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REVIEW

# *PNPLA3* I148M variant in nonalcoholic fatty liver disease: Demographic and ethnic characteristics and the role of the variant in nonalcoholic fatty liver fibrosis

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## Abstract

Patatin-like phospholipase domain-containing 3 (PNPLA3 or adiponutrin) displays anabolic and catabolic activities in lipid metabolism, and has been reported to be significantly associated with liver fat content. Various studies have established a strong link between the 148 isoleucine to methionine protein variant (I148M) of PNPLA3 and liver diseases, including nonalcoholic fatty liver disease (NAFLD). However, detailed demographic and ethnic characteristics of the I148M variant and its role in the development of nonalcoholic fatty liver fibrosis have not been fully elucidated. The present review summarizes the current knowledge on the association between the *PNPLA3* I148M variant and NAFLD, and especially its role in the development of nonalcoholic fatty liver fibrosis. First, we analyze the impact of demographic and ethnic characteristics of the *PNPLA3* I148M variant and the presence of metabolic syndrome on the association between *PNPLA3* I148M and NAFLD. Then, we explore the role of the *PNPLA3* I148M in the development of nonalcoholic fatty liver fibrosis, and hypothesize the underlying mechanisms by speculating a pro-fibrogenic network. Finally, we briefly highlight future research that may elucidate the specific mechanisms of the *PNPLA3* I148M variant in fibrogenesis, which, in turn, provides a theoretical foundation and valuable experimental data for the clinical management of nonalcoholic fatty liver fibrosis.

**Key words:** *PNPLA3* I148M variant; Polymorphism; Nonalcoholic fatty liver disease; Nonalcoholic fatty liver fibrosis



**Core tip:** In this review, we summarize the association between the *PNPLA3* I148M variant and nonalcoholic fatty liver disease (NAFLD), and especially its role in nonalcoholic fatty liver fibrosis. The variant is associated with NAFLD, but is predominant in women, not in men. The association may vary among different ethnic populations, but is not affected by the presence of metabolic syndrome. We speculate there is a pro-

fibrogenic network that the *PNPLA3* I148M variant may promote the development of fibrogenesis by activating the hedgehog signaling pathway, which, in turn, leads to the activation and proliferation of hepatic stellate cells, and excessive generation and deposition of extracellular matrix.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined histologically or by proton magnetic resonance spectroscopy as hepatic fat accumulation (steatosis) exceeding 5% in the absence of excessive ethanol consumption, drugs, toxins, infectious diseases or any other specific etiologic factors of liver disease[1]. NAFLD embraces a morphological spectrum of hepatic diseases, ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). NASH is the late stage of NAFLD, in which hepatic inflammation and fibrosis co-exist. In a proportion of patients, NASH can progress towards cirrhosis and even hepatocellular carcinoma (HCC)[2]. With a general prevalence of 25%-30%, NAFLD currently represents the most common cause of liver dysfunction, and is now the most prevalent liver disorder in Western countries[3].

It is well known that metabolic risk factors such as obesity, insulin resistance, type 2 diabetes mellitus and dyslipidemia are deeply associated with the pathophysiology of NAFLD[2,4]. Moreover, genetic mutations also play a significant role in predisposition to the development and progression of NAFLD[5].

In 2008, a single nucleotide polymorphism (SNP) in the patatin-like phospholipase domain-containing 3 (*PNPLA3*, also known as adiponutrin) gene, or rs738409 polymorphism, which represents a substitution from cytosine to guanine that results in a switch from isoleucine to methionine at residue 148 (I148M), was reported to be significantly associated with liver fat content[6].

Since then, extensive investigations of the association between the *PNPLA3* I148M variant (or rs738409 polymorphism) and NAFLD have been carried out, and various studies have established a strong link between the *PNPLA3* I148M variant and the development and progression of NAFLD, including nonalcoholic fatty liver fibrosis[7-12]. These results indicate that this variant may be a potential modifier of NAFLD, especially nonalcoholic fatty liver fibrosis. However, detailed demographic and ethnic characteristics of the I148M variant and its role in the development of nonalcoholic fatty liver fibrosis, along with the specific molecular mechanisms, have not been fully elucidated. Therefore, the present review summarizes the current knowledge on the association between the *PNPLA3* I148M variant and NAFLD, and the variant's role in the development of nonalcoholic fatty liver fibrosis.

## EXPRESSION AND FUNCTION OF THE *PNPLA3* GENE AND *PNPLA3* I148M VARIANT

The *PNPLA3* gene is located in the long branch of human chromosome 22, and encodes a transmembrane polypeptides chain containing 481 amino acids[13]. PNPLA3 protein is highly expressed on the endoplasmic reticulum and lipid membranes of hepatocytes as well as adipose tissue[14], and changes in the expression are closely associated with the nutrient status[15]. Rae-Whitcombe and colleagues reported that the promoter region of the *PNPLA3* gene is regulated by glucose and insulin[16]. Consistently, *PNPLA3* mRNA levels have been demonstrated to decrease after fasting and increased by refeeding in mice[17]. The nutritional regulation of *PNPLA3* has further been confirmed, as the gene is shown to be regulated by sterol regulatory element binding protein 1c (SREBP-1c) in mouse liver and human hepatocytes[17-19], which responds in turn to insulin and glucose.

With the conserved patatin domain at its N-terminal, the PNPLA3 protein demonstrates a predominant triglyceride hydrolase activity with mild lysophosphatidic acid acyltransferase activity[13]. It has been shown that substitution of methionine for isoleucine at residue 148 does not alter the orientation of the catalytic dyad, but the longer side chain of methionine restricts access of substrate to the catalytic serine at residue 47[20]. The size of the substrate-access entry site is significantly reduced in mutants, which limits the access of palmitic acid to the catalytic dyad[21]. Recently, Kumari and colleagues determined that the *PNPLA3* I148M variant induced an increase in lipogenic activity, leading to increased hepatic triglyceride synthesis[22]. Similarly, Li *et al*[23] generated transgenic mice over-expressing PNPLA3 in the liver and observed that the *PNPLA3* I148M variant exerted three effects on hepatic triglyceride metabolism: increased synthesis of fatty acids and triglyceride; impaired hydrolysis of triglyceride; and depletion of triglyceride long-chain polyunsaturated fatty acids. These findings suggest that the increase in hepatic triglyceride levels associated with the *PNPLA3* I148M variant is induced by multiple changes in triglyceride metabolism. These previous studies showed that acid modification within the catalytic patatin domain of the *PNPLA3* protein acts as a kind of "gain of function" mutation enhancing the accumulation of lipids in the hepatocytes.

## *PNPLA3* I148M VARIANT AND NAFLD

In 2008, Romeo and colleagues first reported a genome-wide association study to explore the genes associated with susceptibility to NAFLD[6]. They demonstrated that the *PNPLA3* 148M allele was robustly associated with increased liver fat content, and the association remained highly significant after adjusting for body mass index (BMI), diabetes status, ethanol use, as well as global and local ancestry. In addition, the *PNPLA3* I148M variant was also found to be associated with elevated serum aminotransferase levels[6,24] and increased computed tomography-measured hepatic steatosis and histological NAFLD[25]. A series of subsequent candidate gene studies[26,29,36,37] have verified the association between the *PNPLA3* I148M variant and NAFLD.

### *PNPLA3*I148M variant is associated with NAFLD in adults

The *PNPLA3* I148M variant is reported to be dose-dependently associated with increased levels of serum triglyceride, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[26]. In addition, numerous studies have demonstrated that the *PNPLA3* I148M variant is associated with liver fat content[27-29]. These findings confirm that the *PNPLA3* I148M variant is associated not only with fat accumulation in the liver, but also with liver injury since aminotransferases are the most sensitive liver function parameters. Liver injury is believed to be triggered by lipotoxicity, which results from hepatic fat accumulation. It has been previously reported that liver necrosis induced by intracellular lipotoxicity parallels liver fat accumulation[30], and the degree of steatosis correlates with the severity of liver injury in NAFLD[31].

Currently, liver biopsy is used as the gold standard for diagnosis of NAFLD. Although it is expensive and not ethically feasible, especially in uninvestigated patients, there are still some studies on NAFLD based on histological diagnosis. The *PNPLA3* I148M variant has been confirmed to be strongly associated with an increased risk of histological NAFLD[32]. In a case-control study, patients who were homozygotes of the 148M allele had higher steatosis scores (33.3% ± 4.0%) compared with heterozygotes of the 148IM allele (26.3% ± 3.5%) and 148I allele (14.9% ± 3.9%), indicating that the variant was significantly associated with the degree of liver steatosis[27].

### *PNPLA3 I148M variant is associated with pediatric NAFLD*

NAFLD is not only a disease affecting the adult population, but also a leading liver disease in children worldwide[8,33]. A study of Hispanic children and adolescents in the Unites States showed that the 148M allele was associated with higher liver fat content and lower HDL cholesterol levels[34]. This is consistent with the observation that Hispanic children who were homozygotes of the 148MM allele were susceptible to increased hepatic fat when dietary carbohydrate intake was high[35]. In addition, a study of obese Taiwanese children also showed that the *PNPLA3* I148M variant was associated with an increase in ALT levels and an increased risk of NAFLD[36,37].

In a more extensive study of pediatric patients with biopsy-proven NAFLD, the *PNPLA3* I148M variant was associated with the severity of steatosis, hepatocellular ballooning and lobular inflammation, and the presence of NASH and fibrosis, but not with BMI, adiposity, lipid levels, insulin resistance and ALT levels[8]. In another large study[7] to determine the association between SNPs and the histological severity of NAFLD, 223 children with histologically confirmed NAFLD were investigated. It was observed that the 148M allele was associated with an earlier presentation of the disease, but not with histological severity. However, the association was marginal in the multivariate analysis ($P = 0.045$).

Therefore, although the currently available findings suggest that the *PNPLA3* I148M variant confers genetic susceptibility to liver injury in children at a young age, most subjects studied were obese children or pediatric NAFLD patients, and the samples were relatively small in most of the studies. Thus, well-designed large studies that include pediatric NAFLD patients and matched healthy children are required to confirm the association. At the very least, a meta-analysis would offer valuable information.

## ASSOCIATION BETWEEN *PNPLA3* I148M VARIANT AND NAFLD IS AFFECTED BY GENDER AND PROBABLY BY ETHNICITY, BUT NOT BY METABOLIC SYNDROME

The *PNPLA3* I148M variant shows a potential sexual dimorphism on NAFLD susceptibility[9,32]. In a gender-specific analysis of a NASH cohort, Speliotes *et al*[32] observed that the effect of the *PNPLA3*I148M variant on histological NAFLD was higher in women than in men. Indeed, a meta-regression analysis showed a negative correlation between male gender and the effect of the *PNPLA3* I148M variant on liver fat content[9].

The above findings suggest a predominant association between the *PNPLA3* I148M variant with NAFLD in women, but not in men. It is known that estrogen levels are different in men and women, and estrogen is a critical hormone involved in lipid metabolism. Therefore, the gender differences may mainly result from the variations in the hormone, the variation in the gene, or the interaction of the two. However, it is necessary to test whether there is a true and reproducible interaction between estrogen and *PNPLA3* I148M in well-defined population-based cohorts.

The prevalence of NAFLD differs among different populations. Hispanics have been demonstrated to have a higher prevalence of hepatic steatosis compared with European-Americans, whereas African-Americans have a lower prevalence[38]. In addition, Asian-Indian men have

more liver fat and are more insulin-resistant than BMI- and age-matched white individuals[39].

Romeo and colleagues found that the frequencies of the 148M allele matched the prevalence of NAFLD in the Dallas Heart Study, and Hispanics had a higher frequency of the 148M allele (49%) compared with European Americans (23%) and African Americans (17%)[6]. Another study by Wagenknecht *et al*[40] suggested that the *PNPLA3* I148M variant contributed to the variation in NAFLD across multiple ethnicities. These findings indicate that the *PNPLA3* I148M variant may explain ethnic differences in the prevalence of NAFLD, and that some of the ethnic variations in NAFLD are genetic.

On the other hand, in a study of 144 biopsy-proven NAFLD patients and 198 controls in Malaysia, the *PNPLA3* I148M variant was associated with susceptibility to NAFLD (OR = 2.34; 95%CI: 1.69-3.24)[12]. However, the association remained similar in three ethnic groups, namely Chinese (OR = 1.94; 95%CI: 1.12-3.37), Indian (OR = 3.51; 95%CI: 1.69-7.26) and Malay (OR = 2.05; 95%CI: 1.25-3.35), which indicates no effect of ethnicity on the association between the *PNPLA3* I148M variant and NAFLD. Nevertheless, these three ethnic groups all belong to Asian populations, which may be different from Hispanics, Europeans and Africans in terms of association between the *PNPLA3* I148M variant and NAFLD.

NAFLD is now considered the hepatic manifestation of metabolic syndrome[41]. Insulin resistance in adipose tissue induces an excess of free fatty acid supply to the liver, which may lead to lipotoxicity, oxidative stress, and apoptosis[42]. Whether the association between the *PNPLA3* I148M variant and NAFLD is confounded by the presence of metabolic syndrome has been investigated. Although a few studies have suggested an association between the *PNPLA3* I148M variant and metabolic syndrome, such as insulin resistance[26,43], other studies have failed to reveal the association[9,32,44,45]. For example, in a study of 592 cases with European ancestry, there were no associations of the *PNPLA3* I148M variant with BMI, triglyceride levels, high- and low-density lipoprotein levels, or diabetes[32]. Moreover, a study of 330 German subjects showed that the *PNPLA3* I148M variant was strongly associated with fatty liver, but not with insulin resistance or estimates of liver injury[44]. In addition, in a study of 218 French type 2 diabetic patients, the *PNPLA3* I148M variant was not correlated with visceral obesity and was inversely associated with carotid intima media thickness, suggesting that fatty liver associated with the *PNPLA3* I148M variant may not be linked to metabolic disorders[45]. Indeed, in a recent meta-analysis, all included studies showed a lack of a significant difference among genotypes for BMI, glucose and insulin levels, and homeostasis model assessment of insulin resistance[9].

Furthermore, there appears to be no association between the *PNPLA3* I148M variant and metabolic syndrome in children. In a study of obese children and adolescents, the *PNPLA3* I148M variant was associated with increased levels of ALT and AST, but not with glucose tolerance and insulin sensitivity[46]. The *PNPLA3*I148M variant also conferred susceptibility to hepatic steatosis in obese youths, but without increasing insulin resistance[47].

In summary, the *PNPLA3* I148M variant is associated with NAFLD both in adults and children, and the association is affected by gender and ethnicity, but not by the presence of metabolic syndrome (Table 1).

## ROLE OF THE *PNPLA3* I148M VARIANT IN NONALCOHOLIC FATTY LIVER FIBROSIS

Nonalcoholic fatty liver fibrosis represents a necessary pathological pathway that patients with NAFLD undergo and then progress to cirrhosis, HCC and end-stage liver disease, and poses a noteworthy economic burden worldwide. Liver fibrosis is a reversible wound-healing response to continuous chronic liver injuries[48], and the most characteristic hallmark is the excessive production and accumulation of intrahepatic extracellular matrix (ECM), including fibronectin, type I collagen, proteoglycan, *etc*., which eventually lead to hepatic structural change and dysfunction. Therefore, whether or not to control or reverse liver fibrosis affects the prognosis of patients to a great extent. However, challenges remain, as the underlying specific pathogenesis of liver fibrosis is still unclear.

Various studies have established that the *PNPLA3* I148M variant is significantly associated with the development of fibrogenesis and the severity of nonalcoholic fatty liver fibrosis[7,8,10,11,32,49]. In 2010, Valenti and colleagues demonstrated that the *PNPLA3* I148M variant influenced both the presence of NASH (OR = 1.5; 95%CI: 1.12-2.04) and the severity of liver fibrosis (OR = 1.5; 95%CI: 1.09-2.12) in a large series of 591 biopsied patients with NAFLD independently of the degree of obesity, diabetes and steatosis[11]. In addition, Rotman *et al*[7] carried out a study in a large cohort of 894 adults and 223 children with histopathological markers of NAFLD, and confirmed that the *PNPLA3* I148M variant was associated with portal ($P < 0.001$) and lobular inflammation ($P = 0.005$), Mallory-Denk bodies ($P = 0.020$), and fibrosis ($P < 0.001$). Furthermore, in an observational cross-sectional study of 899 European patients with chronic liver diseases, there was a prominent association between the *PNPLA3* I148M variant and enhanced liver stiffness by using a non-invasive transient elastography[10]. This association between the *PNPLA3* I148M variant and the severity of fibrosis in patients with histologically confirmed NAFLD was replicated in a case-control analysis (OR = 3.37; 95%CI: 2.85-3.97; $P < 0.001$)[32]. More importantly, consistent with previous findings in adults, a prospective study of 149 consecutive Caucasian children and adolescents with biopsy-proven

**Table 1 Studies evaluating the association between the *PNPLA3* I148M variant and nonalcoholic fatty liver disease**

| Ref. | Population/Ethnicity country | *n* | Age | Diagnosis criteria | Key findings |
|---|---|---|---|---|---|
| Wang *et al*[26] | Asian<br>Tai Wan | 879 | Adult | US | Increase in TG, ALT and AST |
| Sookoian *et al*[27] | Caucasian<br>Argentina | 266 | Adult | US<br>Liver biopsy | Increased liver fat and liver Injury |
| Kollerits *et al*[28] | Italy/Austria/United States | 4290 | Adult | NA | Increase in ALT and AST |
| Xu *et al*[29] | Chinese<br>China | 651 | Adult | US | Increased ALT, GGT and related to development and progression of NAFLD |
| Speliotes *et al*[32] | Caucasian<br>United States | 1597 | Adult | Liver biopsy | Increased risk of histological NAFLD, but not associated with metabolic syndrome |
| Rotman *et al*[7] | Caucasian<br>United States | 1117 | Adult<br>Pediatric | Liver biopsy | Earlier presentation of NAFLD in pediatric patients |
| Valenti *et al*[8] | Caucasian<br>Italian | 149 | Pediatric | Liver biopsy | Associated with steatosis, NASH and fibrosis |
| Goran *et al*[34] | Hispanic<br>United States | 327 | Pediatric | MRS | Higher liver fat and lower HDL-C |
| Davis *et al*[35] | Hispanic<br>United States | 153 | Pediatric | MRI | Increased liver fat when dietary carbohydrate intake |
| Lin *et al*[36] | Asian<br>Tai Wan | 520 | Pediatric | US | Increased ALT and risk of NAFLD |
| Viitasalo *et al*[37] | Caucasian<br>Finland | 481 | Pediatric | NA | Increase in ALT |
| Sookoian *et al*[9] | Meta-analysis | | | | A negative correlation between male sex and the variant on liver fat, and a lack of significant difference among genotypes for metabolic syndrome |
| Romeo *et al*[6] | Hispanic/<br>European American/<br>African American<br>United States | 9229 | Adult | H-MRS | Hispanics have a higher frequency of the 148M allele than European Americans and African Americans |
| Zain *et al*[12] | Chinese, Indian and Malay<br>Malaysia | 342 | Adult | Liver biopsy | No effect of ethnicity on the association between the variant and NAFLD |
| Browning *et al*[38] | White/Black/Hispanic<br>United States | 2287 | Adult | H-MRS | Frequency of hepatic steatosis varied with ethnicity and gender |
| Petersen *et al*[39] | Caucasian/<br>Eastern Asian/<br>Asian-Indian/Black/<br>Hispanic<br>United States | 482 | Pediatric<br>Adult | Proton MRS | Asian-Indians have increased liver fat and prevalence of insulin resistance compared with all other ethnic groups |
| Wagenknecht *et al*[40] | Hispanic American/<br>African American<br>United States | 1214 | Adult | Abdominal CT scanning | Hispanic Americans have a higher frequency of the 148M allele than African Americans |
| Kantartzis *et al*[44] | Caucasian<br>Germany | 330 | Adult | H-MRS<br>MRT | Higher liver fat but not insulin sensitivity, lipids, or liver enzymes |
| Petit *et al*[45] | Caucasian<br>France | 218 | Adult | H-MRS | Not associated with BMI or visceral fat area |
| Romeo *et al*[46] | Caucasian<br>Italy | 475 | Pediatric | US | Increased ALT and AST, but not glucose tolerance and insulin sensitivity |
| Santoro *et al*[47] | Caucasian/<br>Hispanic/<br>African American<br>United States | 85 | Pediatric | MRI | Increase susceptibility to hepatic steatosis, but without increasing insulin resistance |

PNPLA3: Patatin-like phospholipase domain-containing 3; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; US: Ultrasonography; H-MRS: Hydrogen magnetic resonance spectroscopy; MRI: Magnetic resonance imaging; MRT: Magnetic resonance tomography; CT: Computed tomography; TG: Triglyceride; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index; NA: Not available.

NAFLD showed stronger evidence that the *PNPLA3* I148M variant significantly influenced the occurrence of fibrosis ($P = 0.01$) irrespective of confounding factors[8].

Recently, a meta-analysis established a significant association between the *PNPLA3* I148M variant and advanced nonalcoholic fatty liver fibrosis[49]. In a dominant model, patients with PNPLA3 148MM or 148IM exhibited a significantly increased risk of developing advanced fibrosis compared with 148Ⅱ carriers (OR = 1.29; 95%CI: 1.21-1.38). In line with the dominant model, a recessive model yielded a similar strength of the association (OR = 1.32; 95%CI: 1.20-1.45)[49]. Therefore, there is little doubt that there exists an association between the *PNPLA3* I148M variant and nonalcoholic fatty liver

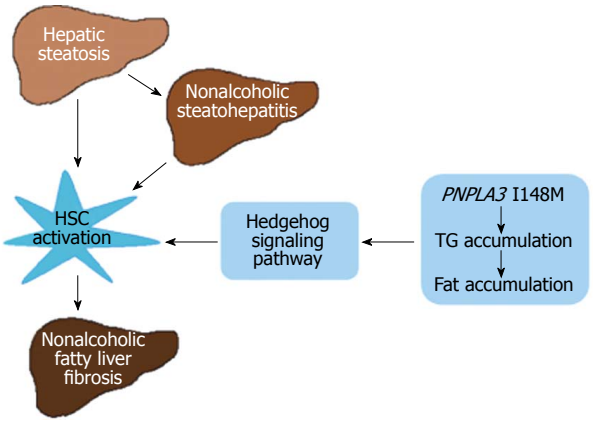


**Figure 1 Simplified schematic model showing the hypothetical molecular mechanism by which the *PNPLA3* I148M variant participates in the development and progression of nonalcoholic fatty liver fibrosis.** The hedgehog signaling pathway links *PNPLA3* with the activation of hepatic stellate cells, which is considered as the central part of fibrogenesis. PNPLA3 protein exhibits activities of lysophosphatidic acid acyltransferase and acylglycerol hydrolase to maintain the Triglyceride (TG) balance in the liver. The "gain function" of the *PNPLA3* I148M variant causes TG accumulation in the liver, which accelerates the progression of nonalcoholic fatty liver disease. HSC: Hepatic stellate cell.

fibrosis. Continuous research on the strategies for potential prevention or even curative intervention of nonalcoholic fatty liver fibrosis is warranted.

However, the specific mechanism of the *PNPLA3* I148M variant in the development and progression of nonalcoholic fatty liver fibrosis is still not clear. Up to now, abnormal activation of hepatic stellate cells (HSCs) characterized by retinoid loss was considered as the key contributor to fibrogenesis irrespective of the underlying disease[50]. The hedgehog (Hh) signaling pathway, consisting of Hh ligands, transmembrane protein receptors patched and smoothened, and Gli family transcription factors, is one of the most classic signaling pathways participating in the process of cell differentiation and proliferation during embryonic development[51,52].

Recent studies have shown a strong association between the Hh signaling pathway and the development and progression of nonalcoholic fatty liver fibrosis[53-55]. Guy *et al*[53] demonstrated that the activation of the Hh pathway paralleled histological severity of injury and liver fibrosis in a cross-sectional immunohistochemical study of a large cohort of biopsy-proven adult NAFLD patients. Moreover, a study of 56 children with NAFLD at the University of California, San Diego, United States, also showed significant associations between sonic Hh grade, the numbers of Hh-ligand-producing cells, Hh-responsive cells, and fibrosis stage[55]. In addition, it has been reported that the Hh signaling pathway regulates the HSC-to-myofibroblast transition[56,57], the expansion of hepatic progenitor cells[53,54], and the expression of cholangiocyte chemokines[58,59]. Meanwhile, cholangiocytes and hepatic progenitor cells can activate the Hh signaling pathway by generating Hh ligands[59] and increasing the expression of Gli2[54] (a Hh-regulated target gene), which, in turn, activates HSCs. Based on the available evidence, it is speculated that cross-talk between the Hh signaling pathway and activated HSCs, as well as progenitor cells and cholangiocytes, forms a pro-fibrogenic network together and leads to excessive generation and deposition of ECM and eventually fibrogenesis. Accordingly, we hypothesize that the *PNPLA3* I148M variant promotes the development of fibrogenesis by activating the Hh signaling pathway, which, in turn, leads to the activation and proliferation of HSCs, and excessive generation and deposition of ECM (Figure 1). To test this hypothesis, future studies are needed to established *PNPLA3* I148M transgenic mouse models, which can be used to establish transgenic mouse models of nonalcoholic fatty liver fibrosis. With such models, the role of the *PNPLA3* I148M variant in nonalcoholic fatty liver fibrosis and the underlying mechanisms can be further explored. Consequently, the association between the *PNPLA3* I148M variant and the Hh signaling pathway, and the precise mechanisms at molecular, cellular and genetic levels by which the *PNPLA3* I148M variant participates in the development of fibrogenesis are expected to be elucidated, which will lay a theoretical foundation and provide valuable experimental data for the clinical management of nonalcoholic fatty liver fibrosis.

## CONCLUSION

The *PNPLA3* I148M variant is associated with NAFLD, but is predominant in women, not in men. The association may vary among different ethnic populations, but is not affected by the presence of metabolic syndrome. The *PNPLA3* I148M variant may promote the development of fibrogenesis by activating the Hh signaling pathway, which, in turn, leads to the activation and proliferation of HSCs, and excessive generation and deposition of ECM. Further studies are needed to understand the underlying mechanisms.

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