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HUMAN GENETICS

Study of the Role of Genes Involved in the Metabolism of Histamine in the Development of Allergic Respiratory Diseases

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Abstract—The interaction of genetic, epigenetic, and environmental factors underlies the pathogenesis of allergic diseases. Allergic rhinitis and atopic bronchial asthma are closely related and often concurrent allergic airway diseases. The chronic recurrent course of these diseases establishes the importance of further and more profound studies of the mechanisms underlying the development of these pathologies. Histamine is one of the most significant inflammatory mediators secreted during allergic reactions. The aim of the research was to study the role of polymorphic variants of the *AOC1*, *HRH2*, *HRH3*, *ALDH7A1*, *ADCYAP1*, *HNMT*, *PSAP*, and *SCG3* genes involved in the histamine metabolism in the development of different endophenotypes of the allergic airway diseases in individuals living in the Republic of Bashkortostan. DNA samples of 358 individuals with allergic airway diseases of different ethnicity (Russians—165, Tatars—143, Bashkirs—50) and 200 controls with unweighted heredity in allergic diseases (Russians—75, Tatars—83, Bashkirs—42). Genotyping of polymorphic variants was performed by real-time PCR and PCR-RFLP analysis. It was revealed that the rs104979793**CC* genotype and the rs104979793**C* allele of the *AOC1* gene were associated with allergic airway diseases and asthma with concomitant allergic rhinitis in Russians. A significant increase in total IgE level was revealed in Russian patients with allergic airway diseases with the rs1049793**CC* genotype of the *AOC1* gene compared to carriers of the rs1049793**CG* and rs1049793**GG* genotypes. The association of the *C* allele of the rs17525472 polymorphic variant localized near the *SCG3* gene with allergic rhinitis in Russians was established. The results revealed that *AOC1* and *SCG3* genes involved in the metabolism of histamine are related to the development of different endophenotypes of allergic airway tract diseases in children.

Keywords: histamine, gene, polymorphic variant, allergic rhinitis, bronchial asthma

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INTRODUCTION

Allergic diseases are common chronic diseases of a multifactorial nature. The most well-known allergic diseases include asthma, allergic rhinitis (AR), and atopic dermatitis. Asthma and AR are complex diseases that manifest themselves as chronic inflammation of the upper and lower respiratory tract. The mucous membranes of the nasal cavity and bronchi in individuals with asthma and AR have a common profile of allergens and inflammatory mediators; pathomorphological studies show a similar cellular composition of the inflammatory infiltrate of the nasal and bronchial mucosa in patients. Asthma and AR are closely related and are often combined with each other. It is assumed that these diseases may be different stages of a single process, a single disease, the basis of which is sensitization of the upper respiratory tract and bronchi [1].

Asthma is a multifactorial and heterogeneous disease, often characterized by wheezing and shortness of breath caused by inflammation and hyperresponsiveness of the respiratory tract, and the heritability of the disease varies from 55 to 74% in adults and reaches 90% in children [2]. It has been shown that more than 80% of patients with allergic asthma have associated symptoms of AR, while 20% to 50% of patients with AR have clinical manifestations of asthma [3]. AR is a disease often characterized by immunoglobulin E-mediated inflammation of the nasal mucosa, which develops and progresses under the influence of aller-

gens [4]. It is known that the symptoms of AR are not life-threatening, but they are often distressing and negatively affect work and quality of life; the heritability of AR is more than 65% [5]. Around 400 million people suffer from AR worldwide, and the number of patients has been increasing in recent decades owing to increased industrialization and air pollution [3]. The development of allergic diseases is based on a complex interaction between genetic predisposition and exposure to various environmental factors, the most important of which are allergens. A number of genome-wide association studies (GWAS) have shown that asthma and AR share a large number of both different and common polymorphic variants of genes (*IL33*, *IL1RL1*, *IL13, RAD50*, *C11orf30*, *LRRC32*, *TSL*, etc.) associated with the development of diseases and their individual phenotypes [6].

Histamine plays a central role in the pathogenesis of allergic diseases, enhances the secretion of Th2 cytokines (IL-5, IL-4, IL-10, and IL-13), and inhibits the production of Th1 cytokines (IFN-γ, IL-12, IL-2), promoting a shift in the balance of T cells towards Th2 lymphocytes. Histamine also regulates the functions of monocytes, macrophages, neutrophils, eosinophils, B cells, and dendritic cells [7]. Histamine synthesis begins with α-decarboxylation of L-histidine by the enzyme histidine decarboxylase; the biological effects of histamine are realized through interaction with the HR1, HR2, HR3, and HR4 receptors. Histamine is broken down by the enzymes histamine N-methyltransferase (HNMT) and diamine oxidase (DAO or AOC1), and a wide range of genes encoding proteins responsible for the synthesis and metabolism of histamine are known (*HDC*, *HRH1*, *HRH2*, *HRH3*, *HRH4*, *HNMT*, and *AOC1*) [8]. A number of studies have been carried out on polymorphic loci of genes involved in histamine metabolism in patients with allergic diseases, the results of which revealed polymorphic variants of genes associated with the risk of developing allergopathologies, as well as with the sensitivity of patients to the use of antihistamines in individuals of various origins [9, 10]. A number of studies have also been carried out in the Republic of Bashkortostan on the analysis of genes involved in histamine metabolism, as a result of which polymorphic variants of genes associated with the risk of development and characteristics of the clinical course of asthma were identified (*HRH1*, *HRH4*, *HNMT*, *AOC1*) [11–13]; however, analysis of polymorphic variants of genes of histamine receptors *HRH2* and *HRH3*, aldehyde dehydrogenase 7 family member A1 *ALDH7A1*, adenylate cyclase-activating polypeptide 1 *ADCYAP1*, prosaposin *PSAP*, secretogranin 3 *SCG3,* amine oxidase copper containing 1 *AOC1*, and histamine N-methyltransferase *HNMT* genes in groups of individuals from the Republic of Bashkortostan with different endophenotypes of allergic airway diseases (AAD) was not previously carried out.

The purpose of this work is to study the role of polymorphic variants of *AOC1*, *HRH2*, *HRH3*, *ALDH7A1*, *ADCYAP1*, *HNMT*, *PSAP*, and *SCG3* genes involved in histamine metabolism in the development of various endophenotypes of AAD in individuals living in the Republic of Bashkortostan.

MATERIALS AND METHODS

DNA samples from 558 unrelated individuals aged 2 to 18 years from the Republic of Bashkortostan were used as research material. The total sample of patients consisted of 358 individuals with AAD of various ethnicities (Russians—165, Tatars—143, Bashkirs—50). All studied individuals with AAD were patients of the Bashkir State Medical University Clinic, City Clinical Hospital No. 21 in Ufa, and the State Budgetary Healthcare Institution of the Russian Children's Clinical Hospital (Ufa). The diagnosis of diseases was established on the basis of family history, medical history, clinical examination results, and additional laboratory methods (allergy skin test, immunoglobulin E (IgE) level, general blood test, rhinoscopy). During the analysis, the combined group of patients was divided into several subgroups: the total sample of patients including all individuals with asthma and AR, patients with asthma (without AR), patients with AR (without asthma), and patients with asthma with concomitant AR. As a control, a group was used that included 200 essentially healthy individuals with an uncomplicated heredity for allergic diseases (Russians—75, Tatars—83, Bashkirs—42), with a low level of total IgE in the blood serum and indicators of respiratory function within normal limits.

DNA samples were isolated from peripheral blood using phenol-chloroform extraction. Genotyping of polymorphic variants of *AOC1* (rs1049793, p.His664Asp) and *HNMT* (rs11558538, p.Thr105Ile) genes was carried out using RFLP analysis; for *HRH2* (rs2067474, c.-525-493G>A) and *HRH3* (rs3787429, p.Arg196His), *ALDH7A1* (rs13182402, c.517+395T>C), *ADCYAP1* (rs2231187, c.456A>G; p.Lys152=), and *PSAP* (rs11000016, g.71819460C>T) genes and polymorphic locus rs17525472 (g.51677471T>C) localized near the *SCG3* gene, it was performed by the real-time PCR method.

For a comparative analysis of the frequencies of alleles and genotypes in groups, the chi-square test was used for 2 × 2 contingency tables (with Yates' correction); in case of statistically significant differences, the odds ratio (OR) and 95% confidence interval (CI95%) were assessed (MS Excel 2016, Plink 1.9). The type of distribution of quantitative data was assessed by the Kolmogorov–Smirnov test. To assess the equality of the general variance, Levene's test was used; if the data distribution was normal and the general variance was equal, comparison of two groups was performed by the Student's *t*-test; comparison of three or more was performed by one-way analysis of vari-

ance. Nonparametric tests were used if the distribution was not normal or the condition of equality of variances was not met (Mann–Whitney *t*-test and Kruskal–Wallis *H*-test). The meta-analysis was performed using the Plink 1.9 and WinPepi v.11.32 software packages.

RESULTS

A study of polymorphic variants of eight genes involved in histamine metabolism (*AOC1*, *HRH2*, *HRH3*, *ALDH7A1*, *ADCYAP1*, *HNMT*, *PSAP*, *SCG3*) in patients with AAD and in the control group of individuals from the Republic of Bashkortostan was carried out (Table 1). An association analysis of the analyzed polymorphic gene variants with the risk of developing AAD, clinical manifestations of asthma only and AR only, and asthma with concomitant AR was performed. The frequency distribution of genotypes of polymorphic variants corresponded to the Hardy–Weinberg equilibrium ($p > 0.05$).

Statistically significant differences in the distribution of allele and genotype frequencies between samples of AAD patients and controls were revealed when analyzing the polymorphic variant rs1049793 of the *AOC1* gene (Table 1). In Russians, a higher frequency of the rs1049793**CC* genotype and the rs1049793**C* allele of the *AOC1* gene in AAD patients (50.93 and 71.43%) than in the control was revealed (35.14%, $p = 0.02$; OR = 1.92; 95%CI 1.09–3.38 and 60.14%, $p = 0.01$; OR = 1.66; 95%CI 1.1–2.49).

Further, a more differentiated analysis of the associations of polymorphic variants of genes with clinical manifestations of asthma and AR only, as well as asthma with concomitant AR, and with the level of total IgE was carried out. In the group of Russians with asthma with concomitant AR, a significantly higher frequency of the rs1049793**CC* genotype and the rs1049793**C* allele (56.94 and 74.31%) than in controls was also established (35.14%, $p = 0.008$; OR = 2.44, 95%CI 1.25–4.76 and 60.14%, $p = 0.01$; OR = 1.92, 95%CI 1.17–3.15). Allele rs1049793**G* of the *AOC1* gene was significantly less common in patients with AAD (28.57%, $p = 0.01$; OR = 0.60, 95%CI 0.40–0.91) and patients with asthma with concomitant AR (25.69%, $p = 0.01$; OR = 0.52, 95%CI 0.32–0.86) than in the control of Russian ethnicity (39.86%). A significant increase in the level of total IgE was found in Russian patients with AAD and carriers of the rs1049793**CC* genotype (432.9 ± 45.89) of the *AOC1* gene, compared to patients with rs1049793**CG* and rs1049793**GG* genotypes (291.6 ± 23.72 and 251 ± 64.87, respectively, $p = 0.04$).

A study of polymorphic variants rs2231187 of the *ADCYAP1* gene and rs11558538 of the *HNMT* gene was carried out in samples of patients and controls from the Republic of Bashkortostan. Analysis of the distribution of alleles and genotypes frequencies of the rs2231187 polymorphic variant of the *ADCYAP1* gene revealed a tendency to an increase in the frequency of occurrence of the rs2231187**A* allele in patients with AAD (83.0%) and asthma with concomitant AR (83.82%) of Bashkir ethnicity compared with controls (71.43%, $p = 0.06$ and $p = 0.07$, respectively); a similar trend was found in the group of Tatars with AAD ($p = 0.08$). A tendency toward association of the rs11558538**T* allele of the *HNMT* gene was revealed with the development of asthma with concomitant AR in Bashkirs ($p = 0.08$).

In a comparative analysis of the distribution of alleles and genotypes frequencies of the polymorphic variant rs17525472 of the *SCG3* gene between groups of patients with AAD and control, it was revealed that the rs17525472**C* allele is significantly more common in individuals with AR of Russian ethnicity (17.74%) than in the control sample (8.67%, $p = 0.03$; OR = 2.27, 95%CI 1.09–4.72). The frequency of the rs17525472**TT* genotype and the rs17525472**T* allele in the group of patients with AR was significantly lower (67.74 and 82.26%) than in the control group in Russians (82.67%, $p = 0.04$; OR = 0.44, 95%CI 0.20–0.98 and 91.33%, $p = 0.03$; OR = 0.44, 95%CI 0.21–0.91).

In order to summarize the obtained data and discover common markers of the risk of developing allergic diseases in individuals of different ethnicities, a meta-analysis of associations of the studied polymorphisms with the development of AAD in Russians, Tatars, and Bashkirs was carried out. No statistically significant differences were found between the samples of patients with AAD and controls, but a tendency toward an association of the rs1049793**C* allele of the *AOC1* gene with the development of AR was identified (Table 2, $p = 0.07$), which suggests a possible role of this gene not only in the development of AAD in Russians but also in a combined group of individuals of different origins.

DISCUSSION

The growing prevalence of AAD in the world makes the problem of preventing allergic pathologies one of the most important problems of modern clinical medicine. A deeper understanding of the molecular genetic features of the pathogenesis of allergic diseases can contribute to their timely diagnosis and increase the effectiveness of treatment. In this work, we studied a number of polymorphic loci of *AOC1*, *HRH2*, *HRH3*, *ALDH7A1*, *ADCYAP1*, *HNMT*, *PSAP*, and *SCG3* genes involved in histamine metabolism in patients with AAD and controls from the Republic of Bashkortostan.

The *AOC1* gene is located in chromosomal region 7q36.1 encodes the protein copper-containing amine oxidase 1, also known as DAO, which catalyzes the oxidative deamination of histamine (https://omim.

Table 1. Frequencies of alleles and genotypes of polymorphic variants of genes involved in histamine metabolism in patients with AAD and in controls

Polymorphic variant/group		Genotypes			Alleles		*N*
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
AOC1, rs1049793		*CC*	*CG*	*GG*	*C*	*G*	
Patients	Russians	82 (50.93) $p = 0.02$ OR = 1.92 (1.09–3.38)	66 (40.99)	13 (8.07)	230 (71.43) $p = 0.01$ OR = 1.66 (1.1–2.49)	92 (28.57) $p = 0.01$ OR = 0.6 (0.4–0.91)	161
	Tatars	65 (45.77)	63 (44.37)	14 (9.86)	193 (67.96)	91 (32.04)	142
	Bashkirs	15 (30.0)	25 (50.0)	10 (20.0)	55 (55.0)	45 (45.0)	50
Control	Russians	26 (35.14)	37 (50.0)	11 (14.86)	89 (60.14)	59 (39.86)	74
	Tatars	35 (43.21)	41 (50.62)	5 (6.17)	111 (68.52)	51 (31.48)	81
	Bashkirs	18 (42.86)	18 (42.86)	6 (14.29)	54 (64.29)	30 (35.71)	42
HRH2, rs2067474		*GG*	*GA*	*AA*	*G*	*A*	
Patients	Russians	147 (90.74)	14 (8.64)	1 (0.62)	308 (95.06)	16 (4.94)	162
	Tatars	128 (90.78)	13 (9.22)	–	269 (95.39)	13 (4.61)	141
	Bashkirs	41 (82.0)	9 (18.0)	–	91 (91.0)	9 (9.0)	50
Control	Russians	68 (90.67)	7 (9.33)	–	143 (95.33)	7 (4.67)	75
	Tatars	76 (92.68)	6 (7.32)	–	158 (96.34)	6 (3.66)	82
	Bashkirs	36 (85.71)	5 (11.9)	1 (2.38)	77 (91.67)	7 (8.33)	42
HRH3, rs3787429		*CC*	*CT*	*TT*	*C*	*T*	
Patients	Russians	51 (31.10)	88 (53.66)	25 (15.24)	190 (57.93)	138 (42.07)	164
	Tatars	59 (41.84)	53 (37.59)	29 (20.57)	171 (60.64)	111 (39.36)	141
	Bashkirs	16 (32.0)	27 (54.0)	7 (14.0)	59 (59.0)	41 (41.0)	50
Control	Russians	25 (33.33)	41 (54.67)	9 (12.0)	91 (60.67)	59 (39.33)	75
	Tatars	32 (38.55)	41 (49.4)	10 (12.05)	105 (63.25)	61 (36.75)	83
	Bashkirs	17 (40.48)	18 (42.86)	7 (16.67)	52 (61.9)	32 (38.1)	42
ALDH7A1, rs13182402		*AA*	*AG*	*GG*	*A*	*G*	
Patients	Russians	133 (81.60)	27 (16.56)	3 (1.84)	293 (89.88)	33 (10.12)	163
	Tatars	107 (76.43)	32 (22.86)	1 (0.71)	246 (87.86)	34 (12.14)	140
	Bashkirs	41 (82.0)	7 (14.0)	2 (4.0)	89 (89.0)	11 (11.0)	50
Control	Russians	57 (76.0)	17 (22.67)	1 (1.33)	131 (87.33)	19 (12.67)	75
	Tatars	65 (79.27)	17 (20.73)	–	147 (89.63)	17 (10.37)	82
	Bashkirs	32 (76.19)	10 (23.81)	–	74 (88.1)	10 (11.9)	42
ADCYAP1, rs2231187		*AA*	*AG*	*GG*	*A*	*G*	
Patients	Russians	76 (47.2)	62 (38.51)	23 (14.29)	214 (66.46)	108 (33.54)	161
	Tatars	80 (57.55)	48 (34.53)	11 (7.91)	208 (74.82) $p = 0.08$ OR = 1.46 (0.96–2.23)	70 (25.18) $p = 0.08$ OR = 0.69 (0.45–1.05)	139
	Bashkirs	33 (66.0)	17 (34.0)	–	83 (83.0) $p = 0.06$ OR = 1.95 (0.97–3.95)	17 (17.0) $p = 0.06$ OR = 0.51 (0.25–3.95)	50

Table 1. (Contd.)

Polymorphic variant/group		Genotypes			Alleles		*N*
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
ADCYAP1, rs2231187		*AA*	*AG*	*GG*	*A*	*G*	
Control	Russians	34 (45.33)	36 (48.0)	5 (6.67)	104 (69.33)	46 (30.67)	75
	Tatars	40 (48.78)	30 (36.59)	12 (14.63)	110 (67.07)	54 (32.93)	82
	Bashkirs	20 (47.62)	20 (47.62)	2 (4.76)	60 (71.43)	24 (28.57)	42
HNMT, rs11558538		*CC*	*CT*	*TT*	*C*	*T*	
Patients	Russians	127 (78.4)	31 (19.14)	4 (2.47)	285 (87.96)	39 (12.04)	162
	Tatars	105 (75.54)	34 (24.46)	–	244 (87.77)	34 (12.23)	139
	Bashkirs	36 (72.0)	13 (26.0)	1 (2.0)	85 (85.0)	15 (15.0)	50
Control	Russians	58 (78.38)	13 (17.57)	3 (4.05)	129 (87.16)	19 (12.84)	74
	Tatars	67 (81.71)	15 (18.29)	–	149 (90.85)	15 (9.15)	82
	Bashkirs	36 (85.71)	6 (14.29)	–	78 (92.86)	6 (7.14)	42
PSAP, rs11000016		*CC*	*CT*	*TT*	*C*	*T*	
Patients	Russians	117 (71.78)	44 (26.99)	2 (1.23)	278 (85.28)	48 (14.72)	163
	Tatars	93 (66.43)	46 (32.86)	1 (0.71)	232 (82.86)	48 (17.14)	140
	Bashkirs	41 (82.0)	9 (18.0)	–	91 (91.0)	9 (9.0)	50
Control	Russians	55 (74.32)	18 (24.32)	1 (1.35)	128 (86.49)	20 (13.51)	74
	Tatars	53 (65.43)	27 (33.33)	1 (1.23)	133 (82.1)	29 (17.9)	81
	Bashkirs	33 (80.49)	6 (14.63)	2 (4.88)	72 (87.8)	10 (12.2)	41
SCG3, rs17525472		*TT*	*TC*	*CC*	*T*	*C*	
Patients	Russians	119 (73.91)	40 (24.84)	2 (1.24)	278 (86.34)	44 (13.66)	161
	Tatars	109 (77.86)	26 (18.57)	5 (3.57)	133 (82.1)	29 (17.9)	140
	Bashkirs	37 (75.51)	10 (20.41)	2 (4.08)	84 (85.71)	14 (14.29)	49
Control	Russians	62 (82.67)	13 (17.33)	–	137 (91.33)	13 (8.67)	75
	Tatars	63 (76.83)	19 (23.17)	–	145 (88.41)	19 (11.59)	82
	Bashkirs	33 (78.57)	7 (16.67)	2 (4.76)	73 (86.9)	11 (13.1)	42

N—total number of individuals; *n*—number of groups, allele and genotype frequencies in brackets, %; *p*—significance level, indicated at $p < 0.09$; OR—odds ratio and 95% confidence interval (in parentheses).

org/entry/104610); polymorphic variant rs1049793 affects the level of expression of the *AOC1* gene in blood serum (https://www.ensembl.org). The present study revealed an association of the rs1049793**CC* genotype and the rs1049793**C* allele of the *AOC1* gene with the development of AAD and asthma with concomitant AR in Russians, which is consistent with our previously published findings on the association of the rs1049793**C* allele with asthma and reduced spirography rates in Russians [12, 13] and confirms the significance of the *AOC1* gene in the development of allergic inflammation. A number of published works by other authors also show the role of the rs1049793 polymorphic variant and the expression protein of the *AOC1* gene in the development of AAD. E. García-Martín et al. showed that, in patients with AAD of European origin carrying the rs1049793**GG* genotype of the *AOC1* gene, symptoms of allergy are significantly more common with low IgE levels than in carriers of alternative alleles [14]. It was found that the level of protein expression of this gene in blood serum is higher in patients with atopic asthma and AR than in the control group of individuals from Egypt; a positive correlation was also established between the severity of allergic diseases and the level of expression of the protein encoded by the *AOC1* gene [15]. It was found that the lower the catabolic activity of the AOC1, the lower the peak nasal inspiratory flow rate in European adult patients with persistent AR [16].

The *ADCYAP1* (18p11.32) gene encodes pituitary adenylate cyclase-activating protein (PACAP). The PACAP protein is involved in histamine metabolism [10], as well as the endogenous regulation of smooth muscle tone of the respiratory tract in asthma [17]. In

Table 2. Results of a meta-analysis of the association of polymorphic loci of the studied genes with the development of AR in individuals of Russian, Tatar, and Bashkir ethnicity

Gene	SNP	A1	A2	*N*	Model with fixed effect		Model with random effect		*Q*	I^2
					P	OR	*P*(R)	OR(R)		
AOC1	rs1049793	*G*	*C*	3	0.07	0.69	0.07	0.69	0.49	0
HRH2	rs2067474	*A*	*G*	3	0.36	1.45	0.36	1.45	0.58	0
HRH3	rs3787429	*T*	*C*	3	0.75	1.06	0.75	1.06	0.41	0
ALDH7A1	rs13182402	*G*	*A*	3	0.26	1.36	0.26	1.36	0.39	0
ADCYAP1	rs2231187	*G*	*A*	3	0.56	0.88	0.46	0.77	0.15	47.98
HNMT	rs11558538	*T*	*C*	3	0.94	0.98	0.94	0.98	0.81	0
PSAP	rs11000016	*T*	*C*	3	0.29	1.31	0.41	1.32	0.24	30.35
SCG3	rs17525472	*C*	*T*	3	0.15	1.60	0.75	1.24	0.06	71.74

A1 and A2 are alleles; *N* is the number of groups included in the study; *P* is *p*-value fixed; *P*(R) is *p*-value random; OR(R) is odds ratio (random); *Q* is Cochran's heterogeneity criterion; I^2 is assessment of the statistical heterogeneity index.

the present study, only trends toward association of the polymorphic variant rs2231187 of the *ADCYAP1* gene with the development of AAD in Bashkirs and Tatars were found; at the same time, we previously showed that the rs2231187**A* allele of the *ADCYAP1* gene was associated with childhood-onset asthma in Bashkirs [12]. Lower expression of the ADCYAP1 protein was found in the nasal epithelium of patients with chronic rhinosinusitis from Croatia compared to controls, and the lowest level of ADCYAP1 expression was observed in patients with severe forms of the disease. It was shown that inflammation in the nasal mucosa of patients with chronic rhinosinusitis can be regulated through ADCYAP1 signaling [18]. The data obtained may indicate a specific role for the *ADCYAP1* gene in the pathogenesis of various allergic diseases; however, further research is necessary to confirm it.

Polymorphic variant rs11558538 localized in exon 4 of the *HNMT* gene (2q22.1) encodes the amino acid substitution Thr105Ile. The HNMT protein plays an important role in histamine degradation through methylation by histamine N-methyltransferase. According to our previously published study, it was shown that the rs11558538**T* allele of the *HNMT* gene was associated with reduced MEF25 values in Tatars with asthma [13]. However, this work revealed a tendency toward association of the rs11558538**T* allele of the *HNMT* gene with asthma with concomitant AR development in Bashkirs, which did not reach the level of statistical significance. The results obtained are ambiguous and also require additional studies of this gene in allergic diseases patients. At the same time, a number of published works confirm the role of the *HNMT* gene in the pathogenesis of AAD. L. Fernández-Novoa et al. showed that the rs11558538**T* allele of the *HNMT* gene was associated with a decrease in the activity of the HNMT enzyme [19]. An association of the rs1801105**TT* genotype and the rs1801105**T* allele of the *HNMT* gene with the asthma development in children of European origin was established [20]. An association of the rs11558538**T* allele of the *HNMT* gene with pronounced clinical symptoms of AR in pediatric individuals from Mexico was identified [9].

The secretogranin 3 *SCG3* gene is localized in the chromosomal region 15q21.2. The SCG3 protein belongs to the family of neuroendocrine secretory granin proteins, which are the precursors of a number of biologically active proteins. Some granins have been shown to function as auxiliary proteins in the sorting and proteolytic processing of prohormones (www.ncbi.nlm.nih.gov/gene/29106). GWAS revealed that the rs17525472 polymorphic variant was associated with severe asthma in Europeans with a high level of significance [21]. This work shows that the rs17525472**C* allele is associated with AR development, which is partly consistent with the results of GWAS and confirms the role of this gene in the development of allergopathologies.

Thus, a study was carried out of polymorphic variants of eight genes involved in histamine metabolism in patients with AAD and individuals in the control group from the Republic of Bashkortostan. An associ-

ation of the rs1049793**CC* genotype and the rs1049793**C* allele of the *AOC1* gene with the AAD and asthma with concomitant AR in Russians was found, and also revealed a significant increase in the level of total IgE in patients with AAD who are carriers of the rs1049793**CC* genotype. An association of the rs17525472**C* allele of the *SCG3* gene with the AR development in Russians was established. The results of the study indicate the role of allelic variants of the studied *AOC1* and *SCG3* genes involved in the metabolism of histamine in the pathogenesis of AAD, which can be used in the preparation of new modern methods for the early diagnosis of allergic pathologies.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the bioethics committees of the Bashkir State Medical University (protocol no. 28 of October 29, 2012) and the Institute of Biochemistry and Genetics, Ufa Federal Research Center, Russian Academy of Sciences (protocol no. 7 of February 10, 2011).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed voluntary consent was obtained from each of the participants included in the study.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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