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The Role of Polymorphism Of Cytokin Genes Against Inflammation And Anti-Inflammation In Patients With Bronchus-Lung Diseases

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ABSTRACT

In the article, the authors revealed the latest modern data on the analysis of literature on the polymorphism of pro- and anti-inflammatory cytokine genes that are most significant in the development of bronchopulmonary diseases. It has been shown that the secretion of pro-and anti-inflammatory cytokines TNF-α, IL-4, IL-1b, IL-6, IL-10 can change in these diseases. The article analyzes the polymorphic properties of genes encoding cytokines, depending on the concentration of these molecules and the course of the disease.

A detailed study of the polymorphic properties of cytokine genes contributes to the development of criteria for predisposition to the development of recurrent bronchitis in children with lymphotic-hypoplastic diathesis and to substantiate the possibility of a new approach to therapy.

Key words: recurrent bronchitis, lymphatic-hypoplastic diathesis, gene polymorphisms, cytokines.

In recent years, the incidence of recurrent and chronic respiratory pathology in the general structure of childhood morbidity has increased in all developed countries [9]. According to the statistics of the Republic of Uzbekistan, in the

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general structure of the disease, respiratory diseases account for 24 per 100,000 population, and 31.62 cases for the first time. Currently, the proportion of bronchitis with recurrent recurrence is increasing. Including 50% of children develop bronchitis [24,28,40]. In the Russian Federation, recurrent bronchitis (RB) occurs in 16.4 cases per 1,000 children. Out of 1000 children, 40-50 are infected at the age of 1-3 years, 75-100 - at the age of 4-6 years, and 30-40 - at the age of 7-9 years. Pathology is more common in people living in environmentally unfavorable places. In particular, at the age of 3-6 years, the incidence is 5-6 times higher than in those living in a favorable environment, with 250 cases per 1,000 children [8,21,42]. Recurrence of bronchitis increases the risk of decreased ventilation function, aggravates bronchial hyperreactivity and promotes the formation of diffuse reactions and the formation of hypersensitivity, leading to the formation of chronic forms of bronchopulmonary diseases [5,20,25,27,55,63]. Many factors influence the development and course of respiratory diseases, among which cytokine status disorders are of particular importance [53,54,66]. Many researchers consider cytokines to be one of the important biomarkers of the inflammatory reaction of the respiratory tract [7,49].

At present, cytokines are isolated as an independent system of regulation of the basic functions of the body, along with the nervous and endocrine systems. Their main function is considered to be the maintenance of hemostasis when pathogens enter the body and tissue integrity is compromised [49,54]. One of the important results of human genome research was the emergence and rapid development of a qualitatively new branch of medicine - molecular medicine [3,5]: the specificity of molecular medicine as a science is its specificity, based on the molecular structure of the human genome. It focuses on the correction of the pathological process in a particular individual, taking into account the characteristics of his genome [2,10,44]. Their role in the pathogenesis of many diseases allows, on the one hand, to predict the risk of developing pathology or its severity, on the other hand, to choose an individual specific treatment for a

particular patient [10,30,31]. It's another important feature is prophylactic orientation, as complete information about the genome can be obtained long before the onset of the disease and allow it to be eliminated [44]. The identification of genetic traits that lead to the development of respiratory diseases in humans, as well as allowing them to develop resistance, is based on human genetic polymorphism, indicating differences in genes that respond to character determination among humans (presence of two or more qualitative variants) [31]. In recent years, much attention has been paid to the role of genetic polymorphisms in the development of pathological conditions. The most dangerous in the formation of many diseases is the combination of unpleasant alleles of several genes in the presence of predisposing factors to a particular disease [38]. One of the promising directions in the assessment of genetic predisposition to many recurrent diseases, including respiratory diseases, is to determine their association with certain gene-candidates [41]. It is known that two main approaches are used in the examination of genetic determinants: candidate and position mapping. Candidate mapping analyzes disease association or association with polymorphic variants of genes associated with the development of the pathology being investigated [34,11,19,35]. Based on modern data on the pathogenesis of airway damage, the genes for inflammation and anti-inflammatory cytokines are one of these gene-candidates [6,22]. Their role in the pathogenesis of many diseases allows, on the one hand, to predict the risk of developing the pathology or its course, severity, on the other hand, to choose an individual specific treatment for a particular patient [31]. It is known that [76] the intensity of cytokine synthesis is genetically selected. Polymorphisms of many cytokine genes have now been described, and the number of polymorphic domains in a single gene can reach several dozen [48]. They can be located in the encoding areas of the gene - the exon, as well as in the non-coding introns, and it is more important that this gene be in the promoter areas. It is these areas of DNA that determine the amount of the protein component [30]. It has been found that cytokine gene variants are

associated with susceptibility to many diseases, their course characteristics and severity, as well as high and low levels of cytokines produced [73]. The IL-4 gene is located on the long shoulder of chromosome 5 and has 4 exons. Genetic polymorphism is characteristic for the IL-4 gene. The most important is rs 2243250 (C589T). An increase in transcription factor binding has been shown in the presence of a polymorphic T allele for the IL-4rs2243250 gene [68]. An increase in IL-4 activity associated with rs 2243250 has also been demonstrated [68]. According to the literature, people who maintain the T allele for IL-4 are at risk of developing chronic obstructive pulmonary disease (COPD) [1]. Against this study, Hegab A.E. et al. [57] reported that the rs 2243250 polymorphism was not associated with the development of this disease. Cytogenetic location of IL-6 is 7p15.3. Numerous single-nucleotide polymorphisms have been identified in the sequence encoding the IL-6 gene, as well as in the promoter region. The most frequently observed and well studied is rs1800795 (G174C). It is characterized by the appearance of cytosine (C) instead of guanine (G) at 174 locations of the promoter. High concentrations of IL-6 are observed in homozygous carriers of the "wild" G allele [47,74]. The IL-10 gene is located at the 1q32.1 locus, and about 194 polymorphisms have now been identified in the gene. But the most important is rs1800896 (A1082G) [69]. The presence of the G allele variant is associated with higher IL-10 synthesis, while the A allele leads to a decrease in IL-10 synthesis in vitro [71]. In the European population, the occurrence frequency of the G allele reaches 30%. Currently, the polymorphism property of the TNF-α gene is the most widely studied. A study of the TNF-α gene located on the short shoulder of chromosome 6 revealed 43 polymorphisms, 9 of which were associated with malignant tumors of varying etiology, course, and outcome, as well as cardiovascular and respiratory diseases [61]. It was found that if the TNF-α (-308A/ G) homozygous genotype is associated with the AA allele, it increases the relative risk of developing chronic respiratory diseases by 6.4 times, and with the GG allele increases this risk by 2,4 times, while the heterozygous genotype (AG)

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reduces this risk by 1,9 times [18]. It is known from the literature that due to the presence of the A allele of G308A polymorphism, the expression of the TNF-α gene increases tenfold, which under certain conditions is reflected in the body's immune reactions, leading to the development of inflammatory processes in a systemic form, even septic shock [75]. The results of a study by Pikuza O.I. and co-authors [29] showed an increase in TNF-α (-308) A\A genotype frequency in patients prone to acute bronchitis and chronic disease progression, and this condition was considered a marker of increased risk of disease. In addition, the authors observed a decrease in the A\G genotype frequency in such patients (-308), which was included in the protective marker and assessed as a low risk of developing acute bronchitis. However, in studying the polymorphism and frequency distribution of alleles of the IL-6 (-174) C/G and IL-1 + 3953S / T genotypes, the authors did not identify a significant difference with the control group. The expression and production of TNF-α is controlled by mutations and polymorphisms (SNP-sister nucleotide polymorphisms) of genes, depending on whether they are located in the promoter or structural part of a series of cytokines [17]. The effect of polymorphism of regulatory regions of the cytokine gene on the amount of protein synthesized has been studied by a number of researchers [46]. Rizvanova F.F. co-authors. [31] and Sovalkin V.I. co-authors. [72] reported that polymorphisms of the TNF-α, IL-6, and IL-8 genes affect the nature of the inflammatory response. However, the authors identified two polymorphic domains with a single nucleotide exchange: -308 (G → A) and 238 (G → A), which affects the amount of product synthesized. According to Marieke Emonts [65], in alleles of congenital immune response genes, including TNF-α-863A, TNF-α 376G, TNF-α 238G, IL10-1082A, and IL6-C174G alleles may cause changes in cytokine production in the promoter sequence, which leads to a change in the inflammatory reaction, which in turn leads to the development of a tendency to otitis. The role of this mutation in the development of chronic purulent otitis media analyzed by Bayke E.V. and co-authors [4]. The authors found that the C/C genotype of the

C3953T and T31C polymorphisms of the IL1β gene, the G1082A A/A and C819T TT polymorphisms of the IL10 gene were important in the formation of disease susceptibility. Polymorphic variants of the IL1β gene (C/C genotypes of the C3953T and T511C polymorphisms) and IL10 (G1082A A/A genotype) coexist with chronic purulent otitis media under 14 years of age, and the C174G polymorphism of the IL6 gene is prone to disease progression. Henao M.I. and co-authors [56] reported that the polymorphic allele of the TNF-α gene -308A is not the same in tuberculosis infection and is more common in patients with tuberculosis than in healthy people and is a risk factor for the onset and development of the disease. In the study of the association between the allelic polymorphism of the TNF-α, IL-2 gene and the secretion of these cytokines in relation to clinical forms of pulmonary tuberculosis, Churina E.G. and co-authors [45] showed that IL-2 hyposecretion was detected in carriers of the G allele and GG (T-330G) genotype of the IL-2 gene, regardless of the clinical form of the disease. The authors found an increase in cytokine synthesis in patients with disseminated tuberculosis - carriers of the IL-2 gene TT (T-330G) homozygous genotype. Maximum secretion of TNF-α was observed in the control group and in patients with infiltrative tuberculosis in individuals with the TNF-α gene genotype AA (G-308A), but not in patients with this genotype with diffuse tuberculosis. This cytokine hyposecretion was observed in carriers of the TNF-α gene GG (G-308A) homozygous genotype in all controlled groups. Also, E.L. Nikuli's [26] studies have shown that the G allele and GG (T-330) genotype of the IL2 gene, the TT (C-590) genotype of the IL4 gene, and the AA (G-308A) genotype of the TNF-α gene occur in patients with pulmonary tuberculosis with pulmonary infiltrative more were observed than in patients with tuberculosis. Risk of pulmonary tuberculosis development IL2 gene GG (T-330G) genotype; IL4 gene CT and TT (C-590T) genotype, IL10 gene AA (C-592A) genotype; The TNF-α gene has been found to be associated with GA and AA (G-308A) genotypes. In general, the researchers concluded that the polymorphism of the genes of inflammatory cytokines TNF-α,

IL-2 is an important factor in the disregulation of the secretory function of immunocompetent cells, which not only predisposes to the development of tuberculosis, but also aggravates and exacerbates its course. According to HuGE Navigator, bronchial asthma has been linked to polymorphism of the TNF-α gene C1031T, G308A, G238A, C857A, A1078G, while a number of studies have shown that only the TNF-α gene is associated with polymorphism G308A [59,61].

Among the population of the United Kingdom, the United States of America, Mexico, Korea, Japan, and Russia, the 308A allele was most commonly detected in BA [12,50,58,61,62,]. For the Egyptians, the G308 allele was specific for BA [78], while in China, the G and A alleles of the TNF-α gene were detected in BA according to the results of 4 studies [64]. Also, according to Mukhammadieva G.F. and co-authors [23], the TNF-α gene rs1800629 is associated with polymorphic variants in the development of professional BA among the population of the Republic of Bashkortostan. In the study, the authors demonstrated the predominance of G allele and GG genotype encounter. The AA homozygous genotype has not been identified in patients with BA and in healthy individuals.

However, there is evidence that there is no association between the G308 \ 308A allele of the TNF-α gene in the development of bronchial asthma [36,70,79]. The authors observed that the frequency distribution of the GN88 \ 308A alleles of the TNF-α gene in patients living in Belarus with bronchial asthma did not differ reliably from the results of healthy people [36.].

However, studies on the role of genotypes of the TNF-α gene and G308 \ 308A polymorphisms in the synthesis of TNF-α in patients with bronchial asthma are few and contradictory.

Rudenko K.A. and co-authors [36] found that the frequency distribution of the TNF-α gene G308 | 308A polymorphism in the population of the Republic of Adygea in bronchial asthma varied in the groups studied for its effect on TNF-α secretion. Based on the results of the study, the authors found that in bronchial

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asthma, the G308 allele and GG genotype increased production of TNF-α relative to the control group, while the 308A allele and GA genotype decreased.

Features of polymorphism of the cytokines gene TNF-a G-308A, IL-10 S592A, IL-10 S819T, IL-10 G-1082A when studied by Romanova and co-authors [32,33], the TNF-a gene in patients with influenza pneumonia complications (308 G\A) polymorphisms were found to be more common in G allele homozygous carriers.

The authors assessed it as a factor contributing to the disruption of immune defense mechanisms. It has also been observed that the G allele of the IL-10 (1082G/A) gene and the C allele of the IL-10 (592C / A) gene are mostly in the form of homozygous carriers in patients.When the authors studied the distribution of the IL-10 gene (819) C|T) allele variants, they found no differences in the study groups, and found that homozygous carriers of T/T were significantly higher among healthy individuals. No correlation between the severity of pneumonia and genotypes has been identified by the authors.

Also, no differences in serum concentrations of TNF-α and IL-10 cytokines and genetic variants of the polymorphisms studied were observed during the study. Also, no difference was found between serum concentrations of TNF-α and IL-10 cytokines and in the case of genetic variants of the polymorphisms under investigation.

There are also studies on the polymorphism of the IL-10 gene in fetal infections in infants, which revealed the presence of functionally significant polymorphisms in the promoter portion of the IL-10 gene at 592 A\C, -819 T\C, resulting from individual nucleotide exchanges. The observed similarities between single nucleotide exchanges in the interleukin gene and the frequency of fetal period infectious diseases allow the identification of risk groups and genotypes prone to infections. [13].

Uklistaya T.A. and co-authors [43] have shown that patients with chronic obstructive pulmonary disease are carriers of the A allele of the TNF-α gene G-

308A polymorphic locus, which has an increased risk of developing IHD, the IL-1β gene C+3953T polymorphic locus T alley carrier - the development of the risk of arterial hypertension.

Loskutov D.B. and co-authors statistical analysis [18] reported that the observed frequency of homozygous variants of the TNF-α gene AA and GG was higher among patients with chronic respiratory diseases, while among healthy people it was observed that AG heterozygous genotype carriers were more common determined that respiratory diseases are more stable than risk factors for development.

The authors did not identify statistically significant differences when studying allelic variants of the IL-1β gene and explained the absence of the role of the IL- β (+ 3953T / S) gene in the formation of respiratory diseases.

Evaluating the role of polymorphic variants of the cytokines gene TNFa, IL1β in the development of genetic predisposition to respiratory disease in infants, K.B. Danilko and co-authors [14,51] found that the IL1β-511T-IL1β 3953T-IL1RN * A2 haplotype was characterized by a high risk of developing respiratory distress syndrome, while the IL 1b-511T-1IL1b 3953-IL1RN A1 haplotype was found to be less risky.

In addition, signs of predisposition to the development of infectious complications (congenital pneumonia) in patients with respiratory distress syndrome were identified: A1A1 VNTR locus genotype of A1 allele and IL1RN gene and TNFa -308G> A polymorphic site of IL1RN A2 allele AA genotype, respectively; in contrast, the TNFa-308A-LTA 252A haplotypes and IL1β-511C-IL1β 3953T-IL1RN A2 are characterized by a reduced risk of developing congenital pneumonia in infants with respiratory distress syndrome.

Patwari P.P. and co-authors reported that the absence of the IL1RA gene A1 allele in the study of children with nosocomial pneumonia was associated with a higher risk of more severe disease, the need for artificial lung ventilation, acute pneumonia, or the development of acute respiratory distress syndrome. However,

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no similarities were identified with the IL1b-511C> T polymorphic site with the development of bronchopulmonary dysplasia in the Korean population [67].

The results of a study by David S. and co-authors [52] showed that the following genotypes are highly prevalent in the development of bronchial pulmonary dysplasia. CC IL-6-174G> C and GA and AA IL-6-596G> A), GA TNF-a- 308G> A. However, these data were not statistically reliable. The authors concluded that further research is needed to determine which polymorphisms may increase and protect against the risk of bronchial pulmonary dysplasia.

Statistical analysis of a number of authors [38] has shown that different genotypes of the IL-4 gene C-590T polymorphism in children with acute and recurrent obstructive bronchitis do not have similarities. Analysis of the polymorphism of the IL-4 gene C-590T revealed a T/T genotype association (similarity) that developed bronchial asthma in children. Also, in a study by Yarilin A.A. [77], it was found that the IL-4 gene was involved in the formation of recurrent bronchitis in children among a large number of genes.

Studies by Ji-Hong Zhang and other co-authors [60] have shown that a higher probability of asthma is observed in children with a more T/T homozygous genotype of the IL-4 gene than in children with the CC genotype. In children with the T allele, the probability of bronchial asthma was significantly higher and was 3.07 times higher than in children with the C allele.

F.F. Rizvanova [31] found that the IL6 gene (-174) CG and the IL4 gene (-590) CT polymorphisms are characterized by the risk of developing acute lung pathology in children depending on their age and sex. T/C polymorphisms of the TNF-α gene (-308) G/A and the ILlβ gene (+3953) are protective factors against cases of acute bronchitis and nosocomial pneumonia in children.

Summarizing the data, it can be said that the genes of cytokine regulation are currently receiving special attention in the formation of diseases, including the development of diseases of the respiratory organs. Although the problems of respiratory pathology in children are widely covered in the literature and effective

programs for their treatment and prevention have been developed, the identification of the genetic basis of bronchopulmonary diseases remains poorly understood [16], and the data obtained vary widely.

However, studies in recent years have shown that adverse effects usually occur against the background of individual hereditary predisposition to any pathology known today, including diseases of the broncho-pulmonary system.

There are a number of unanswered questions, one of which is the lack of data on available sources on gene polymorphism encoding inflammation and anti-inflammatory cytokines in the development of recurrent bronchitis caused by constitutional features in children.

Identification of genetic markers that determine the predisposition to the development of recurrent bronchitis in patients with lymphatic-hypoplastic diathesis allows not only to understand the molecular mechanisms in the development of the pathological process, but also to identify risk groups and prognostic signs and this gives possibility to use prophylactic algorithms as well as treating standards.

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