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POLYMORPHISM OF GENES LOCALIZED ON THE X-CHROMOSOME AS A MARKER OF PREDISPOSITION TO INFECTIOUS PROCESS CHRONICITY AT HEPATITIS C IN THE ETHNIC GROUP OF MALE YAKUTS

ABSTRACT

The work studied variable sites of six genes localized on the X-chromosome in the Yakut ethnic group - residents of the Republic of Sakha (Yakutia). The candidate TLR7 rs179009 gene was found, the C-allele of which is associated with the chronic course of hepatitis C. The minor C allele is more than 2 times more common in patients with chronic hepatitis C than in the group with spontaneous recovery. It was found that the chances of hepatitis transition to a chronic course are 2.7 times higher in carriers of the C-allele than in carriers of the T-allele rs179009 TLR7. The obtained data confirm the possible significance of the rs179009 polymorphism of the TLR7 gene as a genetic marker of predisposition to the chronicity of the infectious process while viral hepatitis C in the ethnic group of male Yakuts.

Keywords: hepatitis C, single nucleotide polymorphisms, toll-like receptors, X chromosome, chronic infection process, Yakuts, male.

Introduction. In the Republic of Sakha (Yakutia), there is a high incidence of viral hepatitis C (52.4 per 100 thousand of population), which is 1.5 times higher than the average Russian index [2]. The fact that representatives of Yakut men are more involved in the epidemic process than women stands out. In men, liver cirrhosis and hepatocellular carcinoma are more frequent and develop faster [4]. However, it is known that in some patients after hepatitis C virus (HCV) infection spontaneous recovery is possible [14, 21]. Predisposition to the chronic course of hepatitis after acute or latent period is genetically determined and varies significantly among members of different ethnic groups [1, 11, 12, 22]. Thus, according to D.L. Thomas et al., (2009), spontaneous recovery occurs in 36.4% of Caucasians and only in 9.3% of African Americans [12]. However, molecular genetic mechanisms that determine the ethnic and gender features of natural course and outcome of hepatitis C (HC) have not been discovered yet. In this direction, the role of single nucleotide polymorphisms of genes (SNPs) encoding the synthesis of cytokines, interferons and adapter molecules of innate immunity has been actively studied recently [3, 9, 19]. When analyzing gender characteristics of HC and its outcomes, it is necessary to take into account that in men, the genes located on the X chromosome are most susceptible to the influence of SNPs on the functions of antiviral immunity and oncological control due to the absence of the second allele. In the Yakut ethnic group, such studies have not yet been conducted.

Research objective: to improve the personalized prognosis of the course of viral hepatitis C, identify associative links between alleles of single nucleotide polymorphisms of genes localized on the X-chromosome and a predisposition to chronic HCV infection in the male Yakuts ethnic group.

Materials and methods. Presented studies were performed in 2017-2018 on the territory of the Republic of Sakha (Yakutia). The material was collected in the Yakutsk City Clinical Hospital, department for the treatment of patients with viral hepatitis, Gornaya Central District Hospital, Namsk Central District Hospital, Hangalasskaya Central District Hospital in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

In total, molecular genetic studies were performed in 96 Yakut men, including 48 patients with chronic hepatitis C (CHC) and 48 patients with a confirmed spontaneous clearance of the virus. The average age of patients with HC was 53,4 ± 12,5 years, the average body mass index - 26,7. All the examined patients lived on the territory of the Republic of Sakha (Yakutia), including 19 (39,6%) people from the city of Yakutsk and 29 (60,4%) from other uluses (Gornyi, Namsk, Hangalassk). Out of the 48 patients with CHC, 1b - 75,0% (36), prevailed in the structure of genotypes, genotype 2 accounted for 4,2% (2), genotype-3 - 20,8% (10). The control group of persons with spontaneous clearance of HCV (SC) had no significant differences with the experimental one in gender, age and body mass index. All patients have given informed consent to perform a genetic study.

The diagnosis of CHC was made on the basis of medical history, clinical examination, determination of hepatic transaminases activity, detection of anti-HCV IgG and HCV RNA. SC was proved according to the criteria regulated by the sanitary and epidemiological rules of the SP 3.1.3112-13 “Prevention of viral hepatitis C” (decree of October 22, 2013 N 58, registered in the Ministry of Justice of Russia on 19.03.2014 N 31646). Patients with the presence of anti-HCV in the blood were on follow-up monitoring for at least two years, and with repeated negative results of HCV RNA, they were proved to have a spontaneous recovery, if there was no antiviral therapy in the history. Exclusion criteria were patients with cirrhosis, hepatocellular carcinoma, as well as having a combined pathology or co-infection of the liver of a different etiology.

In these patient samples genetic studies of SNP of the following genes were performed: *TLR7* (rs179008); *TLR7* (rs179009); *TLR8* (rs3764879); *IRAK1* (rs3027898); *TAB3* (rs1000129516); *MECP2* (rs1734791). When selecting genes, the authors considered polymorphisms at the X chromosome loci that affect the structure or function of receptors and adapter molecules involved in transmission of intracellular signals — activators of antiviral factors of innate immunity. Molecular genetic studies were performed using an amplifier for real-time PCR Rotor-Gene Q (Qiagen Hilden, Ger-

many). Amplification of certain regions of the genes was carried out using primers and probes of one's own design, synthesized at Sintol Research and Production Company and ZAO Evrogen (table 1).

When analyzing the results of genetic studies, we compared allele occurrence rates. The odds ratio (Odds Ratio, OR) was calculated at a confidence interval level of 95% (Confidence Interval, 95% CI). The significance of differences was assessed after adjusting for multiple comparisons using the average proportion of false deviations of the hypotheses (corrected p-value) [6]. The level of statistical significance was taken at $p \leq 0.05$.

Results and discussion. More than 200 genes are involved in the transmission of the intracellular signal from the pattern recognition receptor to the NFkB transcription factor and its translocation into the nucleus, 13 of which are located on the X-chromosome [25]. This puts the male representatives in unequal conditions, since the absence of the second allele manifests any changes in the variation sites of the genes involved in the innate immune response. According to the literature, males dominate among carriers of HCV antibodies [5, 16]. Perhaps the predominance of males among patients with chronic hepatitis C is associated not only with differences in risk factors for infection, but also due to genetic characteristics of innate immunity reactions. In addition, the predisposition of men to develop HCC in the outcome of HCV is well known. The ratio of females and males in patients with HCC varies from 1: 1.7 in Turkey to 1: 4.1 in Korea [20].

The analysis revealed that out of six SNP only TLR7 rs179009 significantly differed in the frequency of alleles in the group of patients with spontaneous clearance and CHC (table 2). The minor C-allele is more than 2 times more common in patients with chronic hepatitis C than in the group with spontaneous clearance. At the same time, it was established that the chances of HV transition to the chronic course are 2.7 times higher in C-allele carriers than in rs179009 TLR7 T-allele carriers. Despite the long chain of transmission of the intracellular signal, it is Toll-like receptors (TLR) that play a key role in the pathogenesis of HC, since they represent the first viral recognition line that induces the primary "alarm" signal [19]. The recognition of viral RNA initiates signaling along two parallel duplicate paths: from TLR7 / 8 through the MyD88 molecular adapter to the cell nucleus and from TLR3 through the TRIF adapter molecule to the nucleus (the so-called MyD88 independent pathway) [15, 18]. The functional purpose of both signals is the same: ensuring the synthesis of α- and β-interferon and cytokines, which ensure the destruction of the virus and the degradation of viral RNA in the early stage of infection. "Breakdown" of one of the pathways is associated with a violation of the signal transmission rate in the cell and a change in the level of innate immunity genes expression.

Presently, experimental studies of the role of several SNPs of the TLR3 gene localized on the fourth pair of chromosomes have been described [9]. In Caucasians, human macrophages, carriers of the rs13126816 TLR3 G-allele, when in contact with viral antigens, have the ability of rapid and potent interferon-β production [17]. Perhaps for this reason, the G-allele rs13126816 TLR3 is associated with a high incidence of the 1st HCV genotype SC in the Caucasians of North America, African Americans and Latin Americans [17]. The same SNP is associated with the individual's innate resistance to the herpes virus [24]. Unlike the locus described above, another SNR rs3775291 (A/G) TLR3 is in the exon zone. Replacing leucine with phenylalanine in TLR3 protein leads to a loss of receptor activity [23]. The alleles and genotypes of TLR3 SNPs associated with the NF-kB expression level and, as a result, with a decrease in the production of type I interferons have been described [23].

There is significantly less information concerning SNPs of the TLR7 gene. In the present study, no significant differences were found between SNPs in the rs179008 TLR7 variable site and the nature of the HC course. However, other studies established the significance of this SNP in the induction of innate immu-

Table 1

Variable sites of genes and primers for identifying them in real-time PCR

Gene	SNP	Localization, the nature of the replacement	5'->3' primers and probes for real-time PCR
TLR7	rs179008	Chromosome X; exon, not synonymous, Gln-11Leu	F GGTGTTTCCAATGTGGACACTG R ACATCCAGAGTGACATCACAGG 5'(FAM)- TTATGTTAAAAAGGATAAGAATT(A-LNA)G(T-LNA)C– (RTQ1) 5'(R6G)- TTATGTTAAAAAGGATAAGAATT(T-LNA)G(T-LNA)C–(BHQ2)
	rs179009	Chromosome X; intron 2	F TTTGCTAAAGAGCTAAGATGCTAA R TTCAGCTGTCTAAACAGCATCC 5'(FAM)- GTAACTGACAAATACA(G-LNA)TC(T-LNA)TGG – (RTQ1) 5'(R6G)- GTAACTGACAAATACA (T-LNA)C(G-LNA)TGG –(BHQ2)
TLR8	rs3764879	Chromosome X; above reading frame	R TCVTCATTGTTCTGGGACCT F AGATGAARACCTGAAACAACGT 5'- (FAM)-GACTACGGAATGT(G-LNA)AAGT(A-LNA)C-RTQ 5'- (R6G)-GACTACGGAATGTG(A-LNA)AGT(C-LNA)C-BHQ2
IRAK1	rs3027898	Chromosome X; below reading frame	F 5'- AGATGAARACCTGAAACAACGT R 5' – TCVTCATTGTTCTGGGACCT 5'- (FAM)-GACTACGGAATGT(G-LNA)AAGT(A-LNA)C-RTQ 5'- (R6G)-GACTACGGAATGTG(A-LNA)AGT(C-LNA)C-BHQ2
TAB3	rs1000129516	Chromosome X; intron	F 5'-AGGTTGGTTTTGGGTC R 5'-AGAGCACAGTAGTAGG 5'-FAM-TCACAGAAGTGAAGG(T-LNA)A-RTQ1 5'-R6G-TCACAGAAGTGAAGG(C-LNA)A-BHQ2
MECP2	rs1734791	Chromosome X; intron	F 5'-ACAGAATAGTCATAAAATC R 5'- AAGTGCTGGGCCACCA 5'-FAM-AAACAGATGA(T-LNA)AAAAG(A-LNA)AA-RTQ1 5'-R6G-AAACAGATGA(T-LNA)AAAAG(T-LNA)AA-BHQ2

nity reactions [8, 10]. By its nature, this SNP is non-synonymous and is characterized by the replacement of glutamine (Gln) with leucine (Leu) in the encoded protein. As a result, the signal peptide of the TLR7 receptor manifests a functional deficiency [13]. In response to synthetic inducers, low expression of IFNL1 mRNA, IL-10Rβ and IL-28Rα is observed in dendritic cells and hepatocytes of carriers of the minor T-allele [7].

Conclusion. The described immunological phenomena explain the potential significance of genes localized on the X chromosome while HC in the context of ethnic groups and the gender of an individual. The discovered association of TLR7 rs179009 with predisposition to chronicity of HC in male Yakuts complements the idea about the toll-like receptors role in the antiviral defense of the body, which will further let us develop personalized approaches to prognosing the course and outcome of the HCV infection natural course

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Table 2

Associations of gene alleles mapped on the X chromosome with the SC of the hepatitis C virus in the ethnic group of Yakut residents of the RS (Ya)

Gene, variable site	The allele	Group Characteristic		OR (95% CI)	p
		spontaneous clearance (N=48) n(%)	chronic hepatitis C (N=48) n(%)		
TLR7 rs179008	A	35(72,9)	40(83,3)	1,0	
	T	13(27,1)	8(16,7)	0,54 (0,20-1,45)	0,2
TLR7 rs179009	T	40(83,4)	31(64,6)	1,0	
	C	8(16,6)	17(35,4)	2,7 (1,05-7,18)	0,036
TLR8 rs3764879	C	36(75,0)	38(79,1)	1,0	
	T	12(25,0)	10(20,8)	0,79 (0,30-2,05)	0,6
IRAK1 rs3027898	A	40(83,3)	40(83,3)	1,0	
	C	8(16,7)	8(16,7)	1,0 (0,34-2,93)	1,0
TAB3 rs1000129516	A	29(60,4)	30(62,5)	1,0	
	G	19(39,6)	18(37,5)	0,92 (0,40-2,08)	0,92
MECP2 rs1734791	A	37(77,1)	38(79,1)	1,0	
	T	11(22,9)	10(20,8)	0,80 (0,34-2,33)	0,89

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