Genetics and Nonalcoholic Fatty Liver Disease

Subjects: Gastroenterology & Hepatology

Contributor: Marica Meroni, Miriam Longo, Giada Tria, Paola Dongiovanni

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.

Keywords: 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**.

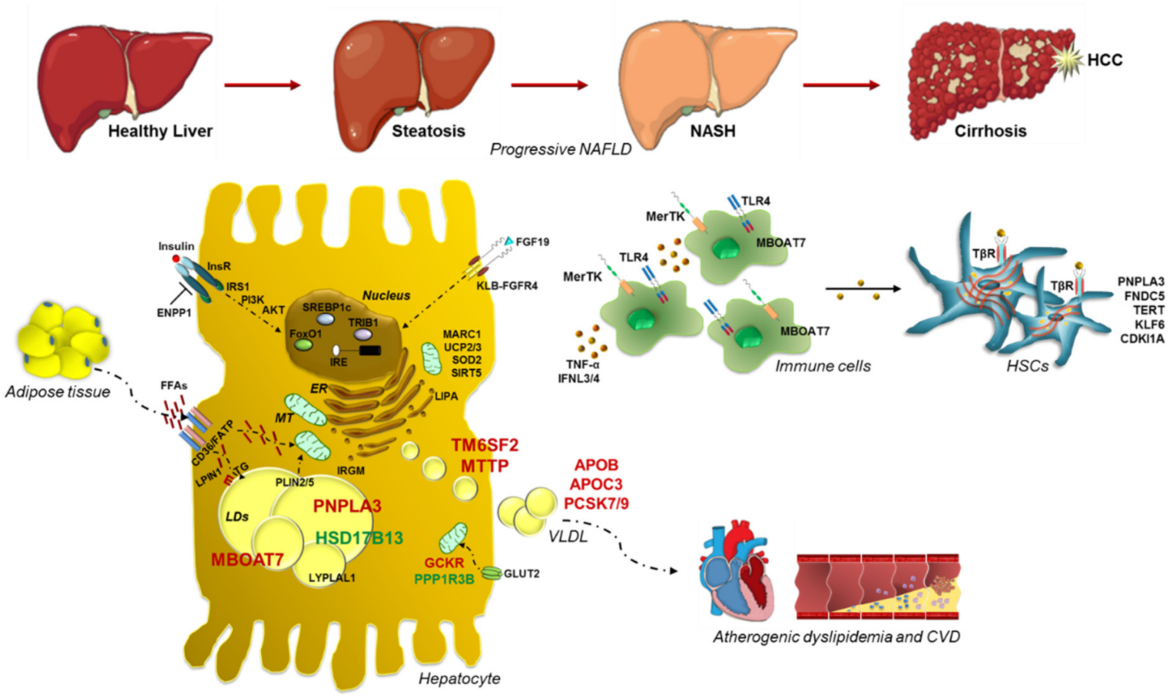

Figure 1. Impact of genetics in NAFLD pathogenesis and progression towards advanced liver damage. Schematic illustration of the most relevant inherited variations involved in progressive NAFLD, shedding light into their functional effects. PNPLA3, localized at the LD surface in hepatocytes, catalyzes 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
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

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
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
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
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

Variant	Gene	Global MAF	Function	Effect	Impact	Phenotype
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.

References

1. Zobair M. Younossi; Aaron Koenig; Dinan Abdelatif; Yousef Fazel; Linda Henry; Mark Wymer; Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **2015**, *64*, 73-84, 10.1002/hep.28431.
2. Mohammed Eslam; Arun J. Sanyal; Jacob George; Brent Neuschwander-Tetri; Claudio Tiribelli; David E. Kleiner; Elizabeth Brunt; Elisabetta Bugianesi; Hannele Yki-Järvinen; Henning Grønbæk; et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* **2020**, *158*, 1999-2014.e1, 10.1053/j.ghttps://doi.org/10.1053/j.gastro.2019.11.312astro.2019.11.312.
3. Mohammed Eslam; Philip N. Newsome; Shiv K. Sarin; Quentin M. Anstee; Giovanni Targher; Manuel Romero-Gomez; Shira Zelber-Sagi; Vincent Wai-Sun Wong; Jean-François Dufour; Jörn M. Schattenberg; et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of Hepatology* **2020**, *73*, 202-209, 10.1016/j.jhep.2020.03.039.
4. Zobair M. Younossi; Linda Henry; Haley Bush; Alita Mishra; Clinical and Economic Burden of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Clinics in Liver Disease* **2017**, *22*, 1-10, 10.1016/j.cld.2017.08.001.
5. George Cholankeril; Robert J. Wong; Menghan Hu; Ryan B. Perumpail; Eric R. Yoo; Puneet Puri; Zobair M. Younossi; Stephen A. Harrison; Aijaz Ahmed; Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. *Digestive Diseases and Sciences* **2017**, *62*, 2915-2922, 10.1007/s10620-017-4684-x.
6. Day, C.P.; From fat to inflammation.. *Gastroenterology* **2006**, *130*, 207-210, https://doi.org/10.1053/j.gastro.2005.11.017.
7. Robert J. Wong; Maria Aguilar; Ramsey Cheung; Ryan Perumpail; Stephen A. Harrison; Zobair M. Younossi; Aijaz Ahmed; Nonalcoholic Steatohepatitis Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States. *Gastroenterology* **2015**, *148*, 547-555, 10.1053/j.gastro.2014.11.039.
8. Christopher D Byrne; Giovanni Targher; NAFLD: A multisystem disease. *Journal of Hepatology* **2015**, *62*, S47-S64, 10.1016/j.jhep.2014.12.012.
9. Marica Meroni; Miriam Longo; Alice Rustichelli; Paola Dongiovanni; Nutrition and Genetics in NAFLD: The Perfect Binomium. *International Journal of Molecular Sciences* **2020**, *21*, 2986, 10.3390/ijms21082986.
10. Paola Dongiovanni; Erika Paolini; Alberto Corsini; Cesare R. Sirtori; Massimiliano Ruscica; Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: From epidemiology to drug approaches. *European Journal of Clinical Investigation* **2021**, *51*, e13519, 10.1111/eci.13519.
11. Paola Dongiovanni; Luca Valenti; Genetics of nonalcoholic fatty liver disease. *Metabolism* **2015**, *65*, 1026-1037, 10.1016/j.metabol.2015.08.018.
12. Marica Meroni; Miriam Longo; Veronica Erconi; Luca Valenti; Stefano Gatti; Anna Ludovica Fracanzani; Paola Dongiovanni; mir-101-3p Downregulation Promotes Fibrogenesis by Facilitating Hepatic Stellate Cell Transdifferentiation During Insulin Resistance. *Nutrients* **2019**, *11*, 2597, 10.3390/nu11112597.
13. Paola Dongiovanni; Marica Meroni; Miriam Longo; Silvia Fargion; Anna Ludovica Fracanzani; miRNA Signature in NAFLD: A Turning Point for a Non-Invasive Diagnosis. *International Journal of Molecular Sciences* **2018**, *19*, 3966, 10.3390/ijms19123966.

14. Stefan Stender; Julia Kozlitina; Børge G. Nordestgaard; Anne Tybjærg-Hansen; Helen H. Hobbs; Jonathan C. Cohen; Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. *Nature Genetics* **2017**, *49*, 842-847, 10.1038/ng.3855.

15. Meroni, M.; Longo, M.; Dongiovanni, P.; Alcohol or Gut Microbiota: Who Is the Guilty?. *Int. J. Mol. Sci.* **2019**, *20*, 4568, https://doi.org/10.3390/ijms20184568.

16. Marica Meroni; Miriam Longo; Paola Dongiovanni; The Role of Probiotics in Nonalcoholic Fatty Liver Disease: A New Insight into Therapeutic Strategies. *Nutrients* **2019**, *11*, 2642, 10.3390/nu11112642.

17. Paola Dongiovanni; Luca Valenti; A Nutrigenomic Approach to Non-Alcoholic Fatty Liver Disease. *International Journal of Molecular Sciences* **2017**, *18*, 1534, 10.3390/ijms18071534.

18. Quentin M. Anstee And Luca Valenti Paola Dongiovanni; Quentin Anstee; Luca Valenti; Genetic Predisposition in NAFLD and NASH: Impact on Severity of Liver Disease and Response to Treatment. *Current Pharmaceutical Design* **2013**, *19*, 5219-5238, 10.2174/1381612811319990381.

19. Paola Dongiovanni; Stefano Romeo; Luca Valenti; Genetic Factors in the Pathogenesis of Nonalcoholic Fatty Liver and Steatohepatitis. *BioMed Research International* **2015**, *2015*, 1-10, 10.1155/2015/460190.

20. Veerle Margrethe Diane Struben; Elizabeth Erickson Hespenheide; Stephen H Caldwell; Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds. *The American Journal of Medicine* **2000**, *108*, 9-13, 10.1016/s0002-9343(99)00315-0.

21. Cecilia Lindgren; Laura M. Yerges-Armstrong; Jun Wu; Ruben Hernaez; Lauren J. Kim; Lyle Palmer; Vilmundur Gudnason; Gudny Eiriksdottir; Melissa E. Garcia; Lenore J. Launer; et al. Genome-Wide Association Analysis Identifies Variants Associated with Nonalcoholic Fatty Liver Disease That Have Distinct Effects on Metabolic Traits. *PLoS Genetics* **2011**, *7*, e1001324, 10.1371/journal.pgen.1001324.

22. Lynne E. Wagenknecht; Ann L. Scherzinger; Elizabeth R. Stamm; Anthony J. G. Hanley; Jill M. Norris; Yii-Der I. Chen; Michael Bryer-Ash; Steven M. Haffner; Jerome I. Rotter; Correlates and Heritability of Nonalcoholic Fatty Liver Disease in a Minority Cohort. *Obesity* **2009**, *17*, 1240-1246, 10.1038/oby.2009.4.

23. Jeffrey B. Schwimmer; Manuel A. Celedon; Joel E. Lavine; Rany Salem; Nzali Campbell; Nicholas J. Schork; Masoud Shiehmorteza; Takeshi Yokoo; Alyssa Chavez; Michael S. Middleton; et al. Heritability of Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2009**, *136*, 1585-1592, 10.1053/j.gastro.2009.01.050.

24. Ira R Willner; Bradford Waters; S Raj Patil; Adrian Reuben; Joseph Morelli; Caroline A Riely; Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *American Journal of Gastroenterology* **2001**, *96*, 2957-2961, 10.1016/s0002-9270(01)03229-4.

25. Janne Makkonen; Kirsi Pietiläinen; Aila Rissanen; Jaakko Kaprio; Hannele Yki-Järvinen; Genetic factors contribute to variation in serum alanine aminotransferase activity independent of obesity and alcohol: A study in monozygotic and dizygotic twins. *Journal of Hepatology* **2009**, *50*, 1035-1042, 10.1016/j.jhep.2008.12.025.

26. Rohit Loomba; Nicholas Schork; Chi-Hua Chen; Ricki Bettencourt; Ana Bhatt; Brandon Ang; Phirum Nguyen; Carolyn Hernandez; Lisa Richards; Joanie Salotti; et al. Heritability of Hepatic Fibrosis and Steatosis Based on a Prospective Twin Study. *Gastroenterology* **2015**, *149*, 1784-1793, 10.1053/j.gastro.2015.08.011.

27. Jeffrey Cui; Chi-Hua Chen; Min-Tzu Lo; Nicholas Schork; Ricki Bettencourt; Monica P. Gonzalez; Archana Bhatt; Jonathan Hooker; Katherine Shaffer; Karen E. Nelson; et al. Shared genetic effects between hepatic steatosis and fibrosis: A prospective twin study.. *Hepatology* **2016**, *64*, 1547-1558, 10.1002/hep.28674.

28. Adam D. Tarnoki; David L. Tarnoki; Pal Bata; Levente Littvay; Janos Osztovits; Gyorgy Jermendy; Kinga Karlinger; Agnes Lannert; Istvan Preda; Robert G. Kiss; et al. Heritability of non-alcoholic fatty liver disease and association with abnormal vascular parameters: A twin study. *Liver International* **2012**, *32*, 1287-1293, 10.1111/j.1478-3231.2012.02823.x.

29. Maya Balakrishnan; Fasiha Kanwal; Hashem B. El-Serag; Aaron P. Thrift; Acculturation and Nonalcoholic Fatty Liver Disease Risk Among Hispanics of Mexican Origin: Findings From the National Health and Nutrition Examination Survey. *Clinical Gastroenterology and Hepatology* **2016**, *15*, 310-312, 10.1016/j.cgh.2016.09.149.

30. Jeffrey D. Browning; Lidia S. Szczepaniak; Robert Dobbins; Pamela Nuremberg; Jay D. Horton; Jonathan C. Cohen; Scott M. Grundy; Helen H. Hobbs; Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. *Hepatology* **2004**, *40*, 1387-1395, 10.1002/hep.20466.

31. Michael Wayne Fleischman; Matthew Budoff; Ifran Zeb; Ng Li; Temitope Foster; NAFLD prevalence differs among hispanic subgroups: The multi-ethnic study of atherosclerosis. *World Journal of Gastroenterology* **2014**, *20*, 4987-93, 10.3748/wjg.v20.i17.4987.

32. Guerrero, R.; Vega, G.L.; Grundy, S.M.; Browning, J.D.; Ethnic differences in hepatic steatosis: An insulin resistance paradox?. *Hepatology* **2009**, *49*, 791-801, https://doi.org/10.1002/hep.22726.

33. P. Dongiovanni; Stefan Stender; A. Pietrelli; Rosellina Margherita Mancina; A. Cespiati; S. Petta; S. Pelusi; P. Pingitore; S. Badiali; M. Maggioni; et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. *Journal of Internal Medicine* **2017**, *283*, 356-370, 10.1111/joim.12719.

34. Di Costanzo, A.; Belardinilli, F.; Bailetti, D.; Sponziello, M.; D'Erasmo, L.; valuation of Polygenic Determinants of Non-Alcoholic Fatty Liver Disease (NAFLD) By a Candidate Genes Resequencing Strategy. *Sci. Rep.* **2018**, *8*, 3702, https://doi.org/10.1038/s41598-018-21939-0.

35. Krawczyk, M.; Bantel, H.; Rau, M.; Schattenberg, J.M.; Grunhage, F.; Pathil, A.; Demir, M.; Kluwe, J.; Boettler, T.; Weber, S.N.; et al. Could inherited predisposition drive non-obese fatty liver disease? Results from German tertiary referral centers.. *J. Hum. Genet.* **2018**, *63*, 621-626, https://doi.org/10.1038/s10038-018-0420-4.

36. Dongiovanni, P.; Rametta, R.; Meroni, M.; Valenti, L.; The role of insulin resistance in nonalcoholic steatohepatitis and liver disease development—A potential therapeutic target?. *Expert Rev. Gastroenterol. Hepatol.* **2016**, *10*, 229-242, https://doi.org/10.1586/17474124.2016.1110018.

37. Paola Dongiovanni; Marica Meroni; Guido Alessandro Baselli; Giulia Alessandra Bassani; Raffaela Rametta; Alessandro Pietrelli; Marco Maggioni; Federica Facciotti; Valentina Trunzo; Sara Badiali; et al. Insulin resistance promotes Lysyl Oxidase Like 2 induction and fibrosis accumulation in non-alcoholic fatty liver disease. *Clinical Science* **2017**, *131*, 1301-1315, 10.1042/cs20170175.

38. Paul Angulo; David E. Kleiner; Sanne Dam-Larsen; Leon A. Adams; Einar S. Bjornsson; Phunchai Charatcharoenwitthaya; Peter R. Mills; Jill C. Keach; Heather D. Lafferty; Alisha Stahler; et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2015**, *149*, 389-397.e10, 10.1053/j.gastro.2015.04.043.

39. Stuart McPherson; Tim Hardy; Elsbeth Henderson; Alastair Burt; Christopher P. Day; Quentin M. Anstee; Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: Implications for prognosis and clinical management. *Journal of Hepatology* **2014**, *62*, 1148-1155, 10.1016/j.jhep.2014.11.034.

40. Serena Pelusi; Salvatore Petta; Chiara Rosso; Vittorio Borroni; Anna Ludovica Fracanzani; Paola Dongiovanni; Antonio Craxi; Elisabetta Bugianesi; Silvia Fargion; Luca Valenti; et al. Renin-Angiotensin System Inhibitors, Type 2 Diabetes and Fibrosis Progression: An Observational Study in Patients with Nonalcoholic Fatty Liver Disease. *PLoS ONE* **2016**, *11*, e0163069-e0163069, 10.1371/journal.pone.0163069.

41. P. Dongiovanni; Luca Valenti; Raffaela Rametta; Ann Daly; Valerio Nobili; Enrico Mozzi; J. B. S. Leathart; Andrea Pietrobattista; Alastair Burt; M. Maggioni; et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. *Gut* **2010**, *59*, 267-273, 10.1136/gut.2009.190801.

42. Aya Kitamoto; Takuya Kitamoto; Takahiro Nakamura; Yuji Ogawa; Masato Yoneda; Hideyuki Hyogo; Hidenori Ochi; Seiho Mizusawa; Takato Ueno; Kazuwa Nakao; et al. Association of polymorphisms in GCKR and TRIB1 with nonalcoholic fatty liver disease and metabolic syndrome traits. *Endocrine Journal* **2014**, *61*, 683-689, 10.1507/endocrj.ej14-0052.

43. Serena Pelusi; Guido Baselli; Alessandro Pietrelli; Paola Dongiovanni; Benedetta Donati; Misti Vanette McCain; Marica Meroni; Anna Ludovica Fracanzani; Renato Romagnoli; Salvatore Petta; et al. Rare Pathogenic Variants Predispose to Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease. *Scientific Reports* **2019**, *9*, 1-10, 10.1038/s41598-019-39998-2.

44. Angelo Baldassare Cefalu'; James Pirruccello; Davide Noto; Stacey Gabriel; Vincenza Valenti; Namrata Gupta; Rossella Spina; Patrizia Tarugi; Sekar Kathiresan; Maurizio R. Averna; et al. A Novel APOB Mutation Identified by Exome Sequencing Cosegregates With Steatosis, Liver Cancer, and Hypocholesterolemia. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2013**, *33*, 2021-2025, 10.1161/atvbaha.112.301101.

45. Mathilde Di Filippo; Philippe Moulin; Pascal Roy; Marie Elisabeth Samson-Bouma; Sophie Collardeau Frachon; Sabrina Chebel-Dumont; Noël Peretti; Jérôme Dumortier; Fabien Zoulim; Thierry Fontanges; et al. Homozygous MTTP and APOB mutations may lead to hepatic steatosis and fibrosis despite metabolic differences in congenital hypocholesterolemia. *Journal of Hepatology* **2014**, *61*, 891-902, 10.1016/j.jhep.2014.05.023.

46. Kitt Falk Petersen; Sylvie Dufour; Ali Hariri; Carol Nelson-Williams; Jia Nee Foo; Xian-Man Zhang; James Dziura; Richard P. Lifton; Gerald I. Shulman; Apolipoprotein C3 Gene Variants in Nonalcoholic Fatty Liver Disease. *New England Journal of Medicine* **2010**, *362*, 1082-1089, 10.1056/nejmoa0907295.

47. Julia Kozlitina; Eric Boerwinkle; Jonathan C. Cohen; Helen H. Hobbs; Dissociation between APOC3 variants, hepatic triglyceride content and insulin resistance. *Hepatology* **2010**, *53*, 467-474, 10.1002/hep.24072.

48. Luca Valenti; Valerio Nobili; Ahmad Al-Serri; Raffaela Rametta; Julian B.S. Leathart; Marco Antonio Zappa; Paola Dongiovanni; Anna Ludovica Fracanzani; Arianna Alterio; Giancarlo Roviaro; et al. The APOC3 T-455C and C-482T promoter region polymorphisms are not associated with the severity of liver damage independently of PNPLA3 I148M genotype in patients with nonalcoholic fatty liver. *Journal of Hepatology* **2011**, *55*, 1409-1414, 10.1016/j.jhep.2011.03.035.

49. Paola Dongiovanni; Marica Meroni; Guido Alessandro Baselli; Rosellina M. Mancina; Massimiliano Ruscica; Miriam Longo; Raffaela Rametta; Annalisa Cespiati; Serena Pelusi; Nicola Ferri; et al. PCSK7 gene variation bridges atherogenic dyslipidemia with hepatic inflammation in NAFLD patients. *Journal of Lipid Research* **2019**, *60*, 1144-1153, 10.1194/jlr.p090449.

50. Tao Huang; Jinyan Huang; Qibin Qi; Yanping Li; George A. Bray; Jennifer Rood; Frank M. Sacks; Lu Qi; PCSK7Genotype Modifies Effect of a Weight-Loss Diet on 2-Year Changes of Insulin Resistance: The POUNDS LOST Trial. *Diabetes Care* **2014**, *38*, 439-444, 10.2337/dc14-0473.

51. Yahya Ashraf; Stéphanie Duval; Vatsal Sachan; Rachid Essalmani; Delia Susan-Resiga; Anna Roubtsova; Josée Hamelin; Stefan Gerhardy; Daniel Kirchhofer; Vincent S. Tagliabracci; et al. Proprotein convertase 7 (PCSK7) reduces apoA-V levels. *The FEBS Journal* **2020**, *287*, 3565-3578, 10.1111/febs.15212.

52. Jonathan Cohen; Alexander Pertsemlidis; Ingrid K Kotowski; Randall Graham; Christine Kim Garcia; Helen H Hobbs; Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nature Genetics* **2005**, *37*, 161-165, 10.1038/ng1509.

53. Massimiliano Ruscica; Nicola Ferri; Chiara Macchi; Marica Meroni; Claudia Lanti; Chiara Ricci; Marco Maggioni; Anna Ludovica Fracanzani; Sara Badiali; Silvia Fargion; et al. Liver fat accumulation is associated with circulating PCSK9. *Annals of Medicine* **2016**, *48*, 384-391, 10.1080/07853890.2016.1188328.

54. Mark Trinder; Gordon A. Francis; Liam R. Brunham; Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease. *JAMA Cardiology* **2020**, *5*, 390-399, 10.1001/jamacardio.2019.5954.

55. Philippe Costet; Bertrand Cariou; Gilles Lambert; Florent Lalanne; Bernard Lardeux; Anne-Laure Jarnoux; Aldo Grefhorst; Bart Staels; Michel Krempf; Hepatic PCSK9 Expression Is Regulated by Nutritional Status via Insulin and Sterol Regulatory Element-binding Protein 1c. *Journal of Biological Chemistry* **2006**, *281*, 6211-6218, 10.1074/jbc.m508582200.

56. Ingrid K. Kotowski; Alexander Pertsemlidis; Amy Luke; Richard S. Cooper; Gloria L. Vega; Jonathan C. Cohen; Helen H. Hobbs; A Spectrum of PCSK9 Alleles Contributes to Plasma Levels of Low-Density Lipoprotein Cholesterol. *The American Journal of Human Genetics* **2006**, *78*, 410-422, 10.1086/500615.

57. Stefania Grimaudo; Stefano Bartesaghi; Raffaela Rametta; Fabio Marra; Rosellina Margherita Mancina; Jussi Pihlajamäki; Dorota Kakol-Palm; Anne-Christine Andréasson; Paola Dongiovanni; Anna Ludovica Fracanzani; et al. PCSK9 rs11591147 R46L loss-of-function variant protects against liver damage in individuals with NAFLD. *Liver International* **2020**, *41*, 321-332, 10.1111/liv.14711.

58. Monica Gomaraschi; Anna Ludovica Fracanzani; Paola Dongiovanni; Chiara Pavanello; Eleonora Giorgio; Lorenzo Da Dalt; Giuseppe Danilo Norata; Laura Calabresi; Dario Consonni; Rosa Lombardi; et al. Lipid accumulation impairs lysosomal acid lipase activity in hepatocytes: Evidence in NAFLD patients and cell cultures. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2019**, *1864*, 158523, 10.1016/j.bbalip.2019.158523.

59. Željko Reiner; Ornella Guardamagna; Devaki Nair; Handrean Soran; Kees Hovingh; Stefano Bertolini; Simon Jones; Marijana Ćorić; Sebastiano Calandra; John Hamilton; et al. Lysosomal acid lipase deficiency – An under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis* **2014**, *235*, 21-30, 10.1016/j.atherosclerosis.2014.04.003.

60. Hernando Lyons; Eleftherios Vouyoukas; Martha Higgins; James J. Maciejko; Clinical and Histologic Liver Improvement in Siblings With Lysosomal Acid Lipase Deficiency After Enzyme Replacement. *Journal of Pediatric Gastroenterology & Nutrition* **2020**, *70*, 635-639, 10.1097/mpg.0000000000002671.

61. Věra Malinová; Manisha Balwani; Reena Sharma; Jean-Baptiste Arnoux; John Kane; Chester B. Whitley; Sachin Marulkar; Florian Abel; Sebelipase alfa for lysosomal acid lipase deficiency: 5-year treatment experience from a phase 2 open-label extension study. *Liver International* **2020**, *40*, 2203-2214, 10.1111/liv.14603.

62. A. Auinger; Luca Valenti; M. Pfeuffer; U. Helwig; J. Herrmann; Anna Ludovica Fracanzani; P. Dongiovanni; S. Fargion; J. Schrezenmeir; D. Rubin; et al. A Promoter Polymorphism in the Liver-specific Fatty Acid Transport Protein 5 is Associated with Features of the Metabolic Syndrome and Steatosis. *Hormone and Metabolic Research* **2010**, *42*, 854-859, 10.1055/s-0030-1267186.

63. Luca Valenti; Benedetta Maria Motta; Anna Alisi; Rita Sartorelli; Giulia Buonaiuto; Paola Dongiovanni; Raffaela Rametta; Serena Pelusi; Silvia Fargion; Valerio Nobili; et al. LPIN1 rs13412852 Polymorphism in Pediatric Nonalcoholic

Fatty Liver Disease. *Journal of Pediatric Gastroenterology & Nutrition* **2012**, *54*, 588-593, 10.1097/mpg.0b013e3182442a55.

64. Claire S. Faulkner; Collin M. White; Vijay H. Shah; Loretta L. Jophlin; A single nucleotide polymorphism of PLIN2 is associated with nonalcoholic steatohepatitis and causes phenotypic changes in hepatocyte lipid droplets: A pilot study. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2020**, *1865*, 158637-158637, 10.1016/j.bbalip.2020.158637.

65. Joëlle Magné; Anna Aminoff; Jeanna Perman Sundelin; Maria Nastase Mannila; Peter Gustafsson; Kjell Hultenby; Annika Wernerson; Greta Bauer; Laura Listenberger; Matt J. Neville; et al. The minor allele of the missense polymorphism Ser251Pro in perilipin 2 (PLIN2) disrupts an α-helix, affects lipolysis, and is associated with reduced plasma triglyceride concentration in humans. *The FASEB Journal* **2013**, *27*, 3090-3099, 10.1096/fj.13-228759.

66. Christina Drevinge; Knut T. Dalen; Maria Nastase Mannila; Margareta Scharin Täng; Marcus Ståhlman; Martina Klevstig; Annika Lundqvist; Ismena Mardani; Fred Haugen; Per Fogelstrand; et al. Perilipin 5 is protective in the ischemic heart. *International Journal of Cardiology* **2016**, *219*, 446-454, 10.1016/j.ijcard.2016.06.037.

67. Kenta Kuramoto; Tomoo Okamura; Tomohiro Yamaguchi; Tomoe Y. Nakamura; Shigeo Wakabayashi; Hidetaka Morinaga; Masatoshi Nomura; Toshihiko Yanase; Kinya Otsu; Nobuteru Usuda; et al. Perilipin 5, a Lipid Droplet-binding Protein, Protects Heart from Oxidative Burden by Sequestering Fatty Acid from Excessive Oxidation. *Journal of Biological Chemistry* **2012**, *287*, 23852-23863, 10.1074/jbc.m111.328708.

68. Yu-Cheng Lin; Pi-Feng Chang; Hsueh-Fang Lin; Kevin Liu; Mei Hwei Chang; Yen-Hsuan Ni; Variants in the autophagy-related gene IRGM confer susceptibility to non-alcoholic fatty liver disease by modulating lipophagy. *Journal of Hepatology* **2016**, *65*, 1209-1216, 10.1016/j.jhep.2016.06.029.

69. Kristin Schwerbel; Anne Kamitz; Natalie Krahmer; Nicole Hallahan; Markus Jähnert; Pascal Gottmann; Sandra Lebek; Tanja Schallschmidt; Danny Arends; Fabian Schumacher; et al. Immunity-related GTPase induces lipophagy to prevent excess hepatic lipid accumulation. *Journal of Hepatology* **2020**, *73*, 771-782, 10.1016/j.jhep.2020.04.031.

70. Marra, F.; Bertolani, C.; Adipokines in liver diseases.. *Hepatology* **2009**, *50*, 957-969, https://doi.org/10.1002/hep.23046.

71. Luca Miele; Venanzio Valenza; Giuseppe La Torre; Massimo Montalto; Giovanni Cammarota; Riccardo Ricci; Roberta Mascianà; Alessandra Forgione; Maria L. Gabrieli; Germano Perotti; et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* **2009**, *49*, 1877-1887, 10.1002/hep.22848.

72. Manfred Bilzer; Frigga Roggel; Alexander L. Gerbes; Role of Kupffer cells in host defense and liver disease. *Liver International* **2006**, *26*, 1175-1186, 10.1111/j.1478-3231.2006.01342.x.

73. Mohammed Eslam; the International Liver Disease Genetics Consortium (ILDGC); Duncan McLeod; Kebitsaone Simon Kelaeng; Alessandra Mangia; Thomas Berg; Khaled Thabet; William Irving; Gregory J Dore; David Sheridan; et al. IFN-λ3, not IFN-λ4, likely mediates IFNL3–IFNL4 haplotype–dependent hepatic inflammation and fibrosis. *Nature Genetics* **2017**, *49*, 795-800, 10.1038/ng.3836.

74. Salvatore Petta; Stefania Grimaudo; Calogero Cammà; Daniela Cabibi; Vito Di Marco; Giusalba Licata; Rosaria Maria Pipitone; Antonio Craxì; IL28B and PNPLA3 polymorphisms affect histological liver damage in patients with non-alcoholic fatty liver disease. *Journal of Hepatology* **2012**, *56*, 1356-1362, 10.1016/j.jhep.2012.01.007.

75. Mohammed Eslam; the International Hepatitis C Genetics Consortium (IHCGC); Ahmed M. Hashem; Reynold Leung; Manuel Romero-Gómez; Thomas Berg; Gregory J. Dore; Henry L.K. Chan; William Irving; David Sheridan; et al. Interferon-λ rs12979860 genotype and liver fibrosis in viral and non-viral chronic liver disease. *Nature Communications* **2015**, *6*, 6422, 10.1038/ncomms7422.

76. Mohammed Eslam; Ahmed M. Hashem; Manuel Romero-Gómez; Thomas Berg; Gregory J. Dore; Alessandra Mangia; Henry Lik Yuen Chan; William Irving; David Sheridan; Maria Lorena Abate; et al. FibroGENE: A gene-based model for staging liver fibrosis. *Journal of Hepatology* **2016**, *64*, 390-398, 10.1016/j.jhep.2015.11.008.

77. Petta, S.; Valenti, L.; Interferon lambda 4 rs368234815 TT > δG variant is associated with liver damage in patients with nonalcoholic fatty liver disease.. *J. Hepatol.* **2017**, *66*, 1885-1893, https://doi.org/10.1002/hep.29395.

78. Petta, S.; Valenti, L.; Svegliati-Baroni, G.; Ruscica, M.; Pipitone, R.M.; Dongiovanni, P.; Rychlicki, C.; Ferri, N.; Cammà, C.; Fracanzani, A.L.; et al. Fibronectin Type III Domain-Containing Protein 5 rs3480 A > G Polymorphism, Irisin, and Liver Fibrosis in Patients With Nonalcoholic Fatty Liver Disease.. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 2660-2669, https://doi.org/10.1210/jc.2017-00056.

79. Mayada Metwally; Ali Bayoumi; Manuel Romero-Gomez; Khaled Thabet; Miya John; Leon A. Adams; Xiaoqi Huo; Rocio Aller; Carmelo García-Monzón; María Teresa Arias-Loste; et al. A polymorphism in the Irisin-encoding gene (FNDC5) associates with hepatic steatosis by differential miRNA binding to the 3′UTR. *Journal of Hepatology* **2018**, *70*, 494-500, 10.1016/j.jhep.2018.10.021.

80. Alexis Gorden; Rongze Yang; Laura M. Yerges-Armstrong; Kathleen A. Ryan; Elizabeth Speliotes; Ingrid B. Borecki; Tamara B. Harris; Xin Chu; G. Craig Wood; Christopher D. Still; et al. Genetic Variation at NCAN Locus Is Associated with Inflammation and Fibrosis in Non-Alcoholic Fatty Liver Disease in Morbid Obesity. *Human Heredity* **2013**, *75*, 34-43, 10.1159/000346195.

81. Cai, W.; Weng, D.H.; Yan, P.; Lin, Y.T.; Dong, Z.H.; Mailamuguli; Yao, H.; Genetic polymorphisms associated with nonalcoholic fatty liver disease in Uyghur population: A case-control study and meta-analysis.. *Lipids Health Dis.* **2019**, *18*, 14, https://doi.org/10.1186/s12944-018-0877-3.

82. Claudia Cicione; Chiara Degirolamo; Antonio Moschetta; Emerging role of fibroblast growth factors 15/19 and 21 as metabolic integrators in the liver. *Hepatology* **2012**, *56*, 2404-2411, 10.1002/hep.25929.

83. Dongiovanni, P.; Crudele, A.; Panera, N.; Romito, I.; Meroni, M.; De Stefanis, C.; Palma, A.; Comparcola, D.; Fracanzani, A.L.; Miele, L.; et al. beta-Klotho gene variation is associated with liver damage in children with NAFLD.. *J. Hepatol.* **2020**, *72*, 411-419, https://doi.org/10.1016/j.jhep.2019.10.011.

84. Kathleen Markan; Meghan C. Naber; Sarah M. Small; Lila Peltekian; Rachel L. Kessler; Matthew J. Potthoff; FGF21 resistance is not mediated by downregulation of beta-klotho expression in white adipose tissue. *Molecular Metabolism* **2017**, *6*, 602-610, 10.1016/j.molmet.2017.03.009.

85. Dushay, J.; Chui, P.C.; Gopalakrishnan, G.S.; Varela-Rey, M.; Crawley, M.; Fisher, F.M.; Badman, M.K.; Martinez-Chantar, M.L.; Maratos-Flier, E.; Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease.. *Gastroenterology* **2010**, *139*, 456-463, https://doi.org/10.1053/j.gastro.2010.04.054.

86. Javier Gómez-Ambrosi; Jose Miguel Gallego-Escuredo; Victoria Catalan; Amaia Rodríguez; Pere Domingo; Rafael Moncada; Víctor Valentí; Javier Salvador; Marta Giralt; Francesc Villarroya; et al. FGF19 and FGF21 serum concentrations in human obesity and type 2 diabetes behave differently after diet- or surgically-induced weight loss. *Clinical Nutrition* **2016**, *36*, 861-868, 10.1016/j.clnu.2016.04.027.

87. Luca Miele; Gary Beale; Gillian Patman; Valerio Nobili; Julian Leathart; Antonio Grieco; Marilena Abate; Scott L. Friedman; Goutham Narla; Elisabetta Bugianesi; et al. The Kruppel-Like Factor 6 Genotype Is Associated With Fibrosis in Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2008**, *135*, 282-291.e1, 10.1053/j.gastro.2008.04.004.

88. Raffaela Rametta; Marica Meroni; Paola Dongiovanni; From Environment to Genome and Back: A Lesson from HFE Mutations. *International Journal of Molecular Sciences* **2020**, *21*, 3505, 10.3390/ijms21103505.

89. Salvatore Petta; Luca Valenti; Fabio Marra; Stefania Grimaudo; Claudio Tripodo; Elisabetta Bugianesi; Calogero Cammà; Andrea Cappon; Vito Di Marco; Giovanni Di Maira; et al. MERTK rs4374383 polymorphism affects the severity of fibrosis in non-alcoholic fatty liver disease. *Journal of Hepatology* **2016**, *64*, 682-690, 10.1016/j.jhep.2015.10.016.

90. S Rüeger; P-Y Bochud; J-F Dufour; B Müllhaupt; D Semela; M H Heim; D Moradpour; A Cerny; R Malinverni; D R Booth; et al. Impact of common risk factors of fibrosis progression in chronic hepatitis C. *Gut* **2014**, *64*, 1605-1615, 10.1136/gutjnl-2014-306997.

91. Bishuang Cai; Paola Dongiovanni; Kathleen E. Corey; Xiaobo Wang; Igor O. Shmarakov; Ze Zheng; Canan Kasikara; Viralkumar Davra; Marica Meroni; Raymond T. Chung; et al. Macrophage MerTK Promotes Liver Fibrosis in Nonalcoholic Steatohepatitis. *Cell Metabolism* **2020**, *31*, 406-421.e407, 10.1016/j.cmet.2019.11.013.

92. José A. Nicolás-Ávila; Ana V. Lechuga-Vieco; Lorena Esteban-Martínez; María Sánchez-Díaz; Elena Díaz García; Demetrio J. Santiago; Andrea Rubio-Ponce; Jackson LiangYao Li; Akhila Balachander; Juan A. Quintana; et al. A Network of Macrophages Supports Mitochondrial Homeostasis in the Heart. *Cell* **2020**, *183*, 94-109.e23, 10.1016/j.cell.2020.08.031.

93. Aloysious Aravinthan; George Mells; Michael Allison; Julian Leathart; Anna Kotronen; Hannele Yki-Järvinen; Ann K Daly; Christopher P Day; Quentin M. Anstee; Graeme Alexander; et al. Gene polymorphisms of cellular senescence marker p21 and disease progression in non-alcohol-related fatty liver disease. *Function of a membrane-embedded domain evolutionarily multiplied in the GPI lipid anchor pathway proteins PIG-B, PIG-M, PIG-U, PIG-W, PIG-V, and PIG-Z* **2014**, *13*, 1489-1494, 10.4161/cc.28471.

94. Rodrigo T. Calado; Joshua A. Regal; David E. Kleiner; David S. Schrump; Nathan R. Peterson; Verònica Pons; Stephen J. Chanock; Peter M. Lansdorp; Neal S. Young; A Spectrum of Severe Familial Liver Disorders Associate with Telomerase Mutations. *PLoS ONE* **2009**, *4*, e7926, 10.1371/journal.pone.0007926.

95. Meroni, M.; Longo, M.; Paolini, E.; Alisi, A.; Miele, L.; De Caro, E.R.; Pisano, G.; Maggioni, M.; Soardo, G.; Valenti, L.V.; et al. The rs599839 A > G Variant Disentangles Cardiovascular Risk and Hepatocellular Carcinoma in NAFLD Patients.. *Cancers (Basel)* **2021**, *13*, 1783, https://doi.org/10.3390/cancers13081783.

96. Paola Dongiovanni; Marica Meroni; Salvatore Petta; Miriam Longo; Anna Alisi; Giorgio Soardo; Luca Valenti; Luca Miele; Stefania Grimaudo; Grazia Pennisi; et al. Neurotensin up-regulation is associated with advanced fibrosis and

hepatocellular carcinoma in patients with MAFLD. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2020**, *1865*, 158765, 10.1016/j.bbalip.2020.158765.

97. Pessayre, D.; Fromenty, B.; NASH: A mitochondrial disease.. *J. Hepatol.* **2005**, *42*, 928-940, https://doi.org/10.1016/j.jhep.2005.03.004.
98. Abdellah Mansouri; Charles-Henry Gattolliat; Tarik Asselah; Mitochondrial Dysfunction and Signaling in Chronic Liver Diseases. *Gastroenterology* **2018**, *155*, 629-647, 10.1053/j.gastro.2018.06.083.
99. Chikako Namikawa; Zhang Shu-Ping; John Raynor Vyselaar; Yasuko Nozaki; Yoshihisa Nemoto; Masafumi Ono; Naoaki Akisawa; Toshiji Saibara; Makoto Hiroi; Hideaki Enzan; et al. Polymorphisms of microsomal triglyceride transfer protein gene and manganese superoxide dismutase gene in non-alcoholic steatohepatitis. *Journal of Hepatology* **2004**, *40*, 781-786, 10.1016/j.jhep.2004.01.028.
100. Ahmad Al-Serri; Quentin M. Anstee; Luca Valenti; Valerio Nobili; Julian B.S. Leathart; Paola Dongiovanni; Julia Patch; Anna Ludovica Fracanzani; Silvia Fargion; Christopher P. Day; et al. The SOD2 C47T polymorphism influences NAFLD fibrosis severity: Evidence from case-control and intra-familial allele association studies. *Journal of Hepatology* **2011**, *56*, 448-454, 10.1016/j.jhep.2011.05.029.
101. Fares, R.; Petta, S.; Lombardi, R.; Grimaudo, S.; Dongiovanni, P.; Pipitone, R.; Rametta, R.; Fracanzani, A.L.; Mozzi, E.; Craxì, A.; et al. The UCP2 -866 G > A promoter region polymorphism is associated with nonalcoholic steatohepatitis. *Liver Int. Off. J. Int. Assoc. Study Liver* **2015**, *35*, 1574-1580, https://doi.org/10.1111/liv.12707.
102. G Serviddio; F Bellanti; R Tamborra; T Rollo; N Capitanio; A D Romano; J Sastre; G Vendemiale; E Altomare; Uncoupling protein-2 (UCP2) induces mitochondrial proton leak and increases susceptibility of non-alcoholic steatohepatitis (NASH) liver to ischaemia-reperfusion injury. *Gut* **2008**, *57*, 957-965, 10.1136/gut.2007.147496.
103. D. A. de Luis; Role of -55CT polymorphism of UCP3 gene on non alcoholic fatty liver disease and insulin resistance in patients with obesity. *Nutr. Hosp.* **2010**, *25*, 572-5576, 10.3305/NH.2010.25.4.4484.
104. Lei Zhong; Raul Mostoslavsky; Fine Tuning Our Cellular Factories: Sirtuins in Mitochondrial Biology. *Cell Metabolism* **2011**, *13*, 621-626, 10.1016/j.cmet.2011.05.004.
105. Chuanhui Dong; David Della-Morte; Liyong Wang; Digna Cabral; Ashley Beecham; Mark S. McClendon; Corneliu Luca; Susan H. Blanton; Ralph L. Sacco; Tatjana Rundek; et al. Association of the Sirtuin and Mitochondrial Uncoupling Protein Genes with Carotid Plaque. *PLoS ONE* **2011**, *6*, e27157, 10.1371/journal.pone.0027157.
106. Connor A. Emdin; Mary E. Haas; Amit V. Khera; Krishna Aragam; Mark Chaffin; Derek Klarin; George Hindy; Lan Jiang; Wei-Qi Wei; Qiping Feng; et al. A missense variant in Mitochondrial Amidoxime Reducing Component 1 gene and protection against liver disease. *PLoS Genetics* **2020**, *16*, e1008629, 10.1371/journal.pgen.1008629.
107. Hamish Innes; Stephan Buch; Sharon Hutchinson; Indra Neil Guha; Joanne R. Morling; Elleanor Barnes; Will Irving; Ewan Forrest; Vincent Pedergnana; David Goldberg; et al. Genome-Wide Association Study for Alcohol-Related Cirrhosis Identifies Risk Loci in MARC1 and HNRNPUL1. *Gastroenterology* **2020**, *159*, 1276-1289.e7, 10.1053/j.gastro.2020.06.014.
108. Panu K. Luukkonen; Anne Juuti; Henna Sammalkorpi; Anne K. Penttilä; Matej Orešič; Tuulia Hyötyläinen; Johanna Arola; Marju Orho-Melander; Hannele Yki-Järvinen; MARC1 variant rs2642438 increases hepatic phosphatidylcholines and decreases severity of non-alcoholic fatty liver disease in humans. *Journal of Hepatology* **2020**, *73*, 725-726, 10.1016/j.jhep.2020.04.021.
109. Jake Mann; Maik Pietzner; Laura B Wittemans; Emmanuela De Lucia Rolfe; Nicola D Kerrison; Fumiaki Imamura; Nita Forouhi; Eric Fauman; Michael E Allison; Jules L Griffin; et al. Insights into genetic variants associated with NASH-fibrosis from metabolite profiling.. *Hum. Mol. Genet.* **2020**, *29*, 3451–3463, 10.17863/cam.55211.
110. Carolin V. Schneider; Kai Markus Schneider; Donna M. Conlon; Joseph Park; Marijana Vujkovic; Inuk Zandvakili; Yi-An Ko; Christian Trautwein; Rotonya M. Carr; Pavel Strnad; et al. A genome-first approach to mortality and metabolic phenotypes in MTARC1 p.Ala165Thr (rs2642438) heterozygotes and homozygotes. *Med* **2021**, *2*, 851-863.e853, 10.1016/j.medj.2021.04.011.