

## Association of GWAS-Based Candidate Genes with HDL-Cholesterol Levels before and after Bariatric Surgery in the Swedish Obese Subjects Study

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**Context and Objective:** The magnitude of weight loss-induced high-density lipoprotein cholesterol (HDL-C) changes may depend on genetic factors. We examined the associations of eight candidate genes, identified by genome-wide association studies, with HDL-C at baseline and 10 yr after bariatric surgery in the Swedish Obese Subjects study.

**Methods:** Single-nucleotide polymorphisms (SNP) ( $n = 60$ ) in the following gene loci were genotyped: *ABCA1*, *APOA5*, *CETP*, *GALNT2*, *LIPC*, *LIPG*, *LPL*, and *MMAB/MVK*. Cross-sectional associations were tested before ( $n = 1771$ ) and 2 yr ( $n = 1583$ ) and 10 yr ( $n = 1196$ ) after surgery. Changes in HDL-C were tested between baseline and yr 2 ( $n = 1518$ ) and yr 2 and 10 ( $n = 1149$ ). A multiple testing corrected threshold of  $P = 0.00125$  was used for statistical significance.

**Results:** In adjusted multivariate models, *CETP* SNP rs3764261 explained from 3.2–4.2% ( $P < 10^{-14}$ ) of the variation in HDL-C at all three time points, whereas *CETP* SNP rs9939224 contributed an additional 0.6 and 0.9% at baseline and yr 2, respectively. *LIPC* SNP rs1077834 showed consistent associations across all time points ( $R^2 = 0.4$ –1.1%;  $3.8 \times 10^{-6} < P < 3 \times 10^{-3}$ ), whereas *LPL* SNP rs6993414 contributed approximately 0.5% ( $5 \times 10^{-4} < P < 0.0012$ ) at yr 2 and 10. In aggregate, four SNP in three genes explained 4.2, 6.8, and 5.6% of the HDL-C variance at baseline, yr 2, and yr 10, respectively. None of the SNP was significantly associated with weight loss-related changes in HDL-C.

**Conclusions:** SNP in the *CETP*, *LIPC*, and *LPL* loci contribute significantly to plasma HDL-C levels in obese individuals, and the associations persist even after considerable weight loss due to bariatric surgery. However, they are not associated with surgery-induced changes in HDL-C levels. (*J Clin Endocrinol Metab* 96: E953–E957, 2011)

Epidemiological studies have provided strong evidence for an inverse relationship between plasma high-density lipoprotein cholesterol (HDL-C) levels and coronary heart disease morbidity and mortality (1–3). Clinical practice guidelines recommend weight loss to raise low levels of HDL-C in overweight and obese individuals with dyslipidemia (4, 5). Bariatric surgery is considered the most reliable method of accomplishing long-term weight loss in

morbidly obese individuals (6) and has also been shown to lead to favorable changes in HDL-C levels. In the Swedish Obese Subjects (SOS) study, severely obese subjects experienced increases in HDL-C of 19 and 14% 2 and 10 yr after bariatric surgery, respectively (7). However, there was large inter-individual variation in the responsiveness of HDL-C levels to weight loss achieved through bariatric surgery in SOS (Supplemental Figs. 1 and 2, published on

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Abbreviations: BMI, Body mass index; GWAS, genome-wide association studies; HDL-C, high-density lipoprotein cholesterol; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism; SOS, Swedish Obese Subjects.

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It is believed that the heterogeneity in HDL-C response to bariatric surgery-induced weight loss may be caused in part by a genetic predisposition. A metaanalysis of cross-sectional genome-wide association studies (GWAS) identified at least 14 replicated loci associated with HDL-C (8). Genetic variants contributing to HDL-C differences among weight-stable individuals may also contribute to differences in weight loss-induced HDL-C changes over time. Therefore, we investigated the cross-sectional associations of single-nucleotide polymorphisms (SNP) from eight GWAS-based candidate genes with HDL-C levels before surgery (baseline) and 2 and 10 yr after surgery in SOS bariatric surgery patients. Furthermore, the associations of SNP with longitudinal changes in HDL-C over 10 yr of follow-up after bariatric surgery were examined.

## Subjects and Methods

### Design of the SOS study

A complete description of the SOS study design, recruitment, and assessment procedures have been published elsewhere (7, 9). The surgery group consisted of 2010 subjects, with surgical treatment techniques including vertical banded gastroplasty ( $n = 1368$ ), banding ( $n = 377$ ), or gastric bypass ( $n = 265$ ). Seven regional ethics review boards approved the study protocol. Informed consent was obtained from all subjects.

### HDL-C assessment

Serum lipid measurements were performed at baseline and the follow-up examinations at yr 2 and 10. All blood samples, which were obtained in the morning after a 10- to 12-h fast, were processed at the primary health care centers and transferred to the Central Laboratory of Sahlgrenska University Hospital. Spectrophotometric methods were used to determine serum HDL-C from 1991–1997 and enzymatic methods used thereafter (Supplemental Table 1). The change in methodologies seemingly did not result in different HDL-C values from 1997–2002. However, an instrument change in 2002 resulted in 13% higher values according to studies at the Central Lab using both methods. Thus, the data included in this report have been adjusted to account for this difference (Supplemental Table 1).

### Genes and SNP selection

Candidate genes for the present study were selected from the first two HDL-C GWAS reports published in 2008 (10, 11). The following genes were included: ATP-binding cassette, sub-family A member 1 (*ABCA1*,  $n = 8$  SNP); apolipoprotein A1/C3/A4/A5 cluster (*APOA5*,  $n = 4$  SNP); cholesteryl ester transfer protein (*CETP*,  $n = 19$  SNP); UDP-GalNAc transferase 2 (*GALNT2*,  $n = 2$  SNP); hepatic lipase (*LIPC*,  $n = 4$  SNP); endothelial lipase (*LIPG*,  $n = 2$  SNP); lipoprotein lipase (*LPL*,  $n = 20$  SNP); and SNP rs7311187, which is located in the vicinity of the methylmalonic aciduria (cobalamin deficiency) cblB type (*MMAB*) and mevalonate kinase (*MVK*) loci. The tagSNP approach was used

for *CETP* and *LPL* (including the GWAS SNP), whereas the SNP for other genes were taken directly from the GWAS reports (10, 11). The tagSNP were selected from the Caucasian data set of HapMap (12) (data release January 23, 2008) using the pairwise algorithm of the Tagger program (13). The pairwise linkage disequilibrium (LD) threshold for the LD clusters was set to  $r^2$  of 0.85 or higher and minimum minor allele frequency to 10%. The final SNP set included 60 SNP with minor allele frequency higher than 0.05 and Hardy-Weinberg equilibrium  $P > 0.05$  in the SOS cohort.

### Genotyping

The SNP were genotyped using the Illumina (San Diego, CA) GoldenGate chemistry and Sentrix Array Matrix technology on the BeadStation 500GX. Genotype calling was done with the Illumina BeadStudio software, and each call was confirmed manually. For quality control purposes, five Centre d'Etude du Polymorphisme Humain control DNA samples (NA10851, NA10854, NA10857, NA10860, and NA10861; all samples included in the HapMap Phase II Caucasian panel) were genotyped in triplicate. Concordance between the replicates as well as with genotypes from the HapMap database was 100%.

### Statistical analysis

Association models were performed using the total association model implemented in MERLIN version 1.1.2 (14). Cross-sectional association models were tested at the baseline, yr-2, and yr-10 examinations. Changes in HDL-C over time were calculated from baseline to yr 2 ( $n = 1518$ ) and yr 2 and 10 ( $n = 1149$ ). The cross-sectional association models included age, sex, body mass index (BMI), smoking, diabetes, and lipid-modifying medications as covariates. Gastric bypass surgery technique (yes or no) was also included as a covariate in the yr-2 and yr-10 models. The HDL-C change over time models included baseline age, sex, BMI of the most recent included exam (yr-2 or -10 BMI), gastric bypass surgery technique (yes or no), weight change, and smoking and lipid-modifying medications at either exam (yes or no). Genotype effect size ( $R^2$ ) was defined as the proportion of total phenotypic variance explained by the genotype. Because multiple SNP ( $n = 60$ ) were used in the association analyses, we applied a multiple testing correction as proposed by Nyholt (15). In our study, the corrected threshold for statistical significance was set to  $P = 0.00125$  as the total effective number of SNP was 40.

To examine the independent contributions of the SNP on cross-sectional HDL-C levels, all significant ( $P \leq 0.00125$ ) SNP from the single-SNP analyses were analyzed with multivariate regression models. Because the significant SNP within the *LIPC* and *LPL* loci were in strong LD ( $r^2 > 0.80$ ), only one significant SNP each from these two gene loci was selected for the final forward regression model. Additionally, because the *CETP* locus had more significant SNP in the single-SNP analyses with LD ranging from 0.002–0.703, we entered all significant *CETP* SNP into a stepwise regression model with backward elimination to remove redundant SNP. The final forward regression models included the *CETP* SNP retained after backward elimination along with one SNP each from *LIPC* and *LPL* and all covariates.

## Results

Overall, SOS subjects lost a significant amount of weight [28.6 (SD 14.1) kg] from baseline to the yr-2 examination

**TABLE 1.** SNP, of the 60 total SNP tested, showing significant cross-sectional associations with HDL-C levels in SOS bariatric surgery patients

SNP	Chr	Map	Gene	Time point					
				Baseline, n = 1771		yr 2, n = 1583		yr 10, n = 1196	
				R <sup>2</sup>	P value	R <sup>2</sup>	P value	R <sup>2</sup>	P value
rs283	8	19,859,378	LPL	0.75	<b>0.0003</b>	0.07	0.28	0.02	0.65
rs328	8	19,864,004	LPL	0.39	0.009	0.62	0.003	1.02	<b>0.0010</b>
rs6993414	8	19,947,198	LPL	0.52	0.003	0.70	0.0014	1.12	<b>0.0005</b>
rs1077834	15	56,510,771	LIPC	0.50	0.003	1.34	<b>3.8 × 10<sup>6</sup></b>	1.09	<b>0.00027</b>
rs1800588	15	56,510,967	LIPC	0.54	0.002	1.14	<b>2.2 × 10<sup>5</sup></b>	0.96	<b>0.0006</b>
rs588136#	15	56,517,790	LIPC	0.60	<b>0.0011</b>	0.96	<b>1.0 × 10<sup>4</sup></b>	0.87	<b>0.00121</b>
rs9989419	16	55,542,640	CETP	1.53	<b>1.9 × 10<sup>7</sup></b>	2.07	<b>9.7 × 10<sup>9</sup></b>	3.27	<b>3.7 × 10<sup>10</sup></b>
rs3764261	16	55,550,825	CETP	3.72	<b>9.4 × 10<sup>16</sup></b>	4.61	<b>1.9 × 10<sup>17</sup></b>	5.03	<b>1.7 × 10<sup>14</sup></b>
rs4783961	16	55,552,395	CETP	0.91	<b>7.4 × 10<sup>5</sup></b>	1.22	<b>1.2 × 10<sup>5</sup></b>	1.28	<b>1.2 × 10<sup>4</sup></b>
rs1800775	16	55,552,737	CETP	2.60	<b>1.7 × 10<sup>12</sup></b>	4.31	<b>1.2 × 10<sup>17</sup></b>	3.88	<b>1.7 × 10<sup>12</sup></b>
rs9929488	16	55,556,073	CETP	0.79	<b>0.00019</b>	1.45	<b>1.8 × 10<sup>6</sup></b>	1.38	<b>5.3 × 10<sup>5</sup></b>
rs9939224	16	55,560,233	CETP	2.14	<b>4.9 × 10<sup>10</sup></b>	2.76	<b>2.9 × 10<sup>11</sup></b>	2.53	<b>3.2 × 10<sup>8</sup></b>
rs7205804	16	55,562,390	CETP	2.64	<b>2.2 × 10<sup>11</sup></b>	3.88	<b>1.2 × 10<sup>14</sup></b>	3.54	<b>2.1 × 10<sup>10</sup></b>
rs289714	16	55,564,952	CETP	1.11	<b>8.2 × 10<sup>6</sup></b>	0.97	<b>8.8 × 10<sup>5</sup></b>	0.68	0.004
rs289719	16	55,567,442	CETP	0.60	<b>0.00118</b>	0.69	<b>0.0010</b>	0.21	0.12
rs12720917	16	55,576,893	CETP	0.28	0.03	0.29	0.03	1.09	<b>0.0005</b>

R<sup>2</sup> is the proportion of total HDL-C variance (percent) explained by the single SNP in the model. Values in *bold* meet the multiple testing threshold for statistical significance of  $P < 0.00125$ . Number of SNP tested for each significant gene locus was as follows *LPL*,  $n = 20$ ; *LIPC*,  $n = 4$ ; *CETP*,  $n = 19$ . The number of subjects with data for all covariates included in the model is represented by  $n$ . The difference in sample size between baseline ( $n = 1771$ ) and yr 2 ( $n = 1583$ ) and yr 10 ( $n = 1196$ ) is not mainly due to dropout but largely reflects the fact that the study had a 13-yr recruitment period and not all subjects had reached the yr-2 or -10 follow-up at the time the analysis data set was frozen. Chr, Chromosome.

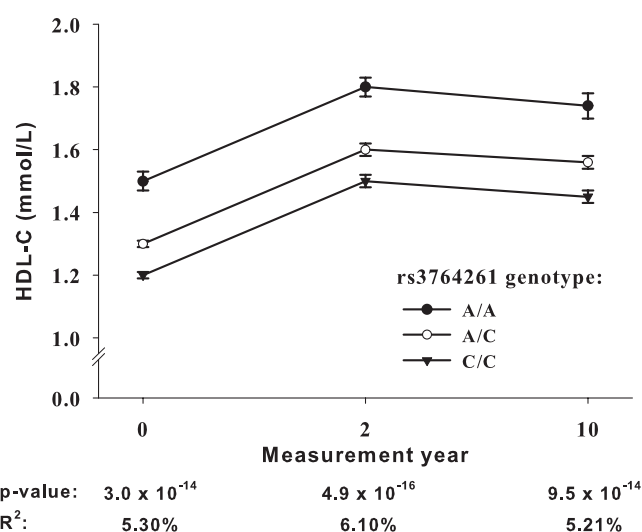
after surgery and experienced a mean HDL-C increase of 0.26 (SD 0.3) mmol/liter (Supplemental Table 2). On average, subjects regained 7.4 (SD 13.4) kg of weight from the yr-2 until yr-10 examinations after surgery and experienced a mean decrease in HDL-C levels [−0.03 (SD 0.3) mmol/liter] (Supplemental Table 2).

All SNP were in Hardy-Weinberg equilibrium. The minor allele frequencies, Hardy-Weinberg equilibrium, and pairwise LD among all included SNP stratified by gene locus can be found in Supplemental Table 3. The results of the single-SNP associations with cross-sectional HDL-C levels for all SNP can be found in Supplemental Table 4. After adjusting for covariates, markers in the *CETP*, *LIPC*, and *LPL* loci showed significant cross-sectional associations with HDL-C (Table 1), with *CETP* SNP rs3764261 showing the strongest association at each time point (Fig. 1). The results of the forward regression models for cross-sectional HDL-C levels at baseline and yr 2 and 10 can be found in Supplemental Tables 5–7. The multivariate regression models showed that *CETP* SNP rs3764261 explained 3.2, 4.2, and 3.8% of the variation in HDL-C at baseline, yr 2, and yr 10, respectively, whereas *CETP* SNP rs9939224 contributed an additional 0.6 and 0.9% at baseline and yr 2, respectively. *LIPC* SNP rs1077834 showed consistent associations with HDL-C across all time points ( $R^2 = 0.4$ – $1.1\%$ ), whereas *LPL* SNP rs6993414 contributed 0.5 and 0.8% at yr 2 and 10, respectively. The percentage of the HDL-C variance explained by these four SNP in three genes was 4.6, 6.8, and 6.1% at baseline, yr 2, and yr 10, respectively.

None of the SNP were significantly associated with bariatric surgery-induced changes in HDL-C (Supplemental Table 8).

## Discussion

We investigated the associations of SNP in candidate genes identified by GWAS with HDL-C levels in morbidly obese



**FIG. 1.** Serum HDL-C levels at baseline (yr 0) and yr 2 and 10 stratified by *CETP* SNP rs3764261 genotype when number of subjects has been maximized globally ( $n = 1132$  for all time points). Mean values are adjusted for age, sex, BMI, smoking, diabetes, and lipid medication. R<sup>2</sup> is the proportion of total HDL-C variance (percent) explained by the SNP in the model.

individuals before and after bariatric surgery-induced weight loss. We found consistent associations between SNP in the *CETP*, *LIPC*, and *LPL* genes and HDL-C levels in cross-sectional analyses both at baseline and after bariatric surgery, thereby replicating previous observations from population-based studies (8, 10). However, we did not observe any associations with bariatric surgery-induced changes in HDL-C levels. Thus, our results indicate that the genetic variants contributing to overall HDL-C levels in apparently weight-stable individuals have little effect on inter-individual variation in the changes of HDL-C in response to the weight loss induced by bariatric surgery.

Few studies have examined the association of gene variants with intervention-induced HDL-C changes over time. Our results are in agreement with those found in the HERITAGE Family Study (16). In White subjects, *CETP* SNP were strongly associated with baseline HDL-C levels, explaining 4.0% of the variance in sedentary-state HDL-C. However, concordant with the present findings, *CETP* SNP were not associated with HDL-C changes after 20 wk of exercise training in HERITAGE subjects (16). Limited studies have examined associations between SNP and spontaneous longitudinal changes in HDL-C (17, 18). A previous study examined the association of variants in the *APOA5*, *LPL*, and *GCK* genes with spontaneous changes in HDL-C over more than 20 yr in over 2800 unrelated individuals (17). The authors found that cross-sectional analyses replicated previous findings, whereas longitudinal analyses showed no evidence that variant associations changed over time, independent of age-related changes, in all but one case (17).

Although the HDL-C methodology changed over time in the SOS study, the results did not differ until 2002, when a 13% difference in HDL values was observed. This difference has been corrected for in the present analyses. If variation associated with the assay methods remained in the data, there should not be systematic differences by genotype, and thus the results of genetic associations should not be affected.

In summary, there was a significant increase in HDL-C (15–29%, depending on surgical intervention) in response to bariatric surgery. HDL-C response to surgery-induced weight loss over time showed large inter-individual variation within the SOS cohort. However, the associations of genetic variation with HDL-C response to weight loss are not clear. Three of the GWAS-based candidate genes for HDL-C levels explored in this study contributed significantly to plasma HDL-C levels at baseline and after bariatric surgery. None of the explored SNP was associated with change in HDL-C and will therefore not be useful in predicting response to treatment. Although a few obser-

vational studies have shown associations of DNA sequence variation with HDL-C fluctuations measured longitudinally, these studies did not target obese subjects or severely obese subjects that underwent voluntary weight losses. Thus, additional studies are needed that examine the genetic associations of HDL-C changes in response to weight loss and weight loss surgery, especially in obese subjects. A better understanding of the SNP-HDL associations in obesity and after weight loss surgery could be used as an aid for improving risk prediction and in determining the best treatment options for obese patients.

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