Published in final edited form as:
Curr Cardiovasc Risk Rep. 2010 October ; 4(6): 461–468. doi:10.1007/s12170-010-0131-7.

Clinical Implications of Lipid Genetics for Cardiovascular Disease

Alanna Strong and **Daniel J. Rader**
University of Pennsylvania School of Medicine, 654 BRB2/3, 421 Curie Boulevard, Philadelphia, PA 19104, USA

Daniel J. Rader: rader@mail.med.upenn.edu

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in the developed world. Epidemiologic data support a strong relationship of atherosclerotic cardiovascular disease (ASCVD) with both elevated low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C). The study of the human genetics of plasma lipid traits, both rare Mendelian disorders as well as common variants, has illuminated multiple genes and pathways involved in the regulation of LDL-C and HDL-C levels. Mendelian disorders of extremes of LDL-C and Mendelian randomization studies of common gene variants associated with LDL-C strongly support a causal relationship between LDL-C and ASCVD, independent of mechanism. In contrast, Mendelian disorders of extremes of HDL-C and Mendelian randomization studies of common genetic variants for HDL-C are inconsistent in their support of a causal relationship between HDL-C and ASCVD. In contrast to LDL-C, a causal relationship between HDL-C and ASCVD may be dependent on the specific mechanism leading to variation in HDL-C levels.

Keywords

Lipid; Lipoprotein; LDL; HDL; Human genetics; Cardiovascular disease; Genome-wide association; Mendelian randomization

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the developed world [1]. The lifetime risk of developing ASCVD is strongly influenced by environmental and behavioral risk factors such as smoking, diet, sedentary lifestyle, obesity, and alcohol consumption, and is also affected by defined medical risk factors including hypertension, diabetes mellitus, elevated low-density lipoprotein cholesterol (LDL-C), and low high-density lipoprotein cholesterol (HDL-C). ASCVD is also a heritable trait, due both to the heritability of the defined medical risk factors as well as to additional genetic factors that independently predispose to disease.

The lipid traits LDL-C and HDL-C are also highly heritable. Study of Mendelian disorders of extremes of LDL-C and HDL-C due to rare mutations of large effect has provided major insights into the regulation of lipoprotein metabolism and its relationship to ASCVD [2].

Correspondence to: Daniel J. Rader, rader@mail.med.upenn.edu.

Disclosure No potential conflicts of interest relevant to this article were reported.

Genome-wide association studies (GWAS) that examine common genetic variants of generally small effect in populations also strongly support a role for genetics in lipid metabolism. This review highlights the lessons learned from rare variants that cause Mendelian lipid disorders of LDL-C and HDL-C as well as the common variants associated with LDL-C and HDL-C discovered through GWAS, with particular attention to the connection between genetically influenced lipid traits and the development of ASCVD.

Mendelian Disorders of LDL Metabolism and Relationship to ASCVD

The study of Mendelian disorders of extremes of LDL-C highlights the strong and causal relationship between LDL-C and cardiovascular disease (CVD) risk: monogenic disorders of hypercholesterolemia consistently increase risk of CVD, whereas Mendelian conditions of hypocholesterolemia consistently protect against CVD [2].

The prototypical example of Mendelian hypercholesterolemia is familial hypercholesterolemia (FH), an autosomal codominant disorder characterized by elevated LDL-C with normal plasma triglycerides, cutaneous and tendon xanthomas, and premature CVD [3]. FH is characterized by delayed LDL clearance from circulation due to mutations in the LDL receptor (LDLR). There are a large number of LDLR mutations (>1000) that cause FH that either result in no receptor production, improper receptor trafficking through the secretory pathway to the cell membrane, impaired receptor internalization, impaired receptor recycling, or impaired LDL binding [4].

Homozygous FH, in which individuals possess two mutant LDLR alleles, occurs in approximately 1 in 1 million persons and is associated with plasma LDL-C concentrations above 500 mg/dL. Homozygous FH is associated with the development of symptomatic ASCVD during childhood or adolescence, which, if left untreated, is often fatal within the first two decades of life. Heterozygous FH, in which individuals carry one mutant LDLR allele, has a prevalence of 1 in 500 people and is characterized by elevated plasma LDL, generally ranging from 200 to 400 mg/dL. Heterozygous FH is associated with the frequent development of premature CVD, which can be delayed or prevented by early treatment to reduce LDL-C levels [3]. The observation that both homozygous and heterozygous FH are associated with a markedly increased risk of developing ASCVD helped to confirm the causal relationship between elevated LDL-C and ASCVD.

Two other Mendelian disorders of elevated LDL-C levels involve proteins that regulate the functional expression of the LDLR and are themselves also associated with premature ASCVD. Autosomal recessive hypercholesterolemia (ARH) is caused by a defect in LDLR adaptor protein (LDLRAP) [5], an adaptor protein that facilitates hepatic LDLR internalization. Loss-of-function mutations in both alleles of LDLRAP prevent clathrin-dependent LDLR internalization, causing impaired LDL uptake and marked hypercholesterolemia [6]. Like homozygous FH, ARH is associated with markedly premature CVD, but generally in the third of fourth decade of life instead of in the first or second [7]. More recently, a new Mendelian disorder of elevated LDL-C was described that also involves dysregulation of LDLR function and is due to gain-of-function mutations in the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9) [8]. PCSK9 is a secreted protein that binds to cell surface LDLR and promotes its lysosome degradation [9]. Gain-of-function mutations in PCSK9 enhance the ability of PCSK9 to bind to the LDLR, which reduces the number of cell surface LDL receptors and LDL clearance [10]. This condition, which has been termed autosomal dominant hypercholesterolemia 3 (ADH3), is also associated with premature coronary disease [8].

The ligand on LDL that binds to the LDLR is a specific sequence on apoB, the large protein that is a major component of LDL. Familial defective apoB100 (FDB) is a dominant

disorder caused by mutations in the LDLR binding site of apolipoprotein (apo) B (most commonly G3500R) that interfere with the ability of apoB to bind to the LDLR, reducing the LDL clearance rate [11]. Cholesterol levels in FDB do not reach as high as those seen in FH and usually range from 250 to 400 mg/dL [12]. Nevertheless, FDB is also associated with premature coronary disease [11, 13].

Finally, sitosterolemia [14, 15] is an autosomal recessive disorder caused by mutations in the ATP-binding cassette transporters ABCG5 or ABCG8 [16]. These proteins form a heterodimer “pump” that transports plant and animal sterols into bile and into the gut lumen for excretion. Loss of ABCG5/8 function results in increased intestinal absorption of plant and animal sterols and reduced excretion in bile, resulting in downregulation of the hepatic LDLR and elevation of plant and animal sterol levels in plasma and in tissues [16, 17]. Sitosterolemia is associated with a significantly greater risk of premature coronary disease [15].

Thus, all of the classic Mendelian disorders of markedly elevated LDL-C levels are characterized by premature ASCVD, strongly supporting the paradigm that substantially elevated LDL-C, regardless of etiology, is a causal and sufficient risk factor for the development of ASCVD.

On the other end of the spectrum are Mendelian disorders of extremely low LDL-C levels. The classic condition of low LDL-C, familial hypobetalipoproteinemia, is caused by mutations in apoB that impair its trafficking and secretion or enhance its catabolism [18, 19]. This condition is associated with LDL-C levels that are generally less than the 5th percentile and, importantly, with a reduced risk of developing coronary disease [19, 20]. The very rare recessive Mendelian disorder abetalipoproteinemia is caused by loss of function mutations in the microsomal triglyceride transfer protein (MTP) [21]. Loss of MTP activity results in defective apoB lipidation in the endoplasmic reticulum (ER), and thus virtually absent secretion of apoB from the liver and intestine [22]. Abetalipoproteinemia is too rare to assess ASCVD prevalence, but an autopsy of an individual with this condition showed absence of atherosclerosis, although the patient was still quite young [23].

Most recently, low frequency loss of function mutations in PCSK9 have been described in association with reduced LDL-C levels [24, 25]. Here, the genetic epidemiology is compelling: heterozygotes for these PCSK9 mutations, who have substantially reduced LDL-C levels, have a markedly reduced lifetime risk of cardiovascular disease [26, 27]. Thus, Mendelian disorders of low LDL-C are consistently associated with protection from coronary disease, again consistent with a causal and necessary role for LDL-C in the development of ASCVD.

Mendelian Disorders of HDL Metabolism and Relationship to ASCVD

Although Mendelian disorders of LDL metabolism show a clear relationship between genetically determined LDL-C levels and risk of CVD, Mendelian disorders of HDL metabolism do not tell nearly as straightforward a story. One of the most dramatic Mendelian disorders of HDL metabolism is Tangier disease, an autosomal codominant disorder caused by loss-of-function mutations in both alleles of the cellular cholesterol transporter ABCA1 that promotes efflux of cholesterol from cells to an apoA-I acceptor [28, 29]. Tangier disease is characterized by extremely low levels of HDL-C (<5 mg/dL) and the accumulation of cholesterol in tissue macrophages, causing hepatosplenomegaly and enlarged, orange tonsils [29]. Despite the extremely low levels of HDL-C, the relationship between Tangier disease and risk of CVD remains uncertain. Tangier disease is too rare to rigorously assess this question, but it can be stated that individuals with Tangier disease do not develop markedly premature ASCVD in childhood or early adulthood similar to that

seen in homozygous FH. The lack of association between Tangier disease and increased risk of CVD may be due in part to the low plasma levels of LDL-C seen in Tangier disease homozygotes.

Importantly, heterozygotes with loss of function mutations in ABCA1 have substantially reduced HDL-C levels (usually 15–30 mg/dL), and because heterozygotes are much more common they can be studied epidemiologically with regard to risk for ASCVD. One study of ABCA1 mutation heterozygotes suggested that a mutation in one allele of ABCA1 is associated with an average decrease in HDL-C of 17 mg/dL but was not associated with increased risk of ischemic heart disease [30•]. In contrast, another study reported that common variants in ABCA1 were associated with reduced HDL-C and increased risk of CVD [31]. This important question of whether haploinsufficiency of ABCA1 causing low HDL-C is associated with increased ASCVD risk remains incompletely answered. Overall, the relationship of ABCA1 mutations that cause reduced HDL-C with CVD is not nearly as clear as might have been predicted based on the strong epidemiologic association between HDL-C and coronary disease.

Another disorder of low HDL-C is caused by recessive deficiency of the enzyme lecithin: cholesterol acyltransferase (LCAT), which esterifies free cholesterol and is essential for HDL maturation. Complete LCAT deficiency is characterized by the inability to esterify free cholesterol in plasma, leading to an inability to form mature HDL, resulting in rapid HDL and apoA-I turnover and plasma HDL-C levels usually lower than 10 mg/dL [32, 33]. This causes progressive corneal opacification due to free cholesterol deposition in the cornea, hemolytic anemia, and progressive renal impairment often leading to end-stage renal disease. Partial LCAT deficiency (ie, fish-eye disease), in which LCAT activity can be detected on LDL but not HDL, is also associated with extremely low plasma HDL-C and corneal opacification but not renal disease [32, 33]. Like Tangier disease, in spite of the extremely low HDL-C levels seen with LCAT deficiency, the association between LCAT deficiency and cardiovascular disease is far from clear. Although one study showed an association between LCAT deficiency and increased carotid intimamedia thickness (IMT) [34], another study on LCAT-deficient homozygotes and heterozygotes showed no increase in IMT, with a trend toward IMT reduction [35•]. Two studies showed that LCAT deficiency in mice is atheroprotective in spite of the reduction in HDL [36, 37], whereas another study showed increased atherosclerosis with LCAT deficiency [38]. As with ABCA1 mutations, the relationship of LCAT deficiency with CVD is not as straightforward as might have been predicted based on the strong epidemiologic association between HDL-C and coronary disease [39].

A third cause of low HDL-C is apoA-I gene deletions and mutations. ApoA-I is the main protein component of HDL and is required for HDL assembly, ABCA1-mediated cholesterol efflux, LCAT activity, and other aspects of HDL metabolism. Individuals with complete deletion of the apoA-I gene or with mutations that prevent the effective transcription or translation of the apoA-I protein [40] have undetectable apoA-I and virtually undetectable HDL-C levels. Importantly, such individuals generally develop markedly premature coronary disease, consistent with the concept that biosynthesis of apoA-I is required for atheroprotection. In contrast, individuals with structural apoA-I gene mutations causing low HDL-C levels usually have no evidence of premature CVD. One of the most well-known apoA-I structural mutations, an R173C substitution termed apoA-I_{Milano}, results in very low plasma HDL-C levels, often less than 20 mg/dL [41]. The catabolism of the mutant apoA-I_{Milano} is considerably faster than that of wild-type apoA-I, whereas the production rate of the lipoprotein is comparable to that of the wild type. In spite of the very low plasma HDL-C levels, apoA-I_{Milano} carriers and carriers of most other apoA-I missense and nonsense mutations are not at increased risk of CVD, although there are some

exceptions to this [42, 43]. One possible conclusion is that mutations that reduce apoA-I biosynthesis and secretion are associated with increased cardiovascular disease risk, whereas mutations that accelerate catabolism but do not interfere with biosynthesis of apoA-I have no impact on cardiovascular risk despite the reduced level of HDL-C.

Mendelian conditions characterized by elevated HDL-C are similarly complicated with regard to association with CVD risk. Loss of function mutations in both alleles of the cholesterol ester transfer protein (CETP), the transfer protein that facilitates exchange of cholesterol esters from HDL to apoB-containing lipoproteins, cause CETP deficiency and markedly elevated plasma HDL-C levels [44]. Despite the elevated HDL-C, the relationship between CETP deficiency and CVD is controversial, with some studies suggesting reduced risk and others suggesting increased risk [45]. Heterozygosity for mutations in CETP has only a modest effect on raising HDL-C levels and also has an inconsistent relationship with CVD [45]. Thus, the major Mendelian form of elevated HDL-C does not provide a clear message regarding the relationship of genetically high HDL-C to ASCVD.

Association of Common Variants with LDL-C and HDL-C and Relationship to Coronary Heart Disease

Although the study of Mendelian disorders has helped in the identification and characterization of key proteins in lipoprotein metabolic pathways, the vast majority of the genetic contribution to variation in plasma lipids in the general population is not explained by the rare mutations that cause Mendelian disorders. Through genotyping of hundreds of thousands of single nucleotide polymorphisms (SNPs) in thousands of phenotyped individuals, genome-wide association studies (GWAS) have been used as an unbiased tool to identify common variants associated with lipid phenotypes and novel genes that contribute in a causal manner to lipid traits in the general population [46, 47•, 48•, 49•, 50•]. GWAS have identified as associated with plasma lipid traits common variants in genes that cause Mendelian LDL and HDL disorders (Table 1), including PCSK9, LDLRAP, LDLR, ABCG5/8, and apoB for LDL-C, and ABCA1, LCAT, ApoA-I, and CETP for HDL-C. GWAS have also identified known targets of LDL-lowering therapies, including HMGCR and NPC1L1, further validating the utility of these studies in identifying lipid-related genes that are potential targets for therapeutic interventions.

The first GWAS for lipid traits, the Diabetes Genetics Initiative, genotyped 3000 individuals of European descent and identified SNPs near *APOE* and *APOB* as strongly associated with LDL-C levels, and SNPs near *CETP*, *LPL* and *LIPC* as genome-wide significant determinants of HDL-C levels [46]. Subsequent GWAS added additional cohorts and involved almost 9000 individuals of European descent [47•, 48•]. Significant SNPs from this group were genotyped in an additional 18,000 individuals. These studies identified 18 loci of genome-wide significance for lipid traits: 7 for LDL-C and 7 for HDL-C, including two novel loci for LDL (the *PSRC1/SORT1* locus at 1p13 and the *CILP2/PBX4* locus at 19p13) and one novel locus for HDL (the *GALNT2* locus at 1q42). The *SORT1* locus has been associated with LDL-C in replication studies in different populations, as have the *GALNT2* and the *CILP2/PBX4* loci [51, 52]. A larger-scale GWAS was reported on approximately 40,000 individuals of European descent [49•] and identified 30 loci as genome-wide significantly associated with lipid traits, including four new loci for LDL-C (*ABCG8* at 2p21, *TIMD4/HAVCR1* at 5q23, *MAFB* at 20q12, and *HNF1A* at 12q24) and six new loci for HDL-C (*FADS1-FADS2-FADS3* at 11q12, *LCAT* at 16q22, *TTC39B* at 9p22, *HNF4A* at 20q13, *PLTP* at 20q13, and *ANGPTL4* at 19p13).

The largest-scale GWAS for lipid traits, the Global Lipids Genetics Consortium (GLGC), was recently published [50•]. This report involved a meta-analysis of over 100,000

individuals of European descent and identified 95 independent loci associated with at least one plasma lipid trait: 21 known lipid loci associated with an additional lipid phenotype for the first time and 59 novel loci that had not been previously reported in association with lipid traits, including 22 loci for LDL-C and 31 for HDL-C. Together, the 95 loci identified in this study account for 25% to 30% of the genetic variance in each lipid trait. The associated SNPs were shown to act additively to influence lipid phenotypes and were shown to be relevant not only to lipid traits in European populations, but also in South Asian, East Asian, and African American populations. Further supporting the importance of these loci in lipid phenotypes, this study also included in vivo evidence in mice regarding the role of three of the novel GWAS hits, *GALNT2*, *PPP1R3B*, and *TTC39B*, on modulating HDL-C levels.

In an accompanying article, detailed studies on the 1p13 locus strongly associated with both LDL-C and coronary heart disease were described [53•]. Greater than 100 SNPs at the 1p13 locus had been genome-wide significantly associated with LDL-C, and the lead SNP at this locus has the strongest statistical association with LDL-C of any SNP in the genome [50•]. The effect size is unusually large for a common variant; homozygotes for the minor allele have an average of 16 mg/dL lower LDL-C than homozygotes for the major allele [47•]. Notably, this same locus on 1p13 had been independently discovered by GWAS as significantly associated with MI and cardiovascular disease [54, 55•]. The minor allele at this locus is associated with substantially higher hepatic mRNA abundance of at least two genes at this locus, *SORT1* and *PSRC1*. The causal SNP at this locus, rs12740374, generates a CEBP binding site, enabling increased transcription of these genes [53•]. Overexpression of *SORT1*, but not *PSRC1*, in the livers of hypercholesterolemic mice resulted in reduced LDL-C, and knockdown of SORT1 in mouse liver resulted in markedly increased LDL-C levels [53•]. Thus, a common variant at the 1p13 locus results in substantially increased transcription of the *SORT1* gene, resulting in increased synthesis of its protein product sortilin, reduced LDL-C levels, and ultimately reduced cardiovascular risk. This provides one of the first examples of how a novel finding from a GWAS can lead to new insights into biology that are relevant to the general population and also supports the strong relationship between genes that regulate LDL-C levels and CVD.

Testing the association of “lipid SNPs” with coronary disease has the potential to provide insight into causality of the lipid–coronary artery disease (CAD) association, an approach known as Mendelian randomization. The GLGC tested the association between significant SNPs for lipid traits and coronary disease and found that 29 of the 95 loci identified were associated with CAD (Table 2) [50•]. Interestingly, most of the associated loci for CAD were in LDL-C genes, supporting the strong causal relationship between LDL-C and CVD risk. Of the HDL-C loci also associated with coronary disease, only KLF14 was associated with HDL-C alone; the other loci were also associated with either LDL-C or triglycerides in addition to HDL-C, and these associations may be responsible for the CVD association.

Common variants generally have a relatively small effect size on the trait of interest. It is possible that with regard to HDL-C (in contrast to LDL-C), a greater effect on HDL-C levels is required in order to detect an association with CAD. Low-frequency variants with greater effect size afford the potential to test this hypothesis. A low-frequency variant N396S in the gene *LIPG* encoding the enzyme endothelial lipase has an allele frequency of about 1% to 2%. It has been shown to be strongly associated with increased HDL-C levels, with an effect size of about 3 to 11 mg/dL per allele copy [56•]. In vitro and in vivo studies have confirmed that this missense variant has reduced lipolytic activity [56•]. It will be of substantial interest to determine through Mendelian randomization whether this variant is associated with coronary disease. More studies of low-frequency variants in genes

associated with HDL-C are required in order to extensively test this critically important concept across a range of different HDL genes.

Conclusions

Both rare Mendelian disorders of lipoprotein metabolism as well as GWAS of common SNPs associated with lipid traits have helped identify and characterize key players in lipoprotein metabolism. Mendelian disorders of LDL-C have provided unequivocal evidence of a strong causal relationship between LDL-C and risk of ASCVD. GWAS have identified additional loci associated with LDL-C, and through Mendelian randomization based on common and low frequency variants have strengthened the causal association between LDL-C and CVD risk. Thus, we can be reasonably confident that pathways influencing LDL-C will likely influence risk of CVD and therefore represent viable therapeutic targets that will affect hard clinical endpoints. The HDL story is clearly more complex, and as we learn more about disorders of HDL metabolism and genome-wide determinants of plasma HDL-C levels, evidence for a uniformly causal relationship between HDL-C and CVD risk is inconsistent. In both cases, a thorough understanding of the biology and molecular mechanisms linking the gene and its pathway to the plasma lipid trait will be critical for validation of that pathway as a new therapeutic target.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

• Of major importance

1. Lloyd-Jones D, et al. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010; 121:948–954. [PubMed: 20177011]
2. Hobbs, DJ. Disorders of lipoprotein metabolism. In: Kasper, DL.; Braunwald, E.; Fauci, AS., et al., editors. Harrison's Principles of Internal Medicine. New York: McGraw Hill Publishers; 2007. p. 2416-2429.
3. Goldstein, J.; Hobbs, H.; Brown, M. Familial hypercholesterolemia. In: Scriver, C.; Beaudet, A.; Sly, W.; Valle, D., editors. The metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001. p. 2863-2913.
4. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009; 29:431–438. [PubMed: 19299327]
5. Garcia CK, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001; 292:1394–1398. [PubMed: 11326085]
6. Mishra SK, Watkins SC, Traub LM. The autosomal recessive hypercholesterolemia (ARH) protein interfaces directly with the clathrin-coat machinery. Proc Natl Acad Sci U S A. 2002; 99:16099–16104. [PubMed: 12451172]
7. Arca M, et al. Autosomal recessive hypercholesterolaemia in Sardinia, Italy, and mutations in ARH: a clinical and molecular genetic analysis. Lancet. 2002; 359:841–847. [PubMed: 11897284]
8. Abifadel M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003; 34:154–156. [PubMed: 12730697]
9. Horton JD, et al. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci. 2007; 32:71–77. [PubMed: 17215125]
10. Cunningham D, et al. Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia. Nat Struct Mol Biol. 2007; 14:413–419. [PubMed: 17435765]
11. Hansen PS. Familial defective apolipoprotein B-100. Dan Med Bull. 1998; 45:370–382. [PubMed: 9777289]

12. Ejarque I, et al. Evaluation of clinical diagnosis criteria of familial ligand defective apoB 100 and lipoprotein phenotype comparison between LDL receptor gene mutations affecting ligand-binding domain and the R3500Q mutation of the apoB gene in patients from a South European population. Transl Res. 2008; 151:162–167. [PubMed: 18279815]
13. Myant NB. Familial defective apolipoprotein B-100: a review, including some comparisons with familial hypercholesterolaemia. Atherosclerosis. 1993; 104:1–18. [PubMed: 8141833]
14. Bhattacharyya AK, Connor WE. Beta-sitosterolemia and xanthomatosis. A newly described lipid storage disease in two sisters. J Clin Invest. 1974; 53:1033–1043. [PubMed: 4360855]
15. Salen G, et al. Sitosterolemia. J Lipid Res. 1992; 33:945–955. [PubMed: 1431587]
16. Berge KE, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science. 2000; 290:1771–1775. [PubMed: 11099417]
17. Oram JF, Vaughan AM. ATP-Binding cassette cholesterol transporters and cardiovascular disease. Circ Res. 2006; 99:1031–1043. [PubMed: 17095732]
18. Tarugi P, et al. Molecular diagnosis of hypobetalipoproteinemia: an ENID review. Atherosclerosis. 2007; 195:e19–27. [PubMed: 17570373]
19. Schonfeld G. Familial hypobetalipoproteinemia: a review. J Lipid Res. 2003; 44:878–883. [PubMed: 12639976]
20. Sankatsing RR, et al. Hepatic and cardiovascular consequences of familial hypobetalipoproteinemia. Arterioscler Thromb Vasc Biol. 2005; 25:1979–1984. [PubMed: 16002743]
21. Sharp D, et al. Cloning and gene defects in microsomal triglyceride transfer protein associated with abetalipoproteinaemia. Nature. 1993; 365:65–69. [PubMed: 8361539]
22. Gordon DA, Jamil H. Progress towards understanding the role of microsomal triglyceride transfer protein in apolipoprotein-B lipoprotein assembly. Biochim Biophys Acta. 2000; 1486:72–83. [PubMed: 10856714]
23. Dische MR, Porro RS. The cardiac lesions in Bassen-Kornzweig syndrome. Report of a case, with autopsy findings. Am J Med. 1970; 49:568–571. [PubMed: 5477641]
24. Cohen J, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005; 37:161–165. [PubMed: 15654334]
25. Zhao Z, et al. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet. 2006; 79:514–523. [PubMed: 16909389]
26. Cohen JC, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006; 354:1264–1272. [PubMed: 16554528]
27. Kathiresan S. A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction. N Engl J Med. 2008; 358:2299–2300. [PubMed: 18499582]
28. Oram JF, Lawn RM. ABCA1. The gatekeeper for eliminating excess tissue cholesterol. J Lipid Res. 2001; 42:1173–1179. [PubMed: 11483617]
29. Hobbs HH, Rader DJ. ABC1: connecting yellow tonsils, neuropathy, and very low HDL. J Clin Invest. 1999; 104:1015–1017. [PubMed: 10525038]
30•. Frikke-Schmidt R, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA. 2008; 299:2524–2532. This study addressed whether heterozygous individuals for four ABCA1 loss-of-function mutations were at increased risk for ischemic heart disease compared with non-carriers. Their data suggests that although carriers of loss-of-function ABCA1 mutations have a 17-mg/dL lower HDL-C level than non-carriers, they are not at increased risk for ischemic heart disease. [PubMed: 18523221]
31. Brousseau ME, et al. Common variants in the gene encoding ATP-binding cassette transporter 1 in men with low HDL cholesterol levels and coronary heart disease. Atherosclerosis. 2001; 154:607–611. [PubMed: 11257261]
32. Kuivenhoven JA, et al. The molecular pathology of lecithin: cholesterol acyltransferase (LCAT) deficiency syndromes. J Lipid Res. 1997; 38:191–205. [PubMed: 9162740]
33. Calabresi L, et al. The molecular basis of lecithin:cholesterol acyltransferase deficiency syndromes: a comprehensive study of molecular and biochemical findings in 13 unrelated Italian families. Arterioscler Thromb Vasc Biol. 2005; 25:1972–1978. [PubMed: 15994445]

34. Hovingh GK, et al. Compromised LCAT function is associated with increased atherosclerosis. Circulation. 2005; 112:879–884. [PubMed: 16061733]

35•. Calabresi L, et al. Functional lecithin: cholesterol acyltransferase is not required for efficient atheroprotection in humans. Circulation. 2009; 120:628–635. This study addressed whether low HDL due to heterozygosity for LCAT mutations is associated with increased risk of CVD compared with non-carriers, using IMT as a marker for preclinical atherosclerotic disease. This study found no association between increased IMT and heterozygosity for LCAT mutations, suggesting that low HDL due to LCAT deficiency is not associated with increased atherosclerotic disease. [PubMed: 19687369]

36. Lambert G, et al. Analysis of glomerulosclerosis and atherosclerosis in lecithin cholesterol acyltransferase-deficient mice. J Biol Chem. 2001; 276:15090–15098. [PubMed: 11278414]

37. Ng DS, et al. Oxidative stress is markedly elevated in lecithin: cholesterol acyltransferase-deficient mice and is paradoxically reversed in the apolipoprotein E knockout background in association with a reduction in atherosclerosis. J Biol Chem. 2002; 277:11715–11720. [PubMed: 11809774]

38. Furbee JW Jr, et al. Lecithin:cholesterol acyltransferase deficiency increases atherosclerosis in the low density lipoprotein receptor and apolipoprotein E knockout mice. J Biol Chem. 2002; 277:3511–3519. [PubMed: 11719520]

39. Rader DJ. Lecithin. cholesterol acyltransferase and atherosclerosis: another high-density lipoprotein story that doesn't quite follow the script. Circulation. 2009; 120:549–552. [PubMed: 19652089]

40. Ng DS, et al. Apolipoprotein A-I Q[-2]X causing isolated apolipoprotein A-I deficiency in a family with analphalipoproteinemia. J Clin Invest. 1994; 93:223–229. [PubMed: 8282791]

41. Franceschini G, et al. Apolipoprotein AIMilano. Disulfide-linked dimers increase high density lipoprotein stability and hinder particle interconversion in carrier plasma. J Biol Chem. 1990; 265:12224–12231. [PubMed: 2115514]

42. Dastani Z, et al. A novel nonsense apolipoprotein A-I mutation (apoA-I(E136X)) causes low HDL cholesterol in French Canadians. Atherosclerosis. 2006; 185:127–136. [PubMed: 16023124]

43. Hovingh GK, et al. A novel apoA-I mutation (L178P) leads to endothelial dysfunction, increased arterial wall thickness, and premature coronary artery disease. J Am Coll Cardiol. 2004; 44:1429–1435. [PubMed: 15464323]

44. Inazu A, et al. Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. N Engl J Med. 1990; 323:1234–1238. [PubMed: 2215607]

45. Barter PJ, et al. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol. 2003; 23:160–167. [PubMed: 12588754]

46. Saxena R, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007; 316:1331–1336. [PubMed: 17463246]

47•. Kathiresan S, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. 2008; 40:189–197. This GWAS identified 18 total loci for lipid traits and six novel loci, including the 1p13 SORT1 locus, as a genome-wide significant determinant of LDL-C. [PubMed: 18193044]

48•. Willer CJ, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet. 2008; 40:161–169. This GWAS identified 11 total loci for lipid traits and six novel loci, including the 1p13 SORT1 locus. This study also found an association between 11 LDL SNPs and CVD. [PubMed: 18193043]

49•. Kathiresan S, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009; 41:56–65. This GWAS identified 30 total loci for lipid traits, with 10 novel loci. [PubMed: 19060906]

50•. Teslovich TM, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2009; 466:707–713. The largest GWAS for lipid traits to date, it identified 95 total loci for lipid traits with 59 novel loci. This study also identified 29 lipid loci also associated with CVD. Many of the significant SNPs were associated with gene expression changes in liver and adipose and were also replicated in three non-European populations. Three novel genes were also overexpressed and/or knocked down in mice and shown to have an effect on lipids. [PubMed: 20686565]

51. Lanktree MB, et al. Replication of genetic associations with plasma lipoprotein traits in a multiethnic sample. J Lipid Res. 2009; 50:1487–1496. [PubMed: 19299407]

52. Nakayama K, et al. Large scale replication analysis of loci associated with lipid concentrations in a Japanese population. J Med Genet. 2009; 46:370–374. [PubMed: 19487539]

53•. Musunuru K, et al. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. Nature. 2009; 466:714–719. This study shows that an SNP in the 1p13 locus creates a CEBP transcription factor binding site and increases hepatic expression of the SORT1 gene. Through overexpression and knockdown studies in mice, this study shows that sortilin affects plasma LDL-C levels by influencing very low-density lipoprotein secretion. [PubMed: 20686566]

54•. Samani NJ, et al. Genomewide association analysis of coronary artery disease. N Engl J Med. 2007; 357:443–453. This is a seminal GWAS of CAD and myocardial infarction. [PubMed: 17634449]

55•. Kathiresan S, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009; 41:334–341. This is a seminal GWAS of CAD and myocardial infarction. [PubMed: 19198609]

56•. Edmondson AC, et al. Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans. J Clin Invest. 2009; 119:1042–1050. This study identified loss of function mutations in LIPG (endothelial lipase) in individuals with high HDL and showed that these mutations lead to reduced lipolytic activity of endothelial lipase. [PubMed: 19287092]

Table 1

Mendelian disorders of LDL-C and HDL-C and association with ASCVD

Disease	Causal gene	Lipid phenotype	Other phenotypes	ASCVD
Familial hypercholesterolemia	*LDLR*	Elevated LDL-C	Tendon xanthomas	Increased
Autosomal dominant hypercholesterolemia 3	*PCSK9*	Elevated LDL-C	Tendon xanthomas	Increased
Autosomal recessive hypercholesterolemia	*LDLRAP*	Elevated LDL-C		Increased
Familial defective apoB-100	*APOB*	Elevated LDL-C		Increased
Sitosterolemia	*ABCG5/8*	Elevated LDL-C	Elevated plant sterols, tendon xanthomas	Increased
Hypobetalipoproteinemia	*APOB*	Reduced LDL-C	Fatty liver	Decreased
PCSK9 deficiency	*PCSK9*	Reduced LDL-C		Decreased
Abetalipoproteinemia	*MTP*	Absent LDL-C	Ataxia, retinal degeneration	Decreased?
Tangier disease	*ABCA1*	Very low HDL-C, low LDL-C	Enlarged, orange tonsils, hepatosplenogemaly	Possibly increased
LCAT deficiency	*LCAT*	Very low HDL-C	Corneal opacification, hemolytic anemia, renal failure	Variable
ApoA-I gene deletions	*APOAI*	Very low HDL-C	Planar xanthomas	Increased
ApoA-I missense mutations	*APOAI*	Low HDL-C	Low HDL	Variable
CETP deficiency	*CETP*	Very high HDL-C	High HDL	Unclear

Apo apolipoprotein; *ASCVD* atherosclerotic cardiovascular disease; *CETP* cholesterol ester transfer protein; *HDL-C* high-density lipoprotein cholesterol; *LCAT* lecithin: cholesterol acyltransferase; *LDL-C* low-density lipoprotein cholesterol

Table 2

Selected genome-wide association study loci for lipid traits and association with ASCVD

Gene	Chromosome	Associated lipid trait	Significant association with ASCVD
ABCAI	9	HDL	–
ABCG5/8	2	LDL	Yes
ABO	9	LDL	Yes
ANGPTL4	19	HDL	Yes
APOAI	11	HDL, LDL, TG	Yes
APOB	2	LDL, HDL, TG	Yes
APOE	19	LDL, HDL, TG	Yes
CETP	16	HDL, LDL, TG	Yes
CILP2/PBX4	19	LDL, TG	Yes
FADS1-2-3	11	LDL, HDL, TG	–
GALNT2	1	HDL, TG	–
HMGCR	5	LDL	Yes
HNF1A	12	LDL	Yes
HNF4A	20	HDL	–
IRS1	2	HDL, TG	Yes
KLF14	7	HDL	Yes
LCAT	16	HDL	–
LDLR	19	LDL	Yes
LDLRAP	1	LDL	–
LIPC	15	HDL, TG	–
LPA	6	LDL, HDL	Yes
LPL	8	TG, HDL	Yes
MAFB	20	LDL	–
NPC1L1	7	LDL	–
PCSK9	1	LDL	Yes
PLTP	20	HDL, TG	–
SORT1	1	LDL	Yes
TIMD4/HAVCRI	5	LDL, TG	–
TRIB1	8	LDL, HDL, TG	Yes
TTC39B	9	HDL	–

ASCVD atherosclerotic cardiovascular disease; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *TG* triglyceride