

# Chapter 2

## Genetics of Lipid Disorders

Marija Stojanova Jordanov

### Abbreviations

ABL	Abetalipoproteinemia
APOA1	apolipoprotein A-I
ApoB	Apolipoprotein B
APOE	apolipoprotein E
CHD	coronary heart disease
CHD	coronary heart disease
CMs	chylomicrons
CVD	cardiovascular disease
EGF	Epidermal growth factor-like domain
EGF-CA	Calcium-binding EGF-like domain
FCH	Familial combined hyperlipidemia
FDA	US Food and Drug Administration
FH	Familial hyperlipidemia
FHBL	familial hypobetalipoproteinemia
FLD	fatty liver disease
HA	hypoalphalipoproteinemia
HDL	High-density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA reductase	hydroxymethylglutaryl-coenzyme A reductase
HoFH	Homozygous Familial Hypercholesterolemia
IDL	Intermediate-density lipoprotein
LCAT	lecithin-cholesterol acetyltransferase
LDL	low-density lipoprotein
LDLa	LDL receptor domain class A
LDLb	LDL receptor repeat class B

---

M. S. Jordanov (✉)

University of Southern California, 2250 Alcazar st, rm 123 A, 90033 Los Angeles, CA, USA  
e-mail: [stojanovamarija982@yahoo.com](mailto:stojanovamarija982@yahoo.com)

© Springer International Publishing Switzerland 2015  
H. Yassine (ed.), *Lipid Management*, DOI 10.1007/978-3-319-11161-2\_2

LDL-C	low density lipoprotein- cholesterol
LDL-C	Low-density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
Lp(a)	Lipoprotein(a)
LPL	lipoprotein lipase
LPL	lipoprotein lipase
mg	milligrams
mg/dl	milligrams/deciliter
ml	milliliter
mmol/l	milimol per litre
PAI-1	Plasminogen activator inhibitor-1
PCSK9	proprotein convertase subtilisin/kexin type 9
PLG	plasminogen
PPAR-alpha	Peroxisome proliferator-activated receptor alpha
PPARs	peroxisome proliferator-activated receptors
VLDL	Very-low-density lipoprotein

## Genetics of Lipid Disorders

Hyperlipidemias is a group of disorders that can be classified as familial or primary caused by specific genetic abnormalities, or secondary to alterations in plasma lipid and lipoprotein metabolism [1]. Hyperlipidemia can be idiopathic, if the cause is not known. Based on which types of lipids are elevated, hyperlipidemias are classified as: hypercholesterolemia, hypertriglyceridemia or if both then combined hyperlipidemia. Increased levels of Lipoprotein (a) may also be classified as a form of hyperlipidemia. Fredrickson classification is the most common approach to classifying the types of the Familial hyperlipidemias and is based on the results of either the electrophoresis or ultracentrifugation and summarized in Table 2.1 [2]. In the first section of this chapter, we discuss the genetic basis for hyperlipidemias classified by Fredrickson. The second section of the chapter discusses the genetic basis of lipid disorders that have been characterized more recently.

## Mendelian Randomization Studies as a Tool to Differentiate Lipid Disorders that Confer Increased Cardiovascular Disease Risk

Recently, genetic epidemiology has increased our understanding of lipid disorders that directly contribute to heart disease. Since genes are randomly assigned during meiosis (which gives rise to the name “Mendelian randomization”), carriers of certain genes that affect a marker of interest will not be systematically different from carriers of other alleles in any other respect, and in consequence there should be no

**Table 2.1** Fredrickson classification of hyperlipidemias

Hyper-lipoproteinemia	Synonyms	Defect type	Increased lipoprotein	Main symptoms	Serum appearance	Estimated prevalence
Type I	Buerger-Grutz syndrome or familial hyperchylomicronemia	Decreased lipoprotein lipase (LPL)	Chylomicrons	Acute pancreatitis, lipemia retinalis, eruptive skin xanthomas, hepatosplenomegaly	Creamy top layer	1 in 1,000,000
	Familial apoprotein CII deficiency	Altered ApoC2				
		LPL inhibitor				
Type II	Familial hypercholesterolemia	LDL receptor deficiency	LDL	Xanthelasma, arcus semilis, tendon xanthomas	Clear	1 in 500 for heterozygotes 1 in 100
	Familial combined hyperlipidemia	Decreased LDL receptor and increased ApoB	LDL and VLDL			
Type III	Familial dysbetalipoproteinemia	Defect in Apo E 2 metabolism	IDL	Tubo-Eruptive Xanthomas & Palmar Xanthomas	Turbid	1 in 10,000
Type IV	Familial hypertriglyceridemia	Increased VLDL production and Decreased elimination	VLDL	Can cause pancreatitis at high triglyceride levels	Turbid	1 in 100
Type V		Increased VLDL production and Decreased LPL	VLDL and Chylomicrons		Creamy top layer & turbid bottom	

confounding. For example, Low-density lipoprotein LDL and high-density lipoprotein HDL are cholesterol fractions among the most commonly measured biomarkers in clinical medicine. Studies have shown that LDL and HDL cholesterol have opposing association with heart disease. For LDL cholesterol, the results of randomized trials of LDL-cholesterol-lowering treatments and from human mendelian diseases are similar and suggest that plasma LDL cholesterol is causally related to risk of myocardial infarction. This is not the case for HDL cholesterol disorders. The results from several Mendelian randomization studies challenge several established views about plasma HDL cholesterol [3] One example was greater HDL cholesterol levels in carriers of an endothelial lipase gene variant (that does not change levels of LDL or triglycerides) was not associated with a decreased risk of myocardial infarction. Hence, solo abnormalities in plasma HDL cholesterol cannot be assumed to be causally related to cardiovascular disease [3]

## Genetic Basis for Fredrickson Classes

### *Familial Chylomicronemia*

Synonyms: **hyperlipoproteinemia type I**, Lipoprotein lipase deficiency, chylomicronemia syndrome

Chylomicrons (from the Greek chylo, meaning juice or milky fluid, and micron, meaning small particle) are lipoprotein particles that consist of triglycerides (85–92%), phospholipids (6–12%), cholesterol (1–3%), and proteins (1–2%) [4]. They transport dietary lipids from the intestines to other locations in the body.

Chylomicrons are one of the five major groups of lipoproteins (chylomicrons, VLDL, IDL, LDL, HDL) that enable fats and cholesterol to move within the water-based solution of the bloodstream [4].

The chylomicronemia is characterized by severe hypertriglyceridemia and fasting chylomicronemia. Genetic causes of the syndrome are rare and include deficiency of lipoprotein lipase (LPL), apolipoprotein C-II, and presence of apolipoprotein CIII which is an inhibitor of LPL. Patients with familial forms of hypertriglyceridemia in combination with secondary acquired disorders (nephrotic syndrome, chronic kidney disease, Cushing's syndrome, and hypothyroidism) account for most individuals presenting with chylomicronemia [5].

Type I hyperlipoproteinemia (chylomicronemia) [6] exists in several forms (Table 2.1):

1. **Type Ia Chylomicronemia** is due to a deficiency of lipoprotein lipase (LPL) or altered apolipoprotein CII, resulting in elevated chylomicrons, the particles that transfer fatty acids from the digestive tract to the liver.
2. **Type Ib Chylomicronemia** is a condition caused by a lack of apolipoprotein CII that is lipoprotein lipase activator.

3. **Type Ic Chylomicronemia** is due to the presence a circulating inhibitor of lipoprotein lipase and hepatic lipase.

Type I hyperlipoproteinemia usually presents in childhood with eruptive xanthomata and abdominal colic. Complications include retinal vein occlusion, acute pancreatitis, steatosis and organomegaly, and lipaemia retinalis

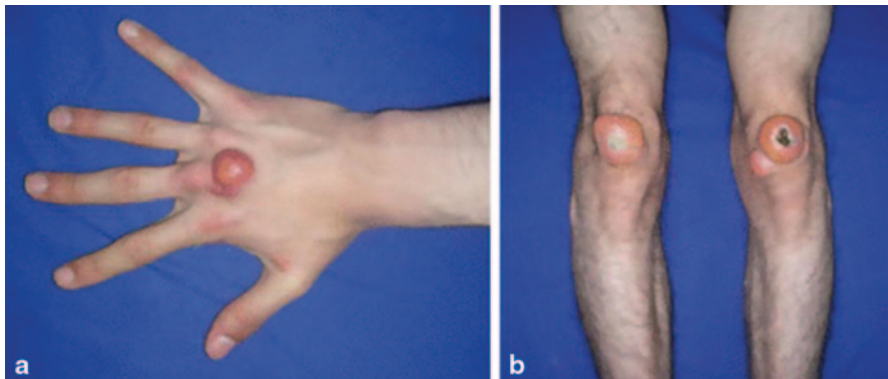
## Treatment

The treatment of patients with genetically inherited LPL and apoC-II deficiency primarily involves restriction of dietary fat to approximately 15% of total calories [7]. The degree of fat restriction (10 to 15 g of fat daily) required to achieve an acceptable plasma triglyceride concentration may be variable. Both unsaturated and saturated fats should be limited. Patients can be given supplements with medium-chain triglycerides as their cooking oils. Medium-chain triglycerides are directly absorbed into the portal vein and do not contribute to the formation of chylomicron triglycerides. However, reports of liver fibrosis have been associated with medium chain triglycerides, and thus they should be used with caution [8]. Treatment of acquired hypertriglyceridemias is covered in Chapter 6.

## *Familial Hypercholesterolemia*

Synonyms: **Type IIA Familial Hypercholesterolaemia**, Hypercholesterolemia, Autosomal Dominant Hyperlipoproteinemia [9]

Familial hypercholesterolemia is a genetic disorder characterized by high cholesterol levels, specifically very high levels of LDL cholesterol (LDL-C) that cause atherosclerotic plaque deposition in arteries and a markedly increased risk of coronary artery disease at an early age. Cholesterol deposits are found in the tendons (xanthomas, Fig. 2.1) and/or around the eyes (xanthelasmas, Fig. 2.2) [10]. The



**Fig. 2.1** Tendinous xanthoma, b. Bilateral ulcerated xanthomas on the extensor knee surface



**Fig. 2.2** a. Tuberos xanthoma of elbow b. Cutaneous xanthoma around the eye. c. Xanthelasma palpebrarum, arcus juvenalis. d. Intertrigenous xanthoma.

most common cardiovascular disease in FH is coronary heart disease (CHD), which may manifest as angina and myocardial infarction; stroke occurs more rarely.

### Clinical Description

High cholesterol levels are not usually symptomatic [10]. Cholesterol deposits can be seen in different places on the body such as in the tendons of the hands, elbows, knees and feet, particularly the Achilles tendon (known as a tendon xanthoma), the eyelids (known as xanthelasma palpebrarum), and the outer margin of the iris (known as arcus senilis corneae).

The underlying cause of cardiovascular disease is the accelerated deposition of cholesterol in the walls of arteries which leads to atherosclerosis. FH causes development of coronary artery disease at a much younger age than would be expected in the general population [11]. This leads in many cases to angina pectoris or heart attacks. The arteries of the brain are less commonly affected, and this may lead to transient ischemic attacks or stroke. Peripheral artery occlusive disease occurs mainly in people with FH who smoke. Atherosclerosis risk is increased further with age and in those who smoke, have diabetes, high blood pressure and a family history of cardiovascular disease [12].

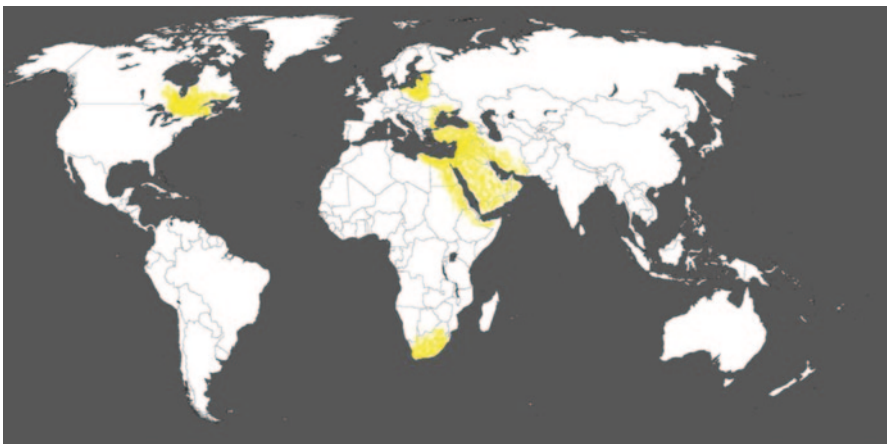
## Mode of Inheritance

The two forms of FH, heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) are inherited in an autosomal dominant manner. Patients who have one abnormal copy of the LDLR gene are heterozygous and patients who have two abnormal copy of the LDLR gene are homozygous. Heterozygous FH is a common genetic disorder, occurring in 1:500 people in most countries [13]. Homozygous FH is much rarer, occurring in 1 in a million births.

Total cholesterol levels of 350–550 mg/dL are typical of heterozygous FH while total cholesterol levels of 650–1000 mg/dL are typical of homozygous FH [14]. LDLR mutations are more common in certain populations. The Africans, French Canadians, Lebanese Christians, and Finns have high rates of specific LDLR mutations that make FH particularly common in these groups. ApoB mutations are more common in Central Europe (Fig. 2.3).

Approximately all affected individuals that are diagnosed with HeFH have an affected parent. If the pathogenic variant found in the affected person cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or de novo mutation in the affected person [9] Even though most individuals diagnosed with HeFH have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

The risk to the siblings of the affected person depends on the genetic status of the parents. If a parent is affected or has a pathogenic variant, the risk to the siblings is 50%. If both parents are affected with HeFH or have a pathogenic variant, the risk to siblings of having HeFH is 75% (50% chance of HeFH and a 25% chance of HoFH) [9].



**Fig. 2.3** Familial Hypercholesterolemia concentrations in the world's populations. Groups with increased prevalence of FH are highlighted

## Molecular Genetics

The most common genetic defects in FH are LDLR mutations (prevalence 1 in 500, depending on the population), ApoB mutations (prevalence 1 in 1000), PCSK9 mutations (less than 1 in 2500) and LDLRAP1 [10].

### a. LDLR

LDLR encodes a mature protein product of 839 amino acids. LDLR has four distinct functional domains that can function independently of each other [9]:

- LDL receptor domain class A (LDLa)
- Epidermal growth factor-like domain (EGF)
- Calcium-binding EGF-like domain (EGF-CA)
- LDL receptor repeat class B (LDLb)

LDLR is made of cell surface proteins involved in endocytosis of LDL cholesterol (LDL-C). Once LDL-C is bound at the cell membrane, it is taken into the cell and to lysosomes where the protein moiety is degraded and the cholesterol molecule suppresses cholesterol synthesis via negative feedback.

Pathogenic variants in LDLR usually reduce the number of LDL receptors produced within the cells or disrupt the ability of the receptor to bind LDL-C. Either way, people with a heterozygous pathogenic variant in LDLR generally have high levels of plasma LDL-C.

### b. ApoB

ApoB is 42,216 base pairs in length, comprising 28 introns and 29 exons. The gene product is the main apolipoprotein of chylomicrons and low density lipoproteins. ApoB has four functional domains [9]:

- Synthesis, assembly, and secretion of hepatic triglyceride-rich lipoproteins
- Binding of lipids and serving as a structural component of very low density lipoproteins (VLDL) and LDL
- Binding of heparin and various proteoglycans found in the arterial wall
- Interaction with the LDL receptor, important for clearance of LDL from plasma

ApoB is generally involved in aiding the binding of LDL-C to its receptor on the cell surface. ApoB pathogenic variants alter the ability of protein to effectively bind LDL-C to LDLR, causing fewer LDL-C particles to be removed from the blood.

### c. PCSK9 (proprotein convertase subtilisin/kexin type 9)

PCSK9 [15] is the gene located on the short (p) arm of chromosome 1 at position 32.3. This gene encodes a protein consisting of 692 amino acids and three main

domains. Mutated alternates in this gene have been linked both with hypercholesterolemia and hypocholesterolemia. “Gain-of-function” is description for mutations that are responsible for hypercholesterolemia because they appear to increase the activity of the PCSK9 protein or to give the protein a new, different function. The consequence of the overactive PCSK9 protein is the significant reduction in the number of LDL receptors on the surface of liver cells. The excess cholesterol is placed abnormally in tissues such as the skin, tendons, and coronary arteries, which greatly increases a person’s risk of having a heart attack.

Other genetic changes in the PCSK9 gene result in an opposite effect – reduced blood cholesterol levels (hypocholesterolemia). These mutations decrease the activity of the PCSK9 protein or decrease the amount of this protein that is produced in cells. This type of mutation is described as “loss-of-function.” The nonsense mutation (*PCSK9142X* *PCSK9679X*) is the most common “loss-of-function” mutation in the PCSK9 gene and leads to an increase in the number of low-density lipoprotein receptors on the surface of liver cells. These additional receptors can remove low-density lipoproteins from the blood more rapidly than usual, which reduces the amount of cholesterol circulating in the bloodstream. Different studies advocate that people with reduced cholesterol levels caused by PCSK9 mutations have a significantly lower-than-average risk of developing coronary heart disease [15].

**Treatment** Guidelines for the management of Familial Hyperlipidemia are discussed in Chapter 6. All individuals with FH should be classified as high risk for cardiovascular disease (CVD) and should be aggressively treated actively to lower their cholesterol levels [9].

**Heterozygous FH** is typically treated with statins [14]. Statins efficiently lower cholesterol and LDL levels, even though sometimes supplemental therapy with other drugs is necessary, such as bile acid sequestrants (cholestyramine or colestipol), nicotinic acid preparations or fibrates [10].

**Homozygous FH** is harder to treat. In individuals with Homozygous FH the LDL receptors are minimally functional, if at all. Only high doses of statins, often in combination with other medications, are modestly effective in improving lipid levels [11]. If medical therapy is not successful at reducing cholesterol levels, LDL apheresis may be used, this filters LDL from the bloodstream in a procedure similar to kidney dialysis [10].

Lomitapide, an inhibitor of the microsomal triglyceride transfer protein was approved by the FDA in December 2012 as an orphan drug for the treatment of homozygous familial hypercholesterolemia [16] In January 2013, The FDA also approved mipomersen, which inhibits the action of the gene apolipoprotein B [17].

Children should be considered for drug treatment with statin-based regimens when:

LDL-C levels are  $\geq 190$  mg/dL ( $\geq 4.9$  mmol/L).

LDL-C levels are  $\geq 160$  mg/dL ( $\geq 4.1$  mmol/L) and at least two other risk factors are present.

A multidisciplinary expert panel in 2006 advised on early combination therapy with LDL apheresis, statins and cholesterol absorption inhibitors in children with homozygous FH at the highest risk [13]

## ***Familial Combined Dyslipidemia***

### **Synonym: hyperlipoproteinemia type IIb**

Combined hyperlipidemia also known as "Multiple-type hyperlipoproteinemia" is a subtype of hypercholesterolemia characterized by increased LDL and triglyceride concentrations, frequently accompanied by decreased HDL. It is the most common inherited lipid disorder, with occurrence of 1/200 persons. In fact, almost 20% from the people who develop coronary heart disease before the age of sixty will have this disorder [1]. The elevated triglyceride levels (>90 mg/dl) are generally due to an increase in VLDL (very low density lipoprotein), a class of lipoprotein that is prone to cause atherosclerosis.

There are two forms of this lipid disorder. This disease is common in patients with metabolic syndrome ("syndrome X", incorporating diabetes mellitus type II, hypertension, central obesity and CH). Excessive free fatty acid production by various tissues leads to increased VLDL synthesis by the liver. Initially, most VLDL is converted into LDL until this mechanism is saturated, after which VLDL levels elevate. Fibrate drugs are used for treatment of both forms and they act on the peroxisome proliferator-activated receptors (PPARs), specifically PPAR $\alpha$ , to decrease free fatty acid production. Statin drugs, especially the synthetic statins (atorvastatin and rosuvastatin) can decrease LDL levels by increasing hepatic reuptake of LDL due to increased LDL-receptor expression. The management of this disease is discussed in more detail in Chap. 6.

## ***Type III Dyslipidemia***

### **Synonyms: Familial dysbetalipoproteinemia**

Type III dyslipidemia, also called type III hyperlipoproteinemia, it is partially caused by mutation in the APOE gene. The effect of this mutation is decrease in the hepatic uptake of APOE-containing lipoproteins and reduction in the conversion of VLDL and IDL to LDL particles [18]. If other factors are not present, remnants do not accumulate to a degree enough to cause hyperlipidemia.

Dysbetalipoproteinemia happens when an ApoE defect (almost always the E2/E2 genotype) occurs in combination with a second genetic or acquired defect that causes either overproduction of VLDL (such as FCHL) or a reduction in LDL receptor activity (such as occurs in heterozygous FH or hypothyroidism). The frequency of the Dysbetalipoproteinemia is estimated to be about 1/10,000. There are other less frequent causes for dysbetalipoproteinemia are ApoE variants such as ApoE3-leiden and ApoE2 (lys146→Gln) can also be causes. Typical for patients with dysbetalipoproteinemia is to have elevated levels of both cholesterol and triglycerides. They are likely to develop premature CVD and are at increased risk for peripheral vascular disease. Clinical signs of dyslipidemia show differently in both genders, and usually do not develop before adulthood in men or before menopause



<http://www.springer.com/978-3-319-11160-5>

Lipid Management

From Basics to Clinic

Yassine, H. (Ed.)

2015, XIV, 269 p. 17 illus., 8 illus. in color., Softcover

ISBN: 978-3-319-11160-5