LeBlanc et al. Supplemental Material

Supplemental Methods

False Discovery Rate (FDR)

The tail-area based FDR for a given p-value, p, is defined as

$$\text{(standard unconditioned) } FDR(p) = \pi_0 F_0(p) / F(p). \qquad [1]$$

where $F_0(p)$ is the cumulative distribution function (cdf) for null SNPs, $F(p)$ is the cdf for all SNPs and π_0 is the *a priori* proportion of null SNPs. In practice the FDR needs to be estimated from the data and a conservative estimate can be obtained by setting π_0 to 1. For p-values, $F_0(p)$ is the cdf for the uniform distribution and $F(p)$ is estimated by the empirical cdf, $q = N_p / N$, where N_p is the number of SNPs with p-values less than or equal to p, and N is the total number of SNPs.

Leveraging pleiotropy by conditional FDR

Conditional FDR exploits the shared polygenic signal between coronary artery disease (CAD) and each secondary trait to increase power for detection of CAD SNPs. Conditional FDR is defined as the posterior probability that a given SNP is null for the first phenotype given that the p-values for both phenotypes are as small or smaller as their observed p-values.

$$\text{Conditional FDR: } FDR(p_1 \mid p_2) = \pi_0(p_2)\, p_1 / F(p_1 \mid p_2), \qquad [2]$$

where p_1 is the p-value for the first phenotype, p_2 is the p-value for the second, $F(p_1 \mid p_2)$ is the conditional cdf and $\pi_0(p_2)$ the conditional proportion of null SNPs for the first phenotype given that p-value for the second phenotype is p_2 or smaller. As with FDR, we obtain a conservative estimate of the conditional FDR by setting π_0 to 1. $F(p_1 \mid p_2)$ is estimated from the data by constructing a two-dimensional grid, with CAD p-value category for columns, and the secondary trait p-value category for rows, and then counting how many SNPs fall into each bin on the grid. The empirical conditional cdf was estimated using the binomial regression model that estimates the probability for falling into a bin conditional on the sum over all bins in one row.

Conjunctional FDR

The conjuctional FDR is defined as follows:

$$FDR_{CAD\ \&\ trait2} = max(FDR_{CAD\ |trait2}, FDR_{trait2\ |\ CAD}). \quad [3]$$

FDR calculations for the Metabochip

To estimate the conditional and conjunctional FDR, the joint distribution for p-values for the primary trait (CAD) and the secondary trait (e.g. T2D), $F(p1,p2)$, needs to be estimated from the observed data. For GWAS data, this is a straightforward process since SNPs on standard GWAS chips can be treated as a random sample of common variants from the human genome and the size of the LD blocks will be unrelated to the effect of the SNPs on the traits of interest. Therefore there is no a priori reason to believe that this estimate of $F(p1,p2)$ is biased. Here we use the CAD metabochip data rather than standard GWAS chip data. Here the estimation of $F(p1,p2)$ will be incorrect if we use the whole dataset. The reason for this is that by design since the metabochip follows up previously described cardiometabolic SNPs with fine mapping. This means that there is non-independence between the size of the LD block and statistical significance. Larger blocks of SNPs will be found for non-null SNPs. As such, an unbiased estimate of $F(p1,p2)$ was obtained from an LD-pruned set of SNPs.

Online Figure Legends

Online Figure I. Pleiotropic Enrichment. Conditional quantile-quantile plot of nominal versus empirical -$\log_{10}$ p-values in Coronary Artery Disease (CAD) as a function of significance of association with A) body mass index (BMI) B) high density lipoprotein (HDL) C) systolic blood pressure (SBP) and D) triglycerides (TG), at the level of $-\log_{10}(p) > 0$, $-\log_{10}(p) > 1$, $-\log_{10}(p) > 2$, $-\log_{10}(p) > 3$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. Due to the linkage disequilibrium structure on the metabochip, a linkage disequilibrium-pruned set of SNPs was used for the quantile-quantile plots. Input p-values were adjusted for shared subjects, if present. Dotted lines indicate the null-hypothesis.

Online Figure II. Stratified replication rates plots showing the average rate of replication ($p < 0.05$) within the CARDIoGRAMplusC4D contributing studies as a function of significance in a secondary trait: (A) C-reactive protein (CRP), (B) type 1 diabetes (T1D), (C) type 2 diabetes (T2D), (D) low density lipoprotein (LDL), (E) high density lipoprotein (HDL), (F) systolic blood pressure (SBP), (G) body mass index (BMI) and (H) triglycerides (TG), at the level of $-\log_{10}(p) > 0$, $-\log_{10}(p) > 1$, $-\log_{10}(p) > 2$, $-\log_{10}(p) > 3$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively.

Online Figure 3 III. Conjunctional FDR Manhattan plot of $-\log_{10}$ (conjunctional FDR) for coronary artery disease (CAD) and type 2 diabetes (T2D; CAD&T2D; navy blue), CAD and type 1 diabetes (T1D; CAD&T1D; light green), CAD and low density lipoprotein (LDL; CAD&LDL; aqua). CAD and high density lipoprotein (HDL; CAD&HDL; dark green), CAD and triglycerides (TG; CAD&TG; fuchsia), CAD and body mass index (BMI; CAD&BMI; mustard yellow). CAD and C-reactive protein (CRP; CAD&CRP; royal blue) and CAD and systolic blood pressure (SBP; CAD&SBP; maroon). SNPs with $-\log_{10}$ (conjunctional FDR) > 2.2 (i.e. overall FDR < 0.05 after Bonferroni correction for eight traits) are shown with large points. A black circle around the large points indicates the most significant SNP in each linkage disequilibrium block and this SNP was annotated with the closest gene which is listed above the symbols in each locus, except for the HLA region on chromosome 6, which was excluded from the analysis. Details for the novel loci with –$\log_{10}$ (conjunctional FDR) > 2.2 are given in Supplemental Table 3.

Online Tables

Online Table I. Correlation due to cross-trait sample overlap and corresponding overlap numbers.

Trait 1	Trait 2	Correlation	Description of overlap
CAD	T2D	0.09 (0.14)	Cases: 26,874 cases unique to T2D 55,780 cases unique to CAD; 7966 shared cases Controls: 75,282 controls unique to T2D 90,982 controls unique to CAD 39,699 shared controls
CAD	T1D	0.03 (NA)	Cases: 7514 cases unique to T1D; 63,746 cases unique to CAD; no shared cases Controls: 5703 controls unique to T1D; 127,339 controls unique to CAD, 3342 shared controls
CAD	LDL	<0.19 (0.10)	188,577 total subjects LDL; 194,427 total subjects CAD, up to which 36,432 are shared subjects
CAD	HDL	<-0.19 (-0.10)	188,577 total subjects HDL; 194,427 total subjects CAD, up to which 36,432 are shared subjects
CAD	TG	<0.19 (0.11)	188,577 total subjects HDL; 194,427 total subjects CAD, up to which 36,432 are shared subjects
CAD	BMI	<0.23 (0.05)	123,865 total subjects BMI; 194,427 total subjects CAD, up to which 37,131 are shared subjects
CAD	SBP	<0.31 (NA)	69,395 total subjects SBP; 194,427 total subjects CAD, up to which 36,545 are shared subjects

Cross-trait correlation of the GWAS test statistics for CAD and each secondary trait calculated using the methods presents in LeBlanc et al. (in prep). Correlation is presented as estimated (observed in data). Where a less than sign, <, is shown, the phenotypic correlation of trait 1 and trait 2 needs to be estimated from epidemiological studies.

Online Table II. Anderson Darling test for enrichment.

	Logp threshold		
	>3	>2	>1
BMD	2.64E-01	2.36E-01	1.20E-01
T2D	**1.70E-03**	5.69E-02	3.47E-01
T1D	**3.58E-04**	**9.56E-04**	3.81E-01
LDL	**1.87E-29**	**4.90E-09**	**7.80E-05**
HDL	**7.65E-06**	8.60E-03	7.47E-02
TG	**1.68E-04**	5.44E-02	5.82E-01
BMI	1.13E-01	**3.48E-06**	**2.10E-03**
CRP	**3.69E-04**	1.60E-02	2.23E-01
SBP*	NA	NA	NA

The bold strata are significant for an overall level of α=0.05 after correction for multiple testing. The set of SNPs (GWAS p>0.1 in the *secondary* trait), i.e., SNPs that are signal depleted in the secondary trait, was used as the comparison set.

*Note that SBP was excluded from the Anderson Darling test since the effect direction was not available and for technical reasons this made the Anderson Darling test unreliable after correction for sample overlap.

Online Table III SNPs that replicate in the WGHS at a nominal p-value of less than 0.05.

SNP	Event	P
rs4888378	CHD	0.0043
rs6905288	MI	0.0048
rs6905288	CHD	0.0066
rs12801636	CHD	0.0088
rs7296651	CHD	0.014
rs7296651	MI	0.017
rs11066320	MI	0.022
rs867764	MI	0.023
rs12801636	MI	0.030
rs1882961	CHD	0.031
rs10747342	MI	0.032
rs10774613	MI	0.034
rs10774613	CHD	0.036
rs2146238	MI	0.037
rs3179840	MI	0.043

MI, myocardial infarction; CHD, coronary heart disease (composed of MI, CHD death, and coronary revascularization)

Online Table IV. Conjunctional FDR (<0.05), after controlling for multiple testing across phenotypes

snp	gene	chr	CAD&T2D	CAD&T1D	CAD&LDL	CAD&HDL	CAD&TG	CAD&BMI	CAD&CRP	CAD&SBP	Min ConjFDR
rs4268379	*SARS*	1	5.07E-02	6.98E-01	**8.30E-04**	4.16E-01	1.00E+00	6.94E-01	4.61E-01	8.89E-01	**LDL**
rs12740374	*CELSR2*	1	3.82E-01	NA	**3.37E-08**	**7.40E-09**	2.22E-01	5.68E-01	3.58E-01	1.00E+00	**HDL**
rs7515901	*MYBPHL*	1	1.00E+00	NA	**2.31E-03**	3.70E-01	1.00E+00	9.68E-01	9.97E-01	1.00E+00	**LDL**
rs10495907	*DYNC2LI1*	2	8.91E-01	1.00E+00	**3.97E-03**	6.77E-01	8.46E-01	9.50E-01	7.41E-01	9.60E-01	**LDL**
rs10186133	*IL1F10*	2	9.63E-01	9.24E-01	4.69E-01	8.11E-01	5.75E-01	1.00E+00	**7.28E-04**	8.89E-01	**CRP**
rs934287	*ICA1L*	2	1.00E+00	3.63E-01	**1.57E-06**	3.28E-01	1.41E-01	2.61E-01	5.17E-01	1.00E+00	**LDL**
rs1250255	*FN1*	2	1.00E+00	1.00E+00	**5.66E-03**	9.04E-01	5.75E-01	9.00E-01	9.97E-01	4.61E-01	**LDL**
rs2176042	*BC017935*	2	**3.36E-03**	NA	4.69E-01	7.07E-03	**5.37E-03**	1.26E-01	7.90E-01	1.99E-01	**T2D**
rs7642590	*MAP4*	3	1.00E+00	NA	6.95E-01	2.89E-01	3.73E-01	4.47E-01	9.17E-01	**2.26E-03**	**SBP**
rs695238	*TRAIP*	3	9.15E-01	NA	9.29E-01	8.35E-03	1.00E+00	3.43E-01	**5.13E-03**	7.44E-01	**CRP**
rs7638389	*BC040632*	3	**5.30E-03**	1.00E+00	1.04E-01	2.89E-01	4.70E-01	2.61E-01	7.90E-01	6.91E-01	**T2D**
rs10512987	*PPP2R3A*	3	1.00E+00	9.58E-01	**3.73E-03**	1.68E-01	7.37E-03	3.43E-01	3.13E-01	8.89E-01	**LDL**
rs7356185	*USP53*	4	1.00E+00	8.93E-01	7.46E-01	9.04E-01	9.27E-01	9.68E-01	1.00E+00	**4.18E-03**	**SBP**
rs1508798	*SNORD123*	5	1.00E+00	9.58E-01	5.85E-01	2.38E-02	**2.34E-03**	1.00E+00	9.17E-01	1.00E+00	**TG**
rs10477741	*C5orf56*	5	6.96E-01	NA	**1.03E-03**	5.68E-01	1.00E+00	1.00E+00	9.47E-01	8.36E-01	**LDL**
rs2814982	*C6orf106*	6	9.63E-01	1.00E+00	**5.20E-04**	**3.03E-03**	8.46E-01	5.06E-01	8.32E-01	1.00E+00	**LDL**
rs1321309	*CDKN1A*	6	8.11E-01	NA	4.69E-01	7.38E-01	**1.86E-03**	1.00E+00	5.74E-01	8.89E-01	**TG**
rs6905288	*VEGFA*	6	3.44E-01	1.00E+00	6.41E-01	**2.56E-03**	**3.46E-03**	8.61E-01	9.97E-01	1.51E-02	**HDL**
rs1564348	*SLC22A1*	6	8.56E-01	1.00E+00	**5.66E-03**	5.15E-01	1.26E-02	9.68E-01	6.32E-01	7.44E-01	**LDL**
rs9365233	*MAP3K4*	6	1.00E+00	1.00E+00	**5.78E-03**	1.00E+00	7.33E-01	5.06E-01	1.00E+00	6.34E-01	**LDL**
rs2237659	*COG5*	7	6.96E-01	1.00E+00	2.60E-02	7.38E-01	**2.66E-03**	8.61E-01	5.17E-01	8.89E-01	**TG**
rs6997340	*NAT2*	8	6.35E-01	9.58E-01	**3.97E-03**	6.22E-01	1.20E-02	9.68E-01	7.41E-01	1.00E+00	**LDL**
rs11204085	*SLC18A1*	8	7.56E-01	NA	9.29E-01	**9.24E-04**	**1.50E-03**	1.00E+00	9.17E-01	1.00E+00	**HDL**
rs343494	*RANBP6*	9	1.00E+00	**5.94E-03**	1.00E+00	6.22E-01	1.00E+00	1.00E+00	9.97E-01	7.44E-01	**T1D**
rs7902355	*TSPAN14*	10	9.63E-01	1.00E+00	3.17E-01	**5.80E-03**	8.46E-01	1.00E+00	9.97E-01	5.75E-01	**HDL**
rs7926335	*PLEKHA7*	11	9.63E-01	NA	9.29E-01	3.70E-01	1.00E+00	9.39E-01	9.97E-01	**7.17E-04**	**SBP**

rs12801636	*PCNXL3*	11	4.70E-01	1.00E+00	3.17E-01	**6.50E-04**	**1.02E-03**	9.26E-01	4.40E-02	6.43E-02	**HDL**
rs644740	*OVOL1*	11	6.35E-01	8.93E-01	1.38E-02	1.15E-02	8.46E-02	1.00E+00	7.90E-01	**2.26E-03**	**SBP**
rs7933887	*ST3GAL4*	11	1.00E+00	NA	1.04E-01	**4.69E-03**	3.73E-01	1.00E+00	1.00E+00	7.91E-01	**HDL**
rs4149033	*SLCO1B1*	12	1.00E+00	1.00E+00	6.41E-01	1.00E+00	**3.98E-03**	9.26E-01	1.00E+00	8.89E-01	**TG**
rs2681472	*ATP2B1*	12	8.11E-01	1.00E+00	1.00E+00	1.00E+00	4.70E-01	1.00E+00	7.90E-01	**3.40E-03**	**SBP**
rs1056618	*AJ276555*	12	1.00E+00	NA	**5.78E-03**	7.38E-01	9.27E-01	5.68E-01	8.32E-01	1.00E+00	**LDL**
rs7398833	*CUX2*	12	9.15E-01	**1.85E-04**	**1.94E-03**	3.70E-01	**3.25E-03**	8.11E-01	2.02E-01	**2.29E-04**	**TG**
rs11066320	*PTPN11*	12	9.63E-01	**4.05E-06**	**1.28E-05**	**8.40E-05**	3.73E-01	1.88E-02	9.17E-01	**5.55E-06**	**T1D**
rs7315519	*RPH3A*	12	8.91E-01	**4.86E-04**	**2.99E-03**	**3.59E-03**	9.27E-01	1.26E-01	1.00E+00	1.21E-01	**T1D**
rs692902	*SPPL3*	12	3.19E-02	9.24E-01	2.75E-01	2.89E-02	7.85E-01	1.00E+00	**4.77E-03**	8.89E-01	**CRP**
rs2708081	*OASL*	12	1.02E-01	3.10E-01	**6.70E-04**	1.94E-01	8.46E-01	9.26E-01	**3.41E-05**	8.89E-01	**CRP**
rs825461	*ZNF664*	12	**4.29E-03**	1.00E+00	9.29E-01	**3.59E-03**	1.65E-01	5.68E-01	1.00E+00	3.60E-01	**T2D**
rs11057830	*SCARB1*	12	9.36E-01	NA	**3.49E-04**	1.95E-02	**2.69E-03**	9.26E-01	9.97E-01	4.09E-01	**LDL**
rs4932370	*FURIN*	15	3.82E-01	9.24E-01	4.69E-01	3.28E-01	3.73E-01	9.50E-01	7.41E-01	**7.93E-05**	**SBP**
rs2072142	*DHX38*	16	9.15E-01	NA	**1.93E-03**	6.22E-01	7.85E-01	8.02E-02	1.00E+00	NA	**LDL**
rs9927309	*CTRB2*	16	**5.30E-03**	**8.50E-04**	9.29E-01	4.64E-01	1.00E+00	9.00E-01	1.00E+00	7.91E-01	**T2D**
rs1838105	*GOSR2*	17	1.00E+00	NA	1.48E-01	**5.97E-03**	6.29E-01	8.11E-01	1.00E+00	8.76E-02	**HDL**
rs12940887	*ZNF652*	17	9.36E-01	NA	7.46E-01	8.89E-02	1.92E-02	8.61E-01	9.97E-01	**5.15E-03**	**SBP**
rs2812	*PECAM1*	17	9.36E-01	NA	6.41E-01	1.24E-01	9.27E-01	8.61E-01	7.41E-01	**3.63E-03**	**SBP**
rs13465	*ILF3*	19	9.63E-01	4.89E-01	**1.62E-03**	2.22E-01	8.46E-01	9.68E-01	1.00E+00	7.44E-01	**LDL**
rs12052058	*SMARCA4*	19	8.91E-01	8.14E-01	**7.34E-06**	7.38E-01	1.00E+00	8.11E-01	5.74E-01	1.00E+00	**LDL**
rs892115	*SPC24*	19	9.63E-01	1.19E-01	**4.75E-03**	9.04E-01	1.00E+00	9.00E-01	6.88E-01	7.44E-01	**LDL**
rs17616661	*KANK2*	19	1.00E+00	6.98E-01	**1.57E-03**	**1.55E-03**	3.29E-01	9.50E-01	5.17E-01	9.60E-01	**HDL**
rs2241718	*CYP2F1*	19	9.63E-01	NA	**2.99E-03**	9.04E-01	5.75E-01	1.00E+00	9.97E-01	NA	**LDL**
rs1415771	*EDEM2*	20	1.00E+00	1.02E-01	5.89E-02	**4.25E-03**	1.00E+00	8.61E-01	1.00E+00	9.60E-01	**HDL**
rs3827066	*ZNF335*	20	1.00E+00	NA	2.75E-01	**1.55E-03**	7.00E-03	9.68E-01	5.74E-01	1.00E+00	**HDL**
rs4822458	*DDT*	22	1.00E+00	8.58E-01	1.00E+00	9.04E-01	**5.76E-03**	9.50E-01	8.66E-01	1.00E+00	**TG**

Independent ($r^2 < 0.2$) of SNP(s) with a conjunctional FDR (conjFDR) < 0.05 (after Bonferonni correction for 8 traits) in Coronary Artery Disease (CAD) given the significance level in the associated phenotype. We defined the most significant CAD SNP in each LD block based on the minimum conjunctional FDR for each associated phenotype. The most significant SNPs in each gene of the LD block are listed along with the associated phenotype that provided the signal. Coronary artery disease (CAD), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG), type 2 diabetes (T2D), C-reactive protein (CRP), body mass index (BMI), systolic blood pressure (SBP), type 1 diabetes (T1D), chromosome number (Chr). Conjunctional FDR values < 0.05, after adjusting for multiple testing across phenotypes are in bold. The most significant phenotype association per gene is shown (min conjFDR). NA indicates that a given SNP was not available for a given trait.

Online Table V. Signed z-scores for the SNPs presented in Supplemental Table 3.

snp	gene	chr	CAD z-score	BMI z-score	T2D z_score	LDL z-score	HDL z-score	TG z-score	CRP z-score	**Min conjFDR**	**Trait**
rs4268379	*SARS*	1	-4.95	1.64	3.57	-12.00	1.85	-0.42	2.09	**8.30E-04**	**LDL**
rs12740374	*CELSR2*	1	8.70	-1.91	-2.22	36.59	-8.37	2.75	-2.24	**7.40E-09**	**HDL**
rs7515901	*MYBPHL*	1	4.48	-0.57	-0.06	9.40	-1.98	0.15	0.43	**2.31E-03**	**LDL**
rs10495907	*DYNC2LI1*	2	-4.22	-0.98	-1.29	-7.81	1.21	-0.96	-1.51	**3.97E-03**	**LDL**
rs10186133	*IL1F10*	2	4.24	-0.10	-0.46	1.84	0.41	1.59	-5.98	**7.28E-04**	**CRP**
rs934287	*ICA1L*	2	5.84	-2.49	0.08	-5.46	-2.20	-2.48	-1.93	**1.57E-06**	**LDL**
rs1250255	*FN1*	2	3.44	-1.22	0.50	-4.75	0.24	-1.25	0.47	**5.66E-03**	**LDL**
rs2176042	*BC017935*	2	-4.33	2.72	-6.59	-1.84	8.47	-7.43	-1.38	**3.36E-03**	**T2D**
rs7642590	*MAP4*	3	-3.96	2.01	-0.75	-1.36	2.11	-2.11	-0.90	**2.26E-03**	**SBP**
rs695238	*TRAIP*	3	-4.04	-2.43	-1.19	0.32	4.38	-0.12	-4.02	**5.13E-03**	**CRP**
rs7638389	*BC040632*	3	3.95	2.62	-5.33	-2.40	1.78	-1.38	-1.44	**5.30E-03**	**T2D**
rs10512987	*PPP2R3A*	3	-4.07	-2.43	-0.09	-3.85	2.50	-4.20	2.36	**3.73E-03**	**LDL**
rs7356185	*USP53*	4	3.80	-0.49	-0.10	1.19	-0.68	-0.18	0.24	**4.18E-03**	**SBP**
rs1508798	*SNORD123*	5	4.24	0.51	0.01	-1.15	2.95	-4.55	-0.83	**2.34E-03**	**TG**
rs10477741	*C5orf56*	5	-4.75	-0.26	-1.88	-4.25	1.49	-0.25	-0.58	**1.03E-03**	**LDL**
rs2814982	*C6orf106*	6	-4.47	-2.16	0.45	4.44	6.75	-0.94	-1.21	**5.20E-04**	**LDL**
rs1321309	*CDKN1A*	6	-4.60	-0.31	-1.65	-1.84	1.11	-4.56	-1.81	**1.86E-03**	**TG**
rs6905288	*VEGFA*	6	-4.52	1.24	-2.53	1.05	6.61	-7.61	-0.44	**2.56E-03**	**HDL**
rs1564348	*SLC22A1*	6	-4.23	0.56	1.31	-9.62	1.67	-3.64	1.77	**5.66E-03**	**LDL**
rs9365233	*MAP3K4*	6	4.57	-1.97	0.23	3.78	-0.32	1.32	-0.04	**5.78E-03**	**LDL**
rs2237659	*COG5*	7	-4.22	1.26	1.63	-3.28	1.00	3.92	1.99	**2.66E-03**	**TG**
rs6997340	*NAT2*	8	4.02	-0.52	1.92	4.07	0.87	6.24	1.54	**3.97E-03**	**LDL**
rs11204085	*SLC18A1*	8	5.23	0.31	1.80	-0.19	-14.03	14.24	0.78	**9.24E-04**	**HDL**
rs343494	*RANBP6*	9	3.53	-0.05	0.73	-0.05	-1.26	-0.15	-0.38	**5.94E-03**	**T1D**
rs7902355	*TSPAN14*	10	4.24	0.63	-0.41	2.21	3.58	-0.45	0.40	**5.80E-03**	**HDL**
rs7926335	*PLEKHA7*	11	-4.25	0.84	-0.78	-0.76	-1.54	-0.29	0.40	**7.17E-04**	**SBP**

rs12801636	*PCNXL3*	11	4.86	1.25	2.25	-1.73	-5.60	4.43	3.28	**6.50E-04**	**HDL**
rs644740	*OVOL1*	11	3.95	0.06	1.94	-3.05	-4.41	2.94	1.40	**2.26E-03**	**SBP**
rs7933887	*ST3GAL4*	11	4.47	-0.29	-0.05	2.80	-3.88	2.10	-0.23	**4.69E-03**	**HDL**
rs4149033	*SLCO1B1*	12	-3.82	1.04	-0.43	1.05	0.00	3.72	0.14	**3.98E-03**	**TG**
rs2681472	*ATP2B1*	12	-3.84	-0.12	1.37	-0.35	0.36	1.41	1.45	**3.40E-03**	**SBP**
rs1056618	*AJ276555*	12	3.96	-1.86	0.30	-3.32	-1.03	0.67	1.30	**5.78E-03**	**LDL**
rs7398833	*CUX2*	12	4.56	-1.45	1.17	-3.81	-2.03	4.08	2.58	**3.25E-03**	**TG**
rs11066320	*PTPN11*	12	5.40	-3.80	0.86	-6.24	-5.54	2.18	0.92	**4.05E-06**	**T1D**
rs7315519	*RPH3A*	12	4.34	-2.76	-0.91	-3.71	-4.36	-0.17	0.18	**4.86E-04**	**T1D**
rs692902	*SPPL3*	12	3.65	0.27	4.76	2.24	2.91	1.02	-9.03	**4.77E-03**	**CRP**
rs2708081	*OASL*	12	5.12	1.28	3.35	4.38	1.97	1.03	-12.98	**3.41E-05**	**CRP**
rs825461	*ZNF664*	12	-4.44	1.84	-4.49	-0.71	6.37	-2.68	-0.35	**4.29E-03**	**T2D**
rs11057830	*SCARB1*	12	-5.26	1.02	0.52	-4.52	3.48	-4.15	-0.54	**3.49E-04**	**LDL**
rs4932370	*FURIN*	15	-5.69	0.75	-2.47	1.31	-1.90	1.50	1.53	**7.93E-05**	**SBP**
rs2072142	*DHX38*	16	-4.27	-3.22	-1.17	-4.90	-0.87	-1.14	-0.06	**1.93E-03**	**LDL**
rs9927309	*CTRB2*	16	4.18	-1.17	5.20	0.62	-1.76	0.12	-0.14	**5.30E-03**	**T2D**
rs1838105	*GOSR2*	17	3.96	-1.40	0.48	2.63	4.19	1.56	0.08	**5.97E-03**	**HDL**
rs12940887	*ZNF652*	17	-3.73	-1.55	0.61	-1.16	2.83	-5.09	-0.54	**5.15E-03**	**SBP**
rs2812	*PECAM1*	17	-4.48	1.27	0.57	1.00	-2.24	-0.79	1.54	**3.63E-03**	**SBP**
rs13465	*ILF3*	19	-4.74	0.57	0.44	-12.12	2.41	-0.95	0.34	**1.62E-03**	**LDL**
rs12052058	*SMARCA4*	19	6.42	-1.52	-1.21	17.44	-1.10	0.10	1.85	**7.34E-06**	**LDL**
rs892115	*SPC24*	19	4.11	-1.18	0.91	6.60	-0.77	0.42	1.65	**4.75E-03**	**LDL**
rs17616661	*KANK2*	19	-4.56	-0.95	-0.62	-4.14	4.41	-2.16	-1.96	**1.55E-03**	**HDL**
rs2241718	*CYP2F1*	19	4.15	0.12	0.88	-3.48	0.18	-1.16	0.38	**2.99E-03**	**LDL**
rs1415771	*EDEM2*	20	-4.22	-1.52	-0.62	2.54	4.03	0.12	0.06	**4.25E-03**	**HDL**
rs3827066	*ZNF335*	20	-4.35	-0.74	-0.22	1.77	-4.33	3.32	-1.82	**1.55E-03**	**HDL**
rs4822458	*DDT*	22	4.21	-0.70	-0.30	0.46	0.26	3.85	-1.08	**5.76E-03**	**TG**

Coronary artery disease (CAD), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG), type 2 diabetes (T2D), C-reactive protein (CRP), body mass index (BMI), systolic blood pressure (SBP), type 1 diabetes (T1D), chromosome number (Chr).

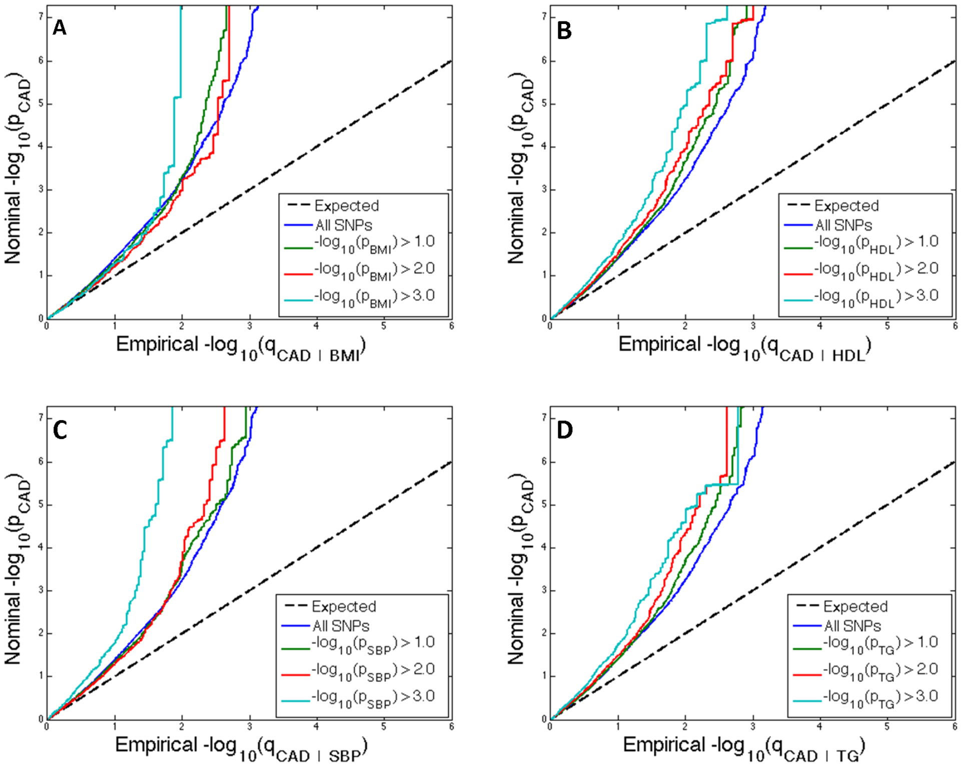
Note that signed z-scores for T1D and SBP are not publically available and are therefore excluded from this table. The most significant phenotype association per gene is shown (min conjFDR).

Online Table VI. Ingenuity Pathway Analysis (IPA) including our novel CAD SNPs and previously published CAD SNPs.

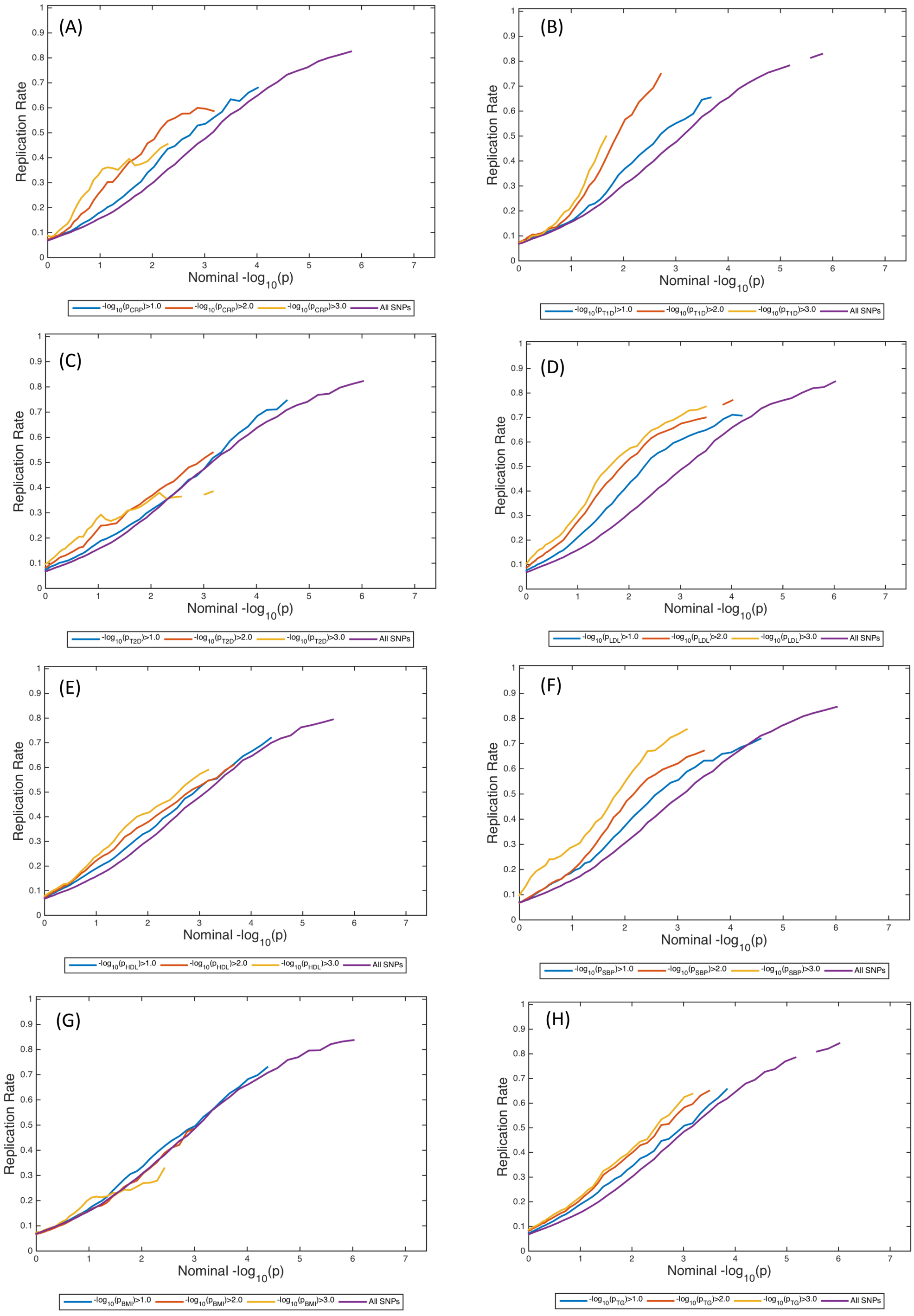
Top Canonical Pathways		
Name	**p-value**	
LXR/RXR Activation	2.22E-14	
Atherosclerosis Signaling	1.36E-11	
FXR/RXR Activation	3.66E-10	
Clathrin-mediated Endocytosis Signaling	2.18E-07	
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	1.57E-05	
Diseases and Disorders		
Name	**p-value**	**#candidate genes**
Cardiovascular Disease	4.24E-14 -5.02E-04	47
Organismal Injury and Abnormalities	9.65E-14 - 5.02E-04	57
Metabolic Disease	1.80E-12 - 3.71E-04	41
Neurological Disease	1.28E-09 - 1.54E-04	29
Psychological Disorders	1.28E-09 - 1.54E-04	26
Molecular and Cellular Functions		
Name	**p-value**	**#candidate genes**
Lipid Metabolism	5.06E-14 - 3.71E-04	40
Molecular Transport	5.06E-14 - 4.12E-04	50
Small Molecule Biochemistry	5.06E-14 - 3.71E-04	51
Vitamin and Mineral Metabolism	1.30E-13 - 3.71E-04	17
Protein Synthesis	1.41E-13 - 4.45E-05	14

*P-values are from a right-tailed Fisher exact test and represent significance of overrepresentation of candidate genes within respective gene groups. P-value ranges indicate values for various disease sub-classifications (not shown).

Online Figure I. Conditional Q-Q plots for BMI, HDL, SBP and TG.



Online Figure II. Stratified replication rates plots



Online Figure III. Conjunctional Manhattan plot