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ASSOCIATION ANALYSIS OF POLYMORPHIC VARIANTS IN *ALDH7A1*, *AOC1*, *PSAP*, *ADCYAP1* GENES INVOLVED IN THE HISTAMINE METABOLISM WITH ASTHMA DEVELOPMENT IN INDIVIDUALS FROM THE REPUBLIC OF BASHKORTOSTAN

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Many environmental and genetic factors are involved in asthma development, among which an important role in the disease formation and response to antihistamine therapy belongs to genes involved in the histamine metabolism (*HRH1*, *HRH2*, *HRH3*, *HRH4*, *HDC*, *HNMT, AOC1*, *MAOB*, *ALDH7A1*, etc.). Histamine is a central mediator of allergic inflammation the release of which leads to contraction of the bronchial smooth muscles, bronchial secretion and edema of the respiratory mucosa. The use of antihistamines performing competitive blockade of histamine receptors leads to inhibition of histamine effects. The aim of this study was to assess the role of polymorphic variants of aldehyde dehydrogenase 7 family member A1 *ALDH7A1* (rs13182402), amine oxidase copper containing 1 *AOC1* (rs1049793), prosaposine *PSAP* (rs11000016), adenylate cyclase activating polypeptide 1 *ADCYAP1* (rs2231187) genes involved in the histamine metabolism in asthma development in individuals from the Republic of Bashkortostan. DNA samples of 846 unrelated individuals of different ethnicity living in the Republic of Bashkortostan were used as the study material. Genotyping of polymorphic variants was performed by real-time PCR and RFLP analysis. The statistically significant association of the rs2231187**AA* genotype and the rs2231187**A* allele of the *ADCYAP1* gene with asthma, the rs2231187**A* allele of the *ADCYAP1* gene with disease manifestation in childhood, the rs2231187**AA* genotype of the *ADCYAP1* gene and the rs13182402**G* allele of the *ALDH7A1* gene with severe and moderate asthma was established in Bashkirs. The rs1049793**CC* genotype and the rs1049793**C* allele of the *AOC1* gene were associated with asthma in Russians. The results of this study are complementary to the previously published data regarding genetic aspects of asthma pathogenesis that suggest the involvement of *ALDH7A1*, *ADCYAP1* and *AOC1* gene polymorphisms in asthma development.

Keywords: bronchial asthma, histamine, pharmacogenetics, association.

Introduction. Asthma is one of the most common chronic diseases in children and adults. The prevalence of asthma in different countries varies from 1 to 18% [7; 9]. The results of a number extensive studies of asthma inheritance based on modern approaches are published nowadays. A number of asthma molecular genetic studies using the candidate gene approach as well as whole-genome analysis of associations are also performed in the Republic of Bashkortostan (RB) [2; 5]. Insufficient control of asthma symptoms observed with even regular taking the recommended antiinflammatory drugs and bronchodilators is a serious problem of modern medicine. The lack of effective asthma control is noted in 20-30% of patients and leads to an increased risk of airway remodeling both disease progression [3]. The modern definition of asthma severity is based on assessing the degree of asthma control [9]. According to the published data, 60-80% of the variability in patients' susceptibility to treatment is due to genetics [11].

Histamine is one of the main inflammatory mediators synthesized and stored in the vesicles of mast cells and basophils. Histamine is assumed to be involved in the allergic reaction immunomodulation through activation of cytokine production, changes in Th1- and Th2-lymphocyte function and regulation of dendritic cells. The inhalation of histamine into the lungs causes the direct bronchoconstriction [7; 14]. Histamine released from storage vesicles into the extracellular space upon immunological stimulation of mast cells and basophils activates the histamine receptors (H1-H4) [14]. The interaction of histamine with H1-receptors stimulates excessive secretion of nasal mucosa and contraction of bronchial smooth muscle, whereas the interaction of histamine with H2-receptors produces the secretion of

gastric acid. H3-receptors are expressed primarily in the central nervous system and operate as autoreceptors in presynaptic histaminergic neurons, suppressing histamine release and modulating other neurotransmitters. H4-receptors are found in cells of the immune system. The action of histamine to H4-receptors activates the secretion of cytokines [10]. The diamine oxidase DAO (AOC1) and histamine-N-methyltransferase HNMT enzymes are actively involved in the initial steps of extracellular and intracellular histamine degradation [4]. Genome-wide association studies found a number of polymorphic variants of genes involved in the histamine metabolism (*PSAP*, *SCG3*, *ADCYAP1*, etc.) associated with asthma (www.genome.gwas.org). Antihistamines are used to treat the symptoms of allergic diseases depending on the histamine release, particularly allergic asthma, and to reduce the frequency of asthma exacerbations [7; 10]. Currently, the first and second generation antihistamines with similar pharmacological effects are used. The main difference between antihistamines is that the second-generation drugs have less adverse effects because they are more selective against peripheral H1 receptors [10].

The frequencies of polymorphic variants of genes involved in the disease pathogenesis varies among geographic regions and populations, which makes a relevance of a molecular genetic study of asthma in groups of people with different origins. The aim of this study is to evaluate the role of polymorphic variants of aldehyde dehydrogenase 7 family member A1 *ALDH7A1* (rs13182402), amine oxidase copper containing 1 *AOC1* (rs1049793), prosaposine *PSAP* (rs11000016) and adenylate cyclase activating polypeptide 1 *ADCYAP1* (rs2231187) genes involved in the histamine metabolism in asthma development in individuals of different ethnicity from the RB.

Materials and methods. The study included 846 unrelated individuals aged 3-67 years from the RB. The group of patients consisted of 421 individuals with asthma of different ethnicities (Russians - 174, Tatars - 142, Bashkirs - 105) from the children's clinic of Bashkir State Medical University of the Ministry of Health of the Russian Federation, the allergology and pulmonology departments of Municipal Clinical Hospital № 21 and Republican Children's Clinical Hospital (Ufa) (239 males, 182 females). The subgroup of individuals with childhood onset asthma consisted of 258 cases with the manifestation of disease before the age of 18 (Russians - 94, Tatars - 111, Bashkirs - 53). The control group included 425 practically healthy individuals (181 males, 244 females) with low levels of total IgE (0-150 IU/ml), without bronchopulmonary and allergic diseases (Russians - 194, Tatars - 145, Bashkirs - 86). The participants or their parents signed an informed consent form. The study was approved by the Bioethics Committee of the IBG UFRS RAS (Protocol № 7 from 10.02.2011).

Genomic DNA was obtained by phenol-chloroform extraction. Genotyping of *ALDH7A1* rs13182402 (c. 517+395T>C), *PSAP* rs11000016 (g. 71819460C>T), *ADCYAP1* rs2231187 (c. 456 A>G, p. Lys152=) genes polymorphisms was performed according to the recommended protocol by using the CFX96 real-time PCR detection system (DNA-Synthesis, Moscow) (Bio-Rad, USA). Genotyping of the *AOC1* rs1049793 (c. 1990C>G, p. His664Asp) polymorphism was conducted by PCR-RFLP analysis. The comparison of allele and genotype frequencies in patient and control groups was based on the chi-square criterion for 2x2 contigency tables, the odds ratio (OR) and 95% confidence interval (CI 95%) were estimated. The statistical analysis of data was performed using the Plink 1.9 and WinPepi v.11.32 programs.

Results and discussion. Insufficient control of asthma is one of the widespread problems of modern medicine. The solution of this problem involves the importance of an extensive and comprehensive analysis of factors involved in the disease pathogenesis, as well as the patients' susceptibility to treatment, which is largely determined by heredity [11]. In the present work the study of polymorphic variants of *ALDH7A1* (rs13182402), *AOC1* (rs1049793), *PSAP* (rs11000016), *ADCYAP1 (*rs2231187) genes involved in the histamine metabolism in asthma patients and control groups from the RB was performed (Table 1). The distribution of genotype frequencies was shown to be consistent with the expected under Hardy-Weinberg equilibrium (p>0,05).

ALDH7A1 plays an important role in the detoxification of aldehydes, catabolism of lysine in the mitochondrial matrix (https://www.ncbi.nlm.nih.gov/gene/501) and degradation of histamine metabolic products [4]. The frequency of the rs13182402**G* allele in patients with severe and moderate asthma of Bashkir ethnicity (18,49%) was significantly higher than in the respective control group (9,52%, p=0,02; OR=2,16; 95%CI 1,11-4,18). Increased frequency of the rs13182402**G* allele was revealed in Bashkirs with severe and moderate-to-severe asthma (18,49%) than in the controls (9,52%, p=0,02; OR=2,16; 95%CI 1,11-4,18). According to the literature, the rs13182402**G* allele was associated with development of other multifactorial diseases, such as esophageal squamous cell cancer and osteoporosis [13]. Genome-wide association analysis revealed that the rs13182402**G* allele with a high level of significance was associated with asthma in individuals of European origin (www.genome.gwas.org)

The association analysis of the *AOC1* rs1049793 polymorphism with asthma development in Russians revealed that the *CC* genotype and the *C* allele were significantly more common in patients (54,07% and 70,35%) than in controls (40,53%; p=0,01; OR=1,73; 95%CI 1,14-2,62 and 62,89%, p=0,03; OR=1,4; 95%CI 1,03-1,91) (Table 1). The obtained data consistent with our previous results, which showed that the rs1049793**CC* genotype and the rs1049793**C* allele were associated with asthma development and low spirometry values in Russians [1]. According to the published data, the rs1049793 polymorphism causes a missense mutation resulting in decreased activity of the AOC1 enzyme involved in histamine degradation. Disorders in the metabolism of histamine may cause to its excessive accumulation in the body both an extensive or prolonged response of receptors to histamine [4; 7]. It was revealed that a haplotype including rare alleles of the *AOC1* rs1049793 and *HNMT* rs11558538 polymorphisms was associated with a more severe course of allergic rhinitis and higher histamine levels in blood serum in children with allergic diseases [6].

The study of the rs2231187 polymorphism of the *ADCYAP1* gene (PACAP, 18p11.32) encoding the PACAP protein involved in the histamine secretion (www.ebi.ac.uk/) in groups from the RB was carried out. The association of the rs2231187**AA* genotype and the rs2231187**A* allele with asthma development in Bashkirs was found (p=0,04; OR=1,83; 95%CI 1,02-3,26 and p=0,03; OR=1,66; 95%CI 1,05-2,63) (Table 1). A higher frequency of the rs2231187**A* allele was observed in Bashkirs with childhood onset asthma (81,13%) compared to controls (68,24%; p=0,02; OR=2,0; 95%CI 1,12-3,59). The rs2231187**AA* genotype was significantly more frequent in Bashkirs with severe and moderate asthma (63,01%) than in controls (47,06%, p=0,05; OR=1,92; 95%CI 1,01-3,63) and in patients with a mild course of asthma (59,38%). According to the literature, a meta-analysis of GWAS studies of

The distribution of allele and genotype frequencies of *ALDH7A1* rs1318240, *AOC1* rs1049793, *ADCYAP1* rs2231187, *PSAP* rs11000016 polymorphisms in case/control groups

Group		Genotypes, n (%)			Alleles, n (%)		N
rs13182402 (*ALDH7A1*)		***AA***	***AG***	***GG***	***A***	***G***	
Cases	Russians	144 (84.21)	25 (14.62)	2 (1.17)	313 (91.52)	29 (8.48)	171
	Tatars	109 (78.42)	28 (20.14)	2 (1.44)	246 (88.49)	32 (11.51)	139
	Bashkirs	77 (73.33)	25 (23.81)	3 (2.86)	179 (85.24)	31 (14.76)	105
Controls	Russians	154 (80.21)	35 (18.23)	3 (1.56)	343 (89.32)	41 (10.68)	192
	Tatars	117 (81.25)	26 (18.06)	1 (0.69)	260 (90.28)	28 (9.72)	144
		68 (80.95)	16 (19.05)	-	152 (90.48)	16 (9.52)	84
rs1049793 (*AOC1*)		***CC***	***CG***	***GG***	***C***	***G***	
Cases	Russians	**93 (54.07) p=0.01 OR=1.73 (1.14-2.62)**	**56 (32.56) p=0.02 OR=0.6 (0.39-0.92)**	23 (13.37)	**242 (70.35) p=0.03 OR=1.4 (1.03-1.91)**	**102 (29.65) p=0.03 OR=0.71 (0.52-0.98)**	172
	Tatars	66 (46.81)	60 (42.55)	15 (10.64)	192 (68.09)	90 (31.91)	141
	Bashkirs	34 (32.69)	54 (51.92)	16 (15.38)	122 (58.65)	86 (41.35)	104
Controls	Russians	77 (40.53)	85 (44.74)	28 (14.74)	239 (62.89)	141 (37.11)	190
	Tatars	59 (41.26)	71 (49.65)	13 (9.09)	189 (66.08)	97 (33.92)	143
	Bashkirs	35 (41.18)	40 (47.06)	10 (11.76)	110 (64.71)	60 (35.29)	85
rs2231187 (*ADCYAP1*)		***AA***	***AG***	***GG***	***A***	***G***	
Cases	Russians	84 (48.84)	61 (35.47)	27 (15.7)	229 (66.57)	115 (33.43)	172
	Tatars	80 (57.14)	50 (35.71)	10 (7.14)	210 (75.0)	70 (25.0)	140
	Bashkirs	**65 (61.9) p=0.04 OR=1.83 (1.02-3.26)**	34 (32.38)	6 (5.71)	**164 (78.1) p=0.03 OR=1.66 (1.05-2.63)**	**46 (21.9) p=0.03 OR=0.6 (0.38-0.95)**	105
Controls	Russians	94 (48.96)	82 (42.71)	16 (8.33)	270 (70.31)	114 (29.69)	192
	Tatars	75 (52.08)	55 (38.19)	14 (9.72)	205 (71.18)	83 (28.82)	144
	Bashkirs	40 (47.06)	36 (42.35)	9 (10.59)	116 (68.24)	54 (31.76)	85
rs11000016 (*PSAP*)		***CC***	***CT***	***TT***	***C***	***T***	
Cases	Russians	128 (74.85)	41 (23.98)	2 (1.17)	297 (86.84)	45 (13.16)	171
	Tatars	97 (69.29)	42 (30.0)	1 (0.71)	236 (84.29)	44 (15.71)	140
	Bashkirs	78 (74.29)	25 (23.81)	2 (1.9)	181 (86.19)	29 (13.81)	105
Controls	Russians	138 (72.25)	49 (25.65)	4 (2.09)	325 (85.08)	57 (14.92)	191
	Tatars	96 (67.13)	44 (30.77)	3 (2.1)	236 (82.52)	50 (17.48)	143
	Bashkirs	59 (70.24)	21 (25.0)	4 (4.76)	139 (82.74)	29 (17.26)	84

Note. N - number of individuals; n – number of the group, the frequency of alleles and genotypes is given in brackets; p – level of significance, indicated only for statistically significant differences ($p < 0,05$); OR – the odds ratio, in brackets – 95% confidence interval

asthma in individuals of European origin found that the *T* allele of the rs1291183 polymorphism localized near the *ADCYAP1* gene was highly significant associated ($4x10^{-6}$) with low percent predicted FEV1 values [8].

The analysis of the genotype distribution and allele frequencies of the *PSAP* rs11000016 polymorphism between asthma patients and controls revealed no statistically significant differences (Table 1). The *PSAP* gene is located in 10q22.1 chromosomal region and encodes a protein fragmented into four homologous sphingolipid activator proteins (saposins A - D) which are involved in the activation of certain lysosomal hydrolases. The mutations of saposin proteins cause a deficiency of lysosomal hydrolase and subsequent lysosomal accumulation disorders [12]. GWAS of individuals of European origin showed that the *PSAP* rs11000019 polymorphism was associated with childhood onset asthma (www.genome.gwas.org).

Meta-analysis of the associations of *ALDH7A1* (rs13182402), *AOC1* (rs1049793), *PSAP* (rs11000016) and *ADCYAP1* (rs2231187) genes polymorphisms with asthma development and clinical severity in Russians, Tatars and Bashkirs revealed no statistically significant differences ($p>0,05$).

Conclusion. In summary, we analyzed the associations of polymorphic variants of the aldehyde dehydrogenase 7 family member A1 *ALDH7A1* (rs13182402), amine oxidase copper containing 1 *AOC1* (rs1049793), prosaposine *PSAP* (rs11000016) and adenylate cyclase activating polypeptide 1 *ADCYAP1* (rs2231187) genes with risk of asthma development and clinical course severity. The association of the rs1049793**CC* genotype and the rs1049793**C* allele of the *AOC1* gene with asthma development in Russians was established. The associations of the rs2231187**AA* genotype and the rs2231187**A* allele of the *ADCYAP1* gene with asthma, the association of the rs2231187**A* allele of the *ADCYAP1* gene with childhood onset asthma, the associations of the 2231187**AA* genotype of the *ADCYAP1* gene and the rs13182402**G* allele of the *ALDH7A1* gene with severe and moderate asthma in Bashkirs were revealed. The results

are important for further understanding the influence of the polymorphic variants of genes involved in the histamine metabolism in the pathophysiology and clinical course of asthma.

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