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APOB-Related Familial Hypobetalipoproteinemia

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Summary

Clinical characteristics

Individuals with biallelic *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) may present from infancy through to adulthood with a range of clinical symptoms including deficiency of fat-soluble vitamins and gastrointestinal and neurologic dysfunction. Affected individuals typically have plasma total cholesterol, LDL cholesterol, and apo B levels below the fifth centile for age and sex. Acanthocytosis, elevated liver enzymes, and hyperbilirubinemia may also be found. The most common clinical findings are hepatomegaly, steatorrhea, and failure to thrive / growth deficiency. In the absence of treatment, affected individuals can develop atypical pigmentation of the retina; progressive loss of deep tendon reflexes, vibratory sense, and proprioception; muscle pain or weakness; dysarthria; ataxia; tremors; and steatohepatitis, fibrosis, and rarely, cirrhosis of the liver.

Individuals with a heterozygous, typically truncating pathogenic variant in *APOB* are usually asymptomatic with mild liver dysfunction and hepatic steatosis. However, about 5%-10% of individuals with heterozygous *APOB*-FHBL develop relatively more severe nonalcoholic steatohepatitis requiring medical attention and occasionally progressing to cirrhosis, albeit very rarely.

Diagnosis/testing

The diagnosis of biallelic *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) or heterozygous *APOB*-FHBL is established in a proband with either biallelic or a heterozygous pathogenic variant(s), respectively, in *APOB* identified by molecular genetic testing

Management

Treatment of manifestations:

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- Individuals with biallelic *APOB*-FHBL: low-fat diet (<30% of total calories) while ensuring adequate caloric intake; high-dose oral fat-soluble vitamin supplementation (vitamin E: 100-300 IU/kg/day; vitamin A: 100-400 IU/kg/day; vitamin D: 800-1200 IU/day; vitamin K: 5-35 mg/week); consideration of oral essential fatty acid supplementation; liver transplantation may be considered for those with end-stage liver disease; standard treatment for ataxia, dysarthria, and loss of night and/or color vision and scotomas; no treatment is typically required for anemia/hemolysis.
- Individuals with heterozygous *APOB*-FHBL: no treatment typically required.

Prevention of primary manifestations: Adoption of a low-fat diet (<30% of total calories) and high-dose oral fat-soluble vitamin supplementation may ameliorate or prevent clinical features of *APOB*-FHBL.

Surveillance:

- Individuals with biallelic *APOB*-FHBL: measurement of growth parameters and assessment for new or progressive signs/symptoms of gastrointestinal issues every 6-12 months; laboratory studies to include lipid profile, liver function tests, vitamin levels, INR, calcium, phosphorus, uric acid, CBC, vitamin B_{12}, folate and TSH every 1-2 years; ophthalmology evaluation and neurologic examination every 6-12 months after age 10 years; hepatic ultrasound and bone mineral densitometry studies every 3-5 years after age 10 years.
- Individuals with heterozygous *APOB*-FHBL: laboratory studies to include lipid profile and liver function tests every 1-2 years; hepatic ultrasound every 3 years after age 10 years in those with elevated liver transaminases.

Agents/circumstances to avoid: Individuals with biallelic *APOB*-FHBL should avoid fatty foods. No dietary restrictions are typically required for those with heterozygous *APOB*-FHBL.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with biallelic *APOB*-FHBL in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include a full lipid profile (including apo B concentration) and/or molecular genetic testing for the *APOB* pathogenic variant(s) identified in the proband.

Pregnancy management: Vitamin A excess can be harmful to the developing fetus. Therefore, women who are pregnant or are planning to become pregnant should reduce their vitamin A supplement dose by 50%. Additionally, close monitoring of serum vitamin A levels throughout pregnancy is recommended. Because vitamin A is an essential vitamin, however, vitamin A supplementation for affected women should not be discontinued during pregnancy.

Genetic counseling

APOB-related familial hypobetalipoproteinemia (*APOB*-FHBL) caused by homozygous (or compound heterozygous) pathogenic variants in *APOB* is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being heterozygous for *APOB*-FHBL and having laboratory findings and (rarely) clinical features, and a 25% chance of being unaffected and not a heterozygote. Heterozygote testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic *APOB* variants in the family are known.

GeneReview Scope

APOB-Related Familial Hypobetalipoproteinemia (FHBL): Included Phenotypes [1]
• Biallelic *APOB*-related FHBL (also referred to as homozygous [or compound heterozygous] FHBL) • Heterozygous *APOB*-related FHBL

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

In this *GeneReview*:

- Biallelic *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) refers to hypocholesterolemia, low plasma LDL cholesterol, and low apolipoprotein (apo) B levels leading to clinical signs and symptoms in untreated individuals who have homozygous or compound heterozygous pathogenic variants in *APOB* that affect the structural integrity of apo B.
- Heterozygous *APOB*-FHBL refers to individuals who have primarily asymptomatic hepatic steatosis with rare clinical symptoms due to a heterozygous, typically truncating pathogenic variant in *APOB*.
- Note: Both heterozygous and biallelic pathogenic variants in *APOB* can also lead to familial hypercholesterolemia (see Genetically Related Disorders). However, the *APOB* pathogenic variants that cause familial hypercholesterolemia are typically located within the LDL receptor binding domain.

Suggestive Findings

Biallelic *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) **should be suspected** in individuals with the following clinical features and supportive laboratory findings.

Clinical findings

- Failure to thrive, with diarrhea
- Fat malabsorption with steatorrhea
- Acquired atypical pigmentation of the retina
- Ataxia with or without absent reflexes
- Hepatomegaly
- Hepatic steatosis

Supportive laboratory findings

- Marked hypocholesterolemia (total cholesterol ~1.0 mmol/L [40 mg/dL])
- Plasma LDL cholesterol (measured or calculated) absent or extremely low
- Plasma apo B absent or very low
- Plasma triglyceride very low
- Plasma HDL cholesterol at a low to average level
- Acanthocytosis
- Abnormal liver transaminases (ALT and AST 1-1.5x the upper reference limit)
- Prolonged international normalized ratio (INR)
- Low serum concentrations of fat-soluble vitamins (A, D, E, and K)

Heterozygous *APOB*-FHBL **should be considered** in individuals with the following laboratory, imaging, and family history findings:

- **Laboratory findings**
  - Plasma total cholesterol level below the 5th percentile for age and sex (~3.0 mmol/L [115 mg/dL])
  - Plasma LDL cholesterol level below the 5th percentile for age and sex (~1.3 mmol/L [50 mg/dL])
  - Plasma apo B level below the 5th percentile for age and sex (~0.5 g/L)
  - Plasma triglyceride level less than 0.5 mmol/L (45 mg/dL)
  - Elevated liver enzymes (AST and ALT) in an otherwise asymptomatic individual
- **Liver ultrasound.** Increased fat content consistent with hepatic steatosis
- **Family history.** First-degree relatives with asymptomatic hepatic steatosis and/or hypocholesterolemia

  Note: Absence of a known family history of first degree relatives with asymptomatic hepatic steatosis and/or hypocholesterolemia does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of biallelic *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) or heterozygous *APOB*-FHBL **is established** in a proband with either biallelic or a heterozygous pathogenic (or likely pathogenic) variant(s), respectively, in *APOB* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of an *APOB* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

When the phenotype and laboratory findings suggest the diagnosis of *APOB*-FHBL, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing. Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

- Perform sequence analysis first.
- If no pathogenic variant or only one pathogenic variant is identified in a symptomatic individual, consider gene-targeted deletion/duplication testing.
- If no pathogenic variant is identified in an asymptomatic individual who has suggestive laboratory, imaging, and/or family history findings, consider gene-targeted deletion/duplication testing.

A multigene panel that includes *APOB* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that include genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in *APOB*-Related Familial Hypobetalipoproteinemia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
APOB	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Tarugi et al [2007]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Large deletions/duplications are very rare [Huang et al 1989].

Clinical Characteristics

Clinical Description

The clinical features of individuals with biallelic *APOB*-related familial hypobetalipoproteinemia (sometimes referred to as homozygous or compound heterozygous *APOB*-FHBL) may resemble those of abetalipoproteinemia, particularly in individuals with truncating *APOB* pathogenic variants shorter in length than apoB-48 (see Genotype-Phenotype Correlations and Molecular Genetics).

Biallelic *APOB*-FHBL

Individuals with biallelic *APOB*-FHBL may present from infancy through to adulthood with a range of clinical symptoms including deficiency of fat-soluble vitamins and gastrointestinal and neurologic dysfunction. However, in contrast to abetalipoproteinemia (mean age of diagnosis 3.8 years), individuals with *APOB*-FHBL can have milder symptoms, and most are diagnosed in adulthood (mean age of diagnosis: 21 years) [Di Filippo et al 2014].

Table 2. Biallelic *APOB*-Related Familial Hypobetalipoproteinemia: Frequency of Select Features

Feature	Frequency		
	Nearly all	Common	Infrequent
Hepatomegaly	●		
Hepatic steatosis	●		
Deficiency in fat-soluble vitamins	●		
Acanthocytosis	●		
NASH/Fibrosis		●	
Steatorrhea/Diarrhea		●	
Fat malabsorption		●	
Failure to thrive		●	
Ophthalmologic impairment		●	
Peripheral neuropathy		●	

Table 2. continued from previous page.

Feature	Frequency		
	Nearly all	Common	Infrequent
Cirrhosis			●

NASH = nonalcoholic steatohepatitis
This table refers only to clinical features in those individuals with biallelic *APOB* pathogenic variants.

Gastrointestinal. Steatorrhea is the primary gastrointestinal manifestation. It can be present starting in infancy and throughout childhood. The severity relates to the fat content of the diet:

- As affected individuals age, they learn to avoid dietary fat, which improves steatorrhea.
- Global caloric deficiency is associated with delayed growth trajectory, with both height and weight typically below the tenth centile without intervention.
- Fat-soluble vitamin malabsorption is severe, and if untreated can lead to irreversible systemic features that affect the eyes (see **Ophthalmologic** below), bones (decreased bone mineral density), and nervous system (see **Neuromuscular** below).
- Hepatic involvement as identified on laboratory studies is frequently stable over many years and may not evolve to be clinically significant.
- Hepatomegaly and hepatic steatosis can be observed in adulthood, and may subsequently progress to steatohepatitis, fibrosis, and (rarely) cirrhosis or (in extremely rare instances) hepatocellular carcinoma.

Endoscopic findings. On a typical diet (e.g., no dietary fat restriction), the intestinal mucosa may have a "gelee blanche" or "white hoar frosting" appearance on endoscopy. Biopsy of the intestinal epithelium may demonstrate lipid-laden epithelial cells.

Hematologic manifestations of biallelic *APOB*-FHBL include the following:

- Acanthocytosis, defined as irregularly spiculated erythrocytes (present from birth)
- Low erythrocyte sedimentation rate
- Low-grade anemia
- Reticulocytosis
- Hyperbilirubinemia
- Hemolysis
- Prolonged INR due to vitamin K deficiency, with easy bruising and prolonged bleeding (present in childhood)

Ophthalmologic manifestations of biallelic *APOB*-FHBL are variable, with the most prominent being an atypical pigmentation of the retina, which can be arrested (though not reversed) with high-dose vitamin A supplementation (see Treatment of Manifestations). However, the eye findings can be averted altogether with early diagnosis and treatment.

- Many affected individuals are asymptomatic until adulthood, when they experience loss of night vision and/or color vision.
- As the disease progresses, affected individuals may experience progressively expanding scotomas.
- Without treatment, progression to complete visual loss may occur.

Note: It is hypothesized that the possible cause of the ophthalmoplegia is vitamin E deficiency leading to cranial nerve demyelination.

Neuromuscular. If untreated, neuromuscular manifestations of biallelic *APOB*-FHBL secondary to the deficiency of vitamin E typically begin in the first or second decade of life. Symptoms include the following:

- Progressive loss of deep tendon reflexes, vibratory sense, and proprioception
- Muscle pain or weakness
- Dysarthria
- Ataxia, broad-based gait
- Tremors

Similar to the ophthalmologic manifestations, the neuromuscular manifestations can also be arrested but not reversed with vitamin supplementation. However, they can be averted altogether with early diagnosis and treatment**.**

Prognosis. In the past, without high-dose fat-soluble vitamin supplementation, affected individuals would typically not survive past the third decade of life, dying with severe neuromyopathy and respiratory failure. With lifelong high-dose oral fat-soluble vitamin treatment, longevity into the seventh and eighth decade of life with relatively minimal symptoms has been observed over 40 years in affected individuals [Dr Robert Hegele, unpublished observations].

Heterozygous *APOB*-FHBL

Individuals with a heterozygous, typically truncating pathogenic variant in *APOB* are usually asymptomatic with mild liver dysfunction and hepatic steatosis. However, about 5%-10% of individuals with heterozygous *APOB*-FHBL develop relatively more severe nonalcoholic steatohepatitis requiring medical attention and occasionally progressing to cirrhosis, albeit very rarely [Vilar-Gomez et al 2021].

Table 3. Heterozygous *APOB*-Related Familial Hypobetalipoproteinemia: Frequency of Select Features

Feature	Frequency		
	Nearly all	Common	Infrequent
Hepatic steatosis	●		
Oral fat intolerance			●
Intestinal fat malabsorption			●

Gastrointestinal. Heterozygous *APOB*-FHBL may be asymptomatic, but fatty liver is common and mild fat malabsorption can occur beginning in young adulthood. These individuals may have liver transaminases that are elevated and often have a three- to five-fold increase in hepatic fat content compared to the typical general population.

Cardiac. Heterozygous *APOB*-FHBL confers protection against atherosclerotic cardiovascular disease, presumably due to lifelong reductions in serum LDL cholesterol concentrations [Sankatsing et al 2005, Peloso et al 2019].

Psychiatric. In a study of more than 800 adults hospitalized in a psychiatric unit, the prevalence of individuals with lipid profiles consistent with being a heterozygote for hypobetalipoproteinemia was higher than expected, although genetic testing for *APOB* pathogenic variants was not performed as part of the study. The authors found some statistically significant associations between low serum LDL cholesterol concentrations and schizophrenia, heteroaggression, and developmental disorders including autism [Cariou et al 2018]. This study did not prove causation.

Prognosis. Individuals with heterozygous *APOB*-FHBL have the potential for their condition to progress from nonalcoholic fatty liver disease to nonalcoholic steatohepatitis, fibrosis, and cirrhosis, particularly in the presence of known risk factors such as alcohol consumption, excessive caloric intake, and liver injury [Sankatsing et al 2005, Welty 2020].

While sibs inheriting a pathogenic variant demonstrate low cholesterol from birth, hepatic steatosis takes years to develop, with 54% of individuals with heterozygous FHBL developing this finding in one study [Sankatsing et al 2005].

Genotype-Phenotype Correlations

The majority of *APOB* pathogenic variants causing biallelic *APOB*-FHBL and heterozygous *APOB*-FHBL are frameshift, nonsense and splice variants resulting in production of a truncated apoB protein (see Molecular Genetics). These are named as a proportion of full-length wild type protein (apoB-100).

- In general, pathogenic variants that lead to truncated proteins that are 30% in length or shorter have more severe signs and symptoms than those whose truncated protein length is predicted to be 32% or longer; the latter tend to have moderate disease.
- It has been hypothesized that longer apoB truncated proteins may be able to maintain some residual capacity to bind lipid and form lipoproteins [Tarugi et al 2007].

Nomenclature

Biallelic *APOB*-FHBL may be referred to as homozygous familial hypobetalipoproteinemia, compound heterozygous familial hypobetalipoproteinemia, or collectively as HHBL.

Prevalence

Heterozygous *APOB*-FHBL due to apoB protein truncations occurs in 1:3000 individuals in the general population [Welty et al 1998]. The estimated incidence of biallelic *APOB*-FHBL is less than one in a million, based on extrapolation from the estimated prevalence of heterozygous *APOB*-FHBL.

In a blood donor cohort with plasma cholesterol below the fifth centile (128 mg/dL), apoB truncations were identified in 0.55% [Tarugi et al 2007].

Genetically Related (Allelic) Disorders

Familial hypercholesterolemia. Pathogenic variants in *APOB* are also associated with familial hypercholesterolemia. Unlike *APOB*-related familial hypobetalipoproteinemia, which is typically caused by truncating variants, *APOB*-related familial hypercholesterolemia is typically caused by missense variants. *APOB* missense variants associated with familial hypercholesterolemia are predominantly within exon 26 and impair LDL receptor binding activity of APOB. This results in a phenotype characterized by severely elevated LDL cholesterol levels that leads to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age, in turn leading to an increased risk for premature atherosclerotic cardiovascular disease and aortic valve disease.

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of Biallelic *APOB*-Related Familial Hypobetalipoproteinemia

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/biallelic *APOB*-FHBL	Distinguishing from biallelic *APOB*-FHBL
ANGPTL3	Familial combined hypolipidemia	AR	Low plasma levels of LDL cholesterol	Very low plasma triglyceride & HDL cholesterol levels

Table 4. continued from previous page.

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/biallelic *APOB*-FHBL	Distinguishing from biallelic *APOB*-FHBL
MTTP	Abetalipoproteinemia	AR	Clinical features may resemble those of persons w/biallelic *APOB*-FHBL.	Mean age of diagnosis 3.8 yrs (vs persons w/biallelic *APOB*-FHBL: mean age of diagnosis 21 yrs)
PCSK9	Hypocholesterolemia w/reduced LDL cholesterol (OMIM 607786)	AD	Low plasma levels of LDL cholesterol	Milder effect on LDL-cholesterol lowering; not assoc w/hepatic steatosis
SAR1B	Chylomicron retention disease	AR	May be clinically similar to biallelic *APOB*-FHBL (failure to thrive, steatorrhea)	Chylomicrons are absent; LDL cholesterol levels are low but not absent.

AD = autosomal dominant; *APOB*-FHBL = *APOB*-related familial hypobetalipoproteinemia; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance

Management

No clinical practice guidelines for *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with biallelic *APOB*-FHBL or heterozygous APOB-FHBL, the evaluations summarized respectively in Tables 5 and 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Biallelic *APOB*-Related Familial Hypobetalipoproteinemia

System/Concern	Evaluation	Comment
General	Growth parameters	To assess for poor growth
Gastrointestinal	Plasma lipid profile: • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglyceride • Apo B	
	Serum concentrations of fat-soluble vitamins (A, D, E, K)	
	Liver transaminases, INR, & bilirubin levels	Prolongation of INR may result from vitamin K deficiency.
	Referral to nutritionist	To provide dietary advice re low-fat diet
	Abdominal ultrasound	To evaluate for steatohepatitis, cirrhosis, &/or hepatocellular carcinoma
Hematologic	Complete blood count	To assess for anemia & erythrocyte morphologic abnormalities, specifically acanthocytosis (a pathognomonic feature)
Ophthalmologic	Referral to ophthalmologist	• For eval of visual acuity & pigmentary retinopathy • Consider electroretinography. [1]

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Referral to neurologist	If evidence of neurologic abnormality (e.g., ataxia, loss of deep tendon reflexes)
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of familial hypobetalipoproteinemia to facilitate medical & personal decision making

HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MOI = mode of inheritance
1. This is a sensitive method to detect early neuropathy [Musialik et al 2020].
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Heterozygous *APOB*-Related Familial Hypobetalipoproteinemia

System/Concern	Evaluation	Comment
Gastrointestinal	Plasma lipid profile: • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglyceride • Apo B	
	Serum concentrations of fat-soluble vitamins (A, D, E, K)	
	Liver transaminases	
	Abdominal ultrasound	If liver transaminases are ↑

Treatment of Manifestations

The following treatment is recommended for individuals with biallelic *APOB*-FHBL to address symptoms and prevent complications [Lee & Hegele 2014]. Treatment is not typically required for heterozygous *APOB*-related familial hypobetalipoproteinemia.

Table 7. Treatment of Manifestations in Individuals with Biallelic *APOB*-Related Familial Hypobetalipoproteinemia

Manifestation/ Concern	Treatment	Considerations/Other
Poor growth	Ensure adequate caloric intake on a low-fat diet.	Working w/nutritionist may be helpful.
Steatorrhea	• Low-fat diet (<30% of total calories) • Oral essential fatty acid supplements may be considered.	Will eliminate steatorrhea & allow absorption of other nutrients essential for growth & development.
Hepatic fibrosis / Cirrhosis	Consider liver transplantation for those w/end-stage liver disease.	
Fat-soluble vitamin deficiencies	High-dose oral fat-soluble vitamins: • Vitamin E (100-300 IU/kg/d) • Vitamin A (100-400 IU/kg/d) • Vitamin D (800-1200 IU/d) • Vitamin K (5-35 mg/wk)	Vitamin K supplementation may improve INR.
Anemia/ Hemolysis	No treatment is typically required.	• Anemia is usually mild. • Iron therapy does not improve anemia in this condition.

Table 7. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Loss of night &/or color vision & scotomas	Standard treatment per ophthalmologist	May incl optical aids
Ataxia	Assistance for coordination problems through established methods of rehab medicine & OT/PT	Canes, walkers, & wheelchairs are useful for gait ataxia.
Dysarthria	Speech therapy	Computer devices are available to assist persons w/severe speech deficits.

INR = international normalized ratio; OT = occupational therapy; PT = physical therapy

Prevention of Primary Manifestations

As outlined in Table 7, adoption of a low-fat diet (<30% of total calories) and high-dose oral fat-soluble vitamin supplementation may ameliorate or prevent clinical features of *APOB*-FHBL.

Surveillance

Table 8. Recommended Surveillance for Individuals with Biallelic *APOB*-Related Familial Hypobetalipoproteinemia

Frequency	Evaluation
Every 6-12 mos	• Measurement of growth parameters • For any new or progressive signs/symptoms of gastrointestinal issues [1]
Every 1-2 yrs	Laboratory investigations: • Lipid profile [2] • Liver function tests [3] • Vitamin A, vitamin E, 25-OH vitamin D • INR • Calcium, phosphate, uric acid • CBC & measurement of vitamin B_{12} & folate levels [4] • TSH [5]
Every 6-12 mos after age 10 yrs	• Ophthalmology eval • Neurologic exam
Every 3-5 yrs after age 10 yrs	• Hepatic ultrasound • Bone mineral densitometry [6]

CBC = complete blood count; INR = international normalized ratio; TSH = thyroid-stimulating hormone

1. Including for hepatomegaly and diarrhea

2. To include total, LDL and HDL cholesterol, triglyceride, and apo B concentrations

3. To include AST and ALT

4. Abnormal vitamin B_{12} and folate levels are not a primary feature of biallelic *APOB*-FHBL. However, the anemia seen in individuals with biallelic *APOB*-FHBL can mask a vitamin B_{12} or folate deficiency, both of which can occur with increased frequency in older individuals and both of which are treatable.

5. Abnormal thyroid function is not a primary feature of biallelic *APOB*-FHBL but is a common co-morbidity in the general population and is also treatable.

6. An affected individual found to have a bone mineral density >1 SD below the lower limit of normal often prompts an increase in vitamin D dosage.

Table 9. Recommended Surveillance for Individuals with Heterozygous *APOB*-Related Familial Hypobetalipoproteinemia

Frequency	Evaluation
Every 1-2 yrs	Laboratory investigations: • Lipid profile [1] • Liver function tests [2]
Every 3 yrs after age 10 yrs	Hepatic ultrasonography if liver transaminases are ↑

1. To include total, LDL and HDL cholesterol, triglyceride, and apo B concentrations
2. To include AST and ALT

Agents/Circumstances to Avoid

Individuals with biallelic *APOB*-FHBL should avoid fatty foods. No dietary restrictions are typically required for those with heterozygous *APOB*-FHBL.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with biallelic *APOB*-FHBL in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include:

- A full lipid profile, including apo B concentration;
- Molecular genetic testing for the *APOB* pathogenic variant(s) identified in the proband. Note: Family members found to be heterozygous for an HBL-related *APOB* variant may benefit from surveillance (see Table 9).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Vitamin A excess can be harmful to the developing fetus. Therefore, women who are pregnant or who are planning to become pregnant should reduce their vitamin A supplement dose by 50%. Additionally, close monitoring of serum vitamin A levels throughout pregnancy is recommended [Lee & Hegele 2014].

Because vitamin A is an essential vitamin, however, vitamin A supplementation for affected women should not be discontinued during pregnancy. Vitamin A deficiency can lead to maternal morbidity.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

APOB-related familial hypobetalipoproteinemia (*APOB*-FHBL) caused by homozygous (or compound heterozygous) pathogenic variants in *APOB* is inherited in an autosomal recessive manner.

Note: The inheritance of *APOB*-FHBL is described as autosomal recessive in this *GeneReview* because clinically manifest FHBL is associated with biallelic pathogenic variants while heterozygous pathogenic variants in *APOB* are primarily associated with biochemical findings in an otherwise asymptomatic individual, with rare exceptions. Because those with heterozygous *APOB*-FHBL occasionally have symptoms, the terms "codominant" and "semidominant" have sometimes been used in the literature to describe the inheritance pattern of *APOB*-FHBL.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an individual with biallelic *APOB*-FHBL are obligate heterozygotes (i.e., presumed to be heterozygous for one *APOB* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *APOB* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Individuals with a heterozygous FHBL-related *APOB* pathogenic variant are usually asymptomatic, with biochemical findings consistent with mild liver dysfunction and hepatic steatosis (see Clinical Description, Heterozygous *APOB*-FHBL). Surveillance, including lipid profiles and liver function tests, is recommended for individuals with heterozygous *APOB*-FHBL (see Table 9).

Sibs of a proband

- If both parents are known to be heterozygous for an *APOB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of having biallelic *APOB*-FHBL, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Individuals with a heterozygous FHBL-related *APOB* pathogenic variant are usually asymptomatic, with biochemical findings consistent with mild liver dysfunction and hepatic steatosis (see Clinical Description, Heterozygous *APOB*-FHBL). Surveillance, including lipid profiles and liver function tests, is recommended for individuals with heterozygous *APOB*-FHBL (see Table 9).

Offspring of a proband. Unless a proband with biallelic *APOB*-FHBL has children with an individual who has biallelic *APOB*-FHBL or heterozygous *APOB*-FHBL, the individual's offspring will be heterozygous for an *APOB* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *APOB* pathogenic variant.

Heterozygote Detection

Molecular genetic testing for at-risk relatives requires prior identification of the *APOB* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who have biallelic *APOB*-related FHBL or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *APOB* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Familial hypobetalipoproteinemia

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. APOB-Related Familial Hypobetalipoproteinemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
APOB	2p24.1	Apolipoprotein B-100	APOB database	APOB	APOB

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for APOB-Related Familial Hypobetalipoproteinemia (View All in OMIM)

107730	APOLIPOPROTEIN B; APOB
615558	HYPOBETALIPOPROTEINEMIA, FAMILIAL, 1; FHBL1

Molecular Pathogenesis

ApoB is essential for the formation of intestinally derived chylomicrons and hepatically derived very low-density lipoprotein (VLDL) and their metabolites, including low-density lipoprotein (LDL). In *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) the mutated apoB is unable to be incorporated and secreted as a

component of a lipoprotein particle, resulting in low levels of LDL cholesterol, and accumulation of fat in the liver (hepatic steatosis). Where both *APOB* alleles are affected (biallelic *APOB*-FHBL) levels of LDL cholesterol will be extremely low and the affected individual will be at risk of developing neuromuscular and ophthalmologic complications as a result of fat-soluble vitamin deficiencies, particularly vitamins E and A.

Truncated proteins are named as a proportion of full-length wild type protein (apoB-100). Apo B proteins shorter than 30% of full-length apoB are not detectable in plasma by Western blot, while those larger than apoB-32 are detectable in plasma. Those individuals with longer truncated proteins that are detectable in plasma are more likely to have moderate disease compared to those with undetectable plasma levels, who typically have severe disease [Tarugi et al 2007] (see Genotype-Phenotype Correlations).

Mechanism of disease causation. Loss of function; typically nonsense, frameshift and splice pathogenic variants; rarely, missense variants

Chapter Notes

Author Notes

Book chapters

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Revision History

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- 13 May 2021 (ma) Review posted live
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