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Evaluation of the epidemiological significance of molecular genetic factors in relation to the intensity of post-vaccination immunity against hepatitis B

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Abstract

Introduction. Hepatitis B retains the status of socially significant infection and remains a major health problem worldwide, including the Russian Federation. The improvement of the effectiveness of the current complex of preventive measures, especially vaccination, is an important task for public health. Although vaccination against hepatitis B is highly successful, 5% to 10% of individuals do not experience a response to vaccine with an adequate level of antibodies to hepatitis B surface antigen (anti-HBs). One of the key factors determining the absence or insufficiency of post-vaccination immunity against hepatitis B may be the single-nucleotide polymorphisms (SNPs) that change gene sequences, including those that determine the mechanism of immunogenesis. Such genetic changes may affect the signaling pathways and result in significant decrease in antibody response to hepatitis B vaccine. Assessment of epidemiological significance of such SNPs is an important task, considering its possible associations with failure to respond adequately to vaccination.

The aim of the study was to determine the effect of SNPs of *IL1B* (*rs1143634*, *rs1143627*), *IL1RN* (*rs4251961*, *rs419598*), *IL6* (*rs1800795*), *IL10* (*rs1800896*), *TULP1* (*rs9380516*), *TLR4* (*rs4986790*), *MERTK* (*rs4374383*) genes on the formation of post-vaccination immunity against hepatitis B.

Materials and methods. Healthcare workers (n = 271) of the Treatment and Rehabilitation Center of the Ministry of Health of the Russian Federation with known vaccination history, data on age, work experience and department of the medical institution were included in this research. The presence and levels of anti-HBs and anti-HBcore IgG antibodies were determined by the ELISA method using the DS-ELISA-ANTI-HBs and DS-ELISA-ANTI-HBc kits, according to the manufacturer's instructions. Genotyping was performed by real time polymerase chain reaction. Statistical analysis of data was carried out using the "Statistica 6.0" software.

Results. Statistically significant differences in the frequencies of *CC* (*rs9380516*) genotypes (p = 0.034; OR 0.497; 95% CI 0.261–0.949) and *CT* (p = 0.044; OR 1.967; 95% CI 1.015–3.812) of the *TULP1* gene in the group of individuals with anti-HBs concentrations of 10–100 IU/l were found in association with the intensity of the post-vaccination response against hepatitis B. Also, for this group, differences were found in the structure of the *TT*/*CT* genotype pair of *IL-10*/*TULP1* genes (*rs1800896*/*rs9380516*) (p = 0.003; OR = 5.39; 95% CI 1.7–17.4) and for the combination of *AA*/*TT* SNP *MERTK*/*IL1RN* genotypes (*rs4374383*/*rs4251961*) (p = 0.003; OR = 7.96; 95% CI 1.7–37.6).

Conclusion. Our study revealed that above variants of genotypes could play a role in predicting an increased risk of low (or absence) post-vaccination immune response against hepatitis B. It seems appropriate to use the relationship between the gene polymorphisms and a low concentration of post-vaccination anti-HBs antibodies in assessing scenarios for the development of the epidemic process of hepatitis B, since the identified associations allow to quantify the risks of poor herd immunity against this infection.

Keywords: *single nucleotide polymorphism, post-vaccination immunity, hepatitis B, anti-HBs, ELISA, PCR*

Ethics approval. The study was conducted with the informed consent of the study participants. The research protocol was approved by the Local Ethics Committee of the Central Research Institute for Epidemiology (Protocol No. 114, April 22, 2021).

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Научная статья
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Оценка эпидемиологической значимости молекулярно-генетических факторов в отношении напряжённости поствакцинального иммунитета против гепатита В

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Аннотация

Введение. Гепатит В, сохраняя статус социально значимой инфекции, остаётся актуальной проблемой здравоохранения в России. Важной задачей является повышение эффективности действующего комплекса противоэпидемических мероприятий, в том числе вакцинопрофилактики. После проведения полного курса вакцинации против гепатита В удельный вес лиц с отсутствием или низкой концентрацией поствакцинальных анти-HBs составляет 5–10%. Одной из причин, детерминирующих отсутствие или недостаточность поствакцинального иммунитета против гепатита В, могут быть однонуклеотидные полиморфизмы (ОНП), в том числе определяющие реализацию механизма иммуногенеза. С учётом возможных ассоциаций ОНП с напряжённостью поствакцинального иммунитета, важной проблемой является оценка их эпидемиологической значимости.

Цель работы — определение влияния ОНП генов *IL1B* (*rs1143634*, *rs1143627*), *IL1RN* (*rs4251961*, *rs419598*), *IL6* (*rs1800795*), *IL10* (*rs1800896*), *TULP1* (*rs9380516*), *TLR4* (*rs4986790*), *MERTK* (*rs4374383*) на формирование поствакцинального иммунитета против гепатита В.

Материалы и методы. Изучаемую группу составили медицинские работники Лечебно-реабилитационного центра Минздрава России (*n* = 271) с установленным прививочным анамнезом, наличием данных о возрасте, стаже работы и отделении медицинского учреждения. Серологические исследования по определению наличия и уровня анти-HBs и анти-HBcore класса IgG выполняли методом ИФА с использованием тест-систем «ДС-ИФА-АНТИ-HBs» и «ДС-ИФА-АНТИ-HBc». Генотипирование проводили методом полимеразной цепной реакции в режиме реального времени. Статистическую обработку полученных данных осуществляли с использованием програмы «Statistica 6.0».

Результаты. В ассоциации с напряжённостью поствакцинального ответа против гепатита В установлены статистически значимые различия частот генотипов *CC* (*rs9380516*) (*p* = 0,034; отношение шансов (ОШ) 0,497; 95% ДИ 0,261–0,949) и *CT* (*p* = 0,044; ОШ 1,967; 95% ДИ 1,015–3,812) гена *TULP1* в группе лиц с концентрацией анти-HBs 10–100 МЕ/л. Для этой группы также выявлены различия генотипов *TT*/*CT* генов *IL10*/*TULP1* (*rs1800896*/*rs9380516*) (*p* = 0,003; ОШ = 5,39; 95% ДИ 1,7–17,4) и сочетания генотипов *AA*/*TT* ОНП *MERTK*/*IL1RN* (*rs4374383*/*rs4251961*) (*p* = 0,003; ОШ = 7,96; 95% ДИ 1,7–37,6).

Заключение. В настоящем исследовании показана роль вариантов генотипов в прогнозировании повышенного риска развития слабого поствакцинального иммунного ответа (или его отсутствия) против гепатита В. Ассоциации полиморфизмов ряда генов с низкой концентрацией поствакцинальных анти-HBs целесообразно использовать при разработке сценариев развития эпидемического процесса гепатита В, поскольку выявленные зависимости позволяют дать количественную характеристику рисков формирования слабого иммунитета против данной инфекции на популяционном уровне.

Ключевые слова: *однонуклеотидный полиморфизм, поствакцинальный иммунитет, гепатит В, анти-HBs, иммуноферментный анализ, полимеразная цепная реакция*

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

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Introduction

Hepatitis B (HB) is an infection controllable through specific preventive measures; the implementation of the country-wide national program of preventive vaccination is the principal and the most effective epidemic control strategy in the system of epidemiological surveillance. Through vaccination programs, Russia has achieved steady and significant improvement in the HB epidemiological situation. Meanwhile, the findings of multiple studies focusing on the analysis of patterns and mechanisms of vaccine-induced immunity against HB demonstrate that 5–10% of the vaccinees who completed the vaccination (a three-dose series on a 0, 1, and 6-month schedule) are defined as non-responders, i.e. they do not develop antibodies or their levels of antibodies are equal to or below the protective level of 10 IU/L [1–3].

Immediate attention should be given to studying the causes of insufficient immune responses in vaccinated people, considering that HB vaccination programs have been adopted by most of the countries. There is no common opinion about the factors causing the problem and about the ways it can be resolved, as antigen presentation and subsequent interactions involved in building both humoral and cell-mediated immunity constitute a complex, multistep process.

As assumed by Abebe et al., the partial or complete failure to produce anti-HBs following a complete immunization series can be caused by dysregulated differentiation of naive B cells into specific antibody-secreting cells and plasmablasts [4]. Kardar et al. attribute low seroconversion rates to diminished production of interleukin-2 (IL-2), interferon-γ, and IL-10 cytokines after HB vaccination [5]. The study conducted by Körber et al. showed that non-responders typically had suppressed IL-10 expression in regulatory B cells [6]. As expected, the administration of a vaccine booster dose resulted in a slight increase in the levels of anti-HBs, which was significantly different from the levels recorded in the control group of individuals with the normal IL-10 expression. Garner-Spitzer et al. have also concluded that absent immune responses to HBsAg-containing vaccines are associated not only with the administered vaccine, but also with genetic characteristics of vaccinated individuals [7].

Immunogenesis is a fairly complex mechanism including a cascade of successive interactions (signaling pathways) inducing immune responses to host-invading antigens. Obviously, by creating new variants of nucleotide sequences, single nucleotide polymorphisms (SNPs) can cause changes both in the subsequent function of non-coding regions of genes and in the amino acid composition of translated polypeptides participating in signaling pathways. Multiple studies address the SNP association, contributing to the extensive experience in studying the impact of human genetic variants in association with different pathological conditions of non-infectious [8–10] and infectious [11] etiology.

The **aim** of the study was to assess the impact of *IL-1B* (*rs1143634*, *rs1143627*), *IL1RN* (*rs4251961*, *rs419598*), *IL6* (*rs1800795*), *IL-10* (*rs1800896*), *TULP1* (*rs9380516*), *TLR4* (*rs4986790*), and *MERTK* (*rs4374383*) SNPs on vaccine-induced immunity against HB.

Materials and methods

The study was conducted in the laboratory of viral hepatitis at the Central Research Institute of Epidemiology (CRIE). The study group was composed of healthcare workers from the Treatment and Rehabilitation Center of the Ministry of Health of Russia (n = 271; men/women — 56/215; mean age 45 ± 10 years), with confirmed vaccination history and employment at the healthcare facility. All the participants signed their informed consent; the study was approved by the CRIE Local Ethics Committee (Minutes No. 114 dated 22/4/2021).

Serological tests for identifying anti-HBs and anti-HBc IgG antibody levels were performed using the enzyme immunoassay (EIA) and DS-EIA-ANTI-HBS and DS-EIA-ANTI-HBc reagent kits (Diagnostic Systems) in accordance with the manufacturer's instructions.

In the study group, the tests for detection of SNPs were performed for the following genes: *IL-1B* (*rs1143634*, *rs1143627*), *IL1RN* (*rs4251961*, *rs419598*), *IL6* (*rs1800795*), *IL-10* (*rs1800896*), *TULP1* (*rs9380516*), *TLR4* (*rs4986790*), and *MERTK* (*rs4374383*). For DNA extraction, we used a Gemolitik reagent and a Ribo-PREP reagent kit (AmpliSens). SNP-containing gene fragments were amplified in a Rotor-Gene Q 6plex thermal cycler (Qiagen). The method of polymorphism detection is based on detection of SNP alleles using allele-specific locked nucleic acid (LNA) probes detectable in 2 or 4 channels of fluorescence detection and designed by the CRIE Research Group for New Methods of Genetic Polymorphism Detection. The obtained results were verified through Sanger sequencing and pyrosequencing [12].

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The sample representativeness was assessed statistically using the Pearson chi-square (χ^2) test for estimating differences between the allele frequencies detected in this study and those reported in the international dbSNP (NCBI) database for group Caucasians (CEU)[1].

The Pearson χ^2 test was based on the standard fourfold table to check whether there is an association between SNPs and levels of post-vaccination anti-HBs. The variables were deemed as statistically significant at $p < 0.05$ when comparing frequencies of individual polymorphisms and at $p < 0.005$ when comparing frequencies of SNP pairwise combinations.

Results

During the first stage of the study, the entire cohort ($n = 271$) was examined for the presence of anti-HBc antibodies using the EIA method to exclude individuals with infection-induced immunity from the further study. Anti-HBc antibodies were detected in 48 (17.7%) participants (95% CI, 13.4–22.8%). In this group of healthcare workers, the mean age was 44 ± 10 years, and the length of occupational employment was 18 ± 11 years. The HB vaccination was reported by 47 participants (25 participants completed full-series immunization more than 5 years ago and 22 participants had full-series immunization less than 5 years ago). Anti-HBs antibodies were detected in 36 (76.6%) participants; in 12 participants, their levels were within a 10 ± 100 IU/L range, and 19 participants had anti-HBs levels higher than 100 IU/L. In 12 healthcare workers, anti-HBs antibodies either were not detected or their levels were below the protective level (10 IU/L).

The division of the healthcare workers into groups of individuals with infection-induced and vaccine-induced immunity against HB was essential for valid assessment of the effectiveness of the preventive measures. 15–20 years ago, the healthcare workers having an occupational exposure to HB and the length of employment over 10 years accounted for 45–50% [13]. At present, the risks for acquiring infection through occupational exposure of healthcare workers have significantly decreased, though not completely eliminated and still requiring close attention.

The study group comprised 223 healthcare workers, who, based on the serological tests, had never been infected with the HB virus (HBV). The mean age in the group was 45 ± 10 years; the length of occupational employment — 20 ± 11 years. Based on the quantitative measurement of anti-HBs antibodies and depending on the anti-HBs antibody levels, the study group was divided into three subgroups: 55 (24.7%; 95% CI, 19.2–30.9%) participants with levels below 10 IU/L; 69 (30.9%; 95% CI, 24.9–37.5%) participants with levels within a 10–100 IU/L range; 99 (42.4%; 95% CI, 37.8–51.2%) participants with levels above 100 IU/L. It should be noted that in the third sub-group, 13 participants had anti-HBs levels higher than 15,000 IU/L, regardless of their vaccination timeframe. Here, we can speak about the pattern when the average levels of post-vaccination anti-HBs antibodies tend to decrease along with the increasing mean age of the participants in the study group. The mean age in the subgroups was as follows: 41 ± 8 years in the group > 100 IU/L; 45 ± 10 years — in the group 10–100 IU/L and 51 ± 8 years — in the group with HB levels < 10 IU/L. The gender factor had no effect on vaccine-induced immunity against the HBV (**Table 1**).

To assess the sample representativeness in the reference-group represented by the group of healthcare workers having post-vaccination anti-HBs antibody levels > 100 IU/L ($n = 99$), we performed a comparative analysis of allele frequency distributions for the studied polymorphisms, using the international dbSNP database (NCBI) (**Table 2**).

The distribution of genotype frequencies for the studied polymorphisms conforms to the Hardy-Weinberg equilibrium and is consistent with the data available for the European (CEU) population in the dbSNP database (NCBI). Therefore, the reference-group data can be used as reference data, against which the results obtained from other study groups can be compared.

The analysis of the identified presence or absence of an association between the levels of post-vaccination antibodies to HBsAg and the studied SNPs showed statistically significant differences between the frequencies of *CC* (*rs9380516*) ($p = 0.034$; OR 0.497; 95% CI, 0.261–0.949) and *CT* ($p = 0.044$; OR 1.967; 95% CI, 1.015–3.812) genotypes of the *TULP1* gene in the group of healthcare workers with anti-HBs antibody levels ranging from 10 to 100 IU/L (**Table 3**). The same group also demonstrated differences for *TT*/*CT* genotypes of *IL-10*/*TULP1* genes (*rs1800896*/*rs9380516*) ($p = 0.003$; OR = 5.39; 95% CI, 1.7–17.4).

In addition to the above pair of SNPs, significant differences were found for *AA*/*TT* genotypes of SNPs in *MERTK*/*IL1RN* (*rs4374383*/*rs4251961*) ($p = 0.003$; OR = 7.96; 95% CI, 1.7–37.6). The comparison of frequency distributions for individual genotypes of *MERTK* (*rs4374383*) and *IL1RN* (*rs4251961*) genes did not show any statistically significant differences.

Table 1. Intensity of post-vaccination immunity against hepatitis B depending on gender, % (95% CI)

Anti-HBs, IU/liter	Men ($n = 46$)	Women ($n = 175$)
< 10	19,5 (9,3–33,9)	26,0 (19,9–33,5)
10–100	39,0 (25,1–54,6)	29,0 (22,5–36,5)
> 100	41,5 (27,0–56,7)	45,0 (37,1–52,3)

[1] Database of Single Nucleotide Polymorphisms (dbSNP). Available at: https://www.ncbi.nlm.nih.gov/snp

Table 2. Comparison of allele frequencies of the reference group of healthcare workers with the database "DbSNP" (NCBI)

Single nucleotide polymorphism	Gene	Substitution	Frequency of rare allele		Difference between allele frequencies	
			dbSNP CEU (*n* = 1000)	reference group (*n* = 99)	χ^2	*p*
rs1143634	*IL1B*	*G > A*	0,247	0,204	1,655	0,199
rs1143627	*IL1B*	*A > G*	0,352	0,362	1,350	0,246
rs4251961	*IL1RN*	*T > C*	0,379	0,299	3,327	0,069
rs419598	*IL1RN*	*T > C*	0,292	0,28	0,103	0,749
rs1800795	*IL6*	*G > C*	0,415	0,428	0,124	0,725
rs1800896	*IL10*	*T > C*	0,453	0,494	1,158	0,282
rs9380516	*TULP1*	*C > T*	0,19	0,159	1,103	0,294
rs4986790	*TLR4*	*A > G*	0,056	0,07	1,237	0,267
rs4374383	*MERTK*	*G > A*	0,376	0,421	1,497	0,222

The combinations of genes with detected associations do not form any linkage groups; they are inherited independently and the gene linkage disequilibrium is 0.0663 for *rs1800896*/*rs9380516* of the *IL-10*/*TULP1* genes and 0.0294 — for *rs4374383*/*rs4251961* of *MERTK*/*IL1RN*.

As opposed to the group of healthcare workers having levels of specific antibodies within a 10–100 IU/L range, the group with low levels of anti-HBs antibodies (< 10 IU/L) did not show any significant differences in polymorphism allele and genotype frequencies.

Discussion

Summarizing data of multiple studies, a number of authors noted that approximately among 10% of the population, the standard HB vaccination schedule (0–1–6 months) does not result in producing antibodies to HBsAg, which would reach the protective level

Table 3. Significant associations regarding the intensity of post-vaccination immunity against hepatitis B

Gene	Genotype	Concentration of anti-HBs, IU/liter		*p*	OR (95% CI)
		> 100 (*n* = 99)	10–100 (*n* = 69)		
TULP1 (*rs9380516*)	*CC*	0,711	0,55	**0,033**	**0,497 (0,261–0,949)**
	CT	0,257	0,405	**0,044**	**1,967 (1,015–3,812)**
	TT	0,03	0,043	0,669	1,424 (0,279–7,276)
IL10/*TULP1* (*rs1800896*/ *rs9380516*)	*CC/CC*	0,164	0,173	0,879	1,066 (0,469–2,424)
	CC/CT	0,082	0,058	0,548	0,685 (0,198–2,371)
	CC/TT	0	0,0145	–	–
	CT/CC	0,329	0,217	0,113	0,564 (0,277–1,150)
	CT/CT	0,134	0,159	0,647	1,225 (0,513–2,925)
	CT/TT	0,02	0,028	0,728	0,705 (0,097–5,133)
	TT/CC	0,216	0,159	0,358	0,686 (0,307–1,536)
	TT/CT	0,041	0,188	**0,003**	**5,397 (1,677–17,367)**
	TT/TT	0,01	0	–	–
MERTK/*IL1RN* (*rs4374383*/ *rs4251961*)	*AA/CC*	0,02	0,014	0,764	0,691 (0,061–7,778)
	AA/CT	0,124	0,058	0,151	0,431 (0,133–1,398)
	AA/TT	0,021	0,144	**0,003**	**7,966 (1,686–37,634)**
	AG/CC	0,061	0,029	0,323	0,448 (0,088–2,288)
	AG/CT	0,144	0,145	0,987	0,993 (0,413–2,388)
	AG/TT	0,299	0,188	0,098	0,536 (0,255–1,129)
	GG/CC	0,02	0,058	0,209	2,892 (0,515–16,259)
	GG/CT	0,124	0,116	0,86	1,089 (0,420–2,826)
	GG/TT	0,175	0,246	0,278	1,519 (0,712–3,242)

Note. Significant associations are highlighted in bold.

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(> 10 IU/L). It has been found that the vaccination failure rate is associated with the older age, existing comorbid pathology [14, 15], obesity, harmful habits [16], and depends on the type of vaccines [17] and on several other factors causing immunosuppression. In addition, the importance of host immunogenetic characteristics cannot be neglected, as the major histocompatibility complex plays a key role in the genetic control of immune responses in normal and pathological conditions.

As the problem is becoming increasingly urgent worldwide, there have been multiple studies addressing the effect of SNPs on vaccine-induced immunity against HB and having resulted in identification of several significant polymorphisms. Researchers tend to focus their attention on the human leukocyte antigen (HLA) system, as it is believed that non-responders have disrupted primary antigen presentation. It is known that lower levels of anti-HBs antibodies (< 10 IU/L) are more frequently detected in combination with HLA-DRB1*0301, DQB1*1302, DRB1*0701 and DRB1*0401 variants. In their turn, DRB1*1301, DRB1*0101 and DRB1*1501 [18] have been more frequently detected in groups of individuals with pronounced post-vaccination response. In their genome-wide association study (GWAS) backed up by multiple verification, Pan et al. detected significant SNP associations located in non-coding regions of HLA class II genes [19], including *rs477515*, *rs28366298* and *rs13204672* (HLA-DRB1), *rs3763316* (BTNL2).

The findings reported by Silvestri et al. are of significant interest. Based on 14 family cases, the researchers proved the fact of hereditary transmission of the HLA class III *C4AQ0* allele associated with suppression of post-vaccination immunity after the full-series vaccination [20].

As demonstrated by several studies, the weak serological response to immunization against HB can also be associated with SNPs not belonging to the major histocompatibility complex. Davila et al. found associations for a number of polymorphisms such as *rs6789153* located close to the *FOXP1* transcription factor gene; *rs1654668* in the *LILRB4* gene encoding leukocyte immunoglobulin-like receptors; *rs1978270* and *rs7029078* belonging to the C5 complement component, as well as *rs854692* and *rs854625* in the *CCL15* gene encoding the C-C motif chemokine ligand 15 [21]. Pan et al. found the association between the *rs12133337* SNP in the CD3Z gene encoding the T-cell surface glycoprotein CD3 zeta chain and the weak vaccine-induced immunity against HB [22]. The *rs2243250* and *rs2227284* polymorphisms in the *IL-4* gene were also found to be associated with diminished immune responses [23]. The summarized data on the SNP effect on vaccine-induced immunity against HB are presented in **Table 4**.

It should be noted that in Russia, the impact of SNPs on vaccine-induced immunity against HB has received no attention until recently, thus making it impossible to compare our results. We detected differences in the distribution of genotype frequencies for the combination of two polymorphic loci in *IL-10*/*TULP1* (*rs1800896*/*rs9380516*) between the group of healthcare workers with anti-HBs antibody levels of 10-100 IU/L and the reference group. The *rs9380516* SNP is also significant by itself as the marker indicating the increased risk of weak vaccine-induced immunity. At

Table 4. SNPs affecting the mechanisms of formation of post-vaccination immunity against hepatitis B (literature data)

Gene	Variant (associated allele)	*P*; OR [95% CI]	Source
HLA-DRB1	*0301	0,01; 0,42 [0,21–0,84]#	[18]
	*0701	0,24; 0,155 [0,14–0,43]#	
	*04	0,009; 0,57 [0,37–0,87]#	
	*1302	0,007; 0,25 [0,09–0,68]#	
BTNL2	*rs477515* (*T*)	2,63e-019; 2,05 [1,75–2,41]	[19]
	rs13204672 (*G*)	1,45e-013; 2,01 [1,67–2,43]	
	rs28366298 (*C*)	1,67e2014; 1,77 [1,53–2,05]	
	rs3763316 (*T*)	3,75e-013; 1,84 [1,56–2,17]	
FOXP1	rs6789153	$9{,}2 \times 10^{-6}$; 1,38 [1,2–1,6]	[21]
LILRB4	*rs1654668* (*T*)	8×10^{-5}; 1,34 [1,16–1,56]	
CCL15	*rs854692* (*T*)	$9{,}6 \times 10^{-4}$; 1,28 [1,11–1,50]	
	rs854625 (*A*)	$1{,}2 \times 10^{-3}$; 1,29 [1,11–1,51]	
CD3Z	*rs12133337* (*C*)	0,033; 1,28 [1,01–1,61]	[22]
IL4	*rs2243250* (*C*)	0,014; 2,04 [1,15–3,64]	[23]
	rs2227284 (*G*)	0,018; 2,25 [1,14–4,44]	

Note. #The study was conducted on a group with high levels of anti-HBs (> 100 IU/liter), therefore, in this case, the odds ratio (OR) value should be interpreted in reverse order relative to the group with a reduced post-vaccination effect.

the moment, there is no clear understanding of the mechanism involved in the identified associations, as the role of the *TULP1* gene and nearby polymorphisms, has been insufficiently studied. There are publications reporting the association of *rs9380516* SNP with some pathological conditions in humans. For example, Salmaninejad et al. [24] and Souzeau et al. [25] have reported the association between *rs9380516* and retinal dystrophies, which is consistent with the findings obtained by Hollander et al. who have reported the association between the above SNP and several inherited retinal diseases [26]. The *rs9380516* SPN has an easily identifiable association with epithelial cancer of the bladder [27]. Kutalik et al. [28] and Rüeger et al. [29] have found that the above SNP is associated with the progression rate of fibrosis and cirrhotic changes in the liver, which are caused by hepatitis C. The literature data and the results of this study, which demonstrate the variability of immune responses in people vaccinated against infectious diseases, give all grounds to believe that further studies will help identify new associations of *rs9380516* in the *TULP1* gene.

The newly identified association between the combination of polymorphisms (*rs4374383*/*rs4251961*) in *MERTK*/*IL1RN* genes and the insufficient production of post-vaccination anti-HBs antibodies comes obviously from the functional impairment of these genes. The *rs4374383* polymorphism is located in the *MERTK* gene encoding proto-oncogene tyrosine-protein kinase MER, which belongs to the TAM (tumor-associated macrophages) family. This enzyme performs a lot of functions, including inhibition of signaling pathways triggered by cytokines and TLR ligands as well as participation in apoptotic cell clearance. Today, researchers have identified the association of the *G*-allele of *rs4374383* with highly intensive development of liver fibrosis in patients with hepatitis C [29, 30]. It has also been found that the *AA* genotype (*rs4374383*) is associated with the reduced expression of the *MERTK* gene, which, consequently, can be seen as a marker of protective effect on nonalcoholic fatty liver disease [31].

Rs4251961 is located in the promoter region of the *IL1RN* gene encoding the interleukin-1 receptor antagonist (IL-1RA). Its main function is to block the pro-inflammatory cascade of responses. It has been found that the C allele of *rs4251961* (*IL1RN*) is associated with elevated levels of several markers of systemic inflammatory process, such as C-reactive protein, fibrinogen, and IL-6 [32]. Our data on the association of the above pair of polymorphisms indirectly correlate with the findings of foreign studies, as the *rs4374383 AA* genotype and the *rs4251961 TT* genotype are apparently typical of individuals with lower activity of the inflammatory profile of immune responses, thus resulting in relatively reduced immunogenicity of vaccines.

This study is the first one in Russia to identify associations between SNPs in some genes participating in regulation of different functions of the human immune system and the patterns of the humoral constituent of the vaccine-induced immunity against HB. It has been found that in the group of healthcare workers, lower levels of post-vaccination anti-HBs antibodies consistently correlate with two paired SNPs in *MERTK*/*IL-1RN* genes (*rs4374383*/*rs4251961*) and *IL-10*/*TULP1* genes (*rs1800896*/*rs9380516*) as well as with the single *rs9380516* SNP of the *TULP1* gene. Note that the above associations were detected only in individuals with lower levels of specific antibodies to HBsAg (10–100 IU/L) and did not apply to the other groups. The results obtained by foreign researchers and the outcome of our study resulting in 3 identified associations out of 9 SNPs give every reason to assume that the impact of SNPs on vaccine-induced immunity is much more versatile and that it needs further research.

The obtained results are significant not only in the context of individual specific characteristics in building the adequate immune response to vaccination, but also for the assessment of post-vaccination herd immunity. The above data can be interpreted from the epidemiological perspective, as they offer quantitative assessment of risks associated with weak protection of the population against HB. Identification of factors, including molecular and genetic factors, which can have an adverse impact on the vaccination, is highly important, especially taking into account the Health National Project launched in Russia in 2006 and the subsequent mass HB vaccination program, the main strategic objective of which is to reach the highest possible level of herd immunity. The more thorough and fuller understanding in this field, including other aspects of the HB-related problem, can significantly contribute to improvement of the epidemiological surveillance system. Today, HB prevention and control measures need priority attention, as the general epidemiological situation, though demonstrating positive trends, is far from being satisfactory.

Conclusion

The obtained results lead to the following conclusions:

1. In the recent years, the risk of occupational infection with HBV among healthcare workers has significantly decreased, as demonstrated by the anti-HBc antibody detection rates in the study groups of healthcare workers — 17.7% (95% CI, 13.4–22.8%).

2. Post-vaccination anti-HBs antibodies at protective levels (> 10 IU/L) were detected in 75.3% of healthcare workers, and high levels of anti-HBs antibodies (> 100 IU/L) were detected in 42.4% of them.

3. Some of the studied SNPs are associated with lower levels of post-vaccination anti-HBs antibodies (10–100 IU/L): *MERTK*/*IL1RN* SNP combinations (*rs4374383*/*rs4251961*) and *IL-10*/*TULP1* SNP combinations (*rs1800896*/*rs9380516*) as well as the *rs9380516* SNP of the *TULP1* gene.

4. The obtained data can be used in preparing scenarios for predicting the development of the HB epidemic process, as the identified associations of SNPs are the core component in quantitative assessment of insufficiently strong vaccine-induced immunity.

СПИСОК ИСТОЧНИКОВ

1. Meier M.A., Berger C.T. A simple clinical score to identify likely hepatitis B vaccination non-responders – data from a retrospective single center study. *BMC Infect. Dis.* 2020; 20(1): 891. https://doi.org/10.1186/s12879-020-05634-y
2. Sjogren M.H. Prevention of hepatitis B in nonresponders to initial hepatitis B virus vaccination. *Am. J. Med.* 2005; 118(Suppl. 10A): 34S–9S. https://doi.org/10.1016/j.amjmed.2005.07.012
3. Pondé R.A.A. Expression and detection of anti-HBs antibodies after hepatitis B virus infection or vaccination in the context of protective immunity. *Arch. Virol.* 2019; 164(11): 2645–58. https://doi.org/10.1007/s00705-019-04369-9
4. Chekol Abebe E., Asmamaw Dejenie T., Mengie Ayele T., Dagnew Baye N., Agegnehu Teshome A., Tilahun Muche Z. The role of regulatory B cells in health and diseases: a systemic review. *J. Inflamm. Res.* 2021; 14: 75–84. https://doi.org/10.2147/JIR.S286426
5. Kardar G.A., Jeddi-Tehrani M., Shokri F. Diminished Th1 and Th2 cytokine production in healthy adult nonresponders to recombinant hepatitis B vaccine. *Scand. J. Immunol.* 2002; 55(3): 311–4. https://doi.org/10.1046/j.1365-3083.2002.01057.x
6. Körber N., Pohl L., Weinberger B., Grubeck-Loebenstein B., Wawer A., Knolle P.A., et al. Hepatitis B vaccine non responders show higher frequencies of $CD24^{high}CD38^{high}$ regulatory B cells and lower levels of IL-10 expression compared to responders. *Front. Immunol.* 2021; 12: 713351. https://doi.org/10.3389/fimmu.2021.713351
7. Garner-Spitzer E., Wagner A., Paulke-Korinek M., Kollaritsch H., Heinz F.X., Redlberger-Fritz M., et al. Tick-borne encephalitis (TBE) and hepatitis B nonresponders feature different immunologic mechanisms in response to TBE and influenza vaccination with involvement of regulatory T and B cells and IL-10. *J. Immunol.* 2013; 191(5): 2426–36. https://doi.org/10.4049/jimmunol.1300293
8. Качнов В.А., Крюков Е.В., Колюбаева С.Н., Кутелев Г.Г., Тыренко В.В. Полиморфизмы генов, ассоциированные с нарушением липидного обмена у людей молодого возраста с риском внезапной сердечной смерти. *Казанский медицинский журнал.* 2021; 102(6): 805–14. https://doi.org/10.17816/KMJ2021-805
9. Мельникова Е.С., Рымар О.Д., Иванова А.А., Мустафина С.В., Шапкина М.Ю., Мартин Б. и др. Ассоциация полиморфизмов генов *TCF7L2*, *FABP2*, *KCNQ1*, *ADIPOQ* с прогнозом развития сахарного диабета 2-го типа. *Терапевтический архив.* 2020; 92(10): 40–7. https://doi.org/10.26442/00403660.2020.10.000393
10. Назарова Е.Л., Демьянова В.Т., Шардаков В.И., Зотина Е.Н., Докшина И.А. Ассоциации полиморфизма ряда генов врожденного иммунитета с риском развития хронических лимфопролиферативных заболеваний. *Гематология и трансфузиология.* 2016; 61(4): 183–9. https://doi.org/10.18821/0234-5730/2016-61-4-183-189
11. Епифанцева Н.В., Витковский Ю.А., Емельянова А.Н. Полиморфизм генов провоспалительных цитокинов при острых кишечных инфекциях. *Инфекция и иммунитет.* 2021; 11(3): 565–9. https://doi.org/10.15789/2220-7619-POP-1268
12. Миронов К.О., Дунаева Е.А., Дрибноходова О.П., Шипулин Г.А. Опыт использования систем генетического анализа на основе технологии пиросеквенирования. *Справочник заведующего КДЛ.* 2016; (5): 33–42.
13. Акимкин В.Г., Семененко Т.А. Эпидемиологическая и иммунологическая эффективность вакцинации медицинских работников против гепатита В. *Эпидемиология и вакцинопрофилактика.* 2017; 16(4): 52–7. https://doi.org/10.31631/2073-3046-2017-16-4-52-57
14. Семененко Т.А. Иммунный ответ при вакцинации против гепатита В у лиц с иммунодефицитными состояниями. *Эпидемиология и вакцинопрофилактика.* 2011; (1): 51–8.
15. Joshi S.S., Davis R.P., Ma M.M., Tam E., Cooper C.L., Ramji A., et al. Reduced immune responses to hepatitis B primary vaccination in obese individuals with nonalcoholic fatty liver disease. *NPJ Vaccines.* 2021; 6(1): 9. https://doi.org/10.1038/s41541-020-00266-4
16. Liu F., Guo Z., Dong C. Influences of obesity on the immunogenicity of hepatitis B vaccine. *Hum. Vaccin. Immunother.* 2017; 13(5): 1014–7. https://doi.org/10.1080/21645515.2016.1274475
17. Yoda T., Katsuyama H. Analysis of antibody-negative medical students after hepatitis B vaccination in Japan. *Hum. Vaccin. Immunother.* 2021; 17(3): 852–6. https://doi.org/10.1080/21645515.2020.1788309.
18. Li Z.K., Nie J.J., Li J., Zhuang H. The effect of HLA on immunological response to hepatitis B vaccine in healthy people: A meta-analysis. *Vaccine*. 2013; 31(40): 4355–61. https://doi.org/10.1016/j.vaccine.2013.06.108
19. Pan L., Zhang L., Zhang W., Wu X., Li Y., Yan B., et al. A genome-wide association study identifies polymorphisms in the HLA-DR region associated with non-response to hepatitis B vaccination in Chinese Han populations. *Hum. Mol. Genet.* 2014; 23(8): 2210–9. https://doi.org/10.1093/hmg/ddt586
20. De Silvestri A., Pasi A., Martinetti M., Belloni C., Tinelli C., Rondini G., et al. Family study of non-responsiveness to hepatitis B vaccine confirms the importance of HLA class III C4A locus. *Genes Immun.* 2001; 2(7): 367–72. https://doi.org/10.1038/sj.gene.6363792
21. Davila S., Froeling F.E., Tan A., Bonnard C., Boland G.J., Snippe H., et al. New genetic associations detected in a host response study to hepatitis B vaccine. *Genes Immun.* 2010; 11(3): 232–8. https://doi.org/10.1038/gene.2010.1
22. Pan L.P., Zhang W., Zhang L., Wu X.P., Zhu X.L., Yan B.Y., et al. *CD3Z* Genetic polymorphism in immune response to hepatitis B vaccination in two independent Chinese populations. *PLoS One.* 2012; 7(4): e35303. https://doi.org/10.1371/journal.pone.0035303
23. Roh E.Y., Song E.Y., Yoon J.H., Oh S., Chang J.Y., Park H., et al. Effects of interleukin-4 and interleukin-12b gene polymorphisms on hepatitis B virus vaccination. *Ann. Hepatol.* 2017; 16(1): 63–70. https://doi.org/10.5604/16652681.1226816
24. Salmaninejad A, Bedoni N, Ravesh Z, Quinodoz M., Shoeibi N., Mojarrad M., et al. Whole exome sequencing and homozygosity mapping reveals genetic defects in consanguineous Iranian families with inherited retinal dystrophies. *Sci. Rep.* 2020; 10(1): 19413. https://doi.org/10.1038/s41598-020-75841-9
25. Souzeau E., Thompson J.A., McLaren T.L., De Roach J.N., Barnett C.P., Lamey T.M., et al. Maternal uniparental isodisomy of chromosome 6 unmasks a novel variant in *TULP1* in a patient with early onset retinal dystrophy. *Mol. Vis.* 2018; 24: 478–84.
26. den Hollander A.I., Lopez I., Yzer S., Zonneveld M.N., Janssen I.M., Strom T.M., et al. Identification of novel mutations in patients with Leber congenital amaurosis and juvenile RP by genome-wide homozygosity mapping with SNP microarrays. *Invest. Ophthalmol. Vis. Sci.* 2007; 48(12): 5690–8. https://doi.org/10.1167/iovs.07-0610

27. Earp M., Winham S.J., Larson N., Permuth J.B., Sicotte H., Chien J., et al. A targeted genetic association study of epithelial ovarian cancer susceptibility. *Oncotarget*. 2016; 7(7): 7381–9. https://doi.org/10.18632/oncotarget.7121
28. Patin E., Kutalik Z., Guergnon J., Bibert S., Nalpas B., Jouanguy E., et al. Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection. *Gastroenterology*. 2012; 143(5): 1244–52.e12. https://doi.org/10.1053/j.gastro.2012.07.097
29. Rüeger S., Bochud P.Y., Dufour J.F., Müllhaupt B., Semela D., Heim M.H., et al. Impact of common risk factors of fibrosis progression in chronic hepatitis C. *Gut.* 2015; 64(10): 1605–15. https://doi.org/10.1136/gutjnl-2014-306997
30. Jiménez-Sousa M.Á., Gómez-Moreno A.Z., Pineda-Tenor D., Brochado-Kith O., Sánchez-Ruano J.J., Artaza-Varasa T., et al. The myeloid-epithelial-reproductive tyrosine kinase (*MERTK*) *rs4374383* polymorphism predicts progression of liver fibrosis in hepatitis C virus-infected patients: a longitudinal study. *J. Clin. Med.* 2018; 7(12): 473. https://doi.org/10.3390/jcm7120473
31. Petta S., Valenti L., Marra F., Grimaudo S., Tripodo C., Bugianesi E., et al. *MERTK rs4374383* polymorphism affects the severity of fibrosis in non-alcoholic fatty liver disease. *J. Hepatol.* 2016; 64(3): 682–90. https://doi.org/10.1016/j.jhep.2015.10.016
32. Reiner A.P., Wurfel M.M., Lange L.A., Carlson C.S., Nord A.S., Carty C.L., et al. Polymorphisms of the IL1-receptor antagonist gene (*IL1RN*) are associated with multiple markers of systemic inflammation. *Arterioscler. Thromb. Vasc. Biol.* 2008; 28(7): 1407–12. https://doi.org/10.1161/ATVBAHA.108.167437

REFERENCES

1. Meier M.A., Berger C.T. A simple clinical score to identify likely hepatitis B vaccination non-responders – data from a retrospective single center study. *BMC Infect. Dis.* 2020; 20(1): 891. https://doi.org/10.1186/s12879-020-05634-y
2. Sjogren M.H. Prevention of hepatitis B in nonresponders to initial hepatitis B virus vaccination. *Am. J. Med.* 2005; 118(Suppl. 10A): 34S–9S. https://doi.org/10.1016/j.amjmed.2005.07.012
3. Pondé R.A.A. Expression and detection of anti-HBs antibodies after hepatitis B virus infection or vaccination in the context of protective immunity. *Arch. Virol.* 2019; 164(11): 2645–58. https://doi.org/10.1007/s00705-019-04369-9
4. Chekol Abebe E., Asmamaw Dejenie T., Mengie Ayele T., Dagnew Baye N., Agegnehu Teshome A., Tilahun Muche Z. The role of regulatory B cells in health and diseases: a systemic review. *J. Inflamm. Res.* 2021; 14: 75–84. https://doi.org/10.2147/JIR.S286426
5. Kardar G.A., Jeddi-Tehrani M., Shokri F. Diminished Th1 and Th2 cytokine production in healthy adult nonresponders to recombinant hepatitis B vaccine. *Scand. J. Immunol.* 2002; 55(3): 311–4. https://doi.org/10.1046/j.1365-3083.2002.01057.x
6. Körber N., Pohl L., Weinberger B., Grubeck-Loebenstein B., Wawer A., Knolle P.A., et al. Hepatitis B vaccine non responders show higher frequencies of $CD24^{high}CD38^{high}$ regulatory B cells and lower levels of IL-10 expression compared to responders. *Front. Immunol.* 2021; 12: 713351. https://doi.org/10.3389/fimmu.2021.713351
7. Garner-Spitzer E., Wagner A., Paulke-Korinek M., Kollaritsch H., Heinz F.X., Redlberger-Fritz M., et al. Tick-borne encephalitis (TBE) and hepatitis B nonresponders feature different immunologic mechanisms in response to TBE and influenza vaccination with involvement of regulatory T and B cells and IL-10. *J. Immunol.* 2013; 191(5): 2426–36. https://doi.org/10.4049/jimmunol.1300293
8. Kachnov V.A., Kryukov E.V., Kolyubaeva S.N., Kutelev G.G., Tyrenko V.V. Gene polymorphisms associated with lipid metabolism disorders in young adults with risk of sudden cardiac death. *Kazanskiy meditsinskiy zhurnal.* 2021; 102(6): 805–14. https://doi.org/10.17816/KMJ2021-805 (in Russian)
9. Mel'nikova E.S., Rymar O.D., Ivanova A.A., Mustafina S.V., Shapkina M.Yu., Martin B. Association of polymorphisms of genes *TCF7L2*, *FABP2*, *KCNQ1*, *ADIPOQ* with the prognosis of the development of type 2 diabetes mellitus. *Terapevticheskiy arkhiv.* 2020; 92(10): 40–7. https://doi.org/10.26442/00403660.2020.10.000393 (in Russian)
10. Nazarova E.L., Dem'yanova V.T., Shardakov V.I., Zotina E.N., Dokshina I.A. Associations of polymorphism in several innate immunity genes with the risk of the development of chronic lymphoproliferative diseases. *Gematologiya i transfuziologiya.* 2016; 61(4): 183–9. https://doi.org/10.18821/0234-5730/2016-61-4-183-189 (in Russian)
11. Epifantseva N.V., Vitkovskiy Yu.A., Emel'yanova A.N. Polymorphism of pro-inflammatory cytokine genes in acute intestinal infections. *Infektsiya i immunitet.* 2021; 11(3): 565–9. https://doi.org/10.15789/2220-7619-POP-1268
12. Mironov K.O., Dunaeva E.A., Dribnokhodova O.P., Shipulin G.A. Using genetic analysis system based on pyrosequencing method. *Spravochnik zaveduyushchego KDL.* 2016; (5): 33–42. (in Russian)
13. Akimkin V.G., Semenenko T.A. Epidemiological and immunological efficacy of health workers vaccination against hepatitis B. *Epidemiologiya i vaktsinoprofilaktika.* 2017; 16(4): 52–7. https://doi.org/10.31631/2073-3046-2017-16-4-52-57 (in Russian)
14. Semenenko T.A. Immune response after vaccination against hepatitis B in patients with immunodeficiency. *Epidemiologiya i vaktsinoprofilaktika.* 2011; (1): 51–8. (in Russian)
15. Joshi S.S., Davis R.P., Ma M.M., Tam E., Cooper C.L., Ramji A., et al. Reduced immune responses to hepatitis B primary vaccination in obese individuals with nonalcoholic fatty liver disease. *NPJ Vaccines.* 2021; 6(1): 9. https://doi.org/10.1038/s41541-020-00266-4
16. Liu F., Guo Z., Dong C. Influences of obesity on the immunogenicity of hepatitis B vaccine. *Hum. Vaccin. Immunother.* 2017; 13(5): 1014–7. https://doi.org/10.1080/21645515.2016.1274475
17. Yoda T., Katsuyama H. Analysis of antibody-negative medical students after hepatitis B vaccination in Japan. *Hum. Vaccin. Immunother.* 2021; 17(3): 852–6. https://doi.org/10.1080/21645515.2020.1788309.
18. Li Z.K., Nie J.J., Li J., Zhuang H. The effect of HLA on immunological response to hepatitis B vaccine in healthy people: A meta-analysis. *Vaccine*. 2013; 31(40): 4355–61. https://doi.org/10.1016/j.vaccine.2013.06.108
19. Pan L., Zhang L., Zhang W., Wu X., Li Y., Yan B., et al. A genome-wide association study identifies polymorphisms in the HLA-DR region associated with non-response to hepatitis B vaccination in Chinese Han populations. *Hum. Mol. Genet.* 2014; 23(8): 2210–9. https://doi.org/10.1093/hmg/ddt586
20. De Silvestri A., Pasi A., Martinetti M., Belloni C., Tinelli C., Rondini G., et al. Family study of non-responsiveness to hepatitis B vaccine confirms the importance of HLA class III C4A locus. *Genes Immun.* 2001; 2(7): 367–72. https://doi.org/10.1038/sj.gene.6363792
21. Davila S., Froeling F.E., Tan A., Bonnard C., Boland G.J., Snippe H., et al. New genetic associations detected in a host response study to hepatitis B vaccine. *Genes Immun.* 2010; 11(3): 232–8. https://doi.org/10.1038/gene.2010.1
22. Pan L.P., Zhang W., Zhang L., Wu X.P., Zhu X.L., Yan B.Y., et al. CD3Z Genetic polymorphism in immune response to hepatitis B vaccination in two independent Chinese populations. *PLoS One.* 2012; 7(4): e35303. https://doi.org/10.1371/journal.pone.0035303

23. Roh E.Y., Song E.Y., Yoon J.H., Oh S., Chang J.Y., Park H., et al. Effects of interleukin-4 and interleukin-12b gene polymorphisms on hepatitis B virus vaccination. *Ann. Hepatol.* 2017; 16(1): 63–70. https://doi.org/10.5604/16652681.1226816
24. Salmaninejad A, Bedoni N, Ravesh Z, Quinodoz M., Shoeibi N., Mojarrad M., et al. Whole exome sequencing and homozygosity mapping reveals genetic defects in consanguineous Iranian families with inherited retinal dystrophies. *Sci. Rep.* 2020; 10(1): 19413. https://doi.org/10.1038/s41598-020-75841-9
25. Souzeau E., Thompson J.A., McLaren T.L., De Roach J.N., Barnett C.P., Lamey T.M., et al. Maternal uniparental isodisomy of chromosome 6 unmasks a novel variant in *TULP1* in a patient with early onset retinal dystrophy. *Mol. Vis.* 2018; 24: 478–84.
26. den Hollander A.I., Lopez I., Yzer S., Zonneveld M.N., Janssen I.M., Strom T.M., et al. Identification of novel mutations in patients with Leber congenital amaurosis and juvenile RP by genome-wide homozygosity mapping with SNP microarrays. *Invest. Ophthalmol. Vis. Sci.* 2007; 48(12): 5690–8. https://doi.org/10.1167/iovs.07-0610
27. Earp M., Winham S.J., Larson N., Permuth J.B., Sicotte H., Chien J., et al. A targeted genetic association study of epithelial ovarian cancer susceptibility. *Oncotarget*. 2016; 7(7): 7381–9. https://doi.org/10.18632/oncotarget.7121
28. Patin E., Kutalik Z., Guergnon J., Bibert S., Nalpas B., Jouanguy E., et al. Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection. *Gastroenterology*. 2012; 143(5): 1244–52.e12. https://doi.org/10.1053/j.gastro.2012.07.097
29. Rüeger S., Bochud P.Y., Dufour J.F., Müllhaupt B., Semela D., Heim M.H., et al. Impact of common risk factors of fibrosis progression in chronic hepatitis C. *Gut.* 2015; 64(10): 1605–15. https://doi.org/10.1136/gutjnl-2014-306997
30. Jiménez-Sousa M.Á., Gómez-Moreno A.Z., Pineda-Tenor D., Brochado-Kith O., Sánchez-Ruano J.J., Artaza-Varasa T., et al. The myeloid-epithelial-reproductive tyrosine kinase (*MERTK*) *rs4374383* polymorphism predicts progression of liver fibrosis in hepatitis C virus-infected patients: a longitudinal study. *J. Clin. Med.* 2018; 7(12): 473. https://doi.org/10.3390/jcm7120473
31. Petta S., Valenti L., Marra F., Grimaudo S., Tripodo C., Bugianesi E., et al. MERTK rs4374383 polymorphism affects the severity of fibrosis in non-alcoholic fatty liver disease. *J. Hepatol.* 2016; 64(3): 682–90. https://doi.org/10.1016/j.jhep.2015.10.016
32. Reiner A.P., Wurfel M.M., Lange L.A., Carlson C.S., Nord A.S., Carty C.L., et al. Polymorphisms of the IL1-receptor antagonist gene (*IL1RN*) are associated with multiple markers of systemic inflammation. *Arterioscler. Thromb. Vasc. Biol.* 2008; 28(7): 1407–12. https://doi.org/10.1161/ATVBAHA.108.167437

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