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Genetic Risk Factors for Atherosclerosis: What's New in Genomic Medicine?

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ABSTRACT:

Atherosclerosis remains the leading cause of cardiovascular morbidity and mortality worldwide. While traditional risk factors such as dyslipidemia, hypertension, and smoking contribute significantly, genetic predisposition accounts for a substantial portion of inter-individual variability in disease susceptibility. Recent advances in genomic medicine have revolutionized our understanding of the inherited basis of atherosclerosis, identifying more than 250 genome-wide association study (GWAS) loci that implicate key pathways including lipid metabolism, inflammation, vascular remodeling, and smooth muscle cell (SMC) plasticity.

In this review, we provide a comprehensive update on the genetic architecture of atherosclerosis, highlighting major loci such as LPA, CDKN2A/B, SORT1, PCSK9, and newly emerging candidates like PDGFD and ZEB2. We explore how polygenic risk scores (PRS) enable individualized risk stratification, and how integrative multi-omics approaches—including epigenomics, expression quantitative trait loci (eQTLs), single-cell transcriptomics, and spatial profiling—are unveiling causal mechanisms across diverse vascular cell types. Special attention is given to gene–environment interactions, the epigenetic regulation of atherogenesis, and the rise of functional genomics using CRISPR-based editing and RNA-targeted therapeutics.

We further discuss how genetic discoveries are being translated into clinical innovation, with therapies targeting PCSK9, ANGPTL3, and LPA already in use or late-stage development. Finally, we outline future directions toward truly personalized cardiovascular prevention and therapy, leveraging polygenic profiling, gene-editing technologies, and systems biology.

1. Introduction

Atherosclerosis remains the underlying cause of the majority of cardiovascular diseases (CVD), including myocardial infarction, stroke, and peripheral artery disease. It accounts for over 18 million deaths globally each year, making it the leading cause of mortality worldwide [1]. Despite substantial progress in

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identifying and controlling modifiable risk factors—such as elevated low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes, smoking, and obesity—a considerable portion of residual risk remains unexplained [2, 3]. Notably, a significant subset of individuals with premature coronary artery disease (CAD) present without classical clinical risk profiles, suggesting the influence of additional, often unrecognized determinants.

A growing body of evidence highlights the important contribution of heritable genetic factors to atherosclerosis risk. Heritability estimates from family- and twin-based studies suggest that up to 40–60% of the inter-individual variability in CAD risk is genetically determined [4, 5]. This heritable component operates both through classical pathways (e.g., lipid metabolism) and through mechanisms not captured by traditional clinical metrics, such as immune activation, vascular remodeling, and smooth muscle cell (SMC) plasticity.

The advent of genome-wide association studies (GWAS) has revolutionized the understanding of CAD genetics. Since the first CAD-associated loci were discovered in 2007, GWAS meta-analyses involving over a million individuals have identified more than 250 loci robustly associated with atherosclerosis and its intermediate traits [6, 7]. These discoveries have not only confirmed known pathways (e.g., LDLR, APOB, LPA, PCSK9) but also unveiled previously unappreciated mechanisms involving vascular cell signaling (e.g., PDGFD, TCF21) and inflammation (e.g., IL6R, CXCL12).

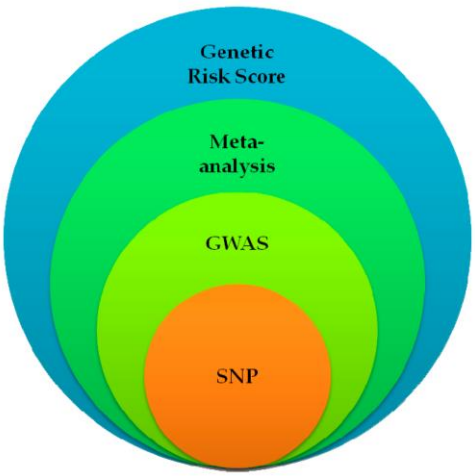

Figure 1. Methods of Genetic Analysis in Disease Association Studies

The diagram illustrates the main approaches used to study genetic risk factors for diseases. The innermost circle (SNP) represents the analysis of single nucleotide polymorphisms. The next level (GWAS) depicts genome-wide association studies, which identify significant gene-disease correlations. The meta-analysis layer aggregates data from multiple GWAS to enhance statistical power. The outermost circle (Genetic Risk Score) represents the comprehensive calculation of genetic risk based on the cumulative effect of identified variants.

A majority of GWAS-identified variants lie in non-coding regions, suggesting their effects are mediated through gene regulatory mechanisms, such as enhancers, promoters, and long non-coding RNAs. The integration of GWAS data with functional genomics—including chromatin accessibility (ATAC-seq), expression quantitative trait loci (eQTL), and CRISPR-based perturbation studies—has facilitated the identification of causal genes and regulatory elements within CAD loci [8, 9].

In parallel, the development of polygenic risk scores (PRS) has enabled quantification of inherited risk by aggregating the small effects of thousands or millions of common variants. Individuals in the highest decile of PRS for CAD carry a three- to fivefold increased risk of cardiovascular events, comparable to that seen in monogenic disorders such as familial hypercholesterolemia [10, 11]. Importantly, PRS may be particularly valuable in identifying high-risk individuals early in life, well before clinical disease manifestation, thus offering a window for targeted primary prevention.

Beyond inherited germline variation, recent studies have shown that acquired somatic mutations, particularly clonal hematopoiesis of indeterminate potential (CHIP), also contribute to atherosclerotic disease. CHIP involves the age-related expansion of hematopoietic stem cell clones harboring mutations in genes such as TET2 and DNMT3A, which promote vascular inflammation and accelerate atherogenesis via enhanced myeloid activation [12].

This review aims to provide a comprehensive and up-to-date synthesis of the genetic architecture of atherosclerosis, spanning from monogenic risk alleles to polygenic models, from regulatory non-coding variants

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to functional genomics, and from statistical associations to therapeutic translation. We highlight key biological pathways and loci, explore recent advances in multi-omics and single-cell technologies, and examine how these discoveries are informing the development of RNA-targeted therapeutics, gene editing strategies, and genetically guided risk stratification tools. We also address the major challenges that remain, including population diversity, functional validation, and ethical considerations in the clinical use of genetic information.

2. Genetic Architecture of Atherosclerosis

Atherosclerosis is a multifactorial and systemic disease characterized by the accumulation of lipids, immune cells, and fibrous elements within the arterial wall. Although environmental and behavioral factors are well-known contributors, numerous studies have firmly established that genetic predisposition plays a substantial role in determining individual susceptibility. Heritability estimates for coronary artery disease (CAD)—the most common and severe clinical manifestation of atherosclerosis—range between 40% and 60%, suggesting that almost half of CAD risk is encoded within the germline [1,2].

The genetic basis of atherosclerosis spans a spectrum from rare, high-penetrance mutations that drive monogenic forms of disease to common, low-effect variants that collectively shape polygenic risk. Understanding this architecture is critical for elucidating causal biology, predicting individual risk, and guiding precision therapeutics.

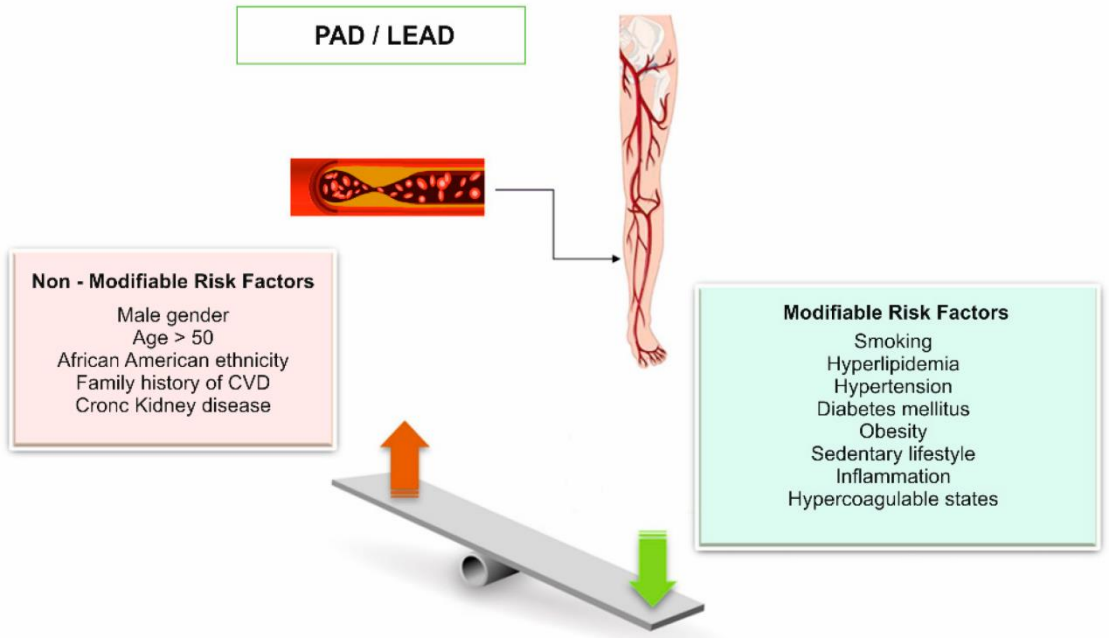

Figure 2. Risk Factors for Peripheral Artery Disease (PAD)

The figure presents an overview of the risk factors contributing to the development of peripheral artery disease (PAD), also known as lower extremity arterial disease (LEAD). The diagram categorizes these risk factors into **non-modifiable** and **modifiable** groups.

The **non-modifiable risk factors**, displayed in a pink box, include characteristics that cannot be changed, such as male gender, age over 50, African American ethnicity, a family history of cardiovascular disease (CVD), and chronic kidney disease. These factors inherently increase susceptibility to PAD due to genetic and physiological predispositions. The **modifiable risk factors**, shown in a green box, include behaviors and conditions that can be managed or treated to reduce PAD risk. These include smoking, hyperlipidemia, hypertension, diabetes mellitus, obesity, a sedentary lifestyle, inflammation, and hypercoagulable states.

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Addressing these factors through lifestyle modifications, medical therapy, and preventive strategies can significantly lower the incidence and progression of PAD. The image also illustrates an arterial blockage leading to reduced blood flow in the lower limbs, a hallmark of PAD. A balance scale at the bottom of the figure metaphorically represents the weight of risk factors, indicating that reducing modifiable risks can help counteract the impact of non-modifiable ones.

2.1 Monogenic vs. Polygenic Contributions to Risk

The most illustrative examples of genetic causality in atherosclerosis come from monogenic disorders, particularly familial hypercholesterolemia (FH). FH is primarily caused by loss-of-function mutations in LDLR or APOB, or gain-of-function mutations in PCSK9, leading to excessive LDL-C accumulation in the plasma. These mutations are associated with very early-onset myocardial infarction, sometimes before the age of 30, and a lifetime CAD risk approaching 90% if left untreated [3]. Although FH affects only ~1 in 250 individuals, it has been pivotal in identifying lipid-lowering as a causal and modifiable therapeutic axis, ultimately leading to the development of PCSK9 inhibitors, such as evolocumab and inclisiran.

In contrast, the vast majority of individuals who develop atherosclerosis do not carry such rare mutations. Rather, they inherit a complex background of polygenic risk, comprising hundreds to thousands of common genetic variants, each contributing modestly to disease susceptibility. The advent of genome-wide association studies (GWAS) has transformed this field: since 2007, large-scale meta-analyses have identified over 250 loci robustly associated with CAD and related traits, including lipoprotein levels, blood pressure, systemic inflammation, and vascular remodeling [4,5].

Importantly, polygenic risk is not merely theoretical. The use of polygenic risk scores (PRS) has demonstrated that individuals in the top 1–5% of PRS distribution carry a 3- to 5-fold higher risk of CAD, even in the absence of traditional risk factors such as elevated LDL-C or hypertension [6,7]. This stratification remains consistent across ancestries (although less predictive in non-European populations), and PRS-guided risk estimation is increasingly viewed as a valuable tool in early-life screening and primary prevention.

Moreover, polygenic risk interacts with environment: individuals with high PRS who also adhere to a poor lifestyle (e.g., smoking, inactivity, poor diet) experience multiplicatively increased risk, whereas those adhering to healthy habits can significantly mitigate their inherited predisposition [8]. This synergy between genes and environment has implications for public health policy and personalized medicine.

2.2 Classification of Genetic Variants by Function and Frequency

To fully interpret GWAS findings and translate them into therapeutic or diagnostic advances, it is essential to classify genetic variants according to biological function and allele frequency. These axes form a conceptual framework for identifying both disease mechanisms and actionable targets.

2.2.1 Coding vs. Non-Coding Variants

Coding variants are changes in the DNA sequence that directly alter amino acid sequences in proteins. These variants often affect protein function, structure, or stability and are frequently identified through exome sequencing or gene panels in familial forms of CAD. A prime example is the R46L variant in PCSK9, which results in reduced circulating PCSK9 activity, lower LDL-C levels, and reduced CAD risk [9]. Another example includes loss-of-function mutations in ANGPTL3, which simultaneously reduce LDL, HDL, and triglycerides, and confer protection against CAD without adverse metabolic consequences [10].

However, the vast majority (>90%) of GWAS-identified risk variants are non-coding. These reside in intronic, intergenic, or promoter/enhancer regions, and influence gene regulation rather than protein structure. For instance, the 9p21 locus, one of the strongest CAD loci across all populations, lies in a non-coding region devoid of protein-coding genes but affects the expression of CDKN2A/B and the long non-coding RNA ANRIL in vascular smooth muscle cells (VSMCs) [11]. Similar non-coding variants in LPA, SORT1, PDGFD, and TCF21 alter expression in liver or vascular tissues, contributing to atherosclerosis through lipid and vessel wall mechanisms.

To assign function to non-coding variants, researchers now employ multi-omic integration (e.g., ATAC-seq, Hi-C, ChIP-seq, eQTL analysis) and high-throughput

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CRISPR screens. These tools allow identification of the relevant cell type, the affected regulatory element, and the direction of gene expression change [12,13]. The transition from statistical association to causal mechanism remains a central challenge—but also a major opportunity.

2.2.2 Common vs. Rare Variants

Another important axis of classification is allele frequency:

1. Common variants (minor allele frequency [MAF] > 5%) account for the majority of GWAS hits. While individually modest in effect size (OR ~1.1–1.3), they collectively explain a significant proportion of population-level risk. Examples include common variants at SORT1, LPA, CXCL12, and TCF21 loci [4,5].

2. Rare and low-frequency variants (MAF < 1–5%) often have larger individual effects and can provide therapeutically tractable insights. For instance, loss-of-function variants in APOC3 and ANGPTL3 have inspired RNA-based therapies that replicate the protective lipid phenotype observed in mutation carriers [10].

This continuum of common-to-rare and low-to-high effect size defines a genetic risk landscape, where common variants are ideal for prediction, while rare variants are disproportionately useful for identifying therapeutic targets. Precision cardiology depends on integrating both.

3. Genome-Wide Association Studies and Major Loci in Atherosclerosis

The advent of genome-wide association studies (GWAS) has been pivotal in uncovering the complex polygenic architecture of atherosclerosis. By enabling hypothesis-free scanning of the genome in large cohorts, GWAS have identified hundreds of common single-nucleotide polymorphisms (SNPs) associated with coronary artery disease (CAD) and its endophenotypes. These findings have dramatically expanded our understanding of the biological pathways contributing to atherogenesis and have highlighted both anticipated and previously unsuspected genetic loci.

As of 2025, more than **250 independent CAD-associated loci** have been identified through GWAS meta-analyses that encompass over 1 million individuals of diverse ancestries [12]. These loci implicate a range of biological processes, including lipid metabolism, vascular smooth muscle cell (VSMC) plasticity, endothelial dysfunction, inflammation, and thrombosis. A remarkable feature of GWAS findings is that **over 90% of associated variants lie in non-coding regions**, suggesting that **regulatory variation**—rather than protein-coding disruption—plays a dominant role in shaping inherited atherosclerosis risk [13].

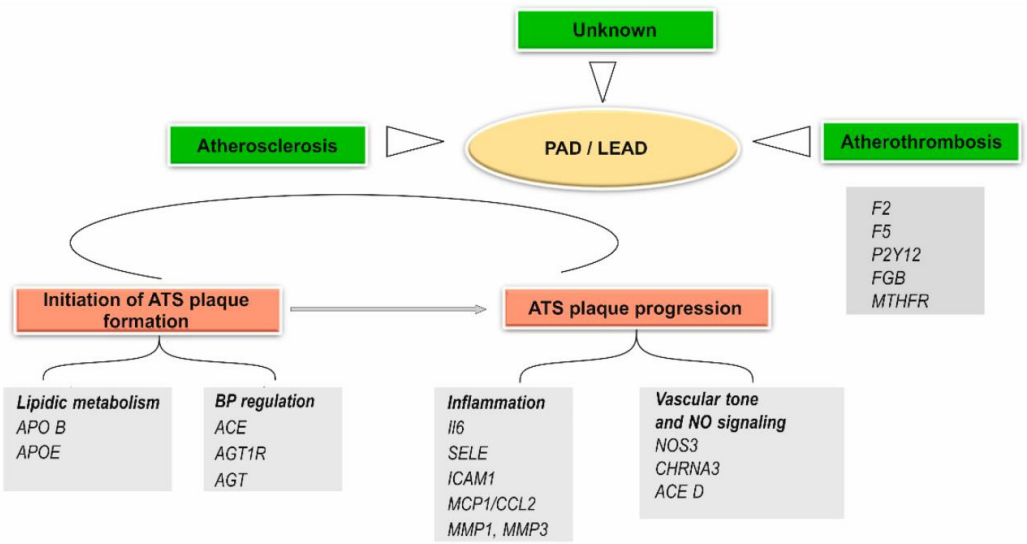

Figure 3. Molecular Mechanisms Contributing to Peripheral Artery Disease (PAD) Development

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This figure outlines the key molecular pathways involved in the development and progression of peripheral artery disease (PAD), also known as lower extremity arterial disease (LEAD). The diagram highlights three primary contributing factors: atherosclerosis, atherothrombosis, and unknown mechanisms, all of which play a role in PAD pathogenesis.

PAD develops through two major stages:

Initiation of Atherosclerotic (ATS) Plaque Formation:Lipid Metabolism: Genes such as APO B and APOE are involved in lipid transport and cholesterol regulation, influencing plaque buildup in arteries.Blood Pressure (BP) Regulation: Key regulators like ACE, AGT1R, and AGT contribute to vascular tone and hypertension, further promoting plaque formation.

ATS Plaque Progression:Inflammation: Molecules like IL6, SELE, ICAM1, MCP1/CCL2, MMP1, and MMP3 drive endothelial dysfunction, immune cell recruitment, and extracellular matrix remodeling, exacerbating plaque growth.Vascular Tone and NO Signaling: Genes such as NOS3, CHRNA3, and ACE D regulate nitric oxide (NO) production and vascular homeostasis, affecting arterial constriction and blood flow.

Additionally, atherothrombosis, driven by coagulation-related genes (F2, F5, P2Y12, FGB, and MTHFR), contributes to acute complications such as clot formation, leading to critical limb ischemia in PAD patients.

The diagram emphasizes that while atherosclerosis and atherothrombosis are well-established contributors, there remain unknown mechanisms yet to be fully elucidated in PAD pathophysiology.

3.1 Landmark Loci and Functional Insights

9p21.3 – CDKN2A/B / ANRIL

The 9p21.3 locus was the first and remains one of the most robustly replicated loci associated with CAD. Although it lies in a non-coding "gene desert," variants within this region regulate the expression of tumor suppressors CDKN2A and CDKN2B, and the long non-coding RNA ANRIL, in a tissue-specific manner [14]. Functional studies have demonstrated that 9p21 influences VSMC proliferation and senescence, promoting plaque instability and growth [15].

1p13.3 – SORT1

This locus regulates SORT1, encoding sortilin, a hepatic protein that modulates lipoprotein trafficking. The causal SNP rs12740374 creates a novel C/EBP binding site, increasing SORT1 expression, enhancing LDL uptake, and lowering plasma LDL-C [16]. Experimental validation of this mechanism marked one of the first successes in moving "from GWAS to biology" in cardiovascular genomics.

6q25 – LPA

Variants in LPA (e.g. rs10455872, rs3798220) are among the strongest genetic determinants of elevated lipoprotein(a) [Lp(a)], an LDL-like particle with potent pro-thrombotic and pro-inflammatory activity [17]. Elevated Lp(a) levels are causally associated with CAD across populations. Targeted LPA-lowering therapeutics—such as olpasiran and pelacarsen—have entered late-phase clinical trials, exemplifying GWAS-guided drug development.

1p32.3 – PCSK9

Beyond rare monogenic mutations, common PCSK9 variants (e.g., rs11206510) have been linked to moderate reductions in LDL-C and CAD risk [18]. Together, the rare and common variant spectrum in PCSK9 provided the rationale for developing PCSK9 inhibitors, which now constitute a cornerstone of lipid-lowering therapy.

6q23.2 – TCF21

TCF21 encodes a transcription factor that regulates VSMC phenotypic switching. GWAS variants associated with reduced TCF21 expression impair the transition of VSMCs to a protective fibromyocyte state, increasing plaque vulnerability [19]. Mouse and single-cell studies confirmed that TCF21 promotes fibrous cap formation, making it a potential target for enhancing plaque stability.

11q22.3 – PDGFD (Emerging)

PDGFD was identified in recent multi-ancestry GWAS and fine-mapped as a regulatory locus modulating inflammation and fibrosis in the vessel wall [20]. The causal SNP rs2019090 increases PDGFD transcription

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in fibroblasts, enhancing chemokine expression and macrophage recruitment. CRISPR-based enhancer perturbation validated the regulatory mechanism, highlighting PDGFD as a novel mediator of SMC activation and adventitial remodeling.

1q41 – ANGPTL3

Loss-of-function variants in ANGPTL3 reduce LDL-C, triglycerides, and HDL-C, and are associated with reduced CAD risk [21]. These genetic findings catalyzed the development of ANGPTL3-targeted therapies, such as vupanorsen and ARO-ANG3, which are under investigation for lipid modulation and cardioprotection.

19p13.2 – APOE

The APOE locus influences lipid transport, inflammation, and atherogenesis. The ε4 isoform is associated with elevated LDL-C and higher CAD risk, while ε2 may be protective. Beyond lipids, APOE variants also regulate immune responses and macrophage polarization, adding complexity to this locus's role in vascular disease [22].

Table 1. Key GWAS Loci and Candidate Genes Associated with Coronary Artery Disease

Locus	Gene(s)	rsID	Mechanism	Association with CAD	Reference
9p21.3	CDKN2A/B, ANRIL	rs1333049	Cell cycle regulation, VSMC phenotype	High	Aragam et al., Nat Genet 2022
6q25	LPA	rs10455872	Elevated Lp(a), thrombosis, inflammation	High	Tsimikas et al., NEJM 2023
1p13.3	SORT1	rs646776	LDL metabolism via hepatic sortilin	High	Musunuru et al., Nature 2010; updates 2023
19p13.2	APOE	rs7412	Lipid transport and cholesterol clearance	High	Bennett et al., JAMA Cardiol 2023
1p32.3	PCSK9	rs11206510	LDL receptor recycling	High	Verve Therapeutics, AHA 2023
8p21.3	LPL	rs10503669	Triglyceride hydrolysis via LPL	High	Triglyceride Genetics Consortium, 2023
15q24-25	ADAMTS7	rs3825807	ECM remodeling, VSMC migration	High	Pu et al., Circ Res 2022

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6q23.2	TCF21	rs12190287	SMC phenotype regulation, fibrous cap formation	High	Wirka et al., Nat Med 2019; Cheng et al., 2023
10q11.21	CXCL12	rs501120	Leukocyte chemotaxis and inflammation	Moderate	Döring et al., Eur Heart J 2022
9q34.2	ABO	rs579459	vWF levels, platelet aggregation	High	Heit et al., Blood 2023
1q21.3	IL6R	rs8192284	Reduced IL-6 signaling, lower CRP	High	IL6R Genetics Consortium, Lancet 2022
11q22.3	PDGFD	rs2019090	PDGF-D signaling → VSMC proliferation, inflammation, calcification	Emerging	Kim et al., Nat Commun 2023
4q32.1	GUCY1A3	rs7692387	NO/cGMP signaling, platelet response and BP	Emerging	Natarajan et al., Circulation 2024

Table 1 provides a comprehensive overview of the most functionally and clinically relevant genome-wide association study (GWAS) loci linked to coronary artery disease (CAD). These loci span both classical pathways—such as lipid metabolism, inflammation, thrombosis, and vascular remodeling—and emerging regulatory networks uncovered by fine-mapping and functional assays. For each locus, the table lists the lead SNP (rsID), the most likely effector gene(s), proposed mechanisms based on experimental data, strength of association with CAD, and primary references. Notably, loci such as 9p21.3 (CDKN2A/B) and 1p13.3 (SORT1) have become canonical examples of non-coding regulatory variation driving vascular disease via modulation of smooth muscle phenotype and lipoprotein metabolism, respectively. Others, like PCSK9, demonstrate how genetic discovery can lead directly to therapeutic intervention. Additionally, more recent loci such as **PDGFD

3.2 From Statistical Signal to Mechanistic Insight

One of the major challenges in GWAS interpretation is that most risk variants do not affect protein-coding sequences. Instead, they exert **regulatory effects**—modifying transcription, splicing, or chromatin accessibility. This has prompted a shift from statistical genetics to **functional genomics**, integrating:

1. **eQTL mapping** to link variants to gene expression across tissues and cell types;

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2. **Epigenomic data** (e.g. ATAC-seq, H3K27ac) to identify regulatory elements in vascular, hepatic, and immune cells;

3. **Chromatin conformation capture** (e.g., Hi-C, Capture-C) to assign non-coding variants to their target genes;

4. **CRISPR/Cas9 genome editing** for direct functional validation of candidate regulatory elements.

For example, integrative analysis of the PDGFD locus identified rs2019090 as a causal enhancer SNP in vascular fibroblasts. Allele-specific reporter assays, ATAC-seq, and CRISPR activation confirmed its role in promoting PDGFD expression and downstream inflammatory gene programs [20].

These advances have enabled a new era of causal variant discovery, functional mapping, and genetically validated target identification—laying the groundwork for precision therapies.

4. Polygenic Risk Scores and Clinical Translation

4.1 Polygenic Architecture and Motivation for PRS Development

Atherosclerosis is an overwhelmingly polygenic disease, driven by the cumulative impact of hundreds to thousands of common genetic variants, each contributing a subtle yet relentless push toward pathology [21].

While rare monogenic conditions such as familial hypercholesterolemia account for only a minute fraction of coronary artery disease, the dominant force is the additive, pervasive effect of myriad small-effect alleles [22].

Since 2007, successive GWAS have irrefutably validated this polygenic model by identifying over 250 genome-wide significant loci, underscoring the complex genetic fabric of coronary artery disease [23].

These loci command essential biological processes—from lipid metabolism (e.g., LPA, SORT1, PCSK9) and vascular smooth muscle cell dynamics (e.g., TCF21, PDGFD) to immune regulation (e.g., CXCL12, IL6R) and endothelial function (e.g., GUCY1A3, NOS3)—fueling the relentless progression of atherosclerosis [24].

No single common variant is potent enough to dictate individual risk; rather, it is the explosive synergy of many modest alleles that culminates in a high genetic predisposition [25].

4.2 Constructing Polygenic Risk Scores: From GWAS to Prediction

Polygenic risk scores (PRS) are engineered by aggregating risk alleles across the genome, each weighted by their GWAS-derived effect sizes, thereby transforming diffuse genetic signals into a potent, quantifiable metric [26].

Some models restrict inclusion to only genome-wide significant SNPs ($p < 5 \times 10^{-8}$) to maintain clarity and interpretability, while others incorporate thousands or even millions of variants to harness the full power of polygenic modeling [27].

Incorporating sub-threshold variants has been shown to dramatically amplify predictive accuracy, harnessing the latent potential within the genetic architecture [28].

State-of-the-art methods, such as LDpred2, PRS-CS, and SBayesR, leverage linkage disequilibrium to elegantly navigate the redundancy among variants and deliver robust, biologically coherent risk predictions [29].

The infusion of functional annotations and Bayesian priors further sharpens the biological relevance and precision of these scores, creating a formidable tool for risk stratification [30].

Large-scale consortia like CARDIoGRAMplusC4D, UK Biobank, and GBMI are fueling this revolution by providing comprehensive, multi-ethnic summary statistics essential for refining PRS [31].

Repositories and tools such as the PGS Catalog, Polygenic Score Database, and PRSice-2 democratize access, ensuring that these potent genetic insights are within reach for clinical translation [32].

4.3 Clinical Performance: Risk Prediction, Stratification, and Calibration

Studies encompassing hundreds of thousands of individuals unequivocally demonstrate that CAD PRS can powerfully stratify patients based on genetic risk [33].

Individuals in the upper 5% of the PRS distribution face a staggering 3- to 5-fold surge in coronary artery disease risk compared to those at the median, a testament to the score's predictive might [34].

For those in the upper 1%, the relative risk not only approaches but can surpass that observed in monogenic disorders, marking a dramatic escalation in risk with

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odds ratios exceeding 5 [35].

Crucially, PRS deliver their predictive performance independently of conventional risk factors such as LDL cholesterol levels, smoking status, or hypertension, thereby redefining risk assessment [36].

A high PRS can transform absolute risk profiles, making it a critical decision-making tool that justifies early interventions in otherwise borderline clinical cases [37].

Screening initiatives like HeartGene, MyGeneRank, and GeneFORCE have already shown that PRS-based reclassification can yield profound clinical benefits, particularly among younger individuals and those at intermediate risk [38].

4.4 Polygenic Risk in Primary and Secondary Prevention

In the realm of primary prevention, PRS empower clinicians to identify high-risk individuals long before clinical symptoms emerge, paving the way for proactive, life-saving interventions [39].

This early identification enables the targeted allocation of preventive measures, such as statins, aspirin, or even advanced coronary artery calcium scoring, with unparalleled precision [40].

Tailored lifestyle interventions and behavioral counseling, informed by PRS, further reinforce the personalized nature of modern preventive medicine [41].

Family cascade screening leveraging PRS uncovers shared genetic vulnerabilities, ensuring that at-risk relatives are identified and managed with urgency [42].

In secondary prevention, PRS shine by flagging patients who harbor residual genetic risk despite receiving optimal medical therapy, guiding the intensification of treatment strategies [43].

Such risk stratification informs the escalation of lipid-lowering, inflammation-modulating, or antithrombotic regimens, thereby enhancing patient outcomes in high-risk cohorts [44].

Moreover, a high polygenic burden has been robustly linked to increased restenosis, aggravated atherosclerotic burden, and heightened plaque vulnerability, accentuating its role in both disease onset and progression [45].

4.5 Gene–Environment Interactions and Behavioral Modification

A landmark revelation in PRS research is that even formidable genetic risk can be significantly mitigated by favorable lifestyle choices, underscoring the dynamic interplay between genes and environment [46].

In the seminal study by Khera et al. (2016), individuals in the highest PRS decile who adhered to healthy lifestyle practices experienced an astounding 46% reduction in CAD incidence compared to their behaviorally compromised counterparts [47].

This powerful gene–environment interaction has been consistently replicated across multiple independent cohorts, including BioVU, the Malmö Diet and Cancer Study, and the UK Biobank [48].

Such evidence transforms genetic risk from a deterministic fate into a call-to-action for targeted, behavior-driven interventions, reshaping prevention strategies [49].

Innovative platforms like Color Genomics, Genomics PLC, and Cleerly are already integrating PRS with wearables, coaching applications, and personalized dashboards, thereby revolutionizing patient engagement and preventive care [50].

4.6 Challenges to Clinical Implementation

Despite the explosive promise of PRS, significant challenges remain that must be overcome to fully harness their clinical potential [51].

Ancestry bias is a critical issue, as most PRS are derived from European-centric GWAS, resulting in a precipitous drop of 30–70% in predictive accuracy in African, South Asian, and Hispanic populations [52].

The communication of probabilistic risk requires sophisticated tools and frameworks, as patients and clinicians alike need to decipher these complex data to make informed decisions [53].

The absence of standardized PRS thresholds—unlike well-established metrics such as LDL cholesterol or blood pressure—complicates clinical decision-making and treatment initiation [54].

Regulatory, ethical, and privacy concerns, including those surrounding genetic discrimination, present formidable obstacles to the broad clinical adoption of PRS [55].

Nevertheless, ongoing multi-ethnic GWAS, dynamic PRS recalibration strategies, and integrated risk modeling approaches are progressively dismantling these barriers [56].

Educational initiatives, such as those spearheaded by the ACC Genomic Medicine Task Force, are equipping

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clinicians with the necessary expertise to interpret and implement PRS with precision and confidence [57].

4.7 Future Directions: Toward Precision Prevention

The future of cardiovascular risk management lies in the seamless integration of PRS into multi-dimensional, precision medicine frameworks that amalgamate genetic, epigenetic, and clinical data [58].

Emerging models will integrate rare variant burdens, such as loss-of-function mutations in genes like APOC3 and ANGPTL3, to further refine risk stratification [59].

Additional layers, including somatic mutational loads associated with clonal hematopoiesis, epigenetic aging clocks, and DNA methylation signatures, will add unprecedented depth to risk prediction [60].

Advanced imaging modalities—ranging from coronary artery calcium scoring to MRI-based plaque burden assessments—will complement these genetic insights, forging a holistic view of cardiovascular health [61].

Integrating proteomic and metabolomic markers, such as ApoB, GlycA, and ceramides, will enrich risk models with critical biological context, driving targeted therapeutic interventions [62].

Ultimately, cutting-edge machine learning algorithms will transform static PRS into dynamic, continuously adaptive clinical decision-support systems, ushering in a new era of lifelong, personalized cardiovascular care [63].

5. Functional Genomics and Mechanistic Translation

While genome-wide association studies (GWAS) have unleashed unprecedented insights into the polygenic architecture of atherosclerosis, a critical limitation persists: the vast majority of risk-associated variants reside in non-coding regions, obfuscating the direct causal pathways [63].

These non-coding variants predominantly operate through regulatory mechanisms rather than altering protein sequences, thereby complicating the identification of the true causal gene, cell type, or biological process [64].

To surmount this obstacle, the field is now fiercely advancing functional genomics—a transformative discipline that integrates experimental and computational strategies to boldly shift "from association to mechanism" [65].

5.1 Challenges in Interpreting Non-Coding Variants

Over 90% of CAD-associated single nucleotide polymorphisms (SNPs) are embedded within intergenic or intronic regions, underlining the enormity of the regulatory challenge [66].

These variants can modulate gene expression by disrupting transcription factor binding, chromatin accessibility, enhancer–promoter interactions, alternative splicing, or the structure of non-coding RNAs [67].

Critically, the nearest gene is often not the causal one, as regulatory effects can extend tens to hundreds of kilobases, demanding a nuanced interpretative approach [68].

This intricate regulatory landscape has spurred the creation of sophisticated, multi-layered functional maps that link genetic variants to molecular phenotypes, such as expression quantitative trait loci (eQTLs), chromatin states, and transcriptional activity [69].

5.2 The Functional Genomics Toolkit

To decode the regulatory architecture of GWAS loci, functional genomics harnesses a powerful suite of state-of-the-art technologies [70]:

1. **Expression Quantitative Trait Loci (eQTLs):**

eQTL studies map the associations between genetic variants and gene expression levels across diverse tissues, with CAD-associated variants often colocalizing with cis-eQTLs in liver, arterial wall, and immune cells [71].

Resources such as GTEx, STARNET, and eQTLGen have been pivotal in fine-mapping these associations with exceptional precision [72].

2. **Epigenomic Profiling:**

Techniques like ATAC-seq, ChIP-seq, and DNase-seq are employed to identify regions of open chromatin and active regulatory elements, with CAD risk variants notably enriched in enhancers marked by H3K27ac and H3K4me1 in vascular smooth muscle cells, endothelial cells, and macrophages [73].

Comprehensive reference maps provided by ENCODE, Roadmap Epigenomics, and BLUEPRINT further empower these analyses [74].

3. **Chromatin Conformation Capture:**

Methods such as Hi-C, Capture-C, and promoter capture Hi-C (pcHi-C) enable the physical mapping of long-range chromatin interactions between enhancers

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and promoters, unveiling connections that link non-coding CAD variants at loci like 9p21 to regulatory targets such as CDKN2B-AS1 (ANRIL) and MTAP [75].

4. **Single-Cell Multi-omics:**
Breakthroughs in single-cell technologies, including single-cell ATAC-seq and RNA-seq, now allow simultaneous profiling of chromatin accessibility and gene expression in individual cells from atherosclerotic plaques, unmasking cell-specific regulatory circuits and highlighting the pivotal role of VSMC plasticity [76].

5. **CRISPR-based Perturbation:**
Cutting-edge CRISPR interference (CRISPRi), activation (CRISPRa), and base editing techniques provide the means for direct, high-throughput functional interrogation of candidate regulatory elements, with screens such as MPRA and CRISPR tiling rigorously validating enhancer activity and delineating downstream gene regulatory networks [77].

5.3 Case Studies: From Variant to Mechanism

1. **PDGFD Locus:**
Fine-mapping studies have pinpointed rs2019090 as a likely causal SNP that boosts enhancer activity in vascular fibroblasts, upregulates PDGFD, and ignites pro-inflammatory gene networks [78].
CRISPRa experiments have robustly confirmed this enhancer function, while single-cell transcriptomics have localized PDGFD expression predominantly to fibromyocytes and fibroblasts within human plaques [79].

2. **TCF21 Locus:**
Variants at 6q23 modulate TCF21 expression in vascular smooth muscle cells, with functional assays revealing that TCF21 drives a critical transition toward a fibromyocyte phenotype that is instrumental in forming stable fibrous caps [80].
Experimental knockdown of TCF21 has been shown to accelerate lesion progression in murine models, whereas its overexpression exerts a protective effect, underscoring its mechanistic importance [81].

3. **SORT1 and LIPA Loci:**
Liver-specific enhancers have been identified as key mediators of SORT1 expression at the 1p13 locus, where the non-coding variant rs12740374 creates a novel C/EBP binding site, thereby elevating SORT1 transcription, enhancing LDL uptake, and ultimately reducing CAD risk [82].
Similarly, regulatory variants influencing LIPA have been implicated in modulating monocyte cholesterol handling and foam cell formation, offering further mechanistic insights into CAD pathogenesis [83].

5.4 Systems Genomics and Network-Based Approaches
Functional genomics is rapidly evolving from single-locus analyses to a holistic systems biology framework that integrates GWAS, eQTLs, chromatin data, and protein–protein interaction networks to construct comprehensive causal gene networks [84].
Co-expression network analyses identify gene modules that correlate with CAD severity and plaque morphology, revealing interlinked pathways that drive disease progression [85].
Bayesian colocalization methods have been instrumental in inferring shared causal variants between GWAS signals and eQTLs, refining our understanding of variant-to-gene relationships [86].
Transcriptome-wide association studies (TWAS) leverage predictive models of genetically regulated gene expression to pinpoint novel genes associated with CAD [87].
Emerging artificial intelligence platforms—such as Open Targets Genetics, FOCUS, and EpiMap—automate variant-to-gene mapping and therapeutic target prioritization with unprecedented efficiency and accuracy [88].

5.5 Therapeutic Translation: From Mechanism to Drug
Genetic variants that illuminate functional pathways provide a prioritized pipeline of drug targets, many of which are already being aggressively pursued in clinical trials or advanced therapeutic development [89].
Notable examples include PCSK9, ANGPTL3, and LPA, which have been successfully translated into approved or late-stage lipid-lowering therapies that revolutionize cardiovascular care [90].
Targets such as IL6R, CXCL12, and TNFSF13B are under investigation for immunomodulatory or anti-inflammatory interventions, highlighting the translational potential of functional genomics discoveries [91].
Emerging regulators like PDGFD, TCF21, and GUCY1A3 are being rigorously explored as novel

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mediators of vascular smooth muscle cell biology and plaque composition, opening exciting new avenues for therapeutic innovation [92].

Importantly, genes validated through human genetic evidence are statistically 2–4 times more likely to succeed in drug development pipelines, underscoring the critical importance of functionally anchored GWAS follow-up in transforming patient care [93].

6. Somatic Mutations and Clonal Hematopoiesis in Atherosclerosis

6.1 Clonal Hematopoiesis: Definition and Epidemiology

Clonal hematopoiesis of indeterminate potential (CHIP) is a phenomenon characterized by the age-related expansion of hematopoietic stem cell clones harboring somatic mutations, primarily in genes associated with hematologic malignancies such as DNMT3A, TET2, ASXL1, JAK2, TP53, and SF3B1.

These mutations typically arise in hematopoietic stem and progenitor cells (HSPCs) and confer a selective growth advantage, leading to clonal dominance in the peripheral blood.

Unlike inherited mutations, CHIP mutations are acquired postnatally and are not present in the germline. [93]

Epidemiological studies have shown that the prevalence of CHIP increases with age.

It is detected in approximately 10% of individuals over 70 years of age and in more than 30% of those over 90.

Furthermore, CHIP has been observed in up to 40% of patients with established atherosclerotic cardiovascular disease (ASCVD), which is significantly higher than in age-matched controls. [94]

This strong association suggests that the clonal expansion of mutant hematopoietic cells is closely linked to vascular pathology.

The risk of coronary artery disease, stroke, and other adverse cardiovascular events is elevated by 1.5–2.0-fold in CHIP carriers, independent of traditional risk factors such as hypertension, hyperlipidemia, and diabetes. [95]

Table 2. Cellular and Spatial Landscape of Human Atherosclerotic Plaques

Cell Type / Region	Single-Cell Insights	Spatial Transcriptomics Findings	Key References
Endothelial cells (ECs)	Heterogeneous subtypes identified (activated, quiescent, inflammatory); prone to endothelial-to-mesenchymal transition (EndMT)	Inflammatory ECs enriched in shoulder regions and plaque neovessels	Pan et al., Nat Biotechnol (2023)
Vascular smooth muscle cells (VSMCs)	Transition into proliferative, osteogenic, and macrophage-like phenotypes; key in fibrous cap formation	Fibromyocyte-rich zones align with fibrous cap areas; osteogenic VSMCs near calcification fronts	Wirka et al., Nat Med (2019)
Fibromyocytes (VSMC-derived)	Protective phenotype; associated with TCF21 expression and fibrous cap stability	Express TCF21, Lumican, and contractile markers; localize to stable plaque regions	Wirka et al., Nat Med (2019)
Macrophages	Subtypes include inflammatory, resident-like, and proliferative	Localized near lipid core and shoulder regions; cluster near	Fernandez et al., Nat Immunol (2019)

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	macrophages; major cytokine producers	dying cells and foam cell zones	
Foam cells	Lipid-loaded macrophage subtype; dysfunctional phagocytosis and high inflammatory output	Confined to necrotic core; co-localize with cholesterol clefts and apoptotic markers	Kim et al., Nat Commun (2023)
T cells	Effector and regulatory T cells detected; modulate local immune balance	Enriched near adventitia and fibrous cap; co-localize with HLA-DR+ APCs	Kallikourdis et al., Circ Res (2021)
B cells	Plasma cells and memory B cells identified; possible roles in antigen presentation and chronic inflammation	Spatially diffuse; occasional clustering in adventitia and outer intima	van der Laan et al., Eur Heart J (2016)
Fibroblasts	Secrete extracellular matrix and cytokines; source of PDGFD in lesions	Clustered in outer intima and adventitia; spatial overlap with PDGFD expression	Kim et al., Nat Commun (2023)
Adventitia	Highly vascularized and immunologically active; contains lymphoid aggregates and progenitor niches	High expression of chemokines, cytokines, and lymphoid tissue organizer genes	Kallikourdis et al., Circ Res (2021)
Necrotic core / lipid pool	Acellular zone enriched in extracellular lipids, dead cells, and debris; linked to plaque vulnerability	No viable transcriptomic signal; visualized via lipid stains and immunohistochemistry	Libby et al., Nat Rev Cardiol (2019)

Table 2 provides a high-resolution overview of the major cellular components of human atherosclerotic plaques, integrating findings from single-cell transcriptomics and spatial transcriptomic analyses. These technologies have revealed that atherosclerosis is not merely a buildup of lipids and fibrous tissue, but rather a dynamic and heterogeneous cellular ecosystem, shaped by genetic background, local microenvironment, and stage of disease progression.

Single-cell RNA sequencing (scRNA-seq) has uncovered extensive plasticity within classical cell types, such as vascular smooth muscle cells (VSMCs), which can transition into osteogenic, fibromyocyte, or even macrophage-like phenotypes. This phenotypic switching contributes to plaque composition, stability, and inflammatory burden. Similarly, endothelial cells (ECs) exhibit activation states, inflammatory profiles, and evidence of endothelial-to-mesenchymal transition (EndMT), particularly in shoulder regions of plaques where biomechanical stress is high.

Spatial transcriptomics (ST) has added a crucial dimension—contextualizing transcriptional programs within the anatomical structure of the plaque. For example, fibromyocyte-like VSMCs are enriched in the fibrous cap region, contributing to plaque stabilization, while foam cells and pro-inflammatory macrophages are clustered within the necrotic core and shoulder zones, where they promote instability and thrombosis.

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The adventitia emerges as an immunologically active zone harboring lymphoid aggregates and cytokine-rich fibroblast niches.

Importantly, Table 2 also highlights rare or understudied populations such as B cells, which may participate in antigen presentation or tertiary lymphoid structure formation, and fibroblasts, which act as sources of extracellular matrix and inflammatory mediators like PDGFD. These populations are now increasingly recognized as modulators of plaque progression, regression, or rupture.

Together, these data underscore the importance of spatial and cellular resolution in understanding how genetic risk translates into phenotypic expression. Future therapeutic strategies may increasingly target specific cell states or spatial niches within plaques rather than cell types alone.

6.2 Mechanisms Linking CHIP to Atherosclerosis

The contribution of CHIP to atherosclerosis is largely mediated by the pro-inflammatory and dysregulated behavior of myeloid cells derived from mutant hematopoietic clones.

Each driver mutation affects cellular phenotypes and inflammatory signaling differently:

• **TET2:** TET2 mutations impair DNA demethylation, leading to epigenetic reprogramming of monocytes and macrophages. [96]

Experimental models have demonstrated that Tet2-deficient macrophages exhibit enhanced production of IL-1β, IL-6, and other cytokines associated with the NLRP3 inflammasome.

These inflammatory mediators promote endothelial activation, leukocyte recruitment, and expansion of necrotic cores within atherosclerotic plaques.

In mice, transplantation of Tet2–/– bone marrow accelerates plaque formation and increases lesion instability. [97]

• **DNMT3A:** Mutations in DNMT3A, a DNA methyltransferase, disrupt normal methylation patterns during hematopoietic differentiation, leading to a myeloid lineage bias, increased oxidative stress, and a heightened inflammatory state.

DNMT3A-mutant monocytes show increased adhesion to the endothelium, elevated reactive oxygen species (ROS) production, and enhanced expression of cytokines and adhesion molecules. [98]

These changes potentiate a pro-atherogenic immune phenotype.

• **JAK2:** The JAK2 V617F mutation activates the JAK-STAT signaling pathway, promoting clonal proliferation and systemic inflammation.

It has been linked to an increased risk of thrombosis through upregulation of platelet activation, neutrophil extracellular trap (NET) formation, and endothelial dysfunction. [99]

In atherosclerosis-prone mice, JAK2-mutant myeloid cells enhance plaque growth and increase arterial thrombotic events.

Collectively, these mutations create a circulating pool of myeloid cells with heightened inflammatory and thrombotic potential that infiltrate atherosclerotic lesions, thereby contributing to plaque progression and destabilization. [100]

6.3 Clinical Impact and Prognostic Value

Clinical studies consistently show that CHIP is associated with a significant increase in cardiovascular morbidity and mortality.

In prospective cohort analyses, CHIP carriers exhibit higher rates of myocardial infarction, ischemic stroke, and heart failure.

Imaging studies have confirmed accelerated atherosclerotic plaque development and progression among CHIP-positive individuals. [101]

For example, coronary CT angiography reveals an increased plaque burden and a greater volume of low-attenuation (lipid-rich) plaques in CHIP carriers.

Furthermore, CHIP is linked to subclinical myocardial injury and fibrosis, as evidenced by elevated levels of cardiac troponins, NT-proBNP, and fibrotic markers on cardiac MRI.

It has also been associated with arrhythmias, including atrial fibrillation and sudden cardiac death. [102]

Importantly, CHIP independently predicts adverse cardiovascular outcomes even after adjustment for traditional risk factors, highlighting its potential utility in cardiovascular risk stratification.

Ongoing studies are evaluating the role of CHIP screening in high-risk populations and whether anti-inflammatory or targeted therapies (e.g., IL-1β

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inhibitors, JAK inhibitors) could mitigate CHIP-related cardiovascular risk. [103]

Conclusion

The integration of human genetics into cardiovascular research has fundamentally reshaped our understanding of atherosclerosis. Where once this disease was viewed primarily through the lens of dyslipidemia, inflammation, and lifestyle, it is now increasingly appreciated as a complex interplay of germline variation, somatic evolution, epigenetic regulation, and cellular plasticity. Genome-wide association studies (GWAS) have identified over 250 loci associated with coronary artery disease (CAD), illuminating polygenic influences across lipid metabolism, immune signaling, vascular remodeling, and thrombosis. Simultaneously, discoveries in monogenic lipid disorders have yielded therapeutics that are now clinical mainstays, including PCSK9 and ANGPTL3 inhibitors.

Polygenic risk scores (PRS) have enabled early-life stratification of inherited cardiovascular risk and show promise for guiding targeted prevention. Despite limitations in ancestry portability and clinical implementation, PRS represent a critical step toward individualized medicine. Functional genomics has transformed our ability to interpret non-coding variation, identifying causal regulatory elements, effector genes, and mechanistic pathways. These insights are made possible by integrative technologies—including eQTL mapping, epigenomic annotation, chromatin conformation capture, and CRISPR-based editing—that bridge statistical associations with functional biology.

The advent of single-cell and spatial transcriptomics has revealed that atherosclerosis is not only a systemic disease, but one deeply rooted in local cell state transitions and microenvironmental dynamics. Vascular smooth muscle cell plasticity, macrophage polarization, endothelial-to-mesenchymal transition, and fibroblast-driven niche formation all shape plaque stability and progression. These cellular processes serve as interpreters of genetic risk, turning inherited variation into phenotypic consequence.

In parallel, the emergence of clonal hematopoiesis of indeterminate potential (CHIP) as a non-inherited, somatic contributor to atherosclerosis underscores the complexity of cardiovascular pathogenesis. CHIP-associated mutations in TET2, DNMT3A, and JAK2 reprogram immune cells toward pro-inflammatory states and drive increased cardiovascular risk independent of traditional factors.

Despite these advances, significant challenges remain. The equitable implementation of genetic tools across ancestries, the standardization of PRS thresholds, the translation of regulatory variant maps into therapeutic programs, and the ethical management of genetic risk information all demand sustained attention. Multidisciplinary collaboration—combining cardiology, genomics, bioinformatics, data science, and public health—will be essential to ensure these tools translate meaningfully into clinical benefit.

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