Review article
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Single nucleotide polymorphisms of the interleukin-1 superfamily members: association with viral hepatitis B and C

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The review provides information on single nucleotide polymorphisms (SNPs) in genes encoding some interleukins belonging to the interleukin-1 (IL-1) superfamily and on their association with different infectious and non-infectious human diseases. It also briefs on the history of SNP discovery and the progress in the related scientific studies till the present time. It gives an insight into some mechanisms of interaction between infectious agents and the human immune system, involving SNPs in some cytokines of the IL-1 superfamily. The review provides data on relationships of SNPs in genes encoding other factors of the immune system, which are associated with the specific characteristics of natural history of chronic hepatitis B and C. It explores the significance of assessment of the SNP-proportion in proinflammatory cytokines and their antagonists of the IL-1 superfamily among the healthy population as well as the ratio of individual SNPs in specific groups of patients as a monitoring parameter for epidemiological surveillance of infectious diseases.

Keywords: *single nucleotide polymorphism, interleukin-1 superfamily, viral hepatitis B and C, review*

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Однонуклеотидные полиморфизмы членов суперсемейства интерлейкина-1: ассоциация с вирусными гепатитами В и С

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Аннотация

В обзоре представлена информация об однонуклеотидных полиморфизмах (single nucleotide polymorphism, SNP) в генах некоторых интерлейкинов (IL), входящих в суперсемейство IL-1, и их связи с различными заболеваниями человека как инфекционной, так и неинфекционной природы. Кратко изложена история обнаружения SNP и развитие научного поиска по данной проблеме до сегодняшнего времени. Описаны некоторые механизмы взаимодействия инфекционных агентов и иммунной системы человека с учётом SNP отдельных цитокинов суперсемейства IL-1. Приведены данные о связи ряда SNP в генах, кодирую-

щих другие факторы иммунной системы, ассоциированные с особенностями течения вирусных гепатитов В и С. Обсуждается значение определения SNP-пропорции провоспалительных цитокинов и их антагонистов суперсемейства IL-1 среди здорового населения и соотношения отдельных SNP у определённых групп пациентов как параметра мониторинга систем эпидемиологического надзора за инфекционными заболеваниями.

Ключевые слова: *однонуклеотидный полиморфизм, суперсемейство интерлейкина-1, вирусные гепатиты В и С, обзор*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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The aim of the review is to provide up-to-date information on the association of polymorphisms in interleukin-1 superfamily genes and some cytokines with human diseases, including viral hepatitis B and C.

As currently assumed, most of the human diseases are multifactorial. The international Human Genome Project completed in 2000 set the stage for a new and important trend in studying molecular and genetic mechanisms in a wide range of autoimmune and infectious diseases. The project provided an insight into the relationship between an individual's susceptibility to different diseases, severity of their development, their outcomes and treatment effectiveness, on the one hand, and single nucleotide polymorphisms, on the other hand. It sparked great interest among scientists, motivating them for thorough research on the new problem.

SNPs are the smallest possible variations of the genetic code or the substitution of one nucleotide base for another. Currently, the related term "single nucleotide variation" (SNV) is becoming quite popular, though it has a more general meaning, including single nucleotide deletions and insertions, which in coding sequences cause the reading frameshift and premature termination of translation, thus affecting adversely the protein synthesis. SNVs will not be discussed in this review. The nonsynonymous substitution, on the one hand, can lead to a missense mutation (incorporation of a different amino acid into the resulting protein and possible alteration of protein properties) or, on the other hand, can result in a nonsense mutation (creation of a stop codon, which causes termination of the transcription). Synonymous substitutions do not lead to substitutions in the protein sequence and, consequently, do not cause any alterations in the encoded protein and disruption of its functions. SNPs are found in both coding and non-coding regions of a gene. Mosrati et al. described 2 polymorphic loci in the promoter region of the *TERT* (telomerase reverse transcriptase, which is a catalytic subunit of the enzyme telomerase) gene, or more specifically, *rs2736100* (*A→C*) and *rs10069690* (*C→T*) with homozygosity for the C and T variants, respectively, associated with an increased risk of developing primary glioblastoma [1].

The new era of molecular diagnostics opened new avenues in exploration of the relationship between SNPs and different human diseases. Most of the research articles published in the early 2000s focused mostly on detection of new SNPs in the human genome, making no attempts to find any correlation relationships with different diseases [2, 3]. The increased interest of researchers from different countries resulted in description of numerous SNPs in the human genome. In their review summarizing the results of multiple studies, Sachidanandam et al. provided a map of 1.42 million SNPs [4]. Currently, the number of identified polymorphisms exceeds the previous number manifold: According to the data generated by the 1000 Genomes Project, more than 40 million SNPs were identified in the human genome. The same period is rich in studies focusing on detection of relationships between SNPs and different diseases. Hijikata et al. reported the identified correlation between the polymorphism of the promoter region of the *MxA* gene encoding myxovirus (MX1, Gene ID: 4599) resistance proteins and the virological response to treatment of patients with chronic hepatitis C (CHC) [5]. Soon after, Grösch et al. found the association between the polymorphism of the *MOR* gene (μ-opioid receptor, Gene ID: 4988) and the risk of idiopathic epilepsy development [6].

The intense interest and fast accumulation of new data on the role of SNPs in development of diseases provided the basis for the International HapMap Project that was launched in 2002 and is still available to researchers worldwide [7]. The main objective of the HapMap Project is full-scale mapping of SNPs in the haploid set of the human genome. Note that conceptually similar studies were conducted in the late 1990s to explore the joint effect of polymorphisms in closely linked genes on some disease processes. Chamberlain et al. and Fujita et al. found the association of polymorphism at the D9S5 locus on chromosome 9 with the

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mutation at the FA locus, which is tightly linked to development of Friedreich ataxia [8, 9].

The interaction between an infectious agent and the human immune system is a complex and multifactorial process involving active participation of cytokines. A significant part of the cytokine system is represented by the interleukin group, which includes the IL-1 superfamily comprising 11 proteins. At the initial stage of an infectious disease, these proteins participate in activation of phagocytosis and synthesis of *arachidonic acid*, which is a precursor in the biosynthesis of prostaglandins and thromboxanes [10]. Previously, this group included only four proteins: IL-1α, -1β, -1RA, and -18. Other cytokines with similar functions were discovered later and were also included in the superfamily. The discovery of new interleukins made it necessary to make changes in the names assigned to interleukins of the above superfamily (**Table 1**).

The simplified scheme of the inflammatory pathway of the IL-1 family can be described as a competitive interaction between IL-1α, -1β, and -1RA (the interleukin receptor antagonist) and 3 receptors for the above interleukins: IL-1R1, -1R2, -1R3 (IL-1RAcP accessory protein). The interaction can result in activation of the proinflammatory or the anti-inflammatory pathway.

Although the IL-1α functions have not been studied to the full extent, Werman *et al*. believe that this interleukin is a signaling molecule functioning as a transcription factor for proinflammatory cytokines [12]. The implementation of the inflammatory pathway becomes possible if IL-1α and IL-1β bind to the IL-1R1 receptor with the participation of IL-1RAcP. If IL-1β binds to IL-1R2 (a decoy receptor), the signal initiating the inflammatory pathway is not transmitted, and the inflammatory process does not develop [13]. The expression of IL-1α and IL-1β genes is different. The alpha-protein continuously persists in epithelial and mesenchymal cells of the healthy body; there are data proving its presence in large quantities during cellular apoptosis [14]. The active IL-1β transcription occurs solely in response to development of a pathologic process. The transcription of cytokine genes, including IL-1, is activated through Toll-like receptors (TLRs) primarily recognizing pathogen-associated molecular patterns (PAMPs), which include bacterial and fungal cell wall components, their nucleic acids and proteins, as well as damage-associated molecular patterns (DAMPs) — endogenous molecules that are released from damaged cells following the infection or any other pathological conditions.

Expression levels of IL-1β and -1RA depend on epigenetic modifications in the respective protein-coding regions, as it was confirmed by Madej *et al.* who conducted the *in vitro* study to compare expression levels of proinflammatory cytokines and their antagonists through dual exposure of isolated monocytes and macrophages to infectious bacteria [14]. We think that the mechanism described above is universal and is implemented in multiple pathological processes, though this assumption needs further studies.

Currently, locus *rs1800587* (-889*C→T*) is one of the most extensively researched IL-1α SNPs. Numerous attempts have been made to identify the association of this polymorphism with different diseases; studies have frequently produced discordant findings. For example, Pšemeneckienė *et al.* [15] identified the association

Table 1. Names of IL-1 superfamily interleukins in the new and previous nomenclatures [11]

The name approved in the previous nomenclature	The name approved in the new nomenclature	Identification number (NCBI Gene ID)
IL-1α	1F1	ID: 3552
IL-1β	1F2	ID: 3553
IL-1RA	1F3	ID: 3557
IL-18	1F4	ID: 3606
IL-36Ra	1F5	ID: 26525
IL-36α	1F6	ID: 27179
IL-37	1F7	ID: 27178
IL-36β	1F8	ID: 27177
IL-36γ	1F9	ID: 56300
IL-38	1F10	ID: 84639
IL-33	1F11	ID: 90865

with high risk of Alzheimer's disease development. In the meantime, Serretti *et al.* and Yildiz *et al.* did not find any proof of the above association [16, 17]. Such controversial findings may be explained by ethnic distribution of the patients: The association between SNPs and Alzheimer's disease was found in patients from Lithuania, though it was absent in Italians, Greeks, and Turks. The similar discrepancies were encountered during attempts to find the association between *rs1800587* (*C→T*) SNP and the risk of posttraumatic osteomyelitis and many other diseases. Asensi et al. and Tsezou et al. reported the positive correlation [18, 19], while Jiang et al. did not find any correlation [20]. Note that the range of diseases associated with the *rs1800587* (*C→T*) polymorphism is quite wide and has not been identified yet. In their recent research, Korobeinikova *et al.* [21] reported the significant prevalence of the homozygous *CC* genotype in patients with a larger size of the primary breast cancer tumor and more unfavorable prognosis for the disease outcome as compared with other genotypes of the same SNP.

As members of the IL-1 superfamily are proinflammatory agents of the immune system, multiple attempts have been made to find the association between sequence variations encoding IL-1 members and the wide range of human diseases. Although results obtained by many researchers give no evidence of any associations, they are highly important for creating a global databank. For example, Picos *et al.* [22] found no association of *rs16944* (-511*C→T*), *rs1143634* (3953*C→T*), and *rs1800587* (-889*C→T*) polymorphisms with gastroesophageal reflux disease. No association between IL-1α nucleotide polymorphisms for *rs1800587* (*C→T*) and *rs17561* (*G→T*) loci and open-angle glaucoma or autoimmune diseases (systemic sclerosis, juvenile idiopathic arthritis, rheumatoid arthritis, multiple sclerosis, and systemic *lupus erythematosus*) was found [23, 24]. Identification of negative correlation relationships can be of great use in finding new genetic targets of the studied diseases. The obtained results can also be used in repeat research with different parameters of study groups, materials and methods.

At present, IL-1β is a more actively researched member of the IL-1 family as compared to IL-1α, which, in our opinion, can be explained by the high significance of SNP for functional activity of the produced protein. Gorący *et al.* [25] found that the presence of the *C*-allele at *rs1143627* (-31*T→C*) located in the promoter region of the IL-1β-coding gene was associated with high probability of a stroke. Okada *et al.* [26] identified the *TT* genotype as a risk factor for pouchitis in patients with ulcerative colitis and its progression. Rech *et al.* [3] studied the impact of the *rs1143627* (-31*T→C*) polymorphism and came to conclusion that the *TT* genotype is associated with chronic gastritis caused by *H. pylori*; they also made assumption that individuals with the *TT* genotype are characterized by significantly higher expression of proinflammatory IL-1β.

Polymorphic variants of locus *rs16944* (-511*C→T*) are in linkage disequilibrium with allelic variants of locus *rs1143627* (-31*T→C*). The most unfavorable combination is represented by the *C*/*T* (-31/-511) haplotype. The above conclusion was made by Oliveira *et al.* [23] when they studied the association of polymorphisms with open-angle glaucoma. Landvik *et al.* [27] were able to identify the linkage group of four IL-1β polymorphisms: -3893*G*, -1464*G*, -511*C,* and -31*T*, which is a risk factor for non-small cell lung cancer caused by the ability of this combination group of nucleotides to boost translation of proinflammatory IL-1β molecules.

IL-1RA encoded by the *IL-1RN* gene is a monomeric glycated protein and binds with similar affinity to IL-1R1 and IL-1β receptors, without any further signal transmission, thus causing an anti-inflammatory effect [28]. This protein is expressed in many tissues of the body: intestine, lungs, lymph nodes, liver, skin, etc. A substantial increase in the IL-1RA production can be indicative of a favorable prognosis in acute conditions, while a decrease in its production implies the prevalence of the proinflammatory profile, which, in its turn, is seen as a chronic process predictor.

The anti-inflammatory property of IL-1RA is successfully used in medical practice. Such severe diseases as rheumatoid arthritis, atherosclerosis, coronary artery disease, diabetes, metabolic syndrome, and others are successfully treated with anakinra, a recombinant form of IL-1 receptor antagonist (IL-1Ra) [29, 30]. Mutations in the nucleotide sequence encoding IL-1RA, such as deletions or insertions of nucleotides can cause an increased risk of nonfunctional protein production, which can result in development of deficiency of the IL-1 receptor antagonist (DIRA) resulting in severe skin and bone inflammation [31].

The *IL-1RN* gene has 5 allelic variants, depending on the number of the incorporated tandem repeats, or variable number tandem repeats (VNTRs) consisting of 86 base pairs and located in intron 2. Allele 2 (IL-1RN*2), which has 2 tandem repeats, is associated with high risk of *carotid artery disease* [32] and coronary heart disease [33]. The IL1RN*2 haplotype is also associated with male infertility [34], while the IL1RN*1/*1 genotype was associated by Tripathy *et al.* with high risk of *chikungunya virus infection* [35].

Ismail et al. demonstrated that IL-1RN *rs419598* (-2018*T→C*) SNPs, the *CT* genotype could be used as a predictor of more aggressive form of rheumatoid arthritis [36]. Lin et al. did not find any association of IL-1RN *rs6743376* and *rs1542176* SNPs with risk of a myocardial infarction [37]. Ibáñez *et al.* found that the protective properties of the *rs380092 T*-allele (*C→T*) were associated with minimization of intimal thickening, which precedes atherosclerosis [38]. Attur et al. found that the CTA-haplotype of *rs419598*/*rs315952*/

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rs9005 loci is associated with lower risk of knee osteoarthritis [39].

Individuals differ in their susceptibility to viral infections and response to the infection process. According to WHO, 30% of individuals with hepatitis C virus infection (HCV) clear the virus spontaneously within the first six months of the infection, without therapeutic intervention, while the remaining 70% of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of liver cirrhosis (LC) ranges between 15% and 30% [40]. The variability of the human genome is one of the critical factors affecting the individual development patterns of infection processes, including viral hepatitis infections. Identification of genetic markers is of high importance for disease development prognosis, for patients' individual responsiveness to treatment regimes, and for computational modeling of an epidemic process, including short-term and medium-term scenarios of its development. Signaling pathways participating in implementation of the immune response are significant areas for finding SNPs affecting the intensity of the infection process in patients with viral hepatitis. At present, studies are focused on the role of SNPs in *HLA-DPB1*, *HLA-DPA1, DQB1*, *DQB2,* and *DQA2* genes belonging to the major histocompatibility complex (MHC) Class II, which, in its turn, is responsible for antigen presentation to $CD4^+$ cells.

According to WHO, hepatitis B and C are diseases causing severe damage to the health of people in many countries. Worldwide, there are 325 million people living with viral hepatitis B and C leading to more than 900 thousand deaths a year. Recognizing the tremendous global burden caused by viral hepatitis, in 2016, WHO adopted the Global Health Sector Strategies on Viral Hepatitis for 2016–2021, calling for global elimination of viral hepatitis. Viral hepatitis is a global challenge that demands researchers conduct scientific studies across the entire spectrum of the problem, including identification of associations between SNPs and hepatitis B and C. The main focus is on search for patterns and risk factors for development of LC and primary liver cancer (PLC), which are the most severe complications of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) (**Table 2**).

Researchers from different countries found several polymorphisms associated with LC and PLC. Most of the studies were performed in China, which is highly endemic for hepatitis B. In their studies, Jiang *et al.* prove the existence of the association of *HLA-DQB1* (Gene ID: 3119) *rs9275319* (A→G) polymorphism with LC and PLC [41, 63]. Cao *et al.* found that in patients with CHB, the *AA* genotype of *rs1800896* (*G→A*) *IL-10* (Gene ID: 3586) could be seen as a risk factor for LC and PLC compared with the *GG* allele [43]. The studies performed among patients with CHB and CHC in European countries also demonstrated associations of some SNPs with higher risks of LC and PLC development. Polish researchers found that patients with CHB were exposed to higher risk of LC development, and this risk was associated with the *IL10 GCCT* haplotype (*1082G/819C/592C/1353T*, ID 3586) [44]. Jiménez-Sousa *et al.* and Cavalli *et al.* found the association between the MERTK *rs4374383 (A→G)*, ID10461, and high risk of LC development in CHC patients in Spain [46, 47].

In addition to associations with LC and PLC, in the recent years there have been identified associations of SNPs with other characteristics inherent in infections caused by hepatitis B and C viruses (**Table 3**).

The meta-analysis of epidemiological studies on identification of the association of SNP *IL-28B* (*IFNL3;* Gene ID: 282617) with hepatitis B and C, which was performed by Jiménez-Sousa *et al.* [52], showed that the *CC* genotype was associated with a higher frequency of spontaneous clearance of hepatitis C virus infection both in patients of Mongolian origin and in patients

Table 2. SNP associations with the development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) and C (CHC)

Gene ID NSBI	Polymorphism	Region of study, source	Study groups	*n*	Identification of association between SNPs and viral hepatitis	Effect
HLA-DQB1 ID: 3119	*rs9275319* (*A→G*)	China [63]	CHB and cirrhosis-patients	702	$P = 1{,}30 \times 10^{-2}$; OR = 1,32; 95% CI 1,06–1,64	*A*-allele – risk of LC
			Healthy population	2601		
		China [41]	Patients with CHB and HCC	1161	$P_{meta} = 2{,}72 \times 10^{-17}$; OR = 1,49	*A*-allele — risk factor for CHB and HCC
			Healthy population	1353		

End of Table 2.

Gene ID NSBI	Polymorphism	Region of study, source	Study groups	*n*	Identification of association between SNPs and viral hepatitis	Effect
IL-6 ID: 3569	*rs1474347* (*C→A,G*)	Egypt [42]	Patients with CHC and LC	22	OR = 5,7; 95% CI 1,05–31,07; $p < 0,05$	*AC* allele is associated with high risk of LC and HCC
			Patients with HCV and HCC	54		
			Comparison group	48		
IL-10 ID: 3586	*rs1800896* (*G→A*)	China [43]	Patients with LC in CHC	241	OR = 2,01; 95% CI 1,10–3,65; $p < 0,05$	*AA* genotype is a risk factor for LC and HCC
			Comparison group	254		
	rs1800896 (-1082*G→A*)/ *rs1800871* (-819*T→C*)/ *rs1800872* (-592*C*/*A*)/ rs1800893 (-1353*C*/*T*) *1082G*/*819C*/ *592C*/*1353T*	Poland [44]	Patients with CHB	857	OR = 2,61; 95% CI 1,58–4,30; $p = 0,0003$	*GCCT* haplotype is associated with risk of LC in CHB
			Comparison group	100		
STAT4 ID: 6775	*rs7574865* (*T→A,G*)	China [45]	Patients with CHB	5902	OR = 1,18; 95% CI 1,07–1,31; $p = 0,001$	G-allele — risk factor for HCC
			Comparison group	7867		
MERTK ID: 10461	*rs4374383* (*A→G*)	Spain [46, 47]	Patients with CHC	208	OR = 2,18; $p = 0,070$	*G* allele is associated with higher risk of liver fibrosis in CHC patients as compared to *A* allele
TLR4[1] ID: 7099	*rs2148356* (*A→T*)	Spain [48]	Patients with CHC and HCC	155	OR = 0,942; 95% CI 0,366–2,426	*T* allele is associated with low risk of HCC and slow progression of CHC
			Patients with CHC	153		
			Comparison group	390		

Note. 95% CI — 95% confidence interval; OR — odds ratio.
[1]A number of studies addressing TLR4 *rs4986790* and *rs4986791* SNPs did not find any association with any parameter for CHB and CHC or obtained results different from those shown in Table 2. Katrinli *et al.* [59] found no association between the *rs4986790* polymorphism and CHB; Pires-Neto Ode *et al.* [60] claimed the absence of any correlation of *rs4986790* and *rs4986791* with CHB and CHC. Sghaier *et al.* [56] identified the *G* allele at locus *rs4986790* as a risk factor for chronic infection with hepatitis B and C viruses.

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Table 3. Simple nucleotide polymorphisms associated with achieving a sustained virological response, spontaneous clearance, and high risk of chronicity in patients with HBV and HCV infections

Gene ID NSBI	Polymorphysm	Region of study, source	Study groups	*n*	Identified SNP and viral hepatitis associations	Effect
HLA-DQB2 C→T ID: 3120	*rs7756516* (*C→T*)	China [49]	Patients with CHB	321	OR = 0,46; 95% CI 0,23–0,91; *p* = 0,0262	*TT* haplotype is associated with non-sustained therapeutic response in patients with CHB
HLA-DQA2 G/T ID: 3118	*rs9276370* (*G→A,T*)		Comparison group	304		
IL-10 ID: 3586	*rs1800896* (*T→C*)	Egypt [50]	Patients with LC in CHC	50	OR = 4,0; 95% CI 1,86–8,8; *p* < 0,05	*GG* genotype is associated with higher susceptibility to HCV
			Comparison group	50		
	rs1800871 (-819*T→C*)	India [51]	Patients with acute hepatic encephalopathy in acute viral hepatitis E combined with CHB	40	OR = 2,4; 95% CI 0,9–6,2; *p* < 0,05	*TC* genotype is a risk factor for acute liver failure
			Comparison group	40		
IL-28B (*IFNL3*) ID: 282617	*rs12979860* (*C→T*)	Metaanalysis [52]	Mongoloid patients	1880	OR = 1,31; 95% CI 0,79–2,15	*CC* genotype implies higher probability of spontaneous clearance
			Caucasian patients	8828	OR = 3,78; 95% CI 2,60–5,50	
		Russia [53]	CHC patients (genotype *CC*)	48	OR = 2,38; 95% CI 1,1–5,11; *p* = 0,025	
			Patients with CHC (other genotype)	76		
	rs4803217 (*C*/*A*)	Poland [54]	Patients with CHC	96	OR = 4,979; 95% CI 1,344–18,444; *p* = 0,016	*A* allele is associated with sustained virological response to CHC (HCV genotype 1) treatment with pegylated interferon and ribavirin
STAT3 ID: 6774	*rs1053004* (*C→T*)	China [45]	Patients with CHB	5242	OR = 1,17; 95% CI 1,07–1,29; *p* = 0,0007	*C* allele suggests higher risk of chronicity following acute hepatitis B
			Comparison group	2717		
HLA-DPB1 ID: 3115	*rs9277378* (*A→C,G,T*)	Thailand [55]	Пациенты с ХГВ Patients with CHB	219	OR = 0,47; 95% CI 0,31–0,72; *p* = 0,001	*A* allele suggests lower risk of chronicity following acute hepatitis B
			Comparison group	123		
	rs4986790[1] (*A→G,T*)	Tunisia [56]	Patients with CHC	174	*p* = 0,031	*T* allele is a risk factor for chronic infection in patients with acute hepatitis C
			Comparison group	360		

End of Table 3

Gene ID NSBI	Polymorphysm	Region of study, source	Study groups	*n*	Identified SNP and viral hepatitis associations	Effect
		China [57]	Patients with CHB	278	OR = 3,29; 95% CI 0,85–5,73; p = 0,008	*G* allele is associated with spontaneous HBsAg seroclearance
	rs4986791[1] (*C→T*)	Saudi Arabia [58]	Patients with HCV	450	*rs4986791*: OR = 0,298; 95% CI 0,201–0,443; p < 0,0001 *rs4986790*: OR = 0,404; 95% CI 0,281–0,581; p < 0,0001	*T* allele of *rs4986791* combined with the *G*-allele of *rs4986790* have a protective effect against HCV
			Comparison group	600		
IFNL4 ID: 101180976	*rs368234815* (*G→TT,T,C*)	Russia [53]	Patients with HCV (genotype *TT*)	48	OR = 2,38; 95% CI 1,1–5,11; p = 0,025	*TT/TT* in combination with the *CC* genotype of *rs12979860* is associated with high probability of spontaneous HCV clearance
			Patients with HCV (other genotype)	76		

of Caucasian origin. The data on the association of combined *TT/TT* genotypes (*IFNL4;* Gene ID: 101180976) and *CC* (*IFNL3;* Gene ID: 282617) [53] with spontaneous clearance are of particular interest. Chinese researchers identified the association between *rs4986790* (*A→G,T*) in *HLA-DPB1* gene (Gene ID: 3115) at and elimination of HBsAg in patients with CHB [57]. The association of the T-allele of *rs4986790* (*A→G,T*), *HLA-DPB1* gene (Gene ID: 3115) with higher risk of chronic infection in patients infected with HCV was found during the examination of a cohort of patients in Tunisia [56]. Shi *et al.* identified that the carriers of the *C*-allele of *rs1053004 STAT3* (Gene ID: 6774), had higher risk of chronicity following acute hepatitis B [45]. In India, Maurya *et al.* found that the *TC* genotype of *rs1800871* (-819 *T→C*), *IL10* gene (Gene ID: 3586), was associated with higher probability of development of fulminant hepatitis E in patients with CHC [51]. Egyptian researchers found the association between the *GG* genotype of *rs1800896*, *IL10* gene (Gene ID: 3586), and higher susceptibility to HCV infection [50].

The STAT3 and STAT4 proteins encoded by the respective genes mediate expression of the genes responsible for the immune response and participate in activation of processes involving cell growth and apoptosis. *IFNL3*, similar to *IFNL4*, has antiviral and antitumor properties; it acts as a ligand for the Class II heterodimeric cytokine receptor consisting of *IL-10RB* and *IFNLR1*; the receptor activates the JAK/STAT-pathway to transmit a signal and trigger an antiviral effect. The *MERTK* gene encodes the MER protein (MER proto-oncogene, tyrosine kinase), which is a member of the TAM RTK (Tyro3, Axl, Mer receptor tyrosine kinase) family of receptor kinases and is a transmembrane protein with 2 domains of fibronectin type-III, 1 domain of tyrosine kinase and 2 immunoglobulin-like domains. MER inhibits the signaling pathways actuated by cytokines and TLR ligands through suppressors of cytokine signaling and participates in clearance of apoptotic cells [61]. TLR4 is a signaling protein transducing a signal to Kupffer cells in the event of hepatitis B and C development, thus activating the synthesis of proinflammatory cytokines, such as TNF-α, IL-1β, -6, -12, -18 as well as anti-inflammatory IL-10, -4, TGFβ cytokines, and others. IL-6 induces the production of proteins of the acute phase of inflammation; in hepatitis B and C, it participates in intensification of hepatocyte mitosis. The synthesis of IL-6 is activated by TLR4 as well as by IL-1 and TNF-α [62]. IL-10 induces the synthesis of Th2, monocytes, macrophages, cytotoxic T lymphocytes, and mast cells; it inhibits the activation of Th1 and NK-cells; it promotes production of collagen by hepatic stellate cells, thus being one of the factors contributing the development of fibrosis and LC. The function of TNF-α is to induce the synthesis of IFN-γ and $CD8^+$.

IL-28B belongs to the type III interferon (λ) with a high antiviral effect achieved through the JAK/STAT-signaling cascade-mediated activation of the protein kinase inhibiting replication of HCV.

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IFN-γ has numerous immune-regulatory properties: It activates macrophages and monocytes, neutrophils, and NK-cells; it stimulates differentiation between T- and B-lymphocytes.

Among the range of less-explored polymorphisms, one of the most promising focus areas is identification of associations between SNPs of the IL-1 superfamily and viral hepatitis, considering a significant biological role of the above proinflammatory cytokines and their antagonists. Currently, there are published results of the studies exploring the association between the members of the IL-1 superfamily and viral hepatitis. Estfanous *et al.* found that for IL-1β *rs1143629* SNPs, the homozygous *AA* variant has a significantly higher rate of occurrence among patients with CHC, though there was no correlation for IL-1β *rs1143634* [64]. IL-18 SNPs (the *GG* genotype of *rs1946518*) were found to be associated with low susceptibility to HCV infection, while the *T*-allele was associated with high risk of infection. Biswas *et al.* found the prevailing *CC* IL-1β -511 (*C/T*) genotype in patients with asymptomatic CHC [65]. As compared to the patients with LC and the control group of healthy people, genotype 2/2 for IL-1RN was more frequently detected in patients with LC; the combination of IL-1β (-511) and IL-1RN genotypes, which was represented by *CC*-1/2, was more typical of asymptomatic CHC, while the *TT*-2/2 combination was more typical of patients with LC.

Associations between polymorphisms and different diseases are being extensively studied in many countries. The understanding of the SNP association with people's susceptibility to different diseases, severity of disease development and outcome, efficiency of antiviral medications is of tremendous significance for epidemiological studies. An important component of the present-day systems of epidemiological surveillance of infectious diseases is designing of precise computational models of epidemic process development. Reliable scenarios of further evolution of epidemic processes cannot be prepared without knowing the SNP proportion among the healthy population and the ratio of SNPs in specific groups of patients. The pressing demand for improved efficiency of epidemic preventive actions adds significance to SNP research and suggests that assessment methods for SNP proportions should be included in the epidemiological surveillance system as monitoring parameters. Considering the significant biological role of proinflammatory cytokines and their antagonists of the IL1 superfamily, exploration of associations between SNPs and viral hepatitis B and C is one of the priority objectives.

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