MONOGENIC DISORDERS CAUSING HYPOBETALIPOPROTEINEMIA

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ABSTRACT

Monogenic mutations leading to hypobetalipoproteinemia are rare. The monogenic causes of hypobetalipoproteinemia include familial hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease, loss of function mutations in PCSK9, and loss of function mutations in angiopoietin-like protein 3 (ANGPTL3) (Familiar Combined Hypolipidemia). This chapter describes the etiology, pathogenesis, clinical and laboratory findings, and the treatment of these rare monogenic disorders.

INTRODUCTION

Monogenic mutations leading to hypobetalipoproteinemia are rare. The monogenic causes of hypobetalipoproteinemia include familial hypobetalipoproteinemia (FHBL), abetalipoproteinemia (ABL), chylomicron retention disease (CMRD), loss of function mutations in PCSK9, and loss of function mutations in angiopoietin-like protein 3 (ANGPTL3) (Familial Combined Hypolipidemia, FCH) (1). Increased understanding of the genetic and the molecular underpinnings of these disorders has allowed a focused prioritization of therapeutic targets for drug development. Table 1 summarizes genetic, lipid, and clinical features of the major hypobetalipoproteinemia syndromes and table 2 provides a new classification of these disorders. Of note the parental lipid profile is normal in abetalipoproteinemia and chylomicron retention disease.

It should be recognized that secondary, non-familial, forms of hypobetalipoproteinemia occur and include strict vegan diet, malnutrition, malabsorption, hyperthyroidism, malignancy, and chronic liver disease. In addition, hypobetalipoproteinemia can also be due to polymorphisms in multiple genes that together result in hypobetalipoproteinemia (polygenic etiology) (2-4). In a study of 111 patients with LDL-C levels below the fifth percentile 36% had monogenic hypobetalipoproteinemia, 34% had polygenic hypobetalipoproteinemia, and 30% had hypobetalipoproteinemia from an unknown cause (2). In a study of women with an LDL-C ≤1st percentile (≤50 mg/dL) 15.7% carried mutations causing monogenic hypocholesterolemia and 49.6% were genetically predisposed to a low LDL-C on the basis of an extremely low weighted polygenetic risk score (4). Of note individuals with monogenic hypobetalipoproteinemia are more likely to have liver steatosis than individuals without a monogenic disorder (2).

Table 1. Characteristics of the Hypobetalipoproteinemia Syndromes					
	Inheritance	**Effected gene**	**Prevalence**	**Lipids**	**Clinical features**
FHBL	ACD	Truncation mutations in Apo B	1:1000 – 1:3000	Apo B <5th percentile, LDL-C 20- 50 mg/dL	Hepatic steatosis Mild elevation of transaminases. Lower prevalence of ASCVD
ABL FHBL	AR AR	MTTP Apo B	<1:1,000,000	Triglycerides < 30 mg/dL, Cholesterol < 30 mg/dL), LDL and Apo B undetectable	Hepatic steatosis Malabsorption, steatorrhea, diarrhea, and failure to thrive. Deficiency of fat-soluble vitamins.
PCSK9	ACD	Loss of function mutations in PCSK9		Heterozygous – mild to moderate reduction in LDL-C Homozygous – LDL-C ~15 mg/dL	Normal health; significantly lower prevalence of ASCVD
FCH	ACD	Loss of function mutations in ANGPTL3	Very rare	Panhypolipidemia	Normal health; significantly lower prevalence of ASCVD
CMRD	AR	SAR1B	Very rare	LDL-C and HDL-C -decreased by 50%, Triglycerides - normal	hypocholesterolemia associated with failure to thrive, diarrhea, steatorrhea, and abdominal distension

ACD- autosomal co-dominant; AR- autosomal recessive; FHBL- familial hypobetalipoproteinemia; ABL- abetalipoproteinemia; FCH- Familiar Combined Hypolipidemia; CMRD- chylomicron retention disease, MTTP- microsomal triglyceride transfer protein; ANGPTL3- angiopoietin-like protein 3; ASCVD- atherosclerotic cardiovascular disease.

Table 2. Classification of Disorders Causing Familial Hypocholesterolemia		
New Name	**Common Name**	**Gene Defect**
Class I: Familial hypobetalipoproteinemia due to lipoprotein assembly and secretion defects		

FHBL-SD1	Abetalipoproteinemia	Microsomal Triglyceride Transfer Protein
FHBL-SD2	Familial Hypobetalipoproteinemia	Apolipoprotein B
FHBL-SD3	Chylomicron retention disease	SAR1B
Class II: Familial hypobetalipoproteinemia due to enhanced lipoprotein catabolism		
FHBL-EC1	Familial Combined Hypolipidemia	ANGPTL3
FHBL-EC2		PCSK9

Modified from (5).

FAMILIAL HYPOBETALIPOPROTEINEMIA

Familial Hypobetalipoproteinemia (FHBL) is a relatively common autosomal semi-dominant disorder most commonly due to truncation mutations in the gene coding for Apo B (1,6-8). The prevalence of heterozygous FHBL is estimated to be 1 in 700 to 3000 (1). Variants that lead to truncated proteins that are 30% in length or shorter have more severe signs and symptoms than those with longer truncated proteins (6,7). The truncated forms of Apo B found in FHBL are generally non-functional (truncation decreases lipidation and secretion) and are catabolized quickly, resulting in markedly reduced levels in the plasma (Apo B <5th percentile and LDL-C typically between 20- 50 mg/dL) (7,8). Although there is one normal allele in heterozygous FHBL, plasma Apo B levels are approximately 25% of normal rather than the predicted 50% (8). These lower-than-expected levels result from a lower secretion rate of VLDL Apo B from the liver, decreased production of LDL Apo B, increased catabolism of VLDL, and extremely low secretion of the truncated Apo B (6-8). Given the reduced substrate (Apo B) for lipid (predominantly triglyceride) loading, fatty liver develops in these patients (6,9). Hepatic steatosis and mild elevation of liver enzymes are common in heterozygous FHBL (6,9). Interestingly, individuals with monogenic hypobetalipoproteinemia had a much greater prevalence of hepatic dysfunction than individuals with polygenic hypobetalipoproteinemia (2). In contrast to non-alcoholic fatty liver disease, FHBL is not associated with hepatic or peripheral insulin resistance (9). This observation, however, does not imply that hepatic steatosis associated with FHBL is benign. There are several reports of steatohepatitis, cirrhosis, and hepatocellular carcinoma in patients with FHBL and it is estimated that 5-10% of individuals with FHBL develop relatively more severe nonalcoholic steatohepatitis (6). Because of the risk of developing liver disease liver function tests should be checked every 1-2 years and a hepatic ultrasound in those with elevated liver transaminases (6). While hepatic fat accumulation is the rule, there is generally sufficient chylomicron production to handle dietary fat. However, oral fat intolerance and intestinal fat malabsorption have been reported (6). On the positive side the decrease in proatherogenic lipoproteins has been associated with a reduced risk of cardiovascular disease (10).

Given the association of FHBL and low LDL-C, Apo B has been an attractive target for drug development. Indeed, unraveling the genetic and molecular mechanisms of FHBL provided the motivation to pharmacologically antagonize Apo B synthesis for therapeutic gains. This culminated in the production of mipomersen, a synthetic single strand anti-sense oligonucleotide to Apo B (11,12). Essentially, anti-sense oligonucleotides contain approximately ~20 deoxyribonucleic acid (DNA) base pairs complementary to a unique messenger ribonucleic acid (mRNA) sequence. The hybridization of the anti-sense oligonucleotide to the mRNA of interest leads to its catabolism via RNase H1, with markedly

reduced mRNA levels and ultimately reduced target protein levels. In this case, mipomersen binds to Apo B mRNA leading to reduced production of the protein, and mimicking (albeit to a lesser extent) FHBL. Mipomersen is the first anti-sense oligonucleotide approved by the United States Food and Drug Administration (FDA) and was commercialized in 2013 with a limited indication for adjunctive LDL-C lowering in patients with homozygous familial hypercholesterolemia (HoFH) (12). It is an injectable agent administered subcutaneously once a week. In the clinical trials, mipomersen was associated with a reduction of LDL-C by 21% in subjects with HoFH and 33% in subjects with heterozygous familial hypercholesterolemia (HeFH) (12). Interestingly, it was also found to lower Lp(a) by 21- 23% (12). While it is highly efficacious in LDL-C lowering, it has side effects, many of which can be predicted based on the experience with FHBL (e.g., hepatic steatosis, elevated liver enzymes) (12). It is also associated with injection site reactions in a considerable number of subjects (12). In May 2018 sales were discontinued due to safety concerns related to increased liver transaminases and fatty liver.

Homozygous hypobetalipoproteinemia (HHBL) is extremely rare (6). These patients are homozygous or compound heterozygous for mutations in the Apo B gene. The clinical manifestations mimic ABL (see below) (6).

ABETALIPOPROTEINEMIA

Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder characterized by very low plasma concentrations of triglyceride and cholesterol (under 30 mg/dL) and undetectable levels of LDL and Apo B (1,7,13,14). The incidence of ABL is < 1 in 1,000,000. HDL-C levels are usually normal or modestly reduced. It is due to mutations in the gene that codes for microsomal triglyceride transfer protein (*MTTP*) (7,13-15). MTTP lipidates nascent Apo B in the endoplasmic reticulum to produce VLDL and chylomicrons in the liver and small intestine, respectively (15,16). Unlipidated Apo B is targeted for proteasomal degradation leading to the absence of Apo B containing lipoproteins in the plasma (and thus markedly reduced levels of LDL-C and triglycerides) (15,16). Similar to FHBL, VLDL production is inhibited (14). The reduced triglyceride export from the liver leads to hepatic steatosis, which rarely may progress to steatohepatitis, fibrosis, and cirrhosis (1,9,13). Additionally, lack of MTTP facilitated lipidation of chylomicrons in the small intestine results in lipid accumulation in enterocytes with associated malabsorption, steatorrhea, and diarrhea (1,7,13). The malabsorption and diarrhea lead to failure to thrive during infancy (1,7,13). A decrease in dietary fat can reduce the gastrointestinal symptoms. Acanthocytosis may encompass 50% of circulating red blood cells (red blood cells with spiked cell membranes, due to thorny projections) due to alterations in the lipid composition and fluidity of red cell membranes (1,13,14). An additional issue of importance related to ABL is deficiency of fat-soluble vitamins (1,13). Early diagnosis of ABL and homozygous hypobetalipoproteinemia is extremely important as vitamin E deficiency culminates in atypical retinitis pigmentosa, spinocerebellar degeneration with ataxia, vitamin K deficiency can lead to a significant bleeding diathesis, vitamin A deficiency can contribute to eye disorders, and vitamin D deficiency can lead to defects in bone formation (1,13). High dose supplementation with fat soluble vitamins early in life can prevent or delay these devastating complications (Table 3) (7,13). Additional treatment measures include a low-fat diet and supplementation with essential fatty acids (Table 3) (7,13).

Table 3. Dietary Recommendations for Abetalipoproteinemia

Fat calories	Less than 10-15% (<15 g/day) of total daily caloric requirement.

	Increase as tolerated.
Essential fatty acids	Ensure 2-4% daily caloric intake of EFAs (alpha-linolenic acid/linoleic acid)
Medium chain triglycerides	May prevent or treat malnutrition
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

Derived from (1)

Given the very low level of atherogenic lipoproteins and lipids associated with ABL, there was interest in inhibiting MTTP therapeutically. Lomitapide is an oral MTP inhibitor that has been developed over the course of many years (12,17). In early trials, it was tested at a relatively high dose and the side effect profile was prohibitive (nausea, flatulence, and diarrhea). The more recent clinical trial program tested lower doses with drug titration in subjects with Homozygote Familial Hypercholesterolemia (HoFH) (12,17). On an intention to treat basis, LDL-C was decreased by 40% and apolipoprotein B by 39% (12). In patients who were actually taking lomitapide, LDL-C levels were reduced by 50% (12). In addition to decreasing LDL-C levels, non-HDL-C levels were decreased by 50%, Lp(a) by 15%, and triglycerides by 45% (12). Lomitapide received the same limited indication as mipomersen for adjunctive treatment of patients with HoFH (12). Besides the gastrointestinal issues already alluded to, its side effect profile includes hepatic steatosis (12). Its long-term safety has not been established.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9)

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) belongs to the proprotein convertase class of serine proteases (18-20). After synthesis, PCSK9 undergoes autocatalytic cleavage. This step is required for secretion, most likely because the prodomain functions as a chaperone and facilitates folding (18,19). PCSK9 is associated with LDL particles and the LDL-receptor (LDLR) (20). In 2003, Abifadel reported the seminal work that mapped PCSK9 as the third locus for autosomal dominant hypercholesterolemia (Familial Hypercholesterolemia- FH) (21). This finding revealed a previously unknown actor involved in cholesterol homeostasis and served to launch a series of investigations into PCSK9 biology. As it turns out, PCSK9 functions as a central regulator of plasma LDL-C concentration (18-20). It binds to the LDLR and targets it for destruction in the lysosome (18-20). Overactivity of PCSK9 results in a decrease in LDLR and an increase in LDL-C levels while decreased activity of PCSK9 results in an increase in LDLR and a decrease in LDL-C.

Since the discovery of gain-of-function mutations in PCSK9 as a cause of FH, investigators have also uncovered loss of function mutations of PCSK9. Loss-of-function mutations in PCSK9 are associated with low LDL-C levels and markedly reduced ASCVD (18,19). In African Americans 2.6 percent had nonsense mutations in PCSK9 that resulted in a 28 percent reduction in LDL-C and an 88 percent reduction in the risk of coronary heart disease (22). The hypolipidemia is not associated with liver abnormalities or other disorders. Interestingly, rare individuals homozygous or compound heterozygotes for loss of function mutations in PCSK9 have been

reported with extremely low levels of LDL-C (~15 mg/dL), normal health and reproductive capacity, and no evidence of neurologic or cognitive dysfunction (20,23,24). Collectively, these observations served as further motivation to pursue antagonism of PCSK9 as a therapeutic target. Antagonizing PCSK9 would prolong the lifespan of LDLR, leading to significant reductions in plasma LDL-C levels. Two fully human monoclonal antibodies (alirocumab and evolocumab) targeting PCSK9 became commercially available in 2015 and inclisiran, a small interfering RNA that inhibits translation of PCSK9 is also available. Other approaches to inhibit PCSK9 are under investigation.

FAMILIAL COMBINED HYPOLIPIDEMIA

Familial combined hypolipidemia (FCH) is due to loss of function mutations in the gene encoding angiopoietin-like protein 3 (ANGPTL3) (25,26). ANGPTL3 inhibits various lipases, such as lipoprotein lipase and endothelial lipase (25,26). Therefore, loss of function mutations in ANGPTL3 relinquishes this inhibition increasing the activity of lipases resulting in more efficient metabolism of VLDL and HDL particles (25,26). In addition, to increasing VLDL clearance the secretion of VLDL is also decreased due to a decrease in free fatty acid flux to the liver (25). LDL clearance is increased but the mechanism remains to be fully elucidated (25). Studies have suggested that ANGPTL3 inhibition lowers LDL-C by limiting LDL particle production due to ANGPTL3 inhibition and increased endothelial lipase activity reducing VLDL-lipid content and size, generating remnant particles that are efficiently removed from the circulation rather than being further metabolized to LDL (27).

Clinically, FCH manifests as panhypolipidemia (decreased triglycerides, LDL-C, HDL-C, apo B, and apo A-I) (25,26,28). Interestingly, heterozygotes for certain nonsense mutations in the first exon of ANGPTL3 have moderately reduced LDL-C and triglyceride levels while compound heterozygotes have significant reductions in HDL-C as well (25,26). Homozygosity or compound heterozygosity for other loss-of-function mutations in exon 1 of ANGPTL3 have no detectable ANGPTL3 in plasma and striking reductions of atherogenic lipoproteins with HDL particles containing only apo A-I and preß-HDL. Individuals who are heterozygous for the loss of function mutations in ANGPTL3 have significantly reduced LDL-C and triglyceride levels and a reduced risk of atherosclerosis (25,26,28).

A pooled analysis of cases of familial combined hypolipidemia was published 2013 (29). One hundred fifteen individuals carrying 13 different mutations in the *ANGPTL3* gene (14 homozygotes, 8 compound heterozygotes, and 93 heterozygotes) and 402 controls were evaluated. Homozygotes and compound heterozygotes (two mutant alleles) had no measurable ANGPTL3 protein. In heterozygotes, ANGPTL3 was reduced by 34-88%, according to genotype. All cases (homozygotes and heterozygotes) demonstrated significantly lower concentrations of all plasma lipoproteins (except for Lp(a)) as compared to controls. Familial combined hypolipidemia is not associated with any comorbidity. In fact, the prevalence of fatty liver was the same as controls. However, ANGPTL3 deficiency is associated with a reduced risk of cardiovascular disease (25,30).

Recently, evinacumab, a human monoclonal antibody against ANGPTL3, was approved for the treatment of Homozygous Familial Hypercholesterolemia (12). Evinacumab decreases LDL-C levels by mechanisms independent of LDL receptor activity (12).

CHYLOMICRON RETENTION DISEASE

Chylomicron retention disease (CMRD), known also as Anderson's disease for the individual who first described the condition in 1961, is a rare inherited lipid malabsorption syndrome (31,32). It is due to mutations in the *SAR1B* gene which codes for the protein SAR1b, a small GTPase, involved in intracellular protein trafficking (31). Mutations in SAR1b result in the failure of pre-chylomicrons to

move from the endoplasmic reticulum to the golgi (31). This disorder usually presents in young infants with diarrhea, steatorrhea, abdominal distention, and failure to thrive, which can improve with a low-fat diet (1,31,32). Patients with CMRD demonstrate a specific autosomal recessive hypocholesterolemia that differs from other familial hypocholesterolemias. CMRD is associated with a 50% reduction in both plasma LDL-C and HDL-C with normal fasting triglyceride levels (31,32). Mutations in SAR1B do not affect VLDL secretion by the liver. The decrease in HDL-C is postulated to be due to a decrease in Apo A-I secretion and cholesterol efflux by the small intestine (31). The mechanism accounting for the decrease in LDL-C is not clear. The usual increase in triglycerides and chylomicron levels following a fat meal is blocked (31). The duodenal mucosa is white on endoscopy and intestinal biopsy reveals cytosolic lipid droplets and lipoprotein-sized particles in enterocytes (31). As one would expect the absorption of fat-soluble vitamins (A, D, K, and E) and essential fatty acids is impaired (31,32). Neurological and eye manifestations are milder and occur at an older age compared to abetalipoproteinemia (1). Red blood cell acanthosis is rare (1). Heterozygotes with mutations in SAR1B are unaffected.

Treatment for individuals with CMRD is similar to that described above for individuals with ABL (32).

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