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Genomic and epigenetic influences on coronary artery disease

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Abstract

Coronary artery disease (CAD), the leading cause of morbidity and mortality worldwide, is a consequence of the interaction of numerous genetic, epigenetic, and environmental factors. Many genes have been recognized by genomic research to contribute to CAD risk through single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs). Epigenetic modifications like DNA methylation, histone adjustments, and non-coding RNAs control gene expression following contact with environmental stressors. This literature review consolidates available evidence on the genomic and epigenetic determinants of CAD and their diagnostic, predictive, and therapeutic implications. An exhaustive search was conducted on PubMed, Scopus, and Web of Science using keywords such as "coronary artery disease" AND "genomics," "epigenetics" AND "CAD," and "DNA methylation" AND "cardiovascular disease," between 2015 and 2025. Genetic loci such as 9p21, PCSK9, and APOE have strong association with CAD susceptibility, and epigenetic changes such as hypermethylation of lipid metabolism genes and disruption of microRNAs contribute to disease pathology. Evidence is highly suggestive of the diagnostic utility of epigenetic biomarkers and polygenic risk scores (PRS), and PRS has the potential to predict CAD risk with up to 80% specificity in high-risk subjects. However, barriers in the shape of genetic heterogeneity, epigenetic assay heterogeneity, and sparse longitudinal data pose an impediment to clinical use. Therapies targeting epigenetic changes, such as microRNA mimics and conditional histone deacetylase inhibitors, are promising but require validation. This review emphasizes the core contribution of genomics to CAD epigenetics, emphasizing the need for standardised assays, combined omics strategies, and large-scale prospective cohorts to enhance precision medicine.

Keywords: coronary artery disease, genomics, epigenetics, polygenic risk scores, DNA methylation.

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1. Introduction

Coronary artery disease (CAD), characterized by the atherosclerotic accumulation of plaque within coronary arteries, is one of the principal causes of worldwide cardiovascular mortality, accounting for approximately 9 million deaths annually [1]. Conventional risk factors like hypertension, dyslipidemia, smoking, and diabetes explain only a fraction of CAD risk, and more and more evidence suggests genetic and epigenetic factors as principal drivers [2]. Genomic analysis, particularly genome-wide association studies (GWAS), has identified over 160 loci associated with CAD, and the strongest replicated locus is on 9p21 [3]. Gene expression is controlled by epigenetic processes, such as DNA methylation, histone modification, and non-coding RNAs (microRNAs and long non-coding RNAs), without altering DNA sequences, acting as mediators of environmental impact on genetic susceptibility [4]. These mechanisms underlie major pathological processes in CAD, including endothelial dysfunction, smooth muscle cell proliferation, and inflammation [5].

The integration of genomic and epigenetic data has transformed CAD from a relatively lifestyle-predisposed condition to a disease with molecular targets that are actionable [6]. Polygenic risk scores (PRS), which aggregate the effects of multiple SNPs, have become powerful risk stratifiers, while epigenetic markers give hints towards disease progression and drug tolerance [7]. However, there are issues that include genetic variation between populations, variation in epigenetic assay sensitivity, and the complexity of gene-environment interaction [8]. Novel epigenetic therapies, such as histone deacetylase (HDAC) inhibitors and microRNA-targeting therapies, are promising but face challenges to clinical application [9]. This review aims to synthesize the latest data on the genomic and epigenetic determinants of CAD, discussing their diagnostic utility, clinical correlations, prognostic significance, and therapeutic potential, with a focus on areas of uncertainty and future directions.

2. Review

2.1 Genomic influences on Coronary Artery Disease

2. 1.1 Established genetic variants

Genome-wide studies identified numerous genetic variants associated with CAD. The strongest CAD-associated locus is on 9p21, which contains CDKN2A and

CDKN2B genes; SNPs such as rs1333049 increase CAD risk by 20–30% per allele [10]. These genes regulate cell cycle progression and smooth muscle growth in vessels, critical processes involved in atherosclerosis [11]. PCSK9 gene variants coding for proprotein convertase subtilisin/kexin type 9 are implicated in low-density lipoprotein cholesterol (LDL-C) concentration and CAD risk, with loss-of-function variants decreasing risk up to 40% [12]. The APOE gene, and more so the ε4 allele, is implicated in dyslipidemia and 1.5-fold increased CAD risk [13]. GWAS have also identified variants in genes for inflammation (IL6R), thrombosis (F5), and endothelial function (NOS3) to highlight the polygenic nature of CAD [14].

2.1.2 Rare variants and copy number variations

Besides common SNPs, rare variants and CNVs are involved in CAD susceptibility. Rare mutations in APOB and LDLR that lead to familial hypercholesterolemia and early CAD have been discovered using whole-exome sequencing [15]. CNVs in the 1q21 and 16p13.11 loci that impinge on lipid metabolism and inflammation genes are detected in 5–10% of CAD cases [16]. The findings demonstrate the utility of genomic profiling of rare variants in accounting for CAD risk.

2.1.3 Polygenic risk scores

Polygenic risk scores (PRS) aggregate the additive effect of multiple SNPs to predict CAD risk. Research by Khera et al. in 2023 demonstrated that PRS with over 6 million SNPs were able to predict CAD in 80% of high-risk individuals accurately better than traditional risk factors, including the LDL-C level [17]. PRS are particularly valuable in younger age groups where traditional risk scores (e.g., Framingham Risk Score) are weaker [18]. However, PRS performance is based on ethnic groups due to genetic heterogeneity, with lower accuracy in non-European groups [19].

2.1.4 Diagnostic challenges

Genomic testing relies on technologies like next-generation sequencing (NGS) and SNP arrays, but the limitations lie in the form of high cost, penetrance heterogeneity, and the need for population-specific reference databases [20]. False negatives are present in the event of rare variants not found in standard panels, while false positives may result from benign polymorphisms [21]. Standardization of genomic assays and correlation with clinical risk factors is necessary to improve diagnostic accuracy.

3. Epigenetic influences on Coronary Artery Disease

3.1 DNA methylation

DNA methylation, cytosine residue methylation, is among the significant epigenetic alterations in CAD. Genes like ABCA1, a cholesterol efflux gene, which are overmethylated, enhance CAD risk and occur in 60% of patients with acute coronary syndrome [22]. Hypomethylation of pro-inflammatory genes like IL6 and TNF enhances endothelial dysfunction and plaque instability [23]. A 2022 study by Zhang et al. identified methylation signatures in peripheral blood leukocytes that are 75% sensitive for CAD progression prediction [24]. Nevertheless, tissue-specific methylation signatures and assay-to-assay variation in sensitivity (e.g., bisulfite sequencing vs. methylation arrays) complicate clinical use [25].

3.2 Histone modifications

Histone modifications like acetylation and methylation regulate chromatin accessibility and gene expression. Histone deacetylase 3 (HDAC3) dysregulation is linked to endothelial dysfunction with increased H3K27me3 marks promoting vascular inflammation [26]. Histone acetyltransferase (HAT) inhibitors reduced atherosclerotic plaque burden by 30% in mice models, suggesting therapeutic potential in a 2021 paper by Chen et al. [27]. However, non-selective effects of histone-modifying drugs limit their use in the clinic [28].

3.3 Non-Coding RNAs

Non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play a central role in CAD. Lipid metabolism-regulating miR-33 is overexpressed in atherosclerotic plaques, while endothelial repair function is maintained by underexpression of miR-126 in CAD [29]. lncRNAs like ANRIL, encoded at the 9p21 locus, regulates atherosclerosis by regulating CDKN2A/B expression [30]. A 2024 meta-analysis has quoted that miRNA panels (e.g., miR-133a, miR-208b) predict acute myocardial infarction with 85% specificity [31]. However, miRNA analysis from plasma is troubled by degradation and low abundance [32].

3.4 Epigenetic biomarkers

Epigenetic biomarkers such as methylation status and miRNA profiles carry prognostic and diagnostic significance. Li et al. in 2023 designed an epigenetic risk score incorporating methylation and miRNA data with 78% accuracy in CAD event prediction [33]. They are particularly useful for diagnosing subclinical atherosclerosis, when conventional imaging can be useless [34]. However, tissue-to-tissue heterogeneity of epigenetic signatures and environmental influences (e.g., diet, smoking) render them hard to standardize [35].

4. Clinical and prognostic implications

4.1 Clinical phenotypes

Genomic and epigenetic patterns characterize CAD presentation. PCSK9 and LDLR variants predispose to early-onset CAD and hypercholesterolemia, while 9p21 variants impart susceptibility to plaque rupture and acute coronary syndromes [36]. Epigenetic changes, such as hypermethylation of ABCA1, are more prevalent in patients with unstable angina, which is associated with higher rates of recurrent events [37]. Downregulation of miR-126 is associated with endothelial dysfunction and stent restenosis in 15–20% of patients after angioplasty [38].

4.2 Prognostic significance

Genetic and epigenetic markers yield prognostic information. An elevated PRS predicts a 2-fold greater risk of major adverse cardiovascular events (MACE) over 5 years [17]. Increased methylation of IL6 and low miR-126 are associated with poor outcomes, such as a 30% increased risk of myocardial infarction [39]. Longitudinal research indicates that repeated epigenetic changes after treatment are

predictive of recurrent events, with 25% of patients maintaining stable patterns of methylation on 1-year follow-up [40].

4.3 Heritable vs. environmental contributions

CAD risk is a compromise between heritability and environment. Genomic loci like 9p21 confer immutable risk, while epigenetic changes can be reversed, which are induced by lifestyle factors like smoking (inducing TNF hypomethylation) and diet (altering miR-33 levels) [41]. Separation between heritable and modifiable risk through integrated omics profiling is crucial for personalized prevention strategies.

5. Mechanisms of genomic and epigenetic pathology

Genomic CAD variants interfere with key pathways, including lipid metabolism (PCSK9, LDLR), inflammation (IL6R), and thrombosis (F5) [42]. PCSK9 variants, for example, augment LDL receptor degradation, increasing circulating LDL-C and promoting atherosclerosis [12]. Epigenetic mechanisms amplify these processes: ABCA1 hypermethylation reduces cholesterol efflux, and miR-33 upregulation inhibits HDL biogenesis [43]. Histone modifications, such as H3K27me3, enhance inflammatory gene expression, promoting macrophage infiltration of plaques [44]. lncRNAs like ANRIL control chromatin remodeling, promoting CDKN2A/B-induced atherosclerosis [30]. These mechanisms highlight the collaborative interplay of genomics and epigenetics in CAD development.

6. Therapeutic implications and challenges

6.1 Genomic-Based therapies

Genetic discoveries have raised directed therapies, such as PCSK9 inhibitors (e.g., evolocumab), that reduce LDL-C by 60% and CAD events by 15% in high-risk patients [45]. Gene editing reagents, including CRISPR-Cas9, are being explored to correct LDLR gene mutations in familial hypercholesterolemia, with proof-of-concept in animal models showing 50% decreases in LDL-C [46]. Off-target effects, however, and moral concerns limit their utilization currently [47].

6.2 Epigenetic therapies

Epigenetic drugs, including HDAC inhibitors (e.g., vorinostat) and miRNA mimics, are under investigation. Wang et al.'s 2023 trial proved that miR-126 mimics reduced endothelial dysfunction in CAD patients by 25% [48]. BET inhibitors, targeting histone acetylation, were promising in reducing plaque inflammation in animal models [49]. Non-specific effects and toxicity remain issues [50].

6.3 Challenges

Therapies are responsive to genomic and epigenetic subtype, and to agreed protocols. PCSK9 inhibitors are second-best in carriers of specific APOE alleles, and epigenetic therapies are hampered by specificity and delivery issues [51]. There is little long-term safety data for epigenetic drugs, and there is a 10% risk of infection [52]. Developing personalized algorithms for treatment that include genomic and epigenetic data is a priority.

7. Limitations and future directions

7.1 Current limitations

Genomic and epigenetic studies are faced with challenges like genetic heterogeneity across populations, variability of sensitivity across epigenetic assays, and small sample sizes (50–200 patients in most of the studies) [53]. Longitudinal epigenetic change data are scarce, particularly for rare variants and lncRNAs [54]. Clinical presentation overlap, such as chest pain between CAD and non-cardiac disease, renders biomarker utility challenging [55].

7.2 Future research

Large-scale, multi-ethnic GWAS and EWAS are needed to validate biomarkers and improve PRS in mixed populations. Multiscale, multi-omics integration (genomics, epigenomics, transcriptomics) with machine learning would enhance risk prediction and therapeutic intervention. Prospective studies comparing dynamic epigenetic changes longitudinally and their response to lifestyle intervention are a priority. RCTs of epigenetic therapy, e.g., miRNA mimics, are needed to establish efficacy and safety.

7.3 Clinical implications

Regular epigenetic and genomic profiling, including PRS and methylation panels, need to be integrated into CAD risk assessment. Point-of-care epigenetic testing may reduce diagnostic time. Patient registries and biobanks will enable large-scale omics research and personalized medicine approaches.

8. Conclusion

Genomic and epigenetic influences have revolutionized our understanding of coronary artery disease, with genetic loci like 9p21 and PCSK9, and epigenetic changes like ABCA1 methylation and miR-126 dysregulation, guiding risk stratification and treatment planning. Polygenic risk scores and epigenetic biomarkers are very diagnostic and prognostic but raise concerns regarding assay standardization, genetic heterogeneity, and therapeutic specificity. Advances in multi-omics integration, standardization of assays, and novel therapies offer precision cardiology, which is capable of enabling earlier diagnosis and tailored treatments to reduce the global burden of CAD.

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