Supplementary Materials for

Genome-Wide Association Scans Identify Novel Loci That Influence Lipid Levels and Risk of Coronary Artery Disease

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Supplementary Online Methods for Willer et al.
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Initial Screening. To survey the genome for variants associated with plasma HDL-C, LDL-C, and triglyceride levels, we combined test statistics from three genome-wide association scans (GWAS): the Finland-United States Investigation of NIDDM Genetics (FUSION)[1,2], the SardiNIA Study of Aging[3,4], and the Diabetes Genetics Initiative (DGI)[5]. In aggregate, the scans include information on plasma lipid levels for 8,816 individuals. Results from the DGI GWAS were obtained by contacting the authors of a previously published study[5], whereas association scans for lipid levels in the SardiNIA and FUSION samples are reported here for the first time. The studies used two different marker sets, and we used information on patterns of haplotype variation throughout the genome to infer missing genotypes "*in silico*" to facilitate comparison between the studies[1,6]. Here we first provide a brief overview of the samples and genotype data available for each study and then provide additional details on the approach used to analyze the GWASs.

Lipid Measurements (GWAS). Fasting lipid measurements for serum total cholesterol, high density lipoprotein cholesterol (HDL-C) concentration, and triglycerides were determined using standard enzymatic methods for the FUSION, SardiNIA, and DGI samples. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.

FUSION GWAS. The FUSION[7] GWAS focused on a set of 1,161 Finnish type 2 diabetes (T2D) cases, 1,174 normal glucose tolerant (NGT) controls, and 122 offspring of case/control pairs (1 T2D, 119 NGT, 2 with impaired glucose tolerance). Cases and controls were matched as previously described, taking into account age, sex, and birth province within Finland; relationships between genotyped individuals were verified using RELPAIR[8] prior to analysis. For the present analysis, we used 773 T2D cases and 1,101 non-diabetic controls not known to be taking lipid-lowering drugs. Samples were genotyped with the Illumina HumanHap300 BeadChip (version 1.0) and with an Illumina GoldenGate Custom Panel (1,536 SNPs) design to improve genomic coverage around T2D candidate genes[2]. Genotypes for a total of 304,581 SNPs that had minor allele frequency (MAF) > 1% and passed quality checks evaluating data completeness (≥ 90.0%), Hardy-Weinberg equilibrium ($p \geq 10^{-6}$), reproducibility in duplicate samples and Mendelian inheritance (≤3 total discrepancies in 79 duplicate samples and 122 parent-offspring sets) were used for analysis. Using information on local haplotype patterns, these 304,581 SNPs were used to estimate genotypes for all polymorphic SNPs genotyped in the HapMap CEU samples[9] (July 2006 phased haplotype release) but not included in either Illumina panel, and these estimated genotypes were also included in the analyses. For the analyses reported here, we focused on the SNPs for which the imputation procedure predicted $r^2>0.30$ between true and imputed genotypes (the average predicted r^2 was 0.89). We evaluated quality of the imputed genotypes by comparing imputed genotypes for 521 markers with those obtained by genotyping 1,215 individuals – overall, we observed an error rate of 1.46% per allele – in line with expectations[1,6].

SardiNIA GWAS. The SardiNIA GWAS examined a total of 4,305 related individuals participating in a longitudinal study of aging-related quantitative traits in the Ogliastra region of Sardinia, Italy. Genotyped individuals had four Sardinian grandparents and were selected for genotyping without regard to their phenotypic values. Relationships between genotyped individuals were verified using RELPAIR[8]. Among the individuals examined, 1,412 were genotyped with the Affymetrix Mapping 500K Array Set. In parallel to the strategy used in the FUSION study, we first used the 356,359 SNPs in this set that had MAF>5% and passed quality control filters evaluating data completeness (>90%), Mendelian transmission (<3 inconsistencies), and Hardy-Weinberg equilibrium ($p > 10^{-6}$) to estimate genotypes for all the polymorphic SNPs genotyped by the HapMap consortium. As with the FUSION data, we focused on the SNPs for which the imputation procedure predicted $r^2>0.30$ between true and imputed genotypes (the average predicted r^2 was 0.86). We evaluated quality of the imputed genotypes by comparing imputed genotypes for 5,305 markers with those obtained by genotyping the Affymetrix Mapping 10K Array in 436 individuals – overall, we observed an error rate of 2.17% per allele – in line with expectations[6]. Taking advantage of the relatedness among individuals in the SardiNIA sample, we carried out a second round of computational analysis to impute genotypes for analysis in an additional 2,893 individuals who were genotyped only with the Affymetrix Mapping 10K Array. In this second round, we identified large stretches of chromosome shared within each family and probabilistically "filled-in" genotypes within each stretch whenever one or more of its carriers was genotyped with the 500K Array Set[10,11]. These 2,893 individuals were mostly offspring and siblings of the 1,412 individuals genotyped at high density (typically, we genotyped two parents or three total

family members with the 500K Array Set in each large nuclear family and then imputed results for the remaining individuals). For the present analyses, we included 4,184 individuals not on lipid-lowering drugs.

DGI GWAS. Results of the DGI GWAS for T2D susceptibility loci and related quantitative traits have been reported elsewhere[5]. Briefly, this study examined 1,464 cases of T2D and 1,467 non-diabetic control individuals matched for age, sex, and BMI. The study resulted in the identification of several T2D susceptibility genes and also in a replicated report of strong association between variants in the *GCKR* gene and triglyceride levels[5]. For this analysis, we considered 2,758 individuals who were not known to be taking lipid-lowering medications. As in the Sardinia GWAS, this study relied on the Affymetrix Mapping 500K Array Set. We collaborated with the DGI investigators to impute and analyze genotypes at SNPs that are polymorphic in the HapMap CEU panel but not included in the 500K Array Set. A total of 347,010 SNPs had MAF > 5%, passed quality control checks for genotype completeness (>95% call rate) and Hardy-Weinberg equilibrium ($p > 10^{-6}$ in controls), were used as input for the imputation procedure.

Association Analysis Relating Genotypes to Lipid Levels. Within each of the three study samples, we then carried out association analyses to relate observed and imputed genotypes to lipid levels. At each SNP, lipid levels were related to allele counts for a reference allele in a regression model that also included sex, age, and age^2 as covariates. For SNPs genotyped in the laboratory, allele counts were discrete (0, 1, or 2), whereas for

SNPs genotyped "*in silico*", allele counts were fractional (between 0.0 and 2.0, depending on the expected number of copies of the allele for each individual). In the FUSION GWAS, diabetic individuals and control individuals were analyzed separately and results combined using the meta-analytic techniques described below. In the DGI GWAS, diabetic individuals and controls were analyzed together, and an additional covariate to indicate T2D status was used to account for differences between the two groups. To allow for relatedness, regression coefficients were estimated in the context of a variance component model that also accounted for background polygenic effects[10]. Deviations from normality can lead to inflation of type I error rates and reduce power for quantitative trait analyses[12]. To help achieve univariate normality we used quantile normalization (inverse normal scores), which involves ranking all trait values and then converting these to z-scores according to quantiles of the standard normal distribution. For each trait, we analyzed both transformed and untransformed trait values. We report p-values from the analysis of the transformed traits, as those are expected to be slightly more accurate. We report effect sizes from the analysis of untransformed traits, as those are easier to interpret. In both cases, analysis included sex, age, and age^2 as covariates, as well as additional covariates appropriate to each dataset (e.g. diabetes status for the DGI data).

As noted above, only individuals who were not taking lipid-lowering therapies were considered, resulting in the exclusion of ~20% of genotyped individuals in the FUSION sample, 4% of genotyped individuals in the SardiNIA sample, and 5% of the genotyped individuals in the DGI sample. Totals in Table 1 refer to the number of individuals with

appropriate trait data and not on lipid-lowering medication. The difference in the proportion of excluded individuals is explained by the higher proportion of older participants and individuals with disease in the FUSION study, resulting in a high prevalence of lipid-lowering therapy. Information on medication usage was not available for ~300 individuals and these were included in our analyses. Thus, we expect a small number among the 8,816 individuals analyzed were being treated with lipid-lowering therapies. Heterogeneity introduced by analyzing both individuals on lipid-lowering medication and individuals not on lipid-lowering medication together might have resulted in a small loss of power, but should not increase false-positive rates.

Meta-Analysis. To summarize results for the four initial scans (773 diabetics from FUSION, 1,101 controls from FUSION, 4,184 individuals from Sardinia, and 2,759 individuals from the DGI) we carried out a meta-analysis. For each marker, we selected an arbitrary reference allele and calculated a z-statistic characterizing the evidence for association in each study (summarizing both the p-value, in its magnitude, and the direction of effect, in its sign). We then calculated an overall z-statistic as a weighted average of the four individual statistics and calculated the corresponding p-value. Weights were proportional to the square-root of the number of individuals examined in each sample and were selected such that the squared weights sum to 1.0. Because the samples include related individuals – who provide redundant information -- a different choice of weights might have increased power. However, we note that our choice of weights is valid and that different choices of weights did not lead to noticeable differences in results (results not shown).

Follow-Up of Findings from Initial Screening. We followed up promising loci identified through meta-analysis of the three genome-wide scans by examining SNPs in additional samples: an additional 970 T2D cases and 1,249 NGT controls from Stage 2 of the FUSION study[1], 1,254 non-fatal myocardial infarction cases and 1,252 controls from the ISIS study in the United Kingdom[13], 1,551 individuals from the SUVIMAX trial of vitamin supplementation[14,15], 861 individuals from the Amish HAPI Heart study[16,17], 3,358 women from the British Women's Heart and Health Study[18] and 1,074 men in the Caerphilly study[19].

Genotyping of the Stage 2 samples for the FUSION study was carried out at the National Human Genome Research Institute (Bethesda, MD) using Sequenom assays. Genotyping of the ISIS samples was carried out at the Centre Nationale de Genotypage (Paris, France) also using Sequenom assays. The HAPI and SUVIMAX samples were genotyped for the whole genome using the Affymetrix Mapping 500K Array Set and Illumina HumanHap300 arrays, respectively. We did not examine genome wide scans for these two samples, but rather focused on markers and regions identified in the initial meta-analysis described above. In the HAPI dataset, we calculated association statistics only for specific markers that are part of the Affymetrix 5.0 chip. In the SUVIMAX dataset, we first imputed genotypes for all markers in the genome[6], and then looked up results for specific markers of interest. Full results of these two studies will be published elsewhere. Genotyping of BWHHS and Caerphilly samples was performed by KBiosciences

(Hoddesdon, UK) using their fluorescence-based competitive allele-specific PCR (KASPar) technology.

Fasting lipid measurements for total cholesterol, HDL-C, and triglycerides were measured using standard enzymatic protocols in the HAPI, SUVIMAX, Caerphilly, BWHHS, and FUSION Stage 2 samples. LDL-C levels were calculated using the Friedewald formula. In the ISIS samples, HDL-C, LDL-C, and triglycerides were all measured directly using standard enzymatic methods and it was not necessary to use the Friedwald formula.

Association analyses and meta-analysis of the Stage 2 samples were parallel to those of Stage 1 samples, with the following exceptions: (1) evidence for association in the HAPI samples, which includes very large Amish pedigrees, was evaluated using SOLAR[20] with procedures implemented and validated by the HAPI investigators; (2) the ISIS study participants were examined in the early 1990's before lipid-lowering therapies became common so that no exclusion based on drug therapy was necessary; (3) triglyceride levels could not be reliably measured in the ISIS myocardial infarction cases, and were not analyzed among those individuals; (4) information on lipid-lowering therapy was not readily available for the majority of FUSION Stage 2 samples and for the SUVIMAX and Caerphilly samples, thus no exclusion criterion was applied to those individuals. The SUVIMAX were collected in 1994-1995, before the use of lipid-lowering drugs became relatively common.

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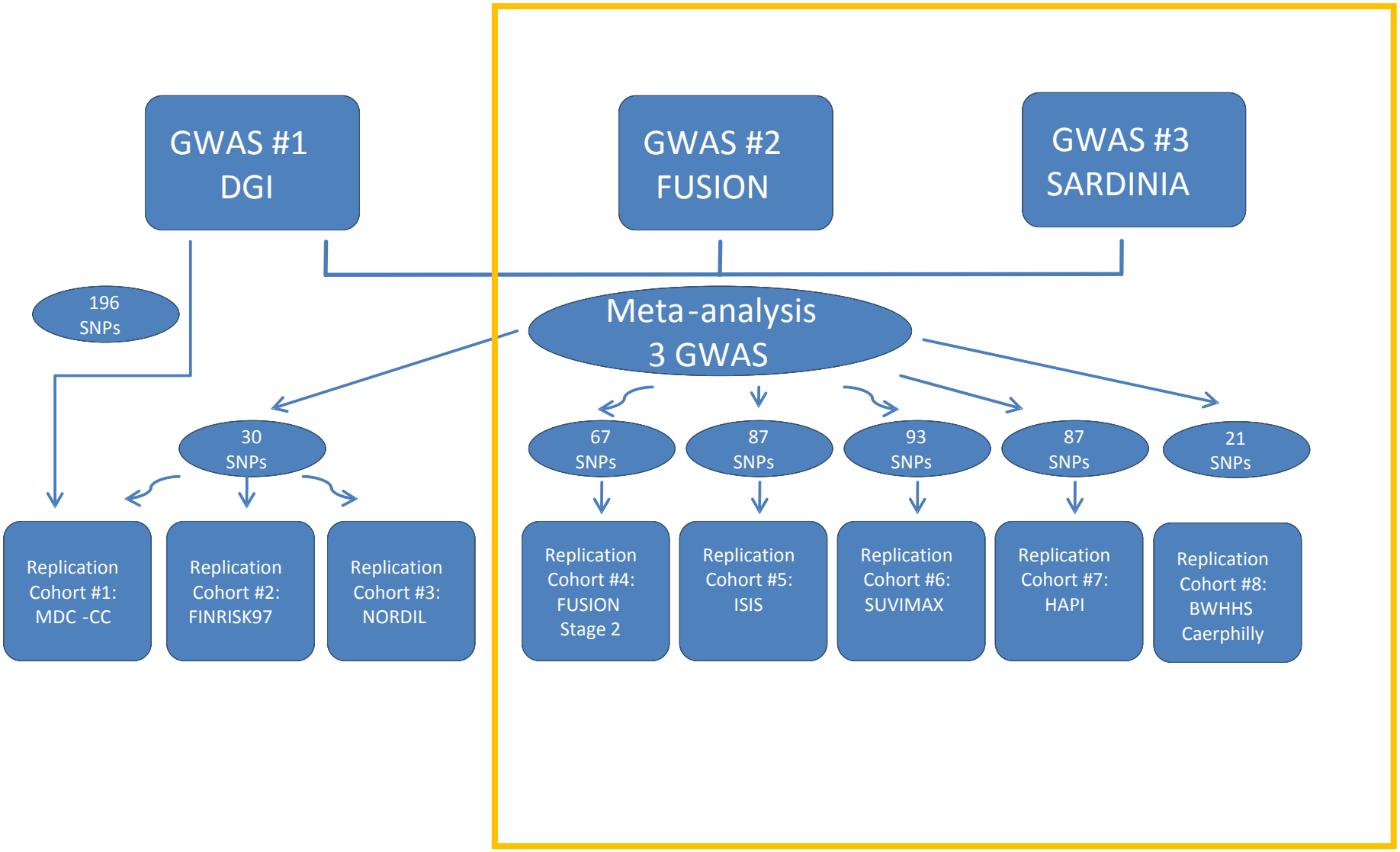
Supplementary Figure 1. Study Design for Meta-analysis of Three Genome Wide Association Scans and Follow-up of Results



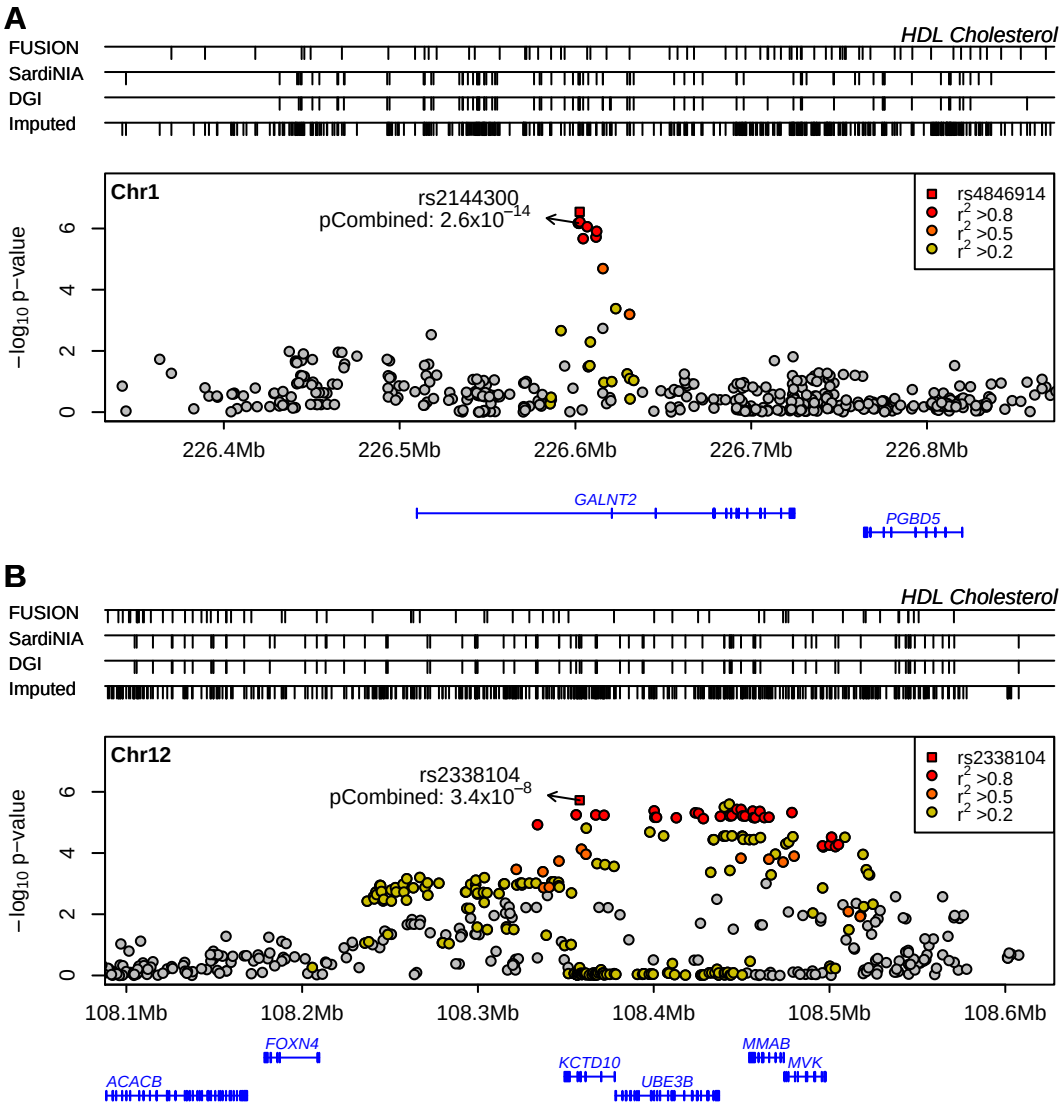
Supplementary Figure 1 Legend. Study Design for Meta-analysis of Three Genome Wide Association Scans and Follow-up of Results

The FUSION sample was genotyped using the Illumina HumanHap300 BeadChip. The 4,305 individuals from the SardiNIA study were genotyped using either the Affymetrix Mapping 10K Array (N = 2,893), the Affymetrix 500K Array Set (N = 976) or both (N = 436) to allow for family-based imputation. A subset of 4,184 individuals not taking lipid medication was used in the analyses described here. The DGI sample was genotyped using the Affymetrix Mapping 500K Array Set, as described previously (Diabetes Genetics Initiative 2007) and in the accompanying report (Kathiresan et al. 2007).

Following imputation of Affymetrix 500K SNPs in FUSION Stage 1 samples, a meta-analysis was performed with DGI and SardiNIA results (N = 8,816), and 87-93 of the most strongly associated SNPs ($p < 7 \times 10^{-5}$) were selected for follow-up in the ISIS, SUVIMAX, and HAPI samples. Included in the SNP set were 17 SNPs in strong linkage disequilibrium ($r^2 > .80$) with other highly significant SNPs that were selected as proxies to protect against genotyping failure of the originally selected SNP. Sixty-seven SNPs ($p < 5 \times 10^{-6}$) were genotyped in the FUSION Stage 2 sample. Following a preliminary analysis of Stage 2 results from the FUSION, ISIS, SUVIMAX and HAPI studies, twenty-one SNPs in the most promising genes were selected for genotyping in the BWHHS and Caerphilly samples. The combined Stage 2 sample includes genotypes for up to 11,569 individuals.

The orange box highlights experiments and data unique to this manuscript. The FUSION and SardiNIA lipid scans are reported for the first time. The meta-analysis of the three original scans of these two scans with the DGI scan and results of follow-up genotyping in six samples (ISIS, HAPI, SUVIMAX, FUSION Stage 2, BWHHS, Caerphilly) are also reported here for the first time. An independent set of follow-up experiments (based on our meta-analysis and on the DGI genome-wide scan) and using a non-overlapping set of follow-up samples are reported in a companion manuscript by Kathiresan and colleagues.

Supplementary Figure 2. Summary of Association in Newly-Identified Loci. Each panel spans 500 kb (except for panels D and F, 800 kb) and shows evidence for association around one of our replicated signals (p-value < 10^{-8}). At the top of each panel, comb diagrams indicate the location of successfully genotyped SNPs in FUSION, SardiNIA, and DGI, and of SNPs imputed. In the middle of each panel, evidence for association is summarized at all evaluated SNPs in Stage 1 samples. The SNP showing strongest evidence for association in the region is highlighted with a red square and other SNPs are colored according to their degree of linkage disequilibrium with this top SNP. In each locus, one of the SNPs followed-up in Stage 2 is highlighted together with a combined p-value taking Stage 1 and Stage 2 data into account. Note that, since we preferentially followed-up Affymetrix 500K SNPs, the strongest association signal and the SNP selected for follow-up do not always match. The bottom panel summarizes gene locations in each region. For visual clarity, some gene labels were omitted in panels D and F. From left to right, the labels for genes appearing in panels D and F are: *SLC25A42*, *TMEM161A*, *MEF2B*, *RFXANK*, *TRA16*, *NCAN*, *HAPLN4*, *TM6SF2*, *SF4*, *KIAA0892*, *GATAD2A*, *TSSK6*, *NDUFA13*, *FLJ44968*, *CILP2*, *PBX4*, *EDG4*, *GMIP*, *ATP13A1*, *ZNF101*, *ZNF14*, *ZNF253*, *ZNF93*, *ZNF682*, *FLJ44894*, *ZNF626*, *ZNF85*, *ZNF430*, *ZNF714*.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HDL Cholesterol
FUSION
SardiNIA
DGI
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r2 >0.5
r2 >0.2
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4
6
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226.5Mb
226.6Mb
226.7Mb
226.8Mb
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PGBD5
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FUSION
SardiNIA
DGI
Imputed
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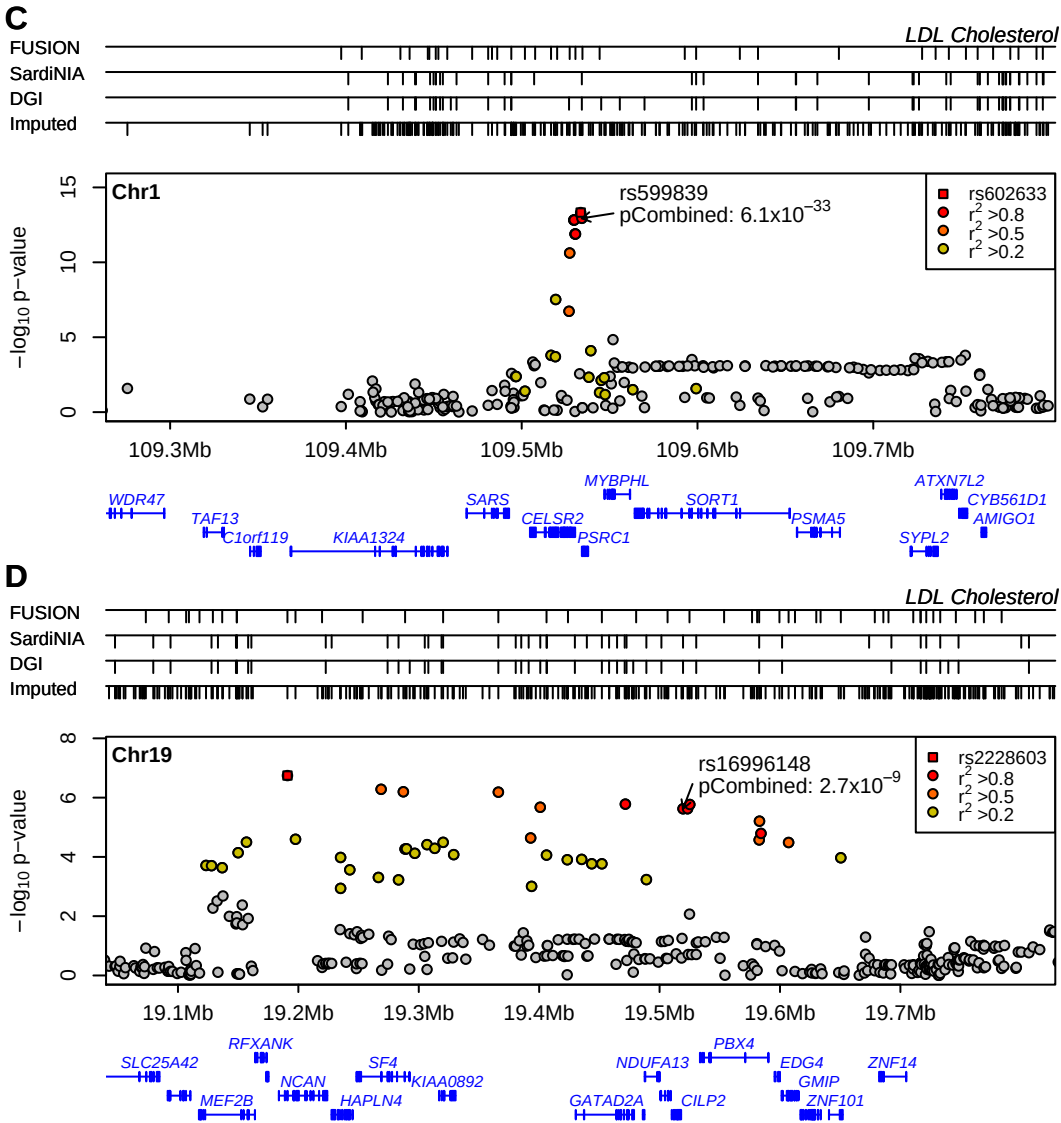
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DGI
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109.5Mb
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C1orf119
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DGI
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19.2Mb
19.3Mb
19.4Mb
19.5Mb
19.6Mb
19.7Mb
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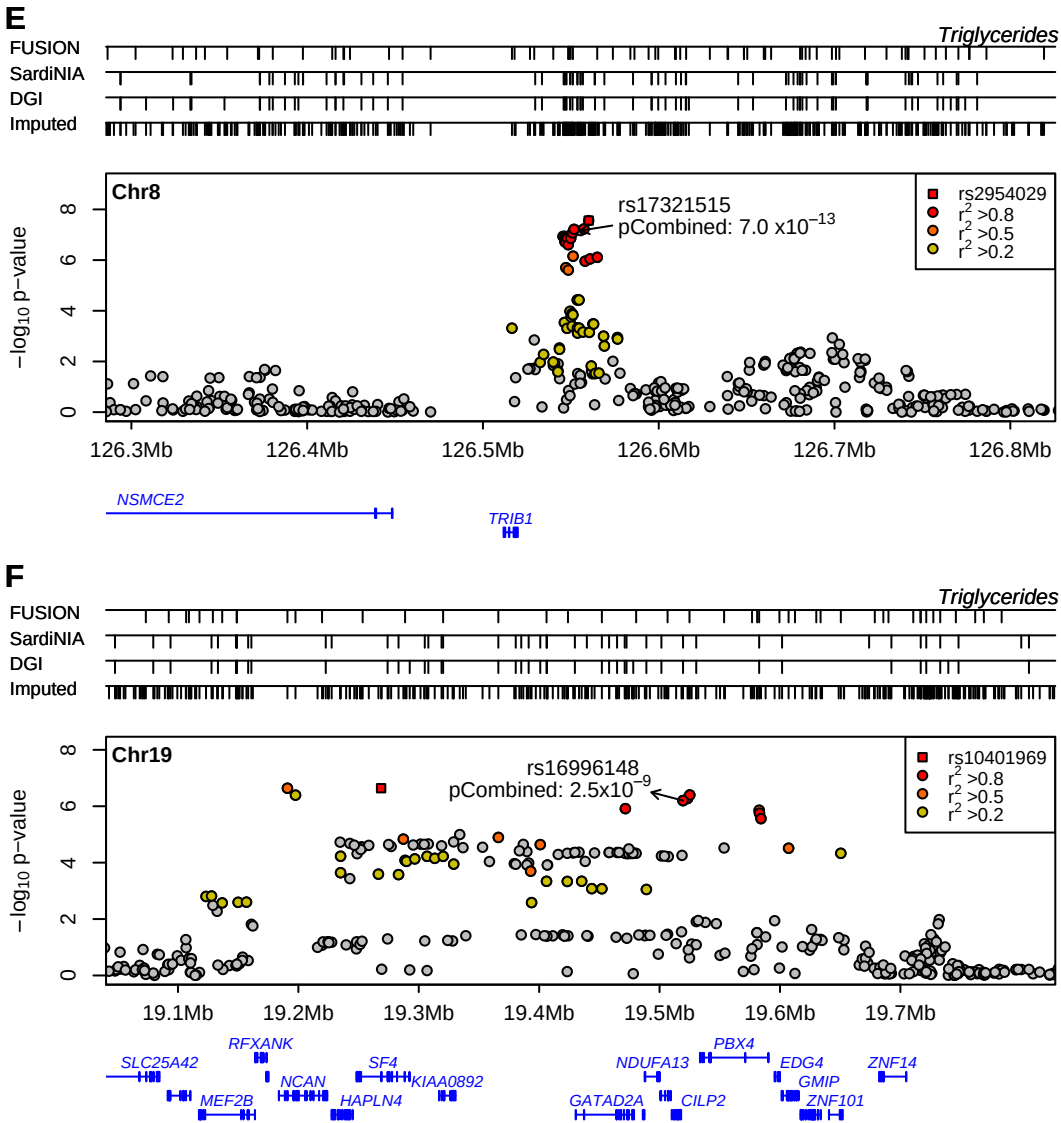
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FUSION
SardiNIA
DGI
Imputed
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r2 >0.5
r2 >0.2
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2
4
6
8
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126.4Mb
126.5Mb
126.6Mb
126.7Mb
126.8Mb
NSMCE2
TRIB1
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DGI
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19.2Mb
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NCAN
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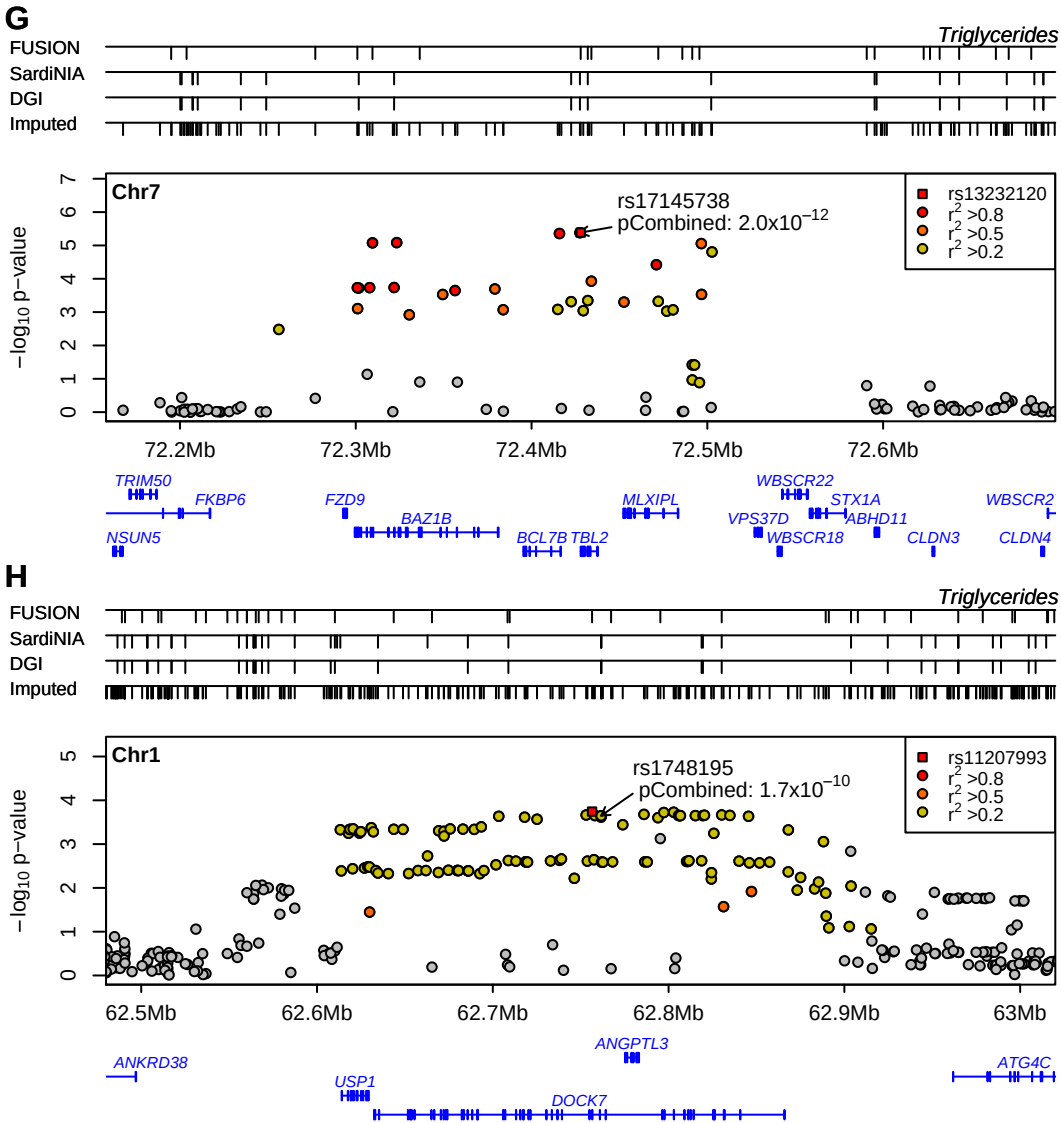
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72.3Mb
72.4Mb
72.5Mb
72.6Mb
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FZD9
BAZ1B
MLXIPL
WBSCR22
STX1A
WBSCR2
VPS37D
ABHD11
NSUN5
BCL7B
TBL2
WBSCR18
CLDN3
CLDN4
H
Triglycerides
FUSION
SardiNIA
DGI
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62.6Mb
62.7Mb
62.8Mb
62.9Mb
63Mb
ANKRD38
ANGPTL3
ATG4C
USP1
DOCK7

Supplementary Table 1. Comparison of Imputed and Genotyped SNP Association Results for FUSION Stage 1 Samples

SNP	Nearby genes	Trait	N genotyped (% of total)	Allele frequency		Association p-values		r^2 between imputed and actual genotypes		Observed allelic concordance
				Imputed	Genotyped	Imputed[a]	Genotyped	Actual	Estimated[b]	
rs1864163	*CETP*	HDL-C	1810 (96.9)	.746	.789	$9.7x10^{-14}$	$4.3x10^{-10}$	.793	.690	.957
rs662799	*APOA5/A4/C3/A1*	TG	1814 (97.2)	.055	.075	$7.6x10^{-9}$	$1.6x10^{-8}$	.813	.716	.978
rs255052	*LCAT*	HDL-C	1865 (99.9)	.189	.189	$1.9x10^{-5}$	$1.9x10^{-5}$	1.00	1.00	1.00
rs6511720	*LDLR*	LDL-C	1746 (95.0)	.104	.111	$2.5x10^{-5}$	$3.4x10^{-7}$	.906	.940	.989
rs17321515	*TRIB1*	TG	1791 (95.6)	.465	.473	$6.3x10^{-5}$	$5.3x10^{-5}$	.970	.981	.986
rs2254287	*B3GALT4*	LDL-C	1774 (96.9)	.474	.481	$1.7x10^{-4}$	$1.9x10^{-4}$	.998	.995	.998
rs2338104	*MVK/MMAB*	HDL-C	1757 (94.1)	.471	.459	$2.2x10^{-4}$	$2.1x10^{-4}$	.971	.966	.981
rs10503669	*LPL*	TG	1783 (95.5)	.910	.917	$2.3x10^{-4}$	$1.4x10^{-4}$	.956	.991	.997
rs562338	*APOB*	LDL-C	1746 (95.0)	.818	.803	.00047	.0058	.924	.917	.990
rs16996148	*CSPG3/CILP2*	TG	1747 (93.2)	.072	.071	.0011	.00080	.976	.968	.999
rs2144300	*GALNT2*	HDL-C	1777 (94.8)	.565	.552	.0014	.00093	.922	.890	.978
rs17145738	*MLXIPL*	TG	1824 (97.7)	.881	.879	.0035	.0035	1.00	1.00	1.00
rs2156552	*LIPG*	HDL-C	1724 (92.0)	.204	.164	.0038	.0046	.861	.833	.964
rs599839	*CELSR2/*	LDL-C	1837 (100)	.236	.228	.0039	.0034	.955	.882	.992
rs12695382	*B4GALT4*	LDL-C	1793 (98.0)	.886	.885	.0043	.0031	.986	.989	.998
rs2197089	*LPL*	TG	1779 (94.9)	.603	.601	.0046	.0052	.974	.971	.993
rs4775041	*LIPC*	HDL-C	1831 (98.1)	.671	.646	.0067	$2.1x10^{-4}$	.734	.726	.920
rs1748195	*ANGPTL3*	TG	1791 (95.9)	.725	.735	.011	.015	.990	.979	.997
rs261332	*LIPC*	HDL-C	1766 (94.2)	.237	.186	.012	.0027	.677	.705	.931
rs1323432	*GRIN3A*	HDL-C	1787 (95.4)	.090	.080	.049	.077	.945	.921	.996
rs11206510	*PCSK9*	LDL-C	1760 (96.2)	.884	.834	.07	$6.8x10^{-5}$	.361	.399	.888
rs11127129	*RBKS*	TG	1761 (94.0)	.282	.305	.13	.07	.910	.966	.969
rs4149268	*ABCA1*	HDL-C	1808 (96.8)	.286	.292	.51	.48	.929	.869	.985

[a] Association results for imputed SNPs were restricted to individuals with successful genotypes for each SNP; these results may differ slightly from those used in the meta-analysis, which was based on all Stage 1 individuals.

[b] The estimated r^2 is the ratio of the observed variance of estimated allele counts to its theoretical expectation of $2pq$ for a genotyped SNP under Hardy-Weinberg equilibrium (as described in Li, Y., Willer, C. J., Ding, J., Scheet, P. & Abecasis, G. R. Markov Model for Rapid Haplotyping and Genotype Imputation in Genome Wide Studies. *Nature Genetics* submitted 2007; p and q are the allele frequencies).

Supplementary Table 2. Comparison of the Most Significant Stage 1+2 Results to Previous Reports of Association

Locus			Evidence for association			Previous evidence for association			
SNP	Chr	Position Mb	Alleles (+/-)[a]	Stage 1+2 p-value	N	Nearby genes	Best proxy among previously reported SNPs	r^2 in HapMap CEU	References
SNPs Associated With HDL Cholesterol									
rs3764261	**16**	**55.6**	**A/C**	**$2.3x10^{-57}$**	16,728	***CETP***	rs7205804	.53	1
rs1864163	**16**	**55.6**	**G/A**	**$6.9x10^{-39}$**	12,340	***CETP***	rs7205804	.32	1
rs9989419	**16**	**55.5**	**G/A**	**$3.2x10^{-31}$**	15,637	***CETP***	rs9989419	1	2
rs12596776	**16**	**55.5**	**G/C**	**$2.8x10^{-8}$**	15,686	***CETP***	rs9989419	.021	2
rs1566439	**16**	**55.6**	**C/T**	**$3.3x10^{-8}$**	13,537	***CETP***	rs9989419	.031	2
rs4775041	**15**	**56.5**	**C/G**	**$3.2x10^{-20}$**	20,082	***LIPC***	rs1800588 (-514 C/T) rs2070895 (-250 G/A)	.004 .004	1,3-7
rs261332	**15**	**56.5**	**A/G**	**$2.3x10^{-15}$**	15,612	***LIPC***	rs1800588 (-514 C/T) rs2070895 (-250 G/A)	.91 .87	1,3-7
rs10503669	**8**	**19.9**	**A/C**	**$4.1x10^{-19}$**	20,087	***LPL***	rs328 (Ser447Ter)	1	1,5,8
rs2197089	**8**	**19.9**	**A/G**	**$1.0x10^{-11}$**	12,300	***LPL***	rs285 (*Pvu* II)	.68	9
rs6586891	**8**	**20**	**A/C**	**$2.9x10^{-9}$**	15,673	***LPL***	rs328 (Ser447Ter)	.083	1,5,8
rs2144300	**1**	**226.6**	**T/C**	**$2.6x10^{-14}$**	20,062	***GALNT2***			
rs2156552	**18**	**45.4**	**T/A**	**$6.4x10^{-12}$**	20,093	***LIPG***	rs2000813 (Thr111Ile or 584C/T)	.07	10
rs4149268	**9**	**104.7**	**C/T**	**$1.2x10^{-10}$**	19,983	***ABCA1***	rs2275542	.88	11
rs2338104	**12**	**108.4**	**G/C**	**$3.4x10^{-8}$**	20,055	***MVK/MMAB***			
rs255052	16	66.6	A/G	$1.2x10^{-7}$	13,190	*LCAT*	rs2292318	.73	12
SNPs Associated With LDL Cholesterol									
rs4420638	**19**	**50.1**	**G/A**	**$3.0x10^{-43}$**	19,395	***APOE/C1/C4***	rs7412[b]	.72[13]	14
rs10402271	**19**	**50**	**G/T**	**$1.2x10^{-9}$**	15,108	***APOE/C1/C4***	rs7412[b]	.03[13]	14
rs599839	**1**	**109.5**	**A/G**	**$6.1x10^{-33}$**	19,372	***CELSR2/PSRC1/SORT1***			
rs6511720	**19**	**11.1**	**G/T**	**$4.2x10^{-26}$**	16,031	***LDLR***	rs688	.0004	15
rs562338	**2**	**21.2**	**G/A**	**$5.6x10^{-22}$**	19,438	***APOB***	rs693	.24	16
rs754523	**2**	**21.2**	**G/A**	**$8.3x10^{-12}$**	15,131	***APOB***	rs693	.25	16
rs693	**2**	**21.1**	**A/G**	**$3.1x10^{-9}$**	11,811	***APOB***	rs693	1	16
rs11206510	**1**	**55.2**	**T/C**	**$3.5x10^{-11}$**	19,394	***PCSK9***	rs505151 rs2495480	.008 .008	17 18
rs16996148	**19**	**19.5**	**G/T**	**$2.7x10^{-9}$**	19,430	***NCAN/CILP2***			
rs2254287	6	33.3	G/C	$5.1x10^{-8}$	16,029	*B3GALT4*			
rs12695382	3	120.4	A/G	$1.0x10^{-6}$	19,391	*B4GALT4*			

Supplementary Table 2 continued. Comparison of the Most Significant Stage 1+2 Results to Previous Reports of Association

Locus			Evidence for association			Previous evidence for association			
SNP	Chr	Position Mb	Alleles (+/-)[a]	Stage 1+2 p-value	N	Nearby genes	Best proxy among previously reported SNPs	r^2 in HapMap CEU	References
SNPs Associated With Triglycerides									
Rs780094	**2**	**27.7**	**T/C**	**$6.1x10^{-32}$**	18,407	***GCKR***	rs780094	1	19
rs11127129	2	28.0	C/G	$4.7x10^{-7}$	18,384	*RBKS/GCKR*			
rs12286037	**11**	**116.2**	**T/C**	**$1.0x10^{-26}$**	18,422	***APOA5/C3/A4***	rs3135506	.98 [c]	20-24
Rs662799	**11**	**116.2**	**G/A**	**$2.4x10^{-15}$**	11,932	***APOA5/C3/A4***	rs662799 (-1131 T/C)	1	22,23,24 ,25
rs2000571	**11**	**116.1**	**A/G**	**$5.7x10^{-8}$**	11,893	***APOA5/C3/A4***	rs662799	.10	22,23,24 ,25
Rs486394	11	116.0	C/A	$7.4x10^{-6}$	12,281	*APOA5/C3/A4*	rs662799	.004	22,23,24 ,25
rs10503669	**8**	**19.9**	**C/A**	**$3.9x10^{-22}$**	18,395	***LPL***	rs328 (Ser447Ter)	1	1,5,8
rs2197089	**8**	**19.9**	**G/A**	**$1.1x10^{-12}$**	11,886	***LPL***	rs285 (*Pvu* II)	.68	9
rs6586891	8	20.0	C/A	$1.1x10^{-6}$	12,306	*LPL*	rs328 (Ser447Ter)	.083	1,5,8
rs17321515	**8**	**126.6**	**A/G**	**$7.0x10^{-13}$**	13,996	***TRIB1***			
rs17145738	**7**	**72.4**	**C/T**	**$2.0x10^{-12}$**	18,425	***MLXIPL***			
rs1748195	**1**	**62.8**	**C/G**	**$1.7x10^{-10}$**	18,243	***ANGPTL3***			
rs16996148	**19**	**19.5**	**G/T**	**$2.5x10^{-9}$**	18,391	***NCAN/CILP2***			
rs4775041	**15**	**56.5**	**C/G**	**$1.6x10^{-8}$**	17,146	***LIPC***	rs1800588 (-514 C/T) rs2070895 (-250 G/A)	.004 .004	1,3-7
rs2144300	1	226.6	C/T	$7.9x10^{-7}$	17,157	*GALNT2*			

[a] The + allele was defined as the allele that was associated with higher trait values.
[b] Evaluation of linkage disequilibrium with rs7412 and rs429358, which together define the *APOE* e2, e3, and e4 alleles, was estimated using data from Coon et al.[13], because these SNPs have not been genotyped in HapMap CEU and could not be successfully genotyped in our samples.
[c] Linkage disequilibrium was evaluated in the FUSION sample because rs3135506 was not in the HapMap CEU database.

Legend: For each of the variants described in Stage 1 + 2 data on Table 3, with the exception of rs1323432, we list the previously reported SNP in strongest LD as defined by r^2. Previous reports were identified by a literature search using search terms ["HDL" or "LDL" or "triglyceride"] and "genetic" in publications from January 2003 to May 2007. Reports for well-studied variants published before 2003 were identified by including the gene name in the search terms. This analysis suggests that for HDL-C, the SNPs near *GALNT2* and near *MMAB/MVK* represent novel association signals. One of the two SNPs identified near *LIPC*, rs4775041, is 49 kb from the *LIPC* gene and not in LD with any previously reported SNP, which suggests that screening narrow regions surrounding candidate genes may fail to identify important regulatory SNPs. At the *APOE* locus, strong association with LDL-C was observed for a SNP in moderate LD with the well-studied rs7412, which is a surrogate for the well-studied *APOE* e2 allele. Also at the *APOE* locus, a second association signal that appears to be independent from those reported in the literature was identified ~80kb from *APOE* (rs10402271). For LDL-C, we found no reports of association with any lipid phenotype for common variants in the *CELSR2/PSRC1/SORT* and *NCAN/CILP2* gene regions. At the *LDLR* locus, a common variant previously reported to be associated with LDL-C, rs688, was not in LD with the SNP reported here, rs6511720 ($r^2 < .001$). For triglyceride levels, SNPs near *GCKR*, *LPL* (2 LD groups), and *APOA5* (2 LD groups) have been reported, although additional associated SNPs near *LPL* (1 LD group) and *APOA5* (2 LD groups) appear to be independent

from previously reported associations. SNPs near *TRIB1, MLXIPL, ANGPTL3, NCAN/CILP2*, and *RBKS* have not, to our knowledge, been reported previously.

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Supplementary Table 3. Complete Stage 2 Results for HDL-C, LDL-C and Triglycerides.

SNP	Chr	Position (Mb)	Alleles	Stage 1 N	Stage 1 P (two sided)	Stage 2 N	Stage 2 P (one sided)	Combined N	Combined P (two sided)	Nearby SNP	r^2
					HDL Cholesterol						
rs3764261	16	55.6	A/C	8,656	$2.8x10^{-19}$	8,072	$6.4x10^{-43}$	16,728	$2.3x10^{-57}$	-	-
rs1864163	16	55.6	G/A	8,656	$3.0x10^{-17}$	3,684	4.4x10-^{28}	12,340	$6.9x10^{-39}$	rs3764261	.18
rs9989419	16	55.5	G/A	8,656	$8.0x10^{-16}$	6,981	$1.8x10^{-17}$	15,637	$3.2x10^{-31}$	rs1864163	.18
rs4775041	15	56.5	C/G	8,656	$2.8x10^{-9}$	11,426	$9.6x10^{-13}$	20,082	$3.2x10^{-20}$	-	-
rs10503669	8	19.9	A/C	8,656	$3.2x10^{-10}$	11,431	$9.4x10^{-11}$	20,087	$4.1x10^{-19}$	-	-
rs261332	15	56.5	A/G	8,656	$1.7x10^{-9}$	6,956	$1.3x10^{-7}$	15,612	$2.3x10^{-15}$	rs4775041	<.01
rs2144300	1	226.6	T/C	8,656	$6.6x10^{-7}$	11,406	$4.0x10^{-9}$	20,062	$2.6x10^{-14}$	-	-
rs2156552	18	45.4	T/A	8,656	$8.3x10^{-7}$	11,437	$7.1x10^{-7}$	20,093	$6.4x10^{-12}$	-	-
rs2197089	8	19.9	A/G	8,656	$3.4x10^{-8}$	3,644	$3.2x10^{-5}$	12,300	$1.0x10^{-11}$	rs10503669	.11
rs4149268	9	104.7	C/T	8,656	$3.3x10^{-7}$	11,327	$2.2x10^{-5}$	19,983	$1.2x10^{-10}$	-	-
rs6586891	8	20	A/C	8,656	$3.5x10^{-5}$	7,017	$9.7x10^{-6}$	15,673	$2.9x10^{-9}$	rs2197089	.11
rs12596776	16	55.5	G/C	8,656	$3.7x10^{-5}$	7,030	.00010	15,686	$2.8x10^{-8}$	rs9989419	.02
rs1566439	16	55.6	C/T	8,656	$2.0x10^{-5}$	4,881	.00021	13,537	$3.3x10^{-8}$	rs9989419	.03
rs2338104	12	108.4	G/C	8,656	$1.9x10^{-6}$	11,399	.00076	20,055	$3.4x10^{-8}$	-	-
rs255052	16	66.6	A/G	8,656	$1.5x10^{-6}$	4,534	.0087	13,190	$1.2x10^{-7}$	-	-
rs1033924	10	58.3	C/G	8,656	$7.7x10^{-7}$	7,014	.19	15,670	$2.1x10^{-5}$	-	-
rs2289114	16	55.5	C/T	8,656	$6.2x10^{-5}$	4,862	.053	13,518	$3.0x10^{-5}$	rs9989419	.14
rs17145738	7	72.4	T/C	8,656	0.00014	8,992	.031	17,648	$6.2x10^{-5}$	-	-
rs16955385	18	9.6	G/A	8,656	$6.3x10^{-7}$	6,976	.40	15,632	.00011	-	-
rs2676034	15	31.4	G/A	8,656	$9.3x10^{-7}$	3,654	.68	12,310	.00011	-	-
rs2185938	9	15.3	A/G	8,656	0.00051	2,385	.062	11,041	.00015	-	-
rs7350947	17	64	C/T	8,656	$2.5x10^{-6}$	3,698	.62	12,354	.00016	-	-
rs475749	3	169.9	G/A	8,656	$2.6x10^{-6}$	3,715	.64	12,371	.00019	-	-
rs174548	11	61.3	C/G	8,656	0.00019	4,882	.13	13,538	.00026	-	-
rs6857	19	50.1	C/T	8,656	0.00056	3,691	.12	12,347	.00042	-	-
rs1323432	9	101.4	A/G	8,656	$2.5x10^{-8}$	8,100	.82	16,756	.00075	-	-
rs10155080	4	166.8	G/T	8,656	$8.5x10^{-5}$	4,815	.41	13,471	.0010	-	-
rs10948262	6	45.9	A/G	8,656	.00020	4,892	.35	13,548	.0013	-	-
rs2285528	15	89.5	C/T	8,656	$1.5x10^{-5}$	4,878	.70	13,534	.0017	-	-
rs4081825	8	82.7	A/C	8,656	.00024	4,902	.42	13,558	.0023	-	-
rs10766360	11	16.9	T/A	8,656	$4.9x10^{-5}$	4,871	.64	13,527	.0024	-	-
rs4884605	13	53.1	C/T	8,656	$1.1x10^{-5}$	3,714	.90	12,370	.0029	-	-
rs2100078	2	209.9	C/A	8,656	$5.8x10^{-5}$	2,397	.90	11,053	.0030	-	-
rs12323921	14	98.4	G/C	8,656	.00015	4,823	.55	13,479	.0031	-	-
rs10942230	5	27	C/T	8,656	.00090	7,014	.25	15,670	.0036	-	-
rs7845766	8	138.4	A/G	8,656	.00018	4,847	.68	13,503	.0067	-	-
rs9599823	13	70.8	C/T	8,656	$6.1x10^{-5}$	4,873	.81	13,529	.0074	-	-
rs2589238	15	94.6	T/C	8,656	$7.0x10^{-5}$	2,407	.97	11,063	.0085	-	-
rs10468017	15	56.5	T/C	8,656	$8.6x10^{-11}$	4,016	$6.2x10^{-8}$	12,672	$7.4x10^{-17}$	rs4775041	.81
rs17482753	8	19.9	T/G	8,656	$1.6x10^{-11}$	7,008	$3.5x10^{-7}$	15,664	$8.5x10^{-17}$	rs10503669	1
rs261334	15	56.5	G/C	8,656	$4.2x10^{-9}$	4,017	.027	12,673	$2.9x10^{-9}$	rs261332	.91
rs4846914	1	226.6	A/G	8,656	$2.9x10^{-7}$	7,029	.00066	15,685	$2.5x10^{-9}$	rs2144300	1
rs4244457	8	19.9	T/C	8,656	.00010	3,702	.00073	12,358	$5.9x10^{-7}$	rs6586891	.86
rs13306677	16	55.5	A/G	8,656	$1.9x10^{-5}$	4,017	.00092	12,673	$1.2x10^{-7}$	rs12596776	1
rs10774708	12	108.4	G/A	8,656	$5.6x10^{-6}$	4,843	.0022	13,499	$9.2x10^{-8}$	rs2338104	1

rs13232120	7	72.4	T/A	8,656	.00014	3,723	.34	12,379	.00064	rs17145738	1
rs683278	18	9.6	A/G	8,656	$4.9x10^{-6}$	4,014	.51	12,670	.00017	rs16955385	1
LDL Cholesterol											
rs4420638	19	50.1	G/A	8,589	$3.2x10^{-21}$	10,806	$4.9x10^{-24}$	19,395	$3.0x10^{-43}$	-	-
rs599839	1	109.5	A/G	8,589	$1.2x10^{-13}$	10,783	$2.7x10^{-21}$	19,372	$6.1x10^{-33}$	-	-
rs6511720	19	11.1	G/T	8,589	$6.8x10^{-10}$	7,442	$3.3x10^{-19}$	16,031	$4.2x10^{-26}$	-	-
rs562338	2	21.2	G/A	8,589	$1.2x10^{-11}$	10,849	$3.3x10^{-12}$	19,438	$5.6x10^{-22}$	-	-
rs754523	2	21.2	G/A	8,589	$7.0x10^{-7}$	6,542	$1.3x10^{-6}$	15,131	$8.3x10^{-12}$	rs562338	.12
rs11206510	1	55.2	T/C	8,589	$7.5x10^{-6}$	10,805	$5.4x10^{-7}$	19,394	$3.5x10^{-11}$	-	-
rs10402271	19	50	G/T	8,589	$9.8x10^{-6}$	6,519	$1.5x10^{-5}$	15,108	$1.2x10^{-9}$	rs4420638	.15
rs16996148	19	19.5	G/T	8,589	$2.4x10^{-6}$	10,841	$8.3x10^{-5}$	19,430	$2.7x10^{-9}$	-	-
rs693	2	21.1	A/G	8,589	$1.2x10^{-7}$	3,222	.0034	11,811	$3.1x10^{-9}$	rs7575840	.26
rs2254287	6	33.3	G/C	8,589	$2.9x10^{-6}$	7,440	.0015	16,029	$5.1x10^{-8}$	-	-
rs2228603	19	19.2	C/T	8,589	$1.8x10^{-7}$	3,176	.056	11,765	$1.3x10^{-7}$	-	-
rs12695382	3	120.4	A/G	8,589	$4.9x10^{-6}$	10,802	.0067	19,391	$1.0x10^{-6}$	-	-
rs1418746	9	5.8	C/T	8,589	$5.1x10^{-6}$	7,491	.060	16,080	$1.1x10^{-5}$	-	-
rs1024637	17	55.4	T/C	8,589	$6.1x10^{-6}$	4,873	.14	13,462	$1.9x10^{-5}$	-	-
rs6692477	1	214.2	A/G	8,589	$1.5x10^{-5}$	12,981	.029	21,570	$2.7x10^{-5}$	-	-
rs7586834	2	153.1	T/C	8,589	$4.4x10^{-6}$	3,219	.46	11,808	$7.2x10^{-5}$	-	-
rs206131	13	31.8	T/C	8,589	.00015	4,830	.08	13,419	.00011	-	-
rs12543503	8	95.9	C/T	8,589	$6.5x10^{-5}$	4,875	.17	13,464	.00017	-	-
rs12451501	17	57.6	G/A	8,589	$1.4x10^{-5}$	7,361	.20	15,950	.00018	-	-
rs17753596	14	65.4	T/G	8,589	$5.0x10^{-5}$	4,851	.20	13,440	.00019	-	-
rs1883515	20	37.5	G/A	8,589	$3.8x10^{-5}$	4,870	.28	13,459	.00026	-	-
rs3887891	1	110.1	T/C	8,589	$2.1x10^{-5}$	3,218	.68	11,807	.00070	-	-
rs762982	22	36.5	C/T	8,589	$1.5x10^{-5}$	6,478	.45	15,067	.00082	-	-
rs9378968	6	5.5	G/A	8,589	$8.6x10^{-7}$	3,212	.97	11,801	.0014	-	-
rs4140745	7	121.3	C/T	8,589	$5.9x10^{-6}$	3,164	.92	11,753	.0018	-	-
rs7644545	3	120.9	A/G	8,589	.00079	4,831	.68	13,420	.016	-	-
rs17265047	19	10.8	C/G	8,589	.00055	10,838	.56	19,427	.028	-	-
rs6857	19	50.1	T/C	8,589	$1.6x10^{-13}$	5,635	$2.7x10^{-10}$	14,224	$5.5x10^{-22}$	rs4420638	.46
rs7575840	2	21.2	T/G	8,589	$4.6x10^{-9}$	3,219	$6.6x10^{-7}$	11,808	$5.4x10^{-14}$	rs754523	.88
rs563290	2	21.2	A/G	8,589	$3.5x10^{-14}$	5,660	$7.9x10^{-6}$	14,249	$7.6x10^{-18}$	rs562338	1
rs3794991	19	19.5	C/T	8,589	$1.7x10^{-6}$	3,245	.13	11,834	$2.9x10^{-6}$	rs16996148	1
Triglycerides											
rs780094	2	27.7	T/C	8,684	$1.7x10^{-14}$	9,723	$2.0x10^{-19}$	18,407	$6.1x10^{-32}$	-	-
rs12286037	11	116.2	T/C	8,684	$1.1x10^{-7}$	9,738	$1.6x10^{-22}$	18,422	$1.0x10^{-26}$	-	-
rs10503669	8	19.9	C/A	8,684	$1.4x10^{-9}$	9,711	$1.6x10^{-14}$	18,395	$3.9x10^{-22}$	-	-
rs662799	11	116.2	G/A	8,684	$4.3x10^{-8}$	3,248	$2.7x10^{-10}$	11,932	$2.5x10^{-15}$	rs12286037	<.01
rs17321515	8	126.6	A/G	8,684	$6.8x10^{-8}$	5,312	$1.0x10^{-6}$	13,996	$7.0x10^{-13}$	-	-
rs2197089	8	19.9	G/A	8,684	$3.1x10^{-11}$	3,202	.0029	11,886	$1.1x10^{-12}$	rs10503669	.11
rs17145738	7	72.4	C/T	8,684	$4.1x10^{-6}$	9,741	$5.0x10^{-8}$	18,425	$2.0x10^{-12}$	-	-
rs1748195	1	62.8	C/G	8,684	.00023	9,559	$4.7x10^{-8}$	18,243	$1.5x10^{-10}$	-	-
rs16996148	19	19.5	G/T	8,684	$6.3x10^{-7}$	9,707	.00024	18,391	$2.5x10^{-9}$	-	-
rs4775041	15	56.5	C/G	8,684	$7.3x10^{-5}$	8,462	$2.9x10^{-5}$	17,146	$1.6x10^{-8}$	-	-
rs2000571	11	116.1	A/G	8,684	$4.7x10^{-5}$	3,209	$8.7x10^{-5}$	11,893	$5.7x10^{-8}$	rs662799	.10
rs2228603	19	19.2	C/T	8,684	$2.3x10^{-7}$	3,206	.027	11,890	$5.9x10^{-8}$	-	-

rs11127129	2	28	C/G	8,684	.00020	9,700	.00032	18,384	$4.7x10^{-7}$	-	-
rs2144300	1	226.6	C/T	8,684	.00049	8,473	.00024	17,157	$7.9x10^{-7}$	-	-
rs6586891	8	20	C/A	8,684	.00024	3,622	.00050	12,306	$1.1x10^{-6}$	rs2197089	.11
rs7120515	11	116.5	A/G	8,684	.00017	3,624	.0047	12,308	$5.1x10^{-6}$	-	-
rs486394	11	116	C/A	8,684	.00017	3,597	.0073	12,281	$7.4x10^{-6}$	rs12286037	.03
rs4808203	19	19.4	T/C	8,684	$4.3x10^{-5}$	3,593	.037	12,277	$1.1x10^{-5}$	rs2228603	.15
rs2409716	8	11	C/T	8,684	$5.0x10^{-6}$	9,690	.048	18,374	$1.4x10^{-5}$	-	-
rs4891590	18	62.9	C/T	8,684	$6.0x10^{-7}$	3,641	.60	12,325	$5.0x10^{-5}$	-	-
rs6456218	6	170.7	C/T	8,684	$2.3x10^{-6}$	5,270	.33	13,954	$6.6x10^{-5}$	-	-
rs7309928	12	46.2	C/G	8,684	$1.4x10^{-5}$	3,642	.32	12,326	$9.5x10^{-5}$	-	-
rs1989827	7	89.9	T/G	8,684	$9.3x10^{-6}$	3,612	.41	12,296	.00012	-	-
rs11229192	11	54.9	A/T	8,684	.00018	3,626	.13	12,310	.00017	-	-
rs10155080	4	166.8	T/G	8,684	.00048	3,588	.082	12,272	.00023	-	-
rs325160	1	44.4	G/C	8,684	$1.3x10^{-5}$	3,613	.54	12,297	.00032	-	-
rs4683029	3	45.1	G/A	8,684	$3.5x10^{-5}$	3,633	.66	12,317	.0011	-	-
rs3739391	8	6.4	A/G	8,684	$3.0x10^{-5}$	5,301	.53	13,985	.0012	-	-
rs4348504	8	23.2	C/T	8,684	.00056	3,598	.26	12,282	.0012	-	-
rs665795	5	3.2	A/G	8,684	$6.7x10^{-5}$	4,087	.57	12,771	.0015	-	-
rs236996	4	88.4	G/A	8,684	$2.3x10^{-5}$	3,614	.89	12,298	.0038	-	-
rs9298535	8	56.6	T/G	8,684	.00077	4,714	.71	13,398	.017	-	-
rs11682534	2	26.7	G/A	8,684	$4.0x10^{-5}$	5,296	.94	13,980	.023	-	-
rs1260326	2	27.6	T/C	8,684	$1.5x10^{-15}$	3,250	$2.8x10^{-8}$	11,934	$5.6x10^{-22}$	rs780094	.93
rs780093	2	27.7	T/C	8,684	$2.0x10^{-14}$	2,782	$7.4x10^{-5}$	11,466	$1.5x10^{-17}$	rs780094	1
rs17120029	11	116.2	T/C	8,684	$1.0x10^{-7}$	2,786	$5.4x10^{-7}$	11,470	$1.9x10^{-12}$	rs12286037	1
rs17482753	8	19.9	G/T	8,684	$2.3x10^{-12}$	5,286	$2.2x10^{-8}$	13,970	$5.9x10^{-19}$	rs10503669	1
rs6982636	8	126.5	G/A	8,684	$2.5x10^{-7}$	2,788	.012	11,472	$2.1x10^{-8}$	rs17321515	1
rs13232120	7	72.4	A/T	8,684	$4.1x10^{-6}$	3,250	.032	11,934	$9.7x10^{-7}$	rs17145738	1
rs1167998	1	62.6	A/C	8,684	.00046	3,227	.00018	11,911	$1.3x10^{-6}$	rs1748195	1
rs3794991	19	19.5	C/T	8,684	$1.2x10^{-6}$	3,278	.11	11,962	$1.8x10^{-6}$	rs16996148	1
rs12617171	2	28	C/T	8,684	.00040	2,407	.0041	11,091	$1.3x10^{-5}$	rs11127129	1
rs4846914	1	226.6	G/A	8,684	.00075	4,081	.0060	12,765	$2.7x10^{-5}$	rs2144300	1
rs2409715	8	11	T/A	8,684	$8.1x10^{-6}$	3,231	.019	11,915	$9.9x10^{-7}$	rs2409716	.94
rs4244457	8	19.9	C/T	8,684	$6.6x10^{-5}$	3,233	.22	11,917	.00014	rs6586891	.86
rs3775214	4	88.4	A/G	8,684	$2.3x10^{-6}$	9,652	.70	18,336	.0040	rs236996	1

Supplementary Table 3. This table summarizes Stage 2 results for all the SNPs evaluated in at least one of the Stage 2 Samples (FUSION, ISIS, SUVIMAX, HAPI, BWHHS, Caerphilly). Marker name, chromosome and position are followed by the trait increasing and decreasing alleles (based on analysis of the combined Stage 1 + 2 data). The number of individuals analyzed in Stage 1, Stage 2 and Stage 1+2 is also given together with the corresponding p-value. Stage 2 p-values are one sided and test for replication of the effect observed in Stage 1. Proxy SNPs ($r^2 > .8$) are indicated in the "Nearby SNP" column and are grouped towards the bottom of each table; these SNPs were examined as a backup, for situations where the target SNP might fail Stage 2 genotyping e. To help evaluate evidence for independent signals within each locus, we also list the highest r^2 between each SNP and other SNPs in the same locus that show stronger evidence for association.

Supplementary Table 4. Summary of Most Significant Stage 1+2 Results.

Locus			Evidence for Association in Stage 2									Summary P-values			Sample sizes		
						P-values (one-sided)						Stage 1	Stage 2	Combined			
SNP	Chr	Pos (Mb)	Alleles (+/-)	Freq (+)	Effect (mg/dl)	FUSION	ISIS	SUVI	HAPI	BWHHS	Caer	(two-sided)	(one-sided)	(two-sided)	Stage 1	Stage 2	Nearby Genes
HDL Cholesterol																	
rs3764261	**16**	**55.6**	**A/C**	**.694**	**3.47**	**$4.6x10^{-16}$**		**$3.3x10^{-9}$**		**$4.0x10^{-20}$**	**$6.9x10^{-4}$**	**$2.8x10^{-19}$**	**$6.4x10^{-43}$**	**$2.3x10^{-57}$**	**8656**	**8072**	***CETP***
rs1864163	**16**	**55.6**	**G/A**	**.799**	**4.12**	**$3.2x10^{-16}$**		**$9.0x10^{-14}$**				**$3.0x10^{-17}$**	**$4.3x10^{-28}$**	**$6.9x10^{-39}$**	**8656**	**3684**	***CETP***
rs9989419	**16**	**55.5**	**G/A**	**.653**	**1.72**	**$8.9x10^{-8}$**	**$1.7x10^{-6}$**	**$3.5x10^{-4}$**	**$3.1x10^{-4}$**			**$8.0x10^{-16}$**	**$1.8x10^{-17}$**	**$3.2x10^{-31}$**	**8656**	**6981**	***CETP***
rs12596776	**16**	**55.5**	**G/C**	**.133**	**1.26**	**.0046**	**.026**	**.0031**	**.68**			**$3.7x10^{-5}$**	**$1.0x10^{-4}$**	**$2.8x10^{-8}$**	**8656**	**7030**	***CETP***
rs1566439	**16**	**55.6**	**C/T**	**.452**	**0.96**		**.049**	**.050**	**$3.6x10^{-4}$**			**$2.0x10^{-5}$**	**$2.1x10^{-4}$**	**$3.3x10^{-8}$**	**8656**	**4881**	***CETP***
rs4775041	**15**	**56.5**	**C/G**	**.674**	**1.38**	**$1.2x10^{-6}$**	**$4.5x10^{-4}$**	**.0017**	**.13**	**$7.4x10^{-5}$**	**.49**	**$2.8x10^{-9}$**	**$9.6x10^{-13}$**	**$3.2x10^{-20}$**	**8656**	**11426**	***LIPC***
rs261332	**15**	**56.5**	**A/G**	**.194**	**1.41**	**$1.3x10^{-7}$**	**.12**	**0.031**	**.018**			**$1.7x10^{-9}$**	**$1.3x10^{-7}$**	**$2.3x10^{-15}$**	**8656**	**6956**	***LIPC***
rs10503669	**8**	**19.9**	**A/C**	**.104**	**2.09**	**.12**	**.0025**	**$1.3x10^{-7}$**	**.43**	**$3.8x10^{-5}$**	**.066**	**$3.2x10^{-10}$**	**$9.4x10^{-11}$**	**$4.1x10^{-19}$**	**8656**	**11431**	***LPL***
rs2197089	**8**	**19.9**	**A/G**	**.418**	**1.38**	**.011**		**$2.7x10^{-4}$**				**$3.4x10^{-8}$**	**$3.2x10^{-5}$**	**$1.0x10^{-11}$**	**8656**	**3644**	***LPL***
rs6586891	**8**	**20**	**A/C**	**.342**	**1.00**	**.013**	**.036**	**.0022**	**.033**			**$3.5x10^{-5}$**	**$9.7x10^{-6}$**	**$2.9x10^{-9}$**	**8656**	**7017**	***LPL***
rs2144300	**1**	**226.6**	**T/C**	**.400**	**1.11**	**.0078**	**.059**	**.055**	**.11**	**$2.1x10^{-4}$**	**$7.1x10^{-5}$**	**$6.6x10^{-7}$**	**$4.0x10^{-9}$**	**$2.6x10^{-14}$**	**8656**	**11406**	***GALNT2***
rs2156552	**18**	**45.4**	**T/A**	**.840**	**1.20**	**$2.6x10^{-4}$**	**$2.3x10^{-4}$**	**.25**	**.26**	**.012**	**.80**	**$8.4x10^{-7}$**	**$7.1x10^{-7}$**	**$6.4x10^{-12}$**	**8656**	**11437**	***LIPG***
rs4149268	**9**	**104.7**	**C/T**	**.355**	**0.82**	**.0037**	**.047**	**.17**	**.31**	**.030**	**.017**	**$3.3x10^{-7}$**	**$2.2x10^{-5}$**	**$1.2x10^{-10}$**	**8656**	**11327**	***ABCA1***
rs2338104	**12**	**108.4**	**G/C**	**.446**	**0.48**	**.30**	**.010**	**.028**	**.22**	**.14**	**.12**	**$1.9x10^{-6}$**	**$7.6x10^{-4}$**	**$3.4x10^{-8}$**	**8656**	**11399**	***MVK/MMAB***
rs255052	16	66.6	A/G	.169	0.74	.012		.28	.13			$1.5x10^{-6}$	.0087	$1.2x10^{-7}$	8656	4534	*LCAT*
rs1323432	9	101.4	A/G	.879	-0.03	.67		.86		.69	.38	$2.5x10^{-8}$	.82	$7.7x10^{-4}$	8656	8176	*GRIN3A*
LDL Cholesterol																	
rs4420638	**19**	**50.1**	**G/A**	**.821**	**6.61**	**.015**	**$1.7x10^{-9}$**	**$3.2x10^{-4}$**	**.048**	**$7.2x10^{-11}$**	**$2.3x10^{-4}$**	**$3.2x10^{-21}$**	**$4.9x10^{-24}$**	**$3.0x10^{-43}$**	**8589**	**10806**	***APOE/C1/C4***
rs10402271	**19**	**50**	**G/T**	**.666**	**2.62**	**.066**	**$2.7x10^{-6}$**	**.075**	**.40**			**$9.8x10^{-6}$**	**$1.5x10^{-5}$**	**$1.2x10^{-9}$**	**8589**	**6519**	***APOE/C1/C4***
rs599839	**1**	**109.5**	**A/G**	**.769**	**5.48**	**$3.8x10^{-4}$**	**$3.2x10^{-5}$**	**$1.6x10^{-4}$**	**.042**	**$6.7x10^{-8}$**	**$1.8x10^{-6}$**	**$1.2x10^{-13}$**	**$2.7x10^{-21}$**	**$6.1x10^{-33}$**	**8589**	**10783**	***CELSR2/PSRC 1/SORT1***
rs6511720	**19**	**11.1**	**G/T**	**.899**	**9.17**	**$1.9x10^{-6}$**		**$2.2x10^{-7}$**		**$9.6x10^{-7}$**	**$3.1x10^{-4}$**	**$6.8x10^{-10}$**	**$3.3x10^{-19}$**	**$4.2x10^{-26}$**	**8589**	**7442**	***LDLR***
rs562338	**2**	**21.2**	**G/A**	**.184**	**4.89**	**.25**	**$5.3x10^{-5}$**	**.0014**	**.013**	**$6.9x10^{-6}$**	**.027**	**$1.2x10^{-11}$**	**$3.6x10^{-12}$**	**$5.6x10^{-22}$**	**8589**	**10849**	***APOB***
rs754523	**2**	**21.2**	**G/A**	**.280**	**2.78**	**$3.5x10^{-5}$**	**$5.3x10^{-3}$**	**$9.0x10^{-4}$**	**.86**			**$7.0x10^{-7}$**	**$1.3x10^{-6}$**	**$8.3x10^{-12}$**	**8589**	**6542**	***APOB***
rs693	**2**	**21.1**	**A/G**	**.417**	**2.44**	**.33**		**$3.0x10^{-4}$**				**$1.2x10^{-7}$**	**.0034**	**$3.1x10^{-9}$**	**8589**	**3222**	***APOB***
rs11206510	**1**	**55.2**	**T/C**	**.808**	**3.04**	**$2.8x10^{-4}$**	**.0082**	**.56**	**.57**	**$5.8x10^{-4}$**	**.012**	**$7.5x10^{-6}$**	**$5.4x10^{-7}$**	**$3.5x10^{-11}$**	**8589**	**10805**	***PCSK9***
rs16996148	**19**	**19.5**	**G/T**	**.887**	**3.32**	**.27**	**$6.7x10^{-5}$**	**.19**	**$2.2x10^{-6}$**	**.22**	**.86**	**$2.4x10^{-6}$**	**$8.3x10^{-5}$**	**$2.7x10^{-9}$**	**8589**	**10841**	***NCAN/CILP2***
rs2254287	6	33.3	G/C	.381	1.91	.10		.020		.095	.061	$2.9x10^{-6}$	.0015	$5.1x10^{-8}$	8589	7440	*B3GALT4*
rs12695382	3	120.4	A/G	.900	2.23	.36	.12	.38	.056	.0058	.71	$4.9x10^{-6}$	.0067	$1.0x10^{-6}$	8589	10802	*B4GALT4*

Supplementary Table 4. Summary of Most Significant Stage 1+2 Results (continued).

Locus			Evidence for Association in Stage 2									Summary P-values					
						P-values (one-sided)						Stage 1	Stage 2	Combined	Sample sizes		
SNP	Chr	Pos (Mb)	Alleles (+/-)	Freq (+)	Effect (mg/dl)	FUSION	ISIS	SUVI	HAPI	BWHHS	Caer	(two-sided)	(one-sided)	(two-sided)	Stage 1	Stage 2	Nearby Genes
									Triglycerides								
rs780094	**2**	**27.7**	**T/C**	**.392**	**8.59**	**$1.2x10^{-6}$**	**.0024**	**.0070**	**.0031**	**$1.4x10^{-9}$**	**.018**	**$1.7x10^{-14}$**	**$2.0x10^{-19}$**	**$6.1x10^{-32}$**	**8684**	**9723**	***GCKR***
rs11127129	2	28.0	C/G	.787	3.77	$4.2x10^{-5}$	.51	.0065	.18	.39	.13	$2.0x10^{-4}$	$3.2x10^{-4}$	$4.7x10^{-7}$	8684	9700	*RBKS/GCKR*
rs12286037	**11**	**116.2**	**T/C**	**.938**	**25.82**	**$9.7x10^{-4}$**	**$8.8x10^{-4}$**	**$9.0x10^{-5}$**	**.0071**	**$3.5x10^{-7}$**	**$3.1x10^{-11}$**	**$1.1x10^{-7}$**	**$1.6x10^{-22}$**	**$1.0x10^{-26}$**	**8684**	**9738**	***APOA5/C3/A4***
rs662799	**11**	**116.2**	**G/A**	**.051**	**16.88**	**$1.2x10^{-6}$**		**$2.5x10^{-5}$**				**$4.3x10^{-8}$**	**$2.7x10^{-10}$**	**$2.4x10^{-15}$**	**8684**	**3248**	***APOA5/C3/A4***
rs2000571	11	116.1	A/G	.170	6.93	.0056		.0028				$4.7x10^{-5}$	$8.7x10^{-5}$	$5.7x10^{-8}$	8684	3209	*APOA5/C3/A4*
rs486394	11	116.0	C/A	.282	1.50		.66	$8.5x10^{-4}$	.10			$1.7x10^{-4}$	.0073	$7.4x10^{-6}$	8684	3597	*APOA5/C3/A4*
rs10503669	**8**	**19.9**	**C/A**	**.895**	**11.57**	**0.46**	**$2.7x10^{-4}$**	**$4.1x10^{-8}$**	**.029**	**$1.2x10^{-6}$**	**.0055**	**$1.4x10^{-9}$**	**$1.6x10^{-14}$**	**$3.9x10^{-22}$**	**8684**	**9711**	***LPL***
rs2197089	**8**	**19.9**	**G/A**	**.582**	**3.38**	**.040**		**.016**				**$3.1x10^{-11}$**	**.0029**	**$1.1x10^{-12}$**	**8684**	**3202**	***LPL***
rs6586891	8	20.0	C/A	.658	4.60		.028	.11	.0022			$2.4x10^{-4}$	$5.0x10^{-4}$	$1.1x10^{-6}$	8684	3622	*LPL*
rs17321515	**8**	**126.6**	**A/G**	**.562**	**6.42**	**$1.8x10^{-4}$**	**.051**	**.012**	**.034**			**$6.8x10^{-8}$**	**$1.0x10^{-6}$**	**$7.0x10^{-13}$**	**8684**	**5312**	***TRIB1***
rs17145738	**7**	**72.4**	**C/T**	**.840**	**8.21**	**.11**	**.060**	**.085**	**.13**	**$1.2x10^{-5}$**	**.0032**	**$4.1x10^{-6}$**	**$5.0x10^{-8}$**	**$2.0x10^{-12}$**	**8684**	**9741**	***MLXIPL***
rs1748195	**1**	**62.8**	**C/G**	**.704**	**7.12**	**.020**	**.057**	**$8.0x10^{-4}$**	**.52**	**.0030**	**$9.3x10^{-4}$**	**$2.3x10^{-4}$**	**$5.4x10^{-8}$**	**$1.7x10^{-10}$**	**8684**	**9559**	***ANGPTL3***
rs16996148	**19**	**19.5**	**G/T**	**.924**	**6.10**	**.13**	**.0052**	**.41**	**$7.5x10^{-4}$**	**.022**	**.62**	**$6.3x10^{-7}$**	**$2.4x10^{-4}$**	**$2.5x10^{-9}$**	**8684**	**9707**	***NCAN/CILP2***
rs4775041	**15**	**56.5**	**C/G**	**.673**	**3.62**	**.32**		**.0080**	**.030**	**.012**	**.014**	**$7.3x10^{-5}$**	**$2.9x10^{-5}$**	**$1.6x10^{-8}$**	**8684**	**8462**	***LIPC***
rs2144300	1	226.6	C/T	.601	4.25	.081		.0012	.67	.011	.21	$4.9x10^{-4}$	$2.4x10^{-4}$	$7.9x10^{-7}$	8684	8473	*GALNT2*

The table summarizes association signals after follow-up of the promising SNPs in Stage 2 samples (same SNPs as Table 3). Column headings are as described for Table 2, except for the addition of one-sided p-values for the Stage 2 samples, in which the same direction of effect observed in Stage 1 was tested. SNPs with a Combined (Stage 1 + 2) p-value < 10^{-5} were included, although we also show *GRIN3A* for completeness because it was significant in the initial scan. SNPs in this table may not match those in Table 2, which only displays the strongest signal at each locus. The discrepancy also reflects our bias towards genotyped Affymetrix 500K SNPs in the Stage 2 follow-up. The Stage 2 and Combined Stage 1+2 p-values for rs12286037 used rs17120029 as a proxy ($r^2 = 1$) in ISIS. For rs4420638, we used rs6857 as proxy ($r^2 = 0.46$) in ISIS because there was no proxy in HapMap in stronger LD with rs4420638. For rs6586891, we used rs4244457 as a proxy ($r^2 = .86$) in FUSION.

Supplementary Table 5. Association between Coronary Artery Disease and HDL Cholesterol Associated SNPs

Locus			HDL-C Association (Current Study)		Association With Coronary Artery Disease (WTCCC)						
					Expanded Reference Set		CAD Cases				
SNP	Chr	Position (Mb)	Alleles (+/-)	P-value (two-sided)	N	Frequency of HDL- Allele	N	Frequency of HDL- Allele	P-value (one sided)	OR (95% CI)	Nearby Genes
rs3764261*	16	55.6	A/C	**$2.3x10^{-57}$**	12301	.658	1926	.664	0.18	1.05 (0.95-1.15)	***CETP***
rs1864163*	16	55.6	G/A	**$6.9x10^{-39}$**	12301	.234	1926	.240	0.12	1.07 (0.96-1.20)	***CETP***
rs9989419	16	55.5	G/A	**$3.2x10^{-31}$**	12277	.398	1923	.404	0.24	1.02 (0.96-1.10)	***CETP***
rs12596776	16	55.5	G/C	**$2.8x10^{-8}$**	12287	.900	1925	.898	0.64	0.98 (0.88-1.10)	***CETP***
rs1566439	16	55.6	C/T	**$3.3x10^{-8}$**	12235	.587	1923	.600	0.059	1.06 (0.99-1.13)	***CETP***
rs4775041	15	56.5	C/G	**$3.2x10^{-20}$**	12073	.704	1910	.689	0.97	0.93 (0.87-1.00)	***LIPC***
rs261332	15	56.5	A/G	**$2.3x10^{-15}$**	12269	.798	1921	.794	0.75	0.97 (0.89-1.06)	***LIPC***
rs10503669	8	19.9	A/C	**$7.6x10^{-19}$**	12286	.901	1925	.909	0.062	1.10 (0.97-1.23)	***LPL***
rs2197089*	8	19.9	A/G	**$1.0x10^{-11}$**	12301	.440	1926	.453	0.041	1.07 (0.99-1.16)	***LPL***
rs6586891	8	20.0	A/C	$3.7x10^{-7}$	12269	.353	1923	.366	0.060	1.06 (0.99-1.13)	*LPL*
rs2144300	1	226.6	T/C	**$2.6x10^{-14}$**	12273	.396	1922	.402	0.25	1.02 (0.95-1.10)	***GALNT2***
rs2156552	18	45.4	T/A	**$4.1x10^{-11}$**	12293	.173	1920	.183	0.060	1.07 (0.98-1.17)	***LIPG***
rs4149268	9	104.7	C/T	**$1.2x10^{-10}$**	12246	.371	1915	.367	0.66	0.99 (0.92-1.06)	***ABCA1***
rs2338104	12	108.4	G/C	**$3.4x10^{-8}$**	12284	.474	1922	.471	0.62	0.99 (0.92-1.06)	***MVK/MMAB***
rs255052	16	66.6	A/G	$1.2x10^{-7}$	12278	.860	1923	.863	0.32	1.02 (0.93-1.13)	*LCAT*
rs1323432*	9	101.4	A/G	$7.7x10^{-4}$	12301	.116	1926	.116	0.47	1.00 (0.90-1.12)	*GRIN3A*

The table summarizes association between coronary artery disease (CAD) and the alleles associated with HDL-C levels in our study. Evidence for association was evaluated in the Wellcome Trust Case Control Consortium panel.

* Genotypes for four SNPs (rs3764261, rs1864163, rs2197089, rs1323432) were imputed in the WTCCC samples using MACH.

Supplementary Table 5. Association between Coronary Artery Disease and Triglyceride Associated SNPs

Locus			Triglyceride Association (Current Study)		Association With Coronary Artery Disease (WTCCC)						
					Expanded Reference Set		CAD Cases				
SNP	Chr	Position (Mb)	Alleles (+/-)	P-value (two-sided)	N	Frequency of TG+ Allele	N	Frequency of TG+ Allele	P-value (one sided)	OR (95% CI)	Nearby Genes
rs780094	2	27.7	**T/C**	**$6.1x10^{-32}$**	12194	0.393	1909	0.395	0.79	1.01 (0.94-1.08)	***GCKR***
rs11127129	2	28	C/G	$4.7x10^{-7}$	12288	0.816	1925	0.815	0.81	0.99 (0.91-1.08)	*RBKS/GCKR*
rs12286037	11	116.2	**T/C**	**$1.0x10^{-26}$**	12280	0.065	1924	0.076	0.0085	1.19 (1.05-1.36)	***APOA5/C3/A4***
rs662799*	11	116.2	**G/A**	**$2.4x10^{-15}$**	12301	0.058	1926	0.060	0.58	1.04 (0.90-1.21)	***APOA5/C3/A4***
rs2000571*	11	116.1	A/G	$5.7x10^{-8}$	12301	0.202	1926	0.202	0.92	1.00 (0.91-1.09)	*APOA5/C3/A4*
rs486394	11	116	C/A	$7.4x10^{-6}$	12222	0.289	1912	0.290	0.90	1.00 (0.93-1.08)	*APOA5/C3/A4*
rs10503669	8	19.9	**C/A**	**$3.9x10^{-22}$**	12286	0.901	1925	0.909	0.12	1.10 (0.97-1.23)	***LPL***
rs2197089*	8	19.9	**G/A**	**$1.1x10^{-12}$**	12301	0.440	1926	0.453	0.083	1.07 (0.99-1.16)	***LPL***
rs6586891	8	20	C/A	$1.1x10^{-6}$	12269	0.353	1923	0.366	0.12	1.06 (0.99-1.13)	*LPL*
rs17321515	8	126.6	**A/G**	**$7.0x10^{-13}$**	12286	0.527	1926	0.554	0.0016	1.12 (1.04-1.19)	***TRIB1***
rs17145738	7	72.4	**C/T**	**$2.0x10^{-12}$**	12282	0.878	1920	0.885	0.24	1.07 (0.96-1.19)	***MLXIPL***
rs1748195	1	62.8	**C/G**	**$1.7x10^{-10}$**	12255	0.652	1923	0.639	0.12	0.94 (0.88-1.01)	***ANGPTL3***
rs16996148	19	19.5	**G/T**	**$2.5x10^{-9}$**	12182	0.915	1921	0.922	0.11	1.11 (0.98-1.26)	***NCAN/CILP2***
rs4775041	15	56.5	**C/G**	**$1.6x10^{-8}$**	12073	0.296	1910	0.311	0.056	1.07 (1.00-1.16)	***LIPC***
rs2144300	1	226.6	C/T	$7.9x10^{-7}$	12273	0.396	1922	0.402	0.51	1.02 (0.95-1.10)	*GALNT2*

The table summarizes association between Coronary Artery Disease and the alleles associated with triglyceride levels in our study. Evidence for association was evaluated in the Wellcome Trust Case Control Consortium panel.

* Genotypes for three SNPs (rs662799, rs2000571, rs2197089) were imputed in the WTCCC samples using MACH.