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CLINICAL REVIEW

Significance of genetic polymorphisms in patients with nonalcoholic fatty liver disease

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Abstract Because of recent advances in genetic research such as genome-wide association studies, the underlying genetic mechanisms of nonalcoholic fatty liver disease (NAFLD) pathophysiology have been elucidated. Here, we present a review of the current literature on the impact of genetic polymorphisms in patients with NAFLD. These genetic polymorphisms, which regulate lipid metabolism, glucose metabolism, and the renin-angiotensin system, are involved in NAFLD onset, steatosis, inflammation, fibrosis, and hepatocellular carcinoma (HCC). Among these genetic polymorphisms, many studies and meta-analyses have demonstrated that position 148 (rs738409 C/G) of the patatin-like phospholipase domain-containing protein (PNPLA3) is a genetic factor associated with NAFLD pathophysiological features, such as hepatic fat level, hepatic inflammation, fibrosis, and HCC. However, the impact of genetic polymorphisms on NAFLD pathophysiology appears to differ among ethnic groups. Therefore, further studies with larger sample sizes are needed for each ethnic group.

Keywords Genetic polymorphism · NAFLD · NASH · Steatosis · Inflammation · Fibrosis

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide. A large Japanese cohort study indicated that 29.7% of the adult population has NAFLD [1]. NAFLD is associated with metabolic syndrome, including obesity, hyperlipidemia, hypertension, and diabetes [2, 3]. Therefore, NAFLD is considered part of the metabolic syndrome [3]. With an increasing number of patients with metabolic disease, the prevalence of NAFLD patients is increasing in Japan [1]. NAFLD encompasses a wide range of diseases, including non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [4, 5]. It has been determined that several environmental factors, such as lifestyle and enteral environment, affect the development of NASH. However, disease state in NAFLD is difference in individual at any body mass index or visceral fat. Furthermore, studies of twin subjects have suggested the heritability of NAFLD [6]. Therefore, NAFLD could be influenced by genetic variants. Indeed, several single-nucleotide polymorphisms (SNPs) have been reported to affect pathophysiology in patients with chronic liver disease including NAFLD through a genome-wide association study (GWAS). Over the last 10 years, many studies have also revealed the role of genetic factors in the development of steatosis, fibrosis, cirrhosis, and HCC in NAFLD. In this review, we discuss the genetic factors implicated in steatosis, steatohepatitis, fibrosis progression, cirrhosis, and HCC in NAFLD patients.

Table 1 Characteristics of genetic polymorphisms involved in lipid metabolism

Gene	Patient ethnicity	Polymorphism	Association	Reference
PNPLA3	Mixed (Hispanic/Caucasian/African American)	rs738409 I148M (C/G)	Steatosis	[8]
PNPLA3	Japanese	I148M (C/G)	Steatosis, fibrosis	[9, 10]
PNPLA3	Taiwan, Pediatric	I148M (C/G)	Steatosis	[18]
MTP	Caucasian (French)	−493 (G/T)	Steatohepatitis	[26]
MTP	Japanese	−493 (G/T)	Intracellular triglyceride accumulation	[27]
MTP	Chinese	rs1800804 (−164T/C) rs1057613 A/G rs3805335 C/T	NAFLD	[29]
APOC3	India	rs651821 C-482T, T-455C	NAFLD, insulin resistance	[29]
APOC3	Caucasian (Italian/United Kingdom)	rs651821 C-482T, T-455C	Favorable lipid profile	[30]
TM6SF2	Mixed (Hispanic/Caucasian/African American)	rs58542926	Hepatic steatosis	[34]
PPARα	Brazilian	Leu162Val	Fibrosis	[38]
PPARα	Chinese	Val227Ala	NAFLD	[40]
PPARγ	Germany	Pro12Ala	NAFLD	[43]
PPARγ	Indian	Pro12Ala	NAFLD, overweight	[44]

PNPLA3 patatin-like phospholipase domain-containing protein, *MTP* microsomal triglyceride transfer protein, *APOC3* apolipoprotein C3, *PPAR* peroxisome proliferator-activated receptor, *NAFLD* nonalcoholic fatty liver disease

Genetic polymorphisms of lipid metabolism (Table 1)

About half of Japanese patients with NAFLD have hyperlipidemia [7]. Lipid metabolism in the liver and peripheral tissue plays a critical role in NAFLD onset and progression. Thus, there are many reports of gene polymorphisms involved in lipid metabolism that are associated with NAFLD and NAFLD fibrosis progression.

Patatin-like phospholipase domain-containing protein (PNPLA3)

A polymorphism in PNPLA3 at position 148 of the protein, which causes an isoleucine (rs738409-C) to methionine (rs738409-G) substitution, was identified as a genetic factor associated with increased hepatic fat level and hepatic inflammation by GWAS [8]. Subsequently, many studies of this polymorphism have been reported. In addition, the rs738409-GG genotype was associated with a higher risk of liver fibrosis, cirrhosis, and HCC [9–11].

The *PNPLA3* gene encodes the protein adiponutrin, which is expressed in the liver [12], where the replacement of isoleucine with methionine reduces its hydrolytic activity for triglycerides [13]. PNPLA3 is also expressed in adipose tissue [14] and the adrenal gland [15], and it is closely related to the major triglyceride hydrolete in peripheral fat tissue [16].

In the Japanese population, the rs738409-GG genotype was associated with susceptibility to NAFLD and with histological fibrosis stage [9, 10]. In addition, the rs738409-G allele was associated with hepatic steatosis as measured by ultrasonography and with overweight in pediatric subjects in Italy and Taiwan [17, 18]. The rs738409-G allele also increases the risk of HCC in patients with NAFLD. Compared to the CC genotype, the GC and GG genotypes exhibit increased risk for HCC (ORs 2.52 and 12.19, respectively) [19]. The frequency of the rs738409-GG genotype is higher among the Japanese (23%) and Hispanic (33%) populations than among the African American (1.6%) or European American (4%) populations [8–10].

Liver steatosis is observed in 18–40% patients after liver transplantation. Finkenstedts et al. reported that the rs738409 genotype of the recipient, but not the donor was associated with post-transplant steatosis [20]. In contrast, in our recent study, an rs738409-GG genotype in the donor was a predictor of post-transplant steatosis (in submission). In addition, the donor *PNPLA3* genotype was reported to be the predictor of post-transplant outcome among liver transplant recipients with hepatitis C virus [21]. Finally, the rs738409-G allele has been reported to be associated with steatosis and/or fibrosis and HCC in other liver diseases, including hepatitis B and C and alcoholic liver disease [22].

Microsomal triglyceride transfer protein (MTP)

MTP has a pivotal role in metabolizing hepatic triglycerides and very low-density lipoproteins (VLDL) for lipid

export from the liver [23]. Therefore, MTP plays an important role in lipid metabolism. Some previous studies reported that functional polymorphisms of MTP were associated with reduced low-density lipoprotein (LDL) levels [24]. Among French and Japanese patients, a polymorphism (promoter −493 G-allele) in the *MTP* gene is correlated with down-regulation of the *MTP* gene, corresponding to NASH and more severe steatosis [25, 26]. In contrast, in a Brazilian study, there was no association between the −493 G/T polymorphism and NAFLD [27]. The frequency of the *MTP* gene polymorphism (−493 GG-genotype) was similar among Japanese (60.7%), French (55.7%), and Brazilian (59.3%) individuals [25–27]. Finally, Peng et al. examined 580 NAFLD patients and 580 healthy controls in China. Multivariate analysis demonstrated that rs1800804 (−164 T/C) was associated with an increased risk of NAFLD, while rs1057613 A/C and rs3805335 C/T were associated with a decreased risk of NAFLD [28].

Apolipoprotein C3 (APOC3)

APOC3 regulates lipoprotein lipase activity. An APOC3 variant (C-482T, T-455C, or both) resulted in a 30% increase in the plasma concentration of apolipoprotein C3 as compared with that in the wild-type. There was also an increase in plasma triglycerides and tetinyl fatty acid ester concentrations by a factor of approximately two after an oral fat-tolerance test. The average hepatic triglyceride content was higher in individuals carrying the *APOC3* rs651821 variant alleles (C-482T, T-455C, or both) than in wild-type homozygotes. In addition, the prevalence of NAFLD was 38% among the *APOC3* variant-allele group and 0% among wild-type homozygotes. Subjects with NAFLD also exhibited marked insulin resistance [29]. In contrast, in Italy and the United Kingdom, the *APOC3* wild-type genotype was associated with a more favorable lipid profile but not with insulin resistance, NASH, or increased fibrosis [30]. Moreover, among Finnish subjects, *APOC3* variants were not associated with liver fat content due to NAFLD [31]. The prevalence of variant *APOC3* alleles was found to be 79.7% in Asian Indian, 66.8% in Italian, and 80% in Finnish individuals [29–31].

Transmembrane 6 superfamily member 2 (TM6SF2)

A *TM6SF2* variant was identified in an exome-wide association study. This variant was not associated with body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR), or alcohol intake. Knockdown of *TM6SF2* in mice increased liver triglyceride content by threefold and decreased VLDL secretion by 50%. Thus, these data indicate that TM6SF2 activity is required for normal VLDL secretion. The *TM6SF2* variant associated with hepatic triglyceride content is an adenine-to-guanine substitution at coding nucleotide 499. Moreover, the *TM6SF2* variant genotype affects inflammation and liver fibrosis stage [32]. However, a recent study in a Japanese cohort demonstrated that the *TM6SF2* genotype was not associated with steatosis, inflammation, or liver fibrosis stage [33]. *TM6SF2* (rs10401969) also influences the total cholesterol level and was associated with a reduction in coronary artery disease events in a large sample of 20,597 cases and 61,046 controls (OR 0.90, $p = 2 \times 10^{-4}$) [34].

Peroxisome proliferator-activated receptor (PPAR)

PPARs are members of a family of nuclear receptors and play an important role in lipid metabolism. Members of the PPAR family include PPARα, PPARγ, and PPARδ. PPARα regulates fatty acid uptake and the oxidation of fatty acids. It is expressed in tissues such as the liver, heart, muscle, and brown adipose tissue [35]. In a Brazilian study, the polymorphism Leu162Val in PPARα was associated with NAFLD fibrosis [36], while in an Italian study, the frequency of the Leu162Val polymorphism did not differ between patients with NAFLD and a control group [37]. However, the frequency of another PPARα polymorphism, Val227Ala, was significantly different between subjects with NAFLD and a control group in China [38]. In Japan, Yamakawa et al. reported that the Val227Ala allele was associated with total cholesterol [39].

PPARγ is expressed in adipocytes, macrophages, and muscle, where it regulates abiogenesis, lipid storage, and glucose metabolism [40]. The polymorphism Pro12Ala in PPARγ among German subjects was more frequently found in NAFLD patients than in controls. However, the Pro12Ala polymorphism was not associated with NAFLD progression [41]. Similarly, in Italian NAFLD patients, Pro12Ala was not associated with NAFLD onset, liver damage, or insulin resistance [37]. Gupta et al. showed that the prevalence of the Pro12Ala variant was higher among Indian NAFLD subjects than among controls. In addition, the Pro12Ala variant was also associated with overweight [42]. This result suggests that the Pro12Ala variant plays a role in obesity-related NAFLD.

Genetic polymorphisms of glucose metabolism (Table 2)

Glucose intolerance, including insulin resistance, is a risk factor for the development of steatosis, NASH, and cirrhosis in patients with NAFLD.

Table 2 Characteristics of genetic polymorphisms involved in glucose metabolism, renin-angiotensin, and others

Gene	Patients ethnicity	Polymorphism	Association	Reference
ENPP1	Caucasian (Italian, United Kingdom)	Lys121Gln	Body weight, dyslipidemia, fibrosis	[48]
IRS-1	Caucasian (Italian, United Kingdom)	Gly972Arg	Dyslipidemia, fibrosis	[48]
Adiponectin	Italian	+45T/G	Hepatic steatosis, necroinflammatory grade	[52]
Adiponectin	Japanese	−493 (G/T)	Steatohepatitis	[53]
AGT	Japanese	rs7079 SNP	Steatohepatitis	
AGTR1	Japanese	rs3772622, rs3772633, rs2276736, rs3772630, rs3772627	NAFLD, fibrosis	[58]
IL28B	Italian	rs12979860 (CC)	Inflammation, fibrosis	[63]

ENPP1 ectoenzyme nucleotide pyrophosphate phosphodiesterase, *IRS* insulin receptor substrate, *AGT* angiotensinogen, *AGTR1* angiotensin II type 1 receptor, *IL28B* interleukin 28B

Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP) and insulin receptor substrate (IRS)

Insulin resistance is a key factor in NAFLD pathophysiology. The presence of metabolic syndrome is associated with the severity of NAFLD [2, 3]. In addition, insulin resistance is associated with liver damage and fibrosis [43]. In hepatocytes, insulin binds to the insulin receptor, activating insulin receptor substrate (IRS)-1 and IRS-2 and in turn leading to the phosphorylation of transcription factors that regulate the glucose level [44]. ENPP1 inhibits the insulin signal and causes insulin resistance [45]. Among the genes involved in the regulation of the insulin signal, it has been reported that genetic polymorphisms of ENPP1 and IRS-1 influence insulin receptor activity and are associated with liver damage [46]. In studies in Italy and the United Kingdom, multivariate analysis revealed that the ENPP1 121Gln and IRS-1 972Arg polymorphisms, present in 28.7 and 18.1% of patients respectively, were independently associated with advanced fibrosis in NAFLD patients. In addition, these polymorphisms were associated with a reduction in AKT status, reflecting insulin resistance and disease severity in patients with NAFLD [46].

Adiponectin

Adiponectin is a cytokine secreted from adipose tissue, also known as an adipokine. Adiponectin plays an important role in hepatic and peripheral glucose metabolism and has an anti-inflammatory function [47]. Several studies have reported that systemic levels of adiponectin are reduced in NASH patients [48] and correlated with liver fibrosis [49]. Musoo et al. demonstrated that in an Italian cohort, an adiponectin genotype (+45T/G) was associated with hepatic steatosis, necroinflammatory grade, and postprandial adiponectin levels [50]. Similarly, associations between +45T/G and HOMA-IR and liver fibrosis were reported among Japanese NAFLD patients [51]. In an Indian population, −11377GG and +45T/G were associated with NAFLD [52]. The frequency of +45GG, a well-known adiponectin SNP, was found to vary in Japanese (NAFLD 10.9%, control 10.4%) and Indian (NAFLD 5.1%, control 0.8%) individuals with and without NAFLD [51, 52].

Genetic polymorphisms of hypertension (Table 2)

Hypertension is one of the diseases included in the diagnosis of metabolic syndrome, and it is associated with the progression of NAFLD [2, 53]. The activity of the renin-angiotensin system influences hypertension and liver fibrosis in chronic liver disease [54].

Angiotensinogen (AGT) and angiotensin II type 1 receptor (AGTR1)

AGT is well known to be an important regulator of blood pressure. Some previous reports have shown that genetic polymorphisms of AGT and angiotensin receptor (AGTR) influence serum AGT levels and hypertension. The frequency of the rs7079-A allele in NASH patients (21.0%) was found to be significantly higher than that in healthy controls (13.0%). Regarding haplotypes of the *AGT* gene, the CTA/- frequency in NASH patients was significantly higher than that in healthy controls. In addition, the diastolic blood pressure in patients with the CTA/- haplotype was significantly higher than that in patients with other haplotypes [55].

Angiotensin II function involves AGTR1. This receptor is expressed on hepatic stellate cells, which play an important role in liver fibrosis progression. Five SNPs (rs3772622,

rs3772633, rs2276736, rs3772630, and rs3772627) in *AGTR1* were found to be significantly associated with NAFLD. Moreover, there was a significant association between rs3773622 genotypes and liver fibrosis [56].

Genetic variants in mediators of inflammation (Table 2)

Interleukin 28B (IL28B)

Genetic polymorphisms of *IL28B* (rs12979860 CC and rs809917 TT) have been reported as predictors of the sustained virological response (SVR) after interferon therapy in patients with chronic hepatitis C [57–59]. Moreover, previous studies have demonstrated that this *IL28B* polymorphism was associated with severity of disease, steatosis, and fibrosis in patients with chronic hepatitis C [60–62]. In Italian patients with NAFLD, multivariate analysis showed that the rs12979860-CC genotype is independently associated with moderate to severe inflammation and severe fibrosis [63]. However, in a cohort of Caucasian North American patients, the rs12979860-CC genotype did not affect the histological features of patients with NAFLD [64]. In contrast, meta-analysis showed that rs8099917-TT was significantly associated with a reduced risk of severe steatosis in patients with chronic hepatitis C [62].

In conclusion, a variety of genetic polymorphisms appear to influence NAFLD onset and the severity of steatosis, necroinflammation, and fibrosis. However, the influence of genetic polymorphisms on NAFLD pathophysiology seems to differ among ethnic groups. Therefore, validation studies in each ethnic group should be performed in the future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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