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Polymorphism in the *CETP* Gene Region, HDL Cholesterol, and Risk of Future Myocardial Infarction: Genomewide Analysis among 18,245 Initially Healthy Women from the Women's Genome Health Study

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Abstract

Background—Recent trial data have challenged the hypothesis that cholesteryl ester transfer protein (CETP) and high-density lipoprotein cholesterol (HDLC) have causal roles in atherothrombosis. One method to evaluate this issue is to examine whether polymorphisms in the *CETP* gene that impact on HDLC levels also impact on the future development of myocardial infarction.

Methods and Results—In a prospective cohort of 18,245 initially healthy American women, we examined over 350,000 singe nucleotide polymorphisms (SNPs) first to identify loci associated with HDLC and then to evaluate whether significant SNPs within these loci also impact upon rates of incident myocardial infarction during an average 10-year follow-up period. Nine loci on 9 chromosomes had one or more SNPs associated with HDLC at genomewide statistical significance ($P<5\times10^{-8}$). However, only SNPs near or in the *CETP* gene at 16q13 were associated with both HDLC and risk of incident myocardial infarction (198 events). For example, SNP rs708272 in the *CETP* gene was associated with a per-allele increase in HDLC levels of 3.1 mg/dL and a concordant 24 percent lower risk of future myocardial infarction (age-adjusted HR 0.76, 95%CI 0.62–0.94), consistent with recent meta-analysis. Independent and again concordant effects on HDLC and incident myocardial infarction were also observed at the *CETP* locus for rs4329913 and rs7202364. Adjustment for HDLC attenuated did not eliminate these effects.

Conclusion—In this prospective cohort of initially healthy women, SNPs at the *CETP* locus impact upon future risk of myocardial infarction, supporting a causal role for CETP in atherothrombosis, possibly through an HDLC mediated pathway.

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Conflict of Interest Disclosures

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Keywords

HDL cholesterol; myocardial infarction; atherosclerosis; genetic association

Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters from high-density lipoprotein cholesterol (HDLC) to other lipoprotein particles, and individuals genetically deficient for CETP often have extremely high HDLC levels[1, 2]. In part on this basis, and because of consistent epidemiologic evidence that elevated levels of HDLC are protective against cardiovascular disease, inhibitors of CETP were developed with the hope that raising HDLC through this mechanism would reduce vascular event rates. However, in the recently reported ILLUMINATE trial of torcetrapib conducted among more than 15,000 individuals at high risk for cardiovascular disease, mortality rates were increased in the active as compared to placebo treatment group[3] leading to considerable debate as to whether CETP and/or HDLC are in fact causal for heart disease and should remain viable pharmacologic targets[4, 5].

One approach to understanding causal pathways is to ascertain if genetic polymorphism known to impact on an intermediate phenotype (such as plasma lipid levels) also impacts on vascular risk[6]. For example, recent work has found that those with polymorphism in *PCSK9* not only have reduced levels of low-density lipoprotein cholesterol (LDLC), but also reduced rates of vascular events[7]. Similarly, recent reports have shown that polymorphism within several other LDL related pathways determine both plasma LDLC levels and vascular risk[8–11]. By contrast, data demonstrating that polymorphism in genes known to affect plasma HDLC levels also affect vascular event rates have been inconsistent, particularly with regard to *CETP*[9, 11–14]. However, such evidence, if available from a prospective cohort study free of selection bias, would support continued investigation into CETP and HDLC as targets for therapy.

To address this issue, we evaluated more than 350,000 single nucleotide polymorphisms (SNPs) across the human genome to first determine genetic loci associated with HDLC and then evaluate whether any significant SNPs within these loci in turn impact upon rates of incident myocardial infarction during an average 10-year follow-up period.

Methods

We evaluated the role of polymorphisms that impact upon HDLC as potential determinants of incident myocardial infarction among participants in the prospective Women's Genome Health Study (WGHS)[15]. In brief, participants in the WGHS include initially healthy American women aged 45 and older with no prior history of cardiovascular disease, cancer, or other major chronic illness who provided a baseline blood sample during the enrollment phase of the Women's Health Study[16] between 1992 and 1995, and who gave consent for blood based analyses related to risks of incident chronic diseases.

All study participants were followed up through March 2007 for incident myocardial infarction events that were adjudicated by an endpoints committee using standardized criteria and full medical record review. The endpoint of myocardial infarction was confirmed if symptoms met World Health Organization Criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiographic criteria. Only confirmed endpoints were included in this analysis.

All study participants had baseline blood samples assayed for total cholesterol, HDLC, direct LDLC, apolipoprotein A-1, and apolipoprotein B-100, and high-sensitivity C-reactive protein (hsCRP) in a core laboratory certified by the national Heart Lung and Blood Institute / Centers for Disease Control and Prevention Lipid Standardization Program; coefficients of variation

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were < 3 percent for total cholesterol, HDL and LDL cholesterol, and < 5 percent for apolipoproteins A-1 and B-100.

As described elsewhere, DNA extracted from the baseline WGHS blood samples underwent SNP genotyping using the Illumina Infinium II assay to query a genomewide set of 318,237 SNP markers (Human HAP300 panel) as well as an additional focused panel of 45,751 SNPs selected to enhance coverage of genomic regions without regard to allele frequency in which we had a strong a priori interest owing to presence of genes thought to be of relevance to metabolic, lipid, inflammatory, and other biological functions[15]. To reduce the potential for population stratification, we evaluated only WGHS participants who were of European ancestry. As previously reported in the WGHS, a principal component analysis using 1,443 ancestry-informative SNPs was used to confirm self-reported ancestry in 99.7 percent of the sample17, leaving 18,245 participants with both self-reported and genetically inferred European ancestry for this study who also had both HDLC and genotype data available. Further, in an additional principal component analysis performed for the exclusion of within European stratification based on 124,931 SNPs chosen to have pairwise disequilibrium $r^2 < 0.4$, no correction for within European ancestry was required[17].

For the current analysis, we first ascertained those loci that contained one or more SNPs that associated with plasma HDLC at a genomewide level of statistical significance ($P < 5\times10^{-8}$) and that had Hardy-Weinberg $P > 10^{-6}$, minor allele frequency greater than 1 percent, and genotyping call rates greater than 90 percent. To evaluate for associations between any of these SNPs and plasma HDLC, we assumed an additive model of inheritance and initially conducted univariate linear regression analysis to test the null hypothesis that HDLC levels did not differ by the number of inherited copies of the SNP minor alleles; in these initial analyses, we adjusted plasma HDLC levels on an *a priori* basis for age, smoking, body mass index, hormone therapy, and menopausal status, and limited the evaluation to non-diabetic women who were not taking lipid-lowering agents.

For any locus containing at least one SNP that was associated with HDLC at a genomewide level of statistical significance, we next sought evidence of association between the significant SNPs in that loci and incident myocardial infarction. Association testing of these SNPs with incident myocardial infarction was performed with age-adjusted Cox proportional hazards models as well as models that additionally adjusted for HDLC, and in fully adjusted models that further controlled for smoking status (current, not current), blood pressure (Framingham categories), diabetes (yes/no), parental history of myocardial infarction before age 60 years (yes/no), LDLC, and log transformed triglycerides (mg/dL).

Haplotype analysis was performed using the haplo.glm program from the haplo.stats analysis package in R[18–20] within blocks of linkage disequilibrium as defined previously[21]. Briefly, this program provided a method for logistic regression of myocardial infarction dependent on inferred haplotypes in a pre-specified block of linkage disequilibrium. The key feature of the haplo.glm algorithm is its use of an expectation maximization procedure to optimize the likelihood of both the logistic model fit and the haplotype inference in an iterative fashion.

To replicate associations at the 2q24.3 locus, we used HDLC measurements from PRINCE cohort for which genotype information was available through the PARC consortium22–25. The genotype data derive from Illumina Human HAP300 genotyping among 670 PRINCE participants, of whom 168 (25.1%) were female.

The study protocol was approved by the Institutional Review board of the Brigham and Women's Hospital, Boston, MA.

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Statuement of responsibility

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as it is written.

Results

Effects of polymorphism on HDLC

Nine loci on 9 chromosomes were identified that contained one or more SNPs that were associated with HDLC at a genomewide level of statistical significance ($P < 5\times10^{-8}$) (Table 1). Eight of these nine loci contain genes known to impact upon HDLC metabolism, while one locus near the genes *COBLL1* and *GRB14* at 2q24.3 appears to be novel [8, 11, 24, 26, 27]. The per-allele shifts in HDLC for the two SNPs with genomewide significance at 2q24.3, rs10490694 and rs7607980, were 1.35 mg/dL ($P=3.9\times10^{-9}$) and 1.29 mg/dL ($P=1.5\times10^{-8}$), respectively. These SNPs were in high linkage disequlibirum (LD; $r^2=0.98$) with minor allele frequencies 12.3% and 12.5%, respectively. The minor allele frequencies of the two SNPs were comparable and their associations with HDLC were significant with consistent direction of effects in separate genetic analysis in the PRINCE population. Specifically, the per-allele shifts were 2.9 mg/dL (P=0.0008) and 3.1 mg/dL (p=0.0004), respectively. The effects were larger among the 168 PRINCE women (both SNPs 7.3 mg/dL) than the 501 men (1.5 mg/dL and 1.7 mg/dL, respectively), and an interaction with gender was observed (P-interaction=0.002 and 0.003, respectively).

At the *CETP* locus, where genomewide associations with HDLC were both most significant and numerous, 20 SNPs were associated with plasma HDLC at a genomewide level of statistical significance (P-values ranging from 3.8×10^{-8} to 3.7×10^{-93}) (Table 2). All of these were also highly associated with apolipoprotein A-1 levels (data not shown). These SNPs spanned about 242 kb of chromosome 16 with most clustered around the *CETP* gene but three mapping to the neighboring *NUP93* gene encoding a nuclear pore protein, and another six in mapping to the neighboring *SLC12A3* and *HERPUD1* genes, respectively encoding a sodium transporter and a protein of uncertain function localized to the endoplasmic reticulum (Figure 1).

As also shown in Table 2, several of the *CETP* SNPs were common (minor allele frequencies between 30 and 48 percent), and several had substantive effects on plasma levels of HDLC. For example, median HDLC levels for homozygous major allele carriers, heterozygotes, and homozygous minor allele carriers at rs70872 [minor allele frequency 0.428] were 50, 52, and 56 mg/dL, respectively ($P = 1.7\times10^{-90}$) such that each minor allele increased HDLC levels by an average 3.1 mg/dL or approximately 6 percent. By contrast, other *CETP* SNPs that were associated with plasma HDLC levels at a genome-wide level of significance were less common or had only marginal absolute effects on plasma HDLC.

Effects of polymorphism on incident myocardial infarction

During follow-up, 198 incident myocardial infarction events were confirmed by the Endpoints Committee. Among the 9 loci in Table 1, only one at 16q3 (the site encompassing the CETP gene) contained SNPs that were both associated with HDLC and also had significant impact on rates of incident myocardial infarction. For example, as shown in Table 3, polymorphism at rs708272 in the *CETP* gene was associated with a per-allele increase in HDLC levels of 3.1 mg/dL and a concordant 24 percent lower risk of future myocardial infarction (age-adjusted hazard ratio 0.76, 95%CI 0.62–0.94; P=0.01) (Figure 2A). The direction and magnitude of effect for rs708272 is consistent with recent meta-analysis involving 38 prior studies [28], indicating external validation.

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Adjustment for HDLC level only partially attenuated the effect of rs708272 on myocardial infarction risk (age and HDLC adjusted hazard ratio 0.84, 95%CI 0.68–1.03; P=0.09), and in subsequent analyses further associations were observed between rs708272 and LDLC and triglycerides, albeit on a much more modest basis. For example, for rs708272, LDLC levels were 123, 122, and 120 mg/dL among GG, GA, and AA participants, respectively (P = 0.0009), while corresponding triglyceride levels were 123, 120, and 114 mg/dL, respectively (P < 0.0001). *CETP* genotype at rs708272 was not associated with age, obesity, smoking, blood pressure, or other major clinical covariates (Table 4). Adjustment for these additional factors (as well as for body mass index, smoking, HRT use, blood pressure, diabetes, and parental history of myocardial infarction before age 60 years) again only marginally attenuated risk from rs708272 (fully adjusted hazard ratio 0.83, 95%CI 0.6–1.04; P=0.1).

As also shown in Table 3, independent effects on both HDLC and on incident myocardial infarction were also observed at rs4329913 (approximately 90 kb from the *CETP* gene; Figure 2B) and rs7202364 (approximately 210 kb from the *CETP* gene; Figure 2C). Three other SNPs showed similar concordant effects on both HDLC and myocardial infarction risk, rs180775 and rs1532624 (both of which were in high LD with rs708272) and rs8051691 (which was in high LD with rs7202364). For these SNPs, adjustment for HDLC or for traditional risk factors again attenuated but did not eliminate effects on risk of incident myocardial infarction (Table 3).

Haplotype analysis was performed to evaluate whether combinations of SNPs at the *CETP* locus might be more strongly associated with myocardial infarction than individual SNPs. Haplotypes were inferred for neighboring SNPs in blocks with little evidence of historical recombination[21, 29] and tested for association with myocardial infarction. These analyses did not reveal stronger associations than were found in the single SNP analysis.

Discussion

Evaluating variation at 9 loci with genomewide significance for HDLC among 18,245 initially healthy American women followed prospectively over an average period of 10 years, we found that common SNPs exclusively in or near the *CETP* gene were also associated with risk of incident myocardial infarction. Effects on HDLC and myocardial infarction were concordant such that SNP alleles associated with increased plasma HDLC (or ApoA1) levels were also associated with decreased vascular risk, and vice versa. SNP-based risk was attenuated but not eliminated by adjustment for either plasma HDLC or traditional risk factors.

At the same time, our genomewide design identified a novel candidate locus for HDLC at 2q24.3. Analysis in the PRINCE population validated the 2q24.3 associations with HDL-C level and furthermore suggested potential gender specific effects. This region contains two genes, *COBLL1* and *GRB14*, the latter of which may be the better candidate for a functional role in determining HDLC levels. *GRB14* encodes and adaptor protein known to form inhibitory interactions with the insulin receptor and other growth receptors and is expressed in the liver, skeletal muscle, and adipose tissue[30, 31]. Mice deficient of *GRB14* have altered patterns of glucose metabolism[32], a biological process that may also be linked to HDLC levels.

As prior epidemiologic work relating polymorphism in the *CETP* gene to vascular risk has been controversial[12–14] and as two recent studies have not found significant relationships[9, 11], external validation of our findings is important for interpretation. In this regard, in a recent comprehensive meta-analysis that included data from 38 prior studies employing a candidate gene approach [28], the same rs708272 SNP uncovered in the WGHS using a genome-wide approach was associated with a 4.5 percent per-allele increase in HDLC and a directionally concordant 5 percent per allele reduction in coronary risk (odds ratio 0.95, 95%CI 0.92 – 0.99).

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For direct comparison, in our data, rs708272 was associated with a 6 percent per allele increase in HDLC and a 17 percent per allele concordant reduction in myocardial infarction after multivariate adjustment (HR 0.83, 95%CI 0.66–1.04). Thus, for the primary observation in this large-scale GWAS linking *CETP* genotype not only to HDLC but also to incident vascular events, external validation is available for rs708272 when prior studies are statistically pooled[28].

While the direction of effect for rs708272 in our data is consistent with that of the meta-analysis, the absolute magnitude of genetic impact on vascular events is somewhat larger. We believe there are several potential explanations for this effect. First, our data are limited to incident myocardial infarction whereas data in the recent meta-analysis includes many forms of coronary heart disease, often inclusive of angina and coronary revascularization, events that may have more to do with atherosclerotic progression than with acute plaque rupture.

Second, our data derive from a prospective cohort study of initially healthy women in which event status was determined solely by occurrence of disease rather than by any selection criteria imposed by the investigators or the patients that could result in inadvertent confounding or bias. In both theory and practice, inadvertent bias introduced in the conduct of even the best case-control studies may, in some situations, be greater in magnitude than the effect under study, particularly when that effect is modest to small in absolute magnitude.

Third, we limited our analysis to a Caucasian population, and thereby reduced the potential for ethnicity-based stratification to adversely impact upon the validity of our data. In this regard, it should be noted that several early candidate gene studies and prior meta-analyses of *CETP* polymorphism were unable to control for such effects and that substantial heterogeneity between studies has previously been observed[12].

We believe it of interest that one of the SNPs most significantly associated with myocardial infarction in our data was rs708272, the SNP that defines the B2 allele of the *CETP* TaqIB polymorphism (and is the core candidate *CETP* SNP defined in the recent comprehensive meta-analysis28). Although using a different genotyping technology, the current data also extend to women early candidate gene work suggesting that the TaqIB polymorphism is associated with myocardial infarction in men with low HDLC levels[33]. In this regard, we note that some reports suggest that the Taq1B polymorphism is acting through linkage disequilibrium to a second SNP in the promoter of the *CETP* gene at position −629 from the transcription start site[34, 35]. This SNP is equivalent to rs1800775, which was the single most strongly associated SNP in our analysis with HDLC (Table 1) and thus again is consistent with previous reports.

The second SNP within 16q13, rs4329913, which was independently associated with a decrease in HDLC and an increase in the risk of myocardial infarction, is relatively far from the transcription start site for the *CETP* gene and within the transcribed region for a gene encoding a solute transporter, *SLC12A3*. Neither *SLC12A3* nor a second neighboring gene *HERPUD1* are obvious candidates for regulation of HDLC levels, perhaps suggesting the effect of rs4329913 is mediated by long range linkage disequilibrium to a causal variant nearer the *CETP* gene or long range effects on transcription at the entire locus. In our data, linkage disequilibrium between rs4329913 and at least one other SNP (rs1800777) nearer the *CETP* gene was as high as D'=0.85, reinforcing the potential for long range linkage effects. Finally, the third SNP in 16q13 independently associated with both HDLC and incident myocardial infarction (rs7202364), is even further from the transcription site for the *CETP* gene and within the *NUP93* gene, another unlikely candidate for effects on HDLC and again suggesting effects mediated through linkage to the *CETP* gene.

In population based epidemiologic studies typically conducted among men of middle-age or older, it has been observed that the risk of coronary heart disease decreases approximately 2

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percent for each 1 percent increase in HDLC[36, 37]. However, in our fully adjusted data, the reduction in risk associated with polymorphism in *CETP* was somewhat greater than this prediction. One possible explanation of this effect is that lifelong elevations of HDLC may confer greater protection from vascular disease than would be anticipated from changes in HDLC that might occur from pharmacologic or dietary interventions begun at midlife. A second possibility is that gender specific differences exist in the relationships between *CETP* polymorphism, HDLC, and vascular risk that were brought out by our study of women. Alternatively, it is possible that the biologic effects of *CETP* polymorphism on myocardial infarction risk are not captured solely through the intermediate phenotype of HDLC (or through the assessment of HDLC at a single point in time). In this regard, adjustment for HDLC only moderately attenuated the magnitude of the per allele relationships we observed between genotype and myocardial infarction risk. Further, as shown in Table 3, modest associations between rs708272genotype and both LDLC and triglycerides were also observed in our data. Nonetheless, even after additional adjustment for these lipid fractions (as well as for a large number of other major risk factors), the per allele hazard ratio for rs708272 was still 0.83. This lack of further attenuation suggests that *CETP* may well impact upon atherothrombosis through additional intermediate pathways and/or intermediate phenotypes that go beyond its primary effects on HDLC.

In sum, in these prospective data, we found specific polymorphisms in or near the *CETP* gene that impact on future risk of myocardial infarction. As such, these data support continued investigation of agents that target CETP as a potential method for vascular risk reduction.

Acknowledgments

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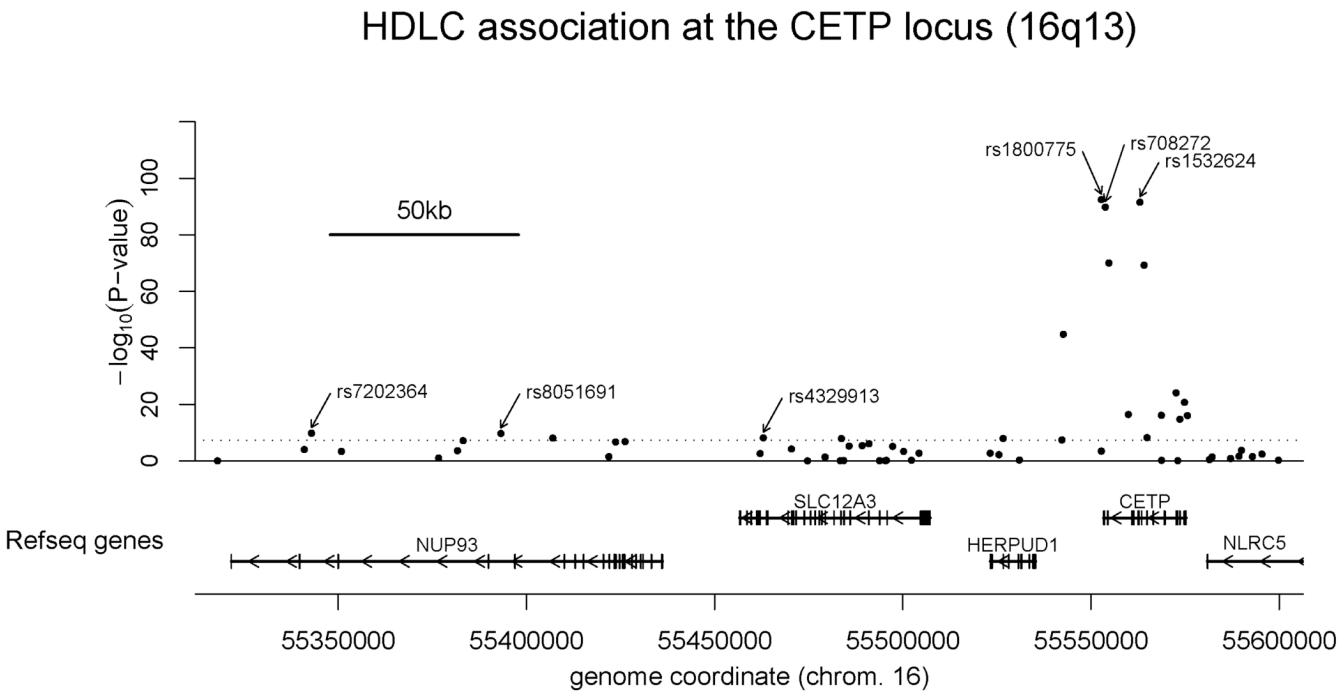

Figure 1.

Genomic context for *CETP*. Plot of genomic region surrounding SNPs with genomewide association with HDLC near the *CETP* gene. Upper panel: SNPs are shown according to their physical location and -$\log_{10}$ of their association P-values with adjusted HDLC. Lower panel: Genes from RefSeq release 30. Only one isoform is indicated when multiple splicing variants are known. Annotated SNPs are discussed in this manuscript.

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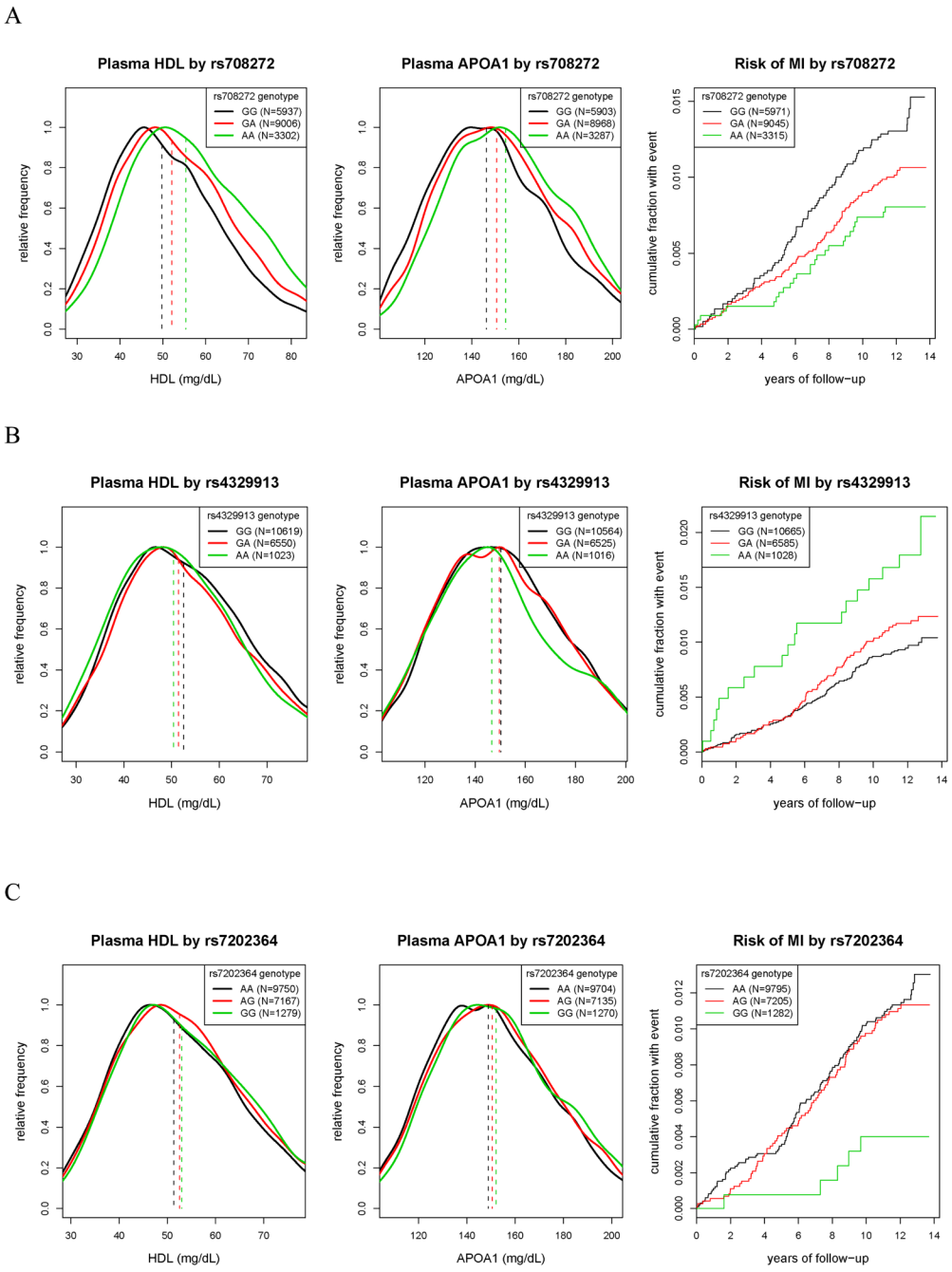

Figure 2.

Distribution of HDLC (left), ApoA1 (middle), and Kaplan Maier estimates of cumulative incidence of myocardial infarction (right) according to the genotype of SNPs at the *CETP* locus. For comparison, in the left and middle panels, the distribution of HDLC and ApoA1 levels for each genotype is scaled to have maximum value of one. Vertical dashed lines indicate median values of lipid fractions by genotype. A) SNP rs708272; B) SNP rs4329913; C) SNP rs7202364

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Table 1

Genetic loci with one or more SNPs associated with HDLC at a genome-wide level of statistical significance.

Locus	N SNPs*	Locus smallest P-value	candidate genes
2q24.3	2	3.9×10^{-9}	*COBLL1, GRB14*
8p21.3	11	1.4×10^{-17}	*LPL*
9q31.1	1	1.6×10^{-8}	*ABCA1*
11q23.3	6	2.8×10^{-12}	*APOA1, APOA4, APOA5, APOC3*
15q22.1	12	1.4×10^{-23}	*LIPC*
16q13	20	3.7×10^{-93}	*CETP*
18q21.1	1	1.4×10^{-9}	*LIPG*
19q13.32	1	2.6×10^{-11}	*APOC1, APOC2, APOC4, APOE*
20q13.12	3	1.9×10^{-14}	*PLTP*

*Number of locus SNPs with $P<5\times10^{-8}$

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Table 2

SNPs in the *CETP* gene with genomewide effects on plasma HDL cholesterol.

SNP*	BP	MAF	M/m	HW-p	HDL-C (mg/dL)			per allele	P
					MM	Mm	Mm	HDL shift (mg/dL)	
rs1800775	55552736	0.486	C/A	0.44	49 (41–59)	52 (43–62)	55 (46–67)	3.09	3.7×10^{-93}
rs1532624	55562979	0.430	C/A	0.57	50 (42–60)	52 (44–63)	56 (46–68)	3.14	3.0×10^{-92}
rs708272	55553788	0.428	G/A	0.28	50 (42–60)	52 (44–63)	56 (46–67)	3.08	1.7×10^{-90}
rs1864163	55554733	0.255	G/A	0.27	54 (45–65)	50 (42–61)	48 (40–58)	−3.10	9.2×10^{-71}
rs7499892	55564090	0.177	G/A	0.96	53 (44–64)	50 (41–60)	47 (40–57)	−3.50	5.5×10^{-70}
rs9989419	55542639	0.395	G/A	0.35	54 (45–65)	51 (43–62)	50 (42–60)	−2.19	1.6×10^{-45}
rs5880	55572591	0.053	G/C	0.16	52 (44–63)	49 (41–59)	45 (39–52)	−3.48	8.2×10^{-25}
rs1800777	55574819	0.036	G/A	0.28	52 (44–63)	49 (40–58)	43 (37–47)	−3.91	1.9×10^{-21}
rs12597002	55559904	0.300	C/A	0.96	53 (44–64)	51 (43–62)	50 (42–60)	−1.39	3.6×10^{-17}
rs4784744	55568685	0.349	G/A	0.90	53 (44–64)	52 (43–62)	50 (41–61)	−1.32	7.4×10^{-17}
rs289744	55575602	0.302	A/C	0.99	51 (43–62)	53 (44–63)	54 (45–64)	1.37	8.8×10^{-17}
rs5882	55573592	0.318	A/G	0.42	51 (43–62)	53 (44–63)	53 (45–64)	1.30	1.7×10^{-15}
rs7202364	55342890	0.267	A/G	0.40	52 (43–62)	53 (44–63)	53 (44–65)	1.10	1.5×10^{-10}
rs8051691	55393212	0.267	C/A	0.44	52 (43–62)	52 (44–63)	53 (44–65)	1.09	1.9×10^{-10}
rs5883	55564853	0.054	G/A	0.13	52 (43–62)	54 (45–64)	58 (49–67)	1.94	5.6×10^{-9}
rs4329913	55462932	0.236	G/A	0.79	52 (43–63)	52 (43–62)	50 (42–60)	−1.03	6.6×10^{-9}
rs1529929	55406996	0.411	G/A	0.09	51 (43–62)	52 (43–63)	53 (44–64)	0.89	8.5×10^{-9}
rs2217332	55526648	0.145	G/A	0.74	52 (44–63)	51 (42–62)	51 (41–62)	−1.23	1.1×10^{-8}
rs13306677	55483695	0.096	G/A	0.90	52 (43–62)	53 (44–64)	53 (45–62)	1.47	1.3×10^{-8}
rs247615	55542263	0.232	A/G	0.76	52 (44–63)	52 (43–62)	51 (43–61)	−0.98	3.8×10^{-8}

M= major allele, m = minor allele

MAF = minor allele frequency

HW-p = Hardy Weinberg P-value

* In order of decreasing significance for association with HDLC

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Table 3

Hazard ratios (95%C) for the risk of incident myocardial infarction according to *CETP* genotype. Data are provided on an individual genotype basis, and on a per-allele basis, adjusted for age and adjusted for multiple risk factors.

SNP	N		Genotype HR (age-adjusted)		Per allele (age-adjusted)		Per allele (HDLC-adjusted)		Per allele (fully-adjusted*)	
		MM	Mm	Mm	HR	P	HR	P	HR	P
rs708272	18245	GG	GA	AA						
		1.0	0.75	0.59	0.76	0.01	0.84	0.094	0.83	0.099
			(0.56–1.02)	(0.38–0.92)	(0.62–0.94)		(0.68–1.03)		(0.66–1.04)	
rs4329913	18190	GG	GA	AA						
		1.0	1.26	1.94	1.34	0.008	1.29	0.021	1.29	0.031
			(0.94–1.69)	(1.19–3.16)	(1.08–1.66)		(1.04–1.6)		(1.02–1.63)	
rs1532624	17719	CC	CA	AA						
		1.0	0.77	0.61	0.78	0.018	0.86	0.15	0.83	0.12
			(0.57–1.04)	(0.40–0.95)	(0.64–0.96)		(0.7–1.06)		(0.66–1.05)	
rs1800775	18211	CC	CA	AA						
		1.0	0.81	0.67	0.82	0.048	0.9	0.31	0.88	0.24
			(0.59–1.11)	(0.45–1.00)	(0.67–1)		(0.74–1.1)		(0.7–1.09)	
rs7202364	18194	AA	AG	GG						
		1.0	0.94	0.32	0.79	0.045	0.81	0.077	0.76	0.042
			(0.71–1.25)	(0.13–0.79)	(0.62–0.99)		(0.64–1.02)		(0.59–0.99)	
rs8051691	18237	CC	CA	AA						
		1.0	0.94	0.32	0.79	0.047	0.81	0.079	0.76	0.043
			(0.71–1.25)	(0.13–0.79)	(0.62–1)		(0.64–1.02)		(0.59–0.99)	

*Fully adjusted model controlled for age (years), body mass index (kg/m^2), smoking status (current, not current), hormone replacement therapy use (yes/no), blood pressure (Framingham categories), diabetes (yes/no), parental history of myocardial infarction before age 60 years (yes/no), LDLC, HDLC, and log transformed triglycerides (mg/dL).

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Table 4

Characteristics of study participants according to rs708272 genotype

	GG	GA	AA	P
N (%)	**5937 (32.5)**	**9006 (49.4)**	**3302 (18.1)**	
Age (yrs)	52.8 (48.9–58.9)	53.0 (49.0–59.0)	52.8 (48.9–58.8)	0.3
BMI (kg/m^2)	24.9 (22.5–28.3)	24.9 (22.4–28.3)	25.0 (22.6–28.3)	0.2
Current smokers (%)	685 (0.12)	1073 (0.12)	404 (0.12)	0.6
Diabetes	150 (0.025)	253 (0.028)	71 (0.022)	0.1
Hypertension	1476 (0.25)	2201 (0.24)	783 (0.24)	0.5
Total Cholesterol (mg/dl)	208 (183–235)	209 (184–237)	210.0 (186.0–237.0)	0.005
HDL-C (mg/dl)	49.7 (41.5–59.6)	52.2 (43.5–62.9)	55.5 (46.4–67.4)	<0.0001
LDL-C (mg/dl)	122.9 (102.1–145.7)	122.2 (100.4–145.5)	119.9 (99.4–143.3)	0.0009
Non=HDL-C (mg/dl)	155.9 (130.8–183.8)	155.0 (129.5–183.1)	151.8 (127.1–179.1)	<0.001
ApoA1 (mg/dl)	146.3 (130.0–164.9)	150.4 (133.3–169.1)	154.1 (137.0–173.1)	<0.001
ApoB (mg/dl)	103.3 (84.2–122.0)	100.1 (84.1–121.6)	98.0 (82.0–118.4)	<0.001
Triglycerides (mg/dl)	123 (85–183)	120.0 (85.0–176.0)	114.0 (81.0–167.8)	<0.0001
Incident MI Events (N)/ Event rate*	80/1.12	92/0.85	26/0.65	0.008

* incident myocardial infarction per 1,000 person years. P value (age–adjusted) from Table 2.