent obtained from all participants.

RESULTS

Demographic and Clinical Data

Demographic and clinical characteristics of the groups were presented in Table 1. There were no statistically significant differences in age and gender distribution between asthma patients and controls (p=0.155 and p=0.622, respectively). Body mass index (BMI) was significantly higher in asthma patients (p<0.001). The smoking rate was significantly elevated in the patient group relative to controls (p<0.001). Regarding pulmonary function parameters, asthma patients showed significantly lower values for FEV_1 (p<0.001), FVC (p<0.001), and FEV_1/FVC ratio (p=0.007), consistent with impaired respiratory function.

Analysis of the -607 Promoter Region (rs1946518)

The -607 C/A polymorphism (rs1946518) in the IL-18 promoter region was genotyped using PCR-RFLP. The 303 bp PCR product was shown in Figure 2a. Following digestion with the Tru1I enzyme, the C allele yielded fragments of 199 bp, 75 bp, and 33 bp, while the A allele produced 101 bp, 98 bp, 75 bp, and 29 bp fragments (Figure 2b).

Table 1. Demographic distribution of the study group

	Control (n=101)	Asthma (n=100)	p
Age (years)	54.88±10.54	52.58±12.26	0.155
Gender, n (%)			
Male	50 (49.5)	53 (53.0)	0.622
Female	51 (50.5)	47 (47.0)	
BMI (kg/m^2)	25.31±4.21	31.22±6.66	**<0.001**
Smoking, n (%)	4 (4.0)	33 (33.0)	**<0.001**
FEV_1 (%)	91.16±10.45	79.27±21.76	**<0.001**
FVC (%)	91.00±12.32	84.05±18.57	**<0.001**
FEV_1/FVC	88.88±7.11	78.34±11.05	**0.007**

BMI: body mass index, FEV: forced expiratory volume, FVC: forced vital capacity, numerical data were presented as mean±standard deviation (minimum-maximum)

The genotype distribution of rs1946518 was consistent with HWE in the study group (χ^2=1.98, p=0.159). As shown in Table 2, the genotype frequencies in the asthma group were CC 49 (49.0%), CA 46 (46.0%), and AA 5 (5.0 %), while in the control group they were CC 64 (63.4%), CA 34 (33.7%), and AA 3 (2.9%). Although both the CA and AA genotypes were more frequent in asthma patients than in controls, neither difference reached statistical significance. For the CA genotype, the odds ratio (OR) compared to the CC genotype was 1.767 with a 95% confidence interval (CI) of 0.991-3.152 (p=0.540), while for the AA genotype it was 2.177 (95% CI: 0.496-9.553, p=0.303). These findings suggest that neither heterozygosity nor homozygosity for the A allele at the -607 position is significantly associated with asthma risk in this population (Table 2).

Analysis of the -656 Promoter Region (rs1946519)

The -656 G/T polymorphism (rs1946519) was analyzed using PCR-RFLP. The 125 bp PCR product is presented in Figure 3a. Following MwoI digestion, two fragments of 92 bp and 33 bp were obtained (Figure 3b).

The genotype distribution of rs1946519 was consistent with HWE in the study group (χ^2=2.46, p=0.117). As shown in Table 2, the genotype frequencies in patients were GG 49 (49.0%), GT 37 (37.0%), and TT 14 (14.0%). In controls, frequencies were GG 55 (54.5%), GT 41 (40.6%), and TT 5 (4.9%). Although the GT genotype showed no statistically significant difference between the asthma and control groups (OR=1.013, 95% CI: 0.563-1.824, p=0.966), the TT genotype was significantly more frequent in the asthma patients than in the control group. The OR for the TT genotype was 3.143 (95% CI: 1.055-9.360, p=0.040), indicating a potential association between this genotype and increased asthma susceptibility (Table 2).

Haplotype Analysis

A total of nine haplotypes were identified and assessed for their association with asthma. The most common haplotype in both groups was CC/GG, observed in 34.7% of controls and 24.0% of asthma patients. Although this haplotype was less frequent in the patient group, the difference did not reach statistical significance (p=0.097).

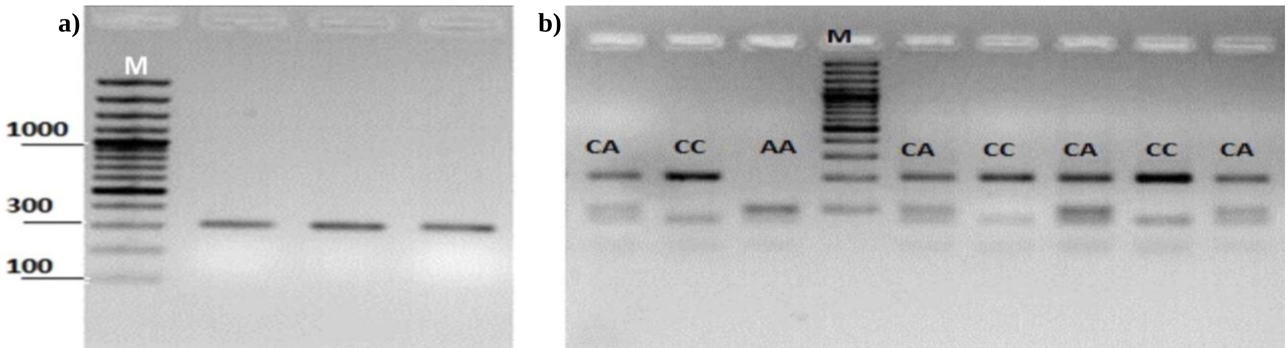

Figure 2. a) 1.5% agarose gel electrophoresis image of -607 promoter region PCR product, **b)** 3% agarose gel electrophoresis image of the -607 promoter gene region restriction with Tru1I enzyme (M: Marker, 100 bp marker)

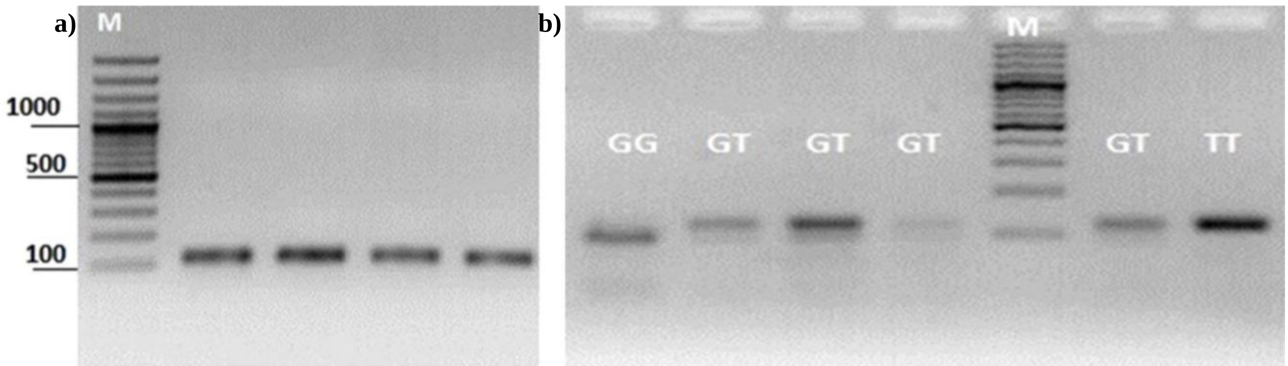

Figure 3. a) 1.5% agarose gel electrophoresis image of -656 promoter region PCR product, **b)** 3% agarose gel electrophoresis image of the -656 promoter region restricted fragments with MwoI enzyme (M: Marker, 100 bp marker)

Table 2. Distribution of IL-18 genotypes among the patients and healthy controls

Polymorphic site	Genotypes	Control (n=101)	Asthma (n=100)	OR (95% CI)	p
rs1946518 (-607)	CC	64 (63.4)	49 (49.0)	(Reference)	
	CA	34 (33.7)	46 (46.0)	1.767 (0.991-3.152)	0.540
	AA	3 (2.9)	5 (5.0)	2.177 (0.496-9.553)	0.303
rs1946519 (-656)	GG	55 (54.5)	49 (49.0)	(Reference)	
	GT	41 (40.6)	37 (37.0)	1.013 (0.563-1.824)	0.966
	TT	5 (4.9)	14 (14.0)	3.143 (1.055-9.360)	**0.040**

IL-18: interleukin-18, OR: odds ratio, CI: confidence interval

Other haplotypes also showed no statistically significant differences between groups, included CC/GT (24.8% vs. 17.0%, p=0.176), CC/TT (4.0% vs. 8.0%, p=0.227), CA/GG (16.8% vs. 23.0%, p=0.273), CA/GT (15.8% vs. 19.0%, p=0.555), and CA/TT (1.0% vs. 4.0%, p=0.212) in controls and in patients, respectively. Rare haplotypes such as AA/GG, AA/GT, and AA/TT were observed infrequently in both groups and also showed no significant differences.

DISCUSSION

Asthma is a complex inflammatory airway disease influenced by genetic predisposition and environmental exposures. IL-18, a pro-inflammatory cytokine, plays a role in asthma pathogenesis, with a specific focus on promoter region polymorphisms. This study explored the -607 C/A and -656 G/T IL-18 promoter polymorphisms and their link to asthma in a Turkish cohort.

Numerous diseases have been associated with IL-18 gene promoter polymorphisms.

Zhou et al. (25) identified significant associations between sarcoidosis and the -607 C/A and -656 G/T polymorphisms. The -607C/-656G haplotype exhibited greater promoter activity than the -607A/-656T haplotype, though no clinical phenotype differences were observed. Abdolahi et al. (26) linked the IL-18 -656 TT genotype to an increased risk of thyroid cancer in a study of 105 patients and 148 controls. Nielsen et al. (27) found that the -607 C/A polymorphism raised Type 1 diabetes susceptibility in Asians but not Europeans. Fouad et al. (28) associated the -607 CC genotype with lupus nephritis, arthritis, and immunological disorders. Conversely, Song et al. (29) reported no link between the -607 C allele and rheumatoid arthritis. Moravej et al. (30) suggested that the T allele at the -656 position confers resistance to visceral leishmaniasis.

IL-18 also plays a significant role in asthma. Kaur et al. (31) investigated the relationship between IL-18, IL-18BP, and IL-18Rα expression and bronchial epithelial function in asthma. They reported that IL-18 and IL-18BP levels were reduced in the bronchial epithelium of asthma patients, while IL-18 was released in sputum with elevated IL-18BP. It was suggested that IL-18 enhanced metabolic activity, wound repair, and cellular differentiation in bronchial epithelial cells, suggesting a potential role in airway epithelial activation in asthma. Wang et al. (32) showed that IL-18 and IL-18Rα expression were increased in Th2 and Th17 cells of allergic asthma patients. House dust mites further amplified these expressions, with similar patterns observed in an ovalbumin-induced asthma model. Their results suggest that targeting IL-18 and IL-18Rα in Th2 cells could be a potential therapeutic approach for asthma. Additionally, Watanabe et al. (33) reported that lower baseline IL-18 levels were associated with poorer treatment response, and the cut-off value was 230.5 pg/mL for IL-18 effectively discriminated non-responders to dupilumab treatment.

Our results reveal a significant decrease in the -607 CC genotype frequency among asthma patients compared to healthy controls, suggesting a potential protective effect. Similarly, Harada et al. (34) identified a functional polymorphism in the IL-18 gene (rs5744247) associated with increased asthma severity in a Japanese population. Although the specific variants differ, both studies support a link between IL-18 promoter region polymorphisms and asthma pathogenesis. Unlike our finding where a particular genotype appears protective, Harada et al. (34) reported a variant (rs5744247 G allele) that was associated with increased IL-18 expression and greater disease severity, indicating that elevated IL-18 activity may contribute to worsened asthma outcomes. Although rs5744247 is distinct from the -607 C/A polymorphism analyzed in our study, both variants are located in the promoter region and are thought to influence IL-18 gene expression. Therefore, the observed association with disease severity in Harada et al. (34) supports the biological relevance of IL-18 transcriptional regulation in asthma.

Our study revealed that the -656 TT genotype was more prevalent in asthma patients, indicating an increased susceptibility. Huang et al. (35) reported that homozygous polymorphism in rs1946519 is associated with an increased risk of chronic obstructive pulmonary disease (COPD). Although their study focused on COPD, the observation that a homozygous variant was linked to increased disease risk is consistent with our finding that the -656 TT genotype is associated with asthma susceptibility, reinforcing the pathogenic significance of IL-18 gene variants across airway inflammatory diseases.

Although haplotype differences were not statistically significant, the reduced frequency of the CC/GG combination in patients suggests a potential protective trend. While this specific haplotype has not been extensively studied in asthma, our preliminary finding merits further investigation in larger cohorts.

Previous studies have connected IL-18 promoter polymorphisms to various inflammatory conditions. For example, -607C/A and -137G/C polymorphisms have been associated with allergic rhinitis in asthma, illustrating distinct impacts on disease pathogenesis (16). Additionally, IL-18 promoter polymorphisms influence COPD susceptibility and severity, emphasizing IL-18's broader relevance in respiratory diseases (36).

Our study demonstrates a significant association between IL-18 promoter polymorphisms and asthma susceptibility. Specifically, the -607 CC genotype appears to exert a protective effect, while the -656 TT genotype is associated with an increased risk of asthma. These findings are in line with those reported by Chen et al. (37), who observed that the TT genotype at the IL-18 rs360715 locus was correlated with elevated serum IL-18 levels in asthma patients, suggesting that this variant may contribute to disease severity through increased cytokine expression. Although our study and that of Chen et al. (37) investigated different polymorphic loci (-607 C/A and -656 G/T vs. rs360715), both support the idea that IL-18 genetic variations can influence asthma pathogenesis by modulating IL-18 expression levels. In our study, the lower frequency of the -607 CC genotype in asthma patients may indicate a protective role, whereas Chen et al. (37) associated the rs360715 TT genotype with higher IL-18 levels and more severe clinical features.

Furthermore, while our research focused on promoter polymorphisms, Chen et al. (37) evaluated multiple IL-18 variants and reported associations between certain genotypes and altered oxygen and carbon dioxide levels in patients. This suggests a broader impact of IL-18 polymorphisms not only on immune dysregulation but also on pulmonary function. Together, these findings underscore the potential of IL-18 as a genetic marker for asthma susceptibility and severity, warranting further investigation into its mechanistic role in disease progression.

The protective role observed for the -607 CC genotype may reflect its potential impact on IL-18 gene transcription. Reduced promoter activity associated with this genotype could lead to lower IL-18 expression, thereby limiting downstream inflammatory responses relevant to asthma pathogenesis. In contrast, the -656 TT genotype might be associated with higher promoter activity and increased IL-18 production, which could enhance Th2-skewed immune responses and airway inflammation. This functional distinction between the genotypes may help explain their opposing associations with asthma susceptibility observed in our study.

This study has several limitations. First, all participants were recruited from a single geographic region and shared a relatively homogeneous ethnic background, which may limit the generalizability of the findings. Second, although genotypic associations were identified, no functional analyses were performed to determine the effects of these polymorphisms on IL-18 gene expression or cytokine levels. Additional investigation in other populations and functional assays is necessary to clarify the biological significance of these polymorphisms.

To our knowledge, this is one of the first studies to examine the relationship between IL-18 promoter polymorphisms and asthma susceptibility in the Turkish population. Although some such polymorphisms have been investigated in other ethnic groups in previous studies, and our findings have provided new population-based information, for the especially rare polymorphism -656 G/T, there is little data available for asthma in other ethnic groups, and the variant has been less frequently studied. These findings add to existing literature that suggests ethnic- and genetic-specific effects on the risk of asthma.

CONCLUSION

The results of the present study showed that IL-18 promoter gene polymorphisms, particularly -607 CC and -656 TT genotypes, are associated with susceptibility to asthma in the Turkish population. Our findings indicate that IL-18 may be a potential genetic marker for classifying individuals with high and low risk for asthma. The modulation of IL-18 pathways may be useful for personalized prevention strategies and therapeutic interventions for asthma. These findings warrant further investigation, including functional studies, to clarify the role of IL-18 promoter variants in asthma onset and progression.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Balıkesir University (29.11.2017, 139).

Conflict of Interest: This manuscript was derived from the master's thesis of the first author, Nil Ocak Yılmaz, and all authors declare that there is no conflict of interest.

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REFERENCES

1. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med. 1989;320(5):271-7.
2. Li Y, Hua S. Mechanisms of pathogenesis in allergic asthma: role of interleukin-23. Respirology. 2014;19(5):663-9.
3. Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science. 1994;264(5166):1733-9.
4. Mukherjee AB, Zhang Z. Allergic asthma: influence of genetic and environmental factors. J Biol Chem. 2011;286(38):32883-9.
5. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: A roadmap to asthma control. Eur Respir J. 2015;46(3):622-39.
6. Bochner BS, Undem BJ, Lichtenstein LM. Immunological aspects of allergic asthma. Annu Rev Immunol. 1994;12:295-335.
7. Kaufman G. Asthma: pathophysiology, diagnosis and management. Nurs Stand. 2011;26(5):48-56; quiz 58.
8. Chini L, Monteferrario E, Graziani S, Moschese V. Novel treatments of asthma and allergic diseases. Paediatr Respir Rev. 2014;15(4):355-62.
9. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. J Allergy Clin Immunol. 2015;135(2):299-310.
10. Akira S. The role of IL-18 in innate immunity. Curr Opin Immunol. 2000;12(1):59-63.
11. Volin MV, Koch AE. Interleukin-18: A mediator of inflammation and angiogenesis in rheumatoid arthritis. J Interferon Cytokine Res. 2011;31(10):745-51.
12. Nolan KF, Greaves DR, Waldmann H. The human interleukin 18 gene IL18 maps to 11q22.2-q22.3, closely linked to the DRD2 gene locus and distinct from mapped IDDM loci. Genomics. 1998;51(1):161-3.
13. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm. 2014;2014:561459.

14. Kretowski A, Mironczuk K, Karpinska A, Bojaryn U, Kinalski M, Puchalski Z, et al. Interleukin-18 promoter polymorphisms in type 1 diabetes. Diabetes. 2002;51(11):3347-9.
15. Cai LP, Zhou LJ, Lu SY, Liang YE, Chen XY, Liu L, et al. Association of IL-18 promoter gene polymorphisms with rheumatoid arthritis: A meta-analysis. Mol Biol Rep. 2014;41(12):8211-7.
16. Wu SQ, Liang W, Wang GL, Li LY, Wang DL, Chen C. Polymorphisms of the IL-18 promoter and bronchial asthma. Mol Med Rep. 2012;6(6):1385-8.
17. Pawlik A, Kaminski M, Kusnierczyk P, Kurzawski M, Dziedziejko V, Adamska M, et al. Interleukin-18 promoter polymorphism in patients with atopic asthma. Tissue Antigens. 2007;70(4):314-8.
18. Sanders NL, Mishra A. Role of interleukin-18 in the pathophysiology of allergic diseases. Cytokine Growth Factor Rev. 2016;32:31-9.
19. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Res Methods. 2009;41(4):1149-60.
20. Rezaieyazdi Z, Delavar P, Rafatpanah H, Ganjali R, Sahebari M, Tabaei S, et al. Interleukin 18 (-137G/C, -607C/A) polymorphisms as genetic biomarkers of susceptibility to systematic lupus erythematosus. Curr Rheumatol Rev. 2024;[Epub ahead of print]. doi: 10.2174/0115733971304493240801094652.
21. Said EM, Soliman MS, Shousha HI, Rashed MS, Elazm AA, Aamer RZ, et al. Interleukin-18 and its gene single nucleotide polymorphisms (SNPs) influence chronic hepatitis C progression. J Infect Dev Ctries. 2018;12(4):257-64.
22. Tavares NA, Santos MM, Moura R, Araújo J, Guimarães R, Crovella S, et al. Interleukin 18 (IL18) gene promoter polymorphisms are associated with type 1 diabetes mellitus in Brazilian patients. Cytokine. 2013;62(2):286-9.
23. Zhou Y, Yamaguchi E, Hizawa N, Nishimura M. Roles of functional polymorphisms in the interleukin-18 gene promoter in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(2):105-13.
24. Chen CC, Tzeng HE, Kuo CC, Lim SNS, Hsu PC, Hsu YN, et al. Significant contribution of interleukin-18 genotypes to childhood acute lymphocytic leukemia risk in Taiwanese. Anticancer Res. 2022;42(11):5283-90.
25. Zhou Y, Yamaguchi E, Hizawa N, Nishimura M. Roles of functional polymorphisms in the interleukin-18 gene promoter in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(2):105-13.
26. Abdolahi F, Dabbaghmanesh MH, Haghshenas MR, Ghaderi A, Erfani N. A gene-disease association study of IL18 in thyroid cancer: Genotype and haplotype analyses. Endocrine. 2015;50(3):698-707.
27. Nielsen C, Hansen D, Husby S, Jacobsen BB, Lillevang ST. Association of a putative regulatory polymorphism in the PD-1 gene with susceptibility to type 1 diabetes. Tissue Antigens. 2003;62(6):492-7.
28. Fouad NA, Baraka EA, Hassan WA. Interleukin-18 gene polymorphisms in systemic lupus erythematosus: Relation to disease status. Egypt J Immunol. 2014;21(1):1-12.
29. Song GG, Bae SC, Kim JH, Lee YH. Interleukin-4, interleukin-4 receptor, and interleukin-18 polymorphisms and rheumatoid arthritis: A meta-analysis. Immunol Invest. 2013;42(6):455-69.
30. Moravej A, Rasouli M, Asaei S, Kalani M, Mansoori Y. Association of interleukin-18 gene variants with susceptibility to visceral leishmaniasis in Iranian population. Mol Biol Rep. 2013;40(6):4009-14.
31. Kaur D, Chachi L, Gomez E, Sylvius N, Brightling CE. Interleukin-18, IL-18 binding protein and IL-18 receptor expression in asthma: a hypothesis showing IL-18 promotes epithelial cell differentiation. Clin Transl Immunology. 2021;10(6):e1301.
32. Wang J, Zhan M, Zhai Y, Wang S, Gu F, Zhao Z, et al. Allergens induce upregulated IL-18 and IL-18Rα expression in blood Th2 and Th17 cells of patients with allergic asthma. Clin Exp Immunol. 2024;217(1):31-44.
33. Watanabe S, Suzukawa M, Tashimo H, Ohshima N, Asari I, Takada K, et al. Low serum IL-18 levels may predict the effectiveness of dupilumab in severe asthma. Intern Med. 2024;63(2):179-87.
34. Harada M, Obara K, Hirota T, Yoshimoto T, Hitomi Y, Sakashita M, et al. A functional polymorphism in IL-18 is associated with severity of bronchial asthma. Am J Respir Crit Care Med. 2009;180(11):1048-55.
35. Huang C, Mei L, Wang A, Zhang X. IL-18 gene polymorphisms were associated with risk of chronic obstructive pulmonary disease in a Chinese Han population. Oncotarget. 2017;9(Suppl 1):109-16.
36. Wang J, Liu X, Xie J, Xu Y. Association of interleukin-18 promoter polymorphisms with chronic obstructive pulmonary disease in male smokers. Int J Immunogenet. 2013;40(3):204-8.
37. Chen LX, Xu CM, Gao F, Zhu MF, Xu MJ, Zhang JR, et al. Associations of IL-18 and IL-9 expressions and gene polymorphisms with asthma. Eur Rev Med Pharmacol Sci. 2020;24(12):6931-8.