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Lack of Association Between *FNDC5* Gene Polymorphisms, Serum Irisin Levels and Allergic Rhinitis

FNDC5 Geni Polimorfizmleri, Serum İrisin Düzeyleri ve Alerjik Rinit Arasındaki İlişkinin Yokluğu

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ABSTRACT

Aim: Allergic rhinitis (AR) is an inflammatory nasal mucosa disease caused by type 1 immunoglobulin E-mediated reactions to allergen exposure. Irisin is a hormone released by skeletal muscles in response to exercise. There are studies that demonstrate the relationship of irisin with inflammation. We aimed to investigate the potential association between irisin coding fibronectin type III domain 5 *FNDC5* gene polymorphisms, serum irisin levels, and AR.

Methods: A case-control study was designed, involving 100 AR patients and 100 healthy controls. Genotyping of rs726344 and rs1746661 SNPs within the *FNDC5* gene was performed using PCR-RFLP method. Serum irisin levels were measured using ELISA.

Results: Genotyping of rs726344 SNP in patients revealed 90% GG and 10% GA genotypes, while in controls, it was 94% GG and 6% GA. The AA genotype was not detected in any case. For rs1746661 SNP, patients had 57% GG, 39% GT, and 4% TT genotypes, while controls had 58% GG, 36% GT, and 6% TT genotypes. No significant difference was found in rs726344 and rs1746661 SNPs between the patients and the control group. Serum irisin levels were 406.3±56.09 ng/ml in patients and 354.3±46.06 ng/ml in controls with no significant difference.

Conclusion: This is the first study aiming to investigate the relationship between the irisin protein, its encoding gene, and AR. No significant association was identified between *FNDC5* gene polymorphisms, serum irisin levels, and allergic rhinitis. While these findings suggest a limited role of these factors in AR, further studies are needed for more comprehensive understanding of the irisin-AR relationship.

Key Words: Allergic Rhinitis, Irisin, *FNDC5*, SNP, Genotyping

ÖZET

Amaç: Alerjik rinit (AR), alerjen maruziyetine bağlı olarak tip 1 immünoglobulin E-aracılı reaksiyonlarla oluşan bir enflamatuar burun mukozası hastalığıdır. İrisin, egzersize yanıt olarak iskelet kasları tarafından salınan bir hormondur. İrisin ile inflamasyon ilişkisini gösteren çalışmalar bulunmaktadır. Bu çalışmada, irisin kodlayan fibronektin tip III domain 5 *FNDC5* gen polimorfizmleri, serum irisin seviyeleri ve AR arasındaki potansiyel ilişkiyi araştırmayı amaçladık.

Yöntem: Çalışma, 100 AR hastası ve 100 sağlıklı kontrol bireyin yer aldığı bir vaka-kontrol çalışması şeklinde dizayn edilmiştir. *FNDC5* geninde bulunan rs726344 ve rs1746661 SNP'lerin genotipleme analizleri PCR-RFLP yöntemiyle gerçekleştirilmiştir. Serum irisin seviyeleri ELISA yöntemi ile ölçülmüştür.

Bulgular: Hasta grubunda rs726344 SNP genotipleme sonuçlarına göre, %90 GG ve %10 GA genotipleri saptanırken, kontrol grubunda sırasıyla %94 GG ve %6 GA genotipleri belirlendi. AA genotipi hiçbir olguda saptanmadı. rs1746661 SNP için ise hastalarda %57 GG, %39 GT ve %4 TT genotipleri, kontrollerde ise sırasıyla %58 GG, %36 GT ve %6 TT genotipleri saptandı. Hastalar ile kontroller arasında rs726344 ve rs1746661 SNP'lerinde genotipik farklılık saptanmadı. Serum irisin seviyesi, hastalarda 406.3±56.09 ng/ml iken, kontrollerde 354.3±46.06 ng/ml olarak bulundu ve aralarında anlamlı farklılık görülmedi.

Sonuç: Bu çalışma, irisin proteininin, kodlayıcı geni ve AR arasındaki ilişkiyi araştırmayı amaçlayan ilk çalışmadır. *FNDC5* gen polimorfizmleri, serum irisin seviyeleri ve AR arasında anlamlı bir ilişki saptanmamıştır. Bu bulgular, bu faktörlerin AR gelişiminde sınırlı bir rolünü göstermekle birlikte, irisin-AR ilişkisinin anlaşılması için ileri çalışmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Alerjik Rinit, Irisin, *FNDC5*, SNP, Genotipleme

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Introduction

In recent years, a continuous increase has been observed in the incidence of allergic rhinitis (AR) (OMIM #607154), a condition which is characterized by symptoms such as nasal congestion, sneezing attacks, and nasal discharge. For this reason, AR is emerging as an important health concern and challenge in modern medicine [1]. AR does not only affect an individual's social life but also results in substantial job loss and significant healthcare costs. The pathogenesis of AR involves nasal mucosal inflammation mediated by a type 1 immunoglobulin E (IgE)-triggered response upon allergen exposure [2]. The prevalence of AR is on the rise, with a global impact affecting approximately 10% to 25% of the population [3]. According to a study conducted in Turkey encompassing 9017 individuals from seven regions, the prevalence of AR was found to be 36.7% [3]. Genetic factors play a pivotal role in the etiology of AR. Although numerous single nucleotide polymorphisms (SNPs) potentially associated with AR have been identified, primarily in genes encoding cytokines and receptors, only a minority of these have demonstrated consistent validity in genetic studies, underscoring the complexity of the genetic landscape [4-7]. The genes contributing to susceptibility to AR have not been characterized to the extent of those associated with asthma and its correlated phenotypes [4].

Irisin, a myokine released from skeletal muscles during regular exercise, emerges as a key player in protecting individuals from metabolic disorders. Functioning as an autocrine, paracrine, and endocrine hormone, irisin stands out as a thermogenic protein capable of converting white adipose tissue into energy-expending brown adipose tissue. Its close associations lie with diseases such as type 2 diabetes, obesity, metabolic syndrome, and osteoporosis [8].

Furthermore, irisin is known to possess anti-inflammatory effects and has been shown to reduce systemic inflammation through various studies [9]. In a knockout mouse model of the fibronectin type III domain 5 (*Fndc5*) gene, which encodes irisin, metabolic parameters deteriorated alongside increased levels of pro-inflammatory cytokines (IL-6 and TNF-alpha) in the serum [8]. Conversely, diminished serum irisin levels have been observed in individuals with acute or chronic inflammation [10]. As a relatively recently discovered hormone, irisin is believed to play a role in development of the AR condition, particularly stemming from its association with systemic inflammation. Our research aims to investigate the relationship between genotypes of the rs726344 and rs1746661 SNPs within the *FNDC5* gene, serum irisin protein levels, and the development and clinical manifestations of AR in both AR patients and healthy control individuals.

Material and Methods

Study Group

The curent control-case study included a patient group of 100 adult individuals aged 18-65 years diagnosed with allergic rhinitis (AR) who presented to the Ear, Nose, and Throat (ENT) Diseases outpatient clinic of Alanya Alaaddin Keykubat University Alanya Education and Research Hospital, and a control group of 100 healthy adult individuals aged 18-65 years. Informed consent forms, signed by all participants, were obtained for the study.

The patient group consisted of Turkish subjects with isolated AR diagnosis and no chronic illnesses. Patients with a history of malignant disease, pregnancy, steroid use, obesity, diabetes, and signs of metabolic syndrome were excluded from the study. Total Immunoglobulin E (IgE) levels, duration of diagnosis, AR type (intermittent, persistent), and disease severity (mild, moderate, severe) were determined for the patients. Elevated serum total IgE levels were identified using a cutoff point of 150 IU/mL [11]. Patients were categorized into two groups based on total IgE levels: those with levels ≤ 150 IU/ml and those with levels > 150 IU/ml. The control group comprised healthy individuals with no previous diagnosis of AR.

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism Analysis

Genomic DNA isolations were performed using Roche High Pure PCR Template Preparation Kit Version 20 (Roche Diagnostics GmbH, Mannheim, Germany) from peripheral blood samples collected in K3 EDTA tubes of both patients and healthy individuals. Following isolation, DNA concentrations and purities were determined by measuring absorbances at wavelengths of 260 nm and 280 nm using Biotek Synergy H1 Multimode Reader Take 3 (BioTek Instruments, Inc.). The gDNA samples were stored at -20°C.

The identification of two intronic SNPs, rs726344 (G>A) and rs1746661 (G>T), within the *FNDC5* gene in both patient and control subjects was carried out using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. Initially, relevant gene regions were amplified using Polymerase Chain Reaction (PCR) with the gDNA of patients and controls. PCR mixture was prepared as described below: 0.4 µmol/L of each primer, 2.5 mmol/L $MgCl_2$, 0.8 mmol/L dNTP mix, 0.05 unit/L Taq DNA polymerase (Thermo Scientific), 0.01 pmol/ml gDNA template, and 1x Taq Buffer were added into PCR grade H_2O adjust total volume to 25 µl. The oligonucleotide primer sequences and PCR conditions for amplification were as follows: For the amplification of the SNP region with ID number rs726344, forward primer: 5'-CAGTGACTTCCCCTGAGCTT-3', reverse primer: 5'-CG-

ACAGTTCTGGGAAACAGA-3'; for the amplification of the SNP with ID number rs1746661, forward primer: 5'-TGGAGAGAGTTATGTAGGGGACA-3', reverse primer: 5'-CTTCCGCAGGCTTTATTCTG-3'. The PCR conditions for both regions were set as follows: initial denaturation at 95°C for 4 minutes, denaturation at 95°C for 45 seconds, annealing at 62°C for 30 seconds, extension at 72°C for 45 seconds, with 40 cycles, and a final extension at 72°C for 7 minutes.

Hpy188I restriction enzyme (New England Biolabs Ltd, UK) was used for genotyping the rs726344 SNP region, and HhaI restriction enzyme (New England Biolabs Ltd, UK) was employed for rs1746661 SNP. Reaction mixtures were prepared following the manufacturer's instructions and incubated overnight at 37°C. After digestion, the cleavage products were resolved on 3.0% (w/v) agarose gel and gels were run at 110 Volt then imaged using G:BOX Chemi XRQ gel documentation system (Syngene, Cambridge, UK). For rs726344, samples were identified as homozygous wild type if three PCR bands were observed at 132 base pair (bp), 92 bp and, 23 bp, homozygous variant genotype, if two PCR bands were observed at 224 bp and 23 bp, heterozygous variant genotype, if four PCR bands were observed at 224 bp, 132 bp, 92 bp, and 23 bp. For the rs1746661, samples were identified as homozygous wild type if a single but actually two PCR bands were present at 125 bp and 123 bp (seem like a single band due to their very close lengths), homozygous variant genotype, if a single PCR band was present at 248 bp, heterozygous variant genotype, if two PCR bands were observed at 248 bp and 125 bp (with 123 bp).

ELISA

The irisin protein levels of serum samples from 100 patients and 100 controls were determined using the enzyme-linked immunosorbent assay (ELISA) method. Blood samples of 5 mL were collected from both patient and control groups into gel tubes and allowed to clot at room temperature. After clotting, the samples were subjected to centrifugation at 2000 rpm for 10 minutes using a refrigerated centrifuge. Following centrifugation, serum samples were divided into portions in 1 mL Eppendorf tubes and stored at -20°C until the day of analysis. On the analysis day, serum samples belonging to both patient and control groups were thawed by taking them out from the deep freezer and allowing them to thaw at room temperature. The levels of serum irisin for both the patient and control groups were determined using the Human Protein Irisin (IS) kit (AFG Bioscience, China) according to the manufacturer's instructions.

Statistical Analysis

The frequencies of categorical variables between patients and controls were compared using the Chi-square test (Fisher's exact test), while continuous variables were compared using Student's t-test or Mann-Whitney test (for non-parametric variables). Shapiro-Wilk test was performed for assessing normality. Allelic and genotypic findings between controls and AR patients for the SNPs were compared using 2x2 contingency tables and two-sided Fisher exact test. The strength of the association was estimated using odds ratio (OR) and 95% confidence intervals (CI). For the comparison of genetic findings and irisin protein levels, the Kruskal-Wallis test was employed. The assessment of Hardy-Weinberg equilibrium was performed using an online calculation tool (https://www.cog-genomics.org/software/stats), while other statistical calculations were carried out using GraphPad Prism 7 software.

Results

Demographic and Clinical Findings

The mean age of the patient group was found to be 38.53 ± 13.01 years (Male n: 40, 40%, Female n: 60, 60%). In the control group, the mean age was 31.17 ± 11.9 years, and the gender distribution was consistent with that of the patient group. The duration of AR diagnosis in patients ranged from 18 to 72 months, with a mean of 29.36 months. Among the patients, 83 had intermittent AR, and 17 were diagnosed with persistent AR. Based on classification, 69 patients had mild AR, 21 had moderate AR, and 10 were classified as severe AR. The patients' total IgE levels were determined to be 169 ± 16.77 IU/ml (mean ± standard error of mean) with a range of 8 to 902.

Genetic Findings

The genotyping analysis of rs726344 SNP revealed that among the participants, the GG genotype was identified in 90 patients (90%) and 94 controls (94%), while the GA genotype was observed in 10 patients (10%) and 6 controls (6%). The AA genotype was not detected among both patients and controls. Regarding the genotyping of rs1746661 SNP, the results showed that among the participants, the GG genotype was determined in 57 patients (57%) and 58 controls (58%), the GT genotype was found in 39 patients (39%) and 36 controls (36%), and the TT genotype was present in 4 patients (4%) and 6 controls (6%) (Table 1). The genotypic findings of the representative cases for rs726344 and rs1746661 are shown in Figures 1 and 2, respectively.

According to the statistical analysis results, no significant difference in genotypic distribution was observed between the patient and control groups for the rs726344 and rs1746661 polymorphisms (Table 1).

According to the Hardy-Weinberg equilibrium analysis results, no significant deviation from Hardy-Weinberg equilibrium was observed for both SNPs (p=0.5781)

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Table 1. *FNDC5* SNP genotypes and allele frequencies in patient and control groups

SNP		n (%) Patients with AR	n (%) Control	OR** (95% CI)	p*
rs726344	*Genotype*	n= 100	n= 100		
	GG	90 (90%)	94 (94%)	Ref.	Ref
	GA	10 (10%)	6 (6%)	0.5745 (0.2006 to 1.518)	0.4353
	AA	0	0	-	-
	Allele	n=200	n=200		
	G	190 (95%)	194 (97%)	Ref.	Ref.
	A	10 (5%)	6 (3%)	0.5876 (0.2122 to 1.599)	0.5876
rs1746661	*Genotype*	n= 100	n= 100		
	GG	57 (57%)	58 (58%)	Ref.	Ref.
	GT	39 (39%)	36 (36%)	0.9072 (0.5088 to 1.609)	0.7682
	TT	4 (4%)	6 (6%)	1.474 (0.3935 to 4.812)	0.7443
	GT+TT	43 (43%)	42 (42%)	0.9599 (0.5395 to 1.705)	>0.9999
	Allele	n=200	n=200		
	G	153 (76.5%)	152 (76%)	Ref.	Ref.
	T	47 (23.5%)	48 (24%)	1.028 (0.6408 to 1.617)	>0.9999

*Fisher chi-square analysis.
**OR, Odds ratio.
CI, confidence interval; AR, allergic rhinitis; Ref, reference.
Genotype comparisons between patient and control groups were conducted using 2x2 contingency tables, with the format GG vs GA for rs726344, GG vs GT, GG vs TT, and GG vs GT+TT for rs1746661. Allele comparisons were performed using 2x2 contingency tables, with the format G vs A for rs726344 and G vs T for rs1746661.

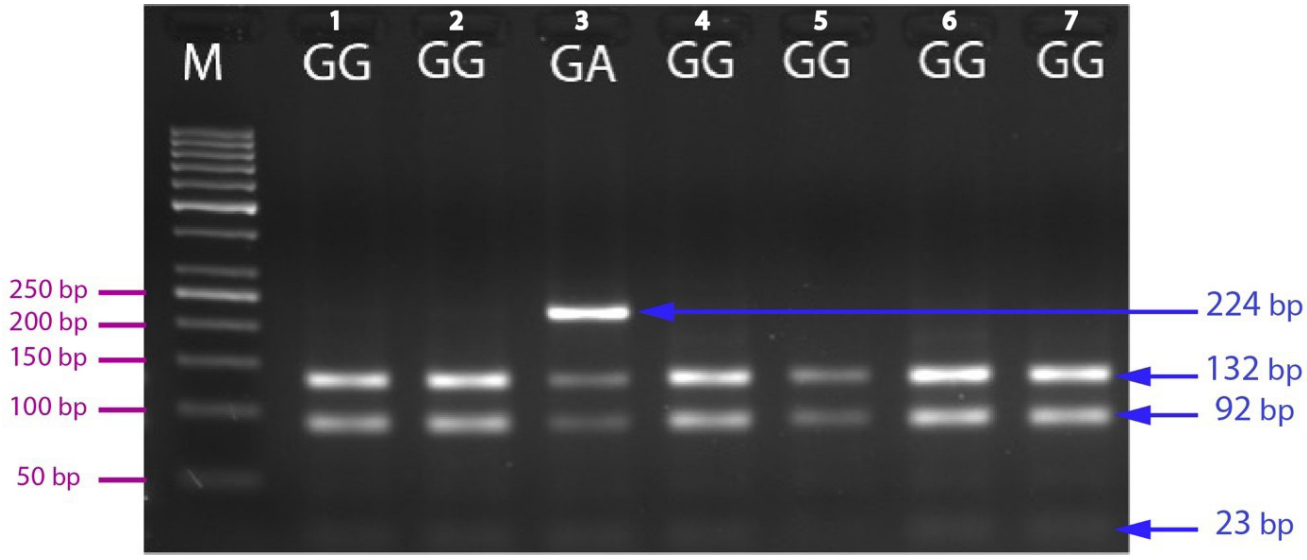

Figure 1. Gel electrophoresis of PCR-RFLP products for representative blood samples for the *FNDC5* gene variant rs726344 (G>A): M, 50 bp DNA molecular weight marker (Thermo Scientific), lanes 1, 2, 4, 5, 6 and 7, GG homozygous wild type; lane 3, GA heterozygous mutant.

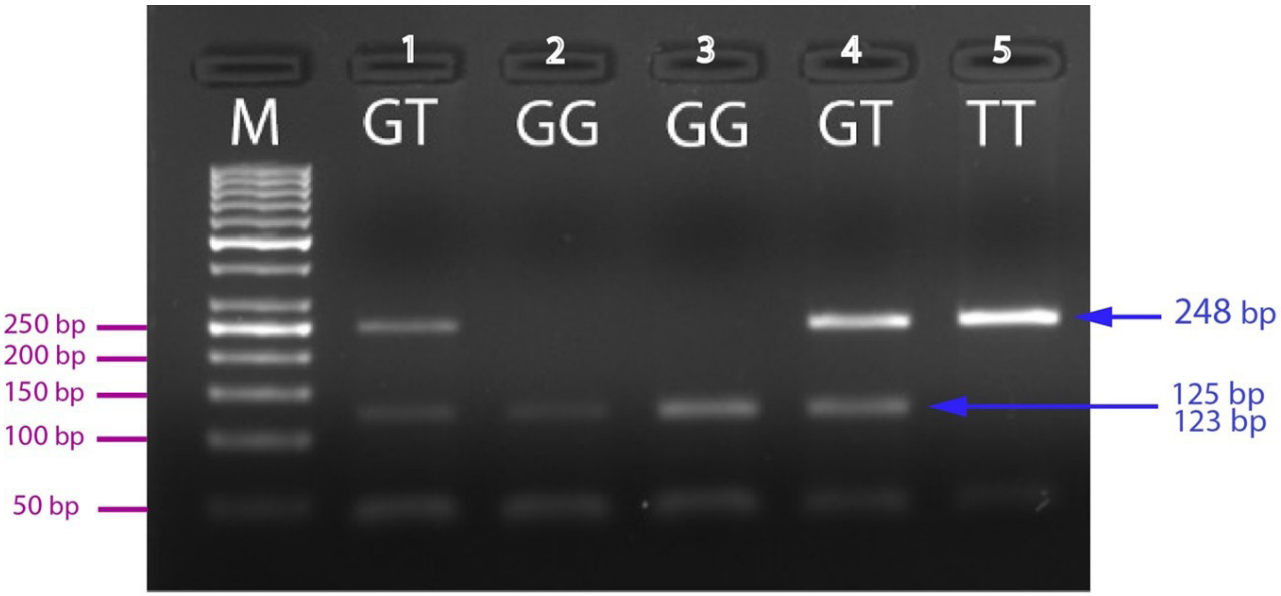

Figure 2. Gel electrophoresis of PCR-RFLP products for representative blood samples for the *FNDC5* gene variant rs1746661 (G>T): M, 50 bp DNA molecular weight marker (Thermo Scientific); lanes 1 and 4, GT heterozygous mutant; lanes 2 and 3, GG homozygous wild type; lane 5, homozygous mutant.

When genotype findings were compared according to the clinical and biochemical data (type of AR, disease severity and IgE levels) of the patients, no statistically significant difference was found for rs726344 polymorphism (Table 2) and rs1746661 polymorphism (Table 3).

Serum Irisin Levels

Serum irisin level in the patient group was 406.3±56.09 ng/ml and 354.3±46.06 ng/ml in the control group. There was no statistically significant difference between the serum irisin levels of the patient and control groups (p=0.757) (Figure 3). Additionally, no statistical difference was found between serum irisin levels of patients and controls with different genotypes for each polymorphism (p>0.05).

Discussion

AR, triggered by IgE-mediated reactions to inhaled allergens, stands as one of the most prevalent chronic disorders globally. In recent years, the incidence of AR has shown a dramatic rise, notably in Europe and Asia, thus elevating it to a concern of global proportions. AR is often accompanied by conditions such as asthma and conjunctivitis. Risk factors encompass inhaled allergens, occupational allergens, and genetic factors. While the contribution of genetic factors to the development of the disease is recognized, AR is noted for its genetic heterogeneity [12]. Given interpopulation variances, further genetic studies are required. The etiopathogenesis of AR remains incompletely elucidated.

Irisin, secreted by muscle tissue, is a hormone formed through cleavage of the membrane protein FNDC5. It is regarded as a mediator of the metabolic improvements induced by exercise. Irisin emerges as a prospective therapeutic target for metabolic and non-metabolic disorders [13].

We aimed to investigate the potential association between *FNDC5* gene polymorphisms, serum irisin levels, and AR. No statistically significant difference was found between serum irisin levels of the patient and control groups. Based on the genotyping of the rs726344 and rs1746661 SNPs within the *FNDC5* gene, no genotypic differences were found to be significant between the patient and control groups. AA genotype of rs726344 was not found in our cohort. It could be due to ethnic differences or the relatively small size of our cohort. Up to date, the associations of these variations have been explored in relation to conditions such as preterm birth, myocardial infarction, obesity, and type 2 diabetes [14-17]. However, their relation to a disease characterized by allergy has not been assessed. Given its close metabolic ties, particularly with metabolic diseases, it appears that irisin, as indicated by our current data, does not contribute to AR pathogenesis.

Over 40% of patients diagnosed with AR exhibit concomitant asthma, whereas individuals afflicted with asthma demonstrate a notably elevated prevalence of concomitant AR [18-19]. Therefore, evaluating asthma studies would be beneficial. Though no study has yet explored the relationship between AR and irisin, data regarding iri-

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Table 2. Comparison of clinical findings in patients with different rs726344 polymorphism genotypes

		GG (n)	GA (n)	OR** (95% CI)	p*
AR Type	**Intermittent**	73	10	0.000 (0.000 to 1.684)	0.2042
	Persistent	17	0		
Severity of AR	**Mild**	62	7	0.9490 (0.2522 to 3.894)	>0.9999
	Moderate + Severe	28	3		
IgE Level (UI/ml)	**≥151**	32	3	1.287 (0.3166 to 4.818)	>0.9999
	≤150	58	7		

*Fisher chi-square analysis.
**OR, Odds ratio; CI, confidence interval; AR, allergic rhinitis.
Genotype comparisons between groups were calculated using a 2x2 probability table as GG vs GA.

Table 3. Comparison of clinical findings in patients with different rs1746661polymorphism genotypes

		GG (n)	GT+TT (n)	OR** (95% CI)	p*
AR Type	**Intermittent**	50	33	2.165 (0.7872 to 5.679)	0.1829
	Persistent	7	10		
Severity of AR	**Mild**	37	32	0.6359 (0.2680 to 1.504)	0.3842
	Moderate + Severe	20	11		
IgE Level (UI/ml)	**≥151**	22	17	0.9613 (0.4462 to 2.110)	>0.9999
	≤150	35	26		

*Fisher chi-square analysis.
**OR, Odds ratio; CI, confidence interval; AR, allergic rhinitis.
Genotype comparisons between groups were calculated using a 2x2 probability table as GG vs GT+TT

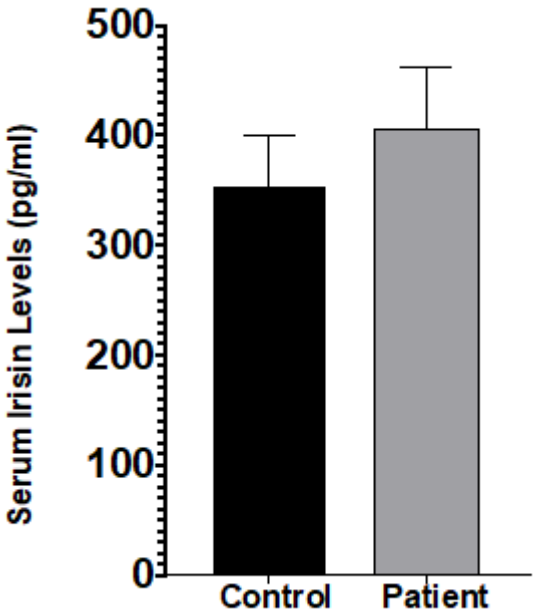

Figure 3. Serum irisin levels in patient and control groups

sin's role in asthma development are intriguing. In a study by Bulut et al. in 2019, immunomodulatory cytokine and irisin concentrations were evaluated in allergic asthmatic patients receiving omalizumab treatment, along with assessing their potential effects on cell surface markers. It was found that irisin and IL-1β concentrations were significantly higher in the serum of severe persistent asthma patients compared to the control group [20]. Asthma, a common chronic airway inflammatory disease, is characterized by a Th2-mediated immune response and excessive expression of inflammatory factors. There are few reports on the relationship between irisin and asthmatic lung injury. In 2022, Sun et al. performed a study wherein irisin was shown to improve overall condition and reduce lung tissue damage in an ovalbumin (OVA)-induced asthma mouse model. Additionally, irisin significantly suppressed inflammation factors in bronchoalveolar lavage fluid and serum, alongside considerably reducing OVA-induced PI3K/AKT phosphorylation. These findings suggest that irisin is an effective active molecule for asthma treatment and suppresses PI3K/AKT pathway phosphorylation in asthma progression and inflammatory factors [21]. Anxiety disorders and depressive states can accompany asthma. Szilasi et al. examined serum irisin levels in asthmatic patients with stress factors. They reported a decrease in irisin levels as stress levels increased [22]. The anti-inflammatory effects of irisin have also been demonstrated in-vitro. A statistically significant reduction in TLR4 protein levels was determined in irisin-treated cells [23].

It is known that physical exercise increases the secretion of the irisin [8]. The relationship between physical exercise-induced irisin secretion and AR remains complex, with varying results from different studies and no clear consensus on its impact on AR symptoms and IgE secretion. Aldred et al. found in 2010 that high-intensity exercise increased IgE secretion in AR patients [24]. Conversely, Tongtako et al. reported that acute and moderate-intensity exercise reduced AR symptoms [25]. The combination of exercise training alone and exercise training coupled with vitamin C supplementation has also been found to reduce rhinitis symptoms in AR patients [25]. These findings are interesting but further studies need to be done to clarify this topic.

Limitations

A limitation of our study is the relatively small size of the study group, which may have impacted the statistical power of our findings. The limited sample size might restrict the generalizability of our results to larger populations. Additionally, our study focused only on specific SNPs. While these SNPs were selected based on their potential relevance to our research question, our study did not encompass the entire sequencing of the *FNDC5* gene. Therefore, it is possible that other DNA variants within the *FNDC5* gene, which were not examined in this study, could play a role in the observed associations or outcomes related to AR. Further investigations involving a larger sample size, as well as a comprehensive analysis of the entire *FNDC5* gene, could provide a more comprehensive understanding of the genetic and molecular mechanisms underlying the relationship between irisin and AR.

Conclusion

Our study is the first to investigate the potential association between *FNDC5* gene polymorphisms, serum irisin levels, and AR. We found no significant association between the studied SNPs, serum irisin levels, and AR, suggesting that these specific genetic variations and irisin concentrations may not play a substantial role in the development of the condition. The findings of current study are preliminary data, the relationship between the irisin pathway and AR development needs to be clarified with further studies. The identification of alternative biological pathways related to AR and allergic diseases is crucial for both a comprehensive understanding of the etiopathogenesis of the disease and developing novel treatment protocols.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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