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Genetics of Lipid Traits and Relationship to Coronary Artery Disease

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Abstract

Despite the critical importance of plasma lipoproteins in the development of atherosclerosis, varying degrees of evidence surround the causal associations of lipoproteins with coronary artery disease (CAD). These causal contributions can be assessed by employing genetic variants as unbiased proxies for lipid levels. A relatively large number of low-density lipoprotein cholesterol (LDL-C) variants strongly associate with CAD, confirming the causal impact of this lipoprotein on atherosclerosis. Although not as firmly established, genetic evidence supporting a causal role of triglycerides (TG) in CAD is growing. Conversely, high-density lipoprotein cholesterol (HDL-C) variants not associated with LDL-C or TG have not yet been shown to be convincingly associated with CAD, raising questions about the causality of HDL-C in atherosclerosis. Finally, genetic variants at the *LPA* locus associated with lipoprotein(a) [Lp(a)] are decisively linked to CAD, indicating a causal role for Lp(a). Translational investigation of CAD-associated lipid variants may identify novel regulatory pathways with therapeutic potential to alter CAD risk.

Keywords

Genetics; GWAS; Mendelian randomization; Lipids; LDL-C; Lipoprotein(a); TG; HDL-C; PCSK9; SORT1; TRIB1; Apolipoprotein A5; Apolipoprotein C3; Lipoprotein lipase; Cholesterol ester transfer protein; Coronary artery disease; Lipid Traits

Introduction

Lipoprotein metabolism plays a central role in atherosclerotic cardiovascular disease by influencing arterial lipid accumulation and atherosclerotic plaque formation [1]. According to the current paradigm, low-density lipoproteins (LDL) and certain triglyceride (TG)-rich lipoproteins enter the arterial intima, where they are taken up by macrophages to form foam cells and also initiate an inflammatory process, both of which form the basis for initiation and progression of atherosclerotic plaques [1]. In contrast, high-density lipoproteins (HDL)

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are believed to facilitate the efflux of cholesterol from arterial macrophages and transport it back to the liver for excretion in a process known as reverse cholesterol transport, thus protecting against atherosclerosis [2]. Consistent with this paradigm, observational epidemiology data demonstrate positive associations of LDL cholesterol (LDL-C) and TG and an inverse association of HDL cholesterol (HDL-C) with coronary artery disease (CAD) risk [3]. Furthermore, randomized controlled trials of LDL-C-lowering interventions, primarily but not exclusively statins, demonstrate consistent reductions in cardiovascular events and strongly support a causal role for LDL in CAD [4]. Conversely, trials of TG-lowering interventions, mostly fibrates, have been less consistent [5], and trials of HDL-C-raising therapies, namely niacin and cholesterol ester transport protein (CETP) inhibitors, have been negative [6], raising questions about the causal role of TG-rich lipoproteins and HDL in atherosclerosis.

Questions about the causal relationship of plasma biomarkers such as lipids with atherosclerosis can be answered by Mendelian randomization, an analytic technique that utilizes the random assignment of genetic variants specific to a biomarker to decipher that biomarker's contribution to a disease process [7]. A large number of genetic variants have been found to be associated with LDL-C, HDL-C, and TG (Figure 1) [8**, 9*]. Genetic variants associated with both plasma lipid traits and CAD offer insight into novel mechanisms by which lipoproteins may causally influence atherosclerosis [8**, 10**]. Here we briefly discuss methods used to investigate the association of lipid variants with CAD and then review loci associated with major plasma lipid traits and their relationship with CAD (Table 1).

Mendelian Randomization to Assess Potential Causality

Monogenic disorders of lipoprotein metabolism due to rare mutations of major effect have provided important insights into lipoprotein metabolism and its relationship to cardiovascular disease [11]. As one example, the Mendelian disorder familial hypercholesterolemia caused by mutations in the LDL receptor (LDLR) gene established the primacy of LDLR in mediating LDL catabolism and confirmed that genetically elevated LDL-C levels are causal for CAD [12]. In the last several years, common variants of relatively small effect have been exploited in large-scale unbiased genome-wide association studies (GWAS) of plasma lipid traits [8**]. These studies identify SNPs that are associated with trait variation at a stringent significance level to correct for multiple comparisons, usually $p < 5 \times 10^{-8}$ [13]. .

An important genetic technique to evaluate the causal nature of biomarkers on disease is Mendelian randomization (Figure 2) [14]. This approach uses the independent assortment of genetic alleles from parents to offspring to construct natural randomized experiments: genetic proxies for intermediate biomarkers are evaluated for association with later disease hypothesized to be caused by the intermediate biomarkers [7]. These studies can overcome confounding and reverse causation by employing genetic variants that are specific to each biomarker and not associated with other disease risk factors [7, 14]. In the case of lipids and cardiovascular disease, Mendelian randomization can powerfully contribute to the evidence for or against the causal effect of plasma lipids on atherosclerosis.

LDL-C Loci and Association with CAD

LDL-C is widely recognized as a causal risk factor for atherosclerotic cardiovascular disease, in large part due to several known Mendelian disorders associated with extremely high LDL-C and premature CAD [15], as well as abundant clinical trial evidence showing that LDL-C lowering reduces cardiovascular risk [4]. Mendelian randomization studies on LDL-C and GWAS for CAD have substantially reinforced the evidence that LDL-C plays a

strong causal role in CAD. Data converge from two directions: 1) GWAS for LDL-C have identified multiple loci that were then shown to be very strongly associated with CAD; and 2) GWAS for CAD have independently identified multiple loci that are also genome-wide significantly associated with LDL-C.

With regard to the first paradigm, there have been several reports involving progressively larger sample sizes of GWAS for lipid traits, culminating in a report by Teslovich et al. for the Global Lipids Genetics Consortium enumerating 95 independent lipid loci, of which 37 were significantly associated with LDL-C at $p < 5 \times 10^{-8}$ [8**]. In a subsequent analysis, the subset of 13 'pure' LDL-C loci, which were not associated with TG or HDL-C at $p < 0.01$, were studied for association with myocardial infarction (MI) in up to 19,139 cases and 50,812 controls [16**]. Of these loci, 23% were concordantly associated with MI at $p < 5 \times 10^{-4}$, i.e. variants associated with higher LDL-C were associated with increased risk of MI and vice versa. A genetic score that combined the 13 'pure' LDL-C variants was significantly associated with MI at $p = 2 \times 10^{-10}$ with an effect size similar to that predicted by observational epidemiology.

With regard to the second paradigm, a recently published GWAS meta-analysis for CAD, incorporating 63,746 cases and 130,681 controls, detailed 46 independent loci that were genome-wide significant for association with CAD [10**]. Remarkably, ~20% of these loci were genome-wide significantly associated with LDL-C in the direction concordant with CAD risk. This discovery of a major enrichment of 'LDL-C genes' in an experiment focused on genes associated with CAD further confirms the indisputable causal relationship between LDL-C levels and CAD. We review here major loci genome-wide significantly associated with both LDL-C and CAD but not with HDL-C or TG.

Critical steps in LDL-C metabolism and their relationship to CAD have been informed by human genetic studies involving the LDLR and its ligand apolipoprotein (apo) B. Loss-of-function mutations in the *LDLR* gene cause familial hypercholesterolemia, an autosomal codominant Mendelian disorder characterized by high LDL-C and premature CAD [11]. Certain mutations in the receptor binding region of the *APOB* gene impair binding of LDL to LDLR and cause a disorder clinically similar to familial hypercholesterolemia called familial defective apoB-100 (FDB), which is also associated with premature CAD [17, 18]. Alternatively, in the condition familial hypobetalipoproteinemia, rare mutations in other regions of the *APOB* gene truncate the apoB protein, reducing LDL-C levels and decreasing CAD risk [19]. Consistent with these studies of Mendelian disorders and rare variants are GWAS: common variation in the *LDLR* and *APOB* genes is also significantly associated with LDL-C levels and these same variants are associated with CAD risk in the expected direction [8**, 10**, 16**].

The story of the adenosine triphosphate-binding cassette (ABC), subfamily G, member 5 and 8 genes on chromosome 2p21 is similar. The ABCG5 and 8 proteins form a heterodimer that transports cholesterol and dietary sterols into bile canaliculi and the gut lumen for excretion [20]. Rare loss-of-function mutations in both alleles of either ABCG5 or 8 cause sitosterolemia, an autosomal recessive disorder characterized by increased circulating levels of plasma sterols and LDL-C and elevated risk of premature CAD [21]. Genetic variants that produce a nonfunctional heterodimer result in increased intestinal plant sterol and cholesterol absorption and decreased sterol excretion, causing a downregulation of hepatic LDLRs and an elevation in LDL-C [22]. More recently, GWAS identified common variants at this locus as significantly associated with LDL-C levels and CAD risk in the 'right' direction [10**], indicating that modest variation in ABCG5/8 expression or function influences LDL-C levels, which in turn influence cardiovascular risk [8**, 16**].

Another variation of this story is that of *PCSK9*, which encodes proprotein convertase subtilisin/kexin type 9. Initially, linkage analysis in families with autosomal dominant hypercholesterolemia who lacked mutations in *LDLR* and *APOB* revealed mutations in *PCSK9* that appeared to be causal [23]. Later, a low-frequency gain-of-function variant was identified as the cause of high LDL-C and early CAD [24]. Sequencing of the *PCSK9* gene in subjects at the low end of the LDL-C distribution yielded two low-frequency loss-of-function nonsense variants in *PCSK9* in individuals of African descent and another low-frequency loss-of-function missense variant in individuals of European descent that were confirmed to be associated with low LDL-C [25]. Strikingly, these variants were definitively shown to be associated with substantially reduced risk of CAD [26]. These findings led to extensive study of the physiology of PCSK9 and LDL metabolism, showing that the PCSK9 protein is secreted by the liver and then binds an extracellular domain of LDLR to target it for lysosomal degradation and prevent it from resurfacing to the cell membrane [27, 28]. Ultimately, common variants at the *PCSK9* locus were also found to be significantly associated with both LDL-C and CAD [10**, 16**, 29], indicating that modest *PCSK9* variation influences CAD risk. In recent randomized trials, monoclonal PCSK9 antibodies have been shown to substantially reduce LDL-C in patients with familial and primary hypercholesterolemia alone and added to a statin without serious adverse events [30, 31*, 32]. PCSK9 is thus an example of a molecular intervention first identified by genetic studies and now being developed as a promising LDL-lowering medication.

One entirely novel pathway uncovered by common variant GWAS is a locus on chromosome 1p13 that was among the first GWAS loci for LDL-C [33] and independently among the first GWAS loci for CAD [33], findings that have held up in the most recent large GWAS meta-analyses for both lipids [8**] and CAD [10**]. Homozygosity for the most significant risk allele, which has a minor allele frequency of about 25% in Caucasians, is associated with a mean 16 mg/dL reduction in LDL-C and an approximate 40% decrease in CAD risk [33, 34]. The causal variant creates a new transcription factor binding site that appears to substantially increase hepatic transcription of several genes including the causal gene *SORT1*, which encodes a protein called sortilin [35**]. Experimental data indicate that genetically increased hepatic sortilin decreases LDL-C by two mechanisms: 1) reduced hepatic production of VLDL, the precursor of LDL, possibly by shunting VLDL from the secretory pathway in the Golgi to the lysosome for degradation [35**]; and 2) increased hepatic uptake of LDL by binding extracellular LDL-C at the hepatic cell membrane and transporting it to the lysosome [36]. This common noncoding variant ascertained by unbiased genetic approaches led to the discovery of a previously unknown modulator of LDL-C metabolism and genetic determinant of CAD risk and a potential therapeutic target to reduce LDL-C and risk for CAD.

Another gene locus identified independently by GWAS for both LDL-C [8**] and angiographic CAD [37] is that involving the *ABO* blood group gene on chromosome 9q34. The glycosyltransferase enzyme encoded by this gene not only influences blood group ABO antigen but also has a host of other protein targets, including von Willebrand factor [38]. While the *ABO* polymorphism is clearly associated with both LDL-C and MI, the molecular bases of these associations remain unknown. *ABO* is a highly pleiotropic locus that has significant associations with a wide range of traits, making it a poor instrument for Mendelian randomization. Its association with MI could well extend beyond LDL-C to include von Willebrand factor and endothelial adhesion markers, such as intercellular adhesion molecule-1, P-selectin, E-selectin, and platelet glycoproteins [39].

In sum, rare Mendelian disorders of LDL-C, low-frequency variants of relatively large effect on LDL-C, and common variants of relatively small effect on LDL-C have all provided a consistent message: genetically increased LDL-C is associated with increased risk of CAD

and genetically decreased LDL-C is associated with decreased risk of CAD. This body of data strongly confirms the causal role of LDL-C in CAD.

Loci Associated with Both LDL-C and TG and Relationship to CAD

Pleiotropic genetic variants that are significantly associated with more than one lipid trait may provide insight into molecular mechanisms of lipoprotein metabolism but are less useful as instruments to assess the causality of specific lipoproteins in atherosclerosis. Nevertheless, it is of interest to review the loci associated with both LDL-C and TG, and their relationship to CAD.

ApoE was identified more than three decades ago as a key regulator of lipoprotein metabolism, in part due to the condition of familial dysbetalipoproteinemia, also called Type III hyperlipoproteinemia. ApoE has three common coding variants in humans: apoE3 (the most common 'wild-type'), apoE4 (Cys112Arg), and apoE2 (Arg158Cys) [40]. Familial dysbetalipoproteinemia is caused by homozygosity for the apoE2 variant. ApoE functions as a ligand for hepatic lipoprotein receptors and mediates the uptake of remnant lipoproteins by the liver [41]. Heterozygosity for the apoE ε2 allele is associated with lower LDL-C levels and reduced CAD risk [40], while heterozygosity for the apoE ε4 allele is associated with higher LDL-C levels and elevated CAD risk [42]. One hypothesis for the higher incidence of CAD in individuals with the apoE ε4 allele involves the higher binding affinity of apoE ε4 for LDLR, which may downregulate LDLR and so decrease clearance of LDL-C [41].

A locus on chromosome 11 is among the most significantly associated with TG concentrations ($p = 7 \times 10^{-240}$) and is also genome-wide significantly associated with both LDLC and HDL-C [8**]. Importantly, this variant is also significantly associated with CAD and was identified on GWAS for CAD [10**]. This complex locus includes the apolipoprotein genes *APOA1*, *APOC3*, *APOA4*, and *APOA5*. Both apoC-III and apoA-V are known to play functional roles in TG metabolism [43]. These two apolipoproteins circulate on chylomicrons and VLDL [44, 45] but have opposite effects: apoC-III inhibits lipoprotein lipase (LPL), promotes VLDL production, and slows hepatic VLDL uptake [43, 46, 47] whereas apoA-V accelerates LPL-mediated hydrolysis of TG-rich VLDL, blocks VLDL production, and facilitates VLDL clearance [48, 49, 50]. Overexpression of the two genes also has contrasting results: *APOC3* increases serum TG [49], while *APOA5* reduces serum TG in mice [51]. While this locus clearly has important implications for human biology and possibly for translational therapeutics, its pleiotropy prevents straightforward conclusions about the causality of specific lipoprotein particles in atherogenesis.

A novel pathway identified by GWAS of lipid traits and of CAD is related to the tribbles homolog 1 (*TRIB1*) gene. Common variants at this locus are significantly associated with TG levels ($p = 3 \times 10^{-55}$), and also with LDL-C ($p = 5 \times 10^{-29}$) in the same direction and with HDL-C ($p = 5 \times 10^{-18}$) in the opposite direction [8**]. A meta-analysis affirmed the genome-wide significant association of this locus with MI [52]. Importantly, the same variant at this locus was found on GWAS meta-analysis to be genome-wide significantly associated with CAD [10**]. The tribbles 1 protein encoded by *TRIB1* is expressed in multiple tissues including the liver. Overexpression of *TRIB1* in liver in mice reduces plasma TG through decreased production of VLDL, while *TRIB1* knockout mice demonstrate elevated TG [53*]. Additional mechanistic work is required to reveal the exact pathways by which hepatic *TRIB1* expression influences lipid levels. The discovery of the robust association of the *TRIB1* locus with all major plasma lipid traits and CAD suggests that upregulation of *TRIB1* could be a novel therapeutic target for dyslipidemia and atherosclerosis.

The angiopoietin-like 3 protein (*ANGPTL3*) locus is noteworthy for its known functional impact on TG metabolism [54]. Common variants at the ANGPTL3 locus are significantly associated with TG ($p = 9 \times 10^{-43}$) and with LDL-C ($p = 2 \times 10^{-17}$) in the same direction [8**]. Exome sequencing of a kindred with familial hypolipidemia demonstrated that ANGPTL3 deficiency leads to reduced TG, LDL-C, and HDL-C levels [55*]. Mechanistic studies demonstrate that the ANGPTL3 protein reversibly blocks the LPL-mediated breakdown of TG-rich particles 56, 57] and is most active after eating [58]. Despite its clear role in metabolism of TG-rich lipoproteins and its association with both TG and LDL-C, the *ANGPTL3* locus has not yet been convincingly shown to be associated with CAD [8**]. If larger studies show that the ANGPTL3 locus is associated with CAD, this protein could become a promising therapeutic target for inhibition.

The genetic loci in this section may impact CAD risk largely through LDL-C, which has been convincingly demonstrated to be a strong causal risk factor. This is particularly likely for apoE, which is most strongly associated with LDL-C. However, the two CAD-associated variants that are orders of magnitude more significantly associated with TG than other lipids, namely those near *APOA5*/*APOC3* and *TRIB1*, may be acting predominantly through TG-rich particles to promote the development of atherosclerotic disease. Future genetic and translational work may uncover a link between atherosclerosis and promising variants, such as *ANGPTL3*, that have strong candidate mechanisms for contributing to atherosclerosis despite the lack of a GWAS significant relationship with CAD.

Loci Associated with TG but not LDL-C and Relationship to CAD

Genetic loci that are associated with TG and not LDL-C are better instruments to address the question of whether TG or TG-rich lipoproteins contribute causally to CAD. Overall, a formal well-powered Mendelian randomization analysis of ‘pure’ TG loci and their relationship to CAD has yet to be performed. One locus that is significantly associated with TG but not LDL-C and is also significantly associated with CAD is the *LPL* gene on chromosome 8. The variant rs264 is associated negatively with TG levels ($p = 5 \times 10^{-46}$), positively with HDL-C ($p = 7 \times 10^{-48}$), and inversely with CAD (i.e. protective) ($p = 3 \times 10^{-9}$) [10**]. Alternatively, another variant (rs12678919) is associated positively with TG ($p = 2 \times 10^{-115}$), inversely with HDL-C ($p = 1 \times 10^{-97}$), and positively with CAD ($p = 7 \times 10^{-4}$) [8**]. The LPL enzyme hydrolyzes TG in TG-rich lipoproteins and is therefore prominent in tissues requiring free fatty acids for energy production or storage, including the heart, skeletal muscle, and adipose tissue [59, 60]. The association of the *LPL* locus with both TG and CAD strongly implicates TG-rich lipoproteins as causal in CAD, and the directionality suggests that upregulation of LPL would be expected to not only reduce TG levels but also to reduce risk of CAD.

Another locus that is associated with TG ($p = 3 \times 10^{-8}$) and HDL-C ($p = 3 \times 10^{-9}$) but not LDL-C is insulin receptor substrate 1 (IRS1) [8**]. The common variant at this locus is associated with CAD at $p = 4 \times 10^{-4}$, which is suggestive but does not meet genome-wide significance [8**]. IRS1 encodes a protein that transmits signals from insulin and insulin-like growth factor receptors to intracellular pathways [61], and it is additionally associated with type 2 diabetes and insulin resistance [62]. If larger studies confirm an association between IRS1 and CAD, this would support a causal role of TG-rich lipoproteins but could also be confounded by the variant’s effect on insulin signalling.

N-acetyltransferase 2 (NAT2) is a locus associated solely with TG [8**]. The common variant at this locus is associated with CAD at $p = 2 \times 10^{-5}$, which, although not genome-wide significant, may indicate a novel mechanism contributing to atherosclerotic risk [8**].

The NAT2 gene encodes an acetylator enzyme that metabolizes drugs and carcinogens [63], but its functional connection to TG metabolism and CAD is unknown.

Variation at the *LPL*, *IRS1*, and *NAT2* loci may contribute to atherogenesis through modulation of plasma TG-rich lipoproteins levels. While awaiting more research and analysis of genetic loci specific to TG, the current data surrounding these variants suggest that TG may be causally related to atherosclerotic cardiovascular disease.

HDL-C Loci and Association with CAD

Plasma levels of HDL-C are strongly inversely associated with CAD risk, a finding consistently observed in numerous prospective studies in many different parts of the world [3]. However, the causal relationship between HDL and CAD remains in substantial doubt. While a detailed review of the Mendelian disorders of HDL is beyond the scope of this review, it is notable that the three known Mendelian causes of extremely low HDL-C—structural mutations in the gene *APOA1* and loss-of-function mutations in the genes *ABCA1* and *LCAT*—are not associated with a clear increased risk of CAD [64]. Conversely, the only known Mendelian cause of extremely elevated HDL-C—loss-of-function mutations in both alleles of CETP—has not been shown to be associated with protection from CAD [64]. Thus, unlike for LDL, the Mendelian HDL disorders have not laid a clean foundation for a causal relationship between HDL and atherosclerosis.

Therefore, low-frequency and common variants associated with HDL-C are particularly important as tools to ascertain the potential causality of HDL using Mendelian randomization. In notable contrast with LDL-C, it appears that the majority of genetic loci that are genome-wide significantly associated with HDL-C but not TG or LDL-C lack significant association with CAD. The largest GWAS for lipids confirmed 12 HDL-C loci from previous GWAS in greater than 100,000 individuals and discovered 36 novel loci for HDL-C, which altogether explained 25 to 30% of the genetic variance in HDL-C [8**]. However, none of these SNPs were associated with CAD at genome-wide significance, and only 1 locus specific to HDL-C, Krüppel-like factor 14 (*KLF14*), was associated with CAD at $p < 0.001$ ($p = 9 \times 10^{-4}$) [8**].

The largest Mendelian randomization study of variants associated with HDL-C and their association with CAD to date was published by Voight et al. in 2012 [16**]. One aspect of this study was a detailed investigation of a low-frequency loss-of-function variant in the *LIPG* gene that encodes the endothelial lipase enzyme, which hydrolyzes HDL phospholipids resulting in accelerated HDL catabolism and reduced HDL-C levels [65]. Early sequencing studies in subjects with high HDL-C identified a missense variant Asn396Ser with a minor allele frequency around 1.5% in Caucasians [66], and a subsequent study confirmed that this variant is a definite loss-of-function variant significantly associated with higher HDL-C levels [67]. In the report by Voight et al., this variant was confirmed to be associated with a genome-wide significant 5.4 mg/dL increase in HDL-C and to have no association with TG, LDL-C, or non-lipid risk factors, making it an excellent tool for Mendelian randomization [16**]. In an adequately powered sample size of 20,913 MI cases and 95,407 controls, there was no evidence that this variant was associated with the expected reduction in CAD risk.

In the same report, the authors further probed a subset of common variants at 14 ‘pure’ HDL-C loci that were not associated with other lipid traits and similarly found that none of these variants were associated with CAD risk [16**]. In addition, a genetic score, which combined these 14 ‘pure’ HDL-C variants to increase statistical power, demonstrated no association with CAD risk. Overall, these results substantively challenge the hypothesis that

HDL-C levels are causally related to CAD. On the other hand, certain HDL loci do have some evidence for association with CAD that may become more robust with increased sample sizes [8**]. Therefore, unlike for LDL-C, the molecular mechanism by which HDL-C is modulated may ultimately determine its impact on CAD risk.

Results from other Mendelian randomization studies that focus on specific genes generally support this conclusion. A low-frequency variant near the gene for lecithin-cholesterol acyltransferase (*LCAT*), an enzyme that promotes HDL-C maturation by converting surface free cholesterol into core-forming cholesterol ester [65], was associated with reduced HDL-C but not with elevated CAD risk in 54,500 individuals [68*]. Similarly, variants near the gene for hepatic lipase (*LIPC*), which hydrolyzes TG in large HDL to form small, dense HDL [65], were associated with higher HDL-C but no difference or even a paradoxical increase in ischemic cardiovascular disease [69, 70]. Additionally, a Mendelian randomization analysis found that SNPs near the gene for adenosine triphosphate-binding cassette protein A1 (*ABCA1*), which facilitates cholesterol efflux from cells to apoA-I [65], were associated with HDL-C levels but not with ischemic heart disease [71]. However, variants in *ABCA1* that were not associated with HDL-C were associated with CAD in prospective studies [72].

One of the strongest loci in the human genome at which common variation influences HDL-C levels is *CETP* [73, 74]. CETP transfers cholesterol esters from HDL to TG-rich lipoproteins in exchange for TG [65], critically impacting HDL metabolism. Three common CETP variants associated with increased HDL-C levels were found to be (weakly) associated with decreased CAD risk [73, 74]. However, these variants are also associated with reduced LDL-C levels [8**, 9*], so the possibility that they affect CAD through changes in LDL-C levels cannot be excluded. Potent pharmacologic inhibitors of CETP, two of which are in late-stage clinical development, not only raise HDL-C levels but also reduce LDL-C levels [75].

Interestingly, a recent GWAS meta-analysis for CAD in 63,746 cases and 130,681 controls found that 4 of the 46 independent loci genome-wide significantly associated with CAD were also genome-wide significantly associated with HDL-C [10**]. However, all were genome-wide significantly associated with LDL-C and/or TG in addition to HDL-C. Indeed, the only locus reported as specific to HDL-C, ankyrin repeat and sterile alpha motif domain containing 1A (*ANKS1A*), did not meet genome-wide significance ($p < 5 \times 10^{-8}$) for its association with HDL-C ($p = 1.65 \times 10^{-5}$). Therefore, unlike the plethora of ‘pure’ LDL-C loci discovered in GWAS for CAD, the number of ‘pure’ HDL-C loci remains essentially zero.

As a whole, evidence from GWAS and Mendelian randomization are consistent with the concept that HDL-C levels per se may not be causally related to the development of atherosclerotic cardiovascular disease. However, existing genetic data do not exclude the hypothesis that the efficiency of an HDL-C metabolic pathway, such as cholesterol efflux, may be related to CAD risk.

Genetics of Lipoprotein(a) and Association with CAD

Lp(a) structurally resembles an LDL-C particle that has one molecule of apolipoprotein B100 and an additional protein, apo(a), covalently bound to apoB-100 [76*]. Plasma levels of Lp(a) are very highly heritable, in the range of 90-95% [77]. Apo(a) is encoded by the LPA gene on chromosome 6q26-27, which evolved from the plasminogen gene and has a variable number of kringle IV type 2 (KIV-2) repeats determined by copy number variation in the KIV-2 domain [78]. Common variants at *LPA* are significantly associated with plasma

Lp(a) levels and are the most important genetic determinants of plasma Lp(a) levels [76*]. These variants are also strongly associated with CAD and indeed the *LPA* locus was among the earliest identified by GWAS for CAD [8**, 10**, 16**]. The modest association of the *LPA* locus with LDL-C likely stems from the ability of high Lp(a) levels to cause an overestimation of LDL-C calculated by the Friedewald equation [79].

The common LPA variants rs10455872 and rs3798220 have been shown to be strongly and independently associated with higher Lp(a) levels, reduced KIV-2 copy number, smaller Lp(a) size, and increased CAD risk [80]. The rs10466872 SNP is located on a noncoding intron of the *LPA* gene, while the rs3798220 SNP is a missense variant leading to an amino acid substitution in the apo(a) protease domain [81]. A meta-analysis demonstrated that the risk alleles of these variants increase CAD risk by 42% and 57%, respectively [82*]. GWAS and Mendelian randomization studies similarly found that the rs3798220 SNP is genome-wide significantly associated with CAD [8**, 16**]. Both Lp(a) variants are also associated with other atherosclerotic conditions, specifically large artery ischemic stroke, peripheral artery disease, and abdominal aortic aneurysm, but not with diseases less related to atherosclerosis, such as cardioembolic stroke, small vessel stroke, intracranial aneurysm, and venous thromboembolism [83]. Thus the genetic data are extremely strong in support of Lp(a) being a causal risk factor for CAD.

The mechanisms by which Lp(a) promotes atherothrombosis remain to be fully elucidated. Apo(a) is homologous to plasminogen in that it contains kringles and a protease domain, although it has only two of plasminogen's five kringles and its protease domain is inactive [76*]. Thus, two mechanisms potentially linking Lp(a) to atherosclerosis are its ability to substitute for LDL-C in the acceleration of macrophage foam cell formation and its action to prevent fibrinolysis by blocking the conversion of plasminogen to plasmin [81]. A third possible pathway involves oxidized phospholipids carried by Lp(a) [84], which have been shown to induce apoptosis in macrophages experiencing endoplasmic reticulum stress [85].

Overall, current genetic evidence supports a robust causal role for Lp(a) in atherosclerotic cardiovascular disease. Additional translational work is required to elucidate the exact mechanisms by which Lp(a) contributes to atherosclerosis and to identify Lp(a)-related therapeutic targets that can alter CAD risk.

Conclusions

Genetic studies of lipids have helped to elucidate the causal mechanisms underlying the development of cardiovascular disease by confirming previously discovered pathways, revealing new clinical targets, and questioning traditional risk factors. GWAS and Mendelian randomization results strongly support a causal association of both LDL-C and Lp(a) with atherosclerotic cardiovascular disease. In the case of TG, investigation of genetic variants specific to TG or analysis of the independent TG effect on pleiotropic variants' associations with CAD would strengthen the currently hypothesized causality of TG in CAD risk. Finally, GWAS and Mendelian randomization studies have failed to demonstrate that the majority of variants specific to HDL-C are genome-wide significantly associated with MI risk, suggesting that HDLC per se may not have a causal relationship to CAD. Instead, there may be a better causal relationship between the functionality of HDL and the flux of cholesterol through the HDL-mediated reverse cholesterol transport pathway [6]. Exome sequencing has revealed more low-frequency and rare variants associated with plasma lipid traits that can be tested for association with CAD. Ultimately translational investigation into the functional consequences of CAD-associated lipid variants is essential for elucidating pathways linking lipids to atherosclerosis and for identifying novel clinical targets to alter cardiovascular disease risk.

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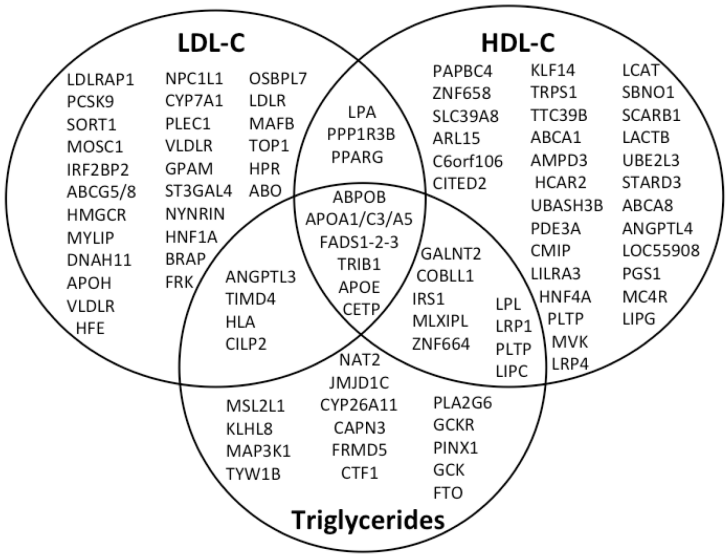

Figure 1.
Known Genetic Loci Genome-Wide Significantly Associated with LDL-C, HDL-C, and Triglycerides ($p < 5 \times 10^{-8}$).

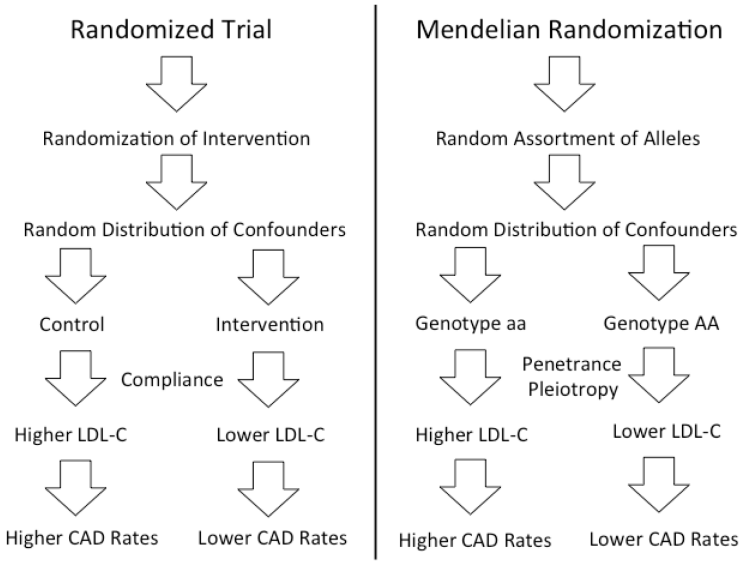

Figure 2.
Comparison of Randomized Trials and Mendelian Randomization Studies.

Table 1

Associations of Lipid Genetic Variants with Coronary Artery Disease

Gene	Chr.	SNP	Primary lipid association	Other genome-wide significant lipid associations	Genome-wide significant association with higher CAD
SNPs associated most significantly with LDL-C					
LDLR	19	rs1122608	+LDL-C	+TC	Yes
ApoB	2	rs515135	+LDL-C	+TC	Yes
ABCG5/8	2	rs6544713	+LDL-C	+TC	Yes
PSCK9	1	rs11206510	+LDL-C	+TC	Yes
SORT1	1	rs602633	+LDL-C	+TC	Yes
ABO	9	rs579459	+LDL-C	+TC	Yes
ApoE	19	rs2075650	+LDL-C	+TG, −HDL-C, +TC	Yes
SNPs associated most significantly with TG					
ApoA1/C3/A5	11	rs964184	+TG	+LDL-C, −HDL-C, +TC	Yes
TRIB1	8	rs2954029	+TG	+LDL-C, −HDL-C, +TC	Yes
ANGPTL3	19	rs7255436	+TG	+LDL-C, +TC	No
NAT2	8	rs1495741	+TG	+TC	No
SNPs associated equally with TG and HDL-C					
LPL	8	rs264	+TG, −HDL-C	none	Yes
IRS1	2	rs2972146	+TG, −HDL-C	none	No
SNPs associated most significantly with HDL-C					
KLF14	7	rs4731702	−HDL-C	none	No
LIPG	18	rs61755018	−HDL-C	−TC	No
LCAT	16	rs16942887	−HDL-C	none	No
LIPC	15	rs1532085	−HDL-C	−TG, −TC	No
ABCA1	9	rs1883025	−HDL-C	−TC	No
CETP	16	rs3764261	−HDL-C	+LDL-C, −TG, +TC	No
ANKS1A	6	rs3822921	−HDL-C[a]	none	No
SNPs associated most significantly with Lp(a)					
LPA	6	rs2048327	Lp(a)	none	Yes

Genome-wide significant $p < 5 \times 10^{-8}$; + or − indicates directionality of change with which CAD allele is associated.

[a] Association is not genome-wide significant.