The role of polymorphic variants of arginase genes (ARG1, ARG2) involved in beta-2-agonist metabolism in the development and course of asthma

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Abstract. Asthma is a common severe disease of the respiratory tract, it leads to a significant impairment in the quality of a patient’s life unless effectively treated. Uncontrolled asthma symptoms are a cause of disease progression and development, they lead to an increase in the patient’s disability. The sensitivity to asthma therapy largely depends on the interaction of genetic and epigenetic factors, which account for about 50–60 % of variability of therapeutic response. Beta-2-agonists are some of the major class of bronchodilators used for asthma management. According to published data, allelic variants of the arginase ARG1 and ARG2 genes are associated with a risk of asthma development, spirometry measures and efficacy of bronchodilator therapy. High arginase activity results in a low level of plasma L-arginine and in a decrease in nitric oxide, and, as a result, in an increase in airway inflammation and remodeling. Arginase genetic polymorphisms (rs2781667 of the ARG1 gene, rs17249437, rs3742879, rs7140310 of the ARG2 gene) were studied in 236 children with asthma and 194 unrelated healthy individuals of Russian, Tatar and Bashkir ethnicity from the Republic of Bashkortostan. Association analysis of the studied polymorphisms with asthma development and course, the sensitivity to therapy in patients was carried out. It was found that the rs2781667* C allele of the ARG1 gene is a marker of an increased risk of asthma in Tatars. In Russians, the association of rs17249437* TT and rs3742879* GG genotypes of the ARG2 gene with a decrease in spirometry measures (FEV1, MEF25) was established. In Russians and Tatars receiving glucocorticoid monotherapy or combination therapy, the association of the rs17249437* T allele and rs17249437* TT genotype of the ARG2 gene with a partially controlled and uncontrolled course of asthma was shown.

Key words: asthma; beta-2-agonists; arginase 1 (ARG1); arginase 2 (ARG2); association; predisposition genes.

For citation: Savelieva O.N., Karunas A.S., Fedorova Yu.Yu., Murzina R.R., Savelieva A.N., Gatiyatullin R.F., Etkina E.I., Khusnutdinova E.K. The role of polymorphic variants of arginase genes (ARG1, ARG2) involved in beta-2-agonist metabolism in the development and course of asthma. Vavilovskii Zhurnal Genetiki i Selektii = Vavilov Journal of Genetics and Breeding. 2020;24(4):391-398. DOI 10.18699/VJ20.631

Роль полиморфных вариантов генов аргиназ (ARG1, ARG2), участвующих в метаболизме бета-2-агонистов, в развитии и течении бронхиальной астмы

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Аннотация. Бронхиальная астма (БА) – широко распространенное тяжелое заболевание дыхательных путей, которое при недостаточно эффективном лечении приводит к значительному ухудшению качества жизни пациентов. Отсутствие контроля над симптомами БА ведет к быстрому прогрессированию, утяжелению заболевания и инвалидизации пациентов. Чувствительность к лекарственной терапии БА во многом зависит от взаимодействия генетических и эпигенетических факторов, которые на 50–60 % определяют вариабельность терапевтического ответа пациентов. Одной из основных групп препаратов, ис-

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Introduction

Bronchial asthma (BA) is a heterogeneous chronic respiratory disease that caused by an interaction of genetic and environmental risk factors. The prevalence of asthma in the world is 1–18%, while a significant proportion of patients have mental risk factors. The prevalence of asthma in the world is a disease that caused by an interaction of genetic and environmental factors. Genomic-wide association studies (GWAS) have been performed to identify genetic variations associated with the development and course of asthma (Kim et al., 2011; Duan et al., 2013; Drake et al., 2014). A number of studies have shown that allelic variants of ARG1 and ARG2 genes are associated with BA development, spirometry measures and the effectiveness of bronchodilator therapy (Li et al., 2006; Salam et al., 2009; Vonk et al., 2010; Duan et al., 2011). The increased expression of arginase genes leads to reduced bioavailability of L-arginine and nitrogen oxide levels in the body, increased production of polyamines and proline, and as a consequence, to increased inflammation and remodeling of the respiratory tract (Li et al., 2006; Cloots et al., 2018; Meurs et al., 2019; Said et al., 2019).

The aim of our research was to analyze the association of arginase 1 (ARG1) rs2781667 and arginase 2 (ARG2) rs17249437, rs3742879, rs7140310 genetic polymorphisms with development and course of asthma in children of different ethnicity.

Materials and methods

DNA samples of 430 unrelated individuals aged 2–17 years from the Republic of Bashkortostan were used in the present study (Table 1). The group of patients consisted of 236 children with bronchial asthma (70 girls, 166 boys) of different ethnicities (Russians – 84, Tatars – 108, Bashkirs – 44). All examined individuals were patients at the children’s clinic at Bashkir State Medical University of the Ministry of Health of Russia (Ufa, Russia) and the Allergology Department of the Republican Children’s Clinical Hospital (Ufa, Russia). The criteria for inclusion of children in the main observation group included the established diagnosis of “bronchial asthma” in accordance with GINA (Global Initiative for Asthma) criteria and the criteria of Russian program documents on BA diagnosis, treatment, and prevention (National Program…, 2012).

All asthma patients were treated for at least three months with inhaled glucocorticosteroids (ICS) monotherapy or the combination of inhaled glucocorticosteroids and long-acting function measurements in response to using beta-2-agonists in asthma patients from Korea was identified, besides genetic variants of the thyroid hormone receptor beta (THRB) gene and the corticotropin-releasing hormone receptor 2 (CRHR2) gene were associated with a more significant bronchodilator response in patients from Europe (Kim et al., 2011; Duan et al., 2013; Drake et al., 2014). A number of studies have shown that allelic variants of ARG1 and ARG2 genes are associated with BA development, spirometry measures and the effectiveness of bronchodilator therapy (Li et al., 2006; Salam et al., 2009; Vonk et al., 2010; Duan et al., 2011). The increased expression of arginase genes leads to reduced bioavailability of L-arginine and nitrogen oxide levels in the body, increased production of polyamines and proline, and as a consequence, to increased inflammation and remodeling of the respiratory tract (Li et al., 2006; Cloots et al., 2018; Meurs et al., 2019; Said et al., 2019).

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beta-agonist (ICS–LABA) in a once-daily dose of 100 to 1000 micrograms of fluticasone propionate, depending on the disease severity. The group of asthma patients on ICS monotherapy was included 187 individuals, patient group receiving ICS–LABA combination therapy was composed of 49 individuals. Patient group with controlled asthma on the background therapy by ICS and ICS–LABA was included 172 individuals, group with partially controlled asthma – 50 individuals, group with uncontrolled asthma – 14 individuals.

The evaluation of respiratory function was performed using a computer spirometer (Erich Jaeger, Germany) with flow–volume curve analysis. The following parameters were assessed (in percent of the expected value present in the computer database of the spirometer): vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), forced expiratory flow between 25 and 75 % of forced vital capacity (MEF75, MEF50, MEF25, respectively). The normal range and reduction in parameters of spirogram (in percent of the standard value) for children under 18 years were assessed according to Klement and Zilber (1993). Patients with clinical asthma symptoms who were unable to perform spirometry were subjected to multiple measurements of peak expiratory flow rate (PEFR).

Assessment of current level of asthma control on the background of at least 3 months of therapy was carried out on the basis of clinical signs for the last 4 weeks (frequency of daytime symptoms and frequency of night waking up per week, the need for drugs to control attacks in a week, activity restriction due to asthma) by using a validated questionnaire “Asthma Control Test”. A group of apparently healthy children without bronchopulmonary, allergic, and autoimmune diseases and any familial history of allergic diseases consisting of 194 individuals (119 girls, 75 boys) of the corresponding ethnicity (75 Russians, 83 Tatars, 36 Bashkirs) served as a control. Children in the control group had low levels of immunoglobulin E (IgE) and no deviations from normal respiratory function according to spirometry or picfluometry data. An informed consent to participate in the study was obtained from all the children over 15 years and parents of children under 15 years participating in the study. The study protocol was approved by the local Bioethical Committees at the Bashkir State Medical University (Protocol no. 28 dated October 29, 2012) and the Institute of Biochemistry and Genetics of the Ufa Federal Research Centre of the Russian Academy of Sciences (Protocol no. 4 dated November 15, 2012).

Genomic DNA was isolated from peripheral blood lymphocytes by phenol-chloroform extraction (Mathew, 1984). Analysis of the rs2781667 (c.57+665C > T) polymorphism of the arginase 1 (ARG1) gene and rs17249437 (c.185-8016T > C), rs7140310 (c.363-1623T > G) and rs3742879 (c.859+101A > G) polymorphisms of the arginase 2 (ARG2) gene was carried out using DNA amplification by the polymerase chain reaction (PCR) with fluorescent detection (FLASH/RTAS) (TestGen, Moscow) according to the manufacturer’s protocol using the CFX96 real-time PCR detection system (Bio-Rad, USA).

Selection of single-nucleotide polymorphisms (SNP) in studied genes was based on literature data, information from databases about variation allele frequencies (over 5 %), their possible regulatory influence on gene expression and functional significance (Li et al., 2006; Salam et al., 2009; Vonk et al., 2010; Duan et al., 2011).

The χ² criterion was used to verify the correspondence of the observed distribution of genotype frequencies to the expected one according to the Hardy–Weinberg equilibrium. A pairwise comparison of allele and genotype frequencies between the patients and controls was based on the χ² criterion for 2 × 2 contingency tables with Yates correction. In the case of significant differences in the studied samples, the odds ratio (OR) and the boundaries of 95 % confidence interval (95 % CI) were estimated. Statistical analysis of quantitative data was performed using parametric and nonparametric tests depending on the scales and the distribution of variables via SPSS v.23 (SPSS Inc.). The distribution of quantitative data was assessed according to the Kolmogorov–Smirnov criterion. The equality of general variances was assessed using Levene’s test. Nonparametric tests (Mann–Whitney t criterion and Kruskal–Wallis H criterion) were used in similar comparisons in the case of abnormal distribution or failed equality of variances. The linkage disequilibrium between polymorphisms

### Table 1. Characteristics of asthma patients and control group

| Parameters                               | Samples       | Russians | Tatars | Bashkirs |
|------------------------------------------|---------------|----------|--------|----------|
| Sample size                              |               | 84       | 108    | 44       |
| Age, years (M ± SE)                      |               | 10.45 ± 0.39 | 10.72 ± 0.31 | 10.34 ± 0.54 |
| Age of asthma onset, years (M ± SE)      |               | 3.85 ± 0.34  | 3.48 ± 0.29  | 3.73 ± 0.47  |
| Total serum IgE levels, IU/mL (M ± SE)   |               | 432.15 ± 46.15 | 431.67 ± 38.86 | 425.30 ± 58.0 |
| FEV1, % of normal (M ± SE)               |               | 62.51 ± 3.59  | 73.27 ± 4.64  | 81.22 ± 8.30  |

**Control group**

| Sample size | 75 | 83 | 36 |
|-------------|----|----|----|
| Age, years (M ± SE) | 11.49 ± 0.43 | 13.54 ± 0.42 | 14.19 ± 0.58 |

Note: M – mean; SE – standard error of mean.
was estimated by applying the D' coefficient, proposed by Lewontin, and Pearson correlation coefficient $r^2$. The EM-algorithm realized in program Haploview version 4.2 was used for definition of haplotype frequencies and for testing of differences in haplotype frequencies distributions (https://www.broadinstitute.org/haploview/haploview).

### Results

Allele and genotype frequencies of four polymorphisms of arginase \( ARG1 \) (rs2781667) and \( ARG2 \) (rs17249437, rs3742879, rs7140310) genes were analyzed in asthma patients and healthy individuals from the Republic of Bashkortostan (Table 2). The distribution of genotype frequencies in all polymorphisms

### Table 2. Distribution of allele and genotype frequencies of \( ARG1 \) rs2781667, \( ARG2 \) rs17249437, rs3742879, rs7140310 gene polymorphisms in asthma patients and control group

| Groups         | N   | Genotypes | Alleles | CC   | CT   | TT   | C    | T    |
|----------------|-----|-----------|---------|------|------|------|------|------|
| **rs2781667**  |     |           |         |      |      |      |      |      |
| Patients       | 84  | 40 (47.62)| 36 (42.86)| 8 (9.52)| 116 (69.05)| 52 (30.95)|      |      |
| Russians       | 84  | 40 (47.62)| 36 (42.86)| 8 (9.52)| 116 (69.05)| 52 (30.95)|      |      |
| Tatars         | 107 | 54 (50.47)| 44 (41.12)| 9 (8.41)| 152 (71.03)| 62 (28.97)|      |      |
| Bashkirs       | 44  | 22 (50.00)| 18 (40.91)| 4 (9.09)| 62 (70.45)| 26 (29.55)|      |      |
| Controls       | 75  | 37 (49.93)| 33 (44.00)| 5 (6.07)| 107 (71.33)| 43 (28.67)|      |      |
| Russians       | 75  | 37 (49.93)| 33 (44.00)| 5 (6.07)| 107 (71.33)| 43 (28.67)|      |      |
| Tatars         | 82  | 34 (41.46)| 32 (39.02)| 16 (19.51)| 100 (60.98)| 64 (39.02)|      |      |
| Bashkirs       | 35  | 17 (48.57)| 17 (48.57)| 1 (2.86)| 51 (72.86)| 19 (27.14)|      |      |
| **rs17249437** |     |           |         |      |      |      |      |      |
| Patients       | 84  | 48 (57.14)| 29 (34.52)| 7 (8.33)| 125 (74.40)| 43 (25.60)|      |      |
| Russians       | 84  | 48 (57.14)| 29 (34.52)| 7 (8.33)| 125 (74.40)| 43 (25.60)|      |      |
| Tatars         | 107 | 43 (40.19)| 53 (49.53)| 11 (10.28)| 139 (64.95)| 75 (35.05)|      |      |
| Bashkirs       | 44  | 17 (38.64)| 21 (47.73)| 6 (13.64)| 55 (62.50)| 33 (37.50)|      |      |
| Controls       | 74  | 31 (41.89)| 36 (48.65)| 7 (9.46)| 98 (66.22)| 50 (33.78)|      |      |
| Russians       | 74  | 31 (41.89)| 36 (48.65)| 7 (9.46)| 98 (66.22)| 50 (33.78)|      |      |
| Tatars         | 82  | 33 (40.24)| 35 (42.68)| 14 (17.07)| 101 (61.59)| 63 (38.41)|      |      |
| Bashkirs       | 36  | 13 (36.11)| 18 (50.00)| 5 (13.89)| 44 (61.11)| 28 (38.89)|      |      |
| **rs3742879**  |     |           |         |      |      |      |      |      |
| Patients       | 84  | 37 (44.05)| 31 (36.90)| 16 (19.05)| 105 (62.50)| 63 (37.50)|      |      |
| Russians       | 84  | 37 (44.05)| 31 (36.90)| 16 (19.05)| 105 (62.50)| 63 (37.50)|      |      |
| Tatars         | 106 | 57 (53.77)| 41 (38.68)| 8 (7.55)| 155 (73.11)| 57 (26.89)|      |      |
| Bashkirs       | 44  | 23 (52.27)| 19 (43.18)| 2 (4.55)| 65 (73.86)| 23 (26.14)|      |      |
| Controls       | 75  | 36 (48.00)| 32 (42.67)| 7 (9.33)| 104 (69.33)| 46 (30.67)|      |      |
| Russians       | 75  | 36 (48.00)| 32 (42.67)| 7 (9.33)| 104 (69.33)| 46 (30.67)|      |      |
| Tatars         | 82  | 42 (51.22)| 37 (45.12)| 3 (3.66)| 121 (73.78)| 43 (26.22)|      |      |
| Bashkirs       | 36  | 17 (47.22)| 17 (47.22)| 2 (5.56)| 51 (70.83)| 21 (29.17)|      |      |
| **rs7140310**  |     |           |         |      |      |      |      |      |
| Patients       | 82  | 63 (76.83)| 19 (23.17)| – | 145 (88.41)| 19 (11.59)|      |      |
| Russians       | 82  | 63 (76.83)| 19 (23.17)| – | 145 (88.41)| 19 (11.59)|      |      |
| Tatars         | 107 | 72 (67.29)| 34 (31.87)| 1 (0.93)| 178 (83.18)| 36 (16.82)|      |      |
| Bashkirs       | 44  | 21 (47.73)| 22 (50.00)| 1 (2.27)| 64 (72.73)| 24 (27.27)|      |      |
| Controls       | 75  | 53 (70.67)| 22 (29.33)| – | 128 (85.33)| 22 (14.67)|      |      |
| Russians       | 75  | 53 (70.67)| 22 (29.33)| – | 128 (85.33)| 22 (14.67)|      |      |
| Tatars         | 83  | 56 (67.47)| 22 (26.51)| 5 (6.02)| 134 (80.72)| 32 (19.28)|      |      |
| Bashkirs       | 36  | 24 (66.67)| 11 (30.56)| 1 (2.78)| 59 (81.94)| 13 (18.06)|      |      |

Note: \( N \) is the number of individuals; \( n \) is the sample size; alleles and genotype frequencies are shown in brackets; \( p \) is the P-value and is shown in the case of statistical significance \( (p ≤ 0.05) \); OR is the odds ratio and 95% confidence interval (in brackets).
corresponded to the Hardy–Weinberg equilibrium \((p > 0.05)\). The association analysis of the studied polymorphisms with asthma development, with clinical and functional parameters of BA (degree of asthma control, age of asthma onset, level of total IgE, spirometry parameters) was carried out.

The arginase 1 \((ARG1)\) gene is located on the chromosome 6 (6q23.2) and contains 8 exons (Vonk et al., 2010). The rs2781667\(^*\) allele frequency in control groups were as follows: 28.67 % in Russians, 39.02 % in Tatars, 27.14 % in Bashkirs. An association of the rs2781667\(^*\) allele with asthma in Tatars \((p = 0.04; OR = 1.57; CI 95\% 1.02–2.41)\) was established. The rs2781667\(^*\)TT genotype and the rs2781667\(^*\)T allele are markers of reduced risk for asthma development in Tatars \((p = 0.03; OR = 0.38; CI 95\% 0.16–0.91)\) and \(p = 0.04; OR = 0.64; CI 95\% 0.41–0.98\), respectively.

The contribution of allelic variants of studied candidate genes to the variability of quantitative traits (IgE level, age of disease onset) was determined by Kruskal–Wallis test (in case of three groups) or Mann–Whitney test (in case of two groups). The analysis of variations in IgE levels among asthma patients of Russian ethnicity with different genotypes of the rs2781667 polymorphism of the \(ARG1\) gene demonstrated higher IgE values in patients bearing the rs2781667\(^*\)CC genotype compared to patients with rs2781667\(^*\)CT and rs2781667\(^*\)TT genotypes. As a result of pairwise comparison of groups, a statistically significant increase of IgE level was observed in patients bearing the rs2781667\(^*\)CC genotype compared with individuals bearing the rs2781667\(^*\)CT genotype \((p = 0.003)\).

| Genotypes            | IgE (M±SE, IU/mL) |
|----------------------|-------------------|
| rs2781667\(^*\)CC    | 520.70 ± 72.47    |
| rs2781667\(^*\)CT    | 331.7 ± 66.28     |
| rs2781667\(^*\)TT    | 471.5 ± 108.3     |
| Kruskal–Wallis test  | H = 8.49, \(p = 0.01\) |
| U Mann–Whitney test  |                   |
| rs2781667\(^*\)CC\(!\)rs2781667\(^*\)CT | U = 354.0, \(p = 0.003\) |
| rs2781667\(^*\)CC\(!\)rs2781667\(^*\)TT  | U = 136.0, \(p = 0.91\) |
| rs2781667\(^*\)CT\(!\)rs2781667\(^*\)TT  | U = 93.0, \(p = 0.18\) |

The \(ARG2\) gene is located at the chromosome region 14q24.1 and contains 8 exons (Vonk et al., 2010). An analysis of allele and genotype frequency distributions of the \(ARG2\) polymorphism rs17249437 showed that the rs17249437\(^*\)C allele was less prevalent in control groups of Russians, Tatars and Bashkirs (33.78, 38.41 and 38.89 % respectively) (see Table 2). No statistically significant associations of the \(ARG2\) polymorphism rs17249437 with asthma were found \((p > 0.05)\). Differences in genotype frequency distribution of rs17249437 polymorphic variant while dividing patients with account for deviations from normal spirometry values in comparison to the controls were revealed. The frequency of the homozygous rs17249437\(^*\)TT genotype (67.74 and 67.74 %) in Russian asthma patients with significant decreases FEV1 and MEF25 was significantly higher than in the control group of individuals \((41.89\%; p = 0.002; OR = 2.91; CI 95\% 1.2–7.05)\) and \(p = 0.02\; OR = 2.91; CI 95\% 1.2–7.05\), respectively). The frequency of the heterozygous rs17249437\(^*\)TC genotype in Russians with significantly reduced FEV1 and MEF25 was lower \((19.35 \text{ and } 22.58\%)\) than in the controls \((48.65\%; p = 0.005; OR = 0.25; CI 95\% 0.09–0.69 \text{ and } p = 0.01; OR = 0.31; CI 95\% 0.12–0.8, \text{ respectively}).

The increased frequency of the \(rs17249437\!^*\!T\) allele \((87.93\%) \text{ and the } rs17249437\!^*\!TT \text{ genotype } (82.76\%) \text{ was detected in Russian patients with partially controlled and uncontrolled asthma, who required treatment with beta-2-agonists more often than three times a week, compared to patients with controlled asthma: } 67.27\% \text{ for the } rs17249437\!^*\!T \text{ allele } (p = 0.004; OR = 3.54; CI 95\% 1.46–8.59) \text{ and } 43.64\% \text{ for the } rs17249437\!^*\!TT \text{ genotype } (p = 0.0006; OR = 6.20; CI 95\% 2.06–18.64). A similar association has been found in asthma patients of Tatar ethnicity. The rs17249437\!^*\!T \text{ allele } (77.59\%) \text{ and the } rs17249437\!^*\!TT \text{ genotype } (58.62\%) \text{ were detected more frequently in patients with partially controlled and uncontrolled asthma, in comparison with children with controlled asthma: } 60.26\% \text{ for } rs17249437\!^*\!T \text{ allele } (p = 0.02; OR = 2.28; CI 95\% 1.14–4.58) \text{ and } 33.33\% \text{ for } rs17249437\!^*\!TT \text{ genotype } (p = 0.02; OR = 2.83; CI 95\% 1.18–6.80).

The study results of the \(ARG2\) polymorphism rs3742879 in children with asthma and individuals of the control group from the Republic of Bashkortostan are presented in Table 2. The rs3742879\!^*\!G allele is less common in all ethnic groups, it was revealed with a frequency of 30.67 % in Russians, 26.22 % in Tatars and 29.17 % in Bashkirs control groups. The association analysis of the \(ARG2\) polymorphism rs3742879 with asthma in individuals of different ethnic origin did not reveal statistically significant differences between groups of patients and controls \((p > 0.05)\). A comparative analysis of allele and genotype frequencies of the rs3742879 polymorphism in asthma patients with different spirometry measures revealed that the rs3742879\!^*\!GG genotype was significantly more frequently (25.81 %) in Russians with significant decrease of FEV1 compared to the control group \((9.33\%, p = 0.03; OR = 3.38; CI 95\% 1.1–10.35).\n
The study of the \(ARG2\) polymorphism rs7140310 did not identify statistically significant differences in the allele and genotype frequency distributions between asthma patients and controls of different ethnicity \((p > 0.05)\). The minor allele frequencies (MAF) in control groups were as follows: 14.67 % in Russians, 19.28 % in Tatars, 18.06 % in Bashkirs. The analysis of rs17249437, rs3742879, rs7140310 polymorphisms of the \(ARG2\) gene in samples of different ethnicity showed significant linkage disequilibrium between rs17249437 and rs3742879 polymorphisms (in Russians \(D' = 0.76\), in Tatars \(D' = 0.85\), in Bashkirs \(D' = 0.9\) in all studied groups). Haplotypes analysis of \(ARG2\) gene polymorphisms did not find statistically significant differences in haplotype frequencies between asthma patients and the control group \((p > 0.05)\).

Discussion

Insufficient control of inflammation in respiratory tract at asthma leads to the disease progression, contributes to increasing the number of severe forms, deaths, and disabilities of patients. Currently, highly effective drugs have been developed and available, many significant mechanisms of asthma pathogenesis have been discovered, but the problem of insufficient asthma control remains one of the most important public health problems. Many studies provide evidence of interethnic differences in genetic markers for the asthma development and
Pathways of arginine metabolism and their relationship to allergen-induced airway obstruction, inflammation, and hyperresponsiveness. Enhanced sensitivity to allergen

The role of polymorphic variants of the arginase genes in the development and course of asthma

Constitutive and inducible NO synthases

Th2-cytokines (IL-4, IL-5, IL-13)

Arginase 1/2

L-Ornithine

Polyamine

L-Proline

Cell proliferation

Airway remodeling

L-arginine

NO

ONOO–

Allergen-induced airway obstruction, inflammation, and hyperresponsiveness. Enhanced sensitivity to allergen
values of total IgE were revealed in Russian patients with the rs2781667*CC genotype. It was found that rs17249437*TT and rs3742879*GG genotypes of the ARG2 gene were associated with a decline in lung function (FEV1, MEF25) in Russian patients. In asthma patients of Russian and Tatar ethnicity association of the rs17249437*T allele and the rs17249437*TT genotype with partially controlled and uncontrolled asthma was established. The results obtained in the present study made it possible to thoroughly understand the molecular basis of BA pathogenesis and to identify genetic markers of efficacy of bronchodilator therapy in BA patients.

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