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# Influence of Cytokine Polymorphisms on the Chronicity of Viral Hepatitis HBV and HCV

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**Abstract**
In recent years, special importance has been attached to the role of polymorphism of cytokine genes - important participants in the immunopathogenesis of viral hepatitis, which determine the nature of the interaction of the pathogen and the macroorganism, affect the chronicity of HBV and HCV infections, and modify the rate of fibrogenesis in the liver. Based on the study of gene polymorphism, it became possible with a high degree of probability to predict the predisposition to the development of viral hepatitis C and the state of resistance. The review presents convincing data on the association of single nucleotide substitutions with the peculiarities of the course of viral hepatitis, on the effect of polymorphism of the genes of cytokines IL-1β, IL-6 and TNFα on the pathogenesis of chronic HBV and HCV infection, response to treatment, and development of complications.

**Keywords:** polymorphisms; interleukin-1β,interleukin-6, interleukin-10, tumor necrosis factor-alpha

## RELEVANCE

The problem of the diversity of the human genome, i.e. genetic polymorphism is the basis for identifying differences between individuals. As you know, genetic polymorphism is supported by mutations and recombinations of genetic material. According to theoretical calculations, the offspring from the crossing of two individuals, differing only in ten loci, which are represented by possible alleles, will be about 10 billion individuals with different genotypes.

The greater the stock of genetic polymorphism in a population, the easier it is to adapt to a new environment and the faster evolution proceeds. However, it is practically impossible to estimate the number of polymorphic alleles using traditional genetic methods, since the very fact of the presence of any gene in the genotype is established by crossing individuals with different forms of the phenotype determined by this gene [9].

In recent years, the association of gene polymorphism with predisposition with various viral diseases, peculiarities of the course of viral hepatitis and its complications has been actively studied [9, 15]. Advances in molecular genetics make it possible to actually isolate and study genetic markers in patients with various diseases in clinical practice. Viruses have a powerful immunosuppressive effect on the cells of the body, which leads to changes in the balance in the cytokine network; on the other hand, genetically determined production of cytokines is triggered in response to infection. Thus, the level of expression of protein products of

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polymorphic cytokine genes determines the quality of the immune response and, accordingly, the course and outcome of the disease [5, 67].

A characteristic feature of molecular medicine as a science based on data on the molecular structure of the human genome is its individual character. It is aimed at correcting the pathological process in a particular person, taking into account the unique features of his genome. Another feature is a preventive orientation, when information about the genome obtained long before the disease can prevent the development of the disease or eliminate it. When studying the pathogenesis of various diseases, much attention is paid to pathogenetic mechanisms, occurring at the cellular and molecular genetic levels, including the role of cytokines. The study of genes that control the activity of cytokines, which are mediators of inflammation, is one of the important tasks in uncovering the pathogenetic links of the initiation and course of diseases, and in identifying a predisposition to diseases in the early stages. Knowledge of their role in the pathogenesis of many diseases allows, on the one hand, to predict the risk of pathology development or the severity of its course, on the other hand, to individually select a specific therapy for a particular patient [56, 34].

At the same time, particular importance is attached to the role of cytokine gene polymorphism - important participants in the immunopathogenesis of viral hepatitis, which determine the nature of the interaction of the pathogen and the macroorganism, affect the chronicity of HBV and HCV infections, and modify the rate of fibrogenesis in the liver. Thus, the functioning of the cytokine system is determined by several factors, primarily genetic factors, therefore, immunogenetic aspects determine the characteristics of the development and progression of viral hepatitis, including genetic ones. The molecular basis of hereditary factors is SNP in the genes of various cytokines and their receptors, which can be localized in the coding or promoter part of the gene. At the same time, SNP in the regulatory part of a gene can affect the level of its expression, which leads to a change in the amount of its product - protein [5, 8]. Based on the study of gene polymorphism, it became possible with a high degree of probability to predict the predisposition to the development of viral hepatitis C and the state of resistance. The phenotype of the host is of decisive importance. Unlike viral hepatitis C, the progression of fibrosis in viral hepatitis B is significantly more correlated with the genotype of the virus, but the polymorphism of the host cytokine genes can determine the development of hepatocellular carcinoma. However, data on studies of genetic factors for the progression of chronic hepatitis B and C are often contradictory and largely depend on the patients' belonging to a particular ethnic population [66, 70].

When HCV and HBV infections interact with the immune system, both adaptive humoral reactions with the formation of virus-specific antibodies and T-cell reactions with the participation of cytokines are activated. In this case, the leading factor in the development of chronic viral hepatitis B and C is insufficient production of cytokines and / or a decrease in the sensitivity of viruses and body cells to them, which is possibly due to the influence of allelic variants of cytokine gene polymorphism [45, 49]. The study of the distribution of allelic variants of the promoter regions of the genes of key immunoregulatory cytokines, as well as the degree of their association with the level of production of the corresponding protein products in patients with slow viral infections, seems to be relevant, since its results can serve as a basis for the development of criteria for predicting the course and outcomes of

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viral infection, as well as used to develop new methods of personalized immunocorrective therapy [23, 74].

Each gene of a cytokine and its receptor has up to 20 allelic variants, which differ mainly in their influence on the final level of cytokine production. Various combinations of allelic variants of cytokine genes can form both their balanced production, characteristic of two main groups of regulatory lymphocytes - Th1 and Th2, and unbalanced [34]. In this case, an individual ensemble of allelic variants of cytokine genes can partly determine the nature of the inflammatory process, its course and outcomes [23, 7].

In the formation of the immune response, the most important place belongs to the polymorphic genes of the cytokines IL-1β, IL-6 and TNFα and the genes of their receptors. In this regard, it is important to study the formation of the body's immune response to the effects of hepatitis C and B viruses, which make it possible to predict the rate of progression of fibrosis and the stability of the response to antiviral therapy [3, 6, 13]. It has been shown that the level of production of cytokines and their antagonists, the level of expression of receptors for cytokines are determined by a human inherited set of allelic variants of cytokine genes and genes of their receptors [2, 75].

***IL-1β gene polymorphism and the risk of developing liver cirrhosis***

The IL-1β gene is located on chromosome 2q14. The most studied polymorphism of the IL-1β gene is a single-nucleotide C-to-T substitution at position –511 of the gene promoter region, leading to an increase in IL-1β secretion [44]. The frequency of occurrence of polymorphism -511C / T does not differ in patients with viral hepatitis of neuropoid origin with different results of treatment [36]. Also, no correlation was found between the prevalence of IL-1B gene polymorphism (at positions –511 and +3954) and spontaneous elimination of HCV in England [58]. Studies have shown that the allele - 511T of the IL-1β gene is more often associated with a more severe degree of liver fibrosis in CHC patients [10]. In a study of patients with CHC in Japan, it was revealed that the genotype - 511TT of the IL-1β gene is an important risk factor for the development of HCC [65]. However, when comparing representatives of the Caucasian and Mongoloid races, the relationship between single nucleotide substitutions at the –511C / T position of the IL-1β gene and the incidence of HCC in the outcome of CHC was not established [72, 73]. The influence of this polymorphism on the course of chronic hepatitis C and antiviral therapy in patients of East Slavic origin has not been fully studied [1].

The influence of IL-1β-31 T / C gene polymorphisms on the state of the immune response in HBV and HCV was established. The CC IL-1β-31 genotype was characterized by suppression of cellular immune responses, which was accompanied by overproduction of proinflammatory cytokines. In this study, differences in the occurrence of genotypes of genes IL-1β -31 T / C and IL-6 -174 G / C between patients with chronic viral hepatitis B and C and healthy people were identified. Patients with chronic viral hepatitis B and C were characterized by an increased frequency of the CC genotype of the IL-1β -31 T / C gene and the CC genotype of the IL-6 -174 G / C gene in comparison with the control group and, probably, more susceptible to the development of this disease in case of contact with pathogenic [61].

***IL-6 gene polymorphism and the risk of developing liver cirrhosis***

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The IL-6 gene is located on chromosome 7p21. Since the late 1990s, several SNPs have been found in the promoter of this gene [64]. The presence of allelic variants in the promoter region of the IL-6 gene leads to different levels of transcription of this gene. It was found that polymorphism of the promoter part of the IL-6 gene (–174 G / C) affects the level of this cytokine in the blood [47]. People with allelic variants GG and GC have a higher serum content of this cytokine than people with the CC genotype [40]. The prevalence of G allele differs in different ethnic groups: among representatives of the European race, this allele is encountered much more frequently than in representatives of other races [16]. So, in Europeans, the frequency of occurrence of the GG allele is 0.54 - 0.62; for Africans, Native Americans, Singaporeans - 0.87 - 1.00. Associations were found between the –174C / G polymorphism of the IL-6 gene and the stage of liver fibrosis in HCV in the indigenous inhabitants of Italy [42]. The allele of the –174C / G polymorphism of the IL-6 gene was more often associated with the development of rapid fibrosis in patients with CHC [39]. It is noteworthy that among the Italian population, the carriage of the –174G allele of the IL-6 gene and a high degree of fibrosis are more common in men [18]. The data of domestic studies are contradictory. In one study, it was shown that the genotypes of the IL-6 gene –174GC and –174CC are significantly more likely to be detected in a rapidly progressing than in a favorable course of the disease [12]. But in another study, conducted in the Tomsk region, among patients with a high degree of inflammatory activity, carriers of the 174GG genotype reliably prevailed. Carriage of genotypes -174CG and -174CC of the IL-6 gene was more common in patients with minimal and moderate inflammation. However, when assessing the value of the –174C / G polymorphism in the promoter region of the IL-6 gene in the development of fibrosis, insignificant differences in the frequencies of variant alleles and gene genotypes were obtained in patients with HCV infection with varying degrees of liver fibrosis [11]. Thus, there are no unambiguous data on the effect of polymorphism in the promoter region –174 G> C of the IL-6 gene on the pathogenesis of chronic HCV infection and on the effectiveness of AVT.

Studies have revealed an increase in serum levels in patients with chronic HCV infection. The overproduction of IL-6 with an increase in its level in the blood serum was significantly more often associated with the carriage of the IL6 –174G allele than the IL6 –174C allele ($p < 0.05$). In addition, an association was found between the presence of cryoglobulinemia and associated systemic manifestations, including the progression of fibrosis and kidney damage, among patients with elevated serum IL-6 levels compared with patients without an increase [6].

A study of patients with chronic viral hepatitis B and C showed an association of the level of IL-1β production in the blood with the IL-6 -174 G / C polymorphism. Carriers of wild-type GG were characterized by a higher synthesis of IL-1β in comparison with the group of heterozygous GC patients and abnormal CC homozygotes. Polymorphic variants IL-1β -31 TS and CC, as well as IL-6 -174 CC, are associated with a higher level of cytolysis, and the genotypes IL-1β -31 TT and IL-6 -174 GC and GG are associated with inactive hepatitis [46] ...

Studies of some authors have shown the effect of IL-6 polymorphisms (-597 and -174) on the severe course of chronic HCV infection [37] and chronic hepatitis B. In studies of another group of authors, no such relationships were found [53, 58].

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***TNF-α gene polymorphism risk of liver cirrhosis development***

Tumor necrosis factor alpha (TNF-α) plays a special role in the formation of the antiviral immune response [30]. TNF-α is a multifunctional cytokine with pronounced pleiotropy, takes part in the formation of the body's defense reactions, stimulates the Th-1 cellular immune response, phagocytic and cytotoxic activity of cells, and regulates the processes of immune inflammation. All this contributes to the progression of liver fibrosis with an increase in the cytokine level TNF-α and IL-1βcontrol the balance between cell proliferation and apoptosis [19]. One of the important biological functions of TNF-α is its participation in the regulation of apoptosis, including in cells damaged by the virus [22]. TNF-α is secreted by various cells, for example, activated macrophages [32], cytotoxic T-lymphocytes in the liver [23].

There are numerous reports in the literature demonstrating changes in TNF-α production in viral infections. An increased level of TNF-α in blood plasma was found during exacerbation of such chronic infections as viral hepatitis, HIV, herpes type I, Epstein-Barr, influenza, poliomyelitis, tick-borne encephalitis, etc. [4, 7]. In CHC, there is an increased level of TNF-α in the blood serum and in the liver parenchyma in patients [28]. HCV stimulates the secretion of TNF-α by human hepatocytes [20]. In particular, it is known that an increase in TNF-α production in chronic viral hepatitis C at an early stage of the infectious process can mediate increased apoptosis of hepatocytes, which leads to the destruction of the liver tissue, followed by a decrease in apoptotic cell death and, as a consequence, the possible development of malignant neoplasms [35]. It is believed that the overproduction of this cytokine is one of the main mechanisms of activation of the infectious process during its transition from the latent state to the phase of clinical manifestations and indicates the progression of the disease.

The TNF-α gene is localized on chromosome 6 in the region where the molecules of the major histocompatibility complex of the first (HLA-A, B, C) and second (HLA-DP, DQ, DR) classes are encoded [21]. The TNFA gene promoter region includes 8 polymorphic regions with single nucleotide substitutions: - 1031T> C, - 863C> A, - 857C> T, - 575G> A, - 376G> A, - 308G> A, - 244G> A, - 238G > A. However, the most significant are the single nucleotide substitutions of guanine for adenine at positions - 308 and - 238, which cause changes in the level of TNF-α production. It has been shown that cells of donors homozygous for genotype A / A synthesize 3 times more cytokine than cells of individuals with genotype G / G [26]. Another polymorphic region of the TNFA gene that affects cytokine production is 238G> A. However, in this case, the replacement of guanine with adenine leads not to an increase but to a decrease in protein production. Stimulation of whole blood cells with lipopolysaccharide showed that cells with the G / A genotype synthesize 1.5 times less TNF-α than cells with the G / G genotype. Thus, single nucleotide substitutions at positions - 308G>A and 238G> A of the TNFA gene are associated with an increase and decrease in the expression level, respectively. Polymorphism - 308G> TNFA gene affects the transcriptional activity of TNFB gene localized in the same cluster [24].

Several SNPs of this gene are known, localized in the main one in the promoter region [33], the most studied of which is the –308G / A polymorphism of the promoter region of the TNF-A gene. Polymorphism of the TNF-α gene at positions –308, –238, –863 of the promoter region affects the expression of TNF-α and is involved in the pathogenesis of many infectious

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diseases. For example, allele - 863A of TNF-α gene is associated with Crohn's disease [27] and human T-lymphotropic virus type I [29]. The results of studies of the involvement of the TNF-α polymorphic gene in the outcomes of acute hepatitis C are controversial, which may be due to different ethnicity of patients, as well as different sample sizes. There is a hypothesis that TNF-α can serve as a prognostic marker of HCV outcomes. It is known that the incidence of spontaneous HCV clearance is different among Caucasians and Africans. In individuals of the Negroid race, the –863A allele of the TNF-α gene is associated with HCV clearance; in addition, the wild-type –863C / –308G haplotype correlates with the persistence of viral infection, although no such relationships were found among the Caucasians [31]. The –863A allele of the TNF-A gene promoter is also associated with viral clearance in HCV patients among the Sicilian population [54, 63]. The involvement of the –308 and –238 polymorphisms of the TNF-A elimination gene of HSV has not been established [17].

Thus, differences in the allele frequencies of the gene IL-4 (C589T), IL-10 (G1082A), TNFα (G308A) were revealed between patients with chronic hepatitis C and healthy individuals in an ethnically homogeneous group of residents of the Odessa region. In the same study, the association of polymorphic markers of the gene IL-10 (G1082A), IL-4 (C589T) and TNFα (G308A), which are located in the promoter regions, with the degree of liver fibrosis in CHC patients was established [14].

According to a meta-analysis conducted by Chen Y. and Pei J. based on the results of 12 studies over the period 2004-2007, no significant association was found between the –308G / A polymorphism of the TNF-α gene and the severity, viral load and frequency spontaneous elimination of HCV among all individuals of different ethnic groups [41]. Although the data of C.Y. Daietal. TNF-apolymorphism at the position –308 correlates with the severity of fibrosis-viral load in CHC [43]. In the mid-faceropoidrasyallele –238, it is more common for patients with hepatitis C compared with uninfected people. Genotype-863CC of the TNF-α gene is more common in patients with CHC, whereas for the –238G / A and –308G / A polymorphisms, such a relationship was not found [71]. Indigenous inhabitants of Mexico have not been found to differ in the prevalence of polymorphism - 238G / A and –308G / TNF-A gene among healthy patients [68]. The –308 allele is often found in the South-East Asian region of cirrhosis at the origin of CHC [71]. The frequency distribution of allelic variants of the –308 G / A polymorphism of the TNF-A gene is not associated with the risk of development and chronicity of viral hepatitis C among the Eastern Slavs living in Western Siberia [8]. Analysis of polymorphic loci of the TNF-A gene in patients of the European population did not reveal associations with the effectiveness of antiviral therapy and with the rate of formation of liver fibrosis in CHC. [51]. The role of SNP –238 G> A of the TNF-α gene in patients of East Slavic origin has not been adequately studied [1].

Niro et al analyzed the effect of TNF-α polymorphism - T1031C, C863A, G308A, and G238A - on hepatitis B virus clearance. 184 patients with chronic hepatitis B and 96 controls with documented clearance were examined. It has been shown that in carriers of the _308 GG genotype and the TCGG haplotype, the prognosis is poor [59].

Genetic analysis revealed a link between polymorphisms in the TNF-α and HBV promoter region located at -308G / A [38, 69], while another study suggested that TNF-αpromoter polymorphisms (positions -238A, -308A, -857, and -31C host, which may determine the

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clinical outcome of HBV infection [48]. These data may indicate a role for TNF-α in the pathogenesis of hepatitis B, as well as in the development of its complications.

Japanese scientists investigated the allele frequencies of the TNFα gene (polymorphisms _238 and _308) in patients with chronic HCV in inactive (n = 50) and active (n = 50) forms and in 40 healthy people. The allele frequencies of the promoter region of the gene did not differ in the groups, but at the same time, the effect of these two types of polymorphism, as well as polymorphism of the TNFα gene and the HLADRB1 haplotype, on the activity of chronic HCV was noted [66].

A number of studies have shown the contribution of the –592A / C, –1082G / A, –819T / C polymorphisms to predisposition to hepatitis C, response to therapy, and disease outcome in Caucasoid and Mongoloid populations [50, 52]. However, the results obtained are often contradictory. Thus, for TNFα and IL10 gene polymorphisms, a number of researchers have not established associations with hepatitis [57, 60, 62].

Studies of the genetic component of chronic viral hepatitis have shown that the IL4RA (Ile50Val) and TNFα (G-308A) genes are involved in the formation of the characteristics of the course of chronic viral hepatitis: the Ile / Val genotype of the IL4RA gene is associated with more pronounced stages of fibrosis, and the G / A genotype of the TNFα gene - with a weak degree of fibrosis. Patients with chronic viral hepatitis who are carriers of the heterozygous genotype for the IL4RA gene (Ile50Val) will have an increased risk of developing liver fibrosis [55].

**CONCLUSION.**

The functioning of the cytokine network in viral infection depends on many reasons, including individual differences in the production of immunoregulatory proteins, due to a number of genetic characteristics. Cytokine genes, for most of which allelic polymorphism has been described, are the most important regulatory genes that control the immune response. The most common allelic variants of cytokine genes are formed as a result of mutations affecting the non-coding introns, the promoter region of genes, as a result of which the structure of the protein product remains the same, and the expression level and the amount of cytokine produced by immunocompetent cells change.

Thus, to date, convincing data on the association of single nucleotide substitutions with the features of the course of viral hepatitis have been obtained only for a small number of polymorphisms, and there are no unambiguous data on the effect of polymorphism in the genes of the IL-1β, IL-6 and TNFα cytokines on the pathogenesis of chronic HBV and HCV infection. response to treatment and development of complications. Considering the presence of a pathogenetic relationship between the course of chronic HBV and HCV infection with the peculiarities of the functioning of the cytokines IL-1β, IL-6 and TNFα, regulation of inflammation and the immune response and the stage of fibrotic changes in the liver, it is of particular interest to assess the role of polymorphisms of these cytokines in the development of chronic HBV and HCV- infection and its complications.

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