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Human genetic insights into lipoproteins and risk of cardiometabolic disease

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Abstract

Purpose of review—Human genetic studies have been successfully used to identify genes and pathways relevant to human biology. Using genetic instruments composed of loci associated with human lipid traits, recent studies have begun to clarify the causal role of major lipid fractions in risk of cardiometabolic disease.

Recent findings—The causal relationship between LDL cholesterol and coronary disease has been firmly established. Of the remaining two major traits, recent studies have found that HDL cholesterol is not likely to be a causal particle in atherogenesis and have instead shifted the causal focus to triglyceride-rich lipoproteins. Subsequent results are refining this view to suggest that triglycerides themselves might not be causal but instead may be a surrogate for the causal cholesterol content within triglyceride-rich lipoproteins. Other studies have used a similar approach to address the association between lipids and lipoproteins and risk of type 2 diabetes. Beyond genetic variation in the target of statin medications (*HGMCR)*, reduced LDL cholesterol associated with multiple genes encoding current or prospective drug targets associated with increased diabetic risk. In addition, genetically lower HDL cholesterol and lower triglycerides appear to increase risk of type 2 diabetes.

Summary—Results of these and future human genetic studies are positioned to provide substantive insights into the causal relationship between lipids and human disease and should highlight mechanisms with important implications for our understanding of human biology and future lipid-altering therapeutic development.

Keywords

Human genetics; lipoprotein metabolism; coronary artery disease; type 2 diabetes

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Conflicts of Interest

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Introduction

Several pragmatic motivating factors continue to encourage ongoing human genetic studies focused on resolving the complete genetic architecture of plasma lipid traits. First, every locus identified for these traits has the potential – when resolved to causal variant(s) and gene(s) – to contribute to our understanding of the biology underlying lipoprotein metabolism in humans[1, 2]. Importantly, some loci will emerge from these studies as potential targets for therapeutically manipulating plasma lipids[3, 4]. Finally, resolving the full contribution of rare and common alleles to these traits also has substantial implications for genetic diagnoses in the dawning era of precision medicine.

Considerable progress has already been made in identifying genetic loci that are robustly associated with variability in plasma lipids. In the most recent genome-wide association study (GWAS) by the Global Lipids Genetics Consortium which included nearly 187,000 individuals, investigators identified 157 independent genetic loci which were significantly associated with at least one of four major lipids and lipoproteins: total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG)[1]. Two observations may lead some to speciously question the utility of performing additional gene mapping studies to identify new loci and resolve existing association signals: current studies only explain a small fraction of the population variance in the trait despite already substantial sample sizes (leading some to wonder if this is the correct approach), and each novel locus is typically associated with increasingly smaller effects on the trait (otherwise the association would likely have been previously identified). If the goal of trait mapping is to understand biology and identify therapeutic targets, however, the variance attributable to either individual or the sum of all loci together is irrelevant. For example, a common variant (rs17238484) in the HMG Co-A Reductase gene (*HMGCR*) has a very modest effect on LDL cholesterol in the population (1.08 mg/dL lower LDL cholesterol for each copy of the minor allele)[5]. Similarly, gain of function variants in *PCSK9* were identified as a cause of autosomal dominant hypercholesterolemia[3]; these specific variants contribute to nearly zero population variance due to their rarity. Despite this, *HMGCR* and *PCSK9* are key elements in the biological pathways of cholesterol biosynthesis and metabolism and substantially effect plasma LDL levels when therapeutically manipulated[6, 7].

Multiple approaches can be used to identify additional loci underlying plasma lipids and to refine the signals within existing loci. In addition to merely increasing sample size (the most obvious means of augmenting statistical power), recent studies have leveraged denser imputation panels[8, 9], studied populations with different or unique genetics[10, 11], and ascertained families with extreme phenotypes[12–14], all of which have enriched our understanding of human lipoprotein metabolism.

In addition to furthering our knowledge of basic human biology, human genetics has the potential to identify causal mechanisms for disease. From a therapeutic perspective it is obviously critical to understand the relationship between genetic loci and risk of disease, as therapeutic manipulation of plasma lipid levels is not a goal unto itself but rather a means to

alter disease. Several studies, reviewed below, have contributed to our understanding of lipoprotein metabolism and risk of cardiometabolic disease.

Human genetic insights into the role of plasma lipids and coronary artery disease

Over 50 years ago, investigators at the Framingham study identified plasma cholesterol as a "factor of risk" for the development of coronary heart disease[15]; subsequent basic science investigation[16] and clinical trial results[6] have firmly established elevated LDL cholesterol as a causal risk factor for coronary artery disease. Prior studies identifying genetic variation in *PCSK9* that associated with both altered LDL cholesterol and risk of coronary disease[4] have successfully accelerated therapeutic development[17, 18] (e.g. *PCSK9* loss of function variants); several recent human genetic studies have contributed to this effort of identifying genetic variation that associates with lipid traits and risk of coronary disease.

Genetic variation modulating LDL cholesterol and risk of coronary artery disease

Nioi et al[19] undertook such a study in which the investigators started with whole genome sequencing (WGS) in 2,636 Icelanders. They imputed the variants discovered by WGS into 119,146 participants with lipid measurements and identified several correlated single nucleotide polymorphisms (SNPs) that were strongly associated with non-HDL cholesterol and which spanned the genes *ASGR1* and *ASGR2*, encoding subunits of the asialoglycoprotein receptor. Nioi et al observed that an intron of *ASGR1* had low WGS coverage likely due to local sequence context and performed additional sequencing in this low coverage area. This led to the discovery of a 12-bp intronic deletion in *ASGR1* which appeared to be responsible for the statistical association between this locus and non-HDL cholesterol. The 12-bp deletion, which causes aberrant mRNA splicing and the subsequent synthesis of a truncated ASGR1 protein, was significantly associated with reduced levels of non-HDL cholesterol (-15.3 mg/dL for carriers), which appeared to be primarily due to lower LDL cholesterol in carriers (-12.5 mg/dL for carriers). Beyond an association with non-HDL cholesterol, the investigators also demonstrated that carriers had a 34% reduced risk of coronary disease compared with non-carriers. Somewhat intriguingly, the 12-bp *ASGR1* deletion was associated with a reduction in coronary disease risk beyond what one might expect based solely on the magnitude of the decrease in non-HDL cholesterol (this comparison was performed using genetic associations in other genes affecting non-HDL cholesterol and coronary disease risk), suggesting there may be non-lipid atheroprotective effects associated with loss of ASGR1.

In addition to identifying potentially novel targets, a human genetic approach can be used to support existing therapeutic targets. We used this type of approach to demonstrate that loss of function mutations in the Niemann-pick C1-like 1 (*NPC1L1*) gene were associated with a reduced risk of coronary artery disease[20]. Despite being approved for therapeutic use in many countries, there was substantial uncertainty over whether or not ezetimibe (a non-statin medication that reduces plasma LDL cholesterol by inhibiting NPC1L1) would reduce coronary artery disease [21, 22]. To address this question, we sequenced *NPC1L1* and found

that approximately 1 in every 650 individuals carried a loss of function allele in *NPC1L1*. These individuals, when compared with those who did not carry *NPC1L1* inactivating mutations, had approximately 12 mg/dL lower LDL cholesterol and 53% reduced risk of coronary artery disease[20]. A large randomized control trial later demonstrated that therapeutic inhibition of NPC1L1 with ezetimibe resulted in lower LDL cholesterol and a significant reduction in risk of recurrent coronary disease[23]. Other protein-altering variants associated with LDL cholesterol and risk of coronary artery disease are listed in Table1.

Are HDL cholesterol and Triglycerides causal factors for coronary artery disease?

Beyond LDL cholesterol, human genetics has the potential to identify lipid phenotypes that are causally related to coronary disease and genes and/or pathways that associate with both causal fractions and risk of disease. While LDL cholesterol has been accepted as a causal factor for coronary artery disease, the epidemiological data implicating HDL and TG as causal factors was unclear. HDL and TG are negatively correlated in population studies and both are correlated with coronary artery disease[24]. The relationship between TG and coronary disease typically disappears, however, when HDL cholesterol is accounted for[24], leading some prior studies to conclude that HDL cholesterol was the likely causal fraction of the two. These types of studies are prone to confounding, however, and approaches using the technique of Mendelian randomization have attempted to address this question for HDL and triglyceride rich lipoproteins (TRL)[25–27]. While previous studies have typically focused on SNPs identified in GWAS studies (where most SNPs are of common frequency in the population), Helgadottir et al[28] recently extended this approach to include low-frequency and rare variants that they discovered to associate with lipid phenotypes. First, using the same lipid associations as were used in Nioi et al[19] discussed above, Helgadottir et al created a genetic risk score (GRS) of associated variants for each of the following: non-HDL cholesterol (defined as HDL cholesterol subtracted from total cholesterol), LDL cholesterol, HDL cholesterol, and triglycerides. They then examined the association between these GRSs and risk of coronary artery disease. This analysis demonstrated a clear causal signal for LDL cholesterol with risk of disease and, in keeping with prior studies, also found no evidence to support a causal role of HDL cholesterol in risk of coronary disease.

In contrast to prior studies, however, the results from Helgadottir et al further support a causal role of non-HDL cholesterol (distinct from that of LDL cholesterol) as opposed to triglycerides themselves. Non-HDL cholesterol is, by definition, all of the cholesterol content in the plasma not carried in HDL and includes cholesterol in very low density lipoproteins, intermediate density lipoproteins, chylomicrons, and lipoprotein(a). Thus, the results of Helgadottir et al may be suggesting that the causal role of TRLs is related to the cholesterol content of the fraction and not the triacylglycerols themselves. While perhaps a subtle distinction, clarifying this mechanistically may have important implications for future therapeutic development. For example, approaches focused on modifying the triacylglycerol content in TRLs may not be as effective for treating coronary disease as lowering total TRL concentration (which would reduce both triacylglycerols and cholesterol content in the plasma). Further development in this area is needed to clarify these points.

Current human genetic evidence is coalescing around lipoprotein lipase (LPL) as one potential mechanism for altering TRL concentration in a manner that alters coronary disease risk, beginning with the observation that loss of function mutations in *APOC3* were associated with lower concentrations of TRLs and reduced risk of coronary disease[29, 30]. *APOC3* is an endogenous inhibitor of LPL, the latter of which functions to hydrolyze triglycerides present in circulating lipoproteins, thereby lowering plasma TRL concentration. As an endogenous inhibitor of LPL, loss of APOC3 function should result in higher LPL activity and loss of an endogenous activator of LPL should result in the opposite effects. Do et al.[31], after sequencing the exomes of nearly 10,000 individuals with and without coronary disease discovered loss of function variants in apolipoprotein A-V (*APOA5*) – an endogenous LPL activator – were associated in a manner that one would expect, where loss of APOA5 associated with higher triglycerides and increased risk of coronary disease. These observations appear to be somewhat generalizable, as loss of function in an additional endogenous LPL inhibitor (*ANGPTL4*) was recently found to associate with reductions in plasma TRLs and lower risk of coronary disease[32]. Similarly, these findings are not limited just to regulatory proteins, as loss and gain of function variants in the *LPL* gene itself are associated with the *a priori* expected alteration in TRL concentration and risk of coronary disease[32]. This allelic series in LPL and its endogenous regulators, in which loss and gain of gene function modulate both the biomarker and risk of disease in the expected direction of effect, increases the confidence in this pathway as a potential target for therapeutic intervention[33]. A partial listing of other protein-altering variants associated with altered plasma lipids and risk of coronary artery disease is provided in Table 1.

Human genetic insights into the role of plasma lipids and type 2 diabetes

HMG Co-A Reductase, LDL cholesterol, and risk of diabetes

As mentioned above, the relationship between plasma lipid traits and coronary disease has been long recognized. Similarly, prior studies have found a relationship between increased risk of type 2 diabetes with reduced HDL cholesterol and elevated TG concentrations (without any such observation for LDL cholesterol)[34–36]. Despite the epidemiological lack of association between LDL cholesterol and risk of diabetes, therapeutic trials of statin medications (which lower LDL cholesterol) have consistently shown an increased risk of diabetes among statin treated patients compared with those on placebo[37]. Whether or not the increased diabetic risk was due to an off-target effect of statins, an artifact of study design, chance, or numerous other possibilities was debated until a study by Swerdlow et al[5] provided human genetic evidence to suggest it was due to an *on-target* effect of statins. By studying genetic variation in *HMGCR*, Swerdlow et al were able to demonstrate that the same genetic variants in *HMGCR* that associated with reduced LDL cholesterol were also associated with increased risk of type 2 diabetes. This result suggests that the increased risk of type 2 diabetes associated with statin use is not due to an off-target effect from statins but rather from inhibiting *HMGCR.* Furthermore, their result suggests that further efforts to make statins more specific in an attempt to reduce diabetes risk may be futile[38]. Importantly, these same variants are also associated with lower risk of coronary artery disease, suggesting that even though statin therapy appears to increase the risk of type 2

diabetes by inhibiting *HMGCR,* the net LDL lowering effect of this mechanism is atheroprotective.

Genetic variation modulating LDL cholesterol and risk of type 2 diabetes

The degree to which this effect extended to other LDL-lowering mechanisms remained unclear until a recent study by Lotta et al.[39] In this study, genetic variants in multiple LDL-associated genes were evaluated for an effect on both type 2 diabetes and coronary artery disease. Similar to Swerdlow, Lotta et al. found that the genetic variants in *HMGCR* that were associated with lower LDL cholesterol were also associated with lower coronary artery disease risk but higher risk of type 2 diabetes. Beyond *HMGCR,* Lotta et al. observed similar effects for genetic variants in *NPC1L1, ABGC5/ABGC8*, and *PCSK9* (all current or potential lipid modifying targets) in which the variants associated with lower LDL cholesterol were also associated with lower coronary artery disease risk but increased risk of type 2 diabetes. The finding that LDL lowering not just by *HMGCR* and statins but also by multiple drug target genetic mechanisms is associated with increased risk of type 2 diabetes has important implications for therapeutic development and future clinical trials.

Are HDL cholesterol and Triglycerides causal factors for type 2 diabetes?

Beyond drugs focused on LDL cholesterol, will therapies focused on TRLs also affect risk of type 2 diabetes? White et al. recently employed a Mendelian randomization technique to estimate the causal role of lipid and lipoproteins in risk of diabetes[40]. Using genetic instruments consisting of SNPs associated with LDL cholesterol, HDL cholesterol, and TGs, the investigators calculated the association between genetically higher lipid levels and both risk of coronary artery disease and type 2 diabetes. Consistent with the results of Lotta et al, White and colleagues found that genetically elevated LDL cholesterol was associated with reduced risk of type 2 diabetes. Beyond LDL cholesterol, they found that both genetically elevated HDL cholesterol and TG were associated with reduced risk of type 2 diabetes (see Table 2). The result that genetically elevated TG concentrations associate with reduced risk of type 2 diabetes is surprising[41] and, due to important implications if valid, deserves further study.

It is important to note, however, that the approach of White et al. is designed to study the biomarker generally and does not necessarily apply to specific genetic mechanisms. Unlike LDL cholesterol, for which Lotta et al. demonstrated to be causally related to type 2 diabetes across multiple genetic mechanisms, the HDL cholesterol and TG association with type 2 diabetes may be dependent on specific mechanisms. For example, while genetically elevated HDL cholesterol in general appears to be protective for type 2 diabetes, Clapham et al. did not find an association for diabetes with a null allele in *ANGPTL8* that associated with higher HDL cholesterol[42], although it is interesting to note that there was a non-significant trend toward protection. Similarly, while the evidence is clear that HDL cholesterol in general is not causal for coronary disease, specific mechanisms that alter HDL cholesterol may affect risk of disease[13]. Finally, we found that a loss of function variant in *ANGPTL4* which associated with reduced TRL and lower risk of coronary artery disease was also nominally associated with a reduction in risk of diabetes[32], raising the possibility that

certain mechanisms resulting in reduced TRL (such as modulators of LPL activity, for example) may protect against both coronary artery disease as well as type 2 diabetes.

Conclusion

With advances in the scale and content of human genetic studies, our view of the genetic architecture underlying plasma lipid biology is coming increasingly into focus. Armed with these tools, investigators are expanding the focus of these studies in new and creative ways to investigate the net cardiometabolic effects of lipoprotein metabolism. Results of these and future studies are poised to provide important insights into the causal relationship between these traits and disease and should highlight important mechanisms for novel therapeutic development.

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References

1. Global Lipids Genetics Consortium. Willer CJ, Schmidt EM, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013; 45:1274–1283. [PubMed: 24097068]
2. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010; 466:707–713. [PubMed: 20686565]
3. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003; 34:154–156. [PubMed: 12730697]
4. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006; 354:1264–1272. [PubMed: 16554528]
5. Swerdlow DI, Preiss D, Kuchenbaecker KB, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet. 2015; 385:351–361. [PubMed: 25262344]
6. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366:1267–1278. [PubMed: 16214597]
7. Dadu RT, Ballantyne CM. Lipid lowering with PCSK9 inhibitors. Nature reviews. Cardiology. 2014; 11:563–575. [PubMed: 24958078]
8. Surakka I, Horikoshi M, Magi R, et al. The impact of low-frequency and rare variants on lipid levels. Nat Genet. 2015; 47:589–597. [PubMed: 25961943]
9. Iotchkova V, Huang J, Morris JA, et al. Discovery and refinement of genetic loci associated with cardiometabolic risk using dense imputation maps. Nat Genet. 2016; 48:1303–1312. [PubMed: 27668658]
10. Tang CS, Zhang H, Cheung CY, et al. Exome-wide association analysis reveals novel coding sequence variants associated with lipid traits in Chinese. Nature communications. 2015; 6:10206.
11. Sidore C, Busonero F, Maschio A, et al. Genome sequencing elucidates Sardinian genetic architecture and augments association analyses for lipid and blood inflammatory markers. Nat Genet. 2015; 47:1272–1281. [PubMed: 26366554]
12. Ripatti P, Ramo JT, Soderlund S, et al. The Contribution of GWAS Loci in Familial Dyslipidemias. PLoS Genet. 2016; 12:e1006078. [PubMed: 27227539]

13. Zanoni P, Khetarpal SA, Larach DB, et al. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. Science. 2016; 351:1166–1171. [PubMed: 26965621]

14. Khetarpal SA, Schjoldager KT, Christoffersen C, et al. Loss of Function of GALNT2 Lowers High-Density Lipoproteins in Humans, Nonhuman Primates, and Rodents. Cell metabolism. 2016; 24:234–245. [PubMed: 27508872]

15. Kannel WB, Dawber TR, Kagan A, et al. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961; 55:33–50. [PubMed: 13751193]

16. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986; 232:34–47. [PubMed: 3513311]

17. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372:1489–1499. [PubMed: 25773378]

18. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372:1500–1509. [PubMed: 25773607]

*19. Nioi P, Sigurdsson A, Thorleifsson G, et al. Variant ASGR1 Associated with a Reduced Risk of Coronary Artery Disease. N Engl J Med. 2016; 374:2131–2141. This impressive study used whole genome sequencing and imputation into nearly 400,000 individuals to find variants in ASGR1 that associate with lower non-HDL cholesterol and reduced risk of coronary disease, also demonstrating the size and scale of studies that will likely be required to find similar protective signals in the future. [PubMed: 27192541]

20. Stitziel NO, Won HH, Morrison AC, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med. 2014; 371:2072–2082. [PubMed: 25390462]

21. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008; 358:1431–1443. [PubMed: 18376000]

22. Krumholz HM. Emphasizing the burden of proof: The American College of Cardiology 2008 Expert Panel Comments on the ENHANCE Trial. Circ Cardiovasc Qual Outcomes. 2010; 3:565–567. [PubMed: 21081745]

23. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372:2387–2397. [PubMed: 26039521]

24. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009; 302:1993–2000. [PubMed: 19903920]

**25. Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013; 45:1345–1352. This was the first study to use multivariable Mendelian randomization to demonstrate that triglyceride-rich lipoproteins are causal for coronary artery disease. [PubMed: 24097064]

26. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015; 36:539–550. [PubMed: 24474739]

27. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012; 380:572–580. [PubMed: 22607825]

28. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. Nat Genet. 2016; 48:634–639. [PubMed: 27135400]

29. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014; 371:32–41. [PubMed: 24941082]

30. Crosby J, Peloso GM, Auer PL, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014; 371:22–31. [PubMed: 24941081]

*31. Do R, Stitziel NO, Won HH, et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature. 2015; 518:102–106. This was the first large-scale sequencing study to show a burden of rare mutations in a gene (APOA5) associated with triglyceride-rich lipoproteins and risk of coronary disease. [PubMed: 25487149]

32. Stitziel N, Stirrups K, Masca N, Erdmann J. Coding Variation in ANGPTL4, LPL, and SVEP1 and the Risk of Coronary Disease. N Engl J Med. 2016; 374:1134–1144. [PubMed: 26934567]

33. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. Nat Rev Drug Discov. 2013; 12:581–594. [PubMed: 23868113]

34. Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. Am J Epidemiol. 1989; 130:1101–1108. [PubMed: 2589303]

35. Lyssenko V, Jonsson A, Almgren P, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med. 2008; 359:2220–2232. [PubMed: 19020324]

36. Wilson PW, Meigs JB, Sullivan L, et al. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med. 2007; 167:1068–1074. [PubMed: 17533210]

*37. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; 375:735–742. This was the first genetic study to explore the causal relationship between statins and type 2 diabetes, finding that lower LDL cholesterol associated with genetic variation in HMGCR was also associated with increased risk of diabetes. [PubMed: 20167359]

38. Frayling TM. Statins and type 2 diabetes: genetic studies on target. Lancet. 2015; 385:310–312. [PubMed: 25262342]

**39. Lotta LA, Sharp SJ, Burgess S, et al. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. JAMA. 2016; 316:1383–1391. This study found that increased risk of type 2 diabetes associated with lower LDL cholesterol across multiple genes encoding current or prospective lipid drug targets. [PubMed: 27701660]

40. White J, Swerdlow DI, Preiss D, et al. Association of Lipid Fractions With Risks for Coronary Artery Disease and Diabetes. JAMA cardiology. 2016; 1:692–699. [PubMed: 27487401]

41. Saleheen D, Rader DJ, Voight BF. Disentangling the Causal Association of Plasma Lipid Traits and Type 2 Diabetes Using Human Genetics. JAMA cardiology. 2016; 1:631–633. [PubMed: 27487162]

42. Clapham KR, Chu AY, Wessel J, et al. A null mutation in ANGPTL8 does not associate with either plasma glucose or type 2 diabetes in humans. BMC endocrine disorders. 2016; 16:7. [PubMed: 26822414]

43. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009; 361:2518–2528. [PubMed: 20032323]

44. Lim ET, Wurtz P, Havulinna AS, et al. Distribution and medical impact of loss-of-function variants in the Finnish founder population. PLoS Genet. 2014; 10:e1004494. [PubMed: 25078778]

*45. Stitziel NO, Stirrups KE, Masca NG, et al. Coding Variation in ANGPTL4, LPL, and SVEP1 and the Risk of Coronary Disease. N Engl J Med. 2016; 374:1134–1144. This study demonstrated that genetic variation across multiple genes leading to loss and gain of LPL function associated with risk and protection of coronary artery disease, respectively, showing a titratable effect on disease for lipoprotein lipase and its endogenous regulators. [PubMed: 26934567]

46. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007; 357:2109–2122. [PubMed: 17984165]

47. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365:2255–2267. [PubMed: 22085343]

48. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014; 371:203–212. [PubMed: 25014686]

49. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 367:2089–2099. [PubMed: 23126252]

50. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014; 384:626–635. [PubMed: 25131982]

Key points

- Human genetic studies have identified hundreds of loci associated with plasma lipid traits which have informed our understanding of the biology underlying lipoprotein metabolism in humans
- Several specific genetic mechanisms that alter plasma lipids and risk of coronary artery disease have now been identified, highlighting potential therapeutic targets
- Current studies support a causal role in coronary artery disease for low-density lipoprotein cholesterol in addition to cholesterol found in lipoproteins other than high-density lipoprotein cholesterol
- Lowering low-density lipoprotein cholesterol through multiple mechanisms increases risk for type 2 diabetes
- Genetically elevated high-density lipoprotein cholesterol and triglycerides are associated with lower risk of type 2 diabetes although this relationship may be dependent on specific mechanisms

Table 1

Protein-altering variants associated with plasma lipids and risk of coronary artery disease

Gene	Protein altering variant(s)	Main plasma lipid alteration	Associated risk of coronary artery disease	Reference
LDLR	Multiple loss of function	Increased LDL cholesterol	Increased	[31]
PCSK9	p.R46L, p.Y142*, p.C697*	Reduced LDL cholesterol	Reduced	[4]
NPC1L1	Multiple loss of function	Reduced LDL cholesterol	Reduced	[20]
LPA	p.I1837M	Increased lipoprotein(a)	Increased	[43]
LPA	Multiple loss of function	Reduced lipoprotein(a)	Reduced	[44]
ASGR1	Multiple loss of function	Reduced non-HDL cholesterol	Reduced	[19]
APOA5	Multiple loss of function	Increased TRL	Increased	[31]
ANGPTL4	p.E40K, multiple loss of function	Reduced TRL	Reduced	[45]
APOC3	Multiple loss of function	Reduced TRL	Reduced	[29, 30]
LPL	p.D36N	Increased TRL	Increased	[45]
LPL	p.S447*	Reduced TRL	Reduced	[45]

LDL = low-density lipoprotein; HDL = high-density lipoprotein; TRL = triglyceride-rich lipoproteins

Table 2

Associations for plasma lipid fractions and risk of cardiometabolic disease

Lipid fraction	Risk of coronary artery disease: genetic estimate	Risk of coronary artery disease: RCT evidence	Risk of type 2 diabetes: genetic estimate	Risk of type 2 diabetes: RCT evidence
Lower LDL cholesterol	Reduced[26–28]	Reduced[6, 23]	Increased[39, 40]	Increased[37]
Higher HDL cholesterol	Null[26–28]	Null[46–49]	Reduced[40]	No evidence
Lower Triglycerides	Reduced[25, 26]	No direct evidence but some indirect evidence for reduced risk[50]	Reduced[40]	No evidence

LDL = low-density lipoproteins; HDL = high-density lipoproteins; Genetic estimate refers to Mendelian randomization studies including multiple genetic variants affecting the trait; RCT evidence = results from randomized control trials of drugs focused primarily on modifying that lipid trait.