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Review Article

Current and Emerging Issues in Familial Hypobetalipoproteinemia-related Steatotic Liver Diseases

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Abstract

Familial hypobetalipoproteinemia (FHBL), caused by apolipoprotein B (*APOB*) variants, disrupts APOB-containing lipoprotein synthesis, leading to reduced serum total cholesterol, low-density lipoprotein cholesterol, and APOB. Heterozygous carriers are often asymptomatic, while homozygotes exhibit severe manifestations like malabsorption, vitamin deficiencies, and hepatic steatosis. In recent years, FHBL has attracted increasing attention due to its association with liver disease and its role as a unique monogenic model of steatotic liver disease independent of cardiometabolic risk factors. Mechanistically, lipid overload, endoplasmic reticulum stress, oxidative damage, and impaired autophagy may drive hepatocellular injury and fibrosis. Challenges include insufficient diagnosis, sparse epidemiological data, and unclear disease progression. Enhanced genetic testing, mechanistic research, and longitudinal studies are critical to improving diagnosis, risk assessment, and therapies for FHBL-associated liver disease.

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Introduction

Familial hypobetalipoproteinemia (FHBL) type 1 (OMIM 615558) is a rare, autosomal codominant monogenic disorder caused by variants in the apolipoprotein B (*APOB*) gene on chromosome locus 2p24.1.[1–3] According to the latest disease classification, it is categorized as lipoprotein assembly and secretion defect type 2, namely FHBL-SD2, commonly known as FHBL (hereinafter referred to as FHBL for FHBL-SD2).[4] Affected individuals exhibit lifelong low plasma levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), or APOB, typically below the 5th percentile for age and gender.[3,5] In the 1980s, Young *et al*. first established the molecular genetic link between FHBL and *APOB*.[6] Epidemiological data from Framingham, USA, showed that heterozygous FHBL (He-FHBL) cases occur in about 1:1,000–1:3,000 individuals, while homozygous or compound heterozygous FHBL (Ho-FHBL) cases are extremely rare, with a prevalence of less than one in a million.[7] Large-scale sequencing studies indicated that APOB protein-truncating variants causing FHBL occur in about 0.1% of the general population.[8] Currently, global epidemiological data are mainly limited to case reports, family studies, or haplotype analyses.

Although FHBL patients are considered protected from atherosclerotic cardiovascular disease due to lifelong low LDL-C,[9] there is increasing recognition that FHBL is frequently associated with hepatic steatosis, and in a subset of cases, progression to steatohepatitis, liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC).[10–13] These hepatic changes can occur in the absence of common cardiometabolic risk factors, distinguishing FHBL from metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease) and steatohepatitis (formerly non-alcoholic steatohepatitis), and positioning FHBL as a unique monogenic model for studying the natural history and molecular mechanisms underlying steatotic liver disease.[14] Recent advances in molecular genetics have refined our understanding of APOB-related pathophysiology, yet critical questions remain unanswered, particularly regarding why some FHBL patients develop progressive liver disease while others remain stable, and what the specific mechanisms and molecular pathways are for the occurrence and development of liver disease.

This review aims to refocus attention on the hepatic aspects of FHBL by (i) summarizing current knowledge of molecular genetics, (ii) analyzing the spectrum and progression of liver disease in affected individuals, (iii) exploring mechanistic hypotheses that may explain liver disease, and (iv) outlining the clinical treatment plan. We aim to establish FHBL not only as a disorder of lipid metabolism but also as a valuable window into the pathogenesis of steatotic liver disease.

Molecular pathogenesis of APOB

The *APOB* gene encodes two tissue-specific isoforms: APOB-100 in the liver and APOB-48 in the intestine, essential for the assembly and secretion of very-low-density lipoprotein (VLDL) and chylomicrons, respectively.[15] Therefore, APOB is a "molecular truck" for lipid transport in the whole body, and

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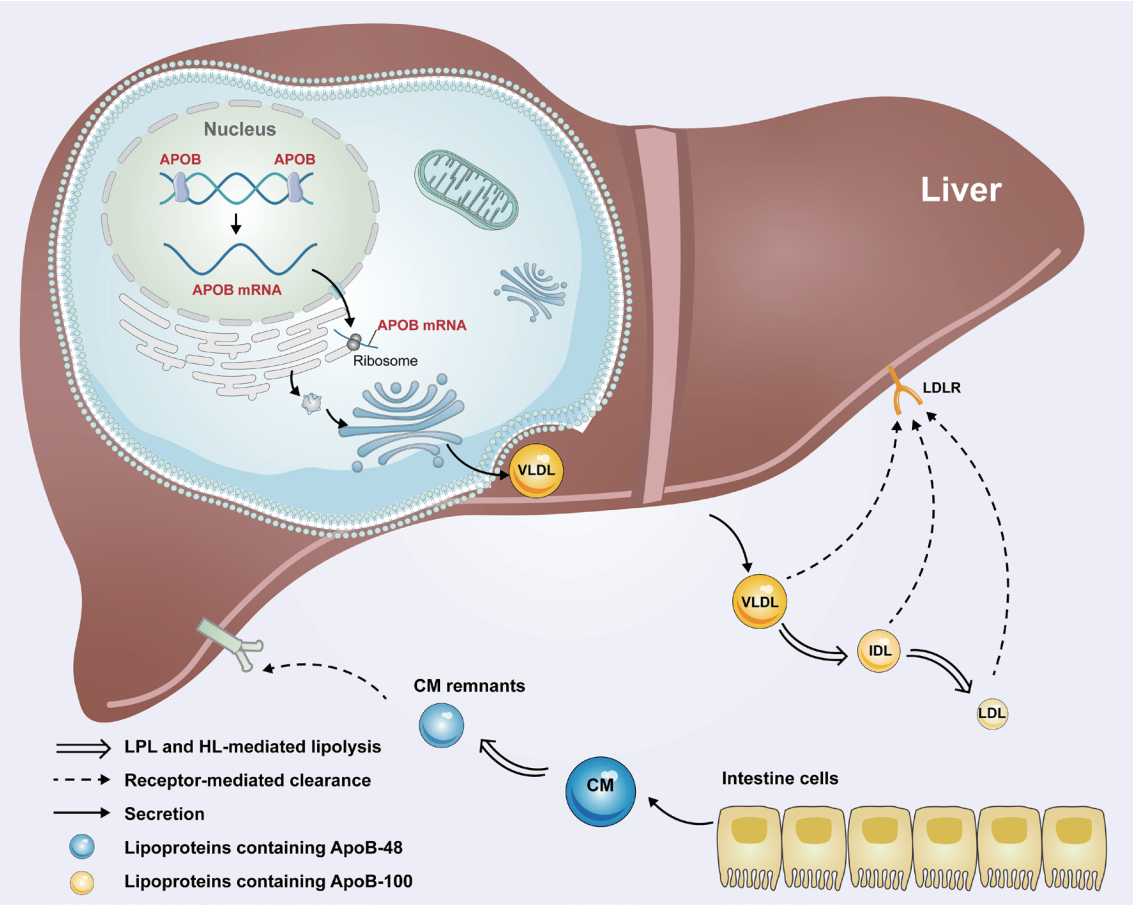

Fig. 1. Normal metabolic pathway of APOB in the body. Under physiological conditions, newly synthesized APOB-100 in hepatocytes is processed in the endoplasmic reticulum and Golgi. Lipids such as triglycerides, cholesterol esters, and phospholipids are added to form VLDL. This process is regulated by lipid availability and microsomal triglyceride transfer protein activity, which is an endoplasmic reticulum–resident chaperone essential for APOB lipidation. In the blood, VLDL is converted to IDL and LDL by interacting with tissue lipoprotein lipase and gradually releasing triglycerides. These particles are ultimately cleared by the LDL receptor on the surface of hepatocytes. In the intestine, APOB -48 packages dietary lipids into chylomicrons. After lymphatic secretion, chylomicrons enter the blood, where LPL converts them to remnant particles. These remnants (containing APOB-48) are cleared by the hepatic LDL receptor and LDL receptor-related protein. APOB, apolipoprotein B; CMs, chylomicrons; CM remnant, chylomicron remnant; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; HL, hepatic lipase.

its function is directly related to the balance of liver–intestinal lipid metabolism (Fig. 1).

To date, more than 140 genetic variants in *APOB* have been identified in FHBL,[7] including missense variants,[16–18] shifted code variants,[19–21] nonsense variants,[11,19,20,22] and splice-site variants.[20,23] Variants can impair every step of the APOB lifecycle, including its synthesis, protein folding, lipidation, VLDL assembly, secretion, and clearance (Fig. 2). Most pathogenic variants result in truncated APOB proteins, and the extent of truncation is a key determinant of functional output: longer truncations (e.g., APOB-80 or APOB-75) may still support partial VLDL secretion, while shorter forms (e.g., APOB-60) behave more like APOB-48.[24] A quantitative relationship has been observed—each 1% truncation correlates with an approximate 1.4% reduction in secretion efficiency.[25] In both humans and mice, truncated APOB proteins have been associated with lower productivity and accelerated clearance rates.[26–28] In addition to truncations, several missense variants in the βα1 domain have been shown to specifically impair APOB-48 secretion[29–31] and enhance post-endoplasmic reticulum (ER) degradation,[31] and variants near the receptor-binding domain can increase low-density lipoprotein catabolism.[18] Beyond classic truncations, *APOB* defects may arise from splice-site variants and mobile element insertions. Minigene assays confirmed that cryptic splicing can generate premature truncations, reclassifying uncertain variants as pathogenic.[32] Recently, an AluYa5 insertion in exon 3 was reported, causing exon skipping and a premature stop codon, undetectable by routine pipelines.[33] These findings stress the need for functional splicing assays and MEI calling in FHBL diagnosis.

Although structural studies have advanced understanding of APOB–low-density lipoprotein receptor interactions,[34] the full structure–function relationships remain incompletely defined. Structure determines function, and these molecular defects form the basis of APOB dysfunction in lipid binding and related processes, setting the stage for subsequent disease progression.

Pathophysiology of the liver in FHBL

Due to the aberrant mutant APOB proteins, hepatic export of triglycerides via VLDL is impaired, resulting in intrahepatic triglyceride accumulation. Possible pathological factors such

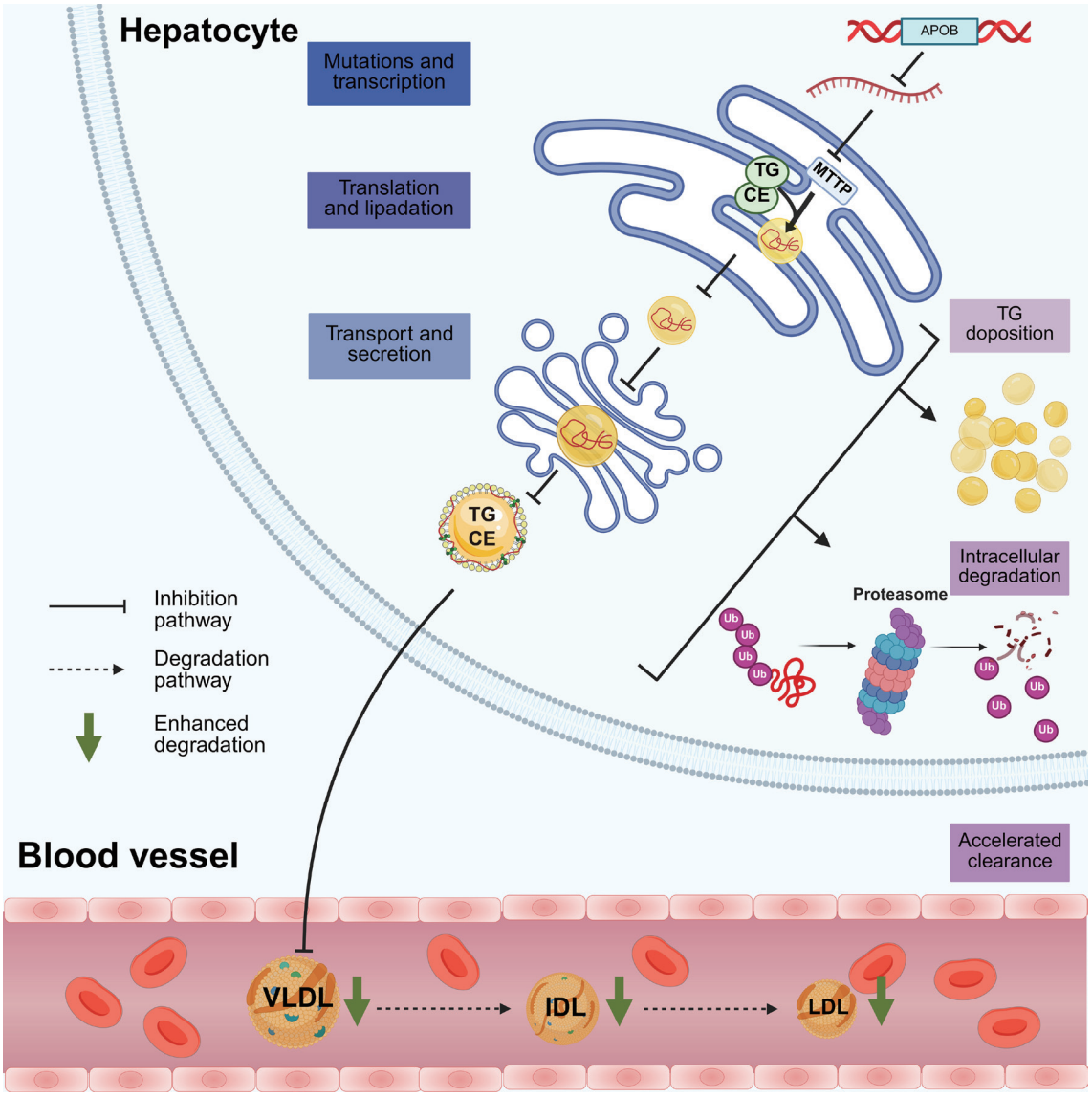

Fig. 2. Mutated APOB-mediated impaired VLDL assembly-secretion-degradation pathway. *APOB* mutations reduce its synthesis, enhance intracellular degradation, and impair its ability to bind triglycerides and cholesteryl esters, leading to decreased VLDL assembly and secretion. Concurrently, the secreted VLDL particles exhibit structural defects, resulting in enhanced vascular clearance and reduced plasma levels. Meanwhile, failed VLDL export increases intracellular triglyceride deposition. APOB, apolipoprotein B; TG, triglyceride; CE, cholesterol esters; MTTP, microsomal triglyceride transfer protein; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein.

as lipid metabolism disorders, ER stress, and autophagy dysfunction are involved in the development of liver diseases (Fig. 3). It is worth noting that hepatic steatosis in FHBL patients often occurs in the absence of systemic insulin resistance[35–38] and does not appear to substantially elevate diabetes risk,[39] indicating that lipid deposition and liver injury in FHBL may primarily result from lipoprotein metabolism abnormalities rather than insulin resistance. While current research has partially revealed the hepatic pathological consequences of FHBL, the exact mechanisms driving steatohepatitis and fibrosis remain elusive.

Abnormal lipid metabolism

To investigate hepatic lipid metabolism dysregulation, Lin *et al*.[40–42] studied APOB-38.9 mutant mice in detail. Compared to wild-type controls, liver triglyceride content increased twofold in heterozygous and fourfold in homozygous mice, consistent with a fatty liver phenotype.[40] The hepatic mRNA expression of sterol regulatory element-binding protein-1c, fatty acid synthase, and stearoyl-CoA desaturase-1 decreased in a gene-dose-dependent manner; in contrast, the key molecules involved in fatty acid β-oxidation, i.e., peroxisome proliferator-activated receptor α and carnitine acyltransferase 1, remained unchanged.[40] This dissociation between suppressed lipogenesis and preserved β-oxidation suggests a compensatory adaptation to hepatic lipid overload, though this adaptation is insufficient to prevent steatosis. Further analysis revealed adaptive metabolic reprogramming in a gene-dose-dependent manner, including downregulation of cholesterol biosynthesis (3-hydroxy-3-methylglutaryl-coenzyme A reductase, ster-

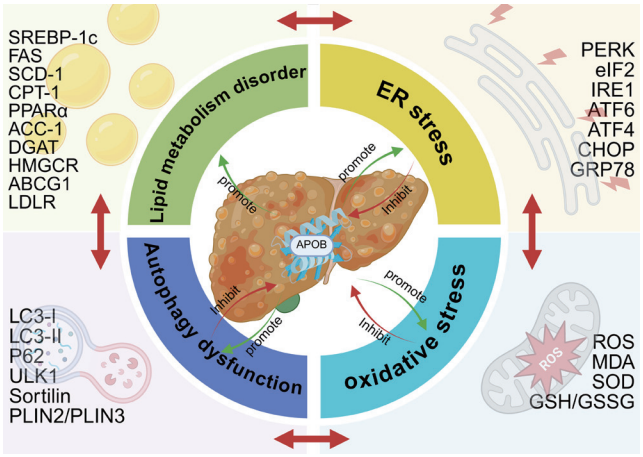

Fig. 3. Pathogenic mechanisms of liver disease in FHBL. The pathological pathways involved in the development of liver disease in FHBL include lipid metabolism disorders, endoplasmic reticulum stress, oxidative stress, and autophagy dysfunction, which are interrelated. The key molecular participants are highlighted in the figure. FHBL, familial hypobetalipoproteinemia assembly and secretion defect type 2; SREBP-1c, sterol regulatory element-binding protein 1c; FAS, fatty acid synthase; SCD-1, stearoyl-CoA desaturase-1; CPT-1, carnitine palmitoyltransferase-1; PPARα, peroxisome proliferator-activated receptor alpha; ACC-1, acetyl-CoA carboxylase-1; DGAT, diacylglycerol O-acyltransferase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ABCG1, ATP-binding cassette transporter G1; LDLR, low-density lipoprotein receptor; LC3-I/II, microtubule-associated protein 1A/1B-light chain 3; ULK1, unc-51-like autophagy activating kinase 1; PLIN2/3, perilipin 2/3; ER, endoplasmic reticulum; PERK, PKR-like ER kinase; eIF2, eukaryotic initiation factor 2; IRE1, inositol-requiring enzyme 1; ATF6, activating transcription factor 6; ATF4, activating transcription factor 4; CHOP, C/EBP-homologous protein; GRP78, glucose-regulated protein 78; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; GSH/GSSG, glutathione/glutathione disulfide.

ol-C5-desaturase, and 7-dehydrocholesterol reductase) and low-density lipoprotein receptor-mediated uptake pathways, coupled with enhanced cholesterol efflux (ATP-binding cassette subfamily G member 5/8).[42] Under the stimulation of high-fat and low-fat diets, liver triglyceride deposition in heterozygous mice significantly increased. Interestingly, dietary composition exerted differential effects: the low-fat diet upregulated the expression of fatty acid synthase and stearoyl-CoA desaturase-1 in both wild-type and heterozygous mice, whereas the high-fat diet inhibited the expression of both in the wild type (not significantly in the heterozygous mice).[41] This implies that dietary fat content modulates hepatic steatosis through distinct pathways, highlighting the complex interaction between genetics and nutrition in FHBL. Furthermore, a pediatric FHBL case (APOB-26.87 variant) presented with cholesterol gallstones, suggesting cholesterol metabolism disorders in the liver.[43] Compared to APOB-38.9 mutant mice, APOB-27.6 mice exhibited greater hepatic triglyceride accumulation and reduced secretion rates.[44] This phenotype arose from two key factors: impaired triglyceride transport/secretion capacity and accelerated plasma clearance of APOB-27.6–containing lipoproteins. The peptide segment differentiating APOB-27.6 from APOB-38.9 appears functionally critical. As this clearance mechanism is APOE-independent, other factors likely mediate lipoprotein particle clearance. Moreover, Hendriks *et al*.[45] developed an FHBL liver organoid model, identifying glucose-driven de novo lipogenesis as the main cause of spontaneous steatosis and fatty acid desaturase 2 as a key regulator. Although the model was based on CRISPR-mediated APOB knockout, which differs from clinical *APOB* variants, it nonetheless highlights the role of dysregulated de novo lipogenesis in disease pathogenesis. This human model system provides a platform for studying cell-autonomous mechanisms and screening drugs that specifically target lipid synthesis in FHBL. The convergence of mouse and organoid models on enhanced lipogenesis as a key driver suggests that targeting this pathway may be beneficial.

Endoplasmic reticulum stress and oxidative stress

Due to the defect in the production of APOB leading to lipid overload in the liver, it can be hypothesized that the lipotoxicity involved may directly trigger ER stress and oxidative stress.[42,46] Clinical evidence supports this hypothesis: liver biopsies from FHBL patients reveal ER and mitochondrial abnormalities.[21] *In vitro* cell models further support this mechanistic link: in MCA cells, overexpression of wild-type APOB-50 and the APOB-50$^{N158–1496}$ truncation mutant induced glucose-regulated protein 78 expression and eukaryotic initiation factor 2 phosphorylation, and further knockdown of APOB-50 significantly attenuated ER stress.[47] This implies that truncated APOB variants may impose a proteotoxic burden on the ER. Meanwhile, ER stress also regulates APOB in turn. In another study, glucosamine-induced ER stress in HepG2 cells suppressed APOB-100 synthesis and enhanced degradation via the ubiquitin–proteasome system,[48] largely mediated by activation of the protein kinase R-like ER kinase (PERK) pathway.[49] Co-transfection experiments of APOB proteins (APOB-15, APOB-50, APOB-100) and PERK modulators further confirmed that PERK activity inhibited both truncated and full-length forms of APOB synthesis, reinforcing the crosstalk between ER stress sensors and APOB regulation. Interestingly, ER stress exhibits a biphasic effect on APOB-100 secretion: moderate fatty acid exposure enhances secretion, while high levels inhibit it.[50] A recent study has shown that under ER stress conditions, the inhibition of protein disulfide isomerase affects the oxidative folding of microsomal triglyceride transfer protein (a protein crucial for APOB lipidation), thereby influencing the unsaturated fatty acid transport process mediated by APOB-100.[51] This further demonstrates the damaging effect of ER stress on the APOB-VLDL pathway.

In addition, oxidative stress can further impair the expression and function of APOB. Pan *et al*. showed that lipid peroxidation promotes APOB-100 degradation via the post-ER presecretory proteolysis pathway and impairs VLDL secretion, while antioxidants such as vitamin E attenuate this effect.[52] Andreo *et al*. identified superoxide anions as key drivers, acting through lipid peroxidation, with superoxide dismutase 1 overexpression or mimetics providing protection.[53] Importantly, APOB-100 degradation depends on lipid peroxide accumulation rather than superoxide levels alone. Consistently, APOB-38.9 mice showed gene dose–dependent lipid peroxidation and upregulation of Cyp4A10.[42] Thus, oxidative stress, particularly lipid peroxidation, is a central regulator of hepatic APOB-100 stability and VLDL secretion. Therefore, antioxidants may help restore lipid and lipoprotein homeostasis within the ER.[54] Worse still, a mutually reinforcing cycle exists between ER stress and oxidative stress,[55,56] inducing a series of apoptotic and inflammatory responses.[57] This ultimately culminates in cellular homeostasis collapse. Multiple lines of evidence have shown that ER stress and oxidative stress contribute not only to lipid dysregulation but also intersect with key inflammatory and fibrogenic pathways that drive progression from hepatic steatosis to steatohepatitis and fibrosis.[46,58,59] Taken together, we reasonably speculate that in FHBL, lipid overload, ER stress, and oxidative stress may interact bidirectionally, though further *in vivo* validation is needed.

Autophagy dysfunction

Autophagy, particularly lipophagy (selective degradation of lipid droplets), is a key pathway for intracellular lipid turnover and cellular homeostasis. In the early stage of hepatic steatosis, lipid droplet–associated protein perilipin-2 undergoes phosphorylation, which recruits microtubule-associated protein light chain 3-II to autophagosomes, leading to the formation of lipophagosomes that subsequently fuse with lysosomes to degrade lipid droplets.[60] During the appropriate stress process, the activation of the three branches of the unfolded protein response in the ER can promote autophagy through various pathways.[61] However, in an excessive ER stress environment, impaired autophagosome–lysosome fusion inhibits lipid droplet autophagy, leading to lipid droplet accumulation and further aggravating ER stress and reactive oxygen species generation in a vicious cycle.[62] Of note, a regulatory link exists between autophagy and APOB. Autophagy can target APOB for degradation via the transmembrane protein sortilin,[63] and sortilin deficiency under lipid overload or ER stress leads to increased APOB secretion. Conlon *et al*.[64] pointed out that liver-specific APOB antisense oligonucleotide treatment induced ER lipid accumulation and stress in the short term (three weeks), but activated ER-selective autophagy and enhanced fatty acid β-oxidation in the longer term (six weeks), thereby preventing cytoplasmic lipid overload. This study provides a new perspective on targeting autophagy for the treatment of FHBL related hepatic steatosis. Previous studies have proved that enhancing lipophagy in hepatocytes significantly reduces steatosis and hepatic inflammation,[65] and macrophage lipophagy mitigates liver inflammation.[66] Therefore, targeting the autophagy pathway may also represent a potential therapeutic strategy, although further experimental evidence is needed.

Hepatic manifestations and clinical heterogeneity in FHBL

FHBL exhibits substantial clinical heterogeneity, with liver disease being a core but variably expressed component. The degree and trajectory of liver involvement appear to be influenced by *APOB* mutation type, residual protein function, and various genetic or environmental modifiers. Therefore, the hepatic outcomes in FHBL vary widely, ranging from isolated hepatic steatosis to steatohepatitis, fibrosis, cirrhosis, and HCC.

Hepatic steatosis and steatohepatitis

Recently, a retrospective study of 15 patients with FHBL revealed a mean onset age of 22.5 ± 15.5 years, with 13 He-FHBL patients and one Ho-FHBL patient presenting hepatic steatosis that correlated strongly with fat-soluble vitamin deficiencies (particularly vitamins A and D), and the only Ho-FHBL patient had mild hepatic steatosis (grade 1).[67] A large non-Hispanic pediatric non-alcoholic fatty liver disease cohort study found that nearly one-tenth of the participants had hypobetalipoproteinemia. Patients with low serum LDL-C exhibited higher hepatic steatosis scores, but no differences were observed in hepatic inflammation or fibrosis scores between different groups.[68] Also, hepatic steatosis has been observed in He-FHBL adolescents aged 13–15 years, including cases with normal serum transaminase levels, suggesting steatosis may occur even in the absence of biochemical liver injury.[69] Patients may maintain their status quo for a considerable time, and only some of them will progress to steatohepatitis or fibrosis,[21,23,70] but the specific proportion has not been supported by large-scale epidemiological data.

Liver cirrhosis and HCC

The exact frequency of liver fibrosis and cirrhosis in patients with FHBL remains uncertain. Although only a small subset of patients progresses to cirrhosis and HCC, recent cohort studies have begun to clarify the cumulative incidence. A cohort study of Ho-FHBL patients demonstrated that three out of four newly diagnosed cases exhibited liver stiffness measurements consistent with clinically significant fibrosis, while six out of nine previously reported cases had biopsy-confirmed hepatic fibrosis, including three cases progressing to cirrhosis.[21] Some case reports described the occurrence of cirrhosis and HCC in He-FHBL[13,71–75] and Ho-FHBL[21,76,77] patients, particularly in young adults,[70] underscoring the critical importance of early recognition and longitudinal monitoring.

Previous studies have pointed out through proteomic and genomic analysis that the level of circulating APOB is negatively correlated with the risk of liver cancer.[78] Recently, Wargny *et al*.[79] demonstrated that individuals with primary low LDL-C levels (including FHBL) showed significantly higher rates of cirrhosis and/or primary liver cancer compared to individuals with LDL-C levels between the 40th–60th percentiles (0.32 vs. 0.07 and 0.69 vs. 0.21 per 1,000 person-years in the CONSTANCES and UK Biobank cohorts, respectively), corresponding to a 4.5-fold and 3.3-fold increased risk. This risk persists independently of obesity, diabetes, alcohol use, and viral hepatitis, even after multivariable adjustment and five-year landmark analysis. FHBL patients showed the high risk, with an incidence density ratio of 4.19 (95% CI, 1.74–10.1) for cirrhosis and/or primary liver cancer, even in the absence of other risk factors. Notably, individuals with LDL-C levels < 1st percentile are associated with a further increased risk (eightfold and fivefold increased risk in the CONSTANCES and UK Biobank cohorts, respectively), suggesting a direct role of low LDL-C in liver disease pathogenesis. In another cohort of 104 adults with primary hypobetalipoproteinemia, the prevalence of hepatic steatosis and significant fibrosis was 31.7% and 14.4%, respectively. Pathogenic *APOB* variants were the strongest risk factor for steatosis (OR = 5.56), affecting nearly half of carriers at an earlier age, and were more frequent in patients with fibrosis, though without statistical significance.[80]

Notably, some long-term follow-up studies report no steatohepatitis or hepatic fibrosis even after decades in some FHBL patients with hepatic steatosis.[81] A 52-year-old Ho-FHBL female patient (c.819-2A>G splice-site variant) was followed up for 40 years.[82] She presented with diarrhea and growth retardation at birth, with undetectable serum LDL-C and APOB levels. After over 40 years of high-dose oral vitamin therapy (vitamins A, D, E, and K), her clinical condition remained stable. However, follow-up data on liver disease were not available, suggesting either no abnormalities or at least no severe hepatic involvement; high-dose oral fat-soluble vitamin therapy may play a role in this process.

Contributing factors to disease progression

The primary factors leading to clinical heterogeneity are zygosity and *APOB* variant sites. Ho-FHBL patients may present with a series of clinical manifestations from infancy to adulthood, involving problems in growth and development, digestive nutrition, hematology, the nervous system, and ophthalmology (Table 1),[3,7,81,83–85] most of which are diagnosed in adulthood (mean age at diagnosis, 21 years old).[83] In a pooled analysis of 55 homozygous cases, 62% exhibited hepatic manifestations, including elevated serum transaminases, fatty liver, hepatomegaly, liver fibrosis, and

Table 1. Summary of genotype-related clinical phenotypes

Genotype	Symptoms		References
Ho- FHBL	Serum lipid levels	Significantly low plasma TC or LDL-C, or APOB	7,83,84
	Serum vitamin levels	Low vitamin E, A, D, K	7,81
	Digestive system manifestations	Elevated serum transaminase levels, steatorrhea, hepatic steatosis, hepatic fibrosis and cirrhosis, hepatocellular carcinoma, hepatomegasia	7,81
	Hematological symptoms	Acanthocytosis	7,83
	Neuromuscular symptoms	Loss of deep tendon reflexes, impaired proprioception, myopathy	7,81,83
	Ophthalmological injury	Night blindness, color vision defects, retinal degeneration, blindness	3,7,81
He- FHBL	Serum lipid levels	Hypolipemia	83
	Digestive system manifestations	Hepatic steatosis and fibrosis	83,85

Ho-FHBL, homozygous or compound heterozygous familial hypobetalipoproteinemia patients; He-FHBL, heterozygous familial hypobetalipoproteinemia patients; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; APOB, apolipoprotein B.

cirrhosis.[76] Abnormal APOB impairs chylomicron assembly and lipid absorption, leading to symptoms such as vomiting and abdominal distension, with endoscopy revealing a characteristic "gelée blanche" appearance.[84] However, He-FHBL patients are usually asymptomatic or have mild liver enzyme abnormalities and simple hepatic steatosis (Table 1). An estimated 5–10% of patients progress to non-alcoholic steatohepatitis, though advanced liver disease is rare.[83]

Shorter truncations typically result in more severe phenotypes,[86] while longer truncations may preserve partial lipoprotein secretion capacity and are associated with milder or subclinical presentations. Data show more severe phenotypes occur with protein-truncating variants (≤30% residual length) than with those preserving ≥32% protein length, the latter generally causing moderate disease.[83] Except for nonsense variants, certain pathogenic variants at critical genomic loci (e.g., the splice variants c.11788+1G>A[67] and c.1471-1G>A[23]) may correlate with aggravated disease manifestations or accelerated progression. Ho-FHBL variants generally lead to more profound systemic and hepatic involvement compared to heterozygous variants. Nevertheless, genotype alone does not fully explain disease variability. Of note, a 48-year-old woman with a homozygous variant of APOB-45.2 remained asymptomatic despite an undetectable LDL-C level and a very low level of APOB.[87]

In addition to genetic factors, additional hits such as alcohol use, hepatitis virus infection, excessive caloric intake, metabolic syndrome, and liver injury can accelerate disease progression.[23] Studies have shown that obesity and insulin resistance are key synergistic factors that accelerate liver fibrosis,[21] and early-onset diabetes (<40 years) is strongly associated with end-stage liver disease. Progression from simple steatosis through steatohepatitis to cirrhosis has been reported in patients consuming 70–80 g of alcohol per day.[23] This discrepancy suggests a multifactorial pathogenesis involving additional modifiers. Additionally, polygenic interactions may contribute to more severe clinical phenotypes. For example, Wang *et al*. reported a patient with multiple rare heterozygous variants (*APOB*, *MTTP*, *PCSK9*, *SAR1B*, *ANGPTL3*),[88] resulting in extremely low serum LDL-C and fat-soluble vitamin levels, though without liver abnormalities. *PNPLA3* and *TM6SF2* have been extensively validated as risk factors for MASLD,[89,90] and the *TM6SF2* E167K and *PNPLA3* I148M variants can promote the profibrotic phenotype of hepatic stellate cells.[91,92] Cases have been reported with combined *APOB* and *PNPLA3* variants leading to fibrosis or cirrhosis,[93] and triple variants (*APOB*, *PNPLA3*, *TM6SF2*) identified in patients with cirrhosis or HCC.[94] These findings underscore the synergistic effect of multiple genetic variants in promoting liver disease progression. Overall, the variability in hepatic outcomes likely reflects the interplay of multiple factors (Fig. 4).

Diagnosis and differential diagnosis

The diagnosis of FHBL requires a comprehensive clinical, biochemical, and genetic approach. Ho-FHBL individuals typically present in infancy with chronic diarrhea, growth retardation, or characteristic endoscopic findings,[81] while He-FHBL individuals are often incidentally detected due to asymptomatic low serum LDL-C or APOB levels, with mildly elevated transaminases or hepatic steatosis on imaging. For suspected patients, a thorough medical history should specifically assess the presence of metabolic disorders and family history. Initial evaluation requires serum lipid profiling, which usually shows significant reductions in total cholesterol, LDL-C, or APOB.[81] Note that excessively truncated APOB proteins may not be detectable in plasma (e.g., APOB-5.44 to APOB-30.40).[95] In addition, the levels of fat-soluble vitamins (A, D, E, K) should be measured to assist in diagnosis. Genetic testing remains the gold standard, with pathogenic *APOB* variants confirming FHBL. In cases of unexpectedly severe liver disease, additional screening for polygenic risk variations (*ANGPTL3*, *PCSK9*, *MTTP*, *PNPLA3*, *TM6SF2*, etc.) is warranted. FHBL must be distinguished from other inherited and secondary causes of hypolipidemia.[4,7] The detailed differential diagnosis is shown in Table 2.

For patients with hepatic involvement, further assessment should incorporate non-invasive tools and, where indicated, histopathology. Additional testing is recommended to further determine genetic susceptibility to alcohol consumption and viral hepatitis.[10] It is important to emphasize that although MASLD and FHBL share hepatic steatosis as a common phenotype, they differ fundamentally in etiology and serum lipid profiles, although sometimes there are common manifestations in metabolic characteristics. Current guidelines (ABLRDF 2022, Japan 2024) provide structured diagnostic frameworks for FHBL (Table 3).[3,7]

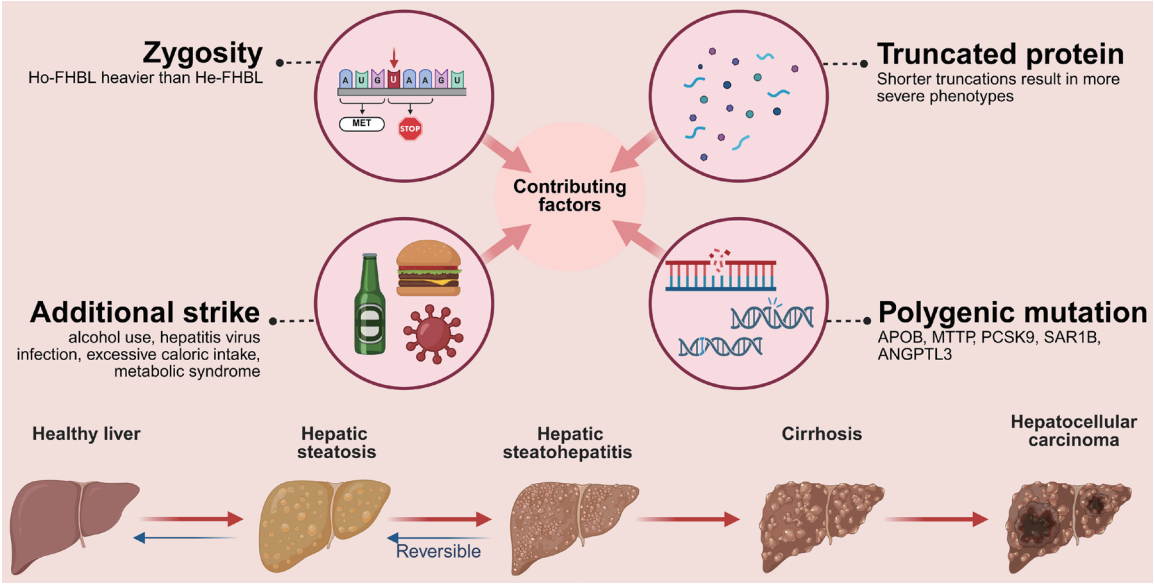

Fig. 4. Contributing factors to liver disease progression in FHBL. The progression of liver disease in FHBL patients involves numerous factors, mainly including zygosity, truncated protein length, additional insults, and polygenic mutations. The progression and prediction of the disease need to be analyzed based on specific circumstances. FHBL, familial hypobetalipoproteinemia assembly and secretion defect type 2; MAFL, metabolic dysfunction-associated fatty liver; MASH, metabolic dysfunction-associated steatohepatitis; APOB, apolipoprotein B; MTTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SAR1B, secretion-associated RAS-related GTPase 1B; ANGPTL3, angiopoietin-like 3.

Treatment

The treatment of FHBL aims to correct metabolic abnormalities, prevent and manage complications, and optimize long-term outcomes. The cornerstone of treatment is adherence to a low-fat diet combined with vitamin supplementation. In a 40-year follow-up of three homozygous patients, high-dose vitamins and strict dietary fat control maintained symptom stability, with only one case developing mild liver steatosis, inflammation, and fibrosis in late adulthood.[82] Clinical management should be individualized according to the genotype and phenotype severity. For He-FHBL patients with markedly low APOB-containing lipoprotein levels, treatment and follow-up should be conducted at the same level as for Ho-FHBL patients. Prognosis depends on genetic variants, environmental exposures, timeliness of diagnosis, patient adherence, and other contributing factors.

Nutrition

Ho-FHBL patients, as well as He-FHBL patients with gastrointestinal symptoms, should maintain adequate caloric intake while limiting fat intake to <30% of total caloric intake, ideally around 20%,[81,83] with some guidelines even recommending <10%–15%.[4] Medium-chain triglycerides are preferred.[84] Attention should be paid to controlling the proportion of total fat intake in infants to address growth retardation and intestinal lipid malabsorption.[3,7,81,96] Effective treatment has been reported using formula diets containing 25% total fat, primarily composed of medium-chain triglycerides.[29] Notably, some patients showed gastrointestinal symptom improvement after spontaneously adopting a markedly low-fat or gluten-free diet.[23,97] Oral supplementation with essential fatty acids is also recommended.[7,81]

Vitamin supplementation

For all Ho-FHBL patients, adequate vitamin supplementation is essential to prevent and potentially ameliorate complications, particularly those involving the nervous system and vision. High-dose vitamin E is especially important, as it may prevent retinal degeneration and neurological symptoms.[98] Recommended vitamin E dosages include 100–300 IU/kg/day in high-dose regimens,[81,96] and 50 IU/kg/day as a maintenance dose.[84] Even high doses may only raise serum vitamin E levels to approximately 30% of the lower limit of normal. Vitamin A supplementation (100–400 IU/kg/day) is recommended to prevent ophthalmic complications.[7,81,99–102] The treatment goal should be at the lower normal limit to avoid toxicity. Supplementation with vitamin D (800–1,200 IU/day), vitamin K (5–35 mg/week or 5 mg/day), iron, folic acid, and vitamin B_{12} should be considered when clinically indicated.[7] Of note, some studies found no evidence supporting vitamin E supplementation in He-FHBL patients,[103] although certain guidelines recommend its use in more symptomatic cases.[4]

Management of liver injury

For all patients with liver injury, long-term follow-up is indispensable. Dietary interventions, regular exercise, and weight reduction represent fundamental strategies for managing liver involvement,[104–106] which can reduce liver fat content and alleviate steatohepatitis and fibrosis to a certain extent. Vitamin E has been proposed as a potential treatment option.[104] Notably, a recent randomized controlled trial conducted in a population with metabolic dysfunction-associated steatohepatitis demonstrated that daily administration of 300 mg of vitamin E significantly improved hepatic steatosis, inflammation, and fibrosis.[106] Previously, the PIVENS trial also demonstrated that vitamin E (800 IU/day) was effective in improving hepatic steatosis and lobular inflammation, as well as in reducing serum alanine and aspartate aminotransferase levels.[108] Therefore, oral administration of vitamin E is a valuable treatment option for patients with FHBL combined with liver injury. Finally, in cases of liver decompensation and HCC, liver transplanta-

Table 2. Differential diagnosis framework for FHBL and various forms of hypolipidemia

I. Primary/genetic causes		
Disease/Factor	**Inheritance pattern**	**Key differentiator**
Abetalipoproteinemia (ABL)	Autosomal recessive	Undetectable serum LDL-C and APOB; Severe malabsorption, acanthocytosis, retinopathy, or neurological disorders in infancy/childhood; Caused by the *MTTP* gene mutation
Chylomicron retention disease (CRD)	Autosomal recessive	Low serum LDL-C, TC, and HDL but normal serum TG; Severe malabsorption in infancy/childhood; Caused by the *SAR1B* gene mutation
PCSK9 deficiency	Autosomal dominant	Low but detectable serum LDL-C with no specific clinical complications; Caused by *PCSK9* loss-of-function mutation
A*NGPTL3* deficiency	Autosomal dominant	Low levels of all major serum lipoprotein fractions (LDL-C, HDL-C, TC, etc.) with no specific clinical complications; Caused by *ANGPTL3* loss-of-function mutation

II. Secondary causes		
System	**Etiology**	**Key Differentiator**
Pharmacological		Clear history of statin use/estrogen or anti-estrogen therapy/PCSK9 inhibitors/Ezetimibe, etc
Nutritional	Malnutrition	History of starvation/eating disorders; improves with feeding
	Steatorrhea/Malabsorption Syndromes	History of gluten intolerance/Crohn's disease/short bowel syndrome/chronic pancreatitis, etc. Often presents with chronic diarrhea, bloating, and weight loss.
Endocrine	Hyperthyroidism	Symptoms of hyperthyroidism and abnormal thyroid function.
Hepatic	Advanced cirrhosis/Severe liver failure	Accompanied by jaundice, ascites, elevated bilirubin/INR, low albumin, etc
Hematologic/Oncologic	Megaloblastic anemia	Low serum Vitamin B12 and/or folate levels
	Cancer	Signs of cachexia and weight loss. Evidence of active malignancy on imaging or biopsy
Inflammatory	Infection/Inflammation	Elevated acute phase reactants. Symptoms of active inflammatory disease or chronic infection
Renal	Chronic kidney disease	Hypolipidemia can be caused by long-term dialysis combined with malnutrition and chronic inflammation

FHBL, familial hypobetalipoproteinemia; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; APOB, apolipoprotein B; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; ANGPTL3, angiopoietin-related protein 3.

tion should be considered as a potential treatment.

Future perspective

Familial hypobetalipoproteinemia, primarily caused by *APOB* variants, disrupts lipoprotein metabolism, leading to markedly reduced plasma LDL-C and APOB levels. The disorder exhibits significant genotypic and phenotypic heterogeneity. Ho-FHBL patients often present with severe multisystem complications, while He-FHBL ones may remain asymptomatic or only develop mild hepatic manifestations. Advances in molecular genetics have elucidated the role of *APOB* variants in impairing VLDL assembly, secretion, and clearance, with genotype-phenotype correlations emphasizing the impact of truncation length on disease severity.

Despite research progress, critical gaps still remain. Epidemiological data are skewed toward Western populations, necessitating global studies to clarify regional prevalence and genetic diversity. The mechanisms underlying FHBL related hepatic steatosis, particularly fibrosis, are incompletely understood and warrant further in-depth investigation. The interplay between FHBL and modifier genes highlights the need for comprehensive genetic profiling to predict disease progression. In particular, the lack of reliable prognostic biomarkers limits our ability to identify patients at risk of advanced liver disease. Multi-omics approaches, including lipidomics, transcriptomics, and microbiome profiling, may uncover novel biomarkers and therapeutic targets in the future.

From a translational perspective, clarifying *APOB* variants and truncation length–kinetics can aid in predicting residual protein function, the likelihood of hepatic involvement, and the necessity for long-term management and surveillance. Recognition of ER stress, oxidative injury, and autophagy dysfunction not only advances mechanistic understanding but also points to potential therapeutic options, such as antioxidants or ER stress–targeted interventions, which may complement standard management. Epidemiological evidence reinforces the importance of genetic testing and early recognition to enable tailored surveillance and nutritional interventions, while clinical data indicate that oral vitamin E may be a valuable therapeutic choice for FHBL patients

Table 3. Overview of current FHBL diagnostic criteria

Organization (Year)	Diagnostic items	
ABLRDF (2022)[3]	Clinical features	Ho-FHBL: Fat malabsorption; Infant/childhood growth retardation; Hepatic steatosis or more severe; Early-onset neurologic & ophthalmic abnormalities. He- FHBL: Usually asymptomatic; Hepatic steatosis; Elevated plasma liver enzymes
	Blood biochemistry	Depends on the specific mutation and the number of affected alleles; Reduced fat-soluble vitamins (A, D, E, K) depend on Reduced plasma lipid levels (TC, LDL-C, APOB)
	Genetic testing	Gold standard
Labour and Welfare of Japan (2024)[7] (For patients with Ho-FHBL)	Clinical features	Gastrointestinal: symptoms related to fat malabsorption; Neuromuscular: ataxia, spastic paralysis, peripheral sensory neuropathy, deep tendon reflex attenuation, etc.; Ophthalmological: night blindness, retinitis pigmentosa, blindness, etc.
	Laboratory tests	plasma LDL-C level <15 mg/dL and/or plasma APOB level <15 mg/dL; Acanthocytosis
	Genetic testing	pathogenic mutations in the *APOB* gene
	Differential diagnosis	Abetalipoproteinemia, chylomicron retention disease, hyperthyroidism
	Definite FHBL	Laboratory test first item plus laboratory test second item or any one of clinical manifestations, plus differential diagnosis and genetic testing

ABLRDF, the AβLipoproteinemia and Related Disorders Foundation; Labour and Welfare of Japan, the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of the Ministry of Health, Labour and Welfare of Japan; Ho-FHBL, homozygous or compound heterozygous familial hypobetalipoproteinemia patients; He-FHBL, heterozygous familial hypobetalipoproteinemia patients; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; APOB, apolipoprotein B.

with liver injury, pending confirmation in prospective FHBL-specific trials.

Conclusions

Early diagnosis via lipid profiling and genetic testing is pivotal. Management focuses on dietary fat restriction, lipid-soluble vitamin supplementation, and vigilant monitoring of liver injury. Emerging therapies targeting metabolic pathways (e.g., vitamin E) show promise but require validation in FHBL-specific cohorts. Gene therapy represents a future-oriented strategy for FHBL, with the potential to correct *APOB* defects and prevent progressive liver injury. The ultimate goal is to bridge molecular insights with tailored therapeutic strategies, providing more ideas for the diagnosis and management of FHBL.

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Conflict of interest

JGF has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Writing – original draft (TWL, TYR), writing – review & editing, funding acquisition, and conceptualization (JGF). All authors have made significant contributions to this study and have approved the final manuscript.

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