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Review Article

Decoding 17-Beta-hydroxysteroid Dehydrogenase 13: A Multifaceted Perspective on Its Role in Hepatic Steatosis and Associated Disorders

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Abstract

Chronic liver disease (CLD) represents a significant global health burden, with hepatic steatosis-associated disorders—such as metabolic dysfunction-associated steatohepatitis (MASH), alcoholic liver disease, and hepatitis C virus infection—being major contributors. Recent genome-wide association studies have identified the rs72613567:TA variant in the 17-beta-hydroxysteroid dehydrogenase 13 (*HSD17B13*) gene as a protective factor against the development and progression of these conditions. In this review, we summarized the current evidence surrounding the *HSD17B13* rs72613567 variant, aiming to elucidate its impact on CLD risk and outcomes, and to explore the potential mechanisms behind its hepatoprotective effects. The rs72613567:TA variant induces a splice donor site mutation, resulting in a truncated, non-functional HSD17B13 protein. Numerous studies have demonstrated that this loss-of-function mutation confers protection against the development of cirrhosis and hepatocellular carcinoma (HCC) in patients with MASH, alcoholic liver disease, and hepatitis C virus infection. Moreover, the rs72613567:TA variant has been associated with reduced liver enzyme levels and improved survival in HCC patients. Integrating this variant into genetic risk scores has shown promise in predicting the progression of fatty liver disease to cirrhosis and HCC. Furthermore, inhibiting *HSD17B13* expression through RNA interference and small molecule inhibitors has emerged as a potential therapeutic strategy for MASH. However, the precise molecular mechanisms underlying the hepatoprotective effects of the *HSD17B13* rs72613567 variant remain to be fully elucidated. Future research should focus on clarifying the structure-function relationship of *HSD17B13* and its role in liver pathophysiology to facilitate the development of targeted therapies for CLD associated with hepatic steatosis.

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Introduction

Chronic liver disease (CLD) represents a significant global health challenge, accounting for approximately two million deaths annually and placing increasing pressure on healthcare systems worldwide, both in industrialized and developing nations.[1] The impact of CLD is particularly pronounced among middle-aged populations, where it ranks as the fourth leading cause of mortality.[2] The most common causes of CLD include chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcoholic liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD). Historically, viral hepatitis, particularly HBV in Asian countries, has been the predominant cause of CLD. However, recent advances in treatment and management have shifted the global burden of liver disease towards MASLD.[3] One of the most severe sequelae of CLD is hepatocellular carcinoma (HCC), currently the fifth most common malignancy worldwide and the fourth leading cause of cancer-related mortality.[4–6] This underscores the critical importance of effective CLD management and prevention strategies to reduce liver-related morbidity and mortality.[7]

While several environmental risk factors, including smoking, polyaromatic hydrocarbons, vinyl chloride, and aflatoxin, contribute to CLD development, a strong genetic component is also present.[8–11] Numerous genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) associated with an increased risk of CLD and HCC.[12] Among the most robust and widely validated genetic determinants of CLD susceptibility are variants in genes involved in lipid metabolism and hepatic lipid accumulation.[13–17] In particular, the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*, also known as adiponutrin) rs738409 C>G (I148M) variant is associated with increased hepatic fat content and elevated risk of MASLD, ALD, and HCC. Variants in genes that regulate glucose and lipid metabolism—such as glucokinase regulator (hereinafter referred to as *GCKR*) rs1260326 T>C (P446L) and transmembrane 6 superfamily member 2

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(*TM6SF2*) rs58542926 C>T (E167K)—also contribute to CLD risk.[14–18]

In contrast, a novel loss-of-function mutation (rs72613567:TA) in the 17-beta-hydroxysteroid dehydrogenase 13 (*HSD17B13*) gene has been identified as a protective factor against MASLD, other chronic liver diseases, and HCC, especially in at-risk individuals.[19,20] This variant leads to a splice donor site mutation, resulting in a truncated, nonfunctional HSD17B13 protein. This discovery has sparked considerable interest in the role of the *HSD17B13* gene in CLD development and progression.

This review aimed to consolidate and critically analyze the existing knowledge surrounding the *HSD17B13* rs72613567 variant in patients with various hepatic disorders. Our objective was to provide a comprehensive overview of the mechanisms through which the HSD17B13 protein influences liver disease development and to explain how its truncation, caused by the rs72613567:TA splice mutation in the *HSD17B13* gene, may confer protective effects. By synthesizing and evaluating the available evidence, we endeavored to offer a nuanced understanding of the *HSD17B13* rs72613567 variant's impact on liver health. This knowledge may inform future research and clinical applications in CLD prevention and management, ultimately improving patient outcomes and advancing the field of hepatology.

HSD17B13: a liver-specific gene with implications in lipid metabolism and liver disease

The *HSD17B13* gene, located on chromosome 4q22.1, exhibits highly liver-specific expression.[21] Although identified as a liver lipid droplet (LD)-associated protein, the precise function of *HSD17B13* remains largely unknown. Generally, the 17β-hydroxysteroid dehydrogenase family catalyzes the interconversion between 17-keto- and 17-hydroxysteroids. While most HSD17B enzymes regulate the activity of lipid sex hormones, several members also participate in diverse metabolic processes, including fatty acid metabolism, cholesterol synthesis, and bile acid production.[22] Initially designated *SCDR9* after its cloning from a human liver cDNA library, *HSD17B13* is one of the most recently characterized members of the *HSD17B* family. Although it was originally thought to participate in sex hormone metabolism due to its structural similarity to *HSD17B11*, subsequent studies have shown that *HSD17B13* primarily contributes to liver-specific fatty acid metabolism within lipid droplets. LDs are organelles with a phospholipid monolayer surface covered by specific proteins and a neutral lipid core of triacylglycerol and sterol esters. In addition to their primary function of lipid storage, LDs are involved in various metabolic and cell signaling processes and are associated with numerous diseases, including dyslipidemia, atherosclerosis, metabolic syndrome, and MASLD.[23–26] Notably, increased *de novo* lipogenesis and abnormal LD accumulation are also involved in the pathogenesis of HCC.[27,28]

In the context of CLD, several LD-associated proteins have been identified as contributors to the pathogenesis of MASLD by influencing lipid metabolism pathways. Among these proteins, members of the perilipin family regulate the access of lipases and lipase co-factors to lipid substrates within LDs, thereby controlling lipolysis.[29–33] The cell death-inducing DFFA-like effector family of proteins also plays roles in hepatic LD biology.[34–37] Additionally, PNPLA3 is involved in the release of retinyl-palmitate, the storage form of retinol. Retinoids, which are metabolites of retinol, regulate gene transcription by binding to nuclear hormone receptors. Impaired PNPLA3 expression reduces retinol release from hepatic stellate cells (HSCs), the primary site of retinol storage and a key player in hepatic fibrogenesis. Similarly, *HSD17B13* exhibits retinol dehydrogenase (RDH) activity and functions as a binding protein for adipose triglyceride lipase (ATGL), facilitating the interaction between CGI-58 and ATGL on hepatocyte lipid droplets.[38–40] Its expression is induced by liver X receptor α via sterol regulatory element-binding protein 1c, a transcription factor crucial for lipid metabolism.[41] Overexpression of *HSD17B13* enhances ATGL and RDH-mediated lipolysis, resulting in increased lipid droplet accumulation in the liver. Similar to *PNPLA3*, *HSD17B13* can activate HSCs, contributing to hepatic fibrosis. The genetic variant *HSD17B13* rs72613567:TA leads to a loss of function in the *HSD17B13* gene and its enzymatic activity. Functional studies have shown that this variant produces a prematurely truncated, unstable protein with reduced enzymatic activity due to altered mRNA splicing. Consequently, impaired *HSD17B13* activity results in decreased retinoid and lipid droplet accumulation, offering protection against hepatic steatosis. Conversely, reduced HSC activation provides protection against liver fibrosis and the progression of chronic liver disease (Fig. 1).

The genetic interplay of *PNPLA3* and *HSD17B13* in liver disease progression

The rs738409 C>G SNP in the *PNPLA3* gene, which encodes the I148M protein variant, is recognized as the most significant genetic determinant of hepatic steatosis and MASLD. The I148M mutation impairs PNPLA3's retinyl-palmitate lipase activity, leading to increased lipid accumulation within HSCs. Consequently, these lipid-laden HSCs adopt a proinflammatory and profibrogenic phenotype, contributing to disease progression.[42] In addition, the I148M variant's loss of PNPLA3-mediated triglyceride hydrolase activity results in the accumulation of catalytically inactive PNPLA3 on LD surfaces, which strongly correlates with hepatic triglyceride deposition and MASLD progression.[43] Recent genome-wide association studies have not only confirmed *PNPLA3* as a significant risk factor for MASLD but have also highlighted substantial contributions from variants in other genes, notably *TM6SF2* and *HSD17B13*.[44] Both PNPLA3 and HSD17B13 proteins play crucial roles in retinol metabolism.[45] Consequently, the interaction between *HSD17B13* and *PNPLA3* variants has garnered increasing scientific attention. A study involving Japanese patients with MASLD demonstrated that carrying the *HSD17B13* rs6834314 G allele mitigated the previously reported hepatic fibrogenic effect associated with the *PNPLA3* rs738409 (I148M) GG genotype.[46] Further research revealed that carrying *HSD17B13* rs72613567:TA reduced the risk of cirrhosis development associated with *PNPLA3* rs738409:G in both sexes. However, the protective effect against subsequent HCC development was observed exclusively in males.[47] Moreover, the combined presence of the *PNPLA3* rs738409 minor allele and the *HSD17B13* rs72613567 major allele has been identified as a risk factor for HCV-related HCC.[48]

These findings collectively suggest that variants in the *HSD17B13* and *PNPLA3* genes may interact in the pathogenesis of both MASLD and HCV-related HCC, underscoring the complex genetic landscape underlying these hepatic disorders. This intricate interplay between genetic variants highlights the need for comprehensive genetic profiling in patients with CLD, as it may provide valuable insights into disease progression and potential therapeutic targets.

HSD17B13 genetic variants: protective effects and implications in chronic liver diseases

Extensive research on CLD has explored the interplay be-

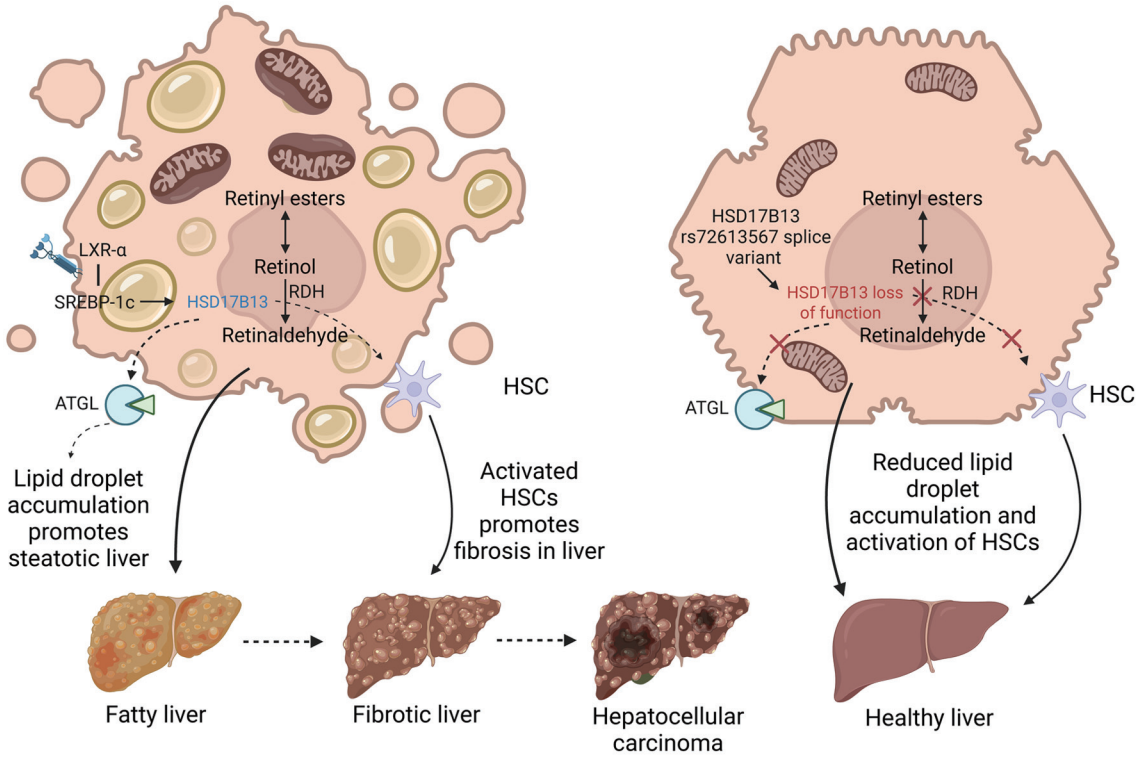

Fig. 1. The overexpression of *HSD17B13* leads to increased lipid droplet accumulation in the liver by enhancing the activities of ATGL and RDH. Concurrently, the activation of hepatic stellate cells contributes to hepatic fibrosis. The genetic variant *HSD17B13* rs72613567:TA results in a loss of function of the HSD17B13 gene and its enzymatic activities, providing protection against liver fat accumulation, fibrosis, and the progression of chronic liver disease. ATGL, adipose triglyceride lipase; HSC, hepatic stellate cell; HCC, hepatocellular carcinoma; LXR-α, liver X receptor α; SREBP-1c, sterol regulatory element-binding protein 1c.

tween the *HSD17B13* rs72613567 variant and *PNPLA3* rs738409 and delved into the specific role of *HSD17B13*, with numerous studies dedicated to elucidating its distinct contributions to the disease. This intensified scientific interest was catalyzed by a pivotal 2014 study that demonstrated significantly elevated HSD17B13 protein expression in the hepatocytes of patients with MASLD.[26] Subsequently, a comprehensive U.S. investigation analyzed exome sequence data from 46,544 individuals to explore correlations between *HSD17B13* SNPs and serum transaminase levels.[19] Notably, the authors identified a novel association between the splice variant rs72613567:TA in *HSD17B13* (allele frequency 26%) and reduced alanine aminotransferase (ALT) concentrations.[19] In addition, the rs72613567:TA variant demonstrated a significant protective effect against liver diseases, with an allele dose-dependent reduction in the risk for both ALD and MASLD. Specifically, the risk reduction for ALD was 42% among heterozygotes and 53% among homozygotes, while for MASLD, it was 17% among heterozygotes and 30% among homozygotes. Moreover, the variant was associated with a decreased risk of metabolic dysfunction-associated steatohepatitis (MASH), though no significant effect on steatosis was observed. Furthermore, the rs72613567:TA variant showed a nominal association with reduced risk of cirrhosis in both alcoholic and non-alcoholic liver disease. In patients with ALD, the risk reduction was 42% among heterozygotes and 73% among homozygotes, while for MASLD, it was 26% among heterozygotes and 49% among homozygotes.[19] In summary, growing evidence indicates that the *HSD17B13* rs72613567:TA variant is associated with a reduced risk of MASLD and ALD. This variant is also linked to lower ALT concentrations and a decreased risk of progression to MASH and cirrhosis.

Further exploration of *HSD17B13* genetic variants revealed another significant polymorphism, rs143404524.[49] This SNP, a deletion and frameshift mutation, results in the production of a truncated protein, likely conferring a loss of function. Notably, the rs143404524 variant had a higher prevalence in African-American individuals and was associated with a reduced risk of CLD.[49] Additionally, rs62305723, located downstream of *HSD17B13*, demonstrated strong linkage disequilibrium with rs72613567 (D′ = 0.995, r^2 = 0.93) and exhibited a similar pattern of association with MASLD histology and liver enzymes.[45] However, these two additional *HSD17B13* SNPs require extensive validation before being considered liver-protective, akin to the *HSD17B13* rs72613567 variant.

The pivotal role of the *HSD17B13* rs72613567 variant in MASLD predisposition was corroborated in a case-control study of 429 patients with histologically confirmed MASLD and 180 controls.[50] This study revealed that the minor TA allele significantly reduced the risk of MASH and fibrosis. Moreover, this splice variant correlated with decreased HSD17B13 levels in hepatocytes. The protective effect of the *HSD17B13* rs72613567 polymorphism against hepatic fibrosis has been extensively validated across numerous studies and diverse geographical regions.[51–55] These investigations have included patients with MASLD, ALD, and HCV infection. The comprehensive nature of this evidence underscores the potential clinical significance of this genetic variant in predicting and potentially managing liver disease progression. Interestingly, a large-scale U.S. study involving 9,342 Hispanic Latinos demonstrated an association between the *HSD17B13* rs72613567:TA variant and lower rates of suspected MA-

SLD, as well as reduced Fibrosis-4 scores.[56] These findings substantially reinforce the hypothesis that the *HSD17B13* rs72613567:TA variant may exert antifibrogenic effects.[56]

While the precise molecular mechanisms behind the effects of *HSD17B13* SNPs against MASLD remain unclear, emerging evidence provides valuable insights into their hepatoprotective action. The exact pathways through which *HSD17B13* SNPs confer protection against MASLD are still under investigation. However, current evidence suggests that this genetic variant primarily acts by reducing hepatocyte ballooning and portal inflammation.[57] This hypothesis is supported by a multicenter study conducted across Europe, which examined 586 patients diagnosed with Wilson's disease.[58] The study found a significant association between the *HSD17B13* rs72613567:TA minor allele and a milder hepatic disease presentation in these patients.[58] This finding not only supports the broader hepatoprotective effects of this genetic variant but also highlights its potential clinical relevance in diverse liver pathologies.

HSD17B13 in hepatocellular carcinoma: From gene expression to genetic variants and clinical implications

Recent investigations have elucidated the potential significance of the *HSD17B13* gene in advanced hepatic pathologies, particularly in HCC. A comprehensive transcriptomic analysis revealed a profound downregulation of *HSD17B13* mRNA expression in HCC specimens compared to adjacent non-neoplastic tissue, with a fold change exceeding 30.[59] This observation was further substantiated by a quantitative proteomic study comparing global proteome profiles between HCC with multiple or single lesions and their respective noncancerous counterparts.[60] Notably, the HSD17B13 protein was downregulated in patients with multiple HCC lesions but not in those with solitary lesions, suggesting that HSD17B13 may serve as a potential biomarker for differentiating primary HCC with single and multiple lesions. A study focusing on hepatitis B virus (HBV)-related HCC found that diminished HSD17B13 expression in peritumoral tissue was associated with worse recurrence-free survival (hazard ratio: 0.41, 95% confidence interval [CI]: 0.20–0.83, $p < 0.05$).[61] Mechanistically, HSD17B13 was found to impede G1/S cell cycle progression in HCC cells, suggesting a potential pathway through which HSD17B13 may influence clinical outcomes in HCC patients. These findings are consistent with recent studies demonstrating that HSD17B13 expression is downregulated in HCC samples, and that elevated HSD17B13 levels correlate with a favorable prognosis in HCC.[62–64]

At the genetic level, a large-scale European study examined the association between the *HSD17B13* rs72613567 variant and HCC risk in a cohort of 3,315 patients with HCC and cirrhosis, compared to 33,337 healthy controls.[20] The study revealed that the TA allele of the rs72613567 variant was significantly less prevalent in patients with ALD and HCC compared to healthy controls (odds ratio [OR]: 0.64, 95% CI: 0.46–0.87, $p = 0.005$). Notably, the protective effect of the TA allele against HCC was consistently observed in patients with MASLD (OR: 0.64, 95% CI: 0.49–0.83, $p < 0.05$) and chronic HCV infection (OR: 0.71, 95% CI: 0.60–0.85, $p < 0.05$). Two additional studies demonstrated that the presence of the TA allele was associated with a reduced risk of cirrhosis (OR: 0.79, 95% CI: 0.72–0.88, $p < 0.05$) and HCC (OR: 0.77, 95% CI: 0.68–0.89, $p < 0.05$) in individuals with alcohol use disorder.[47,48] In HCV-infected individuals, the major allele of *HSD17B13* rs72613567 was identified as an independent risk factor for HCC (OR: 2.00, 95% CI: 1.23–3.26, $p < 0.05$) when coexisting with the *PNPLA3* minor allele and a history of alcohol abuse.[48] This finding underscores the potential interplay between genetic factors and environmental exposures in modulating HCC risk.

A recent study involving 111,612 individuals from the Danish general population, including 497 patients with cirrhosis and 113 with HCC, demonstrated that the *HSD17B13* rs72613567 TA allele reduced cirrhosis and HCC risk and conferred protection against liver-related mortality both in the general population and among patients with cirrhosis.[65] The authors also demonstrated that the ALT-lowering effect of rs72613567:TA was amplified by increasing adiposity, alcohol consumption, and genetic risk of fatty liver disease. Conversely, another study conducted with 487 European patients with portal hypertension caused by viral hepatitis or ALD failed to demonstrate a protective association against hepatic decompensation and mortality.[66] A recent meta-analysis confirmed the protective effect of rs72613567 on HCC through pooled analysis (OR: 0.64, 95% CI: 0.53–0.77, $p < 0.05$), corroborating its protective role in other categories of liver diseases, including any liver disease (OR: 0.73, 95% CI: 0.61–0.87), cirrhosis of any etiology (OR: 0.81, 95% CI: 0.76–0.88, $p < 0.05$), ALD (OR: 0.82, 95% CI: 0.74–0.90, $p < 0.05$), and alcohol-related cirrhosis (OR: 0.77, 95% CI: 0.65–0.90, $p < 0.05$).[67] The protective rs72613567 variant has not only been associated with reduced risk of HCC but also with a survival benefit, as shown in a sample of 439 UK Biobank patients with MASLD and ALD as dominant etiologies.[68] To investigate whether the *HSD17B13* rs72613567 variant plays a role in the development or progression of chronic liver disease without fatty liver, we conducted a case-control study focusing on HBV etiology and found no association with HCC development or prognosis in HBV-infected individuals.[69] Based on current evidence, the *HSD17B13* rs72613567 TA allele appears to confer specific protection against the development and progression of liver diseases associated with hepatic steatosis, including MASLD, ALD, and HCV infection, but not against other CLD. A summary of studies investigating the association of the protective *HSD17B13* rs72613567 variant with CLD is presented in Table 1.

Integrating *HSD17B13* rs72613567 into genetic risk scores: Advancing predictive models for chronic liver disease progression

The identification of the *HSD17B13* rs72613567 variant as hepatoprotective, confirmed by rigorous scientific inquiry, has sparked two seminal studies that integrate this genetic marker into predictive models for CLD progression to cirrhosis and HCC. These investigations represent a significant advancement in hepatology and genetic risk assessment. In one Danish study, researchers developed a genetic risk score (GRS) for fatty liver disease, specifically evaluating the risk of progression to cirrhosis and HCC.[70] This investigation combined their patient cohort with 334,691 individuals from the UK Biobank, creating a robust sample size for analysis. The GRS, which incorporated three genetic variants in the *PNPLA3* (I148M), *TM6SF2* (E167K), and *HSD17B13* (rs72613567) genes, demonstrated a remarkable predictive capacity. Notably, individuals from the general population carrying specific combinations of these variants exhibited up to a 12-fold increased risk of cirrhosis and a 29-fold elevated risk of HCC. These findings highlight the potential of genetic profiling to stratify population-level risk for severe liver disease outcomes, representing a paradigm shift in preventive hepatology. A parallel investigation focused on patients diagnosed with MASLD (n = 160,979) within a larger cohort of 423,252

Table 1. Summary of key studies on the association between the *HSD17B13* rs72613567 variant and chronic liver diseases

Study	Sample size	Population	Key findings
Abul-Husn *et al*. (2018)[19]	83,717	USA (Multi-ethnic)	rs72613567:TA associated with decreased ALT and reduced risk of ALD and MASLD, including cirrhosis
Ma *et al*. (2019)[45]	1,085	USA (Caucasian)	rs72613567:TA linked to favorable histological features in MASLD
Pirola *et al*. (2019)[50]	609	Argentina (Hispanic)	rs72613567:TA reduces risk of MASH and fibrosis
Luukkonen *et al*. (2020)[51]	202	Europe (Caucasian)	rs72613567:TA increases phospholipids and protects against fibrosis in MASLD
Chen *et al*. (2018)[52]	1,536	China (Han)	rs72613567:TA associated with reduced ALD risk
About *et al*. (2019)[53]	80	Europe (Caucasian)	rs72613567:TA associated with less liver fibrosis in HCV patients
Israelsen *et al*. (2019)[54]	325	Denmark	rs72613567:TA linked to lower fibrosis stage in ALD (not statistically significant)
Ting *et al*. (2020)[55]	165	Southeast Asia (Multi-ethnic)	rs72613567:TA associated with lower odds of MASH and liver-related complications
Kallwitz *et al*. (2019)[56]	9,342	USA (Hispanic)	rs72613567:TA linked to lower rates of suspected MASLD and lower FIB-4 scores
Ferenci *et al*. (2019)[58]	586	Europe (Caucasian)	rs72613567:TA associated with milder Wilson's disease
Stickel *et al*. (2020)[47]	6,171	Europe (Caucasian)	rs72613567:TA associated with lower risk of cirrhosis and HCC in alcohol misusers
Yang *et al*. (2019)[20]	36,652	Europe (Caucasian)	rs72613567:TA protective against HCC development in ALD patients
De Benedittis *et al*. (2018)[48]	440	Europe (Caucasian)	Combined PNPLA3 minor allele:G and HSD17B13 major allele:T increase HCV-related HCC risk
Demirtas *et al*. (2020)[69]	323	Türkiye	rs72613567 not associated with HCC in HBV patients
Gellert-Kristensen *et al*. (2020)[65]	111,612	Denmark	rs72613567:TA reduces cirrhosis and HCC risk, lowers liver-related mortality
Scheiner *et al*. (2021)[66]	487	Europe (Caucasian)	rs72613567 not protective against hepatic decompensation and mortality
Innes *et al*. (2020)[68]	439	UK	rs72613567 associated with reduced HCC risk and improved survival

ALD, alcoholic liver disease; ALT, alanine aminotransferase; FIB-4, fibrosis-4 index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

UK Biobank participants.[71] This study developed a more comprehensive GRS utilizing five genetic variants: *PNPLA3* rs738409 C/G, *TM6SF2* rs58542926 C/T, *GCKR* rs1260326 T/C, *MBOAT7* rs641738 C/T, and *HSD17B13* rs72613567:TA. The resulting five-parameter GRS significantly amplified MASLD's effect on various disease outcomes. Specifically, the GRS was associated with increased odds ratios for cirrhosis (OR: 2.77, 95% CI: 2.29−3.36), HCC (OR: 1.59, 95% CI: 1.28−1.98), other liver diseases (OR: 2.09, 95% CI: 1.95−2.24), cardiovascular diseases (OR: 1.39, 95% CI: 1.34−1.44), renal diseases (OR: 1.56, 95% CI: 1.48−1.65), and malignancies (OR: 1.07, 95% CI: 1.05−1.10). These two GRS models exemplify the clinical potential of incorporating *HSD17B13* rs72613567 into risk assessment strategies. By integrating this variant with other established genetic markers, these scores offer a more refined and accurate approach to predicting liver disease progression. This advancement in genetic risk stratification holds profound implications for personalized medicine in hepatology, potentially enabling early intervention strategies and tailored patient management based on individual genetic profiles.

HSD17B13 as a therapeutic target: From genetic insights to novel treatment strategies

The management of MASLD remains primarily focused on lifestyle modifications, with the primary objectives of achieving and maintaining significant weight loss and addressing associated metabolic comorbidities. Recent advancements in pharmacological interventions have yielded promising results, notably the approval of a thyroid hormone receptor beta-selective agonist by the Food and Drug Administration for the treatment of MASH, which has demonstrated efficacy in reducing fibrosis.[72] Concurrently, numerous phase 2 and 3 clinical trials are underway, investigating a variety of therapeutic agents with distinct mechanisms of action, all aimed at mitigating fibrosis in patients with MASH. In this context, the *HSD17B13* gene has emerged as a potential therapeutic tar-

get, supported by both *in vivo* and *in vitro* studies indicating that suppression of *HSD17B13* expression yields favorable outcomes in MASLD. A pilot study from Japan confirmed this hypothesis, demonstrating that reductions in liver stiffness measurements were independently associated with weight loss, particularly in individuals carrying the *HSD17B13* rs6834314 protective variant.[73] Additionally, two large cohort studies revealed that the protective effect of the *HSD17B13* rs72613567 variant on liver fibrosis risk was particularly significant in patients with traditional risk factors, such as obesity, advanced age, female sex, and diabetes mellitus.[65,74] These findings suggest that individuals at higher risk for MASLD progression and related comorbidities may benefit most from therapies targeting *HSD17B13*.

The inhibition of HSD17B13 expression primarily utilizes RNA interference (RNAi) therapeutic approaches. RNAi is a biological process in which small RNA molecules suppress protein translation by binding to complementary messenger RNAs. RNAi-based therapeutics, particularly those utilizing small interfering RNAs (siRNAs), represent a developing strategy for inhibiting specific disease-associated genes. Recent data from phase 1/2 clinical trials on pioneering siRNA therapeutics designed to downregulate *HSD17B13* expression have demonstrated dose-dependent reductions in transaminases and liver stiffness, with no reported treatment-related serious adverse events.[75] In addition to siRNA-based therapies, small molecule inhibitors of HSD17B13 are also being investigated. An experimental drug (INI-678) has shown promise in reducing key biomarkers of liver fibrosis, including α-smooth muscle actin and type 1 collagen, along with changes in the metabolome, in a human liver cell-based 3D liver-on-a-chip model.[76] Using human cell lines and primary mouse hepatocytes, a selective HSD17B13 inhibitor, BI-3231, demonstrated promising outcomes by significantly enhancing hepatocyte proliferation, cell differentiation, and lipid homeostasis. This was achieved by mitigating the lipotoxic effects of palmitic acid in hepatocytes.[77] These findings underscore the potential role of HSD17B13 in modulating inflammation and fibrosis in MASLD. Another preclinical study explored the effects of HSD17B13 antisense oligonucleotide (ASO) in an *in vivo* model of MASH-like hepatic fibrosis.[78] The findings revealed that while *HSD17B13* gene expression was suppressed and hepatic steatosis was modulated, there was no significant impact on fibrosis.[78]

While these preliminary results are encouraging, it is important to note that these studies are still in the early stages of clinical development. The long-term effects of *HSD17B13* inhibition on MASLD progression require further investigation and longer observation periods. Should these therapeutic approaches prove successful, future research may explore their applications in managing other liver diseases associated with hepatic steatosis. It is also crucial to recognize that a single SNP is unlikely to play a major role in the development and progression of MASH, given the complex and multifactorial pathophysiology of the condition. While genetic studies provide preliminary evidence that *HSD17B13* is involved in the disease process, the potential impact of ethnicity on the associations between *HSD17B13* variants and chronic liver disease remains underexplored. This warrants further investigation, particularly since the HSD17B13:TA allele is most prevalent in East Asians (27–40%) and Europeans (22–31%), while being less common in Hispanic Americans (9%) and African (1–8%) populations.[65]

In summary, the evolving landscape of MASLD management encompasses both established lifestyle interventions and emerging pharmacological strategies. Targeting *HSD17B13* through RNAi and small molecule inhibitors represents a promising therapeutic avenue, particularly for high-risk individuals. However, continued research and long-term clinical trials are essential to fully determine the efficacy and safety of these novel approaches in the treatment of MASLD and related liver disorders.

Conclusions

This comprehensive review synthesizes the current evidence on the impact of the HSD17B13 rs72613567:TA variant on the risk and progression of CLD associated with hepatic steatosis. The rs72613567 variant induces a loss-of-function mutation in the HSD17B13 enzyme, a liver-specific lipid droplet protein that plays a pivotal role in regulating hepatic lipid homeostasis. This hepatoprotective genetic variant produces protein products devoid of enzymatic activity, thereby altering the normal function of HSD17B13. Intriguingly, HSD17B13 expression exhibits a dichotomous pattern in different liver pathologies. Downregulation of *HSD17B13* has been observed in HCC tissues, while paradoxically, upregulated expression of *HSD17B13* has demonstrated a protective effect against both CLD and HCC. This apparent contradiction underscores the complex interplay between *HSD17B13* expression and liver pathophysiology. The malleability of HSD17B13's enzymatic activity in response to large domain truncations and deletions presents an intriguing avenue for therapeutic intervention. This susceptibility to structural modifications implies the possibility of modulating the enzyme's activity through targeted gene expression interference or direct inhibition using synthetic small molecules.[79] However, translating this promising concept into clinical practice requires further investigation. To fully realize the therapeutic potential of HSD17B13 modulation, two critical steps are necessary. Firstly, a comprehensive elucidation of HSD17B13's structure is essential to identify potential targets for intervention. Secondly, a thorough characterization of its biochemical function is crucial to understanding the downstream effects of its modulation. These steps are key to clarifying the precise role of HSD17B13 in the development and prognosis of CLD associated with hepatic steatosis. In conclusion, while the HSD17B13 rs72613567:TA variant presents a promising target for therapeutic intervention in CLD, further research is needed to fully elucidate its structure-function relationship and its complex role in liver pathophysiology. This knowledge will be instrumental in developing targeted therapies that could potentially alter the course of CLD associated with hepatic steatosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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