Ağrı Medical Journal

Research Article/ Araştırma Makalesi

DOI: 10.61845/agrimedical.1619321

Investigation of HIF1A gene polymorphisms in patients with allergic rhinitis

Alerjik rinitli hastalarda HIF1A geni polimorfizmlerinin araştırılması

Bünyamin Yaşar[1], Hüseyin Günizi[2], Durkadın Demir Ekşi[1,3]*

ABSTRACT

Aim: Allergic rhinitis (AR) is a chronic inflammatory disease caused by IgE-mediated hypersensitivity to environmental allergens. In Türkiye, AR prevalence ranges between 11.8% and 36.4%. The Hypoxia Inducible Factor 1 Subunit Alpha (HIF1A) gene plays a significant role in hypoxia and inflammation-related pathways, and its polymorphisms have been associated with various inflammatory diseases. The association of C1772T and C111A polymorphisms in the HIF1A gene with AR was aimed to be investigated in this study.

Materials and Methods: The study included 100 AR patients and 100 healthy controls. Single Nucleotide Polymorphism (SNP) analyses were performed using PCR-RFLP and validated by Sanger sequencing. Serum total IgE levels were measured, and patients were classified based on disease severity and duration. Genotype findings were compared with patients' clinical features.

Results: The C111A SNP was non-polymorphic in both groups, as all individuals had the wild-type CC genotype. The C1772T SNP showed no significant differences in genotype or allele frequencies between patients and controls. Similarly, no significant associations were observed in patient subgroups stratified by disease severity, frequency, or serum IgE levels.

Conclusion: This study demonstrated that these two polymorphisms in the HIF1A gene are not associated with AR development in the studied cases. However, the literature indicates that HIF1A mRNA and protein levels affect AR. Results may vary due to genetic and environmental factors. Further studies investigating alternative polymorphisms in the HIF1A gene and its expression levels are needed to better understand the relationship between AR and HIF1A.

Keywords: Allergic Rhinitis, Hypoxia Inducible Factor 1 Subunit Alpha, HIF1A, Single Nucleotide Polymorphism

ÖZ

Amaç: Alerjik rinit (AR), çevresel alerjenlere karşı IgE aracılı aşırı duyarlılık nedeniyle gelişen kronik inflamatuar bir hastalıktır. Türkiye'de AR prevalansı %11,8 ile %36,4 arasında değişmektedir. Hipoksi ile İndüklenebilir 1-Alfa (HIF1A) geni, hipoksi ve inflamasyonla ilişkili biyolojik yolaklarda önemli rol oynar ve bu genin polimorfizmleri, çeşitli inflamatuar hastalıklarla ilişkilendirilmiştir. Bu çalışmada, HIF1A genindeki C1772T ve C111A polimorfizmlerinin AR ile ilişkisinin araştırılması amaçlanmıştır.

Materyal ve Method: Çalışmaya 100 AR hastası ve 100 sağlıklı kontrol dahil edilmiştir. Tek Nükleotid Polimorfizmi (SNP) analizleri, PCR-RFLP kullanılarak yapılmış ve Sanger dizileme ile doğrulanmıştır. Serum total IgE seviyeleri ölçülmüş ve hastalar, hastalık şiddeti ve süresine göre sınıflandırılmıştır. Genotip bulguları, hastaların klinik özellikleriyle karşılaştırılmıştır.

Bulgular: C111A polimorfizmi, hasta ve kontrol gruplarında homozigot yabanıl tip (CC) olarak bulunmuştur. C1772T polimorfizmi ise genotip ve alel frekansı açısından hasta ve kontrol gruplarında anlamlı fark göstermemiştir. Alt grup analizlerinde de fark bulunmamıştır.

Sonuç: Bu çalışma, HIF1A genindeki bu iki polimorfizmin incelenen olgularda AR gelişimiyle ilişkili olmadığını göstermiştir. Ancak literatürde HIF1A mRNA ve protein seviyelerinin AR üzerindeki etkileri gösterilmiştir. Genetik ve çevresel faktörler nedeniyle sonuçların popülasyonlar arasında farklılık gösterebileceği bilinmektedir. HIF1A genindeki alternatif polimorfizmler ve ekspresyon seviyelerinin incelenmesi ile AR ve HIF1A ilişkisinin daha iyi anlaşılabileceği sonucuna varılmıştır.

Anahtar Kelimeler: Alerjik Rinit, Hipoksi ile İndüklenebilir 1-Alfa, HIF1A, Tek Nükleotid Polimorfizmi

1.Alanya Alaaddin Keykubat University, Graduate School of Education, Department of Molecular Medicine

2.Antalya City Hospital, Department of Otolaryngology

3.Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Medical Biology

Gönderilme Tarihi: 13/01/2025
Kabul Tarihi: 31/01/2025
Yayınlanma Tarihi: 01/02/2025

*Sorumlu Yazar
Durkadın Demir Ekşi,
Department of Medical Biology, School of Medicine, Alanya Alaaddin Keykubat University, Antalya 07425, Türkiye,
durkadin.eksi@alanya.edu.tr
ORCID: 0000-0002-5887-3141

Cite this article: Yaşar B, Günizi H, Ekşi DD. Investigation of HIF1A gene polymorphisms in patients with allergic rhinitis. Ağrı Med J. 2025; 3(1): 13-18.

Introduction

Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa caused by immunoglobulin E (IgE)-mediated responses to environmental allergens such as pollen, mold, animal dander, and dust mites. These allergens trigger the release of histamines and activate inflammatory cells such as eosinophils and macrophages, resulting in hallmark symptoms like nasal congestion, sneezing, itching, and watery eyes, which significantly impact patients' daily lives (1, 2). AR is one of the most common allergic diseases worldwide, affecting 15% of people (1). Adolescents aged 13-14 years with AR showed a prevalence of 15.2% across 25 countries, while children aged 6-7 years with AR had a prevalence of 11.1% across 16 countries (3). In Türkiye, AR prevalence differs by gender and region. Women exhibit a higher prevalence rate of 31.4% compared to men at 28.0%. Regionally, AR is least common in Southeastern Anatolia (21.0%) and most prevalent in the Marmara region (36.1%) (4). AR manifests in two primary forms: seasonal and perennial. Seasonal AR is commonly associated with allergens like pollen and grasses, while perennial AR stems from continuous exposure to allergens such as house dust mites, mold, and occupational irritants (5). AR is classified into two categories based on duration: intermittent and persistent. In intermittent AR, the impact of symptoms on daily life is limited to fewer than 4 days per week or less than 4 consecutive weeks. In contrast, in persistent AR, symptoms persist for more than 4 days per week or exceed 4 consecutive weeks (1).

Hypoxia-inducible factor 1-alpha (*HIF1A*) is a transcription factor that plays a pivotal role in cellular responses to hypoxia. This protein regulates key biological processes like angiogenesis and cell survival under low oxygen conditions (6). Emerging evidence suggests *HIF1A* involvement in AR and sinusitis development. For instance, studies demonstrate that *HIF1A* activation in nasal epithelial cells upon allergen exposure modulates the expression of vascular endothelial growth factor (VEGF) and other inflammatory mediators, elucidating its role in nasal airway inflammation (7). Wang et al. investigated the therapeutic effects of the *HIF1A* antagonist YC-1 in ovalbumin-induced allergic rat models. YC-1 administration significantly downregulated key inflammatory regulators, including nuclear factor kappa B (NF-κB), p65, and peroxisome proliferator-activated receptor gamma (PPARα) (8). AR is a complex disease influenced by genetic and environmental factors. Genetic factors are estimated to contribute 70-90% to AR's etiology, supported by single nucleotide polymorphism (SNP) analyses and familial studies (9). However, challenges such as small sample sizes and comorbid conditions like asthma and atopic dermatitis have limited the replicability of genetic findings (10). Despite existing studies on *HIF1A* gene polymorphisms and their potential link to AR (11), further research is necessary to elucidate these associations. The current study aims to contribute to a deeper understanding of AR pathogenesis and to the development of novel diagnostic and therapeutic strategies.

Material and Methods

Study Population

This study included 100 adult patients diagnosed with AR and 100 healthy individuals as the control group. The participants were recruited from the Alanya Alaaddin Keykubat University Education and Research Hospital's otolaryngology clinic. AR patients with a history of malignancy, pregnancy, steroid use for any medical condition, obesity, diabetes, or metabolic syndrome were excluded from the study. The control group consisted of healthy participants with no prior treatment for AR or history of malignancy treatment. Ethical approval was obtained from the Alanya Alaaddin Keykubat University Clinical Research Ethics Committee (Approval No: 11-03, dated 23.06.2021). Informed consent was obtained from all participants.

Clinical Examination

Patients with AR underwent clinical examination and biochemical tests. Serum total IgE levels were measured, with 150 IU/ml taken as the threshold. Patients were classified based on AR severity (mild, moderate, and severe) and the duration of symptoms (intermittent or persistent AR).

Sample Collection and Genomic DNA Extraction

Two milliliters of peripheral blood samples were collected from all individuals in K_3EDTA tubes and stored at +4°C until DNA extraction. Genomic DNA was extracted using the Roche High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH, Germany) according to the manufacturer's protocol. The quantity and purity of the isolated DNA samples were determined using the BioTek Synergy™ H1 multimode microplate reader (BioTek Instruments, Inc., Winooski, USA) and a Take3 plate through spectrophotometric measurement.

Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR-RFLP) Analysis

PCR amplification targeted two specific regions of the *HIF1A* gene (NM_001530.4), encompassing the C1772T (rs11549465) and C111A (rs779897997) polymorphisms. The forward and reverse oligonucleotide primers used for the PCR were as follows, respectively: Forward primer; 5′-AAGGTGTGGCCATTGTAAAAACTC-3′, reverse primer; 5′- GCACTAGTAGTTTCTTTATGTATG-3′ (Tm: 59oC), forward primer; 5′-GGATAAGTTCTGAACGTCGA-3′, reverse primer; 5′-ATCCAGAAGTTTCCTCACAC-3′ (Tm: 55oC). Reaction conditions included initial denaturation at 95°C for 4 minutes, followed by 35 cycles of denaturation, annealing, and extension, and a final extension step at 72°C for 7 minutes. RFLP was employed to genotype the amplified DNA fragments. The HphI restriction enzyme (New England Biolabs, UK) was used for the genotyping of the C1772T polymorphism, the BglII restriction enzyme (New England Biolabs, UK) was used for the genotyping of the C111A polymorphism according to the manufacturer's instructions. Digested products were electrophoresed on 2% agarose gel for 45 minutes at 110 volts. At the end of the process, the digested samples were visualized using a Syngene G:Box Chemi XRQ imaging system (Syngene, UK). Based on the band patterns, individuals were identified as having homozygous wild type, heterozygous, or homozygous variant genotypes.

Sanger Sequencing

Ten patients or healthy controls with different genotypes were randomly selected. To validate the RFLP findings, DNA samples from these individuals were analyzed using Sanger-based DNA sequencing. The electropherograms were analyzed using the NCBI Blast tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Statistical Analysis

Data were analyzed using chi-square tests (or Fisher's exact tests for categorical variables) and t-tests or Mann-Whitney tests for continuous variables. Allelic and genotypic distributions were compared between groups using 2x2 contingency tables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Hardy-Weinberg equilibrium was assessed using an online calculator (https://www.cog-genomics.org/software/stats), and other analyses were performed using GraphPad Prism 7 software (GraphPad Software, San Diego, CA, USA). Statistical significance was determined with a p-value of 0.05.

Results

The study included 100 patients with AR and 100 healthy controls. The demographic data of the patient and control groups, including gender and age, are shown in Table 1.

Table 1. Demographic Data of Patient and Control Groups

	AR Patients	Controls
n	100	100
Male (%) / Female (%)	41 (41%) / 59 (59%)	27 (27%) / 73 (73%)
Mean age ± Standard deviation	38.45 ± 13.24	30.99 ± 11.96

Clinical Findings

Total IgE levels ranged from 8.0 to 902.0 UI/ml, with a mean value of 171.1 ± 172.5 UI/ml. The clinical characteristics of the patients with AR, including the duration of AR diagnosis, severity of AR, and classification of AR based on symptom duration (intermittent or persistent), are provided in Table 2.

Table 2. Clinical Characteristics of AR Patients

Mean Duration of Diagnosis (months) (min-max)		28 (18-60)
Disease Severity	Mild	70
	Moderate	19
	Severe	11
Symptom Duration	Intermittent	84
	Persistent	16

Molecular Genetic Findings

Genomic DNA samples from patients and controls were analyzed for SNPs rs11549465 (C1772T) and rs779897997 (C111A) in the *HIF1A* gene's exon 12 and exon 2, respectively.

DNA fragments of 347 bp and 187 bp for the two target regions were obtained through PCR, respectively. The gel images of PCR products digested with the respective restriction enzymes were analyzed. Through these images, homozygous wild-type, heterozygous variant, and homozygous variant genotypes were determined (Figure 1). DNA samples representing all genotypes confirmed the presence of the expected polymorphisms by Sanger sequencing. The corresponding electropherograms are presented in Figure 2.

The genotyping for C1772T SNP was performed using the HphI restriction enzyme, and its results showed that both patients and controls predominantly had the wild-type genotype (CC) at 68%, while heterozygous (CT) and homozygous mutant (TT) genotypes were observed at 27% and 5% among patients and at 29% and 3% among controls, respectively. These results indicated no statistically significant difference in genotype or allele frequencies between patients and controls ($p > 0.05$) (Table 3). For the C111A SNP, all individuals, both patients and controls, were found to have the wild-type CC genotype. As a result, no further statistical analysis was performed for this SNP (Table 3).

The minor allele frequency (T) for C1772T was determined to be 0.185 in patients and 0.175 in controls. For this SNP, the p-value for deviation from Hardy-Weinberg equilibrium was calculated as 0.316698 in patients, while no deviation from Hardy-Weinberg equilibrium was observed in the control group (p=1) (Table 4).

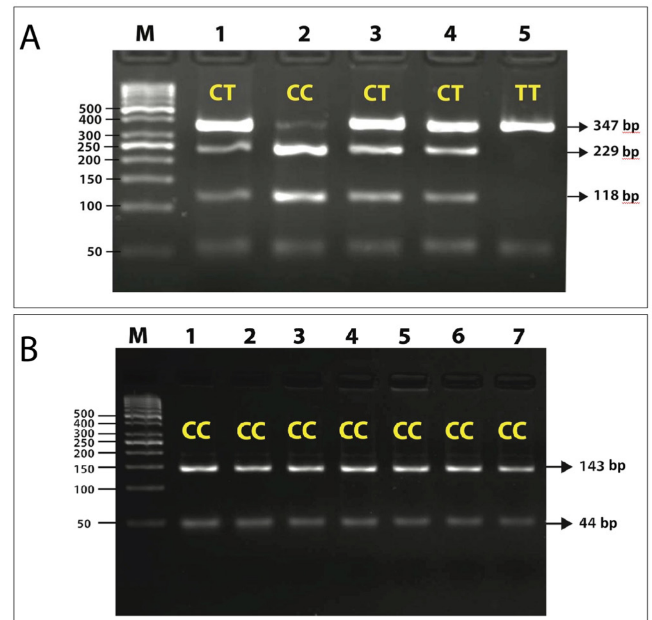

Figure 1. Gel electrophoresis image of enzyme digestion of PCR amplicons. (A) HphI enzyme digestion of the SNP C1772T (rs11549465) PCR amplicon (347 bp) produced 347 bp, 229 bp, and 118 bp fragments for the heterozygous genotype (CT), 229 bp and 118 bp fragments for the homozygous C allele (CC), and a single 347 bp fragment for the homozygous T allele (TT). (B) BglII enzyme digestion of the SNP C111A (rs779897997) PCR amplicon (187 bp) generated 143 bp and 44 bp fragments for the homozygous C allele (CC), no heterozygous (CA) or homozygous A allele (AA) genotypes observed. M: Marker; 1-5: Case numbers (Panel A); 1-7: Case numbers (Panel B); bp: Base pair.

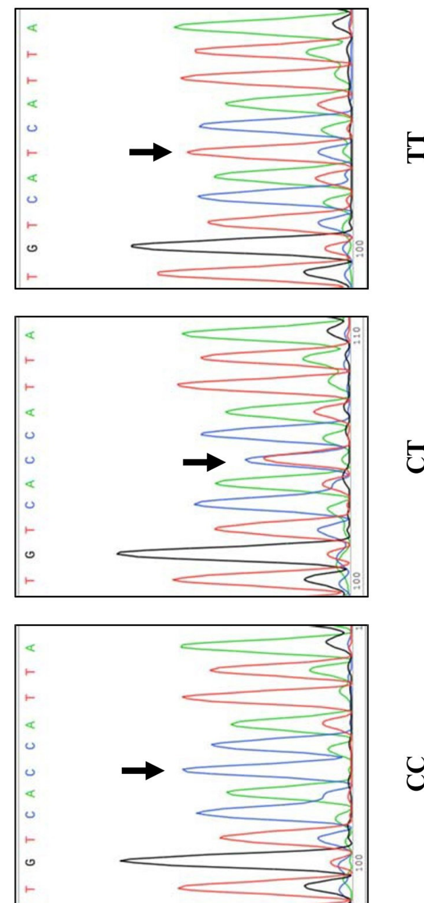

Figure 2. Sanger sequencing electropherograms. (A) Electropherograms displaying the SNP C1772T (rs11549465) genotypes: CC, CT, and TT. (B) Electropherogram showing the SNP C111A (rs779897997) genotype: CC. Black arrows indicate the position of the SNPs.

Table 3. *HIF1A* SNP Genotypes and Allele Frequencies in Patient and Control Groups

SNP		n (%) Patients	n (%) Control	OR** (95% CI)	p*
C1772T	Genotype	n= 100	n= 100		
	CC	68 (68%)	68 (68%)	Ref	Ref
	CT	27 (27%)	29 (29%)	1.074 (0.5849 – 1.986)	0.8745
	TT	5 (5%)	3 (3%)	0.6000 (0.1545 – 2.406)	0.7189
	CT+TT	32 (32%)	32 (32%)	1.000 (0,5475 – 1.826)	>0.9999
	Allele	n=200	n=200		
	C	163 (81.5%)	165 (82.5%)	Ref	Ref
	T	37 (18.5%)	35 (17.5%)	0.9345 (0.5568 – 1.560)	0.8965
C111A	Genotype				
	CC	100	100		
	CA	0	0	-	-
	AA	0	0	-	-
	Allele	n=200	n=200		
	C	200	200		
	A	0	0	-	-

*Fisher's chi-square analysis.**OR, Odds ratio; CI, confidence interval; Ref, reference; -, not calculated. Genotype comparisons between patient and control groups were calculated as CC vs. CT, CC vs. TT, and CC vs. CT+TT using a 2x2 contingency table, while allele comparisons were calculated as C vs. T using a 2x2 contingency table.

Table 4. Rare Allele Frequency and Deviation from Hardy-Weinberg Equilibrium in Patient and Control Groups

SNP	Position	Rare Allele Frequency		p* (HWE)	
			Control	Patient	Control
C1772T	Exon 12	0.185	0.175	0.316698	1
C111A	Exon 2	0	0	-	-

*The p-value for deviation from Hardy-Weinberg equilibrium in patients and controls

-, not calculated

No statistically significant differences in C1772T genotypes were observed among the patient subgroups stratified by disease frequency (intermittent/persistent), disease severity (mild/moderate + severe), or serum total IgE levels (≥151 IU/mL vs. ≤150 IU/mL) (p > 0.05) (Table 5).

Discussion

AR is a chronic inflammatory disease of the respiratory system caused by hypersensitivity to environmental allergens. It affects over 500 million individuals globally, significantly reducing quality of life and imposing economic burdens (12). These statistics indicate that AR is not only a medical challenge but also a public health concern that requires urgent attention. The disease is exacerbated in agricultural regions with pollen exposure like Alanya, Türkiye particularly in areas with significant industrialization and rapid population growth. The etiology of AR is multifactorial, involving a complex interplay between genetic and environmental factors. Studies on genetic predisposition have highlighted the potential role of SNPs in influencing AR susceptibility. SNPs can alter gene expression and protein function, thereby affecting immune responses (13). For example, studies in monozygotic twins have demonstrated a concordance rate of 45%-60% for AR, compared to only 25% in dizygotic twins, suggesting a strong genetic component (13). Similarly, having a first-degree relative with AR or related atopic diseases significantly increases the risk of developing AR (9). However, despite these findings, genetic studies in AR remain limited, particularly in the Turkish population.

Table 5. Genotypic Distribution and Comparison of *HIF1A* C1772T Polymorphism Based on Patient Clinical Characteristics

		CC (n)	CT+TT (n)	OR** (95% CI)	p*
Symptom Duration	Intermittent	58	26	1.338 (0.4211 – 3.955)	0.7706
	Persistent	10	6		
Disease Severity	Mild	46	24	0.6970 (0.2699 – 1.837)	0.4932
	Moderate + Severe	22	8		
IgE levels(UI/ml)	151 and above	25	15	0.6589 (0.2792 – 1.570)	0.3850
	150 and below	43	17		

*Fisher's chi-square analysis. **OR, Odds ratio; CI, confidence interval. Genotype comparisons between groups were calculated as CC vs. CT+TT using a 2x2 contingency table.

Our study focused on the relationship between the C1772T and C111A polymorphisms in the *HIF1A* gene and AR. The *HIF1A* gene encodes a transcription factor that plays a critical role in cellular adaptation to hypoxic conditions. *HIF1A* has been implicated in various inflammatory and respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), and bronchitis (14, 15). Hypoxia is a hallmark of numerous pathological conditions and is known to influence the inflammatory pathways involved in AR. Experimental studies have shown that *HIF1A* expression increases significantly in airway epithelial cells exposed to allergens, such as ovalbumin (OVA), under hypoxic conditions (16). However, our results did not reveal a statistically significant association between the studied SNPs and AR, suggesting that other genetic or environmental factors may play a more prominent role in the Turkish population.

The significance of *HIF1A* in respiratory diseases has been supported by multiple studies. For instance, SNPs in the *HIF1A* gene have been linked to various conditions, including preeclampsia, multiple sclerosis, and lumbar disc degeneration (17-19). Variations in the *HIF1A* gene have previously been associated with COPD, lung cancer, and other extra-pulmonary diseases. A Phenome-Wide Association Study (PheWAS) was conducted in Philadelphia, USA, to investigate the relationship between SNPs in the *HIF1A* gene and AR, acute bronchitis, and bronchiolitis. In a European cohort of 4348 cases and 18794 controls, the A allele of the SNP rs79865957 was found to be significantly associated with AR (allele frequency 0.08%, OR 2.86, beta 1.05, SE 0.25, and P value 3.48E-05). On the other hand, in an African American cohort of 2234 cases and 21463 controls, the T allele was significantly associated with acute bronchitis and bronchiolitis (allele frequency 0.18%, OR 0.32, beta 1.21, SE 3.36, and P value 0.0001) (11). Based on the literature, it is understood that SNPs in the *HIF1A* can play a role in the development of diseases such as acute bronchitis, bronchiolitis, and AR. Furthermore, research on murine models has demonstrated that the combination of hypoxia and allergen exposure significantly

upregulates *HIF1A* mRNA levels, highlighting its role in airway inflammation and remodeling (16). These findings underscore the importance of further genetic studies to explore alternative SNPs and their potential contribution to AR pathogenesis.

In Türkiye, other gene variations have been investigated in patients with AR. Yilmaz and colleagues examined the impact of Transporter Associated with Antigen Processing (*TAP*) polymorphisms on AR in the Turkish population. In this study, a total of 239 individuals, including 113 AR patients and 126 healthy controls, were included. No significant association was found between *TAP1* (I333V) and *TAP2* (A565T) polymorphisms and AR (20). Gulen et al. aimed to evaluate the FcγRIIa polymorphism in Turkish children with atopic asthma and allergic rhinitis. The results showed that the distribution of the R131R genotype and the frequency of the 131R allele were significantly higher in the patient groups compared to the controls, suggesting a potential genetic association with both asthma and allergic rhinitis. The study concludes that the FcγRIIa gene 131R allele is an important genetic risk factor for susceptibility to these conditions (21). We previously investigated the association between serum Wingless-Type MMTV Integration Site Family, Member 3A (WNT3A) protein levels, *WNT3A* gene polymorphisms, and AR. Our results showed significantly higher serum WNT3A levels in AR patients ($p < 0.0001$), and ROC curve analysis revealed a moderate diagnostic value for WNT3A (AUC = 0.67). We also identified a significant association between the rs3121310 polymorphism and the GA genotype in controls ($p < 0.05$), but no significant correlation was found between this polymorphism and clinical parameters in AR patients. Our findings suggest that WNT3A may play a role in AR (22). We also investigated the association between fibronectin type III domain 5 (*FNDC5*) gene polymorphisms (rs726344 and rs1746661) and AR. No significant differences were found in genotype distribution for both SNPs between AR patients and controls. Based on these findings, we concluded that FNDC5 gene polymorphisms do not appear to be associated with AR in our study population (23). In addition to genetic factors, environmental influences and geographical diversity play a critical role in AR prevalence. Türkiye, located at the crossroads of Asia and Europe, exhibits significant genetic diversity, which may influence the distribution and impact of SNPs on AR. These results suggest that the genetic architecture of AR in the Turkish population may differ from other populations, necessitating further large-scale studies to identify population-specific genetic markers.

Current study is the first case-control investigation of *HIF1A* polymorphisms in Turkish AR patients. Our findings suggest that the C1772T and C111A polymorphisms in the *HIF1A* gene do not play a significant role in the development of AR, indicating that these polymorphisms are not clinically relevant biomarkers for this condition. However, previous studies have highlighted the role of changes in *HIF1A* mRNA and protein levels in inflammatory processes. Our results underscore the importance of investigating expression levels of this gene in future studies. Advances in genomic technologies, such as next-generation sequencing can facilitate the identification of novel SNPs and their functional roles. In this context, focusing on other polymorphisms or expression levels that may serve as potential biomarkers could contribute to the development of better diagnostic and therapeutic strategies. The limitations of our study include the relatively small sample size and the investigation of only two specific polymorphisms. Future studies should focus on larger populations and explore additional polymorphisms in the *HIF1A* gene, as well as the gene's expression levels. Furthermore, prospective studies investigating the interaction between environmental factors and genetic variations could provide deeper insights into the pathogenesis of AR.

In conclusion, our findings contribute to the growing body of research on the genetic basis of AR, emphasizing the need for further investigations with larger sample sizes and a broader scope of genetic markers. Genetic studies are crucial not only for understanding disease mechanisms but also for developing personalized therapeutic approaches tailored to specific populations. Given the increasing prevalence of AR, particularly in regions with rapid urbanization and industrialization, advancing our knowledge of its genetic and environmental determinants is essential for improving diagnosis, prevention, and treatment strategies.

Author Contributions

Conceptualization, D.D.E.; **Data collection and processing,** B.Y., H.G., D.D.E.; **Data analysis and interpretation,** B.Y., D.D.E.; **Literature review,** B.Y., D.D.E.; **Writing,** B.Y., D.D.E.; **Review and editing,** B.Y., H.G., D.D.E.; **Supervision**, D.D.E.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

Ethical Approval

Ethical approval was obtained from the Alanya Alaaddin Keykubat University Clinical Research Ethics Committee with approval number 11-03, dated 23.06.2021.

Funding

This study was funded by the Alanya Alaaddin Keykubat University Scientific Research Projects Coordination Unit with the project number 2021-04-01-LTP02.

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