**ONLINE APPENDIX**

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**Supplemental Methods**

**Statistical analysis**

In each replication study individually, we tested for association with CAD using a linear mixed model with fixed effects of genotype and principal components of ancestry and a kinship matrix as random effects. Results were combined within ancestry groups and then across all studies using inverse-variance weighted fixed effects meta-analyses.

**Bioinformatics analysis**

***Annotation of novel loci:*** To identify any association between novel loci and gene expression traits we performed a systematic search for expression quantitative trait loci (eQTLs) in the monocyte and macrophage expression study from the Cardiogenics consortium (1), the Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task (STARNET) RNA-seq dataset (2) and over 100 studies included in the GRASP database (3). To identify candidate causal SNPs at the new loci we functionally annotated each of the lead variants as well all SNPs in high linkage disequilibrium (LD) SNPs (*r2* > 0.8) using Haploreg V3 (4). Non-synonymous variants were analyzed using SIFT (5) and Polyphen-2 (6). Conservation was assessed by GERP (7) and SiPhy (8). Overlap with regulatory elements including chromosome state segmentation, DNase hypersensitivity, and transcription factor binding as determined by the ENCODE (9) and Roadmap Epigenome projects (10), and predicted effects on transcription factor binding based on regulatory motifs from TRANSFAC (11) and JASPAR (12) were identified using Haploreg V3 (4) and the UCSC genome browser. Variants were then scored using three different bioinformatics tools that help prioritize causal disease variants. Combined Annotation Dependent Depletion (CADD) (13) incorporates a range pathogenicity prediction tools to provide a genome-wide score (C-score) for each test variant from its pre-calculated database of ~8.6 billion genetic variants. High scores indicate variants that are not stabilized by selection and are more likely to be disease-causing and low scores indicate evolutionary stable non-damaging variants. The top 10% of likely functional variants will have a C-score >10 and top 1% of variants will have a C-score >20. Genome-wide annotation of variants (GWAVA) (14) predicts the functional impact of noncoding variants based on a number of genomic and epigenomic annotations and provides scores between 0 and 1 with higher scores indicating variants that are more likely to be functional. RegulomeDB (15) annotates and scores variants based on a number of datasets, including ENCODE, and scores variants in seven categories. Scores of 1 and 2 identify variants that are likely to affect transcription factor binding, a score of 3 identifies variants that are less likely to affect binding, scores of 4, 5 and 6 relate to variants with minimal binding evidence and a score of 7 is for variants with no regulatory annotation.

**Supplemental Table 1: Sources of cases and controls in the discovery study**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | Case definition | Control definition | Cases | Controls | Reference | |
| ATVB | Case-control | MI in men or women ≤ 45 years of age | No history of thromboembolic disease | 1,428 | 1,069 | [1](#_ENREF_8)6 |
|  |  |  |  |  |  |  |
| BHF-FHS | Case-control | CAD cases were recruited from the British Heart Foundation Family Heart Study and supplemented by additional cases from WTCCC-CAD2 | Controls were selected from the UK 1958 Birth Cohort | 2,833 | 5,912 | 17,18 |
|  |  |  |  |  |  |  |
| BioVU | Case-control | Cases with MI or CAD were ascertained from the Vanderbilt University Medical Center Biorepository by searching the electronic medical record for ≥ 2 instances of ICD-9 codes 410.x – 414.x | Controls were individuals from the Vanderbilt University Biorepository who did not have any record of ICD-9 codes 410.x – 414.x | 4,587 | 16,556 | 19 |
|  |  |  |  |  |  |  |
| Duke | Case-control | MI or coronary stenosis ≥ 50% | Controls were > 50 years old without coronary stenosis > 30% and without history of MI, coronary artery bypass grafting, percutaneous coronary intervention, or heart transplant | 660 | 515 | [20](#_ENREF_12) |
|  |  |  |  |  |  |  |
| EPIC CAD | Nested case-control | The EPIC (European Prospective Study into Cancer and Nutrition) study sub-cohorts from the UK were used. Subjects were collected in collaboration with general practitioners, mainly in Cambridgeshire and Norfolk. Cases were individuals who developed fatal or non-fatal CAD during an average follow-up of 11 years ending June 2006. Participants were identified if they had a hospital admission and/or died with CAD as the underlying cause. CAD was defined as cause of death codes ICD-9 410-414 or ICD-10 I20-I25, and hospital discharge codes ICD-10 I20.0, I21, I22, or I23 according to the International Classification of Diseases, 9th and 10th revisions, respectively. | Controls were study participants who remained free of any cardiovascular disease during follow-up (defined as ICD-9 401-448 and ICD-10 I10-I79) | 1,386 | 7,037 | [21](#_ENREF_13) |
|  |  |  |  |  |  |  |
| FIA3 | Nested case-control | Cases of MI occurring in participants from Vasterbotten Intervention Program (VIP), WHO’s Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study in northern Sweden and the Mammography Screening Project (MSP) in Vasterbotten | Individuals free of MI from VIP and MSP | 2,473 | 2,047 | 22,23 |
|  |  |  |  |  |  |  |
| GoDARTS CAD | Case-control | The GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) study is a joint initiative of the Department of Medicine and the Medicines Monitoring Unit (MEMO) at the University of Dundee, the diabetes units at three Tayside healthcare trusts (Ninewells Hospital and Medical School, Dundee; Perth Royal Infirmary; and Stracathro Hospital, Brechin), and a large group of Tayside general practitioners with an interest in diabetes care. Cases were first-ever CAD event, defined as fatal and non-fatal myocardial infarction, unstable angina, or coronary revascularization. | Controls were free of CAD, stroke, and peripheral vascular disease | 1,568 | 2,772 | [24](#_ENREF_16) |
|  |  |  |  |  |  |  |
| EGCUT |  | CAD or MI cases were ascertained from the Estonian Biobank (Estonian Genome Center at the University of Tartu) using the medical history and current health status that is recorded according to ICD-10 codes (CAD defined with ICD-10 I20-I25). | Controls were selected from the Estonian Biobank (Estonian Genome Center at the University of Tartu) who did not have any record of cardiovascular diseases (ICD-10 I10-I79). | 392 | 777 | [25](#_ENREF_17) |
|  |  |  |  |  |  |  |
| German CAD North |  | The German North cohort includes individuals from GerMIFS4, PopGen, and HNR with MI or CAD. | Controls were derived from population-based studies in Germany. | 4,464 | 2,886 | [26-28](#_ENREF_18) |
|  |  |  |  |  |  |  |
| German CAD South |  | The German South cohort includes samples from GerMIFS3 and Munich-MI with MI or CAD. | Controls were derived from population-based studies in Germany. | 5,255 | 2,921 | 29,30 |
|  |  |  |  |  |  |  |
| HUNT | Case-control | MI Cases were retrospectively identified as HUNT 2 and HUNT 3 participants diagnosed with acute MI (ICD-10 I21 or ICD-9 410) in the medical departments at the two local hospitals in Nord-Trøndelag County from December 1987 to June 2011. | Controls were selected among HUNT 2 and HUNT 3 participants with available DNA (N = 70,300) after excluding individuals with the following hospital diagnosed or self-reported conditions in themselves or known 1st and/or 2nd degree family members: MI, angina, heart failure, stroke, aortic aneurysm, atherosclerosis, intermittent claudication, and registered percutaneous coronary angioplasty procedures or bypass surgery. | 2,351 | 2,348 | [31](#_ENREF_23) |
|  |  |  |  |  |  |  |
| Bio*Me* Biobank | Case-control | CAD cases were ascertained from the Bio*Me* Biobank using the electronic health record with ICD9 codes 410.xx to 414.xx and abnormal stress test or abnormal coronary angiography | Controls were individuals from the Bio*Me* Biobank who did not meet the criteria for cases | 704 | 1,729 | NIH dbGaP Study Accession phs000388.v1.p1 |
|  |  |  |  |  |  |  |
| MDC | Prospective cohort | Prevalent and incident nonfatal or fatal MI | Participants free of CHD at baseline and during follow-up | 2,283 | 4,511 | [32](#_ENREF_24) |
|  |  |  |  |  |  |  |
| MHI | Case-control | Cases were ascertained from the Montreal Heart Institute Biobank. CAD was defined as the presence of MI, percutaneous coronary intervention, or coronary artery bypass grafting | Controls were individuals from the Montreal Heart Institute Biobank who were free of history of MI, percutaneous coronary intervention, or coronary artery bypass grafting | 3,990 | 6,585 | 33,34 |
|  |  |  |  |  |  |  |
| OHS | Case-control | Cases had angiographically confirmed coronary artery disease (>1 coronary artery with >50% stenosis) and did not have type 2 diabetes; ≤ 50 years old for males and ≤ 50 years old for females | Asymptomatic males > 65, females > 70 | 1,024 | 2,267 | [35](#_ENREF_27) |
|  |  |  |  |  |  |  |
| PAS-AMC | Case-control | Symptomatic CAD before 51 years of age, defined as MI, coronary revascularization, or evidence of at least 70% stenosis in a major epicardial coronary artery | More than 95% of the controls are from the same region as cases | 728 | 808 | [36](#_ENREF_28) |
|  |  |  |  |  |  |  |
| PennCath | Case-control | Cases had angiographically confirmed coronary artery disease (>1 coronary artery with 50% stenosis); ≤ 55 years old for males and ≤ 60 years old for females | Normal coronary angiography in men > 40 years old and women > 45 years old | 683 | 156 | [37](#_ENREF_29) |
|  |  |  |  |  |  |  |
| PROCARDIS | Case-control | Symptomatic CAD before age 66. CAD was defined as clinically documented evidence of myocardial infarction, coronary artery bypass grafting, acute coronary syndrome, coronary angioplasty, or stable angina | No personal or sibling history of CAD before age 66 | 2,490 | 2,220 | [38](#_ENREF_30) |
|  |  |  |  |  |  |  |
| VHS | Case-control | Documented MI, coronary artery bypass grafting, CAD (by angiography) in males ≤ 45 years old and females ≤ 50 years old | Normal coronary angiography in males > 60 years old or females > 65 years old. | 176 | 164 | [39](#_ENREF_31) |
|  |  |  |  |  |  |  |
| WHI | Prospective cohort | Cases were individuals from the Women’s Health Initiative who had incident MI, coronary revascularization, hospitalized angina or death due to coronary disease | Participants free of CHD on follow-up | 2,860 | 14,960 | [40](#_ENREF_32) |
|  |  |  |  |  |  |  |
| Discovery study total | |  |  | **42,335** | **78,240** |  |

ATVB: Italian Atherosclerosis, Thrombosis, and Vascular Biology Study; BHF-FHS: British Heart Foundation Family Heart Study; BioVU: Vanderbilt University Medical Center Biorepository; GoDARTS: Genetics of Diabetes Audit and Research Tayside; FIA3: First-time incidence of myocardial infarction in the AC county 3; EGCUT: Estonian Genome Centre, University of Tartu; EPIC: European Prospective Study into Cancer and Nutrition; HUNT: Nord-Trøndelag health study; IPM: Mt. Sinai Institute for Personalized Medicine Biobank; MDC: Malmo Diet and Cancer Study-Cardiovascular Cohort; MHI: Montreal Heart Institute Study; OHS: Ottawa Heart Study; PAS-AMC; Premature Atherosclerosis Study at Academic Medical Center Amsterdam; PennCath: University of Pennsylvania Catheterization Study; PROCARDIS: Precocious Coronary Artery Disease Study; VHS: Verona Heart Study; WHI: Women’s Health Initiative. MI: myocardial infarction; CAD: coronary artery disease.

**Supplemental** Table 2: **Sources of cases and controls in the replication study**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study (Ancestry) | Design | Case definition | Control definition | N Cases | N Controls | Reference |
| BRAVE (SA) | Case-control | First-ever troponin-confirmed acute MI | Hospital controls frequency matched by age and sex | 2,971 | 2,784 | N/A |
| CCHS (EA) | Prospective cohort | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | Participants from the CCHS cohort who were free from coronary disease at baseline and after follow-up | 2,020 | 6,087 | [41](#_ENREF_33) |
| CIHDS/ CGPS (EA) | Case-control | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | Age- and sex-matched population controls free from coronary disease | 8,079 | 10,367 | [41](#_ENREF_33) |
| EPIC-CVD (EA) | Case-cohort | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | A randomly-selected subcohort of participants from the EPIC cohort who were free from coronary disease at baseline and after follow-up | 3,873 | 7,914 | [42](#_ENREF_34) |
| MORGAM (EA) | Case-cohort | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | A randomly-selected subcohort of participants from the MORGAM cohorts who were free from coronary disease and stroke at baseline and after follow-up | 2,153 | 2,118 | 43,44 |
| PROMIS (SA) | Case-control | First-ever troponin-confirmed acute MI | Hospital controls frequency matched by age and sex | 10,137 | 11,935 | [45](#_ENREF_37) |
| PROSPER (EA) | Nested case-control | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | Age- and sex-matched participants from the PROSPER trial free of coronary disease at baseline and after follow-up | 641 | 638 | [46](#_ENREF_38) |
| WOSCOPS (EA) | Nested case-control | Fatal and non-fatal MI and other coronary events according to ICD-10 codes I20-I25 | Age-matched men from the WOSCOPS trial free of coronary disease at baseline and after follow-up | 659 | 687 | [47](#_ENREF_39) |
| Replication study total | |  |  | **30,533** | **42,530** |  |

EA: European Ancestry; SA: South Asian Ancestry; BRAVE: Bangladesh Risk of Acute Vascular Events Study; CCHS: Copenhagen City Heart Study; CGPS: Copenhagen General Population Study; CIHDS: Copenhagen Ischaemic Heart Disease Study; EPIC-CVD: European Prospective Investigation into Cancer and Nutrition Study; MORGAM: MOnica Risk, Genetics, Archiving and Monograph project; PROMIS: Pakistan Risk of Myocardial Infarction Study; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk clinical trial; WOSCOPS: West of Scotland Coronary Prevention Study; N/A: None available.

**Supplemental Table 3: Discovery, replication and combined findings for the 28 variants that reached an association P value with CAD of < 1 x 10-6 in the discovery cohort**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **Discovery** | | | | **Replication** | | | | **Meta-analysis** | |
| **Exome Chip ID** | **CHR** | **POS** | **Gene** | **Allele1/2** | **Allele1Freq** | **Cases/Controls** | **Odds Ratio (CI 95%)** | **P-value** | **Het P-value** | **Cases/Controls** | **OR (CI 95%)** | **P-value** | **Het P-value** | **OR (CI 95%)** | **P-value** |
| exm-rs16986953 | 2 | 19942473 | none | A/G | 0.08 | 36376/59528 | 1.11 (1.07-1.15) | 8.17x10-08 | 0.02 | 12253/20131 | 1.05 (1.00-1.11) | 0.06 | 0.22 | 1.09(1.06-1.12) | 5.95x10-08 |
| exm-rs1250229 | 2 | 216304384 | none | T/C | 0.26 | 42332/78235 | 1.08 (1.06-1.1) | 1.22x10-12 | 0.18 | 30531/42529 | 1.01 (0.99-1.03) | 0.38 | 0.02 | 1.05 (1.03-1.06) | 3.48x10-09 |
| exm-rs2943634 | 2 | 227068080 | none | A/C | 0.33 | 42332/78233 | 0.95 (0.93-0.97) | 1.57x10-07 | 0.02 | 30523/42511 | 0.99 (0.96-1.01) | 0.31 | 0.73 | 0.96 (0.95-0.98) | 2.85x10-06 |
| exm-rs2943641 | 2 | 227093745 | none | T/C | 0.36 | 42331/78228 | 0.95 (0.93-0.97) | 1.95x10-07 | 0.02 | 30531/42528 | 0.99 (0.97-1.01) | 0.3 | 0.38 | 0.97 (0.95-0.98) | 3.11x10-06 |
| exm-rs2972146 | 2 | 227100698 | none | G/T | 0.36 | 42328/78220 | 0.95 (0.93-0.97) | 2.01x10-07 | 0.04 | 22453/32163 | 0.99 (0.96-1.01) | 0.33 | 0.31 | 0.96 (0.95-0.98) | 1.55x10-06 |
| exm275853 | 2 | 233633460 | *KCNJ13,GIGYF2* | A/G | 0.35 | 42332/78229 | 1.06 (1.04-1.08) | 1.46x10-08 | 0.5 | 30528/42521 | 1.03 (1.01-1.06) | 0.007 | 0.88 | 1.05 (1.03-1.06) | 1.48x10-09 |
| exm2255118 | 2 | 233699415 | *GIGYF2* | G/A | 0.45 | 42333/78238 | 1.05 (1.03-1.07) | 9.10x10-08 | 0.13 | 30532/42526 | 1.02 (1.00-1.05) | 0.03 | 0.97 | 1.04 (1.03-1.06) | 4.02x10-08 |
| exm359878 | 3 | 153839866 | *ARHGEF26* | G/C | 0.13 | 39258/62925 | 0.92 (0.89-0.95) | 8.28x10-09 | 0.43 | 20394/30594 | 1 (0.96-1.04) | 0.9 | 0.74 | 0.94 (0.92-0.97) | 1.75x10-06 |
| exm414316 | 4 | 95496882 | *PDLIM5* | T/C | 0.31 | 42335/78234 | 0.95 (0.93-0.97) | 5.97x10-07 | 0.4 | 30532/42528 | 0.98 (0.95-1.00) | 0.1 | 0.83 | 0.96 (0.95-0.98) | 6.41x10-07 |
| exm473551 | 5 | 121413208 | *LOX* | T/C | 0.17 | 42327/78220 | 1.07 (1.04-1.09) | 1.72x10-07 | 0.15 | 30524/42522 | 1.02 (1.00-1.05) | 0.1 | 0.57 | 1.05 (1.03-1.07) | 5.02x10-07 |
| exm-rs3130683 | 6 | 31888367 | *C2* | C/T | 0.14 | 39494/72267 | 0.91 (0.88-0.94) | 7.87x10-08 | 0.85 | 30450/42485 | 0.91 (0.88-0.95) | 2.97x10-05 | 0.54 | 0.91 (0.89-0.94) | 1.04x10-11 |
| exm-rs1053924 | 6 | 32120715 | none | T/C | 0.30 | 39497/72302 | 0.94 (0.92-0.97) | 7.07x10-07 | 0.99 | 20396/30592 | 0.95 (0.92-0.98) | 0.0005 | 0.36 | 0.95 (0.93-0.96) | 1.52x10-09 |
| exm-rs11042937 | 11 | 10745394 | none | T/G | 0.49 | 42335/78234 | 1.05 (1.03-1.07) | 3.21x10-08 | 0.94 | 30533/42527 | 1.03 (1.00-1.05) | 0.02 | 0.28 | 1.04 (1.03-1.06) | 1.18x10-08 |
| exm-rs11172113 | 12 | 57527283 | *LRP1* | C/T | 0.41 | 42335/78234 | 1.06 (1.04-1.08) | 1.78x10-08 | 0.008 | 28503/36433 | 1.06 (1.03-1.08) | 1.16x10-06 | 0.25 | 1.06 (1.04-1.07) | 9.25x10-14 |
| exm2267392 | 12 | 111385296 | none | G/A | 0.50 | 39502/72328 | 0.95 (0.93-0.97) | 7.90x10-07 | 0.53 | 30530/42528 | 0.99 (0.96-1.01) | 0.24 | 0.36 | 0.97 (0.95-0.98) | 6.58x10-06 |
| exm2271796 | 12 | 112354531 | none | C/T | 0.17 | 39495/72302 | 0.94 (0.91-0.96) | 5.27x10-07 | 0.53 | 30510/42501 | 0.99 (0.96-1.02) | 0.4 | 0.61 | 0.96 (0.94-0.98) | 1.74x10-05 |
| exm1038037 | 12 | 112375990 | *TMEM116* | C/A | 0.17 | 39495/72314 | 0.93 (0.91-0.96) | 2.91x10-07 | 0.47 | 30526/42517 | 0.99 (0.96-1.02) | 0.42 | 0.6 | 0.96 (0.94-0.98) | 1.29x10-05 |
| exm-rs17696736 | 12 | 112486818 | *NAA25* | G/A | 0.45 | 39501/72325 | 1.06 (1.04-1.08) | 8.20x10-09 | 0.36 | 20396/30595 | 1.02 (0.99-1.05) | 0.12 | 0.78 | 1.05 (1.03-1.06) | 1.64x10-08 |
| exm1049349 | 12 | 124427306 | *CCDC92* | A/T | 0.32 | 42327/78211 | 0.95 (0.93-0.97) | 4.32x10-07 | 0.02 | 30526/42524 | 0.98 (0.96-1.01) | 0.16 | 0.1 | 0.96 (0.95-0.98) | 1.43x10-06 |
| exm-rs11057830 | 12 | 125307053 | *SCARB1* | A/G | 0.15 | 42331/78237 | 1.09 (1.06-1.11) | 3.69x10-10 | 0.2 | 20395/30592 | 1.07 (1.03-1.11) | 0.0003 | 0.58 | 1.08 (1.06-1.10) | 4.61x10-13 |
| exm-rs247616 | 16 | 56989590 | none | T/C | 0.32 | 42333/78214 | 0.95 (0.93-0.97) | 1.01x10-07 | 0.06 | 30529/42528 | 0.96 (0.93-0.99) | 0.0008 | 0.19 | 0.95 (0.94-0.97) | 4.29x10-10 |
| exm-rs3764261 | 16 | 56993324 | none | A/C | 0.32 | 42334/78231 | 0.95 (0.93-0.97) | 4.04x10-08 | 0.08 | 22451/32162 | 0.97 (0.94-0.99) | 0.06 | 0.12 | 0.95 (0.94-0.97) | 4.56x10-09 |
| exm-rs1800775 | 16 | 56995236 | none | A/C | 0.49 | 38810/62756 | 0.95 (0.93-0.96) | 2.21x10-08 | 0.13 | 22445/32148 | 0.97 (0.95-1.00) | 0.03 | 0.28 | 0.96 (0.94-0.97) | 9.83x10-09 |
| exm-rs2000999 | 16 | 72108093 | HPR | A/G | 0.20 | 38338/71604 | 1.07 (1.04-1.1) | 7.57x10-08 | 0.64 | 20393/30592 | 1.03 (1.00-1.06) | 0.07 | 0.06 | 1.05 (1.03-1.08) | 7.64x10-08 |
| exm1323676 | 17 | 40257163 | *DHX58* | C/T | 0.17 | 38763/61511 | 1.07 (1.04-1.1) | 5.93x10-07 | 0.05 | 18534/24193 | 1.02 (0.98-1.05) | 0.4 | 0.34 | 1.05 (1.03-1.07) | 4.96x10-06 |
| exm2272546 | 17 | 62401118 | *PECAM1* | T/C | 0.47 | 42332/78229 | 0.95 (0.93-0.97) | 1.82x10-07 | 0.46 | 30533/42528 | 0.98 (0.96-1.00) | 0.04 | 0.5 | 0.96 (0.95-0.98) | 1.15x10-07 |
| exm-rs6504218 | 17 | 62408299 | none | A/G | 0.47 | 42333/78225 | 0.95 (0.93-0.97) | 9.72x10-08 | 0.47 | 29890/41889 | 0.98 (0.96-1.00) | 0.07 | 0.64 | 0.96 (0.95-0.98) | 1.72x10-07 |
| exm1356489 | 17 | 73926121 | *FBF1* | A/C | 0.22 | 41935/77408 | 0.95 (0.92-0.97) | 9.13x10-07 | 0.35 | 11664/13189 | 0.97 (0.93-1.02) | 0.23 | 0.7 | 0.95 (0.93-0.97) | 9.27x10-07 |

Chr, Chromosome; POS, Position (HG19); Allele 1 Freq, frequency of allele 1; OR, Odds Ratio; CI, Confidence interval; Het P-value, heterogeneity P-value. A Bonferroni corrected p value of 1.7x10-5 f (n=29,383 SNPs) would indicate significant heterogeneity.

**Supplemental Table 4: List of variants in high LD with each of the novel CAD associated variants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Locus Name** |  | **Lead Variant** | **Number of variants in high LD (r2>0.8)** |
| ***CETP*** |  | rs1800775 | 1 |
| ***SCARB1*** |  | rs11057830 | 8 |
| ***LRP1*** |  | rs11172113 | 1 |
| ***MRVI1-CTR9*** |  | rs11042937 | 7 |
| ***C2*** |  | rs3130683 | 14 |
| ***KCNJ13-GIGYF2*** | | rs1801251 | 111 |

Number of variants in high LD (r2 > 0.8) with each lead variant in 1000G phase 1 EUR data, identified using Haploreg V3.

**Supplemental Table 5: Notable associations between novel CAD variants and gene expression in *cis***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **Transcript** | **Tissue** | **CAD associated SNP** | **P value** | **Direction** | **Best eSNP** | **P value** | **r2 (Lead variant and Best eSNP)** |
| ***CETP*** | *CETP* | Monocytes48 | rs1800775 | 1.75x10-08 | + | rs7205804 | 5.96x10-16 | 0.77 |
|  | *CETP* | Monocyte1 | rs1800775 | 1.31x10-07 | + | rs7205804 | 2.08x10-10 | 0.77 |
|  | *CETP* | Monocytes49 | rs1800775 | 2.64x10-06 | + | rs7205804 | 2.79x10-10 | 0.77 |
|  | *CETP* | Liver2 | rs1800775 | 1.93x10-07 | + | rs36229491 | 1.43x10-11 | 0.45 |
| ***SCARB1*** | *SCARB1* | Intestine50 | rs11057841 | 3.88x10-06 | NA | rs11057841 | 3.88x10-06 | 0.92 |
| ***LRP1*** | *LRP1* | Omental adipose51 | rs11172113 | 1.55x10-10 | NA | rs11172113 | 1.55x10-10 | Same SNP |
|  | *LRP1* | Subcutaneous adipose51 | rs11172113 | 9.22x10-08 | NA | rs11172113 | 9.22x10-08 | Same SNP |
|  | *LRP1* | Internal mammary artery2 | rs11172113 | 1.59x10-07 | - | rs11172113 | 1.59x10-07 | Same SNP |
|  | *LRP1* | Atherosclerotic aortic arterial wall2 | rs11172113 | 8.77x10-06 | - | rs11172113 | 8.77x10-06 | Same SNP |
| ***C2*** | *CYP21A2* | Whole blood52 | rs3130683 | 1.41x10-28 | NA | rs3130287 | 1.41x10-28 | 0.87 |
| ***KCNJ13-GIGYF2*** | *GIGYF2* | Whole blood53 | rs1801251 | 8.68x10-12 | + | rs6717841 | 8.68x10-12 | 1 |
|  | *GIGYF2* | Whole blood52 | rs1801251 | 1.78x10-11 | NA | rs1801251 | 1.78x10-11 | Same SNP |
|  | *KCNJ13* | Intestine50 | rs1801251 | 1.65x10-10 | NA | rs6738386 | 1.65x10-10 | 1 |

CAD; coronary artery disease; CAD associated SNP; CAD associated lead or high LD proxy SNP with an eQTL association; SNP; single nucleotide polymorphism; Direction, + indicates higher expression with the CAD risk allele; NA, not available; Best eSNP; SNP at the locus with highest P value for eQTL association.

**Supplemental Table 6: Association P-values of CAD variants with selected cardiovascular risk factors**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Locus | Locus Name | Lead Variant | LDL | HDL | TG | SBP | DBP | PP | BMI | T2D | Smoking |
| New Loci |  |  |  |  |  |  |  |  |  |  |  |
| 2q37 | *KCNJ13-GIGYF2* | rs1801251 | 0.13 | 0.7 | 0.9 | 0.88 | 0.66 | 0.81 | 0.27 | 0.05 | 0.69 |
| 6p21 | *C2* | rs3130683 | 0.001 | 0.29 | 1.2x10-4 | 0.21 | 0.93 | 0.04 | 0.21 | **2.7x10-5** | 0.38 |
| 11p15 | *MRVI1-CTR9* | rs11042937 | 0.62 | 0.24 | 0.48 | 0.004 | 0.01 | 0.03 | 0.16 | 0.98 | 0.73 |
| 12q13 | *LRP1* | rs11172113 | 0.53 | 0.05 | 0.26 | 0.22 | 3 x10-4 | 0.29 | 0.17 | 0.64 | 0.44 |
| 12q24 | *SCARB1* | rs11057830 | **2.6x10-5** | 0.002 | **8.3x10-5** | 0.06 | 0.07 | 0.36 | 0.41 | 0.76 | 0.18 |
| 16q13 | *CETP* | rs1800775 | **8.5x10-24** | **3.3x10-644** | **1.3x10-26** | 0.71 | 0.24 | 0.37 | 0.16 | 0.69 | 0.89 |
| Known Loci |  |  |  |  |  |  |  |  |  |  |  |
| 1p32 | *PCSK9* | rs11206510 | **2.4x10-57** | 0.16 | 0.001 | 0.86 | 0.28 | 0.45 | 0.07 | 0.29 | 0.78 |
| 1p32 | *PPAP2B* | rs17114036 | 0.6 | 0.18 | 0.19 | 0.40 | 0.72 | 0.03 | 0.03 | 0.40 | 0.18 |
| 1p13 | *SORT1* | rs602633 | **1.5x10-261** | **3.5x10-14** | 0.003 | 0.93 | 0.73 | 0.72 | 0.06 | 0.03 | 0.73 |
| 1q21 | *IL6R* | rs4845625 | 0.87 | 0.95 | 0.53 | 0.27 | 0.20 | 0.90 | 0.09 | 0.63 | 0.08 |
| 1q41 | *MIA3* | rs17465637 | 0.62 | 0.78 | 0.86 | 0.59d | 0.98d | 0.21d | 0.59 | 3.5x10-4 | 0.65 |
| 2p24 | *APOB* | rs515135 | **1.1x10-178** | 0.009 | 1.4x10-4 | 0.64 | 0.10 | 0.23 | 0.08 | 0.74 | 0.13 |
| 2p21 | *ABCG5-ABCG8* | rs6544713 | **4.8x10-83** | 0.16 | 0.001 | 0.90 | 0.90 | 0.69 | 0.03 | 0.50 | 1.00 |
| 2p11 | *VAMP5-VAMP8-GGCX* | rs1561198 | 0.02 | 0.36 | 0.13 | 0.98 | 0.95 | 0.02 | 0.02 | 0.72 | 0.75 |
| 2q22 | *ZEB2* | rs2252641 | 0.49 | 0.15 | 0.21 | 0.02 | 0.03 | 0.89 | 0.12 | 0.05 | 0.52 |
| 2q33 | *WDR12* | rs6725887 | **1.3x10-5** | 0.1 | 0.04 | 0.94 | 0.09 | 0.01 | 0.19 | 0.00 | 0.54 |
| 3q22 | *MRAS* | rs9818870 | 0.31 | 0.51 | 0.85 | 0.04 | 0.02 | 0.001 | 0.06 | 0.12 | 0.76 |
| 4q12 | *REST-NOA1* | rs17087335 | 0.31 | 0.66 | 0.37 | 0.58 | 0.51 | 0.09 | 0.22 | 0.40 | 0.38 |
| 4q31 | *EDNRA* | rs1878406 | 0.94 | 0.32 | 0.52 | 0.09 | 0.81 | 0.01 | 0.65 | 0.82 | 0.79 |
| 4q32 | *GUCY1A3* | rs7692387 | 0.68 | 0.85 | 0.19 | 0.01 | **3.4x10-5** | 0.75 | 0.55 | 0.04 | 0.10 |
| 5q31 | *SLC22A4-SLC22A5* | rs273909 | **2.3x10-5** | 0.03 | 0.35 | 0.88 | 0.47 | 0.38 | 0.78 | 0.88 | 0.80 |
| 6p21 | *ANKS1A* | rs17609940 | 0.72 | 0.003 | 0.02 | 0.25 | 0.14 | 0.85 | 0.02 | 0.24 | 0.73 |
| 6p21 | *KCNK5* | rs10947789 | 0.28 | 0.22 | 0.68 | 0.62 | 0.02 | 0.34 | 0.23 | 0.99 | 0.79 |
| 6p24 | *PHACTR1* | rs9369640 | 0.18 | 0.16 | 0.12 | 0.02 | 0.02 | 0.06 | 0.03 | 0.92 | 0.95 |
| 6q23 | *TCF21* | rs12190287 | 0.1 | 0.14 | 0.19 | 0.85 | 0.26 | 0.68 | 0.72 | 0.69 | 0.55 |
| 6q25 | *LPA* | rs3798220 | **6.1x10-11** | 0.84 | 0.69 | 0.14 | 0.61 | 0.10 | 0.17 | - | 0.93b |
|  |  | rs2048327 | **1.3x10-6** | 0.64 | 0.009 | 0.47 | 0.49 | 0.05 | 0.001 | 0.58 | 0.35 |
| 6q26 | *PLG* | rs4252120 | 0.04 | 0.04 | 0.79 | 0.73 | 0.73 | 0.54 | 0.25 | 0.92 | 0.72 |
| 7p21 | *HDAC9* | rs2023938 | 0.36 | 0.8 | 0.11 | 0.01 | 0.73 | 0.004 | 0.55 | 0.74 | 0.53 |
| 7q22 | 7q22 | rs10953541 | 0.03 | 0.03 | 0.32 | 0.72 | 0.54 | 0.43 | 0.44 | 0.27 | 0.86 |
| 7q32 | *ZC3HC1* | rs11556924 | 0.09 | **1.3x10-5** | 0.002 | 1.3 x10-4 | **1.79x10-5** | 0.18 | 0.008 | 0.14 | 0.66 |
| 7q36 | *NOS3* | rs3918226 | 0.2 | 0.28 | 0.32 | **1.1x10-6** | **2.2x10-9** | 0.28 | 0.47 | - | - |
| 8p21 | *LPL* | rs264 | 0.09 | **8.3x10-77** | **2.4x10-84** | 0.98 | 0.79 | 0.97 | 0.11 | 0.01 | 0.42 |
| 8q24 | *TRIB1* | rs2954029 | **2.1x10-50** | **2.7x10-29** | **1x10-107** | 0.38 | 0.75 | 0.20 | 0.02 | 0.72 | 0.33 |
| 9p21 | *CDKN2BAS1* | rs4977574 | 0.09 | 0.14 | 0.99 | 0.73 | 0.18 | 0.51 | 0.63 | 0.04 | 0.50 |
|  |  | rs3217992 | 0.8 | 0.58 | 0.63 | 0.58 | 0.07 | 0.78 | 0.53 | 0.01 | 0.31 |
| 9q34 | *ABO* | rs579459 | **2.4x10-44** | 0.08 | 0.01 | 0.19 | 0.001 | 0.25 | 0.84 | 0.16 | 0.64 |
| 10p11 | *KIAA1462* | rs2505083 | 0.48 | 0.79 | 0.38 | 0.39 | 0.17 | 0.02 | 0.99 | 0.28 | 0.57 |
| 10q11 | *CXCL12* | rs501120 | 0.28 | 0.81 | 0.9 | 0.54 | 0.14 | 0.46 | 0.67 | 0.74 | 0.98 |
|  |  | rs2047009 | 0.7 | 0.36 | 0.47 | 0.67 | 0.02 | 0.12 | 0.54 | 0.50 | 0.88 |
| 10q23 | *LIPA* | rs2246833 | 0.13 | 0.23 | 0.12 | 0.39 | 0.61 | 0.48 | 0.24 | 0.48 | 0.86 |
|  |  | rs11203042 | 0.04 | 0.89 | 0.003 | 0.69 | 0.57 | 0.39 | 0.98 | 0.61 | 0.39 |
| 10q24 | *CYP17A1-CNNM2-NT5C2* | rs12413409 | 0.45 | 0.67 | 0.26 | **2x10-9** | **8.8x10-6** | **5.7x10-8** | **2.2x10-8** | 0.81 | 0.64 |
| 11p15 | *SWAP70* | rs10840293 | 0.02g | 0.36g | 0.65g | 3.2x10-4g | 3.7x10-4g | 0.26g | 0.31g | 0.3g | 0.41g |
| 11q22 | *PDGFD* | rs974819 | 0.41 | 0.36 | 0.37 | 0.99 | 0.76 | 0.69 | 0.5 | 0.41 | 0.73 |
| 11q23 | *ZNF259-APOA5-APOA1* | rs964184 | **2x10-26** | **6x10-48** | **6.6x10-224** | 0.24 | 0.96 | 0.10 | 0.9 | 0.15 | 0.63 |
| 12q24 | *SH2B3* | rs3184504 | **4.2x10-12** | **4.1x10-12** | 0.03 | **1.7x10-9** | **2.3x10-14** | 0.11 | **9.4x10-6** | 0.63 | 0.01 |
| 12q24 | *KSR2* | rs11830157 | 0.52 | 0.43 | 0.26 | 0.31 | 0.37 | 0.24 | 0.27 | 0.33 | 0.63 |
| 13q12 | *FLT1* | rs9319428 | 0.38 | 0.63 | 0.73 | 0.84 | 0.11 | 0.39 | 0.001 | 0.62 | 0.89 |
| 13q34 | *COL4A1-COL4A2* | rs4773144 | 0.001 | 0.96 | 0.84 | 0.52 | 0.69 | 0.41 | 0.16 | 0.54 | 0.43 |
|  |  | rs9515203 | 0.05 | 0.28 | 0.03 | 0.001 | 0.01 | 0.04 | 0.18 | 0.02 | 0.53 |
| 14q32 | *HHIPL1* | rs2895811 | 0.42 | 0.36 | 0.54 | 0.18 | 0.76 | 0.31 | 0.83 | 0.08 | 0.54 |
| 15q22 | *SMAD3* | rs56062135 | 0.93f | 0.61f | 0.29f | 0.15f | 0.37f | 0.87f | 0.13f | 0.46f | 0.73f |
| 15q25 | *ADAMTS7* | rs7173743 | 0.34 | 0.46 | 0.99 | 0.04 | 0.92 | 0.002 | 0.10 | 0.02 | 0.02 |
|  |  | rs3825807 | 0.99 | 0.49 | 0.51 | 0.69 | 0.25 | 0.1 | 0.12 | 0.003 | 1.3x10-4 |
| 15q26 | *MFGE8-ABHD2* | rs8042271 | 0.71c | 0.75c | 0.95c | 0.54c | 0.95c | 0.23c | 0.41c | 0.08c | 0.93c |
| 15q26 | *FURIN-FES* | rs17514846 | 0.39 | 0.07 | 0.02 | **1.2x10-5** | 0.004 | 8.5x10-5 | 0.13 | 0.40 | 0.90 |
| 17p13 | *SMG6* | rs2281727 | 0.08 | 0.03 | 0.37 | 0.39 | 0.68 | 0.16 | **3.6x10-6** | 0.69 | 0.87 |
| 17p11 | *RAI1-PEMT-RASD1* | rs12936587 | 0.15 | 0.35 | 0.03 | 0.87 | 0.61 | 0.64 | 0.004 | 0.44 | 0.44 |
| 17q21 | *UBE2Z* | rs15563 | 0.03 | 0.16 | 0.36 | 0.72 | 0.14 | 0.14 | 0.68 | 4.8x10-4 | 0.27 |
| 17q23 | *BCAS3* | rs7212798 | 0.83a | 0.23a | 0.26a | 0.03a | 0.13a | 0.02a | 0.83a | 0.55a | 0.17a |
| 18q21 | *PMAIP1-MC4R* | rs663129 | 0.61 | **5.5x10-9** | 0.001 | 0.58 | 0.91 | 0.07 | **8.8x10-53** | 0.002 | 0.25 |
| 19p13 | *LDLR* | rs1122608 | **8.5x10-57** | 0.16 | 0.53 | 0.95 | 0.66 | 0.88 | 0.02 | 0.86 | 0.46 |
| 19q13 | *ZNF507-LOC400684* | rs12976411 | 0.31 | 0.17 | 0.39 | 0.75 | 0.89 | 0.77 | 0.26 | 0.01 | 0.97 |
| 19q13 | *APOE-APOC1* | rs2075650 | **1.7x10-214** | **9.7x10-26** | **2.3x10-21** | 0.49 | 0.95 | 0.69 | **1.25x10-8** | 0.003 | 0.39 |
|  |  | rs445925 | **6.6x10-397** | **1.9x10-10** | **3.6x10-39** | - | - | - | 0.08 | - | 0.80 |
| 21q22 | *KCNE2* | rs9982601 | 0.04 | 0.06 | 0.49 | 0.11 | 0.26 | 0.46 | 0.36 | 0.46 | 0.55 |
| 22q11 | *POM121L9P-ADORA2A* | rs180803 | 0.76e | 0.84e | 0.58e | 0.56e | 0.64e | 0.57e | - | 0.53e | 0.02e |
|  |  |  |  |  |  |  |  |  |  |  |  |

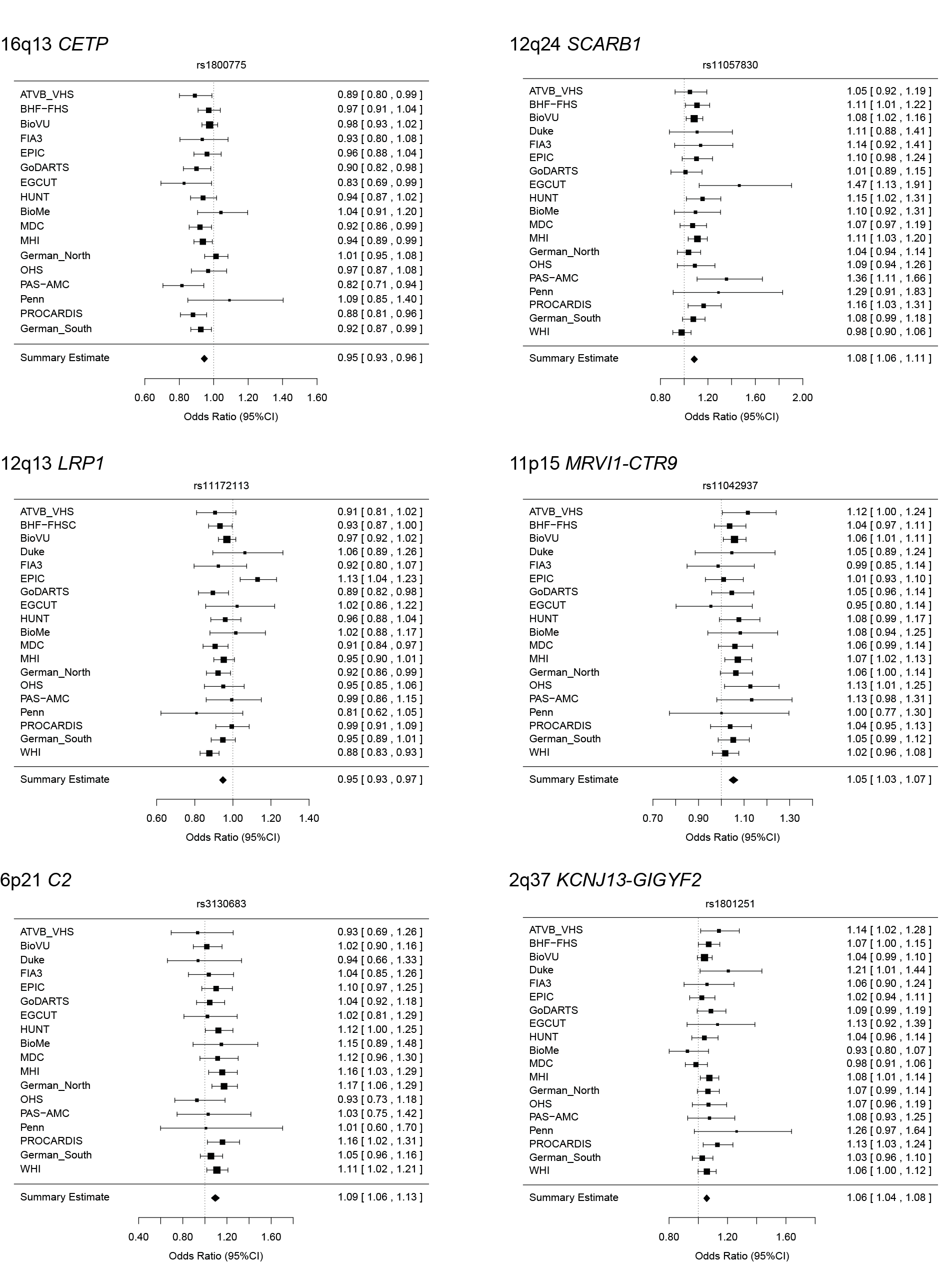
LDL, plasma LDL-cholesterol level; TG, plasma triglyceride level; HDL, plasma HDL-cholesterol level; T2D, type-2 diabetes; SBP, systolic blood pressure DBP, diastolic blood pressure; PP pulse pressure (defined as systolic pressure minus diastolic pressure); BMI, body mass index; T2D, type-2 diabetes.

A Bonferroni corrected p value of 8.32x10-5 f (n=600 tests) was applied to denote significance. P-values lower than this are shown in bold.

a rs7213603 was used as a proxy for rs7212798, *r*2=0.94. b rs9457925 was used as a proxy for rs3798220 *r*2=1. c rs7164299 was used as a proxy for rs8042271, *r*2=0.64. d rs17011681 was used as a proxy for rs17465637 *r*2=1.e rs5760293 was used as a proxy for rs180803 *r*2=0.57. f rs17293632 was used as a proxy for rs56062135 *r*2=0.94. g rs360156 was used as a proxy for rs10840293 *r*2=0.96.

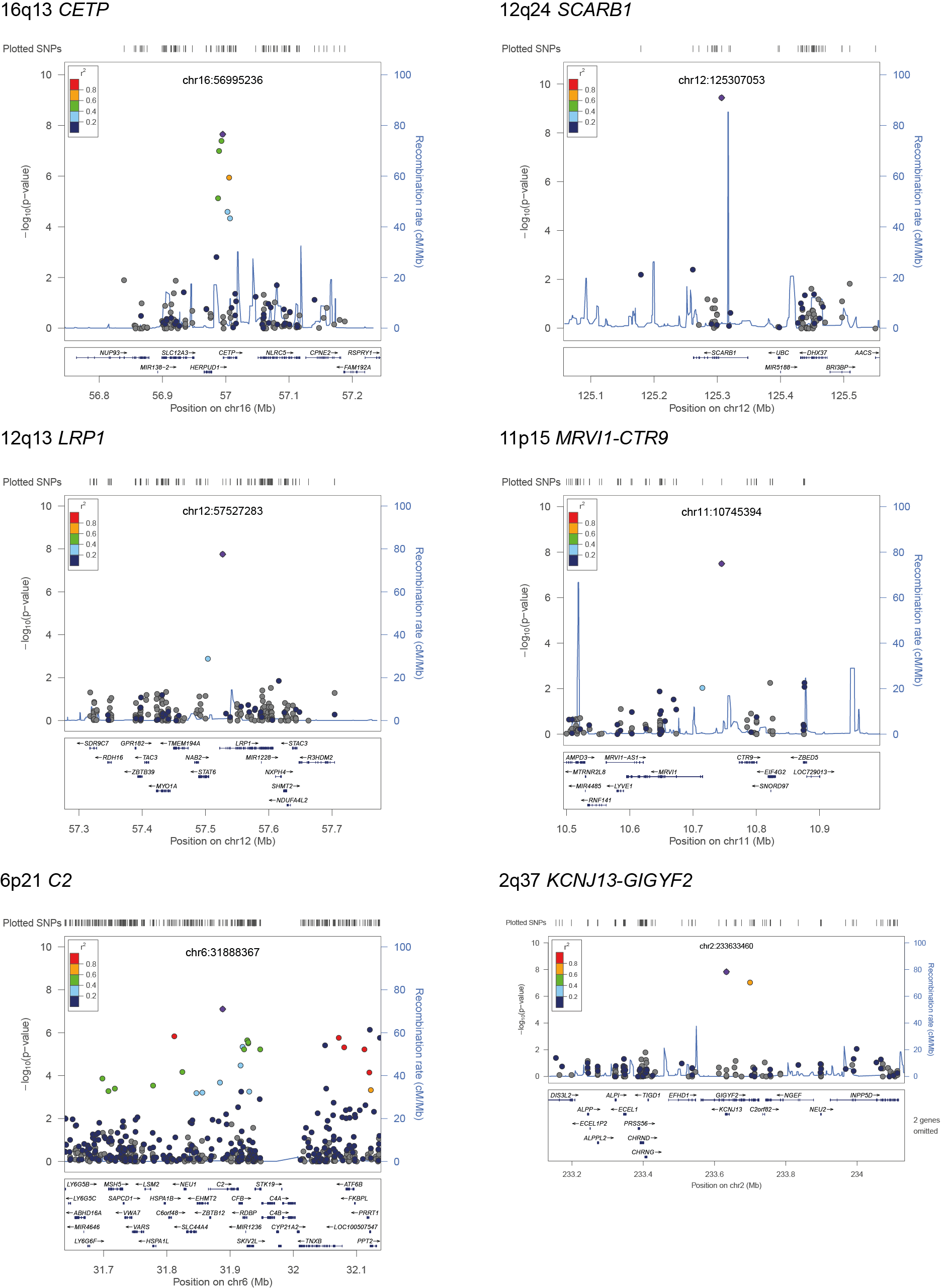
The maximum sample size available for each trait are: HDL-cholesterol level, 187,167; LDL-cholesterol level, 173,082; TG level, 177,860; SBP, 69,899; DBP, 69,909; PP, 74,079; BMI, 339,224; T2D cases 34,840 and controls 114,981; Smoking, 41,150.

**Supplemental Figure 1**: **Forest plots of the six novel CAD loci**



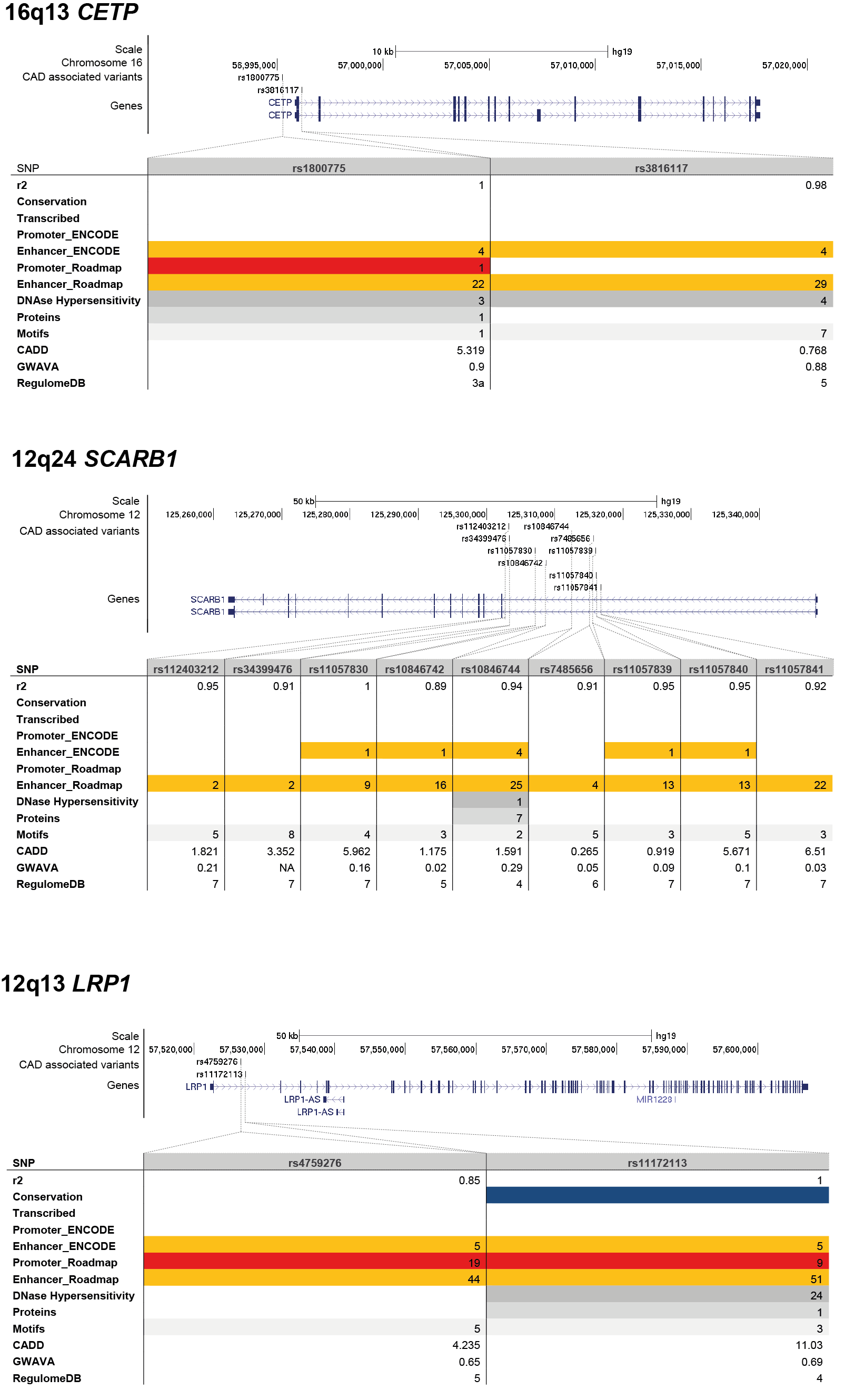
Forest plots for association of each of the novel loci with coronary artery disease in the discovery studies. Plots illustrate effect size (Odds ratio, log scale) and 95% confidence intervals (CIs) observed in each contributing study.

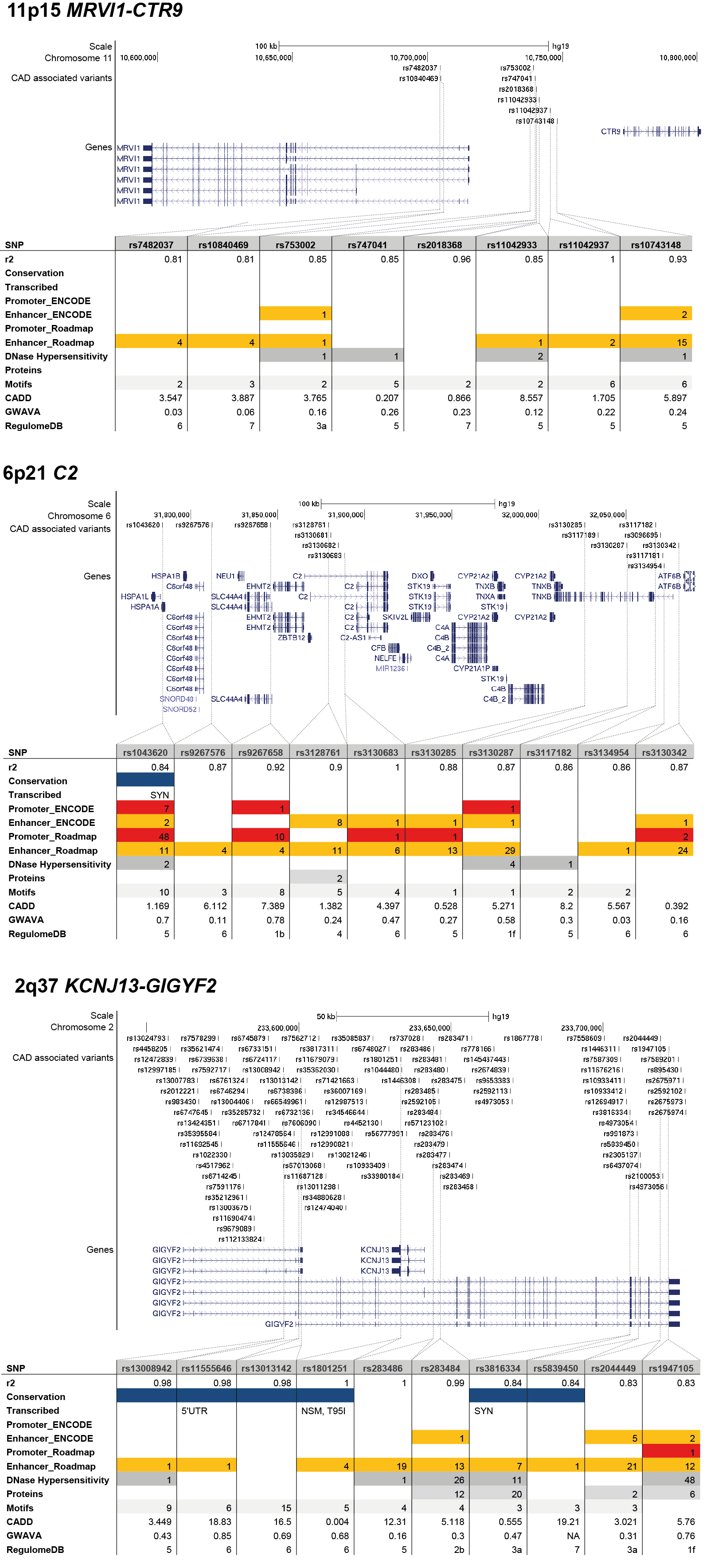
**Supplemental Figure 2**: **Regional association plots for the six novel CAD loci**



Regional association plots are shown for each of the novel loci in the discovery analysis. Regional plots show SNPs plotted by their positions on chromosomes against –log10 p-value for their association with CAD. The top SNP in each region is highlighted in purple. The SNPs surrounding each top SNP are color coded to reflect their LD with this variant LD (r2) calculations were based on the 1000 Genomes March 2012 release (EUR). Genomic coordinates refer to the hg19 sequence assembly. Plots were generated using Locus Zoom.

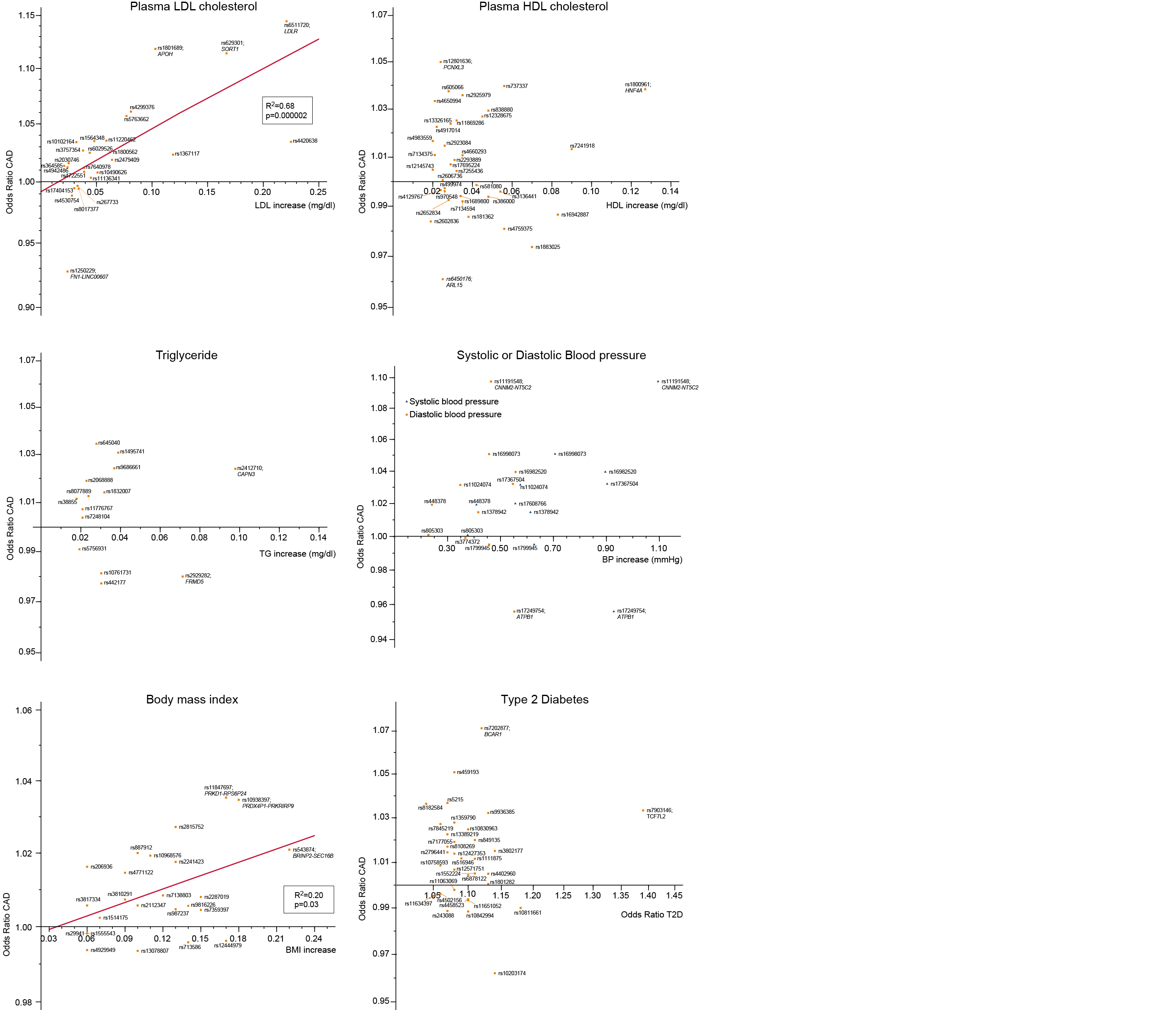
**Supplemental Figure 3. Functional annotation of CAD associated SNPs at the six novel loci.**



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Each figure shows a UCSC genome browser (hg19) snapshot of the CAD associated variants as well as nearby genes. Regulatory annotation generated using Haploreg V3 (see Methods), is shown in tabular form and summarizes the regulatory features overlapping each CAD associated variant including promoter and enhancers based on chromatin state segmentation from ENCODE and Roadmap epigenome, DNase hypersensitivity, bound proteins and predicted disruption of transcription factor binding motifs. The numbers in each block represent the number of observations of each feature. Functional prediction scores for each variant from CADD, GWAVA and RegulomeDB are also shown in the lower three rows of each table. Due to the high number of variants at the 2q37 and 6p21 loci only a selection of variants are included.

**Supplemental Figure 4. Comparison of magnitude of associations with risk factor and CAD for selected variants**

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For variants (or proxies) available on the exome array that have a genome-wide significant association with a traditional risk factor the relative magnitudes of the reported association with the risk factor and the observed association with CAD in our data are plotted. For only two risk factors (LDL-cholesterol and BMI) was there a significant correlation.

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