Supplementary Information

Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease

1. Overview

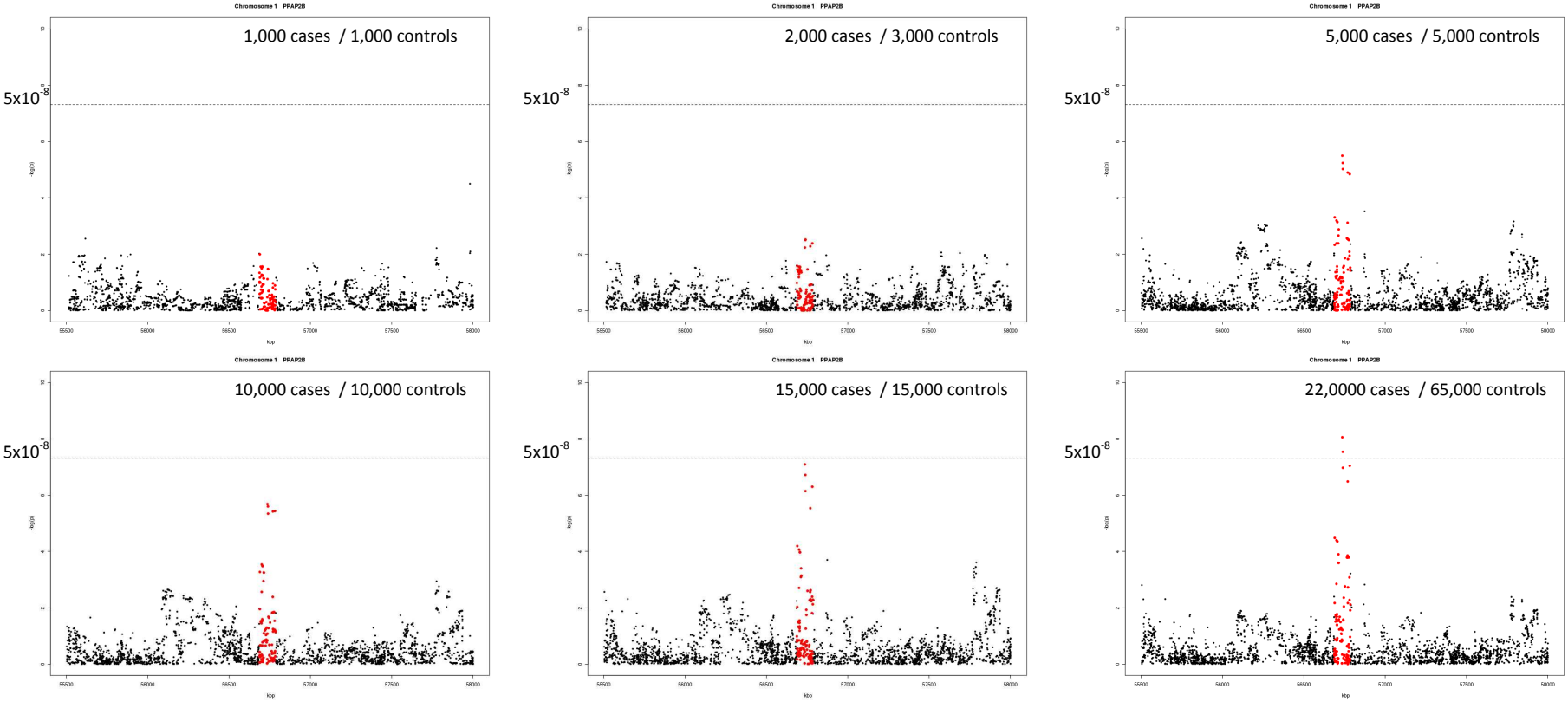
A. Figures

B. Tables

C. Supplementary Note

2. Supplementary Figures

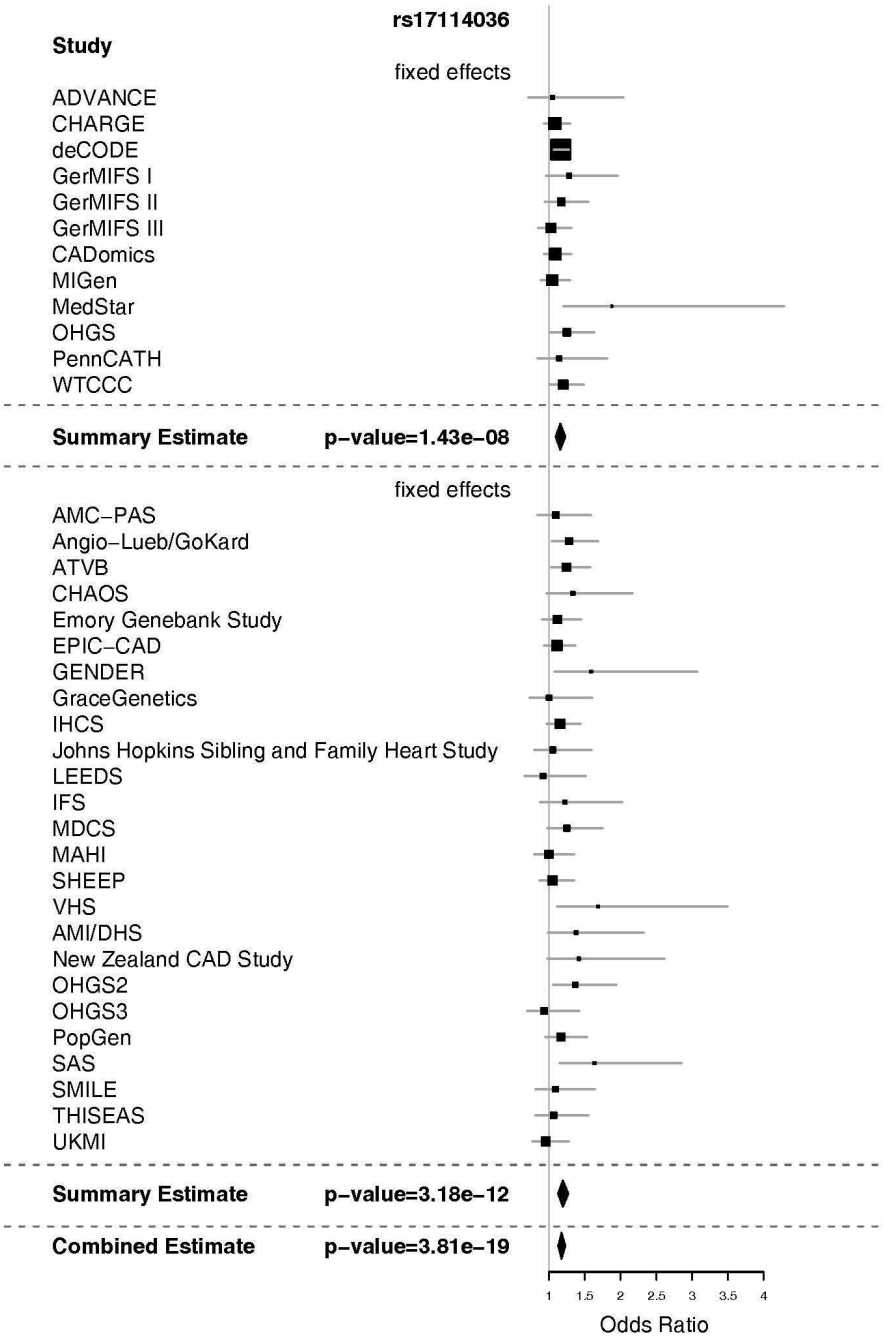
Supplementary Figure 1: GWA studies ask for large numbers. The figure represents the P for association with coronary disease at the chromosome 1p32.2 locus (denoted by red dots) depending on the number of cases and controls studied.



Nature Genetics: doi.10.1038/ng.784

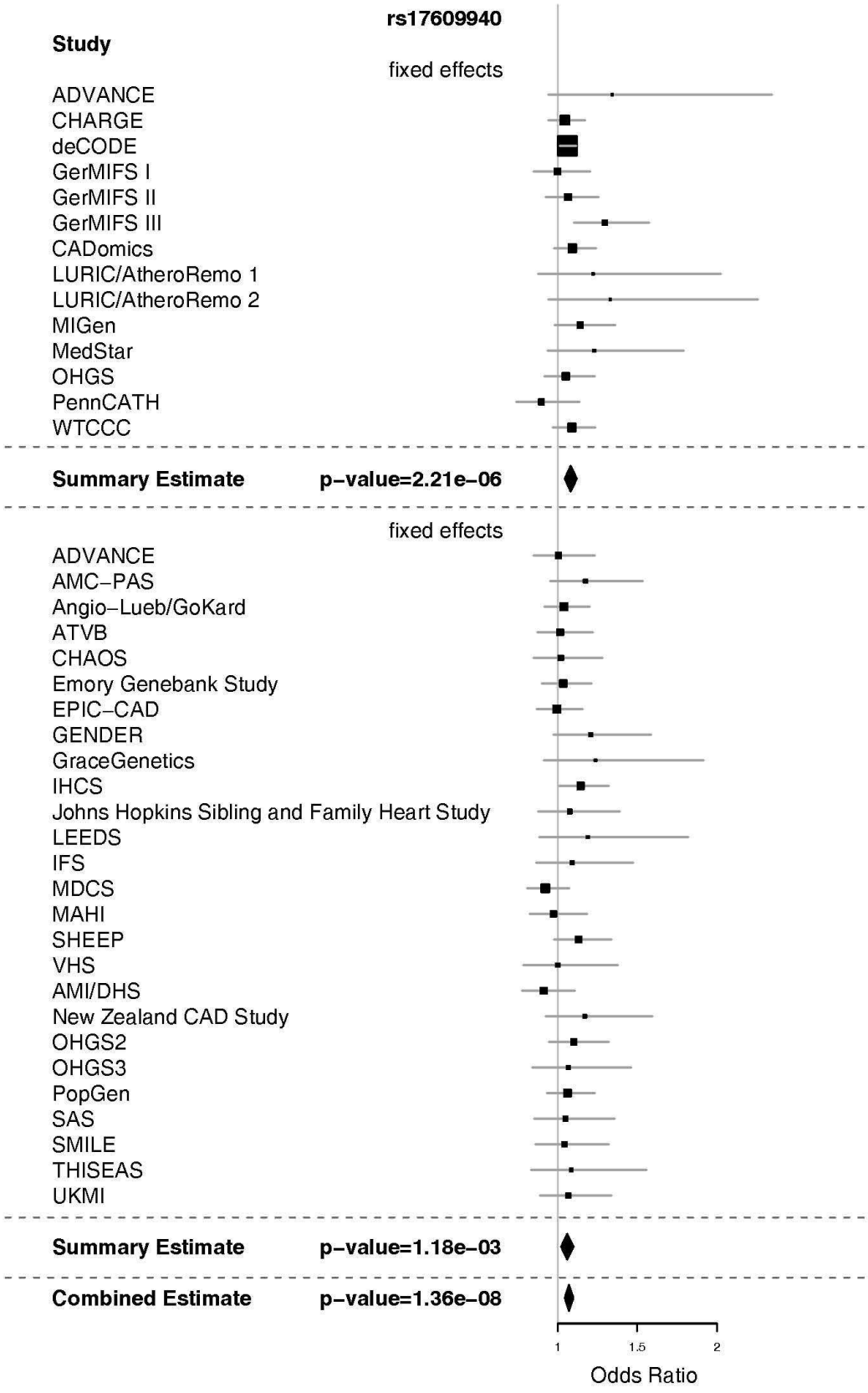
Supplementary Figure 2a: Forest plots of the 13 novel coronary disease loci. Single-study boxes and lines indicate odds ratios and 95% confidence intervals. Box sizes are determined by the weight of the study. Explanation of study abbreviations is provided in Supplementary Table 1.

1p32.2



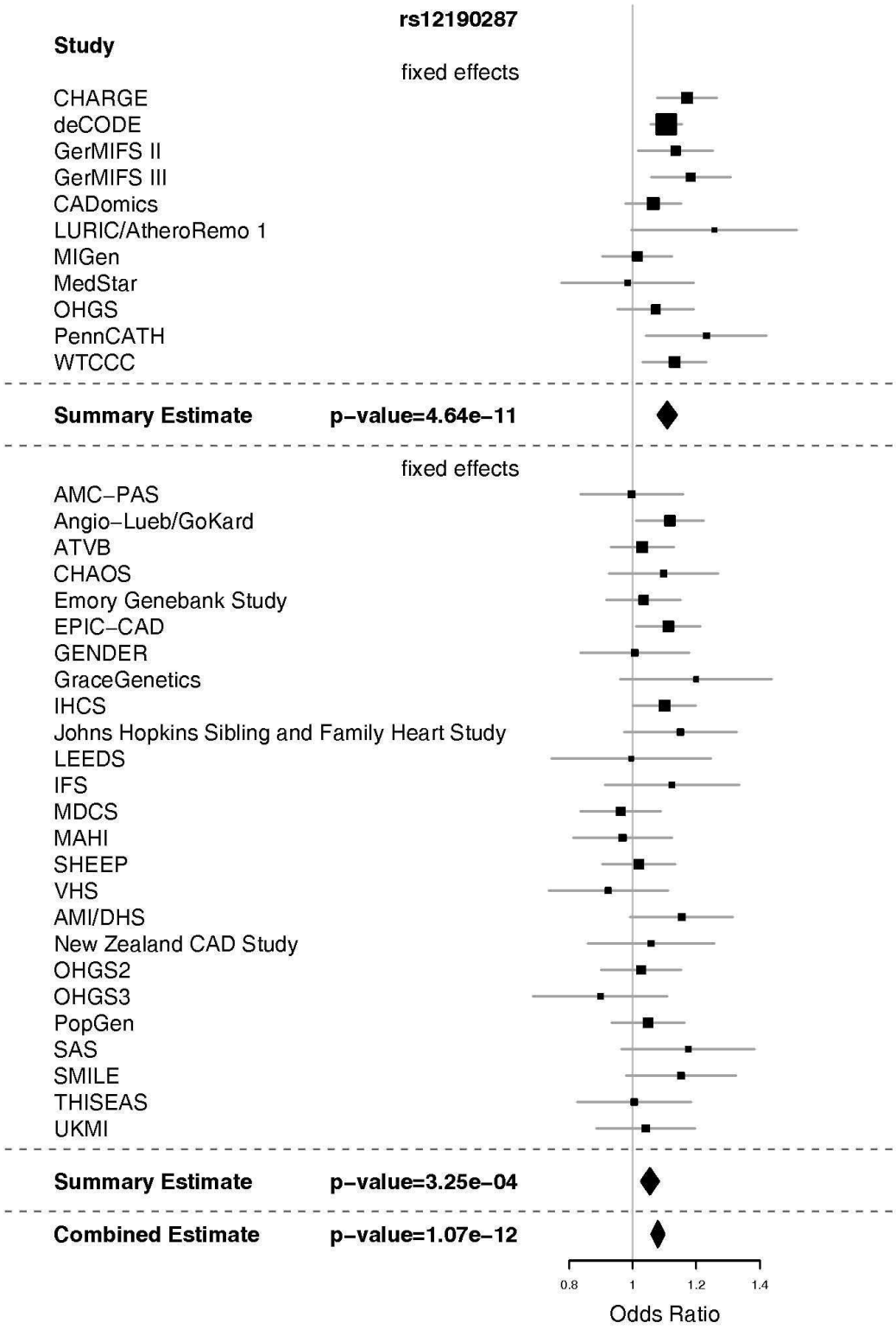
Nature Genetics: doi.10.1038/ng.784

6p21.31



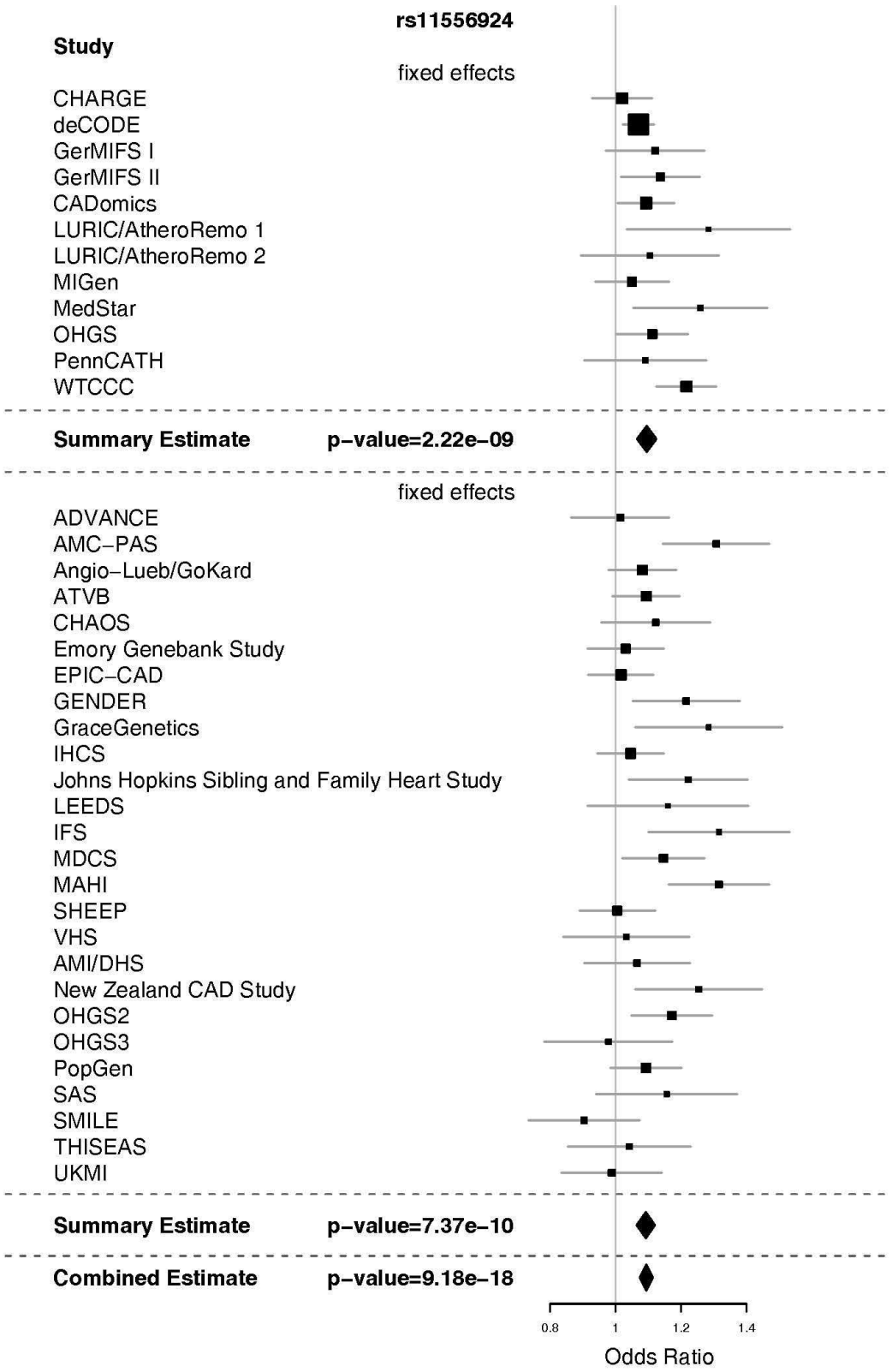
Nature Genetics: doi.10.1038/ng.784

6q23.2



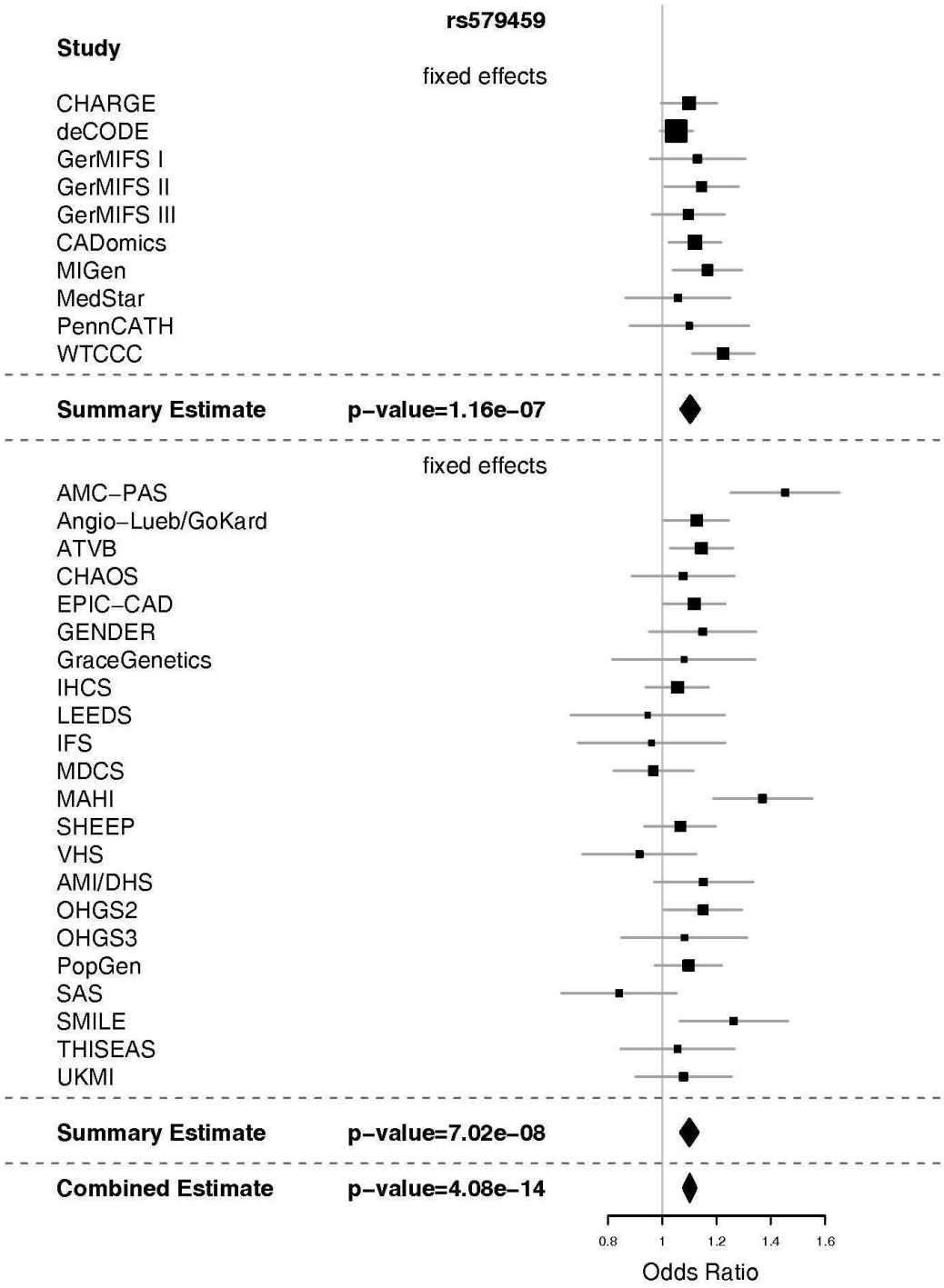
Nature Genetics: doi.10.1038/ng.784

7q32.2



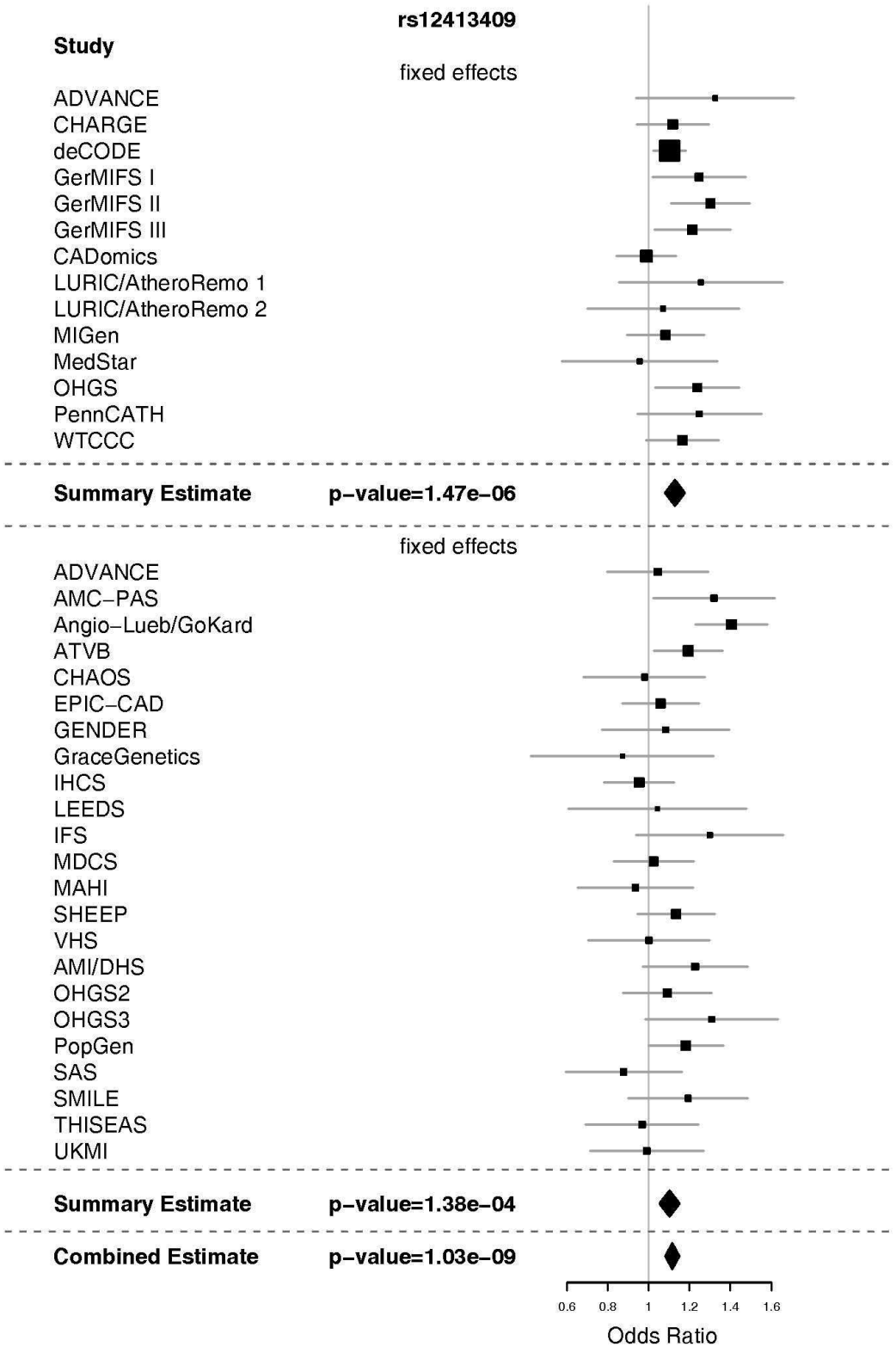
Nature Genetics: doi.10.1038/ng.784

9q34.2



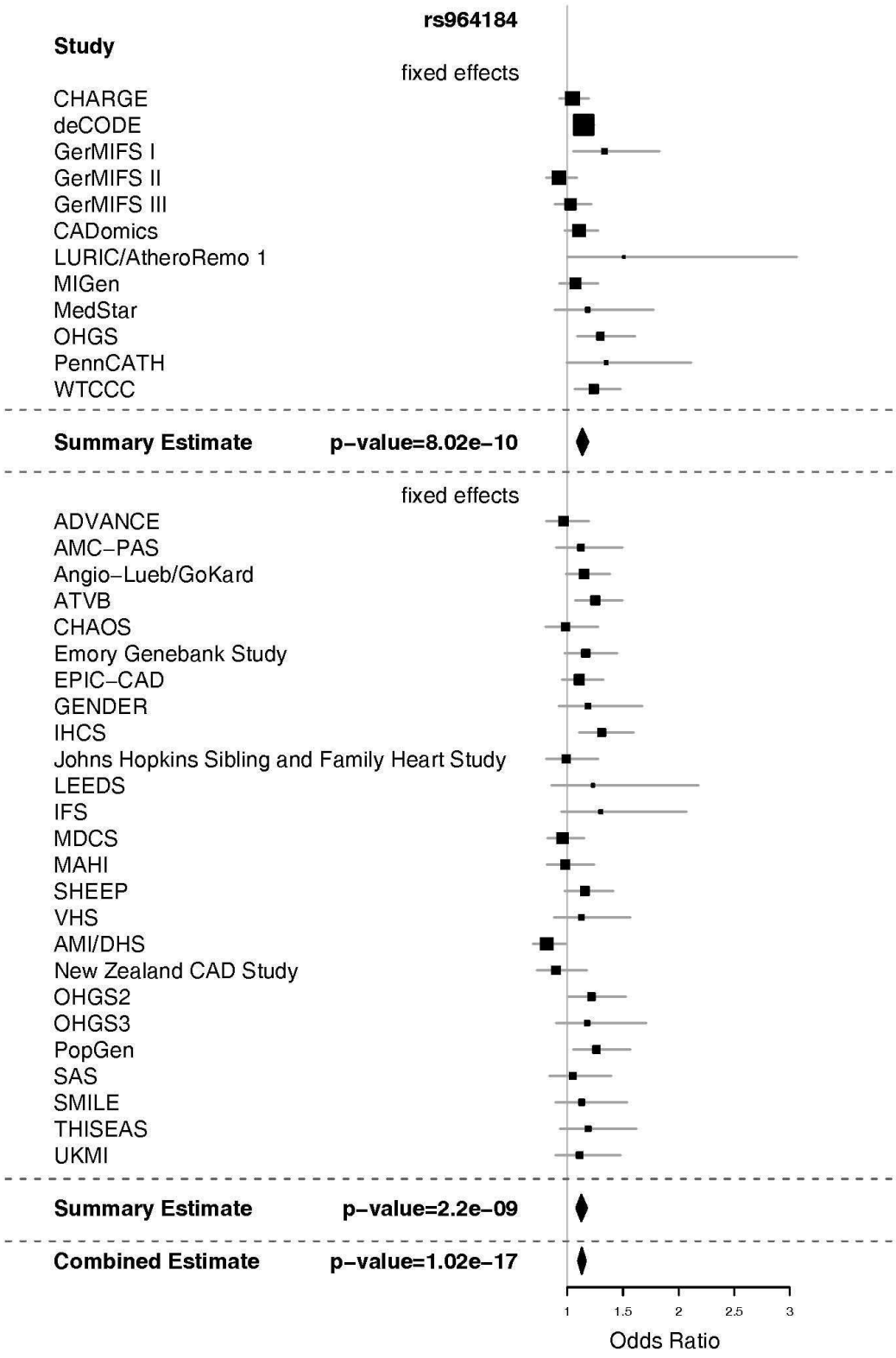
Nature Genetics: doi.10.1038/ng.784

10q24.32



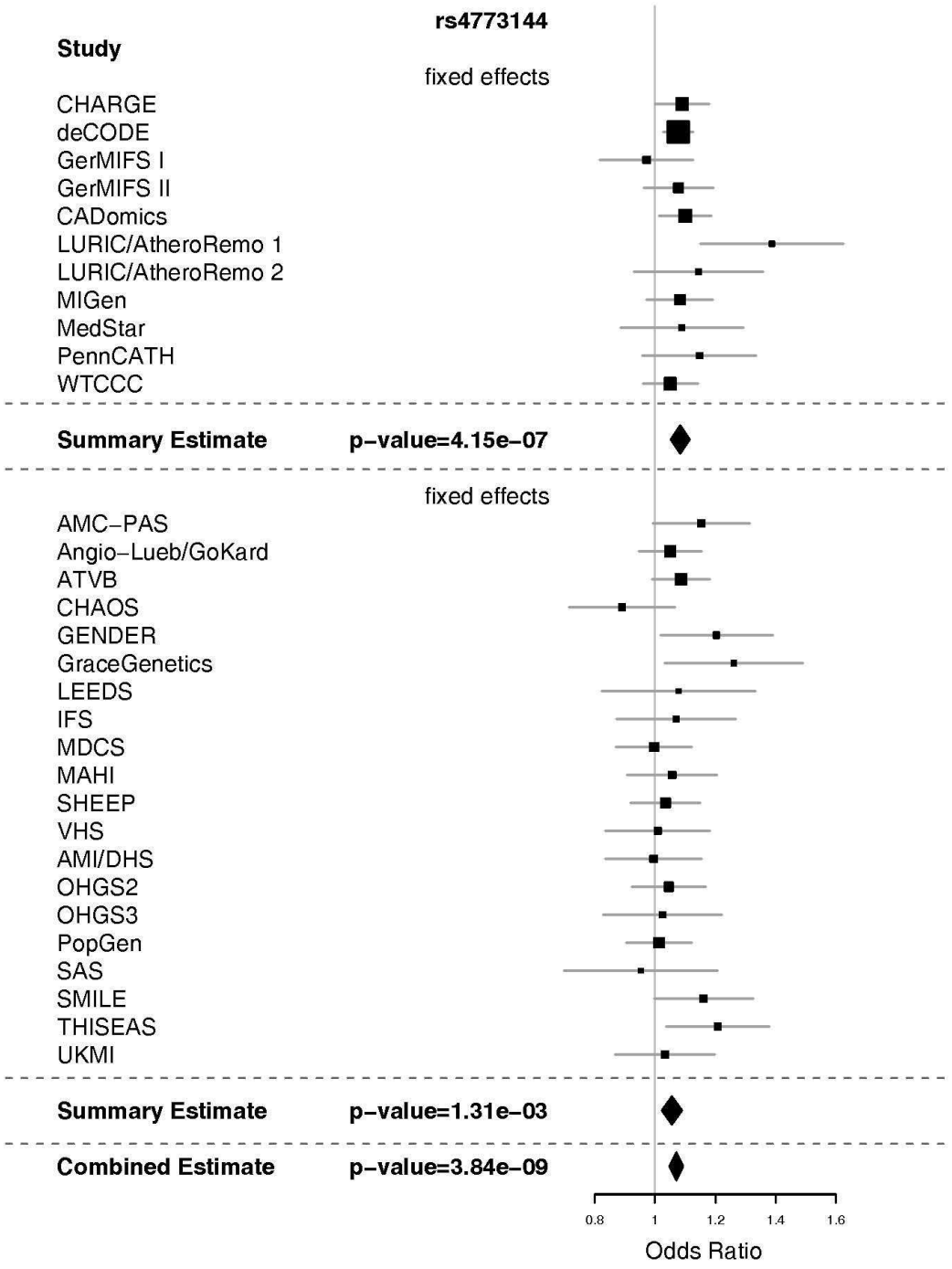
Nature Genetics: doi.10.1038/ng.784

11q23.3



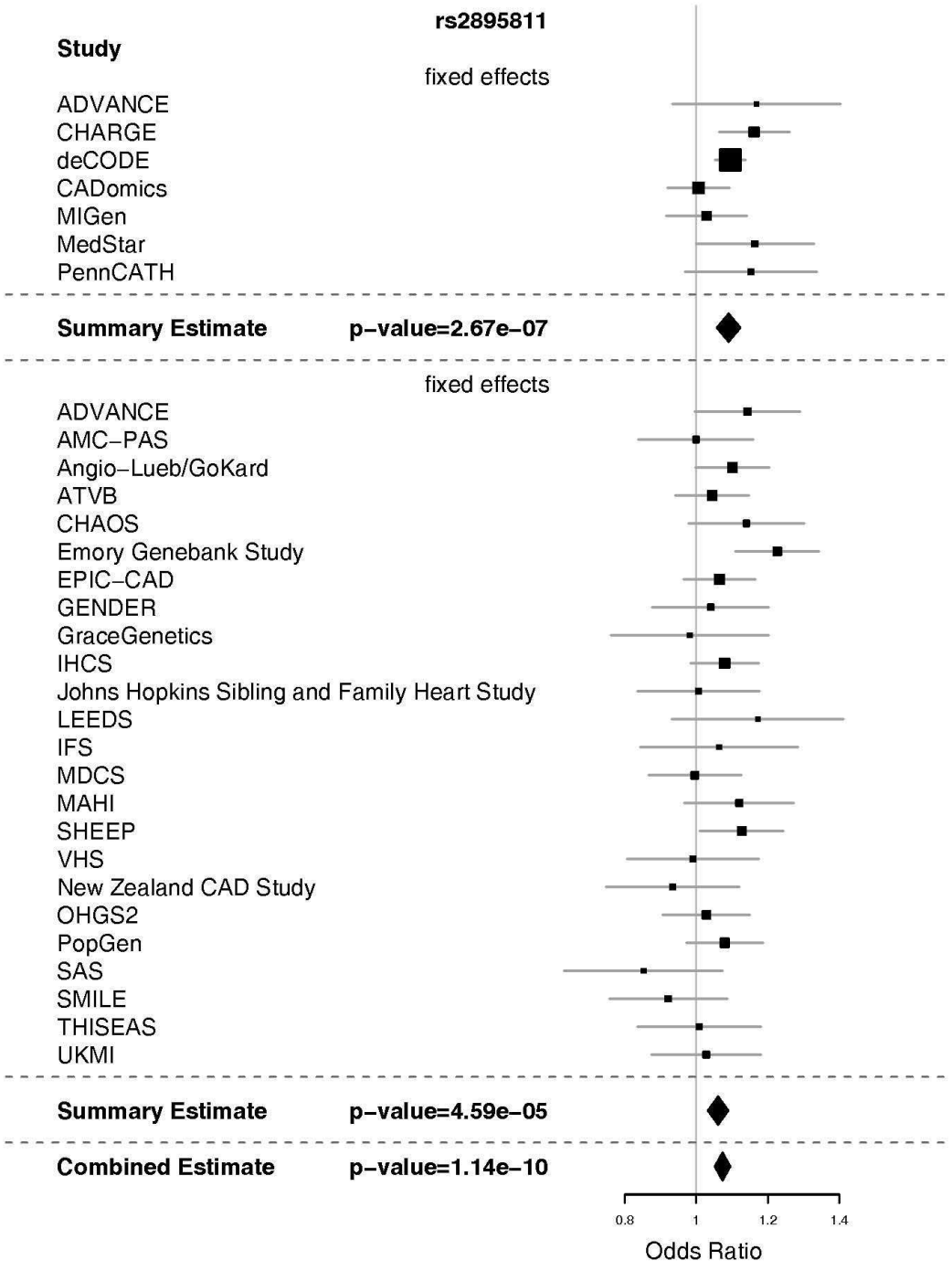
Nature Genetics: doi.10.1038/ng.784

13q34



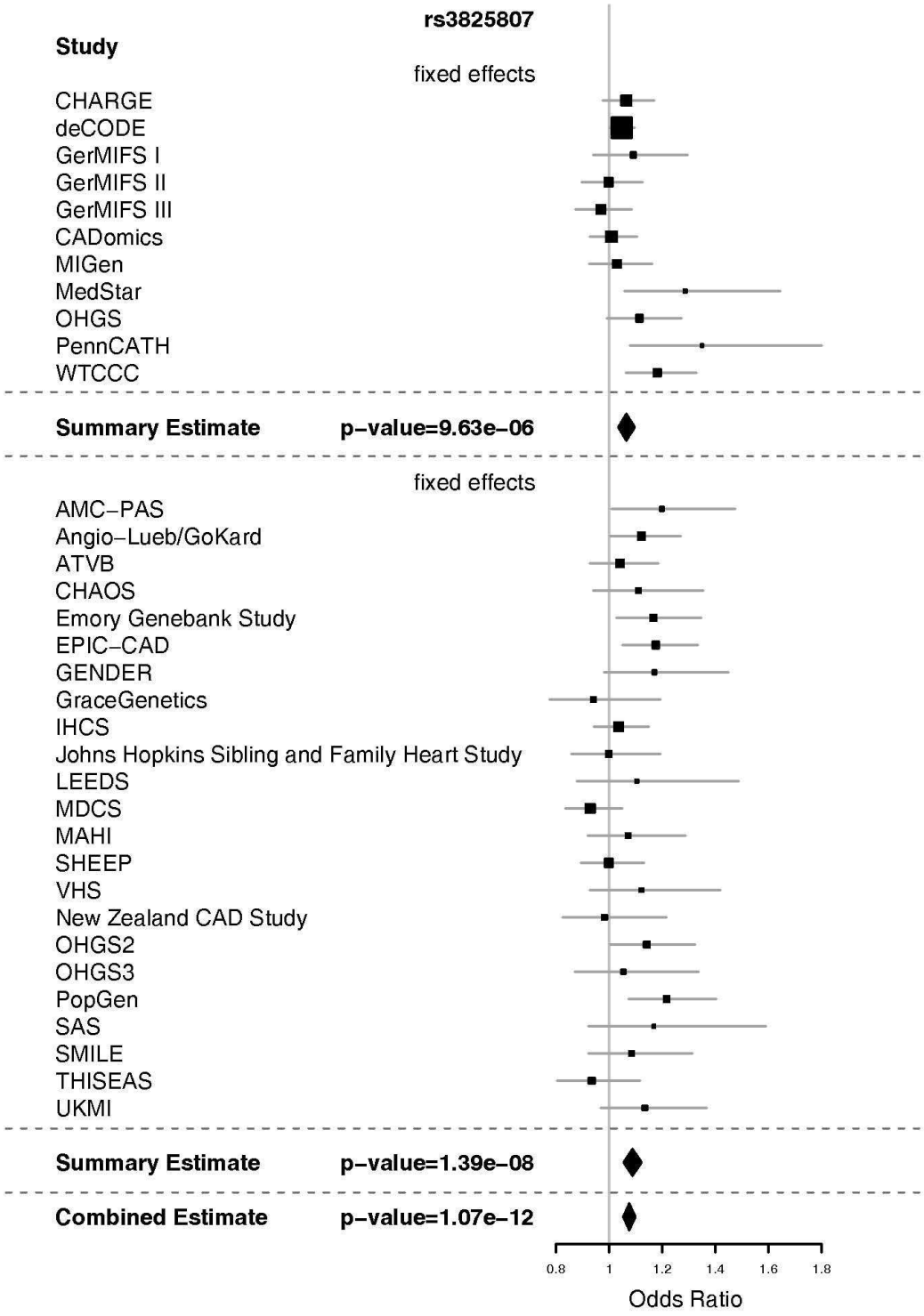
Nature Genetics: doi.10.1038/ng.784

14q32.2



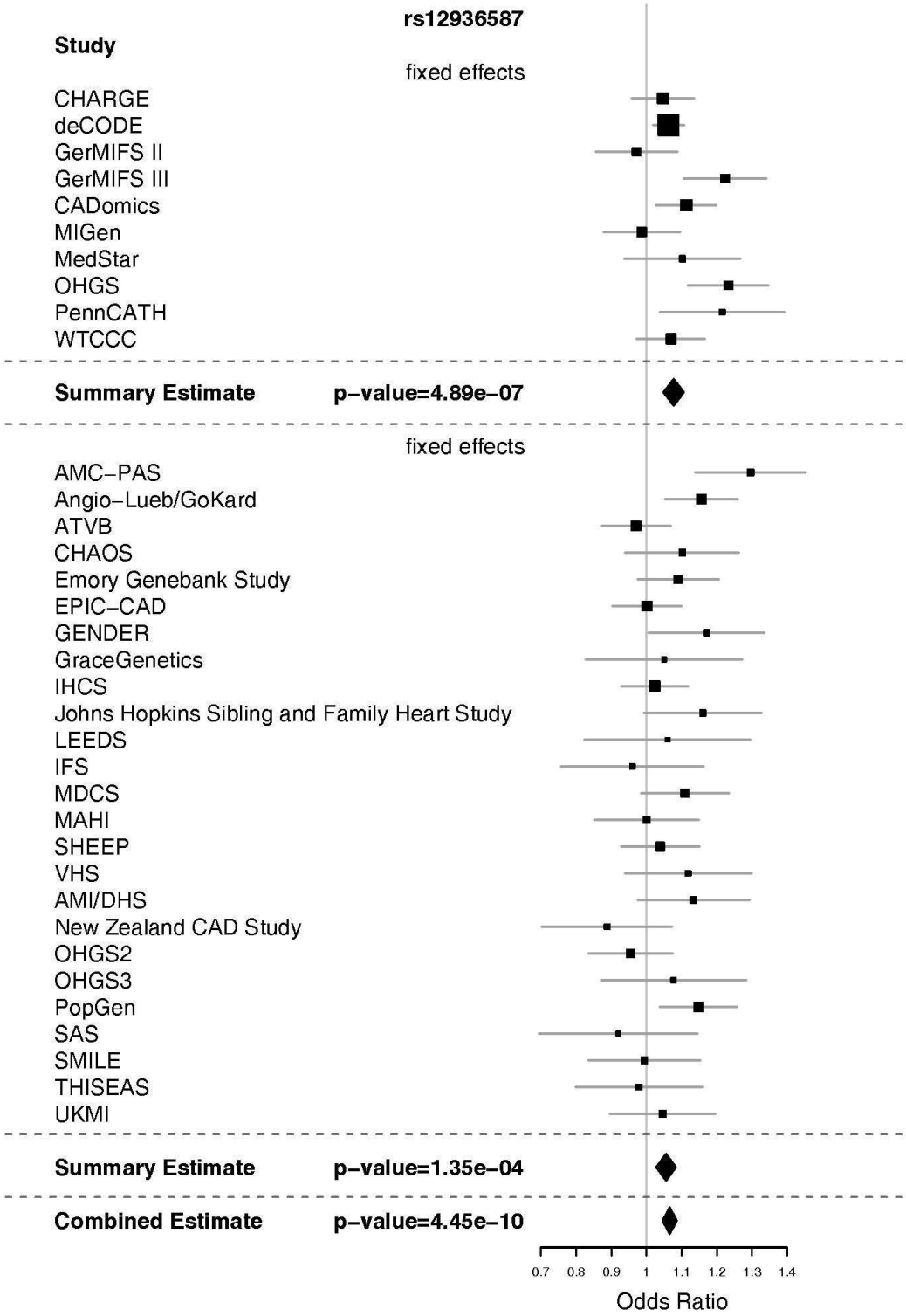
Nature Genetics: doi.10.1038/ng.784

15q25.1



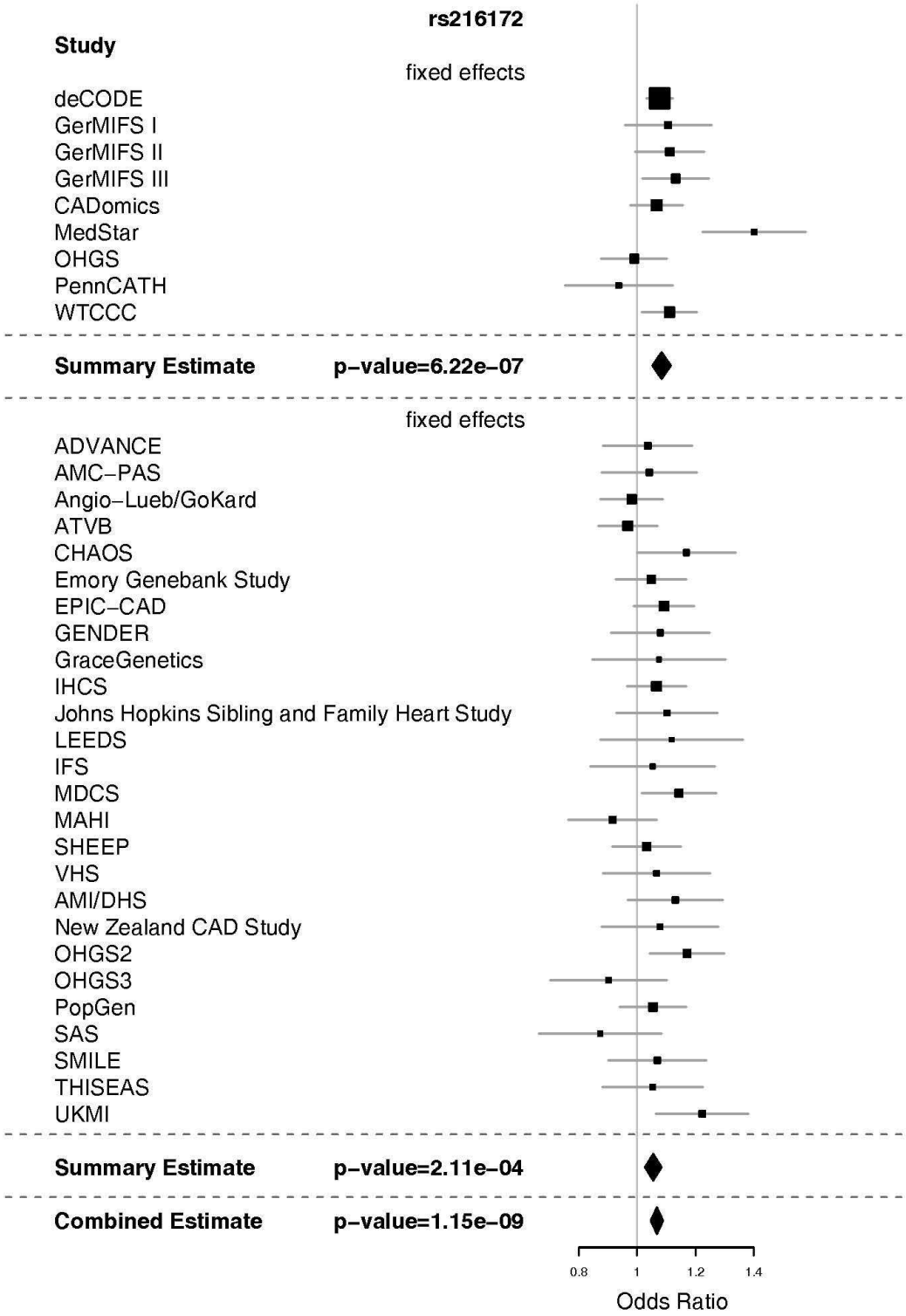
Nature Genetics: doi.10.1038/ng.784

17p11.2



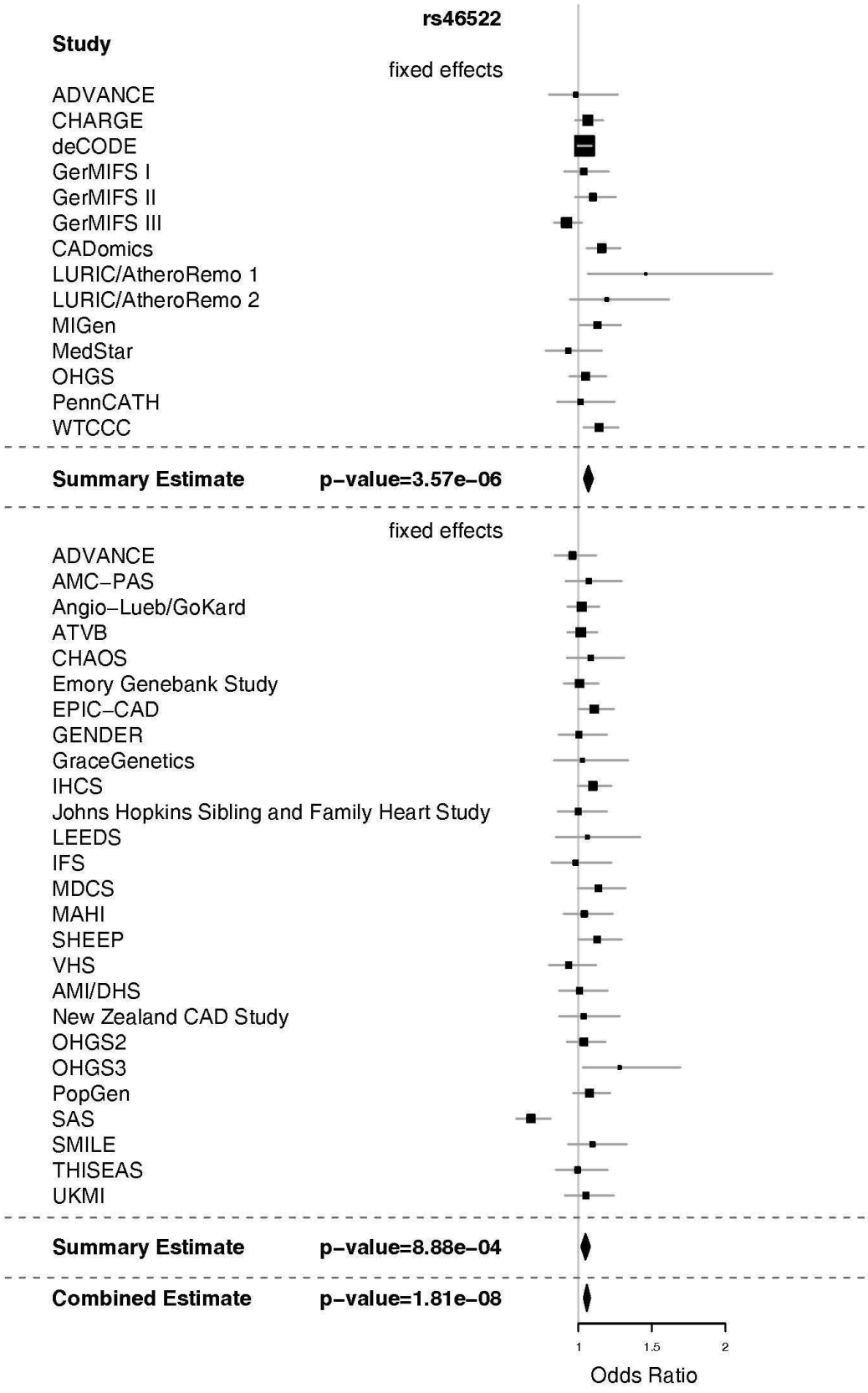
Nature Genetics: doi.10.1038/ng.784

17p13.3



Nature Genetics: doi.10.1038/ng.784

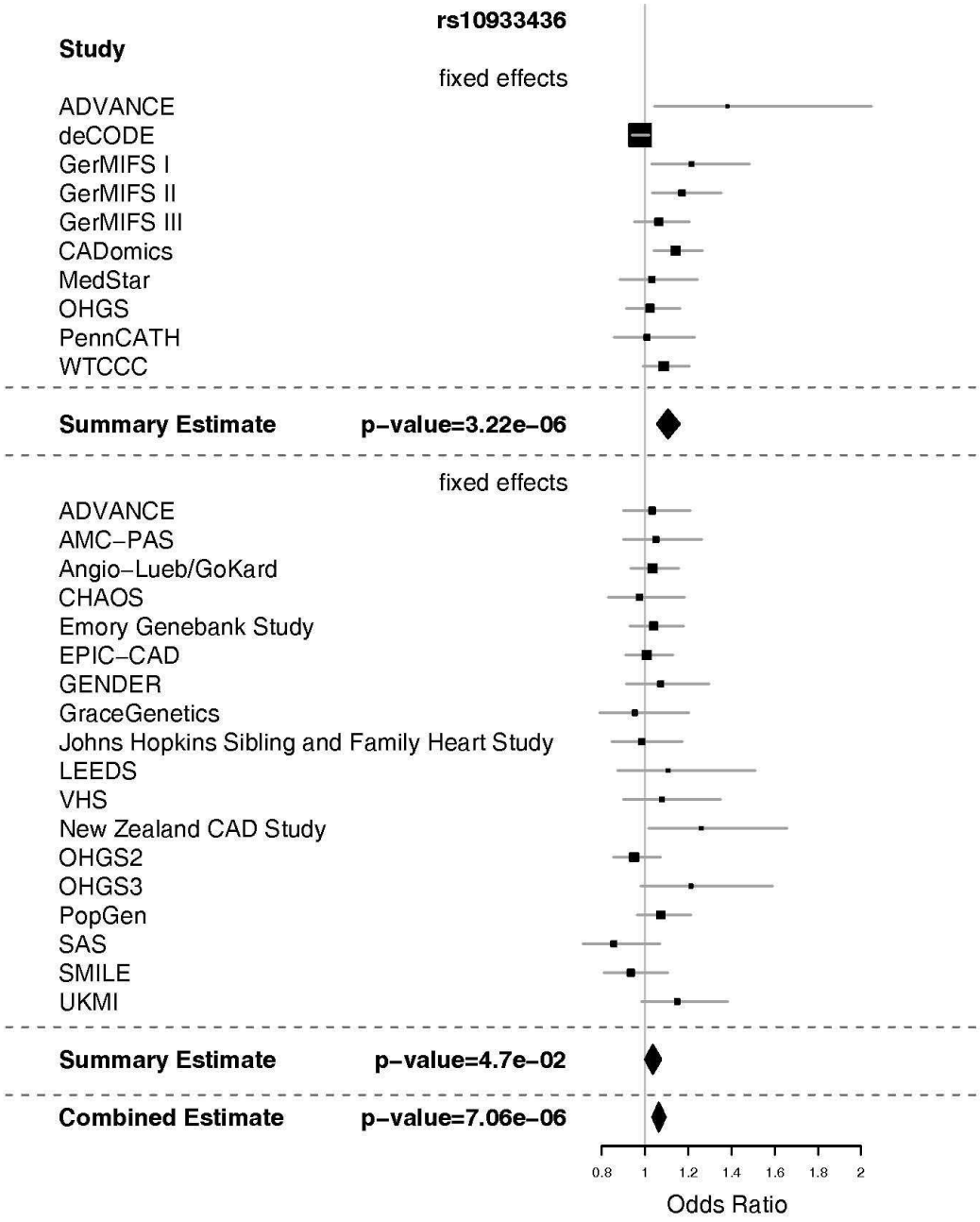
17q21.32



Nature Genetics: doi.10.1038/ng.784

Supplementary Figure 2b: Forest plots of the 10 loci detected in discovery phase but not meeting replication criteria. Explanation is provided in Supplementary Figure 1a.

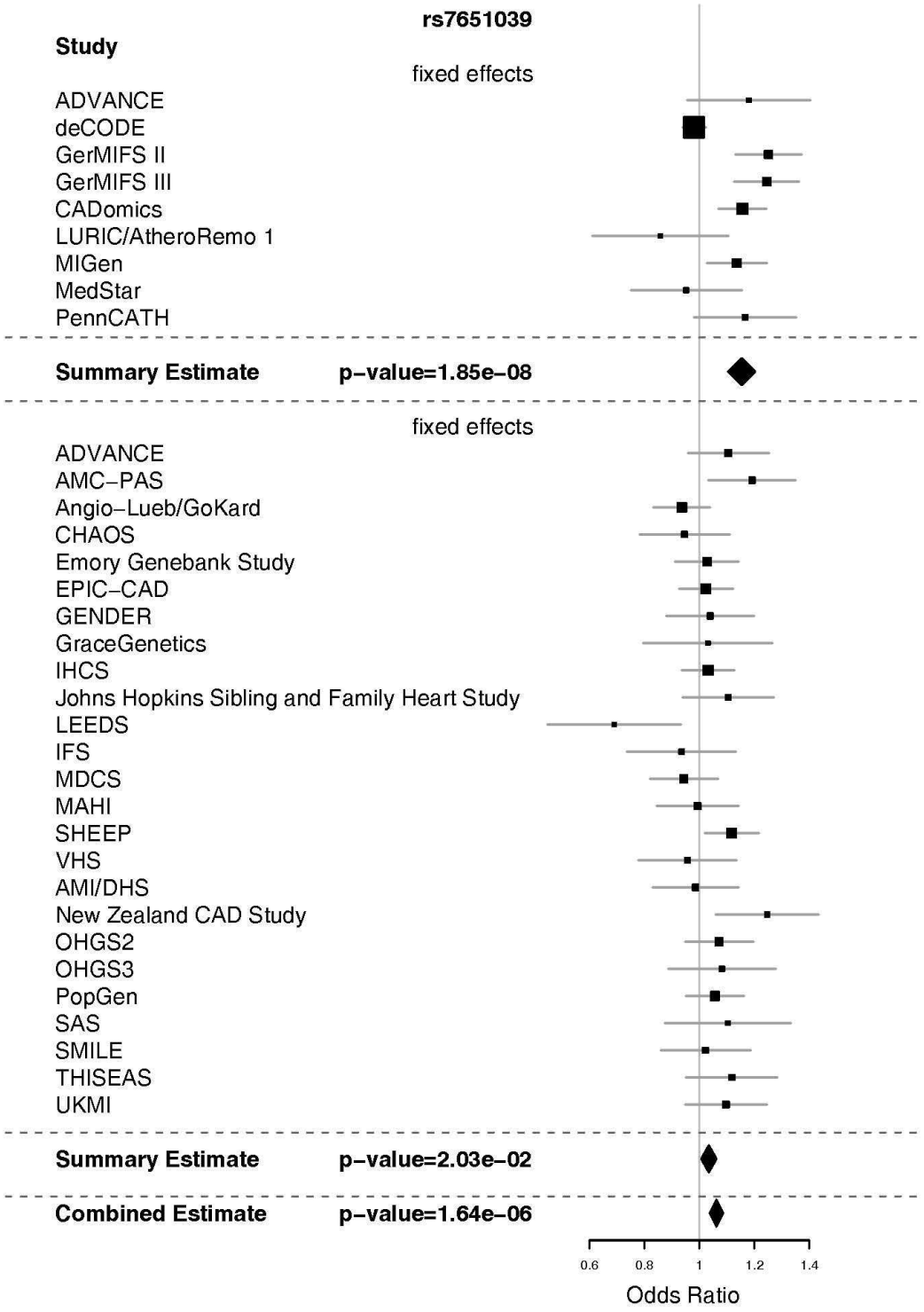
2q37



In the discovery phase, DeCODE was excluded as outlier as defined in the analysis plan.

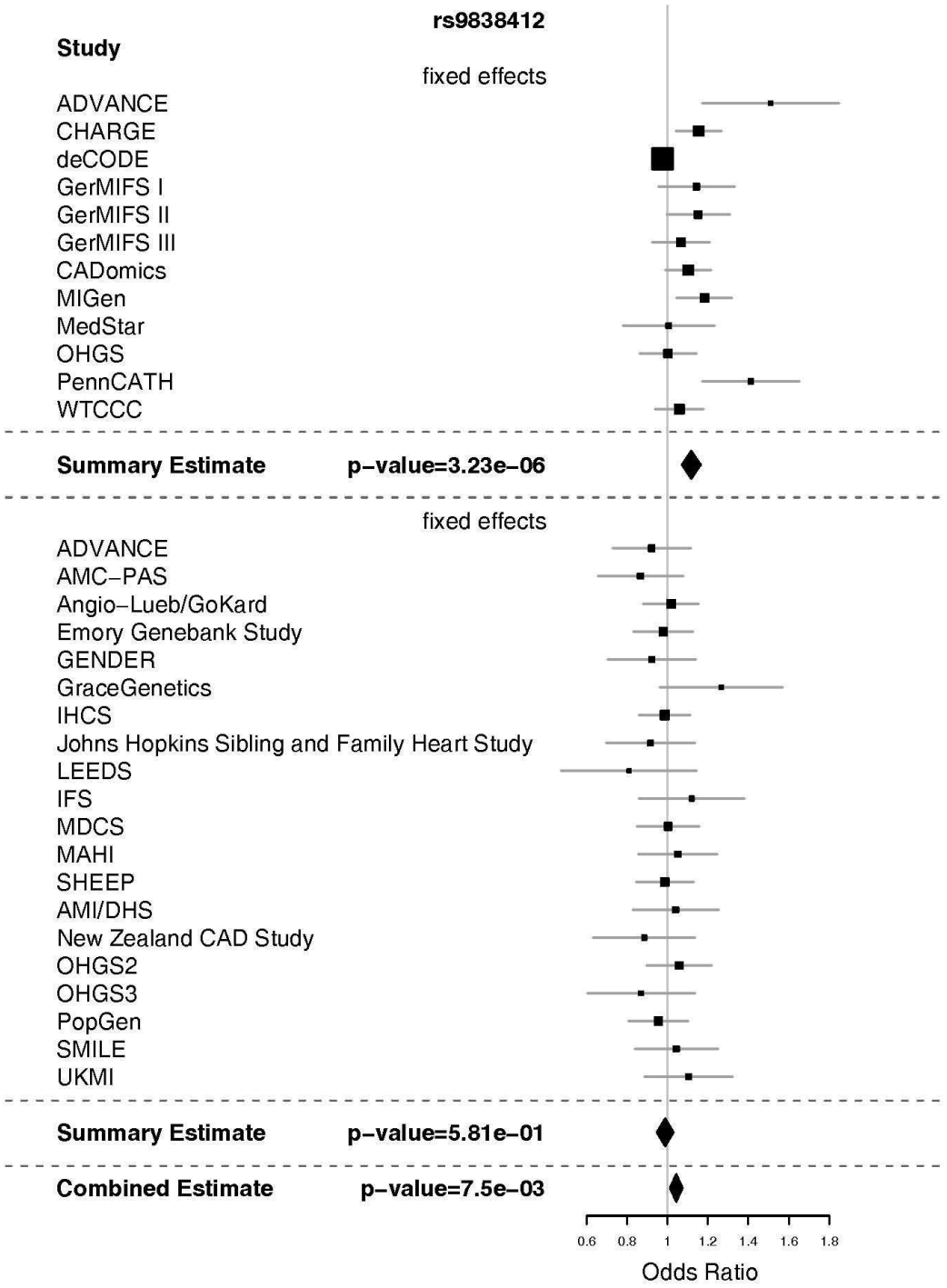
Nature Genetics: doi.10.1038/ng.784

3p24



In the discovery phase, DeCODE was excluded as outlier as defined in the analysis plan.

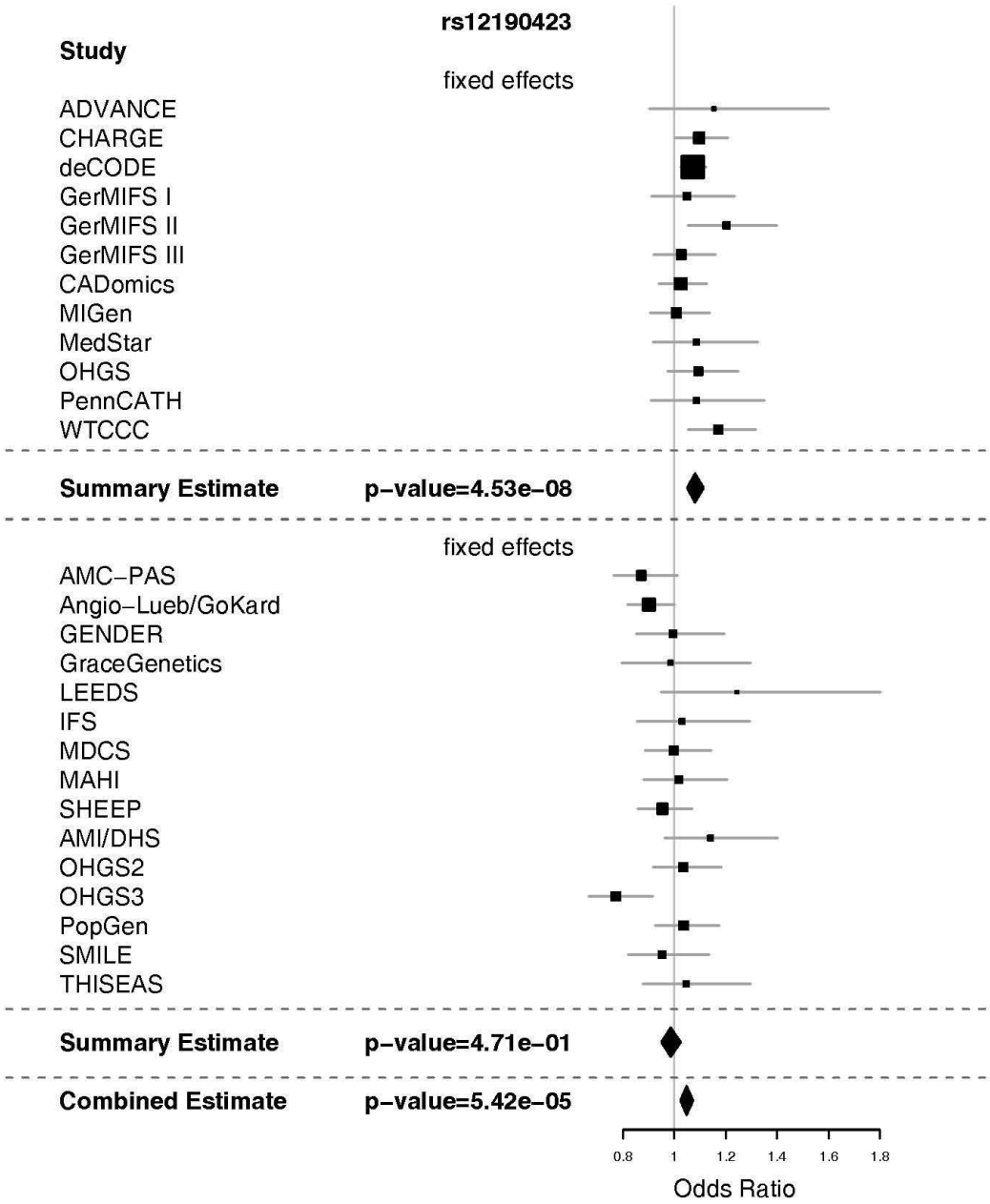
Nature Genetics: doi.10.1038/ng.784



In the discovery phase, DeCODE was excluded as outlier as defined in the analysis plan.

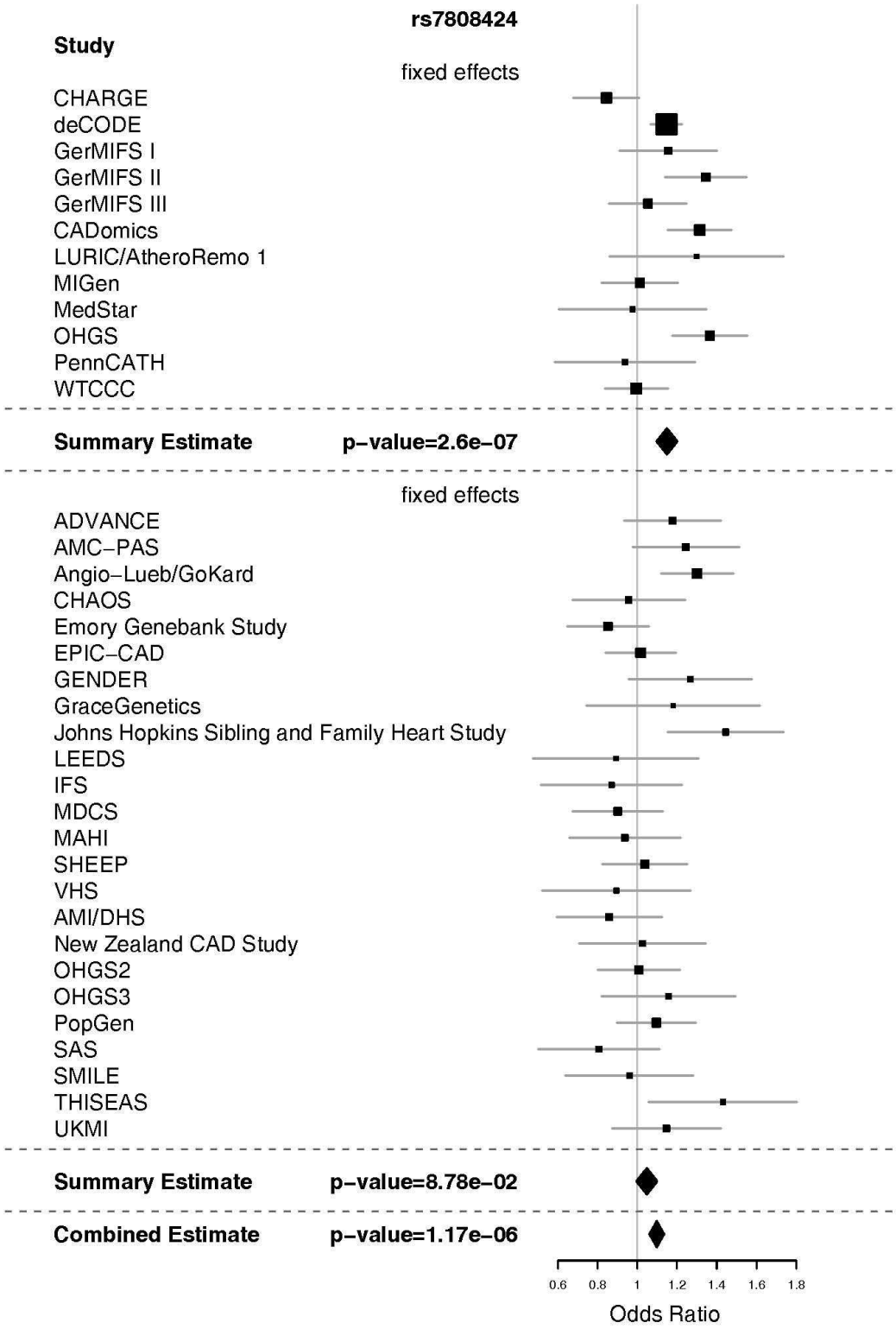
Nature Genetics: doi.10.1038/ng.784

6q13



Nature Genetics: doi.10.1038/ng.784

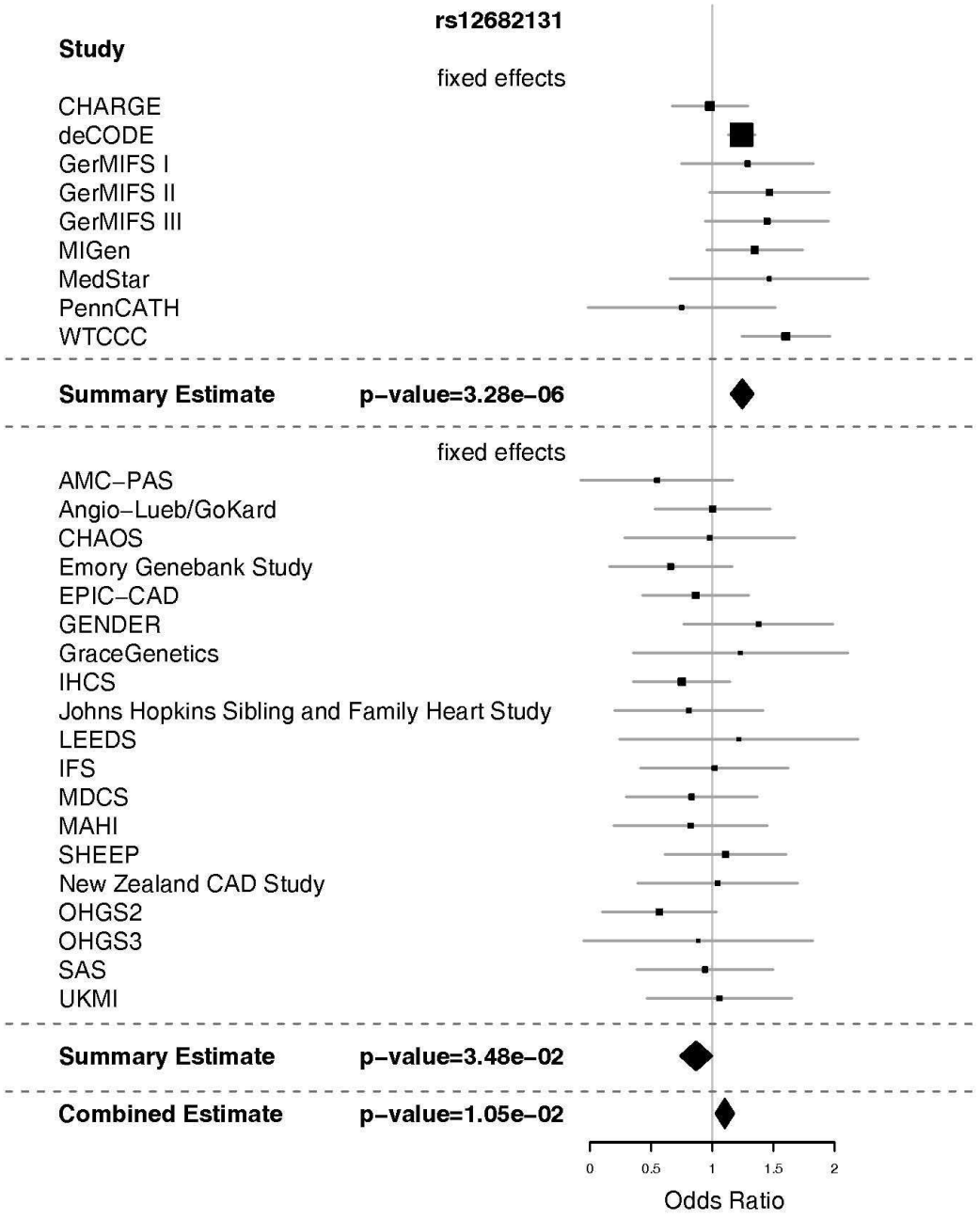
7q31



In the discovery phase, CHARGE was excluded as outlier as defined in the analysis plan.

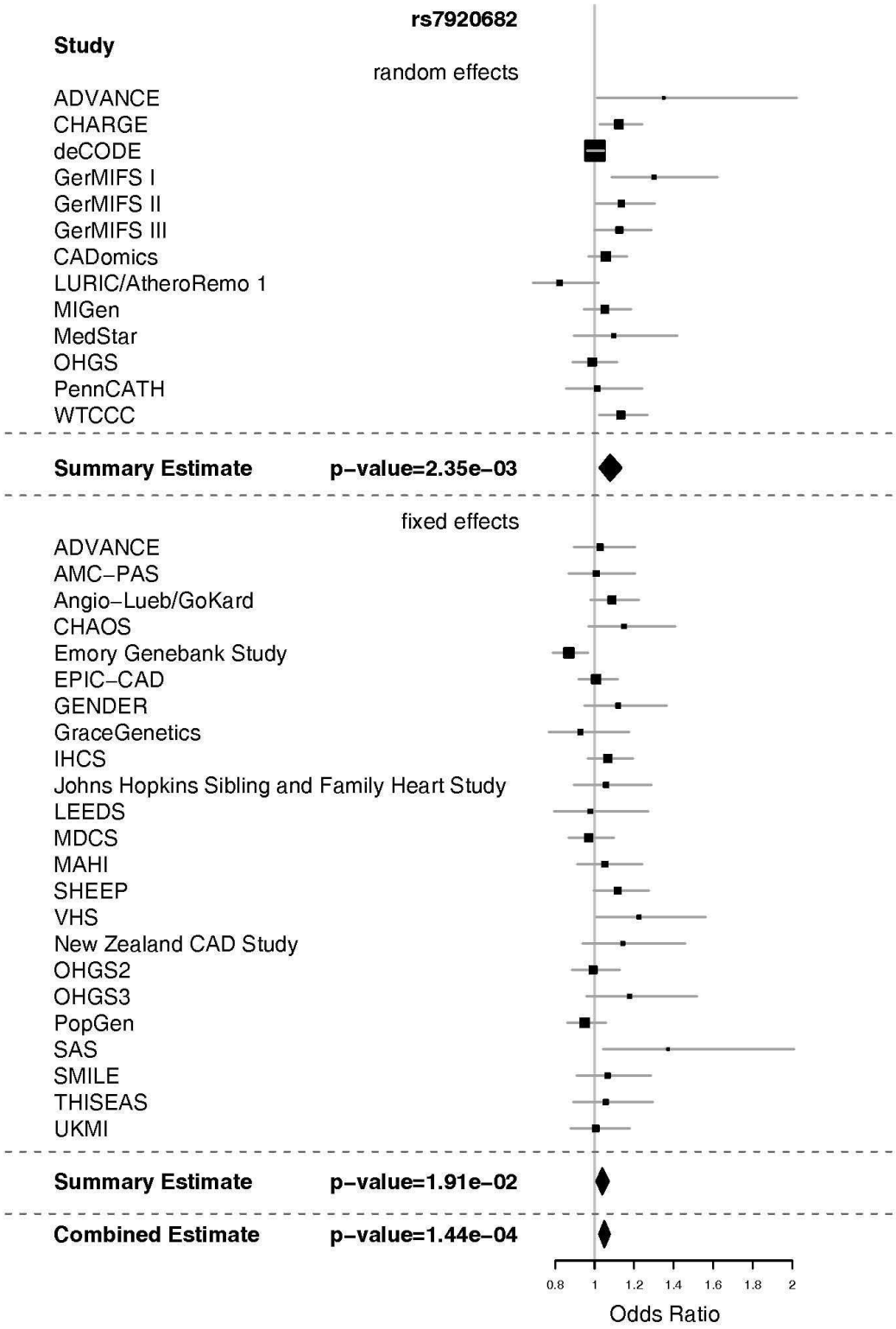
Nature Genetics: doi.10.1038/ng.784

8q24.2



Nature Genetics: doi.10.1038/ng.784

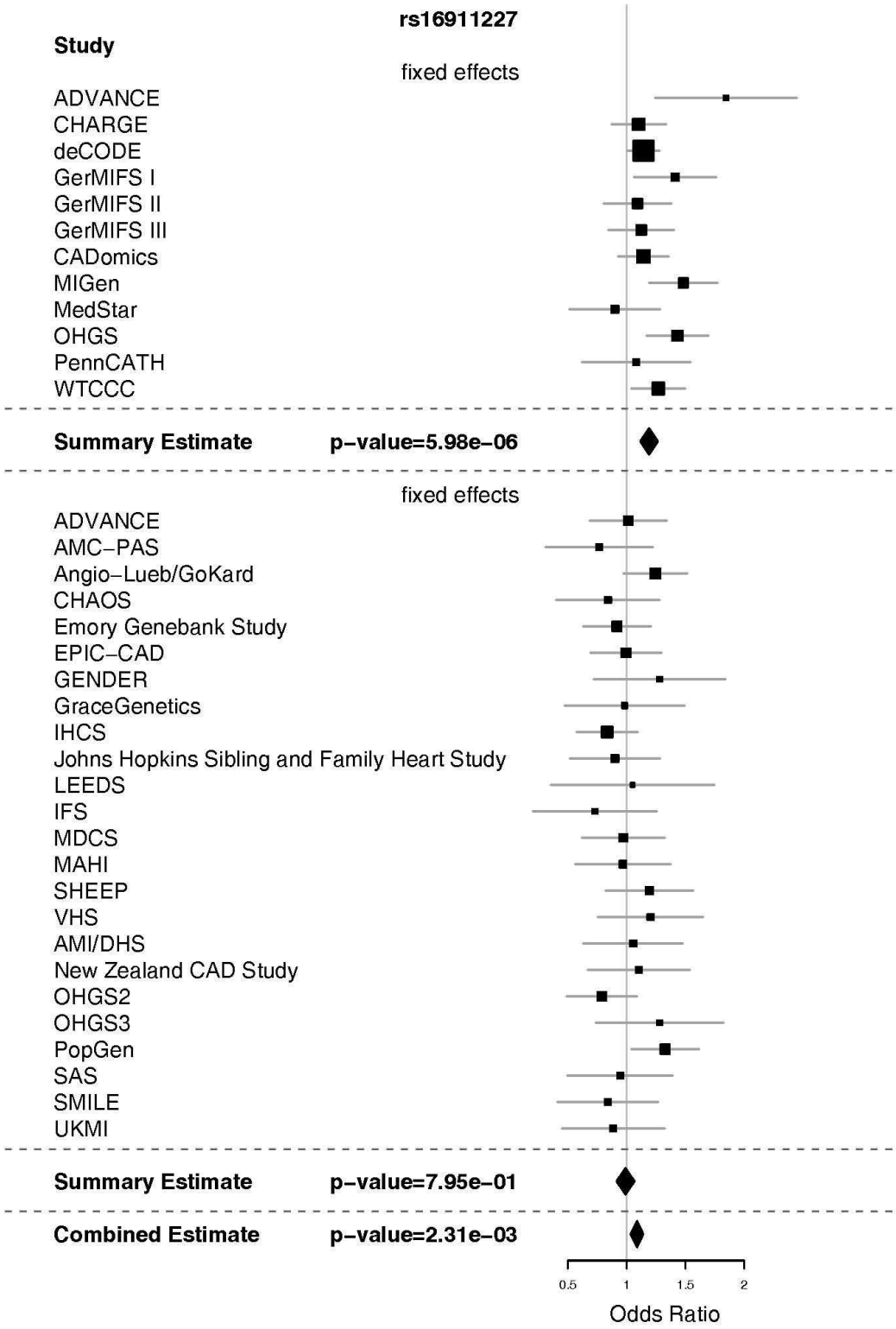
10p11.2



In the discovery phase, this region had been selected based on SNP rs2505083 (P = 3.26E-06). For technical reasons, SNP rs7920682 was selected instead for replication.

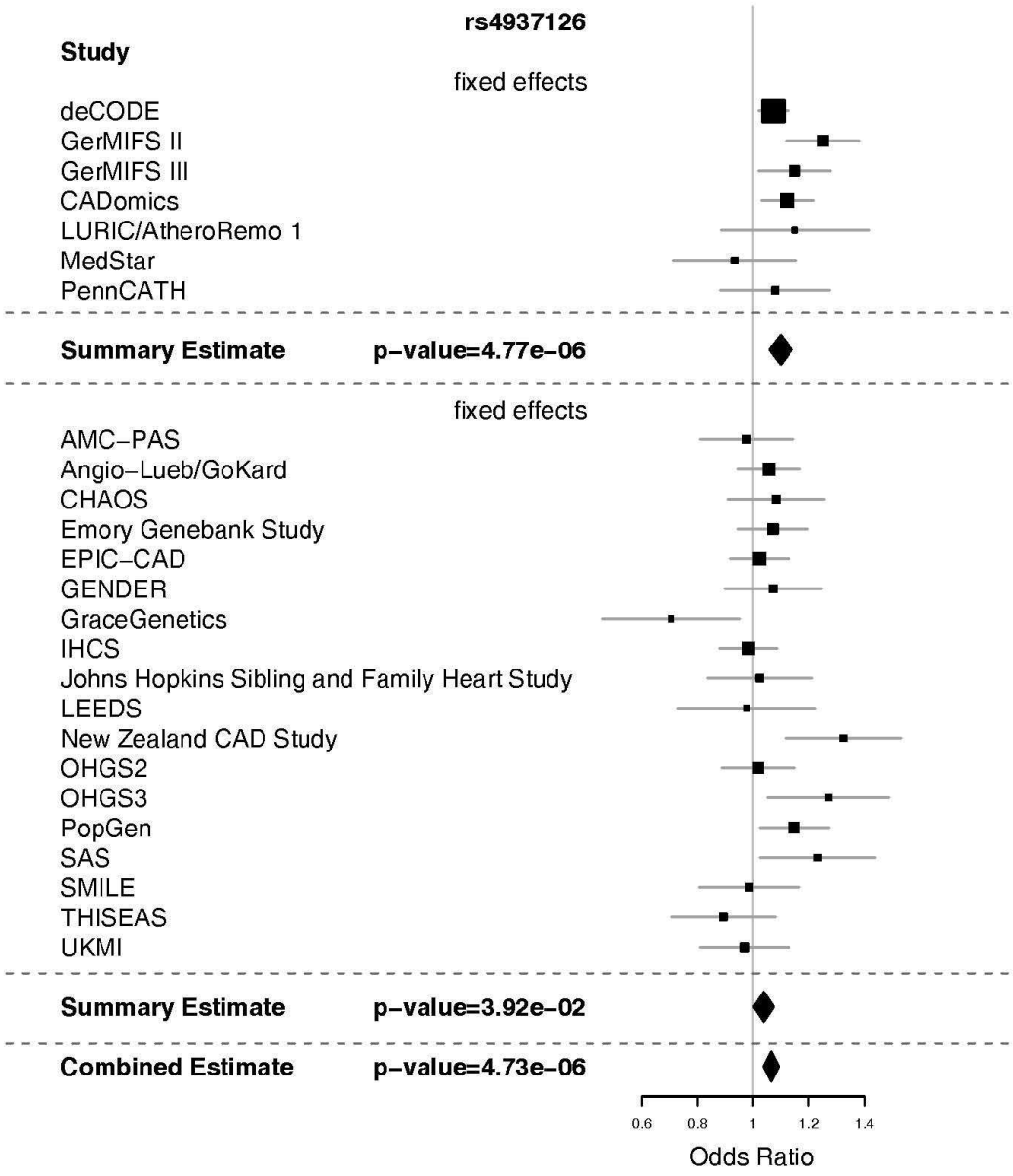
Nature Genetics: doi.10.1038/ng.784

10q21



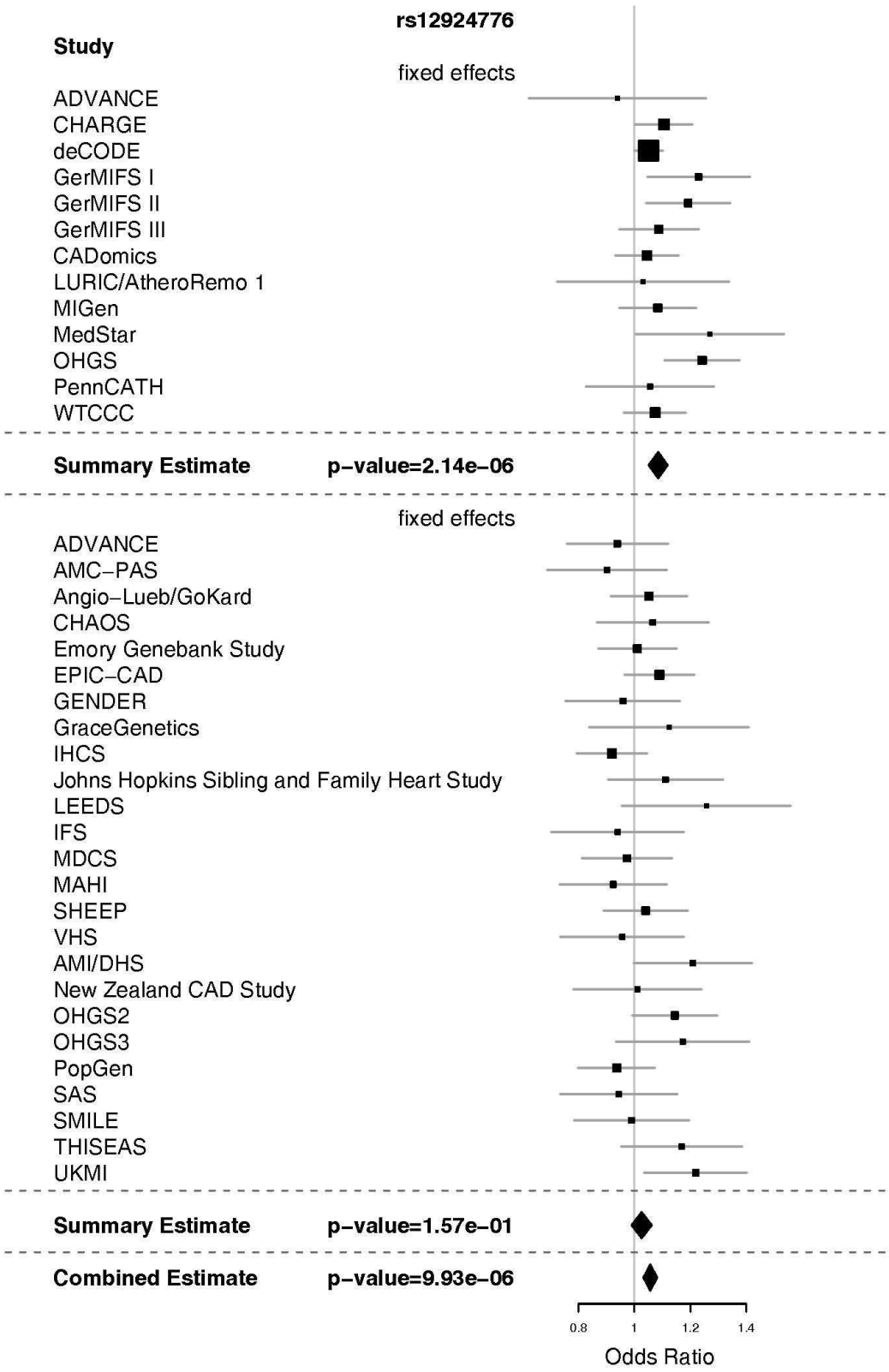
Nature Genetics: doi.10.1038/ng.784

11q24



Nature Genetics: doi.10.1038/ng.784

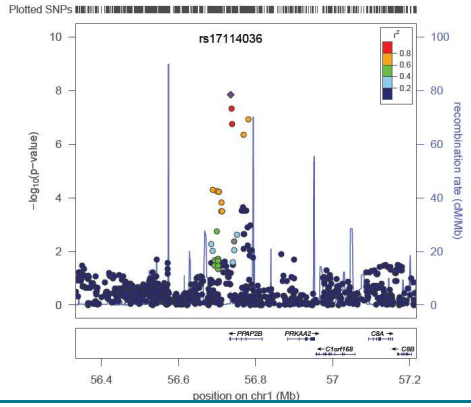
16q24



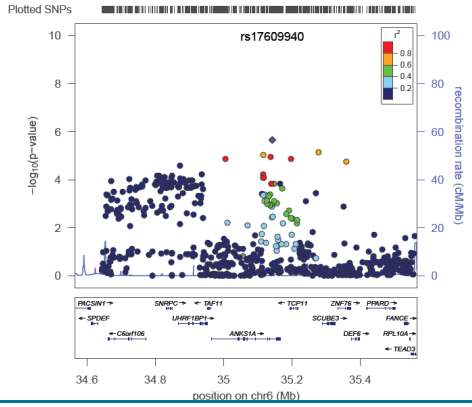
Nature Genetics: doi.10.1038/ng.784

Supplementary Figure 3: Regional association plots of the 13 novel CAD loci.

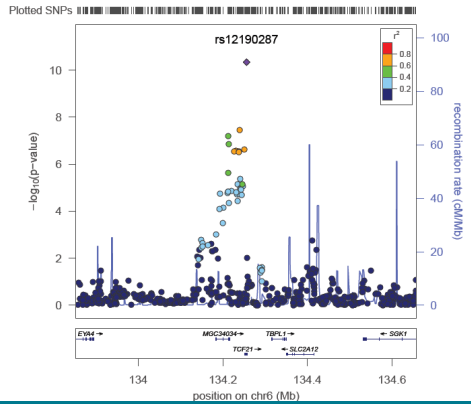
1p32.2



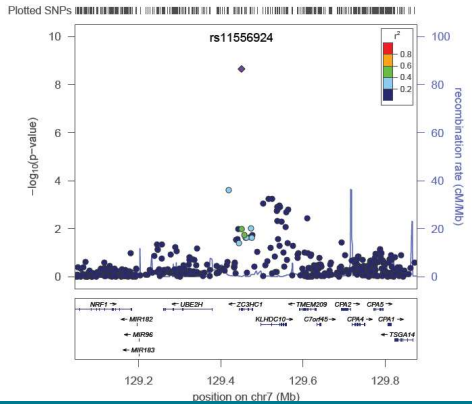
6p21.31



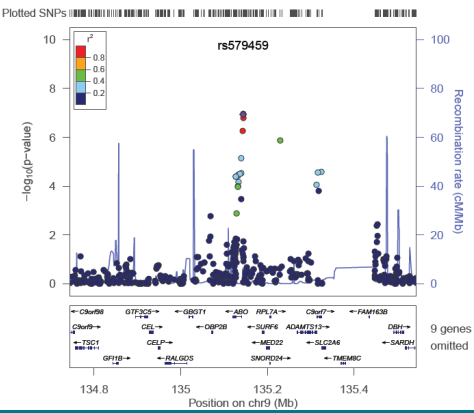
6q23.2



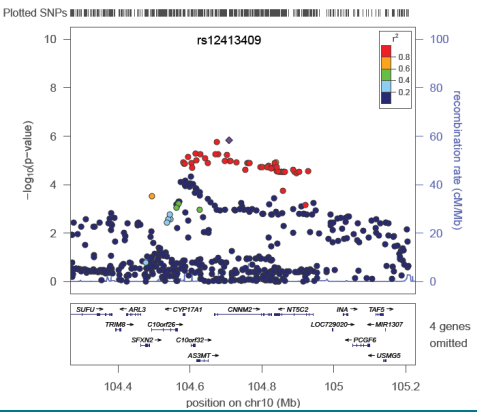
7q32.2



9q34.2

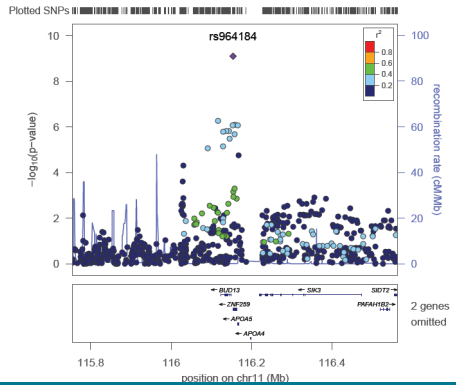


10q24.32

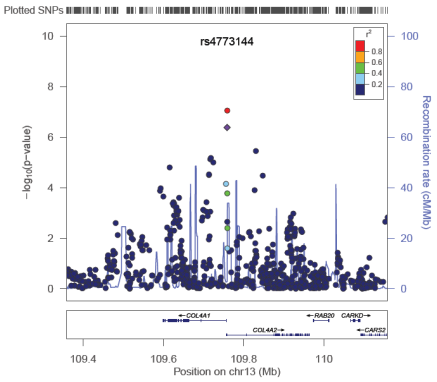


Nature Genetics: doi.10.1038/ng.784

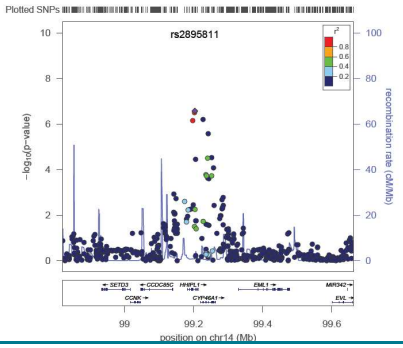
11q23.3



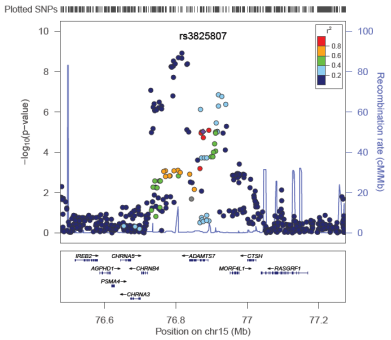
13q34



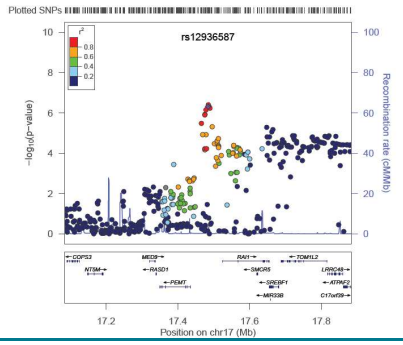
14q32.2



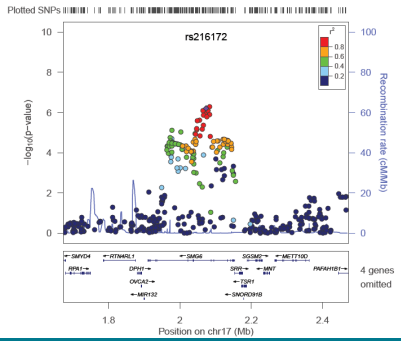
15q25.1



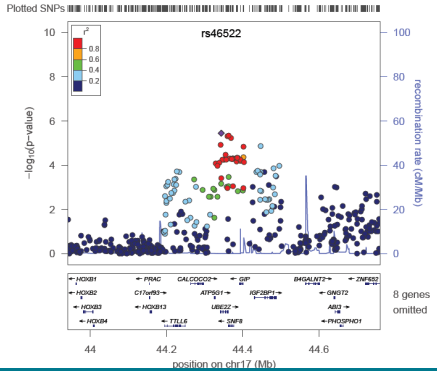
17p11.2



17p13.3

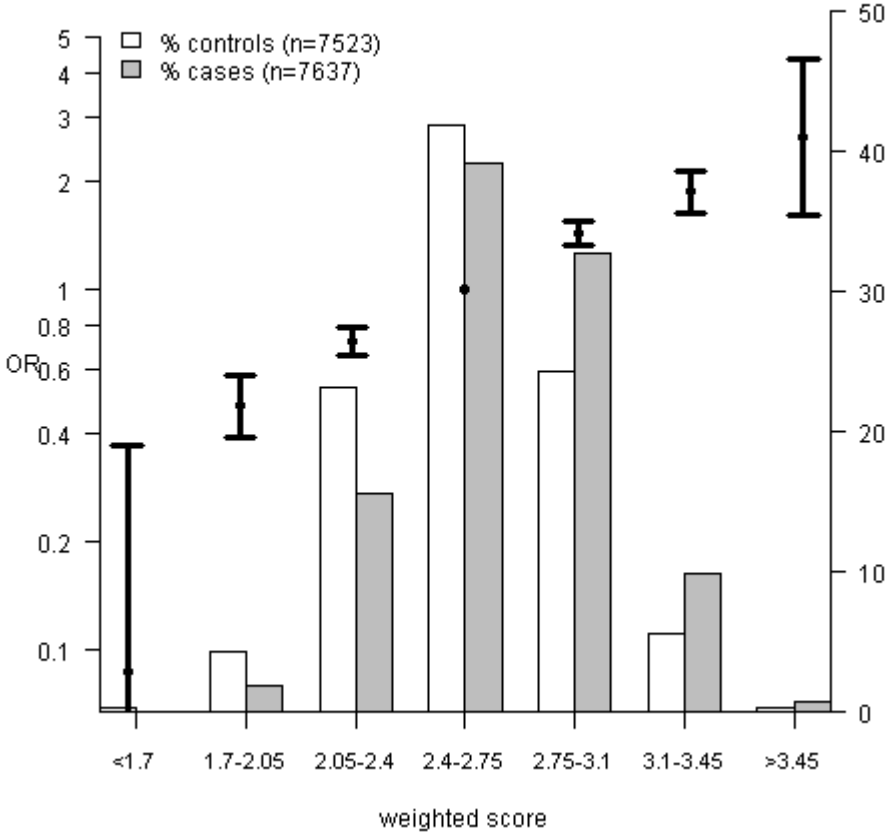


17q21.32



Nature Genetics: doi.10.1038/ng.784

Supplementary Figure 4: Distribution of categories of the weighted risk score. A weighted score, based on all risk alleles per individual multiplied by their log odds ratio, is shown for cases (dark bars) and controls (light bars). The brackets depict the respective odds ratios (95% confidence intervals) for coronary artery disease when compared with the middle category (n=15,171).



Nature Genetics: doi.10.1038/ng.784

3. Supplementary Tables

Supplementary Table 1a: Description of probands (cases/controls) in participating GWA studies in the discovery phase.

Study	Full name	N	% MI	% female	M (SD) Age	M (SD) BMI	CAD definition	Control definition	Ref
ADVANCE	Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology	278/ 312	50.4	57.9/ 59.0	45.8 (6.2)/ 45.3 (5.7)	31.2 (7.1)/ 26.5 (5.7)	Clinical non fatal CAD (men ≤45 yrs, women ≤55 yrs) including AMI (enzymes), typical angina with ≥1 artery with >50% stenosis, positive non invasive test, or PCI or CABG	No history of clinical CAD, CVA, or PAD	[1]
CADomics	Coronary Artery Disease and Omics	2078/ 2952	58.3	21.9/ 50.5	60.8 (10.1)/ 55.3 (10.8)	29.4 (5.1)/ 27.0 (4.7)	CAD: >50% stenosis in 1 major coronary artery and/or MI based on ECG and enzymes	Population sample with no history of MI	--
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology	2287/ 22024	48.0	33.4/ 59.6	60.0 (7.9)/ 63.1 (8.0)	28.1 (7.4)/ 27.5 (8.0)	CHD: definite or probable MI, PTCA or CABG, or ECG MI	None of the conditions that define CAD	[2]
deCODE CAD		6640/ 27611	54.7	36.3/ 61.9	74.8 (11.8)/ 53.7 (21.5)	27.7 (4.7)/ 27.0 (5.4)†	MI: MONICA criteria (<75 yrs) or discharge diagnosis of MI; CAD: PCI or participation in CVD genetics program with self-report of CABG or PCI, or discharge diagnosis of angina pectoris, MI or chronic ischaemic heart disease	Population sample	[3]
GERMIFS I	German Myocardial Infarction Family Studies	884/ 1604	100.0	49.4/ 50.8	50.2 (7.8)/ 62.6 (10.0)*	27.4 (3.6)/ 27.7 (4.5)	MI (<65 yrs) with >1 1st degree sibling with severe CAD (PTCA; MI; CABG)	Population sample	[4]
GERMIFS II		1222/ 1287	100.0	33.1/ 48.3	51.4 (7.5)/ 51.2 (11.9)*	29.0 (3.8)/ 27.4 (4.6)	MI (<60 yrs); 59.4% with family history of CAD	Population sample	[5]
GERMIFS III (KORA)		1157/ 1748	100.0	20.1/ 48.9	58.6 (8.7)/ 55.9 (10.7)*	27.0 (3.6)/ 27.1 (4.5)	MI (<60 yrs); MONICA criteria	Population sample	--
LURIC/ AtheroRemo 1	Ludwigshafen Risk and Cardiovascular Heath Study	652/ 213	71.9	20.3/ 46.0	61.0 (11.8)/ 58.3 (12.1)	27.7 (4.4)/ 27.4 (4.2)	Symptoms of angina pectoris, NSTEMI, STEMI, or >50% coronary stenosis	No coronary lesions or minor stenoses (<20%)	[6]

Nature Genetics: doi.10.1038/ng.784

Study	Full name	N	% MI	% female	M (SD) Age	M (SD) BMI	CAD definition	Control definition	Ref
LURIC/ AtheroRemo 2		486/ 296	79.0	23.4/ 48.6	63.7 (9.4)/ 56.4 (12.7)	27.1 (3.8)/ 26.8 (4.0)	Symptoms of angina pectoris, NSTEMI, STEMI, or >50% coronary stenosis	No coronary lesions or minor stenoses (<20%)	[6]
MedStar		874/ 447‡	48.1	33.0/ 54.6	48.9 (6.4)/ 59.7 (8.9)	31.7 (6.8)/ 31.3(7.9)	Angiography (≥1 coronary vessel with >50% stenosis); ≤55 for males and ≤60 for females.	Angiography normal, >45 yrs	[7]
MIGen	Myocardial Infarction Genetics Consortium	1274/ 1407	100.0	37.2/ 39.9	42.4 (6.6)/ 43.0 (7.8)*	27.6 (5.2)/ 25.8 (4.4)	MI (men <50 yrs / women <60 yrs)	Hospital-based, community based, or nested case-control	[8]
OHGS1	Ottawa Heart Genomics Study	1542/ 1455	61.6	24.1/ 48.0	48.7 (7.3)/ 75.0 (5.0)	28.5 (4.9)/ 26.0 (4.0)	Angiographic (>50% stenosis)	Asymptomatic	[9]
PennCATH		933/ 468‡	50.3	23.7/ 51.9	52.7 (7.6)/ 61.7 (9.6)	29.8 (5.6)/ 28.9 (6.4)	Angiography (≥1 coronary vessel with >50% stenosis); ≤60 for males and ≤65 for females.	Angiography normal, men >40 yrs / women >45 yrs	[8,10]
WTCCC§	Wellcome Trust Case Control Consortium	1926/ 2938	71.5	20.7/ 50.0	49.8 (7.7)/§	27.6 (4.2)/§	Validated MI, CABG, PTCA or angina with positive non-invasive testing <66 yrs	Unselected	[11]

M(SD) = mean (standard deviation); AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass surgery; CAD = coronary artery disease; CVA =cerebrovascular accident; CHD = coronary heart disease; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = Non-ST-Elevated Myocardial Infarciation; PTCA = percutaneous transluminal coronary angioplasty; STEMI = ST segment elevation myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention;

***** for cases age at diagnosis; for controls age at recruitment

† Information on BMI in the deCODE study is available for 81.7% of the cases and 66.8% of the controls.

‡ Cases: Angiographic CAD (>50% stenosis in at least 1 vessel); controls: Angiography normal or <10% stenosis in all vessels

§ WTCCC controls comprised of an equal number of subjects from the 1958 Birth Cohort and from the National Blood Service (NBS) Donors. The latter were recruited in equal 10 years age bands from 11 to 70 yrs of age. Additional phenotypes are not available for these controls.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 1b: Description of the genotyping methods in participating GWA studies in the discovery phase.

Study	Platform	Calling	Genotyped SNPs	Imputation algorithms / NCBI build / HapMap	Total SNPs	QC at study center
ADVANCE	Illumina 550k v3	BeadStudio	561,466	BIMBAM / 36 / r22a	3,732,514	Sample call rate >0.985 SNP call rate >0.95 HWE p >0.001
CADomics	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	602,459	IMPUTE / 36 / r22a	2,588,156	Sample call rate >0.97 SNP call rate >0.98 HWE p(controls) >10^{-4} MAF >0.01
CHARGE*	Illumina HCNV370 Duo BeadChip	BeadStudio	353,202	MACH/36/ r22	2,533,153	Sample call rate >0.97 SNP call rate >0.97 HWE p(controls) >10^{-6} MAF >0.01
CHARGE*	Affymetrix 6.0	Birdseed	589,253	MACH/35/r21	2,516,204	Sample call rate >0.95 SNP call rate >0.90 HWE p>10^{-6}
	Affymetrix 500K (Nsp 250K and Sty 250K) + MPS 50k	BRLMM	534,982	MACH/36/ r22,	2,543,887	Sample call rate >0.97 SNP call rate >0.97 Subject heterozygosity <5 SD from mean No excessive Mendelian errors
	Illumina Infinium HumanHap 550K	BeadStudio	530,683	MACH/36/ r22,	2,586,725	Subject call rate >0.975, heterozygosity <0.336, match on sex, no IBS outliers, SNP call rate >=0.98, HWE p >10^{-6}, MAF >0.01
deCODE CAD	Illumina HH300/HHCNV370	BeadStudio		Impute / 36		Sample call rate >0.98 SNP call rate >0.96
GerMIFS I	Affymetrix Mapping 500K Array Set	BRLMM	262,338(NSP)/ 238,378(STY)	MACH / 36 / r22a	2,543,887	Sample call rate >0.97 SNP call rate >0.98 HWE p(controls) >10^{-4} MAF >0.01
Study	**Platform**	**Calling**	**Genotyped SNPs**	**Imputation algorithms / NCBI**	**Total SNPs**	**QC at study center**

Nature Genetics: doi.10.1038/ng.784

				build / HapMap		
GerMIFS II	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	909,622	MACH / 36 / r22a	2,543,887	Sample call rate >0.97 SNP call rate >0.98 HWE p(controls) >10^{-4} MAF >0.01
GerMIFS III (KORA)	Affymetrix Genome-Wide Human SNP Array 5.0 / 6.0	BRLMM-P	503,590(5.0)/ 904,954(6.0)	MACH / 36 / r22a	2,536,369	Sample call rate >0.97 SNP call rate >0.98 HWE p(controls) >10^{-4} MAF >0.01
LURIC/ AtheroRemo 1	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	905,484	NA	905,484	SNP call rate >0.9†
LURIC/ AtheroRemo 2	Affymetrix Mapping 500K Array Set	DM-3	492,555	NA	492,555	SNP call rate >0.9†
MedStar	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	869,223	MACH / 36 / r22a	2,749,197	Sample call rate >0.95 SNP call rate >0.95 HWE – NA MAF – NA
MIGen	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	727,496	MACH / 35	2,557,744	Sample call rate >0.95 SNP call rate >0.95 HWE p(controls) >10^{-6} MAF >0.01
OHGS 1	Affymetrix Mapping 500K Array Set / Genome-Wide Human SNP Array 6.0	BRLMM/ Birdseed	325,040	Impute / 36 / r22	2,469,454	SNP call rate >0.95 HWE p(controls) >10^{-3} MAF >0.05
PennCATH	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed	869,223	MACH / 36 / r22a	2,749,197	Sample call rate >0.95 SNP call rate >0.95 HWE – NA MAF – NA
WTCCC	Affymetrix Mapping 500K Array Set	CHIAMO	477,459	IMPUTE / 36	2,614,446	Sample call rate >0.97 SNP call rate >0.98 HWE p(controls) >10^{-4} MAF - NA

ADVANCE = Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology; GerMIFS = German Myocardial Infarction Family Studies; WTCCC = Wellcome Trust Case Control Consortium; CHARGE = Cohorts for Heart and Aging Research in Genomic Epidemiology; LURIC = Ludwigshafen Risk and Cardiovascular Heath Study; OHGS = Ottawa Heart Genomics Study
QC = quality control; HWE = test for deviation from Hardy-Weinberg equilibrium; MAF = minor allele frequency
* Four entries for Charge refer to the studies AGES, ARIC, Fram HS, and RS
† Further criteria in LURIC/AtheroRemo: Removed samples based on relatedness, incorrect gender, outliers in the MDS map

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 1c: Results from the study-wise quality control in the discovery phase.

Study	Before QC	Missing	PCA/MDS	λ	MAF cases	MAF controls	Info	HWE	After QC
ADVANCE	3,833,253	610,578	no	1.049	1,775,204	1,772,952	1,571,572	198,254	1,543,559
CADomics	2,588,156	122,138	no	1.061	134,061	131,297	86,588	2,947	2,337,127
CHARGE	2,520,243	173,312	yes	1.007	0	0	33,481	0	2,327,692
deCODE CAD	2,459,609	36	no	1.022	59,090	58,019	37,729	16,349	2,355,027
GerMIFS I	2,543,887	472,639	no	1.29	301,682	260,131	293,368	10,565	1,864,784
GerMIFS II	2,543,887	152,466	no	1.006	148,341	149,095	107,446	1,757	2,249,971
GerMIFS III (KORA)	2,543,887	270,720	no	1.105	234,333	150,771	142,827	2,930	2,086,787
LURIC/AtheroRemo 1	905,484	902	yes	0.993	147,379	150,222	0	26,711	724,149
LURIC/AtheroRemo 2	492,555	944	yes	1.079	69,762	69,951	0	20,671	398,173
MedStar	2,749,197	170,263	no	1.002	259,611	261,741	91,296	7,351	2,317,029
MIGen	2,536,312	162,017	yes	1.03	111,426	111,611	94,588	6,324	2,263,277
OHGS 1	2,469,454	280,801	yes	1.066	176,845	175,775	157,023	18,086	2,033,144
PennCATH	2,749,197	175,608	no	0.997	258,332	262,513	96,812	11,212	2,311,218
WTCCC	2,614,446	264,412	yes	1.058	245,401	243,671	187,478	13,240	2,128,989

SNPs were excluded based on missing frequency in cases or controls > 0.02 (Missing), minor allele frequency in cases (MAF cases) or controls (MAF controls) < 0.01, quality of the imputation (INFO) < 0.5, deviation from Hardy-Weinberg equilibrium in controls (HWE) $p < 0.0001$. Some studies performed principal components analysis (PCA) or multidimensional scaling (MDS) and excluded results outliers or adjusted for the components. Single study results were adjusted by the variance inflation factor λ estimated from genotyped data only.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 2a: Description of probands (cases/controls) in participating studies for replication.

Study	N cases/controls	% MI	% female	M (SD) Age	M (SD) BMI	Ref
Acute Myocardial Infarction Gene Study/Dortmund Health Study (AMI/DHS)	809/1132	44.1	0.0/53.1	52.2 (8.2)/52.6 (13.7)	28.0 (4.7)/27.5 (4.9)	
ADVANCE	970/703	67.4	25.2/38.0	62.7 (8.0)/65.8 (2.9)	29.1 (5.2)/28.3 (5.3)	
AMC-PAS	611/688	81.5	22.9/32.3	41.0 (7.5)/46.7 (17.9)	n. a.	12
Angio-Lueb/GoKard	1,958/1,483	42.4	19.1/52.1	55.1 (6.9)/52.2 (13.3)	28.4 (4.8)	
CHAOS	693/1,792	n. a.	19.5/58.5	63.1 (10.2)/53.0 (7.7)	26.7 (4.1)/n. a.	
Cleveland Clinic GeneBank/OHGS2 (CC/OHGS2)	1,912/933	60.5	24.1/50.3	48.9 (7.3)/74.3 (5.8)	29.1 (5.4)/26.6 (4.4)	
EPIC-CAD	2,154/2,149	30.5	35.3/35.3	71.7 (8.3)/64.4 (7.9)		13
GENDER	925/688	0.0	26.6/34.9	62.1 (10.9)/46.9 (17.8)		14
GraceGenetics	660/663	86.6	24.1/43.0	65.2 (11.8)/41.0 (13.2)	26.9 (4.4)/n. a.	15
INTERHEART/EpiDREAM/OHGS3	1076/2076	64.1	20.1/53.8	63.7(9.9)/62.0(10.2)	27.4(4.5)/29.1(7.5)	
Intermountain Heart Collaborative Study (IHCS)	2,656/1,458	46.0	26.0/53.0	53.4 (7.1)/68.3 (7.2)	30.3 (6.3)/28.8 (6.1)	16-17
Irish Family Study (IFS)	604/755	67.9	19.9/55.5	51.8 (7.3)/56.9 (7.8)	28.5 (4.2)/28.1 (4.9)	18
Italian Atherosclerosis Thrombosis and Vascular Biology (IATVB)	1,693/1,668	50.0	11.4/11.6	39.4 (4.9)/39.3 (5.0)	26.7 (4.2) / 25.0 (3.3)	8
LEEDS	1,236/881	100.0	22.0/10.9	62.2 (11.3)/32.9 (10.2)		
Malmo Diet and Cancer Study (MDCS)	2,115	50.1	21.4	63.7 (5.9)	n. a.	
Mid-America Heart Institute (MAHI)	809/671	76.0	32.0/39.0	62.0 (13)/61.0 (12)	29.0 (6.0)/28.0 (6.0)	19
PopGen	2,131/1,566	60.2	18.9/0	61.2 (8.2)/51.2 (14.4)	27.9 (4.4)/26.7 (4.1)	
SAS	1,250/930	52.6	24.1/52.9	63.2 (10.1)/66.2 (11.5)		20
Study of Myocardial Infarction in LEiden (SMILE)	549/638	100.0	0/0	56.3 (9.0)/57.3 (10.8)	27.1 (3.4)/26.8 (3.5)	21
Stockholm Heart Epidemiology Program (SHEEP)	1,213/1,561	100.0	30.0/32.0	59.2 (7.1)/59.8 (7.1)	26.6 (4.1)/25.6 (3.7)	22
The Emory Genebank Study	1,738/1,099	53.0	27.0/51.0	57.8 (12.0)/ 66.3 (13.1)	29.1 (6.2)[a]/27.7 (10.5)[b]	3
The Johns Hopkins GeneSTAR Research Program (Genetic Study of Atherosclerotic Risk)	378/1,528	47.0	21.0/45.6	49.3 (8.1)/ 45.6 (12.6)	29.6 (5.5)[c]/28.6 (6.1)[d]	23
The New Zealand CAD Study	495/460	83.0	28.0/42.0	61.1 (10.4)/ 68.0 (6.6)	n. a.	24
THISEAS	502/1,050	59.4	16.3/51.6	59.4 (14.4)/55.6 (14.6)		25
UKMI	772/734	100.0	26.8/31.3	56.3 (12.1)/55.7 (10.9)	27.2 (4.8)/26.0 (3.7)	5,26-27
Verona Heart Study (VHS)	1,040/368	60.3	20.5/34.2	61.3 (10.0)/58.9 (12.2)	26.8 (3.5)/25.4 (3.4)	28

Number of individuals with BMI information [a] 1,623; [b] 421; [c] 278; [d] 1,506.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 2b: Description of the genotyping methods in participating studies for replication.

Study	Genotyping Platform
AMI/DHS	Sequenom
ADVANCE	TaqMan OpenArray
AMC-PAS	Sequenom
Angio-Lueb/GoKard	Sequenom
CHAOS	Sequenom
CC/OHGS2	Affymetrix 6.0
EPIC-CAD	Sequenom
GENDER	Sequenom
GraceGenetics	Sequenom
INTERHEART/EpiDREAM/OHGS3	Affymetrix 6.0
IHCS	Sequenom
IFS	Sequenom
IATVB	Affymetrix 6.0
LEEDS	Sequenom
MDCS	Sequenom
MAHI	Sequenom
PopGen	Sequenom
SAS	Sequenom
SMILE	Sequenom
SHEEP	Sequenom
The Emory Genebank Study	Centaurus (Nanogen)
The Johns Hopkins GeneSTAR Research Program	Illumina HumanHap 1M BeadArray
The New Zealand CAD Study	Centaurus (Nanogen)
THISEAS	Sequenom
UKMI	Sequenom
VHS	Sequenom

For explanation of study abbreviations, see Supplementary Table 1b.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 3: Detailed results for previously known loci.

	Risk	Risk allele	Meta-analysis											Replication (no outlier)									Combined Analysis			
SNP	allele	frequency	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	Outlier	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	P	OR	95% CI	
rs599839	A	0.78	2.89E-10	1.113	1.076	1.150	0.34	0.65	0.00	19.77	0.10	83873															
rs11206510	T	0.82	4.81E-04	1.083	1.036	1.133	0.09	0.47	0.00	13.15	0.36	49603		1.66E-04	0.93	0.90	0.97	0.45	0.11	0.66	41.63	0.01	49248	9.10E-08	1.08	1.05	1.11
rs17465637	C	0.74	1.36E-08	1.144	1.092	1.200																					
rs6725887	C	0.15	1.12E-09	1.140	1.093	1.190	0.00	0.63	0.00	7.04	0.85	77954															
rs2306374	C	0.18	3.34E-08	1.115	1.072	1.158	0.04	0.35	0.00	12.49	0.41	77843															
rs12526453	C	0.67	1.15E-09	1.096	1.064	1.128	0.48	0.73	0.02	23.28	0.03	83050															
rs3798220	C	0.02												9.62E-12	1.54	1.36	1.74	0.49	0.05	0.72	25.41	0.02	32500				
rs4977574	G	0.46	1.35E-22	1.290	1.226	1.357	0.61	0.78	0.30	33.44	0.00	84256															
rs1746048	C	0.87	5.78E-05	1.087	1.043	1.131	0.29	0.62	0.00	18.25	0.15	84159		6.58E-05	1.09	1.04	1.14	0.27	0.00	0.56	31.67	0.11	48761	2.12E-10	1.09	1.07	1.13
rs3184504	T	0.44	6.35E-06	1.073	1.041	1.106	0.51	0.00	0.96	16.30	0.04	67746															
rs1122608	G	0.77	9.73E-10	1.136	1.090	1.183	0.09	0.47	0.00	13.13	0.36	83938	DeCODE														
rs9982601	T	0.15	4.22E-10	1.178	1.119	1.240	0.20	0.61	0.00	11.26	0.26	80459	DeCODE														

OR, odds ratio; CI, confidence interval. All effects are from fixed effects models except for rs4977574 in discovery phase (random effects). Note that rs3798220 was not represented on the chips with adequate quality and that some SNPs were not included on the replication array.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 4: Detailed results for all SNPs in replication.

	Risk	Risk allele	Meta-analysis											Replication (no outlier)									Combined Analysis			
SNP	allele	frequency	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	Outlier	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	P	OR	95% CI	
rs17114036	A	0.91	1.43E-08	1.156	1.10	1.22	0.25	0.00	0.62	14.68	0.20	80870		3.18E-12	1.19	1.13	1.25	0.24	0.00	0.54	31.75	0.13	52356	3.81E-19	1.17	1.13	1.22
rs2404715	C	0.92	1.21E-07	1.143	1.09	1.20	0.26	0.00	0.62	14.81	0.19	82259		4.79E-09	1.17	1.11	1.24	0.19	0.00	0.52	25.96	0.21	45227	3.75E-15	1.16	1.12	1.20
rs10933436	A	0.49	3.22E-06	1.106	1.06	1.15	0.17	0.00	0.59	9.65	0.29	57487	DeCODE	4.70E-02	1.04	1.00	1.07	0.01	0.00	0.19	17.21	0.44	35003	7.06E-06	1.06	1.04	1.09
rs7651039	C	0.54	1.85E-08	1.153	1.10	1.21	0.41	0.00	0.74	11.96	0.10	49472	DeCODE	2.03E-02	1.03	1.01	1.06	0.27	0.00	0.55	32.84	0.11	50631	1.64E-06	1.06	1.04	1.09
rs9838412	C	0.79	3.23E-06	1.118	1.07	1.17	0.15	0.00	0.55	11.72	0.30	82314	DeCODE	5.81E-01	0.99	0.95	1.03	0.00	0.00	0.53	12.19	0.88	38400	7.50E-03	1.04	1.01	1.08
rs17609940	G	0.75	2.21E-06	1.081	1.05	1.12	0.12	0.00	0.50	14.77	0.32	83997		1.18E-03	1.06	1.02	1.10	0.00	0.00	0.48	16.14	0.91	53415	1.36E-08	1.07	1.05	1.10
rs12190423	G	0.61	4.53E-08	1.081	1.05	1.11	0.00	0.00	0.75	9.68	0.56	82410		4.71E-01	0.99	0.95	1.02	0.27	0.00	0.60	19.07	0.16	28316	5.42E-05	1.05	1.02	1.07
rs12524865	C	0.70	2.95E-07	1.083	1.05	1.12	0.00	0.00	0.66	8.10	0.70	82374		7.68E-03	1.05	1.01	1.08	0.09	0.00	0.44	23.14	0.34	45071	2.29E-08	1.07	1.04	1.09
rs12190287	C	0.62	4.64E-11	1.109	1.08	1.14	0.00	0.00	0.89	9.17	0.52	78290		3.25E-04	1.05	1.02	1.08	0.00	0.00	0.48	18.07	0.80	52598	1.07E-12	1.08	1.06	1.10
rs7808424	G	0.12	2.60E-07	1.149	1.09	1.21	0.34	0.00	0.68	15.17	0.13	81541	CHARGE	8.78E-02	1.05	0.99	1.10	0.29	0.00	0.57	32.26	0.09	46894	1.17E-06	1.10	1.06	1.14
rs11556924	C	0.62	2.22E-09	1.095	1.06	1.13	0.11	0.00	0.50	12.35	0.34	80011		7.37E-10	1.09	1.06	1.12	0.33	0.00	0.59	37.44	0.05	54189	9.18E-18	1.09	1.07	1.12
rs12682131	G	0.93	3.28E-06	1.246	1.14	1.37	0.00	0.00	0.80	6.68	0.57	73958		3.48E-02	0.87	0.76	0.99	0.00	0.00	0.54	12.71	0.81	40030	1.05E-02	1.10	1.02	1.19
rs651007	T	0.19	5.53E-07	1.099	1.06	1.14	0.01	0.00	0.11	10.07	0.43	77802		8.84E-08	1.10	1.06	1.14	0.15	0.00	0.48	26.98	0.26	46942	2.36E-13	1.10	1.07	1.13
rs579459	C	0.21	1.16E-07	1.103	1.06	1.14	0.00	0.00	0.71	6.66	0.67	77138		7.02E-08	1.10	1.06	1.14	0.33	0.00	0.60	31.23	0.07	46840	4.08E-14	1.10	1.07	1.13
rs7920682*	A	0.54	2.35E-03	1.078	1.03	1.13	0.55	0.17	0.76	26.95	0.01	81546		9.16E-03	1.04	1.01	1.07	0.31	0.00	0.58	31.74	0.08	47348	1.44E-04	1.05	1.02	1.08
rs16911227	G	0.93	5.98E-06	1.190	1.10	1.28	0.00	0.00	0.93	10.27	0.51	82546		7.95E-01	0.99	0.92	1.07	0.00	0.00	0.50	18.60	0.72	48134	2.31E-03	1.09	1.03	1.15
rs12411886	C	0.89	1.72E-06	1.129	1.07	1.19	0.00	0.00	0.67	8.45	0.67	79283		5.75E-04	1.09	1.04	1.15	0.32	0.00	0.59	33.81	0.07	49285	5.59E-09	1.11	1.07	1.15
rs12413409	G	0.89	1.47E-06	1.129	1.07	1.19	0.00	0.00	0.62	9.51	0.73	80940		1.38E-04	1.10	1.05	1.16	0.08	0.00	0.42	23.98	0.35	48801	1.03E-09	1.12	1.08	1.16
rs964184	G	0.13	8.02E-10	1.134	1.09	1.18	0.46	0.00	0.73	20.52	0.04	82562		2.20E-09	1.13	1.08	1.17	0.28	0.00	0.56	33.20	0.10	52930	1.02E-17	1.13	1.10	1.16
rs4937126	G	0.69	4.77E-06	1.099	1.06	1.14	0.16	0.00	0.60	7.15	0.31	47284		3.92E-02	1.04	1.00	1.08	0.42	0.00	0.67	29.35	0.03	38469	4.73E-06	1.06	1.04	1.09
rs4773144	G	0.44	4.15E-07	1.083	1.05	1.12	0.00	0.00	0.68	6.75	0.75	77113		1.31E-03	1.06	1.02	1.09	0.00	0.00	0.55	16.11	0.65	37681	3.84E-09	1.07	1.05	1.09
rs4624107	C	0.44	7.03E-07	1.086	1.05	1.12	0.41	0.00	0.75	10.25	0.11	66494		1.09E-03	1.05	1.02	1.09	0.00	0.00	0.55	15.99	0.66	42654	6.75E-09	1.07	1.05	1.09
rs2895811	C	0.43	2.67E-07	1.090	1.06	1.13	0.13	0.00	0.56	6.91	0.33	63184		4.59E-05	1.06	1.03	1.09	0.00	0.00	1.00	22.53	0.49	51054	1.14E-10	1.07	1.05	1.10
rs3825807	A	0.57	9.63E-06	1.065	1.04	1.10	0.54	0.09	0.77	21.74	0.02	80849		1.39E-08	1.09	1.06	1.12	0.23	0.00	0.54	28.39	0.16	48803	1.07E-12	1.08	1.05	1.10
rs12924776	T	0.20	2.14E-06	1.085	1.05	1.12	0.00	0.00	0.74	10.72	0.55	83114		1.57E-01	1.03	0.99	1.06	0.03	0.00	0.30	24.70	0.42	50889	9.93E-06	1.06	1.03	1.08

Nature Genetics: doi.10.1038/ng.784

	Risk	Risk allele	Meta-analysis											Replication (no outlier)									Combined Analysis			
SNP	allele	frequency	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	Outlier	P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	P	OR	95% CI	
rs1231206	A	0.37	8.69E-07	1.075	1.04	1.11	0.39	0.00	0.70	16.30	0.09	81442		2.11E-04	1.06	1.03	1.10	0.00	0.00	0.05	20.04	0.46	43570	8.52E-10	1.07	1.05	1.09
rs216172	C	0.37	6.22E-07	1.084	1.05	1.12	0.42	0.00	0.73	13.79	0.09	57235		2.11E-04	1.06	1.03	1.09	0.00	0.00	0.68	24.03	0.52	54303	1.15E-09	1.07	1.05	1.09
rs12936587	G	0.56	4.89E-07	1.077	1.05	1.11	0.46	0.00	0.74	16.81	0.05	76952		1.35E-04	1.06	1.03	1.09	0.23	0.00	0.53	31.12	0.15	52648	4.45E-10	1.07	1.04	1.09
rs12449964	C	0.56	4.02E-07	1.078	1.05	1.11	0.42	0.00	0.71	17.33	0.07	77873		2.38E-03	1.05	1.02	1.08	0.25	0.00	0.56	28.02	0.14	45088	8.43E-09	1.06	1.04	1.09
rs46522	T	0.53	3.57E-06	1.066	1.04	1.10	0.42	0.00	0.69	22.29	0.05	83867		8.88E-04	1.05	1.02	1.08	0.10	0.00	0.43	27.91	0.31	53766	1.81E-08	1.06	1.04	1.08

OR, odds ratio; CI, confidence interval. All effects are from fixed effects models except for rs7920682 in discovery phase (random effects).

*In the discovery phase, this region had been selected based on SNP rs2505083 (p = 3.26E-06). For technical reasons, SNP rs7920682 was selected instead for replication.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 5: Detailed results for SNPs in putatively associated loci.

SNP	Gene(s) in region	Risk allele	Risk allele frequency	Meta-analysis										
				P	OR	95% CI		I^2	95% CI		Q	P (Q)	n	Outlier
rs17672135[1]	*FMN2*	T	0.85	1.07E-01	1.035	0.993	1.079	0.39	0.00	0.68	21.45	0.06	84091	
rs383830[1]	*APC*	T	0.78	1.02E-01	1.029	0.994	1.064	0.43	0.00	0.70	21.20	0.05	83548	
rs6922269[1]	*MTHFD1L*	A	0.28	7.38E-05	1.063	1.031	1.095	0.50	0.07	0.73	25.86	0.02	83946	
rs17228212[2]	*SMAD3*	C	0.31	3.82E-01	1.014	0.983	1.046	0.43	0.00	0.70	20.99	0.05	84169	WTCCC
rs8055236[1]	*CDH13*	G	0.80	2.73E-02	1.039	1.004	1.075	0.14	0.00	0.53	15.18	0.30	80936	
rs7250581[1]	*VSTM2B*	G	0.77	2.24E-01	1.023	0.986	1.060	0.24	0.00	0.61	14.51	0.21	81100	
rs688034[1]	*SEZ6L*	C	0.68	5.62E-01	1.009	0.979	1.040	0.32	0.00	0.65	17.73	0.12	84005	WTCCC

OR, odds ratio; CI, confidence interval. All effects are from fixed effects models.

1. WTCCC. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-678 (2007).
2. Samani, N.J.*, et al.* Genomewide association analysis of coronary artery disease. *N Engl J Med* **357**, 443-453 (2007).

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 6: Association analysis of novel regions assuming different modes of inheritance and estimating the likely mode of inheritance.

SNP	Band	Gene in region	Risk allele	P additive	P dominant	P recessive	θ_1	P_1	θ_2	P_2	P_3	MOI
rs17114036	1p32.2	*PPAP2B*	A	$1.43 \cdot 10^{-08}$	$9.87 \cdot 10^{-02}$	$7.63 \cdot 10^{-10}$	0.05	0.659	0.21	0.059	<0.001	rec
rs17609940	6p21.31	*ANKS1A*	G	$2.21 \cdot 10^{-06}$	$4.30 \cdot 10^{-03}$	$1.57 \cdot 10^{-06}$	0.07	0.111	0.15	<0.001	<0.001	rec
rs12190287	6q23.2	*TCF21*	C	$4.64 \cdot 10^{-11}$	$1.00 \cdot 10^{-04}$	$1.12 \cdot 10^{-08}$	0.06	0.036	0.16	<0.001	<0.001	add
rs11556924	7q32.2	*ZC3HC1*	C	$2.22 \cdot 10^{-09}$	$6.88 \cdot 10^{-06}$	$1.70 \cdot 10^{-07}$	0.09	0.004	0.17	<0.001	<0.001	add
rs579459	9q34.2	*ABO*	C	$1.16 \cdot 10^{-07}$	$1.18 \cdot 10^{-08}$	$1.50 \cdot 10^{-02}$	0.11	<0.001	0.17	0.001	0.298	dom
rs12413409	10q24.32	*CYP17A1, CNNM2, NT5C2*	G	$1.47 \cdot 10^{-06}$	$2.11 \cdot 10^{-02}$	$1.52 \cdot 10^{-05}$	0.18	0.122	0.28	0.014	<0.001	rec
rs964184	11q23.3	*ZNF259, APOA5, APOA1*	G	$8.02 \cdot 10^{-10}$	$1.59 \cdot 10^{-09}$	$6.00 \cdot 10^{-04}$	0.12	<0.001	0.27	<0.001	0.026	add
rs4773144	13q34	*COL4A1, COL4A2*	G	$4.15 \cdot 10^{-07}$	$8.99 \cdot 10^{-06}$	$3.00 \cdot 10^{-04}$	0.08	0.001	0.14	<0.001	0.022	add
rs2895811	14q32.2	*HHIPL1, CYP46A1*	C	$2.67 \cdot 10^{-07}$	$1.20 \cdot 10^{-03}$	$2.71 \cdot 10^{-06}$	0.05	0.072	0.16	<0.001	<0.001	rec
rs3825807	15q25.1	*ADAMTS7*	A	$9.63 \cdot 10^{-06}$	$1.60 \cdot 10^{-03}$	$1.35 \cdot 10^{-05}$	0.05	0.071	0.12	<0.001	<0.001	rec
rs12936587	17p11.2	*Rall, PEMT, RADS1*	G	$4.89 \cdot 10^{-07}$	$2.00 \cdot 10^{-04}$	$3.05 \cdot 10^{-06}$	0.06	0.021	0.14	<0.001	<0.001	add
rs216172	17p13.3	*SMG6, SRR*	C	$6.22 \cdot 10^{-07}$	$5.87 \cdot 10^{-08}$	$4.00 \cdot 10^{-04}$	0.09	<0.001	0.15	<0.001	0.059	dom
rs46522	17q21.32	*UBE2Z*	T	$3.57 \cdot 10^{-06}$	$1.55 \cdot 10^{-05}$	$6.17 \cdot 10^{-05}$	0.08	<0.001	0.13	<0.001	0.027	add

P additive, dominant and recessive = association p-values assuming an additive, dominant and recessive mode of inheritance. θ_1 and θ_2 = log odds ratios corresponding to the heterozygous and homozygous effects, modeled in a bivariate response (see Online Methods for further explanation); P_1 = P value for testing H_0: $\theta_1 = 0$; P_2 = P value for testing H_0: $\theta_2 = 0$; P_3 = P value for testing H_0: $\theta_1 = \theta_2$;MOI = estimated mode of inheritance.

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 7: Results in subgroups for regions with genome-wide significance.

Known regions																					
	Risk	Males					Females					Young					Old				
SNP	allele	P	OR	95% CI		n	P	OR	95% CI		n	P	OR	95% CI		n	P	OR	95% CI		n
rs11206510	T																4.82E-03	1.087	1.026	1.152	20446
rs599839	A	5.69E-07	1.127	1.075	1.180	32165	4.69E-06	1.149	1.082	1.219	30111	1.05E-08	1.193	1.123	1.267	46195	5.49E-06	1.106	1.059	1.155	51279
rs6725887	C	2.75E-04	1.116	1.052	1.184	30409	1.02E-05	1.184	1.098	1.276	29164	1.34E-04	1.162	1.076	1.255	44371	8.95E-06	1.133	1.072	1.197	49603
rs2306374	C	8.88E-05	1.112	1.055	1.173	30330	3.69E-03	1.106	1.033	1.184	29123	2.89E-06	1.183	1.103	1.270	44320	1.42E-06	1.130	1.075	1.187	49528
rs12526453	C	1.15E-06	1.107	1.062	1.153	31792	4.78E-05	1.117	1.059	1.178	29676	1.28E-04	1.109	1.052	1.170	45571	1.33E-02	1.091	1.018	1.168	50688
rs4977574	G	1.08E-45	1.314	1.266	1.365	32410	1.12E-13	1.202	1.145	1.261	30278	1.41E-42	1.410	1.342	1.481	46462	1.44E-32	1.240	1.197	1.285	51553
rs1746048	C	4.03E-03	1.086	1.027	1.149	32334	3.42E-04	1.143	1.063	1.230	30255	3.63E-05	1.164	1.083	1.251	46406	4.71E-06	1.133	1.074	1.195	51512
rs3184504	T	9.84E-04	1.078	1.031	1.128	24070	6.12E-04	1.215	1.087	1.359	25245	2.86E-05	1.161	1.083	1.245	36715	1.03E-05	1.097	1.053	1.143	41633
rs1122608	G	9.59E-07	1.118	1.069	1.170	32181	1.63E-01	1.042	0.984	1.104	30159	1.74E-07	1.169	1.102	1.239	46266	4.76E-04	1.078	1.034	1.125	51342
rs9982601	T	1.32E-05	1.130	1.070	1.195	29976	9.12E-02	1.062	0.990	1.140	28912	6.49E-09	1.246	1.156	1.341	44152	1.13E-03	1.091	1.035	1.150	48652
Novel regions																					
	Risk	Males					Females					Young					Old				
SNP	allele	P	OR	95% CI		n	P	OR	95% CI		n	P	OR	95% CI		n	P	OR	95% CI		n
rs17114036	A	8.33E-06	1.180	1.097	1.270	30150	7.15E-03	1.129	1.034	1.234	29159	4.94E-03	1.142	1.041	1.252	44420	1.54E-05	1.159	1.084	1.240	48812
rs17609940	G	1.22E-05	1.108	1.058	1.160	32261	2.94E-02	1.066	1.006	1.130	30166	5.72E-04	1.114	1.047	1.184	46293	1.87E-03	1.070	1.025	1.116	51358
rs12190287	C	8.70E-06	1.103	1.056	1.103	28820	1.78E-02	1.070	1.012	1.132	27837	2.91E-03	1.091	1.030	1.156	42148	5.86E-06	1.098	1.055	1.144	46789
rs11556924	C	2.88E-07	1.116	1.070	1.116	29882	9.61E-03	1.073	1.017	1.133	28538	4.96E-08	1.159	1.099	1.222	43516	1.20E-05	1.093	1.050	1.137	47871
rs579459	C	2.56E-07	1.140	1.084	1.140	30067	3.98E-03	1.102	1.031	1.177	27860	2.04E-04	1.142	1.065	1.225	40262	8.11E-04	1.086	1.035	1.140	46290
rs12413409	G	1.12E-03	1.120	1.046	1.120	32349	1.28E-04	1.185	1.086	1.293	30210	3.20E-06	1.232	1.128	1.345	46344	7.45E-05	1.135	1.066	1.208	51446
rs964184	G	2.38E-06	1.144	1.082	1.210	31423	3.64E-03	1.215	1.066	1.386	29560	1.25E-07	1.219	1.132	1.311	45337	2.20E-03	1.086	1.030	1.146	50294
rs4773144	G	3.19E-05	1.098	1.051	1.098	27987	6.74E-03	1.083	1.022	1.147	27527	1.63E-04	1.115	1.053	1.179	41699	3.64E-04	1.078	1.034	1.123	46180
rs2895811	C	7.35E-04	1.088	1.036	1.088	21228	1.01E-02	1.078	1.018	1.142	23579	9.91E-03	1.113	1.026	1.207	33246	2.95E-05	1.099	1.052	1.150	37523
rs12936587	G	2.22E-03	1.108	1.062	1.156	29036	4.87E-02	1.056	1.000	1.116	26019	1.23E-04	1.115	1.055	1.179	41351	2.50E-05	1.086	1.045	1.129	45735
rs216172	C	2.41E-06	1.069	1.024	1.117	32199	6.71E-03	1.078	1.021	1.139	28219	1.59E-09	1.181	1.119	1.247	44758	2.78E-04	1.074	1.033	1.116	49277
rs3825807	A	6.70E-04	1.072	1.030	1.115	30288	9.97E-03	1.068	1.016	1.124	28999	5.18E-04	1.098	1.041	1.157	44389	1.78E-03	1.061	1.022	1.102	48896
rs46522	T	6.78E-06	1.091	1.050	1.133	26477	4.98E-03	1.073	1.021	1.126	30098	3.84E-05	1.110	1.056	1.167	46186	9.08E-04	1.062	1.025	1.101	51256

Males = test of all male cases versus all male controls; Females = test of all female cases versus all female controls; Young = test of all cases with early age of onset (<=50 years) versus all controls; Old = test of all cases with late age of onset (>50 years) versus all controls.
OR = per allele odds ratio; CI = confidence interval.
All effects are from fixed effects models except for rs964184 in females (random effects).

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 8: Results in subgroup of cases with myocardial infarction and angiographically defined CAD versus controls.

Known regions											
	Risk	Myocardial infarction					Angiography				
SNP	allele	P	OR	95% CI		n	P	OR	95% CI		n
rs11206510	T	1.33E-03	1.096	1.036	1.159	22157	4.31E-01	1.040	0.943	1.147	7347
rs599839	A	4.28E-08	1.124	1.078	1.172	53489	1.84E-05	1.226	1.117	1.346	7355
rs6725887	C	4.89E-07	1.145	1.086	1.208	51314	3.77E-03	1.266	1.079	1.485	4323
rs2306374	C	8.45E-10	1.163	1.108	1.221	51206	7.03E-02	1.140	0.989	1.314	4255
rs12526453	C	8.56E-07	1.097	1.057	1.138	52750	2.67E-01	1.098	0.931	1.296	7155
rs4977574	G	1.02E-19	1.326	1.248	1.409	53808	1.01E-19	1.430	1.324	1.545	7364
rs1746048	C	8.19E-06	1.123	1.067	1.182	53732	2.41E-02	1.138	1.017	1.272	7285
rs3184504	T	1.17E-06	1.105	1.061	1.151	42287					
rs1122608	G	2.37E-05	1.091	1.048	1.136	53482	9.53E-05	1.201	1.095	1.317	7290
rs9982601	T	4.73E-08	1.223	1.138	1.315	47928	2.51E-03	1.200	1.066	1.351	5307
Novel regions											
	Risk	Myocardial infarction					Angiography				
SNP	allele	P	OR	95% CI		n	P	OR	95% CI		n
rs17114036	A	7.14E-06	1.157	1.086	1.234	51047	5.51E-05	1.351	1.167	1.563	5329
rs17609940	G	3.42E-04	1.078	1.035	1.123	53680	1.05E-01	1.086	0.983	1.200	7324
rs12190287	C	5.91E-08	1.114	1.071	1.159	48181	2.22E-02	1.108	1.015	1.209	5965
rs11556924	C	9.06E-09	1.113	1.073	1.155	52572	7.49E-04	1.142	1.057	1.234	7251
rs579459	C	5.16E-07	1.127	1.075	1.180	48418					
rs12413409	G	6.50E-07	1.168	1.099	1.242	53689	1.88E-02	1.179	1.028	1.352	7360
rs964184	G	9.67E-06	1.122	1.066	1.181	52381	3.71E-06	1.309	1.168	1.467	6513
rs4773144	G	3.41E-05	1.089	1.046	1.134	47318	2.98E-03	1.174	1.056	1.305	4260
rs2895811	C	3.91E-05	1.102	1.052	1.154	37421					
rs12936587	G	1.52E-06	1.096	1.056	1.138	47155	4.24E-05	1.193	1.096	1.298	4957
rs3825807	A	1.53E-04	1.071	1.034	1.110	51074	2.03E-05	1.202	1.104	1.308	5428
rs216172	C	2.40E-06	1.094	1.054	1.135	51527					
rs46522	T	6.47E-04	1.062	1.026	1.099	53580	8.03E-02	1.073	0.992	1.162	7135

OR = per allele odds ratio; CI = confidence interval.
All effects are from fixed effects models except for rs4977574 (random effects in myocardial infarction) and rs12526453 (random effects in angiography).

Nature Genetics: doi.10.1038/ng.784

***Supplementary Table 9**:* Description of probands from population-based cohorts ARIC and KORA.

Study	Full name	N	% female	M (range) Age	M (SD) BMI	% Hypertension	% Diabetes	% Smoker	M (SD) HDL	M (SD) LDL
ARIC	Atherosclerosis Risk in Communities	9694	47.1	54 (45-64)	27.0 (4.9)	27.0	8,7	24.6	50.5 (16.7)	137.7 (37.8)
KORA F3	KOoperative Gesundheitsforschung in der Region Augsburg	1644	50.6	62.5 (35-79)	28.1 (4.5)	47.1	11.0	48.2	58.1 (16.9)	130.1 (32.7)
KORA F4	KOoperative Gesundheitsforschung in der Region Augsburg	1814	51.3	60.9 (32.81)	28.2 (4.8)	37.2	9.2	54.0	56.5 (14.5)	139.9 (35.0)

M (SD) = mean (standard deviation); BMI = body mass index (kg/m^2); Hypertension = actual Hypertension (> 160/95 mmHg) or medicamentous controlled hypertension; Diabetes = self-report of diabetes mellitus; Smoker = self-report of current or former smoking; HDL = HDL cholesterol (mg/dl); LDL = LDL cholesterol (mg/dl)

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 10: Effects of novel coronary disease loci on traditional risk factors in combined analysis of ARIC and KORA F3/F4 (n = 13,171).

SNP	Phenotype	KORA F4 Effect (95% CI)	KORA F3 Effect (95% CI)	ARIC Effect (95% CI)	Combined Effect (95% CI)	P
rs17114036	HDL	0.665 (-0.934 to 2.265)	2.014 (0.024 to 4.003)	-0.315 (-1.075 to 0.444)	0.094 (-0.555 to 0.743)	0.7764
	LDL	-2.409 (-6.546 to 1.727)	0.22 (-3.901 to 4.342)	0.857 (-1.055 to 2.769)	0.272 (-1.326 to 1.872)	0.7381
	TotalChol	-1.623 (-6.216 to 2.969)	2.536 (-2.521 to 7.595)	0.695 (-1.341 to 2.731)	0.579 (-1.167 to 2.326)	0.5157
	BMI	0.801 (0.243 to 1.36)	0.34 (-0.217 to 0.898)	-0.231 (-0.476 to 0.013)	-0.008 (-0.216 to 0.2)	0.9387
	Diabetes	1.469 (0.933 to 2.314)	1.268 (0.809 to 1.989)	0.924 (0.774 to 1.102)	1.012 (0.867 to 1.18)	0.8792
	Hypertension	0.976 (0.753 to 1.265)	0.929 (0.71 to 1.216)	1.038 (0.923 to 1.168)	1.013 (0.917 to 1.12)	0.7856
	Smoking	1.137 (0.885 to 1.459)	0.989 (0.759 to 1.29)	0.981 (0.873 to 1.104)	1.005 (0.911 to 1.11)	0.9088
rs17609940	HDL	0.341 (-0.765 to 1.448)	0.34 (-1.011 to 1.691)	0.651 (0.126 to 1.176)	0.566 (0.119 to 1.014)	0.0130
	LDL	1.58 (-1.281 to 4.442)	-0.374 (-3.17 to 2.421)	-1.241 (-2.563 to 0.081)	-0.686 (-1.79 to 0.416)	0.2225
	TotalChol	2.828 (-0.346 to 6.004)	-0.017 (-3.45 to 3.414)	-1.24 (-2.646 to 0.165)	-0.504 (-1.709 to 0.699)	0.4112
	BMI	1.19 (2.233 to 4.841)	0.149 (-0.228 to 0.526)	-0.164 (-0.333 to 0.004)	-0.072 (-0.216 to 0.07)	0.3194
	Diabetes	0.852 (0.636 to 1.142)	0.927 (0.698 to 1.231)	0.944 (0.832 to 1.071)	0.929 (0.834 to 1.034)	0.1794
	Hypertension	1.004 (0.84 to 1.201)	1.151 (0.96 to 1.379)	0.989 (0.913 to 1.072)	1.013 (0.946 to 1.084)	0.6999
	Smoking	1.067 (0.896 to 1.269)	0.929 (0.776 to 1.112)	0.973 (0.897 to 1.056)	0.98 (0.916 to 1.05)	0.5815
rs12190287	HDL	0.327 (-0.598 to 1.253)	-0.75 (-2.033 to 0.531)	0.006 (-0.427 to 0.441)	-0.005 (-0.381 to 0.37)	0.9778
	LDL	-2.803 (-5.194 to -0.412)	0.3 (-2.353 to 2.955)	-0.531 (-1.626 to 0.563)	-0.774 (-1.706 to 0.157)	0.1035
	TotalChol	-2.485 (-5.14 to 0.169)	0.58 (-2.678 to 3.839)	-0.72 (-1.884 to 0.442)	-0.851 (-1.864 to 0.16)	0.0992
	BMI	-0.184 (-0.507 to 0.139)	0.423 (0.065 to 0.78)	-0.093 (-0.233 to 0.046)	-0.047 (-0.168 to 0.073)	0.4416
	Diabetes	0.958 (0.754 to 1.216)	1.164 (0.891 to 1.519)	0.949 (0.856 to 1.052)	0.972 (0.889 to 1.063)	0.5429
	Hypertension	0.987 (0.848 to 1.148)	1.105 (0.931 to 1.312)	0.995 (0.93 to 1.063)	1.005 (0.949 to 1.065)	0.8427
	Smoking	1.044 (0.902 to 1.208)	1.071 (0.903 to 1.271)	1.023 (0.956 to 1.094)	1.032 (0.974 to 1.093)	0.2823
rs11556924	HDL	-0.015 (-0.953 to 0.921)	-1.083 (-2.162 to -0.003)	-0.263 (-0.696 to 0.169)	-0.321 (-0.69 to 0.048)	0.0886
	LDL	1.461 (-0.96 to 3.883)	2.232 (-0.001 to 4.465)	0.487 (-0.603 to 1.579)	0.913 (0.004 to 1.823)	0.0488
	TotalChol	2.406 (-0.28 to 5.094)	2.91 (0.168 to 5.651)	0.358 (-0.802 to 1.518)	0.972 (-0.02 to 1.965)	0.0549
	BMI	0.02 (-0.307 to 0.347)	0.238 (-0.064 to 0.54)	0.115 (-0.024 to 0.254)	0.121 (0.003 to 0.239)	0.0440
	Diabetes	1.024 (0.802 to 1.306)	1.131 (0.903 to 1.417)	1.025 (0.924 to 1.136)	1.04 (0.953 to 1.135)	0.3754
	Hypertension	0.969 (0.831 to 1.13)	1.038 (0.898 to 1.201)	1.076 (1.006 to 1.15)	1.055 (0.997 to 1.116)	0.0616
	Smoking	1.098 (0.947 to 1.272)	0.987 (0.854 to 1.14)	0.991 (0.927 to 1.06)	1.005 (0.95 to 1.064)	0.8362

Nature Genetics: doi.10.1038/ng.784

SNP	Phenotype	KORA F4 Effect (95% CI)	KORA F3 Effect (95% CI)	ARIC Effect (95% CI)	Combined Effect (95% CI)	P
rs579459	HDL	0.723 (-0.35 to 1.798)	-0.44 (-1.829 to 0.949)	0.438 (-0.064 to 0.941)	0.399 (-0.033 to 0.832)	0.0704
	LDL	0.955 (-1.822 to 3.733)	0.477 (-2.398 to 3.352)	1.865 (0.597 to 3.133)	1.537 (0.467 to 2.608)	0.0049
	TotalChol	0.999 (-2.084 to 4.083)	0.326 (-3.204 to 3.856)	2.059 (0.712 to 3.406)	1.719 (0.554 to 2.884)	0.0038
	BMI	0.124 (-0.25 to 0.5)	-0.204 (-0.593 to 0.184)	0.016 (-0.145 to 0.178)	0.003 (-0.135 to 0.142)	0.9633
	Diabetes	1.231 (0.947 to 1.601)	0.98 (0.737 to 1.304)	1.06 (0.941 to 1.192)	1.073 (0.97 to 1.187)	0.1690
	Hypertension	1.149 (0.965 to 1.367)	0.89 (0.738 to 1.072)	1.029 (0.952 to 1.111)	1.026 (0.961 to 1.096)	0.4311
	Smoking	0.999 (0.845 to 1.182)	1.054 (0.876 to 1.268)	1.039 (0.961 to 1.123)	1.034 (0.969 to 1.105)	0.3062
rs12413409	HDL	-0.258 (-1.702 to 1.184)	0.032 (-1.647 to 1.711)	0.197 (-0.557 to 0.952)	0.09 (-0.531 to 0.712)	0.7755
	LDL	2.245 (-1.485 to 5.977)	-0.69 (-4.165 to 2.785)	-1.207 (-3.109 to 0.695)	-0.532 (-2.055 to 0.99)	0.4933
	TotalChol	3.315 (-0.825 to 7.456)	0.412 (-3.853 to 4.678)	-1.573 (-3.595 to 0.448)	-0.472 (-2.143 to 1.199)	0.5797
	BMI	0.552 (0.046 to 1.058)	-0.033 (-0.502 to 0.436)	0.181 (-0.061 to 0.424)	0.2 (0.001 to 0.398)	0.0484
	Diabetes	0.955 (0.657 to 1.388)	1.007 (0.718 to 1.412)	0.938 (0.781 to 1.125)	0.953 (0.822 to 1.105)	0.5288
	Hypertension	0.928 (0.731 to 1.178)	0.995 (0.795 to 1.245)	0.82 (0.727 to 0.925)	0.868 (0.788 to 0.956)	0.0043
	Smoking	0.937 (0.746 to 1.175)	1.084 (0.867 to 1.354)	0.963 (0.856 to 1.084)	0.979 (0.891 to 1.077)	0.6719
rs964184	HDL	1.305 (0.07 to 2.54)	1.463 (-0.079 to 3.005)	2.149 (1.54 to 2.758)	1.926 (1.411 to 2.441)	$2.28 \cdot 10^{-13}$
	LDL	-0.619 (-3.816 to 2.577)	-0.851 (-4.045 to 2.342)	-2.155 (-3.711 to -0.599)	-1.698 (-2.98 to -0.417)	0.0094
	TotalChol	-4.893 (-8.435 to -1.352)	-3.42 (-7.338 to 0.497)	-4.711 (-6.344 to -3.078)	-4.577 (-5.964 to -3.19)	$9.84 \cdot 10^{-11}$
	BMI	0.012 (-0.419 to 0.444)	0.332 (-0.1 to 0.765)	-0.096 (-0.293 to 0.1)	-0.017 (-0.183 to 0.147)	0.8330
	Diabetes	0.858 (0.633 to 1.163)	0.908 (0.666 to 1.237)	0.927 (0.804 to 1.069)	0.913 (0.811 to 1.029)	0.1381
	Hypertension	1.014 (0.828 to 1.243)	1.089 (0.886 to 1.339)	0.918 (0.836 to 1.007)	0.955 (0.883 to 1.032)	0.2483
	Smoking	1.269 (1.045 to 1.541)	0.919 (0.748 to 1.13)	1.039 (0.944 to 1.143)	1.055 (0.974 to 1.141)	0.1829
rs4773144	HDL	-1.18 (-2.086 to -0.274)	1.233 (0.137 to 2.328)	0.183 (-0.244 to 0.611)	0.078 (-0.286 to 0.443)	0.6724
	LDL	1.567 (-0.779 to 3.913)	-1.184 (-3.454 to 1.085)	0.994 (-0.084 to 2.073)	0.736 (-0.164 to 1.636)	0.1090
	TotalChol	1.029 (-1.575 to 3.634)	-0.109 (-2.897 to 2.678)	1.02 (-0.126 to 2.167)	0.881 (-0.1 to 1.863)	0.0786
	BMI	0.201 (-0.115 to 0.519)	-0.228 (-0.535 to 0.079)	0.08 (-0.057 to 0.218)	0.052 (-0.064 to 0.169)	0.3794
	Diabetes	1.139 (0.899 to 1.443)	1.11 (0.885 to 1.391)	0.978 (0.884 to 1.083)	1.017 (0.933 to 1.109)	0.6934
	Hypertension	1.06 (0.913 to 1.23)	1.043 (0.901 to 1.207)	0.974 (0.912 to 1.04)	0.995 (0.941 to 1.052)	0.8849
	Smoking	0.965 (0.837 to 1.113)	1.024 (0.884 to 1.185)	0.993 (0.929 to 1.061)	0.993 (0.939 to 1.05)	0.8172
rs2895811	HDL	-0.464 (-1.376 to 0.448)	-0.458 (-1.882 to 0.965)	0.208 (-0.264 to 0.681)	0.023 (-0.378 to 0.426)	0.9071
	LDL	-0.636 (-2.995 to 1.723)	0.795 (-2.151 to 3.742)	-0.501 (-1.691 to 0.689)	-0.376 (-1.375 to 0.623)	0.4609
	TotalChol	-0.604 (-3.223 to 2.014)	0.473 (-3.145 to 4.091)	-0.957 (-2.223 to 0.308)	-0.767 (-1.854 to 0.319)	0.1664
	BMI	0.096 (-0.222 to 0.415)	-0.241 (-0.639 to 0.156)	0.062 (-0.09 to 0.214)	0.035 (-0.094 to 0.165)	0.5934
	Diabetes	1.124 (0.891 to 1.419)	0.761 (0.564 to 1.027)	0.941 (0.841 to 1.054)	0.949 (0.862 to 1.045)	0.2926
	Hypertension	1.008 (0.868 to 1.171)	1.055 (0.873 to 1.276)	0.98 (0.911 to 1.054)	0.992 (0.933 to 1.056)	0.8193
	Smoking	0.995 (0.862 to 1.148)	1.077 (0.891 to 1.302)	0.938 (0.871 to 1.009)	0.962 (0.904 to 1.024)	0.2284

Nature Genetics: doi.10.1038/ng.784

SNP	Phenotype	KORA F4 Effect (95% CI)	KORA F3 Effect (95% CI)	ARIC Effect (95% CI)	Combined Effect (95% CI)	P
rs3825807	HDL	-0.343 (-1.272 to 0.585)	1.028 (-0.125 to 2.182)	-0.223 (-0.648 to 0.2)	-0.116 (-0.482 to 0.249)	0.5336
	LDL	1.036 (-1.364 to 3.438)	-0.532 (-2.922 to 1.857)	0.482 (-0.588 to 1.552)	0.415 (-0.489 to 1.32)	0.3684
	TotalChol	-0.053 (-2.72 to 2.612)	-0.537 (-3.471 to 2.396)	0.483 (-0.653 to 1.62)	0.295 (-0.689 to 1.28)	0.5568
	BMI	0.314 (-0.01 to 0.639)	-0.138 (-0.462 to 0.184)	0.107 (-0.028 to 0.244)	0.102 (-0.015 to 0.219)	0.0877
	Diabetes	1.055 (0.831 to 1.339)	1.251 (0.984 to 1.589)	1.084 (0.979 to 1.199)	1.101 (1.009 to 1.2)	0.0298
	Hypertension	1.085 (0.932 to 1.263)	1.057 (0.906 to 1.234)	1.018 (0.954 to 1.087)	1.032 (0.976 to 1.091)	0.2592
	Smoking	0.963 (0.832 to 1.114)	0.938 (0.804 to 1.095)	0.981 (0.919 to 1.048)	0.973 (0.92 to 1.029)	0.3411
rs12936587	HDL	-0.188 (-1.107 to 0.73)	0.151 (-1.041 to 1.344)	-0.133 (-0.562 to 0.296)	-0.114 (-0.484 to 0.255)	0.5435
	LDL	0.777 (-1.598 to 3.153)	0.681 (-1.786 to 3.15)	-0.807 (-1.888 to 0.274)	-0.368 (-1.282 to 0.545)	0.4296
	TotalChol	0.428 (-2.208 to 3.066)	-0.053 (-3.084 to 2.976)	-0.914 (-2.064 to 0.235)	-0.63 (-1.625 to 0.365)	0.2149
	BMI	-0.036 (-0.357 to 0.285)	0.195 (-0.137 to 0.529)	-0.109 (-0.248 to 0.028)	-0.06 (-0.179 to 0.057)	0.3143
	Diabetes	0.921 (0.727 to 1.167)	1.043 (0.815 to 1.335)	0.979 (0.884 to 1.085)	0.979 (0.897 to 1.069)	0.6428
	Hypertension	0.989 (0.851 to 1.149)	1.108 (0.944 to 1.3)	0.948 (0.888 to 1.013)	0.973 (0.919 to 1.029)	0.3465
	Smoking	0.853 (0.738 to 0.986)	1.055 (0.9 to 1.237)	1.076 (1.007 to 1.15)	1.036 (0.979 to 1.096)	0.2144
rs216172	HDL	-0.193 (-1.135 to 0.747)	NA	-0.172 (-0.617 to 0.271)	-0.176 (-0.578 to 0.225)	0.3892
	LDL	-0.37 (-2.805 to 2.064)	NA	-0.834 (-1.954 to 0.286)	-0.753 (-1.77 to 0.264)	0.1471
	TotalChol	-0.742 (-3.445 to 1.96)	NA	-0.67 (-1.86 to 0.519)	-0.682 (-1.771 to 0.406)	0.2195
	BMI	-0.062 (-0.391 to 0.267)	NA	0.009 (-0.133 to 0.152)	-0.001 (-0.133 to 0.129)	0.9777
	Diabetes	1.145 (0.901 to 1.456)	NA	1.037 (0.933 to 1.151)	1.053 (0.957 to 1.16)	0.2851
	Hypertension	1.032 (0.885 to 1.204)	NA	1.03 (0.962 to 1.102)	1.03 (0.968 to 1.097)	0.3381
	Smoking	1.021 (0.881 to 1.184)	NA	0.993 (0.927 to 1.064)	0.998 (0.937 to 1.062)	0.9601

Results from fixed effects meta-analysis based on beta-coefficients and standard errors from linear (total cholesterol, LDL, HDL, BMI) and logistic (hypertension, diabetes, smoking) regression analysis of the single studies. Shown are estimated pooled regression coefficients with 95% confidence intervals. HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, TotalChol = total cholesterol, BMI = body mass index.

Nature Genetics: doi.10.1038/ng.784

Additional Table 11: Non-synonymous or splice-site variants in linkage disequilibrium (r^2 > 0.8, D´>0.9) with lead SNPs (from HapMap CEU).

Band	Lead SNP	Proxy SNP	Distance from lead SNP	r^2	D´	Gene	Coding change	Type
7q32.2	rs11556924		0	1	1	*ZC3HC1*	R363H	non-synonymous
14q32.2	rs2895811	rs7158073	7,747	0.82	0.95	*HHIPL1*	V691A	non-synonymous
15q25.1	rs3825807		0	1	1	*ADAMTS7*	S214P	non-synonymous
17q21.32	rs46522	rs2291725	50,535	1	1	*GIP*	S103G	non-synonymous
		rs2291726	50,657	0.94	1	*GIP*	c.258-73A>G	cryptic splice-site alteration

Nature Genetics: doi.10.1038/ng.784

Additional Table 12: eQTL results for the known and novel coronary disease loci.

								SNP with strongest association with expression [c]		
Band	**SNP**	**Position**	**Gene (Transcript)**	**Tissue**	**E** [a]	**P**	**P_{adj}** [b]	**SNP (r^2)** [d]	**P**	**P_{adj}** [e]
Novel loci reported in this study										
6q23.2	rs12190287[C]	134256218	*TCF21* (NM_003206)	Omental	+	1.2×10^{-8}				
"	"	"	*TCF21* (NM_003206)	Liver	+	2.3×10^{-8}				
17p11.2	rs12936587[G]	17484447	*PEMT* (ILMN_1745806)[f]	Monocytes	-	3.1×10^{-9}				
"	"	"	*RASD1* (ILMN_1740426)[f]	Monocytes	+	2.0×10^{-14}				
"	"	"	*SMCR3* (HSS00330572)	Subq	+	9.9×10^{-12}	0.73	rs12945496 (0.85)	1.5×10^{-13}	0.48
17q21.32	rs46522[T]	44343596	*UBE2Z* (NM_023079)	Blood	+	1.7×10^{-12}	0.82	rs12453394 (0.93)	9.9×10^{-13}	0.33
Previously reported loci										
1p13.3	rs599839[A]	109623689	*PSRC1* (ILMN_1671843)[g]	Monocytes	-	7.7×10^{-21}				
"	"	"	*PSRC1* (ILMN_1671843)[g]	Macrophages	-	4.8×10^{-20}				
"	"	"	*PSRC1* (ILMN_2315964)[g]	Macrophages	-	9.8×10^{-7}				
"	"	"	*PSRC1* (NM_032636)	Subq	-	1.3×10^{-9}	0.66	rs4970834 (0.60)	2.7×10^{-11}	0.19
"	"	"	*CELSR2* (NM_001408)	Liver	-	2.8×10^{-70}	1	rs646776 (0.89)	5.0×10^{-73}	0.78
"	"	"	*PSRC1* (NM_032636)	Liver	-	1.2×10^{-182}	0.97	rs646776 (0.89)	1.4×10^{-193}	0.51
"	"	"	*SORT1* (AK000757)	Liver	-	4.7×10^{-213}	0.86	rs646776 (0.89)	3.8×10^{-227}	0.49
"	"	"	*SORT1* (NM_002959)	Liver	-	2.1×10^{-141}	0.94	rs646776 (0.89)	4.8×10^{-147}	0.75
"	"	"	*PSRC1* (NM_032636)	Blood	-	2.1×10^{-24}	0.14	rs660240 (0.85)	1.1×10^{-26}	0.00085
3q22.3	rs2306374[C]	139602642	(hCT1951505.1)	Subq	+	3.7×10^{-6}				
9p21.3	rs4977574[G]	22088574	*CDKN2B* (NM_078487)	Omental	-	5.0×10^{-6}	0.98	rs2383207 (0.90)	1.0×10^{-6}	0.82
19p13.2	rs1122608[G]	11024601	*SMARCA4* (NM_003072)	Omental	+	9.2×10^{-6}	0.69	rs7258189 (0.70)	4.6×10^{-6}	0.71
21q22.11	rs9982601[T]	34520998	*MRPS6* (NM_032476)	Blood	+	5.6×10^{-11}	0.55	rs7278204 (0.84)	2.7×10^{-11}	0.19

All expression associations with $P < 10^{-5}$ where the coronary artery disease SNP is the strongest expression SNP (eSNP) in the region for the given genes or is in high correlation ($r^2 \geq 0.60$) with the strongest eSNP. [a]Direction of effect. [b]P for correlation tested conditional on the SNP that shows most significant correlation with expression. [c]The SNP in the 1 Mb window that shows the strongest correlation with expression. [d]Correlation r^2 between the coronary artery disease-associated SNP and the SNP that shows strongest correlation with expression. [e]P for correlation tested conditioned on the coronary artery disease-associated SNP. [f]A proxy, rs2955359, with $r^2 = 0.85$ with rs12936587 was tested. [g]A proxy, rs646776, with $r^2 = 0.89$ with rs599839 was tested. A more detailed explanation of the table contents and analyses is provided in Supplementary Methods.

Nature Genetics: doi.10.1038/ng.784

Additional Table 13: Evidence of cis effects through allelic expression (AE) imbalance using a first generation AE map (Ge B, Pokholok DK, Kwan T, et al. Global patterns of cis variation in human cells revealed by high-density allelic expression analysis. Nat Genet 2009;41:1216-22). Only CARDIoGRAM lead SNPs located within one or more of the 7785 significant measure AE windows reported by Ge et al. are included. Entries with high LD (r2 > 0.5) are shaded in grey.

CARDIOGRAM lead SNP			Measured AE window			Allelic expression association						Transcript overlapping AE window			
rs	chr	position	Start position	End position	No. of Measured SNPs	Start position	End position	Tag-SNP	Nominal P	Significance level*	r^2 between Tag & lead SNPs	Start position	End position	GENE SYMBOL	locuslink ID
Novel Loci															
Window based AE association															
rs17114036	1	56735409	56748430	56770370	6	56684634	56741065	rs7525717	3.14E-05	0.005	0.0495	56732526	56817845	PPAP2B	8613
rs11556924	7	129450732	129403173	129445118	9	129416799	129485998	rs2242488	2.80E-05	0.005	0.235	129445361	129478469	ZC3HC1	51530
rs579459	9	135143989	135141266	135182445	13	135122575	135149361	rs579459	4.48E-06	0.001	1	135115608	135454453	ABO	28
rs12413409	10	104709086	104747699	104804152	12	104618863	104859028	rs3897401	1.18E-07	0.001	0.0323	104668061	104828334	CNNM2	54805
rs12413409	10	104709086	104839458	104842638	3	104618863	104921574	rs12764154	1.37E-07	0.001	0.0187	104837903	104943041	NT5C2	22978
rs12413409	10	104709086	104859028	104867025	4	104695402	104991787	rs1926030	1.19E-12	Genome-wide	0.081	104837903	104943041	NT5C2	22978
rs3825807	15	76876166	76845627	76886593	4	76869486	76912484	rs12438008	4.76E-08	0.001	0.3049	76838600	76890830	ADAMTS7	11173
rs216172	17	2073254	2142838	2150203	6	2045089	2163008	rs216219	5.68E-12	Genome-wide	0.7454	1909882	2153819	SMG6	23293
rs46522	17	44343596	44329733	44333352	3	44305495	44408827	rs2291726	9.89E-10	Genome-wide	0.9334	44325127	44328229	ATP5G1	516
rs46522	17	44343596	44359722	44360508	3	44305495	44408827	rs318095	1.73E-09	Genome-wide	1	44340828	44362724	UBE2Z	65264
rs46522	17	44343596	44362496	44369126	5	44305495	44408827	rs2291726	5.37E-10	Genome-wide	0.9334	44340828	44362724	UBE2Z	65264
rs46522	17	44343596	44362496	44369126	5	44305495	44408827	rs2291726	5.37E-10	Genome-wide	0.9334	44362459	44377171	SNF8	11267
rs46522	17	44343596	44329733	44333352	3	44305495	44408827	rs2291726	9.89E-10	Genome-wide	0.9334	44390916	44400954	GIP	2695
High confidence full transcript AE association															
none															

Nature Genetics: doi.10.1038/ng.784

Known Loci

Window based AE association

rs6725887	2	203454130	203727576	203742096	5	203440515	203809573	rs10188105	4.57E-06	0.001	0.059	203587846	203659747	ALS2CR16	130029
rs6725887	2	203454130	203727576	203742096	5	203440515	203809573	rs10188105	4.57E-06	0.001	0.059	203484415	203557439	ALS2CR8	79800
rs6725887	2	203454130	203727576	203742096	5	203440515	203809573	rs10188105	4.57E-06	0.001	0.059	203346117	203444953	ICA1L	130026
rs6725887	2	203454130	203727576	203742096	5	203440515	203809573	rs10188105	4.57E-06	0.001	0.059	203708717	203799345	NBEAL1	65065
rs6725887	2	203454130	203727576	203742096	5	203440515	203809573	rs10188105	4.57E-06	0.001	0.059	203453574	203485194	WDR12	55759
rs3184504	12	110368991	110436550	110446964	3	110317972	110614582	rs593226	5.23E-07	0.001	0.314	110608254	110679289	ACAD10	80724
rs3184504	12	110368991	110436550	110446964	3	110317972	110614582	rs593226	5.23E-07	0.001	0.314	110374401	110521863	ATXN2	6311
rs3184504	12	110368991	110436550	110446964	3	110317972	110614582	rs593226	5.23E-07	0.001	0.314	110565880	110608173	BRAP	8315
rs3184504	12	110368991	110436550	110446964	3	110317972	110614582	rs593226	5.23E-07	0.001	0.314	110328134	110373809	SH2B3	10019
rs3184504	12	110368991	110610448	110625616	4	110365692	110713097	rs3809276	2.09E-09	Genome-wide	0.154	110608254	110679289	ACAD10	80724
rs3184504	12	110368991	110610448	110625616	4	110365692	110713097	rs3809276	2.09E-09	Genome-wide	0.154	110688728	110732165	ALDH2	217
rs3184504	12	110368991	110610448	110625616	4	110365692	110713097	rs3809276	2.09E-09	Genome-wide	0.154	110374401	110521863	ATXN2	6311
rs3184504	12	110368991	110610448	110625616	4	110365692	110713097	rs3809276	2.09E-09	Genome-wide	0.154	110565880	110608173	BRAP	8315
rs3184504	12	110368991	110610448	110625616	4	110365692	110713097	rs3809276	2.09E-09	Genome-wide	0.154	110328134	110373809	SH2B3	10019

High confidence full transcript AE association

rs17464857**	1	220829332	NA	NA	NA	220804104	221023703	rs17532708	1.09E-08	0.001	0.253	220977180	220990625	FAM177B	400823

*Significance level is based on permutation analysis and is compartamentalized into three categories: 0.001< P < 0.005, 7.6x10–9 (genomewide) < P <0.001, P < 7.6x10–9 (genomewide)

**This AE imbalance was missed by window based approach either because of low-magnitude AE or due to window partitions excluding informative sections of the transcript

Nature Genetics: doi.10.1038/ng.784

Additional Table 14: Novel and known coronary artery disease loci associated with other traits and diseases.

Region	Lead SNP for CAD	Other trait mapped to the region	Lead SNP for other trait	r^2	D´	P for CAD of lead SNP for other trait	Reported genes in region	Ref
1p13.3	rs646776	LDL cholesterol	rs12740374	1.00	1.00	1.64E-09	CELSR2, PSRC1, SORT1	8
1p13.3	rs646776	Lp-PLA2 activity and mass	rs599839	1.00	1.00	2.89E-10	PSRC1	29
9p21.3	rs4977574	Glioma	rs4977756	0.47	0.95	4.05E-15	CDKN2A, CDKN2B	30
9p21.3	rs4977574	Intracranial aneurysm	rs1333040	0.67	1.00	6.99E-09	CDKN2A,CDKN2B	31
9q34.2	**rs579459**	**Angiotensin-converting enzyme activity**	**rs495828**	**1.00**	**1.00**	**1.63E-07**	**ABO**	32
9q34.2	**rs579459**	**Hematological and biochemical traits**	**rs495828**	**1.00**	**1.00**	**1.63E-07**	**ABO**	33
9q34.2	**rs579459**	**Pancreatic cancer**	**rs505922**	**0.38**	**0.88**	**7.14E-06**	**ABO**	34
9q34.2	**rs579459**	**Plasma E-selectin levels**	**rs651007**	**0.95**	**1.00**	**5.53E-07**	**ABO**	35
9q34.2	**rs579459**	**Protein quantitative trait loci**	**rs505922**	**0.38**	**0.88**	**7.14E-06**	**ABO**	36
9q34.2	**rs579459**	**Serum soluble E-selectin**	**rs579459**	**0.38**	**0.88**	**1.16E-07**	**ABO**	37
9q34.2	**rs579459**	**Soluble levels of adhesion molecules**	**rs649129**	**1.00**	**1.00**	**1.09E-07**	**ABO**	38
9q34.2	**rs579459**	**Venous thromboembolism**	**rs505922**	**0.38**	**0.88**	**7.14E-06**	**ABO**	39
10q24.32	**rs12413409**	**Intracranial aneurysm**	**rs12413409**	**1.00**	**1.00**	**1.47E-06**	**CNNM2**	**{Yasuno, 2010 #476}**
10q24.32	**rs12413409**	**Systolic blood pressure**	**rs11191548**	**1.00**	**1.00**	**1.31E-05**	**CYP17A1, AS3MT, CNNM2, NT5C2**	**{Newton-Cheh, 2009 #485}**
11q23.3	**rs964184**	**HDL cholesterol**	**rs964184**	**1.00**	**1.00**	**8.02E-10**	**APOA1, APOC3, APOA4, APOA5**	**{Aulchenko, 2009 #486}**
11q23.3	**rs964184**	**Hematological and biochemical traits**	**rs7350481**	**0.28**	**0.81**	**8.50E-06**	**APO-A cluster**	**{Kamatani, 2010 #478}**
11q23.3	**rs964184**	**LDL cholesterol**	**rs12272004**	**0.51**	**1.00**	**2.19E-02**	**APOA1, APOA4, APOA5, APOC3**	**{Aulchenko, 2009 #486}**
11q23.3	**rs964184**	**LDL cholesterol**	**rs6589566**	**0.31**	**1.00**	**2.15E-06**	**APOA1,APOC3,APOA5**	**{Wallace, 2008 #487}**
11q23.3	**rs964184**	**Lp-PLA2 activity and mass**	**rs12286037**	**0.59**	**1.00**	**4.98E-04**	**ZNF259**	**{Suchindran, 2010 #474}**
11q23.3	**rs964184**	**Plasma carotenoid and tocopherol levels**	**rs12272004**	**0.51**	**1.00**	**1.29E-02**	**APOA5**	**{Ferrucci, 2009 #488}**
11q23.3	**rs964184**	**Triglycerides**	**rs964184**	**1.00**	**1.00**	**8.02E-10**	**APOA1, APOC3, APOA4, APOA5**	**{Kathiresan, 2009 #473}**
15q25.1	**rs3825807**	**Lung adenocarcinoma**	**rs1051730**	**0.21**	**0.51**	**7.00E-01**	**CHRNA3, CHRNA5**	**{Landi, 2009**

Nature Genetics: doi.10.1038/ng.784

15q25.1	**rs3825807**	**Smoking behavior**	**rs1051730**	**0.21**	**0.51**	**7.00E-01**	**NR**	**#489} {Thorgeirsson, 2010 #490}**

Region	Lead SNP for CAD	Other trait mapped to the region	Lead SNP for other trait	r^2	D´	P for CAD of lead SNP for other trait	Reported genes in region	Ref
12q24.12	rs3184504	Celiac disease	rs653178	1.00	1.00	2.20E-06	SH2B3	{Dubois, 2010 #491}
12q24.12	rs3184504	Chronic kidney disease	rs653178	1.00	1.00	2.20E-06	ATXN2	{Kottgen, 2010 #492}
12q24.12	rs3184504	Diastolic blood pressure	rs3184504	1.00	1.00	6.35E-06	SH2B3	{Levy, 2009 #493}
12q24.12	rs3184504	Diastolic blood pressure	rs653178	1.00	1.00	2.20E-06	ATXN2, SH2B3	{Newton-Cheh, 2009 #485}
12q24.12	rs3184504	Hematocrit	rs11065987	0.69	0.96	5.62E-07	SH2B3, ATXN2	{Ganesh, 2009 #494}
12q24.12	rs3184504	Hemoglobin	rs11065987	0.69	0.96	5.62E-07	TRAFD1	{Ganesh, 2009 #494}
12q24.12	rs3184504	Plasma eosinophil count	rs3184504	1.00	1.00	6.35E-06	SH2B3	{Gudbjartsson, 2009 #495}
12q24.12	rs3184504	Systolic blood pressure	rs3184504	1.00	1.00	6.35E-06	SH2B3	{Levy, 2009 #493}
12q24.12	rs3184504	Type 1 diabetes	rs3184504	1.00	1.00	6.35E-06	SH2B3	{Barrett, 2009 #496}
17p13.3	**rs216172**	**Aortic root size**	**rs10852932**	**0.73**	**0.90**	**5.23E-05**	**SMG6, SRR, TSR1, SGSM2**	**{Vasan, 2009 #497}**

Selection is based on the report in the NHGRI catalogue of published GWAS with genomewide level of significance ($P<5x10^{-8}$), based on a 1 mega base maximum distance and linkage disequilibrium ($r^2>0.2$) between the SNPs. Novel loci are in bold. Date of access June 28th 2010.
Lead SNP for other trait: SNP has documented $P < 5x10^{-8}$ for association with other trait listed (reference in superscript)
r^2, D': Linkage disequilibrium between lead SNP for coronary artery disease and lead SNP for other trait (HapMap)
P for CAD of lead SNP for other trait: P for association of the lead SNP from other trait with coronary artery disease in the CARDIoGRAM meta-analysis discovery phase

Nature Genetics: doi.10.1038/ng.784

4. Supplementary Note

1. Additional Methods

SNP selection for replication

SNPs fulfilling the following criteria were taken forward to replication:

(1) Data in meta-analysis discovery phase available and passed quality control in at least 8 out of 14 studies.

(2) $P < 5 \cdot 10^{-6}$ in meta-analysis discovery phase.

(3) At least 2 SNPs within +/- 50 kb with $P < 10^{-5}$ in meta-analysis discovery phase OR no SNP with $R^2 > 0.8$.

(4) Novel, i.e., not previously reported at genome-wide significance in a prior publication.

We identified 27 SNPs that fulfilled these criteria. Of these, four could not be genotyped in most samples because of the design of the replication array, leaving 23 SNPs for replication.

Proportion of explained variance

The proportion of explained variance by the 23 SNPs was estimated using the R^2 introduced by McKelvey and Zavoina [40]. These estimates are likely to be overly optimistic, because they are similarly derived from a subset of the same sample that was part of the discovery phase. Through this, the proportion of overall variance was estimated to be 3.9%.

Expression analysis

To identify coronary disease-associated SNPs that might influence gene expression, we used three whole genome experiments of gene expression: The deCODE study of blood and subcutaneous adipose tissue among Icelandic families [41], the Massachusetts General Hospital (MGH) study of liver, omental and subcutaneous adipose tissue among subjects undergoing Roux-en-Y gastric bypass surgery [42] and the Cardiogenics study of monocytes and macrophages among subjects with coronary artery disease and controls. The deCODE and MGH studies have been previously described [41-42], and the Cardiogenics study is described in detail below. In the deCODE and MGH studies, for SNPs and RNA transcripts within a defined window (one megabase (Mb) window in the deCODE study and two Mb window in the MGH study) centered on each coronary artery disease index SNP, we tested for association between the log of the

Nature Genetics: doi.10.1038/ng.784

average expression ratio of two fluorophores and the allele count (genotype data) or expected allele count (imputed data) using linear regression, with adjustment for age, sex and, in blood, differential cell count. For each locus and transcript we performed additional conditional analyses by including in the regression model either the most strongly associated cis-expression SNP (eSNP) in the region or the coronary artery disease SNP. These conditional analyses were carried out to provide support for the coronary artery disease signal and any detected cis-expression association at the coronary artery disease index SNP being driven by the same underlying causal variant. In the deCODE study, *P*-values were adjusted for relatedness of the individuals by simulating genotypes through the corresponding Icelandic genealogy [43].

The Cardiogenics study includes patients with coronary disease and healthy individuals of European descent recruited in five centers in Cambridge (UK) (n=459 healthy), Leicester (n=161 cases), Lübeck (n=102 cases), Regensburg (n=122 cases) and Paris (n=74 cases) by the Cardiogenics consortium (http://www.cardiogenics.eu). The study was approved by the Institutional Ethical Committee of each participating center. RNA was extracted from monocytes isolated from whole blood with CD14 micro beads (AutoMacs Pro, Miltenyi) and from parallel samples of macrophages cultured for 7 days in macrophage-SFM medium (Gibco/Invitrogen) with 50 $ng.ml^{-1}$ recombinant human M-CSF (R&D Systems GmbH). Genomic DNA was extracted from peripheral blood by standard procedures. Gene expression profiling was performed using Illumina Human Ref-8 arrays (Illumina Inc., San Diego, CA) containing 24,516 probes. mRNA was amplified and labelled using the Illumina Total Prep RNA Amplification Kit (Ambion, Inc., Austin, TX). After hybridization, array images were scanned using the Illumina BeadArray Reader and probe intensities were extracted using the Gene expression module of the Illumina's Bead Studio software. Variance Stabilization Transformation (VST) was applied to the raw intensities and quantile normalization was performed in the R statistical environment [44] using the Lumi and beadarray packages. Whole-genome genotyping was carried out using either the Human Custom 1.2M or the Human Quad Custom 670 arrays from Illumina. Only SNPs present in both arrays were kept for analysis. After filtering, 758 samples and 522,603 SNPs were used for further analyses. The statistical analysis was conducted using R-lm (Anova model) and was adjusted on center. Before analysis, each expression was standardized by removing the mean and dividing by the standard deviation (sd). For the joint analysis of the tag and proxy SNPs, both were introduced in the linear model. When the number of minor homozygotes was < 10 they were grouped with heterozygotes. All probes available on the expression array whose median genomic position is within 500 kilobase distance of the lead SNPs entered the analyses. When a lead SNP was not present on the genotyping array, the best tag was selected using SNAP (http://www.broadinstitute.org/mpg/snap/).

Nature Genetics: doi.10.1038/ng.784

Supplementary Table 4, see shows all expression associations with significance of $P < 1\times10^{-5}$ where the coronary disease SNP is the strongest eSNP in the region for the given genes or is in high correlation ($r^2 \geq 0.60$) with the strongest eSNP.

Allelic expression (AE) imbalance

Recently, the first genome-wide map of *cis*-acting variants identified through allelic expression (AE) imbalance was published [45]. This map was generated using quantitative measurements of AE on Illumina Human1M BeadChips in 53 lymphoblastoid cells of European origin. The investigators used SNPs in both introns and exons of primary transcripts, which were filtered for expression level and allele discrimination in cDNA and then subjected to allele-ratio normalization[45]. They then partitioned the genome into informative AE windows consisting of heterozygous expressed SNPs in the LCL panel. In order to identify windows showing population variation in AE and to identify transcripts with the same AE behavior, the investigators defined differential AE as the mean cDNAheterozygote ratio − gDNAheterozygote ratio (Δhet ratio) greater than 0.05 or less than −0.05 with a 95% confidence interval excluding.{Ge, 2009 #461} Approximately half (17,346/33,383) of the windows showed differential AE (|Δhet ratio| > 0.05) in at least 15% of the LCL samples and were then used in association tests [45]. The AE association was tested in phased chromosomes with Δhet ratio data correlated with local (±250-kb flanking sequence) genotypes [45]. All samples with measured AE values for a given window were used in AE association tests (i.e. the analysis was not restricted to cut-offs used to delineate AE windows or population variability of AE) [45]. The association results at a Bonferroni adjusted genome-wide significance of $P < 7.6\times10^{-9}$ and at a permutation significance level of 0.001 or 0.005 were made available to the public [45]. A total of 7785 AE windows across the genome met a permutation threshold of $P < 0.005$ [45]. Of these, only 2414 windows reached genome-wide significance for allelic imbalance association with a mean ratio of allelic imbalance of 2.61 [45]. A large proportion reached a permutation threshold of 0.0001 (n = 6305) and among these windows the mean ratio of allelic imbalance was 2.14 [45].

We examined whether any of the lead SNPs meeting genome-wide significance for coronary disease in the CARDIoGRAM study were located within one or more of these AE windows. If a CARDIoGRAM lead SNP was found to be within an AE window, its linkage disequlibrium (LD, as estimated by r^2) with the tagging SNP of that window was calculated and included in **Supplementary Table 5**, along with the AE association results for the tagging SNP.

We considered the possibility of false positive AE associations for this AE imbalance map to be relatively high given the small number of samples (n = 53) used to produce it. Thus, in the main manuscript we report only the CARDIoGRAM SNPs that showed very high LD with a tagging SNP in an AE window that also showed genome-wide significance for association with one or more nearby transcripts. Only two of our novel coronary disease loci met this criterion: the lead

Nature Genetics: doi.10.1038/ng.784

SNP for the SMG6 locus on 17p13.3, rs216172, was found to be in high LD (r^2=0.75) with the tagging SNP of an allelic expression window showing association with mRNA levels of the SMG6 transcript (nominal *P* = 5.68 x10-^{12}, Bonferroni-adjusted *P* < 7.6x10^{-9}) and the lead SNP for the *UBE2Z* locus on 17p13.3, rs46522, was found to be in high LD (r2 0.93 to 1) with the tagging SNP of three different AE windows showing association with mRNA levels of several transcripts in the region including *UBE2Z, GIP, ATP5G1* and *SNF8* (nominal P < 1.73x10^{-9}, Bonferroni-adjusted genome-wide significance at P < 7.6x10^{-9} for all SNPs (**SupplementaryTable 5**).

One other CARDIoGRAM lead SNP was found to be within an AE window reported by Ge et al.. The lead SNP for the *ABO* locus on chromosome 9q34.2, rs579459, was the actual tagging SNP for an allelic expression window showing association with mRNA levels of the ABO transcript. However, the statistical evidence of AE association was substantially lower than the other two SNPs (nominal P = 4.48x10^{-6}, permutation P < 0.001 but not genome-wide significant) (**SupplementaryTable 5**). None of the lead SNPs in known loci were found to be in high LD with tagging SNPs in nearby AE windows.

2. Background information on novel coronary artery disease risk loci

Chromosome 1p32.2; rs17114036 located in PPAP2B (LPP3) gene. The *PPAP2B* gene encodes the enzyme lipid phosphate phosphohydrolase 3 (LPP3) . LPPs are integral membrane proteins that catalyse the dephosphorylation of lipid phosphates [46]. Different LPPs perform distinct functions, probably based on integrin binding, their locations, and their abilities to metabolize different lipid phosphates *in vivo* [47], suggesting that previously unrecognized lipid metabolite may exert an important role in atherosclerosis.

Targeted inactivation of PPAP2b in the mouse results in embryonic lethality because of defects in extraembryonic vascular development and gastrulation [48]. Interestingly, generation of a reporter-null allele of PPAP2b/LPP3 in mice and its expression during embryogenesis demonstrate a critical role of PPAP2b during cardiac valve development [49].

Chromosome 6q23.2 – TCF21. *TCF21* (POD-1; Capsulin) encodes a transcription factor of the basic helix-loop-helix family. The *TCF21* product is mesoderm specific, and expressed in embryonic epicardium, mesenchyme-derived tissues of lung, gut, gonad, and both mesenchymal and glomerular epithelial cells in the kidney. Two transcript variants encoding the same protein have been found for this gene [50]. *TCF21* is a tumor suppressor gene which regulates mesenchymal cell transition into epithelial cells. It is frequently lost in human malignancies and is expressed in normal lung airway epithelial cells [51-52].

Nature Genetics: doi.10.1038/ng.784

Involved in epithelial-mesenchymal interactions in kidney and lung morphogenesis that include epithelial differentiation and branching morphogenesis. It is silenced in the majority of head and neck squamous cell carcinomas and non-small-cell lung cancer tumor cells through a chemical change known as DNA methylation, a process that is potentially reversible [53]. *TCF21* plays a role in the specification or differentiation of one or more subsets of epicardial cell types, its mark the spiral septum of the heart and progenitor cells that give rise to the pericardium and coronary arteries [54]. *TCF21* is related to glomerulogenesis and podocyte structure, may be involved in the pathogenesis of early diabetic glomerulopathy in type 2 diabetes [55-56].

Chromosome 7q32.3 - *ZC3HC1* (zinc finger, C3HC-type containing 1, nuclear-interacting partner of anaplastic lymphoma kinase) encodes a nuclear protein that plays an important role in cell cycle control. The product of *ZC3HC1* gene is an essential component of an SCF-type E3 ligase complex - a multi-protein machinery that catalyses the ubiquitination of proteins (such as cyclin B1) before their proteasomal degradation [57-58]. As a part of SCF-type E3 ligase complex, the protein product of *ZC3HC1* targets cyclin B1 in interphase but permits its nuclear accumulation at G2/M phase of the cell cycle [57-58]. By regulation of this oscillating ubiquitination of nuclear cyclin B1 ZC3HC1 plays an important role in temporal control of mammalian cell entry into mitosis [57-58]. *ZC3HC1* was also shown to play an antiapoptotic role in nucleophosmin-anaplastic lymphoma kinase (ALK) mediated signaling events [57-58]. ZC3HC1 protein is expressed in a broad range of human tissues (with the highest expression in heart, skeletal muscle, and testis) [59].

Chromosome 9q34.2 - ABO. The *ABO* (transferase A, alpha1-3-N-acetylgalactosaminyltransferase; transferase B, alpha 1-3-galactosyltransferase) gene encodes proteins related to the first discovered blood group system, ABO [60]. Which allele is present in an individual determines the blood group. The histo-blood group ABO involves three carbohydrate antigens: A, B, and H. Individuals with the A, B, and AB alleles express glycosyltransferase activities that convert the H antigen to the A antigen (by addition of UDP-GalNAc) or to the B antigen (by addition of UDP-Gal). Other minor alleles have been found for this gene. The 'O' blood group is caused by a deletion of guanine-258 near the N-terminus of the protein which results in a frameshift and translation of an almost entirely different protein lacking glycosyltransferase activity [60-61]. Associations of the ABO blood groups with plasma lipoproteins [62] and cardiovascular disease were reported several decades ago [63-65] . In a recent meta-analysis, Wu et al. found a pooled odds ratios of 1.25 (1.14-1.36) for myocardial infarction (MI) in non-O relative to blood group O carriers [66]. Ketch et al reported that patients with non-O blood groups had higher thrombus burden despite less extensive coronary atherosclerosis at the time of acute MI. ABO-related thrombosis is believed to be mediated by A and B glycosyltransferase-modification of von Willebrand Factor (vWF) resulting in impaired proteolysis and higher circulating vWF and Factor VIII [67]. Recently, *ABO* was identified as as the most significant

Nature Genetics: doi.10.1038/ng.784

locus in separate GWAS of VTE [39] and of plasma vWF and Factor VIII [68]. In addition, GWAS also identified *ABO* as a locus for LDL-C [69], and inflammatory risk biomarkers E-selectin, P-selectin and sol-ICAM1 [38 70 37 35] as well as angiotensin-converting enzyme [32]. Taken together, these data suggests that ABO may modulate multiple distinct protein and lipid pathways related to cardiovascular risk factors, atherosclerosis and thrombosis.

Chromosome 11q23.3 -ZNF259. ZNF259 (zinc finger protein 259; ZPR1) functions as a signaling molecule to communicate mitogenic signals from the cytoplasm to the nucleus and interacts with tyrosine kinase receptors, including the epidermal growth factor receptor, in quiescent mammalian cells [71]. This locus includes the apolipoprotein genes *APOA5, APOA4, APOC3* and *APOA1*. ApoA5 decreases plasma triglycerides by enhancing lipoprotein lipase-mediated triglyceride hydrolysis [72]. ApoC3 has opposite effects on plasma triglycerides due to inhibition of triglyceride hydrolysis. Haplotypes within this gene cluster are linked to plasma triglycerides and LDL particle size [73-74].

Chromosome 15q25.1 - ADAMTS7. The protein encoded by *ADAMTS7* gene is a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family. Members of this family have a similar domain organization, including a preproregion, a reprolysin-type catalytic domain, a disintegrin-like domain, a thrombospondin type-1 (TS) module, a cysteine-rich domain, a spacer domain without cysteine residues, and a COOH-terminal TS module [75-76]. ADAMTS are important targets of canonical PTHrP signaling and participate in the degradation of cartilage extracellular matrix proteins [77-78]. ADAMTS7 (b) degrades cartilage oligomeric matrix protein (COMP) and has been implicated in inflammatory arthritis and bone growth [76,78]. Recently, over-expression of *ADAMTS7* was shown to accelerate vascular smooth muscle cell (VSMC) migration *in vitro* and markedly exacerbate neointimal thickening following carotid artery injury *in vivo*. It facilitates intimal hyperplasia through degradation of inhibitory matrix protein COMP. These data implicate *ADAMTS7* in the proliferative response to vascular injury, a process that has parallels to the progressive phase of atherosclerosis. Therefore, ADAMTS-7 was proposed to serve as a novel therapeutic target for atherosclerosis and postangioplasty restenosis [79].

Chromosome 6p21.31 - ANKS1A (ankyrin repeat and sterile alpha motif domain containing 1A, ankyrin repeat and SAM domain containing 1, ankyrin repeat and sterile alpha motif domain containing 1 , odin) appears to be an adaptor protein, presumably coupling EGFR, PDGFR and EphA8 receptors to their downstream signalling pathways [80]. It shows ubiquitous tissue expression and most likely contributes to negative regulation of growth factor signaling [81].

Chromosome 10q24.32 (rs12413409) near CNNM2, CYP17A1 and others: Cyp17A1 / Cyp46A1: both genes encode a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are localized in the endoplasmic reticulum. They are monooxygenases which catalyze many reactions

Nature Genetics: doi.10.1038/ng.784

involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The *Cyp17A1* gene, also known as 17α-hydroxylase/17,20 lyase/17,20 desmolase. It has both 17alpha-hydroxylase and 17,20-lyase activities and is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens [82].

Newton-Cheh et al. reported that the association of Cyp17a1 gene with systolic blood pressure in a large GWA [83]. In addition results from Yamada et al. suggest that *CYP17A1* is a susceptibility locus for increased bone mineral density (BMD) in postmenopausal and premenopausal Japanese women.

Chromosome 13q34 near COL4A1/A2 locus - **COL4A1** (collagen, type IV, alpha 1) encodes one of six forms of type IV collagen-α chains that define structural stability of basement membranes. Two members of COL4A family genes (COL4A1 and COL4A2) are located head-to-head within the same chromosomal locus and share the common bi-directional promoter. A common non-synonymous single nucleotide polymorphism (rs3742207, Gln1334His) of COL4A1 was previously associated with myocardial infarction [84] and most recently with arterial stiffness [85]. Rare mutations in COL4A1 were associated with different presentations of cerebral small vessel disease [86-88] and hereditary syndrome of angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) [89-90]. In the experimental model, the missense mutation of *COL4A1* lead to defective deposition of collagen type IV in the basement membrane and defects in vascular function accompanied by low blood pressure [91].

Chromosome 14q32.2 (rs2895811) in HHIPL1 and near CYP46A1 overlaps with 14q locus identified with linkage analysis in GerMIFS [92]. The Cyp46A1 gene encodes for Cholesterol 24-hydroxylase that is expressed in the brain, where it converts cholesterol to 24S-hydroxycholesterol. Some research groups reported the association of Cyp46A1 polymorphisms with Alzheimer's disease, but others failed to confirm these results. Hedgehog, FGF, VEGF, and Notch signaling pathways network together for vascular remodeling during embryogenesis and carcinogenesis. HHIP1 (HHIP) is an endogenous antagonist for SHH, IHH, and DHH. HHIP1, **HHIP2 (HHIPL1 or KIAA1822**) and HHIP3 (HHIPL2 or KIAA1822L) constitute human HHIP gene family.

Chromosome 17p13.3 - SMG6 (Smg-6 homolog, nonsense mediated mRNA decay factor /C. Elegans/; previously known as chromosome 17 open reading frame 31). The product of this gene is a ribonuclease with endonucleolytic activity involved in nonsense-mediated mRNA decay (NMD, known also as mRNA surveillance) - a quality control mechanism that prevents accumulation of aberrant PTC (premature translation termination codons) - containing transcripts [93]. Specifically, SMG6 contributes to phosphorylation/dephosphorylation cycle of UFP1 - functionally the most important factor of the NMD [93]. The presence of SMG6 in telomeric chromatin indicates its role in telomere metabolism [93]; possibly through an interaction with telomerase [94] and regulation of telomeric

Nature Genetics: doi.10.1038/ng.784

repeat-containing RNAs (TERRA) bioavailability (that may inhibit telomerase activity) [93]. Indeed, depletion in components of NMD machinery (including SMG6) was associated with increased TERRA abundance and augmented telomere damage [93,95-96].

Chromosome 17p11.2 (rs12936587) intergenic between RAI1 and PEMT. *PEMT* gene encodes PHOSPHATIDYLETHANOLAMINE N-METHYLTRANSFERASE an enzyme which converts phosphatidylethanolamine to phosphatidylcholine by sequential methylation in the liver. The protein localizes to the endoplasmic reticulum and mitochondria-associated membranes. The gene is within the Smith-Magenis syndrome region on chromosome 17. Alternate splicing of this gene results in three transcript variants encoding two different isoforms. Mice homozygous for the disrupted *PEMT* gene displayed no abnormal phenotype, normal hepatocyte morphology, normal plasma lipid levels, and no difference in biocomposition [97-98].

RAI1 gene- Retinoic acid-induced protein 1 - is highly similar to its mouse counterpart and is expressed at high levels mainly in neuronal tissues. The protein encoded by this gene includes a polymorphic polyglutamine tract in the N-terminal domain. Expression of the mouse counterpart in neurons is induced by retinoic acid. It is expressed in all tissues examined with higher expression in the heart and brain [99].

Chromosome 17q21.32 (rs46522) in *UBE2Z*, *GIP*, *ATP5G1* and *SNF8*. The associated region on 17q21.32 contains a number of genes, but there are four genes in particular that are considered most likely to be the causal gene in this locus given the location of the lead SNP and the results of the genome-wide allelic expression analyses in this region. The four genes are UBE2Z, GIP, ATP5G1 and SNF8. Three of these genes control basic cellular processes in most eukaryotic cells, and are considered unlikely to mediate a tissue-restricted disease such as atherosclerosis, while one of the genes in this locus, GIP, provides a clear link to the risk factor insulin action and thus insulin resistance, raising the interesting possibility as the causal mechanism of action. Interestingly, the lead SNP is in high LD with two SNPs in GIP (see main text for details). UBE2Z is a ubiquitin conjugating enzyme (E2). Post-translational modification of proteins with ubiquitin or ubiquitin-like proteins controls many signaling networks and requires a ubiquitin activating enzyme (E1) and a ubiquitin protein ligase (E3) in addition to E2 activity [100]. SNF8 is also involved in ubiquitination. SNF8, VPS25, and VPS36 form ESCRT-II (endosomal sorting complex required for transport II), a complex involved in endocytosis of ubiquitinated membrane proteins. SNF8, VPS25, and VPS36 are also associated in a multiprotein complex with RNA polymerase II elongation factor (ELL) [101]. Importantly, it has been demonstrated that SNF8 can interact with ELL and depress the inhibitory activity of ELL against RNA polymerase II [102]. ATP5G1 is part of the mitochondrial machinery that employs energy derived from a proton gradient to synthesize ATP. The F0-ATP synthase subunit is attached to the inner mitochondrial membrane, and transports protons to the F1-ATPase which associates with multiple copies of the

Nature Genetics: doi.10.1038/ng.784

subunit C protein encoded by ATP5G1. Subunit C protein accumulates in the lysosomes of patients affected with ceroid lipofuscinosis. The fourth gene in this group is the most interesting in relation to possible mechanistic links to atheosclerosis, through the risk factor insulin resistance. The GIP gene encodes the gastric inhibitory polypeptide, also known as glucose-dependent insulinotropic polypeptide (GIP), a 42-amino acid hormone that stimulates insulin secretion in the presence of glucose. Its sequence indicates that it is a member of a family of structurally related hormones that includes secretin, glucagon, vasoactive intestinal peptide, and growth hormone-releasing factor. Decreased action of this peptide is well known to be a factor in adult onset type II diabetes. Perhaps more important, however, is the observation that GIP receptors are located on adipocytes, where they may mediate the storage of dietary fat and modify the adipocyte phenotype, providing a link to obesity and insulin resistance.

3. Sources of Funding

The **ADVANCE** study was supported by a grant from the Reynold's Foundation and NHLBI grant HL087647.

Genetic analyses of **CADomics** were supported by a research grant from Boehringer Ingelheim. Recruitment and analysis of the CADomics cohort was supported by grants from Boehringer Ingelheim and PHILIPS medical Systems, by the Government of Rheinland-Pfalz in the context of the “Stiftung Rheinland-Pfalz für Innovation”, the research program “Wissen schafft Zukunft” and by the Johannes-Gutenberg University of Mainz in the context of the “Schwerpunkt Vaskuläre Prävention” and the “MAIFOR grant 2001”, by grants from the Fondation de France, the French Ministry of Research, and the Institut National de la Santé et de la Recherche Médicale.

The **deCODE** CAD/MI Study was sponsored by NIH grant, National Heart, Lung and Blood Institute R01HL089650-02.

The German MI Family Studies (**GerMIFS I-III (KORA)**) were supported by the Deutsche Forschungsgemeinschaft and the German Federal Ministry of Education and Research (BMBF) in the context of the German National Genome Research Network (NGFN-2 and NGFN-plus), the EU funded integrated project Cardiogenics (LSHM-CT-2006-037593), and the bi-national BMBF/ANR funded project CARDomics (01KU0908A).

LURIC has received funding from the EU framework 6 funded Integrated Project “Bloodomics” (LSHM-CT-2004-503485), the EU framework 7 funded Integrated Project AtheroRemo (HEALTH-F2-2008-201668) and from Sanofi/Aventis, Roche, Dade Behring/Siemens, and AstraZeneca.

The **MIGen** study was funded by the US National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute's STAMPEED genomics research program through R01 HL087676. Ron Do from the MIGen study is supported by a Canada Graduate Doctoral Scholarship from the Canadian Institutes of Health Research.

Recruitment of **PennCATH** was supported by the Cardiovascular Institute of the University of Pennsylvania. Recruitment of the **MedStar** sample was supported in part by the MedStar Research Institute and the Washington Hospital Center and a research grant from GlaxoSmithKline. Genotyping of PennCATH and Medstar was performed at the Center for Applied Genomics at the Children's Hospital of Philadelphia and supported by GlaxoSmithKline through an Alternate Drug Discovery Initiative research alliance award (M. P. R. and D. J. R.) with the University of Pennsylvania School of Medicine.

The **Ottawa Heart Genomic Study** was supported by CIHR #MOP--82810 (R. R.), CFI #11966 (R. R.), HSFO #NA6001 (R. McP.), CIHR #MOP172605 (R. McP.), CIHR #MOP77682 (A. F. R. S.).

The **WTCCC** Study was funded by the Wellcome Trust. Recruitment of cases for the WTCCC Study was carried out by the British Heart Foundation (BHF) Family Heart Study Research Group and supported by the BHF and the UK Medical Research Council. N. J. S. and S. G. B. hold chairs funded by the British Heart Foundation. N. J. S. and A.H.G are also supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease and the work described in this paper is part of the research portfolio of the Leicester NIHR Biomedical Research Unit.

The **Age, Gene/Environment Susceptibility Reykjavik Study** has been funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

The **Cleveland Clinic GeneBank** study was supported by NIH grants P01 HL098055, P01HL076491-06, R01DK080732, P01HL087018, and 1RO1HL103931-01.

The collection of clinical and sociodemographic data in the **Dortmund Health Study** was supported by the German Migraine- & Headache Society (DMKG) and by unrestricted grants of equal share from Astra Zeneca, Berlin Chemie, Boots Healthcare, Glaxo-Smith-Kline, McNeil Pharma (former Woelm Pharma), MSD Sharp & Dohme and Pfizer to the University of Muenster. Blood collection was done through funds from the Institute of Epidemiology and Social Medicine, University of Muenster.

The **EPIC-Norfolk study** is supported by the Medical Research Council UK and Cancer Research UK.

Nature Genetics: doi.10.1038/ng.784

The **EpiDREAM study** is supported by the Canadian Institutes fo Health Research, Heart and Stroke Foundation of Ontario, Sanofi-Aventis, GlaxoSmithKline and King Pharmaceuticals.

Funding for Andrew Lotery from the **LEEDS** study was provided by tha T.F.C. Frost charity and the Macular Disease Society.

The **Rotterdam Study** is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Support for genotyping was provided by the Netherlands Organization for Scientific Research (NWO) (175.010.2005.011, 911.03.012), the Netherlands Genomics Initiative (NGI)/ NWO project nr. 050-060-810 and Research Institute for Diseases in the Elderly (RIDE). Abbas Dehghan is supported by a grant from NWO (Vici, 918-76-619).

The **SAS** study was funded by the British Heart Foundation.

The Swedish Research Council, the Swedish Heart & Lung Foundation and the Stockholm County Council (ALF) supported the **SHEEP** study.

SMILE was funded by the Netherlands Heart foundation (NHS 92345). Dr Rosendaal is a recipient of the Spinoza Award of the Netherlands Organisation for Scientific Research (NWO) which was used for part of this work.

The **Verona Heart Study** was funded by grants from the Italian Ministry of University and Research, the Veneto Region, and the Cariverona Foundation, Verona.

The **Atherosclerosis Risk in Communities Study** is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. The authors thank the staff and participants of the ARIC study for their important contributions.

The **KORA** (Kooperative Gesundheitsforschung in der Region Augsburg) research platform was initiated and financed by the Helmholtz Zentrum München - National Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Part of this work was financed by the German National Genome Research Network (NGFN-2 and NGFNPlus) and within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

Nature Genetics: doi.10.1038/ng.784

Work described in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease.
This work forms part of the research themes contributing to the translational research portfolio of Barts and the London Cardiovascular Biomedical Research Unit which is supported and funded by the National Institute of Health Research.

4. The CARDIoGRAM Consortium

Executive Committee: Sekar Kathiresan[1,2,3], Muredach P. Reilly[4], Nilesh J. Samani[5,6], Heribert Schunkert[7]

Executive Secretary: Jeanette Erdmann[7]

Steering Committee: Themistocles L. Assimes[8], Eric Boerwinkle[9], Jeanette Erdmann[7], Alistair Hall[10], Christian Hengstenberg[11], Sekar Kathiresan[1,2,3], Inke R. König[12], Reijo Laaksonen[13], Ruth McPherson[14], Muredach P. Reilly[4], Nilesh J. Samani[5,6], Heribert Schunkert[7], John R. Thompson[15], Unnur Thorsteinsdottir[16,17], Andreas Ziegler[12]

Statisticians: Inke R. König[12] (chair), John R. Thompson[15] (chair), Devin Absher[18], Li Chen[19], L. Adrienne Cupples[20,21], Eran Halperin[22], Mingyao Li[23], Kiran Musunuru[1,2,3], Michael Preuss[12,7], Arne Schillert[12], Gudmar Thorleifsson[16], Benjamin F. Voight[2,3,24], George A. Wells[25]

Writing group: Themistocles L. Assimes[8], Panos Deloukas[26], Jeanette Erdmann[7], Hilma Holm[16], Sekar Kathiresan[1,2,3], Inke R. König[12], Ruth McPherson[14], Muredach P. Reilly[4], Robert Roberts[14], Nilesh J. Samani[5,6], Heribert Schunkert[7], Alexandre F. R. Stewart[14]

ADVANCE: Devin Absher[18], Themistocles L. Assimes[8], Stephen Fortmann[8], Alan Go[27], Mark Hlatky[8], Carlos Iribarren[27], Joshua Knowles[8], Richard Myers[18], Thomas Quertermous[8], Steven Sidney[27], Neil Risch[28], Hua Tang[29]

Nature Genetics: doi.10.1038/ng.784

CADomics: Stefan Blankenberg[30], Tanja Zeller[30], Arne Schillert[12], Philipp Wild[30], Andreas Ziegler[12], Renate Schnabel[30], Christoph Sinning[30], Karl Lackner[31], Laurence Tiret[32], Viviane Nicaud[32], Francois Cambien[32], Christoph Bickel[30], Hans J. Rupprecht[30], Claire Perret[32], Carole Proust[32], Thomas Münzel[30]

CHARGE: Maja Barbalic[33], Joshua Bis[34], Eric Boerwinkle[9], Ida Yii-Der Chen[35], L. Adrienne Cupples[20,21], Abbas Dehghan[36], Serkalem Demissie-Banjaw[37,21], Aaron Folsom[38], Nicole Glazer[39], Vilmundur Gudnason[40,41], Tamara Harris[42], Susan Heckbert[43], Daniel Levy[21], Thomas Lumley[44], Kristin Marciante[45], Alanna Morrison[46], Christopher J. O´Donnell[47], Bruce M. Psaty[48], Kenneth Rice[49], Jerome I. Rotter[35], David S. Siscovick[50], Nicholas Smith[43], Albert Smith[40,41], Kent D. Taylor[35], Cornelia van Duijn[36], Kelly Volcik[46], Jaqueline Whitteman[36], Vasan Ramachandran[51], Albert Hofman[36], Andre Uitterlinden[52,36]

deCODE: Solveig Gretarsdottir[16], Jeffrey R. Gulcher[16], Hilma Holm[16], Augustine Kong[16], Kari Stefansson[16,17], Gudmundur Thorgeirsson[53,17], Karl Andersen[53,17], Gudmar Thorleifsson[16], Unnur Thorsteinsdottir[16,17]

GERMIFS I and II: Jeanette Erdmann[7], Marcus Fischer[11], Anika Grosshennig[12,7], Christian Hengstenberg[11], Inke R. König[12], Wolfgang Lieb[54], Patrick Linsel-Nitschke[7], Michael Preuss[12,7], Klaus Stark[11], Stefan Schreiber[55], H.-Erich Wichmann[56,58,59], Andreas Ziegler[12], Heribert Schunkert[7]

GERMIFS III (KORA): Zouhair Aherrahrou[7], Petra Bruse[7], Angela Doering[56], Jeanette Erdmann[7], Christian Hengstenberg[11], Thomas Illig[56], Norman Klopp[56], Inke R. König[12], Patrick Linsel-Nitschke[7], Christina Loley[12,7], Anja Medack[7], Christina Meisinger[56], Thomas Meitinger[57,60], Janja Nahrstedt[12,7], Annette Peters[56], Michael Preuss[12,7], Klaus Stark[11], Arnika K. Wagner[7], H.-Erich Wichmann[56,58,59], Christina Willenborg[12,7], Andreas Ziegler[12], Heribert Schunkert[7]

LURIC/AtheroRemo: Bernhard O. Böhm[61], Harald Dobnig[62], Tanja B. Grammer[63], Eran Halperin[22], Michael M. Hoffmann[64], Marcus Kleber[65], Reijo Laaksonen[13], Winfried März[63,66,67], Andreas Meinitzer[66], Bernhard R. Winkelmann[68], Stefan Pilz[62], Wilfried Renner[66], Hubert Scharnagl[66], Tatjana Stojakovic[66], Andreas Tomaschitz[62], Karl Winkler[64]

Nature Genetics: doi.10.1038/ng.784

MIGen: Benjamin F. Voight[2,3,24], Kiran Musunuru[1,2,3], Candace Guiducci[3], Noel Burtt[3], Stacey B. Gabriel[3], David S. Siscovick[50], Christopher J. O'Donnell[47], Roberto Elosua[69], Leena Peltonen[49], Veikko Salomaa[70], Stephen M. Schwartz[50], Olle Melander[26], David Altshuler[71,3], Sekar Kathiresan[1,2,3]

OHGS: Alexandre F. R. Stewart[14], Li Chen[19], Sonny Dandona[14], George A. Wells[25], Olga Jarinova[14], Ruth McPherson[14], Robert Roberts[14]

PennCATH/MedStar: Muredach P. Reilly[4], Mingyao Li[23], Liming Qu[23], Robert Wilensky[4], William Matthai[4], Hakon H. Hakonarson[72], Joe Devaney[73], Mary Susan Burnett[73], Augusto D. Pichard[73], Kenneth M. Kent[73], Lowell Satler[73], Joseph M. Lindsay[73], Ron Waksman[73], Christopher W. Knouff[74], Dawn M. Waterworth[74], Max C. Walker[74], Vincent Mooser[74], Stephen E. Epstein[73], Daniel J. Rader[75,4]

WTCCC: Nilesh J. Samani[5,6], John R. Thompson[15], Peter S. Braund[5], Christopher P. Nelson[5], Benjamin J. Wright[76], Anthony J. Balmforth[77], Stephen G. Ball[78], Alistair S. Hall[10], Wellcome Trust Case Control Consortium

Affiliations

1 Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 2 Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; 3 Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, MA, USA; 4 The Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, USA; 5 Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK; 6 Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK; 7 Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany; 8 Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; 9 University of Texas Health Science Center, Human Genetics Center and Institute of Molecular

Nature Genetics: doi.10.1038/ng.784

Medicine, Houston, TX, USA; 10 Division of Cardiovascular and Neuronal Remodelling, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, UK; 11 Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, Germany; 12 Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Lübeck, Germany; 13 Science Center, Tampere University Hospital, Tampere, Finland; 14 The John & Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Canada; 15 Department of Health Sciences, University of Leicester, Leicester, UK; 16 deCODE Genetics, 101 Reykjavik, Iceland; 17 University of Iceland, Faculty of Medicine, 101 Reykjavik, Iceland; 18 Hudson Alpha Institute, Huntsville, Alabama, USA; 19 Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, Canada, K1Y 4W7; 20 Department of Biostatistics, Boston University School of Public Health, Boston, MA USA; 21 National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA, USA; 22 The Blavatnik School of Computer Science and the Department of Molecular Microbiology and Biotechnology, Tel-Aviv University, Tel-Aviv, Israel, and the International Computer Science Institute, Berkeley, CA, USA; 23 Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; 24 Department of Medicine, Harvard Medical School, Boston, MA, USA; 25 Research Methods, Univ Ottawa Heart Inst; 26 Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, Scania University Hospital, Lund University, Malmö, Sweden; 27 Division of Research, Kaiser Permanente, Oakland, CA, USA; 28 Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA; 29 Dept Cardiovascular Medicine, Cleveland Clinic; 30 Medizinische Klinik und Poliklinik, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 31 Institut für Klinische Chemie und Laboratoriumsmediizin, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 32 INSERM UMRS 937, Pierre and Marie Curie University (UPMC, Paris 6) and Medical School, Paris, France; 33 University of Texas Health Science Center, Human Genetics Center, Houston, TX, USA; 34 Cardiovascular Health Resarch Unit and Department of Medicine,

Nature Genetics: doi.10.1038/ng.784

University of Washington, Seattle, WA USA; 35 Cedars-Sinai Medical Center, Medical Genetics Institute, Los Angeles, CA, USA; 36 Erasmus Medical Center, Department of Epidemiology, Rotterdam, The Netherlands; 37 Boston University, School of Public Health, Boston, MA, USA; 38 University of Minnesota School of Public Health, Division of Epidemiology and Community Health, School of Public Health (A.R.F.), Minneapolis, MN, USA; 39 University of Washington, Cardiovascular Health Research Unit and Department of Medicine, Seattle, WA, USA; 40 Icelandic Heart Association, Kopavogur Iceland; 41 University of Iceland, Reykjavik, Iceland; 42 Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda MD, USA; 43 University of Washington, Department of Epidemiology, Seattle, WA, USA; 44 University of Washington, Department of Biostatistics, Seattle, WA, USA; 45 University of Washington, Department of Internal Medicine, Seattle, WA, USA; 46 University of Texas, School of Public Health, Houston, TX, USA; 47 National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, MA and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 48 Center for Health Studies, Group Health, Departments of Medicine, Epidemiology, and Health Services, Seattle, WA, USA; 49 The Wellcome Trust Sanger Institute, The Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; 50 Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle; 51 Boston University Medical Center, Boston, MA, USA; 52 Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; 53 Department of Medicine, Landspitali University Hospital, 101 Reykjavik, Iceland; 54 Boston University School of Medicine, Framingham Heart Study, Framingham, MA, USA; 55 Institut für Klinische Molekularbiologie, Christian-Albrechts Universität, Kiel, Germany; 56 Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany; 57 Institut für Humangenetik, Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Neuherberg, Germany; 58 Institute of Medical Information Science, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Germany; 59 Klinikum

Nature Genetics: doi.10.1038/ng.784

Grosshadern, Munich, Germany; 60 Institut für Humangenetik, Technische Universität München, Germany; 61 Division of Endocrinology and Diabetes, Graduate School of Molecular Endocrinology and Diabetes, University of Ulm, Ulm, Germany; 62 Division of Endocrinology, Department of Medicine, Medical University of Graz, Austria; 63 Synlab Center of Laboratory Diagnostics Heidelberg, Heidelberg, Germany; 64 Division of Clinical Chemistry, Department of Medicine, Albert Ludwigs University, Freiburg, Germany; 65 LURIC non profit LLC, Freiburg, Germany; 66 Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Austria; 67 Institute of Public Health, Social and Preventive Medicine, Medical Faculty Manneim, University of Heidelberg, Germany; 68 Cardiology Group Frankfurt-Sachsenhausen, Frankfurt, Germany; 69 Cardiovascular Epidemiology and Genetics Group, Institut Municipal d'Investigació Mèdica, Barcelona; Ciber Epidemiología y Salud Pública (CIBERSP), Spain; 70 Chronic Disease Epidemiology and Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; 71 Department of Molecular Biology and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, USA; 72 The Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; 73 Cardiovascular Research Institute, Medstar Health Research Institute, Washington Hospital Center, Washington, DC 20010, USA; 74 Genetics Division and Drug Discovery, GlaxoSmithKline, King of Prussia, Pennsylvania 19406, USA; 75 The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; 76 Department of Cardiovascular Surgery, University of Leicester, Leicester, UK; 77 Division of Cardiovascular and Diabetes Research, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, LS2 9JT, UK; 78 LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds, UK

Nature Genetics: doi.10.1038/ng.784

Supplementary References

1. Assimes, T.L., *et al.* Susceptibility locus for clinical and subclinical coronary artery disease at chromosome 9p21 in the multi-ethnic ADVANCE study. *Human Molecular Genetics* **17**, 2320-2328 (2008).
2. Psaty, B.M., *et al.* Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet* **2**, 73-80 (2009).
3. Helgadottir, A., *et al.* A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* **316**, 1491-1493 (2007).
4. Samani, N.J., *et al.* Genomewide association analysis of coronary artery disease. *The New England Journal of Medicine* **357**, 443-453 (2007).
5. Erdmann, J., *et al.* New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nature Genetics* **41**, 280-282 (2009).
6. Winkelmann, B.R., *et al.* Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics* **2**, S1-73 (2001).
7. Reilly, M.P., *et al.* Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. *Lancet* **377**, 383-392 (2011).
8. Kathiresan, S., *et al.* Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nature genetics* **41**, 334-341 (2009).
9. Stewart, A.F., *et al.* Kinesin family member 6 variant Trp719Arg does not associate with angiographically defined coronary artery disease in the Ottawa Heart Genomics Study. *J Am Coll Cardiol* **53**, 1471-1472 (2009).
10. Lehrke, M., *et al.* CXCL16 is a marker of inflammation, atherosclerosis and acute coronary syndromes in humans. *J Am Coll Cardiol* **49**, 442-449 (2007).
11. WTCCC. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-678 (2007).
12. Trip, M.D., *et al.* Frequent mutation in the ABCC6 gene (R1141X) is associated with a strong increase in the prevalence of coronary artery disease. *Circulation* **106**, 773-775 (2002).
13. Day, N., *et al.* EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* **80 Suppl 1**, 95-103 (1999).
14. Agema, W.R., *et al.* Current PTCA practice and clinical outcomes in The Netherlands: the real world in the pre-drug-eluting stent era. *Eur Heart J* **25**, 1163-1170 (2004).
15. Buysschaert, I., *et al.* A variant at chromosome 9p21 is associated with recurrent myocardial infarction and cardiac death after acute coronary syndrome: the GRACE Genetics Study. *Eur Heart J* **31**, 1132-1141 (2010).
16. Anderson, J.L., *et al.* Genetic variation at the 9p21 locus predicts angiographic coronary artery disease prevalence but not extent and has clinical utility. *Am Heart J* **156**, 1155-1162 e1152 (2008).
17. Horne, B.D., Carlquist, J.F., Muhlestein, J.B., Bair, T.L. & Anderson, J.L. Association of variation in the chromosome 9p21 locus with myocardial infarction versus chronic coronary artery disease. *Circ Cardiovasc Genet* **1**, 85-92 (2008).
18. Meng, W., *et al.* Chromosome 9p21.3 is associated with early-onset coronary heart disease in the Irish population. *Dis Markers* **25**, 81-85 (2008).
19. Morgan, T.M., Krumholz, H.M., Lifton, R.P. & Spertus, J.A. Nonvalidation of reported genetic risk factors for acute coronary syndrome in a large-scale replication study. *J Am Med Assoc* **297**, 1551-1561 (2007).

Nature Genetics: doi.10.1038/ng.784

20. Ye, S.*, et al.* Independent effects of the -219 G>T and epsilon 2/ epsilon 3/ epsilon 4 polymorphisms in the apolipoprotein E gene on coronary artery disease: the Southampton Atherosclerosis Study. *Eur J Hum Genet* **11**, 437-443 (2003).
21. Doggen, C.J., Manger Cats, V., Bertina, R.M. & Rosendaal, F.R. Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or prothrombin 20210A. *Circulation* **97**, 1037-1041 (1998).
22. Gigante, B.*, et al.* Variants in the coagulation factor 2 receptor (F2R) gene influence the risk of myocardial infarction in men through an interaction with interleukin 6 serum levels. *Thromb Haemost* **101**, 943-953 (2009).
23. Vaidya, D.*, et al.* Incidence of coronary artery disease in siblings of patients with premature coronary artery disease: 10 years of follow-up. *Am J Cardiol* **100**, 1410-1415 (2007).
24. Gudbjartsson, D.F.*, et al.* Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nature genetics* **41**, 342-347 (2009).
25. Theodoraki, E.V.*, et al.* Fibrinogen beta variants confer protection against coronary artery disease in a Greek case-control study. *BMC medical genetics* **11**, 28 (2010).
26. Brouilette, S., Singh, R.K., Thompson, J.R., Goodall, A.H. & Samani, N.J. White cell telomere length and risk of premature myocardial infarction. *Arterioscler Thromb Vasc Biol* **23**, 842-846 (2003).
27. Steeds, R., Adams, M., Smith, P., Channer, K. & Samani, N.J. Distribution of tissue plasminogen activator insertion/deletion polymorphism in myocardial infarction and control subjects. *Thromb Haemost* **79**, 980-984 (1998).
28. Girelli, D.*, et al.* Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. *The New England journal of medicine* **343**, 774-780 (2000).
29. Suchindran, S.*, et al.* Genome-wide association study of Lp-PLA(2) activity and mass in the Framingham Heart Study. *PLoS Genet* **6**, e1000928 (2010).
30. Shete, S.*, et al.* Genome-wide association study identifies five susceptibility loci for glioma. *Nature genetics* **41**, 899-904 (2009).
31. Yasuno, K.*, et al.* Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nature genetics* **42**, 420-425 (2010).
32. Chung, C.M.*, et al.* A genome-wide association study identifies new loci for ACE activity: potential implications for response to ACE inhibitor. *Pharmacogenomics J* (2010).
33. Kamatani, Y.*, et al.* Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nature genetics* **42**, 210-215 (2010).
34. Amundadottir, L.*, et al.* Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nature genetics* **41**, 986-990 (2009).
35. Qi, L.*, et al.* Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. *Human molecular genetics* **19**, 1856-1862 (2010).
36. Melzer, D.*, et al.* A genome-wide association study identifies protein quantitative trait loci (pQTLs). *PLoS Genet* **4**, e1000072 (2008).
37. Paterson, A.D.*, et al.* Genome-wide association identifies the ABO blood group as a major locus associated with serum levels of soluble E-selectin. *Arterioscler Thromb Vasc Biol* **29**, 1958-1967 (2009).
38. Barbalic, M.*, et al.* Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. *Human molecular genetics* **19**, 1863-1872 (2010).
39. Tregouet, D.A.*, et al.* Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. *Blood* **113**, 5298-5303 (2009).
40. McKelvey, R.D. & Zavoina, W.A. A statistical model for the analysis of ordinal level dependent variables. *J Math Sociol* **4**, 103-120 (1975).
41. Emilsson, V.*, et al.* Genetics of gene expression and its effect on disease. *Nature* **452**, 423-428 (2008).
42. Honeyman, A.L. & Stewart, G.C. Identification of the protein encoded by rodC, a cell division gene from Bacillus subtilis. *Mol Microbiol* **2**, 735-741 (1988).
43. Stefansson, H.*, et al.* A common inversion under selection in Europeans. *Nature genetics* **37**, 129-137 (2005).

Nature Genetics: doi.10.1038/ng.784

44. R Development Core Team. *R: A language and environment for statistical computing*, (R Foundation for Statistical Computing, Vienna, Austria, 2005).
45. Ge, B.*, et al.* Global patterns of cis variation in human cells revealed by high-density allelic expression analysis. *Nature genetics* **41**, 1216-1222 (2009).
46. Brindley, D.N. & Waggoner, D.W. Mammalian lipid phosphate phosphohydrolases. *J Biol Chem* **273**, 24281-24284 (1998).
47. Brindley, D.N., English, D., Pilquil, C., Buri, K. & Ling, Z.C. Lipid phosphate phosphatases regulate signal transduction through glycerolipids and sphingolipids. *Biochim Biophys Acta* **1582**, 33-44 (2002).
48. Escalante-Alcalde, D., Sanchez-Sanchez, R. & Stewart, C.L. Generation of a conditional Ppap2b/Lpp3 null allele. *Genesis* **45**, 465-469 (2007).
49. Escalante-Alcalde, D., Morales, S.L. & Stewart, C.L. Generation of a reporter-null allele of Ppap2b/Lpp3and its expression during embryogenesis. *Int J Dev Biol* **53**, 139-147 (2009).
50. Quaggin, S.E.*, et al.* The basic-helix-loop-helix protein pod1 is critically important for kidney and lung organogenesis. *Development* **126**, 5771-5783 (1999).
51. Shivapurkar, N.*, et al.* Differential methylation of a short CpG-rich sequence within exon 1 of TCF21 gene: a promising cancer biomarker assay. *Cancer Epidemiol Biomarkers Prev* **17**, 995-1000 (2008).
52. Smith, L.T.*, et al.* Epigenetic regulation of the tumor suppressor gene TCF21 on 6q23-q24 in lung and head and neck cancer. *Proc Natl Acad Sci U S A* **103**, 982-987 (2006).
53. Tessema, M. & Belinsky, S.A. Mining the epigenome for methylated genes in lung cancer. *Proc Am Thorac Soc* **5**, 806-810 (2008).
54. Lu, J., Richardson, J.A. & Olson, E.N. Capsulin: a novel bHLH transcription factor expressed in epicardial progenitors and mesenchyme of visceral organs. *Mech Dev* **73**, 23-32 (1998).
55. Makino, H.*, et al.* Altered gene expression related to glomerulogenesis and podocyte structure in early diabetic nephropathy of db/db mice and its restoration by pioglitazone. *Diabetes* **55**, 2747-2756 (2006).
56. Hidai, H., Bardales, R., Goodwin, R., Quertermous, T. & Quertermous, E.E. Cloning of capsulin, a basic helix-loop-helix factor expressed in progenitor cells of the pericardium and the coronary arteries. *Mech Dev* **73**, 33-43 (1998).
57. Bassermann, F., Peschel, C. & Duyster, J. Mitotic entry: a matter of oscillating destruction. *Cell Cycle* **4**, 1515-1517 (2005).
58. Bassermann, F.*, et al.* NIPA defines an SCF-type mammalian E3 ligase that regulates mitotic entry. *Cell* **122**, 45-57 (2005).
59. Ouyang, T.*, et al.* Identification and characterization of a nuclear interacting partner of anaplastic lymphoma kinase (NIPA). *J Biol Chem* **278**, 30028-30036 (2003).
60. Storry, J.R. & Olsson, M.L. The ABO blood group system revisited: a review and update. *Immunohematology* **25**, 48-59 (2009).
61. Lewin, B. *Genes VII*, (Oxford University Press, New York, 2000).
62. Wakley, E.J., Langman, M.J. & Elwood, P.C. Blood group A sub-groups and serum cholesterol. *Cardiovasc Res* **7**, 679-683 (1973).
63. Bronte-Stewart, B., Botha, M.C. & Krut, L.H. ABO blood groups in relation to ischaemic heart disease. *Br Med J* **1**, 1646-1650 (1962).
64. Garrison, R.J.*, et al.* ABO blood group and cardiovacular disease: the Framingham study. *Atherosclerosis* **25**, 311-318 (1976).
65. Morton, N.E. Genetic markers in atherosclerosis: a review. *J Med Genet* **13**, 81-90 (1976).
66. Wu, O., Bayoumi, N., Vickers, M.A. & Clark, P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost* **6**, 62-69 (2008).
67. Jenkins, P.V. & O'Donnell, J.S. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? *Transfusion* **46**, 1836-1844 (2006).
68. Smith, N.L.*, et al.* Novel associations of multiple genetic loci with plasma levels of factor VII, factor VIII, and von Willebrand factor: The CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) Consortium. *Circulation* **121**, 1382-1392 (2010).
69. Chasman, D.I.*, et al.* Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. *PLoS genetics* **5**, e1000730 (2009).

Nature Genetics: doi.10.1038/ng.784

70. Pare, G.*, et al.* Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. *PLoS genetics* **4**, e1000118 (2008).
71. Galcheva-Gargova, Z.*, et al.* The cytoplasmic zinc finger protein ZPR1 accumulates in the nucleolus of proliferating cells. *Mol Biol Cell* **9**, 2963-2971 (1998).
72. Lookene, A., Beckstead, J.A., Nilsson, S., Olivecrona, G. & Ryan, R.O. Apolipoprotein A-V-heparin interactions: implications for plasma lipoprotein metabolism. *J Biol Chem* **280**, 25383-25387 (2005).
73. Mar, R.*, et al.* Association of the APOLIPOPROTEIN A1/C3/A4/A5 gene cluster with triglyceride levels and LDL particle size in familial combined hyperlipidemia. *Circ Res* **94**, 993-999 (2004).
74. Talmud, P.J., Palmen, J., Putt, W., Lins, L. & Humphries, S.E. Determination of the functionality of common APOA5 polymorphisms. *J Biol Chem* **280**, 28215-28220 (2005).
75. Hurskainen, T.L., Hirohata, S., Seldin, M.F. & Apte, S.S. ADAM-TS5, ADAM-TS6, and ADAM-TS7, novel members of a new family of zinc metalloproteases. General features and genomic distribution of the ADAM-TS family. *J Biol Chem* **274**, 25555-25563 (1999).
76. Liu, C.J.*, et al.* ADAMTS-7: a metalloproteinase that directly binds to and degrades cartilage oligomeric matrix protein. *FASEB J* **20**, 988-990 (2006).
77. Bai, X.H.*, et al.* ADAMTS-7, a direct target of PTHrP, adversely regulates endochondral bone growth by associating with and inactivating GEP growth factor. *Mol Cell Biol* **29**, 4201-4219 (2009).
78. Liu, C.J. The role of ADAMTS-7 and ADAMTS-12 in the pathogenesis of arthritis. *Nat Clin Pract Rheumatol* **5**, 38-45 (2009).
79. Wang, L.*, et al.* ADAMTS-7 mediates vascular smooth muscle cell migration and neointima formation in balloon-injured rat arteries. *Circ Res* **104**, 688-698 (2009).
80. Emaduddin, M., Edelmann, M.J., Kessler, B.M. & Feller, S.M. Odin (ANKS1A) is a Src family kinase target in colorectal cancer cells. *Cell Commun Signal* **6**, 7 (2008).
81. Kristiansen, T.Z., Nielsen, M.M., Blagoev, B., Pandey, A. & Mann, M. Mouse embryonic fibroblasts derived from Odin deficient mice display a hyperproliiferative phenotype. *DNA Res* **11**, 285-292 (2004).
82. Hasler, J.A. Pharmacogenetics of cytochromes P450. *Mol Aspects Med* **20**, 12-24, 25-137 (1999).
83. Newton-Cheh, C.*, et al.* Genome-wide association study identifies eight loci associated with blood pressure. *Nature genetics* (2009).
84. Yamada, Y.*, et al.* Genetic risk for myocardial infarction determined by polymorphisms of candidate genes in a Japanese population. *J Med Genet* **45**, 216-221 (2008).
85. Tarasov, K.V.*, et al.* COL4A1 is associated with arterial stiffness by genome-wide association scan. *Circ Cardiovasc Genet* **2**, 151-158 (2009).
86. de Vries, L.S.*, et al.* COL4A1 mutation in two preterm siblings with antenatal onset of parenchymal hemorrhage. *Ann Neurol* **65**, 12-18 (2009).
87. Gould, D.B.*, et al.* Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. *Science (New York, N Y)* **308**, 1167-1171 (2005).
88. Gould, D.B.*, et al.* Role of COL4A1 in small-vessel disease and hemorrhagic stroke. *The New England journal of medicine* **354**, 1489-1496 (2006).
89. Plaisier, E.*, et al.* COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. *The New England journal of medicine* **357**, 2687-2695 (2007).
90. Ronco, P. & Plaisier, E. [Hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANAC): a new basement membrane-disease associated with mutations of the COL4A1 gene]. *Bull Acad Natl Med* **192**, 971-984 (2008).
91. Van Agtmael, T.*, et al.* Col4a1 mutation in mice causes defects in vascular function and low blood pressure associated with reduced red blood cell volume. *Human molecular genetics* **19**, 1119-1128 (2010).
92. Broeckel, U.*, et al.* A comprehensive linkage analysis for myocardial infarction and its related risk factors. *Nature genetics* **30**, 210-214 (2002).
93. Nicholson, P.*, et al.* Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. *Cell Mol Life Sci* **67**, 677-700 (2010).

Nature Genetics: doi.10.1038/ng.784

94. Redon, S., Reichenbach, P. & Lingner, J. Protein RNA and protein protein interactions mediate association of human EST1A/SMG6 with telomerase. *Nucleic Acids Res* **35**, 7011-7022 (2007).
95. Azzalin, C.M. & Lingner, J. The human RNA surveillance factor UPF1 is required for S phase progression and genome stability. *Curr Biol* **16**, 433-439 (2006).
96. Azzalin, C.M., Reichenbach, P., Khoriauli, L., Giulotto, E. & Lingner, J. Telomeric repeat containing RNA and RNA surveillance factors at mammalian chromosome ends. *Science (New York, N Y)* **318**, 798-801 (2007).
97. Walkey, C.J., Cui, Z., Agellon, L.B. & Vance, D.E. Characterization of the murine phosphatidylethanolamine N-methyltransferase-2 gene. *J Lipid Res* **37**, 2341-2350 (1996).
98. Walkey, C.J., Donohue, L.R., Bronson, R., Agellon, L.B. & Vance, D.E. Disruption of the murine gene encoding phosphatidylethanolamine N-methyltransferase. *Proc Natl Acad Sci U S A* **94**, 12880-12885 (1997).
99. Seranski, P.*, et al.* RAI1 is a novel polyglutamine encoding gene that is deleted in Smith-Magenis syndrome patients. *Gene* **270**, 69-76 (2001).
100. Jin, J., Li, X., Gygi, S.P. & Harper, J.W. Dual E1 activation systems for ubiquitin differentially regulate E2 enzyme charging. *Nature* **447**, 1135-1138 (2007).
101. Kamura, T.*, et al.* Cloning and characterization of ELL-associated proteins EAP45 and EAP20. a role for yeast EAP-like proteins in regulation of gene expression by glucose. *J Biol Chem* **276**, 16528-16533 (2001).
102. Schmidt, A.E., Miller, T., Schmidt, S.L., Shiekhattar, R. & Shilatifard, A. Cloning and characterization of the EAP30 subunit of the ELL complex that confers derepression of transcription by RNA polymerase II. *J Biol Chem* **274**, 21981-21985 (1999).

Nature Genetics: doi.10.1038/ng.784