REVIEW

Genetic background in nonalcoholic fatty liver disease: A comprehensive review

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Author contributions: All authors contributed to writing the paper and had full control over preparation of manuscript; all authors approved the final draft manuscript.

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Abstract

In the Western world, nonalcoholic fatty liver disease (NAFLD) is considered as one of the most significant liver diseases of the twenty-first century. Its development is certainly driven by environmental factors, but it is also regulated by genetic background. The role of heritability has been widely demonstrated by several epidemiological, familial, and twin studies and case series, and likely reflects the wide inter-individual and inter-ethnic genetic variability in systemic metabolism and wound healing response processes. Consistent with this idea, genome-wide association studies have clearly identified Patatin-like phosholipase domain-containing 3 gene variant I148M as a major player in the development and progression of NAFLD. More recently, the transmembrane 6 superfamily member 2 E167K variant emerged as a relevant contributor in both NAFLD pathogenesis and cardio-vascular outcomes. Furthermore, numerous case-control studies have been performed to elucidate the potential role of candidate genes in the pathogenesis and progression of fatty liver, although findings are sometimes contradictory. Accordingly, we performed a comprehensive literature search and review on the role of genetics in NAFLD. We emphasize the strengths and weaknesses of the available literature and outline the putative role of each genetic variant in influencing susceptibility and/or progression of the disease.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Genetics; Genome-wide association studies; Patatin-like phospholipase domain-containing 3; Transmembrane 6 superfamily member 2; Candidate gene studies

Core tip: Nonalcoholic fatty liver disease (NAFLD) is regarded as the most significant liver disease from the twenty-first century in the Western world. Although its development is surely driven by environmental factors, it is also regulated by genetic background. The role of heritability has been widely demonstrated by several studies, likely reflecting the diverse genetic variability in systemic metabolism and wound healing response processes. Accordingly, we performed a review of the literature on the role of genetics in NAFLD and

outlined here the putative role of each genetic variant in influencing susceptibility and/or progression of the disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) consists of a spectrum of disorders characterized predominantly by macrovesicular hepatic steatosis in absence of significant alcohol consumption. In this context, it is correct to discriminate between a condition of simple fatty liver, where the only histological finding is the presence of steatosis, and a state of nonalcoholic steatohepatitis (NASH), featured by hepatocellular injury and inflammation, with or without fibrosis[1]. NAFLD is regarded as the most relevant liver disease of the twenty-first century. Indeed, it has been estimated that NAFLD affects approximately 1 billion individuals worldwide[2]. It is the number one cause of altered aminotransferases in the Western world[3], where at least one third of the population is affected[4]. Importantly, a considerable proportion of NAFLD subjects (20%-30%) develop NASH, and this condition, as opposed to simple fatty liver, is a potentially progressive hepatic disorder that can lead to end-stage liver disease and hepatocellular carcinoma (HCC)[5]. In addition, several lines of evidence clearly demonstrated that all NAFLD/NASH patients are at high risk of cardiovascular diseases, type 2 diabetes (T2D), kidney failure, and colorectal cancer[6]. In this complex scenario, NAFLD development is surely driven by environmental factors - particularly dietary habits and a sedentary lifestyle - but it also requires a background of genetic susceptibility. Indeed, the real explanation for the wide inter-individual variability in the occurrence of NAFLD and progression to NASH - after correction for environmental factors - is provided by heritability. Much data has been accumulated over the years about the burden of heritability in NAFLD, as provided by epidemiological, familial, twin studies, and case series[7-10]. Furthermore, racial and ethnic differences have been reported in the prevalence of NAFLD, where it is most common in East Asian Indians, followed by Hispanics, Asians, Caucasians, and less frequently in African Americans[11-13]. In addition to differential exposure to metabolic risk factors, genetic variability in metabolism and wound healing response have surely influenced - at least in part - such differences. Not by chance, a great amount of evidence on the role of genetics in NAFLD/NASH has

been produced during the last 10-15 years. Genetic studies can be divided into two categories: candidate gene studies and genome-wide association studies (GWAS). A GWAS is a hypothesis-free method for testing the association between all common variants in the human genome and polymorphic traits, such as diseases, drug response, and others. It is a powerful and statistically poorly biased method. On the other hand, candidate gene studies are generally derived from the results of previous genomic/proteomic and/or animal studies, where then a candidate gene is selected to investigate its putative role in the pathogenesis of a disease through a case-control single nucleotide polymorphism (SNP) study, with all potential methodological limits inherent to such type of study[14].

In this review, we have attempted to perform a comprehensive summary of the literature on the role of genetics in NAFLD/NASH, including the most recent evidence on genetic variants identified both by GWAS and candidate gene studies. Furthermore, we emphasize the strengths and weaknesses of the available literature for each variant, trying also to outline their putative role in NAFLD/NASH susceptibility and disease progression (Figure 1). Despite recent progress, several key issues remain to be addressed in the next years, particularly the details about the interaction between genetic background and acquired risk factors in disease pathogenesis and response to current treatments.

GENETIC VARIANTS AFFECTING NAFLD IDENTIFIED BY GWAS

Romeo *et al*[15] was the first to report that the rs738409 C>G SNP in the Patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene, encoding the isoleucine to methionine variant at protein position 148 (I148M), was strongly associated with increased liver fat content. Since then, several other pieces of evidence have highlighted the role of PNPLA3 in the development and progression of NAFLD. Furthermore, other SNPs have been identified by GWAS (Table 1). Among them, transmembrane 6 superfamily member 2 (TM6SF2) E167K variant is currently emerging as another relevant contributor both for NAFLD pathogenesis and cardiovascular outcomes.

PNPLA3

The *PNPLA3* (also known as adiponutrin) gene encodes a transmembrane polypeptide chain exhibiting triglyceride hydrolase activity[16], which is highly expressed on the endoplasmic reticulum and lipid membranes of hepatocytes and adipose tissue[17]. PNPLA3 activity is regulated by glucose and insulin[18], mainly *via* pathways involving the sterol regulatory element binding protein-1c, as demonstrated both
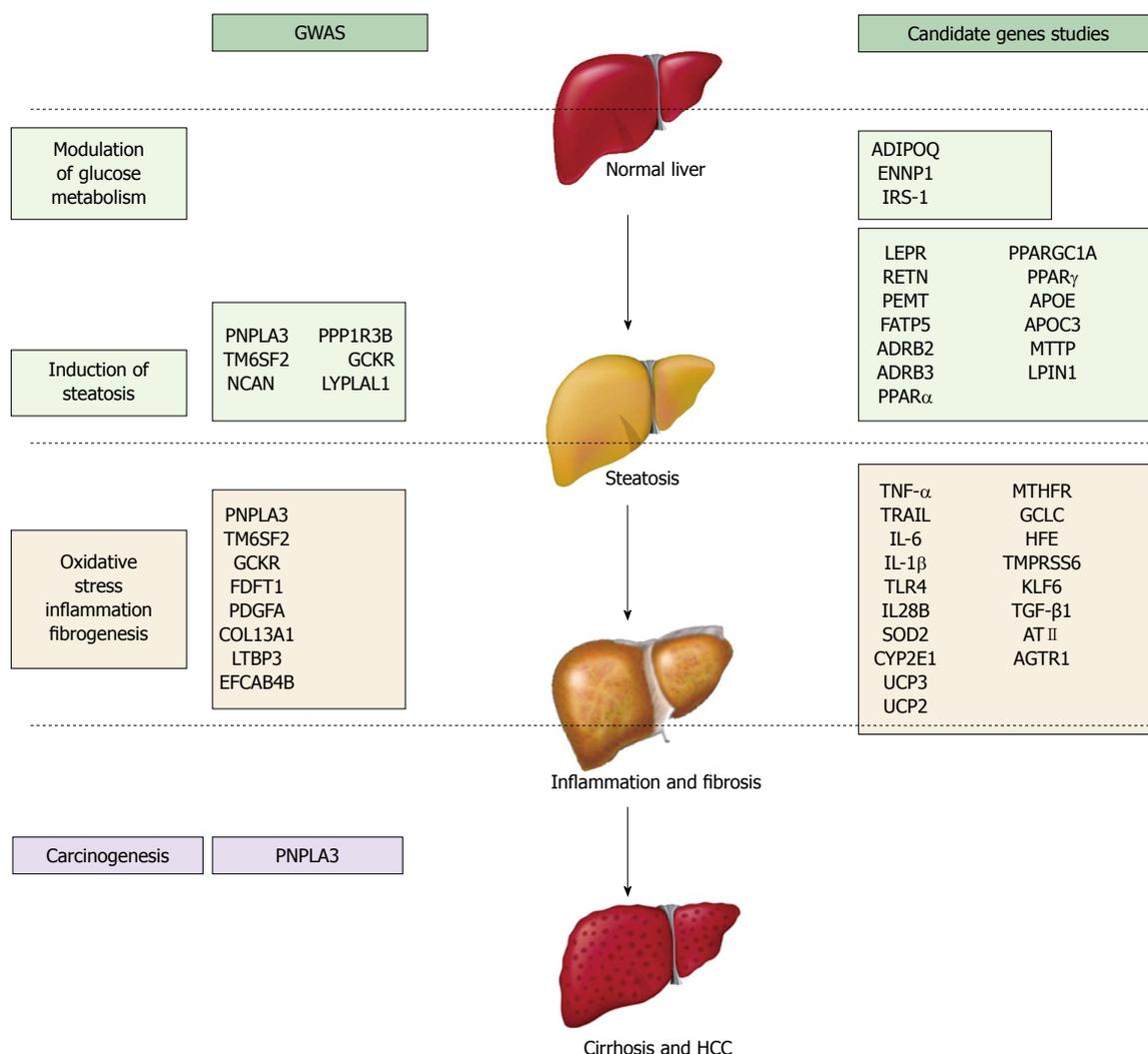
Figure 1 Hematic overview of the main genetic variants potentially involved in nonalcoholic fatty liver disease/nonalcoholic steatohepatitis susceptibility and progression. GWAS: Genome-wide association studies; HCC: Hepatocellular carcinoma.

in animal models and human hepatocytes[19]. The I148M variant - a SNP with a risk allele frequency of 21%-28% in European populations - impairs the phospholipase activity of the enzyme, thus reducing lipid catabolism, although it might also gain new functions[17] with a resulting increase in the synthesis of phosphatidic acid[20]. In addition, the PNPLA3 variant has been associated with a loss of retinyl-palmitate lipase activity in stellate cells[21]. Taken together, these data support a link between the PNPLA3 variant and the above reported wide spectrum of liver damage. As previously mentioned, the first report on the PNPLA3 I148M variant in NAFLD came from the GWAS by Romeo *et al*[15]. These authors identified the relationship between this SNP and liver fat content, and this association remained significant after adjusting for metabolic factors, ethanol use, and ancestry. Of great relevance, the link between PNPLA3 I148M variant and NAFLD is not confounded by the presence of metabolic syndrome (MS) and its features; indeed, even if some authors reported an interplay

between insulin resistance (IR) and the variant[22,23], most studies did not find such association, as confirmed by a recent meta-analysis[24]. Interestingly, this independent association between the PNPLA3 I148M variant and NAFLD could be more relevant in women than in men, as highlighted by Speliotes *et al*[25] in a gender specific analysis performed on a histological NASH cohort. Beyond these gender differences, however, the PNPLA3 I148M variant could explain, at least in part, the variations in NAFLD prevalence across different multiple ethnicities. Indeed, the original report by Romeo *et al*[15] already found that the frequencies of the 148M allele matched the prevalence of NAFLD in the Dallas Heart Study[11], such that Hispanics had the highest frequency of the 148M allele (49%), followed by European Americans (23%) and African Americans (17%). These ethnic differences were subsequently confirmed by other investigators[26]. Over the last few years, several studies not only have further emphasized how the PNPLA3 I148M variant is associated robustly with liver fat content[27,28]

Table 1 Genetic variants involved in susceptibility and/or progression of nonalcoholic fatty liver disease identified by genome-wide association studies

Gene	SNP	Association with
PNPLA3, patatine-like phospholipase domain containing 3	rs738409	Steatosis
		NASH/necroinflammation
		Severity of fibrosis
		HCC development
TM6SF2, transmembrane 6 superfamily member 2	rs58542926	Steatosis
		NASH/necroinflammation
		Severity of fibrosis
		Reduced cardiovascular risk
NCAN, neurocan	rs2228603	Steatosis
PPP1R3B, protein phosphatase 1 regulatory subunit 3b	rs4240624	Steatosis
GCKR, glucokinase regulatory protein	rs780094	Steatosis
		Severity of fibrosis
LYPLAL1, lysophospholipase-like 1	rs12137855	Steatosis
FDFT1, farnesyl diphosphate farnesyl transferase 1	rs2645424	NAFLD activity score
PDGFA, platelet-derived growth factor alpha	rs343062	Severity of fibrosis
COL13A1, collagen type XIII alpha1	rs1227756	Lobular inflammation
LTBP3, latent transforming growth factor-beta-protein 3	rs6591182	Lobular inflammation
EFCAB4B, EF-hand calcium binding domain 4B	rs887304	Lobular inflammation

SNP: Single nucleotide polymorphism; NASH: Nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease; HCC: Hepatocellular carcinoma.

but also revealed the link between the variant and the severity of liver injury, in terms of portal and lobular inflammation and Mallory-Denk bodies[29], presence of NASH, and severity of histological liver fibrosis[25,30] or liver stiffness measurement values[31]. This interplay between the PNPLA3 I148M variant and advanced fibrosis in patients with NASH has been further confirmed by a recent meta-analysis[32]. It is noteworthy that the role of PNPLA3 in NAFLD susceptibility and progression has been reported also in pediatric patients. In this line, the 148M allele was associated with higher liver fat content in Hispanic[33] and obese Taiwanese children[34], and with histological hallmarks of severity of liver injury - steatosis, hepatocellular ballooning and lobular inflammation, and presence of NASH and fibrosis - in Caucasian children and adolescents[35]. Interestingly, the PNPLA3 genotype seems to influence steatosis development also in chronic hepatitis C (CHC) patients, and it has been independently associated with the progression of CHC, including fibrosis, cirrhosis, and HCC occurrence[36,37]. Furthermore, it has been associated with susceptibility to steatosis in patients with chronic hepatitis B[38] and with cirrhosis and HCC development in patients with alcohol abuse[39,40]. Recently, the association between the *PNPLA3* variant I148M and the risk of HCC development has been robustly validated in patients with NAFLD[41,42], and it has been estimated that the homozygous carriers of the p.148M mutation carry a 12-fold increased HCC risk as compared to p.I148 homozygotes[43]. Considering all the aforementioned effects of PNPLA3 genotype on not only NAFLD, but also on alcoholic liver disease and CHC, some authors have proposed defining a novel clinical entity based on the presence of PNPLA3 risk allele - PNPLA3-associated steatohepatitis ("PASH") - *i.e.*, patients with fatty liver disease in whom PNPLA3

appears to be a major driver of disease progression in combination with ethanol consumption and Western diet[44]. Furthermore, PNPLA3 genotype has been evaluated as a possible modifier of NAFLD-associated systemic alterations. Our group recently examined the presence of carotid atherosclerosis in a Sicilian NAFLD cohort and its relation with several SNPs, including PNPLA3[45]. We found that the prevalence of carotid plaques and intima media thickness thickening was significantly higher in PNPLA3 GG compared to CC/CG genotype, particularly among patients under 50 years. This finding was also confirmed in a validation cohort from Northern Italy, where PNPLA3 GG genotype was independently associated with intima media thickness progression. Recently, Musso *et al*[46] associated the PNPLA I148M variant with the presence of chronic kidney disease, a well-known marker of a higher cardiovascular risk in NAFLD. Finally, a recent study by Sevastianova *et al*[23] evaluated whether weight loss was able to decrease liver fat in homozygous carriers of the G allele of PNPLA3; investigators found that liver fat content decreased significantly more in the 148MM group than in the 148Ⅱ after a short course of low carbohydrate diet, although 148Ⅱ and 148MM patients lost similar amounts of body weight. Overall, although the major role of PNPLA3 in susceptibility and progression of fatty liver has been widely elucidated, further research is needed to fully understand the role of PNPLA3 genotype on systemic alterations and treatment outcomes in patients with NAFLD/NASH.

TM6SF2

One of the most recently described and intriguing genetic factors in NAFLD scenario is the nonsynonymous variant rs58542926 (c.449 C>T) within a gene of mostly unknown functions called TM6SF2 at the 19p13.11 locus, which encodes an E167K

amino acid substitution. This variant is in strong linkage disequilibrium with other variants around the 19p13.11 locus that were previously reported by another GWAS (see further) to be risk factors for NAFLD[47], suggesting that the new and old signals could be the same, even if conditional analyses indicate that TM6SF2 rs58542926 may be the real causal variant underlying the association at this locus. The first evidence on this new SNP originated from three independent groups. Kozlitina *et al*[48] performed an exome-wide association study in a multiethnic, population-based cohort derived from the Dallas Heart Study, identifying the association between hepatic triglycerides content - evaluated by proton magnetic resonance spectroscopy - and the TM6SF2 variant rs58542926. In addition, the investigators highlighted the association between the TM6SF2 variant with higher serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels - as surrogate for NASH - and with reduced plasma levels of triglycerides and low-density lipoprotein (LDL)-cholesterol. Finally, they performed a functional analysis for the TM6SF2 in mouse models by silencing the gene *via* adeno-associated viral vectors. Silencing of the gene showed a 3-fold increase in hepatic triglycerides levels and a decrease in plasma levels of triglycerides, LDL- and high-density lipoprotein (HDL)-cholesterols and very low density lipoprotein (VLDL). Overall, their results demonstrated that the *TM6SF2* gene regulated hepatic triglyceride secretion and that the functional impairment of TM6SF2 promoted NAFLD. The second study conducted by Mahdessian *et al*[49] reported a positive correlation between hepatic TM6SF2 mRNA and plasma triglycerides levels and identified the subcellular localization and function of TM6SF2. Indeed, TM6SF2 was mainly localized in the endoplasmic reticulum and endoplasmic reticulum-Golgi intermediate compartment in human hepatoma cells. The TM6SF2 silencing in hepatoma cell lines reduced the expression of genes involved in the synthesis of triglycerides and the secretion of triglycerides-rich lipoprotein, demonstrating that TM6SF2 not only regulated hepatic lipoprotein secretion but also the hepatic synthesis of triglycerides. The third study reported by Liu *et al*[50] analyzed the relationship between the TM6SF2 rs58542926 SNP and the severity of liver disease in patients with biopsy-proven NAFLD. The authors found that the TM6SF2 rs58542926 SNP was associated with necroinflammation, ballooning, and advanced liver fibrosis. Taken together, these three studies provided evidence that the TM6SF2 variant was associated with the development of NAFLD/NASH *via* the deregulation of hepatic lipid metabolism. However, not all the authors reported unequivocal findings. Two studies, one from China[51] and one from South America[52], have been unable to replicate the relationship between TM6SF2 and NAFLD. This may be due ethnic differences in the frequency of carriage of the SNP and

to the analysis of underpowered cohorts. Conversely, another study from China[53] confirmed, once again, the association between the *TM6SF2* 167K allele and NAFLD after adjusting for age, sex, body mass index, and presence of T2D. Thus, the reasons for such discrepancies have not yet been elucidated fully. The most interesting aspect about this variant, however, lies in its key role for the elucidation of the mechanistic basis of progressive NAFLD and for the development of a novel point of view on the association between NAFLD and cardiovascular disease. Consistent with this line, Dongiovanni *et al*[54] found that 188 (13%) out of 1201 subjects who underwent liver biopsy for suspected NASH were carriers of the E167K variant and that they had lower serum lipid levels than noncarriers, more severe steatosis, necroinflammation, ballooning, and fibrosis and were more likely to have NASH and advanced fibrosis after adjusting for metabolic factors and the I148M PNPLA3 risk variant. In addition, E167K carriers had lower risk of developing carotid plaque; in Swedish obese subjects assessed for cardiovascular outcomes, E167K carriers had higher ALT and lower lipid levels but also a lower incidence of cardiovascular events. Consequently, carriers of the TM6SF2 E167K variant seem to be more at risk for progressive NASH, but at the same time they could be protected against cardiovascular diseases. Furthermore, Musso *et al*[46] found that the TM6SF2 T allele was associated with higher eGFR and with a lower prevalence of albuminuria and chronic kidney disease - another known marker of an increased risk for cardiovascular disease in NAFLD. In other words, TM6SF2 may act as a switch gene able to disconnect the risk of NAFLD/NASH progression from cardiovascular risk.

Other genetic variants influencing NAFLD identified by GWAS

In 2011, Speliotes *et al*[47] aimed to discover additional genetic variants influencing NAFLD susceptibility using a genome wide analysis of hepatic steatosis assessed by computed tomography (CT) in large population based samples. First, authors confirmed the prominent role of rs738409 of PNPLA3 as the main genetic risk factor for NAFLD. In addition, they identified four other SNPs. These were localized in or near the genes neurocan (NCAN - rs2228603), protein phosphatase 1, regulatory (inhibitor) subunit 3B (PPP1R3B - rs4240624), glucokinase regulator (GCKR - rs780094), and lysophospholipase-like 1 (LYPLAL1 - rs12137855). NCAN, GCKR, and LYPLAL1, together with PNPLA3, were associated with both increasing CT hepatic steatosis and histological NAFLD, whereas PPP1R3B was associated with CT-assessed steatosis but not histological NAFLD. NCAN is involved in mechanisms of cell adhesion and in lipoprotein metabolism, and its locus was subsequently casually related to the TM6SF2 minor allele (see above). LYPLAL1 likely exerts a complementary function to the PNPLA3

protein in trigliceride catabolism. The protein product of GCKR has been proposed to interfere with glucose and lipid homeostasis *via* the interaction with hepatic glucokinase and the consequent increased activity of the enzyme[55], ultimately raising the hepatic glycolytic flux, *de novo* lipogenesis, and triglyceride levels[56]. Several genetic association studies have confirmed the connection between GCKR rs780094 and NAFLD[57-60], including progression of the disease and fibrosis[61]. These findings were further confirmed by a recent meta-analysis[62] that demonstrated a similar effect size of such association in both Asian and non-Asian populations.

Finally, Chalasani *et al*[63] reported another GWAS in 2010, identifying other variants conferring susceptibility to occurrence of NAFLD and disease progression. On a cohort of patients with biopsy-proven NAFLD, investigators demonstrated an association between severity of histological NAFLD activity score and SNP rs2645424 in the gene encoding farnesyl diphosphate farnesyl transferase 1 - an enzyme involved in cholesterol biosynthesis. Strangely, they did not identify PNPLA3 as a risk factor. However, other associations were reported, including SNP rs343062 on chromosome 7 (near platelet-derived growth factor alpha gene) with the degree of fibrosis; SNP rs1227756 on chromosome 10 in the collagen type XIII alpha1 (*COL13A1*) gene, rs6591182 on chromosome 11 (near latent transforming growth factor-beta-protein 3 gene), and rs887304 on chromosome 12 in EF-hand calcium binding domain 4B (*EFCAB4B*) gene with lobular inflammation; and SNP rs2499604 on chromosome 1, rs6487679 on chromosome 12, rs1421201 on chromosome 18, and rs2710833 on chromosome 4 with serum levels of ALT. However, all of them require extensive validation in larger cohorts.

POTENTIAL GENETIC FACTORS INFLUENCING NAFLD/NASH IDENTIFIED BY CANDIDATE GENES STUDIES

Several genes have been identified as potential candidates in the pathogenesis and progression of fatty liver. In order to give a schematic overview, we roughly divided all candidate genes into two categories: genes influencing glucidic or lipid metabolism - directly or indirectly involved in fatty liver development (Table 2) - and genes involved in mechanisms of liver injury (Table 3).

Genes influencing glucidic or lipidic metabolism with a potential role in NAFLD pathogenesis
Ectonucleotide pyrophosphatase/phospho-diesterase1 or plasma cell antigen-1 and insulin receptor substrate 1: Insulin resistance - the hallmark of NAFLD pathophysiology - is strongly related to disease progression. Not by chance, SNPs of genes included in the hepatic insulin signalling pathway have consistently been reported to influence IR and to be potential causes of hepatic injury[64]. Among them, the ectonucleotide pyrophosphatase/phosphodiesterase1 (ENPP1)/plasma cell antigen-1 Lys121Gln SNP enhances the interaction between the ENPP1 membrane glycoprotein and the insulin receptor, resulting in inhibition of insulin receptor activity. This SNP has been associated with an increased risk of T2D[65]. Furthermore, the loss-of-function Gly972Arg SNP of IRS-1 - part of the machinery involved in the insulin signaling pathway - decreases activity of IRS-1, thereby inhibiting insulin receptor autophosphorylation and activity[66] and thus increasing the risk of IR and T2D[67]. Dongiovanni *et al*[68] analyzed the role of these two SNPs in influencing liver damage in 702 patients with biopsy-proven NAFLD from Italy and the United Kingdom, finding that both were independently associated with a marked reduction of insulin signaling activity and with increased the severity of liver fibrosis. Interestingly, the effect of the ENPP1 and IRS-1 SNPs on the severity of liver fibrosis was independent of ethnic background, as it was observed in patients from both Italy and the United Kingdom, thus emphasizing how hepatic IR has a causal role in the progression of liver damage in NASH.

Adiponectin: Adiponectin is a relevant adipocytokine associated with IR and T2D[69]. Several papers have demonstrated a significant decrease in the serum levels of adiponectin in NASH patients[70] and a reduced expression of its receptor in livers with NASH compared to those with simple steatosis[71]. Furthermore, adiponectin has been associated with liver fibrosis and inflammation[72,73], suggesting that it might be directly or indirectly involved in NASH pathogenesis. Variants in adiponectin (ADIPOQ) - the gene encoding adiponectin - have been investigated in order to find potential associations with NAFLD and its severity. Musso *et al*[74] showed that the at-risk ADIPOQ SNPs 45TT and 276GT were significantly more prevalent in NAFLD than in the general population and that they were associated with the severity of liver disease and with an atherogenic postprandial lipoprotein profile in NASH, independent of fasting adipokine and lipid levels. Consistent with this line, a Japanese study highlighted how such SNPs were associated with IR and progression of liver fibrosis in NAFLD Japanese patients[75]. However, these findings were not replicated in other cohorts. Although hypoadiponectinemia and IR were observed also in Chinese NAFLD patients, the 45TT and 276GT SNPs were not directly associated with NAFLD, even if they might have indirect effects on systemic metabolism and/or NAFLD pathogenesis by influencing serum ALT, body mass index, IR, and plasma adiponectin concentration[76]. It is possible that ethnic differences could explain the discrepancies among these studies.

Table 2 Genes influencing glucidic or lipid metabolism with a potential role in nonalcoholic fatty liver disease pathogenesis evaluated by candidate gene studies

Gene	Functions of encoded protein	SNP
ENPP1, ectonucleotide pyrophosphatase/ phosphodiesterase1 or PC-1	Interaction with the insulin receptor with consequent reduction of insulin receptor activity	rs1044498
IRS-1, insulin receptor substrate 1	Part of the machinery involved in insulin pathway as transductor of insulin receptor signaling	rs1801278
ADIPOQ, adiponectin	Relevant adipocytokine associated with insulin resistance, type 2 diabetes, and NAFLD pathogenesis	rs2241766 rs1501299
LEPR, leptin receptor	Receptor of leptin, a hormone synthesized by adipocytes that regulates food intake, insulin action, thermogenesis, and immune system	rs62589000 rs6700986 rs1137100 rs1137101 rs8179183
RETN, Resistin	Adipocytokine involved in lipid metabolism, hepatic insulin resistance, inflammatory cascade reactions, and fibrogenesis	rs3745367
PEMT, phosphatidylethanolamine N-methyltransferase	Enzyme involved in the *de novo* synthesis of phosphatidylcholine in the liver, a biochemical pathway essential for VLDL formation	rs7946
FATP5, Fatty Acid Transport Protein 5	Transporter involved in the hepatic uptake of fatty acids	rs56225452
ADRB2 and *ADRB3*, β-adrenergic receptor 2 and 3	β-adrenergic receptors, with several functions including regulation of basal metabolism and induction of lipolysis	rs4994 rs1042714 rs2053044 rs11168070 rs11959427 rs1042711
PPARα, peroxisome proliferative activated receptor α	Transcription factor whose activation improves steatosis, inflammation, and fibrosis in pre-clinical models of NAFLD	rs1800206
PPARGC1A, peroxisome proliferator-activated receptor γ coactivator 1-α	PGC-1α, involved in mitochondrial functions, oxidative stress, gluconeogenesis, and lipogenesis	rs8192678 rs2290602
PPARγ, peroxisome proliferative activated receptor γ	Transcription factor whose activation improves IR, restores adipose tissue insulin sensitivity, and decreases fatty free acids flux to the liver	rs1801282
APOE, apolipoprotein E	Mediator of remnant lipoprotein binding to LDL receptors to favor the clearance of chylomicrons and VLDL	N/A
APOC3, apolipoprotein C-Ⅲ	A constituent of plasma VLDL, chylomicrons, and HDL-C that inhibits lipoprotein lipase and triglycerides clearance	rs2854116 rs2854117
MTTP, microsomal triglyceride transfer protein	Transfer protein involved in apoB-lipoprotein assembly	rs1800591 rs1800804 rs1057613 rs3805335
LPIN1, lipin 1	Phosphatase specifically involved in metabolic pathways between adipose tissue and liver	rs13412852

SNP: Single nucleotide polymorphism; NAFLD: Nonalcoholic fatty liver disease; HDL-C: High-density lipoprotein-cholesterols; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein.

Leptin receptor: Leptin is a hormone synthesized by adipocytes that regulates food intake, insulin action, thermogenesis, and the immune system[77]. Several studies[78,79] have demonstrated the association between serum leptin levels and risk of NASH, although results have been sometimes conflicting[80]. Accordingly, the leptin receptor has been investigated due to its potential relevance in the modulation of leptin sensitivity: common variants in the human leptin receptor (*LEPR*) gene have been related with obesity and lipid metabolism[81], IR and T2D[82], and NAFLD[83-86]. The LEPR G3057A variant has been associated with the risk of NAFLD in Chinese diabetic patients[83], whereas Swellam *et al*[84] showed that NAFLD occurrence was associated with another SNP in LEPR - rs6700986 - in an Egyptian cohort. Furthermore, Zain *et al*[85] investigated the relationship between polymorphisms in LEPR and NAFLD across different Asiatic ethnic groups (Malayan, Indian, and Chinese). Two SNPs (LEPR rs1137100 and rs1137101)

were associated with susceptibility to NAFLD and NASH; and, intriguingly, analysis of gene-gene interaction showed a potential interplay between the *LEPR* and *PNPLA3* genes. Finally, Lys656Asn SNP of LEPR was associated with metabolic factors - namely IR, obesity parameters, and glucose levels - in patients with NAFLD[86]. Thus, LEPR variants may be involved in the occurrence and progression of NAFLD by influencing insulin sensitivity and/or lipid metabolism, even if further evidence should be provided to reinforce such observations.

Resistin: Resistin (RETN) is an adipokine with relevant metabolic actions and a potential role in NAFLD pathogenesis. Indeed, murine models showed that RETN is able to modulate lipid metabolism and hepatic IR[87,88] and may also participate in inflammatory cascade reactions known to be involved in NASH development[89] and in processes of fibrogenesis[90]. Many SNPs of *RETN* gene have been investigated as

Table 3 Genes potentially involved in mechanisms of liver injury in nonalcoholic fatty liver disease evaluated by candidate gene studies

Gene	Functions of encoded protein	SNP
TNF-α, tumor necrosis factor-α	Proinflammatory cytokine also involved in the regulation of insulin resistance, release of free fatty acids, and apoptosis in hepatocytes	rs1800629 rs361525 rs1799964 rs1800630
TRAIL, TNF-related apoptosis -inducing ligand	Protein functioning as a ligand that induces celluar apoptosis	rs6763816 rs4491934
IL-6, interleukin-6	Proinflammatory cytokine produced by adipocytes, hepatocytes, and immune cells also involved in the modulation of insulin resistance	rs1800795
IL-1β, interleukin-1β	Member of IL-1 family cytokine, mainly produced by adipose tissue	rs16944
TLR4, toll-like receptor 4	Receptor involved in the interaction with bacterial endotoxins capable to favor hepatic injury and a proinflammatory systemic status	rs4986790
IL28B, interleukin-28B	Cytokine belonging to the type Ⅲ Interferon family	rs12979860
SOD2, superoxide dismutase 2	Manganese-dependent mitochondrial enzyme involved in protection from cellular injury induced by superoxide radicals	rs4880
CYP2E1, cytochrome P450 2E1	Part of the cytochrome P450 complex	rs2031920
UCP3, uncoupling protein 3	Mitochondrial anion carrier involved in the metabolism of superoxide radicals and in the modulation of lipid homeostasis	rs1800849 rs11235972
UCP2, uncoupling protein 2	Similar to uncoupling protein 3	rs695366
MTHFR, methylenetetrahydrofolate reductase	Enzyme involved in the methylation of homocysteine to methionine	rs1801133 rs1801131
GCLC, Glutamate-cysteine ligase catalytic subunit	Limiting enzyme in the formation of glutathione, a relevant endogen antioxidant	rs17883901
HFE, hemochromatosis	Crucial protein for the regulation of iron homeostasis *via* the modulation of the expression of hepcidin	rs1800562 rs1799945
TMPRSS6, trans-membrane protease serine 6	Matriptase-2, which cleaves the membrane-bound hemojuvelin, the co-receptor required for hepcidin expression in the liver	rs855791
KLF6, kruppel-like factor 6	One of the Kruppel-like factors, a family of transcriptional factors that regulate cellular proliferation, differentiation, and apoptosis	rs3750861
TGF-β1, transforming growth factor β1	In the liver, a promoter of hepatic fibrosis *via* the activation of hepatic stellate cells	rs1800471
ATⅡ, angiotensin Ⅱ	Part of the renin-angiotensin system, also advocated as an inducer of TGF-β1 production and accumulation of extracellular matrix in the liver	rs699
AGTR1, Angiotensin Ⅱ Type 1 Receptor	Type 1 Receptor of Angiotensin Ⅱ	rs3772622 rs3772633 rs2276736 rs3772630 rs3772627

SNP: Single nucleotide polymorphism; TGF: Transforming growth factor.

potential risk factors for MS and its components[91]. A Chinese study[92] investigated the role of the RETN intronic +299G/A SNP in a NAFLD setting and found that patients with both T2D and NAFLD had the highest plasma RETN levels compared with diabetic patients without evidence of NAFLD and with controls. Furthermore, the AA genotype at the +299 site of the *RTEN* gene was found to be an independent risk factor for the development of NAFLD in T2D patients at multivariate analysis. However, further studies are needed to confirm this simple association.

Phosphatidylethanolamine N-methyltransferase: Phosphatidylethanolamine N-methyltransferase (PEMT) is a relevant enzyme involved in the *de novo* synthesis of phosphatidylcholine in the liver[93], a biochemical pathway essential for VLDL formation. Thus, PEMP is involved in the flux of lipid between the liver and plasma, where lack of phosphatidylcholine caused severe steatosis in mice models[94]. A higher frequency of a nonsynonymous sequence variation (V175M) in the *PEMT* gene, which results in a loss-of-function in the encoded protein, was reported in patients with biopsy-proven NAFLD compared with subjects with normal hepatic triglyceride content assessed by magnetic resonance or by liver biopsy[95]. Similarly, Dong *et al*[96] found that the occurrence of the V175M variant allele was significantly more frequent in 107 Japanese patients with biopsy-proven NASH than in 150 healthy controls. Conversely, Jun *et al*[97] did not find any difference in PEMT genotype frequency between NAFLD patients and controls, and Romeo *et al*[98] demonstrated a lack of any association between the V175M allele and hepatic triglyceride content - assessed by proton magnetic resonance spectroscopy - in their cohort derived from the Dallas Heart Study, a population-based sample from Dallas, Texas[99]. Overall, the available evidence is not enough to firmly consider PEMT as a relevant genetic factor for NAFLD susceptibility and more studies are needed in this setting.

Fatty acid transport proteins: Fatty acid transport proteins (FATPs) are critically involved in the uptake of fatty acids[100], and two different FATP isoforms are expressed in the liver, namely FATP2 and FATP5[101].

Mice models have emphasized the role of FATP5 in increasing the hepatic uptake and trafficking of fatty acids, so that gain-of-function polymorphisms may result in increased steatosis[102]. Auinger *et al*[103] investigated the consequences of the rs56225452 FATP5 promoter polymorphism on lipid and glucose metabolism and on features of MS in a cohort derived from the Metabolic Intervention Cohort Kiel - a prospective population-based cohort study of the town of Kiel, in Germany, on natural incidence of the MS[104] - and subjects with histologically proven NAFLD. Triglycerides, ALT, and postprandial insulin levels were higher in subjects with the A allele compared with GG homozygotes in the Metabolic Intervention Cohort Kiel cohort, whereas in NAFLD patients, the A allele was associated with higher ALT only. However, the impact of body mass index on the severity of steatosis differed according to FATP5 promoter SNP, suggesting that this polymorphism may be associated with MS and - probably indirectly - with liver damage in NAFLD. Additional independent studies are needed to fully clarify this interesting, even if still unclear, association.

β-adrenergic receptors: β-adrenergic receptors (ADRB) play an important role in regulating basal metabolism, mostly by stimulating lipid mobilization through lipolysis. Several polymorphisms have been detected in *ADRB* genes that influence IR, hypertriglyceridemia, and features of MS[105-108]. These polymorphisms were evaluated in NAFLD settings, although with conflicting results. A Japanese study involving 63 patients with biopsy-proven NASH analyzed a W64R codon substitution in *ADRB3* gene: the R allele frequency in patients with NASH was significantly higher compared with controls[109]. Other authors examined two nonsynonymous polymorphisms involving the *ADRB2* gene (*Gln27Glu* and *Arg16Gly*): no significant association with fatty liver was observed for the Arg16Gly allele, whereas the Gln27Glu heterozygotes showed a higher prevalence of fatty liver compared with those without the mutation at univariate analysis, even if this association was not confirmed at multivariate analysis[106]. Loomba *et al*[110] have published the most relevant study on ADRB2 in 2010. The authors evaluated whether common variants at *ADRB2* gene in twins were associated with plasma γGT levels - a well-known significant predictor of the MS as well as NAFLD[111,112]. Interestingly, five SNPs in ADRB2 were associated with levels of γGT, and ADRB2 haplotypes displayed pleiotropic effects on γGT and triglyceride levels, suggesting that adrenergic pathways may act as a link between genetic susceptibility to NAFLD and MS.

Peroxisome proliferative activated receptor α, peroxisome proliferative activated receptor γ, and peroxisome proliferator-activated receptor γ coactivator 1-α: Peroxisome proliferative activated receptor (PPAR) α is a transcription factor belonging, together with PPARγ and PPARβ/δ, to the NR1C nuclear receptor subfamily. PPARα activation improves steatosis, inflammation, and fibrosis in pre-clinical models of NAFLD[113], whereas PPARγ improves IR and has been reported to restore adipose tissue insulin sensitivity and decrease fatty free acids flux to the liver[114]. Regarding PPARα SNPs and NAFLD, a Chinese study evaluated the frequency of the val227ala variant on patients with NAFLD compared with control subjects[115]. As the distribution of PPARα val227ala polymorphism was significantly different between the two groups, the authors hypothesized that the Val227 isoform - the one predominant in NAFLD subjects - has lower activity than the Ala227 isoform, thus resulting in a reduced lipid catabolism and an increased risk for NAFLD. Another PPARα variant examined in a setting of NAFLD is the loss-of-function Leu162Val. Dongiovanni *et al*[116] did not find any association between this SNP and the risk of NAFLD occurrence and histological severity, although it was independently related to IR. The same study also assessed the Pro12Ala loss-of-function SNP in *PPARγ2* gene. Even if this polymorphism had been identified as an important mediator for the development of obesity, IR, and T2D[117], no significant association with NAFLD susceptibility and severity was found. Importantly, this SNP was not even associated with IR in this cohort. Similar conclusions were argued by a recent meta-analysis[118] including 1697 cases and 2427 controls derived from eight studies[116,119-125]. No clear evidence of an association between the Pro12Ala polymorphism and susceptibility to NAFLD emerged. The protein PGC-1a is encoded by the peroxisome proliferator-activated receptor γ coactivator 1-α (*PPARGC1A*) gene and regulates mitochondrial functions, oxidative stress, gluconeogenesis, and lipogenesis[126]. The Gly482Ser SNP in *PPARGC1A* gene has been repeatedly associated with T2D, hypertension, and obesity in clinical studies[127-129] and also with an impaired capability of PGC-1α to decrease fat deposition in cultured hepatocytes[130]. In this line, it was also associated with the development of NAFLD in Taiwanese obese children after controlling for body mass index, sex, and PNPLA3 genotype[131]. Yoneda *et al*[132] examined 15 SNPs in PPARGC1A in the Japanese population; they found that rs2290602 SNP was associated with NASH, with an odds ratio (OR) of 2.73 for the T allele. In addition, AST and ALT values of NAFLD patients with the TT genotype were significantly higher than those of patients with the GT or GG allele. However, this association was not further confirmed; a study among the Chinese Han people did not find any association between rs2290602 SNP in *PPARGC1A* gene and NAFLD[133].

Apolipoprotein E and apolipoprotein C-Ⅲ: Apolipoprotein E plays a key role in the metabolism of cholesterol and triglycerides. Indeed, it mediates the binding of the remnant lipoproteins to LDL receptors to favor the clearance of chylomicrons and VLDL from the bloodstream. Two SNPs within the apolipoprotein

E (*APOE*) gene have been identified, resulting in three different alleles (e2, e3, e4) and six *APOE* genotypes with different binding powers[134]. Some association studies investigated the role of *APOE* genotypes on NAFLD/NASH susceptibility with conflicting results. The *APOE* 3/3 genotype was associated with an increased risk of NASH in a cohort of Turkish patients[135], whereas the *APOE* 3/4 genotype had a protective effect[136]. Conversely, Lee *et al*[137] showed no significant difference in *APOE* genotypes distribution among 116 Korean NAFLD patients and 50 controls. However, a protective effect of the e4 allele on fatty liver disease was later shown by Yang *et al*[138] on a large Korean population. Finally, an Italian hospital-based case-control study including 310 NAFLD cases and 422 controls showed that APOE e4 allele carriers had a 2-fold reduction of NAFLD risk compared with e3 homozygotes[139]. The discrepancies between these studies might be attributable to several factors, including different sample sizes, ethnic variability, possible inclusion of alcohol consumers, and lack of clear adjustments for potential metabolic confounders. Apolipoprotein C-Ⅲ is a major constituent of plasma VLDL, chylomicrons, and HDL-C, which inhibits lipoprotein lipase and triglyceride clearance[140]. Two SNPs in the promoter region of the *APOC3* gene - -482C > T and -455T > C, which are in strong linkage disequilibrium with each other - have been repeatedly associated with MS and coronary artery disease[141]. Based on these findings, several studies investigated the association between SNPs of *APOC3* gene and NAFLD occurrence, although with conflicting results. Petersen *et al*[142] firstly reported that ApoC3 T-455C and C-482T promoter SNPs predispose Indian men to liver fat accumulation by altering lipid metabolism and IR. Similar positive results were obtained in Indian[143] and Southern Han Chinese cohorts[144]. However, this association was not further replicated in other studies conducted on Italian[145], British[145], American[146], Finnish[147], German[148], Belgian[149] and Chinese Han[150] subjects. A recent meta-analysis confirmed the absence of a robust association and, therefore, the lack of a causal pathogenetic role of *APOC3* gene polymorphisms in patients with NAFLD[151]. These contrasting findings raise doubts about the methodology and quality of some of these studies, particularly about the methods used to diagnose NAFLD and to adjust for confounders.

Microsomal triglyceride transfer protein: Microsomal transfer tryglicerides protein is a transfer protein involved in apoB-lipoprotein assembly[152]. A large number of common genetic polymorphisms in the microsomal triglyceride transfer protein (*MTTP*) gene have been identified. The G allele of MTTP - 493 G>T polymorphism has been associated with impaired MTTP transcription, and, thus, with a reduced export of triglycerides from hepatocytes and increased susceptibility to NAFLD[153]. Accordingly, the G allele frequency was significantly higher in Japanese patients with NASH, and the severity of NASH was higher in patients with the G/G genotype than in patients with the G/T genotype[154]. Similarly, the -493 G/G genotype was reported to be associated with more severe liver disease and a more atherogenic lipoprotein profile in an Italian cohort[155]. Furthermore, in diabetic French patients, this SNP was associated with elevated ALT as a surrogate marker for NASH[156]. However, other studies did not confirm these reports. Oliveira *et al*[157] did not find any association between - 493 G>T polymorphism and NAFLD in a Brazilian cohort. Similarly, Peng *et al*[158] did not find any significant association between the - 493 G>T polymorphism and the risk for NAFLD in a Chinese Han population, even if other SNPs were found to be associated with NAFLD susceptibility. Specifically, in that study, the rs1800804 T/C was associated with an increased risk of NAFLD, while the rs1057613 A/G and rs3805335 C/T SNPs were associated with a decreased risk. Carulli *et al*[159] found that the distribution of MTTP polymorphisms was not significantly different between NAFLD patients compared with the control group nor associated with clinical or histological characteristics. Finally, a recent meta-analysis including 11 case-control studies with a total of 636 cases and 918 healthy controls revealed that MTP - 493G > T polymorphism was correlated overall with an increased risk of NAFLD among both Caucasian and non-Caucasian populations[160]. However, it should be noted that some of the studies included in the meta-analysis evaluated also featured superimposed NAFLD in HCV-infected patients.

Lipin 1: Lipin 1 is a phosphatase expressed specifically by adipose tissue and liver. It seems to be critically involved in metabolic pathways linking adipose tissue and liver[161]. Several polymorphisms of lipin 1 (LPIN1) have been associated with occurrence of MS and its components[162]. In particular, the LPIN1 rs13412852 T allele was associated with lower body mass index and insulin levels[163]. An Italian study[164] evaluated the LIPIN1 rs13412852 C>T polymorphism in pediatric patients with NAFLD. Investigators demonstrated that the TT genotype, even if underrepresented in pediatric NAFLD patients, was associated with less severe dysplipidemia and a lower prevalence and severity of NASH even after adjustment for genetic - PNPLA3 genotype - and metabolic confounders.

Genetic variants involved in mechanisms of liver injury in NAFLD/NASH
Tumor necrosis factor-α and tumor necrosis factor-related apoptosis-inducing ligand: Tumor necrosis factor-α is an important proinflammatory cytokine involved in the regulation of IR, release of free fatty acids, and induction of apoptosis in hepatocytes under stimuli driven by oxidative stress[165]. Thus, it is not surprising that serum tumor necrosis factor (TNF)-α levels were found to be higher in patients with NASH compared with healthy controls[70] and

Macaluso FS *et al*. Genetic background in NAFLD

that elevated levels have been associated with the occurrence of both NAFLD and NASH[166]. Two polymorphisms of the promoter of *TNF-α* gene have been linked to an increased susceptibility of NAFLD: TNF2 allele (at position -308) and TNFA allele (at position -238)[167,168], both associated with higher TNF-α serum levels[169,170]. However, consistency of this association is still debated[171,172]. Valenti *et al*[167] found that the prevalence of the -238, but not of the -308, TNF-α polymorphism was higher in Italian patients with NAFLD than in controls and that patients with NAFLD positive for both TNF-α polymorphisms had higher IR but a lower number of associated risk factors for steatosis. Furthermore, Tokushige *et al*[171] determined the prevalence of six TNF-α promoter region polymorphisms in a group of Japanese patients with NAFLD and in control subjects. Surprisingly, there were no significant differences in the allele frequencies of any of the six polymorphisms between patients and controls. However, they found that two polymorphisms - -1031C and -863A - were significantly higher in the NASH group compared with subjects with simple steatosis only and that they were associated with an increased homeostasis model assessment for IR (HOMA-IR) score. Finally, negative results were also derived from a prospective cohort of Chinese patients with NAFLD, since *TNF-α* gene polymorphisms were not shown to be associated with NAFLD nor with significant fibrosis[172]. A recent meta-analysis[173] comprising several studies on this topic[167,168,171,172,174-177] concluded that there was a significant difference in TNF-α -238 genotype distribution between NAFLD and control, while there was no clear association between TNF-α -308 genotype and susceptibility for NAFLD. Overall, it is still unclear whether TNF-α polymorphisms are critically involved in NAFLD and/or NASH pathogenesis, probably due to ethnic differences and incomplete control for confounding metabolic factors in most of the studies. Finally, another member of the TNF family, TNF-related apoptosis-inducing ligand (TRAIL), should be mentioned. A Chinese study[178] found that soluble TRAIL levels were significantly higher in NAFLD subjects than in controls and positively correlated with triglyceride concentrations in NAFLD patients and that the AA/TT genotypes of TRAIL at position 1525/1595 conferred a lower risk of NAFLD occurrence and a less severe form of steatosis in NAFLD patients.

Interleukin (IL)-6 and IL-1β: IL-6 is a proinflammatory cytokine produced by adipocytes, hepatocytes, and immune cells, involved in both inflammation and IR[179]. Experimental models have investigated its role in NAFLD pathogenesis and progression, although the results were often contradictory[180-182], whereas certain polymorphisms of the *IL-6* gene were associated with NAFLD susceptibility. A small Italian study[159] found that the *IL-6* -174C variant C - an allele associated with IR, T2D, and MS in some cohorts[183,184] but not in others[185] -

was more prevalent in NAFLD than in healthy subjects, associated with increased insulin levels and HOMA-IR, and an independent predictor of NAFLD and NASH. Intriguingly, this finding is in contrast with other studies reporting that it was the *IL-6* -174 G variant that was associated with metabolic abnormalities[186,187]. IL-1 family cytokine members are produced mainly by human adipose tissue; certain IL-1 cytokines - such as IL-1α, IL-1β, IL-18 - have proinflammatory properties, while others - IL-1 receptor antagonist, for example - are anti-inflammatory[188]. Interestingly, IL-1α and IL-1β were shown to have a role in the transition from steatosis to steatohepatitis and liver fibrosis[189]. Based on these findings, Interleukin-1β-511 T/C polymorphism, a functional variant that affects DNA-protein interactions *in vitro*[190], was determined in 63 Japanese NASH patients and 100 healthy volunteers[109]. The authors found that Interleukin-1β -511 T allele frequency and the T/T genotype frequency were significantly higher in NASH patients than in control subjects.

Toll-like receptor 4: Bacterial overgrowth and endotoxemia have recently emerged as two relevant factors in the pathogenesis of NASH[191]. Indeed, the interplay between toll-like receptor 4 (TLR4) and endotoxins results in the release of several mediators capable of favoring hepatic injury and a proinflammatory systemic status[192]. Variants encoded in the ectodomain of the *TLR4* gene, D299G and T399I, have been linked with endotoxin hyporesponsiveness[193] and with possible effects on inflammatory and metabolic disorders like atherosclerosis, IR, MS, and T2D[194,195]. Animal models showed a potential direct link between TLR-4 and Kupffer cells in the pathogenesis of steatohepatitis[192], and, notably, Guo *et al*[196] demonstrated that the D299G and T399I variants were associated with protection from hepatic fibrosis by reducing TLR4-mediated inflammatory and fibrogenic signalling and lowering the apoptotic threshold of activated hepatic stellate cells. Regarding the interaction between NAFLD and TLR-4 polymorphisms in humans, a recent case-control study[197] revealed that the frequency of the heterozygous mutation at position -299 was significantly lower in patients with NAFLD than in controls. However, further studies are needed to clarify the protective role of such polymorphisms in NAFLD pathogenesis and progression.

IL-28B: Several studies repeatedly showed that genetic variations around the *IL-28B* gene strongly predict the spontaneous and treatment-induced clearance of hepatitis C viral infection[198,199]. In particular, IL-28B rs12979860 CC and IL-28B rs8099917 TT genotypes were shown to be closely related to the achievement of a sustained virological response following antiviral therapy[200-202]. Furthermore, other studies revealed a link between IL-28B polymorphisms and the severity

of CHC in terms of steatosis[203,204], necroinflammatory activity[205], and fibrosis[206-208]. Our group reported on a cohort of 160 patients with histological diagnosis of NAFLD that IL-28B rs12979860 CC genotype was associated with the histological severity of liver disease, independently of HOMA and hyperuricemia - well-known risk factors for liver damage in NAFLD[209]. Interestingly, the at-risk CC rs12979860 variant was associated with severe necroinflammation, particularly in subjects with the PNPLA3 G allele, thus leading to hypothesize a potential interplay between these two genes. Such findings were recently confirmed by Eslam *et al*[210] on a large cohort, including 3129 patients with CHC, 555 with chronic hepatitis B, and 488 with NAFLD. The authors demonstrated that rs12979860 genotype acted as a strong predictor of tissue inflammation and fibrosis among all these chronic liver diseases, independent of the underlying etiology. However, Garrett *et al*[211] did not confirm these findings on their North American Caucasian patients with NAFLD, even if they enrolled a cohort of severe obese NAFLD patients evaluated for bariatric surgery, and, therefore, very different from our cohort. Overall, these data suggest an effect of *IL-28B CC* genotype in patients at lower metabolic risk only, and not in obese patients, where the burden of metabolic alterations on NAFLD severity likely overcomes the role of the genetic background.

Superoxide dismutase 2 and cytochrome P450 2E1: The superoxide dismutase 2 (*SOD2*) gene encodes for the mitochondrial enzyme manganese-dependent superoxide dismutase, a protein that protects cells from injury induced by superoxide radicals[212]. Interestingly, oxidative stress is regarded as a relevant factor involved into the transition from simple steatosis to steatohepatitis[213]. A common polymorphism in the *SOD2* gene - C47T, rs4880 - has been related to relatively efficient protein function by *in vitro* studies[214,215], and *SOD2* variants have been investigated in settings of alcoholic liver disease with inconsistent results[216,217]. Regarding the role of SOD2 C47T polymorphism in NAFLD, a small study performed on 63 Japanese subjects revealed an increased prevalence of the lower activity homozygous T genotype among patients with NASH compared with controls[154]. Similar conclusions were drawn from a cohort of obese Egyptian children with steatosis or NASH[218]. Al-Serri *et al*[219] performed a two-step analysis of the relevance of this SNP in NAFLD: the preferential transmission of alleles from parents to affected children in 71 family trios and a classical case-control study involving a cohort of 502 European patients with fatty liver. Investigators demonstrated that *SOD2* genotype - together with *PNPLA3* genotype, T2D, and histological severity of NASH - was associated with an advanced stage of fibrosis. Conversely, a Chinese study did not find any significant difference in the frequencies of the three

SOD2 genotypes among patients and controls but highlighted how the frequency of the SOD2 C variant was higher in the NASH group than in subjects with simple steatosis and in controls[220]. The same study evaluated another gene potentially involved in NAFLD pathogenesis: cytochrome P450 2E1 (CYP2E1), encoding for cytochrome P450 2E1 - another enzyme related to superoxide radicals in humans. Indeed, induction of CYP2E1 is a central process involved in generating oxidative stress in both alcoholic and nonalcoholic steatohepatitis[221]. However, evidence about a potential role of *CYP2E1* gene SNPs in NAFLD pathogenesis are elusive. On the one hand, the above mentioned study[220] did not report any association between the CYP2E1 -1053C>T variation (*1/*5 - rs2031920) and increased susceptibility to NAFLD or NASH in Chinese subjects; on the other hand, Varela *et al*[222] found that the CYP2E1 *5 variant was positively associated with liver injury in obese women with NASH, and similar positive results were also found on a Chinese population[223]. It is likely that ethnic differences and the incomplete understanding of the real effect of SOD2 and CYP2E1 genotypes on related enzymatic activities could be the main reasons underlying these conflicting results.

Uncoupling protein 3 and uncoupling protein 2: Uncoupling protein 3 is a mitochondrial anion carrier selectively expressed in skeletal muscle - the major site of thermogenesis in humans - involved in the metabolism of superoxide radicals and in the modulation of energy and lipid homeostasis[224-226]. The rs1800849 -55C/T polymorphism of uncoupling protein (UCP) 3 has been associated with an increased susceptibility to T2D and obesity and with an atherogenic lipid profile[227-229]. Interestingly, the rs1800849 UCP3 -55CT genotype was also associated with IR, increased adiponectin levels, the presence of moderate-severe steatosis, and NASH in a small Spanish study[230]. Furthermore, an interesting Chinese paper aiming to evaluate the frequency of four nonsynonymous SNPs in the *UCP3* gene in a pediatric cohort found a higher prevalence of another variant - rs11235972 GG genotype - among patients with NAFLD compared with control subjects[231]. Similar to UCP3, UCP2 is involved in the regulation of mitochondrial lipid efflux and oxidative metabolism. Its increased hepatic expression has been reported both in experimental models and in NASH patients as a protective mechanism against liver injury progression[232]. A promoter region polymorphism of UCP2 - -866 G>A variant - is able to influence the extrahepatic expression of UCP2 and insulin release and sensitivity, although the overall metabolic impact is still controversial[233]. A recent Italian paper investigated the role of this SNP in patients who underwent liver biopsy for suspected NASH[234]. UCP2 -866 A/A genotype was associated with a reduced risk of NASH after adjustment for age, sex, body

mass index, impaired fasting glucose or diabetes, and PNPLA3 I148M allele and with a reduced risk of steatosis grade G2-G3 and NASH in patients without, but not in those with, impaired fasting glucose/diabetes. Concerning the metabolic traits, the UCP2 A/A genotype was associated with higher total serum cholesterol levels but not with serum HDL, triglycerides or impaired fasting glucose/diabetes. Overall, SNPs in *UCP* genes may confer susceptibility or protection to NAFLD/NASH, even if further evidence needs to be provided.

Methylenetetrahydrofolate reductase: Homocysteine is an intermediate amino acid formed during methionine metabolism in the liver. Today, hyperhomocysteinemia is regarded as a risk factor for liver diseases *via* the promotion of oxidative and endoplasmic reticulum stress, and the activation of proinflammatory factors[235,236]. Methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a metabolic pathway fundamental for the methylation of homocysteine to methionine. Several genetic polymorphisms in the *MTHFR* gene have been identified, and among them, the C677T polymorphism (rs1801133) and the A1298C (rs1801131) - inducing both a reduction of MTHFR activity - were extensively investigated[237,238] in the setting of NAFLD[239-242]. Sazci *et al*[239] analyzed the frequency of C677T and A1298C polymorphisms of *MTHFR* gene in a Turkish cohort comprising 57 NASH patients and 324 healthy controls, showing that the MTHFR 1298C allele in all NASH patients, the C677C/C1298C compound genotype in women, and the C677C/A1298C compound genotype in men were genetic risk factors for NASH. Similarly, Catalano *et al*[240] recently identified the MTHFR A1298C heterozygous polymorphisms as a weak predictor for NAFLD severity in an Italian cohort. However, the relationship between MTHFR polymorphisms and NAFLD remains controversial. Franco Brochado *et al*[241] did not find any association between the MTHFR C677T and A1298C polymorphisms and NAFLD and its severity. Similarly, Serin *et al*[242] showed that the MTHFR C677T polymorphism was not a risk factor for NAFLD in their Turkish cohort. As a consequence, more rigorous work needs to be performed in this field.

Glutamate-cysteine ligase catalytic subunit: The glutamate-cysteine ligase catalytic subunit (*GCLC*) gene codes the catalytic subunit of the heterodimeric γ-Glutamate-cysteine ligase, the limiting enzyme in the formation of glutathione, a relevant endogen antioxidant. The base T in the position -129, as opposed to base C, determines a sharp decrease in the promoter activity of the *GCLC* gene and was identified as a significant independent risk factor for myocardial infarction in a Japanese population[243].

In addition, mitochondrial glutathione depletion has been associated with the development of alcoholic steatohepatitis due to the increased sensitivity of hepatocytes to the pro-oxidant effects of cytokines generated by ethanol metabolism[244]. Interestingly, Oliveira *et al*[157] found that, among 131 biopsy-proven NAFLD patients, the presence of at least one T allele in the -129 C/T polymorphism of the *GCLC* gene was independently associated with NASH detection, with an OR of 12.14. Thus, such polymorphism could be an important factor in the development of liver injury mediated by oxidative stress.

Hemochromatosis and trans-membrane protease serine 6: Human hemochromatosis protein (HFE) is crucial for the regulation of iron homeostasis *via* modulation of the expression of hepcidin[245]. Excessive hepatic iron deposition is a frequent histological feature of NASH, and it has been investigated as a potential contributor to oxidative stress in the liver, and thus as a second hit promoter[246]. In this regard, even if the C282Y and H63D mutations of the *HFE* gene - common in Caucasians and responsible for most cases of hereditary hemochromatosis - are well-known causes of potential iron overload, their prevalence and relevance in patients with NAFLD have been variable, depending on the examined cohorts. The first reports about the association between HFE mutations and NAFLD came in the late 1990s and showed a positive correlation between these two conditions[247,248]. Later, Lee *et al*[249] identified the presence of H63D mutation as an independent factor associated with NAFLD in the Korean population, and Nelson *et al*[250] suggested that the presence of the C282Y mutation was a risk factor for the development of advanced hepatic fibrosis among American Caucasian patients with NASH. Nonetheless, other studies have not confirmed such associations. Indeed, even if several reports suggested that increased ferritin levels may be markers of histological damage, the HFE mutations did not consistently contribute to hepatic fibrosis in NAFLD[251] nor to its susceptibility[252]. The poor relevance of HFE mutations in NAFLD have been resumed by a recent meta-analysis including 610 cases and 7298 controls[253]: authors found no associations between iron-overloading HFE mutations and NAFLD susceptibility or severity. However, other genetic variants influencing iron deposition may be involved in NAFLD/NASH pathogenesis. Beta-globin mutations have been identified as a good genetic predictor of parenchymal iron overload in Italian patients with NAFLD and have been associated with a two-fold higher risk of severe fibrosis[254]. More recently, the rs855791 C>T polymorphism of the trans-membrane protease serine 6 (*TMPRSS6*) gene - encoding for matriptase-2, which cleaves the membrane-bound hemojuvelin, a co-receptor required for hepcidin expression in the liver[255] - has been associated with

lower hepatic iron stores, ferritin levels, and ballooning in 216 patients with histological NAFLD[256].

Kruppel-like factor 6: The kruppel-like factor 6 (KLFs) are a family of zinc finger-containing transcriptional factors that regulate cellular processes, such as proliferation, differentiation, and apoptosis[257]. In the liver, injury and/or cytokines are able to induce *KLF6* gene expression, which in turn plays an essential role in the transactivation of several genes involved in the development of liver fibrosis, mainly *via* the activation of hepatic stellate cells[258]. Miele *et al*[259] reported the association between a functional polymorphism in the *KLF6* gene - IVS1-27G>A SNP (rs3750861) - and the severity of NAFLD. In particular, they demonstrated increased levels of total and wild type KLF6 expression in patients with NAFLD and higher steatosis, inflammation, and fibrosis, whereas KLF6 IVS1-27G>A SNP was associated with reduced fibrosis, and thus, acted as a protective factor against NASH progression. Intriguingly, the effects of KLF6 genotype on NAFLD/NASH pathogenesis may also involve the modulation of metabolic pathways: Bechmann *et al*[260] observed that KLF6 IVS1-27G wild-type allele was associated with increased fasting glucose and insulin levels and with decreased hepatic insulin sensitivity *via* the reduced expression of glucokinase. KLF6 increased PPARα activity, whereas KLF6 loss led to PPARα repression and attenuation of lipid and glucose abnormalities[261].

Transforming growth factor-β1, angiotensin Ⅱ, and angiotensin Ⅱ type 1 receptor: The transforming growth factor (TGF)-β1 is a well-known promoter of hepatic fibrosis that contributes to the activation of hepatic stellate cells[262]. TGF-β1 production can be stimulated by angiotensin Ⅱ (AT Ⅱ), part of the renin-angiotensin system that has been advocated as a potential inducer of extracellular matrix accumulation[263]. A higher frequency of a pro-fibrotic TGF-β1 SNP (Arg/Arg at codon 25) has been identified in patients with hypertension compared with controls[264]. Furthermore, this TGF-β1 SNP and an AT Ⅱ variant in the promoter region of the gene (AT-6 G>A), leading to a higher transcription of AT, were both associated with increased hepatic fibrosis in patients with CHC[265]. Based on these findings, Dixon *et al*[266] investigated these two polymorphisms in a group of severely obese patients with NASH. The investigators found a positive association between AT-6 A/A polymorphism and severe fibrosis, even if such correlation was lost after correction for gender. However, patients with both high AT Ⅱ and TGF-β1 producing polymorphisms had a higher risk of advanced fibrosis. In addition, animal models had demonstrated that the Angiotensin Ⅱ Type 1 Receptor (*AGTR1*) gene could be implicated in the susceptibility to NAFLD[267]. In this line, none of the five variants of the *AGTR1* gene were associated with susceptibility to NAFLD in a multi-ethnic Asiatic cohort composed of Malayan, Indian, and Chinese subjects, with the exception of the Indian subgroup, where the rs2276736, rs3772630, and rs3772627 were found to be protective against NAFLD and NASH[268]. Furthermore, five SNPs of *AGTR1* gene (rs3772622, rs3772633, rs2276736, rs3772630, and rs3772627) were significantly associated with NAFLD in a Japanese cohort[269]. All in all, the potential involvement of the renin-angiotensin system in NAFLD/NASH pathogenesis is still unclear, and further research is needed.

CONCLUSION

In the complex pathogenetic puzzle of NAFLD, genes clearly act as major disease modifiers affecting NAFLD occurrence and severity and sometimes cardiovascular risk as well. To date, the PNPLA3 gene variant is the most validated susceptibility factor for steatosis, NASH, fibrosis, and HCC, despite a number of other genetic variants contributing to liver damage. However, even if the identification of these variants helped us to understand better NAFLD in terms of both clinical phenotypes and pathogenetic mechanisms, their utility in clinical practice and in the individual patients is far from being relevant. Therefore, further efforts should be done to generate a genetic map useful to stratify the hepatic and non-hepatic risk of NAFLD patients and to define better therapeutic approaches in terms of both lifestyle intervention and new pharmacological therapies.

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