

# Genetic Investigation of Chronic Viral Hepatitis C

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## Abstract

**Aim:** The aim of the study was a comparative analysis of genotypic variants of TNF- $\alpha$  and CTLA-4 genes in patients with chronic hepatitis C and liver cirrhosis and their effect on the course of the disease. **Materials & Methods:** The material for the molecular genetic study was the peripheral blood of the examined persons. DNA isolation was carried out according to the standard procedure with some modifications and using the reagents of the "Interlab service" company (Russia). Identification of alleles of gene polymorphism was carried out using polymerase chain reaction. **Results:** The analysis of the effect of TNF- $\alpha$  gene genotypes on the course of the disease indicates an increased risk of CVHC development with both moderate and highly active course of the disease in carriers of the G/A+A/A genotype combination. **Conclusion:** The data obtained allow us to conclude that the carriage of the "G" allele and the combination of genotypes A/G+G/G of the-A49G polymorphism of the CTLA-4 gene are associated not only with a decrease in the risk of CVHC development, but also with a lower intensity of inflammation and fibro-formation in the liver and a high probability of favorable course of the disease.

**Keywords:** Hepatitis C; Gene; TNF- $\alpha$ ; Treatment; Polymorphism

## Introduction

The problem of the spread and treatment of chronic viral hepatitis C continues to be one of the significant problems of internal medicine. The urgency of the problem of hepatitis C is determined by the high epidemiological and socio-economic significance of this disease, as well as the widespread occurrence, severity of the course and the frequency of development of chronic forms. [1-4] It is HCV infection that is the main reason for the formation of the entire group of chronic liver diseases-chronic hepatitis, cirrhosis, hepato carcinoma. [5-7] At the same time, the study of this issue is not only medical, but also socio-economic in nature. It is believed that chronic hepatitis C is always potentially dangerous, but the pathogenesis of this disease is not fully understood. This will require a search for new approaches and new fundamental research. [8-10]

## Aim of the Research

The aim of the study was a comparative analysis of genotypic variants of TNF- $\alpha$  and CTLA-4 genes in patients with chronic hepatitis C and liver cirrhosis and their effect on the course of the disease.

## Materials and Methods

The main group of the study included 107 patients with Chronic Viral Hepatitis C (CVHC). To assess the association of polymorphic markers of TNF-4 and CTLA-4 genes, patients with CVHC were divided into three subgroups. The first subgroup includes patients with moderate activity, Chronic Hepatitis C (CHC) (n=33). The second subgroup consisted of patients with a high degree of CHC activity (n=37). The third subgroup included patients with liver cirrhosis (n=37). The criteria for inclusion in the study were clinical, biochemical and instrumental verification of the diagnosis with the definition and

stage and severity of the disease, as well as the detection of hepatitis C virus RNA by the Amplisens HCV-FRT test system detected by Polymerase Chain Reaction (PCR) on a RotorGene 6000 device [Table 1].

As a comparison group, a population control was used, which was represented by DNA samples (n=81) of apparently healthy donors without chronic liver infection.

The material for the molecular genetic study was the peripheral blood of the examined persons. DNA isolation was carried out according to the standard procedure with some modifications and using the reagents of the "Interlab service" company (Russia). Identification of alleles of gene polymorphism was carried out using polymerase chain reaction.

## Results and Discussion

Comparative analysis of genotypic variants of the TNF- $\alpha$  marker-G308A revealed the accumulation of A/G and A/A genotypes in the group of patients with chronic hepatitis C and recorded differences in the distribution of these genotypes

**Table 1: Comparison group, a population control.**

Control (n=81)	Main group (n=107) 24,3%		
	1 subgroup (patients with a moderate degree of CHC activity) (n=33)	2 subgroup (patients with a high degree of CHC activity) (n=37)	3 subgroup (patients with liver cirrhosis) (n=37)
9.9%	30.3%	25.3%	18.9%

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between patients and individuals of the control group. The total frequency of genotypes G/A+A/A in the study and control groups was 24.3% and 9.9%, respectively. The calculated total contribution of these genotypes to the development of CVHC turned out to be highly significant, while the odds ratio was OR=3.0 (X<sup>2</sup>=6.4; P=0.01; OR=3.0; 95% CI 1.248-6.875), which indicates a 3-fold increase in the risk of developing CVHC in carriers of this combination of genotypes.

Also, significant differences in the total frequency of genotypes containing the mutant allele "A" were found between the control group (9.9%) and patients of subgroups I and II (30.3% and 25.3%, respectively). At the same time, the risk of developing CVHC in a moderately active form in carriers of these genotypes was 4 times higher (X<sup>2</sup>=7.3; P=0.007; OR=4.0; 95% CI 1.401-11.24), and highly active CVHC was 3 times higher (X<sup>2</sup>=4.3; P=0.04; OR=3.0; 95% CI 1.029-8.358) compared with representatives of the general population sample that do not contain this combination of genotypes. The total share of G/A+A/A genotypes in the subgroup of patients with liver cirrhosis were also higher than in the control sample (18.9% versus 9.9%, respectively). However, despite the fact that the odds ratio, reflecting the degree of risk of developing cirrhosis for a given genotype, turned out to be higher than one (OR=2.1), this difference did not reach the level of statistical significance (X<sup>2</sup>=1.9; P=0.2; OR=2.1; 95% CI 0.7089-6.395) [Figure 1].

Our data indicate an increased risk of developing CVHC with both moderate and highly active course of the disease in carriers of a combination of genotypes G/A+A/A, but they do not confirm the relationship between the carriage of this combination of genotypes and the development of CVHC with an outcome in cirrhosis. To assess the effect of genotypes G/A+A/A on the severity of CVHC and the development of an unfavorable outcome, we also compared the frequency of this combination between different subgroups. It turned out that the frequency of the combination of genotypes G/A+A/A decreases

linearly with an increase in the activity of the pathological process in the liver and the development of cirrhosis, however, the difference in the indicator between the studied subgroups turned out to be insignificant (p>0.05). The most likely reason for the observed phenomenon is that, as mentioned above, as a result of the expression of the TNF- $\alpha$  gene with such genotypes, a smaller amount of tumor necrosis factor with normal activity will be produced, and, therefore, its effect as an activator of the fibro genesis process will be weakened. This was confirmed by the fact that in the subgroup of patients with a moderate degree of CVHC activity, a significant predominance of the homozygous genotype A/A (12.1% versus 2.5%) was revealed in comparison with the control group. In subgroups of patients with highly active CVHC and liver cirrhosis, the difference in the frequency of occurrence of the A/A genotype with that in the healthy population was statistically insignificant (p>0.05).

The study also investigated the total frequency of the genotypes of the CTLA-4 gene containing the mutant allele (A/G+G/G) for a more complete representation of the role of this allele. It was shown that in the main and control groups the total frequency of A/G+G/G was 74.8% and 67.9%, respectively. However, even the total contribution of genotypes carrying the mutant allele "G" to the development of CVHC turned out to be insignificant (X<sup>2</sup>=1.1; P=0.3; OR=1.4; 95% CI 0.7396-2.653), which indicates that there is no increase in the risk of CVHC development in carriers of this combinations of genotypes. Differences in the total frequency of genotypes containing the mutant allele "G" were also insignificant between the control group (67.9%) and patients of II and III subgroups (70.3% and 67.6%, respectively). And only in patients with moderately active CVHC, the difference of this indicator with the control (87.8% versus 67.9%) was statistically significant. It should be noted that a significant difference in the total frequency of genotypes containing the mutant allele was also noted between patients with moderately active CVHC and patients with liver

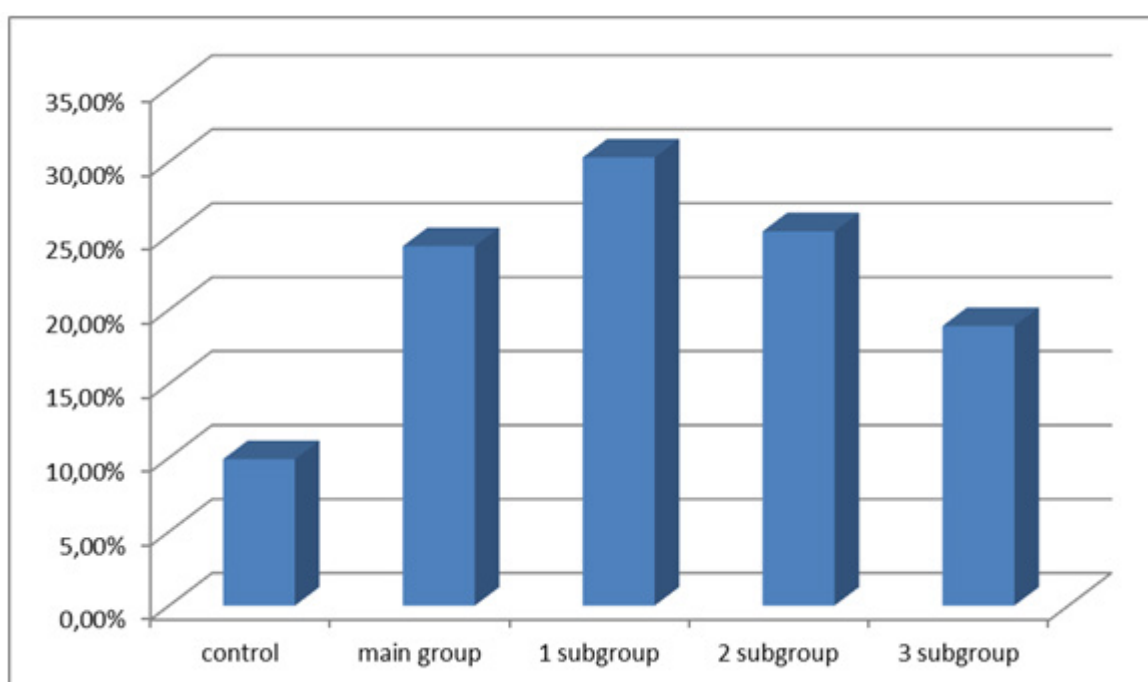


Figure 1: The total frequency of the genotypes of the CTLA-4 gene.

cirrhosis. This fact is another confirmation of the connection between the accumulation of the mutant allele “G” of the-A49G polymorphism of the CTLA-4 gene with a low activity of the inflammatory process and fibrosis in the liver.

### Conclusion

The data obtained allow us to conclude that the carriage of the “G” allele and the combination of genotypes A/G+G/G of the-A49G polymorphism of the CTLA-4 gene are associated not only with a decrease in the risk of CVHC development, but also with a lower intensity of inflammation and fibro-formation in the liver and a high probability of favorable course of the disease.

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