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Meta-analysis of genome-wide association studies of HDL cholesterol response to statins

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Abstract

Background—In addition to lowering low density lipoprotein-cholesterol (LDL-C), statin therapy also raises high density lipoprotein-cholesterol (HDL-C) levels. Inter-individual variation in HDL-C response to statins may be partially explained by genetic variation.

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Methods and Results—We performed a meta-analysis of genome-wide association studies (GWAS) to identify variants with an effect on statin-induced HDL-C changes. The 123 most promising signals with $P<1\times10^{-4}$ from the 16,769 statin-treated participants in the first analysis stage were followed up in an independent group of 10,951 statin-treated individuals, providing a total sample size of 27,720 individuals. The only associations of genome-wide significance ($P<5\times10^{-8}$) were between minor alleles at the *CETP* locus and greater HDL-C response to statin treatment.

Conclusion—Based on results from this study that included a relatively large sample size, we suggest that *CETP* may be the only detectable locus with common genetic variants that influence HDL-C response to statins substantially in individuals of European descent. Although *CETP* is known to be associated with HDL-C, we provide evidence that this pharmacogenetic effect is independent of its association with baseline HDL-C levels.

Keywords

Pharmacogenetics; HDL-Cholesterol; Statins; Genome-wide association study

Introduction

The drug class of 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, better known as "statins", are widely prescribed and effective for the prevention and management of cardiovascular disease (CVD).[1] While the major CVD benefit of statins is due to reduction in plasma low density lipoprotein cholesterol (LDL-C)[2], statins also produce moderate increases, ranging from 4 to 10%, in levels of high density lipoprotein cholesterol (HDL-C).[3, 4] This is of particular interest since HDL-C levels are inversely related to CVD risk in the general population and in patients treated with statins.[5, 6] However, a causal role of low HDL-C as a determinant of increased CVD risk is controversial.[7]

The increase in HDL-C after statin therapy varies among individuals.[3] This might be partly due to genetic variation. Previous studies that have investigated associations between genotype and statin-induced changes in HDL-C[8–10] have focused primarily on variants within the *CETP* gene that are known to affect circulating HDL-C levels[11] and risk of coronary artery disease.[12] To address whether additional loci have an effect on statin-induced changes in HDL-C levels, we conducted a large-scale meta-analysis of genome-wide association studies (GWAS) using datasets from both randomized controlled trials (RCTs) and cohort studies in the large Genomic Investigation of Statin Therapy (GIST) consortium that previously identified four loci associated with LDL-C response to statins. [13]

Methods

Study populations

The GIST consortium assembled data from seven RCTs and eleven prospective population-based studies. The initial analysis (first stage) was performed in 16,769 statin-treated individuals; 8,506 individuals from six RCTs (ASCOT UK, CARDS, CAP, PRINCE,

PROSPER, and TNT) and 8,263 statin-treated individuals from ten observational studies (AGES, ARIC, ASCOT UK-observational, BioVU, CHS, FHS, Health ABC, HVH, MESA, and the Rotterdam Study). Further investigation (second stage) was performed in 10,951 statin-treated individuals from two RCTs (ASCOT Scandinavia and JUPITER) and two observational studies (ASCOT Scandinavia – observational and GoDARTS), which were used to test for replication of findings from the first stage. Details of the first and second stage studies, including their genotyping and quality control (QC) information, can be found in the Supplementary Notes 1, 2 and 3 and Supplementary tables 1 and 2.

Subjects

Response to statin treatment was principally studied in statin-treated individuals only. Those treated with placebo were excluded from the analyses of RCTs and those not treated with statins were excluded from observational studies. HDL-C measurements were obtained before and after start of statin treatment. Only subjects with non-missing phenotypes and covariates were included. Those of reported or suspected non-European ancestry were excluded.

Outcome measurements

The response to statin treatment was defined as the difference between the natural log-transformed on- and off-treatment HDL-C levels (ln (on-treatment HDL-C) – ln (off-treatment HDL-C)). The corresponding linear regression coefficients thus reflect the fraction of differential HDL-C increase (relative increase) per copy of the coded allele in the additive genetic model. For observational studies, on-treatment HDL-C levels were calculated for all different prescribed statins, at any dosage, for any indication, and for any treatment episode extending at least four weeks prior to on-treatment HDL-C measurement. Characteristics of on- and off-treatment HDL-C levels and statins used in each study are shown in Supplementary Table 2. For each individual, at least one off-treatment HDL-C measurement and at least one on-treatment measurement were required. Subjects with missing on- or off-treatment measurements were excluded, with the exception of the GoDARTS study for which missing off-treatment HDL-C levels were estimated using imputation methods, as described previously.[14] In RCTs, when multiple on- or off-treatment measurements were available, the mean of the measurements was used.

Genotyping and imputation

Genotyping, quality control, data cleaning and imputation were performed independently in each study using different genetic platforms and software as outlined in Supplementary Table 3. In all studies, genotyping was performed using either Illumina, Affymetrix, or Perlegen genotyping arrays. Genotype data from each study had been imputed to the HapMap phase 2 reference panel [15], except for JUPITER which was imputed to the 1000genomes pilot data, using either MACH, Impute, or BIMBAM software [16–18], resulting in a total of approximately 2.5 million SNPs for analysis.

GWAS analysis

Each study independently performed the GWAS on the difference between natural log-transformed on- and off-treatment HDL-C levels, according to a common, central analysis protocol. To reduce confounding by possible association with off-treatment HDL-C levels, analyses were adjusted for the natural log-transformed off-treatment HDL-C levels. Linear regression was used, with SNPs represented by an additive genetic model and with imputed SNPs represented by expected allele dosage. Analyses were additionally adjusted for age, sex, and study specific covariates (e.g ancestry principal components (PCs), site, or country). FHS made use of a linear mixed effects model considering the kinship matrix in the analysis, hereby accounting for familial correlations within FHS. Analyses in the observational studies were, if the information was available, additionally adjusted for the time interval between on- and off-treatment HDL-C measures (mean follow-up times per study are provided in Supplementary Table 2) and for the natural logarithm of the statin dose equivalent, as defined in Supplementary Table 4. This table shows the dose for different statins for the LDL-C response; dividing the statin dosage for an individual drug by its dose equivalent shown in Supplementary Table 4 gives the standardized statin dosage.

Quality control and Meta-analysis

Within each study, SNPs with minor allele frequency <1% or imputation quality <0.3 were excluded from the analysis. QQ-plots were assessed for each study to check that there were no between study differences nor evidence for systematic bias within studies (Supplementary Figure 1). The software package METAL was used to perform the meta-analysis.[19] A fixed effects, inverse variance weighted approach was used. To correct for possible inflation of the test statistic, e.g. due to small amounts of potential population sub-structure, genomic control was performed by adjusting the within-study findings and the meta-analysis results for the genomic inflation factor.

Second stage

SNPs with p-values $<1\times10^{-4}$ in the first stage meta-analyses were selected for further investigation in the second stage. A maximum of two SNPs per locus (with a maximum 100 kB distance between SNPs) were selected, with the choice based on statistical significance. A total of 123 SNPs in 83 loci were selected for the second stage, which was performed in the GoDARTS study, the JUPITER trial, and the RCT and observational arm of the ASCOT Scandinavia study. GWAS data and response to statin treatment were available for these studies. Analysis was performed as for the first stage. Results of the first and second stage were combined using a fixed effects, inverse variance weighted meta-analysis using METAL.

Interaction analysis

The interaction effect of the lead *CETP* SNP rs247616 with the binary treatment indicator for statin versus placebo allocation was assessed in five of the participating RCTs (ASCOT Scandinavia, ASCOT UK, CARDS, JUPITER, and PROSPER). For these analyses, placebo treated individuals in the RCTs were included. The total sample size was 17,857, with 8,978 statin treated individuals and 8,879 placebo treated individuals. Regression models were

applied to the combined population of statin and placebo treated subjects by adding to the model extra terms including treatment (statin (=1) or placebo (=0)) allocation and the product of treatment allocation with SNP minor allele dose.[20] Interaction coefficients of the five studies were combined in a fixed effects, inverse variance weighted meta-analysis using METAL. In addition, we also performed our main analysis for the *CETP* SNP rs247616 in only the placebo users of the five RCTs included in the interaction analysis.

Effect of genetic determinants of HDL-C levels on statin-induced HDL-C response

We performed a look-up in our GWAS results for all known genome-wide significant genetic variants associated with HDL-C levels, obtained from the most recent Global Lipids Genetics Consortium (GLGC) paper.[11] Of the 80 variants, 78 were available in our GWAS on statin induced HDL-C response. Subsequently, we examined whether a multi-SNP genotypic risk score constructed from these GLGC variants was associated with the level of statin induced HDL-C response, using publicly available summary level data from the GLGC (http://csg.sph.umich.edu//abecasis/public/lipids2013/). The joint effect of the 78 genetic variants on statin-induced HDL-C response was examined by means of a data-driven inverse-variance weighted approach, described previously by Dastani *et al*, [21] and accomplished through the gtx-package [22] (Genetics ToolboX, http://cran.r-project.org/web/packages/gtx) in the R statistical software environment.[23] Analogous to deriving a pooled estimate from the results of individual studies in conventional meta-analysis, this approach combines the causal estimates of multiple genetic variants, defined as the ratio of their association with statin response to their association with HDL-C levels.

Conditional analysis

Conditional analysis were performed in two of the participating studies, ASCOT UK (both RCT and observational – genotype data available for n=3,804) and CARDS (genotype data available for n=1194). Conditional analysis was conducted within GCTA software[24], using the *–cojo* method, which performs conditional and joint analysis with model selection. The genome-wide meta-analysis summary statistics from the combined analysis of both first-stage and second-stage data were used as the input data. Analysis was restricted to chromosome 16, containing the only genome-wide significant result from the meta-analysis, in order to determine whether the *CETP* region contains more than one independent signal of association. Within the GCTA analysis, MAF was restricted to 1% and a p-value cut-off of 5×10^{-7} was used as the selection threshold. LD was calculated between pairwise SNPs, but any SNPs further than 10 Mb apart were assumed to be in linkage equilibrium.

Variance explained

Two secondary analyses were performed to investigate the heritability of this pharmacogenetic trait. Firstly, the genome-wide heritability was calculated in GCTA[24] by estimating h^2 using GREML analysis, according to all HapMap SNPs with MAF 1%, with reference to the genomic relatedness matrix generated within GCTA. Secondly, the percentage variance explained for the HDL-C response to statins adjusted for baseline HDL-C was calculated specifically for the lead *CETP* SNP rs247616 using R software[23] by including the dosage data for this SNP as a continuous predictor variable within the model. Firstly, the HDL-C response trait was regressed against all non-genetic covariates. The

residuals from this model were used as the residual trait. In a second stage linear regression analysis the residual trait was regressed against the lead SNP and PCs. The R^2 calculated from this second fitted linear regression model was used to estimate the percentage of the trait variance explained. Both analyses were performed using the ASCOT-UK dataset, as individual level raw genotype data are required. The combination of both the RCT and observational sub-cohorts of ASCOT-UK gave a total sample size of N = 2,055 statin-treated participants. The explained variance analysis in R was additionally performed in the CARDS study, including 1,194 statin-treated participants. The linear regression models used exactly the same data and covariates as from the primary GWAS analysis.

Results

First-stage meta-analysis

In the first stage of this analysis, six randomized controlled trials (n=8,506 statin recipients) and ten observational studies (n=8,263 statin recipients) were included (Supplementary Notes 1 and 2 and Supplementary Tables 1 and 2). Three SNPs at the *CETP* locus (chromosome 16) were identified as genome-wide significant ($P<5\times10^{-8}$) for their association with HDL-C response to statin treatment (Figures 1 and 2 and Table 1). The most significant association was for SNP rs247616 (MAF=0.324, β=0.011, SE=0.002, $P=5.95\times10^{-10}$) (Figure 3), indicating that carriers of the minor allele of this SNP respond to statins with a 1.1% greater per-allele increase in HDL-C compared with non-carriers. The average increase in HDL-C during statin treatment across all studies was 0.045 mmol/L. This additional 1.1% per-allele increase in HDL-C is equivalent to a 0.046 mmol/L increase for carriers of one copy of the CETP SNP. We found no other loci associated with HDL-C response to statin treatment at a genome-wide significant level at this first stage.

Second-stage meta-analysis

We selected 123 SNPs from 83 loci with $P<1\times10^{-4}$ in the first stage meta-analysis for further investigation in the second stage, which included 10,951 statin-treated individuals from two RCTs and two observational studies (Supplementary Note 3 and Supplementary Tables 1 and 2). The second stage meta-analysis confirmed the significant association between genetic variants within the *CETP* loci and HDL-C response from the first stage meta-analysis (rs247616: MAF=0.327, β=0.005, SE=0.001, $P=1.59\times10^{-5}$) as $P<6\times10^{-4}$, the Bonferroni p-value threshold for testing 123 SNPs (Table 1, Figure 2, and Supplementary Table 5). The combined effect from the first and second stage meta-analysis for the *CETP* rs247616 SNP was genome-wide significant (MAF=0.326, β=0.007, SE=0.001, $P=8.52\times10^{-13}$) (Table 1, Figure 2, and Supplementary Table 5). No other locus reached statistical significance ($P<4\times10^{-4}$) in the second stage meta-analysis or in the combined meta-analysis ($P<5\times10^{-8}$) for association with HDL-C response to statin treatment (Figure 1 and Supplementary Table 5). Indeed, Supplementary Table 5 (ordered by the combined meta-analysis p-values) shows that the three SNPs within *CETP* which were genome-wide significant in the first stage, were the only SNPs that reached Bonferroni significance in the second stage and genome-wide significance in the combined meta-analysis.

Interaction analysis

To exclude the possibility of confounding in the association between *CETP* and HDL-C response to statin treatment, two analyses were performed. First the main analysis for the *CETP* SNP rs247616 was repeated in the placebo users using data from five of the participating RCTs. In addition, in the same studies we tested for interaction between the *CETP* lead SNP rs247616 and randomized statin or placebo allocation. Supplementary Figure 2 shows the results for the association between HDL-C change during follow-up and rs247616 stratified for placebo and statin users. Table 2 shows a significant P-value for interaction in the meta-analysis combining the five studies (P-3.52×10^{-3}, β=0.007, SE=0.002) for the *CETP* SNP, indicating that genetic effects of *CETP* on baseline HDL-C contribute at most only in part to genetic effects on HDL-C response in the statin-treated group, as the genetic effect is modified by the use of statin treatment.

Effect of genetic determinants of HDL-C levels on statin-induced HDL-C response

SNPs previously shown to be associated with HDL-C levels (n=78)[11] were assessed for their association with statin-induced HDL-C response in our meta-analysis. After Bonferroni correction, rs3764261 (*CETP*) was the sole genetic variant associated with statin-induced HDL-C response amongst the 78 examined variants (Supplementary Table 5). Joint analysis of the HDL-C associated variants demonstrated that predisposition to high HDL-C levels is associated with increased statin-induced HDL-C response (Figure 4). This amounted to a 2.9% fractional increase (β=0.029, SE=0.003, P=1×10^{-19}) in statin-induced HDL-C response per SD increase in genetically raised HDL-C levels. Excluding the *CETP* SNP (rs3764261) from the model did not materially change the results (β=0.029, SE=0.005, P=1×10^{-8}). Testing for heterogeneity did not reveal any indication of pleiotropic effects(P=0.64).

Conditional analysis

The conditional analysis within GCTA resulted in only one remaining SNP selected in the model, namely the lead SNP rs247616 within the *CETP* locus, with a joint p-value of 9.96×10^{-10} and joint β=0.0104, equal to its unconditional effect size estimate. As can be seen from the locus zoom plot in Figure 3, the other two genome-wide significant hits are in high LD with the lead SNP, and after conditioning on the lead SNP, the GCTA conditional analysis results show that no other SNPs within chromosome 16 have significant residual association, with the minimum conditional p-value being p~3×10^{-5}. Hence we conclude that there is only one independent signal within the *CETP* association.

Variance explained

From genome-wide data of the ASCOT-UK datasets, the trait heritability for HDL-C response to statins was estimated as h^2 = 17.8% (SE = 0.154) although this was non-significant (p=0.125). There was insufficient power to run the GCTA analysis in the CARDS dataset, due to smaller sample size. The trait variance explained by the lead *CETP* SNP rs247616 alone was calculated to be 0.04% from ASCOT-UK and 0.01% from CARDS, both non-significant (p=0.38 and p=0.54, respectively).

Discussion

In this study we have performed a meta-analysis of GWAS including over 27,700 statin-treated individuals, investigating genetic variants associated with variation in HDL-C response to statin treatment. We identified three genetic variants in the *CETP* locus that were highly significantly associated with a larger HDL-C response to statin treatment. No other SNPs met the genome-wide criterion for association of HDL-C change with statin use.

CETP plays an important role in HDL-C metabolism by promoting the exchange of cholesteryl esters in HDL particles with triglycerides in apolipoprotein B-containing particles, leading to increased HDL catabolism and lower HDL-C levels. Increases in HDL-C levels after statin treatment are probably partly the result of a reduction in CETP mediated lipid transfer[25], as was also shown in mice expressing human CETP.[26] Statin treatment decreases CETP activity up to 30%.[27, 28] Previously it has been shown that genetic variants within *CETP* are associated with differences in CETP concentration.[29] The three SNPs associated with HDL-C response to statins in the present study are located 2.5–7 kb upstream of the *CETP* gene and are in high linkage disequilibrium (Figure 3).[30] The minor alleles of these SNPs have been shown to be associated with lower *CETP* mRNA expression levels in liver tissue and with higher HDL-C levels.[30, 31]

Previous studies investigating the association between SNPs in the *CETP* locus and the HDL-C response to statin treatment have yielded inconsistent results. Several studies showed associations with a greater HDL-C response [8, 10], whereas others showed no significant associations.[12, 32–34] These discrepancies could be explained by limited sample sizes and by the investigation of different genetic variants in these studies. An alternative explanation could be the fact that the effect of statins on HDL-C response is relatively small and depends on statin dose and type.[3, 4] Since the power to detect genetic effects on these small variations is low in single studies, the results from the present large meta-analysis, with replication, provide strong evidence that genetic variation at the *CETP* locus is associated with HDL-C response.

The results of six randomized clinical trials and ten observational studies were combined in the first stage of the current study. Different statins were investigated in the trials and used within the observational studies, resulting in combining several types of statins in our analysis. This and the variation in statin dosages during follow-up for an individual are a limitation of the current study, since the pharmacogenetic impact might be dependent on specific statin types and dose. To address this possible limitation, the individual study analyses were adjusted for statin equivalent dose based on effect on LDL-C levels, making the different statin types likely more comparable with respect to clinical effectiveness on HDL-C levels. Combining RCTs and observational cohort might also result in heterogeneity between the study types. To reduce the possibility of large heterogeneity we aimed to mimic the design of a RCT in the observational studies, by including only new statin-users. Comparing heterogeneity of the RCTs and observational studies included in the first stage showed no evidence of large heterogeneity (p=0.761, data not shown).

Another possible limitation of the current study is the association of the identified genetic variant with baseline HDL-C concentration. As shown in previous large GWAS studies, the *CETP* SNP rs3764261 is strongly associated with HDL-C levels.[11, 31] In pharmacogenetic studies investigating lipid responses to drug exposure, it is important to eliminate the effect of the association between baseline lipid levels and the investigated genetic variants.[13] To reduce the impact of these possible confounding effects, our response to treatment analyses were adjusted for baseline HDL-C levels. In addition, interaction analyses in five of the RCTs, with direct modeled comparison with a random assignment to a placebo group, suggested little or no influence of the association between the *CETP* SNPs and baseline HDL-C levels on the genetic effect on HDL-C response to statin treatment. It is, however, possible that mechanisms underlying the effects of CETP on HDL-C levels are also involved in mediating statin effects on HDL-C.

All genetic data in the current study was imputed to up to 2.5 million autosomal SNPs based on data from the HapMap project.[15] In addition, in our analysis we excluded genetic variants with a minor allele frequency <1%, restricting our analysis to common genetic variants. Imputation based on the more recent 1000 Genomes project could reveal more associations with rare genetic variants.[35] Future studies using exome sequencing data and investigating rare variants may identify additional associations between genetic variants and statin-induced HDL-C response. However, the non-significant estimate of heritability attributable to common variation in our analysis may indicate that the observed increase in HDL-C levels after statin-treatment may be mainly due to environmental rather than genetic effects.

The implications of the present findings regarding genetic effects on the efficacy of statins for reductions in risk of CVD are uncertain. Based on the strong inverse relationship of HDL-C with CVD, the greater statin-induced increase in HDL-C among carriers of the minor vs. major alleles of the three *CETP* SNPs reported here may confer a greater protective effect of statins on CVD in patients carrying the minor allele. However, a recent study employing Mendelian randomization found that genotypes associated with plasma HDL-C levels were not associated with the impact on CVD risk that would be predicted by the magnitude of the genotypic effects on HDL-C.[7] Moreover, two large clinical trials have failed to show reduction of CVD events by nicotinic acid-induced increases in HDL-C in patients with well-controlled LDL-C levels.[36, 37] Hence, whether greater genetically-mediated HDL-C increases with statin treatment confer increased protection from CVD remains unknown.

In conclusion, this study is the largest meta-analysis of GWAS for HDL-C response to statin treatment conducted to date. The findings suggest that *CETP* may be the only locus in which common genetic variants are significantly associated with a substantial HDL-C response to statin treatment in individuals of European descent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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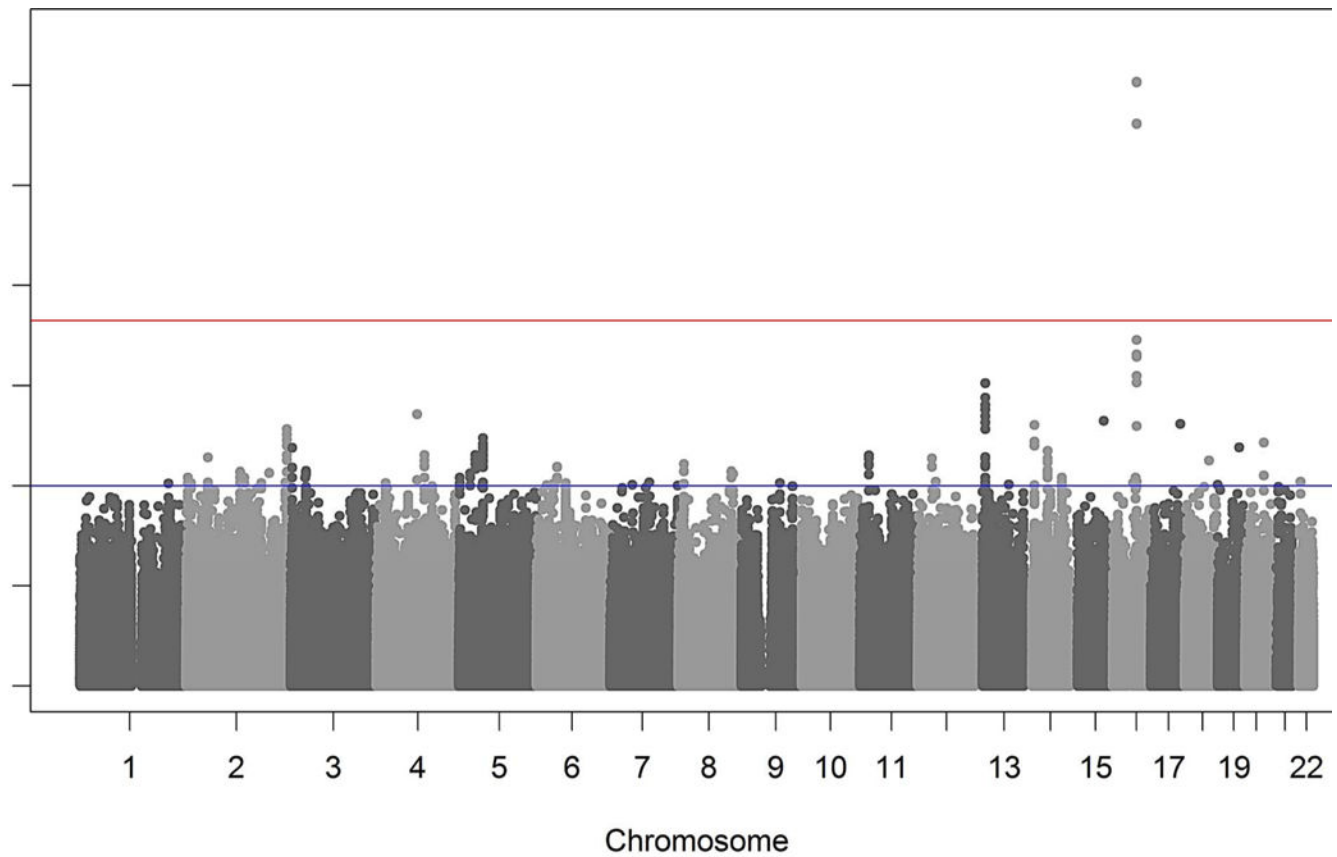
Figure 1.
Results of the GWAS meta-analysis. Manhattan plot presenting the $-\log_{10}$ P-values from the combined stage 1 and 2 meta-analysis on HDL-C response to statin treatment. The top (red) line represents the genome-wide significant P-value 5×10^{-8}, the second (blue) line represents the P-value 1×10^{-4}, the threshold used for selecting SNPs to take forward to the second stage. Hence the results of these SNPs come from the lager combined meta-analysis, whereas all other results are taken from the stage 1 discovery meta-analysis.
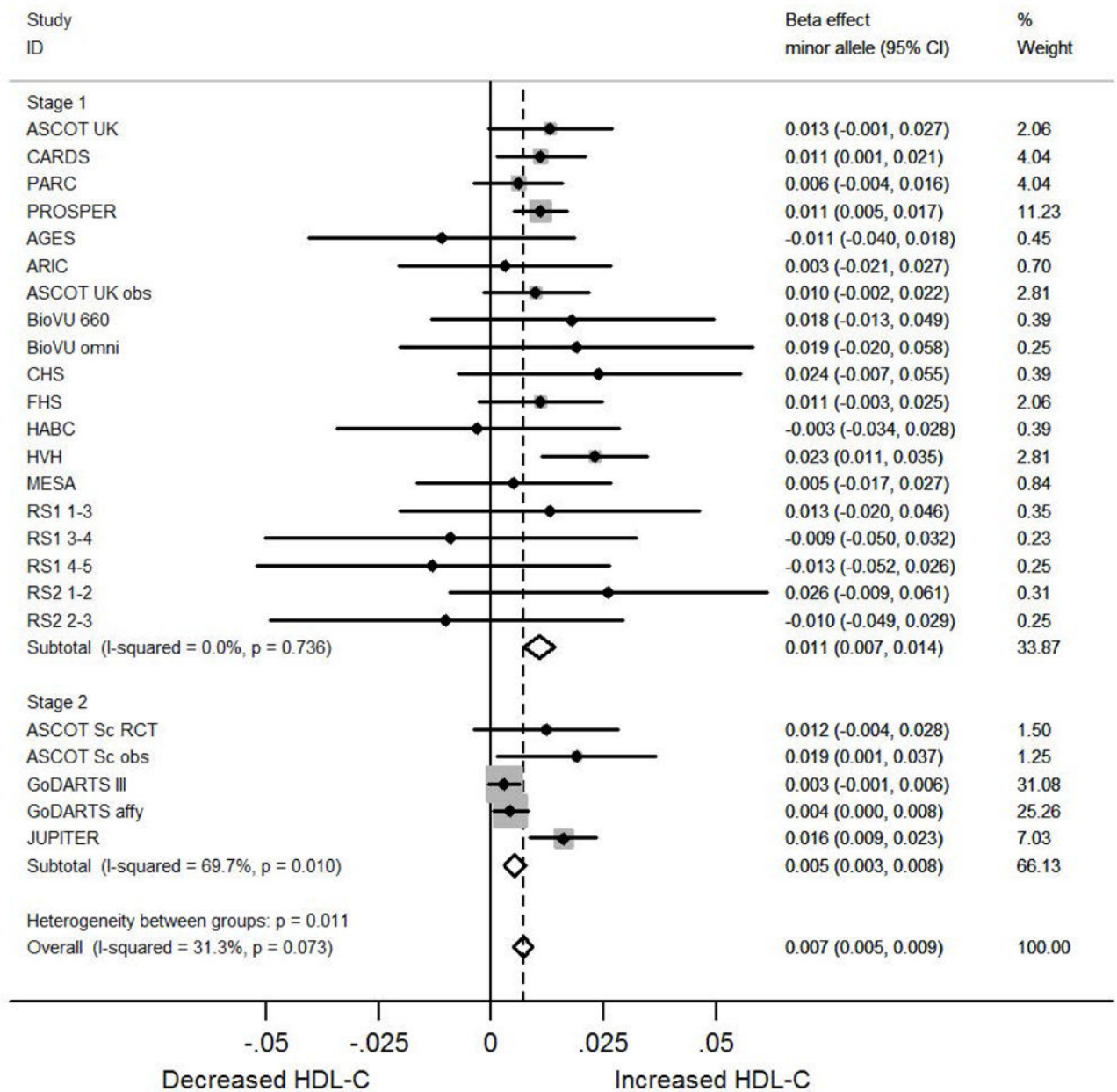
Figure 2.
Forest plot showing the association in each study and overall association of the lead *CETP* SNP rs247616 with HDL-C response to statin treatment. Beta represents fractional HDL-C change for each copy of the minor allele.
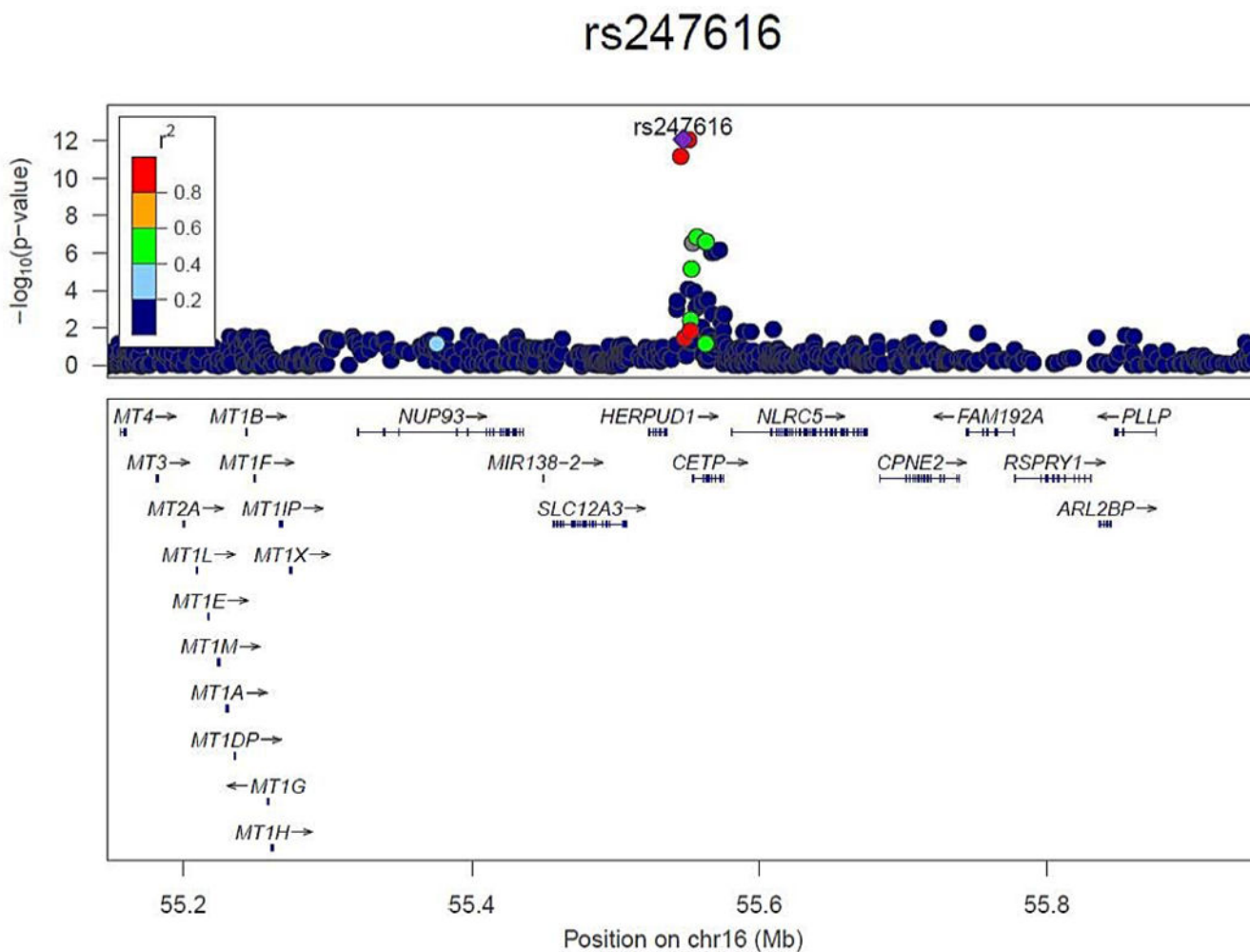
Figure 3.
Regional association plot of the *CETP* region that was genome-wide significant for association with HDL-C response to statin treatment, using the results of the combined meta-analysis (generated using LocusZoom [39]). The color of each SNP is based on the LD (r^2) with the lead SNP rs247616 (shown in purple). The RefSeq genes in the region are shown in the lower panel.
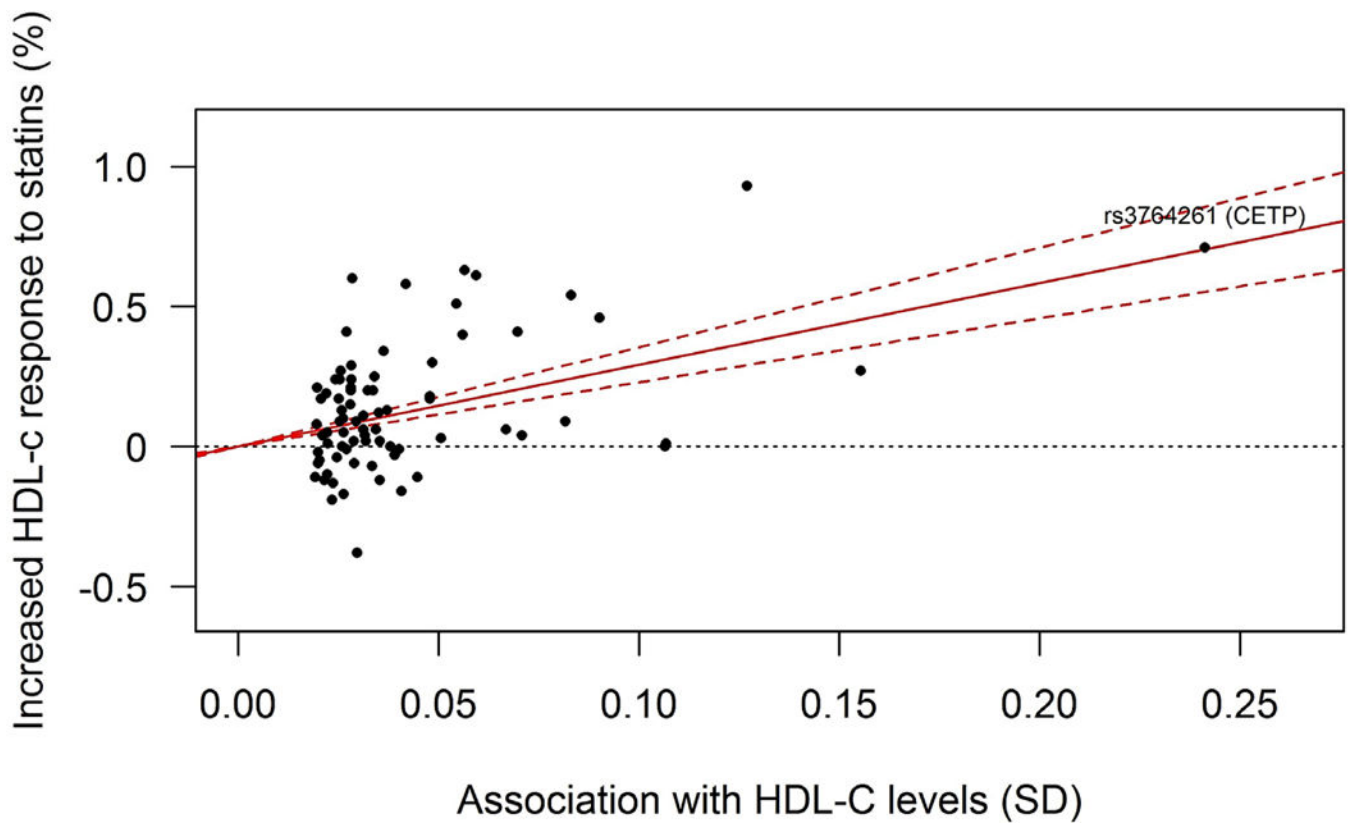
Figure 4.
Plot of the per-allele association of genetic variants with HDL-C levels (x-axis, per allele in SD units, as reported by Willer *et al.* [11]) against the association with HDL-C response to statin treatment (y-axis, percentage) (generated using [22]). The regression line shows the linear relationship between these two variables, with 95% confidence boundaries.

Table 1

Association of *CETP* SNP rs247616 (chromosome 16, bp 55547091) with HDL-C response after statin treatment in the stage 1, stage 2, and combined GWAS meta-analyses.

Phase	N	Coding allele	Non-coding allele	Frequency coding allele	Beta*	SE	% extra increase#	P-value
Stage 1	14693	T	C	0.324	0.011	0.002	1.1	5.95×10^{-10}
Stage 2	10961	T	C	0.327	0.005	0.001	0.5	1.59×10^{-5}
Combined	25654	T	C	0.326	0.007	0.001	0.7	8.52×10^{-13}

*
Beta for difference between the natural log transformed on- and off-treatment HDL-C levels, adjusted for natural log transformed off-treatment HDL-C, age, sex, and study specific covariates. The beta reflects the fraction of differential HDL-C lowering in carriers vs. non-carriers of the SNP; a positive beta indicates a better statin response (larger HDL-C increase).

#
This percentage reflects the % extra HDL-C increase in carriers vs. non-carriers of the SNP.

Table 2

Interaction between *CETP* rs247616 and statin vs. placebo allocation on HDL-C response. Meta-analysis of data from 5 RCTs.

SNP	N	Coding allele	Non-coding allele	Frequency coding allele	Interaction Beta	Interaction SE	Interaction P-value
rs247616	17857	T	C	0.341	0.007	0.002	3.52×10^{-3}

Interaction beta and SE refer to statistics from linear regression modelling the difference between the natural log transformed on- and of-treatment HDL-C levels adjusted for natural log transformed off-treatment HDL-C, age, sex, and study specific covariates, and including an interaction term between SNP and statin or placebo allocation. The interaction p-value refers to the significance of the SNP-by-statin or placebo allocation interaction term in the regression model.