Review Article

Genes Associated with Low Serum High-density Lipoprotein Cholesterol

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Abstract

Atherosclerosis is the main cause of death in the world through causing ischemic heart disease (IHD). Altered serum lipid level is the most important risk factor for coronary artery disease (CAD). Many studies reveal a strong inverse association between low levels of high density lipoprotein cholesterol (HDL-C) and increased risk of IHD. On the other hand, plasma levels of HDL-C has a strong hereditary basis. This review focuses on recent data about genetic defects that reduce the level of HDL-C.

In order to investigate possible genes linked to low HDL-C disorder, we reviewed previous studies; we searched current medical literature from September 1990 through January 2013 for the genetics causes of low HDL-C levels.

Genetic defects in ATP binding cassette protein (ABCA1), apolipoprotein (APO) A1, lecithin cholesteryl acyl transferase, Lipoprotein lipase (LPL), and angiopoietin-like 3 proteins (ANGPTL3) associated with low HDL-C. Other potentially important candidates involved in low HDL-C syndromes are metabolic disorders including sphingomyelin phosphodiesterase 1 and glucocerebrosidase. Also Molecular variations in many genes such as ABCAI and APOAI, TRIB1 and Apo E, lipoprotein lipase (LPL), WW domain-containing oxidoreductase (WWOX), Hepatic lipase (HL), lecithin cholesteryl acyl transferase and some linkage analysis have been associated with reduced HDL-Status.

Low HDL-C syndrome has a strong genetic basis and is correlated with an increased risk of CAD.

Keywords: CAD, genetic defects, HDL-C

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Introduction

Altered lipid profiles are one of the major determinants of cardiovascular disease (CVD), which is the first cause of death in developed countries. Many prospective cohort studies suggest that HDL-C is a significant, independent risk factor for heart attack and a 1% lower HDL value is related to a 3% to 4% increase in CAD.[1,2] It has been established that about 40% of patients with CAD have low HDL-C.[3] Low HDL-C is a component of the metabolic syndrome and is defined as HDL-C level <40 mg/dL according to current guidelines.[4,5] Epidemiological studies have shown that lipid levels are influenced by environmental factors (including demographics, sex, diet, alcohol consumption, smoking, obesity, exercise, and hypertension)as well as genetic factors (such as variants in genes that play a role in the synthesis, processing, or catabolism of plasma lipoprotein) and their interactions as well as ethnic diversities.[6] Studies have shown that approximately 25%–80% of the inter-individual variation in plasma lipid phenotypes can be explained by genetic polymorphisms.[7] HDL-C levels have a strong genetic component; approximately up to 70% of variations in human populations are due to genetic factors.[8] HDL plays an important role in reverse cholesterol transport (RCT); in addition, it has anti-oxidant, anti-inflammatory and antithrombotic activities.[9] The main aim of this article is to review the article about genetic variants related to low levels of high-density lipoprotein cholesterol.

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Materials and Methods

Search strategy

We searched the medical literature for clinical studies examining low HDL-C levels in patients with CAD. Primary sources used to identify clinical studies included: MEDLINE literature , Google scholar, Scopus and PubMed; using the search terms "lipoprotein", "HDL-C", "low HDL-C," "lipid", "hypoalphalipoproteinemia", "polymorphism", "coronary artery disease", " variation", "genetic defect" and "atherosclerosis". To review genetic studies from September1990 through January 2013, our search was restricted to genetic studies in clinical settings published in English. We also excluded studies published prior to1990 largely to reflect important advances in genetic basis of low HDL-C. We first identified 102 records and then excluded those, which 1) were not about Low HDL-C patients, 2) were not in English, or 3) were duplicate publications (Figure 1).

HDL-C

HDL is the smallest and densest plasma lipoprotein and mediates the displacement of cholesterol from peripheral cells to the liver for reprocessing or excretion from the body.[10] Most HDL in the plasma is in the form of spherical particles which vary in size, density of hydration, and apolipoprotein composition.[11] They

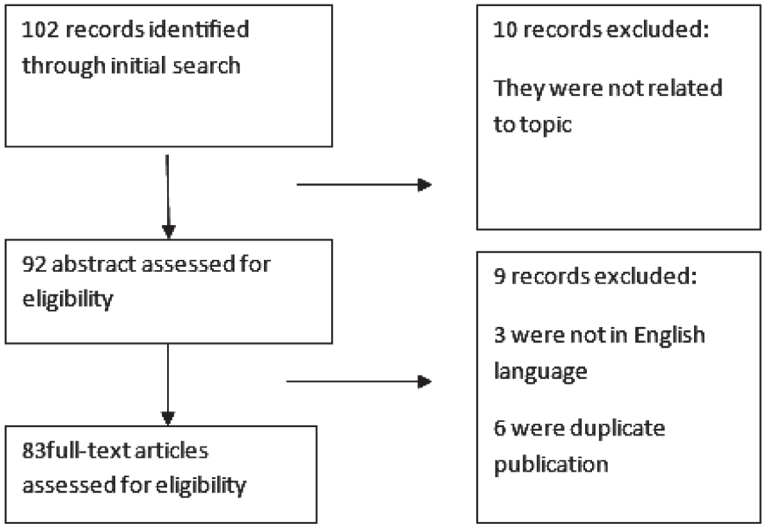

Figure1. Flow diagram of studies assessed and included.

consist of a fatty core that contains cholesterol esters with a small amount of triglycerides, surrounded by a surface layer of phospholipids, unesterified cholesterol and apolipoprotein.[12] The main structural proteins of HDL are apolipoprotein A-I (Apo A-I) and ApoA-II; nevertheless, HDL contains other proteins, including lecithin cholesterol acyl-transferase (LCAT), serum paraoxonase (PON1), platelet-activating factor acetylhydrolase (PAF-AH), Apo E, ApoA-IV, cholesterol ester transfer protein (CETP), and phospholipid transfer protein (PLTP).[13] Nascent HDL particles are produced by the liver and the small intestine. Remodeling of these particles occurs as they circulate in plasma so that they attract excess free cholesterol from extra hepatic cells and other types of lipoprotein particles.[14] LCAT, with Apo AI as a cofactor, esterifies free cholesterol into cholesterol esters that are hydrophobic and therefore sequestered into the core of the particles to produce large HDL-C particles. HDL particles may also become smaller as a result of the action of cholesterol ester transfer protein (CETP), which exchanges the cholesterol ester in HDL for triglycerides in VLDL and IDL. Hepatic lipase can then hydrolyze HDL triglycerides, reducing particle size. There are two major HDL particle sizes in plasma on the basis of the main apolipoprotein, namely HDL2 particles that are larger and less dense containing only Apo AI, and HDL3 particles that contain both Apo AI and Apo AII.[14,15] Although "HDL" and "HDL-C" are often used interchangeably, "HDL" refers to the lipoprotein particle and its properties, whereas "HDL-C" refers to its measured levels.[16] According to the US National Cholesterol Education Program (NCEP), low levels of high-density lipoprotein cholesterol (HDL) or hypoalphalipoproteinemia (HA) is defined as HDL-C levels lower than 40 mg/dL.[17] HDL-C levels below 20 mg/dL are referred to as very low HDL-C levels and these patient often have severe hypertriglyceridemia (triglyceride >500 mg/dL).[18] Low HDL-C levels are highly prevalent in some populations; Azizi et al., have shown the prevalence of metabolic syndrome in Iran to be about 32% and low HDL-C level is the most frequent component of metabolic syndrome in Iranian patients.[19]

Rare syndromes associated with low HDL-C

Reduced levels of HDL-C are found in patients with hypertriglyceridemia and in patients who have inherited disorders associated with CAD. Rare hereditary conditions associated with low HDL-C include LCAT deficiency with a prevalence below 1/1,000,000 with two reported forms including the Fish Eye Disease (FED) and Familial Lecithin cholesteryl acyl transferase Deficiency (FLD), Tangier disease (TD) and familial hypoalphalipoproteinemia (FHA) both of which are caused by mutations in ABCA1 gene and approximately 100 cases have been identified worldwide (1/ 120,000,000).[20–22] All of these single genes only affect small fractions of the general population.[15] Tangier disease is characterized by an almost complete absence of HDL cholesterol in plasma, accumulation of cholesterol esters in various tissues and enlarged orange tonsils (Figure 2). FHA is a disorder characterized by moderately low HDL cholesterol (20–35 mg/dL).[23] Homozygosity and heterozygosity for mutations in ABCA1 cause TD and the milder forms of FHA, respectively. Another type of FHA caused by apolipoprotein AI mutations is FED and FLD that are characterized clinically by corneal opacifications (Figure 2) and HDL-C <5mg/dL. Both are caused by LCAT mutation[24]; in FLD, lack of LCAT activity affects both the esterification of HDL (α-LCAT activity) and LDL (β-LCAT activity) while in FED, only α-LCAT activity is impaired.[24] Overall, very low HDL-C, recognized by HDL-C levels <20 mg/dL, have been seen in patients with Tangier disease, lecithin-cholesterol acyltransferase deficiency, apolipoprotein A-I mutations(which characterized with xanthomas Figure 2) and people with secondary causes such as malignancy and androgen use.[18]

Population study relate to low HDL-C

Analyses of data from family and twin studies have shown that HDL-C levels have a strong genetic basis[25] Surveys have showed a substantial prevalence of low HDL-C in different countries. The Pan-European survey of HDL-C in a large (n = 8545) population revealed the prevalence of low HDL-C in 33% of men and 40% of women, and very low HDL-C in 14% (both genders).[58] Rutherford et al., reported that the prevalence of isolated low HDL-C phenotype was 28.8% in Philippine women.[26] On the average, HDL-C levels are lower in men than women, and are lower in whites than blacks. In the general American adult population, approximately 15% of men and 5% of women have HDL-C < 35 mg/dL[27] Although low HDL-C level has a strong genetic basis;

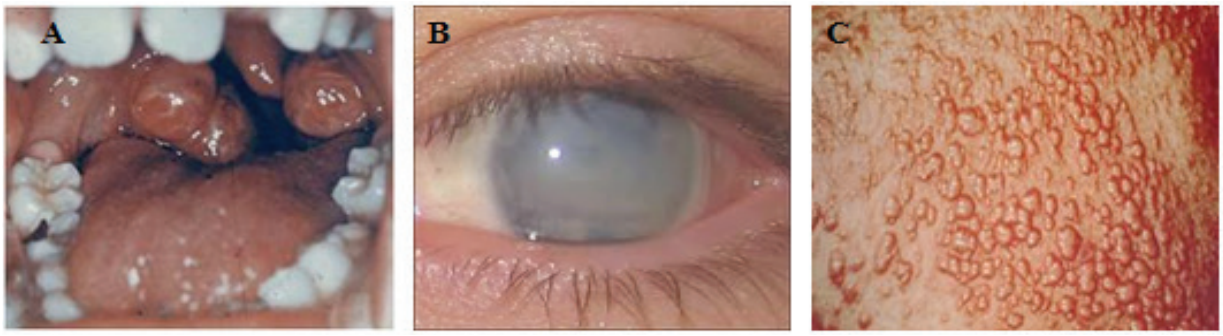

Figure 2. Patients with Tangier disease manifest enlarged orange tonsils **(A).** The hallmark physical findings in LCAT deficiency is corneal opacifications **(B)** and xanthomas **(C)** in patient with apolipoprotein A-I mutations.

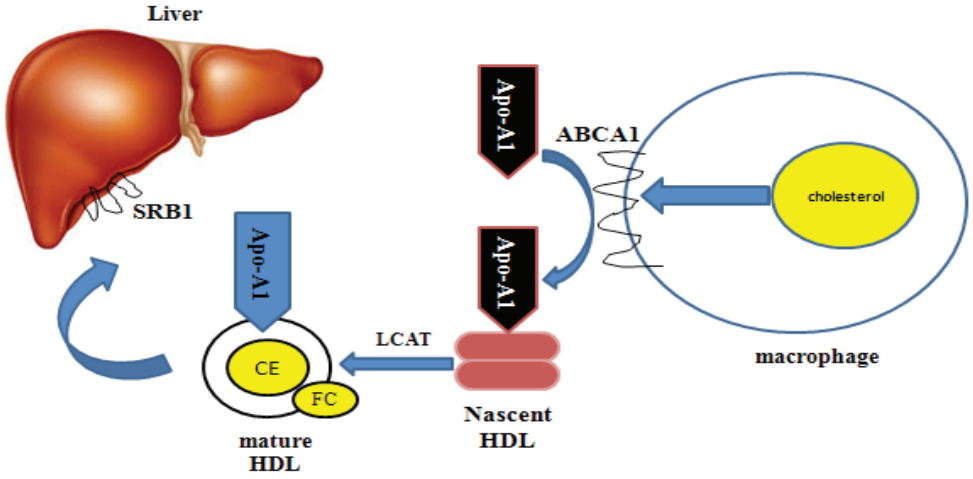

Figure 3. ABCA1 facilitates the efflux of phospholipids and cholesterol to Apo A-I to generate nascent discoidal high HDL particles. LCAT uses HDL phospholipids and cholesterol to esterify cholesterol and produce globular HDL particles. HDL cholesterol esters are removed by scavenger receptor class BI (SRB1) in the liver.[28,29]

this genetic inheritance is complex and along with many other complex traits determines the level of HDL-C. The most common genetic disorder of HDL-C is FHA which is a common finding in patients with premature CAD.[50] We will discuss more about the genes that can affect HDL-C level.

Monogenic candidates associated with low HDL-C

ABCA1 transporter

The ATP-binding cassette transporter (ABCA1) located on 9q31 is a member of the ABC1 subfamily. This protein moves phospholipids and cholesterol across the cell membrane to HDL-C and has an important role in the initial phase of reverse cholesterol transport (Figure 3). Homozygosity and heterozygosity mutations in this gene have been associated with Tangier disease, an autosomal-recessive disorder characterized by deposition of cholesterol esters in organs, and familial high-density lipoprotein deficiency, respectively.[28,29] Low cellular cholesterol efflux due to mutant ABCA1 leads to reduced apolipoprotein A-I stability and rapid catabolism of HDL-C.[30] Over 90 structural variants have been known to cause low HDL-C, most of which are in coding areas, whereas only a few are located in intronic regions[31,32]; e.g., a single defective allele in exon 4 ABCA1 at C254T changing a proline to a leucine (P85L) may be associated with low HDL-C.[33]

Lecithin cholesteryl acyl transferase

LCAT (16q22.1), a member of the lipase superfamily, is a plasma enzyme synthesized by the liver and the small intestine. It esterifies free cholesterol molecules with acyl groups derived from lecithin and plays an important role in HDL-C maturation.[34] The LCAT deficiency syndrome was first described by Norum and Gjone in 1967 with an autosomal recessive mode of inheritance. Homozygous mutations in the LCAT gene result in a complete deficiency known as familial LCAT deficiency (FLD), characterized by severe corneal opacities, hyperlipidemia, anemia, proteinuria and renal failure. Compound heterozygous mutation typically gives rise to the Fish-Eye Disease (FED) which is characterized only by corneal opacifications, eventually leading to loss of vision. In both diseases, there are HDL-C levels below the 5th percentile, elevated TGs and decreased LDL-C. Eighty causative mutations in LCAT have been described while functional mutations in LCAT were found in 29% of patients with low HDL-C.[35–37]

Apolipoprotein A-I

Apo A-I is the major protein component of HDL-C and a key determinant of HDL-C level and metabolism.[38] The Apo A-I gene is located on chromosome 11q23-q24 and Apo AI deficiency is associated with CAD. Homozygous loss of Apo AI is characterized by complete absence of Apo AI, HDL-C level <5 mg/dL, normal levels of LDL-C and triglycerides. Patients may exhibit xanthomas or mild to moderate corneal opacifications. Heterozygous carriers have plasma HDL-C and Apo AI levels that are

about 50% of the normal values and do not present any specific clinical signs.[39,40] Defects in the Apo A-I gene may be due to deletion, nonsense mutation and chromosomal aberration. Most Apo A-I gene mutations have been related to low HDL-C levels and increased risk of CAD. In contrast, at least two APOAI variants (APO-AI $_{Paris}$ and APO-AI $_{Milano}$) have been linked to cardio protection despite low HDL-C levels.[41–44]

Lipoprotein lipase

The Lipoprotein lipase (LPL) gene located on chromosome 8p22 plays an important role in hydrolysis of core triglycerides of chylomicrons and VLDL and enhances the HDL-C level by processing HDL to its mature form.[45,46] Many mutations have been identified in LPL; it's may occur because of base-pair substitutions, rearrangements, and splice site mutations.[47,48] LPL deficiency is an autosomal recessive disorder known as Type I hyperlipoproteinemia or familial chylomicronemia. LPL deficiency is associated with low HDL-C levels in the both homozygous and heterozygous states; as well as low levels of LDL-C.[49,50]

Metabolic Disorders and low HDL-C Level

The metabolic syndrome is a multiplex risk factor for CAD. Low levels of HDL-C are found in patients with this syndrome who have inherited the genetic defect in pathways which are linked to HDL metabolism.[51] Niemann-Pick is a metabolic disorder with an autosomal recessive pattern that is caused by mutations in the SMPD1gene (11p15.4–p15.1).Recognized by sphingomyelin accumulation in the reticuloendothelial organs and the brain due to deficiency of sphingomyelinase, this disease is associated with low HDL-C levels because increased sphingomyelin impairs the binding of LCAT to HDL.[52–54] Gaucher disease is another metabolic storage disease due to recessive mutation in the *GBA* gene that is located on chromosome 1and causes deficiency of glucocerebrosidase. Lack of glucocerebrosidase causes lipid accumulation in cells and certain organs and many studies report that reduced glucocerebrosidase linked to low HDL-C levels.[54–56] Diabetes is classified as part of the metabolic syndrome. Elevated levels of plasma triglycerides and reduced concentrations of HDL-C are very common in patients with diabetes, particularly NIDDM.[57,58] One possibilities is that altered lipid flux in the liver due to insulin resistance might reduce the hepatic production of apolipoprotein A-I and thus lower HDL-C levels.[59]

ANGPTL3 Mutations

Angiopoietin-like 3 protein (ANGPTL3) is located on 1p31.3 and is expressed primarily in the liver. This gene encodes a member of a family of secreted proteins that function in angiogenesis. In addition, it acts as dual inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL), and increases plasma HDL-C. Patients with the loss-of-function mutation in ANGPTL3 have significantly lower plasma HDL cholesterol levels than individuals with no mutation.[60,61]

Extremely low levels of HDL-C

Very low level of HDL-C is defined by HDL-C <20 mg/dL which may be due to hypertriglyceridemia or liver failure; in the absence of these conditions, it has been observed in patients with Apo A-I deficiency, Tangier diseases and LCAT deficiency.[18] The monogenic disorders described previously are rare and altogether, they may account for only a small fraction (~1%) of low HDL-C in the general population.[62] A large number of studies have failed to demonstrate the most important single-gene effect on HDL-C in the general population.[15] Tangier disease was first described by Fredrickson in a 5-year old boy from Tangier Island in Chesapeake Bay, USA in 1960.[63] In large population studies, mutations in the ABCA1 gene were found in patients with Tangier disease.[24] The apolipoprotein A-I deficiency was recognized in1991 by Matsunaga in a Japanese woman.[64] Mutations that lead to Apo A-I deficiency are characterized by absence or low levels of HDL.[65] In population studies, such as PRIME that included 9,711 men, Apo A-I deficiency was found to be related to coronary heart disease.[66] LCAT deficiency was first described by Norum and Gjone in a 33 year old Norwegian woman in1967.[35] Many studies have shown different mutations in the LCAT gene that lead to LCAT deficiency and low HDL-C levels.[36]

Linkage analysis and low HDL-C

Detection of new chromosomal loci is promising for discovery of new genes responsible for HDL-related disorders. In recent years, linkage analysis has been relatively successful at identifying susceptibility genes for HDL-C levels (Table1); Wilson et al., recognized two families with Tangier disease (TD), showed 9q31 linkage and established this region containing gene encoding the ABCA1.[67] Soro et al., found linkage between the low HDL-C and three loci in data analysis of 25 families with low HDL-C. The highest statistical evidence was observed at 8q23, with a two-point LOD score of 4.7 under a recessive mode of inheritance and a multipoint LOD score of 3.3. Linkages related to low HDL-C have been also seen for loci on 16q24.1–24.2 and 20q13.11.[68] Kontio et al., conducted a whole-genome scan for the loci regulating plasma HDL-C levels in 35 well-defined Finnish extended pedigrees with probands having low HDL-C levels, and discovered five loci with the strongest confirmation of linkage on chromosomes 4p12, 6p24, 6p12, 15q22 and 22q11.[69] Daneshpour et al., investigated possible genes linked to low HDL-C and metabolic syndrome in 107 Iranian families and found that 8q22–24; 11q23–25 and 16q23–24 regions are very likely to contain genes that control HDL-C levels in Iranian families with the metabolic syndrome.[70]

Association studies

A common and important mission in genetic association studies is the identification of SNPs and SNP interactions associated with a disease. Nowadays, results of genetic association studies are gathered in databases such as the database of Genotypes and Phenotypes (dbGaP) or the catalog of human genome. Many gene association studies have investigated HDL-C levels over the years. Here we will summarize only the main conclusions of common genetic polymorphisms related to low HDL-C (Figure 4). Daneshpour et al., showed TaqI polymorphism at -629CIA in CETP gene to be associated with low HDL-C in Tehran. In another study, Daneshpour et al., identified that there is no significant relationship between HDL cholesterol levels and Hepatic lipase C-514T polymorphism in Tehran.[72,73] Zarkesh et al., revealed that the genetic polymorphism of Apo E, a structural protein of HDL-C, is significantly associated with HDL-C concentrations. Serum HDL-C decreases in the presence of E4 allele.[74] Saez et al., stated that the 5' end and intron 8 of the WWOX gene are associated with HDL levels; WWOX encodes a protein which contains 2 WW domains and a short-chain dehydrogenase/ re-

Table 1. Summary of the most important genome-wide linkage analyzes identified for HDL-C.[71]

Locus	Number of Families	LOD Score	Study
2q21.3	330 families (Framingham Heart Study)	3.5	Arya, et al.
4q21.21	13 French-Canadian families	4.6	Yu, et al.
5p13.3	101 Caucasian families (NHLBI Study)	3.6	Peacock, et al.
6q23.1 (HDL3-C)	330 families (Framingham Heart Study)	4.0	Yang, et al.
7p15-22	388 Caucasian families (Gene Quest)	3.76	Yang, et al.
7q31.32	295 African-American diabetic sib pairs	4.3	Adeyemo, et al.
8q23.1-24.22	25 Finnish families	4.7.	Soro, et al.
8q23.1-24.22	10 Mexican-American families (San Antonio Heart Study)	4.9	Almasy, et al.
9p21.3	27 Mexican-American families	3.4	Arya, et al.
11q23.3	105 families from Utah	3.5	Kort, et al.
12q14.1	292 pedigrees (Quebec Family Study)	4.1	Bosse, et al.
15q22.31	10 Mexican-American families (San Antonio Heart Study)	3.3	Almasy, et al.
15q21-26	388 Caucasian families (Gene Quest)	6.69	Yang, et al.
16q22.3-23.1	10 Mexican-American (San Antonio Heart Study)	4.3	Mahaney, et al.
16q22.3-23.1	48 Dutch and Finnish families	3.4	Pajukanta, et al.

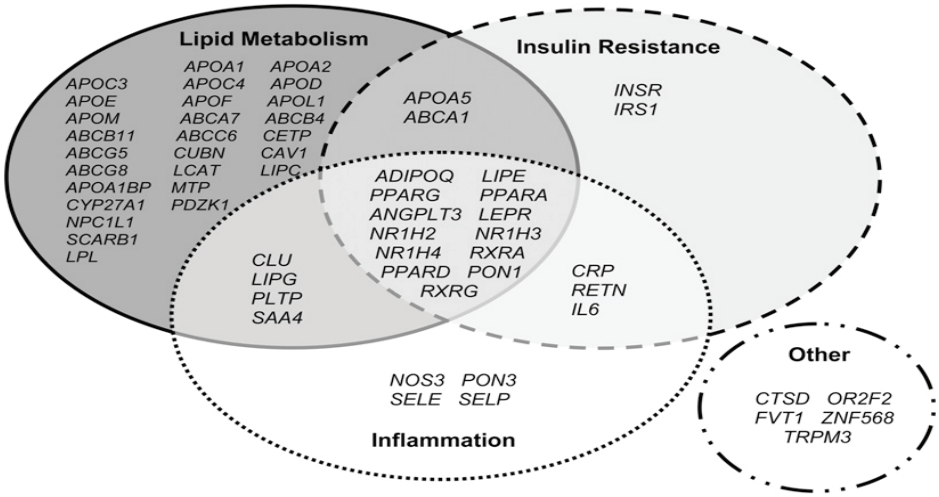

Figure 4. Gene polymorphisms that directly influence HDL metabolism, as well as genes that may indirectly influence HDL-C concentrations (diabetes, insulin resistance, and inflammation).[81]

ductase domain (SRD).This gene plays an important role in steroid metabolism.[75] Hepatic lipase encoded by the hepatic lipase gene (LIPC) is involved in metabolism of several lipoproteins. Juo et al., investigated that promoter polymorphisms of hepatic lipase gene influence HDL2 concentration in African American men.[76] TRIB1 is located on 8q24 and is one of the potential candidate genes that play an important role in cholesterol metabolism and the atherosclerosis process. Aung et al., have indicated that some TRIB1 polymorphisms and TRIB1 over-expression are related to low HDL-C levels.[77] Many studies show thatABCA1, apolipoprotein (Apo)A1M1, ApoA1M2, ApoB, ApoAIV, Apo CIII, SRB1 and the LPL gene polymorphisms are associated with HDL-C concentrations.[78–80]

Discussion

In this article, we review genetic studies that addressed genetic factors contributing to low levels of HDL-C. Coronary heart disease is a major cause of death and disability worldwide and low levels of HDL-C are the most common plasma lipid abnormality observed in patients with established coronary heart disease.[82] HDL is the smallest and densest lipoprotein because it contains the highest proportion of protein. The liver synthesizes this lipoprotein which then circulates and attracts excess free cholesterol from hepatic cells and other types of lipoproteins. Apo A-I and Apo A-II are the main structural proteins of HDL.[13,14] Low HDL-C and very low HDL-C levels defined as HDL-C <40 mg/dL and <20 mg/dL, respectively, are prevalent in patients with both the metabolic syndrome and CAD.[17,18,71] It is well recognized that HDL-C is affected by both genetic backgrounds and environmental factors, including demographics, diet, alcohol consumption, smoking, obesity, and some drugs.[83] Genetic defects associated with low levels of HDL-C consist of ABCA1, APOAI, LCAT, LPL, some metabolic disorders and ANGPTL3 mutations.[28,37,40,48,52,54,60] On the other hand,

studies have revealed that polymorphisms in many genes such as ABCAI, APOAI, TRIB1 , Apo E, LPL, WWOX, HL, LCAT and special chromosomal regions are related to low HDL-C.[70,71,80,81] Raising HDL-C levels is one of the targets in the recent National Cholesterol Education Program ATP III report.[16] Two concepts are important for identifying HDL-regulating genes in terms of regulating plasma HDL-C concentrations; first, the most significant impact of being aware of the defective genes can be effective in helping treatment and can suggest new interventions to inhibit or increase HDL-mediated reverse cholesterol transport. Second, finding HDL-regulating genes have helped in understanding previously unknown mechanisms of some HDL-regulating drugs and currently several therapeutic approaches are under development based on genetic studies.[70,82]

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