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Inherited Disorders of Lipoprotein Metabolism

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

AD	autosomal dominant	CAD	coronary artery disease	FTF	failure to thrive	RP	retinitis pigmentosa
AR	autosomal recessive	CHD	congenital heart defects	HDL-C	high density lipoprotein cholesterol	PAD	periphery artery disease
APOB	apolipoprotein B	DM	diabetes mellitus	LDL-C	low-density lipoprotein cholesterol	PMH	personal medical history
ASCVD	atherosclerotic cardiovascular disease	FH	family history	MI	myocardial infarction		

Conditions	Genes (mode of inheritance)	Age of onset	Frequency	Clinical features	Mechanism and most common alterations	References
Atherosclerotic cardiovascular diseases due to elevated lipoprotein(a) (Lp(a))	*LPA* (AD); complex trait	Adult (variable; earlier with very high Lp(a))	Common but risk variable (High Lp(a) has a frequency of 1/5)	Often asymptomatic. Premature ASCVD (MI, CAD), ischemic stroke, aortic valve stenosis, increased clotting; often independent of LDL-C.	Elevated Lp(a) promotes atherogenesis, inflammation, and thrombosis via apo(a) and oxidized phospholipids; KIV-2 repeat copy number variation (major determinant of Lp(a) levels).	9848878, 4378929, 28183512, 41141607
Familial hypercholesterolemia (homozygous HoFH and heterozygous HeFH)	*LDLR* (AD/AR), *APOB* (AD/AR), *PCSK9* (AD/AR)	HoFH: CHD in childhood / adolescence. HeFH: if untreated, CHD events can occur in the 30s–50s (men) and 40s–60s (women)	HeFH up to ~1:300 worldwide. HoFH up to ~ 1:250,000. Occurrence of mutations: *LDLR* (90%), *APOB* (8%), *PCSK9* (2%)	Elevated LDL-C (>190 mg/dL HeFH, >400 mg/dL HoFH, FH/PMH of early-onset ASCVD, tendon xanthomas, early-onset corneal arcus).	*LDLR* (LDL receptor), *APOB* (apolipoprotein B) and *PCSK9* (proprotein convertase subtilisin/Kexin type 9) play key role in cholesterol clearance. FH is a major risk factor for early-onset CHD. Children with FH should be screened at age 2. Common genetic variants (polygenic risk score) can modify the phenotype.	25939291, 36196022, 31838973, 39751968 , 41824590, 32507592, 37130090
Autosomal Recessive Hypercholesterolemia (ARH)	*LDLRAP1* (AR)	Early childhood	Rare (<1 in every 1,000,000 people)	Xanthomas by age 5–10; risk of ASCVD in the 20s or 30s.	*LDLRAP1* encodes low-density lipoprotein receptor adapter protein 1. Mutations in the *LDLRAP1* gene causing ARH deficiency lead to severely elevated LDL cholesterol, resembling HoFH.	31734096, 35187127, 30876877
Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)	*APOE* (AR)	Age >20 in men and post-menopause in women. Poor diet can cause earlier onset	Frequency 1:825 to 1:250	Increased cholesterol and triglycerides, low LDL-C levels, tuberoeruptive and palmar xanthomas, premature CHD, and PAD.	Most of cases due to homozygous ε2 isoform of *APOE* (ε2ε2 genotype is diagnostic). Variable penetrance.	7175379, 2313204, 1357300,
Hypobetalipoproteinemia FAMILIAL, 1; FHBL1	*APOB* (AR/AD), *PCSK9* (AD/AR)	Variable	Rare (1/3000)	Heterozygotes often have LDL-C < 5th percentile (80 mg/dL) and individuals with *APOB* truncations may have hepatic steatosis. AR cases: hypocholesterolemia and impaired absorption of fat-soluble vitamins, leading to retinal degeneration, neuropathy, and coagulopathy.	Reduced serum cholesterol and beta-lipoprotein disrupts fat absorption and transport, often causing hepatic steatosis and, in severe cases, vitamin E deficiency, with symptoms ranging from asymptomatic to severe fat malabsorption. Defective apoB protein due to *APOB* truncating mutations. Loss of function *PCSK9* mutations leads to enhanced PCSK9 activity and decreased LDL absorption.	36003908, 15818469, 21874758, 1562615, 2901434, 21981844, 32039990
Hypobetalipoproteinemia FAMILIAL, 2; FHBL2	*ANGPTL3* (AR)	Early childhood (2-16 years old), but can be detected in infancy (incidentally)	Rare; ~10% of severe hypobetalipoproteinemia cases in studied cohorts	Very low LDL-C, triglycerides, and HDL-C (combined hypolipidemia); typically mild phenotype without severe malabsorption or neurologic complications.	Homozygous or compound heterozygous mutations in *ANGPTL3*. Loss-of-function *ANGPTL3* mutations increase lipase activity, leading to reduced LDL, triglycerides, and HDL levels.	19075393, 22247256, 20942659, 19075393
Abetalipoproteinemia	*MTTP* (AR)	Infancy / early childhood	Extremely rare (~15 reported cases)	Very low LDL-C. Infancy: FTF, diarrhea, steatorrhea; childhood: progressive ataxia, RP. Acanthocytosis, anemia, fat-soluble vitamin deficiency, neuropathy.	Mutations in the *MTTP* gene inhibit the production of microsomal triglyceride transfer protein (MTP), preventing the absorption and transport of fats and fat-soluble vitamins (A, D, E, K).	8361539, 12630961, 32039990
Severe hypertriglyceridemia, Lipoprotein Lipase (LPL) Deficiency, Combined	*LMF1* (AR)	LMF1 deficiency may present in late adulthood	Extremely rare (only a few families with pathogenic *LMF1* mutations)	From mild (abdominal pain, nausea, vomiting, recurrent pancreatitis, hepatosplenomegaly, lipemia retinalis, eruptive xanthomata) to severe (renal failure, uncontrolled DM).	Lipase maturation factor 1 (LMF1) plays a role in the post-translational activation of lipoprotein lipase (LPL). Severe hypertriglyceridemia is caused by biallelic loss-of-function *LMF1* variants. Homozygous missense variants cause partial loss of LM1 function and lead to hypertriglyceridemia and multifactorial chylomicronemia syndrome.	22135386, 19820022, 17994020, 39537501
Multifactorial chylomicronemia syndrome	*LPL* (AD), *APOC2, GPIHBP1, APOA5, LMF1*	Adulthood	~1% population	Hypertriglyceridemia (>880 mg/dL) often in the context of other conditions such as diabetes, hypertension, and/or obesity, pancreatitis, premature coronary artery disease. Limited response to lipid lowering medication increases likelihood of a pathogenic variant vs. polygenic etiology.	Two-hit hypothesis (genetic predisposition plus a secondary factor such as uncontrolled diabetes or nephrotic syndrome), partial function of lipoprotein lipase pathway which results in elevated VLDL and chylomicrons.	39238074, 37994661, 31035285

Familial hyperchylomicronemia Syndrome (aka Lipoprotein Lipase Deficiency [LPLD], Type 1 Hyperlipoproteinemia, or Familial Chylomicronemia Syndrome [FCS])	*LPL* (AR), *APOC2*, *GPIHBP1*, *APOA5*, *LMF1*	First decade of life	1-10 individuals per million	Extremely high triglyceride levels (up to ~10,000 mg/dL), severe abdominal pain, recurrent pancreatitis, fatigue, hepatosplenomegaly, lipemia retinalis, eruptive xanthomas.	~80% of cases due to *LPL* mutations, 20% due to mutation in other genes related to the function of lipoprotein-lipase (apolipoprotein C-II [*APOC2]*, apolipoprotein A-V [*APOA5]*, high-density lipoprotein binding protein 1 [*GP1HBP1]*, and lipase maturation factor 1 [*LMF1]*), resulting in plasma elevated triglycerides and chylomicrons.	8755931, 2110364, 32472350, 30183397, 39238074
Sitosterolemia (Phytosterolemia or Xenosterolemia)	*ABCG5* (AR), *ABCG8* (AR)	Early childhood	1 in 50,000	Tendon xanthomas and rarely corneal arcus and xanthelasma. Presence of xanthomas may be out of proportion with elevated LDL-C level. If untreated, patients develop severe CAD, MI, and other complications. Patients may also have anemia, thrombocytopenia, splenomegaly.	*ABCG5* and *ABCG8* encode for the ABC transporter proteins (sterolin-1 and sterolin-2). Mutations result in accumulation of plant sterols in the blood. Sitosterolemia can be clinically misdiagnosed as familial hypercholesterolemia.	11452359, 18441155, 15375183, 17976197, 27104173
Cerebrotendinous xanthomatosis (CTX)	*CYP27A1* (AR)	Infancy through adulthood	Rare. Intrafamilial variability	Infancy: diarrhea; childhood: cataracts; adolescent: tendon xanthomas; adult: neurological impairment (ataxia, dementia, psychiatric disturbances, parkinsonism, neuropathy, seizures).	*CYP27A1* (sterol 27-hydroxylase) is crucial to breaking down cholesterol to acids used in the digestion of fats (bile acids). *CYP27A1* mutations lead to increased level of cholestanol and bile alcohols in blood and increased level of cholesterol and cholestanol in tissues.	33630770, 23759795
Tangier disease	*ABCA1* (AR)	infancy with some features presenting later in life	1 in 1,000,000	Very low HDL (<5 mg/dL) and very low ApoA1 (<30 mg/dL) plasma levels, orange tonsils, platelet abnormalities, peripheral neuropathy, and premature coronary artery disease.	*ABCA1* codes for the AT-binding cassette transporter A1 which is involved in the efflux of cholesterol to form HDL particles.	32022754, 31751110
LCAT deficiency, fish eye disease	*LCAT* (AR)	infancy with some features presenting later in life	Rare	Low HDL-C (<10 mg/dL), elevated triglycerides and VLDL levels, anemia, kidney disease, increased risk for CAD; Individuals with fish-eye disease may have corneal opacification.	Partial or complete absence of the LCAT enzyme which is involved in the metabolism of HDL particles. Loss of function leads to low HDL levels. Fish-eye disease has partial enzyme activity. Some patients may have lipoprotein-X.	33867422, 38404612, 34256778, 30503707
LPX–mediated hypercholesterolemia	*LCAT* (AR)	Variable depending on etiology	Rare	Leads to severe elevations in cholesterol levels. Rather than atherosclerosis, Lp-X accumulation can lead to hyperviscosity syndrome, renal disease, and xanthomatosis.	Lipoprotein X (Lp-X), an abnormal lipoprotein, lacks apolipoprotein B100 and is rich in unesterified cholesterol and phospholipids. Increased Lp-X levels are seen primarily in cholestatic liver diseases, and other rare conditions such as lecithin cholesterol acyltransferase (LCAT) deficiency, partial FLD (fish-eye disease), graft versus host liver disease, and after lipid infusions. The only known genetic etiology of LPX–mediated hypercholesterolemia is seen with LCAT deficiency, in which mutations in the LCAT enzyme are implicated.	40555623, 40555623, 34256778
Cholesteryl ester transfer protein (CETP) deficiency, CETP-Related Hyperalphalipoproteinemia (HALP)	*CETP* (AR)	Variable, most individuals are asymptomatic	Carrier frequency: 0.27%-0.98% (more common in Asian ancestry, possible founder effect)	Elevated plasma levels of HDL-C and decreased LDL-C levels found on a routine lipid profile testing. Generally asymptomatic with no obvious clinical signs.	CETP is a plasma glycoprotein that mediates the exchange of triglycerides and cholesteryl esters between lipoproteins and regulates plasma HDL-C levels. Mechanisms of disease include biallelic (homozygous or compound heterozygous) CETP-related HALP or heterozygous CETP-related HALP due to loss of function variants. The amount of residual CETP activity correlates with the degree of elevation of HDL-C.	8318066, 11730826, 34207236
Apolipoprotein A-I (ApoA-I) deficiency	*APOA1* (AR)	Variable	Rare	Low serum concentrations of HDL-C and Apo A-I. Atherosclerosis, increased coronary risk, planar xanthomas and corneal opacities, premature coronary heart disease, amyloidosis.	*APOA1* encodes ApoA-I, an apoprotein involved in HDL metabolism. Deletions, rearrangements, nonsense or frameshift mutations in the *APOA1* gene result in the impaired production and secretion, or impaired function and increased catabolism of ApoA-I, leading to low serum levels of low HDL-C levels.	20616715, 29396262, 23043194
Hepatic lipase deficiency	*LIPC* (AR)	Variable, including early childhood	Very rare (fewer than 10 families have been reported)	Elevated levels of total cholesterol and triglycerides, moderate levels of LDL-C and HDL-C; premature atherosclerosis.	Hepatic lipase is a protein secreted by the liver that hydrolyzes phospholipids and triglycerides of plasma lipoproteins. Biallelic loss-of-function variants in the *LIPC* gene result in reduced or deficient lipolytic activity, leading to elevated plasma lipids. Heterozygotes for *LIPC* variants might also have detectable dyslipidemia phenotypes.	9885775, 39518997; 35204909

Created 9/2026