HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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THE ROLE OF *Ile105Val* POLYMORPHISM OF THE *GSTP1* GENE IN THE DEVELOPMENT OF ALLERGIC PATHOLOGY IN THE CHILDREN POPULATION OF THE INDUSTRIAL CENTER OF WESTERN URAL

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Introduction. A modern approach to the diagnostic support of patients with allergic diseases involves the introduction of innovative developments in the field of precision medicine, the development, identification and use of reliable biomarkers, including the determination of individual genetic variability in living conditions at various territories of the Russian Federation. **The aim** of the study is to investigate the role of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in the development of allergic pathology and its connection with the characteristics of the formation of the immune profile in the child population of the industrial center of the Western Urals. **Materials and methods.** The observation group consisted of 34 children with allergic pathology. The comparison group included 37 children, relatively healthy, without allergies. Markers of hypersensitivity and cytokine status were studied using enzyme-linked immunosorbent assay. Genotyping was performed using real-time polymerase chain reaction. **Results.** In the group of children with allergic pathology, an increase in the eosinophilic-lymphocyte index was shown by 1.8 times, total IgE concentration by 4.7 times, a change in the level of serum cytokines IL-10 by 1.3 times and IL-4 by 1.8 times relative to the comparison group (p=0.005-0.038). Genetic analysis of the *Ile105Val* polymorphism of the *GSTP1* gene revealed a 2.0-fold increase in the frequency of the homozygous *AA* genotype in the observation group (p=0.01). Allele *A* was associated with the development of allergies in the examined children (OR=2.36; 95% CI=1.16-4.79), while allele *G* had a protective value (OR=0.33; 95% CI= 0.12-0.89). An increase in the concentration of total IgE and blood eosinophils in carriers of the *AA* genotype was shown to be 4.6 times and 1.9 times, respectively, relative to owners of the *AG* and *GG* genotypes (p=0.013-0.031). **Conclusion.** Allele *A* and genotype *AA* of the polymorphic variant *Ile105Val* of the *GSTP1* gene in children with allergic pathology act as sensitivity markers associated with the formation of allergies, a significant increase in total IgE, blood eosinophils and the anti-inflammatory cytokine IL-4, and can be considered as promising indicators of pathophysiological conditions associated with risk of development of atopic processes (allergic pathology) in children (RR=1.61; 95% CI=1.06-2.44) living in the Western Urals.

Keywords. Genetic polymorphism; *GSTP1* gene; immunoglobulin E; eosinophils; IL-4.

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Introduction. The prevalence of allergic diseases, including asthma, atopic dermatitis, allergic rhinitis, conjunctivitis, chronic rhinosinusitis and food allergies, accounts for more than 40% of the population in industrialized countries, and is constantly increasing in developing countries, reducing people's quality of life. The significant increase in the number of allergy cases is due to factors such as environmental pollution, climate change, loss of biodiversity, urbanization, and changing lifestyles and eating habits. The variability of the population's sensitivity to the adverse effects of chemicals is associated with the level and duration of exposure, which significantly depend not only on the development of industry and the type of production, but also on the geographical features and meteorological conditions of the region, as well as concomitant diseases, period of life and genetic predisposition to exposure to xenobiotics [5, 6].

The ability to metabolize xenobiotics is determined by the level of activity of enzyme in biotransformation systems, which depends on the sex, age and genetic characteristics of the organism. Glutathione-S-transferases (GSTs) belong to a multigene family of enzymes that metabolize a wide range of exogenous and endogenous electrophilic compounds, with a high degree of gene polymorphism, which determines the individual level of enzymatic activity. All human tissues express GST, but each tissue has a unique expression profile. Studies show the dominance of GSTP1 (π class) in the respiratory tract, its role in antioxidant protection and the association of polymorphism of this enzyme with the development of allergic inflammation [3, 16].

The aim of the study is to investigate the role of the Ile105Val polymorphism of the GSTP1 gene (rs1695) in the development of allergy pathology and its connection with the characteristics of the formation of the immune profile in the child population of the industrial center of the Western Urals.

Materials and methods. We examined the school-age children of a large industrial center of the Perm region; the observation group included 34 children with allergic pathology: allergic rhinitis, allergic contact dermatitis, atopic dermatitis, asthma with a predominance of the allergic component. The comparison

group included 37 relatively healthy children. The groups were comparable by gender, age, and ethnicity (p>0.05). All legal representatives of the examined children signed voluntary informed consent to participate in the study.

Quantitative indicators of leukocyte fractions were studied using a hematology analyzer "Drew-3" (USA). The content of total IgE, interleukins (IL-6, IL-4, IL-10), tumor necrosis factor (TNFalfa), interferon gamma (IFNgamma) was determined by commercial test systems (Vector-Best, Xema, Russia) using the enzyme immunoassay method on an analyzer "Elx808IU" (BioTek, USA). DNA for genetic analysis was isolated using the sorbent method. The *Ile105Val* polymorphism of the glutathione-S-transferase *GSTP1* gene (rs1695) was studied by real-time polymerase chain reaction on a thermal cycler "CFX96" (Bio-Rad, USA) using SNP-screen kits (Synthol, Russia).

The collected data were analyzed using Statistica 10.0 software (Statsoft, USA). The results are presented as the arithmetic mean and standard error of the mean (M±m) or frequency (%). In the absence of a normal distribution, a normalizing log-transformation was used. The significance of differences between groups in quantitative characteristics was determined using Student's t-test, qualitative variables were compared using the chi-square test (χ^2), differences were considered significant at the p<0.05 level. Genetic analysis data were processed in the "Gene-Expert" program, and genotype frequencies were calculated using the Hardy-Weinberg equilibrium. Allele frequency data were analyzed by logistic regression analysis with calculation of odds ratio (OR), relative risk (RR) and 95% confidence interval (95% CI).

Results and discussion. The identified features of the immune profile of children in the group with allergic pathology (Table 1) indicate characteristic changes in cellular parameters with an increase in the number of blood eosinophils by 1.5 times and the eosinophil-lymphocytic index by 1.8 times relative to the comparison group (p=0.012-0.037), while the References range for this indicator was exceeded in 97.1% of the studied samples. The level of general sensitization in terms of total IgE content significantly exceeded the comparison indicators, on average 4.7 times (p=0.005). Serum levels of cytokine mediators also significantly increased relative to the levels of the comparison group in terms of IL-10 content by 1.3 times and IL-4 and INFgamma by 1.8 times, respectively (p=0.008-0.038).

The genetic analysis of the *Ile105Val* polymorphism of the *GSTP1* gene (Table 2) revealed a 2.0-fold increased frequency of occurrence of the homozygous *AA* genotype in the group of examined children with allergic pathology relative to the comparison group (additive model: p=0.01). In this case, carriage of the *A* allele can be considered as a marker of sensitivity associated with the development of atopic diseases (OR=2.36; 95% CI=1.16-4.79), while the *G* allele probably performs a protective function (OR=0.33; 95% CI=0.12-0.89). The distribution of allele and genotype frequencies corresponded to Hardy-Weinberg equilibrium (χ^2=0.02-0.22; p=0.64-0.88). Calculation of the relative risk showed an increase in the probability of developing allergic health disorders by 1.7 times in owners of the *A* allele compared with carriers of the *G* variant in the examined group (RR=1.61; 95% CI=1.06-2.44).

A study of hypersensitivity markers in children with allergic pathology associated with carriage of the *Ile105Val* polymorphic variant of the *GSTP1* gene (Table 3)

Table 1

Basic and immune parameters in examined children with allergic diseases

Parameter	Observation group	Comparison group	p
Age, years	11.41±0.59	11.26±0.32	0.838
Gender, girls/boys, %	61.8/38.2	62.2/37.8	1.000
Total IgE, IU/cm^3	201.99±108.63	43.27±18.27	0.005
Eosinophils, %	4.18±1.20	2.70±0.67	0.037
Eosinophilic-lymphocytic index	0.105±0.033	0.059±0.014	0.012
IL-10, pg/cm^3	3.60±0.62	2.78±0.47	0.038
IL-4, pg/cm^3	1.70±0.54	0.92±0.20	0.008
IL-6, pg/cm^3	2.23±1.05	1.49±0.25	0.167
INFgamma, pg/cm^3	1.82±0.56	1.02±0.22	0.009
TNFalfa, pg/cm^3	2.09±0.64	1.55±0.26	0.122

Table 2

Results in the study of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in children with allergic pathology

Genotype, allele	Observation group, %	Comparison group, %	p	OR (95% CI)
Multiplicative model (chi-square test)				
A	73.5	54.1	0.02	2.36 (1.16-4.79)
G	26.5	45.9		0.42 (0.21-0.86)
Additive model (Cochran-Armitage test for linear trends)				
AA	52.9	27.0	0.01	3.04 (1.13-8.17)
AG	41.2	54.1		0.60 (0.23-1.52)
GG	5.9	18.9		0.27 (0.05-1.39)

Table 3

Features of hypersensitivity indicators in children with allergic pathology associated with the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695)

Показатель	Genotype		p
	AA	*AG+GG*	
Total IgE, IU/cm^3	320.04±193.40	69.17±39.57	0.013
Total IgE >100.0 IU/cm^3	61.1%	25.0%	0.045
Eosinophils, %	5.33±2.12	2.88±0.70	0.031
Eosinophils >3.0%	55.6%	18.8%	0.039

determined significantly higher levels of total IgE concentration and relative content of blood eosinophils, increased by 4.6 times and 1.9 times respectively in carriers with the *AA* genotype relative to those with heterozygous *AG* and variant homozygous *GG* genotypes (p=0.013-0.031). The proportion of samples exceeding the References value in carriers of the *AA* genotype was significantly higher, by 2.4 times for total IgE and 3.0 times for blood eosinophil content, 61.1% and 55.6%, respectively (p=0.039-0.045).

Allergic diseases are mediated by the specific influence of environmental factors and an imbalance of innate and adaptive immune reactions with the development of a pathological allergic inflammatory process [4]. It is believed that environmental changes, associated primarily with an increase in the level of chemical contamination, are the leading factor in the rapid spread and progression of allergic pathology [15]. Many pollutants exhibit oxidative properties, promoting the activation of free radical oxidation processes and the development of oxidative stress, which in turn can also provoke the progression of allergies through the regulation of signaling pathways (NF-κB) and activation of the production of proinflammatory mediators (IL-6, IL-1, TNF), increasing the expression of the corresponding genes even at very low levels of exposure [13, 14].

GSTP1 is the main enzyme of this group in the lung epithelium, which accounts for up to 90% of the activity; therefore, genetic polymorphism of the GSTP1 coding sequence is crucial in the implementation of antioxidant protection and detoxification of aerogenic chemical compounds. The GSTP1 gene is mapped to chromosome 11q13.2 and consists of seven exons and six introns. The *Ile-105Val* polymorphism of the *GSTP1* gene (rs1695) is located in the coding region near the ligand-binding site, in which adenine (A) is replaced by guanine (G) at position 313 of exon 5 (*313A>G*), which leads to the replacement of the amino acid isoleucine (Ile) by valine (Val) in codon 105 and changes in the physicochemical properties and secondary structure of the protein, modification of the catalytic activity of the enzyme [17].

Studies show an association of the *Ile105Val* polymorphism of the *GSTP1* gene with an increased risk of decreased pulmonary function, asthma and allergies as a result of exposure to exhaust gases and industrial pollutants, and variant genotypes are prone to earlier development of symptoms and a more severe course of various forms of allergic pathology [1, 9]. At the same time, data regarding individual polymorphic variants of *Ile105Val GSTP1* are quite contradictory due to differences in study design, exposure level, gender, age and ethnicity of participants. Various polymorphic variants of *GSTP1* gene can significantly differ in the level of expression, changes in the catalytic activity of the enzyme or substrate specificity, and also depend on the level of exposure to toxicants [7, 18]. For example, the Val-variant of the GSTP1 enzyme exhibits greater catalytic activity towards diol epoxides of polycyclic aromatic compounds and lower catalytic activity towards 1-chloro-2,4-dinitrobenzene compared to the Ile-variant. Factors such as the possibility of gene interactions with other components of the antioxidant defense system (other *GST* or *NQO1* genotypes) or environmental factors should be taken into account. It has been shown that the protective effects of *GSTP1* genotypes on the negative effects of diesel exhaust particles, observed at lower levels and exposure patterns, can be reversed when children are exposed to multiple environmental stressors at an early age [10]. The current inconsistency in research results may therefore be explained by variations in enzyme activity towards different pollutants and depending on specific environmental conditions or research methodology.

It is worth noting a number of scientific works that are consistent with our results and indicate a possible protective role of the *G* allele (*Val*) and a decrease in the frequency of the *GG* genotype in patients with atopy [2]. An increased risk of asthma in children carrying the *IleIle* (*AA*) genotype has been reported in both areas with high and low levels of air pollution [11]. Controlled human exposure studies examining the effect of *GSTP1* polymorphism on the association between exposure to exhaust air pollution and respiratory disease and allergy also showed increased allergic inflammation, elevated IgE and histamine levels in carriers of the *AA* genotype [12].

A modern approach to patients with allergic diseases must combine accurate diagnosis and personalized treatment, new developments in the field of precision medicine, phenotyping and endotyping of diseases, as well as the identification and use of reliable biomarkers, including the determination of individual genetic variability in conditions of exposure to harmful factors of production and the environment [8]. The results obtained in this research require further study due to the limited sample size, taking into account possible gene and gene-environment interactions and population characteristics of the examined group.

Conclusion. A study of the association of the genetic polymorphism *Ile105Val* of the *GSTP1* gene with the development of allergic pathology in children showed a shift in the vector of immune regulation towards Th2-inflammatory responses – an increase in the production of total IgE, the number of blood eosinophils and IL-4 (p=0.005-0.037). The identified shift in immune parameters in children with allergic pathology was reliably associated with individual genetic variability in *Ile105Val* polymorphism of the *GSTP1* gene, and the *A* allele of *Ile105Val* polymorphism acts as a marker of sensitivity (OR=2.36; 95% CI=1.16-4.79) and the risk of allergy formation (RR=1.61; 95% CI=1.06-2.44) and can be considered as a promising prognostic criterion, a marker of individual risk of developing atopic processes in children in industrialized areas of the Western Urals.

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EPIDEMIOLOGICAL PREVALENCE OF MEASLES IN THE RUSSIAN FEDERATION, NEIGHBOURING AND FOREIGN STATES

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This article analyzes the statistical studies results of the epidemiological prevalence of measles infection in Russia, neighboring and foreign countries for the period from 2017 to 2023. A comparative characteristic of the measles incidence has been carried out in the Russian Federation, Ukraine, Georgia, Kazakhstan, and the USA. The effect of immunization results on morbidity is shown. The increasing risks of outbreaks of morbidity associated with migrations and import processes during the import of the causative agent of measles infection have been identified.

The reasons for the lack of vaccination against measles among the entire population are considered. Data on vaccination coverage among residents of the Russian Federation are provided. Social groups that are less resistant to outbreaks of the disease due to the lack of immunization have been identified. All risks and possible complications due to high morbidity among the entire population are reflected. The restrictive measures influence related to the unfavorable epidemiological situation of COVID-19 was noted. The relationship is presented between the introduced restrictive measures related to the new coronavirus infection and the reduction of measles outbreaks among different countries, as well as the general incidence. The prevention importance is shown among children and adults, as well as the importance of timely detection of new measles infection outbreaks.

Keywords: measles; morbidity; epidemiological situation, vaccination.

Introduction. Measles is a highly contagious acute viral disease that is transmitted by airborne droplets and can lead to serious complications and death.

The incubation period of measles infection ranges from 9 to 17 days. Infected people are contagious from 4 days before the appearance of the rash and up to 4 days after the appearance of the rash in vaccinated people.

Measles virus is transmitted by airborne droplets through aerosolised secretions, as a part of the contents of the nasopharynx, secretions from coughing, sneezing, talking, breathing. The pathogen can spread considerable distances with airflow.

The disease begins with fever and usually at least one of three symptoms: cough, rhinitis and conjunctivitis. Filatov-Koplik spots are small whitish-gray dots surrounded by a corolla of hyperemia. They are located on the mucous membrane of the cheeks opposite the second molars and make it possible to clinically diagnose measles a day or two before the rash appears.

The rash appears in 3-4 days after the onset of fever, first on the face and behind the ears. Then it spreads to the trunk and extremities, coinciding with the development of the adaptive immune response. Fever and catarrhal symptoms usually peak along with the rash, which persists for 3-4 days. Measles in vaccinated patients occurs in a mild form, there is no stage in the manifestation of infection.

Diagnostic studies of measles consist of the collection of anamnesis, examination, assessment of the manifestation of the main symptoms of the disease, as well as laboratory and instrumental methods of investigation.

Specific prevention. The main method of protecting the population from measles, rubella and mumps is vaccination.

Immunization of the population against measles, rubella, and mumps is carried out within the framework of the National Calendar of Preventive Vaccinations and the Epidemic Indications Preventive Vaccination Calendar.

Children and adults who received vaccinations under the National Preventive

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