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INVESTIGATION OF THE ROLE OF CYTOKINE GENES POLYMORPHISMS IN THE DEVELOPMENT OF THE URTICARIA IN THE REPUBLIC OF BASHKORTOSTAN

ABSTRACT

At present, there is a steady increase in the incidence and prevalence of allergic skin diseases in the world, affecting up to 25% of the population in different countries. Urticaria is an etiologically heterogeneous group of diseases and conditions characterized by the formation of itching rashes on the skin. According to epidemiological studies, at least once during a lifetime this pathology is observed in 15-25% of the population. Urticaria is a polyethological disease. Allergic mechanisms of tissue damage are involved in the development of the allergic form of hives. Cytokines play a key role in all stages of development and maintenance of allergic inflammation. The purpose of this study was to investigate the polymorphic loci of interleukins genes IL4 (rs2243250), IL4R (rs1805010), IL10 (rs1800872), IL13 (rs20541) and tumor necrosis factor gene TNF (rs1800629) in patients with hives and in the control group of individuals. The material for the study was DNA samples of 102 unrelated individuals with urticaria, and 153 healthy individuals living in the Republic of Bashkortostan. The DNA was isolated by phenol-chloroform extraction. Genotyping of polymorphic loci was carried out by real-time PCR. As a result of the analysis, we showed that the rs1800629*G allele and the rs1800629*G/G genotype of the TNF gene polymorphism are the markers of an increased risk of developing of chronic urticaria, rs2243250*C allele of the IL4 gene – of the acute urticaria, and the rs1800629*G/A genotype of the TNF gene is a marker of the urticaria with concomitant allergic diseases development. The data obtained by us are in part consistent with the results of other authors. Thus, in patients from Japan and Canada, the SNP rs2243250 of the IL4 gene is associated with the development of atopic dermatitis. The association of the TNF gene rs1800629 polymorphism with the development of bronchial asthma and atopy is indicated in patients from the USA and Spain. As in our study, patients with allergic dermatoses from Japan did not have an association of the IL4R gene SNP rs1805010 with the development of the disease. Nevertheless, a number of other studies have shown the association with the development of various allergic diseases of all the polymorphic loci we studied. Thus, this study shows an association with the development of urticaria of polymorphic variants of the TNF and IL4 genes.

Keywords: urticaria, association analysis, cytokines, genes, polymorphic variants.

INTRODUCTION

At present, there is a steady increase in the incidence and prevalence of allergic skin diseases in the world, which affects up to 25% of the population in different countries. Allergic dermatoses account for 20% in the structure of allergic diseases, and take 50 to 66% in the structure of childhood allergopathology [1]. One of the most common allergic dermatoses, found in people of different ages, is urticaria. Urticaria is a toxic-allergic dermatosis, characterized by the rapid occurrence of multiple itchy rashes (blisters) of red color on the skin and mucous membranes. According to epidemiological studies, at least once during a lifetime this pathology is observed in 15-25% of the population [2].

Urticaria is a classic polyethological disease, i.e. its symptoms can be caused by various factors. The main risk factors for the development of acute urticaria are food products, medicines and insect bites. The situation with chronic urticaria is more complicated: many factors that cause its aggravation are known, but it is possible to reveal its cause in no more than 10% of cases. At the same time, the pathogenesis of urticaria due to allergic reactions of the immediate type has been studied quite well. Allergic mechanisms of tissue damage are involved in the development of this form of hives. The leading mechanism of development of urticaria is a reagin-dependent mechanism of damage.

Cytokines play a key role in all stages of development and maintenance of allergic inflammation. In many studies, a significant association of single nucleotide polymorphisms (SNPs) of cytokines and their receptors genes with the development of allergic diseases has been demonstrated [4, 6, 8, 9, 13]. The association of polymorphic loci of cytokine genes with the development of allergic dermatoses, in particular atopic dermatitis (AD), has been shown in numerous studies conducted in patients from Japan [12,13], Korea [7], Czech Republic [6], Canada [9] and the United States [14]. In addition, the association of polymorphic variants of cytokine genes with the development of other allergic diseases, in particular bronchial asthma, has been identified [4, 15, 18]. Nevertheless, a number of other authors do not confirm this data [8; 16].

In our study, we analyzed SNPs of *IL4* (rs2243250), *IL4R* (rs1805010), *IL10* (rs1800872), *IL13* (rs20541) and *TNF* (rs1800629) genes in urticaria and in the control group of individuals living in the Republic of Bashkortostan.

MATERIALS AND METHODS

The study of polymorphic loci of cytokine genes was carried out in 102 unrelated individuals with urticaria living in the Republic of Bashkortostan. All examined individuals were patients of the Department of allergy at Municipal Clinical Hospital No. 21 in Ufa. Diagnosis of the disease was established by qualified doctors on the basis of clinical, general laboratory and additional research methods in accordance with the criteria of the program documents for the diagnosis, treatment and prevention of diseases. The sample of patients with urticaria included individuals with different forms of the disease. The acute form (with the duration of the disease up to 6 weeks) was observed in 47 patients, chronic (with duration of the disease more than 6 weeks) – in 55 patients. In addition, the patients were divided into two groups depending on the presence or absence of concomitant allergic diseases (allergic conjunctivitis , allergic rhinitis, atopic dermatitis, bronchial asthma, angioedema, or combinations thereof). The control group consisted of 153 practically healthy individuals, comparable in sex and age with patients and not having a hereditary burden of atopic diseases. Informed consent to participate in this study was obtained from all of its participants.

The isolation of DNA from peripheral blood lymphocytes was carried out by a standard phenol-chloroform extraction method. Amplification of polymorphic loci of cytokine genes was carried out using real-time polymerase chain reaction (PCR) of DNA synthesis.

RESULTS AND DISCUSSION

Five polymorphic variants of cytokine genes (*IL4* (rs2243250, c.-590C>T), *IL4R* (rs1805010), *IL10* (rs1800872, c.-627C>A), *IL13* (rs20541, p.Arg144Gln) and *TNF* (rs1800629)) were studied in patients with urticaria and individuals of the control group living in the Republic of Bashkortostan. The frequency distribution of the genotypes of all the polymorphic loci studied in the control groups of healthy individuals corresponded to the Hardy-Weinberg equilibrium.

The study of polymorphic locus rs2243250 of *IL4* gene revealed its association with the development of acute urticaria. In this group of patients rs2243250*C allele was determined in 79.35% of individuals, whereas in the control the frequency was lower and was 67.4% (p = 0.0247, OR = 1.86 (95% CI 1.08- 3.21)). In patients with chronic disease, the differences in rs2243250*C allele frequencies with control were less pronounced: here it was detected only in 63.2% of cases (p> 0.05). Statistically significant differences in the distribution of alleles and genotypes frequencies of a given polymorphic locus between healthy individuals and patients with urticaria with or without concomitant allergic diseases have also not been identified.

Association analysis of the SNP rs1805010 of *IL4RA* gene revealed a tendency to increase in patients with chronic urticaria when compared with the control, the frequency of rs1805010*Val/Val genotype, which was 19.3% and 9.9%, respectively (p = 0.054). In the group of patients with acute disease, this genotype was detected only in 8.7% of patients. Comparative analysis of the frequency distribution of alleles and genotypes of SNP rs1805010 of the IL4RA gene in patients with urticaria with concomitant allergic diseases and without them did not reveal statistically significant differences with the control group.

In the study of the rs1800872 polymorphism of the *IL10* gene, no statistically significant differences in the distribution of frequencies of alleles and genotypes between hives patients and controls were found neither. This SNP is not associated with either acute or chronic disease. It should be noted that the association of the polymorphic locus rs1800872 of the *IL10* gene with the development of urticaria was not detected, regardless of the presence or absence of concomitant allergic diseases.

A comparative analysis of the distribution of alleles and genotypes frequencies of the *IL13* gene rs20541 polymorphism in patients with urticaria and in the control group showed that in patients with chronic urticaria there is a tendency to increase of the frequency of rs20541*Arg/Gln genotype. It was detected in 54.6% of individuals from this group, and in in 40.1% controls (p = 0.06). In patients with acute urticaria, the rs20541*Arg/Gln genotype was found in 48.9% of individuals, however, these differences did not reach the level of statistical significance. Minor differences were found when control group was compared to the group of patients with hives with concomitant allergic diseases. In this group, the rs20541*Arg/Arg genotype was detected in 45% of individuals, and the rs20541*Arg/Gln genotype – in 55%. Their frequencies in the controls were, respectively, 52.5% and 40.1% (p> 0.05). The rs20541*Arg/Arg genotype was found in 46.3% of patients with urticaria without concomitant allergic diseases, and an insignificant tendency for the rs20541*Arg/Gln genotype to show an increase in frequency compared with the control (51.3%, p=0.09).

Analysis of the polymorphic locus rs1800629 of the *TNF* gene indicated the association with the development of chronic urticaria of rs1800629*G

allele and rs1800629*G/G genotype. The frequency of rs1800629*G allele was 83.9% in patients and 90.7% in the control group of individuals (p = 0.037, OR = 0.53 (95% CI 0.29-0.97)). The rs1800629*G/G genotype was detected in 67.9% of patients with chronic urticaria and 82.4% of controls (p = 0.0164, OR = 0.45, (95% CI 0.23-0.87)). The frequency of rs1800629*G/A genotype, in contrast, was higher in patients, where it was 32.1%, than in control - 16.7% (p> 0.05). In addition, we discovered the association of the SNP rs1800629 of the TNF gene with the development of urticaria with concomitant allergic diseases. In patients, the rs1800629*G/A genotype frequency was higher than that in controls (29.1% and 16.7%, respectively, p = 0.0179, OR = 2.05 (95% CI = 1.12- 3.75)). In contrast, the rs1800629*G/G genotype and the rs1800629*G allele are more often found in the control group of individuals. The rs1800629*G/G genotype frequency was 69.6% in patients and 82.4% in controls (p = 0.017, OR = 0.49 (95% CI 0.27-0.89)), and the rs1800629*G allele frequency was 84.2% and 90.7%, respectively (p = 0.02, OR = 0.54 (95% CI 0.32-0.93)).

The data obtained by us are in part consistent with the results of other authors. Thus, in patients from Japan and Canada, the rs2243250 polymorphism of the *IL4* gene is associated with the development of AD [9, 13]. However, the authors of the study conducted in China, found no association of this polymorphic locus with the development of allergic dermatoses [16]. As in our work, patients with allergic dermatoses from Japan did not have an association of the *IL4R* gene rs1805010 with the development of the disease [14], however, a large number of studies of polymorphic variants of this gene showed its role in the development of AD and other allergic diseases [17]. A number of studies conducted in Canada, Japan and other countries showed the association of SNP rs20541 of the *IL13* gene with the development of AD [9,12], which, however, is not confirmed by others [16]. Earlier, the association of the SNP rs1800872 of the *IL10* gene with the development of AD in India [5] and with an increased IgE level in patients from Korea [11] and with the development of AD in patients from the Republic of Bashkortostan [3] was found. The association of *TNF* gene SNPs with the development of allergic dermatoses was not found in some works conducted in Macedonia and Great Britain [19]. Nevertheless, the association of the rs1800629 with the development of asthma and atopy in patients from the USA and Spain has been shown [10, 18].

CONCLUSION

In this paper, we analyzed the polymorphic variants of the cytokine genes: rs2243250 of the *IL4* gene, rs1805010 of the *IL4R* gene, rs1800872 of the *IL10* gene, rs20541 of the *IL13* gene and rs1800629 of the *TNF* gene, in patients with hives and controls. As a result of the study, it was revealed that the rs1800629*G allele and the rs1800629*G/G genotype of the *TNF* gene polymorphism are the markers for the increased risk of chronic hives, and the rs2243250*C allele of the *IL4* gene polymorphism is the marker of increased risk of acute urticaria development. The marker of an increased risk of development of urticaria with concomitant allergic diseases is the rs1800629*G/A genotype of the *TNF* gene polymorphism. The rs1800629*G/G genotype and rs1800629*G allele of this polymorphic locus are markers of a reduced risk of hives with concomitant allergic diseases.

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APPROBATION OF THE MOLECULAR GENETIC METHOD FOR THE DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION IN YAKUTIA

ABSTRACT

In this paper we presented the results of approbation of the PCR method for the diagnosis of Helicobacter pylori infection based on the amplification of the *16S rRNA* marker gene of bacterial DNA isolated from samples of gastric mucosa tissue from patients with gastroduodenal diseases in Yakutia.

Keywords: Helicobacter pylori, gastroduodenal diseases, PCR, *16S rRNA* gene, histology, Yakutia.

INTRODUCTION

Helicobacter pylori (*H. pylori*) as considered is a main cause of the development of various gastroduodenal diseases, such as chronic gastritis, erosion and stomach ulcer in humans [1, 3, 5]. In 1994, the International Agency for Research on Cancer classified *H. pylori* infection to the I group of carcinogen (obvious carcinogens), along with some of the radionuclides and radiation [23]. Due to the fact that *H. pylori* is currently associated not only with certain gastroduodenal diseases, but also with severe oncological pathologies, it becomes necessary to specifically diagnose this infection. At present, in clinical practice, there are many different methods for diagnosing *H. pylori* [7, 11-13]. The variety of methods for detection of this infection can be divided into invasive (require fibrogastroduodenoscopy) and non-invasive. The main and most frequently used methods for diagnosing *H. pylori* infection are presented in Table 1. In addition, each of the method has its advantages and disadvantages [11-13]. The disadvantage of many non-invasive methods is their inaccuracy, and the invasive methods – risks of complications, as well as their duration and labor intensity. In clinical practice, the histological examination method is widely used, which allows at the same time to

Table 1

The main detection methods of *Helicobacter pylori*

Invasive methods*	Non-invasive methods**
Histological method: examination of a tissue sample of the gastric mucosa for *H. pylori*	ELISA: a study of feces for the presence of *H. pylori* antigens (using monoclonal antibodies)
Microbiological method: cultivation of *H. pylori* on substratum from a sample of gastric mucosa tissue	ELISA: detection of IgG antibodies to *H. pylori* in serum
PCR method: investigation by polymerase chain reaction on the presence of *H. pylori* DNA from a sample of the gastric mucosa tissue	Rapid urease test (CLO-test, Campylobacter-like organism test)
	Urea breath test (13C, 14C carbamide)
	PCR method: investigation by polymerase chain reaction for the presence of *H. pylori* DNA in saliva or feces

*- Require an endoscopic examination with a targeted biopsy and further study of gastrobiopsies;
** - Not require an endoscopic examination.