SUPPLEMENTAL MATERIAL

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Supplementary Data

ADAMTS7 and *CHRNB4-A3-A5* gene expression in vascular cells:

Cells were cultured to confluence in media under conditions recommended by the suppliers (Lonza and ATCC). Total RNA from cultured cells was extracted using Trizol (Invitrogen P/N 15596-018). DNAse digestion was performed with the Turbo DNAfree kit from Ambion (P/N AM1907). cDNA was generated according to the manufacturer's protocol with the SuperScript® III First-Strand Synthesis System (Invitrogen 18080-051). Real-time quantitative PCR (q-PCR) measurements were performed on an Applied Biosystems 7900HT Fast Real-Time PCR System using the TaqMan® Gene Expression Master Mix (P/N 4369016) and the following TaqMan probes: ACTB (Hs01060665_g1), GAPDH (Hs02758991_g1), TBP (Hs00427620_m1), ADAMTS7 (Hs00276223_m1), CHRNB4 (Hs00609520_m1), CHRNA3 (Hs01088199_m1), CHRNA5 (Hs00181248_m1). The standard cycling protocol was 95°C 10min, 40x (95°C 15s, 60°C 1min). Delta Cts were calculated as follows: $(Ct_{ACTB} + Ct_{GAPDH} + Ct_{TBP})/3 – Ct_{TARGET\ GENE}$). Fold changes are derived from delta delta Cts based on formula $FC = 2^{-dCt}$. Graphs were generated using GraphPad Prism 6.04.

ADAMTS7 and *CHRNB4-A3-A5 gene* expression in response to cigarette smoke extract (CSE):

RNA preparation and q-PCR were conducted as described above except RNA was extracted using RNeasy Mini Kit from Qiagen (Valencia, CA), reverse transcription was done using High-Capacity cDNA Reverse Transcription Kit from Life Technologies (Grand Island, NY), and cDNA samples were quantified for expression of *ADAMTS7* and *CHRNB4-A3-A5* genes by Taqman and normalized to *GAPDH*. Graphs were generated using GraphPad Prism 6.04. Results were presented as means ± SEM, and data were analyzed using Student's t-Test.

Regulatory features of the chr. 15q25.1 region: UCSC browser images were integrated using data from the ENCODE project (http://genome.ucsc.edu/cgibin/hgTracks?db=hg19&hubUrl=http://ftp.ebi.ac.uk/pub/databases/ensembl/encode/integration_data_jan2011/hub.txt, PMID 22955616) and the NIH Roadmap Epigenomics Project (http://genome.ucsc.edu/cgibin/hgTracks?db=hg19&hubUrl=http://vizhub.wustl.edu/VizHub/RoadmapRelease4.txt, PMID 25693563).

Supplementary Figure 1. Flow chart of study strategy. The current study had five inter-related components. First, as part of the quality control, we investigated the association of smoking status with CHD risk within each study. Second, for all the SNPs (± 50 KB) at the 45 established CHD loci, effect estimates from each study in association with CHD risk were obtained and pooled to identify the strongest variant ("lead variant") at all the established CHD loci. Third, we conducted gene-smoking interaction analyses for 45 CHD variants with the most significant association with the CHD risk in our study population as well as for 5 variants previously reported in association with smoking behavior. Fourth, for loci demonstrating differential CHD associations by smoking status, we mapped the interaction region, examined linkage disequilibrium (LD) across the region and performed conditional analyses to identify independent genetic signals. Finally, for loci exhibiting interaction, we assessed their eQTL patterns of local genes in available datasets and examined expression of these genes in in multiple cell types that play prominent roles in smoking-CHD pathobiology.

Supplementary Table 1. Description of the participating studies with information available on "ever-smoking" status, CHD risk and genotypes at the 50 candidate loci. Information on "ever-smoking" was available in 29 studies, yielding a total sample size of 60,919 CHD cases and 80,243 controls. All studies recruited participants of European ancestry, except in PROMIS (South Asian), LOLIPOP (South Asian) and FGENTCARD (Lebanese).

Supplementary Figure 2. Association of "ever-smoking" status with CHD in participating studies. As expected, in all the participating studies, association of "ever-smoking" status with CHD risk was directionally consistent with an increased risk of CHD.

Supplementary Figure 3. Comparison of the lead variants with the top previously reported CHD variants at the candidate loci. Effect estimates for SNP association with CHD for (i) the most significant SNP that we identified at established CHD loci in the current study population (larger than any previously published) as well as for (ii) SNPs previously reported at these established CHD loci in prior GWA studies. Of the 45 established CHD loci, we identified 32 for which we found a more significant SNP in association with CHD risk in our dataset than the previously reported variant.

Supplementary Figure 4. Association of reported variants with smoking behavior in the Tobacco Genetics Consortium (n=140,000). Data on rs302543 was not available in sufficient studies; hence was not analyzed in the current gene-CHD smoking interaction analyses.

Supplementary Table 2. Association of top variants at established CHD loci in our study population. Effect estimates for SNP association with CHD for the most significant SNP that we identified at established CHD loci in the current study population (larger than any previously published) as well as for SNPs previously reported at these established CHD loci in prior GWA studies. Of the 45 established CHD loci, we identified 32 for which we found a more significant SNP in association with CHD risk in our dataset than the previously reported variant.

Supplementary Table 3. Stratified (Never-smokers" and "Ever-Smokers") and Gene-smoking interaction analyses in CHD for the CHD and smoking behavior loci. Of the 50 candidate variants, we identified effect-modification by "ever-smoking" status on CHD for the lead variants at two distinct loci, rs7178051, at the *ADAMTS7* CHD locus, and rs1051730, at the *CHRNB4-A3-A5* genes smoking behavior locus). Although associated with different traits and located in distinct LD blocks, these two variants reside only ~224 KBs apart on chr.15q25.1 and indeed are in weak linkage disequilibrium (LD) (r2 = 0.22).

Supplementary Figure 5a. Association by smoking status of the *APOE* εpsiolon genotypes with CHD in PROMIS. The OR for CHD among ε4 carriers in "never-smokers" was 1.10 which was similar to the CHD OR of 1.11 observed in "ever-smokers".

Supplementary Figure 5b. Forest plot displaying interaction beta across the participating studies.

Supplementary Figure 5c. Forest plot displaying interaction beta across the participating studies by ethnicity

Supplementary Figure 6. (a) Unadjusted associations of chromosome 15q21.1 variants with CHD (red triangles) and smoking behavior (cigarettes per day, CPD; grey circles); (b) analyses adjusted for rs7178051, rs11638490, rs1051730 and rs684513 in association with CHD and CPD; (c) analyses of rs7178051 and rs1051730 with MI risk in PROMIS (9,025 MI cases and 8,506 controls)

Supplementary Figure 7. Unadjusted effects of 15q21.1 lead variants on CHD stratified by smoking status in the CARDIoGRAMplusC4D consortium and analyses of variants with smoking behavior in the Tobacco and Genetics Consortium (TGC) in 140,000 participants.

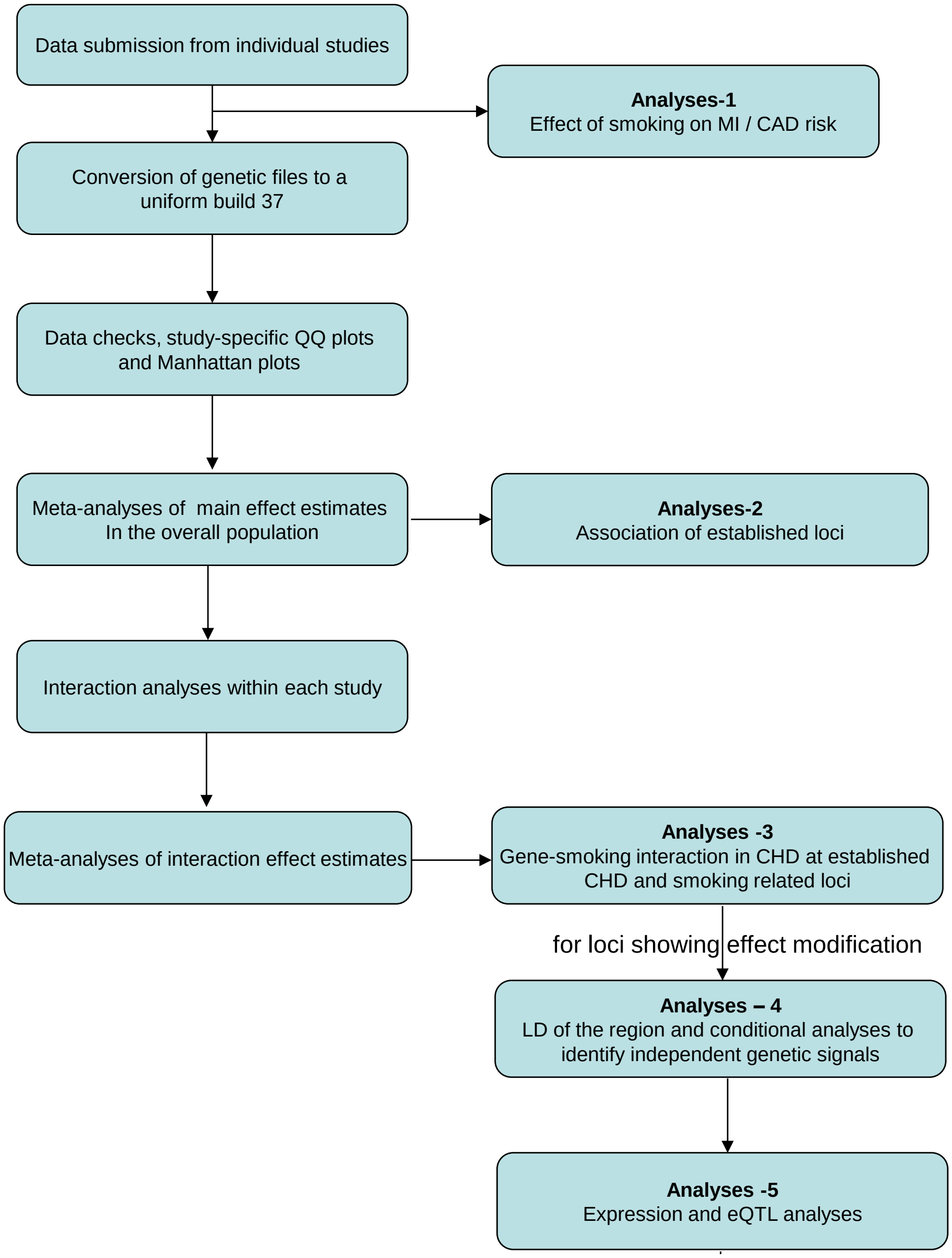
Supplementary Table 4. Association of rs7178051 with MI risk in PROMIS in participants by smoking status who do not carry the minor allele for rs1051730 and rs684513 variants

Supplementary Table 5. Association of rs7178051 (top CHD SNP) and rs1051730 (top CPD SNP) mutually adjusted for each other in 9,025 MI cases and 8,506 controls in PROMIS

Supplementary Figure 8. Genome browser view of regulatory features at the CHD and smoking behavior loci on Chr15q21.1. ChIP-seq experiments were performed on confluent HCASMC for TCF21, Jun, JunD, CEBP and H3K4me1, H3K27me3, H3K27ac. DNAaseI hypersensitivity data for human AoSMC were acquired from the ENCODE project. Human aortic tissue H3K4me1, H3K9me3, H3K27me3, and H3K36me3 ChIP-seq data were acquired from the NIH Roadmap Epigenomics Project. *ADAMTS7* was associated with RNAseq reads and an active transcription mark, H3K36me3, whereas the *CHRNB4-A3-A5* genes had low/absent RNAseq reads and were positive for repressive marks H3K27me3 and H3K9me3 HCASMC = human coronary artery smooth muscle cells; AoSMC = human aortic smooth muscle cells. TF = transcription factor.

Supplementary Figure 9. *ADAMTS7* and *CHRNB4-A3-A5* mRNA levels were measured in HCASMC, HCAEC, HAoSMC, HAoEC, HAoAF, and the THP-1 cell line. Cells were cultured to confluence, total RNA was extracted and cDNA generated. q-PCR was performed for *ACTB, GAPDH, TBP, ADAMTS7, CHRNB4, CHRNA3, CHRNA5*. Delta Cts were calculated as follows: $(Ct_{ACTB} + Ct_{GAPDH} + Ct_{TBP})/3 – Ct_{TARGET\ GENE})$. Fold changes are derived from delta delta Cts based on formula FC = 2^{-dCt}. Graphs were generated using GraphPad Prism 6.04.

Supplementary Figure 1. Flow chart of study strategy

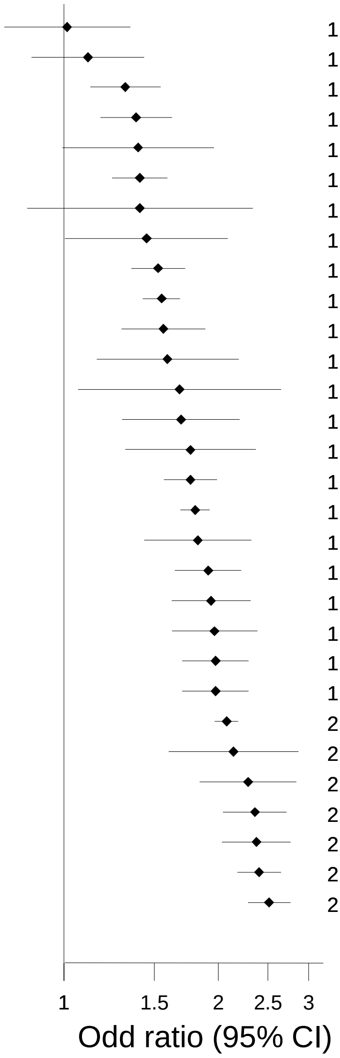


Supplementary Table 1. Description of the participating studies with information available on “ever-smoking” status, coronary heart disease risk and genotypes at the 50 candidate loci

Study Name	**Location**	**Ethnicity**	**Age (years) Mean (SD)**	**Platform**	**Number of CHD cases**	**Number of controls**	**Ever smokers in CHD cases (%)**	**Ever smokers in controls (%)**
Medstar	USA	European	48.9(6.4)/59.7(8.9)	GWAS	873	445	52.5	49.8
STR	USA	European	78.9(9.7)/73.1(11.0)	Metabochip	359	1367	33.4	31.6
ROTTERDAM	Netherlands	European	41.6(6.0)/51.0(11.8)	GWAS	1099	4963	23.2	24.4
EPIC-Norfolk	UK	European	71.8(8.18)/60.3(9.3)	Metabochip	1822	1335	67.0	54.3
PennCath	USA	European	52.7 (7.6)/61.7(9.6)	GWAS	415	156	79.8	54.5
OHGS	Canada	European	49.0(7.3)/74.5(5.5)	GWAS	3686	3269	67.5	50.3
CARDIOGENICS	Europe	European	57.0(8.8)/53.5(7.0)	GWAS	354	349	74.6	40.4
DILGOM	FINLAND	European	56.6(9.5)/51.7(13.6)	Metabochip	143	3773	59.4	42.8
MIGEN	USA & Europe	European	42.4 (6.6)/43.0(7.8)	GWAS	5221	4188	46.79	36.87
CADOMICS	Germany	European	59.3(10.8)/59.3(10.8)	GWAS	2080	2958	63.75	52.84
AGES	ICELAND	European	76.4 (5.4)/79.1(5.5)	GWAS	873	445	52.58	49.89
GERMIFSII	Germany	European	55.0(6.8)/51.1(12.9)	GWAS	450	466	61.1	13.09
PIVUS	Sweden	European	65.0(7.2)/70.2(0.2)	Metabochip	94	858	65.96	50
Cleveland Clinic	USA	European	61.7(11.1)/73.0(5.7)	GWAS	2345	335	73.22	54.33
FRAMINGHAM	USA	European	64.5(12.8)/75.2(12.2)	GWAS	259	4202	72.9	60.6
LOLIPOP	UK	South Asian	59.3(9.7)/52.4(10.2)	GWAS	2289	3238	33.9	22.5
EPIC-CVD	Europe	European	71.8(8.18)/60.3(9.3)	Metabochip	8964	11613	66.24	50.59
FGENTCARD	Lebanon	Middle-eastern	61.0(11.1)/55.6(11.6)	GWAS	1556	432	67.1	54.8
SCARF-SHEEP	Sweden	European	57.6(7.3)/50.5(7.0)	Metabochip	1520	1883	73.7	59.2
MORGAM	Europe	European	64.5(7.3)/60.9(7.8)	Metabochip	1955	1955	79.9	71.1
DUKE	USA	European	57(9.7)/63(8.7)	GWAS	1172	824	54.69	41.1
Diabetes Heart Study	USA	European	59.3(10)/61.5 (9.35)	Metabochip	686	450	65.3	49.3
COROGENE	FINLAND	European	66.0(11.8)/56.7(11.3)	GWAS	2197	1893	62.8	50.1
GoDARTS	Scotland	European	61.5(10.5)/61.8(9.5)	Metabochip	723	1948	74.8	61.1
THISEAS	GREECE	European	57.6(7.3)/50.5(7.0)	Metabochip	448	752	79.02	57.3
PROMIS	Pakistan	South Asian	54.2(10.6)/53.5(10.0)	GWAS	6990	6626	57.7	36.02
PROCARDIS	Europe	European	53.6(8.1)/60.9(13.1)	GWAS	5719	1674	72.2	51.3
WTCCC	United Kingdom	European	53.5(9.6)/44(0)	GWAS	1935	1446	76.07	56.02
deCODE	Iceland	European	74.8(11.8)/53.7(21.5)	GWAS	4037	10253	83.87	67.02
Family Heart Study	USA	European	64.5+12.8/75.2(12.2)	GWAS	439	3430	64.01	41.11

Supplementary Figure 2. Association of “ever-smoking” status with coronary heart disease in participating studies

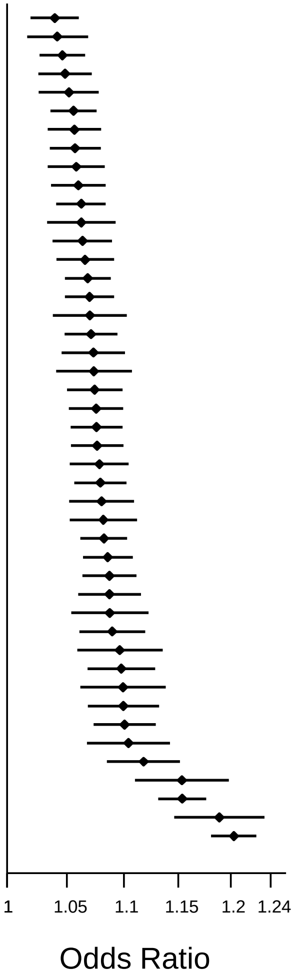
Study	**Cases (% smokers)**	**Controls (%smokers)**	**OR (95% CI)**
Medstar	873(52.58%)	445(49.89%)	1.01 (0.76, 1.35)
STR	359(33.43%)	1367(31.68%)	1.11 (0.86, 1.43)
ROTTERDAM	1099(23.2%)	4963(24.38%)	1.32 (1.12, 1.54)
EPIC-NORFOLK	1822(67.01%)	1335(54.31%)	1.38 (1.18, 1.62)
PennCath	415(79.76%)	156(54.49%)	1.40 (0.99, 1.96)
OHGS	3686(67.53%)	3269(50.32%)	1.41 (1.24, 1.59)
CARDIOGENICS	354(74.58%)	349(40.4%)	1.41 (0.85, 2.33)
DILGOM	143(59.44%)	3773(42.8%)	1.45 (1.01, 2.09)
MIGEN	5221(46.79%)	4188(36.87%)	1.53 (1.35, 1.72)
Cadomics	2080(63.75%)	2958(52.84%)	1.55 (1.43, 1.69)
AGES	873(52.58%)	445(49.89%)	1.56 (1.29, 1.88)
GERMIFSII	450(61.11%)	466(13.09%)	1.59 (1.16, 2.19)
PIVUS	94(65.96%)	858(50%)	1.68 (1.06, 2.65)
Clevland Clinic Study	2345(73.22%)	335(54.33%)	1.69 (1.30, 2.20)
FRAMINGHAM	259(72.97%)	4202(60.66%)	1.77 (1.32, 2.37)
LOLIPOP	2289(33.99%)	3238(22.58%)	1.77 (1.57, 1.99)
EPIC-CVD	8964(66.24%)	11613(50.59%)	1.80 (1.69, 1.93)
FGENTCARD	1556(67.16%)	432(54.86%)	1.82 (1.43, 2.32)
SCARF-SHEEP	1520(73.75%)	1883(59.16%)	1.91 (1.65, 2.22)
MORGAM	1955(79.9%)	1955(71.1%)	1.94 (1.62, 2.31)
DUKE	1172(54.69%)	824(41.14%)	1.97 (1.62, 2.39)
Diabetes Heart Study	686(65.31%)	450(49.33%)	1.97 (1.70, 2.29)
COROGENE	2197(62.81%)	1893(50.13%)	1.97 (1.70, 2.29)
GoDARTS	723(74.83%)	1948(61.09%)	2.07 (1.97, 2.19)
THISEAS	448(79.02%)	752(57.31%)	2.14 (1.60, 2.86)
PROMIS	6990(57.7%)	6626(36.02%)	2.28 (1.84, 2.84)
PROCARDIS	5719(72.2%)	1674(51.31%)	2.36 (2.04, 2.72)
WTCCC	1935(76.07%)	1446(56.02%)	2.37 (2.03, 2.77)
deCODE	4037(83.87%)	10253(67.02%)	2.40 (2.18, 2.65)
FAMILY HEART STUDY	439(64.01%)	3430(41.11%)	2.51 (2.28, 2.76)



Supplementary Figure 3. Comparison of the lead variants with the top previously reported coronary heart disease variants at the candidate loci

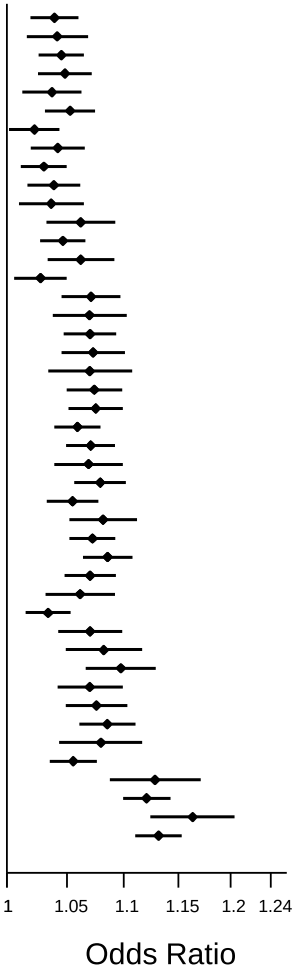
Lead CHD variants

Chr.	Closest gene	Variant	Effect allele	P-value
13q12.3	FLT1	rs9319428	A	1.09e-04
7q22.3	COG5	rs12539895	C	1.25e-03
2p11.2	GGCX*	rs6738645	G	2.335e-06
6p21.2	KCNK5	rs10947789	T	2.023e-05
6p21.31	ANKS1A*	rs12203818	G	5.688e-05
10p11.23	KIAA1462*	rs17294968	G	2.965e-08
17p13.3	SMG6*	rs2760751	G	7.508e-07
2p21	ABCG8*	rs4245791	C	1.959e-07
17q21.32	UBE2Z*	rs16941382	C	2.053e-06
17p11.2	RAI1*	rs8080061	C	3.313e-07
6q23.2	TCF21*	rs10457618	C	7.151e-09
5q31.1	SLC22A4	rs273909	G	2.324e-05
1q21.3	IL6R*	rs4845579	C	8.001e-07
2p24.1	APOB*	rs488507	T	1.255e-07
6q26	LPA*	rs7770628	C	6.375e-12
13q34	COL4A2*	rs750597	T	7.295e-11
7p21.1	HDAC9	rs2023938	C	1.116e-05
19p13.2	LDLR*	rs3786722	C	5.532e-10
4q31.22	EDNRA	rs1878406	T	1.125e-07
10q24.32	CYP17A1*	rs11191454	A	7.642e-06
9q34.2	ABO	rs579459	C	6.322e-10
7q32.2	ZC3HC1	rs11556924	C	1.267e-10
8q24.13	TRIB1*	rs2954021	A	1.691e-11
12q24.12	SH2B3*	rs653178	C	1.435e-11
4q32.1	GUCY1B3*	rs10517620	G	1.228e-09
10q23.31	LIPA	rs2246833	T	1.816e-12
14q32.2	HHIPL1*	rs2146238	G	1.153e-08
1p32.3	PCSK9	rs11206510	T	2.407e-08
15q25.1	ADAMTS7*	rs7178051	C	5.714e-16
11q22.3	PDGFD	rs974819	T	1.353e-15
15q26.1	FURIN*	rs6227	T	1.305e-13
1q41	MIA3*	rs2133189	T	2.001e-10
2q22.3	ZEB2*	rs16824790	T	1.859e-07
3q22.3	MRAS*	rs2345270	A	2.611e-10
19q13.32	APOE*	rs6857	T	2.46e-07
21q22.11	KCNE2*	rs8131284	C	4.01e-11
8p21.3	LPL*	rs343	C	1.041e-07
10q11.21	CXCL12*	rs10900001	C	1.811e-10
1p13.3	SORT1*	rs629301	T	1.613e-13
11q23.3	APOA5*	rs10790162	A	1.03e-08
6q25.3	SLC22A3*	rs3125055	A	2.651e-13
1p32.2	PPAP2B*	rs4634932	T	2.363e-13
6p24.1	PHACTR1*	rs9349379	G	3.217e-46
2q33.2	WDR12*	rs7560547	G	3.94e-20
9p21.3	CDKN2BAS1*	rs1537371	A	5.551e-86



Reported CHD variants

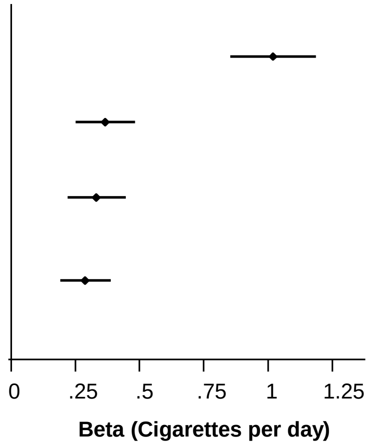
Variant	Effect allele	Pvalue
rs9319428	A	1.09e-04
rs12539895	C	1.25e-03
rs1561198	T	2.359e-06
rs10947789	T	2.023e-05
rs12205331	C	2.939e-03
rs2505083	C	7.518e-07
rs2281727	G	3.39e-02
rs6544713	T	2.563e-3
rs15563	G	1.511e-3
rs12936587	G	5.198e-4
rs12190287	C	7.257e-4
rs273909	G	2.324e-05
rs4845625	T	1.340e-06
rs515135	C	1.331e-04
rs4252120	T	1.195e-02
rs4773144	G	2.642e-08
rs2023938	C	1.116e-05
rs1122608	G	5.539e-10
rs1878406	T	1.125e-07
rs12413409	G	9.905e-04
rs579459	C	6.322e-10
rs11556924	C	1.267e-10
rs2954029	A	1.927e-09
rs3184504	T	3.119e-11
rs7692387	G	2.929e-06
rs2246833	T	1.816e-12
rs2895811	C	5.108e-07
rs11206510	T	2.407e-08
rs7173743	T	4.725e-13
rs974819	T	1.353e-15
rs17514846	A	2.514e-10
rs17464857	T	3.388e-04
rs2252641	C	3.468e-04
rs9818870	T	3.448e-07
rs2075650	G	6.613e-07
rs9982601	T	1.452e-10
rs264	G	7.086e-07
rs501120	T	1.331e-08
rs602633	G	3.374e-12
rs9326246	C	1.009e-04
rs2048327	C	3.233e-08
rs17114036	A	1.737e-10
rs9369640	A	2.658e-31
rs6725887	C	5.200e-18
rs1333049	C	8.118e-37



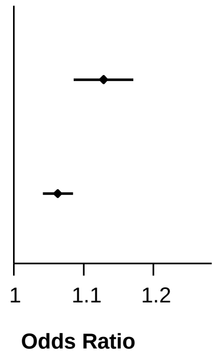
*lead variant observed in our study population differed with the reported variant

Supplementary Figure 4. Association of reported variants with smoking behavior in the Tobacco Genetics Consortium

CHR	SNP	Gene	EA	N	Beta (95% CI)	*P-value*
15q25.1	rs1051730	CHRNA3	A	73853	1.02 (0.85, 1.19)	2.75x10-73
10q23.32	rs1329650	LOC100188947	G	73853	0.37 (0.25, 0.48)	5.67x10-10
19q13.2	rs3733829	CYP2A6	G	73853	0.33 (0.22, 0.45)	1.04x10-8
8p11.21	rs6474412	CHRNB3	T	84956	0.29 (0.19, 0.39)	1.04x10-8



CHR	SNP	Gene	EA	N	OR (95% CI)	*P-value*
Ever-versus never smokers						
9q34.2	rs3025343	DBH	A	143023	1.13 (1.09, 1.17)	3.56x10-8
Former never current smokers						
11p14.1	rs6265	BDNF	C	64924	1.06 (1.04, 1.08)	1.84x10-8



Information on rs3025343 was not available in all participants in the CARDIoGRAMplusC4D consortium; hence excluded from analyses. EA. Effect allele

Supplementary Table 2. Association of top variants at established coronary heart disease loci in our study population

		Lead variant observed in our study population at established CHD Loci						Association of reported variant at established CHD loci in our study population					
Chr	**Locus**	**SNP**	**Position (Mb)**	**Effect allele**	**Beta**	**SE**	**P-value**	**SNP**	**Position (Mb)**	**Effect allele**	**Beta**	**SE**	**P-value**
13q12.3	FLT1	rs9319428	28973621	A	0.04	0.01	1.09E-04	rs9319428	28973621	A	0.04	0.01	1.09E-04
7q22.3	COG5	rs12539895	107091849	C	0.04	0.01	1.25E-03	rs12539895	107091849	C	0.04	0.01	1.25E-03
2p11.2	GGCX*	rs6738645	85783128	G	0.05	0.01	2.34E-06	rs1561198	85809989	T	0.04	0.01	2.36E-06
6p21.2	KCNK5	rs10947789	39174922	T	0.05	0.01	2.02E-05	rs10947789	39174922	T	0.05	0.01	2.02E-05
6p21.31	ANKS1A*	rs12203818	35251317	G	0.05	0.01	5.69E-05	rs12205331	34898455	C	0.04	0.01	2.94E-03
10p11.23	KIAA1462*	rs17294968	30300420	G	0.05	0.01	2.97E-08	rs2505083	30335122	C	0.05	0.01	7.52E-07
17p13.3	SMG6*	rs2760751	2028106	G	0.05	0.01	7.51E-07	rs2281727	2117945	G	0.02	0.01	3.39E-02
2p21	ABCG8*	rs4245791	44074431	C	0.06	0.01	1.96E-07	rs6544713	44073881	T	0.04	0.01	2.56E-04
17q21.32	UBE2Z*	rs16941382	45043508	C	0.06	0.01	2.05E-06	rs15563	47005193	G	0.03	0.01	1.51E-03
17p11.2	RAI1*	rs8080061	17776389	C	0.06	0.01	3.31E-07	rs12936587	17543722	G	0.04	0.01	5.20E-04
6q23.2	TCF21*	rs10457618	134188626	C	0.06	0.01	7.15E-09	rs12190287	134214525	C	0.04	0.01	7.26E-03
5q31.1	SLC22A4	rs273909	131667353	G	0.06	0.01	2.32E-05	rs273909	131667353	G	0.06	0.01	2.32E-05
1q21.3	IL6R*	rs4845579	151770138	C	0.06	0.01	8.00E-07	rs4845625	154422067	T	0.05	0.01	1.34E-06
2p24.1	APOB*	rs488507	21393689	T	0.06	0.01	1.26E-07	rs515135	21286057	C	0.06	0.01	1.33E-05
6q26	LPA*	rs7770628	161018174	C	0.07	0.01	6.38E-12	rs4252120	161143608	T	0.03	0.01	1.20E-02
13q34	COL4A2*	rs750597	111029256	T	0.07	0.01	7.30E-11	rs4773144	110960712	G	0.07	0.01	2.64E-08
7p21.1	HDAC9	rs2023938	19036775	C	0.07	0.02	1.12E-05	rs2023938	19036775	C	0.07	0.02	1.12E-05
19p13.2	LDLR*	rs3786722	11161537	C	0.07	0.01	5.53E-10	rs1122608	11163601	G	0.07	0.01	5.54E-10
4q31.22	EDNRA	rs1878406	148393664	T	0.07	0.01	1.13E-07	rs1878406	148393664	T	0.07	0.01	1.13E-07
10q24.32	CYP17A1*	rs11191454	104660004	A	0.07	0.02	7.64E-06	rs12413409	104719096	G	0.07	0.02	9.91E-05
9q34.2	ABO	rs579459	136154168	C	0.07	0.01	6.32E-10	rs579459	136154168	C	0.07	0.01	6.32E-10
7q32.2	ZC3HC1	rs11556924	129663496	C	0.07	0.01	1.27E-10	rs11556924	129663496	C	0.07	0.01	1.27E-10
8q24.13	TRIB1*	rs2954021	126482077	A	0.07	0.01	1.69E-11	rs2954029	126490972	A	0.06	0.01	1.93E-09
12q24.12	SH2B3*	rs653178	112007756	C	0.07	0.01	1.44E-11	rs3184504	111884608	T	0.07	0.01	3.12E-11
4q32.1	GUCY1B3*	rs10517620	156676558	G	0.08	0.01	1.23E-09	rs7692387	156635309	G	0.07	0.01	2.93E-06
10q23.31	LIPA	rs2246833	91005854	T	0.08	0.01	1.82E-12	rs2246833	91005854	T	0.08	0.01	1.82E-12
14q32.2	HHIPL1	rs2895811	100133942	C	0.05	0.01	5.11E-07	rs2895811	100133942	C	0.05	0.01	5.11E-07
1p32.3	PCSK9	rs11206510	55496039	T	0.08	0.01	2.41E-08	rs11206510	55496039	T	0.08	0.01	2.41E-08
15q25.1	ADAMTS7*	rs7178051	79118296	C	0.08	0.01	5.71E-16	rs7173743	79141784	T	0.07	0.01	4.73E-13
11q22.3	PDGFD	rs974819	103660567	T	0.08	0.01	1.35E-15	rs974819	103660567	T	0.08	0.01	1.35E-15
15q26.1	FURIN*	rs6227	91425232	T	0.08	0.01	1.31E-13	rs17514846	91416550	A	0.07	0.01	2.51E-10
1q41	MIA3*	rs2133189	222814442	T	0.08	0.01	2.00E-10	rs17464857	222762709	T	0.06	0.01	3.39E-05
2q22.3	ZEB2*	rs16824790	146106518	T	0.08	0.02	1.86E-07	rs2252641	145801461	C	0.03	0.01	3.47E-04
3q22.3	MRAS*	rs2345270	137325390	A	0.09	0.01	2.61E-10	rs9818870	138122122	T	0.07	0.01	3.45E-07
19q13.32	APOE*	rs6857	45392254	T	0.09	0.02	2.46E-07	rs2075650	45395619	G	0.08	0.02	6.61E-07
21q22.11	KCNE2*	rs8131284	35607496	C	0.09	0.01	4.01E-11	rs9982601	35599128	T	0.09	0.01	1.45E-10
8p21.3	LPL*	rs343	19810787	C	0.09	0.02	1.04E-07	rs264	19813180	G	0.07	0.01	7.09E-07
10q11.21	CXCL12*	rs10900001	44695585	C	0.09	0.01	1.81E-10	rs501120	44753867	T	0.07	0.01	1.33E-08
1p13.3	SORT1*	rs629301	109818306	T	0.10	0.01	1.61E-13	rs602633	109821511	G	0.08	0.01	3.37E-12
11q23.3	APOA5*	rs10790162	116639104	A	0.10	0.02	1.03E-08	rs9326246	116611733	C	0.08	0.02	1.01E-05
6q25.3	SLC22A3*	rs3125055	160736787	A	0.11	0.02	2.65E-13	rs2048327	160863532	C	0.05	0.01	3.23E-08
1p32.2	PPAP2B*	rs4634932	56996191	T	0.14	0.02	2.36E-13	rs17114036	56962821	A	0.12	0.02	1.74E-10
6p24.1	PHACTR1*	rs9349379	12903957	G	0.14	0.01	3.22E-46	rs9369640	12901441	A	0.11	0.01	2.66E-31
2q33.2	WDR12*	rs7560547	203757916	G	0.17	0.02	3.94E-20	rs6725887	203745885	C	0.15	0.02	5.20E-18
9p21.3	CDKN2BAS1*	rs1537371	22099568	A	0.18	0.01	5.55E-86	rs1333049	22125503	C	0.12	0.01	8.12E-37

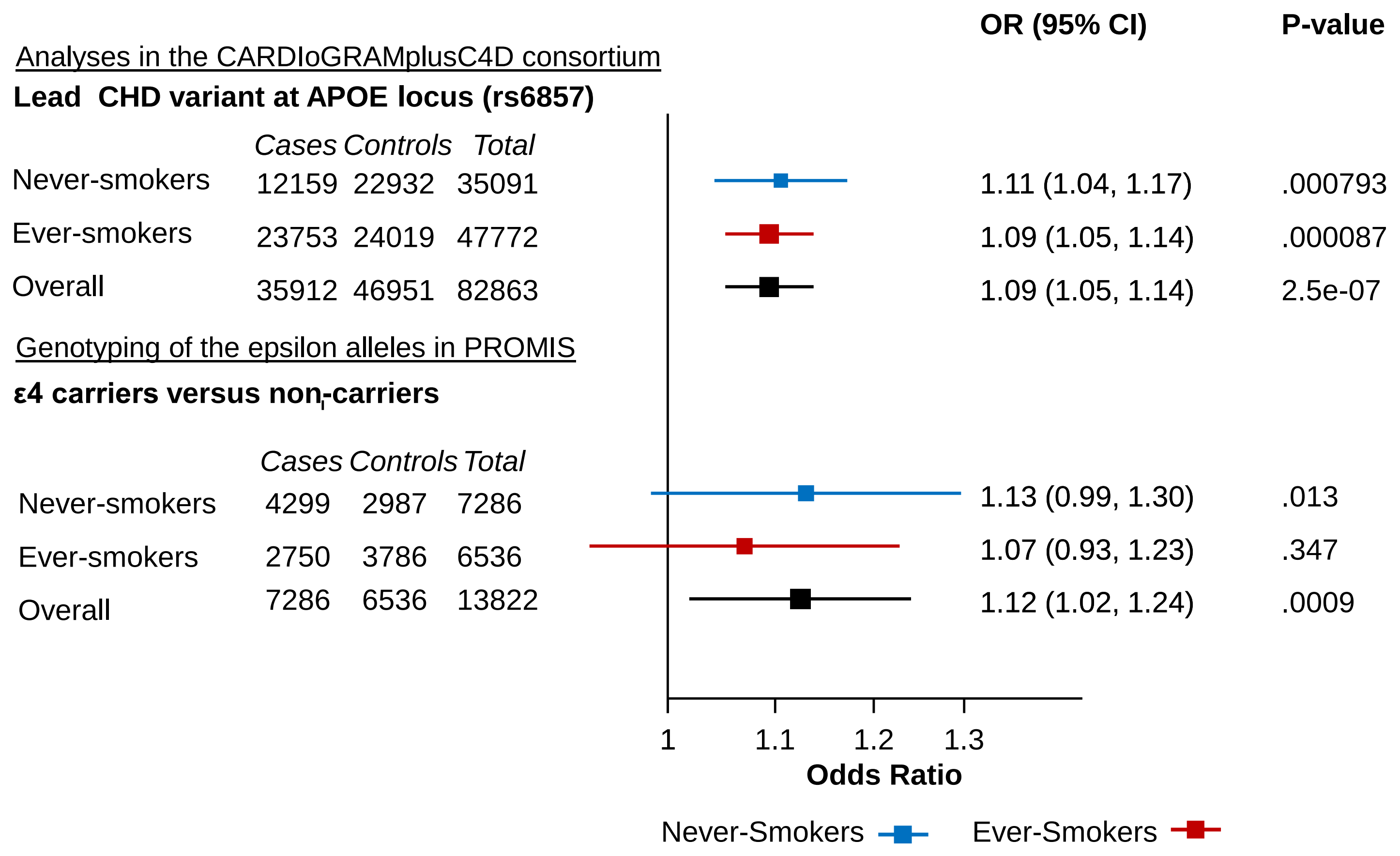
***lead variant observed in our study population differed with the reported variant**

Supplementary Table 3. Stratified (Never-smokers” and “Ever-Smokers”) and Gene-smoking interaction analyses in coronary heart disease for the coronary heart disease and smoking behavior loci

				Never-Smokers						Ever-Smokers						
Chr	**Locus**	**variant**	**Allele (E/R)***	**Cases**	**Controls**	**Total**	**Beta**	**SE**	**P-value**	**Cases**	**Controls**	**Total**	**Beta**	**Se**	**P-value**	**INTERACTION P-value**
CHD RELATED LOCI																
15q25.1	**ADAMTS7**	**rs7178051**	**T/C**	**21232**	**38713**	**59945**	**-0.13**	**0.02**	**1.30E-16**	**39585**	**40749**	**80334**	**-0.05**	**0.01**	**2.49E-04**	**8.57E-05**
14q32.2	HHIPL1	rs2895811	T/C	16542	29114	45656	-0.08	0.02	2.68E-06	31524	30816	62340	-0.04	0.01	8.16E-03	9.45E-03
1q41	MIA3	rs2133189	T/C	14475	23848	38323	0.12	0.02	6.31E-09	24428	22522	46950	0.06	0.02	7.19E-04	0.05057
6p21.2	KCNK5	rs10947789	T/C	21232	38713	59945	0.02	0.02	1.56E-01	39585	40749	80334	0.06	0.01	1.37E-05	0.0949
10q24.32	CYP17A1	rs11191454	A/G	18470	29062	47532	0.10	0.02	7.84E-05	38155	35437	73592	0.05	0.02	1.12E-02	0.1088
12q24.12	SH2B3	rs653178	T/C	18206	32975	51181	-0.10	0.02	3.44E-09	33647	34874	68521	-0.05	0.01	8.95E-05	0.1131
5q31.1	SLC22A4	rs273909	A/G	19247	33076	52323	-0.09	0.02	5.05E-05	38049	36478	74527	-0.04	0.02	3.18E-02	0.1144
11q22.3	PDGFD	rs974819	T/C	20559	38198	58757	0.11	0.02	5.73E-11	38923	40371	79294	0.07	0.01	7.70E-07	0.1426
9q34.2	ABO	rs579459	T/C	21232	38713	59945	-0.06	0.02	1.37E-03	39585	40749	80334	-0.08	0.02	7.52E-08	0.1598
13q12.3	FLT1	rs9319428	A/G	21232	38713	59945	0.06	0.02	3.13E-04	39585	40749	80334	0.03	0.01	4.07E-02	0.1619
2p11.2	GGCX	rs6738645	T/G	20377	37440	57817	-0.02	0.02	1.35E-01	38382	39181	77563	-0.06	0.01	1.07E-06	0.1687
2p21	ABCG8	rs4245791	T/C	18906	34620	53526	-0.07	0.02	1.35E-05	37169	38266	75435	-0.04	0.01	1.52E-03	0.2016
17p13.3	SMG6	rs2760751	A/G	18484	31315	49799	-0.07	0.02	8.19E-05	33722	32479	66201	-0.05	0.01	1.76E-03	0.2017
21q22.11	KCNE2	rs8131284	T/C	20827	32578	53405	-0.12	0.02	1.25E-07	39353	37234	76587	-0.08	0.02	2.36E-05	0.2254
15q26.1	FURIN	rs6227	T/C	17094	31503	48597	0.11	0.02	1.08E-09	30978	32908	63886	0.07	0.01	4.87E-06	0.2261
1p32.3	PCSK9	rs11206510	T/C	19080	30813	49893	0.07	0.02	1.91E-03	33026	28327	61353	0.09	0.02	2.76E-06	0.2742
6q23.2	TCF21	rs10457618	T/C	20553	37945	58498	-0.05	0.02	4.98E-03	38909	40166	79075	-0.07	0.01	2.07E-07	0.315
6q25.3	SLC22A3	rs3125055	A/T	19496	31336	50832	0.13	0.02	3.32E-08	37193	35724	72917	0.10	0.02	8.24E-07	0.3191
2q33.2	WDR12	rs7560547	A/G	11452	16774	28226	-0.15	0.03	5.62E-07	23827	22810	46637	-0.19	0.02	8.83E-15	0.3584
6q26	LPA	rs7770628	T/C	21050	37955	59005	-0.06	0.01	9.27E-05	39044	39559	78603	-0.07	0.01	1.30E-08	0.3634
13q34	COL4A2	rs750597	A/T	21232	38713	59945	-0.07	0.02	4.00E-06	39585	40749	80334	-0.06	0.01	3.46E-06	0.3881
7p21.1	HDAC9	rs2023938	T/C	20178	31202	51380	-0.05	0.02	6.02E-02	39137	36961	76098	-0.08	0.02	3.44E-05	0.3987
10q11.21	CXCL12	rs10900001	C/G	20029	30278	50307	0.09	0.02	1.04E-04	38286	35107	73393	0.10	0.02	3.91E-07	0.4158
1p13.3	SORT1	rs629301	T/G	17401	28346	45747	0.11	0.02	9.86E-08	32124	30718	62842	0.09	0.02	2.42E-07	0.419
4q31.22	EDNRA	rs1878406	T/C	20568	31970	52538	0.08	0.02	8.06E-05	39177	37144	76321	0.06	0.02	2.96E-04	0.4329
17p11.2	RAI1	rs8080061	T/C	16313	26850	43163	-0.04	0.02	1.63E-02	28987	28172	57159	-0.07	0.02	3.06E-06	0.4536
1p32.2	PPAP2B	rs4634932	T/C	14428	21600	36028	0.18	0.03	3.47E-09	29796	27171	56967	0.12	0.03	4.61E-06	0.4825
3q22.3	SOX14	rs2345270	A/G	13811	22661	36472	0.07	0.02	4.94E-04	24704	21225	45929	0.10	0.02	8.78E-08	0.4994
10q23.31	LIPA	rs2246833	T/C	17742	32340	50082	0.09	0.02	1.29E-07	32175	34064	66239	0.07	0.01	1.85E-06	0.5051
1q21.3	IL6R	rs4845579	T/C	20933	37873	58806	-0.06	0.02	9.71E-04	39323	39994	79317	-0.06	0.02	2.39E-04	0.5327
4q32.1	GUCY1B3	rs10517620	A/G	19324	32464	51788	-0.08	0.02	7.83E-06	34925	34047	68972	-0.07	0.02	3.04E-05	0.6146
6p21.31	ANKS1A	rs12203818	A/G	18318	34529	52847	-0.05	0.02	1.61E-02	36527	37975	74502	-0.05	0.02	1.25E-03	0.6371
7q32.2	ZC3HC1	rs11556924	T/C	15973	28497	44470	-0.08	0.02	3.03E-06	30026	30932	60958	-0.06	0.01	6.85E-06	0.6466
17q21.32	UBE2Z	rs16941382	T/C	21013	37746	58759	-0.06	0.02	8.19E-04	39402	40002	79404	-0.05	0.02	6.75E-04	0.7015
8p21.3	LPL	rs343	A/C	16096	25458	41554	-0.10	0.03	3.00E-04	35930	33164	69094	-0.09	0.02	8.97E-05	0.7019
11q23.3	APOA5	rs10790162	A/G	18776	28882	47658	0.11	0.03	2.31E-05	38184	34895	73079	0.09	0.02	9.36E-05	0.7106
8q24.13	TRIB1	rs2954021	A/G	16449	27132	43581	0.08	0.02	3.67E-06	29253	28441	57694	0.07	0.01	9.83E-07	0.7373
19p13.2	LDLR	rs3786722	A/C	21232	38713	59945	-0.07	0.02	7.01E-05	39585	40749	80334	-0.07	0.01	1.92E-06	0.7522
2p24.1	APOB	rs488507	T/G	20559	37688	58247	0.06	0.02	1.06E-03	38310	39748	78058	0.07	0.02	3.32E-05	0.7576
19q13.32	APOE	rs6857	T/C	12159	22932	35091	0.10	0.03	7.93E-04	23753	24019	47772	0.09	0.02	8.68E-05	0.7612
10p11.23	KIAA1462	rs17294968	A/G	21232	38713	59945	-0.05	0.02	4.26E-04	39585	40749	80334	-0.05	0.01	1.87E-05	0.8262
7q22.3	COG5	rs12539895	A/C	18206	32975	51181	-0.05	0.02	2.02E-02	33647	34874	68521	-0.04	0.02	2.34E-02	0.8558
6p24.1	PHACTR1	rs9349379	A/G	19819	33838	53657	-0.15	0.02	9.37E-21	37887	37825	75712	-0.14	0.01	3.62E-27	0.9004
9p21.3	CDKN2BAS1	rs1537371	A/C	21232	38713	59945	0.19	0.01	2.45E-37	39585	40749	80334	0.18	0.01	1.73E-50	0.9201
2q22.3	ZEB2	rs16824790	T/C	15330	27420	42750	0.09	0.03	1.13E-03	30004	33753	63757	0.08	0.02	4.67E-05	0.9841
SMOKING RELATED LOCI																
15q25.1	**CHRNA3**	**rs1051730**	**A/G**	**20559**	**38198**	**58758**	**-0.04**	**0.02**	**1.65E-02**	**38923**	**40371**	**79294**	**0.03**	**0.01**	**1.53E-02**	**2.37E-04**
10q23.32	LOC100188947	rs1329650	T/G	19339	32588	68973	-0.01	0.02	0.49	34925	34047	68973	-0.022	0.0141	0.1032	**0.5291**
19q13.2	CYP2A6	rs3733829	A/G	18875	31953	50829	0.01	0.02	0.465	33453	33237	66691	-0.005	0.01	0.7142	0.4924
11p14.1	BDNF-AS	rs6265	T/C	21232	38713	59946	-0.06	0.02	1.72E-03	39585	40749	80334	-0.03	0.02	3.79E-02	0.4163
8p11.21	CHRNB3	rs6474412	T/C	19269	30935	50205	-0.01	0.02	6.15E-01	34736	31498	66234	-0.01	0.02	6.61E-01	0.7113

*(E/R) – (effect allele / reference allele)

Supplementary Figure 5a. Association by smoking status of the *APOE* locus with coronary heart disease in the CARDIoGRAMplusC4D consortium and PROMIS



Analyses in the CARDIoGRAMplusC4D consortium

Lead CHD variant at APOE locus (rs6857)

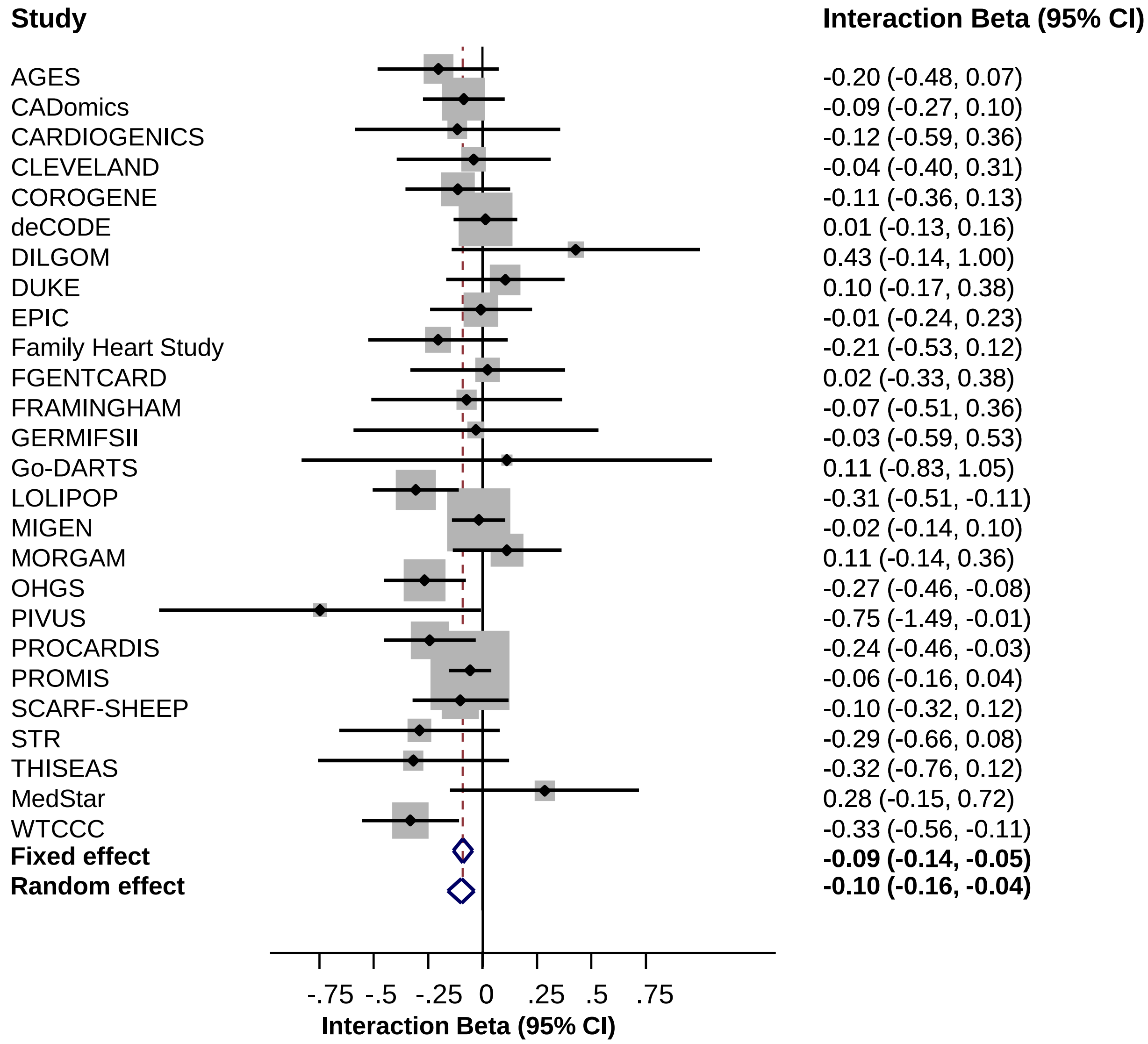
	Cases	*Controls*	*Total*	**OR (95% CI)**	**P-value**
Never-smokers	12159	22932	35091	1.11 (1.04, 1.17)	.000793
Ever-smokers	23753	24019	47772	1.09 (1.05, 1.14)	.000087
Overall	35912	46951	82863	1.09 (1.05, 1.14)	2.5e-07

Genotyping of the epsilon alleles in PROMIS

ε4 carriers versus non-carriers

	Cases	*Controls*	*Total*	**OR (95% CI)**	**P-value**
Never-smokers	4299	2987	7286	1.13 (0.99, 1.30)	.013
Ever-smokers	2750	3786	6536	1.07 (0.93, 1.23)	.347
Overall	7286	6536	13822	1.12 (1.02, 1.24)	.0009

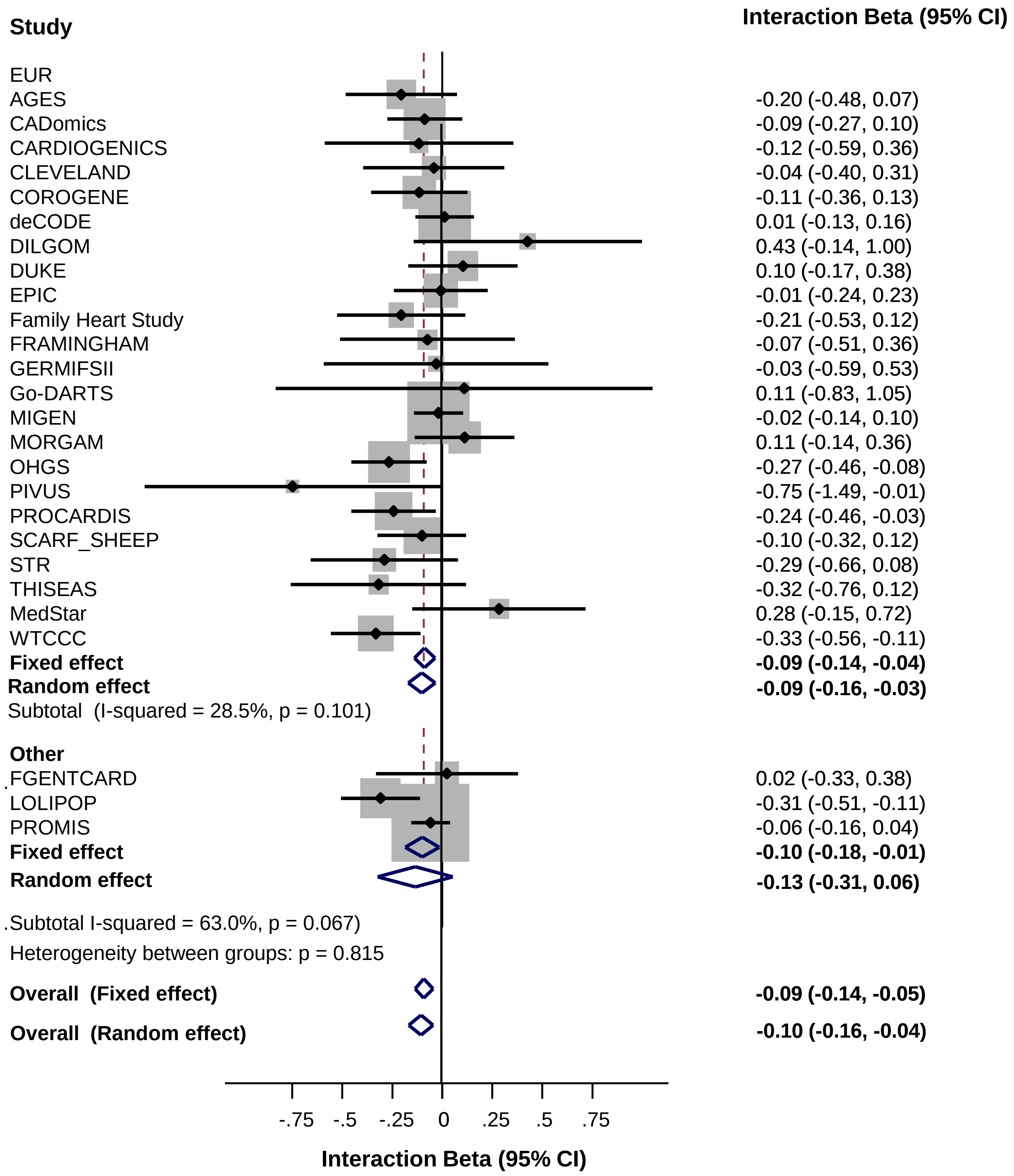
Supplementary Figure 5b. Forest plot displaying interaction beta across the participating studies



Study	Interaction Beta (95% CI)
AGES	-0.20 (-0.48, 0.07)
CADomics	-0.09 (-0.27, 0.10)
CARDIOGENICS	-0.12 (-0.59, 0.36)
CLEVELAND	-0.04 (-0.40, 0.31)
COROGENE	-0.11 (-0.36, 0.13)
deCODE	0.01 (-0.13, 0.16)
DILGOM	0.43 (-0.14, 1.00)
DUKE	0.10 (-0.17, 0.38)
EPIC	-0.01 (-0.24, 0.23)
Family Heart Study	-0.21 (-0.53, 0.12)
FGENTCARD	0.02 (-0.33, 0.38)
FRAMINGHAM	-0.07 (-0.51, 0.36)
GERMIFSII	-0.03 (-0.59, 0.53)
Go-DARTS	0.11 (-0.83, 1.05)
LOLIPOP	-0.31 (-0.51, -0.11)
MIGEN	-0.02 (-0.14, 0.10)
MORGAM	0.11 (-0.14, 0.36)
OHGS	-0.27 (-0.46, -0.08)
PIVUS	-0.75 (-1.49, -0.01)
PROCARDIS	-0.24 (-0.46, -0.03)
PROMIS	-0.06 (-0.16, 0.04)
SCARF-SHEEP	-0.10 (-0.32, 0.12)
STR	-0.29 (-0.66, 0.08)
THISEAS	-0.32 (-0.76, 0.12)
MedStar	0.28 (-0.15, 0.72)
WTCCC	-0.33 (-0.56, -0.11)
Fixed effect	**-0.09 (-0.14, -0.05)**
Random effect	**-0.10 (-0.16, -0.04)**

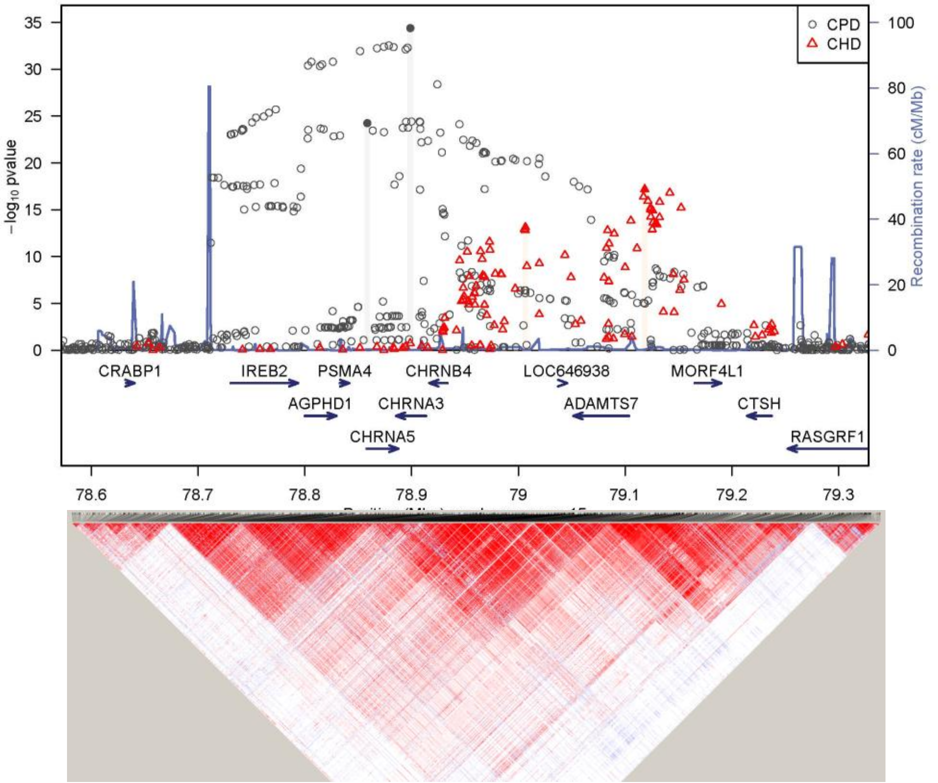
Overall (I-squared = 31.0%, p = 0.068)

Supplementary Figure 5c. Forest plot displaying interaction beta across the participating studies by ethnicity

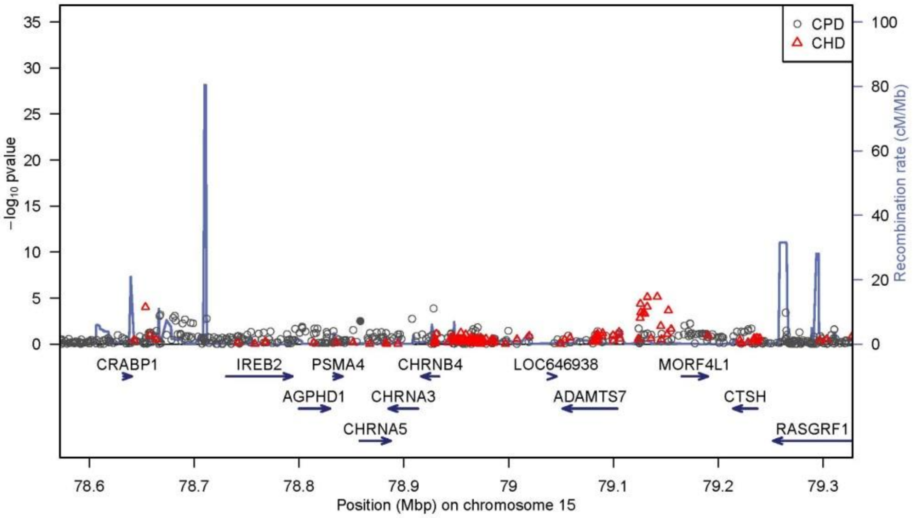


Supplementary Figure 6. (a) Unadjusted and (b) adjusted associations of chromosome 15q21.1 variants with coronary heart disease (CHD, red triangles) and smoking behavior (cigarettes per day, CPD; grey circles)

(a) Main effects on CHD risk and CPD behavior (unconditional)

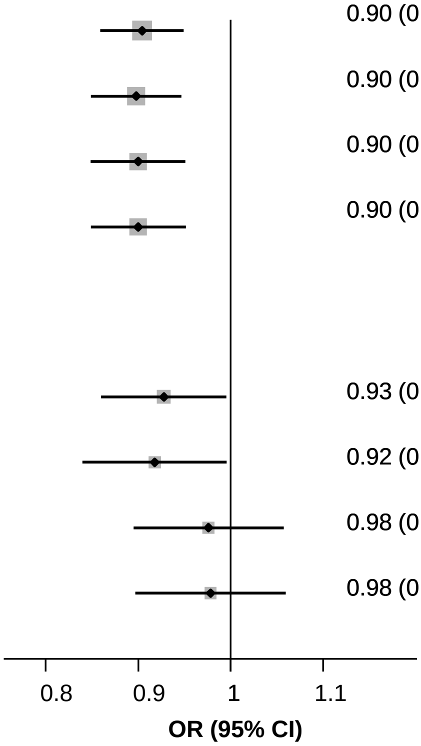


(b) analyses conditioned on rs717805, rs11072794, rs1051730 and rs684513



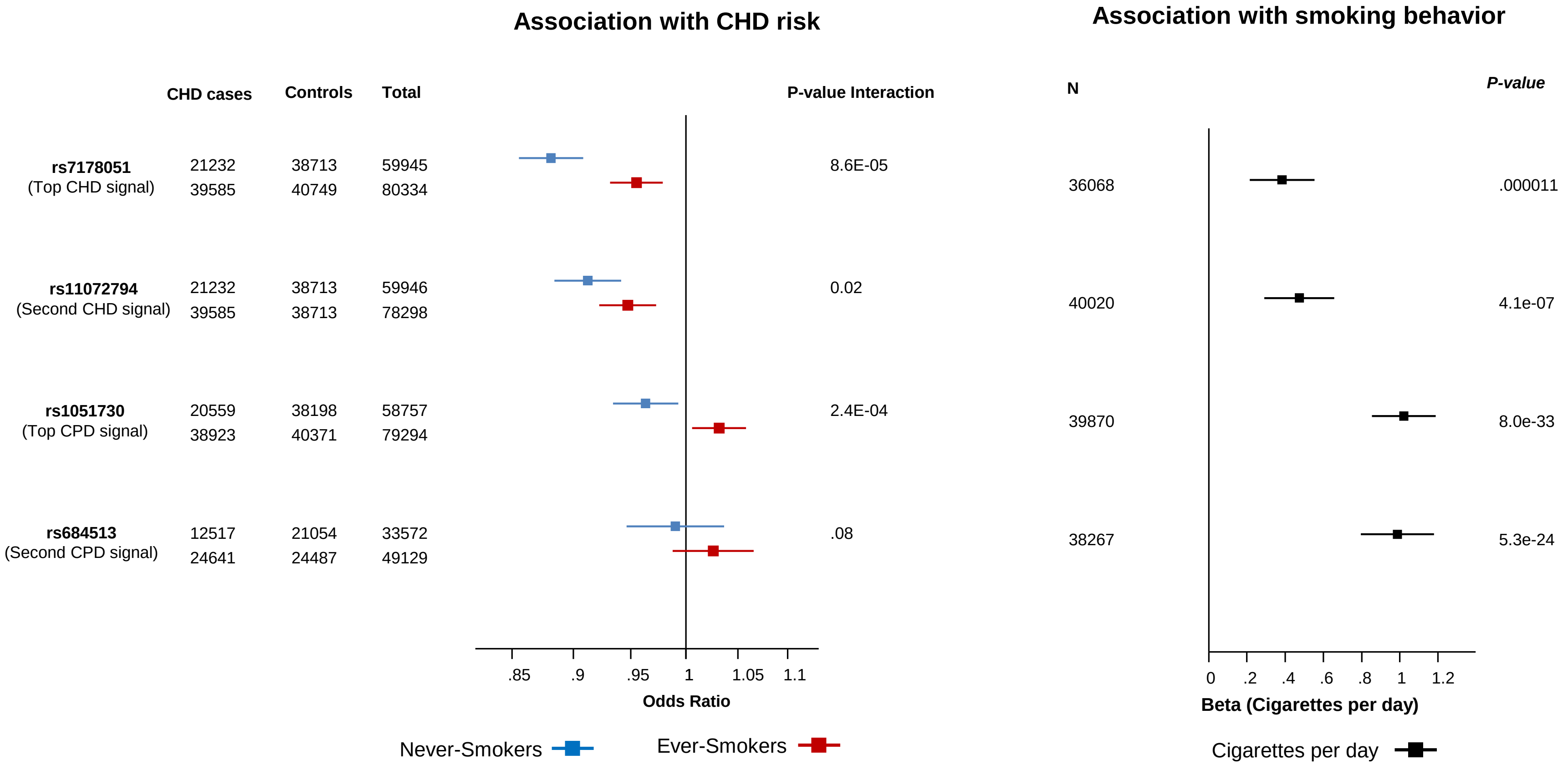
Supplementary Figure 6c – Analyses of rs7178051 and rs1051730 with MI risk in PROMIS (9,025 MI cases and 8,506 controls)

	OR (95% CI)	*P-value*
Association of rs7178051 on MI risk		
unadjusted	0.90 (0.86, 0.95)	1.3E-05
adjusted for rs11072794 (Second CHD signal)	0.90 (0.85, 0.95)	1.5E-05
adjusted for rs1051730 (Top CPD signal)	0.90 (0.85, 0.95)	5.3E-05
adjusted for rs684513 (Second CPD signal)	0.90 (0.85, 0.95)	6.0E-05
Association of rs1051730 on MI risk		
unadjusted	0.93 (0.86, 1.00)	0.03
adjusted for rs684513 (Second CDP signal)	0.92 (0.84, 1.00)	0.03
adjusted for rs7178051 (Top CHD signal)	0.98 (0.89, 1.06)	0.97
adjusted for rs11072794 (Second CHD signal)	0.98 (0.90, 1.06)	0.82



The current analyses used data from a customized cardiometabochip that was genotyped in 9,025 MI cases and 8,506 controls from the PROMIS study

Supplementary Figure 7. Unadjusted effects of 15q21.1 lead variants on coronary heart disease and smoking behavior



	CHD cases	Controls	Total	P-value Interaction	N	*P-value*
rs7178051 (Top CHD signal)	21232 39585	38713 40749	59945 80334	8.6E-05	36068	.000011
rs11072794 (Second CHD signal)	21232 39585	38713 38713	59946 78298	0.02	40020	4.1e-07
rs1051730 (Top CPD signal)	20559 38923	38198 40371	58757 79294	2.4E-04	39870	8.0e-33
rs684513 (Second CPD signal)	12517 24641	21054 24487	33572 49129	.08	38267	5.3e-24

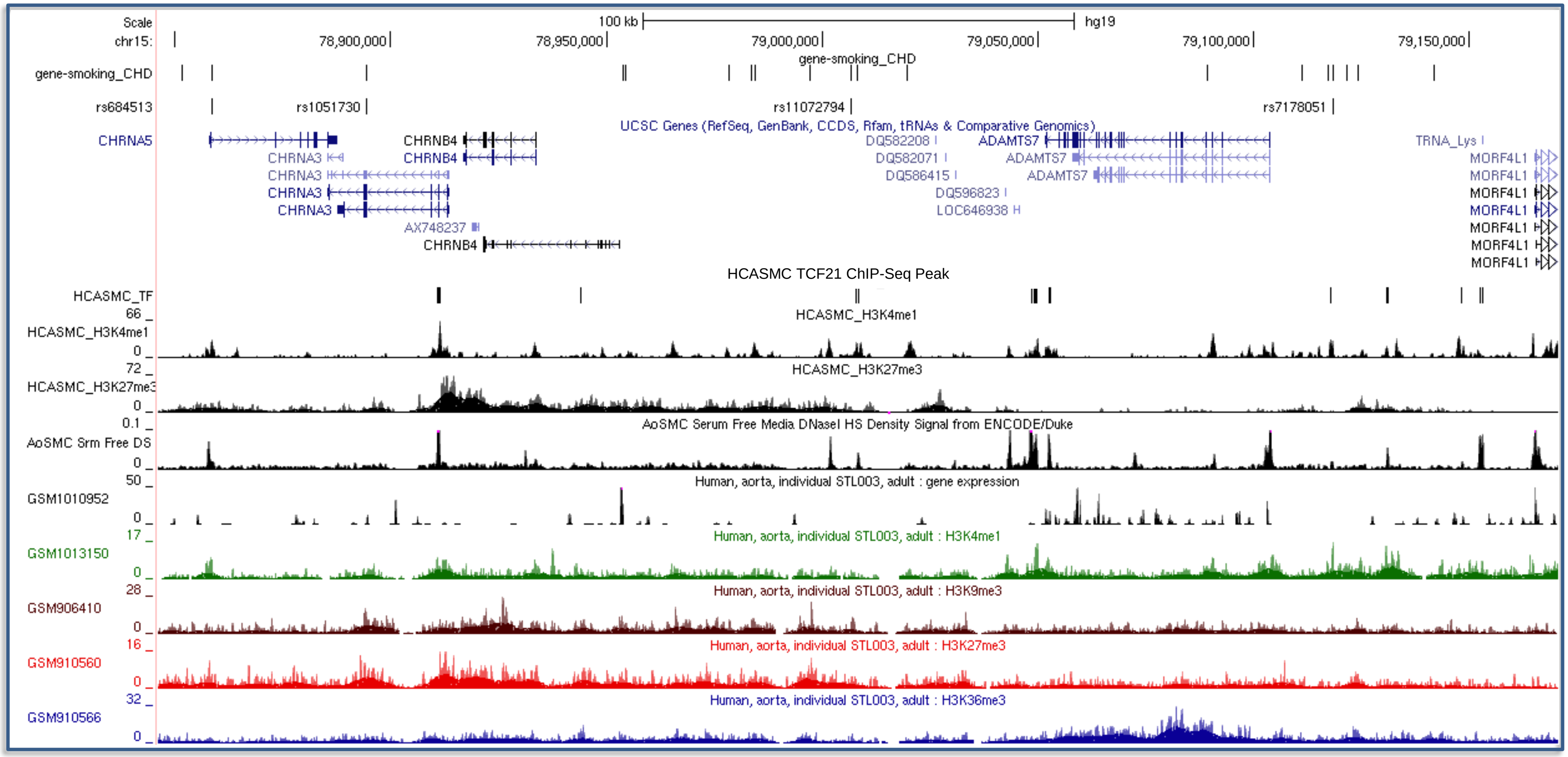
Supplementary Table 4. Association of rs7178051 (top CHD SNP) and rs1051730 (top CPD SNP) mutually adjusted for each other in 9,025 MI cases and 8,506 controls in PROMIS

PROMIS (9,025 MI cases and 8,506 controls)			
	OR	Se	P-value
rs7178051 (unadjusted)	0.90	0.02	1.31E-05
adjusted for rs1051730 using logistic regression	0.91	0.02	6.78E-05
adjusted for rs1051730 using GCTA	0.91	0.02	2.60E-05
rs1051730 (unadjusted)	0.96	0.02	0.076
adjusted for rs7178051 using logistic regression	1.00	0.03	0.875
adjusted for rs7178051 using GCTA method	1.00	0.02	0.80

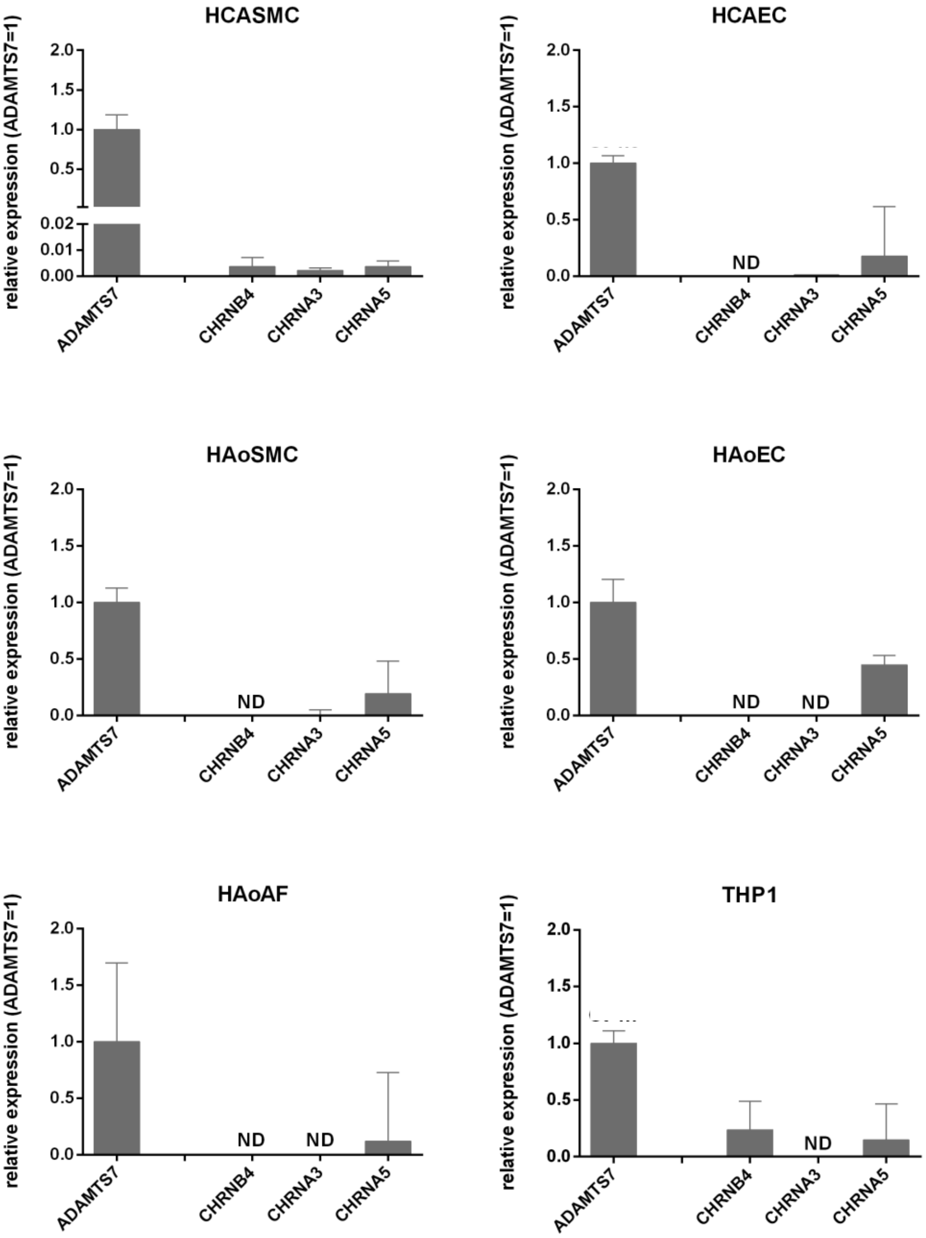
Supplementary Table 5. Association of rs7178051 with MI risk in PROMIS in participants by smoking status who do not carry the minor allele for rs1051730 and rs684513 variants

PROMIS				
	Cases	**Controls**	**OR**	**P-value**
Never-smokers	2110	2787	0.88	0.01
Ever-smokers	2982	2026	0.94	0.21
Current meta-analyses utilizing data from all participants				
Never-smokers	21232	38713	0.88	1.30x 10^{-16}
Ever-smokers	39585	40749	0.95	2.49 x10^{-04}

Supplementary Figure 8. Genome browser view of regulatory features at Chr15q21.



Supplementary Figure 9. Expression of *ADAMTS7* and *CHRNB4-A3-A5* mRNAs in HCASMC, HCAEC, HAoSMC, HAoEC, HAoAF and THP-1 cells.



HCASMC = human coronary artery smooth muscle cells; HCAEC = human coronary artery endothelial cells; HAoSMC = human aortic smooth muscle cells; HAoEC = human aortic endothelial cells; HAoAF = human aortic adventitial fibroblasts; THP-1 = human acute monocytic leukemia cell line; ND = not detected.