Apolipoprotein Genetic Pathway Reference — Addendum

A standalone supplement to the Lipoprotein Pathway Reference

Reference build: GRCh38. Standalone educational reference. Contains no personal health information.
Version: April 2026

1. Introduction and Scope

This addendum supplements the prior Lipoprotein Pathway Reference. The original reference covered the broad lipoprotein machinery — LDLR clearance, HMGCR biosynthesis, statin pharmacogenomics, intestinal absorption (NPC1L1, ABCG5/8), the ATP-citrate lyase / bempedoic acid axis, PCSK9 monoclonal antibody pharmacogenomics, triglyceride-rich lipoprotein and remnant metabolism at a high level, HDL metabolism and reverse cholesterol transport, the LPA core variants, and the oxidation/NAFLD interface.

What was under-represented was the apolipoprotein protein family itself: the structural and regulatory proteins that ride on lipoprotein particles and dictate their metabolic fate. This addendum fills those gaps. Specifically:

- APOB extended series — variants beyond rs1367117, rs693, rs5742904 already in the prior report.
- The 11q23 APOA5/APOA4/APOC3/APOA1 cluster — full deep-dive including rs964184 (top GWAS tag) which was missing.
- APOC2 — entirely absent from the prior reference; obligate LPL cofactor.
- APOA1 promoter and rare functional variants beyond what was covered.
- Extended LPA variants beyond the three standard GWAS tags (rs10455872, rs3798220, rs140570886).
- APOE regulatory layer (TOMM40 poly-T, promoter SNPs, intron 1 regulators) beyond the two isoform-defining SNPs.
- Supporting cast genes omitted entirely: GPIHBP1, LMF1, CREB3L3, APOM, APOH, APOL1, APOF, APOBR.

Sources are restricted to peer-reviewed primary literature, GWAS Catalog, OMIM, and PharmGKB annotations. Effect sizes and p-values are cited where available. Variants with mixed or controversial replication are flagged in the variant tables.

2. Pathway Biology — The Apolipoprotein Layer

2.1 Why apolipoproteins deserve a dedicated layer

Lipoproteins are not just lipid droplets. Each particle's metabolic fate — whether it is taken up by a receptor, hydrolyzed by lipoprotein lipase, transferred via CETP, or cleared in the liver — is dictated by the apolipoprotein cargo on its surface. The major classes are summarized below.

Class	Members	Functional role
ApoB family	ApoB-100 (VLDL/IDL/LDL/Lp(a)); ApoB-48 (chylomicrons)	Structural anchor. One ApoB per particle. ApoB count equals atherogenic particle count.
ApoA family	ApoA-I, ApoA-II (HDL structural); ApoA-IV, ApoA-V (TG-rich regulators)	ApoA-I is the major HDL scaffold (~70% of HDL apolipoprotein mass). ApoA-V is a low-abundance LPL activator. ApoA-IV rides on chylomicrons and acts as a satiety signal.
ApoC family	ApoC-I, ApoC-II, ApoC-III	Small exchangeable cofactors. ApoC-II activates LPL (obligate). ApoC-III inhibits LPL and impairs hepatic remnant uptake.
ApoE	single gene with three common isoforms (ε2, ε3, ε4)	Universal remnant clearance ligand. Binds LDLR and LRP1.
Apo(a)	LPA gene product	Kringle-rich plasminogen homolog. Covalently linked to one

Class	Members	Functional role
		ApoB-100 to form Lp(a).

2.2 The 11q23 cluster as a haplotype unit

Four functionally interlocking apolipoproteins sit within ~50 kb of each other on chromosome 11q23: APOA5, APOA4, APOC3, APOA1. They are inherited together as haplotypes. This is why a single tag SNP — rs964184, located in the intergenic region — captures most of the cluster's effect on triglycerides and CHD risk in GWAS.

rs964184 is the single strongest signal at this locus across multiple meta-analyses (Teslovich, Nature 2010, 466:707; Willer, Nat Genet 2013, 45:1274; Klarin, Nat Genet 2018, 50:1514). Per-allele effects: triglycerides increased by approximately 16 mg/dL, HDL-C decreased by approximately 1 mg/dL, and CHD risk increased by approximately 13% per copy of the G allele. This was missing from the prior reference.

Conditional analyses suggest at least two independent signals at this locus: one tagged by rs964184 (intergenic), and a second tagged by rs651821 in the APOA5 5'UTR. Recent work (PMC8770627) implicates GATA4 binding to the rs651821 site as a mechanism, with the T allele (protective) supporting APOA5 transcription and the C allele (risk) impairing it.

2.3 The LPL co-activation triangle

Lipoprotein lipase is the enzyme that hydrolyzes triglycerides on circulating lipoproteins. Its activity depends on three factors that the prior reference covered unevenly:

1. LPL itself — covered in prior reference (rs328 S447X, rs268 N291S, rs1801177 D9N).
2. ApoC-II — obligate cofactor. Without ApoC-II, LPL is inactive regardless of expression. Entirely missing from prior reference.
3. GPIHBP1 — anchors LPL to the capillary endothelium and shuttles TG-rich particles to it. Missing from prior reference. Loss-of-function causes severe chylomicronemia (Beigneux, Cell Metab 2007). Autoantibodies against GPIHBP1 cause acquired chylomicronemia (Beigneux, NEJM 2017, 376:1647).

ApoC-III is the natural inhibitor of this triangle. APOC3 LoF variants (R19X, IVS2+1G>A, A23T) reduce TG by ~40% and CHD by ~40% — establishing ApoC-III as a causal CHD target (TG/HDL Working Group, NEJM 2014, 371:22). The ApoC-III antisense drug volanesorsen (approved for familial chylomicronemia) and the siRNA olezarsen recapitulate this genetic phenotype.

2.4 Hepatic transcriptional regulation: CREB3L3

CREB3L3 (also called CREBH) is a hepatic transcription factor that coordinately regulates APOA4, APOA5, APOC2, and FGF21 expression. LoF carriers have hypertriglyceridemia (Lee, J Lipid Res 2016, 57:1420). This is the upstream master regulator of the LPL-cofactor axis and was absent from the prior reference.

2.5 The APOE regulatory layer

The prior reference covered the two isoform-defining SNPs: rs429358 (Cys112Arg, ε4-defining) and rs7412 (Arg158Cys, ε2-defining). Together these define the ε2/ε3/ε4 isoforms. What was not covered is that APOE expression level — independent of isoform — is modulated by promoter and intronic variants (rs405509, rs440446, -491A>T) and by the adjacent TOMM40 poly-T length polymorphism.

rs405509 (-219G>T) has independently replicated as an Alzheimer's risk modifier in multiple cohorts (Bullido, Nat Genet 1998, 18:69; Lescai, Neurobiol Aging 2011). The TOMM40 poly-T claim is more controversial: positive reports (Roses, Pharmacogenomics J 2010) have not consistently replicated (Chu, Neurobiol Aging 2011), and the variant requires repeat-aware genotyping (e.g., ExpansionHunter) rather than standard SNP calling.

2.6 Sphingosine-1-phosphate axis: APOM

ApoM is a low-abundance HDL apolipoprotein that carries sphingosine-1-phosphate (S1P), a bioactive lipid mediator with vascular and immune effects. Approximately 95% of plasma S1P is bound to HDL via ApoM. ApoM-bound S1P signals through S1P receptors on endothelial cells, modulating barrier function and inflammation (Christoffersen, JBC 2008, 283:18765; Christoffersen, J Lipid Res 2012, 53:2198). The functional significance of

common APOM variants is still being defined; rs805296 (-778T>C) tags a haplotype with modestly altered ApoM expression.

2.7 Population-restricted variants: APOL1

APOL1 G1 (rs73885319 + rs60910145) and G2 (rs71785313) are non-synonymous variants that arose in sub-Saharan Africa and confer trypanolytic activity against Trypanosoma brucei rhodesiense (Genovese, Science 2010, 329:841). They are essentially absent in non-African populations. In African-ancestry individuals, two-allele carriage (G1/G1, G1/G2, or G2/G2) confers substantially elevated risk for FSGS, hypertensive nephropathy, HIV-associated nephropathy, and lupus nephritis. Cataloged here for completeness; expected absent in European-ancestry individuals.

3. Gene Catalog by Functional Category

3.1 APOB extended series

The prior reference covered rs1367117 (T2488T near-missense, GWAS LDL-C tag), rs693 (XbaI synonymous), and rs5742904 (R3500Q, familial defective ApoB / FDB-1). The variants below extend the catalog.

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs515135	5' near-gene	Tag SNP for APOB locus haplotype	—	LDL-C / CHD GWAS signal; Klarin, Nat Genet 2018
rs562338	Intronic	LDL-C signal independent of rs1367117	—	GLGC; Willer, Nat Genet 2013
rs1042031	E4181K	Missense near LDLR-binding domain	—	Mild LDL-C effect; Boekholdt, Circulation 2003
rs1801701	R3531C (FDB-2)	Familial defective ApoB allele 2; reduces LDLR affinity ~30%	LDLR binding requires basic-residue cluster	Pullinger, J Clin Invest 1995, 95:1225 — milder than R3500Q
rs934197	Intronic	LDL-C tag signal	—	GLGC meta-analysis
(rare series)	ApoB truncations (e.g., R463W, R532W)	Truncated ApoB cannot assemble VLDL	MTTP-dependent assembly fails	Familial hypobetalipoproteinemia (FHBL); Schonfeld, J Lipid Res 2003 — protective vs CHD but causes hepatic steatosis

Cofactor note: APOB itself is not enzymatic; it is structural. Assembly into VLDL requires MTTP (covered at rs1800591 in the prior reference) and adequate phosphatidylcholine supply, which depends on choline status.

PCSK9–APOB interaction: PCSK9 binds the EGF-A domain of LDLR; the LDLR–ApoB binding site sits at residues 3359–3369 of ApoB. R3500Q and R3531C disrupt the binding site, mimicking PCSK9 gain-of-function in phenotype but through a different mechanism. Compound carriage of PCSK9 GOF + APOB FDB is additive (Soutar & Naoumova, Nat Clin Pract Cardiovasc Med 2007, 4:214).

3.2 The APOA5 / APOA4 / APOC3 / APOA1 cluster on 11q23

3.2.1 — Cluster-tagging variant (rs964184)

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs964184	11q23 intergenic (between BUD13 and ZNF259)	Top GWAS tag for the entire cluster haplotype	Tags ↑APOC3, ↓APOA5 expression patterns	Per-G allele: ↑TG ~16 mg/dL, ↑CHD OR 1.13. $P < 5\times10^{-50}$. Teslovich Nature 2010; Willer 2013; Klarin 2018

rs964184 is missing from the prior reference and is the single most important addition. It tags the cluster haplotype and remains a CHD signal in conditional analyses, suggesting an independent regulatory effect beyond the individual gene-level variants.

3.2.2 — APOA5 (LPL activator)

APOA5 is a low-abundance plasma protein (~0.1 µg/mL — orders of magnitude less than APOC3) but a major LPL activator. Heterozygous LoF causes severe hypertriglyceridemia in mice (Pennacchio, Science 2001, 294:169).

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs662799	-1131T>C promoter (in prior ref)	Reduced APOA5 expression	—	C allele ↑TG ~30%; Do, Nature 2013, 493:96 — covered for completeness
rs3135506	S19W (signal peptide)	Reduces secretion efficiency	Signal peptide processing	W allele ↑TG ~20%; Pennacchio, Hum Mol Genet 2002, 11:3031
rs2266788	3'UTR T>C	Disrupts miR-485-5p binding site	miRNA-mediated regulation	Tag SNP for ↑TG haplotype; Caussy, Hum Mol Genet 2014, 23:2091
rs2075290	Intronic / APOA5*-12238	Tag SNP — strong LD with rs662799	—	TG association in Asian cohorts; Hsu, Atherosclerosis 2008
rs10750097	Promoter region	Independent CHD signal	—	Klarin, Nat Genet 2018
rs651821	-3A>G (5'UTR)	Disrupts GATA4 binding site	GATA4 is hepatic TF that drives APOA5 expression	C allele (risk) ↓APOA5; T allele (protective). $P=4.5\times10^{-76}$ for hyperlipidemia in Chinese cohort. PMC8770627

Cofactor note: APOA5 acts as an LPL activator and is itself dependent on hepatic transcriptional drive (CREB3L3, GATA4 binding sites in the promoter and 5'UTR). Intervention does not act on APOA5 directly; downstream LPL substrate management (omega-3 EPA/DHA at high dose, fibrates, and TG-lowering agents like tirzepatide) bypass the genetic loss.

3.2.3 — APOC3 (LPL inhibitor)

APOC3 inhibits LPL and impairs hepatic remnant uptake. APOC3 loss-of-function is one of the cleanest Mendelian-randomization findings in lipid genetics — supporting the entire ApoC-III antisense / siRNA drug class (volanesorsen, olezarsen).

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs138326449	R19X LoF (in prior ref)	Premature stop	—	~39% ↓TG, ~40% ↓CHD; TG/HDL Working Group, NEJM 2014, 371:22
rs76353203	IVS2+1G>A (splice LoF)	Splice donor disruption	—	Same phenotype as R19X; Jorgensen, NEJM 2014, 371:32
rs147210663	A23T	Reduced secretion	—	TG-lowering, CHD-protective LoF
rs140621530	Lancaster Amish LoF	Functional null	—	Pollin, Science 2008, 322:1702
rs5128	3'UTR SstI (S2 allele)	C→G in 3'UTR	Possibly affects mRNA stability	G allele (S2) ↑TG; meta-analysis Song, Atherosclerosis 2006
rs2854117	-482C>T (insulin response element)	Disrupts insulin-mediated APOC3 suppression	Insulin signaling regulates hepatic APOC3	T allele ↑APOC3 expression, ↑TG; Li 2004
rs2854116	-455T>C	Insulin response element (linked to rs2854117)	—	Haplotype tag for promoter risk variant
rs4520	T2854C 3'UTR	Tag SNP; LD with cluster haplotype	—	↑TG signal in some cohorts

Pharmacological context: APOC3 antisense oligonucleotide (volanesorsen, approved for familial chylomicronemia syndrome) and siRNA (olezarsen, in late-stage trials) recapitulate the genetic LoF phenotype: ~70-80% TG reduction. The genetic data validates the drug class (Witztum, NEJM 2019, 381:531; Tardif, Eur Heart J 2022, 43:1401).

3.2.4 — APOA4 (chylomicron, satiety signal)

APOA4 is secreted by enterocytes, rides on chylomicrons, and acts as a satiety signal in addition to its lipoprotein role. Less studied than the others in the cluster.

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs675	T347S (in prior ref)	Modest postprandial TG effect	Chylomicron assembly	Lefevre, J Lipid Res 1994 — small effect
rs5110	Q360H (in prior ref)	Affects LCAT activation	LCAT cofactor function	Modest HDL-C effect
rs5104	5' region tag	Promoter haplotype tag	—	Weak independent effect; usually inherited as haplotype with rs675/rs5110

APOA4 is the weakest contributor to the 11q23 cluster's lipid effects. The APOA4-1/APOA4-2 dimorphism (rs675) modulates postprandial TG response slightly. Clinical relevance is mostly population-genetic.

3.2.5 — APOA1 (HDL scaffold)

APOA1 is the major HDL structural protein (~70% of HDL apolipoprotein mass). Plasma ApoA-I tracks HDL-C and is a stronger predictor of CHD than HDL-C alone in some cohorts (Walldius, Circulation 2004).

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs670	-75 G>A (MspI)	Disrupts a transcription factor binding site in the promoter	—	A allele ↑APOA1 expression → ↑HDL-C ~3-5%; meta-analysis Juo, Genet Epidemiol 1999. Conflicting reports in some cohorts (al-Bustan, BMC Med Genet 2013)
rs5069	-83 C>T promoter	Modulates promoter activity	—	Modest HDL effect; less replicated
rs2070665	Intronic	LD with promoter haplotype	—	Tag SNP
rs5070	Intron 3 G>A	Splice-region tag	—	HDL signal in Asian cohorts

Rare functional variants (cataloged for context only — gnomAD AF <0.001):

- APOA1 Milano (R173C) — autosomal dominant; carriers have very low HDL-C but paradoxically reduced atherosclerosis. Sirtori, Circulation 2001, 103:1949.
- APOA1 Paris (R151C) — phenotype similar to Milano. Daum, Atherosclerosis 1999.
- APOA1 Zaragoza (L144R) — familial amyloidosis with very low HDL.

3.3 APOC2 — the obligate LPL activator

APOC2 is required for LPL activity. Without ApoC-II, LPL is inactive regardless of expression level. ApoC-II deficiency causes familial chylomicronemia syndrome indistinguishable phenotypically from LPL deficiency (Breckenridge, NEJM 1978, 298:1265). This gene was entirely absent from the prior reference.

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs9610291	5' regulatory tag	Tag SNP for APOC2 locus	—	Modest TG effect; GLGC
rs5167	3'UTR variant	Possibly affects mRNA stability	—	Limited replication
(rare)	APOC2 deficiency mutations	LoF; functional null	—	Familial chylomicronemia syndrome; Connelly, J Lipid Res 1987, 28:1048

Cofactor / supplement context: APOC2 itself is the cofactor for LPL. LPL also requires GPIHBP1 for endothelial anchoring (Section 3.6). APOC2-mimetic peptides (e.g., D6PV) are in preclinical development for familial chylomicronemia syndrome. Endogenous APOC2 supply is genetically determined and cannot be supplemented.

3.4 LPA extended variants

The prior reference covered rs10455872, rs3798220, and rs140570886. Additional independent signals identified through dense association mapping and conditional GWAS:

rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
rs7770628	Intronic	Independent CHD signal after conditioning on rs10455872	—	Conditional GWAS; Clarke, NEJM 2009, 361:2518
rs55730499	Intronic	CARDIoGRAM signal	—	Schunkert, Nat Genet 2011, 43:333
rs41272110	G+1/in (KIV-9 splice)	Splice variant in apo(a)	Affects apo(a) protein production	Lower Lp(a); Lim, Nat Genet 2014, 46:543
rs1853021	Promoter	Pentanucleotide repeat tag	—	Modulates apo(a) transcription
rs1800769	Promoter PNR	Variable repeats (5-11) of TTTTA	Repeat-aware genotyping required	Repeat number inversely correlates with Lp(a); Trommsdorff, J Clin Invest 1995, 96:150
rs9457951	LPA region	Independent signal	—	Saleheen, Lancet Diabetes Endocrinol 2017
rs74617384	Recently identified	LoF effect on apo(a)	—	Lower Lp(a) and CHD; Coassin, Eur Heart J 2017, 38:1823

OxPL-apoB biomarker: oxidized phospholipids on apoB-containing particles are a Lp(a)-related biomarker because Lp(a) preferentially carries OxPL. Plasma OxPL-apoB (E06 antibody assay) tracks plasma Lp(a) and independently predicts CHD events (Tsimikas, NEJM 2005, 353:46). Not a SNP — but worth tracking as an emerging Lp(a)-axis biomarker.

3.5 APOE regulatory layer (beyond ε2/ε3/ε4 isoforms)

The prior reference covered rs429358 (Cys112Arg, ε4-defining) and rs7412 (Arg158Cys, ε2-defining). The regulatory layer below modulates APOE expression independently of isoform.

Gene / rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
APOE rs405509	-219G>T promoter	Disrupts transcription factor binding	Promoter-driven APOE expression	T allele ↓APOE expression; modulates AD risk independent of isoform; Bullido Nat Genet 1998, 18:69; Lescai 2011
APOE rs440446	Intron 1 G>C	Linked to promoter haplotype	—	Tag SNP for APOE expression haplotype
APOE -491A>T	Promoter (rare)	Reduces transcription	—	Independent AD association; Bullido, Nat Genet 1998
TOMM40 rs10524523	Poly-T variable repeat	T-length affects TOMM40 + APOE expression	Variable-length repeat (VLR), not a SNP — requires repeat-aware genotyping (e.g., ExpansionHunter)	MIXED EVIDENCE: positive reports (Roses, Pharmacogenomics J 2010, 10:375) have not consistently replicated (Chu,

Gene / rsID	Common name	Functional consequence	Cofactor / context	Evidence / effect
				Neurobiol Aging 2011, 32:2107.e1)
TOMM40 rs2075650	Intronic	LD with APOE ε4 in Europeans	—	Strong AD GWAS signal driven by APOE ε4 LD

Cross-reference: The prior Dementia Genetic Report and Lipoprotein Pathway Reference both discuss APOE ε2/ε3/ε4 in detail. The regulatory layer above is relevant even in ε3/ε3 individuals because expression-level modulation continues to operate.

3.6 Supporting cast — LPL machinery and HDL functional axis

These genes are entirely absent from the prior reference and are biologically essential at the intersections of apolipoprotein cargo, LPL machinery, and HDL function.

Gene	Role	Key SNPs / variants	Cofactor / context	Evidence
GPIHBP1	Anchors LPL to capillary endothelium; transfers TG-rich particles to LPL	rs72691625 (G56R partial LoF); rs141935764; rare LoF series	GPI-anchored protein on endothelium	Beigneux, Cell Metab 2007, 5:279. Autoimmune chylomicronemia from anti-GPIHBP1 antibodies — Beigneux, NEJM 2017, 376:1647
LMF1 (TMEM112)	LPL maturation factor in ER; required for proper folding	Rare LoF causes chylomicronemia	ER chaperone for LPL	Péterfy, Nat Genet 2007, 39:1483
CREB3L3 (CREBH)	Hepatic transcription factor; coordinately regulates APOA4, APOA5, APOC2, FGF21	rs139739064 (LoF tag); rare missense series	ER membrane-bound TF; activated by ER stress / fasting	Lee, J Lipid Res 2016, 57:1420 — LoF carriers have hypertriglyceridemia
APOM	Sphingosine-1-phosphate carrier on HDL; functional HDL component	rs805296 (-778T>C); rs9404941	Carries ~95% of plasma S1P	Christoffersen, JBC 2008, 283:18765; J Lipid Res 2012, 53:2198
APOH (β2-glycoprotein I)	Primary antigen of antiphospholipid antibodies; lipid-binding	rs8178847 and others	Antiphospholipid syndrome target	Mehdi, J Mol Biol 2008. CHD relevance via aPL syndrome
APOL1	HDL-associated; trypanolytic factor	G1 = rs73885319 + rs60910145; G2 = rs71785313	African-ancestry-restricted; absent in Europeans	Genovese, Science 2010, 329:841 — kidney disease in two-allele African-ancestry carriers; expected absent in European-ancestry individuals

Gene	Role	Key SNPs / variants	Cofactor / context	Evidence
APOF	CETP modulator; inhibits CETP-mediated lipid transfer	Limited common-variant data	—	Wang, J Lipid Res 2007, 48:2622
APOBR	Apolipoprotein B receptor; binds chylomicron remnants in macrophages	Limited common-variant data	—	Brown, Atherosclerosis 2000

4. Category → Gene → Cofactor → Supplement Target Map

This table mirrors the format of the prior Lipoprotein Pathway Reference Section 3 but covers only the addendum genes.

Category	Key genes	Cofactors / substrates	Supplement / nutrient targets
A.1 APOB extended	APOB	MTTP-mediated assembly; phosphatidylcholine	Choline (PC precursor); MTTP function indirectly via vitamin E + omega-3 if VLDL export is impaired (relevant for FHBL phenotype only)
A.2 11q23 cluster (APOA5/A4/C3/A1)	APOA5, APOA4, APOC3, APOA1	ApoC-II (LPL cofactor); insulin-mediated APOC3 suppression	Omega-3 EPA/DHA (TG reduction independent of cluster); volanesorsen / olezarsen (Rx, drug targets)
A.3 APOC2	APOC2	GPIHBP1 endothelial anchor; LPL substrate	No supplement; APOC2-mimetic peptides in development (Rx)
A.4 APOA1 promoter	APOA1	Transcription factor binding at -75/-83	No direct supplement; lifestyle factors (exercise, alcohol moderation) modulate APOA1 expression
A.5 LPA extended	LPA	Apo(a) covalent linkage to ApoB-100 via Cys disulfide	No effective supplement; PCSK9 mAb ~25-30% reduction; apo(a) ASOs (pelacarsen, olpasiran, lepodisiran) in trials
A.6 APOE regulatory	APOE, TOMM40	Promoter TF binding; APOE expression level	No direct supplement; cardiovascular and Alzheimer's risk factors modulate downstream
A.7 LPL machinery + HDL function	GPIHBP1, LMF1, CREB3L3, APOM, APOH, APOL1, APOF, APOBR	GPI anchoring (GPIHBP1); ER chaperone (LMF1); S1P (APOM)	No direct supplements for these genes; conventional TG-lowering interventions act downstream

5. Complete SNP Lookup Reference (Addendum)

All SNPs cataloged in this addendum, in a single lookup format. Coordinates are GRCh38. Where multiple common names exist, the most frequent in the literature is shown. This table is paired with the companion files apolipoprotein_addendum_rsids.txt and apolipoprotein_addendum_positions.bed for direct use with bcftools, VEP, or snpEff.

Gene	rsID	Common name	Category	GRCh38 (approx)
APOB	rs515135	5' near-gene	A.1	2:21001388
APOB	rs562338	Intronic	A.1	2:21008012
APOB	rs1042031	E4181K	A.1	2:21006292
APOB	rs1801701	R3531C (FDB-2)	A.1	2:21036459
APOB	rs934197	Intronic	A.1	2:21013867
11q23	rs964184	Cluster intergenic tag	A.2	11:116648917
APOA5	rs3135506	S19W	A.2	11:116789958
APOA5	rs2266788	3'UTR T>C	A.2	11:116787802
APOA5	rs2075290	APOA5*-12238	A.2	11:116782552
APOA5	rs10750097	Promoter	A.2	11:116657561
APOA5	rs651821	-3A>G 5'UTR (GATA4)	A.2	11:116789997
APOC3	rs76353203	IVS2+1G>A LoF	A.2	11:116831204
APOC3	rs147210663	A23T	A.2	11:116830807
APOC3	rs140621530	Lancaster Amish LoF	A.2	11:116830638
APOC3	rs5128	3'UTR SstI (S2)	A.2	11:116829907
APOC3	rs2854117	-482C>T (IRE)	A.2	11:116829908
APOC3	rs2854116	-455T>C (IRE)	A.2	11:116829935
APOC3	rs4520	T2854C 3'UTR	A.2	11:116830038
APOA4	rs5104	Promoter haplotype	A.2	11:116821128
APOA1	rs670	-75 G>A (MspI)	A.2	11:116836706
APOA1	rs5069	-83 C>T	A.2	11:116836564
APOA1	rs2070665	Intronic	A.2	11:116836200
APOA1	rs5070	Intron 3 G>A	A.2	11:116835000
APOC2	rs9610291	5' regulatory	A.3	19:44949250
APOC2	rs5167	3'UTR	A.3	19:44946086
LPA	rs7770628	Intronic	A.5	6:161058098
LPA	rs55730499	Intronic	A.5	6:161005610
LPA	rs41272110	G+1/in (KIV-9 splice)	A.5	6:160585824
LPA	rs1853021	Promoter	A.5	6:161035000
LPA	rs1800769	Promoter PNR	A.5	6:161092000
LPA	rs9457951	LPA region	A.5	6:161005000

Gene	rsID	Common name	Category	GRCh38 (approx)
LPA	rs74617384	Protective LoF	A.5	6:161080000
APOE	rs405509	-219G>T	A.6	19:44905578
APOE	rs440446	Intron 1 G>C	A.6	19:44906745
TOMM40	rs10524523	Poly-T tag	A.6	19:44899792
TOMM40	rs2075650	Intronic	A.6	19:44892362
GPIHBP1	rs72691625	G56R	A.7	8:14693517
GPIHBP1	rs141935764	Coding region	A.7	8:14688550
CREB3L3	rs139739064	LoF tag	A.7	1:221152565
APOM	rs805296	-778T>C	A.7	20:57424716
APOM	rs9404941	Promoter region	A.7	6:31621000
APOH	rs8178847	Coding region	A.7	17:66212290
APOL1	rs73885319	G1 S342G	A.7	22:36265860
APOL1	rs60910145	G1 I384M	A.7	22:36265988
APOL1	rs71785313	G2 indel	A.7	22:36266000

Note: GRCh38 coordinates above are best-effort and provided as a guide for positional fallback. For precise variant calling, always resolve through dbSNP, Ensembl VEP, or the GWAS Catalog REST API using the rsID. The companion bcftools script also includes gene-region scans (Section 7) that catch any variant whose precise coordinate is slightly off.

6. Risk-Allele Orientation Quick Reference

The bcftools script includes strand-orientation spot-check entries for the variants below. APOA5 and APOC3 are minus-strand genes — alleles may appear as complements in some VCFs; if VCF REF/ALT is the reverse complement of the dbSNP forward-strand REF/ALT, flip the genotype interpretation.

rsID	Gene	REF	ALT	Risk allele	Note
rs964184	11q23	C	G	G	TG-raising and CHD-raising allele; top GWAS tag
rs651821	APOA5	T	C	C	C disrupts GATA4 binding → ↓APOA5 → ↑TG
rs2854117	APOC3	C	T	T	T disrupts insulin response element → ↑APOC3
rs5128	APOC3	C	G	G (S2)	S2 allele in 3'UTR; ↑TG
rs670	APOA1	G	A	G (ref)	A allele is HDL-raising / protective; G is the more common allele
rs7770628	LPA	C	T	T	Independent CHD signal after conditioning on rs10455872
rs1801701	APOB	C	T	T	FDB-2 partial LDLR-binding loss
rs405509	APOE	G	T	T	T allele ↓APOE expression

rsID	Gene	REF	ALT	Risk allele	Note
rs73885319	APOL1	A	G	G (G1)	Expected ABSENT in European-ancestry individuals

7. ClinVar Pathogenicity / PharmGKB Annotation Status

The variants in this addendum are predominantly common-variant lipid-modifying SNPs without ClinVar pathogenic classifications or PharmGKB clinical annotations of level 1A/1B. The rare functional variants (APOB R3531C, APOC3 LoF series, APOC2 deficiency, APOA1 Milano/Paris/Zaragoza, GPIHBP1 LoF, CREB3L3 LoF) have ClinVar entries with variable significance levels.

Variant	ClinVar status	PharmGKB annotation	Comment
APOB R3500Q (rs5742904)	Pathogenic (FDB)	Level 3	Already in prior reference — FDB-1
APOB R3531C (rs1801701)	Likely pathogenic / risk factor (FDB-2)	—	Milder ApoB-LDLR binding defect than R3500Q
APOC3 R19X (rs138326449)	Benign for FCS / protective for CHD	Level 3	Net cardioprotective
APOC3 IVS2+1 (rs76353203)	Same protective phenotype	—	Replicated in Pakistani cohort (Saleheen 2017)
APOA5 -1131T>C (rs662799)	Common variant; not pathogenic	Level 3	Strong TG-raising association
rs964184 (11q23)	Common variant; not pathogenic	Level 3	Top GWAS tag
GPIHBP1 (LoF series)	Pathogenic for chylomicronemia	—	Heterozygous carriers may have moderate hypertriglyceridemia
APOL1 G1, G2	Risk factor for kidney disease (African ancestry)	Level 1A (HIV nephropathy / FSGS)	Expected ABSENT in European-ancestry individuals
APOE rs405509	Common variant	—	Mixed AD-association evidence
TOMM40 poly-T	Common variant	—	Mixed evidence; requires repeat-aware genotyping

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9. Companion Files for VCF Querying

This addendum is paired with three companion files that live alongside it and enable direct interrogation of a per-sample VCF:

apolipoprotein_addendum_rsids.txt — flat list of rsIDs suitable for bcftools view -i 'ID=@apolipoprotein_addendum_rsids.txt'.

apolipoprotein_addendum_positions.bed — GRCh38 BED file with chrXX naming, suitable for bcftools view -R apolipoprotein_addendum_positions.bed. Provides positional fallback for SNPs whose rsIDs are not in the VCF ID column, and full gene-region scans for the 11q23 cluster, APOC2, LPA, APOE/TOMM40, GPIHBP1, LMF1, CREB3L3, APOM, APOH, and APOL1.

apolipoprotein_addendum_query.sh — bash script that runs the rsID and positional queries, computes call rate, runs region scans, and (if BAM or CRAM is provided) runs samtools mpileup spot-checks on the highest-impact variants for strand and depth confirmation. Modeled on the parkinson_pd_query.sh script structure.

Variant types not addressable by standard SNP query and flagged in the script:

- TOMM40 poly-T variable-length repeat (rs10524523) — requires repeat-aware caller such as ExpansionHunter or GangSTR.
- LPA KIV-2 copy number variation — already noted as a limitation in the prior reference.
- LPA pentanucleotide repeat (rs1800769) — requires repeat-aware caller.