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Review

Genetic Variants in Liver Cirrhosis: A Review of Classification, Mechanisms, and Clinical Relevance

CIRRHOSIS

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Abstract

Background/Objectives: Cirrhosis represents a significant global health burden, driven by diverse etiologies including viral hepatitis, alcohol-associated liver disease, and non-alcoholic fatty liver disease (NAFLD). While environmental factors play a key role, individual susceptibility and disease progression vary widely, underscoring the importance of genetic predisposition. This review systematically examines the influence of inherited genetic variations on cirrhosis development and clinical outcomes, aiming to provide a mechanistic framework for understanding these associations and their implications for personalized hepatology. **Methods**: We conducted a comprehensive literature review of studies investigating genetic contributors to cirrhosis, focusing on germline variants with established or potential clinical relevance. Key databases (PubMed, Scopus, and Web of Science) were searched for peer-reviewed articles published up to [insert date]. Genetic variants were categorized into four functional groups: ethnicity-associated polymorphisms, liver enzyme–related genes, immune-modulating variants, and metabolism-related genetic changes. Polygenic risk scores and genotype-based prognostic tools were also evaluated. **Results**: Our analysis highlights critical genes, including *PNPLA3*, *HSD17B13*, and *TM6SF2*, which influence cirrhosis risk through mechanisms such as lipid metabolism dysregulation and hepatic inflammation. Ethnicity-specific polymorphisms and immune-related variants further modulate disease susceptibility. Polygenic risk scores demonstrate promise in stratifying patients, though clinical utility requires further validation. **Conclusions**: Genetic factors significantly contribute to cirrhosis heterogeneity, offering insights into individualized risk assessment and therapeutic targeting. Future research should prioritize translating these findings into actionable clinical strategies, integrating genetic profiling into hepatology practice. This review provides a structured foundation for understanding the genetic architecture of cirrhosis and its implications for precision medicine.

Keywords: genetic polymorphisms; liver cirrhosis; PNPLA3; HSD17B13; polygenic risk scores

Introduction

Cirrhosis represents the final common pathway of chronic liver injury and remains a major contributor to global morbidity and mortality [1]. It is characterized by progressive fibrosis, regenerative nodule formation, and the eventual disruption of normal hepatic architecture and function [1]. Common etiologies include chronic viral hepatitis (hepatitis B and C), excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD), autoimmune liver diseases, cholestatic disorders, and metabolic overload states such as hemochromatosis and Wilson's disease [2,3]. While

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cirrhosis may initially remain asymptomatic, its progression from compensated to decompensated stages marks a significant decline in quality of life, with manifestations including jaundice, gastrointestinal bleeding, ascites, encephalopathy, and increased risk of hepatocellular carcinoma [1,4].

Diagnosis typically relies on clinical evaluation supported by biochemical tests such as liver function panels, coagulation markers, and serological profiles for viral and metabolic etiologies [4]. Non-invasive fibrosis assessment tools—including the AST to Platelet Ratio Index (APRI), Fibrosis-4 score, and transient elastography—aid in detecting advanced liver disease [4]. Although liver transplantation remains the only definitive curative option in selected patients, medical management focuses on addressing the underlying cause, preventing complications, and delaying disease progression [1,5].

Despite well-recognized environmental and lifestyle risk factors, it is increasingly evident that individuals with similar exposures exhibit differing susceptibilities to cirrhosis, suggesting a strong genetic component in disease onset and progression [6]. Recent genome-wide association studies (GWAS) and candidate gene investigations have identified key variants associated with liver disease risk, particularly in the setting of NAFLD, alcoholic liver disease, and autoimmune liver disorders [6–9]. Among the most studied are missense variants in *PNPLA3*, *TM6SF2*, and *HSD17B13*, which modulate steatosis, inflammation, and fibrosis [8,9].

Advances in genetic epidemiology have also enabled risk stratification through polygenic risk scores and the recognition of mosaic chromosomal alterations (mCAs), further refining predictive models in chronic liver disease [10,11]. Genetic profiling, including *PNPLA3* genotyping, may enhance prognostication and inform therapeutic prioritization [11]. Importantly, some variants such as loss-of-function mutations in *HSD17B13* may confer protection against disease progression, presenting potential targets for future therapeutic intervention [12].

This review aims to provide a structured classification of genetic variants implicated in cirrhosis pathogenesis, categorized across four mechanistic domains: ethnicity-related polymorphisms, liver enzyme–associated genes, immune-mediated variants, and metabolism-related loci. By synthesizing current evidence, we seek to outline the mechanistic roles and clinical relevance of these variants, and explore their application in risk assessment, prognosis, and potential genotype-guided therapy.

Rationale for a Genetic Framework in Cirrhosis

Cirrhosis develops in response to chronic liver injury, yet not all individuals exposed to known risk factors, such as alcohol use or metabolic dysfunction, progress to advanced fibrosis. This clinical variability strongly suggests the involvement of inherited genetic factors in determining disease susceptibility and trajectory [6]. Emerging genomic studies have demonstrated that specific genetic variants can influence liver injury, fibrosis progression, and the transition from steatosis to steatohepatitis, underscoring the importance of incorporating genetic insight into cirrhosis pathogenesis [6,8,9].

Multiple studies have identified key genetic loci associated with cirrhosis, with the most consistent findings involving variants in *PNPLA3*, *TM6SF2*, *MBOAT7*, and *HSD17B13* [8,9]. These genes impact diverse processes including lipid metabolism, hepatocellular injury, and fibrogenesis. Importantly, the presence of these variants not only increases disease risk but also appears to modify disease phenotype and severity, reinforcing the need for genotype-based risk models [8,9]. These loci also demonstrate pleiotropic effects across a range of hepatic and systemic phenotypes, as supported by phenome-wide association studies (PheWAS), reinforcing the interconnected nature of liver disease and systemic metabolism [21].

The cumulative effect of genetic susceptibility can now be quantified using polygenic risk scores, which combine multiple loci to stratify patients according to their inherited risk [10]. This approach has been further refined by integrating mosaic chromosomal alterations (mCAs), which reflect post-zygotic genomic instability and have been independently associated with increased cirrhosis risk [10]. Such integration of germline and somatic genomic markers may enhance prediction models beyond

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traditional clinical parameters. However, the clinical application of polygenic risk scores remains limited by variability in algorithms, lack of ancestry calibration, and incomplete validation across real-world cohorts [63].

From a prognostic standpoint, genotyping for *PNPLA3* and related loci may allow earlier identification of high-risk individuals, even in the absence of advanced disease [11]. Moreover, certain variants may influence treatment response or offer protective effects; for example, a protein-truncating mutation in *HSD17B13* has been associated with reduced risk of progression to steatohepatitis and cirrhosis, suggesting its potential utility as a therapeutic target [12].

Taken together, these findings highlight the need for a structured framework to classify genetic variants relevant to cirrhosis. Such a model can support translational application in hepatology by informing screening, prognosis, and future personalized interventions.

Classification of Genetic Variants in Cirrhosis Pathogenesis

Recent studies have demonstrated that cirrhosis susceptibility is shaped by a wide range of inherited variants that influence lipid metabolism, immune modulation, hepatocellular integrity, and population-specific risk profiles [6,8]. While many individual variants have been described, their interpretation remains fragmented in the literature, complicated by inconsistencies in study design, population bias, and variable replication of genetic signals [13]. Most reviews focus on specific genes or disease subtypes. In this review, we propose a novel, clinically oriented classification of genetic risk factors for cirrhosis into four mechanistic domains: ethnicity-based polymorphisms, liver enzyme–related variants, immune-mediated genetic changes, and metabolism-associated genes. These categories are developed based on functional roles observed across current evidence and aim to support translational application in diagnosis, prognostication, and therapy [9,70]. The corresponding framework is summarized in Table 1.

Table 1. Mechanistic Classification of Genetic Variants in Cirrhosis Pathogenesis.

Classification Domain	Representative Genes	Primary Mechanism	Associated Liver Conditions
Ethnicity-based variants	*MBOAT7*, *HFE*, CNVs	Population-level susceptibility differences	Hemochromatosis, NAFLD
Liver enzyme–related variants	*HSD17B13*, *ALPL*, *TM6SF2*	Modulation of hepatocellular injury markers	NAFLD, alcohol-related liver disease
Immune-related genetic variants	*HLA*, *TERT*, *PTPN22*	Autoimmunity, telomere maintenance	Autoimmune hepatitis, cryptogenic cirrhosis
Metabolism-related variants	*PNPLA3*, *ADH1B*, *CIDEB*	Lipid metabolism, alcohol metabolism	NAFLD, NASH, alcoholic liver disease

Ethnicity-Based Genetic Variants

Genetic variation is not uniformly distributed across populations, and ethnicity-specific polymorphisms can significantly influence the risk, phenotype, and progression of liver diseases. Multiple studies have highlighted the importance of considering ethnic background when evaluating genetic contributions to cirrhosis [14,15]. Population-specific copy number variations (CNVs), observed in Israeli, African, and Latin American populations, may represent benign structural variants or may confer increased susceptibility to chronic liver disease depending on the context [14,16,22]. These CNVs often overlap with genes involved in immune regulation, lipid metabolism, and iron transport — pathways critical to hepatic homeostasis. Notably, ethnic variation also shapes

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the penetrance of variants such as PNPLA3, which may confer significant fibrosis risk even in non-obese individuals in certain populations [71].

One notable example is the *MBOAT7* rs641738C>T variant, which has been associated with liver fibrosis and NAFLD predominantly in individuals of European ancestry [15]. Although its role in hepatocellular carcinoma (HCC) remains inconsistent across populations, the variant appears to modulate hepatic lipid remodeling, contributing to fibrogenesis. Clinically, this suggests that patients of European descent with NAFLD may benefit from targeted genotyping for *MBOAT7*, particularly in cases of ambiguous fibrosis progression or family history of advanced liver disease.

Similarly, mutations in the *HFE* gene—most notably C282Y and H63D—have varying prevalence across ethnic groups. While rare in Jordanian Arabs, these mutations are common among Northern Europeans and contribute to hereditary hemochromatosis, a known cause of secondary cirrhosis [14–16]. In clinical practice, ethnic-specific screening for *HFE* variants may support early diagnosis of iron overload syndromes in high-risk populations and prompt preventive phlebotomy to avoid irreversible liver injury.

The differential distribution of Mendelian disease variants further underscores the clinical relevance of ethnic background in cirrhosis risk assessment [17,18]. For example, studies in African ancestry populations have revealed distinct linkage disequilibrium patterns, facilitating fine mapping of liver-related loci [18]. However, the continued use of race and ethnicity as proxies in genetic research, despite their biological ambiguity, necessitates caution and reinforces the need for ethically grounded study designs [19].

From a translational standpoint, these findings argue for the integration of **ancestry-aware genetic screening panels**, especially in regions with genetically admixed populations. Validation of these variant effects across populations remains essential to avoid misclassification of genetic risk [20].

Liver Enzyme–Related Genetic Variants

Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) serve as crucial biochemical markers of hepatic injury, inflammation, and cholestasis. While elevations in these enzymes often guide the diagnosis and monitoring of liver disease, interindividual variability in baseline enzyme levels can result from inherited genetic factors. These enzyme-modifying variants may contribute to under-recognition of disease in some patients or signal an increased risk of fibrosis progression in others, independent of traditional risk factors [23,24]. Recent Mendelian randomization studies have also linked hematologic traits and inflammatory markers to variation in liver enzyme levels, reinforcing their systemic genetic modulation [25,32].

A notable protective variant is the **HSD17B13 rs72613567:TA** splice mutation, which has been associated with **lower ALT levels** and a **reduced risk of chronic liver disease**, particularly in patients with steatosis [22,26,33]. Clinically, its presence may suggest a more benign course in NAFLD and NASH, and it could influence decisions regarding surveillance intensity or treatment escalation.

Another important variant is **TM6SF2 rs58542926**, which impacts lipid handling in hepatocytes. While it predisposes to hepatic steatosis and elevated ALT/AST levels, it paradoxically results in lower circulating LDL and triglycerides [24,36]. This biochemical dissociation may obscure cardiovascular risk while exacerbating liver disease — a phenomenon relevant for both hepatologists and primary care providers.

Genetic variants in ***ALPL***, the gene encoding tissue-nonspecific alkaline phosphatase, have been associated with altered ALP levels even in the absence of cholestatic disease. In particular, rare coding mutations have been linked to abnormal bone and liver profiles, with implications for the diagnosis of conditions like adult hypophosphatasia [27,31]. Persistent ALP elevation without imaging evidence of biliary obstruction may warrant targeted genetic evaluation in selected cases. Genome-wide studies have identified loci associated with elevated ALP and metabolic outcomes, including diabetes risk, highlighting the broader clinical relevance of ALPL variants [28,29].

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Variants near ***PPP1R3B*** and in ***GCKR*** also modulate liver enzyme levels and hepatic fat content. For instance, *GCKR rs780094* is associated with elevated ALT and triglycerides but lower fasting glucose, influencing both metabolic and hepatic risk [30,34]. These patterns underscore the value of integrating genomic data with routine biochemistry for more nuanced interpretation of liver profiles.

Furthermore, the **PNPLA3 I148M** variant, while often associated with normal or mildly elevated transaminases, confers a **substantial increase in fibrosis and cirrhosis risk**, suggesting that enzyme levels alone may not reflect disease severity in genetically susceptible individuals [24,37,71].

Table 2. Liver Enzyme–Modifying Genetic Variants and Their Clinical Implications.

Gene	Variant	Enzyme Affected	Effect	Clinical Implication
HSD17B13	rs72613567:TA	ALT	↓ ALT, protective effect in steatosis	Lower risk of progression to steatohepatitis or cirrhosis [22,33]
TM6SF2	rs58542926	ALT, AST	↑ liver enzymes, ↑ fat, ↓ blood lipids	Misleading cardiovascular profile; higher liver risk [24,36]
ALPL	Rare coding variants	ALP	Abnormal levels without cholestasis	May mimic liver disease; consider bone disorders [27,31]
GCKR	rs780094	ALT	↑ ALT, ↑ triglycerides, ↓ fasting glucose	Links metabolic syndrome with hepatic fat [34]
PNPLA3	rs738409 (I148M)	Often normal ALT	↑ risk of fibrosis despite mild labs	Enzyme levels underestimate severity [24,37]

Immune-Related Genetic Variants

Chronic inflammation is central to the progression of most liver diseases, and immune-mediated mechanisms are increasingly recognized as major contributors to cirrhosis. Genetic variants that affect immune tolerance, antigen presentation, and cytokine signaling can predispose individuals to persistent hepatic inflammation, autoimmunity, or aberrant responses to environmental insults. These immune-related variants do not operate in isolation but often interact with other metabolic or viral factors to accelerate fibrotic progression [39,40]. Epigenetic mechanisms such as DNA methylation may further modulate immune gene expression in this setting, influencing inflammation severity and fibrosis risk [38,42].

A key genomic region involved in immune modulation is the **human leukocyte antigen (HLA) complex**, particularly **HLA class II genes** such as *HLA-DRB1*, *DQA1*, and *DQB1*. These loci are highly polymorphic and have been linked to several autoimmune liver conditions, including autoimmune hepatitis and primary biliary cholangitis [53,54]. Specific HLA alleles influence **T cell antigen presentation**, thereby affecting susceptibility to immune-triggered liver injury. Clinically, HLA typing may support diagnostic confirmation in patients with ambiguous serologic profiles and guide immunosuppressive strategies in autoimmune liver diseases. Specific HLA alleles influence T cell antigen presentation, thereby affecting susceptibility to immune-triggered liver injury [53,54]. Additional studies have correlated specific haplotypes with disease severity and therapeutic response, particularly in autoimmune hepatitis [52,55].

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Beyond HLA, **non-HLA immune-regulatory genes** also modulate cirrhosis risk. Variants in **PTPN2 and PTPN22** influence **T cell and B cell homeostasis**, playing a role in immune tolerance breakdown and autoantibody production [40]. These genes have been implicated in broader autoimmune susceptibility and may partially explain overlapping features between autoimmune liver disease and systemic conditions. [40,51,56].

The ***TERT (telomerase reverse transcriptase)*** gene is another immune-relevant locus with dual roles in **genomic stability and immunosenescence**. Mutations in *TERT* have been associated with **shortened telomeres**, impaired regenerative capacity, and increased fibrosis risk [47,49]. Clinically, these variants may contribute to more rapid liver decompensation and poorer post-transplant outcomes[45,47,49]. This telomere dysfunction likely contributes to a pro-fibrotic phenotype, possibly through enhanced inflammatory signaling and regenerative failure [48,50]. Some studies also suggest links between *TERT* variants and **inflammatory amplification pathways**, though mechanistic understanding is still evolving.

Emerging research has highlighted the relevance of **regulatory non-coding variants**, including expression quantitative trait loci (eQTLs), that influence the **transcriptional activity of immune-related genes** [41,46]. These variations can modify cytokine profiles or affect the threshold for immune activation, providing a molecular basis for variable clinical presentations [41,46,57].

Furthermore, studies of **somatic mutations in immune cells** have revealed potential roles for clonal hematopoiesis and immune cell dysfunction in cirrhosis development, especially in the setting of cryptogenic or autoimmune liver injury [43,44]. Although not yet ready for routine clinical use, these findings underscore the dynamic interplay between inherited and acquired immune-genetic factors in liver disease.

From a translational perspective, immune-related variants may offer **diagnostic value** in atypical liver presentations, help tailor **immunomodulatory therapies**, or even serve as targets for future interventions aimed at **fibrosis attenuation or immune reprogramming**.

Metabolism-Related Genetic Variants

Metabolic dysregulation, particularly in lipid and alcohol metabolism, plays a pivotal role in the pathogenesis and progression of cirrhosis. Genetic variants affecting pathways of fatty acid oxidation, lipogenesis, insulin resistance, and alcohol degradation can significantly modulate an individual's risk of developing steatosis, steatohepatitis, and ultimately fibrotic liver disease [58,59]. These metabolic-related polymorphisms are often polygenic and exhibit pleiotropic effects, with implications that extend beyond the liver to broader metabolic and cardiovascular health [60,61]. Additionally, they may synergize with low-grade inflammation to promote fibrogenesis through convergent inflammatory-metabolic signaling pathways [70].

Among the most extensively studied is the **PNPLA3 I148M (rs738409)** variant, which encodes a loss-of-function substitution that impairs triglyceride hydrolysis in hepatocytes. This variant is strongly associated with hepatic steatosis, NASH, fibrosis, and even hepatocellular carcinoma [72–74]. Importantly, the risk conferred by *PNPLA3* is **independent of BMI or lifestyle factors**, making it a powerful **genetic risk marker** in both lean and obese NAFLD patients. Its presence may warrant more aggressive surveillance or earlier intervention, even in the absence of abnormal liver enzymes [75].

The **ADH1B and ALDH2** genes, which encode alcohol dehydrogenase and aldehyde dehydrogenase enzymes, are critical for alcohol metabolism. Variants such as **ADH1B rs1229984 (His48)** and common alleles in *ALDH2* influence the rate of ethanol clearance and the accumulation of acetaldehyde, a hepatotoxic intermediate [65–67]. These polymorphisms can affect **both alcohol sensitivity and liver injury susceptibility**, offering a genetic explanation for interindividual variability in alcohol-related cirrhosis risk. Ethnic variation in these alleles also underlines the need for population-specific approaches to alcohol-related liver disease screening and counseling [68,69].

Variants in **GCKR and CIDEB** have been implicated in hepatic lipid handling and metabolic syndrome traits. For instance, ***GCKR rs780094*** affects hepatic glucose uptake and lipogenesis,

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promoting triglyceride accumulation and NAFLD, particularly when coupled with insulin resistance [34,76]. Similarly, ***loss-of-function mutations in CIDEB*** have been associated with protection from cirrhosis in population studies, offering a potential **therapeutic target** for future anti-steatotic strategies [35]. Other lipid droplet regulators beyond PNPLA3 and CIDEB are also under investigation, with potential to further clarify the cellular basis of hepatic resilience [62].

Collectively, these metabolism-related variants serve not only as disease modifiers but also as potential tools for **genotype-informed risk prediction** and **treatment prioritization**. Understanding their interactions with diet, alcohol, and insulin signaling pathways may open avenues for **precision nutrition**, pharmacogenomics, and personalized lifestyle counseling in at-risk individuals.

Table 3. Metabolism-Related Genetic Variants and Clinical Implications in Cirrhosis.

Gene	Variant	Pathway Affected	Clinical Impact	Implication
PNPLA3	rs738409 (I148M)	Lipid metabolism	↑ Steatosis, ↑ NASH, ↑ fibrosis, ↑ HCC	High-risk NAFLD genotype; risk persists despite normal BMI or labs [72,74]
ADH1B, *ALDH2*	rs1229984, common alleles	Alcohol metabolism	↑ Acetaldehyde accumulation; variable alcohol tolerance	Explains ethnic differences in alcohol-related liver risk [65,67,69]
GCKR	rs780094	Glucose/lipid regulation	↑ Hepatic lipogenesis; ↑ ALT, ↑ triglycerides	Strong link with metabolic NAFLD; useful in lean NASH [34]
CIDEB	LoF mutations	Lipid droplet dynamics	↓ Risk of steatosis and cirrhosis	Potential protective genotype; future therapeutic target [35]

Abbreviations: NASH – Non-alcoholic steatohepatitis; HCC – Hepatocellular carcinoma; LoF – Loss of function.

Implications for Diagnosis and Risk Stratification

Despite advances in imaging and biochemical scoring tools, the accurate prediction of cirrhosis development and progression remains a major clinical challenge. Conventional models such as the Fibrosis-4 score or APRI index often lack sensitivity in early disease or among patients with atypical phenotypes. In this context, genetic data offer a compelling opportunity to enhance diagnostic precision and personalize risk assessment, especially in asymptomatic individuals or those with ambiguous liver function profiles [10].

One of the most promising tools is the use of **polygenic risk scores (PRS)**, which aggregate the cumulative impact of multiple genetic variants to stratify individuals according to inherited susceptibility. Studies have shown that PRS models incorporating variants in *PNPLA3*, *TM6SF2*, *HSD17B13*, and others can significantly improve risk prediction for NAFLD and its progression to cirrhosis [10]. The inclusion of **mosaic chromosomal alterations (mCAs)** alongside germline variants further refines these models, offering a layered view of both inherited and acquired genomic instability as contributors to liver disease.

Importantly, genetics may uncover **"silent risk" profiles** — individuals with normal liver enzymes or minimal fibrosis who carry high-risk genotypes. For example, ***PNPLA3 rs738409*** homozygosity is strongly associated with progressive fibrosis even in non-obese patients and may justify earlier imaging or biopsy, despite reassuring biochemical findings [11]. Similarly, ***HSD17B13***

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loss-of-function variants may offer protective information, identifying patients with fatty liver who are at low risk of progression and who may not require aggressive follow-up [12].

In clinical practice, these insights could be incorporated into **personalized cirrhosis risk calculators**, integrating genetic data with conventional metrics to enhance predictive accuracy. Additionally, genotype-informed screening strategies could be particularly useful in:

- First-degree relatives of patients with cryptogenic cirrhosis,
- Lean individuals with metabolic risk factors but no overt liver disease,
- Populations with high prevalence of high-risk alleles (e.g., *PNPLA3* in South Asians and Hispanics).

While genotyping is not yet routine in hepatology clinics, the decreasing cost of sequencing and growing evidence base suggest that **genetic markers will soon complement or even precede** current non-invasive assessments in select patients. However, challenges remain around standardization, ancestry calibration, and external validation of risk models in real-world populations [64]. Importantly, this approach may also reduce unnecessary liver biopsies and enable earlier intervention in high-risk genotypic subsets.

Finally, genetic risk models raise critical questions about **how early we should intervene** and whether lifestyle or pharmacologic interventions have **differential effects based on genetic background** — topics that merit urgent research.

Therapeutic and Prognostic Implications

While the role of genetics in cirrhosis risk prediction is increasingly recognized, its true clinical value lies in guiding therapeutic decisions and informing prognostic expectations. The integration of genetic data into care pathways could eventually support a more stratified approach to treatment intensity, surveillance, and even drug development.

Among the most clinically actionable variants is ***PNPLA3 rs738409***. Patients homozygous for the I148M allele have consistently demonstrated increased hepatic fat, inflammation, fibrosis, and hepatocellular carcinoma (HCC) risk — independent of body mass index, alcohol intake, or metabolic comorbidities [73–75]. This genotype may identify a subgroup of NAFLD or ALD patients who would benefit from early therapeutic intervention, even before conventional thresholds are met. Moreover, I148M status could inform HCC screening intervals or treatment thresholds, particularly in resource-limited settings.

Conversely, the ***HSD17B13 rs72613567*** variant offers a rare example of a protective allele. Patients carrying this loss-of-function mutation exhibit a **significantly lower risk of progressing from steatosis to steatohepatitis and cirrhosis** [12]. As a result, this gene is now being explored as a potential **therapeutic target**, with early-stage drug development focused on mimicking its effects. Clinically, it may justify **de-escalation of monitoring or pharmacotherapy** in select low-risk patients.

From a prognostic standpoint, **genetic risk stratification may help refine transplant listing criteria or post-transplant surveillance strategies**. For instance, in recipients with high-risk genotypes such as *PNPLA3* or *TM6SF2*, closer monitoring for disease recurrence or graft steatosis may be warranted. Additionally, variants like ***CIDEB*** loss-of-function mutations, which appear protective against cirrhosis in large population cohorts, could serve as **biomarkers for favorable natural history** [35].

Beyond known gene–disease associations, the availability of **polygenic risk scores (PRS)** and **mosaic chromosomal alterations (mCAs)** allows for a more comprehensive approach to prognosis [10]. Incorporating these tools may help **identify patients who require early referral to hepatology**, closer imaging surveillance, or prioritization for antifibrotic therapies as they emerge.

Furthermore, emerging therapies — including **anti-fibrotic agents, metabolic modulators, and gut-liver axis interventions** — may be variably effective based on genetic background. The ability to **predict treatment response by genotype** remains an evolving but promising area, raising the potential for future pharmacogenomic personalization.

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Limitations of Current Genetic Approaches

While genetic discoveries have undoubtedly enriched our understanding of cirrhosis pathogenesis, several limitations hinder their immediate translation into routine clinical practice. These challenges span both **scientific constraints** and **implementation barriers**, and must be acknowledged to guide responsible application and future research.

First, the **heritability of cirrhosis remains only partially explained** by currently identified variants. Despite robust genome-wide association studies (GWAS), the majority of risk in complex liver diseases such as NAFLD and alcoholic liver disease is still attributable to **unknown or unmeasured genetic factors** [6,64]. Many identified variants, including *PNPLA3* and *TM6SF2*, have moderate effect sizes, and their predictive power may be limited outside of polygenic models. Moreover, the **mechanistic roles of several loci remain incompletely understood**, restricting their use in therapeutic targeting.

Second, **population bias in genetic research** significantly affects the generalizability of findings. Most GWAS have been conducted in populations of European ancestry, limiting their application to ethnically diverse groups [18,63]. Variants that are common and pathogenic in one population may be rare or benign in another. This raises important questions about **equity in genetic risk prediction**, particularly for underrepresented communities, and underscores the urgent need for more **diverse, ancestry-aware genomic studies** [19].

Another major barrier is the **interpretational complexity** of polygenic risk scores (PRS). While PRS offer a promising way to capture the cumulative impact of multiple low-penetrance variants, their clinical utility remains uncertain. Differences in scoring algorithms, ancestry calibration, and lack of prospective validation hinder their adoption [63,64]. Additionally, PRS may be confounded by **environmental and epigenetic interactions** that are not accounted for in static DNA-based models.

From a clinical implementation standpoint, **cost, accessibility, and data integration challenges** persist. Although the cost of sequencing has dropped significantly, most hepatology clinics still lack infrastructure to interpret, store, and act on genetic information. The absence of **standardized guidelines** on when and how to use genotyping in chronic liver disease further contributes to variability in clinical practice.

Finally, **ethical concerns** related to genetic testing — including privacy, incidental findings, and the use of ethnicity as a proxy for biology — remain unresolved [13,19]. These issues are particularly relevant in liver disease, where socioeconomic disparities intersect with genetic risk and healthcare access.

Future Directions

The expanding landscape of liver genomics offers unprecedented opportunities to transform the diagnosis, management, and prevention of cirrhosis. However, realizing this potential will require addressing current limitations and developing structured pathways for clinical implementation.

One of the most promising directions is the **integration of genomic data with clinical and biochemical models** to create comprehensive, risk-adaptive algorithms. Incorporating polygenic risk scores, protective variants (such as *HSD17B13*), and high-risk genotypes (such as *PNPLA3*) into existing fibrosis scoring systems may yield more precise tools for early detection and individualized surveillance [10,12]. These models could guide decisions regarding imaging frequency, biopsy thresholds, and therapeutic initiation, particularly in at-risk but asymptomatic individuals.

In parallel, there is a need to develop **clinical-grade genotyping panels** tailored for hepatology practice. Such panels should prioritize high-evidence variants associated with disease progression, drug metabolism, and treatment response, and be validated across diverse populations. As genetic testing becomes more accessible, the creation of **specialist-led frameworks** to interpret and apply results in routine care will be essential.

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On the therapeutic front, genetics may shape the future of **precision hepatology**. Variants like *HSD17B13* and *CIDEB*, which confer protection against cirrhosis, offer **novel targets for antifibrotic therapies or metabolic modulation** [12,35]. Pharmacogenomic approaches may also refine eligibility or dosing for emerging treatments targeting lipid metabolism, insulin sensitivity, or gut-liver signaling.

Research must also expand into **understudied populations**. Most genetic insights have been derived from European ancestry cohorts, limiting the generalizability of risk models [6,63]. Future studies should prioritize inclusive design, enabling ancestry-aware tools that can equitably benefit all patients with liver disease [64].

Beyond individual genes, emerging technologies such as **multi-omics**, **single-cell sequencing**, and **machine learning** are poised to deepen our understanding of liver disease heterogeneity. These tools may uncover noncoding regulatory elements, transcriptomic patterns, and tissue-specific dynamics that elude traditional genotyping methods [13].

Finally, **ethically grounded implementation frameworks** are critical. As genetic data becomes more integrated into clinical care, attention must be paid to data privacy, informed consent, and equity in access — ensuring that the benefits of genomic hepatology are broadly and responsibly realized.

Conclusions

Cirrhosis remains a complex and heterogeneous condition, with clinical outcomes that vary widely despite similar environmental exposures. Accumulating evidence supports a significant role for genetic variation in modulating disease susceptibility, phenotype, and progression. In this review, we proposed a functional classification of cirrhosis-associated genetic variants into four mechanistic domains—**ethnicity-based polymorphisms, liver enzyme–related genes, immune-mediated variants, and metabolism-related loci**—to provide a structured lens through which to interpret emerging genomic insights.

Key variants such as *PNPLA3*, *TM6SF2*, *HSD17B13*, and *ADH1B* offer clinically relevant information that may refine risk stratification, guide surveillance intensity, and even inform therapeutic development. The integration of polygenic risk scores, protective alleles, and genotype–phenotype correlations holds promise for advancing personalized hepatology. However, limitations related to population bias, unexplained heritability, and translational infrastructure must be addressed to realize this potential.

As genomic technologies continue to evolve, the application of liver genetics in clinical practice will require not only technical innovation but also ethically grounded, patient-centered frameworks. Bridging the gap between molecular insight and bedside utility will be essential in delivering precision medicine to those at risk of — or already living with — cirrhosis.

Abbreviations

Abbreviation	Definition
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
ALD	Alcohol-related liver disease
HCC	Hepatocellular carcinoma
GWAS	Genome-wide association study
PRS	Polygenic risk score

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mCAs	Mosaic chromosomal alterations
LoF	Loss of function
CNVs	Copy number variants
HLA	Human leukocyte antigen
TERT	Telomerase reverse transcriptase
PTPN2/PTPN22	Protein tyrosine phosphatase non-receptor type 2 / 22
LFTs	Liver function tests
BMI	Body mass index
ADH1B	Alcohol dehydrogenase 1B
ALDH2	Aldehyde dehydrogenase 2
PNPLA3	Patatin-like phospholipase domain-containing 3
TM6SF2	Transmembrane 6 superfamily member 2
HSD17B13	Hydroxysteroid 17-beta dehydrogenase 13
MBOAT7	Membrane-bound O-acyltransferase domain-containing 7
GCKR	Glucokinase regulatory protein
CIDEB	Cell death–inducing DFFA-like effector B
ALPL	Alkaline phosphatase, liver/bone/kidney isozyme
PPP1R3B	Protein phosphatase 1 regulatory subunit 3B

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