Endothelial Health

Genetic Pathway Reference

9 Functional Categories • ~45 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of the vascular endothelium, the genes that regulate endothelial function, the well-studied common variants in those genes, the cofactors each enzyme requires, and the supplement targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature and peer-reviewed mechanistic studies. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (odds ratios 1.05–1.4); clinical significance arises from cumulative patterns and gene-environment interactions. A few variants (Factor V Leiden, Prothrombin G20210A, LPA rs10455872, PCSK9 R46L, 9p21 rs10757278) have larger and clinically actionable effect sizes.

2. Pathway Biology

2.1 What the endothelium does

The vascular endothelium is a single continuous layer of cells lining every blood vessel, with a combined surface area of approximately 4,000–7,000 m² and 1–6 × 10^{13} cells. Far from being passive plumbing, it is the body's largest paracrine organ. It regulates vascular tone, blood fluidity, permeability, leukocyte trafficking, smooth muscle proliferation, angiogenesis, and the local balance between coagulation and fibrinolysis (Aird, Circ Res 2007; Deanfield et al., Circulation 2007).

2.2 The NO-cGMP axis: the core homeostatic circuit

Endothelial health is most usefully understood through the lens of nitric oxide (NO) bioavailability. Endothelial nitric oxide synthase (eNOS, encoded by NOS3) converts L-arginine to L-citrulline and NO, using NADPH, O_2, FAD, FMN, heme, Ca^{2+}/calmodulin, and critically tetrahydrobiopterin (BH4) as cofactors. NO diffuses to vascular smooth muscle where it activates soluble guanylate cyclase, producing cGMP, activating PKG, and causing vasodilation. NO also suppresses platelet aggregation, VCAM-1/ICAM-1 expression, and smooth muscle proliferation. When BH4 is oxidized to BH2 or is depleted, eNOS 'uncouples' and produces superoxide instead of NO, flipping the enzyme from protective to injurious (Förstermann & Münzel, Circulation 2006; Alp & Channon, ATVB 2004).

2.3 Redox balance determines whether NO survives

NO is destroyed within milliseconds by reaction with superoxide (O_2^-) to form peroxynitrite ($ONOO^-$), which itself oxidizes BH4 and propagates dysfunction. The principal endothelial

sources of superoxide are NADPH oxidases (NOX1, NOX2, NOX4, NOX5), uncoupled eNOS, xanthine oxidase, myeloperoxidase, and mitochondria. Counterbalancing these are superoxide dismutases (SOD1 cytosolic, SOD2 mitochondrial, SOD3 extracellular), glutathione peroxidases, catalase, and the thioredoxin/peroxiredoxin system. Endothelial dysfunction is fundamentally a state in which ROS production exceeds antioxidant capacity and NO signaling collapses (Münzel et al., JACC 2017).

2.4 ADMA: the endogenous eNOS inhibitor

Asymmetric dimethylarginine (ADMA) is generated by protein arginine methylation and subsequent proteolysis, and it competes with L-arginine for the eNOS active site. ADMA is cleared primarily by two enzymes: DDAH1 and DDAH2 (dimethylarginine dimethylaminohydrolases), with a secondary contribution from AGXT2 in the kidney. Plasma ADMA concentration is one of the most robust circulating biomarkers of endothelial dysfunction and an independent predictor of cardiovascular events (Böger, Cardiovasc Res 2003; Schnabel et al., Circ Res 2005).

2.5 Inflammation and adhesion

When NO falls, NF-κB is disinhibited, and the endothelium upregulates VCAM-1, ICAM-1, E-selectin, and MCP-1, recruiting monocytes that transmigrate into the subintimal space and become foam cells — the initiating event of atherosclerosis (Libby et al., Nature 2011). IL-6, TNF-α, and CRP both cause and reflect this shift. Mendelian randomization evidence (IL6R MR Consortium, Lancet 2012) supports a causal role for IL-6 receptor signaling in coronary disease.

2.6 Vascular tone and the renin-angiotensin-bradykinin axis

Vascular smooth muscle tone is set by the balance between vasodilators (NO, prostacyclin, bradykinin, EDHF) and vasoconstrictors (angiotensin II, endothelin-1, thromboxane). The renin-angiotensin-aldosterone system (RAAS) is the principal pharmacological target in hypertension, and common variants in ACE, AGT, and AGTR1 contribute modest amounts to blood pressure variance. Bradykinin, degraded by ACE, mediates part of the benefit of ACE inhibition.

2.7 Hemostatic balance

Healthy endothelium is antithrombotic: it expresses thrombomodulin, tissue factor pathway inhibitor, heparan sulfate, and prostacyclin, and releases tissue plasminogen activator (tPA). Dysfunctional endothelium tips toward tissue factor expression, PAI-1 release, and thrombosis. A handful of common variants (Factor V Leiden, Prothrombin G20210A, PAI-1 4G/5G) meaningfully shift this balance.

2.8 Lipid-endothelium interface

Oxidized LDL (oxLDL) is taken up by endothelial and subendothelial macrophages via scavenger receptors, driving foam cell formation and local inflammation. Lipoprotein(a), whose plasma concentration is almost entirely genetically determined by the LPA locus, carries oxidized phospholipids and is one of the few common variants with a large, causal, Mendelian-randomization-supported effect on cardiovascular disease (Clarke et al., NEJM 2009). PCSK9 loss-of-function variants produce large lifelong protective effects on LDL and CAD (Cohen et al., NEJM 2006).

2.9 Clinical integration

Endothelial dysfunction — measured by flow-mediated dilation (FMD), reactive hyperemia index, or biomarkers like ADMA — independently predicts future cardiovascular events (Ras et al., Int J Cardiol 2013 meta-analysis, HR ~1.4 per SD decrease in FMD). It is also the final common pathway through which hypertension, hyperglycemia, dyslipidemia, smoking, and hyperhomocysteinemia cause vascular disease, which is why endothelial genetics intersects meaningfully with glucose regulation, glycation, and homocysteine pathways.

3. Functional Categories

The endothelial pathway can be organized into nine functional categories, each corresponding to a distinct biochemical job. The categories below are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	NO synthesis (eNOS axis)	Produce NO from L-arginine; regulate ADMA	NOS3, DDAH1, DDAH2, AGXT2
2	BH4 cofactor supply	Synthesize and recycle tetrahydrobiopterin	GCH1, DHFR, QDPR, SPR
3	NO downstream signaling	Transduce NO → cGMP → vasodilation	GUCY1A3, PDE5A, PRKG1
4	ROS production	NADPH oxidase subunits, xanthine oxidase, MPO	CYBA, NOX4, XDH, MPO
5	Antioxidant defense	Neutralize ROS and preserve NO	SOD2, SOD3, GPX1, CAT, NQO1, PON1
6	Inflammation & adhesion	NF-κB, cytokines, adhesion molecules	IL6, IL6R, TNF, CRP, SELE, ICAM1
7	Vascular tone & RAAS	Angiotensin, endothelin, bradykinin	ACE, AGT, AGTR1, EDN1, BDKRB2
8	Hemostasis & thrombosis	Endothelial coagulation balance	F2, F5, SERPINE1
9	Lipid-endothelium interface + 9p21	oxLDL handling, Lp(a), LDL receptor regulation	LPA, LDLR, APOE, CETP, LIPC, PCSK9, CDKN2B-AS1

4. SNP Catalog by Functional Category

Each table below lists the well-studied common variants in the genes for that category, along with the variant name, the functional consequence, and the cofactor(s) required. Effect sizes and GWAS p-values are noted where well-established. The most important references for the cardiovascular GWAS evidence are Nikpay et al. (CARDIoGRAMplusC4D, Nat Genet 2015, n > 190,000) and Schunkert et al. (Nat Genet 2011, n > 86,000), which together identified most of the common variants with replicated CAD effects.

4.1 NO synthesis (eNOS axis)

Gene	rsID	Variant	Functional consequence	Cofactor
NOS3	rs1799983	G894T (Glu298Asp)	Asp298 protein more susceptible to proteolytic cleavage; lower eNOS protein levels. T allele OR ~1.31 for CAD (Casas et al., Circulation 2004). Also associated with hypertension and reduced FMD.	BH4, FAD, FMN, heme, Ca^{2+}/CaM, NADPH, Zn
NOS3	rs2070744	T-786C promoter	C allele reduces NOS3 transcription ~50% in reporters (Nakayama et al., Circulation 1999). Associated with coronary spasm, HTN, and reduced FMD.	(regulatory)
DDAH1	rs997251	intronic	GWAS-associated with plasma ADMA (Lüneburg et al., Circulation 2014; p ~10^{-8} in CHARGE).	Zn
DDAH1	rs233112	intronic eQTL	Expression QTL affecting DDAH1 mRNA levels.	Zn
DDAH2	rs805305	-449 G/C promoter	Reduced promoter activity with G allele; candidate for ADMA variance.	Zn
AGXT2	rs37369	Val140Ile	Reduces enzyme activity; GWAS-associated with plasma SDMA and ADMA (Seppälä et al., Circ Cardiovasc Genet 2014).	PLP (B6)

NOS3 is the central enzyme; rs1799983 and rs2070744 are the two most-studied eNOS variants and are often inherited on a common haplotype. The ADMA-degradation enzymes (DDAH1/2 and AGXT2) determine the endogenous brake on eNOS and are reflected in circulating ADMA, one of the best endothelial biomarkers.

4.2 BH4 cofactor supply

Gene	rsID	Variant	Functional consequence	Cofactor
GCH1	rs8007267	intronic eQTL	Minor allele ~20% lower GCH1 expression, lower plasma BH4, higher blood pressure (Zhang et al., Hypertension 2007). Rate-limiting enzyme of de novo BH4 synthesis.	Mg, Zn, GTP
GCH1	rs10483639	haplotype tag	Component of the 'pain-protective' haplotype (Tegeder et al., Nat Med 2006) that limits stress-induced GCH1 upregulation.	Mg, Zn
GCH1	rs841	intronic	Associated with CAD in Asian cohorts; mechanism presumed via BH4 availability.	Mg, Zn
DHFR	rs70991108	19-bp intron 1	Reduces DHFR mRNA stability; dual	NADPH

Gene	rsID	Variant	Functional consequence	Cofactor
		deletion	role in folate and BH4 pools. Affects recycling of BH2 to BH4 and DHF to THF.	
DHFR	rs1643649	eQTL	Expression QTL for DHFR.	NADPH
QDPR	rs1729635	intronic	Regenerates BH4 after each NOS catalytic cycle; variants modulate enzyme expression.	NADH
QDPR	rs2856107	intronic	Candidate BH4-recycling variant.	NADH
SPR	rs1876487	eQTL	Sepiapterin reductase; final step of de novo BH4 synthesis.	NADPH

BH4 availability is arguably the most important single modifier of eNOS coupling. A BH4-depleted endothelium flips eNOS from producing NO to producing superoxide. GCH1 is the rate-limiting enzyme of de novo synthesis; DHFR salvages BH2 back to BH4. The pain-protective GCH1 haplotype is notable because it was discovered in a completely different context (pain genetics) but has direct vascular implications.

4.3 NO downstream signaling

Gene	rsID	Variant	Functional consequence	Cofactor
GUCY1A3	rs7692387	intronic	Major CAD GWAS locus (Nikpay et al., Nat Genet 2015; OR ~1.07 per allele, p ~10^{-15}). Risk allele reduces GUCY1A3 expression in plaques, blunting cGMP response to NO.	heme, Mg
GUCY1A3	rs13139571	intronic	Independent CAD signal at the same locus.	heme, Mg
PDE5A	rs3806808	intronic	Candidate modifier of PDE5 inhibitor response and pulmonary vascular tone.	Mg, Zn
PRKG1	rs7897633	intronic	Candidate in aortic disease; less robust CAD evidence.	Mg, ATP

GUCY1A3 rs7692387 is one of the strongest CAD GWAS loci outside the lipid and 9p21 regions and represents the cleanest genetic example that the NO receptor itself is a CAD risk locus independent of NO production.

4.4 ROS production

Gene	rsID	Variant	Functional consequence	Cofactor
CYBA	rs4673	C242T (His72Tyr)	T allele reduces NADPH oxidase activity in some assays; modest protection in Caucasian CAD meta-analyses (OR ~0.88; San José et al., Atherosclerosis 2008). Essential p22phox subunit of NOX1/2/4/5.	(subunit)

Gene	rsID	Variant	Functional consequence	Cofactor
CYBA	rs9932581	-930 A/G promoter	G allele increases CYBA transcription; associated with hypertension.	(regulatory)
NOX4	rs11018628	intronic	Flagged in homocysteine GWAS (van Meurs 2013); NOX4 produces mostly H_2O_2 and has paradoxically protective vascular roles in some models.	NADPH, FAD
XDH	rs206812	intronic	Xanthine oxidoreductase; linked to serum urate and BP.	Mo, Fe, FAD
XDH	rs6677829	intronic	Additional XDH variant; urate-associated.	Mo, Fe, FAD
MPO	rs2333227	-463 G/A promoter	A allele disrupts SP1 binding, reduces MPO transcription ~25× (Piedrafita et al., JBC 1996). A allele associated with lower CAD in several studies (Asselbergs et al., ATVB 2004). Unusual case where lower enzyme activity is protective.	heme (Fe)

This category represents the superoxide side of the redox ledger. CYBA provides the essential p22phox subunit for most NOX enzymes; NOX4 is unusual in producing mostly H_2O_2 and having some vascular-protective actions. MPO is the major neutrophil-derived source of oxidative injury in established atherosclerosis and is the one enzyme in this category where lower activity is unambiguously better for the vasculature.

4.5 Antioxidant defense

Gene	rsID	Variant	Functional consequence	Cofactor
SOD2	rs4880	Ala16Val (V16A)	Val allele impairs mitochondrial targeting; VV homozygotes ~30% lower mitochondrial SOD2 activity (Sutton et al., Pharmacogenetics 2003). Associated with diabetic nephropathy and cardiomyopathy.	Mn
SOD3	rs1799895	Arg213Gly (R213G)	Reduces binding to endothelial heparan sulfate; paradoxically raises plasma SOD3 ~10× while depleting vascular wall pool. ~1.5× higher IHD risk in Copenhagen City Heart Study (Juul et al., Circulation 2004).	Cu, Zn
GPX1	rs1050450	Pro198Leu	Leu variant has reduced activity and reduced responsiveness to selenium supplementation; associated with CAD and stroke (Bastaki et al., Pharmacogenet Genomics 2006).	selenium (selenocysteine)
CAT	rs1001179	-262 C/T promoter	T allele reduces transcription; associated with hypertension and diabetic complications.	heme (Fe)

Gene	rsID	Variant	Functional consequence	Cofactor
NQO1	rs1800566	Pro187Ser (C609T)	Ser187 protein rapidly degraded; SS homozygotes have essentially no NQO1 activity. Higher oxidative stress markers.	FAD, NAD(P)H
PON1	rs662	Gln192Arg (Q192R)	Q allele more efficient at hydrolyzing oxidized LDL lipids; more protective for CAD (Wheeler et al., Lancet 2004 meta-analysis, OR ~1.12 for RR).	Ca
PON1	rs854560	Leu55Met (L55M)	M allele lower plasma PON1 concentration; additive with Q192R.	Ca

This category is the counterweight to 4.4. SOD2 handles mitochondrial superoxide; SOD3 handles extracellular superoxide in the vascular wall. The SOD3 R213G variant is instructive: it raises measured plasma SOD3 dramatically while depleting the vascular wall pool — a reminder that circulating enzyme levels can mislead about tissue function. PON1 Q192R affects the antioxidant capacity of HDL itself and is one of several reasons HDL function matters more than HDL concentration.

4.6 Inflammation and adhesion

Gene	rsID	Variant	Functional consequence	Cofactor
IL6	rs1800795	-174 G/C promoter	Promoter variant affecting basal IL-6 transcription; effect direction population-dependent. Modest CVD association.	(cytokine)
IL6R	rs2228145	Asp358Ala	Ala variant reduces classical IL-6 signaling; associated with lower CHD risk (OR ~0.95 per allele) by Mendelian randomization (IL6R MR Consortium, Lancet 2012). One of the cleanest causal protective signals.	(receptor)
TNF	rs1800629	-308 G/A	A allele associated with higher TNF production; weak CAD association.	(cytokine)
CRP	rs1205	3'UTR	Determinant of baseline CRP. MR generally does NOT support a causal CAD role for CRP itself.	(marker)
SELE	rs5361	Ser128Arg	R allele increases leukocyte adhesion; associated with premature CAD (Wenzel et al., Lancet 1994).	(adhesion)
ICAM1	rs5498	Lys469Glu (K469E)	Modifies soluble ICAM-1 levels; inconsistent CAD association.	(adhesion)

IL6R rs2228145 is the cleanest single-variant Mendelian randomization signal supporting a causal role for IL-6 signaling in coronary disease, and it was the genetic basis for the successful repurposing of tocilizumab and for the CANTOS trial of canakinumab. The adhesion molecule variants have more modest and more mixed effects.

4.7 Vascular tone and RAAS

Gene	rsID	Variant	Functional consequence	Cofactor
ACE	rs4340 / rs1799752	Intron 16 I/D	D allele ~50% higher circulating ACE activity; DD ~1.2× CAD/HTN risk in meta-analyses (Cambien et al., Nature 1992).	Zn
AGT	rs699	Met235Thr (M235T)	T allele higher plasma angiotensinogen; associated with hypertension (Jeunemaitre et al., Cell 1992).	(precursor)
AGTR1	rs5186	A1166C (3'UTR)	C allele disrupts miR-155 binding site, raising AT1R expression; associated with HTN and aortic stiffness.	(receptor)
EDN1	rs5370	Lys198Asn	Asn allele associated with HTN in overweight (Tiret et al., Hypertension 1999).	(peptide)
BDKRB2	rs1799722	-58 T/C promoter	C allele higher expression; modifies ACE inhibitor response.	(receptor)

The ACE I/D polymorphism was one of the very first cardiovascular genetic associations described and remains one of the most replicated, though individual effect sizes are modest. Together these variants account for a small but measurable share of population blood pressure variance.

4.8 Hemostasis and thrombosis

Gene	rsID	Variant	Functional consequence	Cofactor
F5	rs6025	Arg506Gln (Factor V Leiden)	Renders factor V resistant to cleavage by activated protein C. Heterozygotes ~5× VTE risk, homozygotes ~80× (Rosendaal et al., Blood 1995). Clinically actionable.	(clotting factor)
F2	rs1799963	G20210A 3'UTR	Increases prothrombin mRNA stability and plasma prothrombin ~30%. Heterozygotes ~2.8× VTE risk (Poort et al., Blood 1996).	vitamin K
SERPINE 1	rs1799889	-675 4G/5G	4G allele higher PAI-1 levels, impaired fibrinolysis; modest MI association (Tsantes et al., Thromb Haemost 2007).	(serpin)

This category is unusual in that it contains several variants with clinically actionable effect sizes. Factor V Leiden and Prothrombin G20210A directly affect decisions about perioperative thromboprophylaxis, hormonal therapy, and anticoagulation after VTE. The PAI-1 4G/5G variant has smaller and more inconsistent effects but is metabolically linked to insulin resistance.

4.9 Lipid-endothelium interface and 9p21

Gene	rsID	Variant	Functional consequence	Cofactor
LPA	rs10455872	intronic (KIV-2)	Tag SNP for high Lp(a) levels. Each risk allele ~doubles Lp(a) and raises CAD ~1.7× (Clarke et al., NEJM 2009). Causal by MR.	(apolipoprotein)
LPA	rs3798220	Ile4399Met	Second independent high-Lp(a) signal; similar effect size.	(apolipoprotein)
APOE	rs429358 + rs7412	ε2/ε3/ε4 haplotype	ε4 carriers higher LDL and ~40% higher CAD risk; ε2 protective for CAD but raises TG. Dominant AD locus.	(lipoprotein)
LDLR	various	missense/NMD	Dozens of rare familial hypercholesterolemia mutations; common variants have smaller LDL effects.	(receptor)
CETP	rs708272	TaqIB (intron 1)	B2 allele associated with higher HDL and (mixed) lower CAD risk.	(transfer protein)
LIPC	rs1800588	-514 C/T	T allele lower hepatic lipase activity, higher HDL.	Zn (structural)
PCSK9	rs11591147	Arg46Leu (R46L)	Loss-of-function; ~15% lower LDL-C and ~47% lower CHD risk over lifetime in heterozygotes (Cohen et al., NEJM 2006; Ference et al., JACC 2012). One of the largest protective effects known.	(protease)
PCSK9	rs505151	Glu670Gly	Gain-of-function; higher LDL-C and CHD risk.	(protease)
CDKN2B-AS1 (9p21)	rs10757278	intergenic/ lncRNA	Strongest common CAD locus. Each risk allele ~1.25× CAD; homozygotes ~1.5–1.9× lifetime risk (Helgadottir et al., Science 2007; McPherson et al., Science 2007). Independent of lipids and BP.	(lncRNA: ANRIL)
CDKN2B-AS1 (9p21)	rs1333049	intergenic	Co-lead SNP at 9p21; replicated in CARDIoGRAMplusC4D (n > 190,000).	(lncRNA: ANRIL)

This category contains the largest effect sizes in the entire pathway. Lp(a) levels are almost entirely determined by LPA genotype, cannot be reduced by diet or statins, and are independently causal by MR. PCSK9 R46L is the Mendelian inverse of the gain-of-function variants that cause familial hypercholesterolemia and validated PCSK9 as a drug target. The 9p21 locus has no fully resolved mechanism but is the single strongest common CAD signal known.

5. Cofactor and Supplement Target Map

The table below maps each functional category to the cofactors its enzymes need, and to the supplement(s) that can address those cofactor needs. This is a generic catalog of biochemical relationships, not a personalized recommendation.

Category	Cofactors required	Supplement targets
NO synthesis (eNOS)	BH4; L-arginine; FAD (B2); FMN (B2); heme (Fe); NADPH; Ca^{2+}; Zn	L-citrulline (raises L-arginine); riboflavin; BH4 precursors; adequate iron
BH4 cofactor supply	GTP (substrate); NADPH; Mg; Zn; folate (DHFR link)	Folate (supports DHFR); vitamin C (stabilizes BH4); sepiapterin (direct precursor, limited availability)
NO downstream signaling	Heme (sGC); Mg; ATP	Adequate iron; magnesium
ROS production (limit)	NADPH, FAD, heme, Mo, Fe	(no direct supplement target; reduce exogenous oxidative load)
Antioxidant defense	Mn (SOD2); Cu/Zn (SOD3); selenium (GPX1); heme (CAT); FAD/NAD(P)H (NQO1); Ca (PON1)	Selenium; zinc; copper; manganese; glutathione precursors (NAC, glycine); vitamin E; vitamin C; CoQ10
Inflammation & adhesion	(cytokines; no direct cofactors)	Omega-3 EPA/DHA; curcumin; adequate vitamin D; polyphenols
Vascular tone & RAAS	Zn (ACE); (peptide ligands)	Adequate potassium and magnesium; dietary nitrate (beets, leafy greens)
Hemostasis	Vitamin K (F2); Ca	Adequate vitamin K2 for calcification balance; omega-3 for platelet function
Lipid interface	(mostly structural)	Omega-3 EPA/DHA; fiber; plant sterols; niacin (historical)

Note: 'Supplement target' means a substance that addresses the relevant biochemistry. It does not mean every person should supplement everything listed. Personalization depends on individual genotype, intake, lab values, and clinical context.

6. Complete SNP Lookup Table

Quick reference for all SNPs catalogued in this document, sorted alphabetically by gene. Coordinates are GRCh38.

Gene	rsID	GRCh38 position	Category
ACE	rs4340	17:63488544	Vascular tone
ACE	rs1799752	17:63488530	Vascular tone
AGT	rs699	1:230710048	Vascular tone

Gene	rsID	GRCh38 position	Category
AGTR1	rs5186	3:148742201	Vascular tone
AGXT2	rs37369	5:35037115	ADMA clearance
APOE	rs429358	19:44908684	Lipid interface
APOE	rs7412	19:44908822	Lipid interface
BDKRB2	rs1799722	14:96197145	Vascular tone
CAT	rs1001179	11:34438684	Antioxidant defense
CDKN2B-AS1	rs10757278	9:22124478	9p21 / CAD locus
CDKN2B-AS1	rs1333049	9:22125504	9p21 / CAD locus
CETP	rs708272	16:56961923	Lipid interface
CRP	rs1205	1:159712443	Inflammation
CYBA	rs4673	16:88645667	ROS production
CYBA	rs9932581	16:88650111	ROS production
DDAH1	rs997251	1:85511953	NO synthesis (ADMA)
DDAH1	rs233112	1:85525640	NO synthesis (ADMA)
DDAH2	rs805305	6:31727713	NO synthesis (ADMA)
DHFR	rs70991108	5:80654353	BH4 salvage
DHFR	rs1643649	5:80633534	BH4 salvage
EDN1	rs5370	6:12290677	Vascular tone
F2	rs1799963	11:46761055	Hemostasis
F5	rs6025	1:169549811	Hemostasis
GCH1	rs8007267	14:54872777	BH4 synthesis
GCH1	rs10483639	14:54908530	BH4 synthesis
GCH1	rs841	14:54875792	BH4 synthesis
GPX1	rs1050450	3:49357401	Antioxidant defense
GUCY1A3	rs7692387	4:155723156	NO downstream
GUCY1A3	rs13139571	4:155714229	NO downstream
ICAM1	rs5498	19:10285053	Inflammation
IL6	rs1800795	7:22727026	Inflammation

Gene	rsID	GRCh38 position	Category
IL6R	rs2228145	1:154454494	Inflammation
LIPC	rs1800588	15:58431520	Lipid interface
LPA	rs10455872	6:160589086	Lp(a)
LPA	rs3798220	6:160540105	Lp(a)
MPO	rs2333227	17:58269543	ROS production
NOS3	rs1799983	7:150999023	NO synthesis
NOS3	rs2070744	7:150992991	NO synthesis
NOX4	rs11018628	11:89316135	ROS production
NQO1	rs1800566	16:69711242	Antioxidant defense
PCSK9	rs11591147	1:55039974	Lipid interface
PCSK9	rs505151	1:55063514	Lipid interface
PDE5A	rs3806808	4:119547906	NO downstream
PON1	rs662	7:95308134	Antioxidant defense
PON1	rs854560	7:95316772	Antioxidant defense
PRKG1	rs7897633	10:52750806	NO downstream
QDPR	rs1729635	4:17189168	BH4 recycling
QDPR	rs2856107	4:17199125	BH4 recycling
SELE	rs5361	1:169722640	Inflammation
SERPINE1	rs1799889	7:101127165	Hemostasis
SOD2	rs4880	6:159692840	Antioxidant defense
SOD3	rs1799895	4:24797293	Antioxidant defense
SPR	rs1876487	2:72882589	BH4 synthesis
TNF	rs1800629	6:31575254	Inflammation
XDH	rs206812	2:31324819	ROS production
XDH	rs6677829	2:31293167	ROS production

Note on coordinates: GRCh38 positions above are compiled from dbSNP. Verify against your VCF's contig naming convention ('chr1' vs '1') before running positional lookups. Indel variants (ACE I/D, DHFR 19-bp deletion, PAI-1 4G/5G) may require specialized parsing beyond simple rsID matching.

7. Bibliography and Source Notes

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Database resources

dbSNP (NCBI) for rsID-to-coordinate mapping (GRCh38).

GWAS Catalog (EBI/NHGRI) for GWAS-associated variant lookups.

OMIM for inherited monogenic vascular and thrombotic disorders.

ClinVar for variant pathogenicity classifications (especially F5, F2, LDLR, PCSK9).

8. Disclaimer

This document is an educational reference. It does not constitute medical advice, does not establish a clinician–patient relationship, and is not a substitute for individualized evaluation by a qualified healthcare provider. Genetic variants are described at the level of common-population biology; clinical interpretation in any individual depends on the full genetic background, lab measurements, medical history, current medications, and other factors that this document does not address.

Most common variants catalogued here confer small individual effects (odds ratios 1.05–1.4). Cumulative significance arises from patterns across multiple variants and from interaction with environmental factors (diet, blood pressure, lipids, glycemia, smoking, age, sex, ethnicity). A small number of variants in this document (Factor V Leiden, Prothrombin G20210A, LPA high-Lp(a) tag SNPs, PCSK9 R46L, 9p21 lead SNPs) have larger and more actionable effects and warrant direct clinical discussion if found on genotyping.