



## Assessment of Association Cytochrome P450 Gene Polymorphism with Pathogenesis and Course of HCV in Uzbek Population

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### Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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### ABSTRACT

**Aims:** The assessment of polymorphisms CYP2C9\*2 (430C>T; rs1799853) and CYP2E1\*1B (–C9896G, rs2070676) role of the genes of cytochrome P450 in pathogenesis of the chronic viral hepatitis C (HCV) in Uzbek population became the main aim.

**Place and Duration of Study:** The molecular and genetic study of biomaterial was accomplished under Department of Molecular Medicine and Cellular Technologies of SRIH&BT (Scientific Research Institute of Hematology and Blood Transfusion), MoH RUz in the period of 2013-2016.

**Methodology and Study Design:** Genotyping assay of polymorphism of the genes under study was accomplished by the standard polymerase chain reaction (PCR). Peripheral blood of 107 patients with diagnosis chronic viral hepatitis C included in the main group and 81 relatively healthy donors (test group) was used for the molecular and genetic study of CYP2E1\*1B and CYP2C9\*2 polymorphisms.

**Results:** Comparative analysis revealed differences in the distribution of allele frequencies of polymorphisms 430C > T CYP2C9 gene and gene C9896G CYP2E1 \* 1B in groups of patients with

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chronic HCV group and population control. In the main group of patients with chronic HCV mutant allele "T" » CYP2C9 gene met significantly more frequently in comparison with the control group population. Thus, the highest frequency of the mutant allele of the "T", as compared with the control group was observed in patients with moderate HCV activity. This is the lowest frequency of this genotype was observed in the subgroup of patients with liver cirrhosis. Our studies have shown that the accumulation of the mutant allele «G» CYP2E1 \* 1B gene was also the case in almost all subgroups of patients with chronic HCV. The frequency of heterozygous genotype CYP2E1\*1B polymorphism in the population control group was 13.6%. It should be noted that the highest frequency component of genotype C/G was detected in the group of patients with chronic HCV with high activity. The data obtained indicate an association genotype C/G with the activation process of inflammation and fibrotic changes.

**Conclusion:** The results showed a high frequency of mutant allele "T" polymorphism 430C > T CYP2C9 with HCV, which allows us to consider the CYP2C9 gene as a factor of a favorable outcome of chronic hepatitis C. The association between the expression of CYP2E1 \* 1B and progression of the disease with activation fibrosis-formation in individuals of Uzbek population is an important factor in the development of personalized therapy.

*Keywords: Chronic viral hepatitis C; polymorphism; gene CYP2E1; gene CYP2C9; cytochrome P450.*

## 1. INTRODUCTION

Chronic viral hepatitis is one of the causes of liver cirrhosis. However, not all cases of HCV infection are associated with the development of fibrosis or cirrhosis. Despite considerable progress in the study of chronic hepatitis C development mechanisms, its clinical form and outcome, the question of the molecular and genetic aspects of the pathogenesis of this disease remains poorly known. At the same time identifying linkages gene polymorphism with the risk of development and course of the disease is still relevant for each population group, in view of the variability of allele frequencies in different populations.

It is assumed that during chronic HCV may be due to genes polymorphism of cytochrome P450. Cytochrome P450 (CYP) is a group of enzymes performing not only the metabolism of drugs and other xenobiotics, but also participate in the synthesis glucocorticosteroid hormones, cholesterol, bile acids, prostanoids (thromboxane A2 and prostacyclin) [1,2]. The greatest number of cytochrome P450 found in liver [3-6]. The relative number of individual isoenzymes of cytochrome P-450 in the human body is different. Thus, CYP3A4 content is 28%, CYP2C9 - 18%, CYP1A2 - 13%, CYP2E1 - 7%, CYP2A6 - 4%, which is of great clinical value, since it can affect the development of liver diseases [7]. However, the possible role of individual cytochromes P450 in the pathogenesis of chronic liver disease is determined not only by their content in this organ, but also the functional activity.

In recent years, in addition to the generally accepted theory in the development of autoimmune chronic liver diseases, it attaches great importance to violations of the balance between the synthesis of free radicals and antioxidant defense capacity. Free radical oxidation is an essential element of the inflammatory process. The reason for increasing the concentration of reactive oxygen species (ROS) can be enhanced synthesis of active compounds, or change in the activity of enzymes responsible for their biotransformation. In reactions with participation of one of the cytochrome P450 isoenzymes - CYP2E1 always formed ROS such as superoxide and hydrogen peroxide, which can cause lipid peroxidation [8,9]. Due to the excessive accumulation of lipid peroxidation products (LPO) is activated stellate cells with increased collagen they produce. The literature describes the relationship between the level of expression of CYP2E1 isoform of cytochrome P450 and the rate of progression of liver fibrosis. Numerous studies point to the damaging effect of liver oxidative stress-induced overexpression CYP2E1 [1,8-11]. One of the polymorphisms of CYP2E1 gene - version of CYP2E1 \* 1B (polymorphism -C9896G, rs2070676 (TaqI)), leads to an increased level of production of the enzyme CYP2E1, high rate of metabolism of xenobiotics and increased formation of lipid peroxidation products [12]. However, information on the role of polymorphism of CYP2E1 -C9896G in the pathogenesis of chronic HCV is fragmented and ambiguous.

Isoenzymes cytochrome P450 2C9 (CYP2C9), which is the main enzyme metabolism of many drugs is associated with the development of disorders in the liver induced by pharmacological agents (Drug-induced liver injury, DILI). One of the basic mechanisms of DILI is based on the hypothesis that changes in the production of reactive metabolites associated with genetic variability [13-15]. It is found that allelic variant CYP2C9 \* 2 (430C>T, rs1799853) are characterized by a significant decrease CYP2C9 enzyme activity [16].

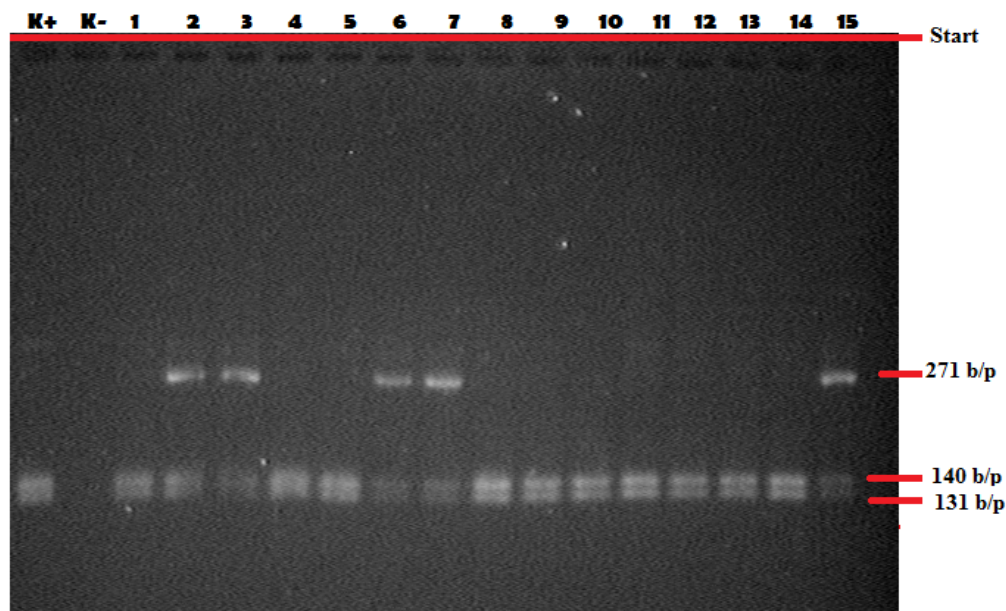
In this way, the aim of our study was to assess the role of polymorphisms of CYP2C9 \* 2 (430C>T; rs1799853) and CYP2E1 \* 1B (-C9896G, rs2070676) genes cytochrome P450 in the pathogenesis of chronic HCV in the Uzbek population, as well as its relationship with the severity of the pathological process and the development of liver cirrhosis.

## 2. MATERIALS AND METHODS

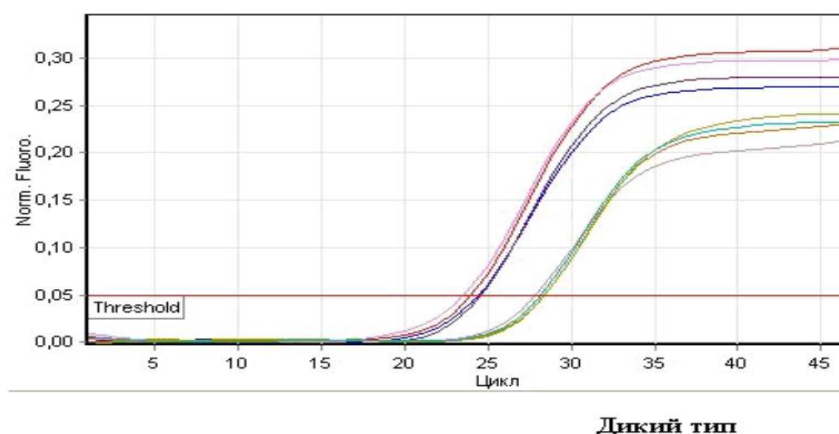
As the peripheral blood of 107 patients with a diagnosis of the chronic viral hepatitis C (the HCV), which were included in the main group, and peripheral blood of 81 healthy donors of probation (control group) material for molecular genetic studies CYP2E1\*1B and CYP2C9\*2

polymorphism is used. The main group of HCV patients was divided into three subgroups, which included patients with moderately active chronic HCV (33), a highly chronic HCV (37) and liver cirrhosis (37). When selecting individuals take into account their national identity. Patients in both groups were persons of Uzbek nationality the total floor at the age of 20 to 60 years.

Venous blood sampling was conducted in an amount of 3.5 ml EDTA. Isolation of DNA was carried out according to standard procedures, identification of polymorphism alleles was performed using polymerase chain reaction on a programmable thermal cycler («Applied Biosystems», USA) followed by digestion with restriction enzyme fragments of DNA according to the recommendations of the manufacturer (Pictures 1 and 2). Products of amplification of DNA fragments were separated on 2.3% agarose gels and, after staining with ethidium bromide was detected in the transmitted UV light. Genomic DNA was amplified using specific primers. Polymorphism CYP2E1 (9896S>G) (10q24.3) unused primer structure: (F) 5' <ATGSSAGGAASAAASTATSA> 3'; (R) 5' <5'SAGAGTTGGCASTACGACTG> 3'. For CYP2C9\*2 (10q23.33) (430C>T) - 5'-GGGGAAGAGGAGCATTGAGGCC-3'; 5'-CAGTAGAGAAGATAGTAGTCCAG-3'.



**Picture 1. Electrophoregram detecting gene polymorphism CYP2E1 after enzymatic restriction**  
 Note: K+ - positive control K - negative control, 1,4,5,8,9,10,11,12,13,14 - wild genotype (genotype C / C);  
 2,3,6,7 - heterozygous genotype (genotype C / T)



**Picture 2. The result of PCR in real time for CYP2C9 gene (wild type gene identification - the norm)**

The frequency of allele and genotype variants (f) is calculated as follows:  $f = n / 2N$  and  $f = n / N$ , respectively, where n - the occurrence of variant (allele or genotype), N - sample size. The significance of the differences in the two groups were calculated using the odds ratio (OR) of the event, which was calculated using the standard formula:  $OR = a / b \times d / c$ , where a and b - the number of patients who have the mutant allele was detected or absent, respectively, c and d - number of persons in the control group, in which the mutant allele was identified or absent, respectively. In order to describe the relation of allele and genotype frequencies of genes using the Hardy-Weinberg equilibrium. The relative deviation of the observed expected heterozygous (factor D) was calculated according to the formula:  $D = (hobs-hexp) / hexp$ , where hobs and hexp - the expected and observed heterozygous, respectively. To calculate the ratio OR with 95% confidence intervals (CI),  $\chi^2$  and p values used package «OpenEpi 2009, Version 2.3» statistical programs.

### 3. RESULTS AND DISCUSSION

Our study showed that the purity of the gametes of "wild" type of polymorphism CYP2C9\*2 in a group of healthy donors at 7.1 times the frequency of the mutant gametes (87.6% vs. 12.3%). Accordingly, the frequency of a genotype "wild" type polymorphism CYP2C9\*2 (C/C) was 75.3% in the studied population and the heterozygous genotype C/T - 24.7%. Homozygous genotype of the mutant allele in a group of healthy donors has not been found by us that may be indicative of its low population incidence.

Comparative analysis revealed differences in the distribution of frequencies of alleles polymorphism 430C>T CYP2C9 gene in a group of patients with chronic HCV and population control group (Table 1). It has been shown that in patients with chronic HCV has been an accumulation of the mutant allele. In the total group of patients with chronic HCV (core group) mutant allele "T" met more frequently in comparison with the control group of the population (13,1%;  $\chi^2 = 4.2$ ;  $P = 0.04$ ;  $OR = 2.1$ ; 95%CI 1.024, 4.288 ), but the difference was unreliable. Reliably high frequency of mutant allele "T", as compared with the control group (19,7%) was observed in patients with moderately active chronic HCV. In patients with chronic HCV high activity was observed decrease in the frequency of the mutant allele, although in this case, as in the case of liver cirrhosis, the difference with the control was unreliable. Thus, traced a clear connection between the high frequency of the mutant allele "T" with a more favorable course of chronic HCV.

The study showed that in the distribution of genotype frequencies of the polymorphism 430C>T gene CYP2C9 noted the predominance of homozygous for the "wild" allele genotype C/C in both groups (control and main), and in all three subgroups. The lowest frequency of occurrence in the studied groups of patients and control - taking into account the absence of the studied samples homozygous for the mutant allele genotype - characterized by a heterozygous genotype C/T. This is the lowest frequency of this genotype was observed in the subgroup of patients with liver cirrhosis. Comparative analysis of the frequency of heterozygous genotype C/T

**Table 1. The frequency of allele and genotype distribution of polymorphism CYP2C9\*2 and CYP2E1\*1B gene cytochrome P450 in patients with chronic HCV, liver cirrhosis and healthy donors**

Gene/ polymorphism	Group	n	The frequency of alleles				The frequency of genotypes					
			C		T		C/C		C/T		T/T	
			N	%	n	%	N	%	N	%	N	%
<b>CYP2C9*2</b>	The main group	107	186	86,9	28	13,1	79	73,8	28	26,2	-	0
	1 subgroup: moderately active HCV	33	53	80,3	13	19,7	20	60,6	13	39,4	-	0
	2-subgroup: highly active HCV	37	68	91,9	6	8,1	31	83,8	6	16,2	-	0
	3-subgroup: liver cirrhosis	37	65	87,8	9	12,2	28	75,7	9	24,3	-	0
	Control group: healthy donors	81	142	87,6	20	12,3	61	75,3	20	24,7	-	0
<b>CYP2E1*1B</b>	The main group	107	181	84,6	33	15,4	78	72,9	25	23,4	4	3,7
	1 subgroup: moderately active HCV	33	55	83,3	11	16,7	24	72,7	7	21,2	2	6,1
	2-subgroup: highly active HCV	37	60	81,1	14	18,9	24	64,9	12	32,4	1	2,7
	3-subgroup: liver cirrhosis	37	66	89,2	8	10,8	30	81,1	6	16,2	1	2,7
	Control group: healthy donors	81	151	93,2	11	6,8	70	86,4	11	13,6	0	-

polymorphism 430C>T CYP2C9 gene among the studied subgroups revealed that the highest figure was in patients with moderately active chronic HCV (39,40%;  $\chi^2 = 1.8$ ;  $P=0.2$ ;  $OR=2.0$ ; 95%CI 0.8375, 4.693). In patients with highly active chronic HCV genotype frequency of the C/T it was 1.5 times lower than the value of this indicator in the control group (16,2%), and patients with cirrhosis frequency genotype C/T was substantially the same as the control. The received data may indicate that genotype C/T associated with the stage is moderately active chronic HCV, when the disease is more suitable for, and fibrosis-formation process is not expressed. This gives grounds to assess allele carriers of the "T" and the genotype C/T polymorphism 430C>T CYP2C9 gene as a

positive factor, associated with a lower risk of liver damage and progression of fibrosis in chronic HCV.

The purity of the gametes of "wild" type of polymorphism CYP2E1\*1B in a group of healthy donors to 13.7 times higher than the frequency of the mutant gametes (93.2% vs. 6.8%). However, in the group of patients, this ratio decreased chronic HCV, indicating that the accumulation of the mutant allele. It was shown that the accumulation of the mutant allele «G» occurred in almost all subgroups of patients with chronic HCV. Statistically significant allele frequency difference «G» with the control was detected in the total group of patients with chronic HCV (15,4%;  $\chi^2 = 6.6$ ;  $p = 0.01$ ;  $OR = 2.503$ ; 95% CI

1.22 -5.12), and in two subgroups: the first - 16.7% ( $X^2 = 5.2$ ,  $P = 0.02$ ,  $OR = 2.7$ ; 95% CI 1.126, 6.69) and in the second - 18.9% ( $X^2 = 7.9$ ,  $P = 0.005$ ;  $OR = 3.2$ ; 95% CI 1.377, 7.452). In the subgroup of patients with liver cirrhosis increased frequency of the mutant allele in comparison with the control was also the case, however, the difference was unreliable. Thus, the correlation between the high frequency of the mutant allele «G» polymorphism CYP2E1 with the activation of chronic HCV.

The frequency of genotype homozygous for the "wild" allele C/C in the group of population control was 86.4%. The study showed that the observed genotype prevalence in the distribution of genotypes CYP2E1 polymorphism frequencies C/C not only in the control group, but in the group of patients with chronic HCV. Homozygous genotype for the mutant allele G/G in a group of healthy donors has not been identified by us. However, in the total group of patients with chronic HCV genotype G/G met with a frequency of 3.7%. In the subgroup of patients with chronic HCV moderately active this figure was the highest and reached 6.1%.

The frequency of heterozygous genotype CYP2E1\*1B polymorphism in the population control group was 13.6% ( $X^2 = 2.8$ ;  $P = 0.1$ ;  $OR = 1.9$ ; 95% of 0.8916, 4.222). Comparative analysis of the frequency of the genotype C / G in the section on the group showed that the highest this figure was highly active in patients with chronic HCV (32,40%;  $X^2 = 5.7$ ;  $P = 0.02$ ;  $OR = 3.0$ ; 95% 1.197, 7.795). In patients with chronic HCV moderately active and patients with liver cirrhosis, genotype frequency of the C/T was also increased, but the difference with the control was unreliable. Estimation of total contribution genotypes carrying the mutant allele (C/G + G/G), also showed the highest value of the index for the group of patients with highly active chronic HCV (35,1%;  $X^2 = 7.3$ ;  $P = 0.01$ ;  $OR = 3.4$ ; 95% 1.364, 8.711), although a significant difference to the control was observed for patients with moderately active chronic HCV (27,3%;  $X^2 = 3.0$ ;  $P = 0.08$ ;  $OR = 2.4$ ; 95% CI 0.8819, 6.457). The received data may indicate that genotype C/G is associated with a highly active stage of chronic HCV, when activated by the processes of inflammation and fibrosis-formation and increases the risk of liver cirrhosis. This gives reason to evaluate polymorphism CYP2E1 \* 1B as the factor with the predictor value allele «G» and genotype C/G in relation to chronic HCV activation and progression of liver fibrogenesis.

Analysis of deviations, according to the Hardy-Weinberg law, expected and observed genotype frequencies of the polymorphism 430C>T CYP2C9 gene in the studied group of patients with chronic HCV showed that the expected frequency of homozygous C/C was almost equal to or close to the observed - the difference ranged from 0.7 to 6.0% (Table 2). The deviation in the frequency of homozygous T/T could not be established due to the lack of recent patients in the study sample. Difference between expected and observed frequency of heterozygotes was greater, with the maximum difference in performance was observed in the subgroup of patients with chronic moderately active the HCV, where it was 19.8%.

Assessment of the relative deviation from the expected heterozygous observed on the basis of heterozygote deficiency index (D) showed that in all observed groups D index was negative, indicating an excess of heterozygotes locus 430C>T CYP2C9 gene in the sample. In assessing the relative deviation from the expected heterozygous observed in the studied subgroups, it was shown that patients with moderately active chronic HCV, the figure was the most significant (-0.198). This fact speaks of heterozygote excess locus 430C>T CYP2C9 gene in this subgroup.

Analysis of expected and observed frequency deviation genotypes polymorphism CYP2E1\*1B shows that, according to the distribution of Hardy-Weinberg equilibrium, in subgroups of patients with chronic HCV difference of expected and observed frequency of homozygotes for the allele "wild" type (C/C) ranged from 1.4 to 4 5%, and homozygotes for the mutant allele (G/G) - from 25.0 to 55.5% (Table 2). In the control group, the deviation in the frequency of homozygous G / G could not be established because of their absence in the test sample. Difference between expected and observed frequency of heterozygotes was 5.5% (patients with highly active chronic HCV) to 23.7% (patients with moderately active chronic HCV). Assessment of the relative deviation from the expected heterozygous observed showed that in all groups (except the second sub-group) index D has a positive value, indicating that the deficit of heterozygotes locus -C9896G CYP2E1 gene in the sample. In the group of patients with moderately active chronic HCV relative deviation of the observed expected heterozygous was the most significant (0.31). Patients with highly active chronic HCV, as well as the group of healthy donors, on the contrary, an excess of

**Table 2. Analysis of deviation expected and observed genotype frequencies of polymorphisms CYP2C9\*2 and CYP2E1\*1B gene cytochrome P450 in patients with chronic HCV, liver cirrhosis and healthy donors**

Gene/ polymorphism	Group	The frequency of genotypes						D
		C/C		C/T		T/T		
		Obs	Exp	Obs	Exp	Obs	Exp	
CYP2C9*2	The main group	0,755	0,738	0,228	0,26,2	0,017	0	-0,130
	1 subgroup: moderately active HCV	0,645	0,606	0,316	0,394	0,039	0	-0,198
	2-subgroup: highly active HCV	0,844	0,838	0,149	0,162	0,006	0	-0,080
	3-subgroup: liver cirrhosis	0,771	0,757	0,214	0,243	0,015	0	-0,119
	Control group: healthy donors	0,771	0,753	0,214	0,247	0,015	0	-0,134
CYP2E1*1B	The main group	0,716	0,729	0,260	0,234	0,024	0,037	0,111
	1 subgroup: moderately active HCV	0,694	0,727	0,278	0,212	0,028	0,061	0,311
	2-subgroup: highly active HCV	0,658	0,649	0,306	0,324	0,036	0,027	-0,055
	3-subgroup: liver cirrhosis	0,796	0,811	0,193	0,162	0,012	0,027	0,191
	Control group: healthy donors	0,869	0,864	0,127	0,136	0,005	0	-0,066

*Obs – expected genotype frequencies; Exp – observed genotype frequencies*

heterozygotes identified, as evidenced by the negative index value D.

CYP2C9 gene is polymorphic. The currently known allelic variants of the CYP2C9 gene metabolize the substrates determine the speed. The polymorphic gene variant CYP2C9\*2 (430C>T) (rs1799853) is a nucleotide substitution at position 430 in the sequence of nucleotides cytosine (C) to thymine (T), in that the amino acid sequence CYP2C9 leads to replacement of arginine at position 144 to cysteine.

A comparison of the frequency of occurrence of the contact data in the study of the Uzbek population genotype polymorphisms CYP2C9\*2 (C/C - 75.3%, C/T - 24.7%, T/T - 0%) with the literature revealed some differences. Thus, the frequency of occurrence of "wild" genotype polymorphism CYP2C9 in Turkey amounted to 79.4%, and genotype CYP2C9\*2 - 10.6% [17], in China - CYP2C9\*1 - 96.3%, CYP2C9\*2 - 0, 1% [18], in Korea - CYP2C9\*1 - 93.4%, CYP2C9\*2 - 0% [19], in Egypt -CYP2C9\*1 - 82.0%,

CYP2C9\*2 - 12.0% [20] Bolivia - CYP2C9\*1 - 92.2%, CYP2C9\*2 - 4.8% [21], in Russian - CYP2C9\*1 - 82.8%, CYP2C9\*2 - 10.5% [22] Spanish - CYP2C9\*1 - 74.0%, CYP2C9\*2 - 16.0% [23], the French -CYP2C9\*1 - 77.0%, CYP2C9\*2 - 15.0% [18]. The difference between the data on the frequency of genotypes obtained by different researchers, can be explained by several factors, including population characteristics studied groups, genetic drift, natural selection, adaptation of the population to the local environmental conditions. It should be noted that the low frequency of a genotype homozygous for the mutant allele of the "T" polymorphism 430C>T CYP2C9 gene in our study may be associated with the possibility of selective data elimination genotypes.

It is known that allelic variant CYP2C9\*2 gene is characterized by a significant decrease of the enzymatic activity of P450 [16]. In the literature, there is evidence that the autoimmune hepatitis and other forms of hepatitis can alter the hepatic expression of P450 and the activity of enzymes. Violations of cytochrome P450 liver function were



observed in patients with chronic hepatitis B (HBV) [24]. Work has been carried out, showing a decrease in the activity of isoenzyme CYP2C9 in patients with chronic HCV [25]. However, the relationship CYP2C9 gene polymorphisms, particularly 430C>T, the pathogenesis and progression of HCV and cirrhosis of the liver, to date insufficiently evaluated.

Our study showed the prevalence of the contents of the "wild" allele "C" and homozygous genotype C/C polymorphism 430C>T CYP2C9 gene. The lowest incidence in the studied groups of patients and controls was observed for genotypes containing the mutant allele. This is the highest frequency of heterozygous genotype CYP2C9 polymorphism was observed in the subgroup of patients with chronic moderately active HCV. In this way we observed a clear link between the increase in the frequency of the mutant allele "T" polymorphism 430C>T CYP2C9 and more favorable course of chronic HCV. Perhaps when moderately active course of chronic HCV in patients who are carriers of these polymorphisms CYP2C9 characterized by low activity of isoenzyme, there is a reduced production of reactive metabolites that can lead to liver damage. This fact may indicate the value of the tread of the mutant allele and heterozygous genotype polymorphism 430C>T CYP2C9 gene in relation to aggravation of the disease and the occurrence of irreversible complications in chronic HCV.

Deviation analysis of expected and observed frequencies of genotypes showed that the expected frequency of homozygous C/C polymorphism 430C>T CYP2C9 gene was similar to that observed. If the expected value of a genetic marker homozygotes longer observed, one can speak of balancing selection. However, in this case, when the expected and observed frequencies are almost equal, we can talk more about selective neutrality. Nevertheless, the relative deviation of the observed expected heterozygous (D), were the most significant in patients with moderately active the HCV, indicating an excess of heterozygotes locus 430C>T CYP2C9 gene in this group and, consequently, their selective advantage. This fact, given the low degree of severity of the pathological process in the liver of patients in this subgroup, can be considered the allelic variant CYP2C9 gene in HCV as a protective associated with low risk of severe disease.

Information about the role of CYP2E1, in particular polymorphism -C9896G (rs2070676),

in the pathogenesis of chronic HCV is fragmented and ambiguous. However, most researchers suggest that induction of cytochrome P450 2E1 plays a role in the development of fibrosis and the progression of the pathological process in chronic liver disease [8-10,26,11]. The data of several authors [27,5] show that the early stages of chronic hepatitis C is associated with the induction of CYP2E1. At the same time in patients with chronic hepatitis C was found an association between CYP2E1 expression in liver disease progression. Similar results were obtained in studies of S. Sutti et al. [28,11]. They showed that in patients with HCV chronic presence of auto-antibodies against c CYP2E1 associated increase in incidence of necro-inflammation and fibrosis in the liver. In this regard, it has been suggested by researchers that CYP2E1 associated with more severe liver damage in chronic HCV.

Our study showed that the presence of variants of CYP2E1\*1B, defined allele «G» and raises the level of production of CYP2E1 enzyme, typical of the early stages of chronic HCV to a greater extent than for cirrhosis. In this case the total frequency of genotypes carrying the mutant allele «G», in patients with moderately active chronic HCV was 2 times, and in patients with highly active form of chronic HCV - 2.7 times more than in the control group. Increased expression of CYP2E1 causes high speed toxins and xenobiotic metabolism and consequently, increased formation of lipid peroxidation products, leading to oxidative stress and hepatocellular dysfunction, which is one of the factors fibrosis constituting the pathogenic basis of liver cirrhosis. Thus, our results indicate a link between the expression defined allele «G» version of CYP2E1\*1B and progression of the disease with the activation of fibrosis, education, and consistent with those of supporters of ideas about the important pathogenetic role of CYP2E1 in the development of chronic liver disease [29,27,12].

Deviation Analysis of expected and observed frequencies of genotypes of CYP2E1\*1B polymorphism showed that the most significant difference was expected and observed frequency of homozygotes for the mutant allele. D A negative value of the index in the subgroup of patients with highly active chronic HCV indicative of an excess of heterozygotes, whereas in the remaining subgroups of index D has a positive value, indicating that the deficit of heterozygotes locus -C9896G CYP2E1 gene in the sample. In the group of patients with moderately active



chronic HCV relative deviation of the observed expected heterozygous was the most significant.

#### 4. CONCLUSION

In this way we have established a connection between the high frequency of the mutant allele "T" polymorphism 430C>T CYP2C9 and more favorable course of chronic the HCV, allowing to consider this allelic options of the CYP2C9 gene as a positive factor associated with a low risk of liver damages by HCV. This fact is especially important in light of the data on the reversibility of liver fibrosis at shallow lesion body and effective antiviral therapy. Also, we have a relationship between the expression of CYP2E1\*1B and disease progression to fibrosis is the activation of education at the Uzbek population of persons, in connection with which these markers should be considered in a personalized treatment.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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