SCIENTIFIC REVIEWS AND LECTURES

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ROLE OF POLYMORPHISM OF I148M GENE PNPLA3 IN THE PROGRESSION OF LIVER DISEASES IN PATIENTS WITH CHRONIC VIRAL HEPATITIS B, C

Abstract

The article presents an overview of the relationship between I148M, PNPLA3, and fibrosis, liver cancer in patients with chronic hepatitis B and C.

Key words: I148M, PNPLA3, adiponutrin, chronic viral hepatitis B, chronic viral hepatitis C, steatosis, fibrosis, HCC, CHC, CHB, CHD

Introduction

Currently, more than 350 million people are chronically infected with the hepatitis B virus and about 1 million people die each year from the effects of hepatitis B and approximately 130-170 million worldwide are infected with the hepatitis C virus [4].

In the Russian Federation, viral hepatitis B and C are widespread, the total number of patients with chronic viral hepatitis B (HBV) and HBsAg carriers is about 5 million, the number of patients with chronic hepatitis C (HCV) and carriers of hepatitis C virus is at least 2 million people [4].

The Republic of Sakha (Yakutia) is considered hyperendemic region of the Russian Federation for the prevalence of viral hepatitis B, C and D [4]. The level of registration of chronic viral hepatitis does not tend to decrease, the incidence rate in 2011 was 1502.5 per 100 thousand population and is, according to the Reference Center for the Supervision of Viral Hepatitis, the highest in the Russian Federation. According to the register «Chronic viral hepatitis in the Republic of Sakha (Yakutia)» for 2016, 14 391 people are registered, (excluding carriers of hepatitis B virus - 570 people), of them with chronic hepatitis B - 6404, C - 6224, D - 889, mixed - 821, unspecified etiology – 57, liver cirrhosis - 544 patients, 59 patients with primary liver cancer.

The first genetic studies in the pathology of liver disease

It is believed that the additional factors of liver damage in CHB and CHC are pathological conditions such as abdominal obesity, hypertriglyceridemia, insulin resistance, metabolic syndrome leading to steatosis of the liver and its progression to steatohepatitis followed by the development of fibrosis and then cirrhosis.

It is established that the fat content in the liver is determined not only by the way of life and the presence of risk factors, but also associated with genetic factors.

The first studies of genetic polymorphisms in the progression of liver diseases were carried out in 2008 by Romeo S. et al. [15] who found that polymorphism I148M PNPLA3 gene associated with steatosis in patients with non-alcoholic fatty liver disease (NAFLD). After that, a large number of studies have been conducted on the relationship between I148M polymorphism and liver disease [10].

PNPLA3 gene function

It is believed that the PNPLA3 gene located on the long arm of chromosome 22q13.31 is expressed in the membranes of hepatocytes and is responsible for intrahepatic lipid metabolism by coding the synthesis of adiponutrin, a protein regulating the activity of triacylglycerol lipase in adipocytes [24].

I148M polymorphism consists in replacing the sequence from cytosine to guanine, which in turn leads to the replacement of the amino acid isoleucine by methionine in residue 148, which leads to disruption of the mechanism of lipid metabolism in the liver.

The hypotheses of the I148M polymorphism impact:

1. Mutant adiponutrin reduces the activity of triacylglycerol hydrolases, thereby reducing the hydrolysis of triglycerides and increasing their concentration in liver cells [21];

2. Accumulation of free fatty acids in hepatocytes occurs, which leads to the development of oxidative stress, and as a result, a direct cytopathic effect on liver cells takes place [16];

3. An alternative hypothesis is that the substitution of amino acids entails an increase in the activity of the acyltransferase, leading to an increase in the synthesis of triglycerides [5];

4. Adiponutrin affects the differentiation of adipocytes (fat cells) through activation of the PPAR-γ receptor [16].

Influence of I148M polymorphism on the progression of CHC

Since the I148M polymorphism was recognized as a genetic determinant of the development of hepatic steatosis in patients with NAFLD and alcoholic liver disease, it was suggested that this polymorphism is also associated with steatosis and progression of fibrosis in patients with CHC [14].

The prevalence of liver steatosis in CHC patients ranges from 35 to 81% and is associated with progression of liver fibrosis, inefficiency of antiviral therapy, and the development of HCC [10, 1]. Possible risk factors for the development of steatosis in CHC patients include obesity, hyperlipidemia and insulin resistance, as well as direct virus cytopathic effect [29]. In sum, these risk factors, combined with predisposing factors of the body itself, lead to the emergence of steatosis in CHC patients. Also, the degree of development of steatosis depends on the genotype of the virus, in case of chronic HCV infection caused by virus genotype 3a, steatosis of the liver occurs significantly more often than with the 1b genotype of HCV (almost 2-fold). [2]

In 2011, Valenti et al. first reported a possible association between I148M polymorphism and CHC. In the study of two independent groups of patients with CHC, it was found that I148M is associated with the development of not only steatohepatitis, but also liver fibrosis in these patients [19].

Influence of polymorphism I148M on the progression of CHB

The prevalence of liver steatosis in CHB is (according to the data of different authors) from 27 to 51% [11], and its role in the progression of fibrosis and cirrhosis in these patients has not been fully determined [9]. Yet some authors argue that the steatosis of the liver affects the development of fibrosis and the progression of CHB [17].

But whether genetic factors contribute to the development of steatosis and fibrosis in CHB patients is not yet known, although there are reports that I148M polymorphism is an independent predictor of severe steatosis in patients with CHB [20]. Other authors have not reported this genetic association between I148M polymorphism and steatosis in patients with CHB [12]. Data on the effect of I148M polymorphism on the course and progression of CHD are not available at this time. Probable route of influence of polymorphism I148M on the progression of CHC and CHB in combination with various risk factors is presented in Figure 1.

Polymorphism I148M and allele G

It was found that I148M recessive G allele is associated with the highest risk of development of steatosis and severe liver fibrosis and in patients with NAFLD, including patients with CHC and CHB [24, 26, 18].

The effect of I148M polymorphism on a sustained virological response (SVR)

In an early study, Valenti et al. reported that patients with CHC combined with fibrosis (virus genotype 1 and 4) carrying I148M polymorphism less often achieved SVR [19], while others did not observe an association between I148M polymorphism and SVR level [6]. It is possible that the cause of low SVR in antiviral therapy is steatosis, mediated by metabolic rather than genetic factors [6]. However, the effect of I148M polymorphism on the SVR level is still controversial and should be studied in future researches.

The influence of polymorphism I148M on the development and progression of hepatocellular carcinoma (HCC)

In his first study, Valenti et al. demonstrated the relationship of polymorphism I148M to the development of liver cancer [19], which was confirmed later [25], also confirmed by other authors [28, 8]. These reports indicate the important role of I148M polymorphism in the development and progression of HCC in various liver diseases, including patients with CHB and HCV.

Thus, the carriers of polymorphism I148M have a predisposition to HCC, moreover HCC does not depend on the stage of steatosis and cirrhosis, developing in the early stages of liver disease, including CHC, and the polymorphism I148M affects the rapid progression of cancer and low survival of patients with HCC [25].

Effect of I148M polymorphism on liver transplantation efficiency

CHC is the most common cause of liver transplantation in Western countries [7].

A number of studies have demonstrated that the presence of I148M polymorphism in donors and recipients affects the results of liver transplantation in patients with CHC, in particular the frequent development of post-transplant metabolic disorders, diabetes mellitus, steatosis and liver fibrosis, liver transplantation, high incidence of lethal cases [13, 22].

I148M polymorphism and ethnic predisposition

The frequency of the allele G of polymorphism I148M varies depending on ethnicity, with the highest prevalence in early studies among Hispanics (49%), and the approximate frequency of homozygotes is 25%. It is reported that the frequency of homozygotes 148M among the population of Italy is approximately 10% (8-14%). In contrast, the frequency of homozygotes in Germany is lower (5.5%) [27]. Among the Asian population, the frequency of polymorphism 148M, due to the lack of qualitative research at the moment, is not known [26].

I148M polymorphism and other risk factors

It is believed that the presence of I148M polymorphism in combination with risk factors, such as abdominal obesity, insulin resistance, hypertriglyceridemia, impaired carbohydrate metabolism, alcohol consumption leads to faster progression of steatosis, fibrosis and cirrhosis [23].

Mackawy, A. M., et al. [18] showed that I148M polymorphism is not associated with the presence of risk factors such as age, gender, BMI, total cholesterol and triglyceride levels, but found significant association with alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) level and viral load in patients with CHC.

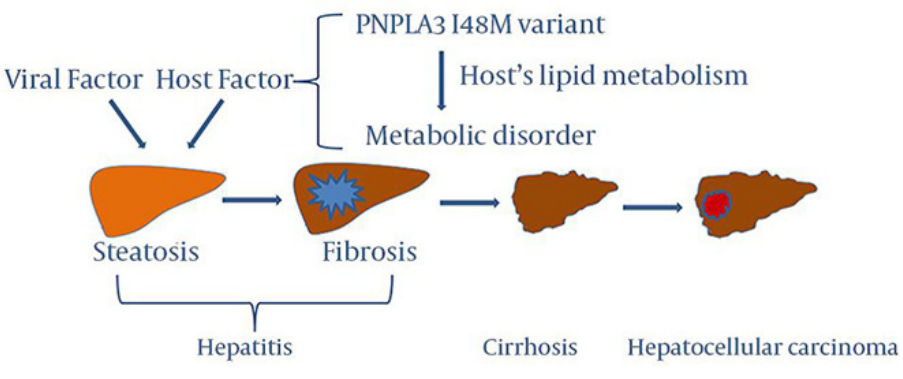

Fig. 1. Probable route of influence of polymorphism I148M on the progression of CHC and CHB in combination with various risk factors.

Conclusion

In conclusion, the results of the studies indicate a significant association of I148M polymorphism with the severity and progression of steatosis, fibrosis and HCC in patients with CHB and CHC, the outcome of liver transplantation depends on the presence of I148M polymorphism in both donors and recipients. It was found that the frequency of polymorphism I148M varies depending on ethnicity. Also, I148M polymorphism was associated with ALT, AST, GGT level in peripheral blood, however, association I148M polymorphism with age, sex, BMI, total cholesterol and triglyceride levels were not observed.

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