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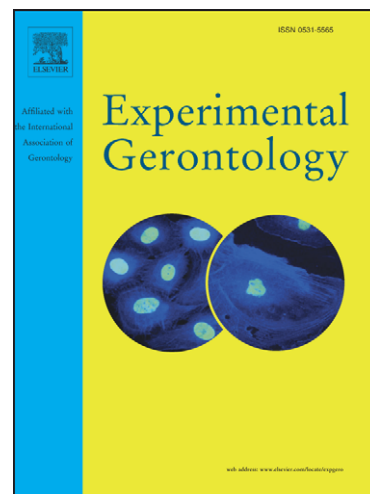
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Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: A systematic in-depth review

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Abstract

High-density lipoprotein (HDL) particles exhibit multiple antiatherogenic effects. They are key players in the reverse cholesterol transport which shuttles cholesterol from peripheral cells (e.g. macrophages) to the liver or other tissues. This complex process is thought to represent the basis for the antiatherogenic properties of HDL particles. The amount of cholesterol transported in HDL particles is measured as HDL cholesterol (HDLC) and is inversely correlated with the risk for coronary artery disease: an increase of 1 mg/dL of HDLC levels is associated with a 2% and 3% decrease of the risk for coronary artery disease in men and women, respectively. Genetically determined conditions with high HDLC levels (e.g. familial hyperalphalipoproteinemia) often coexist with longevity, and higher HDLC levels were found among healthy elderly individuals.

HDLC levels are under considerable genetic control with heritability estimates of up to 80%. The identification and characterization of genetic variants associated with HDLC concentrations can provide new insights into the background of longevity. This review provides an extended overview on the current genetic-epidemiological evidence from association studies on genes involved in HDLC metabolism. It provides a path through the jungle of association studies which are sometimes confusing due to the varying and sometimes erroneous names of genetic variants, positions and directions of associations. Furthermore, it reviews the recent findings from genome-wide association studies which have identified new genes influencing HDLC levels.

The yet identified genes together explain only a small amount of less than 10% of the HDLC variance, which leaves an enormous room for further yet to be identified genetic variants. This might be accomplished by large population-based genome-wide meta-analyses and by deep-sequencing approaches on the identified genes. The resulting findings will probably result in a re-drawing and extension of the involved metabolic pathways of HDLC metabolism.

1. Introduction

1.1. HDL metabolism

High-density lipoproteins (HDL) are a heterogeneous group of particles composed of a core of cholesteryl ester and triglycerides surrounded by an amphipathic layer of free cholesterol, phospholipids and apolipoproteins (apo) (Klos et al., 2007).

HDL particles exhibit multiple antiatherogenic effects (Kontush et al., 2006). They shuttle cholesterol from peripheral cells (e.g. macrophages) to the liver or other tissues in need of large amounts of cholesterol (Bruce et al., 1998), an important step that relieves the peripheral cells from cholesterol burden (Figure 1). The concept for this complex process was first proposed by Glomset et al. 40 years ago (Glomset 1968) and is called reverse cholesterol transport. It is thought to represent the basis for the antiatherogenic properties of HDL (Kontush et al., 2006; Von Eckardstein et al., 2001). Furthermore, HDL has antioxidative properties due to associated antioxidative enzymes and expresses anti-inflammatory activity in various pathways.

Figure 1 illustrates the major routes of lipoprotein metabolism to allow a better understanding of the HDL metabolism (Kwan et al., 2007). HDL precursor particles are secreted as disc-shaped structures by the liver and intestine and can absorb free cholesterol from cell membranes, a process mediated by ABCA1, apoA-I and apoA-IV. While ABCA1 presents the best understood active cholesterol efflux mechanism, the HDL-mediated removal of free cholesterol from the peripheral cells is also aided by other active transporters such as ABCG1 as well as by passive diffusion which can be enhanced by plasma membrane receptors such as SCARB1 (Cavelier et al., 2006). ApoA-I is the major apolipoprotein of HDL and activates the enzyme lecithin:cholesteryl acyltransferase (LCAT), which esterifies the accepted free cholesterol to allow more efficient packaging of the cholesterol for transport. By acquisition of additional apolipoproteins, cholesteryl esters, and triglycerides, HDL₃ particles are transformed into spherical HDL₂ particles (Dieplinger et al., 1985). Reverse cholesterol transport can take three different routes. First, large HDL particles with multiple copies of apoE can be taken up by the liver via the LDL receptor (Bruce et al., 1998). Second, the accumulated cholesteryl esters from HDL can be selectively taken up by the liver mediated by SR-B1 (Acton et al., 1996). This receptor is expressed primarily in liver and nonplacental steroidogenic tissues. Third, cholesteryl esters are

transferred by the cholesteryl ester transfer protein (CETP) from HDL to triglyceride-rich lipoproteins (Bruce et al., 1998). Serum HDL cholesterol levels are influenced by the complexity of these reverse cholesterol transport processes. Disturbances in the concentrations of apoproteins, function of enzymes, transport proteins, receptors, other lipoproteins, and their clearance from plasma can have a major impact on the anti-atherogenic properties in HDL.

1.2. HDLC and epidemiological evidence for antiatherogenic properties

High-density lipoprotein (HDL) particles exhibit multiple antiatherogenic effects (Kontush et al., 2006) and HDL cholesterol (HDLC) concentrations show a strong inverse correlation with the risk of coronary artery disease (CAD) (Lewington et al., 2007). Epidemiological studies highlighted the antiatherogenic function of HDLC and showed that an increase of 1 mg/dL of HDLC levels is associated with a 2% and 3% decrease of the risk for CAD in men and women, respectively (Wilson 1990; Linsel-Nitschke et al., 2005). A recent meta-analysis (Lewington et al., 2007) including prospective observational studies with HDLC measurements available in 150,000 individuals demonstrated a strong negative association with ischemic heart disease mortality in every age group, with no evidence of a threshold beyond which higher HDL cholesterol was no longer associated with lower mortality. On average, 13 mg/dL higher HDL cholesterol was associated with about a third lower ischemic heart disease mortality. Within every age group, the strength of this association was comparable for men and women. Moreover, clinical trials have established that increasing HDLC levels by drugs could reduce CAD risk (Gotto, Jr. 2001; Manninen et al., 1988; Rubins et al., 1999; Kronenberg 2004), thus bringing longer life expectancy. This hypothesis is compatible with observations that familial hyperalphalipoproteinemia often coexists with longevity (Patsch et al., 1981), and that higher HDLC levels are found among healthy elderly aged 85-89 years as compared to those in middle-aged subjects (Nikkila et al., 1990). Accordingly, HDL and molecules involved in HDL metabolism seem to be attractive candidates for longevity-promoting factors (Arai et al., 2004).

Since HDLC levels are under considerable genetic control with heritability estimates of up to 80% (Kronenberg et al., 2002; Perusse et al., 1997; Wang et al., 2005; Goode et al., 2007), the identification and characterization of genetic variants associated with HDLC concentrations can provide useful information related to genotype-phenotype relationships and give new insights in the background of longevity.

This article reviews the current genetic-epidemiological evidence from association studies on genes involved in HDL metabolism. Genetic association studies establish estimates for a difference of mean HDLC levels among subjects with a certain genetic variant compared to the others and thus a measure of association between the genetic background and HDLC outcome in human beings. This overview should provide a path through the jungle of association studies often reporting different names and positions for the same genetic variant under study. Furthermore, the associations are sometimes reported in the direction of the “risk allele”, that is the genetic variant associated with increased CAD risk and thus lower HDLC levels, or in the direction of the “minor allele”, that is the less frequently appearing variant in the population, which may even differ between study populations. Furthermore, it reviews the recent findings from genome-wide association studies, which have identified new genes influencing HDLC levels and provides a first taste on the future. It is not intended to provide an overview on functional studies.

2. Methods on literature search

The literature search for genes previously reported for association with HDLC was performed in PubMed using search terms such as “(meta-analysis OR associat* OR epidemiolog*) AND (polymorphism OR genetic OR mutation) AND HDL AND human” with an Entrez Date in PubMed until April 2008 (EDAT: the date the citation was added to PubMed). Results were complemented by knowledge of the lipid-experienced investigators of this study.

Eligible studies for data extraction were meta-analyses, population-based studies, studies in the general population, healthy control populations, hospital-based controls, control populations selected for not having type 2 diabetes mellitus (T2DM), and case-control studies for cardiovascular disease (CVD) or T2DM. Studies which were included in a meta-analysis were only indirectly considered by showing the results of this meta-analysis in the tables instead of each single study. We did not consider studies with special patient populations other than cardiovascular disease or T2DM (e.g. patients with chronic kidney disease).

Exclusion criteria for our search were studies in a non-English language where only the abstract was available in English and small studies with less than 500 individuals.

Studies which investigated a large number of genetic variants were only considered to provide statistically significant association, if the associations were strong enough to hold for a significance level corrected for the multiple comparisons. This was usually not sufficiently accounted for in the reported associations. Moreover, we omitted studies on polymorphisms with a too low minor allele frequency (MAF) yielding less than about 30 study participants with the minor allele considering the number of individuals investigated.

If the results of a particular polymorphism of a certain study population were considered in more than one publication, only one of these publications was referenced in our tables.

A gene was considered an HDLC candidate gene if at least two eligible studies reported a statistically significant association of genetic variation within or related to the particular gene with HDLC levels. An exception from this rule was made for *LCAT* for which strong functional evidence was available combined with one large and a few small association studies.

Rarely investigated genetic variations that showed a significant association with HDLC levels in at least one large study ($n > 1000$) are listed in an additional table (Table 11).

Tables 1-11 and the Supplementary Table show the results of all eligible candidate gene association studies which were accessible in PubMed until the Entrez Date April 2008. Even though we draw our attention to the fact not to miss the most important studies, we are aware that it might not have been possible to have complete lists of all studies which deal with candidate genes for HDL cholesterol.

It should be noted that identifying the precise rs numbers of some polymorphisms was very tedious if not impossible as rs numbers were often lacking or mistakenly reported and in some of these cases we were only able to derive rs numbers by combining literature reports with databases such as HapMap or NCBI. In some cases the effect size of the investigated SNP on HDL cholesterol was only displayed in a figure and allowed only an approximate estimate of the numerical value.

For the single nucleotide polymorphisms (SNPs) of the candidate genes reported in the Tables 1-9 we imported data from HapMap and constructed an r^2 -plot using HaploView 4.1 to illustrate the correlation of the SNPs reported for each gene. For *APOA1*, *APOC3* and *PON1* no r^2 -plot was constructed since only one or none of the tabulated SNPs was available in HapMap. Furthermore, rs2303790 of *CETP* and rs2066718 of *ABCA1* are not displayed in the r^2 -plots since the MAF of these SNPs was 0.0% for the imported HapMap data.

A further chapter reviews the evidence recently derived from genome-wide association (GWA) studies. SNPs derived from these studies are not listed in Tables 1-11 but are provided in an extra table (Table 12).

3. Results from candidate gene association studies

3.1. Cholesteryl ester transfer protein (CETP)

The *CETP* gene is located on chromosome 16 and consists of 16 exons and 15 introns and is a member of the lipopolysaccharide binding protein gene family (Yamashita et al., 2001). The gene locus is highly polymorphic with several common polymorphisms as well as rare mutations (Thompson et al., 2007).

CETP is a key plasma protein that influences circulating levels of HDLC by mediating the transfer of esterified cholesterol from HDL to apoB-containing particles in exchanges for triglycerides (Tall 1993) (Figure 1). The effect of this transfer is an increase in atherogenic apoB-containing particles and a decrease of HDL (Carlquist et al., 2007). The lipid profile typically seen in subjects with CETP deficiency includes elevated HDL cholesterol levels with LDL cholesterol levels generally in the normal range (Miller et al., 2003). Complete loss of CETP activity due to mutations in the *CETP* gene can result in up to five times the normal HDLC levels, heterozygous deficiency of CETP result in milder (10-30%) increases in HDLC levels (Klos et al., 2007).

A great number of studies investigated the association of *CETP* polymorphisms with HDLC concentrations and the evidence for an association is very clear (Table 1). Although these SNPs are in strong linkage disequilibrium they are not necessarily strongly correlated (Heid et al., 2008; Thompson et al., 2007; McCaskie et al., 2007). SNPs reported in Table 1 that were genotyped in HapMap were for the most part only weakly correlated with each other (Figure 2). Some of the investigated SNPs showed pronounced additive influences on HDLC levels with changes of 2-3 mg/dL per copy of the minor allele. Meta-analyses including more than 10,000 individuals are available for rs708272 (*Taq1B*) and rs5882 (Ile405Val) showing a clear association of these SNPs with HDLC levels (Boekholdt et al., 2003; Boekholdt et al., 2005). Recently, a dense genotyping approach in more than 2000 individuals provided a very clear overview on the genetic variability within this gene and its associations with HDLC levels (Thompson et al., 2007). During the review process of this manuscript, a further meta-analysis on *CETP* was published (Thompson et al., 2008), which

is not included in Table 1 since the Entrez Date in PubMed was after our deadline of April 2008. The results of this meta-analysis which included 26 to 72 studies with 39,581 to 68,134 participants for the three common SNPs rs708272 (*Taq1B*), rs5882 (I405V), and rs1800775 (-629C>A) are in line with the results of the other studies listed in Table 1 and underline the significant influence of the *CETP* gene on HDLC levels.

3.2. Lipoprotein lipase (LPL)

Lipoprotein lipase is a critical enzyme involved in lipolysis of triglyceride-rich lipoproteins, chylomicrons and VLDL (Miller et al., 2004). LPL does not act directly on HDL, but its action on triglyceride-rich lipoproteins has an important indirect effect on HDL metabolism (Lewis et al., 2005) (Figure 1). Familial LPL deficiency is a rare autosomal recessive disorder characterized by absence of LPL activity and a massive accumulation of chylomicrons in plasma. Homozygous deficiency is associated with severe hypertriglyceridemia and marked reductions in high- and low-density cholesterol levels (Klos et al., 2007).

Our literature search identified nine polymorphisms investigated for an association with HDL cholesterol (Table 2 and Supplementary Table). Most of these SNPs showed a significant association with HDLC levels (Table 2), whereas no study found a significant association for the common polymorphism rs285, which is only weakly correlated with the other SNPs (Supplementary Table and Figure 2). Five of the seven SNPs available in HapMap are located in a block of strong linkage disequilibrium (Heid et al., 2008) and especially rs320, rs326, rs13702 and rs10105606 show high correlations (Figure 2). A meta-analysis is available for four common polymorphisms which demonstrated significant associations with HDLC (Wittrup et al., 1999): the minor allele of rs328 (S447X respectively S474X according to NCBI) in >4000 individuals was associated with increased HDLC levels, whereas the minor alleles of rs268 (N291S) in almost 15,000 individuals, Gly188Glu (no rs number available) in >10,000 individuals and rs1801177 (D9N) in >5000 individuals were associated with lower HDLC levels.

3.3. Hepatic lipase (LIPC, HL, HTGL)

The human *hepatic lipase* gene, *LIPC*, is located on chromosome 15q21. It comprises 9 exons and 8 introns, and spans a length of more than 30 kb. It encodes a protein of 449 amino acids with a signal peptide of 23 amino acids (Cai et al., 1989; Ameis et al., 1990). Hepatic lipase is a glycoprotein of approximately 65 kDa and is synthesized in hepatocytes and then secreted and bound to hepatocytes and hepatic endothelial surfaces. Hepatic

lipase specifically catalyzes the hydrolysis of triglycerides, diglycerides and phospholipids in native lipoproteins (Miller et al., 2003). It appears to be involved in the selective uptake of cholesterol ester from HDL (Lambert et al., 2000) (Figure 1). To date, few patients with true hepatic lipase deficiency have been identified. All individuals with complete deficiency have had elevated plasma cholesterol and triglyceride concentrations. Furthermore, deficiency is characterized by abnormally triglyceride-rich HDL and LDL particles as well as high levels of HDLC (Cohen et al., 1999; Holleboom et al., 2008).

Seven SNPs in *LIPC* were reported to be associated with HDLC levels, two of them showing a very consistent association: rs1800588 and rs2070895 (Table 3). On six of the seven SNPs data are available in HapMap, and the r^2 -plot indicates a strong correlation between three of these SNPs which are all located in the promoter region of *LIPC* (Figure 2). A meta-analysis including more than 24,000 individuals is available for rs1800588 (also described as C-514T or C-480T) showing that one or two copies of the minor allele increase HDLC levels by 1.5 and 3.5 mg/dL, respectively (Isaacs et al., 2004).

3.4. Endothelial lipase (EL, LIPG)

Endothelial lipase (encoded by the *LIPG* gene) was discovered in 1999 independently by two different laboratories (Jaye et al., 1999; Hirata et al., 1999) and is a member of the triglyceride lipase gene family. This enzyme derived its name because of its expression by endothelial cells (Jaye et al., 2004). Since overexpression of *LIPG* in mice resulted in marked reduction of HDLC levels (Jaye et al., 1999), this has led to the concept that *LIPG* may play an important role in HDL metabolism. It promotes the turnover of HDL components and it increases the catabolism of apolipoprotein A-I (Figure 1). It was proposed that the endothelial lipase together with the hepatic lipase converts large HDL particles to smaller particles by its phospholipase activity (Jaye et al., 2004). Evidence is increasing that endothelial lipase might play a role in the etiology of the lipoprotein profile characteristic of the metabolic syndrome and an increased activity of this enzyme is linked to the underlying proinflammatory state in the metabolic syndrome (Lamarche et al., 2007).

In our literature search we found five SNPs of *LIPG* which were significantly associated with HDL levels (Table 4). The evidence for an association is less strong as for *CETP*, *LPL* and *LIPC* and the studies available are much smaller than for these three genes. Four of these SNPs were available in HapMap, three of them are strongly correlated with r^2 ranging from 0.31-0.96 (Figure 2).

3.5. Lecithin:cholesterol acyltransferase (LCAT)

LCAT is associated with HDL and esterifies cholesterol in plasma (Figure 1). ApoA-I serves as a cofactor for this reaction (Miller et al., 2004; Klos et al., 2007). Important knowledge on the function of this gene was derived from patients with LCAT deficiency which results in free cholesterol and phosphatidylcholine deposition in membranes followed by corneal opacification (fish-eye disease), anemia, and renal failure (Miller et al., 2004). Homozygous LCAT deficiency is an underlying cause of two conditions: familial LCAT deficiency and fish-eye disease. While the former is associated with the complete loss of LCAT activity, the latter is associated with a change in the substrate specificity of LCAT that becomes inactive toward HDL cholesterol, while retaining its activity toward LDL cholesterol. Both conditions are characterized by severe hypoalphalipoproteinemia, but only familial LCAT deficiency is strongly associated with premature CAD (Sviridov et al., 2007).

Even though *LCAT* is due to its physiological function an important HDL candidate gene, only few large studies investigated the possible role of this gene on HDLC levels. Five polymorphisms of *LCAT* were investigated for an association with HDLC levels, but the findings are not entirely consistent (Table 5). The two SNPs available in HapMap (rs4986970 and rs2292318) are not correlated at all with each other (Figure 2) which could explain the presence of association with HDLC for one SNP (rs2292318) and the lack of association for the other SNP (rs4986970). An influence of *LCAT* on HDLC levels is supported by genome-wide association studies (see below). There is an urgent need for large studies investigating the influence of common and rare genetic variations of this candidate gene on HDLC levels.

3.6. Scavenger receptor class B type 1 (SCARB1, SR-B1)

The *SCARB1* gene has been localized to chromosome 12 spanning a region of 75 kb containing 13 exons. The gene encodes a receptor protein of approximately 80 kDa, whose weight can vary based on its extent of glycosylation. *SCARB1* is highly expressed in liver and steroidogenic tissue (adrenal, ovaries, and testes) (Cao et al., 1997). It was isolated and characterized as a functional hepatic receptor for HDL (Acton et al., 1996). This receptor participates in the selective uptake of cholesterol ester (Miller et al., 2003), and binds a number of ligands with high affinity, including native HDL (Cao et al., 1997). The selective uptake involves the transfer of cholesterol from the HDL particle and the release of the lipid-poor HDL particle into the plasma (Acton et al., 1996) (Figure 1). It should be mentioned that *SCARB1* has predominantly been studied in animal models where it has been shown to

control levels of plasma HDLC and non-HDL cholesterol as well as the propensity for atherosclerosis (Miller et al., 2003), but it has to be determined whether this receptor has an equally important function in humans.

Despite the obvious functional evidence for an influence of *SCARB1* on HDLC levels, the genetic-epidemiological evidence is relatively weak. Our literature search identified five polymorphic sites studied with HDLC levels with inconsistent results (Table 6). The two variants found in HapMap (rs5888 and rs5891) show no correlation with each other (Figure 2). Large genetic epidemiological studies on this gene are required before a final conclusion can be drawn.

3.7. ATP binding cassette transporter A1 (*ABCA1*)

The ATP binding cassette group of transporter proteins is involved in the transfer of various substances across plasma membranes, including ions, peptides, vitamins, and hormones. The *ABCA1* transporter is expressed in liver, macrophages and steroidogenic tissues and plays a pivotal role in the initial phase of reverse cholesterol transport by mediating cholesterol and phospholipid efflux from macrophages to HDL (Miller et al., 2003; Cavelier et al., 2006) (Figure 1). Far more than 1000 polymorphic sites within this gene are known. We appreciate the most important knowledge on *ABCA1* and its influence on HDL metabolism to a rare monogenic recessive disorder, called Tangier disease in which patients carry homozygous mutations in *ABCA1* (Bodzioch et al., 1999; Rust et al., 1999; Brooks-Wilson et al., 1999). This causes a deposition of cholesteryl esters in the reticuloendothelial organs which results in orange-colored tonsils. Cholesterol is entrapped in macrophages due to the heavily disturbed cholesterol efflux. This results in lipid-depleted HDL particles rapidly catabolized and HDL deficiency.

Since the *ABCA1* transporter plays an important physiological role in HDL metabolism, many studies attempted to show an association of this candidate gene with HDLC levels. Table 7 and the Supplementary Table list 19 SNPs of *ABCA1* that were investigated in the literature. However, most studies did not reveal large effects of these polymorphisms on HDLC levels although many included a large number of individuals. An explanation for this failing might be that a lot of rare (population frequency below 1%) and very rare (also called "private") mutations in *ABCA1* with strong effects for each, could sum to an important influence on HDL metabolism (Cohen et al., 2004). These rare mutations are hardly to be pinpointed by association studies due to the small number of mutation carriers even in large

studies. A typical example was recently shown by the Copenhagen City Heart Study (Frikke-Schmidt et al., 2008b) which could demonstrate in more than 9000 participants a pronounced effect for four rare mutations in *ABCA1* on HDL cholesterol levels (a reduction of 17 mg/dL for heterozygotes vs noncarriers, $p < 0.001$).

The r^2 -plot of the 9 available SNPs in HapMap shows that most SNPs are only weakly correlated which suggests that the missing associations of the single SNPs with HDL levels are independent of each other (Figure 2).

3.8. Apolipoprotein A-I (APOA1)

APOA1 is located in the *APOA1/C3/C4* gene cluster on human chromosome 11q23 which harbors also *APOA5*.

As the major protein component of the HDL particle, apoA-I is an important ligand for HDL binding to cellular receptors, including scavenger receptor class B type 1 and *ABCA1* (Rigotti et al., 1997; Remaley et al., 2001). Therefore, apoA-I serves as a cofactor for cholesterol esterification and is an important component of the reverse cholesterol transport (Miller et al., 2003) (Figure 1). The clinical importance of apoA-I is underscored by a premature CVD in families with *APOA1* deficiency and by a marked atherosclerosis in knockout mouse models (Miller et al., 2003). Patients carrying two functionally-relevant mutations in *APOA1* being either homozygous or compound heterozygous, have extremely rare states of complete HDLC deficiency (Funke 1997) and present with two different clinical hallmarks, namely xanthomas or corneal opacities (Von Eckardstein 2006).

In our literature search we found three SNPs (rs670, rs5069 and rs5070) which were investigated for an association with HDLC levels. Mostly, large studies found a significant association with HDLC levels, but further large studies are required (Table 8 and Supplementary Table).

3.9. Apolipoprotein C-III (APOC3)

Apolipoprotein C-III is a component of triglyceride-rich lipoproteins and HDL particle and is transferred to HDL during the hydrolysis of triglyceride-rich lipoproteins (Miller et al., 2004). The major physiological role of ApoC-III appears to be an inhibiting effect on LPL (Figure 1).

For the *APOC3* gene, data on the influence of genetic variability on HDLC levels are heterogeneous. If indeed present, the influence seems to be weak (Table 8).

3.10. Apolipoprotein A-V (APOA5)

APOA5 is located proximal to the *APOA1/C3/C4* gene cluster and was recently described by two groups (Pennacchio et al., 2001; van der Vliet et al., 2001). The human *APOA5* gene consists of four exons and codes a 369 amino acid protein, expressed only in the liver (Hubacek 2005). ApoA-V is predominantly located on TG-rich particles, chylomicrons and VLDL but also on HDL, and there is evidence that ApoA-V serves as an activator of LPL (Hubacek 2005) (Figure 1).

Among the apolipoproteins, *APOA5* is the gene with the most pronounced associations with HDLC levels. Many polymorphisms of *APOA5* were investigated in the literature, and most of them show an association with decreased levels of HDLC (Table 8). Only four SNPs are available in HapMap which are only weakly associated except rs662799 and rs651821 with a strong correlation (Figure 2).

3.11. Ghrelin (GHRL)

Ghrelin was only recently described by Kojima et al. (Kojima et al., 1999). Ghrelin is an endogenous peptide, its active form is composed of 28 aminoacids and circulates in plasma in a concentration of ~800-1000 pg/mL. Ghrelin is an orexigenic peptide predominantly produced by the stomach. Accumulating evidence suggests that ghrelin is a key regulator of body weight (Cummings et al., 2003).

Two studies found a significant inverse association of four polymorphisms with HDLC levels whereas another study found no association of five SNPs with HDLC (Table 9). The effects of the SNPs on HDLC levels seem to be independent from each other since most of the SNPs available in HapMap are not highly correlated (Figure 2).

3.12. LDL-receptor (LDLR)

The LDL-receptor is a cell surface receptor that mediates the uptake of LDL particles from the circulation via receptor-mediated endocytosis (Hobbs et al., 1990). Since this receptor plays an important role in plasma lipoprotein homeostasis (Muallem et al., 2007) (Figure 1), genetic variations in the *LDLR* gene that alter its expression could contribute to inter-individual differences in lipoprotein levels.

Some of the five literature-reported polymorphisms in the *LDLR* gene show an association with HDLC levels, which was not confirmed by other SNPs (Table 9). For the four

SNPs available in HapMap, rs688 and rs5925 showed strong correlations ($r^2=0.96$) (Figure 2).

3.13. Paraoxonase 1 (PON1)

Paraoxonase 1 is a member of the paraoxonase family that includes three isoenzymes; their genes are clustered on chromosome 7q21.3-22.1 (Primo-Parmo et al., 1996). PON1, a HDL-associated enzyme, is partly responsible for the antioxidation properties of HDL by protecting low-density lipoproteins against oxidation (Mackness et al., 1991).

The *PON1* gene has two widely investigated polymorphisms, the Gln192Arg and the Met55Leu, but the results are not entirely convincing (Table 9). A strong linkage disequilibrium exists between the two polymorphisms (Arca et al., 2002).

3.14. Apolipoprotein E (APOE)

ApoE is a part of chylomicrons, VLDL, IDL and of some subspecies of HDL (Sviridov et al., 2007) (Figure 1). The role of *APOE* polymorphism in determining VLDL-LDL levels is well known, but its independent influence on HDLC concentration is still controversial (Sviridov et al., 2007).

A connection between the *APOE* polymorphism and HDLC levels was found in many but not all studies (Table 10). Since *APOE* is the best investigated of all known polymorphisms with far more than 50 publications that investigated an association with HDLC levels, we only referenced large population-based studies with more than 1000 individuals per study. Almost all of these studies found the E2 allele with increased and the E4 allele with decreased HDL levels compared to the E3 allele.

4. Results on rarely investigated genes

Table 11 provides the results on genes rarely investigated which showed a significant association with HDLC levels in at least one large study ($n>1000$). It might be a worthwhile attempt to replicate the shown associations with HDLC in further large studies.

5. Negative results on often investigated genes

Many studies investigated the association of the *APOA4* gene and HDLC levels. The most frequently investigated polymorphisms are the T347S (rs675) and Q360H (rs5110).

Especially the large studies with sample sizes above 1000 did not show a significant association of these polymorphisms with HDLC levels (data not shown).

The same holds true for *APOB*: several studies investigated the association of this gene with HDLC levels. Large studies, however, showed non-significant results (data not shown). A recent genome-wide association study with almost 18,000 individuals from 16 population-based cohorts found apoB to be associated with HDLC levels ($p=4.4 \times 10^{-8}$) (Aulchenko et al., 2008).

6. Common versus rare variants

Common variants are those that appear in the general population with a frequency $>1\%$ or even $>5\%$ of subjects. These variants often show, individually, rather small associations. Kathiresan et al. illustrated, however, that a combining of the information on several of these low-impact common variants can contribute to some extent to the prediction of HDLC levels (Kathiresan et al., 2008a). They studied nine SNPs at nine loci in 5287 subjects, created a genotype score on the basis of the number of unfavorable alleles and found decreasing HDLC levels with increasing genotype scores. Another study (Zietz et al., 2006) investigated five polymorphisms in different genes and found a significant association between the number of rarely occurring genotype combinations and HDLC levels, whereas each single polymorphism was not associated with HDLC levels.

Rare variants are those that appear with $<1\%$ in the general population. Cohen and colleagues (Cohen et al., 2004) investigated whether rare DNA sequence variants collectively contribute to variation in HDLC levels by sequencing *ABCA1*, *APOA1*, and *LCAT* in individuals from a population-based study. Nonsynonymous sequence variants were eight times more common (16% vs. 2%) in individuals with low HDLC (<5 th percentile) than in those with high HDLC levels (>95 th percentile). Biochemical studies indicated that most sequence variants in the low HDLC group were functionally important. The authors concluded that rare alleles with major phenotypic effects contribute significantly to low plasma HDLC levels in the general population. This seminal work started a new era with a focus on rare variants, and it is a consequent step to search these variants after a gene has been pinpointed by common variants to contribute to a certain phenotype.

Other examples for genes with rare variants having an important influence on HDLC levels are the angiotensin-like 4 (*ANGPTL4*) gene (variant E40K, MAF=2%) which was

associated with significantly higher levels of HDLC ($p=4.0 \times 10^{-7}$) in 8726 individuals of the ARIC Study (Romeo et al., 2007) or rare variants in the alcohol dehydrogenase 2 (*ADH2*) gene (MAF=2.8%) (Whitfield et al., 2003) or in the cytochrome P450, family 3, subfamily A, polypeptide 4 (*CYP3A4*) gene (MAF=0.5%) (Yamada et al., 2007) which showed significant associations in 901 and 3787 individuals, respectively.

These studies highlight several important aspects for quantitative traits: 1) multiple common alleles influence trait variation, with each allele conferring a modest effect; 2) although each SNP exerts a modest effect, a combination of SNPs in aggregate can have a substantial influence on HDL levels; and 3) many rare alleles of candidate genes with a strong effect of each allele might have a pronounced influence on the trait under investigation in the studied population. Considering that all common alleles together explain less than 5-10% of HDLC levels in the general population and that HDLC levels are under considerable genetic control with heritability estimates of up to 80% (Kronenberg et al., 2002; Perusse et al., 1997), leaves a wide space for rare variants as well as for genetic regulatory mechanisms not yet well understood.

7. New insights from genome-wide association studies

7.1. Advantages of genome-wide association studies

The recent introduction of microarray technology for genotyping allows the genotyping of several hundreds of thousands genetic variants in a single person in one step. This enables genome-wide association (GWA) studies by genotyping a large number of individuals with phenotypes of interest at reasonable costs. Compared to a hypothesis-driven candidate gene approach as described in the chapters above the hypothesis-free GWA studies can identify new susceptibility genes without making any *a priori* biological assumptions. They permit to identify genes involved in pathways which until now were unknown to be involved in a certain phenotype. GWA studies are therefore a new and very powerful tool to identify genetic contributors to phenotypes and have revolutionized gene hunting (for review see (Kronenberg 2008; McCarthy et al., 2008). There was never a time before in which in such a short time an unbelievable high number of genes for complex diseases and phenotypes has been identified. This holds true for complex diseases such as T2DM (Frayling 2007), cancer as well as continuous variables such as lipids.

The introduction of GWA studies allowed to leave the path of hypothesis-driven search for genes influencing lipid levels, which was based on a limited a priori knowledge on biological and physiological processes involved in lipid metabolism. GWA studies allow to widen the horizon and to detect new genes involved in lipid metabolism. The identification of genes, however, is strongly dependent on the power of GWA studies which is usually quite low considering the fact that 500,000 SNPs and more are investigated at once, which creates a pronounced multiple testing problem with up to 25,000 false positive findings if the conventional significance threshold of $p < 0.05$ is used. A decrease of this threshold to a genome-wide significance level (e.g. $p < 10^{-7}$) and an increase in the number of samples studied increases the power and allows to bring the "real" genes out of the jungle of false positive associations. Therefore, the step from the single study to the meta-analysis was never before as short as in times of GWA studies. The researchers in this field realized immediately that they are more successful when combining their studies, which allows to identify even gene variants modifying the disease risk by only 10% or explaining less than 0.5% of the variance of continuous parameters.

7.2. Findings on HDLC by genome-wide association studies

Until now eight GWA studies on HDLC levels are available (Willer et al., 2008; Kathiresan et al., 2008b; Kooner et al., 2008; Wallace et al., 2008; Heid et al., 2008; Kathiresan et al., 2007; Aulchenko et al., 2008; Cashman et al., 2008). Results from these studies are summarized in Table 12. On the one hand, they have confirmed the following genes which were already known from earlier functional as well as association studies: *CETP*, *LPL*, *LIPC*, *LIPG*, *ABCA1*, *LCAT*, and the *APOA1C3A4A5 gene cluster*. On the other hand, these studies have identified new candidate genes influencing HDLC levels which need further functional characterization.

The most pronounced association of these newly identified genes was observed for *GALNT2* (Willer et al., 2008; Kathiresan et al., 2008b). This gene would not have been identified in an hypothesis-driven approach since it does not have a known function immediately connected to lipid metabolism. *GALNT2* encodes a widely expressed glycosyltransferase that could potentially modify a lipoprotein or receptor. This gene was also found to be associated with triglyceride concentrations (Willer et al., 2008; Kathiresan et al., 2008b). Another newly identified gene region was located near *MVK* and *MMAB*. These neighboring genes are regulated by *SREBP2*. *MVK* encodes mevalonate kinase, which catalyzes an early step in cholesterol biosynthesis, and *MMAB* encodes a protein that

participates in a metabolic pathway that degrades cholesterol (Willer et al., 2008). *GRIN3A* was identified in the initial GWA with a genome-wide significant p value of 2.5×10^{-8} , but was not confirmed in the combined analysis with the replication samples (Willer et al., 2008). *CLPTM1* was found in two independent GWA studies with a combined p value of 5.79×10^{-6} . However, this SNP was not found by other GWA studies (Willer et al., 2008; Heid et al., 2008; Aulchenko et al., 2008; Cashman et al., 2008).

Future GWA studies under way with even larger study samples and meta-analyses in up to 50,000 to 100,000 study participants will elucidate whether the above mentioned new genes or previously known candidate genes mentioned in chapter 3 and 4 but not yet identified in the hitherto published GWA studies will be confirmed. It can be taken for granted that new candidates will be identified with even smaller effect sizes than for the already identified genes.

Except three GWA studies (Heid et al., 2008; Cashman et al., 2008; Aulchenko et al., 2008), previous studies were mainly based on study participants ascertained for T2DM or the metabolic syndrome (Willer et al., 2008; Kathiresan et al., 2008b; Wallace et al., 2008; Kooner et al., 2008; Kathiresan et al., 2007), which could have obscured the results. Therefore, meta-analyses of population-based studies might have an advantage in identifying new candidates for HDLC levels that are not yet distorted by disease processes or medication. Such a meta-analysis of 16 European population-based cohorts has been published very recently (Aulchenko et al., 2008). For HDL cholesterol, eight regions showed genome-wide significant results. The results of the SNPs with the lowest p value for each of these regions are displayed in Table 12. Five of these regions (*LPL*, *ABCA1*, *LIPC*, *CETP*, and *LIPG*) have been identified in earlier GWA studies, *APOB* was for the first time identified in a GWA study for HDL cholesterol, and two regions (*CTCF-PRMT8* and *MADD-FOLH1*) represent entirely novel regions. The *MADD-FOLH1* locus of chromosome 11 represents a gene desert close to the centromere with no known gene on the 550 kb flanking region, and the two genes *MADD* and *FOLH1* flanking the locus have not been implicated in lipid metabolism. The *CTCF-PRMT8* gene encodes a transcriptional regulator, potentially involved in hormone-dependent gene silencing (Aulchenko et al., 2008). Further studies are needed to examine the potential role of these or neighbouring genes in HDL metabolism.

It is of interest that some loci (*LCAT*, *APOA1C3A4A5*, *GALNT2*, *MVK/MMAB*, *CLPTM1* and *GRIN3A*) identified in earlier GWA studies of mostly diseased populations could not be confirmed in the meta-analysis of 16 European population-based cohorts. It can not be

excluded that they were false positives in earlier studies considering that some were of borderline significance in these studies. Another explanation could be that genetic variation in these genes might play a more pronounced role in populations with metabolic disease-relevant disturbances compared to the general population.

7.3. Conclusion from GWA studies on intergenic regions

One of the most important observation of our and other GWA studies is the fact that strong association signals are observed for SNPs in regions hitherto regarded as “intergenic”. For example, we observed for HDLC very strong signals up to 70kb downstream of *LIPG* and *LPL*, and 10kb upstream of *CETP* (Heid et al., 2008). This is particularly remarkable as the usual current candidate gene studies focus on SNPs within the gene ± 5 kb. While our downstream *LPL* SNPs showed some correlation with previously literature-reported SNPs within the gene, our *LIPG* signals were completely independent from SNPs within the gene or from any SNP reported previously in candidate gene studies. The identified *CETP* SNP 10kb upstream (rs8999419) was independent from all of the numerous SNPs reported in candidate gene studies and was even located in a recombination hotspot which strongly supports this region as an independent locus.

These findings are in line with ideas that several regions within and outside of a gene can have independent effects on the gene function and that even regions far away from the gene harboring transcription factor binding sites, miRNAs, other enhancer elements or yet unknown regulatory elements can remotely control gene function. A similar example is reported for chromosomal region 9p21, which was shown to be associated with myocardial infarction (Samani et al., 2007) and T2DM (Scott et al., 2007; Saxena et al., 2007). SNPs with the most significant signals were located more than 100kb upstream of the cyclin-dependent kinase inhibitors *CDKN2A* and *CDKN2B*, which supports either long-range effects on one of these genes or the influence of a gene not yet annotated. This supports the relevance of intergenic regions and calls for future functional studies to address this issue.

As we discussed recently (Heid et al., 2008), the relevance of genetic variation far outside of the gene might have far reaching consequences for candidate gene association studies in general. It is conceivable that plausible candidate genes in the past have been dropped prematurely when no association between intragenic variation and the investigated phenotypes was observed. If these regions are not considered and the variation located there is not in strong linkage disequilibrium with intragenic variation, an association would be

missed. A higher-weighting for intragenic regions in previous candidate gene studies results in a biased search of phenotype-influencing gene regions and should probably be avoided.

In line with these observations, the GWA study approach thus evolves as “*the better candidate gene study*” as it enables a much more comprehensive analysis of all known candidate genes with ad libitum extension beyond gene boundaries and comparability across studies. Previously, candidate gene studies were each investigating different SNPs in different studies with different HDLC measurements and often different analysis models and in most of the studies with a strong focus on the promoter and intragenic regions of these genes.

8. Heterogeneity of low-HDL syndromes

HDL cholesterol levels have a strong genetic determination, with heritability estimates ranging in most cases between 40% and 60% (Wang et al., 2005; Goode et al., 2007; Kronenberg et al., 2002). As it is the case with many intermediate cardiovascular risk phenotypes, low HDLC can be either monogenic or purely environmental or, in most cases is multifactorial / polygenic in origin (Von Eckardstein 2006). The most common inherited form of low HDLC is familial hypoalphalipoproteinemia, which is defined as an HDLC level below the 10th percentile, without secondary cause, and associated with a family history of low HDLC levels. The genetic cause is not fully characterized: some of the cases are due to mutations in HDL structural genes (mostly in one of the three genes *APOA1*, *LCAT* or *ABCA1*), whereas in other cases there appears to be accelerated catabolism of HDL and its apolipoproteins without a specific genetic mutation identified (Klos et al., 2007). In contrast to the rare occurrence of isolated low HDL in hypoalphalipoproteinemia, very low plasma levels of HDLC are also found in patients with genetically disturbed metabolic pathways which are indirectly linked to HDL metabolism. For example, many patients with lipid storage diseases like Gaucher’s disease, Nieman-Pick disease, diabetes mellitus or hypertriglyceridemia present with low HDL cholesterol (Von Eckardstein 2006). In the context of high triglycerides, low HDL cholesterol is not only an early symptom, but also provides a very sensitive marker of impaired glucose tolerance and increased lipolysis (Rohrer et al., 2004). These examples reflect the very heterogeneous nature of HDLC which makes HDL genetics very complex.

9. Relationship between HDLC and triglyceride genes

Many genes control lipolysis of plasma triglycerides, a process that also affects HDLC levels through the delivery of apolipoproteins and phospholipids to HDL (Holleboom et al., 2008). There are several genes influencing both HDLC and triglyceride levels which have been identified by candidate gene and hypothesis-free GWA study approaches. For example associations between common SNPs at the *APOA5* locus and triglyceride concentrations as well as HDLC levels are significant and relatively consistent across studies and populations (Lai et al., 2005). Certain variants of *LPL* are associated with elevated plasma triglyceride and decreased HDLC levels (Busch et al., 2000). The variation of the recognition site for SstI within the 3'-untranslated region of *APOC3* has consistently shown an association with both plasma triglyceride and HDLC levels, whereas common variants of some other promising candidate genes, such as *LIPC*, were not as consistent (Busch et al., 2000).

Recent GWA analyses confirmed on the one hand the association of several loci with prior evidence of an association with triglyceride and HDLC levels (*LPL*, *APOA1C3A4A5*, and partly *LIPC*) (Saxena et al., 2007; Wallace et al., 2008; Kooner et al., 2008; Willer et al., 2008; Kathiresan et al., 2008b; Aulchenko et al., 2008; Cashman et al., 2008), and identified on the other hand new loci (*GALNT2*, *APOB*) with an influence on both HDL and triglyceride levels (Willer et al., 2008; Kathiresan et al., 2008b; Aulchenko et al., 2008).

10. HDLC genes and atherosclerosis

The epidemiological evidence for an inverse association of HDLC concentrations with the risk of coronary artery disease is very strong (Lewington et al., 2007), but the causality of this relationship is hard to prove. Since HDL levels are strongly determined by genetic variants (besides environmental factors), a causal association between HDLC and CAD can be demonstrated by showing an association of these genetic variants with risk of CAD. The idea behind is the concept of Mendelian Randomization (Katan 1986; Davey et al., 2003; Kronenberg et al., 2007) which is based on the fact that it is randomly determined at the time of conception which of the two alleles from the father as well as from the mother will be transmitted to the child. Since the transmitted alleles are of lifelong persistence, these alleles determine to a certain amount also whether a person is exposed e.g. to low HDLC levels and therefore to the CVD risk associated with low HDLC levels. Therefore, the association between the polymorphism and CVD is less influenced by reverse causation or confounding. Reverse causation would mean that CVD influences the polymorphism, which can practically

be excluded. Confounding would mean that e.g. a lifestyle factor such as smoking is associated with the disease (which is often the case) as well as with the polymorphism (which is less probable). Therefore this method is well appropriate to underline a causal relationship which is hardly possible with conventional epidemiological observation studies. The idea of Mendelian Randomization was originally proposed by Katan in the mid eighties (Katan 1986) and was more and more used during the last five years (Davey et al., 2003). To our knowledge, it was the first time applied in 1992 when Sandholzer and colleagues clearly showed that the apolipoprotein(a) gene locus determines the risk for CVD by its strong influence on lipoprotein(a) concentrations (Sandholzer et al., 1992). This seminal work demonstrated that high lipoprotein(a) concentrations are a primary, genetically determined risk factor for CVD, which was discussed controversially at that time since some researchers had believed that high lipoprotein(a) concentrations are a consequence rather than a cause of CVD. The causal relationship between lipoprotein(a) and atherosclerosis by using the Mendelian Randomization approach has been confirmed in the meanwhile by several studies (Kronenberg et al., 1999b; Kronenberg et al., 1999a; Wild et al., 1997; Kamstrup et al., 2008; Koch et al., 1997).

Figure 3A shows some considerations concerning the sample size for Mendelian Randomization projects. If one assumes that a particular polymorphism explains an unusual high 30% of an intermediate phenotype and that this intermediate phenotype explains about 10% of the clinical endpoint, it is expected that the polymorphism itself explains about 3% of the clinical endpoint ($0.30 \times 0.10 = 0.03$). Single polymorphisms of HDLC genes, however, explain at best 3% of the HDLC levels. This would mean that such a polymorphism would explain 0.3% of the clinical endpoint ($0.03 \times 0.10 = 0.003$). These considerations warn us that very large case-control studies are required to demonstrate an association between a polymorphism and a clinical endpoint. This might be the reason why although many association studies found an association between various polymorphisms and HDLC levels, most of them were markedly underpowered to consistently find an association of these polymorphisms with clinical endpoints.

A recent meta-analysis of three polymorphisms within the *CETP* gene (*Taq1B*, I405V and -629C>A) included 92 studies with up to 113,833 healthy participants, and 46 studies on 27,196 coronary cases and 55,338 controls (Thompson et al., 2008). The minor allele of each of the three polymorphisms was associated with a moderate inhibition of CETP activity and, in line with that, modestly higher HDLC levels and, most importantly, with a weakly inverse association with coronary risk. The odds ratios (OR) for coronary disease were

compatible with the expected reductions in risk for equivalent increases in HDLC concentrations demonstrated in prospective studies (Lewington et al., 2007). Figure 3B illustrates these associations for the *Taq1B* polymorphism. These results clearly support a causal association of low HDLC levels with CVD. It also demonstrates that large studies are required to detect an association of this kind with certainty: the meta-analysis on the *Taq1B* polymorphism included 38 studies with a total of 19,035 cases and 32,368 controls. Since the effects of the investigated polymorphisms on HDLC levels were in the usual range expected in association studies, the results and the required sample size will be rather the rule than the exemption.

Even if the Mendelian Randomization approach worked fine e.g. for *CETP*, the situation is less clear for *ABCA1*. A large study of almost 50,000 individuals from Copenhagen showed that heterozygosity for rare loss-of-function mutations in *ABCA1* were associated with substantial, lifelong lowering of plasma levels of HDLC (-17 mg/dL). These variants, however, were not associated with an increased risk of ischemic heart disease (Frikke-Schmidt et al., 2008b). It was speculated that this might be explained by the observation that the lower HDLC levels in these loss-of-function mutations are not accompanied by high triglyceride concentrations and that low HDLC levels per se are not atherogenic. A dysfunctionality of the HDL lipoprotein not necessarily reflected in the HDLC levels could be more important than HDLC levels themselves. This is in line with another study in the Danish population showing that common non-synonymous genetic variation in *ABCA1* predicts risk of ischemic heart disease independent of HDLC concentrations (Frikke-Schmidt et al., 2008a).

11. Conclusions

Several decades of research on the genetic contribution to HDL metabolism have identified a large number of genes contributing to the antiatherogenic HDLC concentrations. The variants detected in these genes together explain only a small amount of less than 10% of the HDLC variance, but the heritability of HDLC is estimated to be up to 80%. This provides an enormous room for further yet to be identified genetic variants. This might be accomplished by genome-wide association studies. Since the low-hanging fruits might already be detected by earlier candidate gene studies and the first genome-wide association studies, future studies in large population-based genome-wide meta-analyses will identify new genes with even smaller effects on HDLC levels. These findings will probably result in a

redrawing or extension of the involved metabolic pathways of HDLC metabolism. On the other hand, in-depth analysis of particular genes by deep-sequencing approaches or similar techniques (Coassin et al., 2008) will extend the previously made observation that a large number of rare alleles considerably contributes to a complex phenotype.

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Figure legends

Figure 1. Illustration of the major normal lipoprotein metabolic pathways. Refer to the text for detailed explanation. Blue arrows refer to points of action of the respective genes in blue. Red arrows refer to activating or inhibiting actions of certain apolipoproteins.

Abbreviations: ABCA1, ATP binding cassette transporter 1; apo, apolipoprotein; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin:cholesteryl acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein-receptor; LIPC, hepatic lipase; LIPG, endothelial lipase; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; SR-B1, scavenger receptor B1; TG, triglycerides; VLDL, very low-density lipoprotein. (Figure adapted from Kwan BCH, Kronenberg F, Beddhu S, Cheung AK: Lipoprotein metabolism and lipid management in chronic kidney disease. *J. Am. Soc. Nephrol.* 18:1246-1261, 2007.)

Figure 2. Correlation of SNPs in various HDLC candidate gene regions. The shading of the diamonds represents the category of the pairwise squared correlation coefficient r^2 between the two SNPs defined by the top left and the top right sides of the diamond. Specific value of r^2 are stated in the diamond. Data for each gene region are derived from HapMap (www.hapmap.org) using the genotyping results based on CEPH families (Utah residents with ancestry from northern and western Europe).

Figure 3. Mendelian Randomization Approach. Panel A shows some considerations concerning the sample size for Mendelian Randomization projects (for explanation see chapter 10 of the text). Panel B shows the results of a recent meta-analysis of the *Taq1B* polymorphism within the *CETP* gene and its association with HDLC levels as well as coronary disease (Thompson et al., 2008) (for details see chapter 10 of the text).

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Table 1: Genetic variants within the *CETP* gene coding for the cholesteryl ester transfer protein and their association with HDLC concentrations.

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs12149545	G-2708A	55550662	G>A	30	(McCaskie et al., 2007)	GP, CVD	W	2683 GP, 556 CVD	≈ +1.9 per copy	<0.001
			G>A	31	(Klerkx et al., 2003)	CVD	W	709	+1.5 / +3.5 (1/2 copies)	0.0016
rs3764261		55550825	G>T	28	(Pare et al., 2007)	CVD, Co	W	1442	n.a.	9x10 ⁻⁶
rs4783961	G-971A	55552395	G>A	49	(Klerkx et al., 2003)	CVD	W	709	+1.2 / +1.9 (1/2 copies)	0.09
rs1800775	C-629 A	55552737	C>A	48	(Borggreve et al., 2005)	P	W	7083	+2.7 / +5.4 (1/2 copies)	<0.001
			C>A	51	(Bernstein et al., 2003)	P	W	847 M, 873 F	+4.2 for homozygotes ^a	<0.002 ^a
			C>A	49	(Kathiresan et al., 2008a)	GP	W	5287	+3 / +5 (1/2 copies)	2x10 ⁻²⁹
			C>A	42-58	(Tai et al., 2003b)	GP	A	4050	+2.2 / +3.4 (1/2 copies) ^a	3.28x10 ^{-9 a}
			C>A	48	(McCaskie et al., 2007)	GP, CVD	W	2683 GP, 556 CVD	≈ +2.7 per copy	<0.001
			C>A	40	(Blankenberg et al., 2004)	CVD Co	W	CVD: 1214 Co: 574	CVD: +2.0 / +3.5 (1/2 copies) Co: +3.3 / +6.1 (1/2 copies)	0.02 0.005
			C>A	44	(Klerkx et al., 2003)	CVD	W	709	+0.8 / +3.9 (1/2 copies)	<0.0001
			C>A	≈ 50	(Eiriksdottir et al., 2001)	MI, Co	W	309 MI, 757 Co	+1.9 / +6.1 (1/2 copies) ^a	<0.0001 ^a
	C>A	48	(Freeman et al., 2003)	CVD, Co	W	498 CVD, 1107 Co	+2.9 / +4.4 (1/2 copies) ^a	<0.001 ^a		
rs708272 ^b	Taq1B, TaqIB G+279A (G=B1, A=B2)	55553789	B1>B2	40-45	(Boekholdt et al., 2005)	M	-	13,677	+1.2 / +3.8 (1/2 copies)	<0.0001
			B1>B2	n.a.	(Boekholdt et al., 2003)	M	-	>10,000	+4.6 for 2 copies	<0.00001
			B1>B2	42	(Borggreve et al., 2005)	P	W	7083	+2.7 / +5.0 (1/2 copies)	<0.001
			B1>B2	44	(Ordovas et al., 2000)	P	W	2916	≈ +2.5 / +4.7 (1/2 copies) ^a	<0.001 ^a
			n.a.	43W/26B	(Klos et al., 2006)	P	W/B	2056 W, 1943 B	n.a. / n.a.	<0.01 / <0.02
			G>A	W: 44 B: 27	(Nettleton et al., 2007)	P	W B	W: 8764 B: 2695	W: +2.3 / +5.8 (1/2 copies) B: +3.8 / +9.8 (1/2 copies)	<0.001 <0.001
			B1>B2	41	(Sandhofer et al., 2008)	P	W	1503	+2 / +5 (1/2 copies)	<0.001
			B1>B2	33-43	(Tai et al., 2003b)	GP	A	4207	+2.5 / +4.4 (1/2 copies) ^a	1.25x10 ^{-10 a}
			B1>B2	40	(Tsujita et al., 2007)	GP	A	1729	M: +1.2 / +3.5 (1/2 copies) F: +1.9 / +6.2 (1/2 copies)	0.096 <0.001
			B1>B2	42	(McCaskie et al., 2007)	GP, CVD	W	2683 GP, 556 CVD	≈ +2.7 per copy	<0.001
			B1>B2	42	(Whiting et al., 2005)	CVD, Co	W	2392 CVD, 827 Co	+1.7 / +3.6 (1/2 copies)	<0.001
B1>B2	40	(Carlquist et al., 2003)	CVD	W	1464	+2.1 / + 3.0 (1/2 copies)	0.003			

		B1>B2	41	(Blankenberg et al., 2004)	CVD, Co	W	1200 CVD, 571 Co	$\approx +2.6 / +4.3$ (1/2 copies) ^a	<0.02 ^a	
		B1>B2	44	(Freeman et al., 2003)	CVD, Co	W	499 CVD, 1105 Co	$\approx +2.1 / +3.6$ (1/2 copies) ^a	<0.001 ^a	
rs34145065 ^c	+784CCC>A	55554147-8	CCC>A	39	(Klerkx et al., 2003)	CVD	W	709	+1.2 / +3.5 (1/2 copies)	0.0009
rs289714		55564952	T>C	18	(Klos et al., 2006)	P	W	2056	M / F	0.018 / <0.001
rs5880	A373P	55572592	A>P G>C	5	(Agerholm-Larsen et al., 2000b)	P, CVD	W	8467 P, 1636 CVD	≈ -5.4 for heterozygotes	<0.001
			C>A	5	(Blankenberg et al., 2004)	CVD, Co	W	1039 CVD, 483 Co	≈ -3.6 for heterozygotes ^a	0.05 ^a
rs5882 =	Ile405Val	55573593	I>V		(Boekholdt et al., 2003)	M		>10,000	+1.9 for homozygotes	<0.00001
rs61212082 ^b	A+16G/Ex14		I>V	32	(Isaacs et al., 2007)	P	W	6421	M: +1.5 / +2.3 (1/2 copies) F: +0.0 / +2.3 (1/2 copies)	0.002 0.007
	aa405		I>V	29	(Pallaud et al., 2001)	P	W	772 M, 780 F	no association	n.s.
	1394I>V		I>V	33	(Agerholm-Larsen et al., 2000a)	P	W	8889	M: $\approx +0.4$ per copy F: $\approx +2.7$ per copy	n.s. <0.001
			C>A	30	(Blankenberg et al., 2004)	CVD Co	W	CVD: 1208 Co: 572	CVD: +1.4 / +3.1 (1/2 copies) Co: +0.3 / +8.4 (1/2 copies)	0.08 0.003
			C>T	30	(Freeman et al., 2003)	CVD Co	W	CVD: 498 Co: 1108	CVD: +1.2 / +3.5 (1/2 copies) Co: +1.5 / +1.5 (1/2 copies)	<0.05 <0.05
rs2303790 ^b	D442G	55574793	D>G	3	(Zhong et al., 1996)	HeEx	A	3469	+4.9 for heterozygotes	<0.001
rs1800777	R451Q; G>A	55574820	R>Q	4	(Agerholm-Larsen et al., 2000b)	P, CVD	W	8467 P, 1636 CVD	≈ -5.4 for heterozygotes	<0.001
	G+82A/Ex15		B1>B2	3	(Blankenberg et al., 2004)	CVD, Co	W	1071 CVD, 532 Co	-3.6 / -5.2 for heterozygotes	0.06 / 0.07

^a pooled estimates and p values.

^b Studies of this SNP with sample sizes <1000 are provided in the Supplementary Table.

^c rs number not fully clarified.

Abbreviations and explanations:

- Chrom. position: means chromosomal position according to NCBI Build 36 as included in Ensembl Release 49.
- Allele: means order of reference allele > risk allele; del, deletion; ins, insertion.
- MAF, minor allele frequency; Car., carriers; if MAF is not available, % Car. is provided.
- Study type: M, meta-analysis; P, population-based; GP, general population; Co, controls; CVD, cardiovascular disease; MI, myocardial infarction; NGT, normal glucose tolerance subjects; DM, diabetes mellitus; HoCo, hospital-based controls; HoSta, hospital staff; HBP, hypertensive patients; HeEx, health examination; Non-DM Co, nondiabetic control subjects; CorAng, coronary angiography; hyperCH, hypercholesterolemic patients.
- Ethnicity: W, Whites; B, Blacks; A, Asians; W-Bra, Caucasian-Brazilians; B-Bra, African-Brazilians; AA, African Americans; NHW, non-Hispanic Whites; H, Hispanics; UK, United Kingdom; Asian-Ind., Asian-Indians.
- HDLC, HDL cholesterol; M, males; F, females; sel., selected; n.s., not significant; n.a., not available.

Table 2: Genetic variants within the *LPL* gene coding for the lipoprotein lipase and their association with HDLC concentrations. ^a

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs1801177	D9N; Asp9Asn	19849988	G>A	4% Car.	(Wittrup et al., 1999)	M	-	5067	-3.1 for heterozygotes	0.002
no rs #	Gly188Glu	19856022	Gly>Glu	1% Car.	(Wittrup et al., 1999)	M	-	10,434	-9.7 for heterozygotes	<0.001
rs268	N291S, Asn291Ser	19857809	A>G	5% Car.	(Wittrup et al., 1999)	M	-	14,912	-4.6 for heterozygotes	<0.001
rs320	HindIII; Int8	19863357	H+>H-	30	(Senti et al., 2001)	P	W	520	+5.5 in H-H- vs. H+H+	0.025
			H2>H1	26	(Holmer et al., 2000)	P	W	1361	M: +3.5 for heterozygotes F 25-44yrs: no association F 45-64yrs: +4.2 for heterozy.	0.0018 n.s. 0.0212
			H+>H-	32	(Corella et al., 2002)	GP	W	906	+1.9 for carriers	0.003
			T>G	17	(Ukkola et al., 2001)	GP	W	568	no association	n.s.
			H+>H-	42% Car.	(Radha et al., 2006)	NGT, DM	A	NGT: 550 DM: 465	NGT: +3.0 in carriers DM: +1.0 in carriers	<0.05 <0.05
			+>-	27-31	(Ahn et al., 1993)	DM, Co	NHW, H	615 NHW, 579 H	higher values in carriers	0.005
rs326		19863719	n.a.	44	(Klos et al., 2006)	P	B	1943	M / F	0.013 / 0.004
rs328 ^b	S447X ^c 1595CG	19864004	S>X	20% Car.	(Wittrup et al., 1999)	M	-	4388	+1.5 for heterozygotes	<0.001
			C>G	W: 10 B: 7	(Nettleton et al., 2007)	P	W B	W: 8968 B: 2677	W: +2.8 / +4.0 (1/2 copies) B: +3.1 / +12.6 (1/2 copies)	<0.001 <0.001
			S>X	11	(Lee et al., 2004)	P	A	4058	+3.1 for carriers	<0.001
			S>X	11	(Komurcu-Bayrak et al., 2007)	P	Turks	1586	M: no association F: +4.0 for carriers	n.s. <0.001
			S>X	29	(Pallaud et al., 2001)	P	W	1552	no association	n.s.
			n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	+ 2.7 for carriers	0.0017
			C>G	9	(Kathiresan et al., 2008a)	GP	W	5287	+3 / +5 (1/2 copies)	3x10 ⁻¹²
S>X	10	(Talmud et al., 2002b)	GP	W	2773	no association	n.s.			
rs13702		19868772	n.a.	50	(Klos et al., 2006)	P	B	1943	M / F	0.009 / 0.006

^a SNPs rs285 and rs10105606 never showed an association in any study but data on these studies are provided in the Supplementary Table.

^b Studies with sample sizes <1000 are provided in the Supplementary Table.

^c Position 474 instead of 447 according to NCBI database.

For abbreviations and explanations, see Table 1.

Table 3: Genetic variants within the *LIPC* gene coding for the hepatic lipase and their association with HDLC concentrations.

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs1077834	T-710C	56510771	T>C	22	(Andersen et al., 2003)	P	W	9121	+3-4% per copy	<0.001
rs1800588 ^b	C-514T ^a	56510967	C>T	25	(Isaacs et al., 2004)	M	Various	>24,000	+1.5 / +3.5 (1/2 copies)	<0.001
	Pos. -480T ^a		C>T	W: 21 B: 53	(Nettleton et al., 2007)	P	W B	W: 8897 B: 2909	W: +2.2 / +3.8 (1/2 copies) B: +1.6 / +4.0 (1/2 copies)	<0.001 <0.001
			C>T	21	(Isaacs et al., 2007)	P	W	6239	≈ +1.3 / +4.3 (1/2 copies) ^d	<0.001 ^d
			C>T	38	(Tai et al., 2003a)	P	A	2170	+2.3 / +2.7 (1/2 copies)	0.001
			C>T	21	(Kathiresan et al., 2008a)	GP	W	5287	+1 / +4 (1/2 copies)	4x10 ⁻¹⁰
			C>T	25	(Talmud et al., 2002b)	GP	W	2773	+1.5 per copy	0.04
			C>T	24	(Whiting et al., 2005)	CVD, Co	W	3319 CVD, 1385 Co	+1.0 / +3.8 (1/2 copies)	0.001
			C>T	51	(Yamada et al., 2007)	HoCo, P	A	5207	≈ +2.5 per copy	<0.001
			C>T	21-24	(McCaskie et al., 2006)	GP, CVD	W	6412	≈ +2.0-2.5 per copy	<0.001
rs2070895	G-250A	56511231	G>A	22	(Andersen et al., 2003)	P	W	9121	+3-4% per copy	<0.001
	1b-280,HL1-280		n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	+ 1.5 for carriers	0.020
			G>A	32	(de Andrade et al., 2004)	P	W	514	M: assoc., F: no assoc.	0.001 / n.s.
			G>A	23	(Grarup et al., 2008)	P	W	5585	+3.9 / +3.9 (1/2 copies)	8x10 ⁻¹⁰
			G>A	22		P	W	8407	+3.9 / +3.9 (1/2 copies)	2x10 ⁻⁷
			G>A	51	(Yamada et al., 2007)	HoCo, P	A	5213	≈ +2.7 per copy	<0.001
			G>A	39	(Ko et al., 2004)	HeEx	A	716	+2.1 for carriers	0.026
rs12594375		56519760	G>A	37	(Iijima et al., 2008)	GP	A	2970	n.a.	0.00003
rs8023503		56527880	C>T	38	(Iijima et al., 2008)	GP	A	2970	n.a.	0.0001
			C>T	33		GP	A	1633	+2.6 / +3.4 (1/2 copies)	0.0007
no rs #	3b-279,HL3-279	56620996 ^c	n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	+ 1.8 for carriers	0.024
rs3829462	+1075C	56640371	A>C	5	(Fang et al., 2002)	HoSta	A	823	+8.0 for heterozygotes	<0.05

^a C-514T and -480T are the same polymorphisms (depending on the nucleotide taking as the transcription start site).

^b Studies with sample sizes <1000 are provided in the Supplementary Table.

^c It is also possible that the known SNP 3b-280 is meant (rs12909325; chrom. position 56620995).

^d pooled estimates and p values.

For abbreviations and explanations, see Table 1.

Table 4: Genetic variants within the *LIPG* gene coding for the endothelial lipase and their association with HDLC concentrations.

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs3813082	-384A>C	45342041	A>C	12	(Hutter et al., 2006)	Co	A	541	+1.3 / +10.2 (1/ 2 copies)	0.021
			A>C	12	(Yamakawa-Kobayashi et al., 2003)	Kids	A	340	+0.7 / +9.8 (1/ 2 copies)	0.0086
rs2000813	584 C/T T111I	45347862	T>I	32	(Paradis et al., 2003)	GP	W	495	M: +1.2 / +2.7 (1/2 copies) F: -0.4 / +1.9 (1/2 copies)	0.82 0.09
			C>T	24	(Hutter et al., 2006)	Co	A	541	+0.5 / +6.1 (1/ 2 copies)	0.048
			C>T	18 / 30	(Tang et al., 2008)	CVD, Co	A	265 CVD, 265 Co	≈ +3.7 in carriers ^a	<0.02 ^a
			C>T	24	(Yamakawa-Kobayashi et al., 2003)	Kids	A	340	-0.6 / +2.6 (1/ 2 copies)	n.s.
			C>T	29	(Ma et al., 2003)	CVD	90% W	372	+1.6 / +6.0 (1/ 2 copies)	0.035
rs2276269	C+42T/ln5	45356000	C>T	44	(Mank-Seymour et al., 2004)	HDL sel. ^b	W	594	decreases HDLC	0.007
rs6507931	T+2864C/ln8	45367006	T>C	42	(Mank-Seymour et al., 2004)	HDL sel. ^b	W	594	decreases HDLC	0.004
rs3744841	2237G>A	45371372	G>A	36	(Yamakawa-Kobayashi et al., 2003)	Kids	A	340	-4.0 / -4.3 (1/ 2 copies)	0.011

^a pooled estimates and p values.

^b Selected according to HDLC levels: high HDLC group with values >60 mg/dL (n=355) and low HDLC group with values <35 mg/dL (n=239).

For abbreviations and explanations, see Table 1.

Table 5: Genetic variants within the *LCAT* gene coding for the lecithin:cholesteryl acyltransferase and their association with HDLC concentrations.

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
no rs #	Gly230Arg	66531921	Gly>Arg	5% Car. ^a	(Miettinen et al., 1998)	see ^a	W	156 low HDLC, 160 high HDLC	variant only in low HDLC group	
rs4986970	Ser208Thr	66533821	S>T	3	(Talmud et al., 2002b)	GP	W	2773	no association	n.s.
	Ser208Thr		S>T	6% Car.	(Boekholdt et al., 2006)	CVD	W	546	no association	n.s.
rs5922	608C/T	66533918	C>T	n.a.	(Zhang et al., 2003)	CVD, Co	A	CVD: 203 Co: 209	increase in HDL no association	0.015 n.s.
			C>T	14% Car.	(Zhu et al., 2006)	Stroke, Co	A	150 stroke, 122 Co	lower HDLC in heterozyg.	<0.05
no rs #	P143L +511C>T	66534134	C>T	6% Car.	(Zhang et al., 2004)	CVD, Co	A	190 CVD, 209 Co	association with low HDLC	<0.01
rs2292318		66543207	G>A	12	(Pare et al., 2007)	CVD, Co	W	1442	increases HDLC	2x10 ⁻⁵

^a 5% carriers in 156 persons with low HDL (8-27 mg/dL) vs. 0% carriers in 160 persons with high HDL (73-139 mg/dL) selected from a large population study.

For abbreviations and explanations, see Table 1.

Table 6: Genetic variants within the *SCARB1* (*SR-B1*) gene coding for the scavenger receptor class B type 1 and their association with HDLC concentrations.

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs5888	A350A (exon8 C-T)	123850701	C>T	48	(Osgood et al., 2003)	P	W	M: 1177 F: 1239	M: +1.2 / +2.3 (1/2 copies) F: 0.0 / +1.2 (1/2 copies)	n.s. n.s.
			C>T	44	(Morabia et al., 2004)	P	W	M: 865 F: 891	M: +1.9 / 2.7 (1/2 copies) F: +0.4 / +0.8 (1/2 copies)	0.0062 n.s.
	C1050T		n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	- 5.1 for carriers	n.s.
			C>T	41	(Roberts et al., 2007)	Families	Amish	M: 428 F: 491	M: no association F: ≈ +4 / +3 (1/ 2 copies)	n.s. 0.04
			C>T	49	(Boekholdt et al., 2006)	CVD	W	546	+2.3 / +1.9 (1/2 copies)	0.03
rs5891		123865495	G>A	3	(Roberts et al., 2007)	Families	Amish	M: 428 F: 491	M: no association F: ≈ +9 / +10 (1/ 2 copies)	n.s. <0.001
rs4238001	Ex.1(G>A)	123914216	G>A	12	(Osgood et al., 2003)	P	W	2465	+0.4 for carriers	n.s.
no rs #	11-bp del ^a	123914499-509	ins>del ^a	4% Car.	(Hsu et al., 2003)	HeEx	A	690	+6.0 for deletion carriers	0.035
no rs #	C-142T	123914515	C>T	14	(Hsu et al., 2003)	HeEx	A	664	+1 / -1 (1/ 2 copies)	n.s.

^a Eleven base pair deletion ranging from position -140 to -150. -140 to -150del mutation identified in the transcription factor binding region of the proximal promoter of the *SCARB1* gene.

For abbreviations and explanations, see Table 1.

Table 7: Genetic variants within the *ABCA1* gene coding for the ATP binding cassette transporter A1 and their association with HDLC concentrations. ^a

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
rs2246298	C(-297)T	106730554	C>T	25	(Shioji et al., 2004b)	GP	A	1625	n.a.	0.0455
rs1800976	G(-273)C	106730530	G>C	40	(Shioji et al., 2004b)	GP HBP	A A	GP: 1626 HBP: 735	+1.9 / +2.7 (1/2 copies) +1.9 / +5.0 (1/2 copies)	0.026 0.026
rs1800977	C69T; C-14T	106730271	C>T	36	(Porchay et al., 2006)	GP	W	5040	no association	n.s.
			C>T	38	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2332	M: +0.7 / +1.9 (1/2 copies) F: -0.3 / 0.0 (1/2 copies)	<0.02 n.s.
rs1800978	G378C	106705799	G>C	13	(Porchay et al., 2006)	GP	W	5040	-1.2 / -2.7 (1/2 copies)	0.03
rs3890182		106687476	G>A	13	(Kathiresan et al., 2008a)	GP	W	5287	-1 / -3 (1/2 copies)	0.003
rs2275542	IMS-JST071749	106684901	n.a.	n.a.	(Shioji et al., 2004b)	GP	A	<1880	n.a.	0.006
rs2515602		106639989	n.a.	27	(Klos et al., 2006)	P	B	1943	M / F	0.034 / <0.001
rs2853578	G596A	106633129	G>A	28	(Whiting et al., 2005)	CVD, Co	W	2468 CVD, 834 Co	-0.2 / +2.8 (1/2 copies)	0.02
rs2066718	V771M 2310G>A	106629076	G>A	3	(Frikke-Schmidt et al., 2004)	P	W	9123	M: trend to higher levels F: higher levels in carriers	0.12 0.02
	G2706A		V>M	5	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2458	M: +2.0 for heterozygotes F: +1.9 for heterozygotes	<0.01 n.s.
			V>M	3	(Clee et al., 2001)	CVD	W	635	no association	n.s.
rs2066715	V825I 2472G>A	106627854	G>A	6	(Frikke-Schmidt et al., 2004)	P	W	9123	M: no association F: ≈ +3.1 in carriers	n.s. 0.0005
	G2868A		V>I	6	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2105	no association	n.s.
			V>I	8	(Clee et al., 2001)	CVD	W	682	no association	n.s.
rs4149313	I883M	106626574	A>G	12	(Frikke-Schmidt et al., 2004)	P	W	9123	M: no association F: increase in heterozygotes	n.s. 0.05
	2648A>G		I>M	22	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2532	no association	n.s.
rs33918808	E1172D	106619453	G>C	3	(Frikke-Schmidt et al., 2004)	P	W	9123	M: no association F: higher levels in carriers	n.s. 0.05
	3515G>C		E>D	5	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2238	no association	n.s.
			E>D	3	(Clee et al., 2001)	CVD	W	644	no association	n.s.
no rs #	32b.+30, ABC32	106606881	n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	- 2.2 for carriers	0.0040

rs2230808	R1587K 4759G>A	106602625	G>A	24	(Frikke-Schmidt et al., 2004)	P	W	9123	M: -1.5 for heterozygotes F: -2.7 for heterozygotes	0.008 0.02
			R>K	33	(Hodoglugil et al., 2005)	GP (no DM)	Turks	2288	no association	n.s.
			R>K	26	(Clee et al., 2001)	CVD	W	779	-1.5 for carriers	0.03
rs41474449	50b.3038, ABC50	106583518- 20	del/ins	n.a.	(Costanza et al., 2005)	P	W	1543	+ 1.6 for carriers	0.043

^a SNPs rs2422493, rs2740483, rs1799777 and rs2230806 never showed an association in any study but data on these studies are provided in the Supplementary Table.

For abbreviations and explanations, see Table 1.

Table 8: Genetic variants within the genes *APOA1*, *APOC3* and *APOA5* coding for apolipoprotein A-I, C-III and A-V, respectively and their associations with HDLC concentrations.^a

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
APOA1										
rs5070	T84C (1280) (HaeIII)	116213230	T>C	W:33/B:47	(Brown et al., 2006)	P	Multi	3831	no association	n.s.
			T>C	23	(Shioji et al., 2004a)	GP	A	1637	+1.9 / +5.4 (1/2 copies)	0.0005
rs5069	MspI RFLP C-151T +83bp; +83 C/T 1046 (C->T)	116213464	T>C	W: 3 B: 31	(Brown et al., 2006)	P	W, B	3831	W: M / F B: M / F	0.0001 / 0.027 n.s. / 0.022
			+>-	3	(Kamboh et al., 1996)	GP	NHW	M: 248 F: 280	M: -3.0 in carriers F: +7.5 in carriers	n.s. 0.009
			+>-	40	(Kamboh et al., 1999)	GP	A	M: 490 F: 291	M: -2.3 / -0.9 (1/2 copies) F: +0.1 / -0.9 (1/2 copies)	n.s. n.s.
			M1>M2	44	(Zaman et al., 1997)	Co	A	1328	-1.2 / -1.3 (1/2 copies)	n.s.
			+>-	5	(Larson et al., 2002)	Co	W	730	≈ +2.0 for carriers	n.s.
APOC3										
rs2854117	-482C>T (9154)	116205352	G>A	W: 73 B: 33	(Brown et al., 2006)	P	Multi	3831	W: M / F B: M / F	n.s. / n.s. n.s. / 0.014
			C>T	27	(Pallaud et al., 2001)	P	W	772 M, 780 F	no association	n.s.
			T>C	27	(Qi et al., 2007)	GP (DM)	W	875	+0.6 / +0.1 (1/2 copies)	n.s.
rs2854116	C-455T, 9127	116205379	A>G	W: 62 B: 30	(Brown et al., 2006)	P	Multi	3831	W: M / F B: M / F	n.s. / n.s. n.s. / 0.045
			T>C	41	(Lahiry et al., 2007)	P	Inuits	1308	-3.1 / -5.4 (1/2 copies)	<0.05
			T>C	38	(Qi et al., 2007)	GP (DM)	W	846	+0.2 / -1.7 (1/2 copies)	n.s.
rs618354 ^c	Fvull	116205987	1>2	49	(Kamboh et al., 1999)	GP	A	M: 478 F: 291	M: -0.9 / -1.3 (1/2 copies) F: +0.1 / -4.2 (1/2 copies)	n.s. 0.029
rs5128	+3175 SstI RFLP 3'-UTR/Sac I 3238C>G	116208850	C>G	9	(Pallaud et al., 2001)	P	W	772 M, 780 F	no association	n.s.
			S1>S2	9	(Russo et al., 2001)	P	W	M: 1219 F: 1266	M: -1.8 in carriers F: +0.4 in carriers	0.04 n.s.
			->+	9	(Hegele et al., 1995)	P	Hutteries	713	-5.0 for heterozygotes	0.0014
			S1>S2	7	(Corella et al., 2002)	GP	W	906	+1.9 for carriers	0.079
			S1>S2	35	(Arai et al., 2005)	GP	A	852	-0.8 / -1.5 (1/2 copies)	0.41

C>G	10	(Qi et al., 2007)	GP (DM)	W	881	+2.4 / -2.0 (1/2 copies)	n.s.
S1>S2	36	(Zaman et al., 1997)	Co	A	1328	+0.2 / +1.5 (1/2 copies)	n.s.

APOA5

rs662799 ^b	-1131T>C	116168917	T>C	6	(Talmud et al., 2002a)	P	UK	1696	-1.5 / -5.4 (1/2 copies)	0.04
			T>C	7-8	(Grallert et al., 2007)	P	W	KORA:1171 SAPHIR: 1596	KORA: -1.2 per copy SAPHIR: -3.5 per copy	n.s 0.00038
			T>C	7	(Lai et al., 2004)	P	W	2256	-1.0 for carriers	n.s.
			T>C	23-30	(Lai et al., 2003)	GP	Chinese Malays Asian-Ind.	Chinese: 2711 Malays: 707 Asian-Ind.: 553	-2.3 / -5.4 (1/2 copies) -1.2 / -8.1 (1/2 copies) 0.0 / -3.1 (1/2 copies)	<0.0001 <0.0001 n.s.
			T>C	34	(Yamada et al., 2007)	HoCo, P	A	5212	≈ -3.3 per copy	<0.001
rs651821	-3A>G	116167789	n.a.	7	(Klos et al., 2006)	P	W	2056	M / F	0.30 / 0.26
			A>G	18-29	(Lai et al., 2003)	GP	Chinese Malays Asian-Ind.	Chinese: 2711 Malays: 707 Asian-Ind.: 553	-2.3 / -5.8 (1/2 copies) -0.8 / -7.3 (1/2 copies) -0.4 / -6.2 (1/2 copies)	<0.0001 <0.0001 0.0913
			T>C	34	(Yamada et al., 2007)	HoCo, P	A	5207	≈ -2.7 per copy	<0.001
			A>G	36	(Yamada et al., 2008)	HoCo	A	2417	-3.9 / -7.0 (1/2 copies)	<0.001
rs3135506 ^b	S19W	116167617	S>W	6	(Talmud et al., 2002a)	P	UK	1660	-1.9 / +1.2 (1/2 copies)	0.02
	56C>G		C>G	6	(Lai et al., 2004)	P	W	2347	-2.0 for carriers	0.008
	+170		C>G	6-7	(Grallert et al., 2007)	P	W	KORA:1116 SAPHIR: 1630	KORA: -1.5 per copy SAPHIR: -2.3 per copy	n.s 0.026
rs2072560	SNP2 IVS3+476G>A +751C/T	116167036	G>A	16-21	(Lai et al., 2003)	GP	Chinese Malays Asian-Ind.	Chinese: 2711 Malays: 707 Asian-Ind.: 553	-1.9 / -3.9 (1/2 copies) -0.4 / -9.3 (1/2 copies) +0.4 / -3.5 (1/2 copies)	0.0003 0.0004 n.s.
			C>T	12% Car.	(Qi et al., 2007)	GP (DM)	W	884	-0.8 for carriers	n.s.
rs3135507	Val153Met V153M	116166698	V>M	7% Car.	(Hubacek et al., 2005)	P	W	2557	M: -0.8 for carriers F: -3.5 for carriers	n.s. <0.01
rs2075291	+553	116166602	G>T	7	(Yamada et al., 2007)	HoCo, P	A	5206	≈ -4.6 per copy	<0.001
	Gly185Cys		G>T	8	(Yamada et al., 2008)	HoCo	A	2417	-5.0 / -11.2 (1/2 copies)	<0.001
			G>T	30	(Hsu et al., 2006)	HeEx	A	677	-2.0 for carriers	n.s.
rs2266788	1259T>C +1891A>G	116165896	T>C	18-23	(Lai et al., 2003)	GP	Chinese Malays Asian-Ind.	Chinese: 2711 Malays: 707 Asian-Ind.: 553	-2.3 / -3.1 (1/2 copies) -0.4 / -6.6 (1/2 copies) -0.4 / -2.3 (1/2 copies)	<0.0001 0.008 n.s.

- ^a SNPs rs670 (*APOA1*), rs4520 (*APOC3*), rs34635405 (*APOC3*), rs2266789 (*APOA5*), rs10750097 (*APOA5*) never showed an association in any study but data on these studies are provided in the Supplementary Table.
- ^b Studies of this SNP with sample sizes <1000 are provided in the Supplementary Table.
- ^c rs number not fully clarified.
- For abbreviations and explanations, see Table 1.

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Table 9: Genetic variants within the genes *GHRL*, *LDLR* and *PON1* coding for ghrelin, LDL-receptor and paraoxonase 1, respectively and their associations with HDLC concentrations. ^a

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
GHRL										
rs3755777	-1500C>G	10308364	C>G	49	(Choi et al., 2006)	Non-DM Co	A	641	-2 for carriers	0.0020
rs26311	-1062G>C	10307926	A>G	12	(Martin et al., 2008)	GP	Canadian	1464	no association	n.s.
			G>C	37	(Choi et al., 2006)	Non-DM Co	A	640	-4 for carriers	<0.0001
rs26312	-994C>T	10307858	C>T	39	(Choi et al., 2006)	Non-DM Co	A	639	-3 for carriers	0.0004
rs26802		10307365	T>G	30	(Martin et al., 2008)	GP	Canadian	1464	no association	n.s.
rs696217	+408C>A	10306457	C>A	18	(Choi et al., 2006)	Non-DM Co	A	636	-2 for carriers	0.0042
	Leu72Met		Leu>Met	7	(Hubacek et al., 2007)	P	W	1189 M, 1364 F	-2.3 for carriers	0.01
rs2075356		10303809	T>C	11	(Martin et al., 2008)	GP	Canadian	1464	no association	n.s.
rs4684677		10303453	T>A	6	(Martin et al., 2008)	GP	Canadian	1464	no association	0.09
rs35684		10301686	A>G	27	(Martin et al., 2008)	GP	Canadian	1464	no association	n.s.
LDLR										
rs2228671	Exon 2	11071912	n.a.	n.a.	(Costanza et al., 2005)	P	W	1543	+3.8 for carriers	0.0056
rs688 = rs57911429	1866C>T Asn591Asn	11088602	C>T	12	(Yamada et al., 2008)	HoCo	A	2417	+1.5 / +8.5 (1/2 copies)	0.0155
	Exon 12/HincII		->+	39	(Hegele et al., 1995)	P	Hutteries	713	-2.3 / -4.3 (1/2 copies)	0.047
rs5925 = rs57369606	2052T>C Val653Val	11091881	T>C	17	(Yamada et al., 2008)	HoCo	A	2417	+1.2 / +5.4 (1/2 copies)	0.043
PON1										
rs662 = rs60480675	Q192R Gln192Arg	94775382	A>G	30 67	(Srinivasan et al., 2004)	P	W B	W: 1232 B: 554	W: +0.1 / +2.3 (1/2 copies) B: -5.4 / -6.7 (1/2 copies)	0.041 0.008
			Q>R	31	(Manresa et al., 2006)	P	W	1364	-0.6 for carriers	n.s.
			Q>R	31	(Senti et al., 2002)	P	W	M: 724 F: 656	M: 0.0 / -0.6 (1/2 copies) F: +0.6 / -1.6 (1/2 copies)	n.s. n.s.
			Q>R	29	(Hegele et al., 1995)	P	Hutteries	738	-3.1 / -3.1 (1/2 copies)	0.001
			Q>R	32	(van Aalst-Cohen et al., 2005)	hyperCH	W	1002	0.0 / -0.8 (1/2 copies)	n.s.
			Q>R	36	(Rios et al., 2007)	CVD, Co	W-Bra	M: 261	M: +1.5 / +2.7 (1/2 copies)	0.035

			46			B-Bra	F: 176 M: 155 F: 120	F: -0.4 / +3.1 (1/2 copies) M: -0.4 / +1.5 (1/2 copies) F: +0.4 / +1.2 (1/2 copies)	n.s. n.s. n.s.	
		Q>R	27 33	(Blatter Garin et al., 2006)	CVD, Co	W	CVD: 710 Co: 199	CVD: -1.2 / -3.5 (1/2 copies) Co: +0.8 / +1.2 (1/2 copies)	n.s. n.s.	
rs3202100 = Met55Leu	94784020	Met>Leu	35	(van Aalst-Cohen et al., 2005)	hyperCH	W	1002	-0.4 / 0.0 (1/2 copies)	n.s.	
rs17434839 =rs57937067		L>M	40 34	(Blatter Garin et al., 2006)	CVD, Co	W	CVD: 710 Co: 199	CVD: 0.0 / 0.0 (1/2 copies) Co: +0.4 / +3.9 (1/2 copies)	n.s. n.s.	
		Leu>Met	43 34	(Rios et al., 2007)	CVD, Co	W-Bra B-Bra	437 275	no association	n.s.	
rs705379	C-107T	94791831	T>C	48 47	(Blatter Garin et al., 2006)	CVD, Co	W	CVD: 710 Co: 199	CVD: -3.1 / -2.3 (1/2 copies) Co: 0.0 / +8.1 (1/2 copies)	0.006 0.001

^a SNPs rs1433099 and rs2738466 of *LDLR* never showed an association in any study but data on these studies are provided in the Supplementary Table.

For abbreviations and explanations, see Table 1.

Table 10: Association of the *APOE* polymorphism coding for apolipoprotein E with HDLC concentrations. ^a

Study name	Sample size	Influence of E2 on HDL	Influence of E4 on HDL	P value ^b
EPIC Norfolk Study (Wu et al., 2007)	22,915	↑	↓	<0.001
ARIC Study (Volcik et al., 2006)	9304 Whites	↑	↓	<0.05
	3187 African Americans	↑	↓	<0.05
Copenhagen City Heart Study (Frikke-Schmidt et al., 2000)	5025 women	↑	↓	<0.001
	4035 men	↔	↓	n.s. / 0.001
Rotterdam Study (Slooter et al., 2001)	5401	↑	↓	<0.0005
Strong Heart Study (Kataoka et al., 1996)	1296 nondiabetic women	↑	↓	0.007
	1040 nondiabetic men	↔	↔	n.s.
	1322 diabetic women	↑	↓	0.040
	752 diabetic men	↔	↔	n.s.
Suita Study (Katsuya et al., 2002)	3997	n.d.	↓	0.003
Framingham Offspring Study (Wilson et al., 1994)	916 women	OR for HDL<35 = 0.80	OR for HDL<35 = 1.15	n.s.
	1034 men	OR for HDL<35 = 1.36	OR for HDL<35 = 1.37	0.11 / 0.06
Cardiovascular Risk in Young Finns Study (Gronroos et al., 2007)	1736	↑	↓	0.04
(Costanza et al., 2005)	1543	↑	n.d.	0.00078
Bogalusa Heart Study (Srinivasan et al., 1999)	1477	↑	↔	<0.05 / n.s.

^a Due to the high number of studies investigating the *APOE* polymorphism, only large (n>1000) population-based studies are provided in this Table.

^b P value from ANOVA comparing the major genotype groups.

n.s., not significant; n.d., not done.

Table 11: Genetic variants in genes rarely investigated, which showed significant association with HDLC levels in at least one large study (n>1000).

rs number	Alias	Chrom. position	Allele	MAF	Study	Study type	Ethnicity	Sample size	Change in HDLC in mg/dL	P value
ALDH2 = aldehyde dehydrogenase 2										
rs671	Glu487Lys	110726149	Glu>Lys	30 28	(Takagi et al., 2001)	P	A	M: 1919 F: 2138	M: -2.3 / -8.5 (1/2 copies) F: -1.9 / -1.9 (1/2 copies)	<0.0001 0.0254
	ALDH2 *1-2		1>2	31 28	(Nakamura et al., 2002)	GP	A	M: 826 F: 1295	M: -1.8 / -3.5 (1/2 copies) F: -1.2 / -0.2 (1/2 copies)	n.s. n.s.
CD36 = CD36 antigen										
rs10499859 ^a		80096746	A>G	33	(Love-Gregory et al., 2008)	HyperGen ^b	AA	2020	+2.5 per copy	2.8x10 ⁻⁴
DGAT1 = acyl CoA:diacylglycerol acyltransferase 1										
rs7003945	C79T	145521273	T>C	43	(Ludwig et al., 2002)	P	W	1322	-1.8 / -1.4 (1/2 copies)	0.019
EDN1 = endothelin-1										
rs5370		12404241	G>T	21	(Pare et al., 2007)	CVD, Co	W	1442	decreases HDLC	1x10 ⁻⁵
MCC = mast cell chymase										
rs1800875	G3255A	24049178	G>A	20	(Fukuda et al., 2002)	P	A	1046	+2.5 / +1.8 (1/2 copies)	0.038
NR1H3 = liver X receptor alpha										
rs11039155	-6G>A	47237338	G>A	11	(Legry et al., 2008)	P	W	2290	+2.1 for carriers	0.007
PPAR-α = peroxisome proliferator activated receptor alpha										
rs1800206	L162V	44992938	L>V	4	(Manresa et al., 2006)	P	W	1204	-4.0 for carriers	<0.05
PPAR-γ2 = peroxisome proliferator activated receptor gamma 2										
rs1805192	Pro12Ala	12396238	Pro>Ala	5	(Tai et al., 2004)	P	A	4038	+1.6 for carriers	0.028
rs3856806	C1431T	12450557	C>T	23	(Tai et al., 2004)	P	A	4038	no association	n.s.
PRKAA2 = AMP-kinase α2 subunit										
rs2796498	1 - 2	56916574	1>2	46	(Spencer-Jones et al., 2006)	GP	W	2275	-1.5 / -2.3 (1/2 copies)	0.01
ZNF202 = Zinc Finger Protein 202										
rs3183878	c.*2T>G Exon10	123101913	T>G	39	(Stene et al., 2006)	P	W	F: 5039 M: 4064	F: no association M: -1.9 for homozygous Car.	n.s. 0.05

^a 15 additional SNPs in *CD36* were significantly associated with HDLC with varying direction of the effects on HDLC (increase or decrease).

^b The HyperGen (Hypertension Genetic Epidemiology Network) Study recruited hypertensive siblings diagnosed before age 60 from sibships with two or more affected persons, normotensive offsprings and random controls. Details on the study are provided in reference (Williams et al., 2000).

For abbreviations and explanations, see Table 1.

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Table 12: SNPs associated with HDLC concentrations in GWA studies. For each study and each gene, the SNP with the best p value is shown.

Gene	Chr.	Chrom. position	rs number	MAF	Study	Results from initial GWAS scan			Results GWAS scan + replication studies	
						Sample size	Change in HDLC	P value	Sample size	P value
<i>CETP</i>	16	55562980	rs1532624	43	(Aulchenko et al., 2008)	19,674	8.24 (z-sc) ^b	9.4x10 ⁻⁹⁴		
		55550825	rs3764261	31	(Willer et al., 2008)	8656	2.42 mg/dL	2.8x10 ⁻¹⁹	8656+8072	2.3x10 ⁻⁵⁷
		55550825	rs3764261	31	(Cashman et al., 2008)	6382	4.0 mg/dL	1.0x10 ⁻⁴¹		
		55552737	rs1800775	49	(Kathiresan et al., 2008b)	2758	2.6 mg/dL	3x10 ⁻¹³	2758+18,554	1x10 ⁻⁷³
		55552737	rs1800775	47	(Heid et al., 2008)	1643	3.99 mg/dL	6.05x10 ⁻¹⁵		
		55542640	rs9989419	39	(Heid et al., 2008)	1643	-2.68 mg/dL	1.86x10 ⁻⁶	8216	8.50x10 ⁻²⁷
		55542640	rs9989419	40	(Wallace et al., 2008)	1636		5.99x10 ⁻³	1636+2631	1.03x10 ⁻¹⁰
		55562390	rs7205804	37-50	(Kooner et al., 2008)				10,536	4.7x10 ⁻⁴⁷
<i>LPL</i>	8	19909455	rs2083637	26	(Aulchenko et al., 2008)	17,922	4.14 (z-sc) ^b	5.5x10 ⁻¹⁸		
		19891970	rs10503669	10	(Willer et al., 2008)	8656		3.2x10 ⁻¹⁰	8656+11,431	4.1x10 ⁻¹⁹
		19864685	rs331	28	(Cashman et al., 2008)	6382	1.5 mg/dL	9.1x10 ⁻⁷		
		19864004	rs328	9	(Kathiresan et al., 2008b)	2758	2.21 mg/dL	3x10 ⁻⁴	2758+18,554	9x10 ⁻²³
		19876926	rs17482753	10	(Heid et al., 2008)	1643	3.70 mg/dL	2.71x10 ⁻⁵	8180	2.82x10 ⁻¹¹
		19896590	rs17411031	27	(Wallace et al., 2008)	1636		2.12x10 ⁻⁵	1636+2631	1.28x10 ⁻¹⁰
		19863719	rs326	22-30	(Kooner et al., 2008)				10,536	1.8x10 ⁻⁸
<i>LIPC</i>	15	56470658	rs1532085	41	(Aulchenko et al., 2008)	19,736	5.03 (z-sc) ^b	9.7x10 ⁻³⁶		
		56461987	rs4775041	33	(Willer et al., 2008)	8656		2.8x10 ⁻⁹	8656+11,426	3.2x10 ⁻²⁰
		56470658	rs1532085	37	(Cashman et al., 2008)	6382	1.8 mg/dL	1.3x10 ⁻¹⁰		
		56510967	rs1800588	21	(Kathiresan et al., 2008b)	2758	1.95 mg/dL	3x10 ⁻⁵	2758+18,554	2x10 ⁻³²
		56514617	rs261332	21	(Wallace et al., 2008)	1636		7.0x10 ⁻³	1636+2631	5.02x10 ⁻⁷
		56530023	rs11858164	27-55	(Kooner et al., 2008)				10,536	7.0x10 ⁻⁸
<i>LIPG</i>	18	45421212	rs4939883	17	(Aulchenko et al., 2008)	16,258	-3.98 (z-sc) ^b	1.6x10 ⁻¹¹		
		45435666	rs2156552	16	(Willer et al., 2008)	8656		8.4x10 ⁻⁷	8656+11,437	6.4x10 ⁻¹²
		45435666	rs2156552	18	(Kathiresan et al., 2008b)	2758	-1.17 mg/dL	0.02	2758+18,554	2x10 ⁻⁷

		45413088	rs7240405	17	(Heid et al., 2008)	1643	-2.77 mg/dL	3.19x10 ⁻⁴	8213	4.67x10 ⁻¹⁰
<i>ABCA1</i>	9	106696891	rs3905000	14	(Aulchenko et al., 2008)	17,913	-4.37 (z-sc) ^b	8.6x10 ⁻¹³		
		106687041	rs4149268	36	(Willer et al., 2008)	8656		3.3x10 ⁻⁷	8656+11,327	1.2x10 ⁻¹⁰
		106687476	rs3890182	13	(Kathiresan et al., 2008b)	2758	-2.21 mg/dL	3x10 ⁻⁵	2758+18,554	3x10 ⁻¹⁰
		106687476	rs3890182	12	(Wallace et al., 2008)	1636		3.8x10 ⁻²	1636+2631	2.09x10 ⁻⁶
		106660656	rs9282541	0-9	(Kooner et al., 2008)				10,536	4.8x10 ⁻⁸
<i>LCAT</i>	16	66582496	rs255052	17	(Willer et al., 2008)	8656		1.5x10 ⁻⁶	8656+4534	1.2x10 ⁻⁷
<i>APOA1C3A4A5</i>	11	116233840	rs12225230	18	(Cashman et al., 2008)	6382	1.5 mg/dL	5.3x10 ⁻⁵		
		116124283	rs28927680	7	(Kathiresan et al., 2008b)	2758	-0.78 mg/dL	0.31	2758+18,554	2x10 ⁻⁵
<i>APOB</i>	2	21059688	rs6754295	25	(Aulchenko et al., 2008)	17,915	2.63 (z-sc) ^b	4.4x10 ⁻⁸		
<i>CTCF-PRMT8</i>	16	66459571	rs2271293	13	(Aulchenko et al., 2008)	17,910	4.99 (z-sc) ^b	8.3x10 ⁻¹⁶		
<i>MADD-FOLH1</i>	11	48475469	rs7395662	39	(Aulchenko et al., 2008)	17,917	2.82 (z-sc) ^b	6.0x10 ⁻¹¹		
<i>GALNT2</i>	1	228361539	rs2144300	40	(Willer et al., 2008)	8656		6.6x10 ⁻⁷	8656+11,406	2.6x10 ⁻¹⁴
		228362314	rs4846914	40	(Kathiresan et al., 2008b)	2758	-1.30 mg/dL	3x10 ⁻⁴	2758+18,554	2x10 ⁻¹³
<i>MVK/MMAB</i>	12	108379551	rs2338104	45	(Willer et al., 2008)	8656		1.9x10 ⁻⁶	8656+11,399	3.4x10 ⁻⁸
<i>CLPTM1</i>	19	50169221	rs16979595	16	(Wallace et al., 2008)	1636		6.11x10 ⁻³	1636+2631	5.79x10 ⁻⁶
<i>GRIN3A</i>	9	103402758	rs1323432	12	(Willer et al., 2008)	8656	1.93 mg/dL	2.5x10 ⁻⁸ ^a	8656+8176	7.7x10 ⁻⁴ ^a

^a *GRIN3A* is shown here because it was significant in the initial scan ($p=2.5 \times 10^{-8}$).

^b z-sc: The ENGAGE consortium provided the effect size on the z-scale.

For abbreviations and explanations, see Table 1.

