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Advances in the Genetics of Nonalcoholic Fatty Liver Disease

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Abstract

Purpose of review: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States and has a strong heritable component. Advances in understanding the genetic underpinnings of NAFLD have revealed important insights into NAFLD pathogenesis, prognosis, and potential therapeutic targets. The purpose of this review is to summarize data on common and rare variants associated with NAFLD, combining risk variants into polygenic scores to predict NAFLD and cirrhosis as well as emerging evidence on using gene silencing as a novel therapeutic target in NAFLD.

Recent Findings: Protective variants in HSD17B13, MARC1 and CIDEB have been identified and a confer 10-50% lower risk of cirrhosis. Together, these as well as other NAFLD risk variants, including those in PNPLA3 and TM6SF2, can be combined to create polygenic risk scores associated with liver fat, cirrhosis, and hepatocellular carcinoma. Genomic analysis of extreme phenotypes including patients with lean NAFLD without visceral adiposity may uncover rare monogenic disorders with pathogenic and therapeutic implications and gene silencing strategies targeting HSD17B13 and PNPLA3 are being evaluated in early phase human studies as treatments for NAFLD.

Summary: Advances in our understanding of the genetics of NAFLD will enable clinical risk stratification and yield potential therapeutic targets.

Keywords

NASH; polygenic risk; rare variant; gene silencing

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as a leading cause of chronic liver disease and accounts for an increasing proportion of liver related morbidity and mortality, including hepatocellular carcinoma. However, only a subset of patients with NAFLD develop advanced liver disease. To date, patients have been risk-stratified based on microscopic features observed on a liver biopsy into nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH), which is considered the progressive form of the disease. More recently, advances in understanding the genetic underpinnings of NAFLD may allow for an improved assessment of disease trajectory and identification of therapeutic targets.

Here, we review the most well characterized genetic variants in NAFLD, their impact on disease severity and potential development as a therapeutic target. This review will outline data on polygenic risk of NAFLD and cirrhosis, the gene-environment interaction, and leveraging genetics to develop novel therapeutic targets and uncover monogenic drivers of disease in lean patients with NAFLD.

HERITABILITY OF LIVER FAT AND FIBROSIS

Familial clustering of liver fat and fibrosis from twin and family studies demonstrated the strong genetic underpinnings to NAFLD and advanced fibrosis (1). A pilot study compared the rate of advanced fibrosis among 39 first-degree relatives of probands with NAFLD cirrhosis and compared this to a population of community-dwelling twin, sib-sib or parent offspring pairs. Using accurate MRI-based biomarkers of liver fat and fibrosis quantified the high risk of advanced fibrosis in first-degree relatives of probands with NAFLD cirrhosis, 17.9% vs 1.4% in the control population (2). These findings were then validated in 2 independent cohorts from the United States and Europe, demonstrating the prevalence of advanced fibrosis in first-degree relatives of probands with advanced fibrosis was 15% (3).

COMMON RISK VARIANTS FOR NAFLD

The implementation of genome wide association studies (GWAS) accelerated the identification of single nucleotide polymorphisms (SNPs) associated with NAFLD (Table 1), and the best characterized common variant associated with NAFLD is the nonsynonymous variant p.I148M in the PNPLA3 gene, initially described by Romeo and colleagues in 2008 (4). The frequency of PNPLA3 risk variant parallels racial/ethnic differences in NAFLD prevalence with an allele frequency of 49% in Hispanics affected compared to 17% in African Americans. Subsequent studies have demonstrated that the PNPLA3 risk variant is associated with an increased risk of hepatic steatosis (4), NASH (5, 6), cirrhosis (7) and hepatocellular carcinoma (8).

In addition, the *TM6SF2* variant p.E167K increases susceptibility to NAFLD, however, is less common with an allele frequency of 7% in Europeans (9). By impeding normal VLDL assembly and decreasing circulating lipids the variant increases the risk of liver disease, including advanced fibrosis and HCC (10, 11), but may mitigate the risk of cardiovascular disease. (12). A polymorphism at rs641738 downstream of *MBOAT7* (13) has an allele

frequency of 37% and likely decreases protein expression with a modest impact on liver fat and fibrosis in European populations. A recent meta-analysis confirmed the effect of the variant on ALT, NAFLD, fibrosis and HCC in Caucasian adults, however, the effect sizes were small compared to variants in PNPLA3 and TM6SF2 (14). Two polymorphisms at rs1260326 (15) and rs780094 (16) in *GCKR* modestly increase liver fat through increased de novo lipogenesis (15) but its association with advanced fibrosis, cirrhosis and hepatocellular carcinoma remains unclear.

COMMON PROTECTIVE VARIANTS FOR NAFLD

Recently, protective variants have also been identified. Splice site variant rs72613567 in *HSD17B13* leads to synthesis of a truncated protein and is associated with lower aminotransferases, lower risk of NASH and nonalcoholic cirrhosis. Importantly, the variant may mitigate the risk associated with PNPLA3 p.I148M (17, 18). In a well-phenotyped cohort of 264 adult patients with NAFLD and magnetic resonance elastography (MRE) assessment, the PNPLA3 and HSD17B13 variants had opposing effects of similar magnitude on liver stiffness and copies of the protective HSD17B13 variant could mitigate the effect of PNPLA3 risk variants on liver stiffness (18). Importantly, the effect of the variant is greatest in the population with risk factors for chronic liver disease including the obese or heavy drinkers (19).

In addition, the rs2642438 (pA165T) missense variant in MARC1, a mitochondrial enzyme, (20, 21) has demonstrated protective effects against liver disease severity with lower fibrosis stage but no impact on steatosis score on histology. A more recent study further characterizes the effect of MARC1 by identifying the effect in rare loss of function variants and demonstrated a decrease in liver aminotransferases and total cholesterol levels. (22)

POLYGENIC RISK SCORES

While the independent contributions of common variants only account for a small portion of the heritability of liver fat and fibrosis, the combination of multiple genetic traits can be incorporated into a polygenic risk score to more accurately risk stratify patients. Leveraging a multi-trait GWAS combining cirrhosis and alanine aminotransferase levels in 5 discovery cohorts and 2 case-control studies, 12 genetic variants including 7 newly identified variants were associated with cirrhosis (7). The top quintile of polygenic risk increased the risk of cirrhosis, OR=2.26 compared to the lowest quintile. Importantly, the gene-environment interaction significantly enhances genetic risk of cirrhosis. In people with a normal BMI who drink < 14 drinks/week the top 1% of genetic risk had a 1.9% risk of cirrhosis compared to 2.6% in the bottom 99%. With morbid obesity or >21 drinks/week the risk of cirrhosis was 27.3% in participants with the top 1% of genetic risk compared to 9.5% in the bottom 99%.

After leveraging a machine learning technique to expand MRI liver fat assessment in the UK Biobank to 30,000 participants Haas and colleagues identified 8 variants associated with liver fat and a polygenic risk score was associated with an increased risk of NAFLD, NASH, cirrhosis and HCC (23).

A recent multi-ancestry study in the million veteran program used a proxy NAFLD definition of chronically elevated ALT without other causes of liver disease and identified 77 loci including 25 without prior associations. They went on to replicate the findings in cohorts with biopsy-proven NAFLD or radiology and replicated 17 SNPs. The genetic risk scores were associated with NAFLD but not evaluated for their association with cirrhosis or HCC (24).

A multiomics study of NAFLD identified 18 variants in 17 genes associated with liver fat and 4 variants associated with cirrhosis, two of which were associated with liver fat PNPLA3 and TM6SF2. Herein, the addition of proteomics significantly enhanced the diagnostic accuracy for NAFLD, cirrhosis and to discriminate cirrhotic vs non-cirrhotic NAFLD (22). In a separate study, a stool metagenomic signature combined with age and serum albumin could accurately distinguish cirrhosis in distinct cohorts from geographically diverse regions (25).

These findings highlight that the clinical utility of polygenic risk scores is not in staging current disease severity but rather can help risk-stratify a patient's disease trajectory. Simple polygenic risk scores involving 4-5 common variants have been associated with the risk of cirrhosis, HCC (10, 26) and may improve the diagnostic accuracy of indeterminate clinical prediction scores including FIB-4 (27). However, longitudinal data on the use of polygenic risk to risk stratify disease progression and guide the frequency of clinical monitoring is an unmet need.

GENETICS TARGETS FOR TREATMENT OF NAFLD

Increasing knowledge of the mechanism of genetic variants in NAFLD has led to the development of multiple new therapeutic targets. Both antisense oligonucleotides (ASO) and RNA interference (RNAi) have been employed to modify expression of genetic targets and have been employed in a Phase II clinical trial of a DGAT2 inhibitor, which significantly decreased hepatic steatosis in patients with NAFLD and type 2 diabetes mellitus (28). Conjugation with a N-acetyl-galactosamine ($GalNAc_3$) moiety allows for delivery to hepatocytes through the asialoglycoprotein receptor, which is highly expressed on hepatocytes allowing for high potency and targeting of the liver (29).

PNPLA3 I148M impacts fatty liver disease by accumulating on lipid droplets and evading ubiquitylation (30). The accumulation of PNPLA3 then sequesters ABDH5 with resultant downstream impact on major adipose triacylglycerol lipase impeding lipolysis (31). In addition, the risk variant leads to a more fibrogenic phenotype of hepatic stellate cells (HSC) (32) through impacting retinol metabolism. Importantly, a high-sucrose diet induced NAFLD in $PNPL3^{I148M}$ knock-in mice with resultant fatty liver (33) and subsequent studies demonstrated that liver-targeted GALNAc3-conjugated antisense oligonucleotide (ASO) mediated silencing ameliorates NASH and fibrosis in a mouse model (34). Currently, a phase 1 clinical trial of a PNPLA3 ASO (NCT04483947) is underway in PNPLA3 I148M carriers (35).

Protective variants in HSD17B13 have been demonstrated to mitigate the risk associated with PNPLA3 risk variants. While in vitro studies suggest that HSD17B13 may have multiple enzymatic substrates, its association with hepatic retinol dehydrogenase activity may be key to its effect on fibrogenesis in NAFLD (36). HDS17B13 variants resulting in a loss of function may counterbalance the fibrogenic impact of PNPLA3 I148M on HSCs through retinol metabolism. Based on genetic data in humans and mechanistic work drug development targeting HSD17B13 has led to two Phase 1 clinical trials utilizing RNAi to inhibit HSD17B13 (NCT04565717 and NCT04202354) (37, 38). Interim analysis of NCT04202354 was presented at the American Association for the Study of Liver Disease (AASLD) annual meeting in 2021 and demonstrated a dose-dependent inhibition on HSD17B13 mRNA with associated decreases in ALT, AST without serious adverse events in 18 patients with suspected NASH (39).

Recently, a multistage rare variant association study involving 542,904 participants with data on liver tests identified 5 coding variants that impact aminotransferases and the risk of liver disease (40). Rare coding variants in CIDEB, which encodes a structural protein found in hepatic lipid droplets, were protective with 33% lower odds of any cause of liver disease and 50% lower odds of cirrhosis. The authors evaluated the effect of the rare coding variant in a subset of the cohort who underwent liver biopsy at the time of bariatric surgery and demonstrated that carriers of rare coding variants had 66% lower odds of a combined outcome of steatosis, NASH or fibrosis than noncarriers. Silencing of CIDEB with siRNA in human hepatic cell lines treated with oleic acid to induce steatosis reduced the mean droplet size suggesting that inhibiting CIDEB may represent a potential therapeutic target in NAFLD.

RARE VARIANTS IN SPECIFIC NAFLD PHENOTYPES

Genomic analysis has also been used to uncover rare monogenic drivers of disease in patients with liver disease of an unknown etiology. In a pilot study including those with non-obese NAFLD, three out of six patients with hepatic steatosis without metabolic syndrome were found to have monogenic disorders including a rare mitochondrial disease, familial partial lipodystrophy and autosomal dominant hypobetalipoproteinemia due to a loss-of-function mutation in APOB (41). A rare variant association study of participants in the UK biobank with MRI-based liver fat assessment revealed that 0.8% of participants with pathologic liver fat had a loss-of-function variant in either *APOB* or *MTTP* (23). Subsequently, a review proposed considering genomic analysis for rare variants in lean patients with NAFLD who lack visceral adiposity to identify potentially actionable rare variants and further elucidate pathogenic mechanisms (42).

CONCLUSIONS

Over the last 15 years there have been significant advances in the understanding of the genetic underpinnings of NAFLD. In addition to uncovering multiple genetic variants that increase the risk of NAFLD, fibrosis and hepatocellular carcinoma, the underlying pathogenetic mechanisms of these variants have been increasingly understood. Therapeutic targets through gene silencing in PNPLA3 and HSD17B13 have now progressed to early

phase clinical trials. While advances in understanding NAFLD genetics has identified targets for drug development, the use of polygenic risk scores to diagnose and stage NAFLD has demonstrated limited diagnostic value. Instead, leveraging genomics to better characterize NAFLD sub-types including lean patients with NAFLD without visceral adiposity has demonstrated utility in uncovering rare monogenic disorders. Future studies in well-phenotyped longitudinal cohorts with NAFLD will be required to evaluate the use of genetics to risk stratify a patient's disease trajectory and guide the frequency of monitoring, which remains an unmet need in the field and an opportunity to further translate increased knowledge of NAFLD genetics into clinical practice.

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KEY POINTS

- NAFLD has a strong heritable component and genome wide association studies have identified common risk variants in PNPLA3, TM6SF2, GCKR and MBOAT7 and protective variants in HSD17B13 and MARC1 associated with NAFLD
- The combination of variants in polygenic risk scores has modest predictive value for disease severity but may enable better prediction of an individual's risk for disease progression.
- Early clinical studies of gene silencing therapies targeting PNPLA3 and HSD17B13 are underway
- Evaluation of rare variants have revealed potential therapeutic targets including CIDEB and may help uncover monogenic disorders in lean patients with NAFLD without visceral adiposity.

Table 1:

Common variants associated with liver fat, fibrosis and hepatocellular carcinoma

Gene	rs number	Coding change	Impact on function	Impact on risk of liver disease	Associated Disease States	Effect Size
PNPLA3	rs738409	Missense	Impedes lipolysis and impacts hepatic stellate cells[30, 31, 32]	Increased	Liver Fat Fibrosis HCC	+++
TM6SF2	rs58542926	Missense	Impedes VLDL assembly and export[10, 11]	Increased	Liver Fat Fibrosis HCC	+++
MBOAT7	rs641738	Missense	Alters transfer of PUFA to lysophospholipids	Increased	Liver Fat Fibrosis	+
GCKR	rs1260326 rs780094	Missense	Increased DNL[15]	Increased	Liver Fat	+
HSD17B13	rs72613567	Splice site variant	Impacts retinol dehydrogenase activity[36]	Decreased	Fibrosis	+++
MARC1	rs2642438	Missense	Mitochondrial enzyme affects cholesterol metabolism[22]	Decreased	Liver Fat Fibrosis	+

Abbreviations: VLDL, very low-density lipoprotein; PUFA, polyunsaturated fatty acid; DNL, de novo lipogenesis; HCC, hepatocellular carcinoma