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About the Genetic Aspects of Chronic Otitis Media (Literature Review)

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Chronic purulent otitis media is recognized as one of the most common pathologies in otirics and is the second most common among ENT-pathology. Worldwide, chronic purulent otitis media affects about 21% of the population, which is about 330 million people, of which 60% have significant hearing loss [3,11]. The prevalence of chronic purulent otitis media in Russia reaches 39.2 people per 1000 population, in 24-63% of chronic purulent otitis media is complicated by the development of cholesteatoma. Bone resorption is detected in 78.8% of cases, which leads to otogenic intracranial and extra-cranial complications [5, 27]. The mortality rate from intracranial complications associated with inflammation in the middle ear cavity and paranasal sinuses is 16.2-50% [13, 33]. Otogenic intracranial complications in adults reach 51.0±22.5%, and in children – 74.3±23.5%.% [13, 17,22,26]. Therefore, chronic purulent otitis media is a medical and socio-economic problem, since most of the patients are of young working age [26].

Modern medical science about the etiopathogenesis of the most common pathologies in the population has come to the idea of the multifactorial nature of their development in more than 90% of all non-infectious forms of pathologies [4]. Their distinctive feature is considered to be the individual manifestation of pathology due to the combination of the effects of genetic and environmental influences and their strength. For each such pathology, a predisposition is determined, depending on hereditary and environmental factors, so there are patients more or less predisposed to the development of a certain disease [7].

Molecular genetics makes it possible to assess the role of candidate genes in the pathogenesis of various diseases. The predisposition to the occurrence of pathology depends on a large number of genes with an additive effect and a variety of independently acting environmental factors.

The predisposition to diseases is based on the genetic diversity (genetic polymorphism) of populations by enzymes, structural, transport proteins, antigenic systems, etc. For almost every disease, it is possible to distinguish the main predisposition genes, whose products play a key role in the initiation of the pathological process, and the secondary ones, whose products play an additional role. Thus, predisposition genes are variants of genes (alleles) that are compatible with the normal course of ontogenesis, but at later stages of development in unfavorable conditions, they lead to various diseases [7].

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Each person's DNA is unique. It contains many different variants of the nucleotide sequences that are specific to a given individual. They are especially numerous at the level of random substitutions (polymorphisms) of single nucleotides (single-nucleotide polymorphism, SNP).

It is the SNP that is particularly important for the molecular diagnosis of diseases. The spectra of genetic polymorphisms depend on geographical conditions, race (ethnic), etc. and they arise as a result of natural selection. Under certain conditions, they can predispose to the development of specific diseases or, on the contrary, prevent them.

Thanks to the success of molecular genetic diagnostics, genes of predisposition to acute and chronic respiratory diseases, bronchial asthma, pathology of the cardiovascular, hematopoietic systems, gastrointestinal tract have been established [9] and many others.

In recent years, an opinion has been formed that a number of infectious diseases also have a hereditary predisposition, that is, not only environmental, but also genetic factors are involved in their development.

The hereditary basis of susceptibility to infectious diseases according to I.A. Goncharova and co authors primarily affects the mechanisms of anti-infectious immunity [7].

Since cytokines are mediators of inflammation, there is no doubt that the study of genes that control the activity of cytokines is an important task in the study of the mechanisms of development and course of diseases and the identification of predisposition to infections. Recent studies have identified genes that affect the predisposition and features of the course of pneumonia, viral hepatitis C, tuberculosis, salmonellosis, tick-borne encephalitis, Lyme disease, etc. [1, 7].

The influence of genetic factors on the development of ENT pathology is actively studied [14, 20, 21].

The works of I. A. Tikhomirova established that IL4 gene polymorphism is associated with the formation of chronic tonsillitis and adenoids in children [21], and according to L. E. Timchuk, IL-1 gene polymorphism contributes to the development of chronic purulent rhinosinusitis [20].

The presence of a hereditary predisposition to the development of acute otitis media in childhood is indicated by many researchers [1, 16, 29, 30, 37].

Despite the obvious role of the infectious agent, perinatal risk factors, and age-related anatomical and physiological features in the etiopathogenesis of acute otitis media in children of the first months of life, great importance is attached to its genetic component.

Recent studies have established that the otitis susceptibility genes are located at loci 17q12

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and 10q22. 3 [29], apolymorphism of the CC16 gene (38 G>A) is associated with the development of secretory otitis media [21].

Patel J. A. and co-authors studied the effect of cytokine polymorphismagens and found that the genetic polymorphism of TNF-308 and IL-6-174 is significantly associated with a predisposition to middle ear inflammation [37].

Larina L. A., using the twin method, proved a higher prevalence of chronic tonsillitis, pharyngitis and tubotitis among twins, compared with children born from a single pregnancy [14].

The genetic aspects of hearing loss are also being studied. The proposed SNPs in the candidate gene selected on the basis of its biological function data are studied [40]. And Grondin Y. co-authors [31] used the method of full-genome associative search and identified new SNPs in the nucleolin gene ($p<0.01$) associated with hearing loss.

Population studies of the candidate gene are often focused on studying SNPs in the coding regions of the gene, and SNPs in non-coding regions of the genome are practically not studied. Polymorphisms of regulatory regions often disregulate the expression of protein isoforms, and polymorphisms of non-coding regions affect the expression of mRNA [28, 31, 38].

Studies in populations identified genes associated with the risk of sensorineural hearing loss, they were conditionally divided into 4 groups responsible for: 1) oxidative stress; 2) maintenance of potassium homeostasis and formation of intercellular contacts; 3) coding of heat shock; 4) genes of predisposition to hearing loss [12].

Often, the cause of differences in the structure of genes is considered to be point mutations, tandem repeats of parts of the gene, deletion of nucleotides or fragments of the gene. This ensures the genetic uniqueness of each person, the variability of the body's reactions to pathogens and environmental factors, and the susceptibility and resistance to a particular pathology [2, 25, 32].

However, the link between a pathology and a mutation of a certain gene does not necessarily prove that genetic polymorphism is its trigger cause, but a possible mechanism of pathogenic effects of the main (not necessarily known) etiological factor and a reliable marker of a genetically determined predisposition to the development of pathology [15, 24, 34, 35].

Polymorphism of cytokine genes in infectious and inflammatory pathologies can be associated with the course and severity of the disease, the effectiveness of drug treatment, this implies the use of these or other drugs and individualize therapy [18, 19].

To date, a sufficient amount of information has been accumulated concerning the etiology of chronic purulent otitis media, the features of the clinical picture of the disease, modern methods of diagnosis and treatment aimed at sanitizing the inflammatory focus in the middle ear and

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preventing the development of recurrent cholesteatomas [6, 11, 41].

The study of the pathogenesis of the inflammatory process in the middle ear by most researchers is reduced to the analysis of disorders of innate immunity associated with changes in the activity of the complement system and lipid peroxidation, the study of factors of dysregulation of humoral immunity and an imbalance of a limited number of pro-inflammatory cytokines in the blood, but does not affect other mechanisms of the occurrence and development of chronic purulent otitis media [8, 10].

Assumptions about the association of the genetic component with the development of acute otitis media were made by foreign scientists in relation to the homozygous genotype A/A of the TNFA gene (-308G / A) and the CX3CR1 gene (Thr280Met) together with the A allele of the IL10 gene (- 1082G/A) and the C allele of the IL1B gene (-511C/T) in the presence of the smoking factor [36, 39, 42, 43].

However, in the development of acute otitis media, its episodic cases, other etiological factors are important, as well as features of the anatomical structure of the eustachian tube, nasopharynx. Therefore, Ustinovich A. A. and co-authors conducted a study on the comparative analysis of the pedigrees of children who underwent acute otitis media in the first months of life and healthy children who did not suffer from otitis media in the first years of life [23].

The authors showed that the frequency of otitis media in the parents of children with acute otitis media was almost 2 times higher than in the parents of children in the control group. The authors confirm the polygenic type of inheritance of the predisposition to acute otitis media, since the frequency of otitis in close relatives of patients with proband is about 2 times higher than in the healthy population, and with subsequent degrees of kinship this frequency quickly decreases (in the first degree of kinship – 36.3%, in the second-10.9%), the frequency of otitis patients is 2.3 times higher than the parents of sick children compared to the control, which indicates an increase in the risk for other family members [23].

In order to study the quantitative contribution of hereditary factors to the formation of a predisposition to acute otitis media, as well as the degree of hereditary predisposition, the authors used the method proposed by D. S. Falconer (1965). The authors indicate that among 99 relatives of the first degree of kinship, 36 suffered from otitis media. This gave a predisposition heritability factor (h2) of 56.8%. Of the 247 relatives of the second degree of kinship, 27 people had otitis media, which gives h2 in 56.0%. The authors concluded that the contribution of hereditary and environmental factors to the development of acute otitis media in the first months of life is approximately the same. At the same time, the predisposition to acute otitis media may not be realized in the absence of adverse external environmental influences [23].

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We can make a preliminary conclusion that the formation of chronic purulent otitis media from acute otitis media will also depend approximately equally on hereditary and environmental factors, but this assumption must be repeatedly rechecked.

In the pathogenesis of chronic purulent otitis media, a number of issues remain unresolved, which makes it impossible to give a complete description of the etiological and pathogenetic factors of its development, as well as molecular and genetic mechanisms associated with cytokine status disorders. In this regard, a comprehensive study of the patterns of development and course of chronic purulent otitis media is considered relevant, including the search for genetic predictors of the severity of the disease, which will allow us to develop personal testing algorithms to assess the predisposition to the development of chronic purulent otitis media, the development of its complicated and severe forms.

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