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## Review Article

# Guidance for the diagnosis and treatment of hypolipidemia disorders



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*Abbreviations:* ABL, abetalipoproteinemia; ABLRDF, Abetalipoproteinemia and Related Disorders Foundation; ALA, alpha-linoleic acid; ANGPTL3, angiopoietin like 3; ApoB, apolipoprotein B; CK, creatine kinase; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EFA, essential fatty acids; EPA, eicosapentaenoic acid; ERG, electroretinogram; FHBL, familial hypobetalipoproteinemia; HDL, high density lipoproteins; HDL-C, HDL-cholesterol; INR, international normalized ratio; LA, linoleic acid; LCT, long chain triglyceride; LDL, low density lipoproteins; LDL-C, LDL-cholesterol; MAG, monoacylglycerols; MCT, medium chain triglycerides;

erides; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SAR1B, secretion associated Ras related GTPase 1B; TG, triglyceride; VLDL, very low density lipoproteins..

The Medical Advisory Panel of the Abetalipoproteinemia and Related Disorders Foundation

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## KEYWORDS

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Triglycerides;  
Cholesterol;  
Fat-soluble vitamins;  
Familial  
hypcholesterolemia;  
Abetalipoproteinemia;  
Hypobetalipoproteinemia;  
Chylomicron retention  
disease

**Abstract:** The Abetalipoproteinemia and Related Disorders Foundation was established in 2019 to provide guidance and support for the life-long management of inherited hypocholesterolemia disorders. Our mission is “to improve the lives of individuals and families affected by abetalipoproteinemia and related disorders”. This review explains the molecular mechanisms behind the monogenic hypobetalipoproteinemia disorders and details their specific pathophysiology, clinical presentation and management throughout the lifespan. In this review, we focus on abetalipoproteinemia, homozygous hypobetalipoproteinemia and chylomicron retention disease; rare genetic conditions that manifest early in life and cause severe complications without appropriate treatment. Absent to low plasma lipid levels, in particular cholesterol and triglyceride, along with malabsorption of fat and fat-soluble vitamins are characteristic features of these diseases. We summarize the genetic basis of these disorders, provide guidance in their diagnosis and suggest treatment regimens including high dose fat-soluble vitamins as therapeutics. A section on preconception counseling and other special considerations pertaining to pregnancy is included. This information may be useful for patients, caregivers, physicians and insurance agencies involved in the management and support of affected individuals.

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## Background

The Abetalipoproteinemia and Related Disorders Foundation (ABLRDF), a non-profit international organization, consists of patients with abetalipoproteinemia (ABL), familial hypobetalipoproteinemia (FHBL) and related hypobetalipoproteinemia disorders, as well as their caregivers, researchers and medical professionals. Early diagnosis and intervention are essential to minimize the deleterious effects of hypobetalipoproteinemia disorders. Nevertheless, it is not uncommon for patients to experience a delay of weeks to years before achieving a diagnosis, despite seeking medical care for adverse symptoms. The Foundation aims to increase awareness of ABL and other hypobetalipoproteinemia disorders in the medical community and provide clinical guidance that is relevant throughout the lifespan. We aspire to lead efforts for comprehensive affordable care including access to specialized professionals, medical assessments that incorporate preconception counseling and genetic testing as well as treatments. Another goal incorporates fundraising to support research developing means to deliver and maintain the efficacy of fat-soluble vitamins and other therapeutic molecules.

To ascertain priorities within the Foundation, we conducted limited, qualitative surveys with patients and held multiple conference calls among the founding members.

These efforts identified several challenges faced by patients and caregivers (Table 1). It became evident that access to necessary fat-soluble vitamins is compromised by cost and inadequate insurance coverage. Out of pocket expenses ranging up to \$800 a month in the United States were reported. Consequently, patients adhere to different vitamin regimens based on their affordability. To address this problem, the medical advisory panel drafted template letters of medical necessity for treating physicians to provide to third party payers when advocating for fat-soluble vitamin coverage on behalf of their patients. In addition, it became apparent that physician awareness of monogenic hypobetalipoproteinemia disorders is suboptimal leading to a delay in diagnosis, substandard treatment and the development of avoidable morbidities. This inattention is perhaps due to the very low prevalence of these diseases and the paucity of published recommendations for their management throughout the lifespan including the peripartum period. These findings illustrate the inconsistencies associated with real-world management of ABL and related hypobetalipoproteinemia disorders. To mitigate these deficiencies, we assembled an international panel of experts to analyze recent literature, summarize known knowledge and propose clinical treatment guidance. Two groups of experts summarized data separately and produced initial written descriptions. Subsequently, these drafts were

**Table 1** Challenges encountered by patients with ABL and related disorders.**Patient burden of disease**

- High daily vitamin pill burden needed to achieve dosage requirements
- Cost of fat-soluble vitamins and their insufficient insurance coverage
- Chronic vitamin treatments and regular physical examinations
- Disabilities leading to unemployment and reliance on social assistance

**Knowledge gaps in the healthcare system**

- Limited awareness of the condition and delay in diagnosis and treatment by the medical community
- Lack of recognition by health insurance organizations and regulatory agencies that ABL and related disorders require high dose vitamin treatments
- Gaps in clinical knowledge of disease evolution with age

**Limited resources for patients and caregivers**

- Paucity of clinical guidance that address management over the lifespan
- Limited availability of dietary guidance
- Inadequate preconception and pregnancy medical counseling
- Absence of a directory of physicians with expertise in disease management
- Patient awareness of available resources

combined and further expanded with the input from additional leaders in the field who agreed to join our panel. All the panel members then critically read, held several discussion meetings, and critiqued the final manuscript. The objective of this article is to provide: (a) information concerning the molecular basis of these conditions; (b) comprehensive and necessary clinical information to various stakeholders involved in the care of these serious monogenic hypobetalipoproteinemia disorders; and (c) guidance for their diagnosis, assessment and treatment. This review builds on our previous classification proposed for these disorders and recommendations provided for their optimal management<sup>1</sup>.

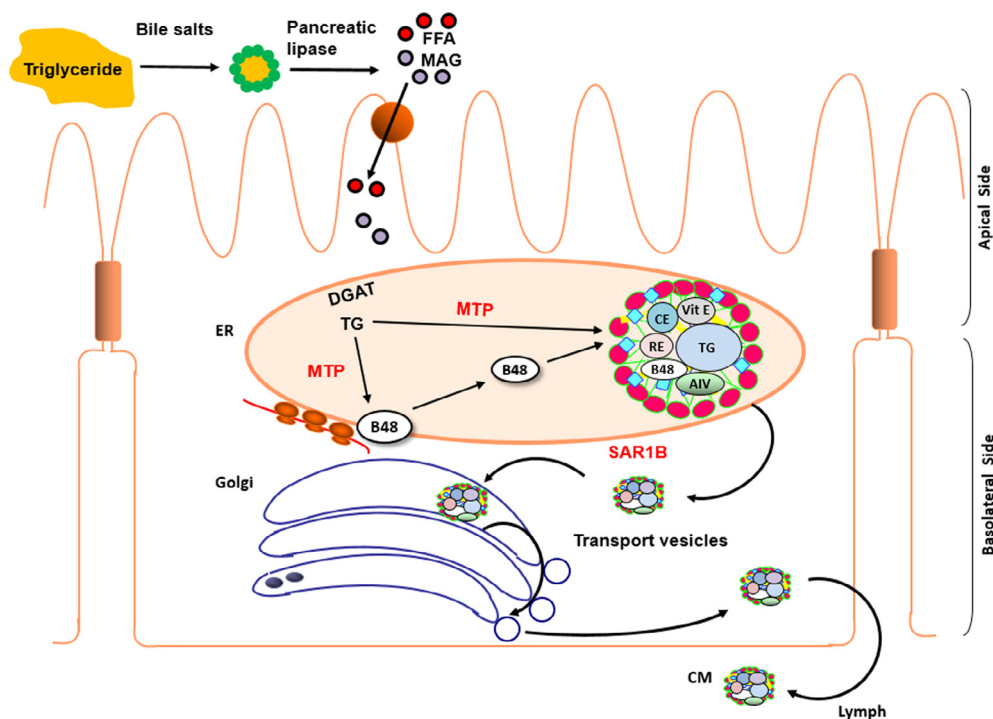
The guidance proposed herein is intended to support patients and clinicians in the management of hypobetalipoproteinemia disorders. In the absence of randomized, placebo controlled clinical trials or meta-analysis, our recommendations are based on isolated published reports and the experience of the ABLRDF medical advisory panel. Additional research is needed to substantiate clinical practice guidelines and is beyond the scope of this review.

We anticipate this document will heighten attention to these under-recognized conditions, including the urgency for improved access to affordable necessary fat-soluble vitamin treatment and medical care.

## Summary of lipoprotein metabolism

Lipoproteins are lipid-protein emulsion particles that transport lipids in blood circulation. They are also critical for the absorption, transport and delivery of fat-soluble vitamins to peripheral tissues. Lipids and proteins in these particles are held together via hydrophobic interactions<sup>2,3</sup>. Apolipoprotein B (apoB)-containing lipoprotein particles are mainly assembled in enterocytes and hepatocytes. En-

terocytes assemble and secrete very large lipoproteins, chylomicrons, to transport dietary fat and fat-soluble vitamins, whereas hepatocytes produce very low density lipoproteins (VLDL) to deliver endogenous lipids to extra-hepatic tissues. Assembly of these particles is dependent on two proteins<sup>4,5</sup>: apoB, a structural protein that acts as a scaffold for lipoprotein integrity, and microsomal triglyceride transfer protein (MTP), a chaperone that transfers lipids and facilitates the assembly of apoB-containing lipoproteins (Fig. 1). In humans, there is one *APOB* gene. In the liver, it is transcribed and translated into apoB100, a single polypeptide of about 4560 amino acids. In the intestine, apoB mRNA undergoes post-transcriptional C-to-U RNA editing with introduction of a TAA stop codon. It is subsequently translated into apoB48, an isoform representing N-terminal 48% of apoB100<sup>6</sup>. ApoB-containing lipoprotein assembly begins in the endoplasmic reticulum (ER). After their assembly, these particles are first transported to the Golgi complex for further maturation and modification and subsequently to the plasma membrane for secretion via exocytosis. Intracellular trafficking of lipoproteins to different organelles is critically dependent on several proteins including secretion associated Ras related GTPase IB (SAR1B). In the circulation, intestine and liver derived lipoproteins undergo lipolysis by endothelial cell-bound lipoprotein lipase. Several proteins inhibit lipoprotein lipase activity, including apoC-III and angiopoietin like proteins (ANGPTLs) 3 and 4. Lipolysis of lipoproteins by lipoprotein lipase yields chylomicron remnants, intermediate density lipoproteins and low-density lipoproteins (LDL). LDL is removed from the circulation by LDL receptors, whereas, remnants and intermediate density lipoproteins are cleared via LDL receptor-related protein 1 (LRP1), proteoglycans and other receptors<sup>7-13</sup>. LDL receptors recognize apoB100 on LDL, internalize the particles, and deliver them to lysosomes for degradation. Subsequently,



**Fig. 1** Schematic diagram highlighting the role of proteins deficient in chylomicron (CM) assembly and secretion by enterocytes in monogenic hypobetalipoproteinemia disorders. Dietary triglycerides (TG) are hydrolyzed in the intestinal lumen. This process requires bile acids secreted from the liver and pancreatic lipase secreted from the pancreas. Hydrolysis yields free fatty acids (FFA) and monoacylglycerols (MAG) which are taken up by enterocytes via specific transporters for the synthesis of TGs by enzymes, such as diacylglycerol acyltransferase (DGAT), present in the endoplasmic reticulum (ER). During translation, apolipoprotein B48 (B48) interacts with ER membrane. Microsomal triglyceride transfer protein (MTP) transfers lipids onto B48 and assists in the assembly of CM. CM containing TG, cholesterol esters (CEs) and fat soluble vitamins (VITs), such as retinyl esters (REs, VIT A), and VIT E (tocopherols) are transported to Golgi via specialized transport vesicles. This transport process is critically dependent on secretion associated Ras related GTPase 1B (SAR1B). Modified from<sup>16</sup>.

intact LDL receptors are sent back to the cell-surface for another round of lipoprotein internalization. To prevent excessive accumulation of cholesterol, LDL receptors are degraded after several rounds of recycling. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a plasma protein, binds to LDL receptors and undergoes endocytosis along with the receptor. In the intracellular compartments, the presence of PCSK9 prevents recycling of LDL receptors to the cell surface and augments their lysosomal degradation<sup>14,15</sup>.

## Description and classification of familial hypobetalipoproteinemia disorders

Primary monogenic FHBL disorders are intricately related to the lipoprotein metabolism summarized above. We have previously proposed a simplified nomenclature based on mechanisms that explain low plasma lipids<sup>1</sup>. The Class I FHBL disorders are due to secretion defects (FHBL-SD), whereas Class II FHBL disorders relate to enhanced catabolism (FHBL-EC). Members in these classes are further defined by the loss-of-function variants in different genes. Class I disorders have significant effects on growth and development in infancy and require early intervention and lifelong monitoring. Class II disorders do not exhibit any

pathologic symptoms or signs; in fact, these variants confer cardiovascular benefit and monitoring is not required. We anticipate that other uncharacterized mechanisms also contribute to FHBL. As such, this classification has flexibility for expansion. Following the discovery of additional causative genes, pathogenic variants and molecular mechanisms, new members can be incorporated within these classes. For example, a *LDLR* variant with truncations in 3'-untranslated region of the *LDLR* mRNA has been associated with low plasma lipids<sup>17</sup>. Following confirmatory studies, this variant may be added as a new member under FHBL Class II. New classes may also be added to the nomenclature if a novel mechanism of hypobetalipoproteinemia is discovered. For instance, a single report described subjects with hypolipidemia possessing mutations in the *LIMAI* gene leading to defects in intestinal cholesterol absorption<sup>18</sup>. An additional class of FHBL for defects in cholesterol absorption may be added following further evidence.

The Class I disorders arise due to secretion defects (SD) in apoB-containing lipoproteins and include FHBL-SD1 (ABL), FHBL-SD2 (FHBL), and FHBL-SD3 (chylomicron retention disease). FHBL-SD1 is an autosomal recessive disorder due to bi-allelic loss-of-function variants in the *MTTP* gene<sup>19-33</sup>. This gene codes for MTP, which as mentioned above is required for the assembly of apoB-containing

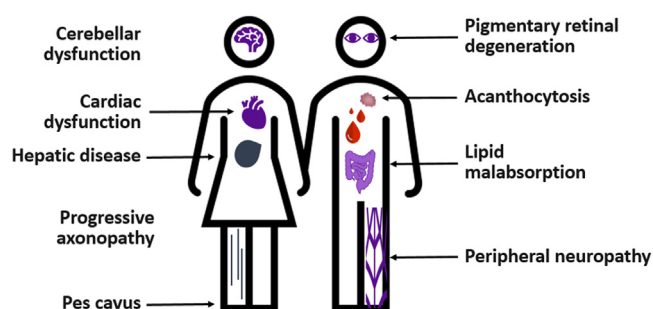
lipoproteins both in the intestine and the liver. Autosomal semi-dominant mutations in the *APOB* gene disable apoB protein from forming lipoproteins and cause FHBL-SD2 with bi-allelic or mono-allelic forms (formerly referred to as “homozygous” or “heterozygous” forms, respectively)<sup>34</sup>. As mentioned previously, the *APOB* gene codes for two tissue-specific isoforms, namely apoB100 and apoB48 in the liver and intestine, respectively. Most pathogenic variants in FHBL result from the synthesis of various truncated forms of the liver-derived apoB100 isoform. However, rare missense pathogenic variants in *APOB* have been reported that produce apoB peptides smaller than apoB48<sup>35,36</sup>. The severity of the disease is generally inversely proportional to length of the variant apoB peptide synthesized; the shorter the peptide, the more severe the phenotype. Patients with FHBL-SD1 and bi-allelic FHBL-SD2 have absent to very low levels of plasma lipids and apoB-containing lipoproteins<sup>37,38</sup>. FHBL-SD3 is an autosomal recessive disease due to bi-allelic loss-of-function variants in the *SAR1B* gene, which encodes SAR1B protein. Loss-of-function variants on both alleles of the *SAR1B* gene profoundly affect secretion of chylomicrons by enterocytes, while one copy of the pathogenic allele is not associated with an abnormal clinical phenotype<sup>39</sup>.

The Class II disorders arise due to enhanced catabolism (EC) of lipoproteins and include FHBL-EC1 (familial combined hypolipidemia) and FHBL-EC2. FHBL-EC1 is an autosomal semi-dominant disorder arising due to loss-of-function variants in the *ANGPTL3* gene<sup>40-42</sup>. Variant ANGPTL3 proteins do not inhibit lipoprotein lipase resulting in enhanced lipolysis of chylomicrons and VLDL and subsequent faster removal of remnant lipoproteins from plasma. FHBL-EC2 is an autosomal semi-dominant disorder due to loss-of-function variants in the *PCSK9* gene, which prevent LDL receptor lysosomal destruction and promote their increased recycling to the liver cell surface. This in turn results in enhanced removal of lipoproteins from circulation leading to reduced plasma LDL-cholesterol (LDL-C) levels<sup>34,43</sup>.

## Diagnosis and assessment of Class 1 disorders

### Familial hypobetalipoproteinemia due to lipoprotein assembly and secretion defect 1 (FHBL-SD1), commonly known as abetalipoproteinemia (ABL, OMIM: 200100)

FHBL-SD1 is an autosomal recessive inherited disorder of fat malabsorption due to impaired formation of apoB-containing lipoproteins. In 1950, Bassen and Kornzweig reported red blood cell acanthocytosis, atypical retinitis pigmentosa and ataxia in a patient<sup>44</sup>. Jampel and Falls observed low serum cholesterol in affected patients in 1958<sup>45</sup>. Salt et al. reported absence of beta-lipoproteins in the serum in 1960 and the syndrome was called “abetalipoproteinemia”<sup>46</sup>. Ultimately, the first causative variants in the *MTTP* gene were described by Wetterau et al. in 1992<sup>19</sup>. Bi-allelic



**Fig. 2** Different organ systems and associated symptoms in FHBL-SD1.

rare pathogenic variants in the *MTTP* gene are causative for the near complete absence of plasma lipids and fat-soluble vitamin deficiency (Table 2). The diagnostic criteria of FHBL-SD1 include: (a) extremely low levels of plasma lipids including cholesterol and TG, (b) absence of apoB-containing lipoproteins including chylomicrons, VLDL, remnants and LDL, (c) low levels of fat-soluble vitamins E, A, K, D and carotenoids, (d) presence of acanthocytosis and (e) bi-allelic pathogenic variants in the *MTTP* gene (either the identical variant on both chromosomes in true homozygosity or two different variants in compound heterozygosity). There is no difference in clinical severity whether both variant alleles are identical or different. Although phenotypic variability exists in FHBL-SD1, the reasons for this are not yet fully understood. Heterozygous parents with a single variant are referred to as “carriers”. Differential diagnostic considerations include: other FHBL disorders, including FHBL-SD2 and -SD3, pancreatic insufficiency including cystic fibrosis, biliary atresia, intolerance to milk proteins, inflammatory bowel disease, intestinal lymphangiectasia, mechanical defects of the small bowel, gluten-sensitive enteropathy, Friedreich ataxia, Refsum disease, spinocerebellar ataxia, acanthocytosis, and ataxia with isolated vitamin E deficiency. Definitive diagnosis is confirmed by sequencing the *MTTP* gene.

The incidence of FHBL-SD1 is reported as less than 1 in 1,000,000<sup>47,48</sup>. In specific founder populations, however, the incidence is significantly higher. For instance, among Ashkenazi Jews, a nonsense variant in the *MTTP* gene found in healthy controls had a carrier frequency of 1:131, which would predict a prevalence of affected individuals with FHBL-SD1 at ~1 in 70,000<sup>49</sup>. Symptoms of FHBL-SD1 are the result of fat malabsorption in the short-term and fat-soluble vitamin deficiencies, in particular vitamin E deficiency, over the long-term. Vitamin E deficiency predominantly influences the ophthalmologic and nervous system (Fig. 2). Gastrointestinal symptoms dominate the clinical picture in infancy and improve within a few days or weeks with a low-fat diet<sup>34</sup>. Due to the rarity of the condition, a diagnosis of FHBL-SD1 may be overlooked at this stage. As the individual matures, but remains untreated, the clinical impact of fat-soluble vitamin deficiency becomes clinically manifest. A description of specific symptoms that may be present to varying degrees of severity and are summarized in

<b>Table 2</b> Key findings in hypobetalipoproteinemia disorders.					
Disease	Gene	Lipids and Lipoproteins (mmol/L) <sup>§</sup>	Ref	Notable Features	Symptoms
<b>Class I: Familial hypobetalipoproteinemia due to lipoprotein assembly and secretion defects</b>					
<b>Bi-allelic FHBL-SD1 (ABL)</b>	<i>MTTP</i>	†TC: 0.87 [0.82-1.02] *LDL-C: <0.04 [0.03-0.13] HDL-C: 0.71 [0.66-0.83] TG: 0.09 [0.10-0.20]	(27)	Acanthocytosis	Fat malabsorption, steatosis, failure to thrive in infancy, early neurologic and ophthalmologic abnormalities
<b>Bi-allelic FHBL-SD2 (FHBL)</b>	<i>APOB</i>	†TC: 0.88 [0.83-1.37] LDL-C: 0.06 [0.04-0.18] HDL-C: 0.77 [0.68-1.23] TG: 0.23 [0.22-0.53]	(27)	Acanthocytosis	Fat malabsorption, steatosis, failure to thrive in infancy, early neurologic and ophthalmologic abnormalities
<b>Mono-allelic FHBL-SD2 (FHBL)</b>	<i>APOB</i>	TC: 2.75 ± 0.62 LDL-C: 1.05 ± 0.43 HDL-C: 1.45 ± 0.52 ††TG: 0.48 [0.34-0.70]	(87)		Usually asymptomatic, possible risk of liver steatosis and fibrosis, Reduced risk for CVD
<b>Bi-allelic FHBL-SD3 (CRD)</b>	<i>SAR1B</i>	TC: 1.49 ± 0.56 LDL-C: 0.69 ± 0.38 HDL-C: 0.46 ± 0.08 ‡TG: 0.73	(89)	↑ CK (up to 10x upper reference limit) Absent chylomicrons	Fat malabsorption, steatosis, failure to thrive in infancy, neurologic and ophthalmologic abnormalities
<b>Class II: Familial hypobetalipoproteinemia due to enhanced lipoprotein catabolism</b>					
<b>Bi-allelic FHBL-EC1 (FCHL)</b>	<i>ANGPTL3</i>	TC: 2.37 ± 0.40 LDL-C: 1.46 ± 0.27 HDL-C: 0.67 ± 0.18 ††TG: 0.54 [0.43-0.58]	(87)		Reduced risk for CVD
<b>Mono-allelic FHBL-EC1 (FCHL)</b>	<i>ANGPTL3</i>	TC: 4.62 ± 1.08 LDL-C: 2.75 ± 0.87 HDL-C: 1.34 ± 0.34 ††TG: 0.97 [0.69-1.60]	(87)		Reduced risk for CVD
<b>Mono-allelic FHBL-EC2</b>	<i>PCSK9</i>	‡‡TC: 4.47 ± 1.14 LDL-C: 2.59 ± 1.11 HDL-C: 1.42 ± 0.41 TG: 1.06 ± 0.43	(88)		Reduced risk for CVD

CVD=cardiovascular disease, CK=creatin kinase, LDL-C=low density lipoprotein cholesterol, HDL=high density lipoprotein, TC=total cholesterol, TG=triglyceride.

<sup>§</sup>The lipid and lipoprotein values are representative means/medians from several studies previously published. Plus-minus values are mean ± SD. To convert cholesterol from mmol/L to mg/dL, multiply by 38.67. To convert TG from mmol/L to mg/dL, multiply by 88.57.

\*Below detection threshold.

†Median [95% interval of confidence].

††Median [25°-75° percentiles].

‡TG in CRD is the same as in controls (0.73 mmol/L).

‡‡Mean ± SD values from nonsense mutations in *PCSK9*142X or 679X.

**Table 2.** The clinical phenotype in adults may differ among probands. The factors contributing to different phenotypes have been poorly characterized and may include genetic and non-genetic influences.

### Gastrointestinal

Infants with FHBL-SD1 experience steatorrhea, vomiting, diarrhea, abdominal pain and distension. These symptoms are aggravated by a diet high in fat, including breast milk. This is a consistent feature of FHBL-SD1 and leads to a rapid failure to thrive in infancy. Endoscopic intestinal

biopsy and electron microscopic examination reveal white mucosa and fat droplets in enterocytes, respectively<sup>50</sup>. The steatorrhea may subside later as affected individuals learn to restrict fat in their diet. Interestingly, Ohashi et al. report adult cases of FHBL-SD1 spared from severe diarrhea and failure to thrive likely due to regional variations in fat intake<sup>32</sup>. Other manifestations include hepatomegaly with fat infiltration and elevated liver enzymes<sup>37</sup>. Hepatic steatosis, steatohepatitis and cirrhosis may develop due to impaired VLDL secretion, although the factors influencing severity and progression of liver disease are poorly understood. Liver

transplantation has been reported in a few patients with cirrhosis and liver failure<sup>51,52</sup>. Nevertheless, cirrhosis has been reported in only a very small number of cases<sup>52-54</sup>. Hepatic steatosis has also been reported in individuals carrying a single *MTP* variant<sup>55,56</sup>.

### Neurologic

Patients present with neurological disorders, predominantly as a consequence of vitamin E deficiency<sup>48,57,58</sup>. The onset of neurologic involvement in FHBL-SD1 typically begins in the first or second decade of life due to progressive axonopathy of the posterior columns, spinocerebellar tracts and peripheral nerves. Reduction and eventual loss of deep tendon reflexes are often the first neurological signs, followed by proprioceptive abnormalities and cerebellar symptoms, including dysmetria, ataxia, and wide-based gait<sup>50</sup>. Lack of voluntary muscle coordination can cause dysarthria and abnormalities in ocular movements<sup>57-60</sup>. Tremors and paresthesias may also occur. In some untreated cases, the neurological manifestations may progress to immobility<sup>18</sup>. Electrophysiological abnormalities may be observed as early as 7 months of age. Sensory nerve fibers frequently show abnormal conduction velocities or amplitudes and H-reflexes are often abnormal<sup>61</sup>.

### Musculoskeletal

Muscle inflammation and weakness have been described. Histologic abnormalities to the myocardium including interstitial fibrosis and enlarged muscle fibers have been described in a patient with heart failure<sup>62,63</sup>. Respiratory failure was described in another patient with severe neuropathy<sup>64</sup>. Skeletal abnormalities including spine curvature disorders and abnormally high foot arches are observed<sup>65</sup>. Vitamin D deficiency is not a consistent finding; however, defects in normal bone growth have been reported<sup>66</sup>.

### Ophthalmologic

The cardinal ocular manifestation of FHBL-SD1 is pigmentary retinal degeneration which is likely secondary to vitamin E and vitamin A deficiencies. Symptoms of retinitis pigmentosa typically begin in childhood and although the course can be varied and gradual, most untreated individuals are legally blind by 40 years. Typically, patients will experience loss of night vision first followed by a loss of color vision and peripheral vision<sup>60</sup>. Less common symptoms include paralysis of the eye muscles and inability to align both eyes simultaneously, including a posterior internuclear ophthalmoplegia, which can affect depth perception<sup>48,67</sup>. Unfortunately, retinal changes can occur despite early initiation of vitamin treatment. On long term follow-up, fundoscopic pigmentary changes and subnormal mixed cone-rod electroretinogram (ERG) amplitudes were observed<sup>68</sup>. A small group of adults who started vitamin A and E treatment even after electrophysiological functions were altered demonstrated stable ERG and electro-oculography over 2-6 years<sup>69</sup>.

### Hematologic

A characteristic hematologic manifestation of FHBL-SD1 is acanthocytosis that can involve up to 50% or more of circulating erythrocytes<sup>59,70,71</sup>. Alterations in the lipid composition and fluidity of red cell membranes are responsible for this defect<sup>59</sup>. Vitamin K, which is involved in the coagulation cascade, may be deficient. Consistent with this, patients with FHBL-SD1 may have a prolonged international normalized ratio (INR)<sup>72,73</sup>. Bleeding tendencies including gastrointestinal bleeding have been reported<sup>48</sup>. A relationship between vitamin E deficiency and hemolysis has been reported<sup>74,75</sup>.

### Blood metabolites

The lipid profile of patients with bi-allelic FHBL-SD1 reveal nearly absent LDL-C, TG and apoB, with most of the cholesterol circulating in high density lipoproteins (HDL)<sup>27</sup>. Lipid soluble vitamins are very low, especially vitamin E (<1/100th of normal) and A. Essential fatty acids (EFAs), linoleic acid (LA) and alpha-linolenic acid (ALA), are also dramatically decreased. Hypothyroidism may occur, although its causality remains unexplained<sup>51</sup>.

### Familial hypobetalipoproteinemia due to lipoprotein assembly and secretion defect 2 (FHBL-SD2), commonly known as familial hypobetalipoproteinemia (FHBL, OMIM: 615558)

**Bi-allelic FHBL-SD2** is caused by pathogenic variants in the *APOB* gene resulting in the synthesis of truncated apoB peptides. Some mutations affect the synthesis of both apoB100 and apoB48, whereas others only affect synthesis of apoB100. Low plasma lipids result due to the inability of the smaller peptides to assemble normal lipoproteins. In the case of larger truncated apoB peptides that can assemble lipoproteins, these lipoproteins are cleared rapidly contributing to hypolipidemia. FHBL-SD2 is an autosomal semi-dominant disease, which means that individuals with one variant allele (i.e. monogenic or "heterozygotes") have a detectable phenotype that is intermediate between individuals with two normal alleles and those with bi-allelic pathogenic variants. The clinical and biochemical presentation of FHBL-SD2 (homozygous or compound heterozygous pathogenic variants of *APOB*) is virtually indistinguishable from FHBL-SD1 (Table 2). Parents of affected individuals possess lipid profile alterations consistent with the heterozygous FHBL-SD2 phenotype, i.e. their lipid levels are intermediate between normal and homozygous FHBL-SD2 individuals. If available, this information may help discern between FHBL-SD1 (*MTP* pathogenic variants) and homozygous FHBL-SD2 (*APOB* pathogenic variants)<sup>76</sup>. Early detection and treatment are needed in FHBL-SD2 to prevent the profound multi-organ dysfunction similar to that outlined for FHBL-SD1. In order to definitively distinguish between FHBL-SD1 and homozygous FHBL-SD2, molecular testing by sequencing the



*MTTP* and *APOB* genes is required<sup>37,77</sup>. Definitive diagnosis of homozygous and heterozygous FHBL-SD2 is further confirmed by sequencing the *APOB* gene: bi-allelic (i.e. true homozygous or compound heterozygous) pathogenic variants indicate the more severe form encompassed by the term “homozygous FHBL” whereas those with a single variant allele are called “heterozygous FHBL”.

**Mono-allelic FHBL-SD2** is relatively common, with a prevalence of 1 in 700 to 3000 based on observed and estimated reports<sup>78</sup>. Peloso et al. report an observed prevalence of *APOB* protein-truncating variants in 0.092% of controls<sup>79</sup>. In contrast to homozygotes, heterozygous FHBL-SD1 are often asymptomatic. Affected individuals have no concerns related to fat-soluble vitamin deficiencies including vitamin E, despite some having very low levels of apoB. Patients have low, but not absent LDL-C. Low LDL-C is defined as <5<sup>th</sup> percentile for age and sex, as derived from National Health and Nutrition Examination Survey data<sup>80</sup>. Due to the decreased hepatic secretion of apoB and TG, an increased incidence of hepatic steatosis and mild elevation in plasma liver enzymes has been reported<sup>55,81</sup>. Furthermore, the clinical expression may depend on the size of the truncated apoB species. Kindreds with short truncated apoB isoforms developing steatosis<sup>82</sup> and cryptogenic cirrhosis have been reported<sup>83</sup>. Some of the clinical and serologic evaluations listed in (Table 3) may also be appropriate for individuals with a more severe presentation of heterozygous FHBL-SD2<sup>78,81,84</sup>. Interestingly, these individuals appear to be protected from cardiovascular disease (CVD)<sup>79</sup>.

### Blood metabolites

ApoB-containing lipoproteins are virtually absent in the plasma of individuals with homozygous FHBL-SD2<sup>27</sup>. Lipid soluble vitamins are very low, particularly vitamin E and A. EFAs are also dramatically decreased, especially ALA. ApoB100 and LDL-C levels in heterozygous FHBL-SD2 plasma are ~24% of those in normal individuals, although the range is wide<sup>80,85</sup>. Variations in lipoprotein profiles between different families have also been reported<sup>86</sup>.

### Familial hypobetalipoproteinemia due to lipoprotein assembly and secretion defect 3 (FHBL-SD3), commonly known as chylomicron retention disease (CRD, OMIM: 246700)

FHBL-SD3 is an extremely rare disease with a few small cohorts described<sup>89-103</sup>. It is due to bi-allelic pathogenic variants in the *SAR1B* gene causing a defect in chylomicron secretion by the intestine. Chylomicrons are assembled in enterocytes, but are not secreted. Heterozygotes for a single pathogenic variant are typically clinically unaffected carriers.

### Gastrointestinal

As with FHBL-SD1 and homozygous FHBL-SD2, gastrointestinal symptoms are observed at the beginning of life. Diarrhea and malabsorption begin in infants shortly after

birth. Other digestive symptoms, such as vomiting or abdominal distension are often present. This malabsorption induces a rapid alteration of the nutritional status with stunting and growth delay in toddlers. Symptoms improve within a few days or weeks with a low-fat diet<sup>100</sup>. Endoscopy reveals white mucosa and lipid laden enterocytes on histology. Although less commonly seen compared to FHBL-SD1 and homozygous FHBL-SD2, hepatomegaly and steatosis is reported to occur in about 20% of FHBL-SD3 patients. No cases of cirrhosis in FHBL-SD3 have been reported to date<sup>83,95,100,104,105</sup>.

### Neurologic

Neurological aberrations, including proprioceptive abnormalities and areflexia, appear only in older children and adolescents, and differentiate this disorder from FHBL-SD1 and homozygous FHBL-SD2. The mean age for the development of neurological abnormalities in FHBL-SD3 is 12 years. Vitamin E status is considered to play a pivotal role in neurological degenerative complications<sup>106,107</sup>. In the largest pediatric cohort, patients with the most severe symptoms also had the lowest vitamin E levels at diagnosis<sup>89</sup>. Severe degenerative symptoms, such as ataxia and sensory neuropathy, have been reported only in a few FHBL-SD3 adults<sup>93,100,101,108</sup>.

### Musculoskeletal

Muscular pain and cramps are possible, but rarely reported by patients. Poor mineralization and delayed bone maturation have been observed potentially as a consequence of malabsorption, malnutrition and vitamin D deficiency<sup>89</sup>.

### Ophthalmologic

Minimal visual abnormalities have been reported in older children with FHBL-SD3, such as nystagmus, mild deficits in the perception of the blue-yellow axis and delayed dark adaptation<sup>100</sup>.

### Blood metabolites

A decrease (~50%) in total cholesterol, LDL-C and HDL-C in the presence of normal TG is a characteristic diagnostic feature of FHBL-SD3<sup>109-113</sup>. In comparison, both FHBL-SD1 and homozygous FHBL-SD2 are associated with a very low plasma TG concentration and undetectable LDL-C (Table 2). Lipid soluble vitamins including vitamin E and A as well as EFAs are dramatically reduced. Unlike the other FHBL disorders; creatine kinase (CK) is selectively elevated in FHBL-SD3. The CK increase is 5-10 times the upper reference limit in some patients and may support the diagnosis<sup>89</sup>. The CK concentration, however, does not correlate well with the severity of the muscular impairment. Finally, acanthocytosis is rare and often transient in FHBL-SD3<sup>89</sup>.

**Table 3** Treatment and dietary guidance for Class 1 disorders.

<sup>1</sup> Annual assessment	
Growth parameters	Height and weight comparison with normal growth charts (as appropriate for age)
Neurologic	Examination with emphasis on cranial nerves, motor and sensory/proprioception, cerebellar, deep tendon reflexes
Ophthalmologic	Fundoscopy
Gastrointestinal	Abdominal distension, hepatomegaly, jaundice
<sup>2</sup> Plasma laboratory tests	Lipid panel, apoB, apoA-I, albumin, liver enzymes, bilirubin, gamma-glutamyl transferase, 25-hydroxy vitamin D, vitamin A, vitamin E, INR, vitamin B12, folate, CBC, reticulocyte count, ferritin, calcium, phosphorus, creatinine, thyroid stimulating hormone
<sup>3</sup> Additional Testing	
Electromyography	
Electroretinography and electro-oculogram	
Ultrasonography of liver; FibroScan/Fibrosis-4 (FIB 4) index	
Bone mineral density testing (DXA)	
Echocardiogram	
<b>Dietary guidance</b>	
Fat calories	Less than 10-15% (<15 g/day) of total daily caloric requirement In infants limit to 5-10% of total calories Amount of dietary fat intake may be increased as tolerated in older children and adults
Essential fatty acids	Ensure 2-4% daily caloric intake of EFAs (alpha-linolenic acid/linoleic acid)
Long chain fatty acids	Not recommended apart from EFAs. Supplementation with DHA and EPA may be considered while monitoring total daily fat intake
Medium chain triglycerides	May prevent or treat malnutrition in infants. Individual assessment of potential benefit is needed. MCT (caprylic and capric acids) provides 8.3 calories/g (14.25 g = 1 tablespoon = 15 ml = 115 kcal). Lauric acid is not recommended.
<b>Vitamin treatment guidance</b>	
<sup>4</sup> Vitamin E	100-300 IU/kg/day (50 IU/kg/day for FHBL-SD3 if diagnosed by age 1)
Vitamin A	100-400 IU/kg/day
Vitamin D	800-1200 IU/day
Vitamin K	5-35 mg/week

<sup>1</sup>Physical and biochemical tests are suggested components of the annual assessment and are not comprehensive.

<sup>2</sup>Lipid panel, apoB, apoA-I do not require repetitive assessment following diagnosis. Plasma vitamin E levels may be measured at time of diagnosis; however, should not be serially monitored as they are not reflective of physiologic homeostasis. Erythrocyte and/or adipose tissue vitamin E level should be measured if possible. (See section 7.2).

<sup>3</sup>Testing is recommended at time of diagnosis or early in the course of the disease and will establish a baseline. Additional testing as clinically indicated to assess for disease stability and/or progression.

<sup>4</sup>Intramuscular injections of 50 mg alpha-tocopherol can be administered once or twice weekly if needed<sup>125</sup>.

## Diagnosis and assessment of class II disorders

### Familial hypobetalipoproteinemia due to enhanced lipoprotein catabolism (FHBL-EC1), commonly known as familial combined hypolipidemia (FCHL, OMIM: 605019)

Hypolipidemia in these individuals is due to enhanced catabolism of lipoproteins resulting from loss-of-function variants in *ANGPTL3* gene. Those with FHBL-EC1 do not have defects in fat and fat-soluble vitamin absorption and transport. Therefore, symptoms associated with fat-soluble vitamin or EFA deficiency are not present<sup>87</sup>. This condition is due to increased hepatic clearance of circulating lipoproteins as a result of increased lipolysis of VLDL. Furthermore, loss-of-function of the *ANGPTL3* gene seems beneficial<sup>114,115</sup>. The lower plasma concentrations of cholesterol and TG likely reduce the risk of developing atherosclerotic

CVD<sup>116</sup>. Despite the presence of low HDL-C concentrations, FHBL-EC1 patients are protected from developing premature atherosclerosis likely due to the concomitant reduction in atherogenic VLDL and LDL. This protective effect has led to the development of a biologic targeting *ANGPTL3*<sup>117</sup>.

### Blood metabolites

Compared to normal individuals, reduction of all plasma lipoproteins and apolipoproteins is seen for both homozygous and heterozygous FHBL-EC1. Bi-allelic *ANGPTL3* pathogenic variants have been shown to have significant reductions in LDL-C, TG, HDL-C, apoB, and apoA-I compared to individuals with two normal alleles<sup>41,118</sup>. Heterozygous individuals show less reduction in plasma LDL compared to homozygous FHBL-EC1<sup>41</sup>. Thus, there is a gene dosage effect (Table 2).

**Table 4** Questions and topics requiring further investigation.**Disease characterization**

- Development of a universal registry for FHBL Class 1 patients and other hypobetalipoproteinemia disorders cataloging demographic, clinical and biochemical data
- Focus on the peripartum period to increase knowledge and improve clinical recommendations
- Determine long term health outcomes in patients adhering to suggested vitamin and dietary interventions
- Preclinical proof of concept research followed by clinical studies demonstrating the clinical efficacy of EFA, DHA and EPA
- Reasons for elevated CK levels in FHBL-SD3 patients
- Development and natural history of hepatic steatosis in heterozygous FHBL-SD2 patients

**Mechanisms of disease and treatment**

- How are fat-soluble vitamins absorbed in patients after oral ingestion of megadoses? Identification and upregulation of these mechanisms may help enhance fat-soluble vitamin absorption
- Role of intestinal HDL in fat-soluble vitamin absorption
- Evaluating new formulations and routes of vitamin delivery to improve systemic delivery and efficacy

**Treatment standardization**

- Identification of clinically feasible and accurate markers of vitamin E status
- Standardization of vitamin E measurement and treatment targets

**Quality of life**

- Integration of social services and other supportive measures aimed to improve health-related quality of life (e.g. very low fat meal recipes)

**Familial hypobetalipoproteinemia due to enhanced lipoprotein catabolism 2 (FHBL-EC2)**

Similar to FHBL-EC1, FHBL-EC2 is also not associated with intestinal malabsorption, fat-soluble vitamin or EFA deficiency. This phenotype results from loss-of-function variants in the *PCSK9* gene, which results in increased clearance of LDL particles by LDL receptors. Patients have low, but detectable LDL-cholesterol without any deleterious systemic involvement. In fact, loss-of-function in *PCSK9* confers substantial protection against coronary atherosclerosis<sup>88</sup>. Extremely rare individuals with bi-allelic loss-of-function variants in *PCSK9* have very depressed levels of LDL-C and apoB containing lipoproteins, but also have no adverse effects<sup>14,88,119-121</sup>. Based on these observations, therapies inhibiting *PCSK9* are available to lower LDL-C levels<sup>122-124</sup>.

**Blood metabolites**

Depending on the type and number of sequence variations, LDL-C concentrations in patients with FHBL-EC2 are 21-40% lower than normal levels (Table 2)<sup>88</sup>.

**Treatment of FHBL Class 1 patients with defects in lipoprotein assembly and secretion**

As previously mentioned, randomized clinical trial evidence is not available to direct the treatment of FHBL Class 1 patients. The following treatment summary, derived from the research and clinical expertise of the ABLRDF medical expert panel, is intended to minimize risk and improve the

well-being of patients. Table 3 shows a framework for clinical assessment, treatment and dietary guidance. The mainstay of treatment for Class 1 disorders consists of three major components: (a) restriction of dietary fat consumption to minimize the steatosis of enterocytes and restore their normal function; (b) consumption of therapeutic doses of fat-soluble vitamins, especially large doses of vitamin E, and; (c) adequate intake of EFAs and micronutrients. All recommendations are best applied with the assistance of a registered dietitian or a specialized provider knowledgeable about FHBL disorders. An emphasis on maintenance of care and adequate follow up is a consequential component of the treatment plan. The gradual progressive nature of FHBL Class 1 disorders requires careful and chronic clinical assessments. Clinical status should direct the frequency of diagnostic testing and intensity of intervention. As such, patient engagement with the healthcare system is essential to maximize outcomes.

**Dietary recommendations**

A very-low fat diet is required in order to alleviate gastrointestinal symptoms and to address failure to thrive in infancy. Breast milk and traditional infant formulas contain a high content of long chain triglycerides (LCT) and are not recommended. A medium chain triglyceride (MCT) commercial formula or skimmed and fortified breast milk (if MCT formula is not available) is preferred. MCT oil, including caprylic acid (8 carbon atoms) and capric acid (10 carbon atoms), bypass the chylomicron fat metabolism pathway and has been successful in several disease states that also re-

quire a very-low fat intake including familial chylomicronemia syndrome and cystic fibrosis<sup>126,127</sup>. The infant formula Monogen (Nutricia) is favored as it contains 90% of its fat content as MCT. The remaining 10% of the fat composition includes arachidonic acid, monounsaturated fatty acids and polyunsaturated fatty acids (including LA, ALA and docosahexaenoic acid (DHA)).

Transitioning from formula to skim milk and low-fat solid foods is advised according to developmental stage. Infants should be restricted to 5-10% of calories from fat while ensuring adequate caloric intake. The amount of dietary fat can be increased with age, as tolerated, but should not exceed 10-15% of total daily caloric intake. Distribution of fat intake throughout the day may minimize symptoms and aid in overall nutrient absorption. Dietary fat intake should be tailored within this framework based on age and caloric needs. Nutrient dense foods as a source of vitamins and minerals should be incorporated within a very-low fat diet. Meal plans that incorporate vegetables, whole grains, proteins, legumes, fruit, and fat-free milk products are encouraged. Psychosocial support may be required with heightened attention for the development of disordered eating patterns. Dietitian consultation is essential for the proper implementation of these recommendations.

Incorporation of EFAs, LA and ALA, to prevent EFA deficiency should be considered. Whole grains, chia seeds, ground flaxseeds as well as 1-2 teaspoons of oils rich in polyunsaturated fatty acids (i.e. flaxseed, soybean oil) are examples of food sources rich in EFAs. Infants whose diet is based on Monogen do not require additional EFA.

The use of prescription grade eicosapentaenoic acid (EPA) and DHA, has been inconsistently recommended in the literature. In alignment with the experience of ABLRDF panel members, controlled quantities (1-3 g/day) of these fatty acids can increase their plasma concentrations. The fat content of EFAs, DHA and EPA supplements should be carefully monitored to avoid exceeding the total daily fat threshold. Additionally, intake of omega-3 polyunsaturated fatty acids varies significantly worldwide, necessitating the need to devise separate dietary recommendations for different countries<sup>51</sup>.

Our panel recommends that the use of MCT oil in FHBL Class I be tailored to the individual<sup>126-128</sup>. MCT oil may be used to increase overall caloric intake particularly in infancy and possibly in pregnancy. It may also improve satiety and help adjust the macronutrient composition of the diet, preventing excessive reliance on carbohydrates in older patients. Importantly, only medical grade MCT oil available via prescription should be used and not over the counter formulations (i.e. coconut oil) that may contain lauric acid (12 carbon atoms), which possesses metabolic properties similar to long chain fatty acids<sup>129</sup>. Gradual introduction of small amounts of MCT oil for low temperature cooking or for supplementation at meals has been utilized in other disease states requiring a very low fat diet<sup>126</sup>. Large doses of MCT oil are neither necessary nor recommended.

## Fat-soluble vitamins

Treatment with high dose fat-soluble vitamins is critical for the prevention of complications. In particular, vitamin E has no carrier protein in plasma and is highly dependent on lipoproteins for intestinal absorption and transport. Over four decades ago, Dr. Herbert Kayden and others recognized that high daily dosages of vitamin E can prevent retinal and neurological adverse effects<sup>69,130,131</sup>. An exceptionally high dose of vitamin E (100-300 IU/kg/day), compared to the recommended dietary allowance for age of 5-30 IU/day in healthy individuals, is required to halt the progression and potentially reverse the neurologic and ophthalmologic sequelae mentioned previously. Similarly, high dose vitamin A (100-400 IU/kg/day), approximately five times the recommended dietary allowance for age, is required<sup>69,76</sup>. Lower doses of vitamin E and vitamin A may be needed for FHBL-SD3 if diagnosed by age 1 (Table 3). Vitamin K levels are less compromised than that of other fat-soluble vitamins in FHBL; however, relatively high oral doses (5-35 mg/week) may be needed. Almost all patients with a Class 1 disorder have shown clinical stabilization with oral vitamin treatment; therefore, parenteral treatment is not generally recommended<sup>37</sup>.

Dosing of vitamin A, D and K can be tailored to plasma vitamin A/ $\beta$ -carotene, 25-hydroxy vitamin D and INR reference intervals, respectively. There are no reliable and easy to perform assays to monitor vitamin E absorption and efficacy. It is widely accepted that neither serum nor plasma vitamin E levels accurately portray vitamin E status. If available, one approach has been to measure erythrocyte tocopherol concentrations. Kayden et al. have reported that the spectrophotometric determination of total tocopherol in erythrocytes is a reproducible method in patients with ABL<sup>132</sup>. In another study, erythrocyte vitamin E levels significantly increased following four months of oral vitamin E treatment (50 IU/kg/d), in FHBL-SD1 and FHBL-SD3 patients, but plasma vitamin E remained very low<sup>133</sup>. Additionally, vitamin E levels in subcutaneous adipose tissue aspirates may be a better representative of whole body status and should be evaluated whenever possible<sup>134</sup>. Data derived from larger cohorts is needed to better assess vitamin E absorption, distribution and remission of symptoms with treatment.

Vitamin E is available in both water and fat-soluble formulations. Limited evidence for the preferred use of one over the other is available based on laboratory testing. Cuerq and colleagues found initial increased bioavailability of tocopherol (a water-soluble derivative of RRR- $\alpha$ -tocopherol) compared with  $\alpha$ -tocopherol acetate (form of fat-soluble vitamin E) in patients with CRD, but not in ABL. At four months, no differences in concentration were observed for patients with either CRD or ABL<sup>133</sup>. In keeping with available evidence, our panel does not advocate for the use of a specific vitamin formulation.

Further complicating the management of vitamin E in Class I disorders is the substantial pill burden. Together with

the other required fat soluble vitamins, the number of daily pills needed to satisfy weight based dose ranges in adulthood is onerous. Because vitamin E deficiency strongly influences patient outcomes and until more efficient treatment methods are available, care to reach dose requirements is critical. Findings from the ophthalmologic and neurologic examination should be used to gauge treatment efficacy and prompt clinical decision making including vitamin dosage adjustments.

In all, the ABLRDF medical advisory panel attests that treatment with fat-soluble vitamins is a medical necessity for Class 1 disorders and advocates for third-party payer coverage. It is the experience of the medical advisory panel that patients without adequate insurance coverage succumb to irreversible progressive morbidities.

## Considerations in pregnancy

Although not systematically evaluated, some men and women with FHBL-SD1 have been shown to be fertile and have completed successful pregnancy and delivery. There is, however, a need for more comprehensive studies to determine fertility in all patients. A multidisciplinary approach to family planning in FHBL Class 1 disorders is favored, including genetic counseling<sup>135</sup>. This will help inform the probability of disease occurrence in the offspring and expand the discussion regarding pregnancy management, including reproductive options. The significance of this counseling is further supported by the availability of effective interventions that may change management should issues arise with respect to conception, pregnancy complication or symptoms in the newborn.

The menstrual pattern is normal in FHBL-SD1. FHBL-SD1 women show normal mid-cycle increases in estrogen, prolactin, as well as luteinizing and follicle stimulating hormones. However, distinctly subnormal increases in luteal phase concentrations of progesterone have been reported<sup>136,137</sup>. This may be secondary to the absence of LDL<sup>136,137</sup>. Insufficient placental biosynthesis of progesterone in patients with FHBL-SD1 has also been reported<sup>136</sup>. For individuals with a Class 1 disorder, we recommend monitoring of progesterone levels throughout pregnancy and consider the use of exogenous progesterone.

The expertise of a lipidologist in conjunction with a registered dietitian is recommended to reconcile a very low fat diet while supporting the increased caloric demands throughout the course of pregnancy. If required, MCT oil may serve as a readily absorbed source of calories. As previously mentioned, careful introduction of MCTs into the diet is required to avoid gastrointestinal discomfort owing to its high osmolarity. If needed, doses of 4-6 tablespoons (385-765 calories) over the course of the day have been shown to be tolerated in other disease states<sup>128</sup>. MCT oil is not a source of EFA. Maternal serum DHA concentration has been correlated to neurocognitive and anti-inflammatory benefits during pregnancy<sup>138</sup>. It is the experience of the ABLRDF panel that

supplementation with DHA (1-3 g/day) can improve plasma concentrations in some FHBL Class 1 disorders. Nevertheless, dosing strategies shown to influence neurodevelopment in the context of FHBL Class 1 disorders are not available. Consistent with the US Preventive Services Task Force recommendation to prevent neural tube defects in pregnancy, a daily supplement of 400-800 µg folic acid is also advised<sup>139</sup>.

Special considerations surrounding the high doses of fat-soluble vitamins in these disorders are warranted. Postpartum hemorrhage due to vitamin K deficiency has been demonstrated as a significant cause for maternal morbidity in FHBL-SD1<sup>140</sup>. Vitamin K deficiency in the fetus may lead to neonatal bleeding and intracranial hemorrhage<sup>141</sup>. An effort to normalize vitamin K levels and INR prior to conception with close surveillance throughout pregnancy is recommended. In addition, vitamin D deficiency in the mother may contribute to fetal hypocalcemia, impaired bone mineralization and enamel defects<sup>142</sup>. Maternal low vitamin A levels have been associated with bilateral ocular colobomata in the infant<sup>141</sup>. Nevertheless, because excess vitamin A can cause toxicity in normal individuals, previous reports have recommended setting a vitamin A goal at the lower limit of normal levels with consideration to reduce the dose by 50% in pregnancy<sup>48,51,143</sup>. Vitamin E supplements should be continued during pregnancy as its deficiency has been shown to increase miscarriages<sup>144</sup>.

## Future work

This manuscript addresses monogenic hypobetalipoproteinemia disorders and their inherent diagnostic and management challenges. Continued work in this area and, in particular surrounding the matters outlined in (Table 1) remains a priority of ABLRDF. Other unresolved issues that require exploration were identified (Table 4). Advances in the preclinical and clinical understanding of pathophysiology will clarify optimal treatment modalities for hypobetalipoproteinemia disorders and likely other conditions of fat malabsorption. Additionally, given the complexity of the problem, strategies to better implement system-based practices that provide social support are warranted. Finally, there is a need for an international registry and collaboration surrounding these rare diseases.

## Conclusions

Early diagnosis, appropriate dietary interventions and sufficient fat-soluble vitamin intake aligned with rigorous follow-up by a multidisciplinary team can lead to successful management of Class I FHBL and other hypobetalipoproteinemia disorders. In this respect, heightened physician awareness and experience managing these disorders is essential. Adequate insurance coverage for fat-soluble vitamins, MCT formulations and regular physical assessments remain an unmet need in this vulnerable population. The ABLRDF

medical advisory panel strongly advocates that fat-soluble vitamins be regarded as medical therapies, and not as dietary supplements, proven to prevent progressive morbidities. Additionally, there is a need for preclinical, clinical and health system research to better understand and document symptoms, pathophysiology and clinical outcomes following therapeutic interventions. It is anticipated that increased knowledge of these understudied disorders and improved access to proper medical care will greatly improve the lives of patients and their families.

## Disclosures

**DB:** Consultant: Intercept Pharmaceuticals; **MB:** Employment: AbbVie; **IG:** Scientific advisory boards: Ionis and Arrowhead; **RAH:** Consultant: Acasti, Aegerion, Akcea/Ionis, Amgen, Arrowhead, Boston Heart, HLS Therapeutics, Novartis, Pfizer, Regeneron, Sanofi and Ultragenyx; **HO:** Scholarship grants: Minophagen Pharmaceutical Co., Ltd., Kowa Company, Ltd., and Tosoh Corporation; **DR:** Scientific advisory boards: Alnylam, Novartis, Pfizer, and Verve. All other authors report no disclosures.

## Authors' contribution

CB, MMH, MDF, NP wrote the original draft of the manuscript. Each author made significant intellectual contributions to the manuscript and participated in the editing and revising process. All authors read and approved the final manuscript.

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