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The Influence of Immunogenetic Factors on the Development and Course of Allergic Rhinitis

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Abstract Allergic diseases are among the most common chronic conditions, characterized by the body's hypersensitivity to certain environmental factors perceived as potentially dangerous. The purpose of this review is to examine current issues related to the molecular genetic factors in the development of allergic rhinitis. This review includes scientific publications from the past 10 years, published in the international databases E-library, Scopus, and Web of Science. Therefore, it can be concluded that studying the molecular genetic factors in the development of allergic rhinitis is relevant and requires further research.

Keywords Allergic rhinitis, Pathogenesis, Gene, Associations, Polymorphism

Allergic rhinitis (AR) is a disease characterized by IgE-mediated inflammation that develops as a result of allergens entering the nasal mucosa [2,10,14]. Worldwide, AR affects 10-30% of adults and up to 40% of children; in Russia, the prevalence of AR in different regions ranges from 18 to 38% [3,7,17,21]. Symptoms developing with AR are not life-threatening; however, they create significant discomfort and sharply reduce a person's ability to work and quality of life [5,11,13].

Late diagnosis of AR and untimely prescription of pathogenetic therapy can lead to complications and the development of asthma [4,6,9,16,18]. The results of epidemiological, pathophysiological, and clinical studies served as the basis for considering AR as a risk factor for asthma or as pre-asthma, i.e., an early stage of a single respiratory disease [1,12,19,22].

Allergic diseases have a complex, multifactorial nature and develop through the interaction of environmental factors and genetic predisposition [8,15,20].

The purpose of this review is to examine current issues regarding the molecular genetic factors in the development of allergic rhinitis.

The review material includes scientific publications from the past 10 years, published in the international databases E-library, Scopus, and Web of Science.

Review results and discussion. Since the late 1980s and early 1990s, active research into the molecular genetic basis of atopy has begun worldwide. Numerous clinical observations, clinical genealogical, population-based, and twin studies have provided compelling evidence of the significance of hereditary factors in the development of atopic diseases [9]. The data obtained by such research methods clearly indicate a genetic predisposition to atopy, and modern molecular genetic studies specify which hereditary factors are most important for this [2].

One effective approach to studying the role of genetic mechanisms in the development of atopy involves identifying a group of genes, the products of which may be directly or indirectly involved in the development of this pathology, the so-called candidate genes. The greatest difficulty in this regard has proven to be the polygenic nature of AR. Therefore, the traditional "gene-disease" framework for studying AR cannot be used in patients with AR. From a genetic perspective, AR is currently considered a multifactorial polygenic disorder, the hereditary transmission of which is carried out by a group of genes [18]. In the 1980s and 1990s, numerous studies were conducted using molecular genetic methods for the purpose of positional cloning and the study of candidate genes. The main characteristics of the AR phenotype were eosinophilia, atopy, and increased IgE levels [5], resulting from the interaction of multiple gene variants. At present, many specific AR candidate genes are already known, the function of the protein products of which is associated with the development of this disease: genes of cytokines and their receptors], the interferon gene – γ IFNG [10], the tumor necrosis factor α gene TNF α, chemokine genes, including the genes of the eotaxin family – RANTES, CCS1, CCL24, CCL26, genes of xenobiotic biotransformation enzymes – GSTM, GSTT, CYP1A1, CYP2C9, CYP2C19, NAT2, the gene of the high-affinity mast cell receptor FcsRI, etc. [14]. According to these researchers, atopic diseases, including allergic rhinitis, should be classified as diseases with an additive polygenic inheritance pattern and a threshold effect, whereby the clinical picture of the disease manifests itself when the combined effects of genetic and environmental factors reach or exceed a threshold value [3]. With a high

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degree of genetic burden, this threshold is reached under conditions common to most people. On the other hand, prolonged and intense exposure to aggressive external factors can also manifest minimally expressed genetic defects. This approach assumes the presence of a significant number of phenotypically healthy individuals in the population with subthreshold defects that may manifest themselves later.

A key link in the pathogenesis of atopic diseases is the production of proinflammatory cytokines and chemokines in these patients, responsible for the development of chronic allergic inflammation [1]. These are primarily IL-4 and the IL-4 receptor, IL-5, IL-6, IL-10, IL-13, IL-18, TNF-α, TGF-β1 (transforming growth factor β) [], GM-CSF (granulocyte-macrophage colony-stimulating factor), IFN-gamma (interferon gamma). For a full-fledged allergic reaction, it is necessary to form a large number of chemokines responsible for the chemotaxis of monocytes, basophils (CCL2), induction and attraction (CCL11 or Eotaxin) of eosinophils to the site of the allergic reaction, and the release of the contents of eosinophil granules (CCL5 or RANTES) [20].

Cytokines are classified based on their biochemical characteristics, types of specific cellular receptors, and biological properties. Cytokines include interferons, interleukins, chemokines, a group of tumor necrosis factors, transforming growth factors, and several others [6]. The main common properties of cytokines, which unite them into an independent regulatory system, include: pleiotropism and interchangeability of biological action, mainly the inducible nature of synthesis in response to the penetration of pathogens (antigens) into the body or damage to tissue integrity, the absence of antigen specificity of action, self-regulation of production and the formation of a cytokine network, and signal transmission through interaction with high-affinity cellular receptor complexes. Within the immune system, cytokines mediate the relationship between nonspecific defense reactions and specific immunity, acting in both directions [7]. Chemotoxic cytokines—chemokines—are small signaling proteins that influence the accumulation of inflammatory cells in the mucous membranes in various diseases [5]. CC chemokines—RANTES (regulated on activation, normal T cell expressed and secreted) and the eotaxin family—influence the activity of eosinophils, which are the main factor in tissue damage in allergic diseases [10]. The study of the genes encoding the corresponding chemokines is currently relevant and is actively carried out worldwide in the molecular genetic study of AR [13].

Tumor necrosis factor-α (TNF-α) is a substance that plays an important role in the regulation of normal differentiation, growth, and metabolism of various cells, and at the same time, it is a potent proinflammatory cytokine. The biological activity of TNF-α is mediated by binding to specific membrane receptors with a molecular mass of 55 kDa (type I or CD120a) and 75 kDa (type II or CD120b). The latter belong to type I transmembrane receptors and are expressed on many cells, including polymorphonuclear leukocytes, endothelial cells, fibroblasts, keratinocytes, etc. Binding of TNF-α to the corresponding receptors leads to the activation of the transcription factors NF kB and AP 1, which in turn regulate the activity of several genes encoding the synthesis of proinflammatory cytokines and other inflammatory mediators and induce programmed cell death (apoptosis). TNF has an activating effect on macrophages [5] and induces the production of other proinflammatory cytokines (IL-1, IL-6). Local TNF production at the site of inflammation ensures the chemotaxis of granulocytes and monocytes into the inflammatory focus, their enhanced degranulation, and increased phagocyte cytotoxicity. TNF is involved not only in protective responses, but also in the destruction and reparation processes that accompany inflammation [17].

TNF-aa gene polymorphism. The tumor necrosis factor α gene is localized on the short arm of chromosome 6 (6p21.3). Allelic variants of the gene located in the promoter region are functionally significant: –863C>A, –850C>T, –376G>A, –308G>A, and –238G>A.

Gene polymorphisms are associated with susceptibility to atopy, type 1 diabetes mellitus, susceptibility to septic shock, arthritis in psoriasis, and migraine (allele –308A) [17].

Despite the obvious clinical and biochemical justification for studying cytokine and growth factor gene polymorphisms in relation to atopy, only a few laboratories worldwide are addressing this issue. Further, clinically and genetically in-depth research into this issue is needed.

RANTES/CCL5 – (Regulated on Activation Normal T cell Expressed and Secreted) – regulates the activity of normal T cell expression and secretion. It is a low-molecular-weight protein (molecular weight in humans ranges between 7.8 and 8.7 kDa). Airway epithelial cells are the main source of RANTES. It belongs to the b family of CC chemokines. It is a regulator of natural immunity – anti-inflammatory cytokines. It is involved in the non-specific protection of the body from bacterial and viral infections. Their main targets are cells belonging to the subpopulations of CD4+/CD45RO+ T lymphocytes, as well as monocytes and eosinophilic granulocytes. RANTES is an integral modulator of many immunological, allergic and inflammatory reactions, participates in the migration and accumulation of lymphocytes, monocytes and eosinophilic granulocytes in inflammatory and pathologically damaged areas of tissues and organs, and is a mediator of angiogenesis [15]. Significant changes in the RANTES level in PC have been described in human autoimmune diseases - asthma, subclinical chronic inflammation, focal alopecia, tumors, as well as in AIDS [21].

The RANTES gene is located on chromosome 17q11.2 12. The polymorphic marker A(-403)G of the CCL5 gene is a single nucleotide substitution G→A at position 403 of the promoter region of the gene.

Several similar studies investigating the A(-403)G marker of the CCL5 gene have not found an association of this marker with bronchial asthma and atopy [14]. Thus, in a study by Yao et al., there was no association of the A(-403)G marker with atopy, the number of eosinophils in the blood, and bronchial hyperreactivity in Asian children. Two studies conducted in the UK demonstrated an association of this marker with atopic bronchial asthma and atopy. It is possible

that such a difference in results can be explained by differences in samples, environmental exposures, and allergens that may be involved in pathogenic mechanisms [19].

Functional analysis showed that the –403 G→A substitution increases promoter transcriptional activity, resulting in increased RANTES production by T cells, megakaryocytes, and mast cells. However, the same study found that the A(–403)G polymorphism does not affect RANTES expression by epithelial cells, which are the main source of RANTES in the airways. Since not all cells produce increased amounts of RANTES, it is possible that this change in protein levels does not exacerbate atopic asthma [6].

The CTLA4 gene is located on chromosome 2q33 and encodes cytotoxic T lymphocyte-associated antigen 4. The CTLA4 gene expression product is involved in T cell activation [14]. This T cell receptor, a transmembrane glycoprotein, is expressed for 2–3 days after T lymphocyte activation. CTLA 4 mediates the suppression of Th2 cell activation, which shifts the balance toward the development of a Th1-dependent response [18]. In this study, we investigated the association of the A(+49)G polymorphic marker of the CTLA4 gene with AR. The A(+49)G polymorphic marker is a single nucleotide substitution A→G at position +49 in exon 1, resulting in an amino acid substitution of threonine to alanine at position 17 of the polypeptide chain. The designation of this polymorphism in the NCBI database is RS231775. Carriers of the mutant allele of the A(+49)G polymorphic marker were found to have increased CTLA 4 expression on the surface of activated T cells [14]. It is also known that the Ala/Ala genotype is associated with decreased CTLA 4 expression on the surface of T cells with subsequent weakening of CTLA 4 function [8].

It should be emphasized that in studies examining the Polish and Japanese populations, no association of this marker with atopic bronchitis was found [8]. However, Korean scientists have established an association of the CTLA 4 gene with atopy [18]. In the same study, an association of the C-Ala haplotype for the A(+49)G marker with atopic bronchitis was found. This can be explained by the fact that the frequencies of alleles and genotypes of the A(+49)G marker vary widely in different populations. Thus, for Koreans, the following genotype frequency distribution was obtained: Ala/Ala - 55-57%, Ala/Thr - 27-34%, Thr/Thr - 9-17% [16], which differs significantly from the distribution of genotype frequencies in people of European descent. Such a difference in frequencies may influence the different contribution of the polymorphic marker to the genetic predisposition to atopic disease depending on the population.

Environmental factors play a significant role in the etiology and pathogenesis of AR. Biotransformation of xenobiotics and endogenous substances, consisting of modification of their physical properties from lipophilic to hydrophilic to facilitate their elimination from the body, is a powerful mechanism for protecting the body from external chemical factors and regulating metabolic reactions [9]. Xenobiotic biotransformation enzymes (XBEs) are involved in the metabolism of leukotrienes and prostaglandins, mediators of allergic inflammation, as well as in the regulation of oxidative stress mechanisms, which plays a significant role in the pathogenesis of atopy [2]. In this regard, XBEs encoded by the genes of the biotransformation system are also an interesting object of research. An important feature of these genes is their polymorphism, with most alleles of these genes causing the formation of biotransformation enzymes with altered activity. This, in turn, leads to a change in the rate and ability to metabolize substrates. Since substrates are a wide variety of substances, both endogenous and exogenous, changes in their metabolism can lead to an increased risk of developing a disease (oncology, allergies, etc.). The biotransformation of xenobiotics is a three-stage process that includes their activation (phase I), detoxification (phase II), and elimination from the body (phase III) [7]. In this case, the enzymes of phases I and II of detoxification play a special role in atopic phenomena. Phase I enzymes bind xenobiotics, forming genotoxic intermediate electrophilic metabolites, which, under the action of phase II enzymes, are converted into water-soluble non-toxic derivatives and eliminated from the body.

Phase 1 (activation) is carried out primarily by a large family of enzymes – cytochromes P450, as well as microsomal epoxide hydrolase and some other enzymes of the detoxification system (esterases, amidases, alcohol dehydrogenases, aldehyde dehydrogenases, etc.) [3]. Their main function is the formation of hydrophilic groups in the xenobiotic molecule, which enables the detoxification of tens of thousands of substances. However, in most cases, phase 1 enzymes carry out metabolic activation of xenobiotics in the cell, which is associated with a significant risk to the cell. Active intermediate electrophilic metabolites are the main substrate for phase 2 enzymes. An important feature of the phase 1 enzyme system is its selective localization and high potency on the main pathways of xenobiotic entry into the body – food (liver, gastrointestinal tract), respiratory (lungs, bronchi) – and a variety of metabolic pathways. However, the enzymes of this system are poorly represented in other organs and tissues, meaning they cannot protect the body from other routes of entry. Finally, they can often lead to the formation of toxic metabolites, i.e., xenobiotic toxicity, for example, converting chloroform into phosgene, a potent liver poison.

The main purpose of phase 2 is to neutralize (deactivate, detoxify) the hydrophilic and often toxic products of phase 1 using various hydrolases and transferases. Unlike phase 1 enzymes, phase 2 enzymes are present in all cells, meaning they function regardless of xenobiotic entry, performing or completing detoxification. Glutathione transferases, glucuronyl transferases, sulfotransferases, acetyltransferases, and others participate in this phase, converting toxic intermediate products of phase 1 metabolism into polar, water-soluble, non-toxic compounds that are excreted from the body. Some of the representatives of phase II enzymes are enzymes of the glutathione S transferase superfamily, which play a key role in ensuring cellular resistance to lipid peroxidation, free radicals, protein alkylation, and in preventing DNA breakage

[5]. In addition, glutathione S transferases play an important role as intracellular carriers of bilirubins and hormones, as well as in the biosynthesis of certain physiologically active substances – prostaglandins [16]. Glutathione S transferases are present in a wide variety of tissues, revealing pronounced intertissue differences. Their concentrations are particularly high in the liver, placenta, lungs, brain, kidneys, and intestines [8].

Glutathione-S-transferases and their role in predisposition to respiratory diseases. Polymorphism of enzymes of the glutathione S-transferase (GST) family determines individual sensitivity to environmental factors [5].

To date, several classes of cytosolic glutathione S transferases have been described in humans: alpha (GSTA), mu (GSTM), pi (GSTP), theta (GSTT), kappa (GSTK), sigma (GSTS), omega (GSTO), and zeta (GSTZ). The division into classes is based on the degree of homology of the amino acid sequences of these enzymes and their immunoreactivity. Some of the genes (GSTM and GSTT) encoding these proteins are considered candidate genes for atopy and associated diseases due to their involvement in the metabolism of leukotrienes and prostaglandins, mediators of allergic inflammation, as well as in the regulation of oxidative stress mechanisms, which play a significant role in the pathogenesis of bronchial asthma (BA) and other diseases [18].

Glutathione S-transferase class M. Glutathione S transferases of class M in humans are expressed predominantly in the lungs. Five different genes encoding glutathione S-transferases have been identified (GSTM1, M2, M3, M4, M5). The gene encoding the GSTM1 enzyme isoform is mapped to the 1p13.3 region, is polymorphic, and has four allelic variants: GSTM1*A, *B, *C, and *0. The first two alleles do not have functional differences between themselves. The *C allele is extremely rare in different populations. The *0 variant is a null allele (a deletion within the gene approximately 10,000 bp long) and is phenotypic and manifests as the absence of the GSTM1 enzyme. Homozygous carriage of the GSTM1 gene deletion (GSTM1 0/0 genotype, “null” genotype) is widely represented in the human population, reaching up to 50% in some population groups [10]. Numerous studies indicate an association of the GSTM1 0/0 genotype with diseases of multifactorial origin. Of particular importance are such widespread chronic respiratory diseases as bronchial asthma and chronic bronchitis. Among adult patients with bronchial asthma, the GSTM1 0/0 genotype is found in 70-80%, and the risk of developing bronchial asthma in the presence of this genotype increases by 3.5 times [17]. An association of this locus with bronchial asthma has also been demonstrated in families of French origin [10].

Thus, individuals with a “null” genotype for the GSTM1 gene are clearly predisposed to chronic upper respiratory diseases.

Glutathione S-transferase class T. The activity of the glutathione S-transferase class T enzyme is almost 10 times higher than the enzymatic activity of proteins of classes A, M, and P. There is evidence that the GSTT1 enzyme binds to the substrate (xenobiotic) more quickly, neutralizes activated xenobiotics more quickly, and enters the new cycle more quickly than other GSTs. GSTT1 detoxifies many environmental pollutants, primarily toxic halogenated hydrocarbons [17]. The GSTT1 gene is mapped to chromosome 22 (22q11.2); its polymorphism is caused by a deletion, which is accompanied by the formation of two types of alleles: functionally active (GSTT1*1) and inactive or null (GSTT1*0). The GSTT1*0 allele results in the absence of enzyme synthesis. An increased frequency of the GSTT1 null allele has been observed in patients with bronchial asthma compared to the control population [2]. GSTT1 can influence the level of eicosanoids (critical mediators in the allergic response) by modulating the level of free radicals [14]. In addition, the role of this enzyme in the utilization of free radical oxidation products has been noted, i.e., it is part of the protection of the lungs from free radical damage and the development of oxidative stress. GSTT1 utilizes oxidized lipids and damaged DNA [16]. In addition, the genes of the detoxification system represent only individual, albeit quite important, elements of the gene network against which the pathological process unfolds in atopy, including AR. The extent to which the phenotypic characteristics of AR depend on the functional characteristics of protein products of other genes involved in the detoxification system, as well as immune response genes, cell membrane receptors, and so on, remains completely unexplored and requires specialized research.

Therefore, studying the GSTT1 gene polymorphism is important because it is expressed in the lungs and the protein is involved in the antioxidant defense of the respiratory tract.

To date, the HuGE Navigator database has published association studies of atopy with more than 80 candidate genes, with consistent, reproducible results obtained for nearly half of them.

Eotaxin Genes. Eotaxins are active eosinophil chemoattractants that influence the recruitment of eosinophils and Th2 lymphocytes during allergic inflammation. The protein products of the eotaxin family of genes play a significant role in the development of allergic reactions. Tumor necrosis factor-α and interleukin-4 are known to stimulate eotaxin transcription in pulmonary fibroblasts and airway epithelial cells [8]. Eotaxin expression is increased in allergic rhinitis [14], and it exerts its activity through its receptor, CCR3, located on eosinophils, Th2 lymphocytes, and basophils [16].

The eotaxin gene (CCS1) is localized on chromosome 17 in the q21 region, spans approximately 3 kb of genomic DNA, and consists of three exons [8]. Its homologs, eotaxin 2 (CCL24) and eotaxin 3 (CCL26), each containing three exons, are mapped to chromosome 7 in the q1 1.23 and q11.2 regions, respectively. Eotaxin and eotaxin 2 have similar properties, while eotaxin 3 exhibits much lower activity.

Genes encoding enzymes of phase I biotransformation. Phase I of xenobiotic biotransformation, or the activation phase, is mainly mediated by a large family of cytochrome P450 isoenzymes (such as CYP1A1, CYP2D6, CYP2C9, CYP2C19), which are localized in the membranes of the

endoplasmic reticulum [22]. The main functions of these enzymes are the formation of hydrophilic groups in the substrate (xenobiotic) molecule, which is what causes detoxification. Numerous studies of the interaction of BC enzymes with the body's immune responses have shown that the activity of cytochrome P450 enzymes is inhibited in one way or another by proinflammatory cytokines (IL1, TNFa, IL6, IL11, INFy) and growth factors (TGFp, KGF, EGF) [21]. There is evidence of inhibition of cytochrome P450-dependent monooxygenases under conditions of pharmacological stimulation of the immune system—upon administration of bacterial lipopolysaccharides, interferon inducers, and synthetic immunomodulators. The superfamily of genes encoding various isoforms of cytochrome P450 enzymes is represented by approximately 100 genes mapped to different chromosomes. The most important enzymes in the metabolism of carcinogens, various polycyclic hydrocarbons, and drugs are representatives of the CYP1 and CYP2 families, expressed mainly in the lungs and liver [19].

Genes of interleukins and their receptors. Interleukins play a key role at all stages of atopic reactions [20]. Of particular importance is IL 4, which switches B lymphocytes to IgE production; IL 5, which attracts eosinophils to the site of inflammation; IL-9, which activates mast cells; IL-13, which duplicates the functions of IL-4 [7]. Interestingly, all of these ILs are located in a single cluster on chromosomal region 5q24 31, for which linkage to atopic diseases and traits has been repeatedly shown. In this regard, IL genes are actively studied in connection with atopy and bronchial asthma (BA). In particular, an association has been established between the 589C/T polymorphism in the IL4 gene promoter region and atopic BA and IgE levels []. A recent large-scale study using case-control designs and family association tests established a link between the haplotype formed by the 589C/T polymorphisms of the IL4 gene and the missense variant Arg130Gln of the IL13 gene with BA, atopic dermatitis, and atopy, determined by skin allergy tests [8].

The IL4 and IL13 genes encode cytokines of the same name, which are critical in IgE-mediated reactions, initiating the Tn2 immune response characteristic of atopic allergies. These genes are located in the chromosomal region 5q31, for which repeated confirmation of a link with A3 has also been obtained. Both cytokines contact target cells through specific receptors, the common subunit of which is the IL4RA gene product, which ensures the overlap of IL 4 and IL 13 signals and, accordingly, the similarity of their biological effects [9]. The IL4RA gene is located in a locus on chromosome 16 linked to atopic diseases and IgE levels; a number of its polymorphisms have a significant impact on the signaling function of IL 4 and IL 13, predisposing to IgE hyperproduction [6]. The cytokines IL-10 and TGF-β, encoded by the IL10 and TGF-β genes, respectively, play a major role in suppressing the allergic immune response to viruses, a number of microbes, and helminths. Their increased expression, for example, explains the paradoxical situation where helminth infestation, which stimulates Th2 immunity, proves to be a protective factor against the development of A3. Accordingly, it has been established that promoter polymorphisms of IL-10 and TGF-β, which reduce gene expression, are associated with A3 and the severity of bronchial asthma and atopy [17].

The high-affinity IgE receptor gene on mast cells (FCER1B). Another candidate for the role of the main gene predisposing to atopy and bronchial asthma is the gene encoding the β chain of the high-affinity IgE receptor. The interaction of antigen-specific IgE with the receptor on mast cells (FceRI) plays a central role in the pathogenesis of allergic diseases. The complete FceRI receptor consists of four subunits: IgE binding α, signaling enhancer (3 and 2 disulfide-linked), and γ, which conduct the ligand signal into the cell. The gene encoding subunit 3 was recognized as a candidate for atopy for two main reasons: 1) the function of its protein product is to significantly (up to 7-fold) enhance signal transduction by γ chains; 2) it is localized on chromosome 11q13 near the D11S97 marker, which has shown close genetic linkage to the hypothetical asthma/atopy locus [15].

Recently, nitric oxide (NO) in exhaled air has become widely used as a marker of allergic inflammation. A gene controlling NO synthase production (NO51) was identified on chromosome 12q. Research in this area is ongoing, and in the future, this marker could be used in the comprehensive diagnosis of allergic diseases. Furthermore, IgE levels were included in the analysis, as allergies mediated by antibodies of this class are the most common.

Five genes were found to be common to all allergic diseases and IgE: HLA DQB1, HLA DRB1, IL4, IL4RA, and MS4A2. These genes can be called syntropic genes when applied to allergic diseases. In addition, five more genes – HLA DQA1, LTC4S, IL13, IL10, TGFB1 – were common to IgE and all allergic diseases, except one: HLA DQA1 and LTC4S are not associated with food allergy, IL13 – with K/OK, IL10 and TGFB1 – with food allergy [7]. Considering that one of the circumstances complicating this kind of analysis is the insufficient study of genes in relation to a specific pathology, it can be assumed that these five genes are also syntropic for allergic diseases. Thus, the genetic determination of atopic rhinitis is not in doubt. However, data on the main locus responsible for the manifestations of the disease have not yet been obtained. In addition, the genetic background does not explain the rapid increase in atopic diseases observed in recent years. The participation of environmental factors in the development of AR in predisposed individuals is obvious. Summarizing the above data, it can be noted that molecular genetic studies of atopic and other allergic diseases are of great scientific and practical importance. These studies will contribute to an in-depth study of the molecular genetic mechanisms of the pathogenesis of these diseases, the creation of their etiological classification, the development of genetic screening to identify predisposed individuals, and the substantiation of more appropriate approaches to therapy and prevention [16].

One of the most promising modern methods for studying complex traits is the method of genome-wide association studies (GWAS), which involves genotyping and testing the

association with the disease of hundreds of thousands of single nucleotide polymorphisms (SNPs) [5]. The 7th GWAS of asthma revealed an association of SNPs localized in the 17ql2-q21 region (ORMDL3 and GSDMB genes) with childhood asthma in Germany and the UK [7]. In recent years, GWAS of asthma have been conducted in various populations around the world; new genes associated with the development of asthma have been discovered in individuals of European origin - DENND1B, PDE4D, RAD50, IL1RL1 /IL18R1, HLA-DQ, IL33, IL6R, SMAD3 and IL2RB; of African origin - ADRA1B, PRNP and DPP10; Mexicans - TLE4, Koreans - CTNNA3, Japanese - TSLP, WDR36. The results of two G WAS for AD have been published, revealing an association with the SNP of region 1 lql3.5 in individuals of European descent [12], and SNPs localized in the regions 5q22.1, 20ql3.33 and lq21.3 (FLG) in Chinese [6]. In GWAS for AR and hay fever in individuals of European descent, an association was established with the SNPs of the genes HLA-DRB4, Cllorf30, LRRC32, TMEM232 and SLC25A46 [15].

Overall, genetic studies have shown that many functionally interconnected genes are involved in the etiopathogenesis of A3. More than 150 A3 candidate genes have been identified, but only about 40 of them have been associated with A3 in more than five independent studies [8]. Among them are genes encoding cytokines (IL4, IL4RA, IL12B, IL13, TNFA, CCL5), the major histocompatibility complex (HLA-DRB1), 32-adrenergic receptors (ADRB2), xenobiotic biotransformation enzymes (GSTM1, GSTP1, and GSTT1), and genes whose protein products are involved in the recognition of conserved microbial structures (CD 14, TLR2, TLR4, CD 14, CARD 15), in the regulation of epithelial barrier function (FLG, SPINK5), positionally cloned genes (ADAM33, DPP10, GPR154), and the ORMDL3 and GSDMB genes, detected in genome-wide association analysis.

The analysis of immunogenetic factors demonstrates that variations in genes responsible for immune regulation play an important role in the susceptibility to allergic rhinitis. Polymorphisms in genes associated with cytokines, immunoglobulin E (IgE) production, human leukocyte antigen (HLA) system, and other immune response mediators can influence the development, severity, and progression of the disease. These genetic variations may affect immune system reactivity, leading to an exaggerated allergic response to environmental allergens.

Furthermore, immunogenetic factors can determine individual differences in clinical manifestations, disease severity, and response to therapy. Understanding these mechanisms contributes to improved diagnostic approaches, early identification of individuals at risk, and the development of more personalized and effective treatment strategies.

In conclusion, immunogenetic determinants play a crucial role in the pathogenesis and progression of allergic rhinitis. Further research in this field will enhance our understanding of the disease mechanisms and support the development of targeted preventive and therapeutic approaches in allergic diseases.

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