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Review Article

Unique Genetic Features of Lean NAFLD: A Review of Mechanisms and Clinical Implications

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Abstract

Non-alcoholic fatty liver disease (NAFLD) affects 25% of the global population. About 20% have a normal body mass index (BMI) and a variant known as lean NAFLD. Unlike typical NAFLD cases associated with obesity and diabetes, lean NAFLD causes liver disease by mechanisms not related to excess weight or insulin resistance. Genetic disorders are among the major factors in developing lean NAFLD, and genome-wide association studies have identified several genes associated with the condition. This review aims to increase awareness by describing the genetic markers linked to NAFLD and the defects involved in developing lean NAFLD.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) comprises a variety of liver disorders defined by an increased amount of fat in the liver without significant alcohol consumption.[1] NAFLD is generally subdivided into nonalcoholic fatty liver (NAFL), characterized by hepatic steatosis and nonalcoholic steatohepatitis (NASH) or steatosis plus hepatitis.[2] NAFLD has become a worldwide concern because it is now one of the main causes of chronic liver disease, requiring an expenditure of more than 100 billion dollars for health care annually in the USA.[3,4] It is associated with increased mortality from hepatic complications, including cirrhosis and hepatocellular carcinoma (HCC), and extra-hepatic complications, such as a higher risk of chronic kidney disease and cardiovascular disease.[5–7] NAFLD is often associated with metabolic syndrome, abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels.

However, approximately 20% of NAFLD patients are not overweight, with a body mass index (BMI) of <23 for Asians and 25 kg/m^2 for Caucasians.[8] These cases have been categorized as lean NAFLD. As with NAFLD, there has been an increase in the prevalence of lean cases, and these patients have a higher mortality rate when compared to the general population.[9] Data from the Third National Health and Nutrition Examination Survey revealed that the unadjusted all-cause mortality in lean NAFLD individuals was 40.9% vs. 17.9% in non-NAFLD lean individuals (p<0.001).[10] There was also higher cardiovascular mortality, 15.1% vs. 3.7%, in lean patients with vs. without NAFLD, respectively (p<0.001).[10] Although this study had a substantial sample size of 5,375 participants, the information regarding cardiovascular disease history was self-reported, which may be a limitation. A comparable study reviewed cases of lean NAFLD from 1999–2021 and found that they were more likely to have acute coronary syndrome.[11]

An Austrian study reported that patients with lean NAFLD had a higher mortality rate from liver-related causes than overweight and obese NAFLD patients (11% vs. 4%), respectively.[12] Similarly, a study evaluating 466 patients with NAFLD revealed that lean patients had a higher prevalence of lobular inflammation (16.2% vs. 7.9%, p=0.011), hepatocellular ballooning (25.7% vs. 15.7%, p=0.014), fibrosis (25.7% vs. 13.2%, p=0.019), and progression to cirrhosis (8.1% vs. 1.7%, p=0.010) compared with overweight patients.[13] Although the study had strong statistical power and NAFLD was confirmed by biopsy, there was a potential for bias as the selection of subjects may have been influenced by their liver enzyme levels.

The clinical differences between lean and obese NAFLD have been investigated. A study that included 92 patients

Keywords: Lean nonalcoholic fatty liver disease; Palatine-like phospholipase domain-containing-3; Transmembrane 6 superfamily member 2; Familial hypobetalipoproteinemia; Abetalipoproteinemia.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ABCA1, ATP-binding cassette A1; ABL, abetalipoproteinemia; ACAT, acetyl-coenzyme A acetyltransferase; ALT, alanine transaminase; ApoB, apolipoprotein B; AST, aspartate transferase; BMI, body mass index; CESD, cholesterol esterase storage disease; DNA, deoxyribonucleic acid; DNL, *de novo* lipogenesis; ER, endoplasmic reticulum; FDA, Federal Drug Administration; FFAs, free fatty acids; FHBL, familial hypobetalipoproteinemia; GCKR, glucokinase regulator; HbA_{1c}, hemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HMCGCoA-R, 3-hydroxy-3-methylglutaryl-CoA reductase; IR, insulin resistance; IU/L, international units per liter; LAL, lysosomal acid lipase; LALD, lysosomal acid lipase deficiency; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LXRs, liver X receptors; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging proton density fat fraction; MTTP, microsomal triglyceride transfer protein; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PNPLA3, palatine-like phospholipase domain-containing-3; RUQ, right upper quadrant; SREBPs, steroid regulation binding proteins; TG, triglycerides; TM6SF2, transmembrane 6 superfamily member 2; VLDL, very low-density lipoprotein; WD, Wolman disease.

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with NAFLD revealed that those who were lean were more commonly women and had a lower prevalence of metabolic syndrome and diabetes ($p<0.001$).[14] Because they lack obesity and may not have typical metabolic risk factors, lean individuals with NAFLD appear to develop liver disease by mechanisms not associated with excess body weight and insulin resistance (IR).[15] In this regard, genetic mechanisms may be involved. The aim of this review is to increase awareness by describing the unique genetic markers associated with NAFLD and the genetic defects involved in the development of lean NAFLD.

Epidemiology

NAFLD

The worldwide prevalence of NAFLD is estimated at 25%, which has increased five-fold since 1997.[3] Around 30% of Americans have NAFL and 5% NASH. Worldwide, 7–30% of NAFL patients progress to NASH.[3] Due to the increase in type 2 diabetes mellitus and obesity, it is estimated that over 100 million Americans will be affected by 2030.[16] Overall, NAFLD is more prevalent in men. However, when women are affected, they tend to have more advanced stages of fibrosis.[17] This is believed to be secondary to the postmenopausal status and lack of estrogen which is protective against fibrosis.[17] The prevalence of NAFLD also differs according to ethnicity. Studies have shown that Hispanics are the most commonly affected, with the prevalence of Hispanic patients originating from Mexico at 33%, Puerto Rico at 18%, and the Dominican Republic at 16%.[18] Studies in twins have demonstrated a 50% heritability of NAFLD.[19] Likewise, the severity of NAFLD has also been associated with genetics. There is evidence of a 12-fold increased risk of severe liver fibrosis in patients with a first-degree family member with NAFLD-associated cirrhosis.[20]

Lean NAFLD

As mentioned above, approximately 10–20% of NAFLD patients are not overweight or obese.[8] About 8–10 million people in the USA have lean NAFLD, including up to 8% of adolescents.[21] Data have revealed that lean NAFLD is most prevalent in Hispanics and Asians (35.1%, 35.6%) followed by White (30%) and Black ethnic groups (11.6%) ($p<0.001$).[22]

Several studies have delineated the demographics of patients with lean NAFLD. A Chinese study in 2021 reviewed data from 4,750 cases of lean NAFLD, including sex, age, BMI, and lipid profile.[23] The prevalence of lean NAFLD was higher in patients >60 years of age and in women ($p<0.001$).[23] A substantial fraction, 26.3%, of patients had total cholesterol >5.2 mmol/L, and 54.2% had triglycerides >1.7 mmol/L.[23] The most common metabolic abnormality was elevated triglycerides.[23] Strengths included good statistical power. However, the cross-sectional design was a limitation. Another study comparing 263 obese and lean NAFLD patients showed that the prevalence of hypertension (61.7% vs. 49.1%, $p=0.190$), dyslipidemia (68.0% vs. 61.4%, $p=0.353$), NASH (63.1% vs. 61.4%, $p=0.710$) and advanced fibrosis (31.6% vs. 26.3%, $p=0.447$) was similar in each group.[24] The study was ethnically diverse with good statistical power. However, it was a cross-sectional design without long-term clinical data. A population-based cross-sectional study in 2021 in China investigated the risk factors for lean NAFLD in 974 cases and found that elevated BMI (although still <25 kg/m^2) and triglycerides were risk factors in the lean group for which lifestyle interventions could be helpful to prevent the occurrence of NAFLD ($p=0.000$).[25] This study had several strengths, including exclusion of any other liver pathologies that could affect the results, careful interpretation of ultrasound results by a single examiner to avoid bias, and a large sample size of 974 patients that provided strong statistical power. However, the cross-sectional design was a limitation of the study.

Genetics and lean NAFLD

The development of genome-wide association studies has allowed the testing of millions of genetic variants using various technologies without bias. This has led to the association of the development of lean NAFLD with several genetic loci, which are discussed below.

Palatine-like phospholipase domain-containing-3 (PNPLA3)

The PNPLA3 protein has been shown to be normally associated with lipase activity toward hepatocyte triglycerides and retinyl esters in hepatic stellate cells.[26] It mediates the rate-limiting step of triglyceride hydrolysis (Fig. 1A).[26]

Substitution of cytosine by guanine at position 148 has been shown to eliminate hepatic lipase activity.[26] This causes the accumulation of hepatic lipid droplets, which can result in steatosis and fibrosis/cirrhosis.[26] Approximately 15% of the population is affected by this genetic defect, and the incidence varies with ethnicity.[27] A cohort study in Texas showed that the variant PNPLA3 was most prevalent in Hispanics (0.49), European Americans (0.23), and, African Americans (0.17).[27] Patients are typically asymptomatic, and hepatic steatosis is diagnosed incidentally on abdominal imaging.[28] There are no characteristic laboratory abnormalities related to this condition, making high clinical suspicion important (Table 1).

Studies have identified PNPLA3 mutations as an etiology of lean NAFLD, and the data showed that the mutations occur more frequently and with greater severity in lean NAFLD patients than in those who are overweight or obese. For example, a cross-sectional study of 540 patients with NAFLD was performed in Japan.[29] A total of 134 lean and 406 obese patients with NAFLD (based on imaging) were enrolled.[29] Patients were excluded if they had hepatitis (autoimmune, viral, drug-induced, or alcoholic), primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease, hemochromatosis, alpha1-antitrypsin deficiency, alcohol intake of >20 g per day or had evidence of hepatic decompensation.[29] Patients were then classified by their BMI as lean (<25 kg/m^2) and obese (≥25 kg/m^2).[29] They underwent percutaneous liver biopsy for the diagnosis and staging of NASH and genomic DNA analysis for PNPLA3 mutations from a venous blood sample.[29] The average characteristics of lean vs. obese patients were 56 vs. 48 years of age, male/female ratio of 57/77 vs. 228/178, BMI 22.8 kg/m^2 vs. 29.8 kg/m^2, HbA_{1c} 6.3% vs. 6.3%, type 2 diabetes 32.9% vs. 36.5%, and total cholesterol 213 mg/dL vs. 212 mg/dL.[29] It was found that lean patients expressed the PNPLA3 mutation significantly more frequently than obese patients (47.8% vs. 36.5%, $p=0.02$) and had lower levels of AST (47 IU/L vs. 51 IU/L, $p=0.0052$) and ALT (71 IU/L vs. 84 IU/L, $p=0.00037$).[29] Finally, multiple logistic regression revealed that lean NAFLD patients with the genotype had a more severe histological grade and fibrosis stage than the affected obese group.[29] The adjusted odds ratio (OR) for lobular inflammation in the lean vs. obese groups was 3.37 vs. 0.99, hepatocyte ballooning was 2.51 vs. 1.46, NAFLD activity score 1.43 vs. 1.06, and fibrosis 1.76 vs. 1.35.[29] The study strengths were good statistical power and the exclusion of any liver diseases that may have impacted

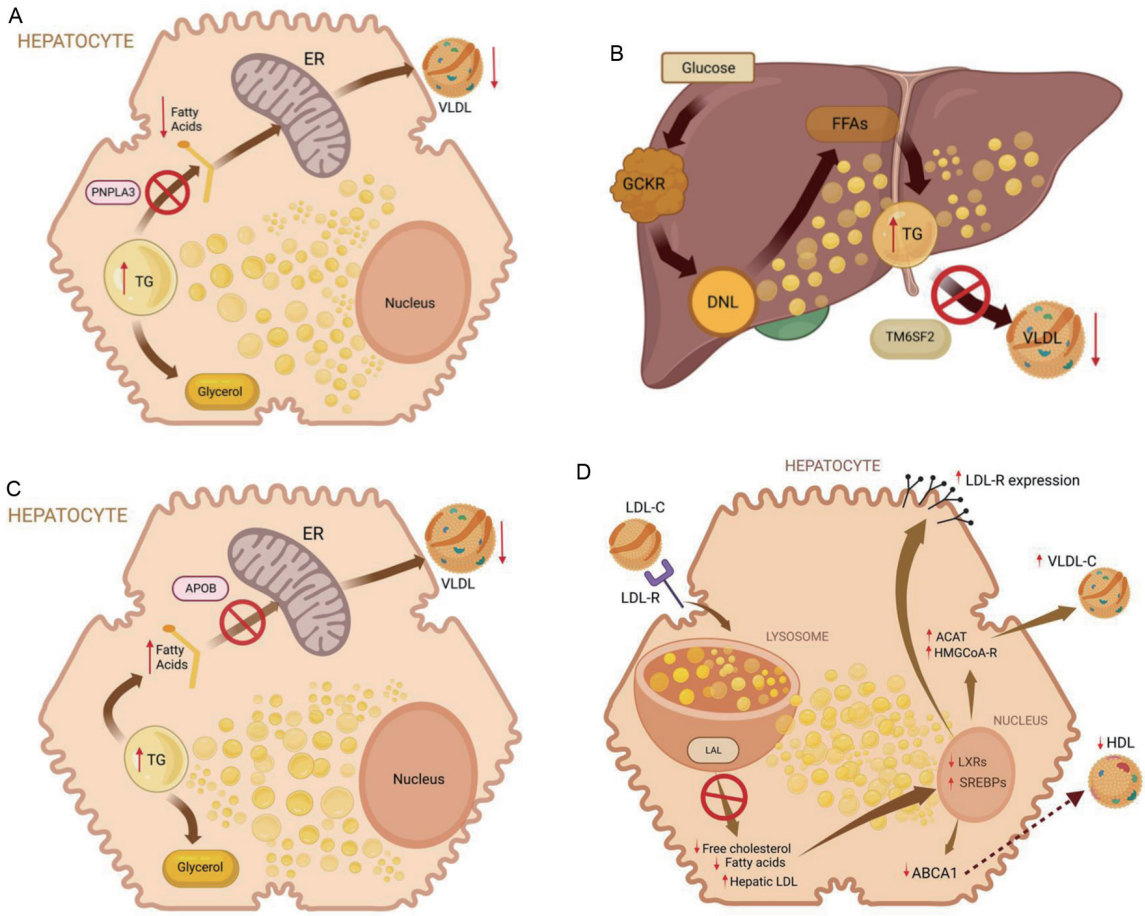

Fig. 1. Pathogenesis of fatty liver according to various etiologies. (A) Due to PNPLA3 defects. Genetic defects in PNPLA3 result in decreased hydrolysis of triglycerides to fatty acids. This leads to increased intrahepatic triglycerides and decreased exportation of VLDL generating hepatic steatosis. (B) Due to TM6SF2 defects. Genetic defects in TM6SF2 decrease the hepatic export of VLDL. This increases intrahepatic triglycerides causing hepatic steatosis. (C) Due to ApoB defects. Genetic defects in ApoB result in decreased packaging of fatty acids in the ER leading to increased intrahepatic triglycerides and decreased hepatic export of VLDL giving rise to hepatic steatosis. (D) Due to LAL defects. Genetic defects in LAL result in decreased lysosomal breakdown of LDL into free cholesterol and fatty acids. This leads to increased intrahepatic LDL, upregulation of LDL receptors, and stimulation of HMGCoA-R with subsequent increased cholesterol production. ABCA1, ATP-binding cassette A1; ACAT, acetyl-coenzyme A acetyltransferase; ApoB, apolipoprotein B; DNL, *de novo* lipogenesis; ER, endoplasmic reticulum; FFAs, free fatty acids; GCKR, glucokinase regulator; HDL, high-density lipoprotein; HMGCoA-R, 3-hydroxy-3-methylglutaryl-CoA reductase; LAL, lysosomal acid lipase; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LXRs, liver X receptors; SREBPs, steroid regulation binding proteins; PNPLA3, palatine-like phospholipase domain-containing-3; TG, triglyceride; TM6SF2, transmembrane 6 superfamily member 2; VLDL, very low-density lipoprotein.

the results. However, as the study was cross-sectional, the patients could not be monitored over time.

Similar results were obtained by *post hoc* analysis of a cross-sectional population study in China.[30] Patients older than 18 years of age were recruited from the Hong Kong government census database between 2008 and 2010, with 1,069 responses.[30] Patients were automatically excluded if they had hepatitis (viral or drug-induced), active malignancy, ≥140 g of alcohol weekly in men or ≥70 g weekly in women, evidence of liver decompensation or contraindication to magnetic resonance imaging (MRI).[30] After exclusion, 904 patients underwent testing for NAFLD.[30] As evidenced by proton-magnetic resonance spectroscopy, NAFLD was diagnosed in patients with intrahepatic fat >5% of liver weight.[30] Of the included population, 259 patients were diagnosed with NAFLD, and 645 were not.[30] All patients underwent genomic analysis of DNA extracted from peripheral leukocytes and analyzed by premade genotyping assays.[30] Patients were subsequently classified as lean (BMI<23 kg/m^2), overweight (BMI 23–24.9 kg/m^2), or obese group (BMI≥25 kg/m^2).[30] Of the 259 patients with NAFLD, 66 were lean (25.5%), 67 were overweight (25.9%), and 126 were obese (48.7%).[30] Patients with fatty livers were an average of 51 years of age, 54.1% were men, 13.5% had type 2 diabetes with an average HbA_{1c} of 5.8%, and 30.5% had hypertension. The average waist circumference was 91 cm in men and 88 cm in women, the average total cholesterol was 5.4 mmol/L, and the triglycerides 1.6 mmol/L.[30] Compared with the group without fatty livers, NAFLD patients had an average ALT of 31 U/L vs. 19 U/L, AST 22 U/L vs. 19 U/L, intrahepatic triglyceride content of 9.8% vs. 1.2%, and liver stiffness measurement of 4.7 kPa vs. 4.1 kPa.[30] The study showed little difference in the prevalence of the PNPLA3 variant among patients without NAFLD, 45.5%, compared with 48.3% in the NAFLD group.[30] However, 30.3% of lean NAFLD patients were found to have a PNLPLA3 mutation compared with 17.9% of overweight and 17.4% of obese NAFLD patients (p=0.003).[30] This study's strengths were a large sample size and three comparison groups. The limitations included an uneven subject distribution because it was a population study, and only

Table 1. Summary of clinical and diagnostic features of genetic causes of lean NAFLD

Gene	Clinical features	VLDL	LDL	HDL	Triglycerides	ApoB	Fat-soluble vitamins	USA source for genetic testing
PNPLA3	Asymptomatic or malaise and RUQ discomfort	No effect	No effect	No effect	No effect	No effect	No effect	ARUP Laboratories, Fulgent Genetics, Speliotes Laboratory
TM6SF2	Asymptomatic or malaise and RUQ discomfort	Low	Low	No effect	Low	No effect	No effect	Fulgent Genetics, Speliotes Laboratory
ApoB FHBL	Failure to thrive, steatorrhea, fat-soluble vitamin deficiencies, hepatic steatosis, hepatomegaly	<Fifth percentile	<Fifth percentile	Normal	<Fifth percentile	<Fifth percentile	Low	Labcorp Invitae, ARUP Laboratories
ApoB ABL	Failure to thrive, steatorrhea, fat-soluble vitamin deficiencies, hepatic steatosis, hepatomegaly	Absent or extremely low	Absent or extremely low	Normal	Absent or extremely low	Absent or extremely low	Low	Labcorp, Invitae, ARUP Laboratories, Fulgent Genetics
LALD	Poor weight gain, diarrhea, steatorrhea, vomiting, hepatomegaly, steatosis	No effect	Elevated	Low	Elevated	No effect	No effect	Mayo Clinic Laboratories, Labcorp

ABL, abetalipoproteinemia; ApoB, apolipoprotein B; FLBL, familial hypobetalipoproteinemia; HDL, high-density lipoprotein; LALD, lysosomal acid lipase deficiency; LDL, low-density lipoprotein; MTTP, microsomal triglyceride transfer protein; PNPLA3, palatine-like phospholipase domain-containing-3; RUQ, right upper quadrant; TM6SF2, transmembrane 6 superfamily member 2; USA, United States of America; VLDL, very low-density lipoprotein.

one ethnic group was studied. The above studies indicate that PNPLA3 mutations can be diagnosed from peripheral venous samples. Unfortunately, treatments specific for patients with this genetic mutation are not available.[31]

Transmembrane 6 superfamily member 2 (TM6SF2)

TM6SF2 is a protein in the endoplasmic reticulum membrane expressed mainly in the liver and intestine.[32] Its primary function is the regulation of very low-density lipoprotein (VLDL) secretion (Fig. 1B).[32] A polymorphism, rs58542926 C>T leads to the substitution of glutamate for lysine to hinder the secretion of hepatic VLDL secretion.[32] This can lead to hepatic steatosis, oxidative stress, fibrosis, and the development of HCC.[33] Data indicate that the prevalence of this condition differs based on ethnicity. The Dallas Heart Study revealed that it is most prevalent in Caucasians (7.2%) followed by Hispanics (4.7%) and, African Americans (3.4%).[33] Patients are typically asymptomatic and hepatic steatosis is diagnosed incidentally on abdominal imaging.[28] Key laboratory findings include low triglycerides and low-density lipoprotein (LDL) due to the decreased hepatic secretion of VLDL (Table 1).[34]

There is evidence that TM6SF2 mutations precede NAFLD in lean individuals and may occur more frequently than in overweight or obese patients. A cross-sectional study investigated TM6SF2 mutations in 528 patients with NAFLD.[35] Patients with biopsy-proven NAFLD were recruited from four hepatology clinics in Australia and Italy.[35] They were excluded if they had viral hepatitis, Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, autoimmune liver disease, decompensated liver disease, drug-induced liver injury, or excessive alcohol intake (>20 g per day in women and >30 g in men).[35] All patients underwent genotyping for TM6SF2 rs58542926 using single nucleotide polymorphism genotyping allelic discrimination.[35] Of 538 patients with biopsy-proven NAFLD, 99 (18%) were lean (BMI<25 kg/m^2).[35] The characteristics of the lean NAFLD group were: average age of 46 years old, 70% men, average BMI 23.2 kg/m^2, ALT 58 IU/mL, 11% had diabetes (average fasting blood glucose 5.3 mmol/L), 25% had hypertension, 43% had dyslipidemia (average HDL 1.5 mmol/L, LDL 3.6 mmol/L, and triglycerides 1.6 mmol/L).[35] Regarding genotyping, lean NAFLD patients expressed the TM6SF2 mutation significantly more frequently than the obese population (26.2% vs. 13.3%, respectively, p=0.005).[35] The severity of liver disease was defined in both groups by liver biopsy findings of fibrosis, ballooning, steatosis, and the NAFLD activity score (NAS).[35] Interestingly, lean patients were found to have a milder fibrosis stage F2-F4 (24% vs. 45%), ballooning (63% vs. 70%), grade 3 steatosis (14% vs. 19%), and NAS (3 vs. 4) than the obese group.[35] This study had a significant number of patients with biopsy-confirmed NAFLD, but its cross-sectional design prevented the ongoing data collection.

Likewise, a retrospective study in Italy found an increased frequency of TM6SF2 mutations in patients with lean NAFLD compared to overweight/obese patients.[36] Patients with biopsy-proven NAFLD were selected from three liver units in Italy.[36] They were excluded if they had viral hepatitis, Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, autoimmune liver disease, drug-induced liver injury, or excessive alcohol intake (>20 g per day in women and 30 g in men).[36] A total of 143 lean (BMI<25 kg/m^2) and 526 overweight/obese patients with NAFLD (BMI>25 kg/m^2) were included.[36] Histologic fibrosis staging of 0–4 was classified by steatosis, lobular inflammation, and hepatocellular ballooning.[36] NASH was defined as the presence of all three components.[36] NAS was also used to further stratify the severity of NAFLD.[36] Additionally, patients underwent extraction of peripheral blood which

was analyzed and genotyped in search of the rs58542926 C>T mutation.[36] The characteristics of lean vs. obese groups were: men (72% vs. 72%), age (46 vs. 49 years), BMI (23 vs. 30 kg/m^2), waist circumference (89 vs. 105 cm), total cholesterol (206 vs. 198 mg/dL), HDL (53 vs. 48 mg/dL), triglycerides (131 vs. 144 mg/dL), AST (41 vs. 41 U/L), and ALT (64 vs. 67 U/L).[36] In terms of chronic conditions in lean vs. obese groups, 20% vs. 37% had hypertension, 11% vs. 26% had diabetes, and 14% vs. 39% had metabolic syndrome.[36] When genotyped, lean patients were significantly more frequently affected by the TM6SF2 mutation than overweight/obese patients (4% vs. 0.3%, respectively, p=0.02).[36] Interestingly, compared with the overweight/obese group, lean patients had less severe grade 3 steatosis (18 vs. 30), lobular inflammation ≥2 (16 vs. 36), ballooning score of 2 (7 vs. 23), and NAS (2.7 vs. 3.9).[36] The strengths of this study included good statistical power with 669 patients with biopsy-proven NAFLD. Weaknesses included a retrospective design. The studies mentioned above demonstrate that it is possible to identify TM6SF2 mutations by analyzing DNA from peripheral leukocytes. Unfortunately, specific treatment for this genetic variation is not currently available.

Apolipoprotein B (ApoB)

ApoB is a critical element of lipoproteins.[37] There are two forms of ApoB. ApoB-48 acts in the small intestine, and ApoB-100 acts in the liver.[37] In the intestine, ApoB-48 allows for the production of chylomicrons and the absorption of dietary fat and fat-soluble vitamins.[37] ApoB-100 is a key component in the liver for packaging lipoproteins and their hepatic exportation (Fig. 1C).[37] Mutations in ApoB lead to fat malabsorption, deficiency of fat-soluble vitamins, and reduced secretion of hepatic lipoproteins.[38] As a result, hepatic triglyceride buildup leads to steatosis and fibrosis.[38] Two conditions associated with mutations in ApoB are classified by the severity of the loss of function, familial hypobetalipoproteinemia and abetalipoproteinemia.[38]

Familial hypobetalipoproteinemia (FHBL): An autosomal codominant disorder, FHBL is characterized by low levels of apolipoprotein B.[38] Approximately 60 different mutations in the ApoB gene have been identified, with a worldwide prevalence of 1 in 3,000 people.[38] There are little data on global/ethnic prevalence. Due to the reduced function of ApoB-48, patients typically present with steatorrhea, fat-soluble vitamin deficiency, and failure to thrive.[39] Additionally, due to the reduction of ApoB-100, they present with hepatic steatosis and hepatomegaly.[39] More severe cases can present with ataxia and atypical retina pigmentation.[39] Characteristic laboratory findings include levels below the fifth percentile of serum ApoB (~150 mg/dL), LDL (~70 mg/dL), and triglycerides (~50 mg/dL; Table 1).[39] As HDL particles do not contain ApoB, HDL levels are usually within the normal range (Table 1).[39] Testing for fat-soluble vitamins (A, D, E, K) can reveal deficiencies (Table 1).[39] The family history, including hypocholesterolemia and hepatic steatosis should be investigated.[39]

There have been several studies on the relationship between FHLB and NAFLD. However, there is limited information regarding lean NAFLD. A case series of five Caucasian patients including three with confirmed FHBL and two with a probable diagnosis based on clinical presentation, laboratory data, and family history, were analyzed to study the association with lean NAFLD.[40] The first patient was a 39-year-old man with a BMI of 24.98 kg/m^2 and confirmed genetic testing. He presented with NASH, mild hepatic fibrosis, and a family history of cirrhosis in his mother and two uncles. His total cholesterol was 101 mg/dL, LDL 34 mg/dL, HDL 59 mg/dL, triglycerides 38 mg/dL, and ApoB 28 mg/dL. The second was a 16-year-old male patient with a BMI of 18.67 kg/m^2 and confirmed genetic testing. He presented with hepatic steatosis and fat malabsorption. The family history was not helpful. His total cholesterol was 87 mg/dL, LDL 8 mg/dL, HDL 82 mg/dL, triglycerides 35 mg/dL, and ApoB 16 mg/dL. The third patient was a 50-year-old woman with a BMI of 21.72 kg/m^2 who deferred genetic testing. She presented with NASH and had a family history of cirrhosis in her father. Her total cholesterol was 134 mg/dL, LDL 43 mg/dL, HDL 82 mg/dL, triglycerides 46 mg/dL, and ApoB 36 mg/dL. The fourth patient was a 12-year-old boy with a BMI of 37.08 kg/m^2 and confirmed genetic testing who presented with NASH. He had a family history of low cholesterol in both parents. His total cholesterol was 74 mg/dL, LDL 33 mg/dL, HDL 31 mg/dL, triglycerides 44 mg/dL, and ApoB 28 mg/dL. The last patient was a 30-year-old woman with a BMI of 26.5 kg/m^2 who deferred genetic testing. She presented with NASH and had a family history of low cholesterol in both parents. Her total cholesterol was 103 mg/dL, LDL<30 mg/dL, HDL 66 mg/dL, triglycerides 37 mg/dL, and ApoB<35 mg/dL. Three patients had a BMI of <25 kg/m^2 indicating that this mutation can cause lean NAFLD.[40] Strengths of this study included the grouping of patients with a rare condition. Weaknesses included the impossibility of establishing a cause-effect relationship and limited generalizability to other populations.

Similarly, genomic analysis of lean individuals with NAFLD recruited patients 18 years of age and older with biopsy-proven NAFLD.[41] Exclusion criteria were significant alcohol consumption within the past 2 years (≥14 drinks/week for men or ≥7 drinks/week for women), active substance use, or other cause of liver disease.[41] A total of six patients were identified as lean NAFLD (BMI≤25 kg/m^2 for non-Asians and ≤23 kg/m^2 for Asians) and underwent whole exome sequencing of germline DNA from a peripheral venous sample.[41] A monogenic mutation of ApoB was identified in one female patient with a BMI of 24.96 kg/m^2.[41] She had biopsy-proven stage 3 fibrosis and an MRI-proton density fat fraction (MRI-PDFF) of 14%.[41] Genomic sequencing revealed a heterozygous frameshift variant and low serum levels of LDL (47 mg/dL), total cholesterol (102 mg/dL), triglycerides (66 mg/dL), and ApoB (39 mg/dL), compared with the respective normal values (<100 mg/dL, <200 mg/dL, <150 mg/dL and >50 mg/dL).[41] Compared to lean NAFLD patients without a genetic mutation, AST, Hb_{A1c}, and insulin were higher (62 vs. 38 U/L, 6.45% vs. 5.8%, 14.5 vs. 13, respectively).[41] Liver histology revealed a higher NAS (6 vs. 4.5) but lower MRI-PDFF (14% vs. 19%) in the affected patient compared to the control.[41] Despite the small sample size, the liver biopsy, MRI, and phenotyping provided detailed and valuable information that were strengths of the study.

Diagnosis of FHBL is made by molecular genetic testing to identify known variants by sequence analysis, including single or multigene testing.[39] Affected patients should have liver function tests every 1–2 years and hepatic ultrasound every 3–5 years.[39] Family members of affected patients are advised to undergo genetic testing for early identification and initiation of preventive measures.[39] Management consists of a low-fat diet (<30% of total calories) and supplementation of high-dose fat-soluble vitamins.[39]

Abetalipoproteinemia (ABL): ABL is an autosomal recessive disorder defined by the absence of ApoB and LDL.[38] The gene product, microsomal triglyceride transfer protein (MTTP), normally initiates the transfer of triglycerides to the ApoB particle to produce VLDL.[38] The loss of function of MTTP prevents ApoB from combining with triglycerides to

form VLDL.[38] This leads to an increase in hepatic triglycerides leading to hepatic steatosis. Over 30 mutations have been identified.[38] The prevalence of this condition has been estimated to be <1 in 1,000,000, with less than 100 cases described in the literature.[42] There are little data on global/ethnic prevalence.

The typical clinical presentation is almost the same as for FHBL. Due to the complete loss of function of ApoB, young patients present with failure to thrive, steatorrhea, fat-soluble vitamin deficiency, hepatic steatosis, and hepatomegaly.[42] Severe features include night or color vision loss, atypical retinal pigmentation, ataxia, and myopathy.[42] In contrast to FHBL, characteristic laboratory findings include absent or extremely low serum ApoB, total cholesterol, LDL, and triglycerides (Table 1).[39] As HDL particles do not contain ApoB, HDL levels are usually within the normal range (Table 1).[39] Patients also have a deficiency of fat-soluble vitamins (A, D, E, K; Table 1).[42] Family history is important as the mode of inheritance is autosomal recessive.[42]

Evidence exists linking abetalipoproteinemia and lean NAFLD. A descriptive study of the genetic, biological, clinical, and histological characteristics of patients with ABL and FHBL was performed.[43] A literature search identified 67 patients with ABL and 41 with FHBL between the ages of 4 months and 42 years old.[43] Patients were included if they had confirmatory genetic testing and were excluded if there was a lack of available retrospective data.[43] Biopsies were described based on steatosis, activity, and fibrosis.[43] Out of the patients with ABL, the mean BMI was 19.7 kg/m^2, and a subgroup of 14 patients followed over time revealed that nine patients maintained a BMI<20 kg/m^2 during adulthood.[43] Typical clinical presentations included 94% of the patients having diarrhea in infancy, 76% having steatorrhea, and 92% failing to thrive.[43] Hepatomegaly was present in nine patients and aminotransferase elevations were present in more than half the cases.[43] All patients had ultrasound evidence of hepatic steatosis with a median kPa of 6.6.[43] Biopsy data were only available for six patients, but all six had steatosis, four fibrosis, and one cirrhosis.[43] Compared to the FHBL group, the ABL cases showed a lower occurrence of liver fibrosis.[43] All ABL cases exhibited severe hypolipidemia and extremely low levels of vitamin E.[43] The average total cholesterol was 0.87 mmol/L, triglycerides 0.09 mmol/L, LDL<0.04 mmol/L, ApoB<0.02 mmol/L.[43] Patients with ABL had significantly lower cholesterol and ApoB than those with FHBL.[43] Although the study had good statistical power, it was weakened by its retrospective design. Diagnosis of ABL is made by molecular genetic testing identifying known variants including single or multigene testing.[39] These patients should have yearly liver function tests and hepatic ultrasound every 3 years.[39,42] Family members of affected patients are advised to undergo genetic testing for early identification and initiation of preventive measures.[39] Management comprises a low-fat diet (10–20% of total calories), essential fatty acids, and fat-soluble vitamin supplementation.[39,42]

Lysosomal acid lipase deficiency (LALD)

The lysosomal acid lipase gene (*LIPA*) normally activates lipase A leading to lysosomal breakdown of triglycerides and cholesterol esters (Fig. 1D).[44] A deficiency of this gene product causes an autosomal recessive condition termed LALD.[44] Hepatic steatosis and dyslipidemia are caused by a buildup of intracellular triglycerides and cholesterol esters, upregulation of LDL receptors increasing intracellular cholesterol intake, and stimulation of the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase with increased cholesterol production.[44] The reported prevalence varies between 1 in 40,000 and 1 in 300,000.[44] Approximately 50 loss-of-function mutations in the *LIPA* gene have been identified and can have varied effects on the residual enzyme function.[44] The most common mutation (50–70%) is an exon eight splice site mutation (E8SJM).[44] Studies have shown that the remaining enzyme activity is inversely proportional to the degree of fibrosis.[44] The characteristic serum lipid profile is elevated LDL, total cholesterol, triglycerides, and low HDL (Table 1).[44,45] The classic clinical presentation is an infant with poor weight gain, diarrhea, steatorrhea, vomiting, hepatomegaly, and steatosis with progression to malnutrition, anemia, ascites, and coma.[44] The median age of diagnosis is 5 years.[44] There is a high mortality rate, with survival generally limited to a year or less.[44]

Diagnosis can be made by several modalities.[44] The dried blood spot test measures the activity of lysosomal acid lipase in serum leukocytes. A genetic analysis of various coding regions of LIPA can also be used.[44] Characteristically, liver biopsy reveals cholesteryl ester crystals and lipid vacuoles with surrounding lysosomal markers.[44] Treatment varies based on severity and clinical presentation but includes lipid-lowering agents, enzyme replacement therapy, and stem cell or liver transplants.[44] Clinically, there are two different phenotypes of LALD, Wolman disease (WD) and cholesteryl ester storage disease (CESD).[44]

WD: This condition has an incidence of approximately 1 in 500 and there are 19 recognized mutations. The most common mutation (30%) is a result of insertions or small deletions.[45] This disorder is characterized by an almost complete lack of LIPA activity.[45] Cases are typically diagnosed around three months of age, and most patients are deceased by six months of age due to the detrimental effects initiated *in utero*.[45] A clinical triad of intestinal malabsorption, liver failure, and adrenal insufficiency has been described.[45] For the diagnosis, LAL assay reveals a lack of *LIPA* enzyme activity.[45]

CESD: CESD has a reported incidence of approximately 1 in 40,000.[44,45] Thirty-two mutations have been identified, of which 50% are caused by missense mutations. Most result in a 1–12% residual activity of LIPA.[45] Usually, it is diagnosed in childhood or adulthood, and the life span varies.[45] A study of 32 children with CESD showed that 84% had hepatomegaly and 88% had splenomegaly.[46] For the diagnosis, LAL assay reveals a low level of *LIPA* enzyme activity. Additionally, liver biopsy findings include an orange color on gross examination and a uniform, diffuse microvesicular steatosis on light microscopy.[47] Genetic testing is generally reliable in these patients even in cases of minor residual activity of the lysosomal lipase.[44] Evidence shows that a human recombinant lysosomal acid lipase called sebelipase alfa can reduce hepatic steatosis. A randomized phase 3 controlled trial of 66 adults and children evaluated the effect of sebelipase alfa 1 mg/kg every other week for 36 weeks with positive outcomes, including a reduction in AST and hepatic fat content (p<0.001).[48]

Diagnostic workup of lean NAFLD

NAFLD is diagnosed by the American Association for the Study of Liver Diseases (AASLD) diagnostic guidelines. However, there is ambiguity in the guidelines for diagnosing lean NAFLD. Potential tools used for the diagnosis of hepatic steatosis include the Hepatic Steatosis Index, the NAFLD Liver Fat Score, and the Lipid Accumulation Product.[49,50] Various imaging techniques are available to detect hepatic steatosis or fibrosis, such as hepatic ultrasound, transient elastography, and liver MRI.[28] After the diagnosis of hepatic steatosis is established, liver fibrosis needs

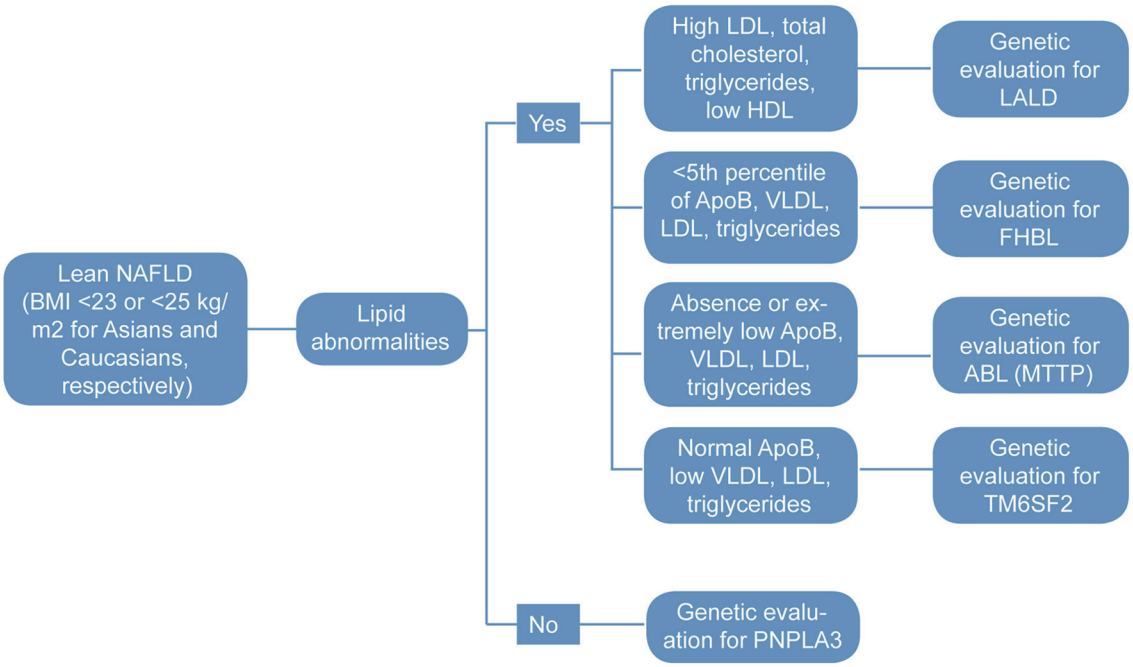

Fig. 2. Algorithm for the diagnosis of genetic causes of lean NAFLD. ABL, abetalipoproteinemia; ApoB, apolipoprotein B; BMI, body mass index; FLBL, familial hypobetalipoproteinemia; HDL, high-density lipoprotein; LALD, lysosomal acid lipase disease; LDL, low-density lipoprotein; MTTP, microsomal triglyceride transfer protein; NAFLD, nonalcoholic fatty liver disease; PNPLA3, palatine-like phospholipase domain-containing-3; TM6SF2, transmembrane 6 superfamily member 2; VLDL, very low-density lipoprotein.

to be assessed.[28] Liver biopsy is the most reliable method for evaluating fibrosis, but it has some drawbacks.[28] Hence, noninvasive methods, such as fibrosis scores, have been developed and are well-validated.[51] The Fibrosis-4 Index, liver stiffness measurement, and the NAFLD fibrosis score are some of the most common noninvasive tests used for NAFLD.[50] Several studies have contrasted these tests in lean and overweight or obese NAFLD patients with comparable values and cut-offs.[51]

A general approach in a lean patient with NAFLD diagnosed on imaging should exclude any secondary causes of hepatic steatosis, including alcohol intake, chronic liver disease, hepatitis, medications, etc. Laboratory data including serum aminotransferases, alkaline phosphatase, and gamma-glutamyl transpeptidase can be helpful in identifying patients with NAFLD. Additionally, LDL, VLDL, HDL, triglycerides, and vitamin A, D, E, and K levels can provide important supporting information on the possible etiology of genetically induced NAFLD (Table 1, Fig. 2). In patients with TM6SF2 defects, key laboratory findings include low LDL and triglycerides due to the decreased hepatic secretion of VLDL.[34] On the other hand, patients with LALD will typically have elevated LDL and triglycerides with a low HDL.[44,45] Both FHBL and ABL will have low levels of ApoB, LDL, triglycerides, and vitamins A, D, E, and K.[40] However, these lab values will be extremely low or absent in patients with ABL[40] (Table 1, Fig. 2).

Treatment of lean NAFLD

Regardless of BMI, the AASLD recommends lifestyle modifications consisting of a low-calorie diet and exercise for the treatment of NAFLD.[52] The main dietary contributors to NAFLD include fructose and sucrose as these increase the production of *de novo* lipogenesis leading to the buildup of hepatic fatty acids.[52] In terms of exercise, sedentary behaviors lead to reduced muscle mass, inflammation, and IR, which contribute to NAFLD.[52] Exercise improves IR in peripheral tissues, and reduces glucose transport from the muscles to the liver thus decreasing hepatic *de novo* lipogenesis.[51] Both aerobic and resistance exercises are comparably effective with recommendations of 40–45 minutes three times a week for 12 weeks.[52]

A single-blind randomized controlled trial investigated the effectiveness of weight loss in lean patients.[53] Patients were recruited from a community screening project using MRI-PDFF and elastography.[53] Patients with a BMI<25 kg/m^2, intrahepatic triglyceride content >5%, 18 years of age and older, and elevated ALT (≥30 U/L in men and ≥19 U/L in women) were included.[53] Patients were excluded if they had hepatitis B or C, HCC, decompensated liver disease, or excessive alcohol intake (>20 g/day in men and >10 g/day in women).[53] A total of 154 patients were included and randomized to a 12-month lifestyle intervention program.[53] The program consisted of an individualized diet plan recommended by a dietitian and an exercise regimen of both aerobic and resistance training for 30 minutes daily for 3 to 5 days a week.[53] Of enrolled patients, 67% achieved NAFLD remission (intrahepatic triglyceride content <5%) with 3–10% body weight loss.[53]

Regarding pharmacotherapy, there is no Federal Drug Administration-approved therapy for either lean or obese NAFLD.[54] Clinical trials are ongoing, and some of the most studied classes are peroxisomal proliferator-activated receptors that participate in the regulation of lipid and glucose metabolism, glucagon-like-peptide-1 receptor agonists that regulate glucose metabolism and have antifibrotic properties, sodium-glucose cotransporter 2 inhibitors that inhibit proximal tubule glucose reabsorption, and vitamin E, which has lipophilic antioxidant properties.[54]

Conclusions

The prevalence of lean NAFLD appears to be rising at the same pace as obese NAFLD. The progression and outcomes of lean NAFLD can be as severe or worse than obese NAFLD. Additionally, the lack of obesity and possible lack of metabolic syndrome markers makes lean NAFLD more likely to be unnoticed or be diagnosed late. The development of genome-wide association studies has enabled the identification of several genes linked to lean NAFLD. It is important to be aware of these genetic causes of lean NAFLD as some are treatable. Future research directions will likely include improvements in diagnostics. More sensitive and specific serological testing should be achievable in the short term. More specific and inexpensive genetic testing obviating the need for genomic sequencing for confirmation would also be helpful. Identifying the genetic causes of lean NAFLD could make possible individualized therapies in which genetic defects are specifically targeted. Finally, more research is required to develop agents that can antagonize the effects of pathogenic mutations with minimal side effects in the treatment of lean NAFLD in the future.

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Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. JT has no conflicts of interest related to this publication.

Author contributions

Proposed concept for review, collected relevant information, drafted the article, and revised the manuscript with critical revisions (JT), edited the article, critical revision of the article, and final approval of the version to be published (GYW).

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