

Supplementary Data File S1

Sr. Number	Genes	Number of Variants	Disease	Pathways
1	ARAP2. (Arf/Rho GAP)	15		Integrin signaling, leukocyte-endothelial adhesion
2	SATB2	15		Endothelial senescence at 9p21/CDKN2A/B locus, VSMC osteogenic programming via RUNX2
3	ELOVL2	14	childhood obesity	PUFA metabolism and lipid homeostasis
4	BABAM2 BRISC/BRCA1-A complex mem2	9	Acute myocardial infarction,	Intersects TNF/NF- κ B and cell-death/DNA-damage axes
5	DLEU7	9	Cardiovascular Diseases	inhibits the B-cell receptors, dampening NF- κ B/NFAT signaling
6	DAB1: (Disabled-1)	8		Activation of the Reelin pathway, Activates NF- κ B, Increases expression of ICAM-1, VCAM, E-selectin
7	CNTN5	8		neuronal adhesion protein
8	ELOVL2-ASI	7	---	lncRNA for ELOVL2
9	MAP2K4	7		Activator of JNK, Promotes endothelial apoptosis and pro-inflammatory gene expression
10	NDOR1 NADPH dependent diflavin oxidoreductase 1	7	diabetic vascular aging	Affects redox-sensitive signaling pathways such as NF- κ B and MAPKs
11	TRAPPC9	4		Promotes NF- κ B signaling
12	GLIS3 β -cell transcript factor	4	Insulinopenia, hyperglycemia,	adult β -cell function, insulin gene transcription
13	TBX2	3	Cardiovascular malformations	Developmental transcription factor, link to cardiac electrical traits and AF.
14	EFNA5. (Ephrin-A5)	2	Cardiovascular development, Atherosclerosis	Monocyte adhesion via EPHA2/EPHA4 and RhoA-cytoskeletal remodeling, Ca ²⁺ /NFAT pathway
15	DOCK2	2	Myocarditis, cardiac graft rejection	Knockdown blunts TNF- α -induced ICAM-1/VCAM-1/MCP-1 and NF- κ B activation.
16	ADAMTSL1	2		Binds fibrillin-1, modulate TGF- β bioavailability.

17	BCAS3	2	Coronary artery disease	Angiogenesis and vascular remodeling, activates CDC42 and actin cytoskeleton.
19	TYW1	2		Modifies tRNA ^{Phe} (wybutosine pathway)
20	RUBCN (Rubicon)	2	acute coronary syndrome (ACS)	LC3-associated phagocytosis (LAP); impairs efferocytosis,
21	PIPOX	2		Glycine/sarcosine metabolism, generate H ₂ O ₂
22	SUGP1	1	CAD, High plasma LDL levels	Cholesterol metabolism, coagulation
23	SULF2	1	Fatty Liver disease. T2DM	impairs TRL clearance and promotes dyslipidemia
24	POR (NADPH–cytochrome P450 oxidoreductase)	1		eNOS/AKT signaling, NO bioavailability, EC dysfunction.
25	RAP1GAP Rap1 GTPase-activating protein	1	myocardial infarction (MI)	Endothelial NO release, Worsen MI via the AMPK/SIRT1/NF-κB pathway
26	NABP1	1	No genetic role in CAD reported yet.	Essential for DNA repair and DDR signaling critical for EC dysfunction, VSMC apoptosis.
27	HDAC9	1	CAD Large artery ischemic stroke	Increasing pro-inflammatory signaling via IKK/NF-κB
28	CD28	1	Acute coronary syndrome (ACS), Rheumatoid arthritis (RA)	Expression on Tregs supports immune regulation and appears protective
29	ITPR1 (IP ₃ receptor 1)	1	CAD	IP ₃ R-mediated Ca ²⁺ release, NO signaling, VSMCs contractility, phenotype switching
30	TSPAN33	1		macrophage activation via NOTCH / TLR
31	PLCB1	1	Coronary artery aneurysm (CAA) Kawasaki disease	Reduce endothelial cell inflammation, Platelet activation pathways downstream of GPCR.
32	KIR2DS4	1	HIV	Reduce CD4+ T-cell counts in chronic HIV-1
33	IL4I1 (interleukin-4–induced-1)	1		Promote regulatory T cells (Tregs). Suppress pro-inflammatory Th17 cells
34	PLCB1	1	Coronary artery aneurysm (CAA) Kawasaki disease	Platelet Ca ²⁺ signaling granule release.
35	TSPAN33	1	---	Macrophage activation via NOTCH / TLR, Increases ADAM10 activity,

36	MAP2K4	1		Lower the threshold for secretion, stabilize thrombi
37	SULF2	1		Reducing local AT/TFPI efficacy
38	ITGA8	1		Regulates differentiation, migration, ECM/fibrotic responses.
39	ARHGAP44	1	Glucose metabolism neuronal development	Associated with HbA _{1c} levels
40	LRP2	1		Renin-angiotensin homeostasis,
41	CDK14	1		Cell-cycle and Wnt signaling
42	TUBB4B β-tubulin isoform	1		GJA1–PI3K/AKT/KLF4 pathway
43	ACAN Aggrecan	1		Promote VSMC apoptosis Plaque instability

ARAP2. (Arf/Rho GAP; integrin trafficking and cell motility)

PCAD cohort, 15 variants, heterozygous. **Control group**; normal, wild type.

Variants: 15 putatively novel variants

ARAP2 encodes a GTPase-activating protein that regulates cell adhesion and migration, notably by modulating integrin endocytosis/recycling and endothelial dynamics. These pathways are central to leukocyte–endothelial adhesion, EC/VSMC migration, and vascular remodeling in atherogenesis, positioning ARAP2 as a biologically plausible modifier of CAD risk. However, no replicated human-genetic association with CAD has been established to date. Therefore, the observed pattern requires validation in larger cohorts and targeted mechanistic cellular assays.

SATB2:

PCAD cohort, 15 variants, heterozygous. **Control group**; normal, wild type.

Variants:

SATB2 influences endothelial cell (EC) senescence and vascular smooth muscle cell (VSMC) phenotype / calcification, making SATB2 a biologically plausible contributor to atherosclerosis and therefore to CAD. SATB2 restrains endothelial senescence at the atherosclerosis-linked 9p21/CDKN2A/B locus and drives VSMC osteogenic programming via RUNX2; although mechanistically compelling, SATB2 is not yet a replicated human CAD locus.

ELOVL2:

PCAD cohort, 14 variants, heterozygous. **Control group**; normal, wild type.

Variants, rs61382946, rs4360130, rs911196, rs113917292, rs12525885, rs3798709, rs3798710, rs17764592, rs10498676, rs72653724, rs60533520, rs3778166, rs56065914, and rs12664138.

Case-restricted heterozygosity across multiple rsIDs suggests a locus-level burden rather than a single causal SNP—very consistent with PUFA-pathway biology. ELOVL2 plays a key role in PUFA metabolism and lipid homeostasis, making it relevant for PCAD patients. While studies in Western populations have not indicated any relationship between ELOVL2 and lipid disorders or atherosclerosis, one Italian study reported association between ELOVL2 variants with childhood obesity. GWAS for red-blood-cell fatty acid composition report signals spanning ELOVL2/ELOVL2-AS1 locus, consistent with this region shaping PUFA composition (inflammatory substrate for atherogenesis).

BABAM2: (BRISC/BRCA1-A complex member 2)

PCAD cohort, 9 variants, homozygous. **Control group**; heterozygous.

Variants:

BABAM2, as a DNA damage/repair (DDR) adaptor modulates TNF/NF-κB and DNA-damage response pathways, both central to vascular inflammation and remodeling in atherosclerosis. However, direct vascular/coronary data for BABAM2 role is sparse. The antisense long non-coding RNA BRE-AS1, transcribed from the BABAM2 locus is elevated in acute myocardial infarction and thus, holds diagnostic and prognostic value for major adverse cardiovascular events. As DNA damage response signaling, particularly under oxidative stress, promotes endothelial

dysfunction, VSMC senescence/apoptosis, and plaque progression, DDR adaptor such as BABAM2 could modulate this axis.

DLEU7:

PCAD cohort, 9 recognized 40 novel variants, heterozygous. **Control** group; normal, homozygous.

Variants: rs3121213, rs797517, rs797519, rs797472, rs797536, rs797537, rs1772872, rs279446

DLEU7 binds and inhibits the B-cell receptors TACI and BCMA, attenuating NF- κ B/NFAT signaling. The BAFF/APRIL $\rightarrow$ TACI/BCMA pathway has been implicated to modulate atherogenesis in murine models where BAFF overexpression reduced hypercholesterolemia and atherosclerosis in hyperlipidemic mice. A variant rs1239948 in the DLEU1/DLEU7 region has been associated with "cardiovascular diseases" phenotype in a functionally reweighted, UK Biobank-based GWAS meta-analysis. However, large, dedicated CAD meta-analyses (e.g., CARDIoGRAMplusC4D/MVP) do not list DLEU7/rs1239948 as a reproducible locus.

DAB1: (Disabled-1; Reelin adaptor)

PCAD cohort, 8 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs1323838, rs7554147, rs7544843, rs6659795, rs7515680, rs12565523, rs12568292, rs1650564482.

DAB1 serves as the principal intracellular adaptor protein mediating Reelin signaling through ApoER2/VLDLR receptors. Within vascular endothelium, Reelin signaling activates NF- κ B and subsequent upregulation of ICAM-1, VCAM-1, and E-selectin expression leading to enhanced leukocyte adhesion and contributing to progression of atherosclerosis. A genome-wide association study identified DAB1 as significantly associated with CAD (odds ratio, 1.29; 95% CI, 1.21-1.38; $P=2.02 \times 10^{-14}$), however, the mechanistic basis for this genetic link was unknown. Given that DAB1 plays essential role in activation of Reelin pathway, a pharmacological inhibition of this signaling cascade may attenuate leukocyte or monocyte adhesion and extravasation, thereby limiting the progression of atherosclerosis. These results provide a compelling mechanistic rationale for further investigation into therapeutic strategies targeting the Reelin pathway inhibition as an approach for modulating adhesion and atherosclerosis development.

CNTN5:

PCAD cohort, 8 novel variants, heterozygous. **Control** group; normal, wild type.

Variants:

CNTN5 is a neuronal adhesion protein, also expressed in vascular cells [46] and has been linked to vascular inflammation. GWAS studies have identified signals near the *CNTN5* locus associated with cardiovascular traits (blood pressure, atrial fibrillation, heart failure), though effects may involve neighboring loci. Murine models suggest CNTN5 perturbation alters cardiovascular parameters, but evidence for direct human disease causation remains limited. Notably, a community-based plasma proteomics study reported higher circulating CNTN5 levels associated with lower incident CVD risk, suggesting a potential protective biomarker signal rather than genetic causation.

ELOVL2-AS1: (lncRNA at the same locus)

PCAD cohort, 7 variants, heterozygous. **Control** group; normal, wild type.

Variants rs17697071, rs4713157, rs60197525, rs4713162, rs5029486, rs4711170, rs1266263

These variants are located within a long non-coding RNA (lncRNA) gene at the ELOVL2 locus on chromosome 6 (approximately 11.0 Mb). While these findings suggest plausible mechanistic connections to plaque inflammation and lipid remodeling, they alone do not establish a definitive role for the antisense lncRNA in atherosclerosis.

ELOVL2 + ELOVL2-AS1 can be treated as a combined *cis* unit: region-based burden (SKAT-O) and haplotype tests. Objective measurement of RBC/plasma FA panels (EPA/DHA/ARA, ratios) would enable medication analysis from genotype to PUFA profile leading to PCAD.

MAP2K4: (MKK4; upstream of JNK)

PCAD cohort, 7 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs2108496, rs1870583, rs28921079, rs57346056, rs1017743, rs12452497, rs4792219.

MAP2K4 is an upstream activator of JNK and can interface with NF-κB signaling. Activation of JNK promotes endothelial apoptosis and the induction of pro-inflammatory gene expression, thus facilitating atherogenesis and indicating MAP2K4 as plausible pro-atherogenic node. However, MAP2K4 is not a replicated CAD/atherosclerosis GWAS locus, hence, these observations require validation in larger cohort and direct mechanistic investigation in relevant cellular models.

NDOR1:

PCAD cohort, 7 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs79850917, rs35844815, rs34983547, rs73563696, rs61466113, rs80043545, rs75016415.

NDOR1 (NADPH-dependent diflavin oxidoreductase 1) is a cytosolic enzyme that transfers electrons from NADPH to redox partners, contributing to Fe-S protein assembly and redox homeostasis. Altered NDOR1 activity can disturb ROS production and scavenging, affecting redox-sensitive signaling pathways such as NF-κB and MAPKs. NDOR1 may contribute to vascular inflammation, and atherosclerotic plaque development by disrupting ROS balance, antioxidant capacity, and downstream redox signaling pathways as supported by an informatics study identifying NDOR1 among genes linked to diabetic vascular aging.

TRAPPC9:

PCAD cohort, 4 novel variants, heterozygous. **Control** group; normal, wild type.

Variants:

TRAPPC9 regulates NF-κB signaling and intracellular trafficking, thereby modulating inflammatory responses in endothelial and myeloid cells. TRAPPC9 activates NF-κB pathway by binding to its core components (NIK, IKKβ). Considering the critical role of NF-κB in vascular inflammation, TRAPPC9 represents a biologically plausible contributor to atherosclerosis. However, direct published evidence associating TRAPPC9 with atherosclerotic plaque formation in vivo or with human CAD is currently limited.

GLIS3: (β-cell transcription; insulin production)

PCAD cohort, 4 variants, heterozygous. **Control** group; normal, wild type.

Variants:

GLIS3 is a β -cell transcription factor that binds islet regulatory regions and drives insulin gene transcription and adult β -cell function. Perturbation increases β -cell stress and apoptosis, predisposing to insulinopenia, hyperglycemia, and diabetes, established risk states for atherosclerosis.

TBX2:

PCAD cohort, 3 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs565422534, rs3782467, rs12423887

TBX5 is a developmental transcription factor integral to cardiac and vascular patterning with crosstalk to SMC differentiation programs. While TBX5 variants are associated with congenital cardiovascular malformations and vascular remodeling, common polymorphisms (rs3825214) show strong, replicated associations with cardiac electrical traits and atrial fibrillation (AF) rather than CAD.

EFNA5: (Ephrin-A5; EphA receptor signaling)

PCAD cohort, 2 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs4957704, rs12656968.

While mechanistic studies in atherosclerosis have predominantly focused on EFNA1, the underlying pathway is highly informative. Pro-atherogenic cues (TNF- α , oxLDL) upregulate endothelial EFNA1 which signals through EPHA2/EPHA4 receptors to promote monocyte adhesion via RhoA-dependent cytoskeletal remodeling and Ca²⁺/NFAT-driven adhesion programs (e.g., VCAM-1). As a cognate ephrin-A ligand, EFNA5 engages the same EphA axis and, given the broader Ephrin/Eph roles in cardiovascular development, atherosclerosis, postnatal angiogenesis, and even fibrosis/calcification, represents a biologically plausible contributor to EC barrier disruption, vascular inflammation and remodeling. Although EFNA5 has not been validated as a replicated locus in genome-wide association studies of CAD, these insights support follow-up investigations with arterial expression quantitative trait locus (eQTL) and colocalization analyses, complemented by in vitro functional assays (e.g., EPHA2 blockade, RhoA activity, ICAM-1/VCAM-1 expression, barrier integrity, and leukocyte adhesion) to establish causality.

DOCK2:

PCAD cohort, 2 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs13360445, rs6879630

DOCK2 promotes pathological vascular remodeling via smooth muscle migration and proliferation following vascular injury leading to narrowing of vessel lumen. It is also implicated in diverse inflammatory conditions and immune responses including myocarditis, cardiac graft rejection, obesity-related inflammation, and metabolic dysregulation. In LDLR^{-/-} mice, Dock2 deficiency reduces atherosclerosis and vascular inflammation, whereas, in human endothelial cells, DOCK2 knockdown blunts TNF- α -induced ICAM-1/VCAM-1/MCP-1 expression and NF- κ B activation, hence, positioning endothelial DOCK2 as a driver of plaque initiation.

ADAMTSL1:

PCAD cohort, 2 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs10810879, rs12346508

ADAMTS-like proteins, including ADAMTSL1, bind fibrillin-1 microfibrils and regulate TGF- β bioavailability, key processes in vascular remodeling and arterial wall integrity [67]. Single-cell and spatial transcriptomic studies have identified *ADAMTSL1* expression in smooth muscle lineage cells within human atherosclerotic plaques, suggesting it as an early diagnostic biomarker. However, direct clinical evidence linking ADAMTSL1 to plaque instability or replicated CAD biomarker status remains limited and requires further investigation.

BCAS3:

PCAD cohort, 2 novel variants, heterozygous. **Control** group; normal, wild type.

Variants:

BCAS3 is implicated in cardiovascular pathogenesis through its fundamental role in angiogenesis and vascular architecture. Evidence from functional murine models and human genetics, including genome-wide association and evolutionary selection studies, correlate BCAS3 to coronary artery disease. Mechanistically, BCAS3 integrates within CAD-related protein networks and governs endothelial polarity and migration by activating CDC42 and reorganizing the actin cytoskeleton, processes critical for angiogenesis and vascular remodeling/repair.

TYW1:

PCAD cohort, 2 variants, heterozygous. **Control** group; normal, wild type.

Variants: rs28867847, rs1796886486

No direct evidence links TYW1 to atherosclerosis or cardiovascular diseases in GWAS studies. TYW1 encodes a radical SAM enzyme that modifies tRNA^{Phe} (wybutosine pathway). While one study reported a genome-wide significant signal between TYW1 and AUTS2 in carotid artery disease, but with limited replication. Although, tRNA modifications and tRNA-derived small RNAs (tsRNAs) influence cellular stress responses, mitochondrial function and processes such as aging, myocardial stress and fibrosis but there isn't direct human association. Considering above, disrupted tRNA modification may skew stress signaling and proteostasis, potentially amplifying vascular inflammation and remodeling.

RUBCN: (Rubicon)

PCAD cohort, 2 variants, heterozygous. **Control** group; homozygous.

Variants:

Rubicon is essential for LC3-associated phagocytosis (LAP), a process critical for efferocytosis. Inadequate LAP impairs apoptotic cell clearance, promoting necrotic core formation. A 2024 study identified a significant association between elevated plasma Rubicon levels and acute coronary syndrome (ACS) with added value beyond standard risk markers. This biomarker evidence positions Rubicon as a clinically relevant player in atherothrombotic disease.

PIPOX:

PCAD cohort, 2 variants, heterozygous. **Control** group; normal, wild type.
Variants: rs36090509, rs12949998

It may generate hydrogen peroxide (H₂O₂) during its enzymatic activity and could contribute to cellular redox homeostasis and oxidative stress responses. It sits in glycine/sarcosine metabolism; higher plasma glycine associates with lower CHD risk in epidemiology, suggesting this pathway modulates cardiometabolic risk [87].

SUGP1:

A single variant was identified exclusively in the control cohort, with all cases homozygous for the reference allele; importantly, this control-specific variant is not indexed in current databases. Several studies have reported SUGP1 and its variant rs10401969 link to CAD and plasma LDL levels, implicating its role in cholesterol metabolism, coagulation, and gene–environment interactions [25]. While the control-specific (putative) variant could represent a protective allele within the studied ancestry context, the finding can be attributed to stochastic variation due to limited sample size. Either way, SUGP1 remains a high-priority candidate within the cholesterol synthesis and LDL clearance node.

SULF2:

PCAD cohort, 1 variant, heterozygous. **Control** group; normal, wild type.
Variants rs6018666

SULF2 modulates the clearance of triglyceride-rich lipoprotein (TRL) remnants by editing heparan sulfate chains on hepatocyte heparan sulfate proteoglycans (HSPGs). Studies in murine and human models have indicated that hepatic SULF2 over-expression (frequently observed during obesity and type 2 diabetes mellitus) impairs remnant clearance and elevates circulating triglyceride levels. Genetic variation in SULF2 (e.g., rs2281279) has been correlated with increased post-prandial triglycerides and heightened SULF2 expression, however, large-scale genetic studies have not established a direct link between this variant and risk of vascular disease or diabetes. Importantly, functional studies have shown its role in post-MI cardiac repair and lipid regulation. These observations warrant targeted investigation to evaluate postprandial triglycerides dynamics and apoB-48/apoB-100 remnant particle levels in human SULF2 variant carriers versus non-carriers.

POR: (Cytochrome P450 oxidoreductase)

PCAD cohort, 1 variant, heterozygous. **Control** group; normal, wild type.
Variants: rs2302429

Cytochrome P450 oxidoreductase (POR) is the obligatory electron donor to microsomal cytochrome P450 enzymes, enabling steroid biosynthesis/ metabolism. Perturbations in POR activity can disrupt sex-steroid balance—particularly estrogen levels, while attenuating downstream endothelial NO bioavailability and promoting vascular inflammation. Furthermore, uncoupling of CYP/POR activity enhances reactive oxygen species (ROS) generation, exacerbating oxidative stress, endothelial dysfunction, and pro-atherogenic signaling pathways. Within Endothelial cells, POR is responsible for maintaining eNOS/AKT signaling, whereas its deficiency leads to activation of vasoconstrictor prostanoids, leading to vascular dysfunction and

hypertension. While POR is not identified as replicated locus for CAD in GWAS studies, these observations provide a strong mechanistic rationale for further investigation in larger cohorts and functional assays in relevant endothelial/VSMC models.

RAP1GAP: (Rap1 GTPase-activating protein)

PCAD cohort, 1 variant, heterozygous. **Control group**; normal, wild type.

Variants: rs1767444.

Rap1 is critical regulator of vascular homeostasis as it mediates endothelial response to sheer stress in vivo, by influencing endothelial NO production [38]. Conversely, RAP1GAP inhibits Rap1 signaling leading to exacerbate myocardial infarction via the AMPK/SIRT1/NF-κB pathway [39]. Although human genetic studies have not established a direct association between RAP1GAP with atherosclerosis, the crosslinked biology is compelling. An augmented antagonizing effect of RAP1GAP against atheroprotective endothelial Rap1, may lead to atherosclerosis progression, meriting targeted testing in endothelial and smooth-muscle cell models.

NABP1: (OBFC2A/hSSB2; SOSS DNA-damage response)

PCAD cohort, 1 variant, heterozygous. **Control group**; normal, wild type.

Variants:

There's no replicated human-genetic association between NABP family genes (NABP1/OBFC2A/hSSB2 or NABP2/OBFC2B/hSSB1) and coronary atherosclerosis to date. But mechanistically they're credible indirect players: NABP1/2 are single-stranded DNA-binding proteins in the SOSS DNA-damage response complex, essential for repairing oxidative DNA lesions—and oxidative DNA damage/DDR signaling is a recognized driver of endothelial dysfunction, VSMC apoptosis/senescence, plaque progression and particularly unstable plaque. In short: biologically plausible, but not yet genetically established.

HDAC9:

PCAD cohort, 1 variant, homozygous. **Control group**; heterozygous.

Variants:

The GWAS study has reported the link associating HDAC9 locus to large artery ischemic stroke and CAD due to atherosclerosis. Mechanistically, HDAC9 promotes vascular inflammation by interacting with IKK/NF-κB and increasing pro-inflammatory signaling in vascular cells, which is a causal route from HDAC9 upregulation to atherogenesis and plaque vulnerability.

CD28:

PCAD cohort, 1 variant, homozygous. **Control group**; heterozygous.

Variants:

Loss of CD28 on T cells marks a pro-inflammatory, cytotoxic phenotype associated with plaque instability and early vascular injury. Conversely, CD28 expression on regulatory T cells (Tregs) supports immune regulation and appears protective against ischemic heart disease. Circulating CD4⁺CD28⁻ T cells are markedly increased in acute coronary syndrome (ACS), and within unstable atherosclerotic plaques, suggesting a possible role in plaque destabilization. In

rheumatoid arthritis (RA), expansion of CD4⁺CD28⁻ T cells correlate with increased carotid intima-media thickness (IMT) and reduced flow-mediated dilatation (FMD), indicating early endothelial dysfunction and atherosclerosis.

ITPR1: (IP₃ receptor 1)

PCAD cohort, 1 variant, heterozygous.

Control group; homozygous.

Variants:

ITPR1 regulates endothelial NO signaling, vascular tone, VSMC phenotype plasticity and inflammation, thereby driving atherosclerosis and coronary artery disease. Mechanistic evidence from cellular and animal models supports its biological relevance to CAD pathways. Specifically, IP₃R-mediated Ca²⁺ release in VSMCs influences contractility, phenotype switching, proliferation and migration, processes central to neointimal formation and atherogenesis.

TSPAN33: (Tetraspanin-33)

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants: rs11767848

TSPAN33 regulates macrophage activation via NOTCH/TLR pathways, driving proinflammatory responses. Ruiz-García et al. reported that Tspan33 is strongly induced during macrophage activation, promotes ADAM10 maturation and NOTCH processing, and enhances TLR-triggered NF-κB–dependent proinflammatory gene expression. Hence, TSPAN33 modulates macrophage inflammatory signaling that is biologically relevant to atherogenesis. However, direct evidence for its causal role in human atherosclerosis has not been established yet.

PLCB1:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants: rs17436253.

A GWAS in Taiwanese children with Kawasaki disease identified a polymorphism (rs6140791) between *PLCB4* and *PLCB1*, associated with increased risk of coronary artery aneurysm (CAA) [59]. Functional studies demonstrated that silencing *PLCB1* and *PLCB4* attenuated endothelial inflammation, implicating these genes in CAA pathogenesis. Importantly, *PLCB1* participates in platelet activation pathways downstream of GPCR agonist signaling (KEGG), linking it to thrombosis that complicates atherosclerosis [60]. Signaling pathway mapping suggests indirect links to other cardiovascular conditions (e.g. cardiomyopathy), but direct, disease-specific studies (e.g. GWAS, functional assays in other cardiovascular contexts) are required to clarify *PLCB1*'s broader relevance in adult cardiovascular context (atherosclerosis, MI or heart failure).

KIR2DS4:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants:

There is currently no direct evidence linking KIR2DS4 to cardiovascular disease. The full-length KIR2DS4 variant has been associated with higher viral load and lower CD4⁺ T-cell counts in individuals with chronic HIV-1 infection. In hematopoietic stem cell transplants, certain KIR2DS4

genotypes are linked with cytomegalovirus (CMV) reactivation rates and overall survival outcomes.

IL4I1: (interleukin-4–induced-1)

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants:

No genetic associations linking IL4I1 to coronary artery disease or stroke have been reported. IL4I1 regulates immune responses following MI by promoting differentiation of regulatory T cells (Tregs), suppressing pro-inflammatory Th17 cells and inhibiting ferroptosis, an iron dependent cell death process that exacerbates ischemic injury. Current evidence suggests IL4I1 as a protective and beneficial immunomodulator post MI rather than a cardiovascular risk factor.

ITGA8: Integrin alpha-8

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants: rs11253580

ITGA8 is a vascular smooth muscle cell marker that regulates differentiation, migration, and extracellular matrix production, thereby influencing vascular remodeling [72] and plaque stability. Single-cell atlases highlight ITGA8 as a contractile-favoring gene that inhibits SMC migration, aligning with plaque stabilizing mechanisms [73]. Despite functional relevance, no genome-wide significant associations with CAD have been reported, suggesting its role may involve expression regulation, rare variants, or tissue-specific effects rather than common variants.

ARHGAP44:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, homozygous.

Variants:

There is no direct evidence linking ARHGAP44 to cardiovascular diseases. Its established associations are with glucose metabolism, neuronal development and with certain cancers. A genome-wide linkage study identified a specific variant (rs56340929) in *ARHGAP44* as significantly associated with longitudinal changes in HbA_{1c} levels in non-diabetic individuals, replicated in both, the Long-Life Family Study and the Framingham Offspring Study.

LRP2:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, homozygous.

Variants:

Murine studies reveal a regulatory role of megalin in the intrarenal renin-angiotensin homeostasis and atherogenesis, indicating renal Ang II as a key mediator of atherosclerosis via its interaction with megalin and angiotensinogen (AGT). Variants that enhance megalin–AGT interactions could heighten RAAS drive, endothelial dysfunction, and vascular inflammation; conversely, attenuating variants may be protective.

CDK14:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants:

There is no direct genetic or experimental evidence linking *CDK14* (PFTK1/PFTAIRE1) to vascular smooth muscle cell (VSMC) proliferation, plaque growth, or atherosclerosis. However, CDK14 regulates cell-cycle and Wnt signaling pathways, both central to VSMC phenotype and plaque biology. Importantly, CDK14 is expressed in cardiovascular tissues and CDKs inhibitors (e.g., p21, p27) are established regulators of VSMC proliferation and neointima formation, making it a plausible candidate for influencing vascular remodeling and plaque growth.

TUBB4B:

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants: rs1836772587

TUBB4B, a β -tubulin isoform, enhances VSMC phenotypic switching, migration, and proliferation via the GJA1–PI3K/AKT/KLF4 pathway, central to vascular inflammation and atheroma progression. Microtubules cytoskeletons govern endothelial barrier and inflammatory signaling (permeability, ICAM-1/VCAM-1 induction, NF- κ B crosstalk). Their pharmacologic interruption results in dampened endothelial inflammation in vitro, as with pretubulysin treatment, and clinically with colchicine, which binds tubulin and reduces vascular inflammation and lowers ischemic events in CAD. While TUBB4B has not emerged as a CAD locus, its pathway is strongly implicated in atherosclerosis.

ACAN: (Aggrecan)

PCAD cohort, 1 variant, heterozygous.

Control group; normal, wild type.

Variants: rs16942383

Aggrecan, a proteoglycan primarily synthesized by phenotypically modulated VSMCs. It accumulates in both stable and unstable atherosclerotic plaques in mice and humans leading to VSMC apoptosis and eventually contributing to plaque instability. Aggrecan is enriched in diseased media and in the neointima of early human carotid artery lesions, but its expression is reduced in calcified plaques. Importantly, ADAMTS5 downregulation enhances aggrecan retention which has been linked to aortic dissection and aneurysm.

Non-coding RNA Gene and Functional Annotation

Gene	Count	Function	Pathway	Disease
LINC01744	18	Transcriptional and epigenetic regulator (lncRNA); linked to proliferation	NF- κ B signaling; inflammatory response; cell-cycle control	Cancer (reported in multiple tumor types); inflammatory disorders (association-based)

		and immune signaling		
TRERNA1	10	lncRNA involved in transcriptional regulation and epithelial–mesenchymal transition (EMT)	TGF- β signaling; EMT programs	Gastroesophageal cancers; metastasis-related phenotypes
TPT1-AS1	9	Antisense lncRNA that may regulate TPT1; influences stress response and apoptosis	PI3K–AKT signaling; apoptosis regulation	Hepatocellular carcinoma; breast cancer (reported)
ELOVL2-AS1	7	Antisense lncRNA linked to regulation of ELOVL2 and lipid homeostasis	Fatty-acid elongation; lipid metabolism	Cardiometabolic traits; aging-related phenotypes (association-based)
LINC02733	7	lncRNA implicated in transcriptional control and cell-cycle regulation (context-dependent)	Cell-cycle checkpoints; p53-related signaling (reported)	Breast and colorectal cancers (reported)
DLGAP2-AS1	6	Antisense lncRNA likely influencing neuronal gene regulation and synaptic biology	Synapse organization; neuronal signaling	Neurodevelopmental/neuropsychiatric disorders (association-based)
LINC02357	6	lncRNA; putative epigenetic and transcriptional regulator	Chromatin regulation; immune/inflammatory signaling (predicted)	Cancer and immune-related disorders (association-based)
DLGAP1-AS2	5	Antisense lncRNA; likely regulates neuronal transcription and synaptic function	Synaptic signaling pathways	Neuropsychiatric/neurodevelopmental disorders (association-based)
LINC01923	5	lncRNA linked to proliferation and migration control	MAPK signaling; transcriptional regulation	Gastrointestinal cancers (reported)

R3HDM2-DT	5	Divergent transcript near R3HDM2; may affect RNA processing/gene regulation	RNA metabolism and processing (predicted)	Cancer (limited functional evidence)
LINC01410	4	lncRNA; putative transcriptional regulator; evidence mainly association-based	Chromatin organization; cell signaling (predicted)	Cancer (reported/association-based)
LINC02893	4	lncRNA; poorly characterized; likely regulatory RNA	Transcriptional regulation (predicted)	Cancer/immune traits (association-based)
LINC01727	3	lncRNA; poorly characterized; regulatory role inferred from expression	Transcriptional regulation (predicted)	Cancer (association-based)
MFSD4A-AS1	3	Antisense lncRNA; may regulate neighboring MFSD4A; implicated in growth control	Cell proliferation pathways; transcriptional regulation	Cancer (reported)
RMEL3	3	lncRNA associated with cell growth and tumor biology (reported)	MAPK signaling; proliferation programs (reported)	Melanoma and other cancers (reported)
TBX5-AS1	3	Antisense lncRNA potentially regulating TBX5; developmental/cardiac relevance	Cardiac development networks; transcriptional regulation	Congenital heart-related traits (inferred); cancers (reported in some datasets)
DKFZP434A062	2	Pseudogene/lncRNA-like transcript; regulatory effects possible (miRNA sponge/transcriptional interference)	Post-transcriptional regulation (predicted)	Cancer susceptibility (association-based)

FAM88F	2	Protein-coding gene; limited characterization; may influence cellular growth	Cellular growth and signaling (predicted)	Cancer (association-based)
HAR1B	2	Brain-expressed lncRNA associated with cortical development	Neurodevelopmental pathways	Neurodevelopmental disorders (association-based)
LINC00635	2	lncRNA; regulatory roles reported in inflammation and tumor biology (context-dependent)	NF- κ B/immune signaling; transcriptional regulation (reported)	Cancer; inflammatory disorders (reported)
LINC00845	2	lncRNA; poorly characterized; inferred regulatory activity	Transcriptional regulation (predicted)	Cancer (association-based)
LINC02500	2	lncRNA; limited annotation; putative regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
LINC02596	2	lncRNA; limited functional annotation; likely regulatory RNA	Chromatin/transcription regulation (predicted)	Cancer/complex traits (association-based)
LINC02800	2	lncRNA; limited annotation; putative transcriptional regulator	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
LINC02930	2	lncRNA; poorly characterized; inferred regulatory activity	Transcriptional regulation (predicted)	Cancer (association-based)
PRPF19-DT	2	Divergent transcript near PRPF19; linked to RNA splicing and DNA	mRNA processing/splicing; DNA damage response	Cancer; genomic instability phenotypes (association-based)

		damage response (via locus)		
PWRN1	2	lncRNA in imprinted region; may regulate chromatin/gene expression	Imprinting and epigenetic regulation	Neurodevelopmental disorders and cancer (association-based)
CDC37L1-DT	1	Divergent transcript near CDC37L1; may relate to chaperone/cofactor regulation	Protein homeostasis signaling (predicted)	Cancer (association-based)
CHAER1	1	Cardiac hypertrophy-associated epigenetic regulator lncRNA	PRC2-mediated chromatin remodeling; hypertrophy pathways	Cardiac hypertrophy; heart failure (reported)
CTB-1121.1	1	Poorly characterized transcript; likely regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
DTNB-AS1	1	Antisense lncRNA; may regulate DTNB; reported in tumor biology contexts	Transcriptional/post-transcriptional regulation	Cancer (reported/association-based)
EMX2OS	1	Antisense lncRNA regulating EMX2 during neurodevelopment	Neurogenesis; cortical patterning	Neurodevelopmental disorders; glioma (reported)
EPCAM-DT	1	Divergent transcript at EPCAM locus; may influence epithelial identity programs	Epithelial differentiation; cell adhesion pathways	Epithelial cancers (association-based)
HERC2P3	1	Pseudogene transcript; potential regulatory roles (miRNA sponge/transcript	Post-transcriptional regulation (predicted)	Cancer susceptibility (association-based)

		ional interference)		
HNRNPD-DT	1	Divergent transcript near HNRNPD (RNA-binding protein locus); may relate to RNA stability regulation	RNA stability and processing (predicted)	Cancer/immune traits (association-based)
LINC01674	1	lncRNA; limited functional data; putative regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
LINC01792	1	lncRNA; poorly characterized; inferred regulatory activity	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
LINC02814	1	lncRNA; limited functional annotation; putative regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
LINC02819	1	lncRNA; limited functional annotation; putative regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
MDN1-AS1	1	Antisense lncRNA; may modulate MDN1 locus; limited functional data	Ribosome/biogenesis-related regulation (inferred)	Cancer (association-based)
MFSD4B-DT	1	Divergent transcript near MFSD4B; limited annotation; potential regulatory RNA	Transcriptional regulation (predicted)	Cancer/complex traits (association-based)
RPL31P11	1	Ribosomal pseudogene transcript; potential regulatory RNA	Post-transcriptional regulation (predicted)	Cancer (association-based)

SENCR	1	Vascular smooth muscle/endothelial lncRNA regulating differentiation and migration	Vascular development; cytoskeletal regulation	Atherosclerosis; coronary artery disease (reported)
SETD4-AS1	1	Antisense lncRNA near SETD4; may affect epigenetic regulation via locus	Chromatin modification/epigenetic regulation (inferred)	Cancer (association-based)

Please consult the manuscript for references.