Familial hypobetalipoproteinemia and abetalipoproteinemia

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Thesis

FAMILIAL HYPOBETALIPOPROTEINEMIA AND ABETALIPOPROTEINEMIA

by

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FAMILIAL HYPOBETALIPOPROTEINEMIA AND ABETALIPOPROTEINEMIA

JIE CHAN

ABSTRACT

Familial hypobetalipoproteinemia (FHBL) and abetalipoproteinemia (ABL) are rare diseases that cause hypocholesterolemia. Studying FHBL and ABL is essential to furthering the field of cholesterol research and has provided many therapeutic targets for hypercholesterolemia. ABL is an autosomal, recessive disease caused by a mutation in MTP, a chaperone protein in the ER that helps fold nascent apoB and transfers lipids onto apoB. FHBL is an autosomal, codominant disease caused by a mutation in APOB, which usually causes a truncated apoB with loss-of-function. ABL and homozygous FHBL have the same clinical symptoms: steatorrhea, neurological dysfunction, vision problems, and non-alcoholic fatty liver. Implementing a low-fat diet routine along with vitamin supplementations will ameliorate most symptoms except for hepatic steatosis. Both ABL and FHBL carry a reduced risk of cardiovascular diseases due to the reduction of atherosclerosis.

Many new therapeutic targets for hypercholesterolemia have been inspired by FHBL and ABL. Lomitapide is an MTP (microsomal triglyceride transfer protein) inhibitor that mimics ABL’s mutant mechanism. Mipomersen is an apoB synthesis
inhibitor, which mimics FHBL’s mutant mechanism. The purpose of both drugs is to treat familial hypercholesterolemia. This literature review suggests other targets: a molecule to permanently bind apoB to MTP which mimics an FHBL mutation, a molecule to prevent PDI from binding to the large M subunit in the heterodimer MTP, and a method to truncate apoB to mimic FHBL mutations. Two new recently-discovered diseases have similar phenotypes as ABL and FHBL: PCSK9 deficiency and familial combined hypolipidemia. Both cause hypocholesterolemia. However, PCSK9 does not have the negative systemic effects such as steatorrhea and neurological dysfunction. In addition, no fatty liver develops. More research into these new diseases can contribute to the field of hypocholesterolemia, which provides new therapeutic targets for hypercholesterolemia.
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LIST OF ABBREVIATIONS

ABL.................................................................................................................. abetalipoproteinemia
ALP...................................................................................................................... alkaline phosphatase;
ALT....................................................................................................................... alanine aminotransferase;
ApoB....................................................................................................................... apolipoprotein B
AST......................................................................................................................... aspartate aminotransferase;
CBC......................................................................................................................... complete blood count;
CM.......................................................................................................................... chylomicrons
DXA....................................................................................................................... dual energy X-ray absorptiometry
EFA.......................................................................................................................... essential fatty acid;
ER.............................................................................................................................. endoplasmic reticulum
FH.............................................................................................................................. familial hypercholesterolemia
FHBL....................................................................................................................... familial hypobetalipoproteinemia
GGT........................................................................................................................ gamma glutamyl transferase;
GI................................................................................................................................. gastrointestinal
HBL........................................................................................................................ hypobetalipoproteinemia
HDL-C.................................................................................................................. high density lipoprotein cholesterol;
HHBL....................................................................................................................... homozygous familial hypobetalipoproteinemia
IDL............................................................................................................................. intermediate density lipoprotein
INR........................................................................................................................... international normalized ratio;
IU................................................................................................................................. international units
LDL........................................................................................................................ low density lipoproteinemia
LDL-C .................................................. low density lipoprotein cholesterol;
LDLR ................................................... liver’s low density lipoprotein receptors
MCTG ..................................................... medium chain triglyceride;
MTP ........................................................ microsomal triglyceride transfer protein
PCSK9 .................................................... proprotein convertase subtilisin kexin type 9
PDI .......................................................... protein disulfide isomerase
RBC ........................................................ red blood cell;
VLDL .................................................... very low density lipoprotein
INTRODUCTION

Plasma cholesterol levels play a major role in determining the quality of our long-term cardiovascular health. Epidemiology and genetic studies demonstrate that plasma low density lipoprotein (LDL) cholesterol levels are directly related to the risk of coronary heart disease, and biochemical studies reveal the mechanism behind such coronary events (Burnett & Hooper, 2008). A high level of plasma LDL cholesterol is associated with an increased risk in myocardial infarctions and strokes due to atherosclerosis. Plasma LDL cholesterol is oxidized in the arteries and is taken in by macrophages. Once the macrophages are packed with lipid vesicles, they are known as foam cells. Accumulation of foam cells within the arterial vessel wall forms fatty streaks. This whole process is called atherosclerosis. Fatty streaks may progress to an unstable fibrous cap. These fibrous caps may unpredictably rupture and form a thrombus, which is a blood clot (Burnett & Hooper, 2008). The blood clot may break off and block circulation at a further downstream site. Occlusions in circulation lead to heart attack and stroke due to oxygen deprivation of cells. Certain drugs can lower plasma LDL cholesterol, and clinical trials with these drugs demonstrate a reduction in both morbidity and mortality from coronary heart disease (Burnett & Hooper, 2008).

An extremely low level of cholesterol is physiologically is also harmful. Hypcholesterolemia is associated with increased morbidity and mortality among
many diseases such as sepsis; some doctors consider hypocholesterolemia an indicator for such diseases. Critically ill patients may exhibit a severely low level of cholesterol. Synthesizing cholesterol is a complex process that demands energy, and bodies in physiologically stressful situations may not absorb or produce enough cholesterol. Low serum cholesterol may become a potential therapeutic target in sepsis among the critically ill (Vyroubal et al., 2008).

Hypocholesterolemia has been hypothesized to be a risk factor for pulmonary tuberculosis as well. Patients with tuberculosis often have hypocholesterolemia, and many other risk factors for tuberculosis are often associated with hypocholesterolemia (Pérez-Guzmán & Vargas, 2006). Cholesterol is vital for a healthy immune system and is essential in macrophage uptake and phagocytosis of mycobacteria. Clinical trials show that a cholesterol-rich diet may accelerate the process of bacteriological sterilization of sputum (Pérez-Guzmán & Vargas, 2006).

Many factors affect our cholesterol levels such as diet, environment, drugs, and genetics. There is much variation in plasma LDL cholesterol levels in the population; up to 50% of the variation is due to genetics (Burnett & Hooper, 2008). Table 1 shows the variation in cholesterol levels in the general population. Plasma LDL cholesterol level is considered to be polygenic because many different genes at various loci control LDL cholesterol levels. However, a small
percentage of the population experience monogenic cholesterol diseases, where one gene will affect the cholesterol level drastically. An example of monogenic hypercholesterolemia is familial hypercholesterolemia (FH), and examples of monogenic hypocholesterolemia are familial hypobetalipoproteinemia (FHBL) and abetalipoproteinemia (ABL) (Burnett & Hooper, 2008).

Table 1. General population distribution of plasma lipid values and apolipoproteins values in mg/dL (Adapted from Kwiterovich Jr, 2013).

<table>
<thead>
<tr>
<th>ApoB-containing lipoprotein</th>
<th>Percentiles</th>
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<tr>
<td></td>
<td>5th</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>80</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>110</td>
</tr>
<tr>
<td>ApoB</td>
<td>60</td>
</tr>
<tr>
<td>Triglycerides men</td>
<td>46</td>
</tr>
<tr>
<td>Triglycerides women</td>
<td>41</td>
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This literature review will evaluate the diseases FHBL and ABL in terms of their clinical symptoms, current treatment, biochemical mechanisms, and implications for future research and studies in cholesterol disease. A brief overview of plasma LDL cholesterol metabolism will provide context for understanding the biochemical mechanisms in FHBL and ABL. Relating the clinical symptoms to the diseases’ biochemical mechanisms will provide insight into current treatment. Although FHBL and ABL are rare orphan diseases, FHBL and ABL research have provided a wealth of information in treating other more common cholesterol dysfunctions such as hypercholesterolemia. Studying FHBL and ABL is a necessity that has been indispensable to furthering the field of cholesterol research.
CHOLESTEROL METABOLISM

Cholesterol has many important biochemical and physiological functions in the body. Cholesterol is a precursor to steroids and biliary acids. Additionally, one third of all cell membranes is composed of cholesterol, which provides fluidity and flexibility to the structure (Vyroubal et al., 2008). Finally, cholesterol participates in cell signaling, particularly in the processes of cell growth and phagocytosis. For example, cholesterol plays a crucial role in lymphocytic signaling during an immune response (Pérez-Guzmán & Vargas, 2006).

Cholesterol is a hydrophobic compound that cannot travel unaccompanied in blood; instead, it needs to be transported in spherical lipoproteins. The core of a lipoprotein is hydrophobic while apolipoproteins and polar phospholipids cover the surface (Welty, 2014). Other hydrophobic compounds in the core may include triglycerides, cholesterol esters, and phospholipids. Apolipoproteins in these complexes stabilize the lipid emulsions and also mediate signaling by acting as a ligand for receptors on the recipient cells (Burnett & Hooper, 2008). Cholesterol from diet is absorbed in the intestines and transported to the liver in chylomicron particles. Additionally, cholesterol can be released from the liver in lipoprotein complexes and redistributed to peripheral tissues. Figure 1 shows the processes of cholesterol absorption and secretion in the intestines and liver.
Figure 1. Cholesterol transportation in lipoproteins. Cholesterol is absorbed in the intestines and transported to the liver by chylomicrons (CM). VLDL is secreted from the liver and eventually becomes metabolized to LDL. The inset shows how triglycerides are added to apoB to form VLDL or CM. This is done by the chaperone MTP (Taken from Burnett & Hooper, 2008).
Different lipoproteins circulate in the blood with cholesterol packed into them: very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and LDL. They are differentiated by the various apolipoproteins, one of which is apolipoprotein B (apoB). ApoB is expressed on lipoproteins made in hepatocytes and enterocytes (Lee & Hegele, 2014). It is an amphipathic glycoprotein that is required for VLDL and LDL formation (Whitfield, Barrett, Bockxmeer, & Burnett, 2004).

VLDL synthesis starts in the liver. A nascent apoB without lipids is stabilized by microsomal triglyceride transfer protein (MTP) in the hepatocyte’s endoplasmic reticulum (ER). ApoB serves as the backbone of VLDL. Then, the chaperone MTP transfers lipids to apoB, eventually packing many neutral lipids into the core to form a VLDL. A triglyceride-rich lipoprotein, the completed VLDL is secreted into circulation by the liver (Burnett & Hooper, 2008).

ApoB synthesized in the liver is different than apoB synthesized in the intestines. Enterocytes make a shorter version called apoB-48 while hepatocytes make a longer version called apoB-100. Both apoBs are transcribed and translated from the same gene, but an mRNA editing process in the intestines causes apoB-48 to contain only 48% of apoB-100 on the side with the amino terminal. The apoB-100 RNA in hepatocytes is unedited. Therefore, triglyceride-and-fatty-acid-rich
chylomicrons from the intestines contain apoB-48 while VLDL from the liver contain apoB-100 (Lee & Hegele, 2014).

Plasma LDL cholesterol levels are influenced by VLDL levels and the activity of the liver’s LDL receptors (LDLR) (Burnett & Hooper, 2008). LDL is a metabolic product of VLDL. When VLDL is released into circulation, lipoprotein lipase on the endothelium hydrolyzes the triglycerides in VLDL. This releases free fatty acids, which are then absorbed and used by the peripheral tissues. The remnant VLDL is either cleared from circulation or converted into IDL and eventually LDL (Kwiterovich Jr, 2013). IDL is either cleared in the liver or is hydrolyzed to LDL by hepatic lipase (Kwiterovich Jr, 2013).

ApoB-100 plays a major role in mediating LDL plasma levels. LDL is eventually cleared by the liver or oxidized in peripheral tissues. LDL clearance in the liver is mediated by LDLR, which recognizes apoB-100 on LDL. Certain mutations in apoB result in decreased LDL plasma levels and hypobetalipoproteinemia (HBL). Meanwhile, loss of function mutations in LDLR tend to cause increased LDL levels and hypercholesterolemia (Burnett & Hooper, 2008).

About 70% of total plasma cholesterol is contained in LDL. Every LDL particle has only one apoB that cannot be passed onto other lipoproteins. As a result, the number of plasma apoB-100 particles is equal to the number of plasma LDL
particles. Therefore, apoB-100 plasma levels are directly related to the incidence of coronary heart disease (Burnett & Hooper, 2008). ApoB-100 plays a large role in regulating cholesterol plasma levels, which in turn affect the development of atherosclerosis, heart attack, and stroke.
MONOGENIC HYPOBETALIPOPROTEINEMIAS

Hypobetalipoproteinemia occurs when total serum cholesterol (<150 mg/dL), LDL cholesterol (<1.8 mmol/L), or total apoB levels (<50 mg/dL) are less than the 5\textsuperscript{th} percentile in a population after adjusting for age, gender, and race (Burnett & Hooper, 2008; Harada et al., 2009). There are two forms of HBL: primary and secondary. Vegan diet, malnutrition, malabsorption, cachexia, hyperthyroidism, severe liver disease, chronic pancreatitis, and certain drugs may cause secondary HBL (Whitfield, Barrett, Bockxmeer, & Burnett, 2004). Meanwhile, primary HBL is rarer and indicates a genetic origin (Tarugi et al., 2007). Two monogenic HBL diseases are familial hypobetalipoproteinemia and abetalipoproteinemia. Mutations in \textit{APOB} cause FHBL, and mutations in \textit{MTP} cause ABL (Tarugi & Averna, 2011).

FHBL can manifest in two forms: heterozygous and homozygous. FHBL heterozygotes tend to be asymptomatic (Sen, Dagdelen, & Erbas, 2007). However, homozygous hypobetalipoproteinemia (HHBL) presents with the same symptoms as ABL (Moutzouri, Elisaf, & Liberopoulos, 2011). HHBL and ABL differ in biochemical mechanism due to a difference in the root genetic mutation, but they present with the same clinical phenotype with varying severity. Both patients are unable to absorb cholesterol from diet or transport cholesterol throughout the bloodstream due to a lack of normal apoB (Hooper & Burnett,
2014). For both diseases, males and females have the same symptoms. Consanguinity is commonly seen in both ABL and HHBL (Lee & Hegele, 2014).

**Clinical Symptoms of HHBL and ABL**

ABL and HHBL have similar phenotypes and clinical symptoms. Both ABL and HHBL patients exhibit steatorrhea, neurological dysfunction, vision problems, and non-alcoholic fatty liver (Table 2) (Zamel, Khan, Pollex, & Hegele, 2008). However, the severity of symptoms may vary due to different mutations (Lee & Hegele, 2014) in *APOB* for HHBL and *MTP* for ABL. Generally speaking, ABL patients tend to have more severe symptoms than HHBL patients. There is a wider range in severity of symptoms among HHBL patients; some patients may be asymptomatic while others have severe neurological and gastrointestinal issues. Diagnosis of HHBL or ABL is usually determined from a lipid profile, blood smear, and clinical symptoms (Lee & Hegele, 2014). Determining the difference between HHBL and ABL requires DNA sequencing and/or a family history.
Table 2. Summary of characteristics in primary HBL (Adapted from Tarugi et al., 2007).

<table>
<thead>
<tr>
<th>Primary HBL</th>
<th>Inheritance</th>
<th>Candidate gene</th>
<th>ApoB levels compared with controls</th>
<th>Clinical characteristics</th>
</tr>
</thead>
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<tr>
<td>FHBL</td>
<td>Codominant</td>
<td>APOB</td>
<td>Reduced (&lt;30%)</td>
<td>Homozygotes: fatty liver, steatorrhea, acanthocytosis, neurological abnormalities Heterozygotes: asymptomatic, fatty liver, loose stools, mild fat malabsorption, gallstones</td>
</tr>
<tr>
<td>ABL</td>
<td>Recessive</td>
<td>MTP</td>
<td>Absence of apoB-containing lipoproteins</td>
<td>Failure to thrive, steatorrhea, fat malabsorption, fatty liver, acanthocytosis, retinitis pigmentosa, progressive spinocerebellar degeneration</td>
</tr>
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</table>
Laboratory Diagnostics of HHBL and ABL

A lipid profile of absent or very low levels of triglycerides (<0.2 mmol/L), LDL cholesterol (<0.1 mmol/L), and apoB (<0.1 g/L) are indicative of HHBL and ABL (Lee & Hegele, 2014). Total cholesterol levels are usually less than half of normal (often 20-45 mg/dl), and triglycerides are only a few milligrams per deciliter (Sen et al., 2007).

Light microscopy of a blood smear will reveal acanthocytosis, which is a condition where the red blood cells are anomalously star-shaped (Anoop & Parker-Williams, 2009). More than 50% of the circulating erythrocytes may be composed of acanthocytes (Figure 2). Anemia may occur as well. The cause of acanthocytosis may be due to a lack of iron, folate, and other nutrients secondary to fat malabsorption. Additionally, accelerated hydroperoxidation of fatty acids may result in hemolysis and anemia (Zamel et al., 2008).
Figure 2. Erythrocytes in FHBL and ABL. The top left slide is from a normal person. The top right slide is from a FHBL heterozygote with an apoB-40.3 mutation. The bottom left slide is from a FHBL heterozygote with an apoB-6.9 mutation. The bottom right slide is from an ABL patient (Taken from Burnett & Hooper, 2008).

Fat Malabsorption and Fat Soluble Vitamin Deficiencies

Symptoms for ABL and HHBL present during infancy or the first 24 months of life. Chronic diarrhea, steatorrhea, and failure to thrive are signs of fat malabsorption. Vomiting and abdominal discomfort and distention may occur. However, these issues disappear when a low-fat diet is in regimen. When the intestinal epithelium
of untreated patients are examined, a “gelee blanche” or “white hoar frosting” appears. The enterocytes appear swollen with a clarified cytoplasm full of intracellular neutral lipid (Lee & Hegele, 2014).

If patients are diagnosed as adults, neurological and eye problems are the most stand-out clinical symptoms (Whitfield et al., 2004). These diagnoses may occur later in life because the cases are less severe. Thus, adult patients did not present with the typical gastrointestinal symptoms as children. Patients diagnosed as adults tend to have retinal degeneration and ataxia in their 20s if there has been no treatment or management of the disease (Lee & Hegele, 2014).

Without early intervention, patients can develop severe conditions including typical retinitis pigmentosa, severe ataxia, dysarthria, and absent reflexes. This can all lead to a shorter life and intense neurological dysfunction. Early diagnosis and treatment can delay or prevent these issues (Whitfield et al., 2004). Without intervention, some patients do not live beyond their 30s (Zamel et al., 2008). These neurological and retinal issues develop because of a deficiency in fat-soluble vitamins.

Deficiencies in vitamins A and E generally cause retinitis pigmentosa or retinal degeneration with varying severity. Symptoms include loss of night vision and/or
color vision (Whitfield et al., 2004). An eye exam may reveal atypical dark pigmentation randomly scattered on the retina, which can progress to expanding scotomas and blindness. Other less commonly observed eye problems include ptosis, ophthalmoplegia, and corneal ulcers (Zamel et al., 2008). Demyelination of cranial nerves due to a vitamin E deficiency can cause the first two conditions while a deficiency in vitamin A can cause corneal ulcers. Lacrimal glands and other ocular tissues depend on vitamin A and its metabolites for normal cell functions and growth (Lee & Hegele, 2014).

When both vitamins E and A are supplemented, retinal degeneration still occurs though at a reduced rate. The human retina expresses both MTP and apoB, so retinopathy could be due to defective inherent proteins rather than a vitamin E deficiency (Burnett & Hooper, 2008).

A deficiency in vitamin E can cause neurological problems because spinocerebellar axons become demyelinated, which eventually leads to immobility. Cerebellar issues occur in forms of ataxia and dysmetria (Pfeiffer, 2014). The posterior column function may be compromised leading to a loss of proprioception and deep tendon reflexes (Burnett & Hooper, 2008). Hyporeflexia, reduced vibratory sensation, muscle weakness, peripheral neuropathy, and a Friedrich’s-like ataxia are other symptoms (Zamel et al., 2008). Vitamin E
supplementation can either delay or prevent these neurological dysfunctions (Lee & Hegele, 2014).

Other fat-soluble vitamins may have slight deficiencies, but vitamin E deficiency is the greatest. Vitamin E is transported in the circulation by apoB-containing lipoproteins. This vitamin is essential for normal neurologic function and development. While the other fat-soluble vitamins A, D, and K are reduced in concentration in the body, these vitamins have other ways of transportation throughout the body. Supplementation with high doses of vitamin E does not normalize the vitamin E levels but only raises the levels to 30% of the lower limit of normal. Meanwhile, high doses of vitamin A can normalize vitamin A levels. Despite transport and absorption issues in the intestines, vitamin A can be transported in plasma by retinol-binding protein, which is not damaged in ABL and HHBL (Zamel et al., 2008). Some patients are reported to experience bleeding tendencies due to a vitamin K deficiency (Aminoff et al., 2012). There are documented cases of rickets due to a vitamin D deficiency or secondary calcium malabsorption (Hasosah, Shesha, Sukkar, & Bassuni, 2010; Narchi, Amr, Mathew, & El Jamil, 2001).
Non-Alcoholic Fatty Liver

In ABL and HHBL patients, liver biopsies may reveal hepatocytes with steatosis, which is also known as fatty liver. Sometimes, hepatic steatosis is reflected by higher serum transaminase levels in a blood sample (Burnett & Hooper, 2008). Fatty liver is defined when lipids accumulate in the liver and weigh more than 5% of the liver weight (Figure 3). On a light microscopy level, more than 5% of hepatocytes contain fatty droplets. Hepatic steatosis appears to be more prevalent in HHBL patients than ABL patients (Zamel et al., 2008). The mechanism for hepatic steatosis has not been elucidated. One explanation is that when apoB is not properly made, the apoB cannot be packed with neutral fatty acids while in the hepatocyte. As a result, the fat stays in the liver, and hepatic steatosis occurs (Harada et al., 2009).
Figure 3. FHBL patient’s liver biopsy. 70-80% of hepatocytes show steatosis (Taken from Ballestri et al., 2009).

Generally, hepatic steatosis is associated with obesity, type-2 diabetes, hyperlipidemia, insulin resistance, hypertension, hepatitis, and effects from certain drugs and toxins (Sen et al., 2007). However, fatty liver appears to have no major negative consequence in the majority of ABL and HHBL patients. Studies show that insulin resistance is dissociated from liver steatosis in HHBL and heterozygous FHBL – this suggests that fatty liver is an indication not a
cause of metabolic dysfunction (Amaro et al., 2010; Della Corte et al., 2013; Visser et al., 2011).

Difference In Genetics Between ABL and FHBL

Both ABL and HHBL have similar symptoms because the diseases have a similar root problem; apoB is not properly made or not made at all. However, the cause for the mutated apoB is different in ABL and HHBL. ABL is a recessive condition that is characterized by a defect in MTP. Meanwhile, FHBL is a codominant condition that is characterized by mutations in apoB itself (Lee & Hegele, 2014). Heterozygotes with FHBL have low LDL cholesterol levels, a resistance to atherosclerosis, and hepatic steatosis; however, they do not have any of the other the malignant symptoms. HHBL and ABL are the most severe forms of HBL (Burnett & Hooper, 2008).

There are more than 30 mutations described for ABL in the MTP gene while there are more than 60 mutations described in the literature for FHBL in the APOB gene (Lee & Hegele, 2014).
**Heterozygotes with FHBL**

FHBL is the most frequent monogenic form of HBL. FHBL is caused by a loss-of-function mutation in the \textit{APOB} gene, usually resulting in a truncated apoB protein (Tarugi et al., 2007). FHBL for both heterozygotes and homozygotes is associated with protection against atherosclerosis and has a prevalence of 1:3000. It is an autosomal codominant disorder (Burnett & Hooper, 2008). The heterozygous form is estimated to be found 1:500-1:1000 (Aminoff et al., 2012).

Heterozygotes with FHBL are generally asymptomatic or may have mild symptoms; however, they generally have hepatic steatosis. Their plasma LDL-cholesterol levels and apoB concentrations are usually below the 50\textsuperscript{th} percentile (Hooper & Burnett, 2013). LDL and apoB concentrations are generally one fourth to one third of the normal concentration (Burnett, Bell, Hooper, & Hegele, 2012b). Total cholesterol levels range from 40-180 mg/dl with the average around 90mg/dl. LDL concentrations are 25-45 mg/dl or less than 50\% of the average. ApoB levels are still very low (Sen et al., 2007).

FHBL heterozygotes can be differentiated from ABL carriers. FHBL heterozygotes exhibit low levels of apoB and LDL-cholesterol while ABL carriers have normal lipid profiles. This is consistent with the inheritance patterns (Lee & Hegele, 2014).
With low circulating plasma LDL levels, heterozygotes have a reduced risk of coronary heart disease, and their lifespan is thought to increase by 10 years on average. Their arterial walls exhibit less stiffness, which is indicative of cardiovascular protection (Burnett et al., 2012b). However, FHBL heterozygotes may still develop fatty liver. Serum liver enzymes ALT, AST, and GGT may be raised (Burnett & Hooper, 2008). Sometimes, oral fat intolerance and intestinal fat malabsorption may be reported (Tarugi et al., 2007). Acanthocytes are sometimes observed in heterozygous FHBL blood samples (Burnett & Hooper, 2008).

Heterozygotes are predicted to live a normal lifespan. There is no specific treatment for heterozygotes, but moderate supplements of vitamin E are sometimes recommended, even though neurological problems rarely occur in heterozygotes. When compared to homozygotes, heterozygotes rarely develop liver pathologies, but periodic clinical and lab examination are still recommended. Genetic counseling is recommended as well (Sen et al., 2007).

**Genetics of ABL**

ABL is due to a rare, autosomal, monogenic recessive mutation in *MTP* ("Abetalipoproteinemia," n.d.). MTP is a chaperone protein that helps add lipids
to apoB in the ER of hepatocytes and enterocytes (Tarugi et al., 2007). MTP is a heterodimer composed of a unique large subunit M and protein disulfide isomerase (PDI). Mutations in the large subunit M of MTP can cause an absence of MTP in ABL patients. MTP is essential for assembly and secretion of apoB from the liver and intestines (Gregg & Wetterau, 1994). In ABL patients, there are no apoB-containing lipoproteins in serum (Lee & Hegele, 2014). ApoB cannot be synthesized, so there is no LDL and VLDL in the blood (Aminoff et al., 2012). Patients with ABL have coronary arteries that are free of atherosclerotic lesions (Zamel et al., 2008). Lipid profiles for an ABL patient include severely low plasma levels of total cholesterol, VLDL, LDL, and nearly no apoB at all (Tarugi et al., 2007). Meanwhile, ABL carriers have normal plasma lipid levels (Tarugi et al., 2007).

Abetalipoproteinemia is a rare metabolic disease with approximately 100 cases described worldwide ("Abetalipoproteinemia," n.d.). Others estimate ABL to occur in 1:100,000 to 1:1,000,000 (Burnett, Bell, Hooper, & Hegele, 2012a; Zamel et al., 2008). Other names for ABL include abetalipoproteinemia neuropathy, acanthocytosis, apolipoprotein B deficiency, Bassen-Kornzweig Syndrome, Betalipoprotein deficiency disease, congenital betalipoprotein deficiency syndrome, and microsomal triglyceride transfer protein deficiency disease ("Abetalipoproteinemia," n.d.).
Current Treatment for Both ABL and FHBL

Treatment and management for both diseases involve a strict low-fat diet along with supplementation of essential fatty acids. High oral doses of fat soluble vitamins are given as well. Prognosis with treatment is generally excellent but may vary, and early diagnosis and treatment can reverse some neurological damage and stop neurological dysfunctions from progressing (Lee & Hegele, 2014). Nutritionists, lipidologists, gastroenterologists, hepatologists, ophthalmologists, and neurologists may be involved in the patient’s treatment plan (“Abetalipoproteinemia | Disease | Overview | Office of Rare Diseases Research (ORDR-NCATS),” n.d.).

Restriction of long-chain fatty acids prevents fat malabsorption and steatorrhea. Fat intake is restricted to 5-20 g/day, which prevents steatorrhea and accelerates growth (Kwiterovich Jr, 2013). Linoleic acid supplements such as 5 g corn oil or safflower oil/d may be given. Medium chain triglycerides (MCTs) as a dietary supplement may be an alternate for a fat source in diet because lipids are necessary for normal growth and development. MCTs are absorbed differently than other fats, which can prevent the intestinal discomfort (Schonfeld, Lin, & Yue, 2005). However, some say that MCTs may produce hepatic fibrosis, so they should be used cautiously if at all (Zamel et al., 2008).
High doses of fat-soluble vitamins are given orally as water emulsions. This process sidesteps the intestinal chylomicron assembly pathway via the portal circulation, so these vitamins can be absorbed. High dose oral vitamins A, E, and K are given. Moderate supplementation of vitamin E concentrations is recommended in those with heterozygous FHBL to prevent neurological problems (Burnett et al., 2012b). Injectable vitamins are also an option (Zamel et al., 2008). Oral Vitamin E is given in daily doses ranging from 2400 to 12000 IU (Zamel et al., 2008). Table 3 shows the overall diet plan for patients with ABL and HHBL.

Table 3. Summary of diet management of ABL and HHBL (Taken from Lee & Hegele, 2014).

<table>
<thead>
<tr>
<th>General</th>
<th>Lipids</th>
<th>Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Ensure adequate caloric intake</td>
<td>-Low fat (&lt;30% of total calories), with reduced long-chain fatty acids</td>
<td>-Oral fat-soluble vitamins:</td>
</tr>
<tr>
<td></td>
<td>-Oral essential fatty acids</td>
<td>-Vitamin E 100–300 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td>-Medium chain triglycerides generally unnecessary</td>
<td>-Vitamin A 100–400 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Vitamin D 800–1200 IU/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Vitamin K 5–35 mg/week</td>
</tr>
</tbody>
</table>

There are no current treatments for non-alcoholic fatty liver (Schonfeld et al., 2005). While the hepatic steatosis appears to be mostly harmless, studies indicate that any additional slight hepatic damage will induce and stimulate
fibrosis (Ballestri et al., 2009). There are reported cases where exercise may be effective in controlling macrovesicular steatosis (Harada et al., 2009).

There are no specific medications and standardized treatment plan for ABL and HBL; each case is managed with specific diet changes that work well for the individual (Lee & Hegele, 2014). See Tables 4 and 5 for general follow-up protocol for ABL and HHBL.
Table 4. ABL and HHBL general follow-up plan after diagnosis (Taken from Lee & Hegele, 2014).

<table>
<thead>
<tr>
<th>Clinical evaluation – every 6–12 months</th>
<th>Laboratory investigations – every year</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Lipids*</td>
</tr>
<tr>
<td></td>
<td>• total cholesterol</td>
</tr>
<tr>
<td></td>
<td>• triglyceride</td>
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<tr>
<td></td>
<td>• LDL-C</td>
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<tr>
<td>Diet</td>
<td>• HDL-C</td>
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<tr>
<td></td>
<td>• apo B</td>
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<tr>
<td></td>
<td>• apo A1</td>
</tr>
<tr>
<td>General</td>
<td>Vitamin supplementation</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>• AST</td>
</tr>
<tr>
<td>GI</td>
<td>• Appetite</td>
</tr>
<tr>
<td></td>
<td>• ALT</td>
</tr>
<tr>
<td></td>
<td>• GGT</td>
</tr>
<tr>
<td></td>
<td>• Total and direct bilirubin</td>
</tr>
<tr>
<td></td>
<td>• ALP</td>
</tr>
<tr>
<td></td>
<td>• Albumin</td>
</tr>
<tr>
<td></td>
<td>• Beta-carotene</td>
</tr>
<tr>
<td>Neurological</td>
<td>• Expected development for age</td>
</tr>
<tr>
<td></td>
<td>• 25-OH vitamin D</td>
</tr>
<tr>
<td></td>
<td>• Plasma or RBC vitamin E</td>
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<tr>
<td></td>
<td>• INR</td>
</tr>
<tr>
<td></td>
<td>• Vitamin B12</td>
</tr>
<tr>
<td></td>
<td>• Muscle pain or weakness</td>
</tr>
<tr>
<td></td>
<td>• Folate</td>
</tr>
<tr>
<td></td>
<td>• Calcium</td>
</tr>
<tr>
<td></td>
<td>• Phosphate</td>
</tr>
<tr>
<td></td>
<td>• Uric acid</td>
</tr>
<tr>
<td></td>
<td>• Thyroid stimulating hormone</td>
</tr>
</tbody>
</table>

Abbreviations: EFA, essential fatty acid; MCTG, medium chain triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; apo, apolipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; RBC, red blood cell; INR, international normalized ratio; CBC, complete blood count; DXA, dual energy X-ray absorptiometry

*lipid profile should absolutely be performed at baseline, however yearly follow-up is not absolutely essential as these levels typically remain stable over the long term
Table 5. ABL and HHBL general follow-up labs and examinations after diagnosis (taken from Lee & Hegele, 2014).

<table>
<thead>
<tr>
<th>Additional investigations: Age &gt; 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic ultrasonography</td>
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<tr>
<td>Neurological examination</td>
</tr>
<tr>
<td>Ophthalmological examination</td>
</tr>
<tr>
<td>Bone mineral density via DXA</td>
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<tr>
<td>Echocardiography</td>
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</table>
BIOCHEMISTRY OF ABL AND FHBL MUTATIONS

The biochemistry behind ABL and FHBL mutations provides context for understanding the clinical presentation of ABL and FHBL. An explanation for the range of severity in FHBL symptoms can be explained biochemically. Additionally, the mechanisms behind each disease can provide research leads for future drug treatments in ABL and FHBL. The unique mutations in ABL and FHBL may provide insight into other cholesterol diseases such as familial hypercholesterolemia and inspire new ideas for treatment.

ABL Mutations Biochemistry

Loss of function mutations in the microsomal triglyceride transfer protein cause ABL. MTP is a chaperone protein in the ER that helps fold nascent apoB and also transfers lipids onto the newly synthesized apoB (Ohashi et al., 2000). MTP is a heterodimer composed of a large subunit M and a common enzyme called protein disulfide isomerase PDI (Figure 4) (Shoulders et al., 1993). The M subunit is an 894 amino-acid 97 kDa protein. The MTP gene is located on chromosome 4q22-24 (Aminoff et al., 2012).
MTP has three major domains: N-terminal beta barrel domain (residues 22–297), middle alpha helical domain (residues 298–603), and the C-terminal domain (residues 604–894). The beta barrel domain facilitates MTP’s binding with the amino terminus of apoB while the alpha helical domain binds MTP to PDI and apoB (Hussain, Rava, Walsh, Rana, & Iqbal, 2012). These two domains are both globular and are homologous to another ancient protein vitellogenin, which is an apolipoprotein in egg laying animals. Meanwhile, the C-terminal domain is responsible for the lipid-binding enzymatic activity of MTP (Zamel, Khan, Pollex, & Hegele, 2008). Amino acids 666-736 in the C-terminal domain are homologous to amino acids 389-584 in cholesteryl ester transfer protein (Aminoff et al., 2012).
This suggests that certain lipid transferring activities are conserved across lipid-transfer enzymes.

MTP mutations can misfold apoB and thus produce a non-functional or non-existent lipoprotein. Additionally, a mutated MTP may be unable to enzymatically transfer lipids to apoB due to a mutation in enzymatic function. In ABL, no VLDL is secreted due to a defective apoB (Lee & Hegele, 2014). Without MTP and lipids, the nascent apoB is rapidly degraded; Figure 5 (Aminoff et al., 2012).

Figure 5. VLDL formation. First, apoB is translated. In conditions lipid-free MTP, apoB is transferred to the cytosol and degraded intracellularly. In conditions with MTP and lipids, triglycerides are packed into the center with apoB on the surface (Taken from Whitfield et al., 2004).
PDI is essential for the MTP complex function, but there are no reports of ABL with mutations in PDI (Wang & Hegele, 2000). Missense mutations in MTP can interfere with PDI binding, which again indicates the importance of PDI in the MTP complex (Burnett & Hooper, 2008). The purpose of PDI seems to be to stabilize the MTP complex because PDI is not involved in any of MTP’s enzymatic activities. PDI’s inherent enzymatic activities are not involved with MTP’s enzymatic activities either (Hussain et al., 2012).

Mutations in MTP in ABL patients usually feature a truncated protein devoid of function. Some other missense mutations have been reported along with less severe symptoms (Tarugi et al., 2007). However, in general, there is uncertainty regarding a relationship between MTP genotype and severity of symptoms (Lee & Hegele, 2014; Wang & Hegele, 2000). More than 30 mutations in MTP have been found. The majority are small point mutations (missense, nonsense, and splicing) that cause splicing errors or premature truncations throughout the gene’s 18 exons (Figure 6). MTP missense mutations may prevent the M subunit from binding with PDI or apoB. If binding does occur, the mutation may prevent MTP from transferring lipids into apoB (Burnett & Hooper, 2008). Most of these mutations are contained within families or ethnic communities (Burnett, Bell, Hooper, & Hegele, 2012a).
Figure 6. MTP gene and ABL mutations. Black boxes are exons (Taken from Zamel, Khan, Pollex, & Hegele, 2008).
**FHBL Mutations Biochemistry**

Loss-of-function mutations in APOB cause FHBL; more than 60 mutations in APOB have been found that cause FHBL. The APOB gene is located on chromosome 2 (Harada et al., 2009). Most mutations that cause FHBL are point mutations that cause splicing errors or premature truncations (Lee & Hegele, 2014). Missense, nonsense, and frameshift splicing mutations in the 29 exons of APOB can lead to truncated forms of apoB (Figure 7). The most common type of mutations for FHBL are missense mutations in the amino terminal region (Burnett et al., 2012b).

![Figure 7](image)

**Figure 7. Selected FHBL mutations in the 29 exons of APOB.** Many mutations are located in exon 26 and are composed of nonsense and frameshift mutations (Taken from Whitfield, Barrett, Bockxmeer, & Burnett, 2004).

The degree of truncation is directly related to the severity of symptoms in FHBL. ApoB-100 is the largest apolipoprotein with 4,536 amino acids. Truncation mutations can result in proteins as short as apoB-2 (2% of full length apoB-100)
or as long as apoB-89 (89% of full length apoB-100). The shorter the truncation, the smaller the number of triglyceride molecules that the apoB can transport (Sen et al., 2007). HHBL patients with apoBs shorter than apoB-48 have the same clinical phenotype as ABL patients. Meanwhile, HHBL patients with longer apoB truncations may have fatty liver as the only symptom of the disease (Lee & Hegele, 2014). A truncated apoB shorter than 54.5 is a risk factor for developing fatty liver (Sen et al., 2007). HHBL patients with mutations longer than apoB-48 have milder symptoms than HHBL patients with shorter mutations (Burnett et al., 2012b).

HHBL patients with the most severe phenotype have truncated apoBs smaller than apoB-30 (Lee & Hegele, 2014). Heterozygotes with apoB mutations shorter than apoB-48, may only have fatty liver and mild fat absorption. Meanwhile, homozygotes with long truncations like apoB-87 are asymptomatic or may just have fatty liver (Burnett et al., 2012b).

Mutated apoBs larger than apoB-29 can be detected in plasma by Western blot analysis; however, shorter truncations are not detectable in plasma and can only be identified by DNA sequencing. Shorter apoBs cannot acquire enough lipids for a hydrophobic core, so they are degraded intracellularly (Burnett & Hooper, 2008). The C terminus of apoB-37 and the C terminus of apoB-42 regulate apoB's intracellular stability and the secretion of apoB from the liver. In vitro
studies show that the initial 884 amino acids on apoB are required for apoB and MTP binding. Therefore, the smallest form of apoB to bind to MTP would be apoB-19.5 (Whitfield et al., 2004).

The apoB secretion rate from the liver is related to the amount of truncation – 1.4% reduction in secretion rate for each 1% of apoB truncated. Smaller apoBs are produced at a slower rate than apoB-100; however, the smaller apoBs are cleared from circulation faster than apoB-100 (Whitfield et al., 2004). For example, apoB-89 is produced 15% more slowly than apoB-100, and apoB-89 lipoproteins are cleared twice as fast as apoB-100 lipoproteins. Lacking the carboxy terminal of apoB increases the affinity for LDLR. Truncations smaller than apoB-70.5 are cleared extremely fast by the kidneys (Schonfeld et al., 2005).

Other mutations in APOB exist outside of truncation mutations. Certain mutations near the N terminal of apoB can increase binding to MTP, which will eventually cause misfolding of apoB due to too tight of a binding. ApoB's βα1 domain near the N-terminal interacts with MTP; Figure 8. Two mutations L343V and R463W occur in this region, which result in a low-cholesterol phenotype for heterozygotes. L343 and R463 are conserved among other mammals, which suggests these particular residues are important (Burnett & Hooper, 2008). Mutations L343V and R463W impair secretion of apoB-100 and VLDL in in vitro studies. There is increased ER retention of apoB and increased apoB binding to
MTP and BiP, which is another general chaperone protein. These mutations alter the folding of the alpha helical domain in the N terminus of apoB (Burnett & Hooper, 2008).

**Figure 8. ApoB-100 gene and apoB five structural domains.** The domains are labeled from left to right: beta alpha 1, beta 1, alpha 2, beta 2, and alpha 3. The site of cleavage to form apoB-48 is shown by the arrow (Taken from Whitfield et al., 2004).

At the other end of the apoB protein, the carboxy terminal regulates LDLR uptake. A lack of the carboxy terminus in apoB-100 results in better LDLR binding thus better LDL uptake and clearance from plasma (Burnett & Hooper, 2008). Mutations in *APOB* affecting the LDLR binding domain like R3527Q are associated with hypercholesterolemia, the opposite phenotype of FHBL. LDL cholesterol and apoB are double the normal levels (Lee & Hegele, 2014). Defects in the carboxy terminus of the LDLR binding domain of apoB cause familial ligand-defective apoB-100, a form of autosomal dominant hypercholesterolemia (Whitfield et al., 2004).
DISCUSSION

There are no discussions in the literature regarding the search for a biochemical cure for FHBL and ABL. Currently both diseases are clinically managed with diet changes and vitamin supplements. Both diseases have excellent prognoses once the proper dietary regimen is established. FHBL and ABL are manageable conditions that do not seem to have a significant decrease in quality of life with treatment. As a result, there is no need to explore risky treatment options in gene therapy or other drastic medications when a low-fat diet with vitamin replacement therapy is sufficient to treat the symptoms. However, depending on coexisting risk factors and conditions, hypothesizing other methods of curing FHBL and ABL may lead to insights that have real world application in this or other cholesterol diseases.

For both diseases, replacing the defective MTP or apoB with a working protein is one curative method. Gene therapy could place a functional MTP or apoB back into the hepatocyte or enterocyte. Enzyme or protein replacement therapy could work as well. Lipoproteins could be directly infused into the patient to increase LDL cholesterol in the plasma. While many of these ideas would be expensive and thus a cost analysis would be needed, the basic idea of placing the normal MTP or apoB back in the body is worthwhile. There would be no need to delete the mutated versions due to the recessive inheritance pattern of ABL and the
codominant inheritance pattern of FHBL. Both the mutated and normal versions could co-exist with a normal phenotype. Such treatments could help determine threshold levels of MTP and apoB required for a normal phenotype and lead to questions such as how much normal MTP needs to exist to override the effects of the mutated MTP? These threshold studies could have implications in the future design of cholesterol-lowering drugs. How much of mutated MTP is needed to turn off the effects of normal MTP is another intriguing question. Lastly elucidating the inheritance pattern of FHBL and ABL can provide further clues as to how to properly dose cholesterol-lowering drugs.

FHBL and ABL are unique diseases in that the disease mutations themselves have inspired treatment for other cholesterol diseases. Recently, two drugs are in the process of clinical trials to treat familial hypercholesterolemia: Lomitapide and Mipomersen. Lomitapide is an MTP inhibitor, which mimics ABL (Davis & Miyares, 2014). Mipomersen is an apoB synthesis inhibitor, which mimics FHBL (Thomas et al., 2013). Studying the biochemistry in FHBL and ABL can provide other therapeutic targets for hypercholesterolemia.

Perhaps another therapeutic target for hypercholesterolemia is a molecule that permanently attaches apoB to MTP. One FHBL mutation in apoB causes increased binding to MTP thus resulting in less VLDL secretion and greater apoB retention in hepatocytes. If a medication could permanently bind apoB to MTP
thus preventing lipoprotein formation, LDL levels could be reduced. However, a side effect and risk of this mechanism is fatty liver because FHBL patients with this mutation have non-alcoholic fatty liver.

Another potential therapeutic target for FH is PDI. MTP requires both the large M subunit and PDI to form a working MTP complex – MTP would not be able to function without proper binding to PDI. Perhaps a molecule could be made to prevent MTP heterodimer formation by targeting PDI. Without MTP, lipids cannot be added to apoB and lipoproteins cannot be made.

ApoB truncation could be a method of treating hypercholesterolemia. The severity of symptoms in HHBL is directly related to the amount by which apoB is truncated; the greater the truncation, the more severe the symptoms. Patients with longer truncated apoBs such as apoB-89 are generally asymptomatic yet appear to have all the cardiovascular benefits. A future cholesterol-lowering medication could incorporate the idea of truncating apoBs to lower plasma LDL cholesterol. Stopping the transcription or translation of apoB earlier can form a truncated protein such as apoB-89. Hypobetalipoproteinemia could be induced except without all the negative symptoms.

The interaction of “opposite” mutations on apoB may provide useful information for future drug treatments in hypocholesterolemia and hypercholesterolemia.
Except for the truncation mutations that delete parts of apoB, most apoB mutations that cause FHBL are near the N terminus while mutations on the carboxy terminus cause hypercholesterolemia. What happens when both mutations are present? The FHBL mutation would interfere with MTP binding thus releasing less VLDL and LDL into circulation; on the other hand, a mutation that decreases LDLR affinity on the carboxy terminus would allow the meager amount of VLDL and LDL to circulate for an even longer period of time. The secretion rate for apoB would not change, but the clearance rate would be decreased. Over time, would LDL levels build up? Would the two mutations cancel out each other and thus produce a normal phenotype? Studies into questions such as these may provide valuable information for future therapeutic designs.

More research into apoB intracellular degradation in hepatocytes could help find new therapeutic targets in cholesterol lowering medication. It is known that in FHBL patients, truncated apoBs that are too short to bind to MTP end up being degraded intracellularly. Studying this mechanism in detail might reveal a way to degrade apoB proteins before binding with MTP. If so then a medication could tag apoB for degradation and be utilized as another approach to treat hypercholesterolemia.
Studies in FHBL and ABL have led to insights in other diseases. For example, one symptom of FHBL and ABL that has already been of interest to many researchers is the non-alcoholic fatty liver. FHBL and ABL helped show that fatty liver is dissociated from insulin resistance. This shows the importance of studying rare diseases that already have excellent management plans; such diseases may play roles in other diseases or help elucidate processes in other diseases.

Recently, new mutations in different genes that display a similar clinical phenotype as FHBL have been identified. Nonsense mutations in proprotein convertase subtilisin kexin type 9 (PCSK9) have been associated with hypocholesterolemia as well, but these mutations do not have the same systemic symptoms such as steatorrhea and conditions caused by fat-soluble vitamin deficiencies (Burnett & Hooper, 2008). PCSK9 is a serine protease that degrades LDLR and regulates the number of LDLRs in the liver – inactivation of PCSK9 causes more LDLRs and thus more LDL uptake from plasma thus resulting in hypobetalipoproteinemia (Harada et al., 2009). Homozygous PCSK9 deficiency is a rare condition, more so than ABL and FHBL, and is autosomal codominant. Loss-of-function mutations are more common in PCSK9 than gain-of-function mutations (Burnett & Hooper, 2008). Heterozygotes have lower plasma LDL cholesterol levels and plasma apoB, and homozygotes do not have as low of LDL and apoB as ABL and HHBL. No fatty liver developments occur in carriers of the PCSK9 loss-of-function mutation (Burnett, Bell, Hooper, & Hegele,
deficiency could lead to other therapeutic targets in lowering cholesterol.

Another condition with a similar clinical phenotype as HHBL and ABL is familial combined hypolipidemia. Familial combined hypolipidemia is another rare condition with extremely low but not absent levels of apoB-containing lipoproteins. This is due to homozygous mutations in angiopoietin-like protein 3 ANGPTL3. Both PCSK9 deficiency and familial combined hypolipidemia are only present in a few number of families in the world (Burnett et al., 2012). More research is necessary in these rare diseases to better understand how LDL levels are manipulated, which can provide future therapeutic targets in lowering cholesterol.
CONCLUSION

Although cholesterol levels are considered to be polygenic, monogenic cholesterol diseases can drastically change a person’s cholesterol levels. ABL and FHBL are monogenic diseases of hypobetalipoproteinemia, which is defined as having total cholesterol, LDL cholesterol, or total apoB levels below the 5th percentile in a population after adjusting for age, gender, and race. ABL is a rare, autosomal, recessive disease caused by a mutation in MTP. FHBL is a rare, autosomal, codominant disease caused by a mutation in APOB. ABL and HHBL have the same clinical symptoms: steatorrhea, neurological dysfunction, vision problems, and non-alcoholic fatty liver. Patients have very low or absent apoB and LDL cholesterol. Neurological and retinal problems are caused by a deficiency in the fat-soluble vitamins. Implementing a low-fat diet routine along with vitamin supplementations will ameliorate most symptoms except for hepatic steatosis. Heterozygous FHBL is generally asymptomatic or may present with mild symptoms with low apoB and cholesterol levels. Both ABL and FHBL cause a reduced risk in cardiovascular diseases.

ABL is caused by mutations in MTP, which is a chaperone protein in the ER that helps fold nascent apoB and then transfers lipid onto apoB. MTP is a heterodimer composed of a large subunit M and PDI. All mutations occur in the M subunit. A defective MTP either cannot fold or cannot transfer lipids to apoB,
which ends up being rapidly degraded. No VLDL is secreted from the liver. There is uncertainty regarding a relationship between MTP genotype and severity of symptoms.

FHBL is caused by loss-of-function mutations in \( APOB \). Most mutations produce a truncated apoB, and a few mutations include missense mutations in the amino terminal region. In HHBL, severity of symptoms is directly related to the degree of truncation. Homozygotes with long truncations like apoB-87 are asymptomatic or may only have hepatic steatosis while homozygotes with short truncations like apoB-48 have severe symptoms. A few FHBL mutations cause increased binding to MTP; apoB is eventually misfolded, and VLDL is not secreted from the liver.

Studying FHBL and ABL contributes to finding new therapeutic targets for hypercholesterolemia. Lomitapide is an MTP inhibitor that mimics ABL’s mutant mechanism. Mipomersen is an apoB synthesis inhibitor, which mimics FHBL’s mutant mechanism. The purpose of both drugs is to treat familial hypercholesterolemia. Other suggested targets include a drug used to permanently bind apoB to MTP, which mimics an FHBL mutation. This way, no apoB and VLDL can be released from the hepatocyte. Preventing PDI from binding to the large M subunit is another target. ApoB truncation is another mechanism to lower cholesterol – HHBL patients with longer truncated apoBs such as apoB-89 are generally asymptomatic yet receive all the cardiovascular
benefits. Additionally, studying how truncated apoBs are degraded might be another approach to treat hypercholesterolemia.

Two new diseases with similar phenotypes as ABL and FHBL are homozygous PCSK9 deficiency and familial combined hypolipidemia. PCSK9 deficiency causes hypocholesterolemia as well but does not cause the negative systemic effects such as steatorrhea and neurological dysfunction. No fatty liver develops either. Familial combined hypolipidemia is caused by homozygous mutations in ANGPTL3. More research into PCSK9 and ANGPTL3 can contribute to the field of hypocholesterolemia, which can give new leads in finding new cholesterol-lowering medication.
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- Boston, MA
- Assist residents with activities of daily living

02/11 – 07/11 Patient Care Safety Aide
- Tufts Medical Center
- Boston, MA
- Provided one-on-one patient observation and report patient condition to nursing and medical staff

Volunteer Work
07/12 – present Pediatric Volunteer
- Boston Medical Center
- Boston, MA
- Engage with pediatric patients in outpatient clinic waiting rooms by reading and working on art projects