ANALYSIS OF ASSOCIATIONS OF POLYMORPHISMS IN THE GENES CODING FOR L4, IL10, IL13 WITH THE DEVELOPMENT OF ATOPIC BRONCHIAL ASTHMA AND ITS REMISSION

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Bronchial asthma is a multifactorial disease underpinned by chronic inflammation. The atopic phenotype of BA implies the presence of similar molecular mechanisms of pathogenesis between the patients. The aim of this study was to analyze the associations between the development of atopic BA/its remission and the following polymorphisms of interleukin genes: IL4 (*rs2243250; C-589T*), IL10 (*rs1800896; G-1082A; rs1800872; C-592A*), and IL13 (*rs20541; Arg130Gln*). Using allele-specific polymerase chain reaction (PCR), we studied the listed SNPs in the mixed urban sample of patients with BA (n = 53) and the controls (n = 30) residing in South Ural. The analysis revealed that genotype AA of IL10 (*rs1800872*) occurred more frequently in the control group (23.3%) than in the patients with atopic BA (5.7%) (OR = 0.197; 95% CI [0.047–0.832]; p = 0.031). No differences in genotype frequencies were observed between the patients with atopic BA and the controls for other studied polymorphisms. Our study failed to demonstrate the association of the listed polymorphisms and BA remission.

Keywords: bronchial asthma in adults, atopy, remission, gene polymorphism, cytokines

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Compliance with ethical standards: the study was approved by the Ethics Committee of South Ural State Medical University (Protocol № 10 dated November 17, 2016). The patients gave informed consent to participate in the study.

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АНАЛИЗ СВЯЗИ ПОЛИМОРФНЫХ ВАРИАНТОВ ГЕНОВ IL4, IL10, IL13 С РАЗВИТИЕМ АТОПИЧЕСКОЙ БРОНХИАЛЬНОЙ АСТМЫ И РЕМИССИЕЙ

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Бронхиальная астма (БА) является многофакторным заболеванием, в основе которого лежит хроническое воспаление. Атопический фенотип предполагает наличие у пациентов сходных молекулярных механизмов патогенеза. Целью работы было провести анализ ассоциации полиморфных локусов генов IL4 (*rs2243250; C-589T*), IL10 (*rs1800896; G-1082A; rs1800872; C-592A*), IL13 (*rs20541; Arg130Gln*) с развитием атопической БА и ремиссией. С помощью аллель-специфичной полимеразной цепной реакции (ПЦР) проведено исследование полиморфных локусов генов больных БА (n = 53) и группы сравнения (n = 30), смешанной городской выборки, проживающих на Южном Урале. Анализ ассоциации полиморфных вариантов генов интерлейкинов с развитием БА показал, что генотип АА IL10 (*rs1800872*) встречается чаще в группе сравнения (23,3%), чем в группе атопической БА (5,7%) (ОШ = 0,197; 95% ДИ [0,047–0,832]; p = 0,031). Для остальных исследованных полиморфных локусов генов интерлейкинов отличий в частотах генотипов между больными атопической БА и группой сравнения не обнаружено. Не удалось показать влияние изученных полиморфных локусов на развитие ремиссии заболевания.

Ключевые слова: бронхиальная астма у взрослых, атопия, ремиссия, полиморфизм генов, цитокины

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Bronchial asthma (BA) is a complex disease arising from a random combination of both allergic and non-allergic factors. BA presents with a diversity of phenotypes. According to epidemiological surveillance reports, the atopic phenotype prevails in the adult population, occurring in 40 to 80% of adult asthmatic individuals. In Russia, atopic BA is diagnosed in 68–78% of adult cases [1].

Genetic predisposition is a significant contributor to asthma development. Familial aggregation of asthma was demonstrated as early as the first half of the 20th century. Twin studies conducted in the second half of the 20th century estimated the heritability of the disease in the range between 36 and 95% [2]. In the past few years, the focus has been on conducting genetic studies of BA in large clnically heterogeneous populations [3]. The analysis of candidate susceptibility genes in phenotypically homogenous cohorts allows identifying groups with similar molecular-genetic origin of the disease. A small homogeneous sample can be sufficient to detect the genetic effect of the analyzed gene [4].

Atopic disorders are regarded as immune response (type I hypersensitivity) caused and/or mediated by class IgE

antibodies against environmental antigens. Immunological reactions underlying atopic disorders can be broken down into few major categories; some of them are implicated in the epidermal barrier dysfunction, while others regulate innate and adaptive immune responses, including IgE sensitization [5].

The list of genes reliably and positively associated with allergies and asthma includes candidate genes coding for cytokines IL4, IL10 and IL13 involved in regulating persistent allergic inflammation [6]. Russian researchers also report an association between the polymorphisms of the aforementioned genes and BA [7, 8].

Most research works on BA genetics focus on the genetic predisposition to this disease [9]. Few studies have looked at its course and progression. Moreover, there is evidence that genetic risk factors for BA identified so far cannot accurately predict the development of the disease or its course [10].

In the literature, the remission rate ranges from 5% in late-onset patients [11] to 65% in children and teenagers [12]. According to our estimates, the remission rate in the adults with atopic BA residing in Chelyabinsk is 22.7%. A positive association with remission is observed in patients with normal BMI, undergoing allergen-specific therapy and eliminating exposure to allergens. Other factors, such as sex, age of onset, disease duration, familial background, co-morbid seasonal or perennial rhinitis, and smoking, do not differ significantly between patients with and without remission [13].

The aim of this study was to analyze the associations between the SNPs in the genes coding for IL4 (*rs2243250; C -589T*), IL10 (*rs1800896; G -1082A; rs1800872; C -592A*), IL13 (*rs20541; Arg130Gln*) and the development of atopic BA /its remission in the mixed sample of Chelyabinsk (South Ural) residents.

METHODS

We conducted a telephone survey of 181 individuals with atopic BA who had been patients of the allergy unit of Chelyabinsk City Clinic № 7 between 1992 and 2018. The diagnosis was established or confirmed by an allergist/immunologist based on clinical, laboratory, instrumental, and skin tests, as recommended by the Guidelines for the Diagnosis and Management of Asthma [14]. The median follow-up period was 8 years [5; 15 years].

The study included patients of both sexes aged 18 to 70 years diagnosed with mild or moderate atopic BA, with confirmed sensitivity to noninfectious allergens, who had been followed up for at least 3 years and gave consent to participate in the study. Patients with comorbid chronic obstructive lung disease, silicosis, tuberculosis, sarcoidosis, bronchiectasis or a history of previous lung surgery were excluded from the study.

Fifty-three patients aged 23–70 years underwent a physical examination; their medical history was taken, including complaints and symptoms of asthma, possible allergies and comorbidities. The patients also took the asthma control test (AST) and the bronchial reversibility test (spirometry). Screening for SNPs in interleukin genes was done using allele-specific polymerase chain reaction (PCR).

The molecular-genetic analysis was conducted at the laboratory of DNA Clinic LLC (Chelyabinsk). Genomic DNA of the patients and controls was isolated from whole-blood lymphocytes using a DNA-Express-Blood reagent kit (DNA-Technology; Russia). Single nucleotide polymorphisms (SNPs) in the genes coding for IL4 (*rs2243250; C-589T*), IL10 (*rs1800896; G-1082A; rs1800872; C-592 A*), and IL13 (*rs20541; Arg130Gln*) were identified using an SNP-express test system (Litech; Russia) and allele-specific PCR.

Spirometry criteria for normal lung function were as follows: the absence of bronchial obstruction defined as the ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) of less than 0.7 before inhalation of a bronchodilator. The bronchodilator test was considered positive if an increase in FEV1 was 12% or more after inhalation of 4 salbutamol doses and an absolute FEV1 increase was over 200 ml [15].

There are a few definitions of asthma remission in the literature varying in length between 1 and 6 years. Some criteria for remission are based on the resolution of clinical symptoms, whereas others require rely on the objective assessment of pulmonary function [16].

Because there is no consensus as to what should be considered BA remission, we defined it as the absence of symptoms (cough, shortness of breath, sensation of suffocation, wheezing) for 1 year in the absence of baseline therapy and short-acting β_2 agonist therapy and the presence of normal pulmonary function observed in a negative spirometry test. Based on this definition, we stratified the patients into 2 groups: with remission of atopic BA (n = 17; 14 men and 3 women) and without remission of atopic BA (n = 36; 14 men and 22 women). The control group consisted of 30 individuals aged 23–73 years (11 men and 19 women) who had no respiratory complaints, no allergies and no family history of allergies.

The obtained data were processed in SPSS Statistics 17.0.1 (SPSS Inc; USA). The analysis was performed using descriptive statstics. Categorical variables were described as absolute and relative frequencies. A median (Me) and an interquartile range [IQR, 25% : 75%] were calculated for quantitative variables. The analysis of quantitative data distribution was done using the Shapiro-Wilk test. In order to compare two means in independent samples, the Mann–Whitney U test was applied. Differences were considered significant at $p < 0.05$.

Allele and genotype frequencies were calculated for the studied SNPs in the candidate genes and compared to the frequencies predicted by the Hardy-Weinberg equation (χ^2 at $p < 0.05$). The two-tailed Fisher exact test was applied to run pairwise comparison of allele and genotype frequencies in the patients and the controls. Associations were analyzed using the odds ratio (OR) and the 95% confidence interval (CI).

RESULTS

The clinical characteristics of patients with atopic BA (n = 53) were as follows: 36 (68%) had polysensitization to indoor,

Table 1. Spirometry test results in patients with atopic BA remission, without remission and in the controls

Parameter	Patients with BA remission, n = 17 (group 1)	Patients without BA remission, (controlled, partially controlled/uncontrolled asthma) (group 2), n = 36	Controls (group 3), n = 30	p (groups 1–3)	p (groups 1–2)
FEV1 %, Me [Q1; Q3]	99 [89.5; 107.8]	84 [74; 97]	104 [95.5; 110]	0.4	0.001
FEV1 increase (ml) after inhalation of salbutamol (400 μg), Me [Q1; Q3]	155 [0; 247.5]	240 [107.5; 445]	167.5 [82.25; 228.75]	0.72	0.013
FEV1 /FVC %, Me [Q1; Q3]	81.5 [76.3; 88.5]	74 [67; 79.75]	83 [80.5; 85.5]	0.69	0.001

Table 2. Genotype frequency distribution for SNPs in the interleukin genes in patients with atopic BA and the controls

Genotype	Patients with atopic BA (*n* = 53), % (*n*)	Control (*n* = 30), % (*n*)	OR (95% CI)	*p*
IL4 (*rs2243250*)				
CC	52.8 (28)	53.3 (16)	0.98 (0.39–2.4)	1.000
CT	43.3 (23)	46.6 (14)	0.876 (0.35–2.15)	0.821
TT	3.8 (2)	0 (0)	0.63 (0.53–0.74)	0.533
IL10 (*rs1800896*)				
GG	37.7 (20)	43.3 (13)	0.79 (0.31–1.97)	0.647
GA	45.3 (24)	30 (9)	1.93 (0.74–4.93)	0.243
AA	17 (9)	26.6 (8)	0.56 (0.19–1.65)	0.397
IL10 (*rs1800872*)				
CC	56.6 (30)	46.6 (14)	1.49 (0.60–3.66)	0.493
CA	37.7 (20)	30 (9)	1.41 (0.54–3.68)	0.632
AA	5.7 (3)	23.3 (7)	0.197 (0.047–.832)	0.031
IL13 (*rs20541*)				
GG	55 (29)	56.6 (17)	0.924 (0.37–2.27)	1.000
GA	34 (18)	30 (9)	1.2 (0.45–3.15)	0.810
AA	11 (6)	13.3 (4)	0.83 (0.21–3.21)	1.000

Table 3. Frequency of SNP genotypes of interleukin genes in patients with atopic BA remission and without it

Genotype	Patients with BA remission (group 1) *n* = 17, % (*n*)	Patients without BA remission (group 2) *n* = 36, % (*n*)	Control (group 3) *n* = 30, % (*n*)	OR (95%CI) for all groups	*p*
IL4 (*rs2243250*)					
CC	52.9 (9)	52.7 (19)	53.3 (16)	1–3 = 1.01 (0.30–3.34) 2–3 = 0.97 (0.37–2.58)	1–3 = 1.000 2–3 = 1.000
CT	47.1 (8)	41.7 (15)	46.6 (14)	1–3 = 0.98 (0.29–3.24) 2–3 = 0.81 (0.31–2.16)	1–3 = 1.000 2–3 = 0.804
TT	0 (0)	5.6 (2)	0 (0)	1–3 = – 2–3 = 0.53 (0.42–0.7)	1–3 = – 2–3 = 0.497
IL10 (*rs1800896*)					
GG	47.1(8)	33.3 (12)	43.3 (13)	1–3 = 0.86 (0.26–2.84) 2–3 = 0.65 (0.24–1.77)	1–3 = 1.000 2–3 = 0.452
GA	35.3 (6)	50 (18)	30 (9)	1–3 = 0.78 (0.22–2.78) 2–3 = 2.3 (0.84–6.45)	1–3 = 0.753 2–3 = 0.133
AA	17.6 (3)	16.7 (6)	26.6 (8)	1–3 = 1.69 (0.38–7.5) 2–3 = 0.55 (0.16–1.8)	1–3 = 0.722 2–3 = 0.375
IL10 (*rs1800872*)					
CC	47.1 (8)	61.1 (22)	46.6 (14)	1–3 = 0.98 (0.29–3.24) 2–3 = 1.79 (0.67–4.79)	1–3 = 1.000 2–3 = 0.322
CA	41.1 (7)	36.1 (13)	26.6 (8)	1–3 = 0.61 (0.17–2.12) 2–3 = 1.31 (0.46–3.71)	1–3 = 0.528 2–3 = 0.794
AA	11.7 (2)	2.8 (1)	23.3 (7)	1–3 = 2.28 (0.41–12.5) 2–3 = 0.094 (0.011–0.814)	1–3 = 0.455 2–3 = 0.019
IL13 Arg130 Gln (*rs20541*)					
GG	52.9 (9)	55.6 (20)	56.6 (17)	1–3 = 1.16 (0.35–3.8) 2–3 = 0.95 (0.36–2.53)	1–3 = 1.000 2–3 = 1.000
GA	29.4 (5)	36.1 (13)	30 (9)	1–3 = 1.02 (0.28–3.28) 2–3 = 1.31 (0.47–3.7)	1–3 = 1.000 2–3 = 0.794
AA	17.7 (3)	8.3 (3)	13.3 (4)	1–3 = 0.71 (0.14–3.6) 2–3 = 0.59 (0.12–2.87)	1–3 = 0.692 2–3 = 0.693

epidermal and plant allergens; 25 (47%) had a family history of allergies; 22 (42%) had early-onset BA (before 18 years of age); 41 (78%) had comorbid allergic rhinitis; 38 (72%) had mild BA, and 15 (28%) had moderate BA. Lung function was normal in the group of patients with remission of atopic BA; no statistical difference in the results of the bronchodilator test was detected between this group of patients and the controls (Table 1). In patients without remission the bronchodilator test was positive, FEV1% and FEV/FVC% were lower than in the controls.

Genotype frequencies were calculated for the total sample of patients with atopic BA relative to the control group and for the subgroups of patients with and without remission. Linkage disequilibrium was detected for all studied loci in the control group; the studied loci were in the Hardy–Weinberg equilibrium for the group of patients with atopic BA.

The analysis of associations between the polymorphisms of interleukin genes and BA development (Table 2) revealed a statistically significant difference in the frequencies of IL10

(*rs1800872*) genotypes: genotype AA was more frequent in the control group (23.3%) than in the group of patients with atopic BA (5.7%) (OR = 0.197; 95% CI [0.047–0.832]; $p = 0.031$) and perhaps had a protective role. No difference in frequencies were detected for other studied SNP between the patients with atopic BA and the controls.

Intergroup comparison revealed a difference in the frequency of IL10 genotypes (*rs1800872*) between the patients without BA remission and the control group: the frequency of AA genotype was 2.8% vs 23.3% (OR= 0.094; 95% CI [0.011–0.814]; $p = 0.019$). Integral assessment of clinical and molecular-genetic data did not reveal any significant associations with BA remission (Table 3).

DISCUSSION

Previous studies of the polymorphic *C-592A* locus of the IL10 gene produced controversial results: some authors reported no association with predisposition to asthma [17], while others observed significant correlations [18, 19]. Previous metanalyses demonstrated an association between the polymorphism *C-589T* of the IL4 gene and the risk for BA in the European population [20] and another association between the polymorphism *Arg130Gln* of the IL13 gene and an increased risk for BA in children and adults [21–23]. According to the literature, the *G-1082A* polymorphism of the IL10 gene predisposes to asthma [24].

It is hypothesized that factors increasing the risk of BA may differ from those affecting its progression [25]. Perhaps, the SNPs studied in this work are not associated with the clinical prognosis of patients with BA. This question needs further investigation in larger patient samples.

CONCLUSIONS

This study presents the first data on the distribution of genotypes of the polymorphic loci *C-589T* (IL4), *G-1082A* (IL10), *C-592A* (IL10), and *Arg130Gln* (IL13) in the mixed sample of urban patients with atopic BA residing in South Ural. Considering the small sample size, the results should be interpreted with caution. So far, many genetic aspects of BA have been studied that contribute to the understanding of the pathogenesis of this multifactorial disease. Further research in this field is needed in order to adapt genetic diagnostic techniques to the clinical setting. The study of SNPs in interleukin genes can become an auxiliary tool for predicting the prognosis of the disease and encouraging patients to adhere to therapeutic regimens.

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