Samarasinghe *et al.*
Egyptian Journal of Medical Human Genetics (2023) 24:53
https://doi.org/10.1186/s43042-023-00433-x

Egyptian Journal of Medical Human Genetics

REVIEW

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Genetic and metabolic aspects of non-alcoholic fatty liver disease (NAFLD) pathogenicity

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease showing a rising prevalence globally. Genetic predisposition plays a key role in the development and progression of the disease pathogenicity.

Main body This paper summarizes genetic associations based on their influence on several metabolic aspects such as lipid metabolism, glucose metabolism, hepatic iron accumulation and cholesterol metabolism toward the NAFLD pathogenicity. Furthermore, we present variations in some epigenetic characters and the microRNA profile with regard to NAFLD.

Conclusion As reported in many studies, the *PNPLA3* rs738409 variant seems to be significantly associated with NAFLD susceptibility. Other gene variants like *TM6SF2* rs58542926, *MBOAT7* rs641738 and *GCKR* variants also appear to be more prevalent among NAFLD patients. We believe these genetic variants may provide insights into new trends in developing noninvasive biomarkers and identify their suitability in clinical practice in the future.

Keywords Non-alcoholic fatty liver disease, Single nucleotide polymorphisms, *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*

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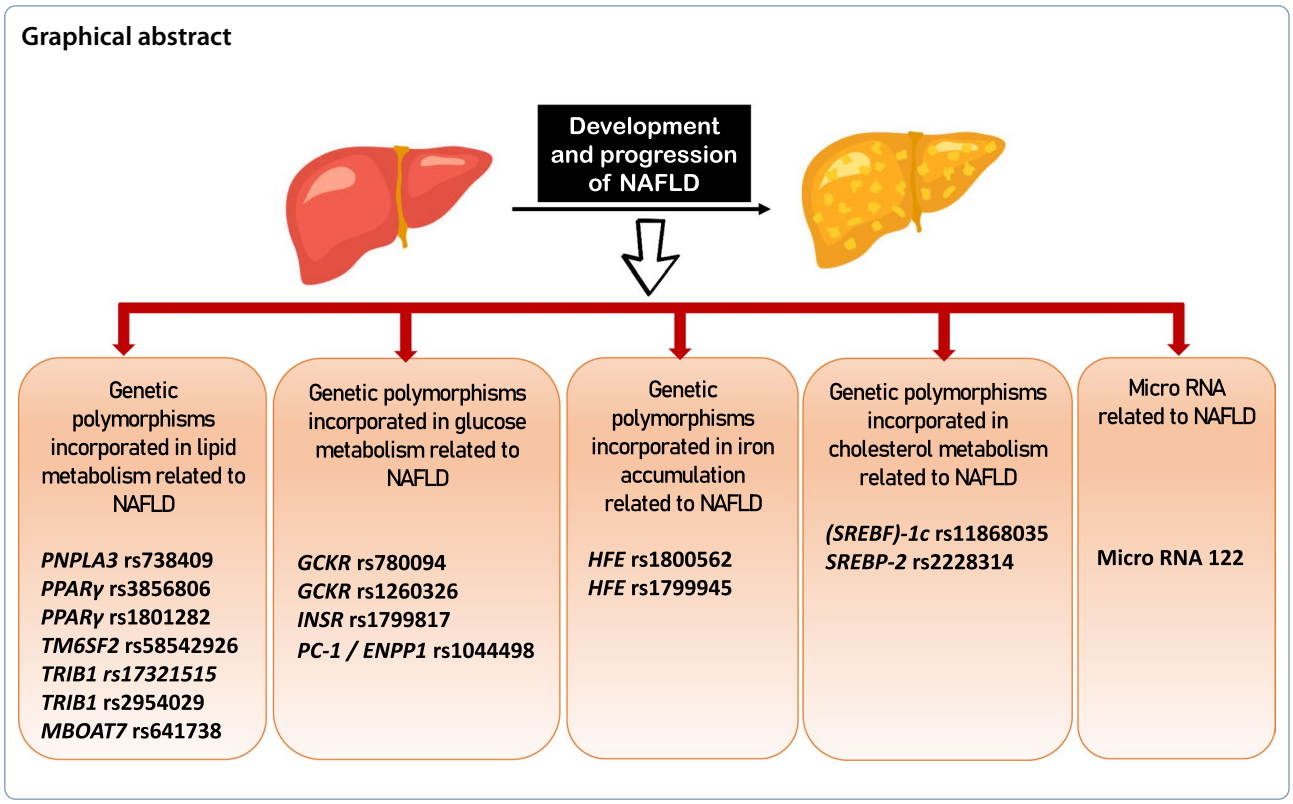

Background

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease covering a wide spectrum of liver pathology (Fig. 1) characterized by accumulation of excess fat in the liver (> 5–10% by weight) in the absence of significant alcohol consumption [1].

NAFLD is considered the liver manifestation of metabolic syndrome [2]. As represented in Fig. 2, several factors could possibly increase the risk for NAFLD. Recent evidences suggest that there is a strong genetic contribution toward susceptibility to NAFLD and its severity [3]. A range of single nucleotide polymorphisms (SNPs) have been implicated in this regard, and in this paper, we aim to investigate the genetic background concerning various metabolic aspects of NAFLD by evaluating literature from several studies that reported genetic variants contributing to NAFLD pathogenicity (Fig. 3). PubMed and google scholar search terms "genetic background of NAFLD" and "genetic studies on NAFLD" were used in selecting high-quality articles for the analysis of our topic of interest.

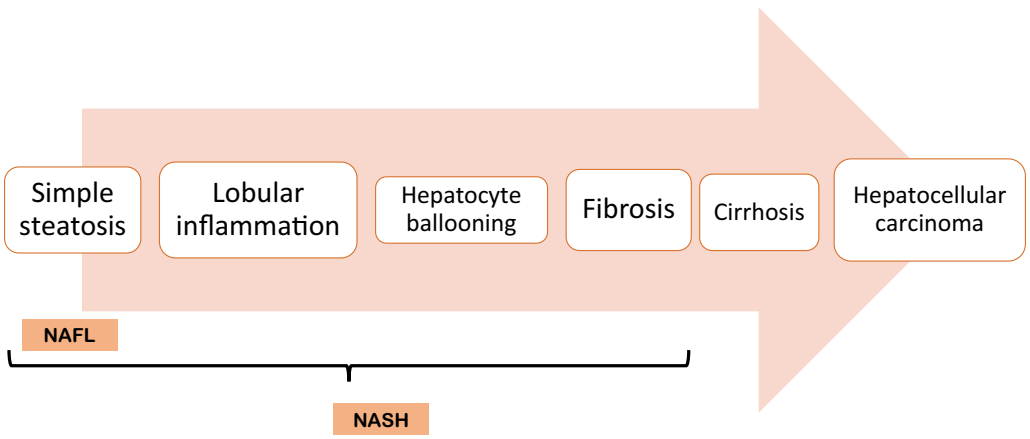

Fig. 1 NAFLD disease spectrum

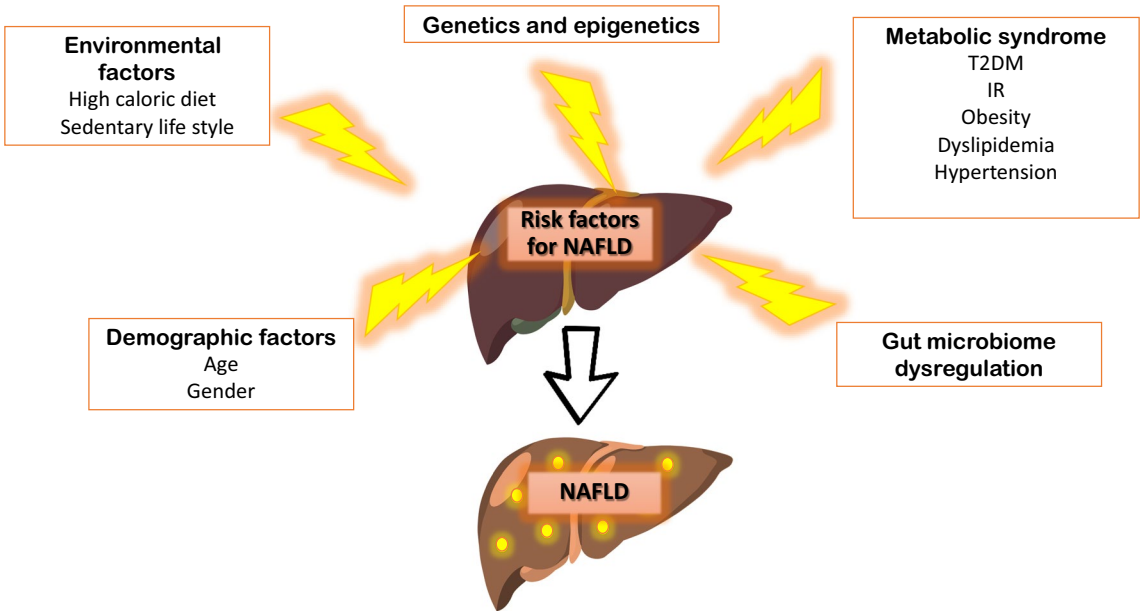

Fig. 2 Risk factors for NAFLD

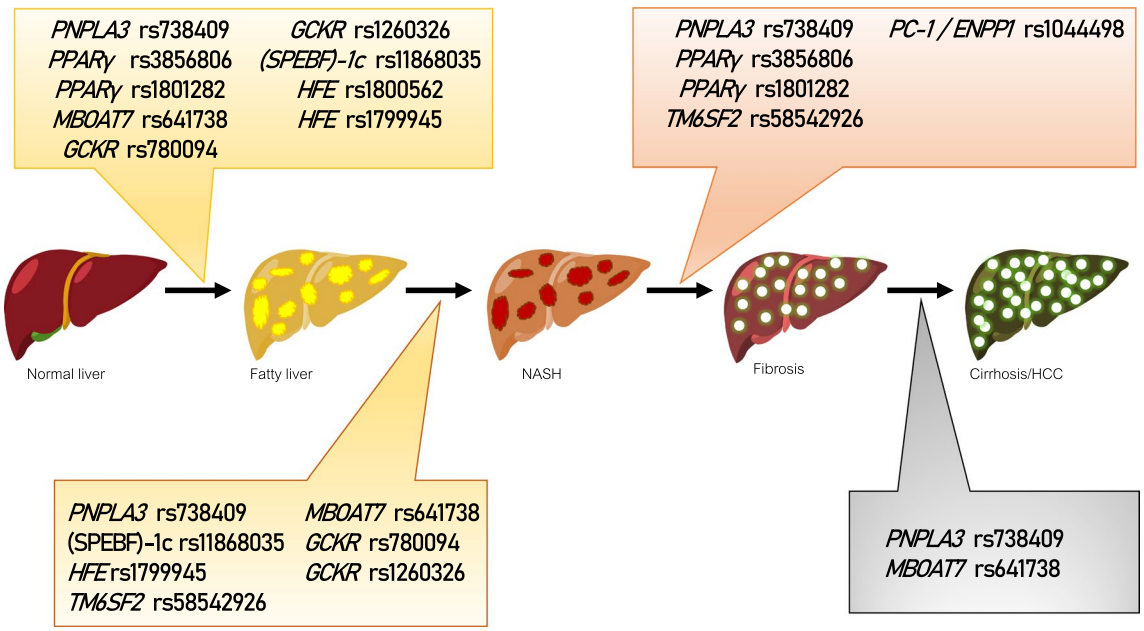

Fig. 3 Schematic representation showing genetic variants involved in different stages of NAFLD progression

Genetic polymorphisms incorporated in lipid metabolism related to NAFLD

PNPLA3 (patatin-like phospholipase domain-containing 3)

PNPLA3 encodes a protein with 481 amino acids that belonging to the patatin-like phospholipase domain-containing protein family, and its function remains unknown [4]. But the progenitor of the family, "patatin," is a lipid acyl hydrolase (LAH) found in potato tubers. Patatin catalyzes the hydrolysis of monoacylglycerols (MAG) and expresses transesterification activity [5]. The human PNPLA family consists of nine members, and they show diverse enzymatic functions. PNPLA2 was previously identified as a major triglyceride hydrolase in the adipose tissue [6, 7], whereas other studies showed that PNPLA3

is a transmembrane polypeptide expressed in adipose tissue, liver and adrenal glands [8–10]. PNPLA3 is confined to the endoplasmic reticulum and on the lipid, droplet surfaces [11]. Several functional roles have been assigned to PNPLA3. These include hydrolase activity [9, 12, 13] a role in lipid droplet remodeling [4, 14] transacylase activity producing alkyl esters [13] and lysophosphatidic acid acyl transferase (LPAAT) activity producing phosphatidic acid triacylglycerol (Fig. 4). Phosphatidic acid is a common precursor for triacylglycerol synthesis [15].

A SNP (rs738409) of cytosine to guanine substitution in *PNPLA3* that changes codon 148 from isoleucine to guanine (I148M) has shown a strong association with NAFLD. Romeo and his colleagues who first reported an association of the *PNPLA3* I148M variant with NAFLD pathogenicity identified this variation to be associated with hepatic fat levels and hepatic inflammation leading to the increased susceptibility to hepatic injury. Furthermore, they observed the carriers of the *PNPLA3* I148M variant, to have elevated serum levels of liver-derived enzymes which are considered as the markers of liver inflammation [16]. He et al. (2009) have shown that the I148M substitution promoted triglyceride accumulation in hepatocytes thus interfering with hepatic triglyceride hydrolysis leading to hepatic steatosis [4]. Further, I148M variant was reported to be associated with higher LPAAT activity leading to steatosis [15].

Yamamoto and his colleagues suggested that *PNPLA3* rs738409 variant is associated with NAFLD progression to cirrhosis and HCC in the Japanese population [17]. Tepper et al. (2018), who further validated this, showed a high frequency of the *PNPLA3* rs738409 [C>G] variant among the Hmong population and that it predisposes to NAFLD/NASH [18]. Valenti et al. (2010) reported that *PNPLA3* I148M in NAFLD patients is strongly associated with severe steatosis and with the presence of NASH and fibrosis in patients from Italy and the United Kingdom. This association was independent of age, basal metabolic rate (BMI) and diabetes. *PNPLA3* rs738409 GG genotype was more prevalent among NAFLD patients, and it was found to influence high-density lipoprotein (HDL) cholesterol and alanine transaminase (ALT) levels [19]. Their study was extended to evaluate the predisposition of the *PNPLA3* I148M variant to NASH and fibrosis in pediatric patients with NAFLD, and they observed that *PNPLA3* rs738409 GG genotype had a very high risk of progressive liver disease in the pediatric cohort [20]. Previously, it was reported that children from different ethnicities including Asians, Americans and Hispanics are more predisposed to develop NAFLD [21].

Alisi et al. (2011) reviewed the genetic background of NAFLD and the metabolic syndrome. The report concludes that both conditions have common genetic origins. They further reported this to be valid for both adults and children [22]. Chan et al. (2017) conducted a retrospective cohort study to evaluate the risk of developing fatty liver in chronic hepatitis B virus (HBV) infected patients without significant alcohol intake. The study revealed that *PNPLA3* rs738409 G allele was significantly associated with the susceptibility to the concurrent development of fatty liver in HBV patients. Furthermore, the study concluded that the concurrent fatty liver in HBV patients is a significant risk factor for progression to HCC in patients without significant alcohol intake [23].

Peroxisome-proliferator-activated receptors (PPARs)

PPARs are hormone receptors that bind to the promoters of the target genes in the ligand (hormone) bound state and activate transcription. There are three isotypes of PPARs, namely PPARα, PPARβ and PPARγ. All the members of PPAR are associated with lipid metabolism and transport. PPARα is expressed mostly in the adipose tissue and the liver. PPARα participates in fatty acid catabolism in the liver [24]. PPARβ mostly expressed in the gut, kidney, heart and the brain. PPARγ expressed mainly in the adipose tissue influences the fatty acid (FA) storage in the adipose tissue. Target genes of PPARγ directly participate in the lipogenic pathways. These include the genes expressing lipoprotein lipase (LPL), adipocyte FA binding protein, acyl-CoA and fatty acid transport protein (FATP) [24]. PPARγ also participates in the body's fat cell differentiation program [25]. Two common variations of *PPARγ*, rs1801282 and rs3856806 are important in the lipid metabolism pathways.

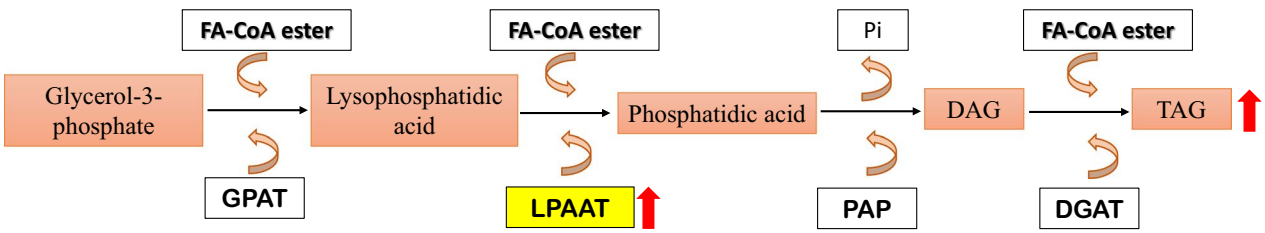

Fig. 4 Lysophosphatidic acid acyl transferase activity of PNPLA3 protein. GPAT, glycerol-3-phosphate acyltransferase; LPAAT, lysophosphatidic acid acyl transferase; PAP, phosphatidic acid phosphatase; DGAT, diacylglycerol acyltransferase

Hui et al. (2008) initially reported a significant association between a *PPARγ* gene variant (rs3856806) and NAFLD through an adiponectin-related pathway [26]. *PPARγ* rs1801282 variant was reported to increase the resistance to oxidative stress, thus increasing susceptibility to develop NAFLD through a Chinese case–control study. Further, it was revealed that both the C/C genotype of *PPARγ* rs1801282 polymorphism and smoking were independent risk factors for NAFLD [27]. Gawrieh et al. (2011) investigated the association of *PPARγ* rs1801282 and *PPARγ* rs3856806 with NAFLD in a North American cohort. The study revealed two haplotypes with two major alleles (CC) and two minor alleles (GT) in the NAFLD cohort are associated with steatosis and fibrosis. Minor alleles (GT) are reported to show a protective form of NASH by lowering the risk for steatosis, inflammation and fibrosis. The study concluded that the two SNPs do not show sufficient individual effects, but an additive effect could possibly promote the risk of developing NAFLD and NASH [28]. Another genetic study on *PPARγ* rs1801282 polymorphism showed that the heterozygous genotype was significantly higher in NAFLD patients [29].

TM6SF2 (transmembrane 6 superfamily member 2)

Transmembrane 6 superfamily member 2 (*TM6SF2*) is identified as a casual gene associated with lipid traits. But its actual function remains unknown. TM6SF4 is expressed predominantly in the liver and intestine [30]. *TM6SF2* is located in the 19q12 locus, and it encodes a protein of 351 amino acids [31]. Protein studies have revealed that TM6SF2 is comprised of 7–10 transmembrane domains, and it is localized in the endoplasmic reticulum (ER) and the ER-Golgi intermediate compartment of human liver cells [32]. TM6SF2 is a functional protein associated with hepatic triglyceride concentration. Functional studies have revealed that TM6SF2 inhibition is associated with reduced very-low-density lipoproteins (VLDL) secretion and elevated cellular triglyceride concentration leading to retention of TGs in hepatic lipid droplets causing a predisposition to fatty liver [30, 33]. But the overexpression of TM6SF2 is associated with reduced lipid droplet content [32]. Therefore, it is possible to suggest that TM6SF2 plays a role in NAFLD development. Another study demonstrated that TM6SF2 can influence total cholesterol levels and is associated with myocardial infarction [33].

Genome-wide association studies (GWAS) have revealed a *TM6SF2* variant (rs58542926) associated with the elevated liver fat level. This variant is an adenine-to-guanine substitution in coding nucleotide 499, which replaces glutamate at residue 167 with lysine (c.499A>G; p.Glu167Lys). This variant was associated with decreased VLDL secretions from hepatocytes [30] and a higher risk of myocardial infarction [33]. An association of the p.Glu167Lys variant with fibrosis in patients with NAFLD [34] was also reported. This variant was highly prevalent in individuals with European ancestry; prevalence was moderate in African Americans and Hispanics and rare in Asians [30, 35]. Dongiovanni et al. (2015) studied suspicion of NASH in severely obese patients of European descent for the possible effect of the *TM6SF2* p.Glu167Lys variant on liver diseases.. The *TM6SF2* p.Glu167Lys variant was found to be associated with a higher prevalence of NASH and advanced fibrosis. Furthermore, the study revealed that the *TM6SF2* p.Glu167Lys carriers are more susceptible to liver damage related to NAFLD. Nevertheless, obese carriers of *TM6SF2* p.Glu167Lys were reported to be protected from cardiovascular risk. They suggest that inhibition of VLDL secretion from hepatocytes may protect against cardiovascular diseases, but on the other hand, it increases the risk of developing severe liver disease [36].

A systematic evaluation done by Holmen et al. (2014) reported that the *TM6SF2* p.Glu167Lys C-allele carriage is a lipid-associated genetic variation influencing total cholesterol levels [33]. Also, strong associations were found between the variant and serum ALT levels [30, 33]. Further, the C>T minor allele in *TM6SF2* p.Glu167Lys was reported to be associated with an increased risk of greater steatosis as well as with the severity of steatohepatitis. The variant genotype also has a strong association with an increased risk of advanced fibrosis independent of gender, age, BMI and diabetes [34]. Sookian et al. (2015) showed that the rs58542926 variant is associated with a higher risk of fatty liver. An allelic test on the study subjects has shown that the T allele was significantly associated with the disease progression. They also reported that TM6SF2 protein expression in the liver was remarkably decreased in NAFLD patients compared with the controls [37].

TRIB1 (tribbles-1)

TRIB1 protein function to regulate cell differentiation, cell division and in protein degradation processes [38]. *TRIB1* polymorphisms are reported to be associated with lipid traits affecting lipid metabolism. Significant association of *TRIB1* polymorphisms, rs17321515 (A>G) and rs2954029 (A>T) with serum TG levels [39, 40] and an association of *TRIB1* rs17321515 with total cholesterol and LDL levels [41] has been reported. Liu et al. (2019) first reported an association of *TRIB1* polymorphisms and the risk of NAFLD. A alleles of rs17321515 and rs2954029 were associated with the risk of NAFLD and rs17321515. A allele was associated with higher LDL

levels in NAFLD [42]. Coronary heart disease (CHD) is a major complication observed in NAFLD; *TRIB1* polymorphisms are implicated in CHD [43] and later studies identified AA and GA genotypes of rs17321515 as those associated with CHD in NAFLD [44]. Serum lipid levels were significantly increased in A allele carriers [44].

MBOAT7 (membrane-bound O-acyltransferase domain-containing 7)

In 2015, Buch et al. reported a gene variant in the membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*) at rs641738 that increased the risk of alcoholic cirrhosis [45]. Later, this variant was shown to be associated with susceptibility to the development and progression of NAFLD [46]. MBOAT7 catalyzes acyl-chain remodeling of phosphatidylinositols (PIs). Mainly, it catalyzes the transfer of polyunsaturated fatty acids like arachidonoyl-CoA to PIs like lysophosphatidylinositol, allowing maintaining the required level of desaturation in cell membranes. The rs641738 T allele reduces MBOAT7 expression affecting PI composition of the hepatocyte plasma membrane favoring hepatocellular fat accumulation and initiating inflammatory responses leading to NASH [46]. In an Italian NAFLD cohort, each *MBOAT7* rs641738 T allele conferred an approximately 80% increased risk of HCC in patients without advanced liver fibrosis [47]. *MBOAT7* variant has been thus implicated to predispose to HCC in non-cirrhotic patients, suggesting it to be a useful biomarker to identify such patients. Luukkonen et al. (2016) also confirmed that this variation was also associated with histological liver damage marked with hepatic phosphatidylinositol remodeling. In a cohort of 3854 patients of European descent, rs641738 was associated with increased hepatic fat content and development of NAFLD [48].

Genetic polymorphisms incorporated in glucose metabolism related to NAFLD

GCKR (glucokinase regulatory protein)

Glucokinase (GCK), the predominant hexokinase isoenzyme in the liver, is also expressed in the β-cells of the pancreas. It is highly sensitive to glucose and plays a key role in glucose metabolism. The activity of GCK is tightly regulated by GCK regulatory protein (GCKR). This protein–protein interaction shows a ligand-dependent and inhibitory GCK activity in response to plasma glucose fluctuations [49].

In 2011, Speolite et al. initially documented that *GCKR* variants were associated with changes in liver and serum lipid levels predisposing to liver fat deposition [50]. *GCKR* rs780094 is an intronic SNP which has shown associations with glucose levels. A GWAS done on the Finnish and Swedish populations [51] has shown that *GCKR* rs780094 polymorphism favors high TG levels and lower glucose levels. The same results were demonstrated in another study done on a European population [52]. Also, this variant showed an association with low insulin resistance and lower T2DM risk [51]. *GCKR* rs1260326, a non-synonymous variant with C to T substitution, substituting leucine for proline (P446L) was also associated with fasting plasma glucose and TG levels [51]. The T allele of rs1260326 C>T and rs780094 C>T variants also showed a clear association with NAFLD and NASH [53]. The rs1260326 T allele was significantly associated with a higher grade of hepatic steatosis in Indian patients but not in Malay and Chinese patients.. When the study was extended to observe the effect of both *GCKR* and *PNPLA3* polymorphisms on the NAFLD risk, *GCKR* rs1260326, *GCKR* rs780094 and *PNPLA3* rs738409 in combination led to a greater risk of developing NAFLD than either of the SNP alone [53].

INSR (insulin receptor) gene

INSR gene coding for the insulin receptor is located on the short arm of chromosome 19 and is composed of 22 exons [54]. Insulin participates in the glucose metabolism pathways through INSR, with liver cells being a major target. Defects in *INSR* lead to IR, a major risk factor for the development and progression of NAFLD.

Impaired secretion of insulin was identified as the major predictor for glucose intolerance in NAFLD patients, and histological severity of NAFLD was directly associated with glucose intolerance independent of adiposity [55]. NAFLD patients had a high prevalence of IR compared to controls. IR in NAFLD patients was associated with higher aspartate transaminase (AST) and ALT levels [56]. IR was reported to be more severe in NASH than in simple fatty liver [57]. The proportion of CT at the *INSR* exon 2-2257 locus was significantly lower in NAFLD than in the controls when compared with the CC genotype [58] the study concluded the protective effect of the CT genotype against NAFLD.

Genetic studies to investigate *INSR* polymorphisms in developing NAFLD are rare. *INSR* Exon 17 is an important motif as it encodes the tyrosine kinase domain of the INSR protein [59]. Therefore, mutations in the exon 17 can directly lead to IR and rs1799817 polymorphism is located in it [60]. Nobakht et al. (2020) who investigated *INS* and *INSR* polymorphisms on NAFLD risk in an Iranian population observed a 90% lower risk for NAFLD in carriers of the *INSR* rs1799817 "TT" genotype when compared with the "CC" genotype and suggested that "TT" genotype has a protective effect for NAFLD risk [54].

PC-1 (plasma cell antigen-1)/*ENPP1* (ectoenzyme nucleotide pyrophosphate phosphodiesterase 1)

ENPP1 is a membrane glycoprotein that binds with INSR and inhibits its effects on glucose metabolism. Thus, overexpression of *ENPP1* can lead to IR [61]. *PC-1/ENPP1* Lys121Gln polymorphism is a gain of function variant causing stronger interaction with INSR.

Dongiovanni et al. (2010) observed the *PC-1/ENPP1* Lys121Gln polymorphism to be associated with increased fibrosis and fibrosis severity in NAFLD patients compared to healthy controls in a European cohort. This variant was also associated with diabetes and metabolic abnormalities in NAFLD patients, suggesting that these abnormalities may occur consequent to IR in them. The study concludes that *PC-1/ENPP1* Lys121Gln polymorphism influences INSR activity thus predisposing to liver damage in NAFLD [62].

Genetic polymorphisms incorporated in hepatic iron accumulation related to NAFLD

HFE polymorphisms

The *HFE* gene shows two common missense mutations (C282Y, H63D) in patients suffering from hereditary hemochromatosis (HH). HH is an autosomal recessive genetic disorder that causes enhanced iron absorption and hepatic iron deposition that can increase the risk of developing cirrhosis and HCC [63, 64].

C282Y, a G to A transition at nucleotide 845 that changes the amino acid cysteine to tyrosine, and H63D a C to G transition at nucleotide 187 that results in a histidine to aspartic acid substitution are reported as the most prevalent genotypes associated with HH [65, 66]. In an Indian population study, C282Y mutation was not present among patients with liver disorders including NASH, but the H63D variant showed 14.8% prevalence among NASH patients, though they did not have iron overload. Two of the NASH patients with hepatic iron load were heterozygous for H63D, and one homozygous patient did not have hepatic iron overload. The study concludes that iron overload in NASH and other liver malignancies is a non-HFE type in Indians. [67]. Saremi et al. (2016) reported a significant association of *HFE* C282Y polymorphism with NAFLD in Iranian patients with T2DM [68]. Hepcidin is the key regulator of iron homeostasis of the body. Nelson et al. (2012) investigated whether the iron loading in NAFLD/NASH is influenced by the hepcidin regulation among *HFE* genotypes and observed a positive correlation between hepatic iron stores and decreased serum hepcidin levels in all the *HFE* genotypes tested (C282Y, H63D and wild type). The study suggests that hepcidin regulation in NAFLD is determined by the iron stores of the body, regardless of *HFE* genotypes. Furthermore, the study found a potential role of *HFE* H63D in NAFLD pathogenesis possibly through an iron-independent pathway [69]. A similar result was found in a Polish study where a higher serum iron level was identified as a risk factor for NAFLD pathogenicity, regardless of *HFE* mutations [70].

Genetic polymorphisms incorporated in cholesterol metabolism related to NAFLD

SREBF (sterol regulatory element-binding factor) polymorphisms

SREBPs are being identified as regulators of cholesterol and lipid metabolism, and there are three members in the human SREBP family named SREBP-1a, SREBP-1c and SREBP-2 [71]. The sterol regulatory element-binding factor *(SREBF)-1c* gene codes for a transcription factor which is involved in de novo lipogenesis and hepatic insulin sensitivity [72]. *(SREBF)-1c* rs11868035 A/G variant is located in the intron region. A allele of this variant together with BMI changes was associated with an increased risk for NAFLD [72]. Furthermore, GA/AA carriers of the NAFLD cohort are reported to show more severe steatosis, higher NAFLD activity score and a higher prevalence of NASH. Also, *SREBF-1c* rs11868035 SNP was associated with impaired glucose homeostasis in NAFLD patients [72]. In contrast, in a Han Chinese population, none of the four common SNPs (rs62064119, rs2297508, rs11868035 and rs13306741) in the *SREBP-1c* gene were associated with the NAFLD risk or with the total cholesterol levels [73]. SREBP-2 is encoded by a separate gene on human chromosome 22q13 and is closely associated with cholesterol synthesis [74, 75]. Studies have shown enhanced SREBP-2 expression and free cholesterol in NAFLD patients compared to healthy controls. This shows that free cholesterol plays an important role in NAFLD, and it is correlated with SREBP-2 expression [76]. Wang et al. (2014) showed that the *SREBP-2* rs2228314 G>C polymorphism increases the risk of NAFLD in the Han Chinese population [77].

Miscellaneous

Steatohepatitic HCC (SH-HCC) is a histological subtype highly associated with metabolic syndrome [78]. Ando et al. (2015) conducted a genetic study with regard to the *CTNNB1* (Catenin beta-1) gene mutations to interpret phenotypic characteristics of SH-HCC. Exon 3 of the *CTNNB1* gene was previously known to be a mutational hotspot region according to the Catalogue of Somatic Mutations in Cancer (COSMIC). The study involved viable tumor tissues of 197 HCCs; 70 SH-HCCs and 127 conventional HCCs (C-HCCs). The mutational analysis revealed that 12 of 84 HCCs had missense mutations of the *CTNNB1* gene with a single SH-HCC case and 11 C-HCC cases. The study concludes that *CTNNB1*

mutations were less frequent in SH-HCC than in C-HCC [79].

Epigenetics

Epigenetic changes that affect gene expression without altering the DNA sequence reveal new perspectives on the pathogenesis of NAFLD. The prevalence of unhealthy diets and physical inactivity has led to the development of NAFLD through epigenetic mechanisms.

Epigenetic alterations of tumor suppressor genes contribute to the HCC emergence. Nishida et al. (2016) examined the DNA methylation levels in HCC and their surrounding non-cancerous liver. The study concludes that the epigenetic alterations in the tumor suppressor genes that are leading to hepatocarcinogenesis could result from oxidative DNA damage in hepatocytes. Furthermore, they have identified that the serum alpha-fetoprotein (AFP) levels and degree of ballooning show independent associations with this oxidative DNA damage [80].

(See Additional file 1 for summary of the NAFLD-associated genetic variants).

MicroRNA

miR-122

MicroRNA 122 (miR-122) was identified as a dominant hepatocyte-specific miRNA accounting for 70% of the liver's total miRNAs. [81]. Pivot roles for endogenous miR-122 were identified as tumor suppression and hepatocyte survival [82]. Also, Esau et al. (2006) showed that miR-122 is a key regulator of cholesterol and fatty acid metabolism in adult liver using mice models [83]. Furthermore, pathogenic repression of miR-122 has been observed in liver diseases such as NASH, cirrhosis and HCCs [84–86]

Tsai et al. (2012) observed key clinical phenotypes of human liver diseases in mice with a targeted deletion of *Mir122a*. These mice developed steatohepatitis, fibrosis and HCC together with disrupted livers which closely resembled disruptions found in human HCC. This study confirms the low expression of miR-122 in chronic liver diseases and HCCs, suggesting the restoration of miR-122 may be a therapy for such diseases [87]. Cheung et al. (2008) tabulated potential targets of miR-122 and pattern of expression regarding human NASH by studying patients with metabolic syndrome with/without suspected NAFLD. Significantly decreased liver tissue miR-122 levels were seen in NASH, and they also observed silencing of miR-122 can activate some lipogenic genes which are expressed in human NASH in vitro. [84]. In contrast to the situation in the liver tissue, Cermelli et al. (2011) reported that serum levels of miR-122 were significantly higher in NAFLD patients when compared with controls. Furthermore, the study shows a positive correlation between miR-122 and disease severity from simple steatosis to steatohepatitis and also with ALT and AST levels.. miR-122 appeared better than ALT, in detecting early disease stages in NAFLD conferring it as a suitable prognostic biomarker [88]. In a case–control study in biopsy-proven NAFLD, Pirola et al. (2015) showed that serum miR-122 level was upregulated in 7.2 folds in both simple steatosis and NASH and a systematic downregulation in miR-122 in the liver tissue in NASH [89]. Schütte et al. (2015) suggest that the high level of circulating miR-122 may be influenced by inflammation or apoptosis of hepatocytes in conditions like NAFLD, indicating miR-122 as a noninvasive biomarker for such HCC-related risk conditions [90]. Zhang et al. (2017) did a weighted gene co-expression network analysis (WGCNA) to identify potential key miRNAs and genes associated with the prognosis of HCC. The study concludes that the hsa-miR-363-5p may be a potential prognostic marker for HCC as its low expression was closely related to better survival of HCC [91]. Gene expression is regulated by upstream regulators (UR) like miRNAs, growth factors, transcription factors and cytokines [92]. Seshachalam et al. (2018) revealed that the miR-1249 is a major activated UR in 112 differentially expressed genes which are specific to NAFLD-HCC. Furthermore, five other miRNAs were also activated as URs in NAFLD-HCC (miR-7159-5p, miR-766-5p, miR-7056-5p, miR-6777-5p and miR-1249-5p). Also, it was found that the miR-4661-5p prominently inhibited UR in NAFLD-HCC [92].

(See Additional file 2 for summary of the included studies representing the association between miR-122 expression and NAFLD).

Association of genetic variations with NAFLD through different ethnicities

Danford et al. (2018) suggested that genetic factors play an important role in ethnic differences for NAFLD susceptibility among individuals [93]. In a large ethnically diverse cohort including African Americans, Japanese Americans, Latinos, native Hawaiians and Whites, *PNPLA3* rs738409 variant showed a similar risk allele association with NAFLD, across all five ethnicities studied, while Latinos showed the strongest among all. Hispanics showed high frequency for this variant, while African Americans showed a lower frequency for the risk allele [94]. Further, Han et al. (2021) reported that this variant has shown increased susceptibility to NAFLD among ethnicities such as Hispanics, African Americans, East Asians, and South Asians [95]. Interestingly, Asians represent a distinct phenotype as "lean NAFLD" showing a BMI lower than the generally accepted obese range [96].

PNPLA3 rs738409 variant has been reported to show associations with this lean NAFLD phenotype found among Asians [95, 97]). *TM6SF2* rs58542926 is another variant associated with lipid traits in NAFLD. Hispanics and Europeans were reported to show similar low frequencies for this variant [94, 98]. Also, this variant was reported to be lower in frequency in Chinese compared to Caucasians [99]. Another important variant associated with NAFLD severity is *MBOAT7* rs641738. This variant was reported to show associations with NAFLD among Caucasians but not among Hispanics and African Americans [100]. Interestingly, among Hispanic obese children, this variant was reported to show a protective role against NAFLD [101]. Two of the reported variants in the *GCKR* (rs780094 and rs1260326) gene were significant genetic determinants of NAFLD, particularly among African Americans and Latinos [94]. Understanding such ethnic variabilities for predisposing to NAFLD is important as it directly affects the generalizability of research data.

Association of NAFLD with COVID-19

A significant association between liver injury and the severity of COVID-19 infection has been reported in multiple studies recently [102–104]. Vrsaljko et al. (2022) showed NAFLD patients had a longer duration of hospitalization in COVID-19 infection together with significant elevations in liver-associated markers and more frequent pulmonary thrombosis [105]. Further, NAFLD patients with advanced fibrosis were reported to have a higher risk of developing severe COVID-19 [106, 107]. Another recent meta-analysis showed that NAFLD is an independent risk factor for severe COVID-19 in younger patients [108]. The presence of cirrhosis was reported to show higher mortality in COVID-19 patients compared to those without underline cirrhosis ($p < 0.001$) [109]. Similar observations were made by Sarin et al. (2020), reporting that obese cirrhotics were more susceptible for liver injury than normal weight cirrhotics in COVID-19 ($p = 0.02$) [110]. Also, obese patients with advanced NAFLD stages, such as in NASH, have been reported to show high likelihood in predisposing to COVID-19 [111]. A Chinese hospital-based study demonstrated that COVID-19 patients with NAFLD had significantly longer viral shredding time compared to non NAFLD patients ($p < 0.0001$). Further, the study reported that COVID-19 patients with NAFLD background had abnormal liver function with high risk of NAFLD progression [112]. In contrast, some reports conclude that the presence of NAFLD does not affect the severity of COVID-19 infection [113, 114]. Multiple studies have shown an important association between metabolic associated fatty liver disease (MAFLD) and COVID-19 severity [110,115].

Future perspectives

Due to the complexity beh ind the NAFLD pathogenesis, identification of favorable drug targets is still emerging. On this regard, defining pathological drivers for NAFLD could be a preferred approach. Toxic alterations in the liver's metabolic homeostasis are the key inducer of hepatic injury in non-alcoholic backgrounds. Genetics plays an important role in this regard as many studies including GWAS have defined loci which can induce metabolic dysfunction. In this review, we showed that such variations could be associated either with multiple stages or only with a specific stage of NAFLD. This is promising as those loci could be used as genetic biomarkers with both diagnostic and prognostic properties toward NAFLD. But to standardize such attempts, future studies should enable translational research with reproducible results with larger sample sizes. The recently proposed early diagnostic MAFLD criteria perform better than NAFLD identification criteria [116,117]. Basically, it combines metabolic syndrome evidences with hepatic steatosis features [118]. A recent Chinese community-based study has further investigated the genetic contribution together with such metabolic dysfunction features toward MAFLD development [119]. Such attempts that combine the metabolic and genetic signatures in defining MAFLD/NAFLD should be encouraged. Although liver biopsy remained the gold standard for diagnosis of NAFLD, it has major limitations due to the invasiveness of the procedure, cost and 10% false negativity [120]. Abdominal ultrasound is an effective NAFLD surveillance strategy, but still has questionable cost-effectiveness [121]. Therefore, genetic biomarkers with metabolic dysfunction features are promising due to noninvasiveness and cost-effectiveness. Future studies should validate such genetic and metabolic data through molecular assays to use them in developing favorable drug targets.

Conclusion

The genetic background of NAFLD is being widely investigated to identify pathogenic gene variants that may predispose to such conditions. Various studies were designed addressing candidate genes which may have some role in NAFLD pathogenicity. In this review, genes having potential roles in processes like lipid metabolism, glucose metabolism, hepatic iron accumulation, cholesterol metabolism and epigenetic characters were addressed in relation to NAFLD pathogenicity. *PNPLA3* rs738409 variant seems to be significantly associated with NAFLD disease susceptibility as studies on this gene variant were replicated in many populations. Also, other gene variants like *TM6SF2* rs58542926, *MBOAT7* rs641738 and *GCKR* variants appear to be more prevalent in the NAFLD susceptibility. Circulating miR-122 was also reported to be

upregulated in NASH validating the circulating miR profile as a prognosis biomarker. Patient characteristics and environmental factors to influence the outcome of the genetic effects. Therefore, factors like age, sex, BMI, co-morbidities such as diabetes mellitus and dietary factors should also be considered when comparing patient and control populations. Liver biopsy, a diagnostic method commonly used to detect NAFLD, is an invasive procedure. Therefore, studies revealing gene variants associated with NAFLD are important in developing noninvasive biomarkers for disease prediction, detection and monitoring prognosis.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
NAFL	Non-alcoholic fatty liver
NASH	Non-alcoholic steatohepatitis
LC	Liver cirrhosis
HCC	Hepatocellular carcinoma
T2DM	Type 2 diabetes mellitus
IR	Insulin resistance
SNPs	Single nucleotide polymorphisms
PNPLA3	Patatin-like phospholipase domain-containing 3
LAH	Lipid acyl hydrolase
MAG	Monoacylglycerols
LPAAT	Lysophosphatidic acid acyl transferase
BMI	Basal metabolic rate
HDL	High-density lipoproteins
ALT	Alanine transaminase
HBV	Hepatitis B virus
PPARs	Peroxisome-proliferator-activated-receptors
FA	Fatty acid
LPL	Lipoprotein lipase
FATP	Fatty acid transport protein
LDL	Low density lipoprotein
TG	Triglyceride
TM6SF2	Transmembrane 6 superfamily member 2
ER	Endoplasmic reticulum
VLDL	Very-low-density lipoproteins
GWAS	Genome-wide association studies
CHD	Coronary heart disease
MBOAT7	Membrane bound O-acyltransferase domain-containing 7
PIs	Phosphatidylinositols
GCKR	GCK regulatory protein
GCK	Glucokinase
INSR	Insulin receptor
AST	Aspartate transaminase
PC-1	Plasma cell antigen-1
ENPP1	Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1
HH	Hereditary hemochromatosis
SREBF	Sterol regulatory element-binding factor
SH-HCC	Steatohepatitic HCC
CTNNB1	Catenin beta-1
COSMIC	Catalogue of Somatic Mutations in Cancer
C-HCCs	Conventional HCCs
AFP	Alpha fetoprotein
miR	Micro RNA
WGCNA	Weighted gene co-expression network analysis
UR	Upstream regulators
MAFLD	Metabolic-associated fatty liver disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-023-00433-x.

Additional file 1: Summery of the NAFLD-associated genetic variants.

Additional file 2: Summery of the included studies representing the association between miR-122 expression and NAFLD.

Acknowledgements
Not applicable.

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Some of the research publications of RCS and MAN related to NAFLD:
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Author contributions
SMS wrote the manuscript. ASH, RCS, KHT, MAN and SDS reviewed the manuscript and provided critical comments. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 14 March 2023 Accepted: 21 August 2023
Published online: 29 August 2023

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