Genetics and Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease worldwide. It is closely related to obesity, insulin resistance (IR) and dyslipidemia so much so it is considered the hepatic manifestation of the Metabolic Syndrome. The NAFLD spectrum extends from simple steatosis to nonalcoholic steatohepatitis (NASH), a clinical condition which may progress up to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). NAFLD is a complex disease whose pathogenesis is shaped by both environmental and genetic factors.

NAFLD heritability personalized medicine lipid handling polygenic risk scores

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disorder of the 21st century, affecting at least one third of the general population [1],[2],[3]. Due to its epidemic proportion, NAFLD constitutes a huge socio-economic and health issue [4] and it is predicted to become the leading cause of hepatocellular carcinoma (HCC) and the main indication of liver transplantation by 2030 [5]. NAFLD is defined by ectopic fat deposition exceeding 5% of liver weight, in absence of alcohol consumption. It embraces a variable phenotypic rainbow of hepatic abnormalities, spreading from uncomplicated steatosis to its progressive form, nonalcoholic steatohepatitis (NASH), characterized by lobular inflammation, hepatocyte ballooning degeneration and fibrosis. NASH may then evolve towards end-stage liver injuries, such as cirrhosis and HCC [6],[7].

NAFLD is epidemiologically related to obesity, insulin resistance (IR) and atherogenic dyslipidemia so much so it is considered the hepatic manifestation of Metabolic Syndrome [8],[9]. Hence, according to a recent international consensus, the nomenclature of NAFLD has been updated from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), to better outline patients in which hepatic steatosis occurs in the presence of obesity or type 2 diabetes (T2D) or metabolic abnormalities [10].

However, NAFLD has an intricate pathogenesis and 50–70% of the individual susceptibility to develop the disease as well as its phenotypic variability are attributable to inherited risk factors [11]. The most robust genetic predictors of NAFLD are single nucleotide polymorphisms (SNPs) in genes regulating hepatic lipid turn-over, reshaping and dismissal, among which patatin-like phospholipase domain-containing 3 (*PNPLA3*), transmembrane 6 superfamily member 2 (*TM6SF2*), membrane bound o-acyltransferase domain-containing 7 (*MBOAT7*) and Glucokinase regulator (*GCKR*) [11]. Even more, along with the heritable variations, gene-environment interactions may also explain the discrepancies in NAFLD phenotypic variability, possibly amplifying the effect due to individual sequence variations [12],[13]. For instance, the associations between common variants and NAFLD may be unmasked by the

increased adiposity, thus enhancing the genetic risk [14]. In addition, among the different actors who play a role in NAFLD pathophysiology, a new point of view is constituted by intestinal dysbiosis, enhanced intestinal permeability and microbial harmful by-products [15],[16].

Nowadays, liver biopsy remains the gold standard procedure for diagnosis of NAFLD and no therapeutic consensus exists for its treatment [9],[17]. However, the combination of inherited factors and dynamic clinical parameters, which can be influenced by lifestyle and pharmacological interventions, may be effective to identify reliable score-based approaches aimed to predict liver damage and to tailor therapeutic options [9],[17].

2. Historical Overture to Discover the Link between Genetics and NAFLD

In the last decade, it has been broadly elucidated that obesity and IR are the leading risk factors for NAFLD. However, at equal body mass index (BMI), there is a widespread variability in the clinical manifestation of NAFLD, supporting the notion that other jeopardizing factors may be engaged into fatty liver onset and progression. Indeed, familial, twin and epidemiological studies pinpoint that both steatosis and fibrosis have a huge inherited component [18],[19].

The first robust evidence regarding NAFLD hereditability has been provided by Struben et al. [20], who studied the familial pattern distribution of cryptogenic cirrhosis in 18 members of 8 kindreds, containing 2 or more afflicted members. These authors revealed that the coexistence of NASH with or without cirrhosis within kindreds suggests a common etiology of these disorders, possibly caused by the shared genetic background and by the elevated frequency of obesity and T2D in these families. Then, large population-based studies more precisely outlined the magnitude of NAFLD predisposition due to genetics. Indeed, Speliotes and colleagues [21] attested the hereditability of hepatic steatosis at 26−27% in a population-based consortia including 6629 subjects of European descent. This estimate has been confirmed by Wagenknecht et al. in 795 Hispanic American and 347 African-American adults who participated to the Insulin Resistance Atherosclerosis Study (IRAS) Family Study [22].

More in detail, in a familial aggregation study, Schwimmer et al. revealed that family members of overweight children with biopsy-proven NAFLD had an increased predisposition to develop hepatic steatosis compared to obese children without NAFLD [23]. Thus, a familial NASH aggregation is frequent, raising up to 18% in subjects having a similarly affected first degree relative [24].

In addition, approximately 60% of the variation in serum alanine aminotransferase (ALT) as well as in circulating insulin concentrations, which are strictly correlated with hepatic fat content, are genetically determined in absence of other confounders, such as viral hepatitis or alcohol abuse, as yielded by the twin studies [25]. Loomba et al. demonstrated that both hepatic steatosis and fibrosis, non-invasively assessed, were tightly connected in monozygotic twins compared to dizygotic ones [26]. In a multivariate generalized model, adjusted for age, gender and ethnicity, the percentages of hereditability of hepatic steatosis and fibrosis were claimed at 52% and 50%, respectively. Moreover, in the same cohort, Cui et al. revealed a high degree (~75.6%) of shared genetic

components between hepatic steatosis and fibrosis, irrespectively of environmental factors [27]. Likewise, cardiovascular comorbidities related to NAFLD, such as carotid plaques formation and abnormal intima-media thickness, have been reported to be strongly hereditable in a cohort of 208 adult Hungarian twins with NAFLD (63 monozygotic and 41 dizygotic pairs) [28].

The large disparity in NAFLD heritability which has been observed in different cohorts may be attributable to ethnicity [18],[19]. Firstly, Wagenknecht and collaborators attested the much greater contribute (33%) of the genetic milieu on NAFLD onset in the Hispanic cohort belonging to the IRAS Family Study, compared to the African American one (14%) [22]. According to these findings, two large multi-ethnic population studies highlighted that Hispanics have a higher risk to develop NAFLD than Europeans [29],[30]. Furthermore, there are discrepancies within the same ethnic group and amongst Hispanics, Mexicans have much higher prevalence of NAFLD compared to Dominicans or those from Puerto Rico [31]. Conversely, it has been confirmed the protection of African-Americans against NAFLD, irrespectively of T2D, overweight and socioeconomic factors, corroborating the role of heritability in NAFLD pathophysiology [11]. Indeed, African-Americans differed in the metabolic response to obesity and IR when compared to either Hispanics or Caucasians, resulting more resistant to triglyceride (TG) accumulation both in adipose tissue and in the liver [32].

A burgeoning number of heritable factors have been recognized as genetic modifier of NAFLD [11]. Specifically, Dongiovanni and colleagues, postulated that hepatic fat content constitutes the main driver of the evolution towards end-stage injuries in genetically predisposed subjects, thus indicating that each genetic variation exerts an effect on the spectrum of NAFLD, directly proportional to its ability to induce fat accumulation [33]. To date, the best known common inherited predictors of progressive NAFLD are the variants in *PNPLA3, TM6SF2*, *MBOAT7* and *GCKR* genes. However, given the challenging genetic framework of NAFLD, an impressive amount of novel inherited risk factors has been picked out through candidate gene association studies, genome wide association studies (GWAS) or exome wide association studies (EWAS). Thus, the most arduous challenge in the study of genetics of NAFLD is to postulate score-based systems which take into account polygenic determinants of NAFLD, that may guarantee the most highly predictive value, the best diagnostic accuracy and the more precise individualized therapy [34],[35].

3. Genetic Signature of Glucose and Lipid Metabolism in NAFLD

In the last decades, it clearly emerged that IR is a key player in NAFLD pathogenesis [36],[37]. In particular, IR strongly predicts the severity of hepatic fibrosis [36], the main determinant of NAFLD prognosis [38], and advanced fibrosis often occurs in NAFLD patients with T2D, even independently of inflammation and NASH [39],[40].Therefore, genetic variants that suppress the activation of insulin signaling may induce fibrosis in NAFLD [41]. The rs1801278 (G972R) loss-of-function mutation in insulin receptor substrate (*IRS1*) and the gain-of-function one in the ectonucleotide pyrophosphatase/phosphodiesterase1 (*ENPP1*) 121Q genes were both related to dyslipidemia, obesity and hepatic fibrosis [41]. On the contrary, the rs2954021 variant in tribbles homolog1 (*TRIB1*), involved in the modulation of hepatic glycogen storage, affected plasma glucose, TG and cholesterol levels [42].

Similarly, other variations in genes governing hepatic lipid handling and release predispose to fatty liver. For instance, variants within Apolipoprotein B (*APOB*), involved in VLDL organization and secretion, have been associated with a protection against cardiovascular complications, due to the lowering of circulating lipoproteins and in turn, they favor severe hepatic fat depot formation, that may foster the progression of liver injury up to HCC [43],[44]. Moreover, even microsomal triglyceride transfer protein (*MTTP*) inherited alterations may prompt VLDL retention [45].

In addition, two common promoter variants in the apolipoprotein C3 (APOC3) (*APOC3* T-455C and C-482T), a component of chylomicrons, VLDL and HDL cholesterol particles, may predispose to steatosis in Indians, but not in other ethnic groups, supporting the notion that genetic factors modulating TG metabolism outside of the liver are less implicated in the onset of progressive NAFLD [46],[47],[48].

Likewise, Dongiovanni et al. [49], elucidated that the proprotein convertase subtilisin/kexin type 7 (*PCSK7*) rs236918 G > C variant affects fasting lipids and hepatic injury in a large cohort of NAFLD subjects, coupling atherogenic dyslipidemia with NASH and hepatic fibrosis. By stratifying patients according to the presence of the PNPLA3 p.I148M allele, the *PCSK7* rs236918 polymorphism was associated with advanced steatosis. Indeed, in hepatoma cells carrying the p.I148M allele in homozygosity, *PCSK7* genetic deficiency decreased the expression of genes involved in DNL, inflammation and fibrosis, even after FFA supplementation [49]. Furthermore, Huang et al. [50], revealed a correlation between the *PCSK7* at-risk allele, hyperinsulinemia and homeostatic model assessment for IR (HOMA-IR) after a high-carbohydrate challenge. *PCSK7* is strongly implicated in lipid homeostasis, since it is localized in a genomic region close to the gene cluster *APOA5/APOA4/APOC3/APOA1*, involved in lipoprotein metabolism regulation. In keeping with these findings, *Pcsk7*$^{-/-}$ mice fed HFD are characterized by elevated plasma apolipoprotein concentrations and enhanced lipoprotein lipase (Lpl) adipose tissue activity [51].

Even more, aberrancies in another member of the proprotein convertase subtilisin/kexin family, PCSK9, have been widely associated with hereditary hypercholesterolemia [52], severe fat deposition [53] and cardiovascular abnormalities [54], due to its impact on LDL uptake. PCSK9 is a nutrient sensor, and it is strongly influenced by nutritional *status*. Indeed, its expression declines in mice after 24 h of fasting. On the contrary, PCSK9 mRNA levels are renewed through SREBP-1c and DNL activation upon high carbohydrate refeeding or insulin stimulation [55]. Loss-of-function mutations in *PCSK9* diminish plasma LDL cholesterol, without inducing steatosis [56]. For example, the *PCSK9* rs11591147 (p.R46L) loss-of-function variant blunted LDL levels and protected against NAFLD, NASH and fibrosis, irrespectively of confounders [57]. Conversely, gain-of-function alterations of *PCSK9* as the rs7552841 variant lead to familial hypercholesterolemia and enhance CAD risk.

Hepatic dysfunctions may be caused even by rare mutations of lysosomal acid lipase (*LIPA*) gene, that induce lysosomal acid lipase (LAL) defects. LAL participates to the hydrolysis of cholesteryl esters, TG and LDL into free cholesterol and fatty acids. Its functional aberrancy fosters un-hydrolyzed compounds accumulation into the hepatocytes, whereby favoring atherogenic dyslipidemia, hepatic steatosis and severe fibrosis [58],[59]. In turn, LAL

restoration using recombinant sebelipase alpha administration in patients for up to 5 years may improves liver enzymes, hepatic features of NAFLD and circulating lipids in patients (clinical trial NCT01488097) [60],[61].

Finally, even variants that alter FFA fluxes into the liver or their catabolism, such as the rs56225452 in fatty acid transport proteins (*FATP5*) or the rs13412852 in Lipin1 (*LPIN1*), may leverage IR and steatosis [62],[63].

4. Genetics of Lipid Droplets

LD accumulation in the liver is the primary hallmark of NAFLD. Compelling evidence indicates that LDs should not be considered as just 'innocent bystander', but conversely, they participate to multiple processes that lead to NASH. LDs are enormously dynamic, modifying their localization, size, lipid and protein composition in response to environmental *stimuli* and energy demand. Hence, they are engaged not only in energy expenditure to produce ATP but also in signaling pathways, acting as hubs that integrate metabolic and inflammatory processes.

Genetic risk factors may play a crucial role as modifiers of lipid composition and LD dimensions, whereby causing the alteration of the expression of LD-associated proteins, which regulates lipid storage. Thus, together with the above-mentioned p.I148M PNPLA3 and *HSD17B13* rs72613567 variants, many other polymorphisms in genes implicated in LD handling have been recently associated with NAFLD. Among them, Perilipin-2 (PLIN2) rs35568725 (Ser251Pro) variant has been associated with IR and atherosclerosis, in two population studies. In particular, PLIN2 protein participates to the formation, stability and trafficking of LDs and in VLDL lipidation. The Ser251Pro mutation induces smaller, but more numerous LDs in hepatocytes, resembling microvesicular steatosis and conveying the risk of NASH in NAFLD patients [64]. The increasing number of small LDs was not translated into enhanced cellular capacity to store fat, but more so into high number of LD-associated proteins on the surface area. Thus, we could speculate that the presence of this variant may enhanced the risk related to PNPLA3 p.I148M carriage in patients. Even more, *PLIN2* variant has been associated with reduced circulating TG and VLDL [65].

Similarly, the common noncoding polymorphism, rs884164 in another LD-associated gene, *PLIN5,* causes a down-regulation of PLIN5 expression, a protein that facilitates the association between LDs and mitochondria. The recruitment of mitochondria to LDs during conditions of high substrate availability may favor lipid catabolism. Thus, PLIN5 hampered expression is associated with a poorer outcome following myocardial ischemia and *PLIN5* deficiency is related to increased oxidative stress in cardiomyocytes [66],[67].

Since the degradation of cellular lipids is mediated by a selective autophagic process, named lipophagy, an impairment in this mechanism induced by genetic defects may dampen lipid β-oxidations, accelerating their accumulation. For instance, the rs10065172 variant in the autophagy-related *IRGM* gene may increase the risk of developing steatosis and *IRGM* knockdown inhibits autophagic flux and increases LD content in HepG2 cells [68]. IRGM is generally localized on endosomes/lysosomes, while in HFD-fed mice it co-localizes with ATGL/PNPLA2 at LD surface, where it recruits autophagic mediators, such as LC3B, in attempt to counteract to steatosis development. Hence, IRGM overexpression protects against hepatic lipid storage [69].

5. Advanced Liver Injuries and Genetic Variants

A series of stressful triggers may precipitate fatty liver up to NASH and severe fibrosis. Among them are included oxidative stress fostered by reactive oxygen species (ROS) overproduction, intracellular organelle derangement, i.e., ER and mitochondrial abnormalities and dysfunctions, innate immune inflammation and pro-inflammatory cytokine and chemokine release [70], intestinal high permeability and gut-derived harmful by-products (due to leaky gut) [71], and HSCs activation to myofibroblasts [72].

Interleukin 28 (*IL28*) gene codifies for the interferon λ3/λ4 (IFNL3/4), and the rs12979860 CC variant has been associated with interferon λ3 over-production [73]. The latter mediates the clearance of hepatitis C virus, and more aggressive NASH and fibrosis in NAFLD patients [74],[75]. In particular, it has been yielded a genetic model to predict significant fibrosis, named FibroGENE, that includes the rs12979860 variant, age, gender and the routinely assessed clinical and biochemical parameters [76]. The rs12979860 is in linkage disequilibrium with the another variant, the *IFNL4* rs368234815 TT > δG. Patients carrying the rs368234815 TT allele are predisposed to develop higher degree of lobular inflammation and fibrosis compared to non-carriers [77]. Contrasting findings have been observed in carriers of the rs3480 A > G variant in the fibronectin type III domain-containing protein 5 (*FNDC5*) gene, encoding irisin, a myokine, that intervenes in HSCs activation and collagen deposition [78],[79]. The minor G allele predisposes to elevated extents of steatosis, likely by modulating irisin expression [79]. Likewise, the rs2228603 polymorphism in Neurocan, the rs12137855 variation in lysophospholipase-like 1 (*LYPLAL1*) and the rs10883437 SNP close to the carboxypeptidase n subunit 1 (*CPN1*) have been coupled to severe NAFLD [80],[81].

Alongside, mounting evidence indicates that the gut-derived fibroblast growth factor (FGF) 19, engaged in lipid and carbohydrate metabolism in response to nutritional *status* through the binding to its hepatic receptor, fibroblast growth factor receptor 4 (FGFR4), is involved in metabolic diseases and NAFLD [82]. Dongiovanni and Crudele et al. [83], demonstrated that the rs17618244 G > A variant in the β-Klotho (*KLB*) gene, encoding the hepatic co-receptor of FGFR4, dampened KLB plasma levels, leading to inflammation, ballooning, fibrosis and to the over-expression of genes involved in lipotoxicity in overweight NAFLD pediatric patients [83]. Furthermore, KLB complexing with others FGFRs also binds the hormone FGF21, released from the liver and adipose tissue. In detail, FGF21 is implicated in glucose and TG uptake by white and brown adipose tissue, through the interaction with FGFR1 [84]. However, FGF21 circulating levels are paradoxically increased in obese patients and in those with NAFLD, as a protective response to KLB down-regulation and to NAFLD-induced adverse effects, e.g., lipotoxicity, oxidative and ER stress [85],[86]. Thus, KLB/FGF19/FGF21 pathway may represent a druggable target in NAFLD patients through the rescue of KLB levels.

Concerning the development of fibrosis, the alternative splicing of the Krueppel-like factor 6 (*KLF6*) gene, that is expressed by the HSCs during their transdifferentiation, associates with mild NAFLD and reduced fibrosis [87]. Conversely, variants in *HFE* and *TMPRSS6* genes likely by predisposing to hepatic iron depot formation are correlated with more severe fibrosis in NAFLD patients [88].

The rs4374383 non-coding variant in the macrophage c-mer tyrosine kinase (*MERTK*), a tyrosine kinase that initiates the removal of dying cells by phagocytes and that mediates HSCs activation, protects against fibrosis in both NAFLD and in viral hepatitis C, eliciting MERTK down-modulation [89],[90]. Consistently, it has been stated that MerTK cleavage in hepatic macrophages is reduced during the transition from simple steatosis to NASH, promoting transforming growth factor β (TGF-β) release and HSCs activation [91]. Novel insights into the role of MERTK in metabolic processes, has been brilliantly proposed by Nicolás-Ávila and colleagues [92], which demonstrated that macrophages may actively entrap materials, including dysfunctional mitochondria ejected from injured cardiomyocytes through dedicated membranous particles enriched in phosphatidyl-serine (PS), with the purpose to maintain the global tissue homeostasis. This peculiar process occurs in MERTK-dependent manner, and it is driven by the cardiomyocytes' autophagy machinery, prompted by cardiac stress. Thus, MERTK depletion abolished the removal of the exhausted mitochondria, hindered autophagic processes and resulted in the inflammasome and autophagy arrest, ultimately compromising mitochondrial fitness. Thus, this novel non-canonical route for the extrusion of cellular waste, including abnormal mitochondria and other organelles into the extracellular space, then scavenged by resident macrophages, may pave the way to potential translational implications on the study of other tissues characterized by high mitochondrial biomass and energy demand, in both healthy and disease status.

Finally, the susceptibility to fibrogenesis and carcinogenesis is also influenced by cellular senescence and cell cycle arrest. Therefore, the rs762623 in cyclin dependent kinase inhibitor 1A (*CDKI1A*) which encodes the cellular senescence marker p21, was significantly associated with disease progression in NAFLD [93]. Likewise, telomerase reverse transcriptase (*TERT*) gene loss-of-function mutations associated with familial cirrhosis and accelerated HCC [94]. Similarly, the rs599839 A > G variant, which causes the overexpression of the oncogene Proline And Serine Rich Coiled-Coil 1 (*PSRC1*), has been associated with enhanced HCC risk in NAFLD patients, irrespectively of fibrosis severity, and with poor prognosis and advanced tumor stage [95]. Even more, the Neurotensin (*NTS*) rs1800832 variant predisposes to cirrhosis and HCC in NAFLD patients likely by affecting NTS protein activity [96].

6. Mitochondrial Dysfunctions: The Tipping Point in the Switching from Simple Steatosis to Steatohepatitis

Growing evidence pinpoints the critical role of organelle abnormalities in the switching from fatty liver towards NASH. Mitochondrial anomalies are closely entangled into the pathogenesis of NAFLD so much so that it has been considered as a mitochondrial disease [97]. During early stages of NAFLD, mitochondrial activity and biomass is adapted in response to IR and to fat accumulation. However, sustained mitochondrial oxidative flux hesitates in exasperated ROS production, triggering phospholipid lipoperoxidation, cellular stress and mitochondrial DNA damage, tissue inflammation and cell death which may precipitate the progression to NASH and more advanced liver injuries [98].

In this context, the knowledge of genetically determined mitochondrial dysregulations may be determinant to predict the course of the disease. Indeed, common polymorphisms in genes regulating mitochondrial homeostasis

have been associated with NAFLD and to its progressive forms. For instance, the rs4880 C47T variant in the superoxide dismutase 2 (*SOD2*) gene, encoding the antioxidant enzyme manganese superoxide dismutase, results in a Valine to Alanine substitution in the signal region addressing the protein to the mitochondrial matrix, where it exerts its function, and the T allele has been related to increased enzymatic activity. Thus, an higher frequency of *SOD2* T/T genotype in biopsy-proven NASH patients compared to healthy controls has been reported [99]. This variant has been further associated with severe fibrosis in NAFLD patients, as a proof of concept that mitochondria-derived oxidative stress is required for fibrosing NASH onset [100].

Alongside, the homozygosity for the −866 G > A mutation in the promoter region of the uncoupling protein 2 (*UCP2*) gene protects against NASH, whereby enhancing hepatic UCP2 expression [101]. The latter is implicated in the regulation of mitochondrial lipid efflux and oxidative metabolism and its hepatic expression increased in NASH patients causing a proton leak and a reduction of redox pressure on the mitochondrial respiratory chain, protecting the hepatic tissue against liver damage worsening [102].

Conversely, a non-coding variant in the promoter (−55C > T, rs1800849) of another member of the UCP family, the uncoupling protein 3 (*UCP3*) gene has been correlated with low insulin sensitivity, IR, reduced adiponectin secretion, moderate-severe hepatic steatosis and inflammation in obese NAFLD individuals [103]. UCP3 is a mitochondrial proton transporter that protects against fatty acid-mediated oxidative stress, uncoupling the oxidative phosphorylation by increasing the proton leak of the inner mitochondrial membrane.

Sirtuins (SIRTs) are a family of nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases embroiled in cellular metabolism. There are 7 distinct SIRTs in mammals (SIRT1–7), which share the catalytic core domain, but they have different subcellular localizations. Indeed, SIRT1, SIRT6 and SIRT7 are mainly localized into the nuclei, SIRT2 is primarily found into the cytoplasm, while SIRT3, SIRT4 and SIRT5 have a mitochondrial distribution [104]. SIRTs along with UCPs may modulate oxidative stress thereby influencing the risk of subclinical atherosclerosis and cardiovascular complications. Indeed, it has been demonstrated that the *SIRT6* rs107251 and the *SIRT5* rs12216101 were associated with an elevated susceptibility to carotid plaques formation, whereas carriers of the T allele of *UCP5* rs5977238 had a lower risk, in 1018 stroke-free subjects from the Northern Manhattan Study (NOMAS) [105]. Even though cardiovascular abnormalities are recurrent in NAFLD patients, the implication of SIRTs genetic variations in this context remains to be fully elucidated.

More recently, a novel common missense variant (rs2642438 A165T) in the mitochondrial amidoxime-reducing component 1 *(MARC1)* gene has been identified. *MARC1,* also known as *MTARC1* or *MOSC1,* encodes the mitochondrial amidoxime reducing component 1, a molybdenum-containing enzyme that regulates endogenous nitric oxide levels and biosynthesis, catalyzing the conversion of nitrite to produce nitric oxide. The A165T variant is located at the N-terminal domain which anchors the protein to the outer membrane of the mitochondria. The threonine to alanine aminoacidic substitution results in a truncating protein making the rs2642438 a loss-of-function mutation. The A165T variant has been associated with protection against all-cause cirrhosis, reduced hepatic fat content and lower levels of liver enzymes [106]. Specifically, in patients affected by alcohol-related cirrhosis *MARC1* and heterogeneous nuclear ribonucleoprotein U like 1 gene (*HNRNPUL1)* variations has been emerged as risk

modifiers of liver damage, in a GWAS of samples from the United Kingdom Biobank [107]. Afterwards, Luukkonen and collaborators [108] investigated the effect of the rs2642438 variant on the severity of NAFLD and they demonstrated that patients carrying the A165T allele had markedly lower prevalence of inflammation and fibrosis, compared to non-carriers. This effect seems to be due to the precise lipid signature that describes A165T allele carriers, displaying increased levels of hepatic polyunsaturated-PC similarly to carriers of the *HSD17B13* rs72613567 variant and opposite to what the same authors observed in *PNPLA3* p.I148M carriers. According to these observations, the wt forms of *MARC1* are related to higher levels of sphingomyelins (i.e., C20:2), Lyso-PC (C14:0 and C15:0) and PC (C34:1 and C40:2) compared to patients carrying the A165T allele, thereby confirming the presence of a distinctive metabolomic pattern by using comprehensive metabolomics data from two population-based studies, including 9135 participants from the Fenland study and 9902 participants from the EPIC-Norfolk cohort [109]. Collectively, these observations pointed out *MARC1* as a potential pharmacologic target for liver diseases without affecting cardiovascular outcomes [110], although further investigations are needed to clarify its function and its role in oxidative stress regulation. A schematic over-view of the main genetic risk factors involved in NAFLD onset and progression is represented in **Figure 1** and in **Table 1**.

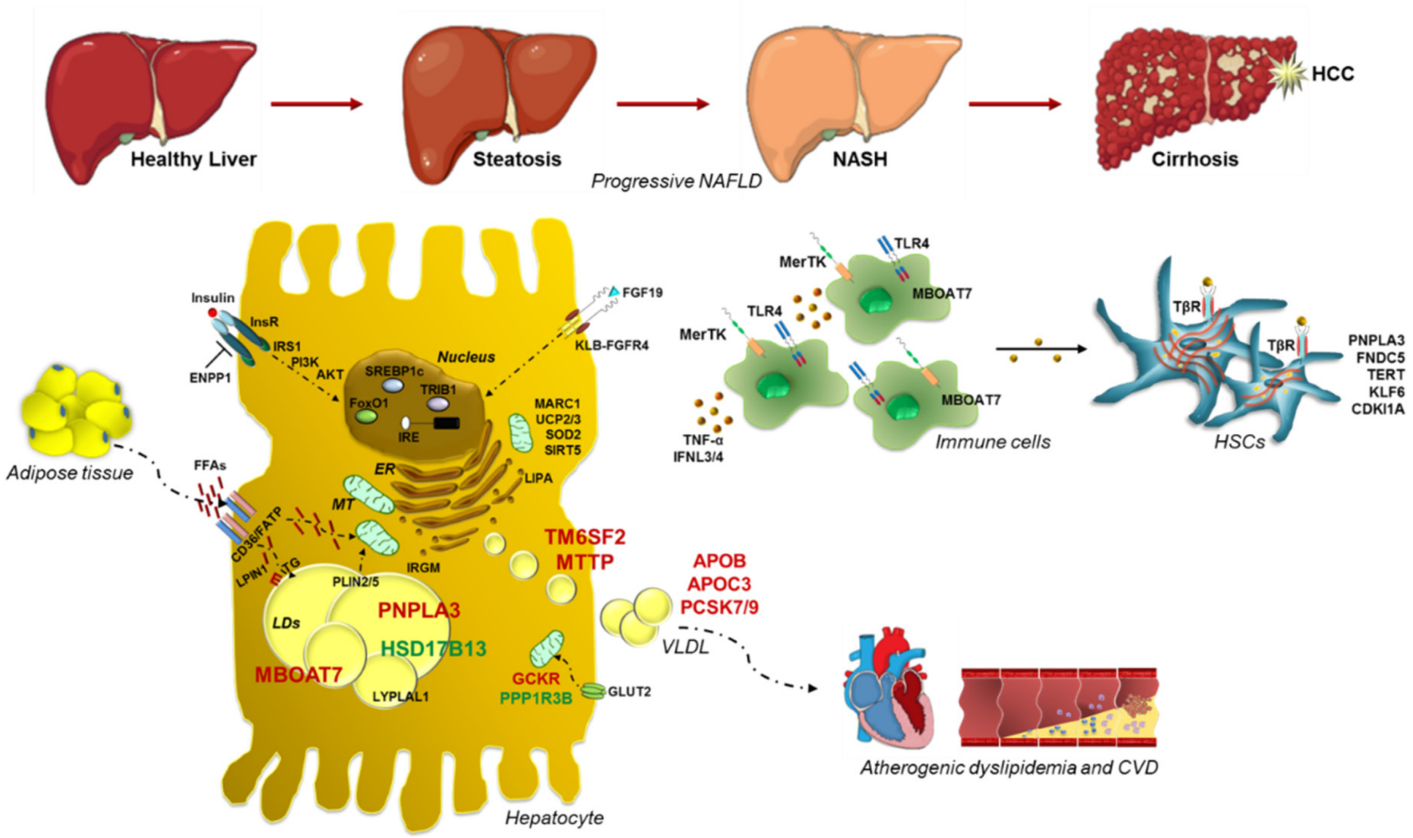

Figure 1. Impact of genetics in NAFLD pathogenesis and progression towards advanced liver damage. Schematic illustration of the most relevant inherited variations involved in progressive NAFLD, shedding light into their functional effects. PNPLA3, localized at the LD surface in hepatocytes, catalyzes TG hydrolysis. The p.148M variant enhances hepatic TG content upon mutant protein accumulation, hampering TG turnover and dismissal. TM6SF2 is implicated in VLDL formation in ER and release, whereas MBOAT7 transfers arachidonoyl-CoA to Lyso-PI, maintaining membrane fluidity. Their variations dampen VLDL secretion and membrane dynamism,

respectively. *Viceversa*, genetic variants in *HSD17B13* and *PPP1R3B* may exert a protective effect against NAFLD. Heritable variations may also influence glucose and insulin signaling, FFA uptake, fat deposition and VLDL turnover, precipitating fatty liver. In addition, IR and elevated FFAs derived from adipose tissue lipolysis exacerbate fat depot formation induced by genetic modifiers, even activating DNL. Recently, common SNPs in modulators of mitochondrial (MT) function have been proposed as active players in the switching from steatosis to NASH and fibrosis, further corroborating the role of organelle abnormalities in these processes. Furthermore, variants in genes regulating inflammatory response and HSCs activation may precipitate fatty liver to worsened conditions. Finally, genetically determined perturbations in circulating lipids may trigger cardiovascular comorbidities. Dotted lines refer to influx and efflux processes into the hepatocyte, whereas solid lines refer to cell activation or to the transition from simple steatosis up to cirrhosis-HCC.

Table 1. Schematic list of the main inherited variations related to the histological hallmarks of NAFLD.

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
rs738409 C > G	*PNPLA3*	0.26 (G)	Lipid remodeling	p.I148M	Loss-of-function	↑ NAFLD, NASH, fibrosis, HCC
rs58542926 C > T	*TM6SF2*	0.07 (T)	VLDL secretion	p.E167K	Loss-of-function	↑ NAFLD, NASH, fibrosis
rs641738 C > T	*TMC4/ MBOAT7*	0.37 (T)	Lipid remodeling	p.G17E	Loss-of-function	↑ NAFLD, NASH, fibrosis, HCC
rs1260326 C > T	*GCKR*	0.29 (T)	Regulation of *DNL*	p.P446L	Loss-of-function	↑ NAFLD, NASH, fibrosis
rs72613567 T > TA	*HSD17B13*	0.18 (TA)	Lipid remodeling	Truncated protein	Loss-of-function	↓ NASH, fibrosis, HCC
rs4841132 G > A	*PPP1R3B*	0.09 (A)	Glycogen synthesis	Non-coding	Gain-of-function	↓ NAFLD, fibrosis, HCC

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
rs1801278 C > T	*IRS1*	0.05 (T)	Insulin signaling	p.G972R	Loss-of-function	↑ Fibrosis
rs1044498 A > C	*ENPP1*	0.34 (C)	Insulin signaling	p.K121Q	Gain-of-function	↑ Fibrosis
rs2954021 G > A	*TRIB1*	0.45 (A)	Regulation of *DNL*	Non-coding	Gain-of-function	↑ NAFLD
rs12137855 C > T	*LYPLAL1*	0.16 (T)	Lipid metabolism	Intronic	Loss-of-function	↑ NAFLD
Several	*APOB*	NA	VLDL secretion	Protein change	Loss-of-function	↑ NAFLD NASH, fibrosis, HCC
Several	*MTTP*	NA	VLDL secretion	Protein change	Loss-of-function	↑NAFLD
rs236918 G > C	*PCSK7*	0.26 (C)	Membrane transferrin receptor shedding and regulation of circulating lipids	Intronic	Gain-of-function	↑ NASH, fibrosis
Several	*PCSK9*	NA	LDL uptake	Protein change	Loss-of-function	No evidence of association with steatosis
Several	*LIPA*	NA	Lipid remodeling	Protein change	LAL deficiency	↑ NAFLD, NASH, fibrosis

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
rs56225452 G > A	*FATP5*	0.16 (A)	FFAs uptake	Non-coding	Gain-of-function	↑ NASH, fibrosis
rs13412852 C > T	*LPIN1*	0.21 (T)	Lipid metabolism	Intronic	Not Defined	↓ NASH, fibrosis
rs35568725 A > G	*PLIN2*	0.02 (G)	Lipid remodeling	p.S251P	Loss-of-function	↑ NAFLD, NASH, IR, atherosclerosis
rs884164 A > G	*PLIN5*	0.19 (G)	Lipid remodeling	Non-coding	Loss-of-function	↑ oxidative stress
rs17618244 G > A	*KLB*	0.15 (A)	FGF19/FGFR4 pathway	p.R728Q	Loss-of-function	↓ NASH, fibrosis
rs4374383 G > A	*MERTK*	0.45 (A)	Innate immunity	Intronic	Loss-of-function	↓ Fibrosis
rs3750861 G > A	*KLF6*	0.07 (A)	HSCs activation	Splice variant IVS1-27G	Loss-of-function	↓ Fibrosis
Several	*TERT*	NA	Telomere maintenance	Protein change	Loss-of-function	↑ Fibrosis, HCC
rs12979860 C > T	*IL28B*	0.36 (T)	Innate immunity	Alternative IFNL3/4 transcription	Loss-of-function	↓ NASH, Fibrosis

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
rs3480 A > G	*FNDC5*	0.42 (G)	HSCs activation	Non-coding	Loss-of-function	↓ Fibrosis
rs4880 C > T	*SOD2*	0.33 (T)	Mitochondrial antioxidant	p.A16V	Loss-of-function	↑ Fibrosis
rs695366 G > A	*UCP2*	0.26 (A)	Mitochondrial lipid metabolism Oxphos	−866 promoter variant	Gain-of-function	↓ NASH, fibrosis
rs2642438 G > A	*MARC1*	0.19 (A)	Mitochondrial detoxification	p.A165T	Loss-of-function	↓ NAFLD, NASH, fibrosis

MAF = minor allele frequency.

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