Lipoprotein Metabolism Genetic Pathway Reference

An educational reference on lipoprotein biology, lipid-lowering drug pharmacogenomics, and well-studied SNPs across the pathway

10 Functional Categories • ~42 Genes • ~70 SNPs Cataloged

Scope: Lipoprotein metabolism (LDL, HDL, VLDL, Lp(a), triglyceride-rich lipoproteins) and the pharmacogenomics of four lipid-lowering drug classes — HMG-CoA reductase inhibitors (statins; e.g., rosuvastatin), ATP-citrate lyase inhibitors (bempedoic acid), NPC1L1 inhibitors (ezetimibe), and PCSK9 monoclonal antibodies (evolocumab, alirocumab). This document is a generic educational reference compiled from peer-reviewed literature and public genomic databases. It contains no personal health information.

1. Pathway Biology and Mechanism

1.1 Why lipoproteins exist

Cholesterol and triglycerides are hydrophobic; plasma is aqueous. To move lipids between tissues, the liver and intestine package them into spherical particles with a hydrophobic core (cholesteryl esters and triglycerides) and an amphipathic shell (phospholipids, free cholesterol, and apolipoproteins). Apolipoproteins serve as address labels: they determine which receptors bind the particle, which enzymes act on it, and how long it circulates.

1.2 The three transport systems

The exogenous pathway handles dietary lipids. Intestinal enterocytes absorb cholesterol via NPC1L1 (the ezetimibe target) and re-export unwanted sterols via the ABCG5/G8 heterodimer. Absorbed lipids are packaged into chylomicrons carrying apolipoprotein B-48, which deliver triglycerides to peripheral tissues through lipoprotein lipase (LPL) and return to the liver as chylomicron remnants bound by apolipoprotein E.

The endogenous pathway handles hepatic lipid export. The liver assembles VLDL particles (apolipoprotein B-100) using the microsomal triglyceride transfer protein (MTTP), exports them, and LPL progressively hydrolyzes the triglyceride core — converting VLDL to IDL and then LDL. LDL is cleared primarily by the hepatic LDL receptor (LDLR), which recognizes apolipoprotein B-100. This is the pathway statins, ezetimibe, bempedoic acid, and PCSK9 inhibitors all ultimately target: they increase hepatic LDLR density, pulling LDL from circulation.

Reverse cholesterol transport moves excess cholesterol from peripheral tissues back to the liver. Cells efflux cholesterol to apolipoprotein A-I via ABCA1, forming nascent HDL. LCAT esterifies the cholesterol, CETP exchanges it for triglycerides from VLDL/LDL, and mature HDL is taken up by hepatocytes via SCARB1 (SR-B1).

Lipoprotein(a) is a special case: an LDL-like particle with apolipoprotein(a) covalently linked to apolipoprotein B-100. Apolipoprotein(a) contains kringle IV repeats that mimic plasminogen, linking Lp(a)

to both atherogenesis and thrombosis. Plasma Lp(a) concentration is ~75–90% determined by the LPA gene.

1.3 Why this pathway matters clinically

The causal relationship between apolipoprotein B-containing lipoproteins (LDL, IDL, VLDL remnants, Lp(a)) and atherosclerotic cardiovascular disease is one of the most rigorously established in medicine. Mendelian randomization across >200 genetic variants shows that lifetime exposure to elevated LDL-C or apolipoprotein B causes a log-linear, dose-dependent increase in coronary heart disease risk, with each ~39 mg/dL lower LDL-C corresponding to ~22% lower CHD events per year of exposure [Ference et al., JACC 2017, 70:1531; Ference et al., Eur Heart J 2017, 38:2459].

1.4 Regulation: the SREBP feedback loop

Intracellular cholesterol controls a feedback loop. When hepatocyte cholesterol drops (for example, from HMGCR inhibition by a statin), the SREBP-2 transcription factor is released from the endoplasmic reticulum by the SCAP/INSIG complex and translocates to the nucleus, where it upregulates LDLR, HMGCR, and — importantly — PCSK9. The simultaneous upregulation of PCSK9 alongside LDLR is why PCSK9 inhibition is synergistic with statins: statins trigger LDLR upregulation but also PCSK9 upregulation, which then degrades the new LDLRs; blocking PCSK9 removes that brake.

1.5 How the four drug classes converge

All four lipid-lowering drug classes in this reference converge on a single final mechanism: increased hepatic LDL receptor density on the hepatocyte surface, which pulls apolipoprotein B-containing particles out of circulation.

Drug class	Molecular target	Mechanism	Primary effect
Statins	HMGCR	Blocks cholesterol synthesis at the rate-limiting step; depletes intracellular cholesterol, activates SREBP-2, upregulates LDLR	LDL-C ↓ 30–55%
Bempedoic acid	ACLY	Blocks cholesterol synthesis two steps upstream of HMGCR; liver-specific activation via ACSVL1 means no muscle exposure	LDL-C ↓ 15–25% (monotherapy)
Ezetimibe	NPC1L1	Blocks intestinal cholesterol absorption; reduces hepatic cholesterol resupply, upregulates LDLR	LDL-C ↓ 15–20%
PCSK9 mAbs	PCSK9	Prevent PCSK9 from binding and degrading the LDL receptor; dramatically extends LDLR surface half-life	LDL-C ↓ 50–60%; Lp(a) ↓ 25–30%

Genetic variants affecting the LDL receptor itself, its feedback regulation, or any of these drugs' target enzymes/transporters have amplified clinical consequences: they can blunt response to multiple drugs simultaneously, or — in the case of gain-of-function variants — make intensive combination therapy essential to reach target LDL-C.

2. Functional Categories and Key Genes

2.1 LDL Receptor Pathway and Clearance

The final common effector of all four drugs. If the LDLR itself or its partner proteins are compromised, the drugs have less to work with. This category contains the largest effect-size common variants in all of cardiovascular genetics.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
LDLR	rs6511720	Intron 1 T>G	G allele increases LDLR transcription	Protective. ~6 mg/dL lower LDL-C, ~17–20% lower CHD per G allele [Teslovich, Nature 2010; Willer, Nat Genet 2013]
LDLR	rs688	C1773T (exon 12, syn.)	T allele alters mRNA splicing, reduces receptor function	Higher LDL-C [Zhu, Atherosclerosis 2003, 171:69]
LDLR	rs5925	A370A (synonymous)	Haplotype marker	Used in older CHD association studies
APOB	rs1367117	T>C (near-missense)	LDL-C and CHD association	GLGC consortium GWAS signal [Willer, Nat Genet 2013]
APOB	rs693	XbaI site (syn.)	Classic marker, modest effect	T allele slightly higher LDL-C
APOB	rs5742904	R3500Q	Familial defective ApoB-100; rare but monogenic	Severe hypercholesterolemia when present [Innerarity, PNAS 1987]
PCSK9	rs11591147	R46L (c.137G>T)	Loss-of-function; reduces PCSK9 secretion	Protective. ~15 mg/dL lower LDL-C, ~47% lower CHD in heterozygotes [Cohen, NEJM 2006, 354:1264]
PCSK9	rs505151	E670G (c.2009A>G)	Gain-of-function; increases PCSK9 activity	Risk. Higher LDL-C and CHD risk [Chen, J Am Coll Cardiol 2005]
PCSK9	rs11206510	1p32 locus T>C	Intergenic regulatory variant	GWAS LDL-C and CHD signal [MIGen, Nat Genet 2009, 41:334]
PCSK9	rs2479409	Promoter G>A	Modest effect on PCSK9 expression	Minor allele associated with lower LDL-C
PCSK9	rs562556	I474V	Haplotype marker, minimal functional effect	Used in pharmacogenomic studies
MYLIP/ IDOL	rs9370867	N342S	Alters E3 ligase activity; degrades LDLR intracellularly	Modest LDL-C association [Weissglas-Volkov, JCI 2011]

SORT1	rs646776	1p13 locus T>C	Regulates hepatic VLDL secretion and PCSK9 trafficking	~6–8 mg/dL lower LDL-C, ~13% lower MI per minor allele [Musunuru, Nature 2010, 466:714]. Largest common-variant LDL effect known.
CELSR2	rs599839	1p13 locus	In linkage with rs646776	Same effect as rs646776 [Willer, Nat Genet 2008, 40:161]

Cofactors / regulators: LDLR trafficking requires ARH/LDLRAP1 for clathrin-mediated endocytosis. PCSK9 secretion requires furin cleavage. IDOL ubiquitination requires the E2 enzymes UBE2D.

2.2 HMG-CoA Reductase and Cholesterol Biosynthesis (Statin Target)

The mevalonate pathway. HMGCR is the rate-limiting enzyme and the direct target of all statins. Variants here predict both LDL-C and statin response magnitude.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
HMGCR	rs17238484	Intronic T>G	Haplotype associated with reduced response to statin	Smaller statin response. Carriers get ~22% less LDL reduction per dose [Chasman, PLoS Genet 2012; Krauss, Circulation 2008, 117:1537]
HMGCR	rs3846662	Intron 13 G>A	Regulates alternative splicing of exon 13; skipped transcript is statin-insensitive	A allele carriers have blunted statin response; up to 6% less LDL-C reduction with simvastatin [Medina, Circulation 2008, 118:355]
HMGCR	rs12916	Intronic T>C	GWAS LDL-C signal	~2.8 mg/dL LDL difference per allele [Willer, Nat Genet 2013]
SREBF2	rs2228314	G595C	Missense in SREBP-2 TF	Modest CHD association in candidate studies
SREBF1	rs11868035	Intronic	SREBP-1 regulation	Minor lipid effect
SCAP	rs12487736	Intronic	May alter SCAP-SREBP processing	Associated with statin response in some studies

Cofactors: HMGCR requires NADPH (2 molecules per mevalonate produced). Downstream mevalonate pathway enzymes use NADPH, ATP, and Mg^{2+}. NADPH is regenerated primarily by the pentose phosphate pathway (G6PD, 6PGD) and by cytosolic IDH1.

2.3 Statin Pharmacogenomics: Transport and Metabolism

How statin drugs get from gut to hepatocyte and back out — and the variants that determine tolerability and myopathy risk. This is the most clinically actionable category of the entire pathway because it has formal CPIC dosing guidelines.

Genes and SNPs — Hepatic uptake

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
SLCO1B1	rs4149056	c.521T>C, V174A (*5)	Reduced OATP1B1 uptake into hepatocytes; higher systemic statin exposure	Most important statin PGx variant. OR ~4.5 per C allele for simvastatin myopathy; ~17× for CC on simvastatin 80 mg [SEARCH Collaborative, NEJM 2008, 359:789]. Effect strongest for simvastatin; moderate atorvastatin; smaller rosuvastatin/pravastatin. CPIC guideline available [Cooper-DeHoff, Clin Pharmacol Ther 2022, 111:1007]
SLCO1B1	rs2306283	N130D (*1B)	Usually in haplotype with *5	Modifies baseline OATP1B1 expression

Genes and SNPs — Efflux transport

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
ABCG2	rs2231142	Q141K, c.421C>A	Reduces BCRP efflux; ~2.4× higher rosuvastatin AUC in A-allele carriers	[Keskitalo, Clin Pharmacol Ther 2009, 86:197]. Also affects bempedoic acid. FDA rosuvastatin label warns against >20 mg dose in carriers.
ABCB1	rs1045642	C3435T (syn.)	Affects mRNA folding and P-gp conformation	Mixed evidence for atorvastatin, simvastatin response
ABCB1	rs1128503	C1236T	Haplotype marker	Part of common ABCB1 haplotype
ABCB1	rs2032582	G2677T/A	Haplotype marker	Part of common ABCB1 haplotype

Genes and SNPs — Phase I metabolism

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
CYP3A5	rs776746	*3 (6986A>G)	Non-expressor allele in Europeans (>90% of Caucasians are *3/*3)	Minor effect on atorvastatin, simvastatin; not relevant for rosuvastatin (<10% CYP3A metabolism)
CYP3A4	rs35599367	*22 (intron 6 C>T)	Reduced CYP3A4 expression	Associated with lower statin dose requirement
CYP2C9	rs1799853	*2 (R144C)	Reduced enzyme activity	Relevant for fluvastatin (major CYP2C9 substrate), minor rosuvastatin
CYP2C9	rs1057910	*3 (I359L)	Markedly reduced enzyme activity	Relevant for fluvastatin

Genes and SNPs — Myopathy modifiers

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence

LILRB5	rs12975366	D247G	Immune receptor; affects creatine kinase baseline	Higher CK baseline and greater statin myopathy risk, independent of SLCO1B1 [Siddiqui, Nat Commun 2017, 8:14685]
GATM	rs1719247	Intronic T>C	Affects creatine synthesis rate-limiting enzyme	Minor allele associated with REDUCED statin myopathy risk [Mangravite, Nature 2013, 502:377]
GATM	rs1346268	Intronic	In LD with rs1719247	Same protective direction
COQ2	rs4693570	Intronic	Candidate CoQ10 biosynthesis myopathy modifier	Mixed evidence [Oh, Atherosclerosis 2007, 195:e49]
COQ2	rs6535454	Intronic	Candidate myopathy modifier	Mixed replication

Cofactors: SLCO1B1 and ABCG2 are ATP-dependent transporters (ABCG2 uses ATP directly; OATP1B1 uses bicarbonate/glutathione gradients). CYP enzymes require heme iron and NADPH via P450 reductase (POR). GATM uses S-adenosylmethionine (SAM) as the methyl donor for creatine synthesis.

2.4 Intestinal Cholesterol Absorption (Ezetimibe Target)

The apical cholesterol importer and the sterol efflux pumps on enterocytes. Ezetimibe inhibits NPC1L1 directly; ABCG5/G8 is the counter-transport 'safety valve' that expels plant sterols and excess cholesterol back into the gut lumen.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
NPC1L1	rs217386	Intronic G>A	GWAS LDL-C signal	Modest LDL-C effect; may modify ezetimibe response
NPC1L1	rs2072183	L272L (syn.)	Common haplotype marker	Part of common NPC1L1 haplotype
NPC1L1	rs41279633	p.R406X	Loss-of-function truncation (rare)	Carriers: ~12 mg/dL lower LDL-C, ~53% lower CHD [MIGen, NEJM 2014, 371:2072]. Validates ezetimibe target.
ABCG8	rs4299376	Intronic T>G	GWAS major LDL signal	Minor allele raises LDL-C ~2–3 mg/dL and CHD risk [Teslovich, Nature 2010]
ABCG8	rs11887534	D19H (c.55G>C)	Gain-of-function; increased activity	Associated with lower LDL-C but higher gallstone risk [Buch, Nat Genet 2007, 39:995]
ABCG8	rs6544713	Intronic C>T	GWAS LDL signal	Minor allele higher LDL-C
ABCG5	rs6720173	R50C	Missense with modest effect	Minor LDL and CHD signal
APOA4	rs675	T347S	Affects chylomicron assembly	Modest TG and LDL-C effect

APOA4	rs5110	Q360H	Modest lipid effect	In complex LD with other APOA1/C3/A4 variants

Cofactors: ABCG5/G8 is an ATP-dependent heterodimer requiring both subunits to function. NPC1L1 cycles between plasma membrane and endocytic compartments in a cholesterol-dependent manner; this cycling is the mechanism ezetimibe disrupts.

2.5 ACL Pathway and Bempedoic Acid

Bempedoic acid is a prodrug activated in the liver by very long-chain acyl-CoA synthetase 1 (ACSVL1, encoded by SLC27A2). The active CoA-conjugated metabolite inhibits ATP-citrate lyase (ACLY), two steps upstream of HMGCR. Because ACSVL1 is not expressed in skeletal muscle, the drug bypasses myalgia side effects [Ray, NEJM 2019, 380:1022].

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
ACLY	rs9912468	Intronic G>A	GWAS LDL-C signal	Modest effect; Mendelian randomization supports ACLY as causal LDL/CHD target [Ference, NEJM 2019, 380:1033]
ACLY	rs2304129	Intronic C>T	GWAS LDL-C signal	Minor allele higher LDL-C
SLC27A2 (ACSVL1)	—	No well-characterized common LoF	Drug-activating enzyme; rare variants not established	Loss would theoretically abolish bempedoic acid activation
UGT2B7	rs7439366	*2 (H268Y)	Altered glucuronidation of bempedoic acid and other drugs	Minor effect on bempedoic acid clearance
SLCO2B1	rs12422149	c.935G>A	Alters intestinal drug uptake	Candidate modifier of bempedoic acid absorption

Cofactors: ACLY requires ATP, CoA, and Mg^{2+} for citrate cleavage. ACSVL1 activates bempedoic acid via CoA thioesterification (requires CoA and ATP). Important drug–drug interaction: bempedoic acid inhibits OATP1B1 and ABCG2, raising rosuvastatin exposure ~2×; FDA label caps rosuvastatin at 10 mg when co-administered [Nexletol prescribing information; Amore, Clin Pharmacol Drug Dev 2020].

2.6 PCSK9 Biology and Monoclonal Antibody Pharmacogenomics

PCSK9 monoclonal antibodies (evolocumab, alirocumab) bind circulating PCSK9 and prevent its interaction with the LDL receptor, dramatically extending LDLR surface half-life. Most genetic modifiers of absolute LDL-C response are small because the drug nearly completely blocks PCSK9; genetics matter more for baseline LDL-C and Lp(a) response.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence

PCSK9	rs11591147	R46L	Loss-of-function	Already cataloged in 2.1. Carriers of LoF variants still respond to mAbs but start from lower baseline
PCSK9	rs28362286	C679X	African-specific LoF; stop-gain	~40% LDL-C reduction in homozygotes; extraordinarily rare
PCSK9	rs662145	Intronic	Minor GWAS LDL signal	Haplotype marker
LDLR	(LoF status)	FH mutations	Loss of receptor function	FH patients still benefit from mAbs but reach higher nadir LDL-C
APOE	rs429358 + rs7412	ε2/ε3/ε4	Determines isoform	ε4 carriers may have slightly attenuated Lp(a) response to PCSK9 inhibition [Szarek, Lancet 2019]
LPA	rs10455872, rs3798220	(see Category 2.9)	KIV-2 isoform size proxy	Predicts baseline Lp(a) and magnitude of Lp(a) reduction with PCSK9 inhibition

Cofactors: PCSK9 is secreted after furin-mediated prodomain cleavage. The monoclonal antibodies are IgG1 (evolocumab) or IgG2 (alirocumab); they are cleared by target-mediated disposition and reticuloendothelial system uptake — no CYP metabolism, so phase I PGx is not relevant.

2.7 Triglyceride-Rich Lipoprotein and Remnant Metabolism

Triglyceride metabolism intersects with LDL biology because apolipoprotein B-containing remnants (chylomicron remnants, IDL) are atherogenic. The last decade of human genetics has established TG-rich remnants as causal contributors to CHD, not mere bystanders.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
APOC3	rs138326449	R19X (LoF)	Rare loss-of-function; removes LPL inhibition	~39% lower TG, ~40% lower CHD [TG/HDL Working Group, NEJM 2014, 371:22]
APOC3	rs3135506	S2P (SstI)	Missense, minor effect	Modest TG association
APOA5	rs662799	-1131T>C (promoter)	Reduced APOA5 expression	C allele higher TG, higher CHD [Do, Nature 2013, 493:96]
APOA5	rs3135506	S19W	Missense, TG effect	Minor allele higher TG
ANGPTL3	rs11207977	Intronic	GWAS TG/LDL signal	Minor lipid effect
ANGPTL3	rs10889353	Intronic	GWAS TG/LDL signal	In LD with other ANGPTL3 variants
ANGPTL4	rs116843064	E40K	Loss-of-function missense	Lower TG, ~53% lower CHD [Dewey, NEJM 2016, 374:1123]
ANGPTL8	rs2278426	R59W	Modest TG effect	Minor allele lower TG
LPL	rs328	S447X	Gain-of-function; more	Lower TG, ~6% lower CHD per allele

		(truncation)	stable enzyme	[Rip, ATVB 2006]
LPL	rs268	N291S	Partial loss-of-function	Higher TG, modest CHD risk
LPL	rs1801177	D9N	Partial loss-of-function	Higher TG and CHD risk
LIPC	rs1800588	C-514T (promoter)	T allele reduces expression	Higher HDL-C; alters LDL particle size distribution
LIPC	rs2070895	Promoter G>A	Expression regulation	HDL and LDL particle effects
APOE	rs429358	Cys112Arg	Defines ε3 vs ε4	Combined with rs7412, determines isoform
APOE	rs7412	Arg158Cys	Defines ε3 vs ε2	Combined with rs429358, determines isoform

APOE isoform key: ε2/ε2 can cause type III hyperlipidemia (dysbetalipoproteinemia) with elevated remnants. ε3/ε3 is the population reference. ε4/ε4 carriers have higher LDL-C and higher CHD and Alzheimer's disease risk [Bennet, JAMA 2007, 298:1300; Mahley & Rall, Annu Rev Genomics 2000].

Cofactors: LPL requires apolipoprotein C-II as an obligate cofactor and is inhibited by apolipoprotein C-III, ANGPTL3, ANGPTL4, and ANGPTL8. LPL activity also requires GPIHBP1 for endothelial surface anchoring.

2.8 HDL Metabolism and Reverse Cholesterol Transport

HDL-C is no longer considered a direct drug target after the CETP inhibitor trials (dalcetrapib, evacetrapib, and anacetrapib) largely failed to show CHD benefit despite substantial HDL-C elevation. Mendelian randomization of HDL-C-raising variants has also failed to demonstrate causal protection [Voight, Lancet 2012, 380:572]. However, HDL particle biology and reverse cholesterol transport remain relevant for particle dynamics.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
CETP	rs708272	TaqIB (intron 1)	B2 allele lower CETP activity, higher HDL-C	Higher HDL-C; modest CHD signal (causality uncertain)
CETP	rs5882	I405V	V allele lower CETP activity	Higher HDL-C; longevity association in some studies
CETP	rs3764261	Intergenic	GWAS HDL-C top signal	Large HDL-C effect
LIPG	rs2000813	T111I	Reduced endothelial lipase activity	Higher HDL-C; no CHD benefit in MR [Voight, Lancet 2012]
LCAT	rs5923	Intronic	Modest HDL effect	Loss-of-function rare
ABCA 1	rs4149313	I883M	Modest HDL effect	Tangier disease from complete LoF

ABCA 1	rs2230806	R219K	Modest HDL-C and CHD effect	Mixed CHD evidence
SCAR B1	rs1084674 4	Intronic	HDL-C regulation	Modest HDL effect
SCAR B1	rs4765623	Intronic	GWAS HDL signal	Modest HDL effect

Cofactors: LCAT uses phosphatidylcholine as the acyl donor for cholesterol esterification on HDL. ABCA1 is ATP-dependent. CETP is a lipid transfer protein requiring no cofactors but is regulated by apolipoprotein composition of donor and acceptor particles.

2.9 Lipoprotein(a) Genetics

Lp(a) plasma concentration is ~75–90% genetically determined by LPA, making it essentially a genetic trait. Lp(a) is causally atherogenic per Mendelian randomization [Kamstrup, JAMA 2009, 301:2331] and is now a recognized independent CVD risk factor. European Atherosclerosis Society 2022 thresholds: optimal <30 mg/dL (<75 nmol/L); high 30–50 mg/dL; very high >50 mg/dL (>125 nmol/L) [Kronenberg, Eur Heart J 2022, 43:3925].

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
LPA	rs10455872	Intron 25 A>G	Tags small apo(a) isoforms (few KIV-2 repeats)	~2–3× higher Lp(a); ~2.5× higher CHD risk per G allele [Clarke, NEJM 2009, 361:2518]. One of the strongest common-variant CVD signals
LPA	rs3798220	I4399M	Missense	Higher Lp(a); ~2× CHD risk in Europeans
LPA	rs140570886	African-ancestry variant	Higher Lp(a)	Population-specific signal
LPA	KIV-2 CNV	Kringle IV-2 copy number	Directly determines apo(a) isoform size	Fewer repeats → smaller isoform → more efficient secretion → higher Lp(a). Inversely correlates with plasma Lp(a). Not a standard SNP — requires CNV assay

Lp(a) treatment note: PCSK9 monoclonal antibodies reduce Lp(a) ~25–30%. Apo(a) antisense oligonucleotides (pelacarsen, olpasiran, lepodisiran) reduce Lp(a) 80–95% and are in outcomes trials. Lp(a) is not meaningfully affected by statins or ezetimibe; bempedoic acid may modestly reduce it.

2.10 Oxidation, Inflammation, and NAFLD-Lipid Interface

The final layer. What happens to lipoproteins after they leave the liver (oxidation) and how hepatic lipid storage intersects with lipoprotein export. NAFLD/MASLD now affects ~25–30% of adults and interacts complexly with circulating lipids: hepatic fat retention can paradoxically LOWER circulating LDL and TG because VLDL export is impaired.

Genes and SNPs

Gene	SNP (rsID)	Variant name	Functional consequence	Effect / evidence
PON1	rs662	Q192R	Alters substrate specificity of paraoxonase-1	R allele: faster paraoxon clearance but slower oxidized lipid hydrolysis; mixed CHD evidence
PON1	rs854560	L55M	Affects enzyme stability	M allele lower PON1 activity
MTTP	rs1800591	-493G>T (promoter)	T allele reduces expression	Lower LDL-C, reduced hepatic VLDL secretion; rare LoF causes abetalipoproteinemia
PNPLA3	rs738409	I148M (c.444C>G)	Loss of triglyceride hydrolase activity; hepatic lipid droplet accumulation	Strongest common NAFLD variant. ~2× NAFLD risk per M allele. Paradoxically LOWER serum TG/LDL because fat is trapped in liver. Higher NASH, fibrosis, HCC risk [Romeo, Nat Genet 2008, 40:1461]
TM6SF2	rs58542926	E167K	Loss-of-function; impaired VLDL secretion	NAFLD risk; paradoxically LOWER LDL-C and TG and LOWER CHD [Kozlitina, Nat Genet 2014, 46:352; Dongiovanni, Hepatology 2015]
HSD17B13	rs72613567	TA insertion (splice)	Loss-of-function; protects against liver injury	Lower NAFLD progression; does not meaningfully affect circulating lipids
GCKR	rs1260326	P446L	Altered glucokinase regulation	Higher TG, lower fasting glucose; complex lipid/glucose effects [Orho-Melander, Diabetes 2008]

Cofactors: PON1 requires Ca^{2+} for enzymatic activity and is anchored to HDL. MTTP uses phosphatidylcholine for lipid loading onto nascent apolipoprotein B. PNPLA3 is a lipase whose activity requires its patatin domain to access lipid droplet surfaces.

3. Summary: Categories → Genes → Cofactors → Supplement Targets

This table maps each functional category to its key genes, the biochemical cofactors those enzymes or transporters require, and the nutrients or supplements most relevant to supporting each step. Supplement relevance is based on published mechanism — individual clinical benefit depends on genotype and baseline status.

Category	Key genes	Cofactors / substrates	Supplement/nutrient targets
2.1 LDLR clearance	LDLR, APOB, PCSK9, SORT1, MYLIP	ATP (clathrin endocytosis); PCSK9 cleavage by furin	No direct supplement. Drug targets: statin, ezetimibe, bempedoic acid, PCSK9 mAb
2.2 HMGCR biosynthesis	HMGCR, SREBF2, SCAP	NADPH (from PPP and IDH1); Mg^{2+}	B3 (NAD/NADP precursor); preserved G6PD activity; statin target
2.3 Statin PGx	SLCO1B1, ABCG2, CYP3A4/5, CYP2C9, LILRB5, GATM, COQ2	ATP (transporters); heme + NADPH (CYPs); SAM (GATM → creatine)	CoQ10 / ubiquinol (controversial but mechanistically plausible for LILRB5/GATM path); creatine (bypasses GATM); riboflavin (supports CYP)
2.4 Intestinal absorption	NPC1L1, ABCG5, ABCG8, APOA4	ATP (ABCG5/8); phospholipids	Plant sterols (compete at NPC1L1); soluble fiber (bile acid sequestration); ezetimibe target
2.5 ACL / bempedoic	ACLY, SLC27A2/ACSVL1, UGT2B7, SLCO2B1	ATP, CoA, Mg^{2+} (ACLY); CoA (drug activation)	Pantothenic acid (B5 → CoA); bempedoic acid target
2.6 PCSK9 mAb PGx	PCSK9, LDLR, APOE, LPA	N/A (antibody pharmacology)	No supplements; drug target
2.7 TG-rich / remnants	APOC3, APOA5, ANGPTL3/4/8, LPL, LIPC, APOE	ApoC-II (obligate LPL cofactor); GPIHBP1 anchoring	Omega-3 EPA/DHA (reduces TG); niacin (TG effect at high dose); exercise (increases LPL)
2.8 HDL / reverse transport	CETP, LIPG, LCAT, ABCA1, SCARB1	Phosphatidylcholine (LCAT); ATP (ABCA1)	Choline (phosphatidylcholine precursor); phosphatidylcholine directly

2.9 Lp(a)	LPA (KIV-2 CNV + rs10455872, rs3798220)	N/A (isoform size driven)	No effective supplement; PCSK9 mAb ~25–30% reduction; ASO drugs in trials
2.10 Oxidation / NAFLD	PON1, MTTP, PNPLA3, TM6SF2, HSD17B13, GCKR	Ca^{2+} (PON1); phosphatidylcholine (MTTP)	Vitamin E (NAFLD); choline (prevents hepatic TG accumulation); olive polyphenols; omega-3

4. Complete SNP Lookup Reference

All SNPs cataloged in this reference, in a single lookup format. Coordinates are GRCh38. Where multiple common names exist, the most frequent in the literature is shown first. This table can be used directly with variant-query tools such as bcftools, VEP, or snpEff.

Gene	rsID	Common name	Cat.	GRCh38 (approx)
LDLR	rs6511720	Intron 1 T>G	2.1	19:11091630 T>G
LDLR	rs688	C1773T (exon 12)	2.1	19:11116926 C>T
LDLR	rs5925	A370A (synonymous)	2.1	19:11113410 C>T
APOB	rs1367117	Near-missense	2.1	2:21044909 G>A
APOB	rs693	XbaI site (syn.)	2.1	2:21006288 C>T
APOB	rs5742904	R3500Q (FH)	2.1	2:21006154 G>A
PCSK9	rs11591147	R46L (protective LoF)	2.1	1:55039974 G>T
PCSK9	rs505151	E670G (risk GoF)	2.1	1:55064852 A>G
PCSK9	rs11206510	1p32 locus T>C	2.1	1:55030366 T>C
PCSK9	rs2479409	Promoter G>A	2.1	1:55030366 region
PCSK9	rs562556	I474V	2.1	1:55058336 A>G
MYLIP	rs9370867	N342S	2.1	6:16129098 A>G
SORT1	rs646776	1p13 locus T>C	2.1	1:109275684 T>C
CELSR2	rs599839	1p13 locus	2.1	1:109279544 A>G
HMGCR	rs17238484	Intronic T>G	2.2	5:75355259 T>G
HMGCR	rs3846662	Intron 13 G>A (splicing)	2.2	5:75360714 A>G
HMGCR	rs12916	Intronic T>C	2.2	5:75360714 region
SREBF2	rs2228314	G595C	2.2	22:41867460 C>G
SREBF1	rs11868035	Intronic	2.2	17:17811551 G>A
SCAP	rs12487736	Intronic	2.2	3:47450789 A>G
SLCO1B1	rs4149056	c.521T>C, V174A (*5)	2.3	12:21178615 T>C
SLCO1B1	rs2306283	N130D (*1B)	2.3	12:21176879 A>G
ABCG2	rs2231142	Q141K	2.3	4:88131171 G>T

ABCB1	rs1045642	C3435T	2.3	7:87509329 A>G
ABCB1	rs1128503	C1236T	2.3	7:87550285 A>G
ABCB1	rs2032582	G2677T/A	2.3	7:87531302 A>C/T
CYP3A5	rs776746	*3 (6986A>G)	2.3	7:99672916 T>C
CYP3A4	rs35599367	*22	2.3	7:99768693 C>T
CYP2C9	rs1799853	*2 (R144C)	2.3	10:94942290 C>T
CYP2C9	rs1057910	*3 (I359L)	2.3	10:94981296 A>C
LILRB5	rs12975366	D247G	2.3	19:54746815 A>G
GATM	rs1719247	Intronic	2.3	15:45361745 C>T
GATM	rs1346268	Intronic	2.3	15:45360093 T>C
COQ2	rs4693570	Intronic	2.3	4:83269940 G>A
COQ2	rs6535454	Intronic	2.3	4:83270169 region
NPC1L1	rs217386	Intronic G>A	2.4	7:44579347 A>G
NPC1L1	rs2072183	L272L (synonymous)	2.4	7:44580914 G>C
NPC1L1	rs41279633	p.R406X (LoF)	2.4	7:44578642 G>A
ABCG8	rs4299376	Intronic T>G	2.4	2:43845437 T>G
ABCG8	rs11887534	D19H	2.4	2:43839060 G>C
ABCG8	rs6544713	Intronic C>T	2.4	2:43847289 C>T
ABCG5	rs6720173	R50C	2.4	2:43826627 C>T
APOA4	rs675	T347S	2.4	11:116820917 A>T
APOA4	rs5110	Q360H	2.4	11:116820955 G>C
ACLY	rs9912468	Intronic	2.5	17:41867460 region
ACLY	rs2304129	Intronic	2.5	17:41868032 C>T
UGT2B7	rs7439366	*2 (H268Y)	2.5	4:69096937 C>T
SLCO2B1	rs12422149	c.935G>A	2.5	11:74914976 G>A
PCSK9	rs28362286	C679X (African LoF)	2.6	1:55065359 T>A
PCSK9	rs662145	Intronic	2.6	1:55061999 C>T
APOE	rs429358	Cys112Arg (ε4 defining)	2.6/2.7	19:44908684 T>C

APOE	rs7412	Arg158Cys (ε2 defining)	2.6/2.7	19:44908822 C>T
APOC3	rs138326449	R19X (LoF)	2.7	11:116830638 G>A
APOC3	rs3135506	S2P (SstI)	2.7	11:116829908 C>G
APOA5	rs662799	-1131T>C (promoter)	2.7	11:116792991 A>G
ANGPTL3	rs11207977	Intronic	2.7	1:62597678 G>A
ANGPTL3	rs10889353	Intronic	2.7	1:62589829 A>C
ANGPTL4	rs116843064	E40K	2.7	19:8364439 G>A
ANGPTL8	rs2278426	R59W	2.7	19:11217515 C>T
LPL	rs328	S447X (protective)	2.7	8:19956018 C>G
LPL	rs268	N291S	2.7	8:19962213 A>G
LPL	rs1801177	D9N	2.7	8:19944198 G>A
LIPC	rs1800588	C-514T (promoter)	2.7	15:58431590 C>T
LIPC	rs2070895	Promoter	2.7	15:58431767 G>A
CETP	rs708272	TaqIB (intron 1)	2.8	16:56957451 G>A
CETP	rs5882	I405V	2.8	16:56973869 A>G
CETP	rs3764261	Intergenic	2.8	16:56959412 C>A
LIPG	rs2000813	T111I	2.8	18:49564395 T>C
LCAT	rs5923	Intronic	2.8	16:67972924 region
ABCA1	rs4149313	I883M	2.8	9:104838305 G>A
ABCA1	rs2230806	R219K	2.8	9:104902327 C>T
SCARB1	rs10846744	Intronic	2.8	12:124794992 G>C
SCARB1	rs4765623	Intronic	2.8	12:124802696 C>T
LPA	rs10455872	Intron 25 A>G	2.9	6:160589086 A>G
LPA	rs3798220	I4399M	2.9	6:160540105 T>C
LPA	rs140570886	African-ancestry	2.9	6:160540000 region
PON1	rs662	Q192R	2.10	7:95308134 A>G
PON1	rs854560	L55M	2.10	7:95316772 A>T

MTTP	rs1800591	-493G>T (promoter)	2.10	4:99618429 G>T
PNPLA3	rs738409	I148M	2.10	22:43928847 C>G
TM6SF2	rs58542926	E167K	2.10	19:19268740 C>T
HSD17B13	rs72613567	TA insertion (splice)	2.10	4:87310241 T>TA
GCKR	rs1260326	P446L	2.10	2:27508073 T>C

Note: GRCh38 coordinates are approximate and provided as a guide. For precise variant calling, always resolve through dbSNP, Ensembl VEP, or the GWAS Catalog REST API using the rsID. Some coordinates above reflect locus positions rather than exact base-pair-level precision.

5. Bibliography and Source Notes

GWAS meta-analyses and lipid genetics consortia

Willer CJ et al. Discovery and refinement of loci associated with lipid levels. Nature Genetics 2013; 45:1274–1283. (Global Lipids Genetics Consortium)

Teslovich TM et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010; 466:707–713.

Klarin D et al. Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program. Nature Genetics 2018; 50:1514–1523.

Kathiresan S et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nature Genetics 2009; 41:334–341. (MIGen)

Causality / Mendelian randomization

Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. European Heart Journal 2017; 38:2459–2472.

Ference BA et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. JAMA 2017; 318:947–956.

Ference BA et al. Mendelian randomization study of ACLY and cardiovascular disease. NEJM 2019; 380:1033–1042.

PCSK9 and LDLR biology

Abifadel M et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genetics 2003; 34:154–156.

Cohen JC et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. NEJM 2006; 354:1264–1272.

Lagace TA et al. Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice. JCI 2006; 116:2995–3005.

Musunuru K et al. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. Nature 2010; 466:714–719.

Statin pharmacogenomics

SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy — a genomewide study. NEJM 2008; 359:789–799.

Cooper-DeHoff RM et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022; 111:1007–1021.

Chasman DI et al. Genetic determinants of statin-induced LDL-C reduction. PLoS Genetics 2012; 8:e1002758.

Medina MW et al. Alternative splicing of HMGCR is associated with plasma LDL cholesterol response to simvastatin. Circulation 2008; 118:355–362.

Siddiqui MK et al. A common missense variant of LILRB5 is associated with statin intolerance and CK elevation. Nature Communications 2017; 8:14685.

Mangravite LM et al. A statin-dependent QTL for GATM expression is associated with statin-induced myopathy. Nature 2013; 502:377–380.

Keskitalo JE et al. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2009; 86:197–203.

Drug-specific evidence

Ray KK et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. NEJM 2019; 380:1022–1032.

Nissen SE et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients (CLEAR Outcomes). NEJM 2023; 388:1353–1364.

Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). NEJM 2015; 372:2387–2397.

Stitziel NO et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. NEJM 2014; 371:2072–2082. (MIGen-Exome)

Sabatine MS et al. Evolocumab and clinical outcomes in patients with cardiovascular disease (FOURIER). NEJM 2017; 376:1713–1722.

Lipoprotein(a)

Clarke R et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. NEJM 2009; 361:2518–2528.

Kamstrup PR et al. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009; 301:2331–2339.

Kronenberg F et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. European Heart Journal 2022; 43:3925–3946.

Triglyceride-rich lipoproteins and ANGPTL pathway

TG and HDL Working Group of the Exome Sequencing Project. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. NEJM 2014; 371:22–31.

Dewey FE et al. Inactivating variants in ANGPTL4 and risk of coronary artery disease. NEJM 2016; 374:1123–1133.

Dewey FE et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. NEJM 2017; 377:211–221.

Do R et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature Genetics 2013; 45:1345.

HDL / reverse cholesterol transport

Voight BF et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. Lancet 2012; 380:572–580.

Bennet AM et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA 2007; 298:1300–1311.

NAFLD genetics and lipid interaction

Romeo S et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature Genetics 2008; 40:1461–1465.

Kozlitina J et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nature Genetics 2014; 46:352–356.

Dongiovanni P et al. TM6SF2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology 2015; 61:506–514.

Databases and resources

NHGRI-EBI GWAS Catalog — https://www.ebi.ac.uk/gwas/

Online Mendelian Inheritance in Man (OMIM) — https://www.omim.org/

dbSNP (NCBI) — https://www.ncbi.nlm.nih.gov/snp/

Ensembl Variant Effect Predictor — https://www.ensembl.org/vep

PharmGKB — https://www.pharmgkb.org/

Clinical Pharmacogenetics Implementation Consortium (CPIC) — https://cpicpgx.org/

This reference is a compilation of published findings as of the date of preparation. Genetic research in lipid metabolism evolves rapidly; new loci are identified regularly in GWAS and exome/genome sequencing studies. Readers should consult GWAS Catalog and PubMed for the most recent evidence when applying this reference to specific clinical or research questions.