Genetic Abetalipoproteinaemia and Hypobetalipoproteinaemia

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Introduction

Inherited diseases of lipoprotein metabolism may give rise to marked hypocholesterolaemia with low or absent levels of betalipoproteins, depending on the gene involved and mode of inheritance of the condition, together with the severity of the mutation or mutations present [1, 2].

The most extreme form of these disorders is abetalipoproteinaemia (Online Mendelian Inheritance in Man (OMIM) 200100), a very rare recessive disorder characterised by the absence of apolipoprotein (apo) B-containing lipoproteins in plasma, leading to a variable clinical phenotype that presents in early childhood with fat malabsorption, steatorrhoea, and failure to thrive, and may include progressive neurological and ophthalmological abnormalities as the patient ages [3]. The molecular basis of this disorder is the inheritance of two mutations in the microsomal triglyceride transfer protein gene (*MTTP*), a chaperone protein critical for the assembly and secretion of apoB in the formation of very low-density lipoprotein (VLDL) and chylomicrons.

Low plasma concentrations of low-density lipoprotein (LDL)-cholesterol and apoB are observed in familial hypobetalipoproteinaemia (OMIM 107730), a codominant disorder of lipoprotein metabolism caused by the inheritance of a mutation in *APOB,* usually giving rise to a truncated apoB protein [4]. Patients are generally asymptomatic, but may be at increased risk of fatty liver disease. Inheritance of two such mutations in *APOB* is known as homozygous familial hypobetalipoproteinaemia and is clinically indistinguishable from abetalipoproteinaemia.

Chylomicron retention disease (OMIM 246700) is characterised by the selective absence of apoB-48 containing particles. Instead of being incorporated into chylomicrons, lipid droplets accumulate within the enterocytes [5]. Clinical findings include fat malabsorption, diarrhoea, abdominal distension, vomiting, and failure to thrive. Patients with chylomicron retention disease inherit two defective copies of secretion associated, Ras related GTPase 1B (*SAR1B*), the product of which is critical for the intracellular trafficking of chylomicron particles.

In recent years, additional causes of inherited hypobetalipoproteinaemia have been found in the proprotein convertase subtilisin kexin 9 (*PCSK9*) and the angiopoietin-like 3 (*ANGPTL3*) genes, although these have not been associated with any clinical symptoms. Loss-of-function mutations in *PCSK9* result in reduced concentrations of LDL-cholesterol in a gene dose-dependent

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A. Garg (ed.), *Dyslipidemias,* Contemporary Endocrinology,
DOI 10.1007/978-1-60761-424-1_14,

manner, leading to a lifetime low risk of cardiovascular disease [6]. Mutations in *ANGPTL3* are associated with recessive familial combined hypolipidaemia, characterised by a reduction in all plasma lipids, including high-density lipoprotein (HDL)-cholesterol [7, 8].

This chapter reviews the molecular basis, pathogenesis, and clinical aspects of these disorders of apoB production and catabolism, focusing on abetalipoproteinaemia, familial hypobetalipoproteinaemia, and chylomicron retention disease.

History

Abetalipoproteinaemia was originally named Bassen–Kornzweig syndrome, after the two physicians who in 1950 described the clinical association of peripheral blood acanthocytosis, atypical retinitis pigmentosa, and ataxia [9]. An autosomal recessive mode of inheritance was suggested, but it was not until 1958 that the observation of low levels of serum cholesterol was made, and in 1960 the absence of beta-migrating lipoproteins by electrophoresis (betalipoproteins) described, leading to the name of the disease being changed to abetalipoproteinaemia [10]. The distinction was then made between abetalipoproteinaemia and homozygous familial hypobetalipoproteinaemia, whereby carriers of familial hypobetalipoproteinaemia have marked hypocholesterolaemia while carriers of abetalipoproteinaemia do not [11].

In 1987, a truncated apoB was found in the plasma of a family with familial hypobetalipoproteinaemia [12], leading to a four-nucleotide deletion being identified in the *APOB* gene [13]. The finding of absent MTTP in hepatic and intestinal microsomes in 1992 suggested that defects in this protein were the cause of abetalipoproteinaemia [14], with mutations subsequently identified in the *MTTP* gene the following year [15, 16].

Chylomicron retention disease was originally named Anderson's disease, after the physician who in 1961 described an infant with fat malabsorption and fat-laden enterocytes on histology, in whom chylomicrons were absent from plasma after meals, and plasma lipids and fat-soluble vitamin levels were low [17]. It was subsequently shown that in Anderson's disease, the enterocytes reacted intensely to monoclonal antibodies to apoB-48, but not to those selectively reactive with apoB-100 [18]. In 1991, the *APOB* gene was excluded as a cause of Anderson's disease [19]. In 2003, mutations in the *SAR1B* gene were identified in patients with Anderson's disease and chylomicron retention disease, revealing that they were, in fact, the same disease [20].

Epidemiology

Data from the Framingham Offspring Study identified persistent hypobetalipoproteinaemia in 1.9% of over 3800 individuals, and a truncated apoB species causing familial hypobetalipoproteinaemia in only one of these subjects [21]. This gives an estimated prevalence of the condition at ~1 in 3000, taking into account that the immunoblot testing method used does not detect circulating plasma apoB of a size less than 30% of the full-length protein. The prevalence of abetalipoproteinaemia and chylomicron retention disease is unknown, but these conditions appear to be extremely rare (<1 in 1 million).

Heterozygous *PCSK9* nonsense mutations can be found in ~2% of Africans and African-Americans [22, 23], which predicts homozygosity in ~1 in 10,000 in these populations.

Etiology and Pathogenesis

Abetalipoproteinaemia

Patients with abetalipoproteinaemia carry two defective copies of the *MTTP* gene on chromosome 4q22–24. The role of MTTP in this disorder was first implicated in 1992, when its activity was not detected in intestinal biopsies of patients with abetalipoproteinaemia [14]; mutations in the *MTTP* gene were subsequently described [16]. *MTTP* encodes an 894 amino acid protein, which forms a heterodimer with the ubiquitous endoplasmic reticulum enzyme protein disulfide isomerise (PDI) [24]. The function of the MTTP heterodimer is to facilitate the transfer of lipids to nascent apoB by a shuttle mechanism [24]; lack of MTTP activity results in insufficient lipidation

of nascent apoB and targets the apoB to a degradation pathway [25], preventing the secretion of triglyceride-rich lipoproteins. Mutations in *MTTP* associated with abetalipoproteinaemia may disrupt production of the normal MTTP protein, disrupt its binding with the PDI subunit, or affect MTTP's lipid transfer activity [26–28].

Familial Hypobetalipoproteinaemia

In familial hypobetalipoproteinaemia, mutations in the *APOB* gene on chromosome 2p23–24 either abolish the expression of apoB or interfere with the translation of full-length apoB leading to formation of prematurely truncated apoB forms [1, 30–32]. These apoB truncations have traditionally been named according to the centile system that also gave the name to apoB-48. The majority of mutations are nucleotide substitutions and deletions in exon 26, which at over 7500 nucleotides is one of the largest exons in the human genome. Several missense mutations in the N-terminal βα1 domain of apoB causing familial hypobetalipoproteinaemia have also been described [33–35]. The mutation R463W was shown to cause impaired secretion of VLDL by impaired endoplasmic reticulum exit and enhanced binding of the mutant protein to MTTP [33]. It is worth noting that missense mutations in the LDL-receptor-binding domain in the carboxyl-terminus of apoB cause familial ligand-defective apoB-100, a form of familial hypercholesterolaemia [36].

In patients with familial hypobetalipoproteinaemia, truncated forms of apoB are produced at lower rates (about 25%) than apoB-100 [37]. The secretion rate was shown to be reduced by about 1.4% for each 1% of apoB truncated [38]. However, for every 10% decrease in apoB length, there is a 13% reduction in the lipoprotein core volume, indicating that the lipid content of secreted apoB-containing lipoproteins is decreased as apoB is shortened [39]. Truncated apoB species shorter than apoB-30 are not detectable in plasma; this appearing to be the minimum length of apoB that is required for MTTP-dependent lipoprotein assembly. Shorter apoB species are unable to acquire sufficient lipid, leading to intracellular degradation rather than secretion [40]. In addition, clearance of the truncated apoB species is faster than the clearance of apoB-100, particularly for the longer truncations such as apoB-89 that contain the LDL-receptor-binding domain, resulting in enhanced LDL-receptor-binding [41].

Linkage analysis in families with familial hypobetalipoproteinaemia without mutations in *APOB* has identified chromosomes 3p21.1–22 and 10q25.1–10q26.11 as susceptibility loci, but the genes responsible remain to be identified [42, 43].

Chylomicron Retention Disease

Mutations in *SAR1B,* a member of the Sar1-adenosine diphosphate (ADP)-ribosylation factor family of small GTPases that control the intracellular trafficking of proteins, are the cause of chylomicron retention disease [20]. SAR1B is needed for the fusion of the intestine specific pre-chylomicron transport vesicle to the Golgi apparatus, allowing transport of chylomicrons through the cellular secretory pathways [44]. Mutations in *SAR1B* result in the inability to secrete chylomicrons, resulting in the accumulation of lipid droplets within the enterocytes.

Other Molecular Causes of Hypobetalipoproteinaemia

PCSK9 is an important regulator of plasma LDL-cholesterol concentrations [45]. It is a protease that binds to the LDL-receptor and targets it for lysosomal degradation within hepatocytes. Gain-of-function missense mutations in *PCSK9* can cause a severe autosomal dominant form of hypercholesterolaemia [46]. In contrast, nonsense and loss-of-function *PCSK9* missense mutations increase the number of LDL-receptors on the cell surface and, therefore, the number of LDL particles able to be internalised by the cell, reducing both circulating LDL-cholesterol concentrations and coronary heart disease risk (Fig. 14.1).

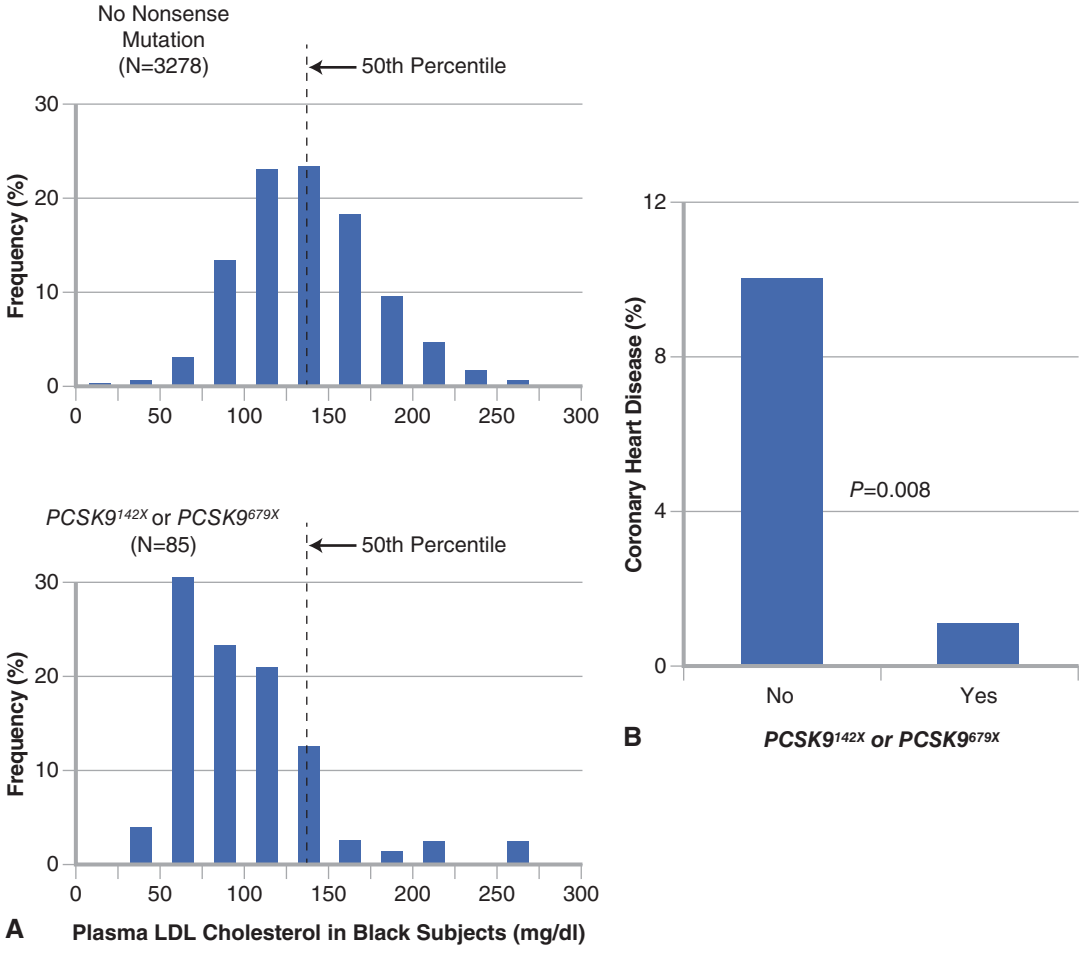

Fig. 14.1 Distribution of plasma LDL cholesterol levels and incidence of coronary heart disease, according to the presence or absence of a *PCSK9*^{142X} or *PCSK9*^{679X} allele. **a** The distribution of plasma LDL-cholesterol levels at baseline among 3278 black subjects who did not carry a *PCSK9* nonsense mutation (*top*) compared to the 85 subjects who carried either *PCSK9*^{142X} or *PCSK9*^{679X}. **b** The percentage of participants from these two groups who had no evidence of coronary heart disease (CHD) at baseline and in whom CHD developed during 15 years of follow-up. *LDL* low-density lipoprotein, *PCSK9* proprotein convertase subtilisin kexin 9. (Adapted from, Cohen 2007) [6]

ANGPTL3 gene mutations are associated with a combined hypolipidaemia. The function of ANGPTL3 appears to be the reversible inhibition of lipase activity, involving endothelial lipase [47], lipoprotein lipase [48], or hepatic lipase [49]. The disruption of ANGPTL3 production would therefore increase lipolysis, enhancing clearance of lipoproteins and decreasing circulating lipid concentrations.

Classification

Lipoprotein disorders causing primary hypocholesterolaemia—abetalipoproteinaemia and hypobetalipoproteinaemia—are classified depending on the lipid biochemical phenotype, gene involved, and mode of inheritance of the condition, together with the severity of the mutation or mutations present (Table 14.1).

Table 14.1 Lipoprotein disorders causing genetic abetalipoproteinaemia and hypobetalipoproteinaemia

Lipoprotein disorder	Gene	Inheritance	Biochemical phenotype	Clinical phenotype
Abetalipoproteinaemia	*MTTP*	Recessive	Absence of LDL and chylomicrons	Variable; includes failure to thrive, steatorrhoea, progressive neurological and ophthalmological abnormalities
Familial hypobetalipoproteinaemia	*APOB*	Codominant	Heterozygous: LDL-cholesterol 30% levels of normal for age and sex Homozygous: absence or very low levels of LDL-cholesterol	Heterozygous: generally asymptomatic, may include fatty liver Homozygous: indistinguishable from abetalipoproteinaemia
Chylomicron retention disease	*SAR1B*	Recessive	Absence of chylomicrons LDL-cholesterol < 50% levels of normal for age and sex	Variable; includes failure to thrive, steatorrhoea, and progressive neurological abnormalities
Familial hypobetalipoproteinaemia	*PCSK9*	Codominant	~40% reduction in LDL per allele	None
Familial combined hypolipidaemia	*ANGPTL3*	Recessive	Reduced levels of all plasma lipoproteins	None

MTTP microsomal triglyceride transfer protein, *LDL* low-density lipoprotein, *APOB* apolipoprotein B, *SAR1B* secretion associated, Ras related GTPase 1B, *ANGPTL3* angiopoietin-like 3

Clinical and Physical Findings

Abetalipoproteinaemia

Abetalipoproteinaemia is associated with multisystem manifestations. Patients with abetalipoproteinaemia typically present in childhood with failure to thrive, growth failure, malabsorption of fat, acanthocytosis, and low plasma cholesterol and vitamin E concentrations [50]. Later in life, retinitis pigmentosa, spinocerebellar ataxia, and myopathy have complicated most of the cases.

Gastrointestinal manifestations of abetalipoproteinaemia include steatorrhoea and fat-soluble vitamin deficiency. Fat malabsorption is a central feature of abetalipoproteinaemia and is usually observed in the neonatal period with diarrhoea, vomiting, and failure to thrive. The severity of the intestinal symptoms relates to the fat content of the diet, and usually decreases with age, in part, due to the avoidance of dietary fat in these patients [51]. A yellow colour of the duodenal mucosa has been observed on endoscopy as a result of intestinal lipid accumulation [52]. A characteristic intestinal histology shows normal villi with enterocytes that are distended with lipid droplets (Fig. 14.2).

Haematological manifestations of abetalipoproteinaemia include acanthocytosis (Fig. 14.3) with acanthocytes comprising 50% or more of circulating erythrocytes [51]. Of interest, normal erythrocytes become acanthocytic after transfusion into abetalipoproteinaemia patients and circulate in plasma [50]. Acanthocytosis in abetalipoproteinaemia could be a result of either vitamin E deficiency or an altered membrane lipid composition. Other abnormalities include low erythrocyte sedimentation rates, decreased red cell survival [53], anaemia, hyperbilirubinaemia and haemolysis [54], and increased international normalised ratio due to vitamin K deficiency [55].

Hepatic manifestations of abetalipoproteinaemia include abnormal liver transaminases with hepatomegaly. Liver biopsies have shown marked hepatic steatosis that may or may not be associated with increased liver transaminase concentrations [50]. Steatosis can progress to steatohepatitis and fibrosis [56], and, importantly, cirrhosis has been reported in abetalipoproteinaemia [57].

Neuromuscular manifestations of abetalipoproteinaemia typically begin in the first or second decade of life, affecting both the central and peripheral nervous system, with either upper

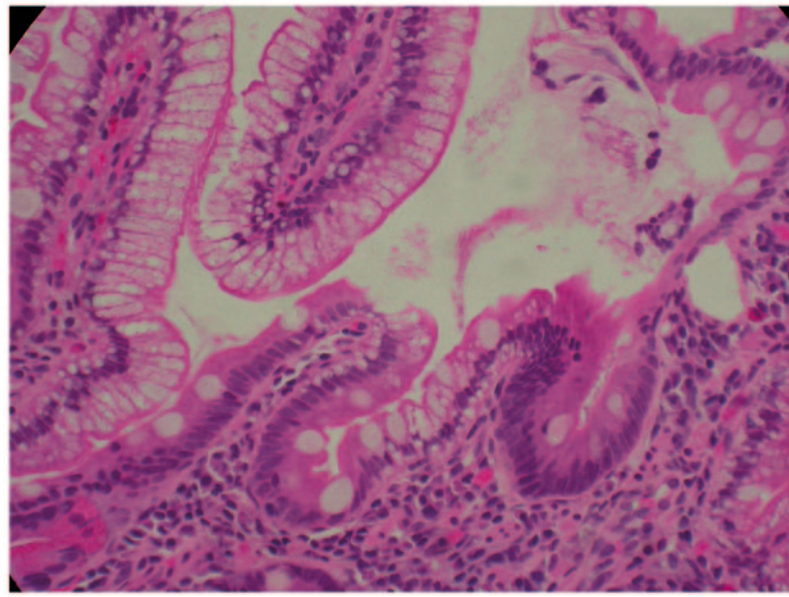

Fig. 14.2 Haematoxylin and eosin-stained light micrograph of the duodenal biopsy from a patient with homozygous familial hypobetalipoproteinaemia, showing marked cytoplasmic microvacuolization of enterocytes (magnification, ×400). (Reprinted with permission, Vongsuvanh [86])

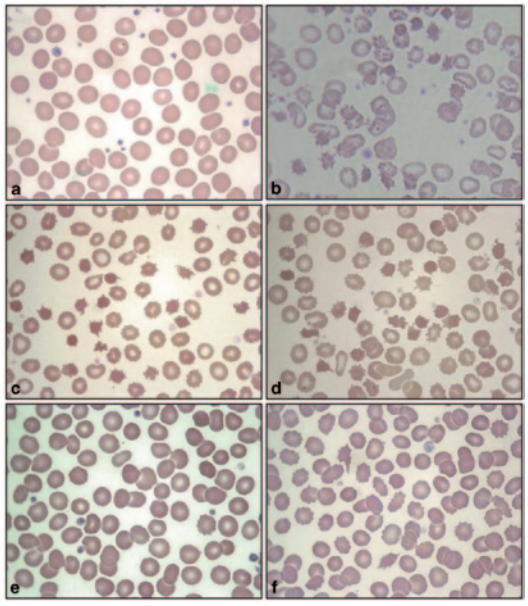

Fig. 14.3 Acanthocytes in abetalipoproteinaemia and familial hypobetalipoproteinaemia. **a** 'Normal' subject. **b** homozygous familial hypobetalipoproteinaemia. **c** and **d** abetalipoproteinaemia. **e** and **f** two different subjects with heterozygous familial hypobetalipoproteinaemia carrying apoB-6.9 mutation

or lower motor neuron abnormalities or both. Neurological signs related to the deficiency of vitamin E include the progressive loss of deep tendon reflexes, vibratory sense and proprioception, muscle weakness and, eventually, a Friedrich's-like ataxia [58].

Ophthalmological manifestations of abetalipoproteinaemia are variable with the most prominent being an atypical pigmentation of the retina characterised by small, irregularly distributed white spots on fundoscopy [59]. Although visual acuity can be affected during the first decade, many patients are asymptomatic until adulthood, with loss of night vision and/or colour vision occurring early in the course of disease. Patients develop annular scotomas with macular sparing that slowly enlarge with progression of the retinopathy. Without treatment, complete visual loss can occur.

Familial Hypobetalipoproteinaemia

Patients with heterozygous *APOB*-linked familial hypobetalipoproteinaemia are often asymptomatic; however, most develop fatty liver (Figs. 14.4 and 14.5), and mild acanthocytosis and fat malabsorption can occur [60, 61]. The clinical and biochemical features of familial hypobetalipoproteinaemia in homozygous and compound heterozygous form are, in general, indistinguishable from those of abetalipoproteinaemia [62]. How-

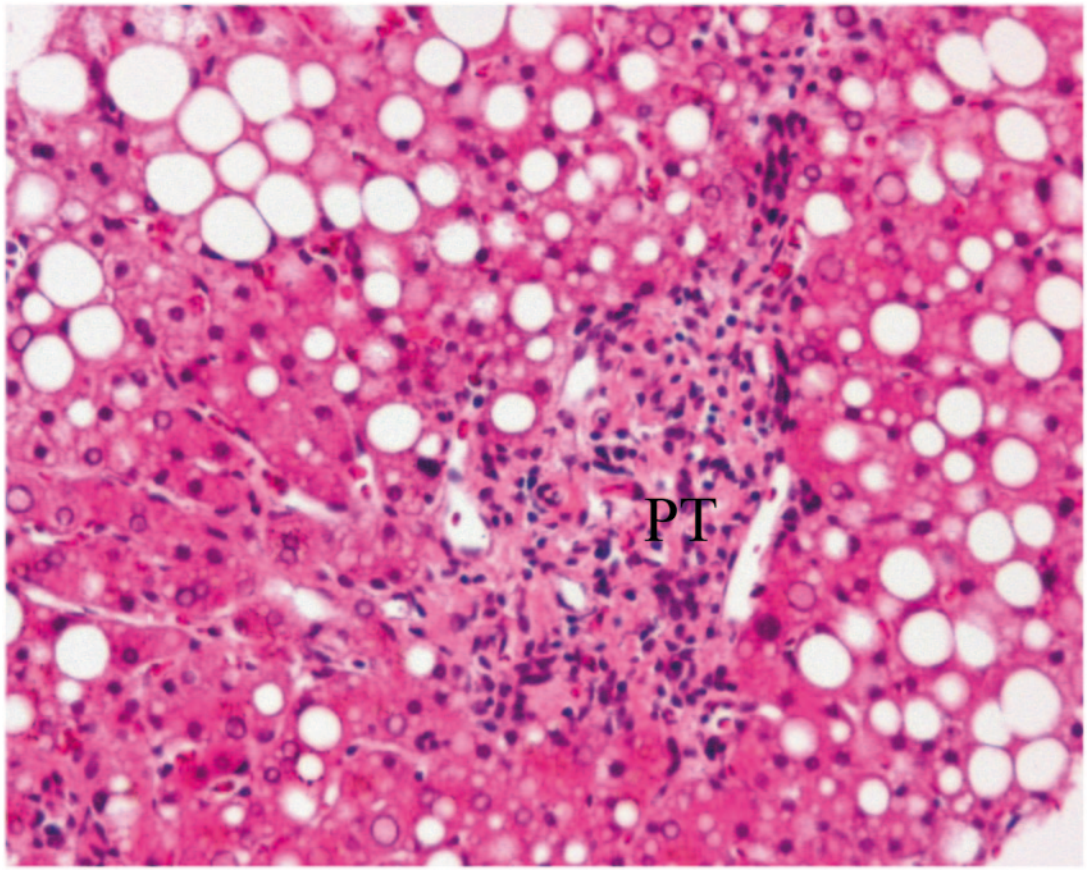

Fig. 14.4 Liver biopsy showing severe macrovesicular steatosis from a patient with heterozygous familial hypobetalipoproteinaemia (H&E, 100×). *PT* indicates portal tract

ever, the clinical features appear to depend on the apoB truncation length, with longer truncations (i.e., greater than apoB-48), as well as those with rare missense mutations who may be asymptomatic, having a milder phenotype.

Familial hypobetalipoproteinaemia might represent a longevity syndrome and be associated with cardiovascular protection due to resistance to atherosclerosis due to a lower lifetime exposure to atherogenic apoB-containing lipoproteins [63]. However, the cardioprotective effects of familial hypobetalipoproteinaemia in humans have, to date, only been shown using the surrogate markers carotid intima-media thickness and distal common carotid arterial wall stiffness [64].

Chylomicron Retention Disease

Chylomicron retention disease presents shortly after birth with diarrhoea, fat malabsorption, and failure to thrive, with vomiting and abdominal distension often present [5, 65]. Acanthocytosis is rare and may be transient. Hepatomegaly and hepatic steatosis may develop in some patients, but do not correlate with liver transaminase levels, along with fat-soluble vitamin deficiencies and their corresponding manifestations. In contrast to abetalipoproteinaemia and familial hypobetalipoproteinaemia, cirrhosis has not been reported in chylomicron retention disease. A white colour of the duodenal mucosa has been observed on endoscopy, with histology like in

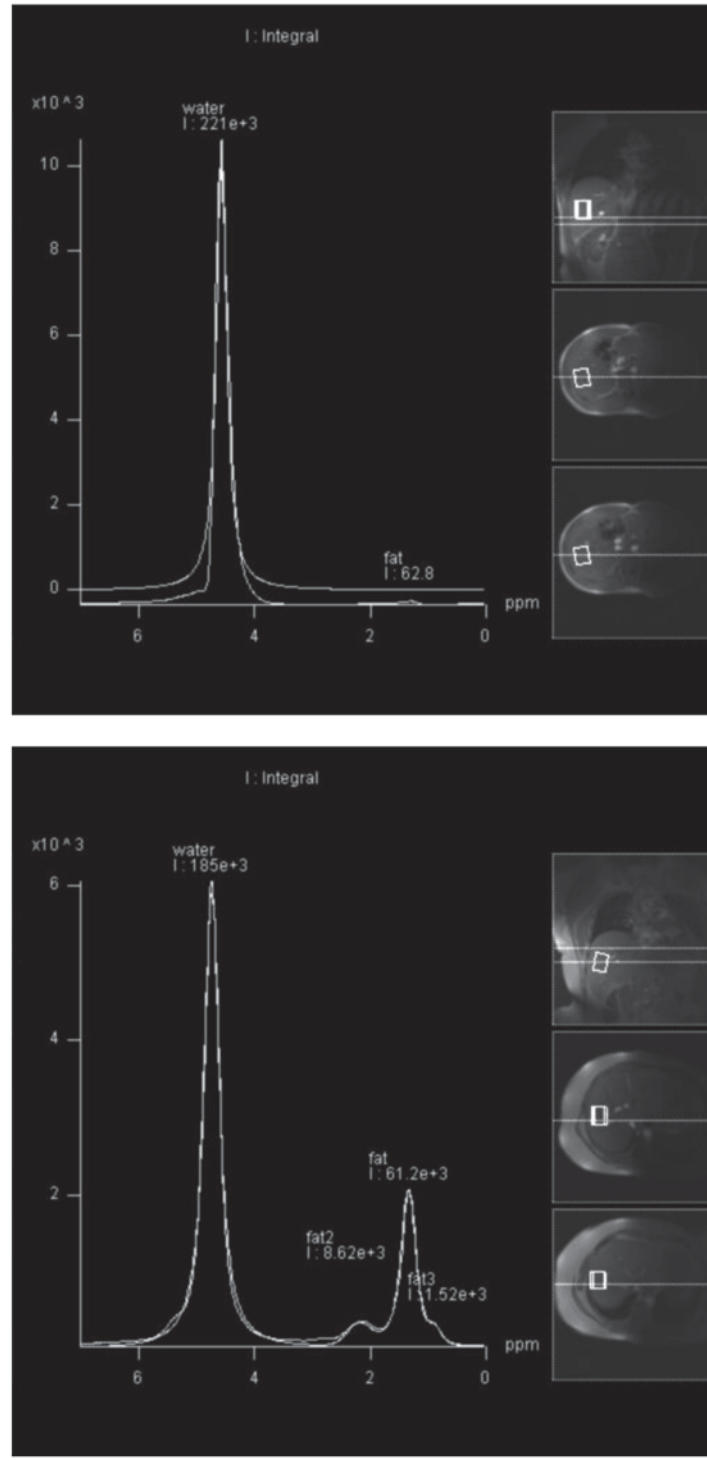

Fig. 14.5 Liver proton nuclear magnetic resonance spectroscopy (^{1}H MRS) in a normal and familial hypobetalipoproteinaemia subject. Liver ^{1}H MRS is shown for a normal subject (*upper panel*), and a heterozygous familial hypobetalipoproteinaemia subject with 28% liver fat (*lower panel*). The area for water and fat peaks are labelled as 'I:'. Percentage liver fat was calculated by 100*fat/(water + fat)

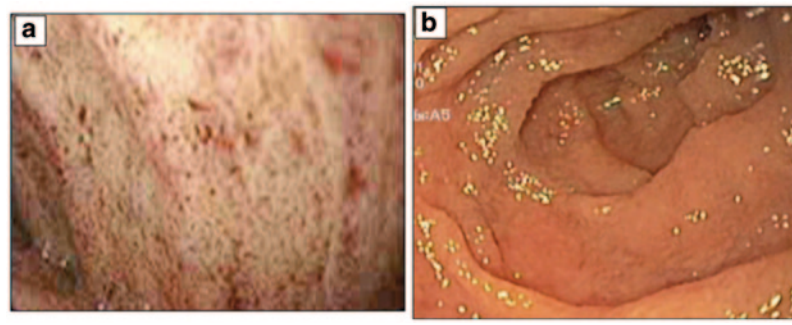

Fig. 14.6 Endoscopy of a chylomicron retention disease patient. Upper endoscopy reveals a white duodenal mucosa in **(a)** chylomicron retention disease compared with **(b)** normal subject (Reproduced with permission from Peretti et al. [5])

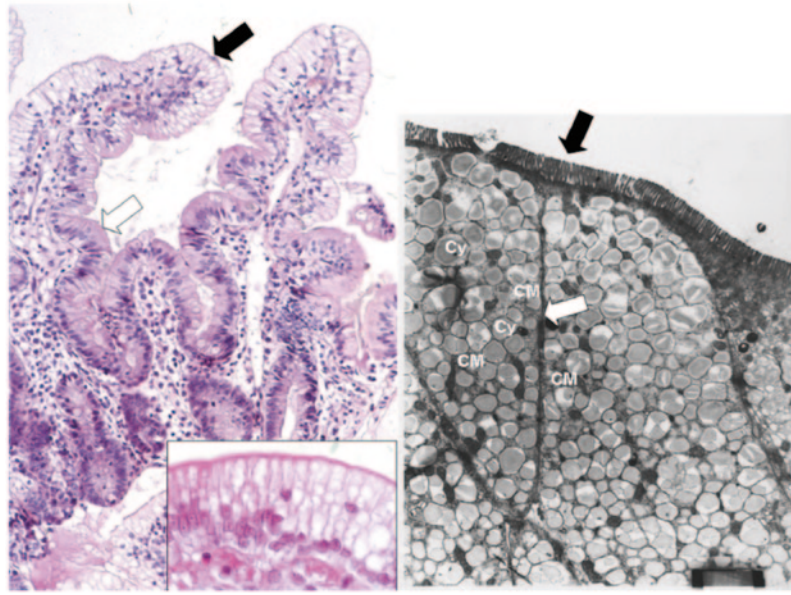

Fig. 14.7 Histology of a jejunal biopsy from a chylomicron retention disease patient. *Left panel*: photomicrograph of haematoxylin–eosin staining showing vacuolisation of enterocytes and well-preserved villous structure. The distribution of vacuolisation, which corresponds to lipid droplets, is heterogeneous: Fat filled enterocytes (*black arrow*) in the upper part of the villus are associated with normal enterocytes in the crypts (*white arrow*) (×20). *Inset*: Higher magnification (×100) of the same patient's biopsy. *Right panel*: Electronic microscopy. The pictures show the apical pole of the enterocytes exhibiting well-preserved microvilli (*black arrow*), numerous chylomicrons (CM) and fat droplets of homogenous size gorging the cytoplasm (Cy). The intercellular membranes demonstrate a complete juxtaposition of intercellular membranes where lipid particles are absent (*white arrow*) (×4000). (Reproduced with permission from Peretti et al. [5])

abetalipoproteinaemia showing vacuolisation of enterocytes in intestinal villi of normal structure (Figs. 14.6 and 14.7).

Approach to the Patient

The usual biochemical trigger for the investigation of genetic abetalipoproteinaemia and hypobetalipoproteinaemia is the finding of marked hypocholesterolaemia with plasma LDL-cholesterol and apoB concentrations below the fifth percentile for age and sex [1]. A personal and family history should be taken and a physical examination conducted. Secondary causes of hypobetalipoproteinaemia should be excluded (see differential diagnosis below) and clinical manifestations such as fat malabsorption, growth failure, fat-soluble vitamin deficiency, fatty liver disease, and neuro-ophthalmological dysfunction

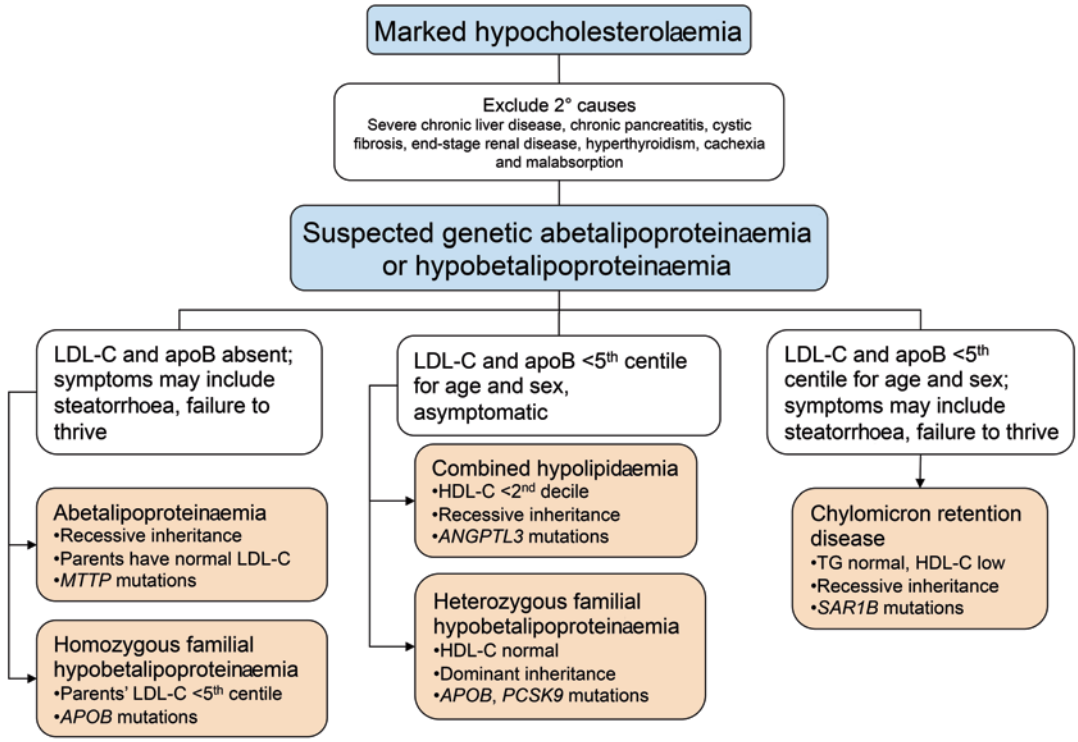

Fig. 14.8 The diagnosis of genetic abetalipoproteinaemia and hypobetalipoproteinaemia. *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *apoB* apolipoprotein B, *TG* triglyceride

sought. A suggested algorithm for the investigation of marked hypocholesterolaemia is shown in Fig. 14.8.

Laboratory Tests

A full fasting lipid profile including total cholesterol, HDL-cholesterol, triglyceride, LDL-cholesterol, and apoB should be performed where genetic abetalipoproteinaemia or hypobetalipoproteinaemia is suspected.

Patients with abetalipoproteinaemia or homozygous familial hypobetalipoproteinaemia will have very low plasma total cholesterol and generally low triglyceride concentrations. LDL-cholesterol, when measured by direct methods, and apoB, will be absent or very low. Vitamin E levels will also be very low, and acanthocytosis may be observed on peripheral blood smear (Fig. 14.3).

Patients with heterozygous familial hypobetalipoproteinaemia typically have plasma LDL-cholesterol and apoB concentrations that are one quarter to one third of normal. The reasons for these lower-than-expected levels may include decreased hepatic secretion of the apoB-containing lipoproteins, or the up-regulation of the LDL-receptor, resulting in an enhanced clearance rate for VLDL and LDL particles produced by the normal allele [37].

Subjects who carry a single *MTTP* mutation (i.e. abetalipoproteinaemia 'carriers') may have normal plasma lipids or may have LDL-cholesterol and apoB concentrations similar to those seen in heterozygous familial hypobetalipoproteinaemia [66].

In chylomicron retention disease, total cholesterol, LDL-cholesterol, and HDL-cholesterol are low, but triglyceride levels are generally normal. The low plasma LDL- and HDL-cholesterol are a consequence of low rates of apoB-100 and apoA-I production [67]. High creatine kinase (4–5x normal) may be seen from infancy, along with deficiencies in fat-soluble vitamins [5].

Molecular Tests

Molecular testing of *MTTP, APOB, SAR1B, PCSK9,* and *ANGPTL3* genes is available in specialist laboratories [68]. Target exonic regions in genomic DNA should be amplified by polymerase chain reaction, ensuring at least 20 base pairs of flanking intronic sequence is included in order to capture any potential splice site mutations. Sequencing should be bidirectional and, if possible, testing of the patient's parents is recommended to confirm that where two mutations are identified, that they originate from two different chromosomes.

In patients with abetalipoproteinaemia where the inheritance pattern is unclear or *MTTP* mutations unable to be identified, then the *APOB* gene should also be sequenced given the clinical and biochemical similarities with homozygous familial hypobetalipoproteinaemia. Likewise, in patients with homozygous familial hypobetalipoproteinaemia, the *MTTP* gene could be sequenced in the event where *APOB* mutations are unable to be found. Alternatively, high-throughput sequencing technology is emerging as a means for screening multiple genes for mutations; massively parallel sequencing could potentially analyse a panel of the genes associated with low cholesterol [69]. This may prove more cost-effective than traditional Sanger sequencing, particularly where multiple genes may need to be sequenced and when the *APOB* gene is involved, which needs over 40 primer sets to cover the whole coding region.

Western blotting can be used as a screening method for mutations in *APOB,* to detect truncated apoB species that are >30% of full-length protein size. DNA sequencing of the region where the mutation is estimated to occur can then be performed. However, truncated apoB species shorter than apoB-30 are not detectable in plasma, so if Western blotting fails to detect an apoB truncation, then sequencing of the first 30% of the *APOB* gene (exons 1–25) should be performed.

Differential Diagnosis

Illnesses and diseases associated with secondary causes of hypobetalipoproteinaemia include severe chronic liver disease, chronic pancreatitis, cystic fibrosis, end-stage renal disease, hyperthyroidism, cachexia, and malabsorption [32, 51]. A vegan diet is associated with ~50% of the general population levels of plasma LDL-cholesterol and triglyceride [70].

Prognosis, Clinical Course, and Complications

Abetalipoproteinaemia and Homozygous Familial Hypobetalipoproteinaemia

The impact on prognosis of age at diagnosis, commencement of a low-fat diet and vitamin replacement therapy, and genotype is variable in abetalipoproteinaemia and homozygous familial hypobetalipoproteinaemia [3, 4, 71]. Early treatment with high-oral doses of vitamin E and A, which are thought to bypass the intestinal chylomicron pathway via the portal circulation, can reduce the potential severity of neuropathy and retinopathy [71–75]. Patients need to be followed regularly for evaluation of symptoms, complications, and to monitor compliance with therapy. A relative paucity of data makes it difficult to predict clinical outcomes based on *MTTP* or *APOB* genotype.

Heterozygous Familial Hypobetalipoproteinaemia

Although the majority of familial hypobetalipoproteinaemia heterozygotes are asymptomatic, most have increased liver transaminases and hepatic steatosis, the long-term consequences of which are unknown [60, 61, 76–78]. Familial hypobetalipoproteinaemia heterozygotes have three- to fivefold greater liver fat content compared to control subjects with no difference in adiposity or insulin resistance [61, 76, 78, 79]. It would seem prudent to monitor biochemically and by imaging techniques the livers of these individuals given a potential increased risk of progression to cirrhosis, particularly in the presence of known risk factors, such as alcohol, caloric excess, and liver injury [32, 77, 80, 81].

Chylomicron Retention Disease

Patients with chylomicron retention disease get better within a few days or weeks with a low-fat diet [5]. No relationship has been found between liver transaminases, hepatomegaly, and hepatic steatosis. Neurological manifestations include hyporeflexia and loss of proprioception in teenagers through to ataxia, myopathy, and sensory neuropathy in adults.

Treatment

Abetalipoproteinaemia

The cornerstone of treatment for abetalipoproteinaemia is dietary modification and the replacement of fat-soluble vitamins [1, 50, 51, 71]. A low-fat diet eliminates steatorrhoea and allows absorption of other nutrients essential for growth and development. Oral vitamin E supplementation (100–300 mg/kg/day orally) in abetalipoproteinaemia is recommended to halt the progression of the neurological disease; however, despite this high dose, serum levels do not fully normalise [50, 51]. Most adult patients with abetalipoproteinaemia who have not received supplements exhibit neuro-ophthalmological complications [50]. Supplementation with a combination of vitamins E and A has been shown to be effective in reducing retinal degeneration [72]. Patients treated with very large oral doses of vitamin E from the age of 16 months do not develop neurological or retinal features, while progression is halted or sometimes even reversed in older patients who already show symptoms of neurological dysfunction [83]. Although serum vitamin E is usually undetectable in untreated abetalipoproteinaemia, supplementation results in trace concentrations, with normal levels in adipose tissue [84]. Erythrocyte and platelet vitamin E have also been used to assess tissue vitamin E status [85]. Oral supplementation of two to four times the recommended daily allowance of vitamin A normalises serum levels. Vitamin D deficiency is not a consistent finding; however, vitamin D replacement should be considered in abetalipoproteinaemia patients, along with other supplementary nutrients such as iron and folate.

There is a need for novel therapeutic approaches to abetalipoproteinaemia as vitamin therapy alone fails to completely control or cure this disease.

Familial Hypobetalipoproteinaemia

In familial hypobetalipoproteinaemia homozygotes, dietary fats should be restricted to prevent steatorrhoea. Long-term high-dose vitamin E and A supplementation should prevent or slow progression of the neuromuscular and retinal degenerative disease [51, 72]. Moderate-dose vitamin E supplementation in familial hypobetalipoproteinaemia heterozygotes with low serum vitamin E concentrations has been recommended to prevent neurological disease [30]. However, this recommendation has been called into question [85].

Chylomicron Retention Disease

There are no specific recommendations for follow-up or treatment of chylomicron retention disease, with therapeutic regimens based on those recommended for abetalipoproteinaemia. Vomiting, diarrhoea, and abdominal distension improve on a low-fat diet of polyunsaturated fatty acids and supplementation with fat-soluble vitamins, particularly vitamin E, can prevent neurological complications [5].

Conclusion

The monogenic hypocholesterolaemic lipid disorders are classified depending on the lipid biochemical phenotype, gene involved, and mode of inheritance of the condition, together with the severity of the mutation or mutations present. These disorders may or may not be associated with clinical manifestations such as fat malabsorption, growth failure, fat-soluble vitamin deficiency, fatty liver disease, and neuro-ophthalmological

dysfunction. We have reviewed the molecular basis, pathogenesis, and clinical aspects of these disorders of apoB production and catabolism, focusing on abetalipoproteinaemia, familial hypobetalipoproteinaemia, and chylomicron retention disease.

Acknowledgements This work was supported by the National Health and Medical Research Council Project Grant 1010133 (to AJH and JRB) and a Practitioner Fellowship from the Royal Perth Hospital Medical Research Foundation (to JRB).

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