

### 28.1 Introduction

Lipoproteins are macromolecular complexes that transport lipids within the blood. The major lipids transported by lipoproteins are triglycerides, cholesterol (both esterified and unesterified), phospholipids and fat-soluble vitamins, especially vitamin E. Lipoproteins also consist of specialized proteins, called apolipoproteins. Apolipoproteins serve a variety of physiological functions in lipoprotein metabolism, including cofactors for enzymes, ligands for cell-surface receptors and structural proteins for lipoproteins [1].

The major classes of lipoprotein particles are chylomicrons and chylomicron ‘remnants’, very-low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL) or ‘VLDL remnants’, low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Their major lipid constituents and functionally significant apolipoproteins are shown below:

Lipoprotein	Major lipids	Major apolipoproteins
Chylomicrons	Triglyceride	ApoB-48, apoC-II
VLDL	Triglyceride	ApoB-100, apoC-II
‘Remnants’	Triglyceride, cholesterol	ApoB-48 or B-100, apoE
LDL	Cholesterol, vitamin E	ApoB-100
HDL	Cholesterol	ApoA-I, apoA-II

A schematic diagram depicting the metabolism of these lipoproteins is shown in Sect. 28.3. Dietary fat, including vitamin E, is absorbed and packaged into triglyceride-rich chylomicrons, which contain a form of apoB, called apoB-48. Triglycerides in chylomicrons are hydrolyzed by the endothelial enzyme lipoprotein lipase (LPL), which requires apoC-II as a cofactor. Deficiency of either LPL or apoC-II causes severe hyperchylomicronemia and hypertriglyceridemia, predisposing to the risk of acute pancreatitis [2]. Once sufficient triglyceride has been hydrolyzed by LPL, the resultant chylomicron remnants are removed from the circulation by the liver via a process that involves the binding of apoE to a putative hepatic remnant (apoE) receptor. Deficiency of apoE

or mutations that affect its receptor-binding affinity cause a defect in the clearance of chylomicron remnants [3].

The liver repackages lipids, including vitamin E, into triglyceride-rich lipoproteins known as VLDL, which contain a form of apoB, called apoB-100. After hydrolysis by LPL, some VLDL remnants are also removed from the circulation by the liver, probably also by binding of apoE to the remnant receptor. However, other VLDL remnants are further processed by another endothelial enzyme called hepatic lipase, with eventual conversion to LDL. Deficiency of hepatic lipase also causes an accumulation of remnant lipoproteins [4]. LDL transports cholesteryl ester and vitamin E to a variety of peripheral tissues, but a significant amount of plasma LDLs are eventually removed from the circulation by the liver via the binding of apoB-100 to the hepatic LDL receptor. Genetic defects in either the LDL receptor or the receptor-binding region of apoB cause a defect in the clearance of LDL from the blood [5, 6].

The metabolism of HDL involves several different enzymes and transfer proteins but is not completely understood [7]. The major apolipoprotein of HDL is apoA-I. The liver and intestine are the sources of apoA-I, which interacts with peripheral cells to remove excess cellular cholesterol via the ATP-binding cassette protein A1 (ABCA1). Unesterified cholesterol associated with nascent HDL is a substrate for the plasma enzyme lecithin: cholesterol acyltransferase (LCAT), resulting in the formation of cholesteryl ester and enlargement of the HDL particle. Genetic defects in apoA-I, ABCA1 and LCAT can cause low levels of HDL, termed hypoalphalipoproteinemia. HDL cholesteryl ester is transferred to apoB-containing lipoproteins (such as LDL) by the cholesteryl ester transfer protein (CETP) and can be returned to the liver via the LDL receptor. HDL may also deliver some cholesterol directly to the liver via the scavenger receptor class BI (SR-BI). The removal of excess cholesterol from peripheral cells and delivery to the liver for excretion in the bile is a process that has been termed 'reverse cholesterol transport'.

Substantial evidence indicates that both lipoprotein remnants and LDL are highly atherogenic. In contrast, a large body of epidemiologic data suggests that HDL may be 'anti-atherogenic'. Lipoproteins can therefore be either atherogenic or anti-atherogenic depending on their composition and physical properties. Therefore the clinical consequences of genetic dyslipidemias are related to the type of lipoprotein that is elevated or decreased. The major complication of elevated chylomicrons is acute pancreatitis. The major sequela of elevated remnants or LDL, as well as of decreased HDL, is premature atherosclerosis. Finally, the primary consequence of markedly decreased VLDL and LDL is retinal and neurologic disease due to vitamin E deficiency [8]. The genetic dyslipoproteinemias can therefore generally be grouped into the following five categories:

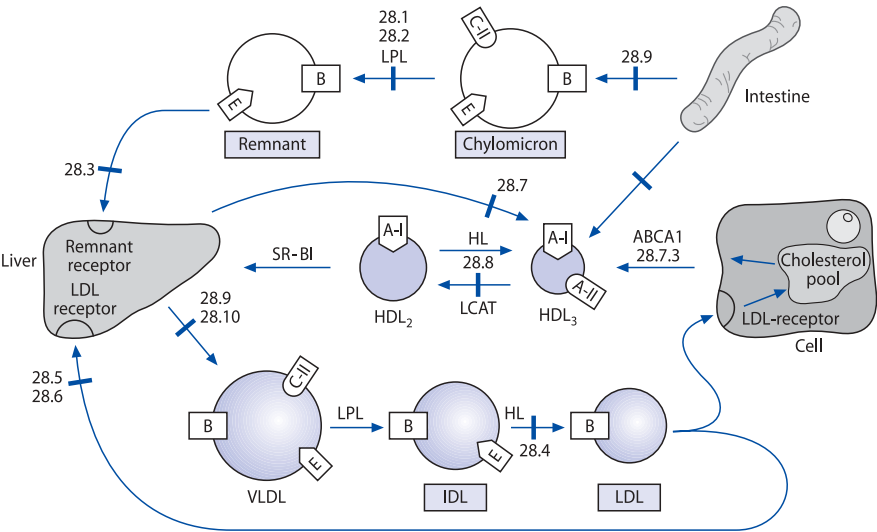
Dyslipoproteinemia (Disorder no.)	Lipoprotein	Clinical consequence
Hypertriglyceridemia (28.1, 28.2)	Chylomicrons (high)	Pancreatitis
'Mixed' hyperlipidemia (28.3, 28.4)	Remnants (high)	Premature atherosclerosis
Hypercholesterolemia (28.5, 28.6)	LDL (high)	Premature atherosclerosis
Hypoalphalipoproteinemia (28.7, 28.8)	HDL (low)	Premature atherosclerosis
Hypolipoproteinemia (28.9, 28.10)	VLDL + LDL (low)	Neurologic disease

For each of these categories of dyslipoproteinemias, there are currently two established genetic causes. This chapter will focus on the appropriate diagnosis of these genetic dyslipoproteinemias.

## 28.2 Nomenclature

No.	Disorder	Affected gene	Primary source	Chromo- somal localisation	MIM
28.1	Lipoprotein lipase deficiency	Lipoprotein lipase (LPL)	Adipose, muscle	8p22	238600
28.2	Apolipoprotein C-II deficiency	Apolipoprotein C-II (apoC-II)	Liver	19q13	207750
28.3	Familial dysbetalipoproteinemia (FD)	A lipoprotein E (apoE)	Liver	19q13	107741
28.4	Hepatic lipase deficiency	Hepatic lipase (HL)	Liver	15q22	151670
28.5.1	Familial hypercholesterolemia (FH) (homozygous)	Low density lipoprotein receptor (LDLR)	Liver	19p13	143890
28.5.2	Familial hypercholesterolemia (FH) (heterozygous)	Low density lipoprotein receptor (LDLR)	Liver	19p13	143890
28.6	Defective apolipoprotein B-100 (FDB)	Apolipoprotein B-100 (apoB-100)	Liver	2p24	107730
28.7.1	Apolipoprotein A-I deficiency (familial)	Apolipoprotein A-I (apoA-I)	Liver, intestine	11q23	107680
28.7.2	Apolipoprotein A-I deficiency (structural mutations)	Apolipoprotein A-I (apoA-I)	Liver, intestine	11q23	107680
28.7.3	Tangier disease	ATP-binding cassette protein A1 (ABCA1)	All tissues	9q31	205400
28.8.1	LCAT deficiency (complete)	Lecithin:cholesterol acyltransferase (LCAT)	Liver	16q22	245900
28.8.2	LCAT deficiency (partial)	Lecithin:cholesterol acyltransferase (LCAT)	Liver	16q22	245900
28.9	Abetalipoproteinemia	Microsomal transfer protein (MTP)	Liver, intestine		200100
28.10.1	Hypobetalipoproteinemia (homozygous)	Apolipoprotein B-100 (apoB-100)	Liver	2p24	107730
28.10.2	Hypobetalipoproteinemia (heterozygous)	Apolipoprotein B-100 (apoB-100)	Liver	2p24	107730

28.3 Metabolic Pathway



**Fig. 28.1.** A schematic diagram depicting lipoprotein metabolism and the known genetic defects affecting lipoproteins. 28.1, Lipoprotein lipase (LPL) deficiency; 28.2, apoC-II deficiency; 28.3, apoE deficiency or mutations; 28.4, hepatic lipase (HL) deficiency; 28.5, LDL receptor deficiency or mutations; 28.6, apoB-100 mutation in receptor binding region; 28.7, apoA-I deficiency or mutations; 28.7.3, ABCA1 deficiency or mutations; 28.8, LCAT deficiency; 28.9, microsomal transfer protein (MTP) deficiency; 28.10, apoB-100 synthesis or truncation mutations. Abbreviations: C-II, apoC-II; B, apoB; E, apoE; A-I, apoA-I; VLDL, very-low-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; HDL, high-density lipoproteins; LPL, lipoprotein lipase; HL, hepatic lipase; LCAT, lecithin:cholesterol acyltransferase; UC, unesterified cholesterol

28.4 Signs and Symptoms

**Table 28.1.** Lipoprotein lipase deficiency

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Abdominal pain	+	+	+	+
	Lipemia retinalis	+	+	+	+
	Eruptive xanthomas	+	+	+	+
Routine laboratory	Triglycerides (P)	↑	↑	↑	↑
	Cholesterol (P)	↑	↑	↑	↑
	HDL cholesterol (P)	↓	↓	↓	↓
Special laboratory	Post-heparin lipase activity (P)	↓	↓	↓	↓
	Apolipoprotein C-II (P)	n	n	n	n

**Table 28.2.** Apolipoprotein C-II deficiency

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Abdominal pain	+	+	+	+
	Lipemia retinalis	+	+	+	+
	Eruptive xanthomas	+	+	+	+
Routine laboratory	Triglycerides (P)	↑	↑	↑	↑
	Cholesterol (P)	↑	↑	↑	↑
	HDL cholesterol (P)	↓	↓	↓	↓
Special laboratory	Post-heparin lipase activity (P)	↓	↓	↓	↓
	Apolipoprotein C-II (P)	n	n	n	n

**Table 28.3.** Familial dysbetalipoproteinemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Palmar xanthomas	n	n	n	+
	Tuberoeruptive xanthomas	n	n	n	+
	Carotid/femoral bruits	n	n	n	+
	Claudication	n	n	n	+
	Angina/MI	n	n	n	+
Routine laboratory	Triglycerides	n	n	n	↑
	Cholesterol	n	n	n	↑
	HDL cholesterol	n	n	n	n
Special laboratory	Lipoprotein electrophoresis	n	n	n	Broad beta
	ApoE genotyping	ApoE-2/2 <sup>a</sup>	ApoE-2/2 <sup>a</sup>	ApoE-2/2 <sup>a</sup>	ApoE-2/2 <sup>a</sup>
	ApoEIEF	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>

<sup>a</sup> The recessive form of familial dysbetalipoproteinemia is associated with the apoE-2/2 genotype. Some dominant forms are associated with other apoE mutations which can only be detected by IEF and not by genotyping alone.

**Table 28.4.** Hepatic lipase deficiency

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Carotid/femoral bruits	n	n	n	+
	Angina/MI	n	n	n	+
Routine laboratory	Triglycerides	n	n	n	↑
	Cholesterol	n	n	n	↑
	HDL cholesterol	n	n	n	↑
Special laboratory	Lipoprotein electrophoresis	n	n	n	Broad beta
	ApoE genotyping	ApoE-3/x	ApoE-3/x	ApoE-3/x	ApoE-3/x
	Post-heparin hepatic lipase activity	↓	↓	↓	↓

**Table 28.5.1** Homozygous familial hypercholesterolemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Cutaneous xanthomas	n	+	+	+
	Tendon xanthomas	n	+	+	+
	Arcus corneae	n	+	+	+
	Carotid/femoral bruits	n	+	+	+
	Aortic flow murmur	n	+	+	+
	Angina/MI	n	+	+	+
	TIA/CVA	n	+	+	+
Routine laboratory	Triglycerides	n	n	n	n
	Total and LDL cholesterol	↑	↑	↑	↑
	HDL cholesterol	↓	↓	↓	↓
Special laboratory	Cardiac ECHO	n	AV disease	AV disease	AV disease
	Carotid Doppler	n	Stenosis	Stenosis	Stenosis
	Exercise ECG	n	Abnormal	Abnormal	Abnormal
	Cardiac catheterization	n	CAD	CAD	CAD
	Fibroblast LDLR assay	↓	↓	↓	↓

**Table 28.5.2.** Heterozygous familial hypercholesterolemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Tendon xanthomas	n	n	n	+
	Arcus corneae	n	n	n	+
	Carotid/femoral bruits	n	n	n	+
	Angina/MI	n	n	n	+
	TIA/CVA	n	n	n	+
Routine laboratory	Triglycerides	n	n	n	n
	Total and LDL cholesterol				
	HDL cholesterol				
Special laboratory	Cardiac catheterization	n	n	n	CAD
	Fibroblast LDLR assay	↓-n	↓-n	↓-n	↓-n

**Table 28.6.** Familial defective apoB-100 (FDB)

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Tendon xanthomas	n	n	n	+
	Arcus corneae	n	n	n	+
	Carotid/femoral bruits	n	n	n	+
	Angina/MI	n	n	n	+
	TIA/CVA	n	n	n	+
Routine laboratory	Triglycerides	n	n	n	n
	Total and LDL cholesterol	↑	↑	↑	↑
	HDL cholesterol	↓-n	↓-n	↓-n	↓-n
Special laboratory	Cardiac catheterization	n	n	n	CAD
	Fibroblast LDLR assay	n	n	n	n
	PCR screen for apoB-3500	+	+	+	+

**Table 28.7.1.** Apolipoprotein A-I deficiency

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Carotid/femoral bruits	n	n	n	+
	Angina/MI	n	n	n	+
Routine laboratory	Triglycerides	n-↑	n-↑	n-↑	n-↑
	Cholesterol	n	n	n	n
	HDL cholesterol	↓	↓	↓	↓
Special laboratory	ApoA-I level	0	0	0	0

**Table 28.7.2.** Apolipoprotein A-I structural mutations

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	None <sup>a</sup>	n	n	n	n
Routine laboratory	Triglycerides	n-↑	n-↑	n-↑	n-↑
	Cholesterol	n	n	n	n
	HDL cholesterol	↓	↓	↓	↓
Special laboratory	ApoA-I level	↓	↓	↓	↓
	ApoA-I IEF	Abnormal	Abnormal	Abnormal	Abnormal

<sup>a</sup> Some dominant mutations in apoA-I causing low levels of HDL have been associated with systemic amyloidosis.

**Table 28.7.3.** Tangier disease

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Arcus corneae	n	n	n	n
	Enlarged orange tonsils	+	+	+	+
	Hepatosplenomegaly	n	n	+	+
	Peripheral neuropathy	n	n	+	+
Routine laboratory	Triglycerides	n	↑	↑	↑
	Cholesterol	n	n	n	n
	HDL cholesterol	↓	↓	↓	↓
Special laboratory	ApoA-I level	↓	↓	↓	↓

**Table 28.8.1.** Familial LCAT deficiency (complete)

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Arcus corneae	n	n	+	+
	Corneal deposits	n	n	n	+
Routine laboratory	Triglycerides	n	n	↑	↑
	Cholesterol	n	n	↑	↑
	HDL cholesterol	↓	↓	↓	↓
	Urea creatinine	n	n	n	↑
	Urine protein	n	n	n	↑
	Hemoglobin	n	n	n	
	Unesterified cholesterol	↑	↑	↑	↑
Special laboratory	LCAT activity	↓	↓	↓	↓
	Cholesterification rate	↓	↓	↓	↓
	Renal biopsy	n	n	n	Abnormal

**Table 28.8.2.** Partial LCAT deficiency (Fish-eye disease)

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Arcus corneae	n	n	+	+
	Corneal deposits	n	n	n	+
Routine laboratory	Triglycerides	n-↑	n-↑	n-↑	n-↑
	Cholesterol	n	n	n	n
	HDL cholesterol	↓	↓	↓	↓
	Urea creatinine	n	n	n	n
	Urine protein	n	n	n	n
	Hemoglobin	n	n	n	n
	Unesterified cholesterol	n	n	n	n
Special laboratory	LCAT activity	↓	↓	↓	↓
	Cholesterification rate	n	n	n	n
	Renal biopsy	n	n	n	n

**Table 28.9.** Abetalipoproteinemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Malabsorption	+	+	+	+
	Deep tendon reflexes	n	n	↓	↓
	Ataxia	n	n	+	+
	Retinal degeneration	n	n	+	+
Routine laboratory	Triglycerides	↓	↓	↓	↓
	Cholesterol	↓	↓	↓	↓
	HDL cholesterol	↓	↓	↓	↓
	Blood smear	Acantho	Acantho	Acantho	Acantho
Special laboratory	ApoB level	0	0		0
	Vitamin E level	↓	↓	↓	↓
	Upper endoscopy and duodenal biopsy	Lipid-laden	Lipid-laden	Lipid-laden	Lipid-laden



**Table 28.10.1.** Homozygous hypobetalipoproteinemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	Malabsorption	+	+	+	+
	Deep tendon reflexes	n	n	+	+
	Ataxia	n	n	+	+
	Retinal degeneration	n	n	+	+
Routine laboratory	Triglycerides	↓	↓	↓	↓
	Cholesterol	↓	↓	↓	↓
	HDL cholesterol	↓	↓	↓	↓
	Blood smear	Acantho	Acantho	Acantho	Acantho
Special laboratory	ApoB level	0	0	0	0
	Vitamin E level	↓	↓	↓	↓
	Upper endoscopy and duodenal biopsy	Lipid-laden	Lipid-laden	Lipid-laden	Lipid-laden

**Table 28.10.2.** Heterozygous hypobetalipoproteinemia

System	Symptoms/markers	Infant	Child	Adolescent	Adult
Clinical findings	None	n	n	n	n
Routine laboratory	Triglycerides	n	n	n	n
	Cholesterol	↓	↓	↓	↓
	HDL cholesterol	n	n	n	n
Special laboratory	ApoB level	↓	↓	↓	↓

## 28.5 Pathological Values

### ■ Hypertriglyceridemias (Elevated Chylomicrons)

No.	Disorder	TG (mmol/l)	Chol. (mmol/l)	HDL-C (mmol/l)	LPL activity	ApoC-II (g/l)
28.1	Lipoprotein lipase deficiency	>10	>6.5	<1.0	0	n
28.2	Apolipoprotein C-II deficiency	>10	>6.5	<1.0	0	0

### ■ Mixed Hyperlipidemias (Elevated Remnant Lipoproteins)

No.	Disorder	TG (mmol/l)	Chol. (mmol/l)	HDL-C	LDL-C	ApoB geno- type	ApoE activity	HL
28.3	Familial dysbeta-lipoproteinemia	>3.0	>5.0	n-↓	↓	n-↑	E-2/2	n
28.4	Hepatic lipase deficiency	>3.0	>5.0	n-↓	↓	n-↑	E-3/X	0

### ■ Hypercholesterolemias (Elevated LDL)

No.	Disorder	TG	Chol. (mmol/l)	HDL-C	LDL-C	ApoB	ApoB PCR <sup>a</sup>
28.5	Familial hypercholesterolemia (FH)						
28.5.1	Homozygous	n	>13	↓	↑	↑	n
28.5.2	Heterozygous	n	>6.5	n-↓	↑	↑	n
28.6	Familial defective apoB-100 (FDB)	n	>6.5	n-↓	↑	↑	Abnormal

<sup>a</sup> PCR assay for detection of apoB-3500 mutation.

### ■ Primary Hypoalphalipoproteinemias

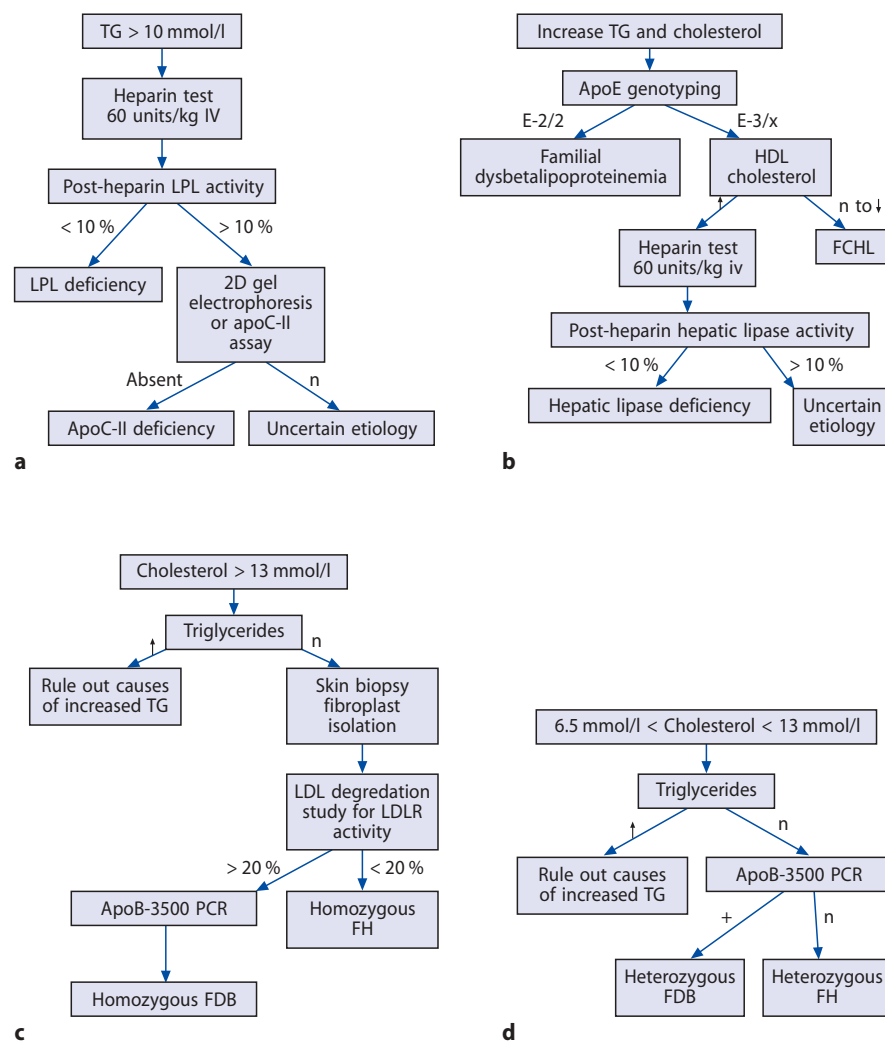
No.	Disorder	TG	Chol.	HDL-C (mmol/l)	LDL-C	ApoA-I (g/l)	LCAT activity	CER <sup>a</sup>
28.7	Apolipoprotein A-I deficiency							
28.7.1	Complete	n	n	<0.25	n	0	n-↓	n
28.7.2	Partial	n	n	<0.50	n	<0.8	n	n
28.7.3	Tangier disease	↑	n	<0.16	↓	<0.1	n	n
28.8	LCAT deficiency							
28.8.1	Complete	↑	↑	<0.25	n-↓	<0.6	0	↓
28.8.2	Partial	n-↑	n-↑	<0.25	n	<0.6	↓	n

<sup>a</sup> Cholesterol esterification rate.

### ■ Primary Hypolipoproteinemias

No.	Disorder	TG (mmol/l)	Chol. (mmol/l)	HDL-C	LDL-C (mmol/l)	ApoB (g/l)	Vit E (μg/ml)
28.9	Abetalipoproteinemia	<0.2	<1.5	n-↓	0	0	<0.2
28.10	Hypobetalipoproteinemia						
28.10.1	Homozygous	<0.2	<1.5	n-↓	0	0	<0.2
28.10.2	Heterozygous	n-↓	1.5-3.0	n	0.5-2.0	<0.6	n

## 28.6 Diagnostic Flow Charts



**Fig. 28.2a–g.** Diagnostic flow charts for genetic dyslipoproteinemias. **a** Hypertriglyceridemia (increased chylomicrons); **b** mixed hyperlipidemia (increased remnants); **c** hypercholesterolemia 1 (increased LDL); **d** hypercholesterolemia 2 (increased LDL); **e** hypoalphalipoproteinemia (decreased HDL); **f** hypolipoproteinemia 1 (decreased LDL); **g** hypolipoproteinemia 2 (decreased LDL). Abbreviations: TG, triglycerides; LPL, lipoprotein lipase; HDL, high-density lipoprotein; FCHL, familial combined hyperlipidemia; LDL, low-density lipoprotein; LDLR, LDL receptor; PCR, polymerase chain reaction; FH, familial hypercholesterolemia; FDB, familial defective apoB; LCAT, lecithin:cholesterol acyltransferase

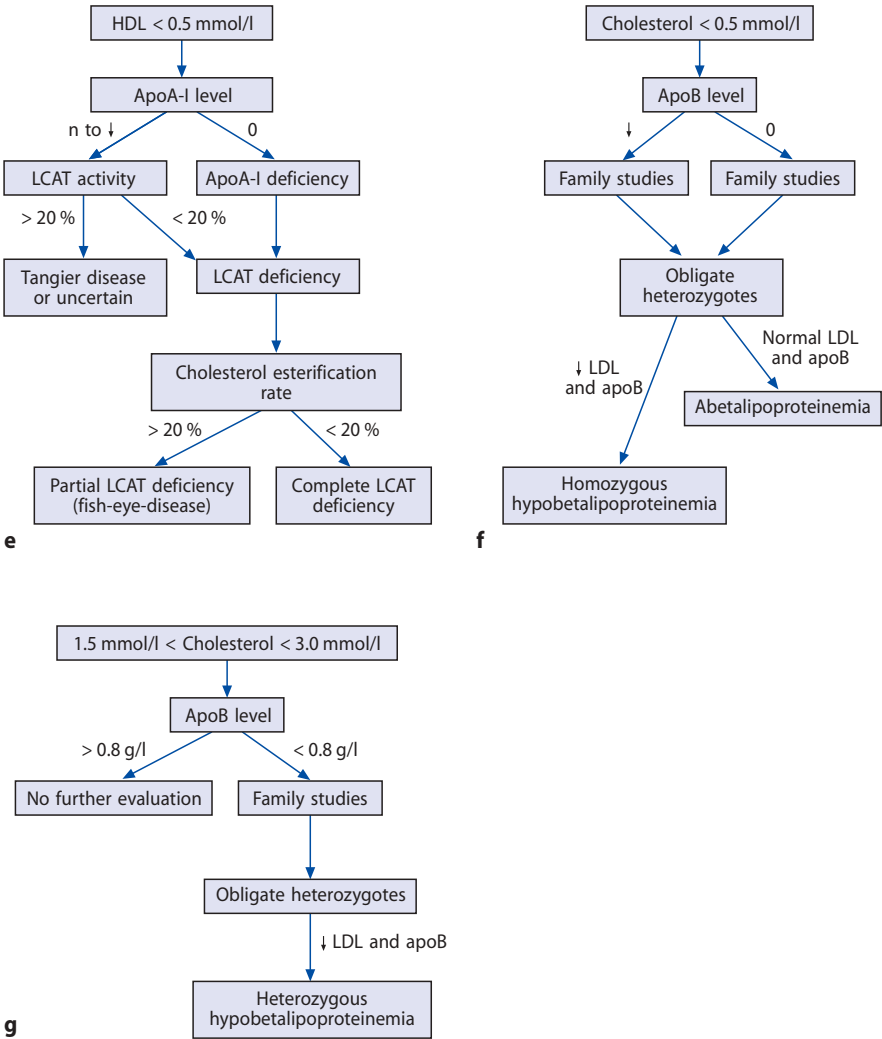


Fig. 28.2e–g

## 28.7 Summary

Inborn errors of lipoprotein metabolism can be divided into several classes, including elevations or reductions in specific types of lipoproteins. The major consequence of genetic lipoprotein disorders is premature atherosclerosis, although pancreatitis and neurologic disease due to vitamin E deficiency are also complications of specific disorders. Most inborn errors of lipoprotein metabolism are diseases of adults; the exceptions are the chylomicronemia syndromes, homozygous familial hypercholesterolemia and abetalipoproteinemia, all of which can present with symptoms in childhood. Lipoprotein disorders are among the most common of monogenic inherited disorders and underlie a significant proportion of premature cardiovascular disease in many societies worldwide. Screening and accurate diagnosis can lead to appropriate therapy to prevent the life-threatening complications of these disorders.

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