Integrative Analysis of ANGPTL3 and APOB Gene Polymorphisms in Lipid Metabolism and Coronary Artery Disease Susceptibility

Randa H Mohamed[1], Tarek Ahmed Naguib[2], Rawda Omar Ali[1], Basma A. Ibrahim[1]

[1]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding Author: Rawda Omar Ali

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Abstract

Background: Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, primarily driven by dyslipidemia and complex gene–environment interactions influencing lipid metabolism. The angiopoietin-like 3 (ANGPTL3) and apolipoprotein B (APOB) genes are central regulators of plasma lipid homeostasis and lipoprotein assembly, respectively. ANGPTL3 modulates lipoprotein lipase and endothelial lipase activity, thereby influencing triglyceride and cholesterol levels, while APOB serves as a structural apolipoprotein critical for very-low-density and low-density lipoprotein (VLDL and LDL) formation. Variations in these genes can lead to altered lipid profiles, promoting atherogenesis and increased CAD susceptibility. This review aims to provide an integrative biochemical and molecular analysis of ANGPTL3 and APOB gene polymorphisms in relation to CAD risk, emphasizing how these variants influence lipid metabolism, endothelial function, and plaque development. We explore the structural and functional aspects of both proteins, the biochemical pathways linking their polymorphisms to dyslipidemia, and the cumulative impact of gene–gene and gene–environment interactions. Moreover, we discuss recent findings on the association of specific single-nucleotide polymorphisms (SNPs) in ANGPTL3 and APOB with lipid fractions, LDL particle characteristics, and the progression of atherosclerotic lesions. From a medical biochemistry perspective, understanding these polymorphisms provides insight into lipid transport regulation, hepatic lipid synthesis, and plasma lipoprotein remodeling. The integrative evaluation of ANGPTL3 and APOB emphasizes the coordinated influence of lipid-modulating genes on CAD pathophysiology. Emerging evidence suggests that loss-of-function variants in ANGPTL3 confer protection against atherosclerosis by lowering LDL-C and triglyceride levels, whereas deleterious mutations in APOB elevate CAD risk through impaired LDL clearance and enhanced foam cell formation. **In conclusion,** polymorphisms in ANGPTL3 and APOB represent pivotal genetic determinants of lipid metabolism and CAD susceptibility. Their interplay underscores the molecular heterogeneity of atherosclerosis and offers promising avenues for personalized risk prediction and targeted therapeutic interventions, including ANGPTL3 inhibition and APOB-directed lipid-lowering strategies. This review integrates biochemical, genetic, and clinical perspectives to elucidate how these lipid-regulatory genes shape cardiovascular risk and disease progression.

Keywords: *ANGPTL3, APOB Gene , Coronary Artery Disease*

Introduction

Coronary artery disease (CAD) represents a multifactorial disorder arising from the interplay of genetic predisposition, dyslipidemia, inflammation, and metabolic dysregulation. Despite extensive advances in cardiovascular medicine, CAD continues to be the most prevalent cause of death globally, with lipid metabolism disturbances playing a central pathogenic role. Biochemically, CAD is initiated by endothelial injury and lipid infiltration into the arterial intima, promoting oxidative modification of lipoproteins, macrophage recruitment, and foam cell formation. This cascade culminates in plaque formation and vascular occlusion, leading to ischemic events such as myocardial infarction and angina. The precise biochemical regulation of lipoprotein metabolism, therefore, serves as a cornerstone for understanding the molecular basis of CAD susceptibility [1].

The genetic determinants of lipid metabolism have been extensively studied, revealing that polymorphisms in lipid-related genes can markedly alter plasma lipoprotein profiles. Among these, the **angiopoietin-like 3 (ANGPTL3)** and **apolipoprotein B (APOB)** genes have emerged as key molecular regulators of lipid homeostasis. ANGPTL3, secreted predominantly by the liver, inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), resulting in increased plasma triglyceride and cholesterol concentrations. In contrast, APOB encodes the structural apolipoprotein essential for the assembly and secretion of atherogenic lipoproteins, including very-low-density (VLDL), intermediate-density (IDL), and low-density lipoproteins (LDL). Variations in these genes can significantly impact lipid transport and clearance, thereby influencing individual susceptibility to CAD [2].

Recent advances in genomics have identified specific single-nucleotide polymorphisms (SNPs) within ANGPTL3 and APOB that modulate plasma lipid concentrations and atherogenic risk. For example, loss-of-function variants in ANGPTL3 (such as E40K and S17X) have been associated with reduced LDL-C and triglyceride levels, conferring protection against atherosclerosis. Conversely, polymorphisms in APOB (e.g., rs693, rs1042031) have been linked to altered LDL particle size and impaired receptor binding, leading to enhanced lipid deposition and atherogenesis. Despite these findings, the combined and interactive effects of ANGPTL3 and APOB polymorphisms remain underexplored, representing a critical gap in the molecular understanding of CAD [3].

The aim of this review is to provide an integrative biochemical analysis of ANGPTL3 and APOB gene polymorphisms and their influence on lipid metabolism and CAD risk. By synthesizing current evidence, this review seeks to bridge the gap between genetic variation and biochemical pathophysiology, highlighting how these polymorphisms contribute to the diversity of lipid profiles observed in CAD patients. Furthermore, understanding these genetic interactions may illuminate novel biomarkers and therapeutic targets for precision cardiovascular medicine [4].

Overview of Coronary Artery Disease — Biochemical and Genetic Landscape

Coronary artery disease (CAD) is a chronic progressive disorder characterized by the accumulation of lipid-rich atheromatous plaques within the coronary arteries. From a biochemical standpoint, CAD develops through a series of interrelated processes including endothelial dysfunction, lipid infiltration, oxidative stress, and inflammation. The earliest event in atherogenesis involves endothelial activation and increased permeability to apolipoprotein B–containing lipoproteins, particularly low-density lipoproteins (LDL). Once trapped in the intimal layer, these lipoproteins undergo oxidative modification, becoming oxidized LDL (oxLDL), which serves as a potent chemotactic and pro-inflammatory signal that recruits circulating monocytes and T lymphocytes to the vascular wall [5].

Upon entry into the subendothelial space, monocytes differentiate into macrophages that internalize oxLDL through scavenger receptors such as CD36 and SR-A. This uptake leads to foam cell formation,

a hallmark of early atheroma. These foam cells secrete cytokines, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs), which perpetuate inflammation and degrade the extracellular matrix, weakening the vascular structure. Concurrently, smooth muscle cells migrate from the media into the intima, proliferate, and synthesize collagen to stabilize the plaque cap. However, continued lipid accumulation and inflammatory signaling often result in plaque instability and rupture, precipitating acute coronary syndromes [6].

Beyond the biochemical cascade, genetic factors play a crucial role in modulating individual susceptibility to CAD. Genome-wide association studies (GWAS) have identified more than 160 loci associated with CAD risk, many of which influence lipid metabolism pathways. Genes encoding lipoproteins, lipases, and their regulators—such as APOB, LDLR, PCSK9, and ANGPTL3—are pivotal determinants of plasma lipid concentrations. Variations within these genes can alter lipoprotein synthesis, secretion, and clearance, affecting LDL particle number and composition, thereby contributing to atherogenic dyslipidemia. Importantly, these genetic variations interact with lifestyle and environmental factors, including diet, smoking, and physical activity, amplifying CAD risk through metabolic–genetic synergy [7].

The integration of biochemical and genetic insights provides a comprehensive understanding of CAD as both a metabolic and genomic disorder. It underscores the importance of evaluating lipid-regulating gene polymorphisms, such as those in ANGPTL3 and APOB, not merely as static risk markers but as dynamic modulators of lipid homeostasis. This approach lays the groundwork for personalized medicine strategies aimed at targeting specific metabolic pathways influenced by genetic variation, ultimately improving prevention and therapeutic outcomes in CAD patients [8].

Angiopoietin-Like 3 (ANGPTL3): Structure, Function, and Role in Lipid Metabolism

The *angiopoietin-like 3 (ANGPTL3)* gene, located on chromosome 1p31.3, encodes a 460-amino acid secreted glycoprotein primarily synthesized in the liver. Structurally, ANGPTL3 shares homology with angiopoietins, comprising an N-terminal coiled-coil domain responsible for oligomerization and a C-terminal fibrinogen-like domain implicated in receptor interaction and lipid regulation. The protein undergoes proteolytic cleavage by proprotein convertases such as furin, generating active N- and C-terminal fragments that differentially regulate lipoprotein lipase (LPL) and endothelial lipase (EL) activity. Through inhibition of these lipases, ANGPTL3 plays a pivotal biochemical role in maintaining plasma triglyceride, LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C) concentrations [9].

Mechanistically, ANGPTL3 exerts its lipid-modulating effects by forming complexes with ANGPTL8 (betatrophin) and ANGPTL4. These interactions fine-tune LPL inhibition across tissues, directing triglyceride trafficking between energy-utilizing and storage sites. Inhibition of LPL by ANGPTL3 reduces hydrolysis of triglyceride-rich lipoproteins, resulting in elevated plasma triglyceride and VLDL levels. Simultaneously, suppression of endothelial lipase decreases HDL catabolism, leading to increased HDL-C. Therefore, ANGPTL3 functions as a central regulator of systemic lipid partitioning, coordinating hepatic lipid secretion and peripheral lipid uptake [10].

Loss-of-function variants of *ANGPTL3* have been associated with familial combined hypolipidemia, characterized by decreased plasma triglycerides, LDL-C, and HDL-C. These variants, including E40K and S17X, impair protein secretion or disrupt lipase inhibition, thereby enhancing LPL activity and accelerating triglyceride clearance. Importantly, carriers of such mutations demonstrate a significantly reduced risk of coronary artery disease, independent of traditional lipid-lowering therapy. This has positioned ANGPTL3 as both a biomarker and a promising therapeutic target for cardiovascular prevention [11].

Pharmacological inactivation of ANGPTL3 using monoclonal antibodies (e.g., evinacumab) or RNA interference has produced profound reductions in LDL-C and triglyceride levels in clinical trials, even in patients with homozygous familial hypercholesterolemia who lack functional LDL receptors. These

findings underscore the biochemical centrality of ANGPTL3 in lipoprotein metabolism and highlight its therapeutic potential in refractory dyslipidemias. Collectively, ANGPTL3 represents a nexus between hepatic lipid biosynthesis, peripheral metabolism, and cardiovascular risk modulation [12].

Apolipoprotein B (APOB): Biochemical Functions and Genetic Variations

Apolipoprotein B (APOB) is a key structural and functional protein central to lipoprotein assembly and lipid transport. The *APOB* gene, located on chromosome 2p24.1, encodes two primary isoforms: APOB-100 and APOB-48, generated through tissue-specific RNA editing. APOB-100, synthesized in the liver, is essential for the assembly and secretion of very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL), while APOB-48, produced in the intestine, facilitates chylomicron formation. These apolipoproteins serve as ligands for the low-density lipoprotein receptor (LDLR), mediating cellular cholesterol uptake and maintaining plasma lipid balance. From a biochemical standpoint, APOB functions as a scaffold protein, embedding within the phospholipid monolayer of lipoproteins to stabilize lipid particles during secretion and transport [13].

The synthesis of APOB is tightly coordinated with lipid availability and microsomal triglyceride transfer protein (MTP) activity. During VLDL assembly in hepatocytes, nascent APOB undergoes co-translational lipidation, a process critical for the formation of secretion-competent particles. Mutations that impair this process can result in defective lipoprotein secretion, leading to hypobetalipoproteinemia, whereas increased APOB production contributes to hyperapobetalipoproteinemia and atherogenic dyslipidemia. The latter condition is characterized by elevated LDL particle number and small dense LDL fractions, both of which exhibit enhanced arterial wall penetration and oxidative susceptibility, promoting atherogenesis [14].

Genetic polymorphisms in *APOB* have been extensively associated with variations in lipid profiles and coronary artery disease (CAD) risk. Common variants, such as rs693 (XbaI), rs1042031 (EcoRI), and the signal peptide polymorphism (SP Ins/Del), have been linked to altered LDL-C levels and impaired LDL receptor binding. For instance, the rs693 variant has been correlated with increased total cholesterol and LDL-C concentrations in multiple populations, while rs1042031 influences LDL particle affinity for the LDLR. These polymorphisms affect APOB structure and function, contributing to interindividual variability in lipoprotein metabolism and cardiovascular susceptibility [15].

Furthermore, elevated plasma APOB concentrations have emerged as one of the strongest biochemical predictors of atherosclerotic cardiovascular disease. Unlike LDL-C, which measures cholesterol content, APOB directly reflects the number of circulating atherogenic particles. Thus, individuals with discordantly high APOB relative to LDL-C exhibit heightened CAD risk, underscoring the clinical importance of APOB as both a biomarker and therapeutic target. Recent advances in antisense oligonucleotide therapies, such as mipomersen, demonstrate the feasibility of reducing APOB synthesis to achieve profound LDL-C lowering and mitigate CAD progression. Together, these findings highlight APOB's dual biochemical and genetic significance in lipid homeostasis and coronary pathology [16].

Mechanistic Links Between ANGPTL3 and APOB in Lipoprotein Regulation

The regulation of plasma lipoproteins represents a tightly coordinated biochemical network in which *ANGPTL3* and *APOB* play synergistic yet distinct roles. ANGPTL3 modulates extracellular lipid processing through inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL), whereas APOB governs intracellular lipoprotein assembly and secretion. Together, these molecules influence the concentration and composition of circulating triglyceride-rich and cholesterol-rich lipoproteins. Biochemically, ANGPTL3-mediated suppression of LPL decreases the hydrolysis of triglyceride-rich VLDL particles, many of which contain APOB-100 as their structural core protein. Consequently, this inhibition leads to reduced clearance and prolonged plasma residence time of VLDL and LDL particles, fostering an atherogenic lipid profile [17].

In hepatocytes, the interplay between ANGPTL3 activity and APOB metabolism is further evidenced by hepatic lipid availability. ANGPTL3 enhances hepatic triglyceride secretion by preserving substrate pools required for VLDL assembly. Increased hepatic triglyceride flux stabilizes nascent APOB, preventing its proteasomal degradation and promoting secretion of large, triglyceride-rich VLDL

particles. Conversely, loss-of-function mutations in *ANGPTL3* lead to reduced lipid supply for APOB lipidation, thereby diminishing VLDL and LDL production. This biochemical mechanism explains why carriers of ANGPTL3 loss-of-function variants exhibit hypobetalipoproteinemia, a phenotype typically associated with decreased APOB levels [18].

Beyond lipid synthesis, ANGPTL3 exerts regulatory effects on APOB-containing lipoprotein metabolism in peripheral tissues. By inhibiting LPL, ANGPTL3 delays the catabolism of VLDL remnants, resulting in increased exposure of APOB-containing particles to oxidative modification. These modified lipoproteins, such as oxidized LDL (oxLDL), can be avidly internalized by macrophage scavenger receptors, promoting foam cell formation and vascular inflammation. Hence, ANGPTL3 indirectly modulates the atherogenic potential of APOB-containing lipoproteins through systemic control of lipase activity and lipid turnover [19].

Emerging genetic studies reveal additive and possibly epistatic interactions between *ANGPTL3* and *APOB* polymorphisms in determining plasma lipid traits. Individuals harboring ANGPTL3 loss-of-function variants concurrently with deleterious APOB alleles demonstrate attenuated hyperlipidemic phenotypes, suggesting compensatory biochemical regulation. This genetic interplay highlights a coordinated lipid-regulatory axis where ANGPTL3 influences lipid substrate availability, while APOB dictates lipoprotein assembly efficiency. Targeting this axis offers a mechanistically grounded therapeutic strategy to modulate atherogenic lipoprotein burden in coronary artery disease [20].

Genetic Polymorphisms of ANGPTL3 Associated with Coronary Artery Disease

Genetic variations in the *ANGPTL3* gene significantly influence lipid metabolism and coronary artery disease (CAD) susceptibility through modulation of lipase activity and lipid transport. Located on chromosome 1p31.3, *ANGPTL3* contains multiple single nucleotide polymorphisms (SNPs) that impact its expression or protein function. Loss-of-function (LOF) variants, such as **E40K (rs2075291)** and **S17X (rs12130333)**, have been consistently associated with lower plasma triglyceride, LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C) concentrations. Mechanistically, these variants impair ANGPTL3 secretion or reduce its inhibitory activity on lipoprotein lipase (LPL) and endothelial lipase (EL), resulting in enhanced clearance of triglyceride-rich lipoproteins. Individuals harboring these variants exhibit a markedly reduced risk of atherosclerotic cardiovascular disease, highlighting ANGPTL3 as a natural protective factor [21].

A pivotal genome-wide association study by Musunuru et al. (2010) identified the E40K variant as one of the strongest genetic determinants of plasma lipid levels across multiple ethnic populations. Carriers of the minor allele displayed up to a 35% reduction in triglycerides and 10–15% lower LDL-C levels compared to noncarriers. Subsequent studies, including the Global Lipids Genetics Consortium meta-analysis, confirmed the cardioprotective nature of *ANGPTL3* LOF variants and demonstrated their independent association with reduced CAD risk, even after adjustment for conventional risk factors [22].

Conversely, certain intronic and regulatory *ANGPTL3* variants have been linked to elevated lipid levels and increased CAD susceptibility. For example, the promoter polymorphism **rs1748195 (C>T)** has been associated with higher serum triglyceride concentrations and subclinical atherosclerosis, particularly among individuals with metabolic syndrome. Functional assays indicate that this variant enhances hepatic *ANGPTL3* transcription, leading to stronger inhibition of LPL and subsequent hypertriglyceridemia. Moreover, epigenetic modifications in the *ANGPTL3* promoter region, influenced by dietary lipids and insulin signaling, can modulate gene expression and alter CAD risk in a gene-environment-dependent manner [23].

Several population-based studies have provided further insights into *ANGPTL3* polymorphisms. In the Italian InCHIANTI cohort, rare coding variants were associated with reduced carotid intima-media thickness, supporting the anti-atherogenic role of reduced ANGPTL3 activity. Similarly, a study in Chinese and Iranian cohorts identified associations between rs2131925 and altered triglyceride levels, reflecting the cross-ethnic relevance of *ANGPTL3* variants. These observations underscore that both coding and non-coding variations in *ANGPTL3* contribute to the complex genetic architecture underlying CAD susceptibility through direct effects on lipid metabolism and vascular inflammation

[24].

Overall, *ANGPTL3* polymorphisms represent functionally diverse molecular determinants that either predispose to or protect against CAD, depending on their impact on lipase inhibition and lipid turnover. Understanding these genetic variants enhances our ability to stratify cardiovascular risk and supports the clinical translation of ANGPTL3 inhibition as a targeted therapeutic strategy for dyslipidemia-driven CAD [25].

Genetic Polymorphisms of APOB and Their Impact on Lipid Profile and CAD

Common *APOB* polymorphisms modulate the biochemistry of atherogenic lipoproteins by altering APOB structure, RNA processing, or regulatory elements that influence expression. Among the most frequently studied are the XbaI variant **rs693** (exon 26), the EcoRI variant **rs1042031** (exon 29), and the signal-peptide insertion/deletion **rs17240441** in the 5′ region. These variants have been repeatedly linked—though with some heterogeneity across ancestries—to shifts in total cholesterol, LDL-C, triglycerides, and LDL particle characteristics. Mechanistically, changes in APOB's primary sequence or its translational handling can affect co-translational lipidation and LDL receptor (LDLR) affinity, thereby modifying particle number and residency time in plasma, both central determinants of coronary atherogenesis. [26]

The **rs693 (XbaI)** variant has shown associations with higher LDL-C and total cholesterol and with CAD across diverse cohorts, consistent with an effect on the abundance or behavior of APOB-containing particles. Population studies (including case–control designs in Mexican and other groups) report that carriers of the risk allele tend to display an atherogenic lipid profile, although effect sizes vary with background diet, adiposity, and metabolic status—highlighting gene–environment interplay. From a biochemical viewpoint, increased LDL particle number (apoB) rather than cholesterol content per particle may be the proximate driver of risk, aligning observed rs693 effects with heightened LDL particle flux into the arterial wall. [27]

The **rs1042031 (EcoRI)** polymorphism, a synonymous change in exon 29, has nonetheless been associated with lipid traits and CAD in several ethnicities, possibly via linkage disequilibrium with functional sites or subtle effects on mRNA structure and translation. Contemporary studies evaluating rs1042031 alongside other lipid-gene variants underscore its contribution to multi-locus risk profiles; in cardiometabolic clusters, carriers may exhibit higher LDL-C and triglycerides and increased CAD odds. While not uniformly replicated, the aggregate evidence supports a modest but directionally consistent relationship between rs1042031 and atherogenic dyslipidemia, warranting inclusion in polygenic models of CAD susceptibility. [28]

For the **signal-peptide Ins/Del (rs17240441)**, early investigations yielded mixed lipid associations; however, larger vascular-outcome cohorts have linked genotype classes to myocardial infarction risk. A plausible biochemical mechanism is that altered signal-peptide length impacts APOB translocation and early secretory pathway kinetics, subtly changing VLDL assembly efficiency and the downstream cascade that sets LDL particle number. Given the small per-allele effects, phenotypic expression likely depends on concurrent metabolic stressors (e.g., insulin resistance) that increase hepatic VLDL output and amplify the lipoprotein consequences of the Ins/Del genotype. [29]

In contrast to common SNPs with modest effects, **familial defective apolipoprotein B-100 (FDB)** most classically **R3500Q**—produces a large, clearly pathogenic impact by diminishing LDLR binding affinity of LDL particles. This defect elevates LDL-C from early life and accelerates coronary disease, offering a powerful human model that validates APOB-LDLR interactions as causal in atherosclerosis. Although rare in the general population, FDB illustrates how single amino-acid substitutions at key receptor-binding loci reshape the biochemical fate of LDL and the tempo of plaque development. [30]

Clinically, these genetic observations dovetail with a robust body of evidence that **apoB concentration** (a count of atherogenic particles) outperforms LDL-C and non-HDL-C for predicting atherosclerotic cardiovascular disease. Because each VLDL/IDL/LDL particle contains exactly one APOB molecule, apoB integrates diverse genetic and metabolic inputs—such as those from *APOB* polymorphisms—into a single, mechanistically proximate risk metric. Accordingly, discordance analyses show that when

LDL-C is "normal" but apoB is elevated, cardiovascular risk tracks with apoB, reinforcing the centrality of particle number as the biochemical driver of atherogenesis. [31]

Combined Effects of ANGPTL3 and APOB Variants in Coronary Pathophysiology

From a medical biochemistry vantage, the most coherent way to integrate *ANGPTL3* and *APOB* genetics is to track their net effect on **apoB particle number** and **triglyceride-rich lipoprotein (TRL) metabolism**—the immediate biochemical drivers of atherogenesis. Loss-of-function (LOF) in *ANGPTL3* lowers triglycerides and LDL-C and, crucially, **reduces circulating apoB-containing particle burden**, shifting the arterial lipid flux downward; conversely, *APOB* risk alleles (or qualitative receptor-binding defects, e.g., FDB) tend to elevate apoB particle number or residence time. In aggregate, these alleles act largely **additively** on the proximate phenotype—apoB particle exposure over time—so individuals inheriting *ANGPTL3* LOF alongside *APOB* risk variants often display a **biochemical attenuation** of the *APOB*-driven atherogenic signature, whereas concurrence of *ANGPTL3* risk variants with *APOB* risk alleles amplifies particle burden and endothelial lipoprotein influx. Formal epistasis remains sparsely demonstrated, but convergent evidence supports **dose–response additivity** on apoB and TRL remnants as the dominant model. [32–34].

Human genetic and interventional data align with this framework. In large cohorts, *ANGPTL3* LOF associates with **lower odds of atherosclerotic cardiovascular disease**, mirroring the lipid changes; pharmacologic antagonism of ANGPTL3 (e.g., **evinacumab**) produces **apoB and LDL-C reductions even in LDLR-deficient states**, indicating that ANGPTL3 acts upstream of LDLR-mediated clearance and can biochemically counterbalance *APOB*-mediated particle generation. Clinically, this means that in carriers of *APOB*-raising variants (or phenotypes with elevated apoB), **ANGPTL3 inhibition** can subtract from the same causal pathway—apoB particle flux—thereby mitigating genetically programmed risk. Such triangulation (human LOF, randomized therapy, and lipid/apoB change) strengthens the causal chain connecting these loci to CAD via particle number biology. [32–33].

At the population level, **polygenic risk scores (PRS)** for CAD integrate hundreds to thousands of lipid-associated variants—including signals near *APOB* and *ANGPTL3*—and stratify risk to magnitudes comparable to monogenic hypercholesterolemia. PRS work mechanistically because many alleles converge on **apoB particle production and processing**; thus, combinations of small-effect *APOB*-proximal alleles with protective *ANGPTL3* alleles (or vice versa) shift the composite score and the biochemical phenotype in predictable directions. Modern PRS frameworks and updated Global Lipids Genetics Consortium (GLGC) catalogs—now spanning **>900 lipid loci**—reinforce that most of the inherited CAD risk attributable to lipids is funneled through **apoB-centric pathways**, with *ANGPTL3* and *APOB* representing canonical, biochemically tractable anchors in that network. [35–36,38].

For clinical translation, the **discordance paradigm** is essential: when LDL-C and apoB disagree, **risk tracks with apoB**. This principle provides a unifying readout for the combined genetic load at *ANGPTL3*, *APOB*, and other lipid loci. Practically, patients with *APOB*-raising genotypes but concurrent *ANGPTL3* LOF may show "normal" LDL-C yet **elevated (or normalized) apoB** depending on allele balance; conversely, concurrent risk alleles can yield **disproportionately high apoB** despite only modest LDL-C elevation. Therefore, measuring apoB captures the **net biochemical result** of multi-locus inheritance and guides targeted therapy—intensifying LDL/apoB lowering and, where appropriate, considering **ANGPTL3-directed therapy** to neutralize residual particle overproduction driven by *APOB* and allied pathways. [34,37–38].

Conclusion

The integration of genetic and biochemical evidence clearly demonstrates that variations in *ANGPTL3* and *APOB* profoundly influence lipid metabolism and the pathophysiology of coronary artery disease (CAD). These genes operate at distinct yet convergent points in lipid regulation—ANGPTL3 modulating extracellular lipase activity and triglyceride hydrolysis, and APOB determining the intracellular assembly and secretion of atherogenic lipoproteins. Their coordinated effects shape the plasma concentration, size, and composition of lipoprotein particles, particularly those carrying apoB, which are the direct mediators of atherogenesis.

From a molecular biochemistry perspective, loss-of-function mutations in *ANGPTL3* reduce lipoprotein particle number, conferring natural protection against atherosclerosis by lowering triglycerides and LDL-C. In contrast, deleterious *APOB* variants or overexpression increase circulating apoB particles and promote lipid retention within the arterial wall. The biochemical interplay between these genes defines an apoB-centered metabolic axis that governs endothelial lipid exposure, oxidative modification, and foam cell formation — processes central to plaque initiation and progression.

Recognizing the joint contribution of *ANGPTL3* and *APOB* polymorphisms advances our understanding of the genetic heterogeneity of CAD and emphasizes the necessity of interpreting lipid disorders through an integrative genomic lens. Clinically, these insights reinforce the superiority of apoB particle concentration over LDL-C as a marker of residual risk and identify ANGPTL3 inhibition as a promising therapeutic strategy to offset genetically determined apoB overproduction.

Ultimately, the relationship between *ANGPTL3* and *APOB* highlights the unity of biochemical and genetic mechanisms underlying coronary atherogenesis. As precision medicine continues to evolve, incorporating these genetic markers into individualized risk models and therapeutic algorithms will enable more accurate stratification of cardiovascular risk and optimized lipid-lowering interventions. Understanding their molecular synergy not only clarifies the biochemical basis of CAD but also illuminates novel pathways for prevention and treatment in the genomic era

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