

**How to Cite:**

Dustbabaeva, N., Razikova, I., Baybekova, V., Pulatovna, N. A., Kamalov, Z., & Zarifovich, K. B. (2022). Immunogenetic characteristics of the clinical course of allergic rhinitis in the UZBEK population depending on the polymorphism of the IL-17A RS2275913 gene. *International Journal of Health Sciences*, 6(S7), 5333-5343. <https://doi.org/10.53730/ijhs.v6nS7.13225>

# **Immunogenetic characteristics of the clinical course of allergic rhinitis in the UZBEK population depending on the polymorphism of the IL-17A RS2275913 gene**

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**Abstract**---Summary Topicality. Over the past decade, according to WHO, there has been an increase in the incidence of allergic diseases. The pathogenesis of allergic diseases is being closely studied, in particular, the role of Th17 cells involved in the pathogenesis of allergic rhinitis and characterized by the predominant synthesis of cytokines IL-17A and IL-17F has been proven. Aim: to study the polymorphism of the IL-17A rs2275913 gene in the Uzbek population and the role in the clinical course, the effectiveness of pharmacotherapy of allergic rhinitis with antihistamines. Material and methods. The study included 118 patients with allergic rhinitis. In 112 patients,

seasonal allergic rhinitis was diagnosed with an exacerbation in summer (94.9%) and in the spring-summer period of pallination (82.2%). The control group included 200 practically healthy individuals. Genotyping of the IL17A rs2275913 polymorphism was performed using the real-time polymerase chain reaction (Real-Time) "SNP-EXPRESS"-RV method. Results. Patients with allergic rhinitis complained of seasonal and year-round symptoms, which included rhinorrhea, nasal obstruction, sneezing, itching, burning sensation in the nose, sniffing, snoring, apnea, voice change and nasality. In these patients, a significant increase in the concentration of IL-17 in the blood serum was revealed before the start of treatment. When analyzing the frequency distribution of the G and A alleles of the IL17A gene, it was registered that the A allele of the IL17A gene was the dominant allele (38.7% versus 19.5%, respectively,  $\chi^2=15.9$ ;  $p<0.05$ ). The G/G genotype of the A/G polymorphism of the IL17A gene was significantly less common in the group of patients with AR compared with practically healthy individuals in the control group. An increase in the frequency of occurrence of the heterozygous variant of the G/A allele of the IL17A gene was found in patients with AR compared with the control (56.9% versus 30.2%, respectively,  $\chi^2=11.9$ ;  $p<0.05$ ; OR=3.1 ). When comparing the A/A genotype of the IL17A gene in groups of patients with AR and healthy individuals, it was noted that the A/A genotype in the group of patients with AR occurs significantly more often than in the control group (14.1% compared with 5.9%, respectively,  $\chi^2=4.6$ ;  $p<0.05$ ). Conclusion. The results of this study showed that the AA rs2275913 genotype of the IL-17A gene is associated with the development of allergic rhinitis in the Uzbek population. This polymorphism can serve as a predictor of allergic rhinitis and provide useful information for the development and implementation of pathogenetically sound methodological approaches to the treatment and prevention of allergic rhinitis. Also, it has been proven that desloratadine (an H1-histamine receptor antagonist) can effectively control clinical symptoms (rhinorrhea, sneezing, nasal itching, nasal congestion), improve rhinoscopy and reduce the production of allergic inflammation mediators, due to its mechanism of action. Desloratadine may be the first choice among 2nd generation antihistamines for the treatment of AR in the presence of the G/A allele of the IL-17A gene (rs2275913) in the genotype of Uzbek patients.

**Keywords**---antihistamines, allergic rhinitis, gene polymorphisms, cytokines.

## Introduction

The increase in the incidence of allergic rhinitis is due to the influence of environmental and hereditary factors. The results of current genetic studies show the role of the association of genes involved in the mechanisms of development of allergic rhinitis [3,12,20]. Here, the most relevant in the pathogenesis of allergic

rhinitis are the genes of cytokines involved in the immune response, development and activation of allergic inflammation. The presence of one or another allelic variant in the cytokine genes involved in the pathogenesis of allergic rhinitis affects the quality of the immune response and, accordingly, the course and outcome of the disease, as well as the variability of the response to ongoing pharmacotherapy [1,2,4].

The interleukin-17 (IL-17) family includes 6 cytokine proteins with a mass of 20–30 kDa, and among them, IL-17A and IL-17F, being the most studied, have the highest protein sequence homology. Members of the IL-17 family are involved in many stages of the immune response and are predominantly secreted by the Th17 cell population [10]. There is evidence that IL-17 plays an important role in the pathogenesis of allergic rhinitis with the most severe monosensitization to birch, steroid-resistant bronchial asthma [7,8,15]. Currently, the polymorphism of the IL-17A and IL-17F genes is being actively studied. It has been shown that IL-17A gene polymorphism is associated with the risk of developing rheumatoid arthritis, non-alcoholic fatty liver disease, and aspirin-induced respiratory disease in Japanese [5,11,13]. The aim of this study was to study the polymorphism of the IL-17A rs2275913 gene in the Uzbek population and the role in the clinical course, the effectiveness of pharmacotherapy of allergic rhinitis with antihistamines.

**Aim:** to study the polymorphism of the IL-17A rs2275913 gene in the Uzbek population and the role in the clinical course, the effectiveness of pharmacotherapy of allergic rhinitis with antihistamines.

**Material and methods.** The study included 118 patients with allergic rhinitis. In 112 patients, seasonal allergic rhinitis was diagnosed with an exacerbation in summer (94.9%) and in the spring-summer period of pollination (82.2%). The control group included 200 practically healthy individuals. Genotyping of the IL17A rs2275913 polymorphism was performed using the real-time polymerase chain reaction (Real-Time) "SNP-EXPRESS" - RV method.

**Results.** Patients with allergic rhinitis have complained of seasonal and persistent symptoms, which include rhinorrhea, nasal obstruction, sneezing, itching, burning sensation in the nose, sniffing, snoring, apnea, voice change and nasality.

In these patients, a significant increase in the concentration of IL-17 was revealed before the start of treatment. The study of the distribution of allele frequencies of G and A of the IL17A gene showed (Table 1) that the A allele of the IL17A gene is the dominant allele (38.7% vs. 19.5%, respectively,  $\chi^2=15.9$ ;  $p>0.05$ ). The data obtained allow us to consider the A allele of the IL17A gene as a risk allele for the development of AR in the examined population.

**Table 1.**  
**Distribution of A/G allele frequencies of IL17A gene polymorphism (rs2275913) in AR patients and healthy individuals**

Polymorphism	Alleles	AR (n=83)	Control group (n=123)	$\chi^2$	<i>p</i>	OR (95% CI)	RR (95%CI)
IL17A rs2275913	G	84 - 67,3%	175 - 86,5%	15.9	<0,05	0.3 (0,21-0,59)	0.7 (0,66-0,88)
	A	48 - 38,7%	37 - 19,5%				

Also, we analyzed the distribution of genotype frequencies of the polymorphism of the studied IL17A gene. Thus, the G/G homozygous genotype of the A/G polymorphic region of the IL17A gene was significantly less common in the group of patients with allergic rhinitis compared to practically healthy controls (Table 2).

**Table 2.**  
**Genotypic frequency of IL-17A rs2275913 polymorphism in patients and regression analysis of prognostic factors**

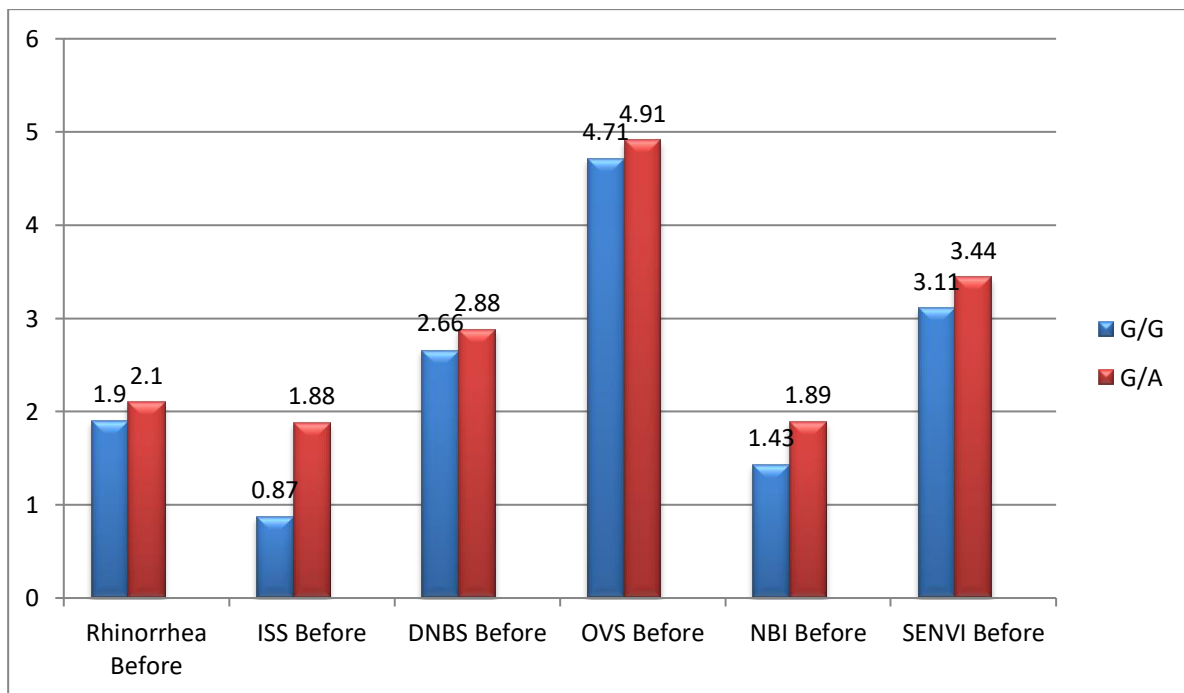
Polymorphism	Genotypes	AR (n=83)	Control Group (n=123)	$\chi^2$	<i>p</i>	OR (95%CI)	RR (95%CI)
IL17A rs2275913	G/G	25-37,9%	75-72,9%	19.	>0,05	0,2 (0,11-0,45)	0,5 (0,34-0,71)
		44-68,1%	34-33,1%	4			
	G/A	37-56,9%	31-30,2%	11.	<0,05	3.1 (1,62-6,06)	1,9 (1,34-2,93)
		32-49,1%	78-72,8%	9			
	A/A	10-14,1%	6-5,9%	4.6	<0,05	4.1 (1.03-16,7)	3,8 (1,0-14,2)
		59-91,9%	100-97,1%				

We found an increase in the frequency of occurrence of the heterozygous variant of the G/A allele of the IL17A gene in patients with allergic rhinitis compared with the control (56.9% versus 30.2%, respectively,  $\chi^2=11.9$ ;  $p<0.05$ ; OR=3, one). When comparing the A/A genotype of the IL17A gene in groups of patients with allergic rhinitis and healthy individuals, it was noted that the A/A genotype in the group of patients with allergic rhinitis occurs significantly more often than in the control group (14.1% compared to 5.9%, respectively,  $\chi^2=4.6$ ;  $p<0.05$ ; OR=4.1; CI95% 1.03-16.7). Statistical analysis showed that carriers of rs2275913 A/A develop allergic rhinitis 4.1 times more often than non-carriers of this genotype.

In patients with allergic rhinitis, there was a significant decrease in the concentration of IL-17 after treatment with the inclusion of desloratadine in pharmacotherapy in cases with the carriage of the G/G allelic variant, and a more pronounced decrease was associated in cases with the carriage of the G/A allelic variant of the IL-17A gene (rs2275913).

To assess the impact on the success of therapy in patients with allergic rhinitis, the difference between the symptoms of allergic rhinitis (rhinorrhea, sneezing, itching in the nose, nasal congestion), indicators of the rhinoscopy picture and mediators of allergic inflammation was evaluated before taking desloratadine with such symptoms of patients and on day 28 treatment. To assess the severity of symptoms of allergic rhinitis, a scoring system was used - the TNSS scale (Total nasal symptom score): 0 points - no symptoms, 1 point - mild symptoms, 2 points - moderately severe symptoms and 3 points - severe clinical symptoms, shown in Fig. 1.

Based on the foregoing, the clinical symptoms of allergic rhinitis by the end of the course of treatment with desloratadine regressed more in patients with heterozygous carriage of alleles: difficulty in nasal breathing - from 2.88 to 0.54 points; the amount of discharge from the nose - from 2.1 to 0.31 points; itching and sneezing - from 1.88 to 0.21 points. Therefore, it can be assumed that the presence of the G / A allele in the genotype of patients with allergic rhinitis is accompanied by a more pronounced pharmacodynamic effect of desloratadine on the synthesis of inflammatory cytokines, which, in turn, determine the development of a systemic allergic inflammatory process and, in particular, the pathological process in the nasal cavity.



**Fig. 1.** Indicators of the rhinoscopic picture before the appointment of desloratadine, depending on the allelic variant of the IL-17A gene. (Note: ISS is itching and sneezing symptom, DNBS is a difficult nasal breathing symptom, OVS is the overall severity of symptoms, NBI is an nasal breathing indicator, SENMI is severity of edema of the nasal mucosa indicator).

The study studied the rs2275913 polymorphism of the IL-17A gene in the Uzbek population and its association with the development of allergic rhinitis. The AA genotype of the IL-17A gene was more common in patients with AR than in practically healthy controls. The found significant difference in the polymorphism of the IL-17A rs2275913 gene between the examined patients with AR and practically healthy control group suggests that this polymorphism plays an important role in the development of AR in the Uzbek population.

The IL-17A gene is located on chromosome 6p12.1 [17]. The rs2275913 allele in the promoter region of the IL-17 gene has been reported to be associated with the risk of ulcerative colitis [6], gastric cancer [14], and atopic dermatitis [15].

It is known from the literature that single nucleotide substitutions of cytokine genes affect the production of cytokines and the development of inflammatory diseases.

Polymorphisms of the IL-17A gene (rs2275913, rs8193036, rs3819024 and rs4711998) and the IL-17B gene (rs1889570, rs763780) have predictive significance for allergic diseases in the IL-17 family [19].

The heterozygous genotype GA SNP IL-17 rs2275913 has been shown to increase the risk of developing asthma in the Asian population [10]. Moreover, Chen et al. demonstrated that IL-17 SNPrs2275913 was involved in several traits associated with rhinitis and asthma that confer a genetic predisposition to childhood asthma [7].

The results of a recent meta-analysis with a total of 5016 participants [18] show that the G allele of rs2275913 in IL-17A is a protective factor for the development of asthma, which is consistent with our results.

Patients receiving desloratadine were divided into 2 subgroups depending on the studied polymorphic allelic variant of the IL-17A gene (rs2275913). The results of the difference in the symptom of rhinorrhea in patients with different allelic variants of the IL-17A gene (rs2275913) are presented in Table 3.

**Table 3.**

**The difference between the symptom of rhinorrhea before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Gene	Alleles	Rhinorrhea before taking desloratadine	Rhinorrhea difference
IL-17A (rs2275913)	G/G	1.9±0,17	0,58±0,08
	G/A	2,1±0,08	0,31±0,03

From the obtained results, it can be seen that the heterozygous carriage of IL-17A is associated with a greater decrease in the symptom of rhinorrhea by 1.87 times

compared with the carriage of the homozygous allelic variant. Moreover, a greater decrease in rhinorrhea in heterozygous carriage is statistically significantly different from the homozygous allelic variant.

The presented results (Table 4) regarding the difference between the symptoms of itching and sneezing demonstrate that in heterozygous carriers of alleles, the frequency of sneezing reduction is significantly 2 times higher compared to carriers of normal allelic variants.

**Table 4.**

**The difference in symptoms of itching and sneezing before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Gene	Alleles	Symptoms of itching and sneezing before taking desloratadine	Difference between itching and sneezing
IL-17A (rs2275913)	G/G	0,87±0,04	0,42±0,03
	G/A	1,88±0,09	0,21±0,08

We also calculated the difference between difficulty in nasal breathing before taking desloratadine and on day 28 of treatment, depending on the allelic variant of the IL-17A gene.

**Table 5.**

**The difference in the symptom of difficult nasal breathing before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Gene	Alleles	Symptom of difficulty in nasal breathing before taking desloratadine	Difficulty in nasal breathing
IL-17A (rs2275913)	G/G	2,66±0,05	0,73±0,04
	G/A	2,88±0,04	0,54±0,06

From the results obtained (Table 5), it can be found that heterozygous carriage is associated with a greater decrease in nasal breathing difficulties by 1.35 times compared with carriage of the homozygous allelic variant. Moreover, a greater decrease in obstructed nasal breathing in heterozygous carriage is statistically significantly different from the homozygous allelic variant.

The effectiveness of therapy on the overall severity of symptoms of allergic rhinitis with fixed doses of desloratadine in patients with various allelic variants of the IL-17A gene (rs2275913) was also studied. Thus, we calculated the difference between the overall severity of symptoms of allergic rhinitis before taking desloratadine and on the 28th day of treatment of the disease.

The results of the difference in the overall severity of symptoms in patients with different allelic variants of the IL-17A gene (rs2275913) are presented in Table 6. The presented results demonstrate that in heterozygous carriers of alleles, the frequency of a decrease in the overall severity of symptoms is significantly higher by 1.3 times compared to carriers of normal options of alleles.

**Table 6.**  
**The difference in the overall severity of symptoms before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Gene	Alleles	The overall severity of symptoms before taking desloratadine	The difference in the overall severity of symptoms
IL-17A (rs2275913)	G/G	4,71±0,41	1,44±0,52
	G/A	4,91±0,37	1,14±0,74

Thus, the analyzed clinical symptoms of allergic rhinitis by the end of the course of treatment with desloratadine regressed more in patients with heterozygous carriage of alleles: difficulty in nasal breathing - from 2.88 to 0.54 points; the amount of discharge from the nose - from 2.1 to 0.31 points; itching and sneezing - from 1.88 to 0.21 points.

In the diagnosis and evaluation of monitoring treatment of allergic rhinitis, anterior rhinoscopy of the nose is important. With allergic rhinitis, a bilateral, not always symmetrical edema of the mucous membrane is revealed, on which there are watery discharges (thick in chronic allergic rhinitis), the mucous membrane is pale or cyanotic, it can be hyperemic, sometimes - nasal polyps.

The results of rhinoscopy were evaluated according to a scale specially developed by the authors [5], in points, nasal breathing was assessed from 1 to 2 points, the severity of swelling of the nasal mucosa was from 1 to 4, the color of the mucous membrane was from 1 to 4, the amount of secretion was from 1 until 3.

After a course of treatment with desloratadine in the group of patients with heterozygous alleles, a significant decrease in the severity of the rhinoscopy pattern of symptoms - nasal breathing from 1.89 to 0.45 points was recorded, in patients with heterozygous alleles, the percentage of nasal breathing recovery is 1.1 times higher ( table 7.).

**Table 7.**

**The difference in the indicators of the rhinoscopic picture before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Gene	Alleles	Nasal breathing rate before taking desloratadine	difference in nasal breathing
IL-17A (rs2275913)	G/G	1,43±0,34	0,53±0,02
	G/A	1,89±0,42	0,45±0,07

When analyzing the rhinoscopic picture during treatment with desloratadine, it was revealed that the severity of swelling of the nasal mucosa in patients with heterozygous alleles decreased from 3.44 to 0.45 points.

During treatment with desloratadine, there was an improvement in the nasal mucosa in patients with heterozygous alleles: the scores for assessing the color of the mucous membrane decreased from 2.61 to 0.49 points, edema and cyanosis, the amount of secretion in the nasal cavity from 0,9 to 0.2 points (Table 8).

**Table 8.**

**The dynamics of indicators of the rhinoscopy picture before the appointment of desloratadine and on the 28<sup>th</sup> day of treatment, depending on the allelic variant of the IL-17A gene**

Indicators of the rhinoscopy picture	Gene IL-17A (rs2275913)			
	Alleles			
	G/G		G/A	
	Before	After	Before	After
Color of the mucosa of the NC	2,2±0,04	0,55±0,07	2,61±0,4	0,49±0,06
Amount of secret in NC	0,8±0,05	0,4±0,03	0,9±0,02	0,2±0,04

## Discussion

Therefore, it can be assumed that the presence of the G / A allele in the genotype of patients with allergic rhinitis is accompanied by a more pronounced pharmacodynamic effect of desloratadine on the synthesis of inflammatory cytokines, which, in turn, determine the development of a systemic allergic inflammatory process and, in particular, a pathological process in the nasal cavity.

Thus, desloratadine can effectively control clinical symptoms (rhinorrhea, sneezing, nasal itching, nasal congestion), improve rhinoscopy and reduce the

production of allergic inflammation mediators, due to its mechanism of action. Desloratadine may be the first choice among 2<sup>nd</sup> generation antihistamines for the treatment of allergic rhinitis in the presence of the G/A allele of the IL-17A gene (rs2275913) in the genotype of Uzbek patients.

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