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Review Article

Genetic Risk Factors for Metabolic Dysfunction-Associated Steatotic Liver Disease

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Metabolic dysfunction-associated steatotic liver disease (MASLD), is the most common cause of liver disease, and its burden on health systems worldwide continues to rise at an alarming rate. MASLD is a complex disease in which the interactions between susceptible genes and the environment influence the disease phenotype and severity. Advances in human genetics over the past few decades have provided new opportunities to improve our understanding of the multiple pathways involved in the pathogenesis of MASLD. Notably, the PNPLA3, TM6SF2, GCKR, MBOAT7 and HSD17B13 single nucleotide polymorphisms have been demonstrated to be robustly associated with MASLD development and disease progression. These genetic variants play crucial roles in lipid droplet remodeling, secretion of hepatic very low-density lipoprotein and lipogenesis, and understanding the biology has brought new insights to this field. This review discusses the current body of knowledge regarding these genetic drivers and how they can lead to development of MASLD, the complex interplay with metabolic factors such as obesity, and how this information has translated clinically into the development of risk prediction models and possible treatment targets. **(Gut Liver 2025;19:8-18)**

Key Words: Metabolic dysfunction-associated steatotic liver disease; Genetic; PNPLA3; Risk stratification; Treatment

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is now the most common chronic liver disease globally,[1] with an ever growing prevalence, increasing from 25.3% in 1990–2006 to 38% in subsequent period of 2016–2019.[2] Defined by the presence of hepatic steatosis in conjunction with metabolic dysfunction, MASLD includes a wide spectrum of clinical phenotypes, from simple steatosis, steatohepatitis, to fibrosis and ultimately cirrhosis. Recognizing the high prevalence and natural history profile of MASLD, the anticipated disease burden in years to come is of great concern.[3] Modelling studies project increasing incidences of hepatocellular carcinoma (HCC), decompensated cirrhosis and MASLD-related mortality by 2030.[4] All this contributes to the bourgeoning socioeconomic health burden worldwide from both the clinical and public health perspectives.[5-7]

As MASLD is usually clinically asymptomatic and insidious, awareness and insight regarding perceived risk may not seem so evident.[8] As such, it remains critical for continued efforts to highlight MASLD amongst all stakeholders, including associated risk factors.

The bi-directional relationship between MASLD and metabolic factors has been well established. With advances in human genetics over the past few decades, our understanding of the multiple pathways, interactions and contributions between the various factors involved in the pathogenesis of MASLD continue to evolve and provide new opportunities in innovative research.[9] Here, we will be focusing on genetic risk factors, which represent significant factors at play in MASLD. Besides potentially identifying at risk individuals at a deeper level, genetic profiling may also allow development of novel biomarkers and targeting of specific gene pathways in a personalized precision medicine approach.

IMPORTANCE OF GENETIC RISK FACTORS

Genetic and epidemiological studies have indicated strong heritability of hepatic fat.[10] This evidence comes from familial aggregation studies that demonstrated that first-degree relatives have up to 12-fold increased risk of MASLD compared to the general population.[11] Another study performed in 2009 revealed that MASLD was more common in siblings (59%) and parents (78%) of children with MASLD, despite adjustments for age, sex, race, and body mass index (BMI). Separately, twin studies suggest between 35% and 61% hereditability for MASLD.[12] Multi-ethnic cohorts also highlight major inter-ethnic variability in MASLD susceptibility, proving that the risks are higher in Hispanics, intermediate in Europeans and lower in individuals of African descent, independent of confounders.[13]

The risk is not limited to the diagnosis of MASLD but also to poorer liver-related outcomes. A recent nationwide multigenerational cohort study performed in 38,000 Swedish adults who are first-degree relatives of patients with biopsy proven MASLD found that the rate of HCC, major adverse liver outcomes, and liver-related mortality was 1.8 times, 1.52 times, and 2.14 times higher respectively than comparator first-degree relatives, illustrating a distinct familial clustering.[14]

Genome-wide association studies (GWAS) cemented the awareness and importance of genetic factors in the pathogenesis of MASLD, and opened up exciting new opportunities to address the unmet need for therapeutics in MASLD. In the age of precision medicine, the identification of patients with specific gene variants may allow individual and targeted treatment via specific genetic pathways.

While there are many genetic factors reported in the literature to be associated with NAFLD,[15] and more recently MASLD,[16] the most well studied and strongest association has been suggested in the following five single nucleotide polymorphisms (SNPs) as summarized in Table 1. These five genes known to be associated with MASLD are all involved in glucose and fat homeostasis regulatory pathways as illustrated in Fig. 1.

1. Patatin-like phospholipase domain-containing protein 3

With the first reported landmark GWAS study in context of MASLD by Romeo *et al.* in 2008,[17] patatin-like phospholipase domain-containing protein 3 (PNPLA3) variant was found to be associated with increased hepatic

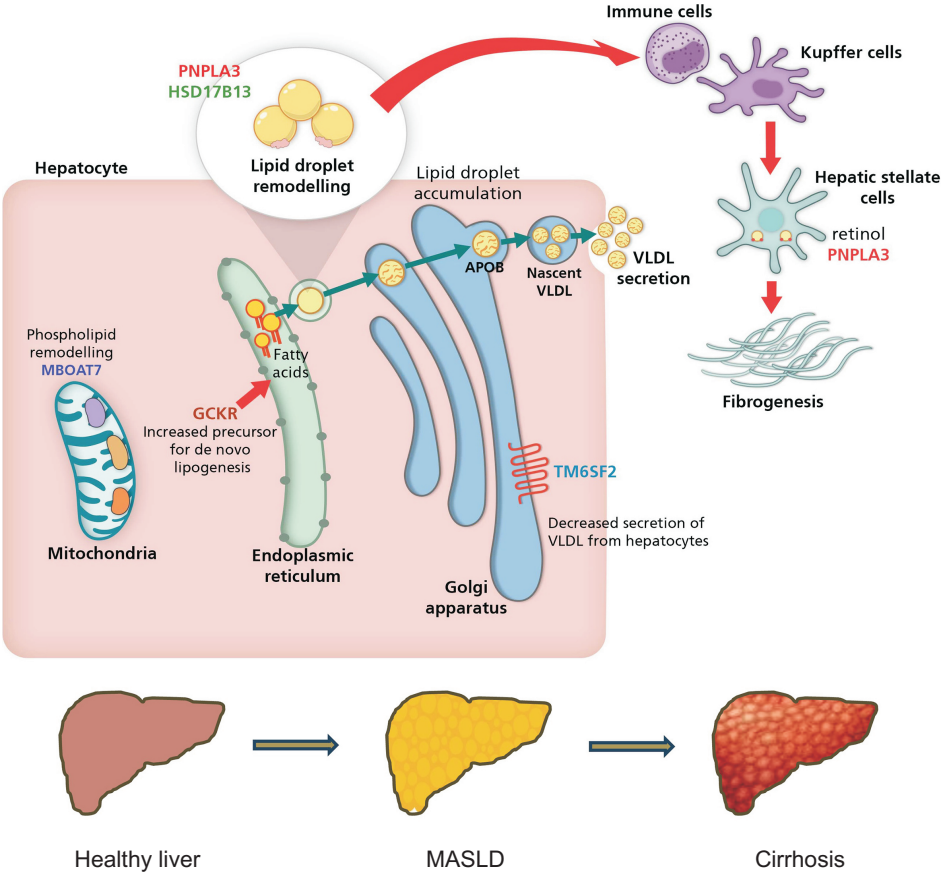

Fig. 1. Genetic loci involved in the susceptibility and pathophysiology of fatty liver disease. PNPLA3, patatin-like phospholipase domain-containing protein 3; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; VLDL, very low-density lipoprotein; APOB, apolipoprotein B; MBOAT7, membrane bound O-acyltransferase domain-containing 7; GCKR, glucokinase regulator; TM6SF2, transmembrane 6 superfamily member 2; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 1. Genetic Variants Associated with MASLD

Gene	Genetic variant	Affected protein	Effect	Pathophysiology	Effect on hepatic steatosis	Effect on NASH	Effect on fibrosis/ cirrhosis	Effect on HCC	Mortality	Reference
PNPLA3	rs738409 C>G	I148M	Complex Gain of function and also loss of function	Lipid droplet remodeling	↑	↑	↑	↑	↑	18-24
TM6SF2	rs58542926 G>A	E167K	Loss of function	Inhibits secretion of VLDL in hepatocytes	↑	↑	↑	↑	-	25-29
MBOAT7	rs641738 C>T	Lysophosphatidylinositol-acyltransferase 1 (LPIAT1)	Downregulation	Phospholipid remodeling	↑	↑	↑	↑	-	30-33
GCRK	rs780094 C>T rs1260326 C>T	Intronic variant P446L	Loss of function	Increases de novo lipogenesis	↑	↑	↑	-	-	34-37
HSD17B13*	rs72613567 T>TA	Splice donor variant	Loss of function	Lipid droplet remodeling	-	↓	↓	↓	↓	38-41

MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; VLDL, very low-density lipoprotein.
*There are many variants within the HSD17B13 gene, including rs6834314 A>G, rs62305723 G>A, rs10433937 T>A, T>C, T>G, rs10433879 G>C, rs61748262 C>A, C>T.

lipid content. The variant is a cytosine to guanine substitution that results in an isoleucine to methionine substitution at position 148 in PNPLA3 gene (rs738409). Subsequent studies have confirmed that this is the most robust, well-replicated genetic variant associated with MASLD.[42] Furthermore, inter-ethnic variability in MASLD is likely accounted for by PNPLA3. Illustrating this, the PNPLA3 allele (rs738409[G], encoding I148M), which was strongly associated with increased hepatic fat levels was found most commonly in Hispanics, who in turn, epidemiologically have the highest susceptibility to MASLD.[17]

PNPLA3 codes for a triacylglycerol lipase that mobilizes polyunsaturated fatty acids from triglycerides. This facilitates the liver's ability to secrete large-sized very low-density lipoprotein (VLDL), which transports triglycerides from the liver to other tissues.[43,44] The current understanding is that the genetic variant is possibly inducing both a gain- as well as a loss of function effect. A loss of function of this allele can hinder the formation and secretion of VLDL,[45] further contributing to triglyceride accumulation in the liver because the liver is less able to export the excess fat.[46,47]

The I148M mutant of PNPLA3 tends to accumulate on the surface of lipid droplets.[48] Recent studies have shown that this protein mutant suppresses adipose triglyceride lipase-mediated lipolysis,[49] by competing for the co-activator comparative gene identification-58 at the surface of the lipid droplets.[46] This gain of function mutation involving transrepression of adipose triglyceride lipase results in impaired lipid turnover and results in accumulation in hepatocytes.[50] Impairment of retinol release from the lipid droplets of hepatic stellate cells resulting in an inflammatory response and fibrogenesis in carriers of the PNPL3 I148M has also been suggested as a contributory mechanism.[51]

Clinically, it is associated with rise in hepatic fat content,[18,52] elevated liver enzymes, fibrosis,[19-21,53] cirrhosis and HCC,[22,23] carrying an odds ratio of 1.91 for MASLD, 2.54 for metabolic dysfunction-associated steatohepatitis (MASH), and 2.68 to 5 for HCC.[24,25] In keeping with these findings, PNPLA3 was also found to be associated with the risk of hepatic decompensation (hazard ratio, 2.1), liver-related mortality (hazard ratio, 3.64)[24] as well as overall mortality.[54]

Interestingly, this effect is independent of alterations in glucose homeostasis or lipoprotein metabolism.[17,24] There is also no association of this variant with BMI, triglyceride levels, high and low-density lipoprotein levels, or diabetes.[17,55] This may be related to the dissociation between the PNPLA3 genetic variant with insulin resistance, estimated from oral glucose tolerance test and measured by the

euglycemic-hyper insulinemic clamp.[56] This has led to the postulation that the effect of PNPLA3 variant on the degree of hepatic steatosis is not related to insulin sensitivity or resistance, but rather that it sets off a multi-step process that is more subtle, sensitizing the liver to metabolic stress due to nutritional calorific excess.[57] In mouse models, PNPLA3 expression is upregulated by carbohydrate feeding through the liver X receptor/sterol regulatory element binding protein-1c pathway.[58] Thus, loss of function of this gene under lipogenic conditions provides a potential explanation for the increased susceptibility of patients carrying the I148M variant to the development of liver steatosis and MASLD.[49] This can also be seen in how morbid obesity acting as a stressor on a specific genetic background may influence susceptibility to MASLD.[57,59] An Italian genetic association analysis found that morbidly obese patients carrying the PNPLA3 148M allele have increased levels of alanine transaminase and aspartate transaminase without any differences in insulin sensitivity or glucose tolerance.[60] This shows that patients with obesity will have a more extreme liver injury with the PNPLA3 148M allele than lean individuals.[61] Among lean persons (BMI <25 kg/m^2), hepatic steatosis in the MM homozygous individuals was at 2.8% versus 1.8% in the II homozygous individuals, whereas in those who were obese (BMI >35 kg/m^2), hepatic fat was 14.2% versus 4.7% in MM than in II individuals, demonstrating that the effect of the M variant increased with increasing BMI.[59] This finding was also replicated in an Asian (Hong Kong) population which found that the median intrahepatic triglyceride increased only mildly in the lean group (1.5% in wild type vs 2.8% in homozygotes), but tripled in the obese subgroup (4.7% in wild type vs 14.2% in homozygotes).[62]

2. Transmembrane 6 superfamily member 2

Transmembrane 6 superfamily member 2 (TM6SF2) regulates the hepatic VLDL secretion pathway.[26] The G to A substitution encoding glutamate to lysine substitution at position 167 at the rs58542926 SNP results in loss of function in the hepatic VLDL secretion pathway, inducing higher liver triglyceride content, resulting in increased susceptibility to liver damage.[27]

This impairment in cholesterol metabolism leads to increased liver fat content, MASH, advanced fibrosis and cirrhosis,[28,63] and even HCC in mouse models,[27] with allelic odds ratio of 1.82 for MASLD and 1.37 for MASH.[25,29] This genetic variation associated with advanced hepatic fibrosis is independent of potential confounding factors such as age, BMI, type 2 diabetes mellitus (T2DM) and PNPLA3 rs738409 genotype.[28,63] While this genetic variant has a moderate to large effect size, it is a generally low frequency variant, and shows inter-ethnic variations in its carriage.[64]

Of note, it is associated with a lower cardiovascular risk, postulated to be due to diminished circulating levels of cholesterol and lipids[65] because these instead accumulate in the liver.[62,63] It has been suggested that TM6SF2 controls hepatic lipid efflux, as loss of function of the gene results in a reduction in lipoprotein secretion (VLDL, triglyceride [TG], and apolipoprotein B), which leads to increased hepatocellular lipid droplet size and TG accumulation in the liver.[66] This variant has also been related to the development of T2DM.[67]

3. Membrane-bound O-acyltransferase domain-containing 7

Membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) encodes lysophosphatidylinositol-acyltransferase 1, which is involved in incorporating arachidonic acid and other unsaturated fatty acids into lysophospholipids, producing a component of cell membranes called phosphatidylinositol.[68] The rs641738 SNP variant linked to 3'UTR of MBOAT7 is associated with the downregulation of MBOAT7, which reduces levels of phosphatidylinositol-containing arachidonic acid and increases levels of saturated lysophosphatidylinositol.[30] This is a proinflammatory molecule involved in macrophage and endothelial cell activation and induces de novo lipogenesis and inhibits beta oxidation in hepatocytes. The downregulation of this gene also favors the accumulation of free arachidonic acid, a known driver of hepatic inflammation.[31,69,70]

This variant is linked with an increased risk of MASLD, inflammation, fibrosis, and HCC.[31,32] It carries allelic an odds ratio of 1.15 (95% confidence interval [CI], 1.05 to 1.26) for MASLD, 1.24 (95% CI, 0.81 to 1.90) for MASH, 1.2 (95% CI, 1.02 to 1.42) for advanced fibrosis and 1.4 (95% CI, 0.99 to 1.98) for HCC.[33] However, the effect size is small compared to PNPLA4 and TM6SF2. No effect on fasting insulin levels was found in population-level GWAS (β=0.009 [95% CI, –0.03 to 0.04], p_z=0.6461), indicating lack of an effect of rs641738C>T on insulin resistance.[33]

4. Glucokinase regulator

Glucokinase regulator (GCKR) is an inhibitor of glucokinase (GCK), and its hepatic concentration is increased in MASLD. The GCKR gene is involved in the glucose control and metabolism in hepatocytes.[71] The rs780094 C>T gene variant has been shown to be related to hepatic steatosis not just in adults,[34] but another loss of function variant rs1260326 C>T SNP was even associated with increased risk of MASLD in obese children and adolescents.[35] The SNP rs1260326 results in a loss of function variant that

increases de novo lipogenesis by inducing glycolytic influx and glucose uptake.[72] GCK, which is inhibited by the GCKR protein, catalyzes the beginning of the glycolytic pathway. With the P446L GCKR variant, this inhibition is reduced, resulting in increased activity of GCK, promoting the glycolytic pathway and elevating concentrations of a precursor for fatty acid biosynthesis, leading to the accumulation of hepatic lipids.[73] This gene is associated with MASLD, MASH, and HCC with allelic odds ratio of 1.38 to 1.49 for MASLD,[36,37] 1.5 for MASH, and 1.52 for fibrosis.[37]

5. Hydroxysteroid 17-beta dehydrogenase 13

Hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) is a hepatic lipid droplet protein which is involved in steroid hormone signaling as well as lipid droplet remodeling,[74] and has multiple polymorphisms including rs72613567 SNP variant, rs143404524, rs62305723. All these variants alter genetic splicing that results in truncated or stable HSD17B13 proteins that have a marked loss of enzymatic activity that protect against liver injury,[38,39] including MASH, ballooning, lobular inflammation and fibrosis. The allelic odds ratios have been reported to be 0.84 for MASLD, 0.86 for MASH, and 0.67 to 0.77 for HCC,[25,40] and each minor allele has been found to decrease the risk of cirrhosis and cirrhosis-associated mortality by 15% (95% CI, 0.74 to 0.98) and 49% (95% CI, 0.32 to 0.81), respectively.[41] The protective role seems to be associated with retinol metabolism, via retinol dehydrogenase activity, inflammation and fibrogenesis rather than simply lipid accumulation in the liver.[75]

Another exciting finding was that rs72613567 interacted with PNPLA3 I148M, mitigating the effects of liver injury as well as that of advanced fibrosis.[76] However, the effect may be influenced by the presence of other factors, as a recent analysis found that the protective effect of HSD17B13 rs72613567 was significant only in selected subgroups of individuals–those aged ≥45 years, women and have class ≥2 obesity or diabetes, and those with PNPLA3 rs738409 CC genotype.[77]

CLINICAL AND TRANSLATIONAL IMPLICATIONS

Given the high effect sizes and genotypic variability associated with MASLD, there was optimism that precision medicine would be translatable to develop new drug targets as well as biomarkers to treat and/or predict MASLD and its liver-related events. Unfortunately, to date, none of the known variants, despite being widely studied, have successfully transitioned into established clinical use. Improvement in risk stratification and development of effective therapies for fatty liver disease remain key unmet clinical needs. Nevertheless, knowledge emerging from genomics could meet this need via use of polygenic risk scores for early disease detection and stratification of severity of fatty liver disease.

1. Risk stratification

There are studies in progress studying the use of these genetic variants as part of risk prediction models.

Bianco *et al.*[78] were able to predict HCC using a polygenic risk score in a European cohort based on PNPLA3, TM6SF2, GCKR, MBOAT7–common genetic variants associated with hepatic fat content (PRS-HFC), and thereafter further adjusted for HSD17B13 as well, in a second score called PRS-5. They showed that the PRS-HFC was significantly associated with increased risk of HCC, estimated to be around 3-fold, in the MASLD cohort, though diagnostic accuracy was only moderate (Table 2).[78] These results have also been shown to be useful in an Asian population.[79] The potential ability to predict HCC was verified with the HCC risk prediction score that was able to identify at risk patients with an area under the curve (AUROC) of 0.96.[32]

Looking beyond HCC, risk scores incorporating genetic variables have also been able to predict incident cirrhosis in patients with NAFLD.[80] The Genetic and Metabolic Staging score incorporates genetic variants with clinical and biochemical parameters to predict liver-related events within the MASLD advanced fibrosis cohort with an AUROC of 0.87 at 1, 3, and 5 years.[81] However, the AUROC drops to 0.7 when applied to the general population, which marks it as suboptimal as a screening tool,[81] though other studies have been promising: a genetic risk score comprising three common variants in PNPLA3, TM6SF2 and HSD17B13 has shown an association of up to 12-fold higher risk of cirrhosis and up to 29-fold higher risk of HCC.[82] This shows that such genetic scores may have the potential to predict the onset and progression of chronic liver disease in the general population. Vicenti and colleagues have also looked into combining the PRS-HFC score with noninvasive fibrosis scores such as NAFLD fibrosis score and fibrosis-4 to improve prediction of cirrhosis and liver events in the overall population.[83] Genetics can possibly even predict liver-related mortality, as the genetic variant PNPLA3 I148M has been found to be associated with increased liver disease mortality with a hazard ratio of 18.2.[54]

Overall, the current evidence suggests that genetic testing does have potential in identifying MASLD patients at higher risk of developing liver-related events including

Table 2. Risk Prediction Scores for Liver-Related Outcomes

Score	Genetic variant and components of score	Method	Cohort	Predicted outcome	AUROC	Diagnostic threshold	Odds ratio	Sensitivity	Specificity	Reference
Genetic risk score	PNPLA3, TM6SF2, HSD17B13	Blood test	General (European) population	Cirrhosis HCC	NA	Combined GRS calculated as sum of risk-increasing alleles with range: 0-6	Up to 12 for cirrhosis Up to 29 for HCC	NA	NA	[82]
Cirrhosis polygenic risk score	PNPLA3, TM6SF2, HSD17B13, MBOAT7, GCKR, TRIB1, APOE, GPAM	Blood test	NAFLD with diabetes and indeterminate FIB-4 (1.3–2.67)	Cirrhosis or portal hypertensive complications	0.73	NA	NA	NA	NA	[80]
PNPLA3-rs738409-GG genotype	PNPLA3				0.78	Presence of GG genotype		0.30	0.93	
HCC risk score*	Age, sex, obesity, T2DM, severe fibrosis, number of risk alleles (PNPLA3, TM6SF2 MBOAT7)	Composite score with clinical, metabolic and genetic factors	NAFLD	HCC	0.96	NA	13.4	0.96	0.89	[32]
Polygenic risk score–hepatic fat content (PRS-HFC)	PNPLA3, TM6SF2, MBOAT7, GCKR	Blood test	NAFLD	HCC	0.64	0.532	3.0	0.43	0.80	[78]
Polygenic risk score considering 5 risk variants (PRS-5)	PNPLA3, TM6SF2, MBOAT7, GCKR, HSD17B13	Blood test	NAFLD	HCC	0.65	0.495	2.9	0.43	0.79	[78]
Genetic and Metabolic Staging (GEMS) scoring system†	PNPLA3, HSD17B13, TM6SF2, male sex, diabetes, low HDL	Composite score of clinical, metabolic and genetic variables	NAFLD and FIB-4 ≥ 1.3	Liver-related events	0.87	Range from 0 to 10 0=total absence of risk of LREs 10=highest risk of LREs, then sub-categorized into five classes: 0–5, 5–6, 6–7, 7–8, 8–10	Risk of LREs increased from 4% in GEMS 0–5, to 91% in GEMS 8–10	NA	NA	[81]

AUROC, area under the curve; HCC, hepatocellular carcinoma; NA, not available; GRS, genetic risk score; NAFLD, nonalcoholic fatty liver disease; FIB-4, fibrosis-4 score; T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein; LRE, liver related events.

*A combined risk score considering acquired and genetic risk factors was developed to predict HCC: 1/(1+e– ((–12.588+(0.162×age)+(0.404×sex: 1 if male, –1 if female)+(0.259×obesity: 1 present, –1 absent)+(0.587×T2DM: 1 present, –1 absent)+(1.299×severe fibrosis: 1 yes, –1 no)+(0.442×number of risk alleles))); †The GEMS score is calculated using the following formula: 1.163–0.438(PNPLA3 CG/GG)+0.421(male sex)–0.413(diabetes)+2.635(55≤age<65)+2.888(age>65)+0.632(low HDL)+0.668(albumin <4 g/dL)+1.935(110,000/mm^3<platelets <150,000/mm^3)+2.605(platelets<110,000/mm^3)+0.602(HSD17B13 TTA/TATA)+0.661(TM6SF2 CT/TT)–1.146(interaction PNPLA3 CG/GG and male sex)+1.641(interaction PNPLA3 CG/GG and diabetes).

HCC, and even of mortality, though challenges remain in the overall ability to extrapolate use of such tests in the general population.

2. Treatment

Even as the space for therapeutics for MASLD remains exciting with recent new findings, the cornerstone for MASLD treatment remains lifestyle modifications.

Data suggests that genetic variations can also affect efficacy and response to lifestyle modification and exercise in MASLD. The presence of G allele in PNPLA3 rs738409 gene polymorphism was associated with greater reduction in intrahepatic TG, body weight, waist-to-hip ratio, blood total cholesterol, and low-density lipoprotein levels in MASLD patients who were enrolled in a 12-month community-based lifestyle modification program.[84] However, there was contrasting findings in a Japanese cohort that found greater reduction in body weight in MASLD patients with the c allele of PNPLA3 rs738409 rather than the G allele.[85] This difference could be accounted for by the lower body weight reduction in the Japanese study, where the dietary intervention is described only as a consultation at baseline visit, as compared to a more intensive regime and personalized meal plan performed by the study by Shen *et al.*[84] Interestingly, the impact of the G allele may be restricted beyond a minimum amount of weight loss. A closer look at the results from the Japanese study yields the finding that among patients with a body weight loss of more than 5%, the reduction of liver stiffness measurement was significantly greater according to the predominance of the G allele. The patient population amongst these two studies also may not be comparable given the higher percentage of advanced fibrosis in the Japanese study, and may suggest that the benefit of the G allele in PNPLA3 rs738409 gene polymorphism may be restricted to early intervention, prior to progression to advanced fibrosis, beyond which the impact may be lost or becomes minimal.

Genetic profiles may also be helpful in predicting response to therapy, which can guide the development of potential therapeutics. A study looking at treatment of NAFLD with silymarin – vitamin E combination was able to produce a decrease in transaminases, but PNPLA3 G-allele carriers responded poorly to the treatment.[86] In patients with T2DM, treatment with exenatide improved liver fat content in patients carrying PNPLA3 148I/I better than in patients with 148M/M.[87] Genetic modulation of therapeutic responses indicates that a genetic-based approach may be the way forward. Having genetically supported drug targets increases the likelihood of successful clinical development by 2-fold.[88] With recent success of drug development in atherosclerosis therapy, such as the PCSK9 story, which was rooted in discovery of drug target based on genetic profiling,[89] optimism persists that similar approaches can be applied to MASLD. Indeed, oligonucleotide-based therapies in the form of antisense oligonucleotide or small interfering RNA (siRNA) that target PNPLA3 and HSD17B13 are already being evaluated in phase 1-2 clinical trials for MASH currently.[90] Early reports do suggest some encouraging results; recently, early phase data pertaining to JNJ-75220795 (also known as ARO-PNPLA3), a hepatocyte-targeted N-acetylgalactosamine–conjugated siRNA against PNPLA3, demonstrated reduction of liver fat content in homozygous subjects for the PNPLA3 I148M variant.[91] The full results from these trials will help to further inform and guide emerging therapeutic strategic approaches in precision medicine. More tools are urgently needed to enable precision medicine as well as personalized medicine to be translated into clinical practice.

CONCLUSION

MASLD is the most common chronic liver disease at present, with increasing prevalence and clinical burden worldwide. The clinical phenotype is affected by a multitude of factors, of which genetic factors play a substantial role. While significant progress has been made in understanding the genomics of MASLD, more needs to be clarified.

Awareness of these factors, how they are related to the underlying pathogenesis and determining their functional impact is crucial to help identify high-risk patients and pave the way to develop novel precision medicine-orientated interventions.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors. Data acquisition: all authors. Data analysis and interpretation: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Approval of final manuscript: all authors.

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