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The Role of Cytokine Genes Polymorphism in the Development of Chronic Viral Hepatitis

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When HCV and HBV infections interact with the immune system, both adaptive humoral reactions with the formation of specific antibodies and the production of cytokines are activated. In this case, the leading factor in the development of chronic viral hepatitis HBV, HCV is insufficient production of cytokines and / or a decrease in the sensitivity of viruses and body cells to them, which is possibly due to the influence of allelic variants of cytokine gene polymorphism [5,7].

In the developing focus of the inflammatory response in viral hepatitis, macrophages and T-lymphocytes mainly accumulate, which synthesize many proinflammatory cytokines, such as IL-1, IL-6, IFN-γ, TNF-α and others [1]. Various xenobiotics cause additional activation of the hepatic tissue, which, in turn, can lead to the launch of the entire cascade of the inflammatory response. This is accompanied by an imbalance of pro- and anti-inflammatory cytokines and impaired cell-cell interactions and expression of cytokine genes on immune cells.

Each cytokine gene and its receptor has up to 20 allelic variants, which differ mainly in their influence on the final level of cytokine production. Various combinations of allelic variants of cytokine genes can form both their balanced production, characteristic of two main groups of regulatory lymphocytes - Th1 and Th2, and unbalanced [3]. In this case, an individual ensemble of allelic variants of cytokine genes can partially determine the nature of the inflammatory process, its course and outcomes [4, 6].

In this regard, the identification of "candidate genes" of chronic viral hepatitis HBV, HCV, mixed infections HBV + HCV, HBV + HDV and occult hepatitis with an outcome in LC, especially in accordance with population differences, can become the basis for predictive molecular prediction of individual predisposition and response to antiviral therapy.

Material and research methods.

To identify possible associations between allelic variants of genes -511C / T of the IL-1B gene, -174 G / C of the IL-6 gene, -238 G / A and -308 G / A of the TNF-A gene with the development of liver cirrhosis against the background of chronic HBV , HCV, HDV infection, the analysis of the distribution of alleles and genotypes was carried out in 67 patients with this form of pathology.

The selection of patients was carried out on the basis of the diagnosis made in the clinic and the written consent of the proband. The distribution of LC patients was carried out according to the Childe-Pugh prognostic system modified by A.I. Khazanova and N.N. Nekrasova on the basis of bilirubinemia, albuminemia, prothrombin index, encephalopathy, ascites and esophageal varices. Comprehensive examination of patients with LC included generally accepted laboratory and instrumental diagnostic methods: clinical examination of the patient by organs and systems, general clinical blood and urine tests, biochemical blood tests, blood tests for specific markers of viral hepatitis in ELISA, blood tests using PCR to assess the qualitative and quantitative the content of the genetic material of HBV viruses, in-depth molecular genetic study of CP patients by single-nucleotide polymorphisms of genes encoding IL1β, IL6 and TNFα, ultrasound of the abdominal organs with Doppler ultrasonography of the portal system vessels, esophagofibrogastroduodenoscopy, puncture liver biopsy followed by hepatological

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morphological examination of the liver, elastometry elastometry. The data obtained were processed statistically on a Pentium-IV personal computer using the Microsoft Office Excel-2010 software package, including the use of built-in statistical processing functions. Methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (□), standard error of the mean (m), relative values (frequency,%), the statistical significance of the obtained measurements when comparing the mean values was determined by the criterion Student's t (t) with the calculation of the error probability (P) when checking the normal distribution (by the kurtosis criterion) and the equality of the general variances (F is the Fisher test). The level of reliability P <0.05 was taken as statistically significant changes.

Research results.

When studying the distribution of alleles and genotypes -511C / T of the IL-1B gene, a high level of reliability was noted for the CC genotype (OR = 0.208; $\chi 2 = 6.176$) with the lowest relative risk, which was also noted for the allelic variant C of this gene, which is undoubtedly , gives us the opportunity to suggest its protective contribution in this group of patients. At the same time, the T allele, with an extremely high level of relative risk and a high level of reliability (OR = 4.639; $\chi 2 = 8.217$), indicates a clear predisposing contribution of this marker to the development of the studied pathology, but despite such a high reliability in the allelic distribution, with Considering the genotypes for the ST genotype, only a tendency towards reliability was noted (OR = 4.286; $\chi 2 = 3.592$), while the indicators of the TT genotype were not significant in this sample (OR = 4.629; $\chi 2 = 2.217$).

Table 1

Frequency of occurrence of allelic variations -511C / T of the IL-1B gene in patients with HBV-induced liver cirrhosis

IL1b – 511C/T	Patients, n = 56	The patients,%	Healthy faces, n = 62	Healthy faces,%	OR	χ^2	95% CI
C	97	86,61	120	96,77	0,216		0.069 >0.216> 0.671
T	15	13,39	4	3,23	4,639	**8.217**	1.491 >4.639> 14.432
CC	45	80,36	59	95,16	0,208	**6.167**	0.055 >0.208> 0.79
CT	7	12,50	2	3,23	4,286	*3.592*	0.851 >4.286> 21.573
TT	4	7,14	1	1,61	4,692	2.217	0.508 >4.692> 43.304

Studies to determine the relationship between SNP -174 G / C of the IL-6 gene with HBV-induced liver cirrhosis in this sample showed (table 2), a high level of reliability was noted for the G allele (OR = 0.305; $\chi 2 = 6.213$) with the lowest relative risk , the trend was also noted for the GG genotype with relative risk indicators of 0.290 and with a high level of significance ($\chi 2 = 5.224$), which indicates its protective contribution in this sample.

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Table 2

Frequency of occurrence of allelic variations -174 G / C of the IL-6 gene in patients with HBV-induced cirrhosis

IL6 – 174G/C	Patients, n = 56	The patients,%	Healthy faces, n = 62	Healthy faces,%	OR	χ^2	95% CI
G	96	85,71	118	95,16	0,305		0.115 >0.305> 0.81
C	16	14,29	6	4,84	3,278	**6.213**	1.235 >3.278> 8.7
GG	43	76,79	57	91,94	0,290	**5.224**	0.096 >0.29> 0.876
GC	10	17,86	4	6,45	3,152	*3,66*	0.928 >3.152> 10.703
CC	3	5,36	1	1,61	3,453	1,26	0.349 >3.453> 34.196

At the same time, the C allele, with an extremely high level of relative risk and a high level of reliability (OR = 3.278; $\chi2$ = 6.213), speaks of a clear predisposing value of this marker, while in the analysis of genotypes with the participation of marker C allele, as in the heterozygous state GC, and in the homozygous state of SS, only a tendency towards reliability was observed, despite the high rates of relative risk.

As can be seen from Table 3, the study of the relationship between SNP -238 G / A of the TNF-A gene in patients with HBV-induced liver cirrhosis in this sample showed a high level of reliability for the G allele (OR = 0.385; $\chi2$ = 4.732) with the lowest relative risk , the same tendency was observed for the GG genotype with the relative risk indices of 0.354 and with a high level of reliability according to Pearson ($\chi2$ = 3.991), which indicates its protective contribution in this sample. At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 2.592; $\chi2$ = 4.732), speaks of a clear predisposing value of this marker, whereas in the analysis of genotypes with the participation of marker allele G, as in the heterozygous state GA, and in the homozygous AA state, the indicators were not reliable, despite the high relative risk indicators.

Table 3

Frequency of Allelic Variations -238 G / A of TNF-A Gene in Patients with HBV-Induced Liver Cirrhosis

TNF-A – 238G/A	Patients, n = 56	The patients,%	Healthy faces, n = 62	Healthy faces,%	OR	χ^2	95% CI
G	95	84,82	116	93,55	0,385396		0.159 >0.385> 0.932
A	17	15,18	8	6,45	2,595	**4.732**	1.073 >2.595> 6.275
GG	43	76,79	56	90,32	0,354396	**3.991**	0.125 >0.354>

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							1.008
GA	9	16,07	4	6,45	2,776596	2.778	0.804 >2.777> 9.585
AA	4	7,14	2	3,23	2,307692	0.935	0.406 >2.308> 13.115

As shown in Table 4, when studying the relationship between SNP -308 G / A of the TNF-A gene with the development of HBV-induced cirrhosis of the liver, a high level of reliability was noted for the GG genotype (OR = 0.431; $\chi 2 = 4.605$) with the lowest relative risk, which it was also noted for the allelic variant G of this gene (OR = 0.423; $\chi 2 = 7.528$), which undoubtedly gives us the opportunity to assume its protective contribution in this group of patients. At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 2.364; $\chi 2 = 7.528$), indicates a clear predisposing contribution of this marker to the development of the studied pathology. Despite the high reliability in the allelic distribution, when considering the heterozygous GA genotype, a relative risk indicator of 1.524 was noted, which indicates its predisposing contribution to the development of this disease, but it is not reliable in the studied sample. Whereas the homozygous AA genotype with the highest relative risk indicator tended to be significant, and it can be assumed that with an increase in the number of examined individuals, this genotype would have significant indicators (OR = 3.152; $\chi 2 = 3.66$).

Table 4

Частота встречаемости аллельных вариаций -308 G/A гена *TNF-A* у пациентов с HBV индуцированным циррозом печени

TNF-A – 308G/A	Patients, n = 56	The patients,%	Healthy faces, n = 62	Healthy faces,%	OR	χ^2	95% CI
G	77	68,75	104	83,87	0,423 077		0.227 >0.423> 0.789
A	35	31,25	20	16,13	2.364	**7.528**	1.267 >2.364> 4.409
GG	31	55,36	46	74,19	0,431 304	**4.605**	0.199 >0.431> 0.937
GA	15	26,79	12	19,35	1,524 39	0.747	0.616 >1.463>3.479
AA	10	17,86	4	6,45	3,152 174	*3,66*	0.928 >3.152> 10.703

Studies of possible associations between allelic variants of the -511C / T genes of the IL-1B gene with the development of liver cirrhosis against the background of chronic HCV infection showed that no significant values were found for any of the genotypes and allelic variants.

Further, the relationship of SNP -308 G / A of the TNF-A gene with the development of HCV-induced

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cirrhosis was investigated. When studying the relationship between SNP -308 G / A of the TNF-A gene with the development of HBV-induced liver cirrhosis, a high level of reliability was found for the G allele (OR = 0.423; $\chi 2$ = 7.045) with the lowest relative risk. A similar trend was observed for the GGdata genotype, but these values did not reach significance (OR = 0.531; $\chi 2$ = 2.367). At the same time, allele A, with a high level of relative risk (OR = 2.364; $\chi 2$ = 7.045), indicates a clear predisposing contribution of this marker to the development of the studied pathology. When considering the heterozygous GA genotype, a relative risk indicator of 0.833 was noted, the reliability indicator did not reach the required significance in the studied sample. Whereas the homozygous AA genotype with the highest relative risk score OR = 4.311 had a very high Pearson significance score, $\chi 2$ = 6.228.

Of particular interest is the study of the relationship between the studied SNPs -511C / T of the IL-1B gene, -174 G / C of the IL-6 gene, -238 G / A and -308 G / A of the TNF-A gene and liver cirrhosis against the background of mixed HBV / HCV infections. The data obtained when studying the distribution of alleles and genotypes -511C / T of the IL-1B gene showed a high level of reliability for the CC genotype (OR = 0.198; $\chi 2$ = 6.251) with the lowest relative risk. Similar values were noted for the C allelic variant of this gene (OR = 0.121; $\chi 2$ = 17.949), which indicates a probable protective effect in this group of patients. At the same time, the T allele, with an extremely high level of relative risk and a high level of reliability (OR = 8.261; $\chi 2$ = 17.949), a high indicator of relative risk indicates a predisposing contribution of this marker to the development of the studied pathology, but despite this, when considering For genotypic features, the homozygous variant of this risk marker of TT did not have significant differences compared to the control group (OR = 4.763; $\chi 2$ = 1.92). When considering the ST genotype, significant changes were noted in the frequency of occurrence of this genotype in comparison with the control group (OR = 4.737; $\chi 2$ = 3.997).

Studies to determine the relationship between SNP -174 G / C of the IL-6 gene in this sample showed a high level of reliability for the G allele (OR = 0.356; $\chi 2$ = 4.096) with the lowest relative risk, the same trend was noted for the GG genotype with relative risk 0.341 but the indicators did not reach significant values according to Pearson's test ($\chi 2$ = 3.447), in this sample. At the same time, the C allele, with an extremely high level of relative risk and a high level of reliability (OR = 2.810; $\chi 2$ = 4.096), speaks of a clear predisposing value of this marker. When analyzing the genotypes for any of the combinations, there were no significant differences between the group of patients and the group of the control group of healthy people.

The study of the relationship between SNP-238 G / A of the TNF-A gene in patients with HBV / HCV-induced liver cirrhosis in this sample showed a high level of reliability for the G allele (OR = 0.250; $\chi 2$ = 10.615) with the lowest relative risk, the same trend was observed and for the GG genotype with relative risk indices of 0.238 and with a high level of Pearson confidence ($\chi 2$ = 8.242), which indicates its protective contribution in this sample. At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 3.993; $\chi 2$ = 10.615) indicates a clear predisposing value of this marker, the heterozygous GA genotype had a high relative risk (OR = 3.728; $\chi 2$ = 4 , 69), but the AA genotype, despite the fact that it carries two significant A alleles, has a high relative risk index (OR = 3.846), but nevertheless had only a tendency towards reliability ($\chi 2$ = 2.773). The study of statistical indicators, the relationship between SNP -308 G / A of the TNF-A gene with the development of HBV / HCV-induced liver cirrhosis, show a high level of reliability for the G allele with indicators (OR = 0.366; $\chi 2$ = 9.637) and GG genotype (OR = 0.364 ; $\chi 2$ = 6.066). At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 2.732; $\chi 2$ = 9.637) proves a clear predisposing contribution of this

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Received 15 December 2020; Accepted 05 January 2021.

marker to the development of the studied pathology. Likewise, the AA genotype in the studied cohort of patients was found 2.25 times more often than in the control group, with a relative risk indicator of 3.625 and a reliability indicator according to Pearson's criterion of 4.484. When considering the heterozygous GA genotype, a relative risk indicator of 1.693 was noted, which indicates its predisposing contribution to the development of this disease, but it is not reliable in the studied sample.

Study of the distribution of alleles and genotypes -511C / T of the IL-1B gene a high level of reliability was noted for the C allele, which was 1.35 times more common in the healthy control group, compared with the control group with a relative risk score of 0.156 and a Pearson confidence criterion of 13.341 ... Both the single C allele and the CC genotype (OR = 0.199; $\chi 2$ = 6.561) with the lowest relative risk were much less common in the group of patients compared with the control group, which suggests its protective contribution in this group of patients. At the same time, the T allele, with an extremely high level of relative risk and a high level of reliability (OR = 6404; $\chi 2$ = 13.341), indicates a clear predisposing contribution of this marker to the development of the studied pathology, but despite such a high reliability in the allelic distribution, with Consideration of genotypes for the ST genotype was not significant (OR = 1.765; $\chi 2$ = 0.38). In turn, when analyzing the TT genotype, the highest relative risk indicators in this sample were noted (OR = 10.609; $\chi 2$ = 7.029).

Studies aimed at studying the possible relationship between SNP -174 G / C of the IL-6 gene with HCV-induced liver cirrhosis in this cohort revealed some correlations. The G parallel and the GG genotype in this sample have a pronounced protective effect with relative risk indices of 0.238 and 0.307 respectively. Whereas the C allele (OR = 4.199; $\chi 2$ = 9.766) and the CC genotype (OR = 9.085; $\chi 2$ = 5.791), on the contrary, made a clear predisposing contribution. The GC genotype had a relative risk index of 1.48, which indicates its predisposing contribution in this pathology, but according to the Pearson significance criterion it was not significant enough.

Determination of the relationship between SNP -238 G / A of the TNF-A gene in patients with HCV-induced liver cirrhosis in this sample showed a high level of significance for the G allele (OR = 0.286; $\chi 2$ = 8.909) with the lowest relative risk and for the GG genotype (OR = 0.279; $\chi 2$ = 6.378). At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 3.5; $\chi 2$ = 8.909) indicates the presence of a clear predisposing value of this marker. When analyzing genotypes with the participation of the marker allele G, both in the heterozygous state of GA and in the homozygous state of AA, the indices were not reliable, despite the high relative risk scores OR = 2.9 and OR = 3.75, respectively.

Statistical indicators obtained when studying the relationship between SNP -308 G / A of the TNF-A gene with the development of HBV / HDV-induced cirrhosis of the liver, indicate a high level of significance noted for the protective allele G with indicators (OR = 0.34; $\chi 2$ = 12.154) and genotype GG (OR = 0.322; $\chi 2$ = 8.316). At the same time, allele A, with a high level of relative risk and a high level of reliability (OR = 2.939; $\chi 2$ = 12.154), speaks of a clear predisposing contribution of this marker to the development of the studied pathology. Likewise, the AA genotype in the studied group of patients was 2.75 times more frequent than in the control group, with a relative risk index of 3.709 and a reliability index according to Pearson's criterion of 4.966. Whereas the heterozygous GA genotype, although it had a relative risk index of 1.914, did not reach its significance in the studied sample.

Thus, we can draw a conclusion about the undoubted contribution of the studied polymorphisms in the development of the studied pathologies. Table 5 presents the summarized data on the results obtained..

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Received 15 December 2020; Accepted 05 January 2021.

Table 5

Summarized data of the obtained results of gene polymorphism IL-1β (–511 C/T), IL-6 (–174 G/C), TNF-A (–238 G/A)

PREPOSITION MARKERS				
	-511C/T *IL-1B*	-174 G/C *IL-6*	-238 G/A *TNF-A*	-308 G/A *TNF-A*
ЦП+HBV	T	C	A	A
ЦП+HCV	-	-	-	A; AA
ЦП+HBV/HCV	T;CT	C	A;GA	A; AA
ЦП+HBV/HDV	T; TT	C; CC	A	A; AA
MARKERS OF RESISTANCE				
	-511C/T *IL-1B*	-174 G/C *IL-6*	-238 G/A *TNF-A*	-308 G/A *TNF-A*
ЦП+HBV	C; CC	G; GG	G; GG	G; GG
ЦП+HCV	-	-	GG	G
ЦП+HBV/HCV	C; CC	G	G; GG	G; GG
ЦП+HBV/HDV	C; CC	G; GG	G; GG	G; GG

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