

Supplementary Information

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Supplementary Methods

Cohort descriptions and cohort-specific methods

ARIC: Atherosclerosis Risk in Communities (ARIC)^{1,2} (NCT00005131), is a population based study of risk factors for atherosclerosis and its sequelae in adults from four U.S. centers. Subjects were aged 45-64 at recruitment in 1987-1989. Institutional Review Board (IRB) approval was obtained at all associated study centers and informed consent was obtained for all participants. ARIC spirometry measurements were performed with a Collins Survey II water-seal spirometer (Collins Medical, Inc.) and Pulmo-Screen II software (PDS Healthcare Products, Inc.). Genotyping was performed using the AffymetrixGeneChip SNP Array 6.0. The current analysis includes 7,224 Caucasian subjects with genotyping data, pulmonary function measures and complete covariate information. Imputation was performed using the 1000 Genomes³ Integrated Phase 1 v3 reference panel (March 2012) in IMPUTE2⁴. Logistic regression was performed using FAST (<https://bitbucket.org/baderlab/fast/wiki/Home>) adjusting for age, sex, pack-years, current and ever smoking, and ancestry.

Cardiovascular Health Study (CHS): The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥ 65 years conducted across four centers⁵ (NCT00005133 and NCT00149435). IRB approval was obtained at participating centers and written informed consent was obtained for all participants. 5,201 predominantly European ancestry 5,201 persons were recruited in 1989-1990 from random samples of Medicare eligibility lists. An additional predominantly African-American cohort of 687 persons was subsequently enrolled for a total sample of 5,888. European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA available using the Illumina 370CNV BeadChip system (for European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for African-American participants, in 2010). Additional genotypes were provided from the ITMAT-Broad-CARE (IBC) Illumina iSELECT chip (for European ancestry participants). Imputation was performed using 1000 Genomes³ Phase 1 v3 haplotypes and minimac⁴ (for European ancestry participants, 2012-11-16) or IMPUTE version 2.2.2 (for African-American participants). Logistic regression was performed in R, adjusting for age, sex, pack-years, current and ever smoking, CHS clinic (4 sites) and PCs 1-5.

COPDGene: Eligible subjects in COPDGene Study (NCT00608764, www.copdgene.org) were of non-Hispanic white or African-American ancestry, aged 45-80 years old, with at least 10 pack-years of smoking and no diagnosed lung disease other than COPD or asthma^{6,7 21,22}. IRB approval was obtained at all study centers, and all study participants provided written informed consent. Illumina (San Diego, CA) performed genotyping on the HumanOmniExpress array. Genotyping at the Z and S alleles was performed in all subjects. Subjects known or found to have severe alpha-1 antitrypsin deficiency were excluded. We performed imputation using MaCH^{8,9 10,11} and minimac^{4 4} (version 2012-10-09) and 1000 Genomes³ Phase I v3 European (EUR) and cosmopolitan reference panels, for whites and African-Americans, respectively. We removed variants with an r^2 value of ≤ 0.3 . We performed logistic regression on cases and controls defined based on pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of genetic ancestry, separately in non-Hispanic whites and African-Americans, using PLINK1.9¹⁰.

Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE; SCO104960, NCT00292552, www.eclipse-copd.com): Details of the ECLIPSE study and genome-wide association analysis have been described previously¹². The ECLIPSE study was approved by the relevant ethics and review boards at the participating clinical centers. All participants provided written informed consent.

Cases and controls were aged 40-75 with at least a 10 pack-year smoking history without other respiratory diseases. Genotyping was performed using the Illumina HumanHap 550 V3 (Illumina, San Diego, CA). Subjects and markers with a call rate of < 95% were excluded. Imputation was performed using MaCH^{8,9} and minimac⁴ (version 2012-10-09) and the 1000 Genomes³ Phase I v3 European (EUR) reference panel. Logistic regression was performed on cases and controls defined by pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of genetic ancestry using PLINK1.9¹⁰.

Expression Quantitative Trait Loci – Lung (eQTL): The lung eQTL study has been described previously¹³. Briefly, patients who underwent thoracic surgery were recruited at three academic sites: Laval University, University of British Columbia (UBC), and University of Groningen, henceforth referred to as Laval, UBC, and Groningen, respectively. Patients from Laval were those undergoing lung cancer surgery, the majority of the UBC patients had lung resection for small peripheral lung lesions with some samples derived from autopsy or at the time of lung transplantation. At Groningen, patients were recruited from those having surgery for various lung diseases, including patients that underwent therapeutic resection for lung tumors and lung transplantation. All patients provided written informed consent, and the study was approved by the ethics committees of the Institut universitaire de cardiologie et de pneumologie de Québec and the UBC-Providence Health Care Research Institute Ethics Board for Laval and UBC, respectively. The study protocol was consistent with the Research Code of the University Medical Center Groningen and Dutch national ethical and professional guidelines. Patients whose lung function could have been influenced by lung diseases other than COPD and lung cancer were excluded. This includes patients with severe alpha-1 antitrypsin deficiency (n=11), amyloidosis (n=1), bronchiectasis (n=3), bronchiolitis obliterans (n=2), bronchopulmonary dysplasia (n=2), cystic fibrosis (n=14), idiopathic pulmonary fibrosis (n=13), langerhans cell histiocytosis (n=1), lymphangioleiomyomatosis (n=1), primary pulmonary hypertension (n=4), sarcoidosis (n=3) and vascular malformation (n=1).

Genotyping was carried out using the Illumina Human1M-Duo BeadChip. Standard genotyping quality controls were performed independently in the Laval, UBC and Groningen cohorts. Genotypes were then imputed with the Michigan Imputation Server¹⁴ using the Haplotype Reference Consortium version 1 (HRC.r1-1) data as reference set. Variants with an r^2 value of ≤ 0.3 were removed from further analysis. Single-marker association tests were performed with PLINK v1.90^{10,11} adjusting for age, sex, smoking status, pack-years, ever smoking status, clinical center and genetic ancestry PC1 to PC10.

Framingham Heart Study (FHS; NCT00005121): Details on pulmonary function in the FHS have been previously published^{15,16}. FHS was IRB-approved at the relevant institutions, and all participants provided written informed consent. We analyzed data from the most recent exam for each of the three generations of families participating in the FHS were analyzed. Genotypes were from the Affymetrix 500K array supplemented by the Affymetrix MIPS 50K. From a total number of 549,781 genotyped SNPs, 412,053 were used with MaCH^{8,9} for haplotype phasing, of which of 137,728 genotyped SNPs were removed by quality control. MaCH/minimac^{4,8,9} were used in this genotype imputation process to impute the FHS sample using the November 2010 release of the 1000 Genomes³ multi-ethnic panel. We used GEE implemented in the R package geepack with independent correlation matrix and clustering based on family, adjusted for sex, age, smoking status, pack years and genetic ancestry principal component 1 (to adjust for population stratification).

KARE: Details on the Korean Association Resource project (KARE) have been previously published^{17,18}. KARE was initiated in 2007 to undertake genome-wide analyses among 10,038 participants in the rural-based Ansung and city-based Ansan South Korean cohorts. The study was approved at appropriate IRBs from participating institutions, and participants provided informed consent. KARE3 data were obtained from the third phenotype collection in 2008; lung function was collected using the Vmax-2130 (Sensor Medics, Yorba Linda, CA, USA). Genotyping was performed using the Affymetrix Genome-Wide Human array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). We performed genotype imputation using IMPUTE2

and the 1000 Genomes³ Phase 3 cosmopolitan panel. Markers were converted to genotype from dosage with call rate $\geq 95\%$, minor allele frequency $\geq 1\%$, p for HWE $\geq 1.0 \times 10^{-5}$, imputation quality score ≥ 0.9 . Logistic regression, adjusting for age, sex, pack-years, principal components, current and ever smoking, was performed using PLINK¹⁹.

LifeLines: The LifeLines Cohort Study is a population-based cohort study established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy aging²⁰⁻²². Between 2006 and 2013, inhabitants of the northern part of The Netherlands and their families were invited to participate, thereby contributing to a three-generation design. Participants visited one of the LifeLines research sites for pre-bronchodilator spirometry following ATS guidelines. All participants signed an informed consent form before they received an invitation for the physical examination. The LifeLines Cohort Study is conducted according to the principles of the Declaration of Helsinki and in accordance with research code University Medical Center Groningen (UMCG), The Netherlands. The LifeLines study is approved by the medical ethical committee of the UMCG. Blood samples for a subset of individuals were genotyped using the Illumina CytoSNP-12v2 array. Independent Caucasian-ancestry samples ($n = 13,436$) have been imputed using the 1000 Genomes³ phase1 v3 reference panels. Genotypes were pre-phased using SHAPEIT²³ and aligned to the reference panels using Genotype Harmonizer (www.molgenis.org/systems/genetics) in order to resolve strand issues. The samples were imputed using minimac⁴ (version 2012-10-09), yielding 28,681,763 SNPs. Associations between genomic dosages with moderate/severe COPD were assessed with logistic regression models adjusted for age, smoking status (never/ever), current smoking (no/yes), pack years smoked and sex. All analysis were performed in software package PLINK version 1.07^{19,24}.

Lovelace: The Lovelace Smokers Cohort (LSC) has been actively enrolling smokers from the Albuquerque, NM metropolitan area since 2001²⁵. All participants provided written informed consent, and the study was approved by the relevant IRB. Enrollment was restricted to current and former smokers age 40 to 74 years old with a minimum of 10 pack-years of smoking and no personal history of lung cancer. A detailed questionnaire written in English was used to collect information on demographics; medical, cigarette smoking, and exposure history; socioeconomic status; diet; and quality of life. Pulmonary function testing was performed at each visit. All participants signed a consent form, and the Western Institutional Review Board approved this project. The GWAS discovery set was comprised of 1200 Caucasian (self-reported) smokers. The HumanOmni2.5-4v1-H BeadChip (Illumina, San Diego, CA) was used to genotype 2,450,000 SNPs in 1200 Caucasian smokers from the LSC. After quality assessment, 1163 subjects with 1,599,980 SNPs remained in the genetic association analysis. Logistic regression was performed using PLINK on white subjects, adjusting for age, sex, pack-years, current and ever smoking, and ancestry.

Multi-Ethnic Study of Atherosclerosis (MESA): MESA is a longitudinal study of subclinical cardiovascular disease and risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease²⁶. Between 2000 and 2002, MESA recruited 6,814 men and women 45 to 84 years of age. Exclusion criteria were clinical cardiovascular disease, weight exceeding 136 kg (300 lb.), pregnancy, and impediment to long-term participation. The MESA Family Study recruited 1,595 African American and Hispanic participants, generally siblings of MESA participants, using the same inclusion and exclusion criteria as MESA except that clinical cardiovascular disease was permitted. The MESA Air Pollution Study recruited an additional 257 participants from Los Angeles and Riverside County, CA, and Rockland County, NY, using the same criteria as MESA, except that participants were ages 50 to 89 who lived in the area more than 50% of the year and had no plans to move in the next five years²⁷. The MESA Lung Study performed spirometry following the 2005 ATS/ERS guidelines in a subset of the MESA and MESA Family Studies and all of the new recruits in the MESA Air Pollution Study²⁸. All participants provided informed consent and the protocols of MESA were approved by the IRBs of collaborating institutions and the National Heart, Lung and Blood Institute.

Participants who consented to genetic analyses were genotyped in 2009 using the Affymetrix Human SNP array 6.0²⁹. The cleaned genotypic data was deposited with MESA phenotypic data into dbGaP as the MESA SHARe project (study accession phs000209); 8,224 consenting individuals (2,685 White, 2,588 non-Hispanic African-American, 2,174 Hispanic, 777 Chinese) were included, with 897,981 SNPs passing study specific quality control (QC). For GWAS, IMPUTE version 2.2.2 was used to perform imputation for the MESA SHARe participants using the cosmopolitan 1,000 Genomes³ Phase 1 v3 March 2012 reference set. Logistic regression was performed using SNPTEST v2.4.0³⁰, adjusting for age, sex, pack-years, current and ever smoking, and ancestry.

National Emphysema Treatment Trial (NETT; NCT00000606, www.nhlbi.nih.gov/health/prof/lung/nett/) and Normative Aging Study (NAS):³¹. NETT was a multicenter clinical trial to evaluate lung volume reduction surgery. All participants provided written informed consent, and the study was approved by the IRB at all participating institutions. Enrolled subjects had severe airflow obstruction by post-bronchodilator spirometry ($FEV_1 < 45\%$ predicted) and evidence of emphysema on computed tomography (CT) chest imaging; exclusion criteria included, but not limited to, history of recurrent infections with significant sputum production or bronchiectasis. A subset of 382 self-reported white subjects without severe alpha-1 antitrypsin deficiency were enrolled in the NETT Genetics Ancillary Study. The Normative Aging Study is a longitudinal study of healthy men established in 1963 aged 21 to 80 years from the greater Boston area, free of known chronic medical conditions. The study was conducted by the Veterans Administration (VA)³², and the local Institutional Review Board approved the study. Controls were of self-reported white ancestry and at least 10 pack-years of cigarette smoking with no evidence of airflow limitation on spirometry on their most recent visit. Genotyping for NETT-NAS was performed using the Illumina Quad 610 array (Illumina, San Diego, CA)^{33,34}. Imputation was performed using MaCH^{8,9} and minimac⁴ (version 2012-10-09) and the 1000 Genomes Phase I v3 European (EUR) reference panel. Logistic regression was performed on cases and controls based on pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry using PLINK1.9^{10,11}.

GenKOLS (Norway): The Norwegian GenKOLS (Genetics of Chronic Obstructive Lung Disease, GSK code RES11080)³⁵ recruited subjects with > 2.5 pack years of smoking history from Bergen, Norway. Subjects with severe alpha-1 antitrypsin deficiency and other lung diseases (aside from asthma) were excluded. The Regional Committee for Medical Research Ethics (REK Vest), the Norwegian Data Inspectorate and the Norwegian Department of Health approved the case-control study. Written informed consent was obtained from all participants. Genotyping was performed using Illumina HumanHap 550 arrays (Illumina, San Diego, CA). Genotype imputation was performed using MaCH^{8,9} and minimac⁴ (version 2012-10-09) and the 1000 Genomes³ Phase I v3 European (EUR) reference panel. Logistic regression was performed on cases and controls defined by pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of genetic ancestry using PLINK1.9^{10,11}.

The Rotterdam Study: The Rotterdam Study is a prospective population-based cohort study founded in 1990 in a suburb of Rotterdam, the Netherlands^{36,37}. The first cohort (RS-I) consists of 7,983 participants, aged 55 years and over. The second cohort (RS-II) was recruited in 2000 with the same inclusion criteria. The third cohort (RS-III) consists of 3,932 participants, aged 45 years and over and was recruited in 2006. The Rotterdam Study was approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. All participants provided written informed consent. Spirometry was performed using the Master Screen® PFT Pro (CareFusion, San Diego, CA). A total of 6,291 subjects for RS I, 2,157 for RS II and 3,048 for RS III passed genotyping quality control. Regression coefficients and their standard errors were determined using the ProbABEL³⁸ program according to an additive model, adjusting for age, sex, pack-years, smoking status, and ancestry.

Subpopulations and intermediate outcome measures in COPD study (SPIROMICS; NCT01969344):

Participants of the NHLBI SPIROMICS study were 40-80 years of age at baseline with a smoking history ≥ 20 pack-years. Recruitment included non-smokers, smokers without COPD, mild-moderate COPD, and severe COPD³⁹. All participants provided written informed consent and the Institutional Review Boards/Ethics Committees of all the cooperating institutions approved the study protocols. Genome-wide genotyping was performed using the Illumina OmniExpress HumanExome BeadChip using standard techniques in the first 571 subjects with COPD and 175 smoking controls. Imputation was performed against 1000 Genomes reference panels using Impute-v2.3.0 using a quality cutoff of 0.9, and association analysis performed using PLINK adjusting for age, sex, pack-years, smoking status, and ancestry.

Studies with Custom Genotyping:

Boston Early-Onset COPD Study (BEOCOPD; ClinicalTrials.gov: NCT01177618). BEOCOPD is an extended pedigree study constructed based on probands under 53 years of age with severe COPD (defined as pre-bronchodilator forced expiratory volume in one second (FEV₁) < 40% predicted) and without severe alpha-1 antitrypsin deficiency^{40,41}. IRB approval was obtained for the study, and all participants provided written informed consent.

International COPD Genetics Network (ICGN): ICGN recruited subjects (FEV₁ < 60% predicted and FEV₁/FVC < 90% predicted between ages 45-65) as probands and then enrolled available siblings and parents of the proband^{42,43}. The study was IRB approved at all relevant institutions and participants provided written informed consent.

Transcontinental COPD Genetics Study (TCGS) – Korea and Poland: TCGS⁴⁴ and comprised of two case-control studies, based in Poland and in Korea. The study was approved by the appropriate IRBs, and all participants provided written informed consent. Both studies recruited individuals between 40 and 80 years of age, with at least 10 pack-years of cigarette smoking; where cases had severe COPD (FEV₁ < 50% predicted) and controls had normal spirometry. Subjects with other lung diseases were excluded. TCGS-Poland enrolled white individuals, and TCGS-Korea enrolled Korean individuals.

Genotyping in BEOCOPD, ICGN, and TCGS:

We genotyped subjects using the Illumina HumanExome v1.2 array with custom content, including top results from prior genome-wide association studies, as previously described⁴⁵. We performed single-variant association analysis adjusting for age, pack-years, sex, and current and ever smoking, together using a covariate additionally indicating study, via a logistic mixed model as implemented in GMMAT version 0.5 in R (version 3.2.0, <http://www.R-project.org/>)⁴⁶ in whites in our family-based studies, and using standard logistic regressions in each of the two TCGS studies.

UK Biobank

Derivation and quality control of FEV₁ and FVC, COPD status, and smoking

The UK Biobank is a resource with approximately 500,000 persons age 40-69 for whom extensive baseline questionnaire data, physiologic measures, and biologic specimens (urine and blood samples) have been obtained⁴⁷. The UK Biobank participants provided informed consent. The UK Biobank's Ethics and Governance Framework guides research ethics principles and policies, the adherence to which is overseen by the independent Ethics and Governance Council. Details of the derivation and quality control of spirometry, smoking, and case-control status were performed as described⁴⁸. Briefly, of 502,682 individuals in UK Biobank, 445,754 individuals had at least two measures of FEV₁ and FVC and spirometry metrics, age, sex, height, and smoking. We used blow quality metrics from the Vitalograph spirometer and compared pre-defined measurements with the blow curve time series. We considered blows as 'acceptable' if their blow quality metrics were blank, ACCEPT, BELOW6SEC ACCEPT, or BELOW6SEC. We assessed back-extrapolated volumes derived from blow curve time series

measurements as previously described⁴⁹ and excluded blows which their back-extrapolated volumes were greater than the larger of either 5% of FVC or 150 mL, leaving 776,927 blows from 387,277 participants. To confirm pre-defined FEV₁ and FVC, we independently derived FEV₁ and FVC from blow curve time series measurements. We further excluded blows which differences between pre-defined and newly derived FEV₁ and FVC were greater than 5%. Following above exclusion, 776,318 blows from 387,052 participants remained in the analysis. Additionally, we assessed if individuals' measures of FEV₁ and FVC were reproducible, allowing differences between the highest measure and others to be up to 250 mL. We defined COPD using modified GOLD criteria (as stated previously) based on highest values of reproducible measures of FEV₁ and FVC; available in 324,299 individuals.

We assigned smoking status to individuals in UK Biobank based on their responses on questionnaires. Never smokers were non-current smokers or smoked occasionally allowing up to 100 life-time cigarettes; ever-smokers were defined as either current, most days (current or all days in the past), or smoked occasionally with > 100 cigarettes. We defined pack-years as packs of cigarettes per day multiplied by years smoked. Pack-years was 0 for never smokers based on VariableID: 20116 smoking status. For ever smokers, we set pack-years to cigarettes per day (VariableID: 2887 in former smokers or VariableID: 3456 in current smokers) divided by 20 multiplied by duration of smoking (VariableID: 2897 minus VariableID: 2867 for former smokers and age at time of study minus VariableID: 3436 in current smokers).

Sample-based genotyping quality control

Details on procedure, imputation, and quality control of genotyping in UK Biobank were published earlier⁵⁰. Briefly, we excluded 968 individuals with outlying heterozygosity or missingness. We further excluded: 1) 378 samples with sex mismatch (reported and genetic sex) 2) 188 samples with >10 3rd degree relatives 3) 652 samples with putative sex chromosome aneuploidy. This left 486,367 samples with genotypes for further analysis.

SNP-based Genotyping quality control

Besides the QC steps described in Bycroft et al. we filtered out: 1) variants with minor allele frequency lower than 1%; 2) variants with imputation quality lower than 0.5; 3) variants not included into the Haplotype Reference Consortium (HRC) imputation panel, as recommended by UK Biobank at the time of analysis. This left us with 7,810,596 variants.

Identification of individuals of European ancestry

To identify individuals of European ancestry, we used K-means clustering on principal components (PCs) provided by UK Biobank. We performed K-means clustering using the first two PCs with number of clusters 3-8 in 486,367 samples passing sample-based quality control. Together with self-reported ethnicity data, we chose 6-cluster model as it reflects the expected broad ethnic groups. This left us 453,958 European individuals for further analysis (an additional 45,865 putative European individuals in addition to 408,093 self-reported white British⁵⁰).

Selecting individuals for genome-wide association analysis

We intersected the individuals passing spirometry QC and sample-based genotyping QC and selected individuals with European ancestry as described above. This left us 321,057 individuals in total. To identify individuals who were outliers in phenotype distribution, we plotted the distribution for each measure (FEV₁, FVC, and FEV₁/FVC) adjusting for sex, age², height, and smoking status

(ever/never). We re-calculated phenotypic adjustment after excluding 10 European samples who were obvious outliers. As stated previously, we defined COPD using modified GOLD criteria for moderate to very severe airflow limitation⁵¹: FEV₁ less than 80% of predicted value and FEV₁/FVC less than 0.7. We excluded 59,358 individuals, who did not match the above criteria. To select completely unrelated individuals for genome-wide association analysis, we removed at least one individual from each related pair, giving preference to cases. Briefly, we created a graph from related pairs using genetic kinship information provided by UK Biobank. For each unconnected component we removed control nodes (healthy individual), starting with the one with the highest degree. If all nodes were cases, we removed the one with the highest degree. We excluded additional 26,855 individuals based on kinship and further 34,035 individuals who had missing information on sex, ever smoking status, pack-years of smoking, and age. We also excluded subjects who had withdrawn consent (updated as of May 2018). After excluding individuals, we were left with 200,792 individuals for genome-wide association analysis of COPD.

Identification of cell types

We tested for enrichment of lung cell type in sets of genome-wide significant variants using SNPsea^{52,53}. Briefly, SNPsea performed three steps: identification of specifically expressed genes, assignment of gene in a locus, and significance testing. We first computed the Euclidean norm of gene expression values in all cell types and divided expression values in each cell type using this value. The score was then converted to nonparametric percentiles. Second, we identified the most specifically expressed gene in a given locus by ranking the score. Finally, we then tested for significance using permutation using matched SNP sets.

We used a single-cell RNA-seq dataset from the study of idiopathic pulmonary fibrosis (540 cells from 6 IPF lung samples and 3 control tissues, available at Gene Expression Omnibus as GSE86618)⁵⁴. We performed quantile normalization of Transcripts Per Kilobase Million (TPM) expression values from the IPF dataset using the preprocessCore package⁵⁵ version 1.43.0 in R⁵⁶ version 3.5.0.

Fine-mapping

We used biomaRt⁵⁷ to annotate variants in each credible set based on the Ensembl Variant Effect Predictor. We defined deleterious variants as those which resulted in non-synonymous, stop, or splice variants (terms: transcript_ablation, splice_acceptor_variant, splice_donor_variant, stop_gained, frameshift_variant, stop_lost, start_lost, transcript_amplification, inframe_insertion, inframe_deletion, missense_variant, and protein_altering_variant). Variants were annotated using Haploreg v4.1⁵⁸.)

Estimation of genetic correlation

We estimated genetic correlation between COPD and 832 diseases/traits in LD Hub⁵⁹.

Target gene identification

DEPICT

DEPICT utilizes pairwise gene correlation data from ~77,000 microarrays to create data-driven “reconstituted” gene sets from a backbone of curated data from GO, KEGG, REACTOME, protein-protein interaction data, and murine phenotypic gene sets. These “reconstituted” gene sets are used to prioritize genes at each GWAS loci based on the similarity each gene’s “reconstituted” gene set membership to the gene set memberships of genes at other GWAS loci⁶⁰.

Methylation quantitative trait loci (mQTL)

Of all genome-wide significant loci, we searched for overlapping methylation quantitative trait loci (mQTL) using previously published data⁶¹. Briefly, lung tissues from 90 severe COPD cases ($FEV_1 < 50\%$ predicted) and 36 control subjects from undergoing lung transplantation, lung volume reduction surgery, or lung nodule resection⁶². All subjects were self-reported former smokers at least 1 month prior to the surgery. A cis-mQTL analysis was performed using the R/Bioconductor package Matrix eQTL (version 2.1.1)⁶³. We tested associations of each CpG site and genetic variants within 500 kb upstream and downstream (from the CpG site) using a linear regression model adjusting for age, sex, smoking pack-years, two principal components of genetic ancestry, batch number, and principal components of methylation data as previous described⁶¹. To determine whether these signals co-localized (rather than being related due to linkage disequilibrium), we performed colocalization analysis between our genome-wide significant loci and mQTL using eCAVIAR⁶⁴ (eQTL and GWAS CAusal Variants Identification in Associated Regions). We tested variants that were significant in both datasets, $P < 0.0027$ in GWAS (equivalent to Z score > 3 , as recommended by the author⁶⁴) and $P < 3.2 \times 10^{-6}$ in mQTL⁶¹. We estimated the posterior probability of a variant being shared in both GWAS and mQTL, using a cut-off of 0.1 as previous demonstrated⁶⁴.

Supplementary Results

Analysis excluding individuals with self-reported asthma

Using the pre-bronchodilator spirometry in diagnosing COPD may include individuals with asthma. We performed additional GWAS by excluding 6,717 self-reported asthma from 21,081 COPD cases in the UK Biobank. While the decreased sample size resulted in less significant associations, we observed highly concordant estimates of effect size between the analysis including and excluding asthma (**Supplementary Figure 7**). One outlier was the variant rs2070600 in *AGER*, which demonstrated a higher OR after excluding individuals with asthma.

Relationship of genome-wide significant variants to smoking

To assess the effect of smoking, we tested association of 82 genetic variants and smoking status (ever- and never- smokers) in the UK Biobank. Of the 82 identified loci, three were associated with cigarette smoking after Bonferroni correction ($P < 0.05/82$) including the strongest association at the known 15q25 locus, but also *IER3* ($P = 9.2 \times 10^{-5}$) at 6p21 and *SPPL2C* ($P = 1.4 \times 10^{-4}$) at 17q21. To test if smoking status could have confounded the association of these variants and COPD, we re-performed the analysis of COPD stratifying by smoking status in the UK Biobank. The lead variants at these latter two loci were highly significant for COPD in never-smokers ($P = 6.7 \times 10^{-13}$ and 2.8×10^{-5} at *IER3* and *SPPL2C* loci, respectively). Seventy-eight of 82 genetic loci were nominally significant in never-smokers ($P < 0.05$) with the exception of four loci including *TESK2*, *RBMS3*, *RIN3*, and *CHRNA3*.

Genetic correlation of COPD and related traits

To gain further insight of genetic contribution of COPD and other traits, we estimated genetic correlation among traits using LDSC in LD hub^{59,65}. In addition to our previously reported correlations between COPD and lung function (FEV_1 and FEV_1/FVC), asthma and height were significant (**Supplementary Table 12**). We additionally identified correlation of COPD and lung cancer ($r_g=0.18$, $P=0.003$). We also tested genetic correlation between COPD and other comorbidities. We were not able to demonstrate genetic correlation of COPD with bone mineral density, major depressive disorder,

coronary artery disease, or type 2 diabetes mellitus (**Supplementary Table 12**). We found suggestive ($P < 0.05$) genetic correlation between COPD and hand grip, angina, and gastroesophageal reflux disease (**Supplementary Table 12**).

Supplementary Information for Select Candidate Target Genes

* empirical pattern of gene expression in tissues from Human Protein Atlas⁶⁶ (broad=expressed in multiple tissues, exclusive=expressed exclusively in lung, none=rarely expressed in lung).

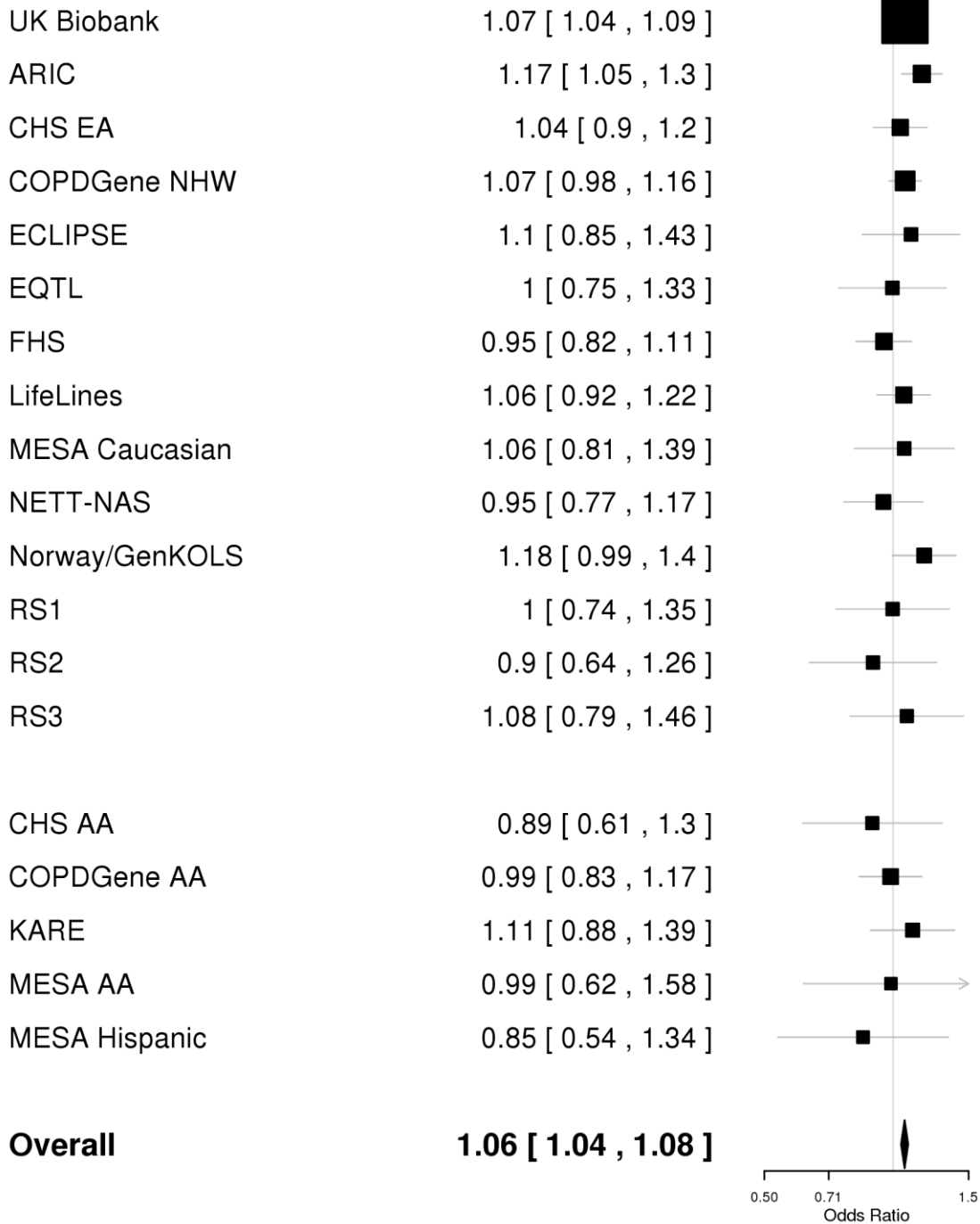
Locus (SNP)	Genes	Expression*	Evidence
1p13.3	<i>DENND2D</i>	Broad	DENN domain containing 2D predominantly expresses in lymph node and appendix ⁶⁶ . It is involved in Rab guanyl-nucleotide exchange factor activity ⁶⁷ .
	<i>CEPT1</i>	Broad	Choline/ethanolamine phosphotransferase 1 encodes an enzyme which functions in the synthesis of choline- or ethanolamine- containing phospholipids ⁶⁸ .
	<i>DRAM2</i>	Broad	DNA damage regulated autophagy modulator 2 encodes the protein that binds microtubule-associated protein 1 light chain 3 and is required for autophagy ⁶⁹ . It is also associated with non-ST elevation myocardial infarction ⁷⁰ and retinal dystrophy ⁷¹ .
	<i>CHIA</i>	Exclusive	Chitinase, acidic encodes a protein that degrades chitin ⁶⁸ . Its expression is specific to lung ^{66,72} . Genetic variants in or around this gene were associated with baseline FEV ₁ and rate of FEV ₁ decline ⁷³ , asthma ⁷⁴⁻⁷⁷ , acid mammalian chitinase activity ^{76,78} , and IgE ⁷⁵ although there were also some null results ⁷⁹ . The protein is involved in T helper-2 (Th2)-mediated diseases and protects pulmonary epithelial cells from growth factor withdrawal- and Fas ligand-induced apoptosis ⁸⁰ . It was induced via a Th2-specific, interleukin-13 (IL-13)-mediated pathway in epithelial cells and macrophages in an aeroallergen asthma model ⁸¹ , and ADAM17/EGFR-dependent pathway ⁸² .
	<i>OVGP1</i>	Broad	Oviductal glycoprotein 1 encodes an epithelial glycoprotein. It is secreted from non-ciliated oviductal epithelial cells and associates with ovulated oocytes, blastomeres, and spermatozoan acrosomal regions ⁶⁸ .
	<i>WDR77</i>	Broad	WD repeat domain 77 encodes an androgen receptor coactivator ⁶⁸ . It may be involved in the early stages of prostate cancer ⁶⁸ .
	<i>ATP5F1 (ATP5PB)</i>	Broad	ATP synthase peripheral stalk-membrane subunit b encodes a subunit of mitochondrial ATP synthase ⁶⁸ . Its hypomethylation was involved in drug resistance in chronic myeloid leukemia ⁸³ .
	<i>FAM212B (INKA2)</i>	Broad	Inka box actin regulator 2 is broadly expressed in multiple tissues including lung ⁶⁸ .

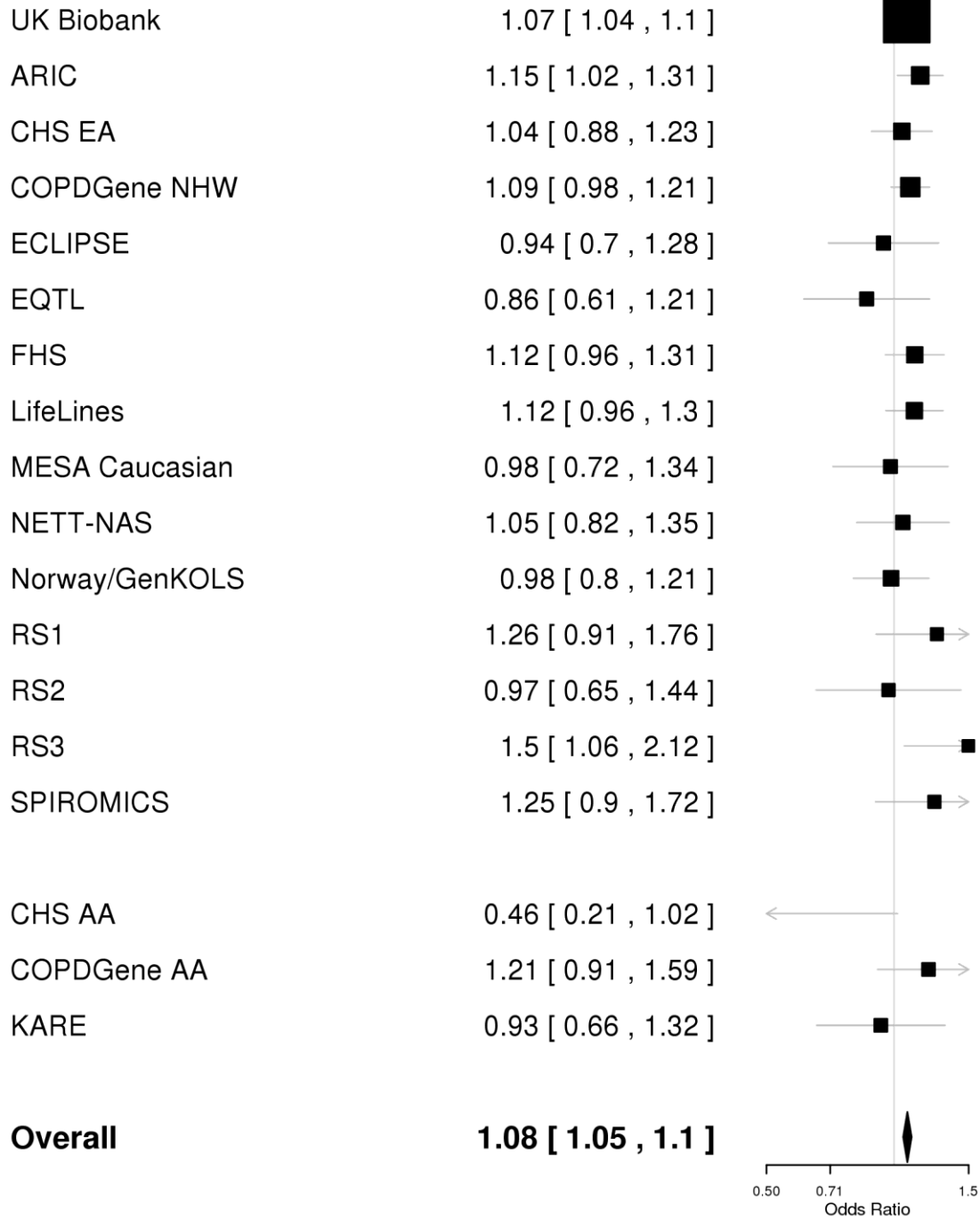
	<i>PROK1</i>	None	Prokineticin 1 induces proliferation, migration, and fenestration in capillary endothelial cells derived from endocrine glands ⁶⁸ . It is induced by hypoxia, and often is complementary to the expression of vascular endothelial growth factor (VEGF) ⁶⁸ . It was involved in angiogenesis in cystic fibrosis ⁸⁴ .
	<i>KCNC4</i>	Broad	Potassium voltage-gated channel subfamily C member 4 encodes a protein that generates atypical voltage-dependent transient current that may be important for neuronal excitability ⁶⁸ . It was related to subacute hypoxia in pulmonary arterial smooth muscle cells ⁸⁵ .
3p14.3	<i>ABHD6</i>	Broad	Abhydrolase domain containing 6 is involved in the control of macrophage activation and inflammation ⁸⁶ .
	<i>ARF4</i>	Broad	ADP ribosylation factor 4 encodes a protein that stimulates the ADP-ribosyltransferase activity of cholera toxin and plays a role in vesicular trafficking and as an activator of phospholipase D ⁶⁸ . It is involved in Golgi stress and susceptibility to pathogens ⁸⁷ .
	<i>IL17RD</i>	Broad	Interleukin 17 receptor D encodes a membrane protein belonging to the interleukin-17 receptor (IL-17R) protein family ⁶⁸ . The gene product affects fibroblast growth factor signaling, inhibiting or stimulating growth through MAPK/ERK signaling ⁶⁸ . It also interacts with TNF receptor 2 (TNFR2) to activate NF-κB ⁸⁸ .
	<i>ARHGEF3</i>	Broad	Rho guanine nucleotide exchange factor 3 encodes a protein that activates RHOA and RHOB, which have a role in bone cell biology ⁶⁸ . Its gene product also regulates a SPARC protein that participates in the assembly and turnover of the extracellular matrix ⁸⁹ . It also has a role in iron uptake ⁹⁰ . Genetic variants in or around this gene were associated with bone mineral density ⁶⁸ .
7p21.1	<i>ITGB8</i>	Broad	Integrin subunit beta 8 is a member of the integrin beta chain family and encodes a single-pass type I membrane protein that binds to an alpha subunit to form an integrin complex ⁶⁸ . The complexes mediate cell-cell and cell-extracellular matrix interactions and this complex plays a role in human airway epithelial proliferation ⁶⁸ and repair ⁹¹ . Its expression was increased in COPD ⁹²⁻⁹⁴ . It is involved in dendritic cell trafficking, and airway inflammation and fibrosis processes ⁹³ . It mediates epithelial homeostasis through an MMP-dependent pathway ⁹⁵ and TGF-β ^{92,96} . It is also regulated by SP3, AP-1, and the p38 pathway ⁹⁷ .
	<i>ABCB5</i>	None	ATP binding cassette subfamily B member 5 belongs to the ATP-binding cassette (ABC) transporter superfamily of integral membrane proteins ⁹⁸ .
	<i>TMEM196</i>	None	Transmembrane protein 196 is a novel functional tumor suppressor and is associated with lung cancer ⁹⁹ .

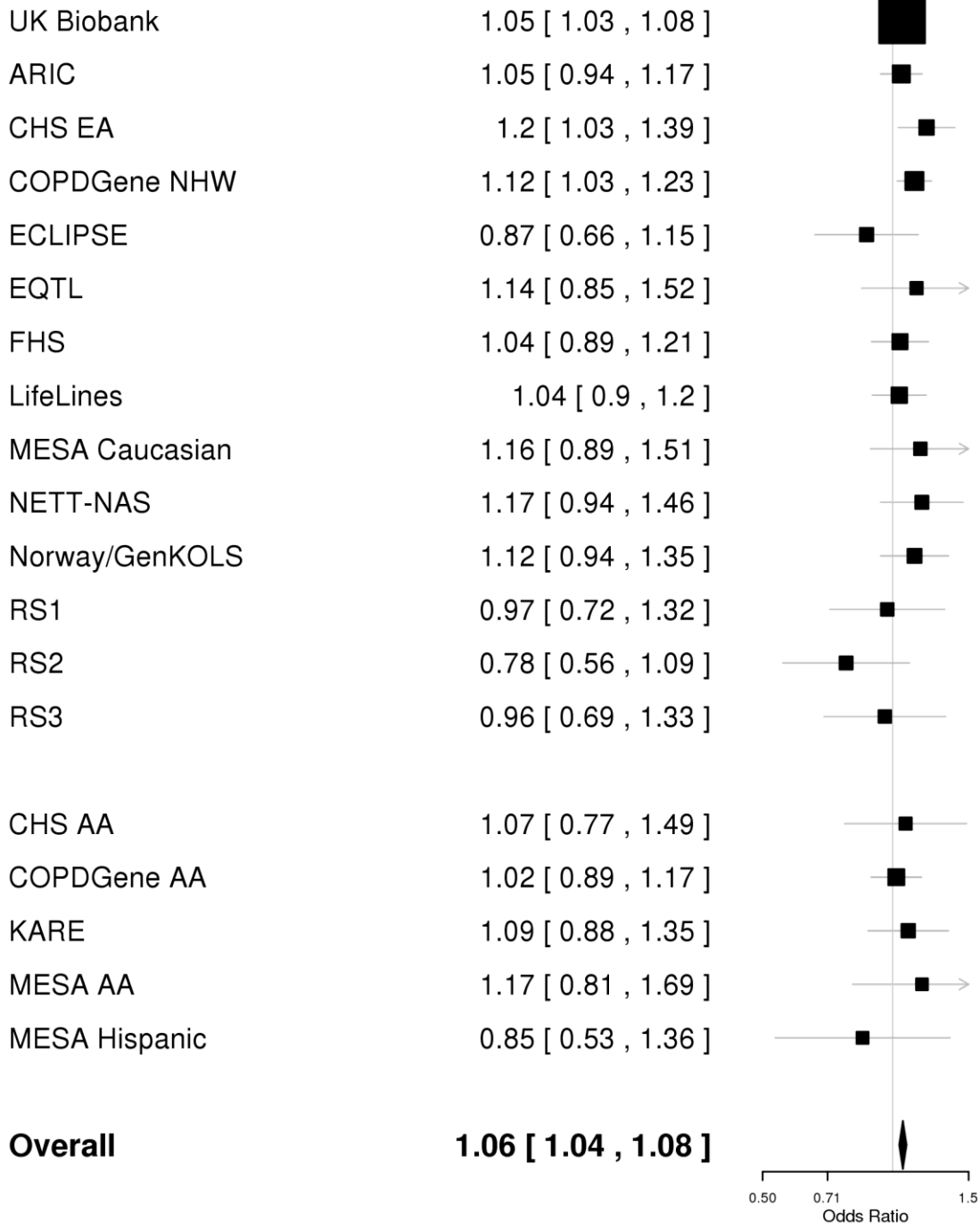
11p15.2	<i>BTBD10</i>	Broad	The gene product of BTB domain containing 10 is an Akt activator ¹⁰⁰ . This gene was associated with neurologic diseases ¹⁰¹ .
	<i>PARVA</i>	Broad	Parvin alpha encodes a member of the parvin family of actin-binding proteins ⁶⁸ . The encoded protein is part of the integrin-linked kinase signaling complex and plays a role in cell adhesion, motility and survival ⁶⁸ .
	<i>MICALCL</i>	Broad	MICAL C-terminal like gene product is predominantly expressed in skin, testis, and lung ⁶⁶ .
15q25.2	<i>ADAMTSL3</i>	Broad	ADAMTS like 3 encodes a gene product that plays a role in cell-matrix interactions or in assembly of specific extracellular matrices ¹⁰² . It was associated with schizophrenia ¹⁰³ and cardiac disorders in tetrasomy ¹⁰⁴ .
	<i>BNC1</i>	None	Basonuclin 1 encodes a zinc finger protein that is present in the basal cell layer of the epidermis and in hair follicles, and in the germ cells of testis and ovary ^{68,105} . Its gene product modulates epithelial plasticity and TGF- β 1-induced loss of epithelial cell integrity ¹⁰⁶ . It is a Pol I and Pol II transcription factor that is associated with epithelial expansion and proliferation ^{107,108} .
	<i>BTBD1</i>	Broad	BTB domain containing 1 encodes a protein that binds topoisomerase I. It is a transcription factor ¹⁰⁹ in the human histone deacetylase family ¹¹⁰ . Its gene product is involved in mesenchymal ¹¹¹ and muscle cell differentiation ¹¹² .

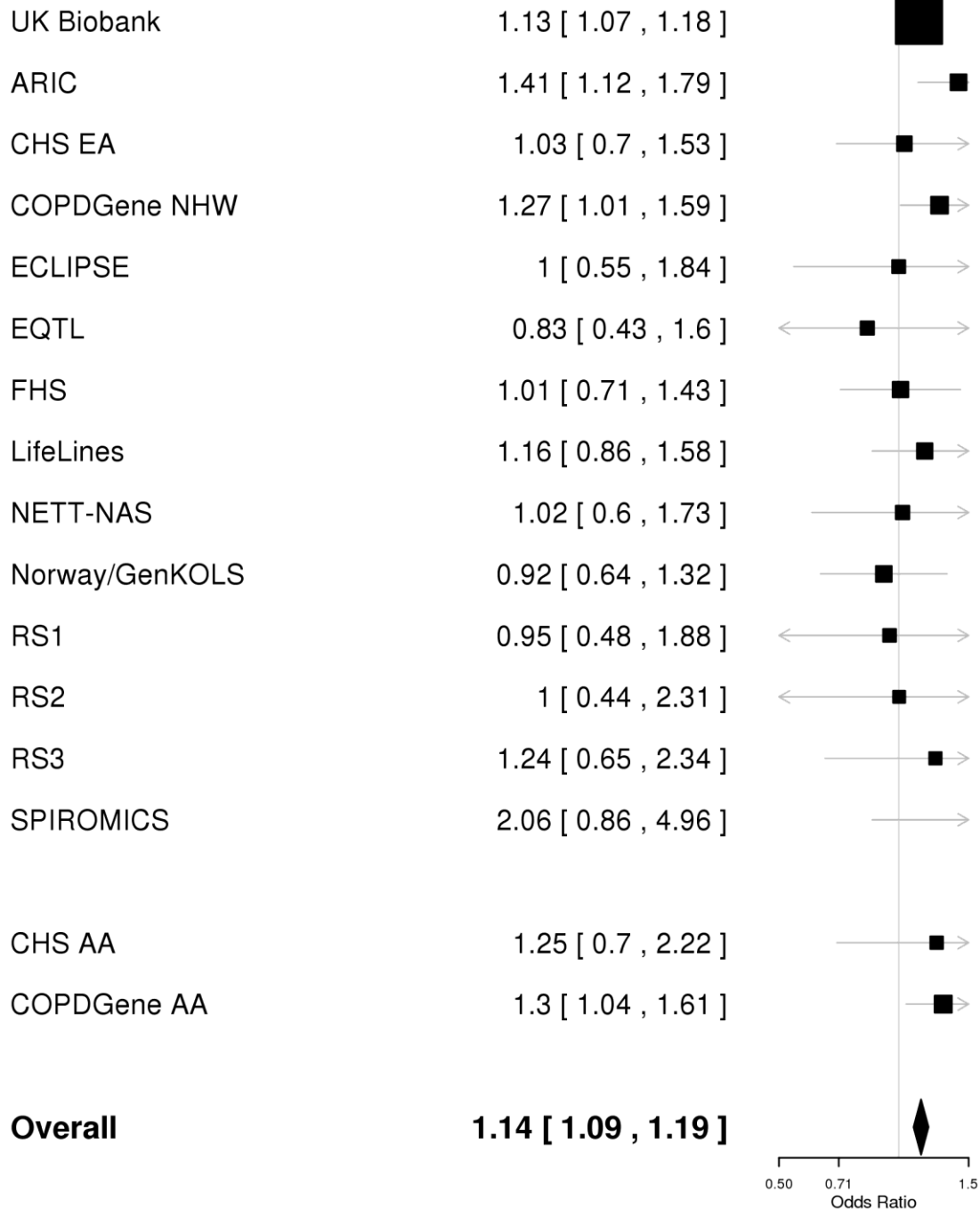
Supplementary Figures

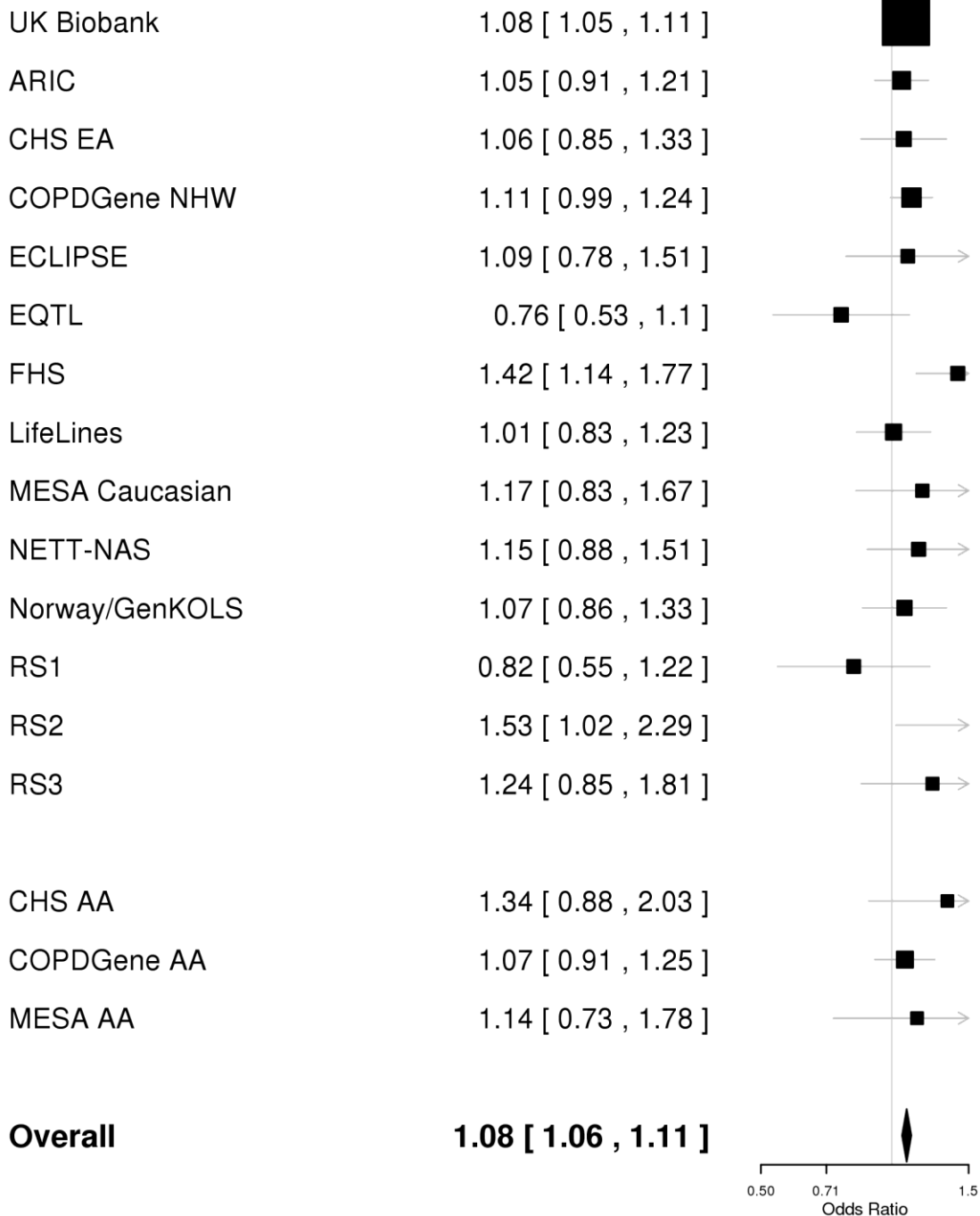
Supplementary Figure 1: Forest plots for 82 genome-wide significant associations

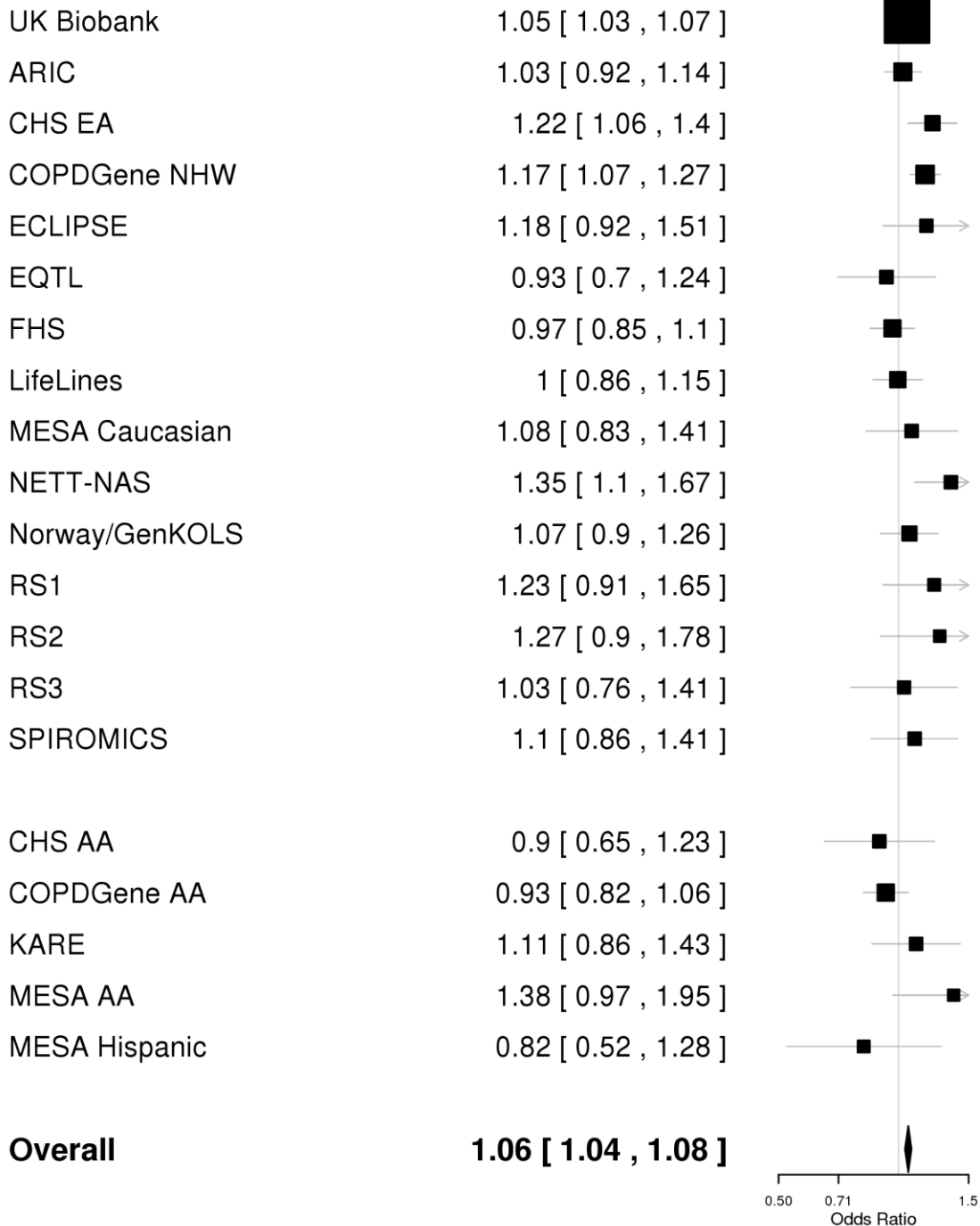
Supplementary Figure 1-1: Forest plot for rs9435731 (*MFAP2* locus at 1p36.13)**1:17306029:A/C rs9435731**

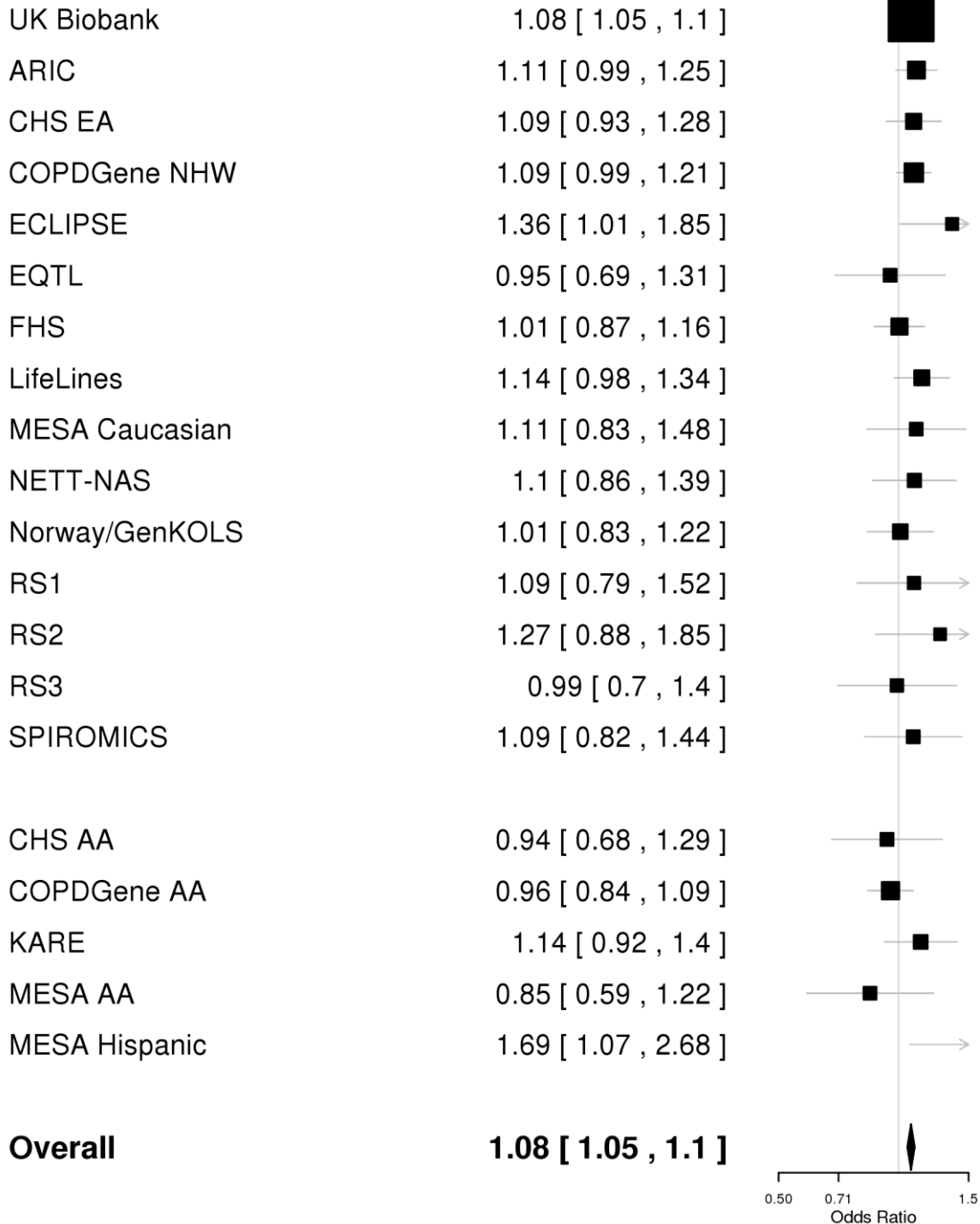
Supplementary Figure 1-2: Forest plot for rs76841360 (*PABPC4* locus at 1p34.3)**1:40060025:A/G rs76841360**

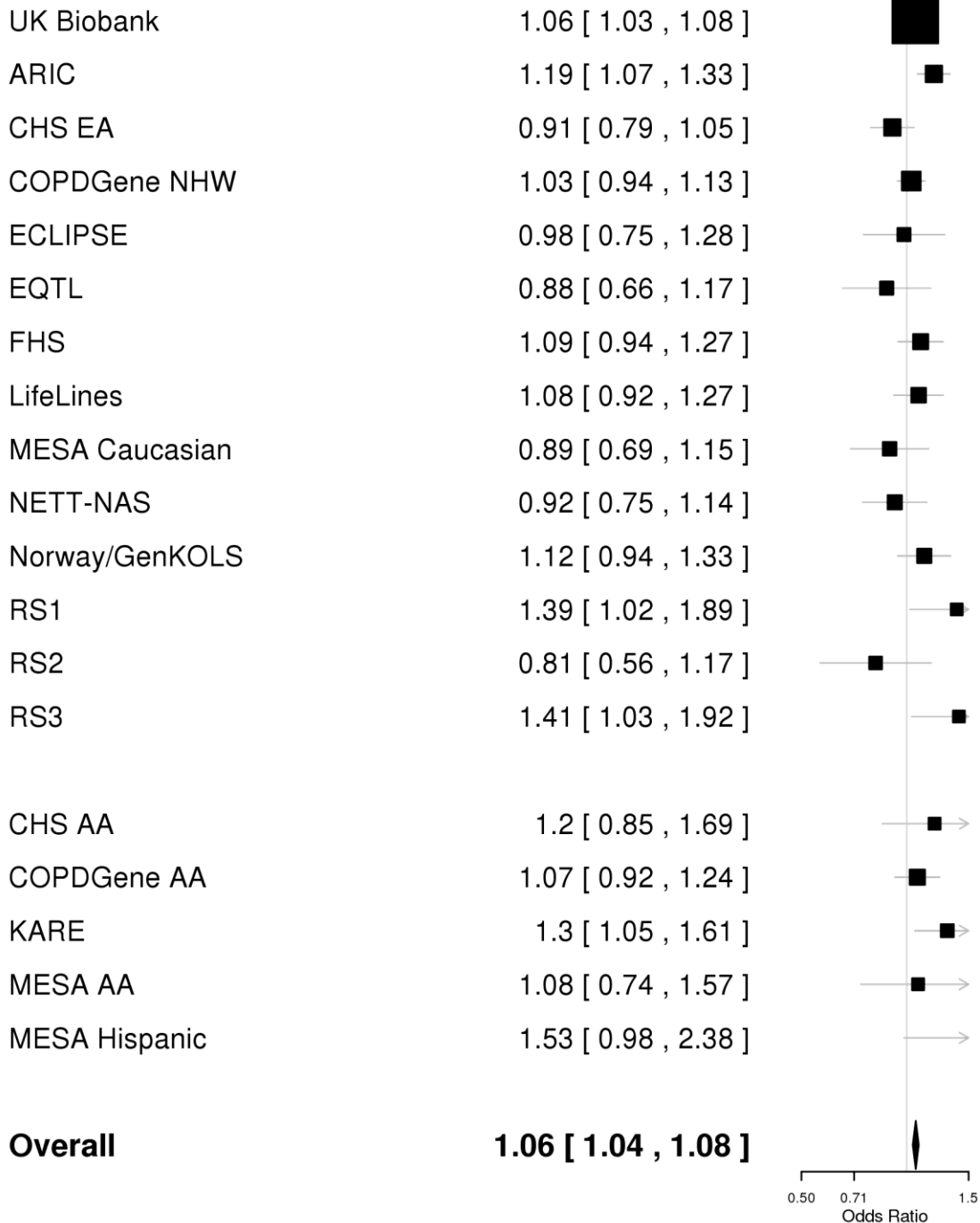
Supplementary Figure 1-3: Forest plot for rs4660861 (*TESK2* locus at 1p34.1)**1:45946636:G/T rs4660861**

Supplementary Figure 1-4: Forest plot for rs72673419 (*C1orf87* locus at 1p32.1)**1:60913143:T/C rs72673419**

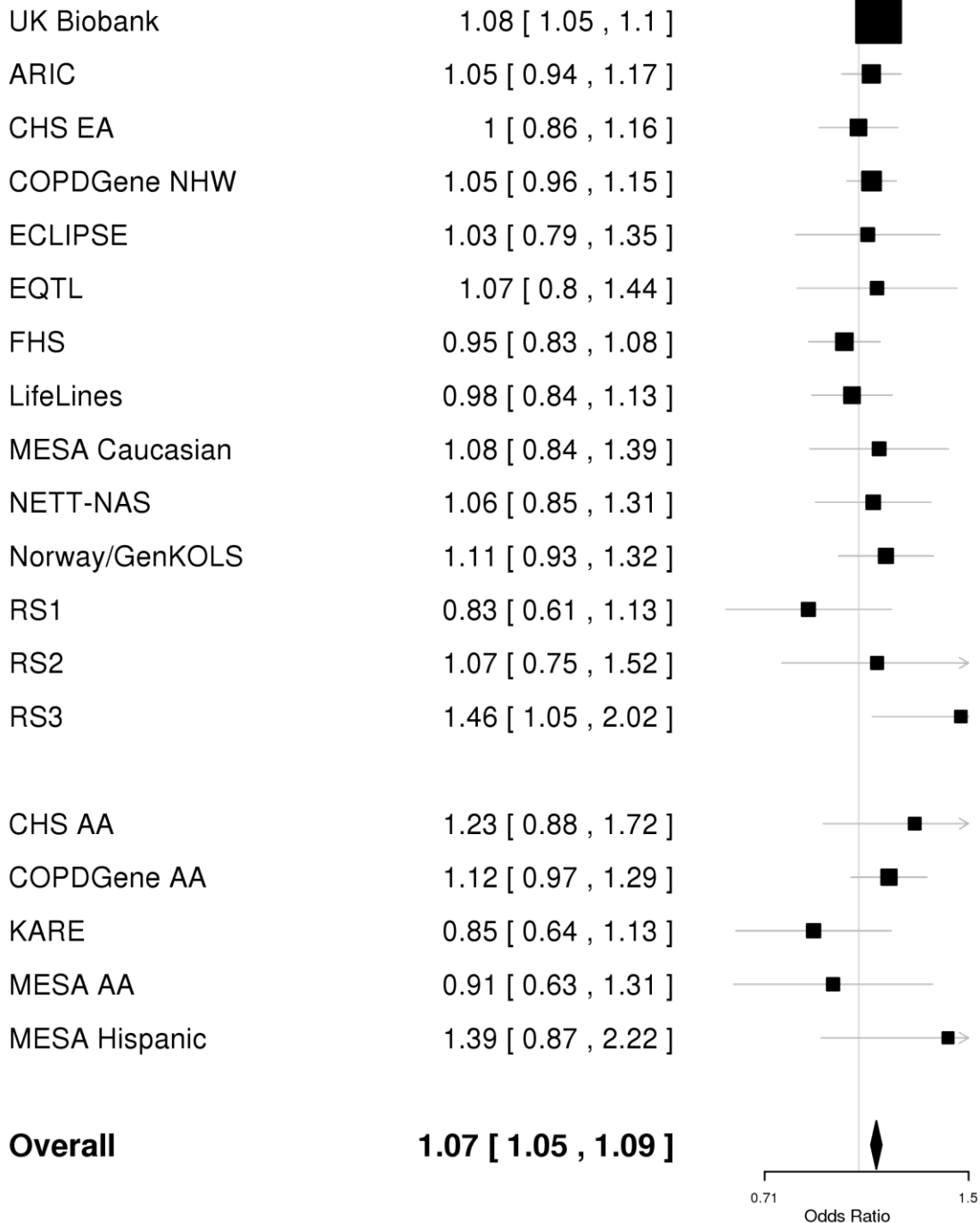
Supplementary Figure 1-5: Forest plot for rs629619 (*DENND2D* locus at 1p13.3)**1:111738108:T/C rs629619**

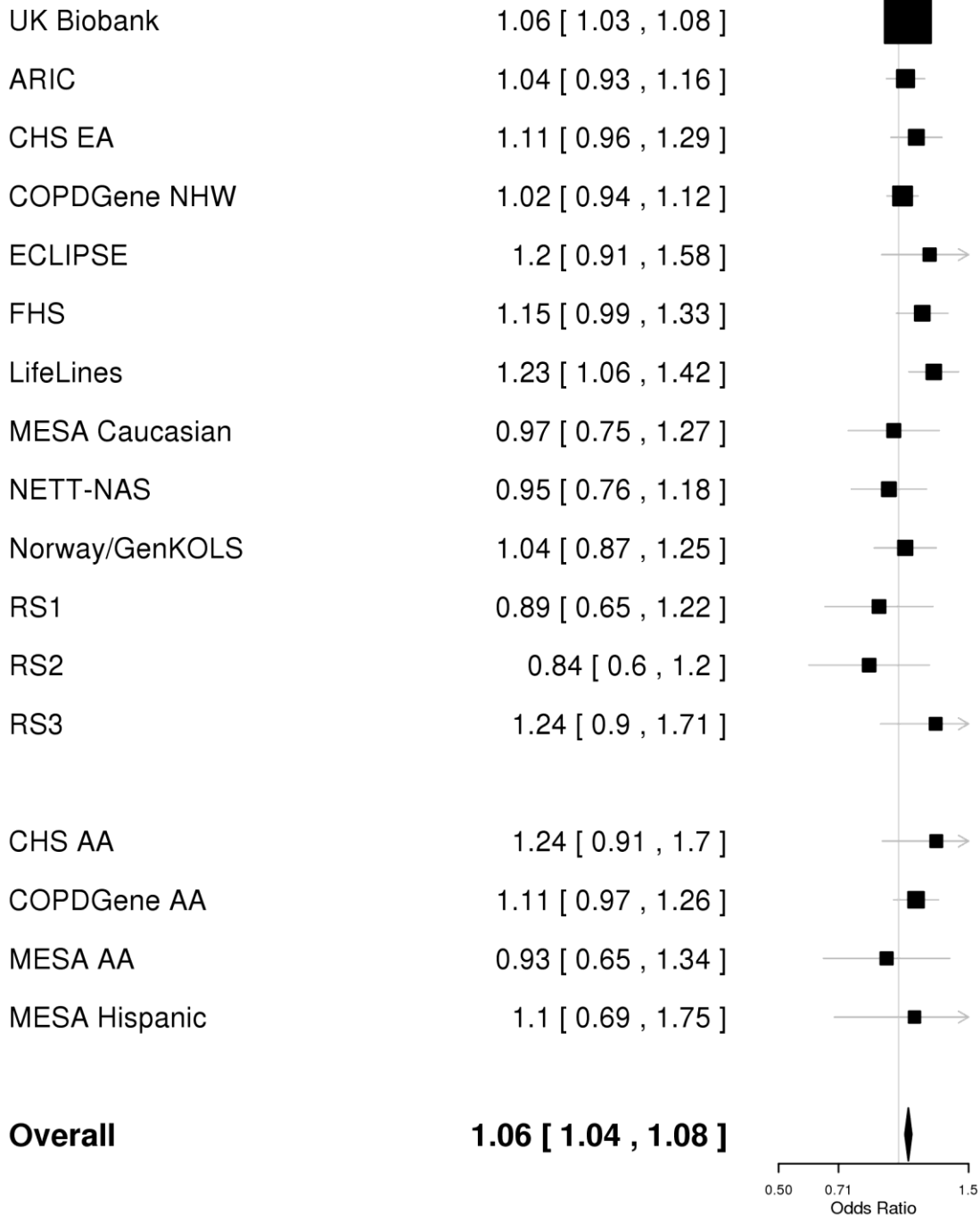
Supplementary Figure 1-6: Forest plot for rs3009947 (*TGFB2* locus at 1q41)**1:218689155:C/T rs3009947**

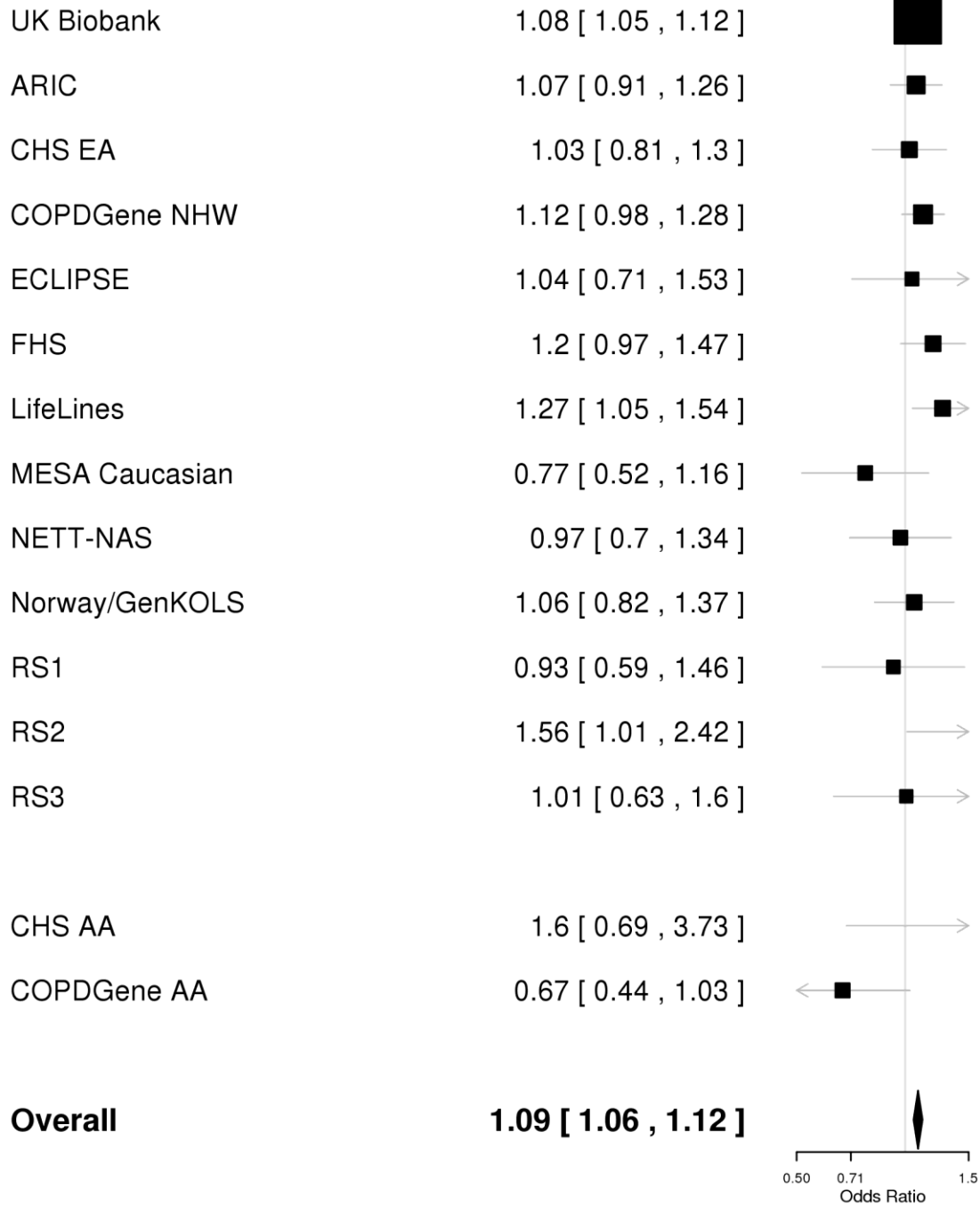
Supplementary Figure 1-7: Forest plot for rs11118406 (*SLC30A10* locus at 1q41)**1:219924894:T/A rs11118406**

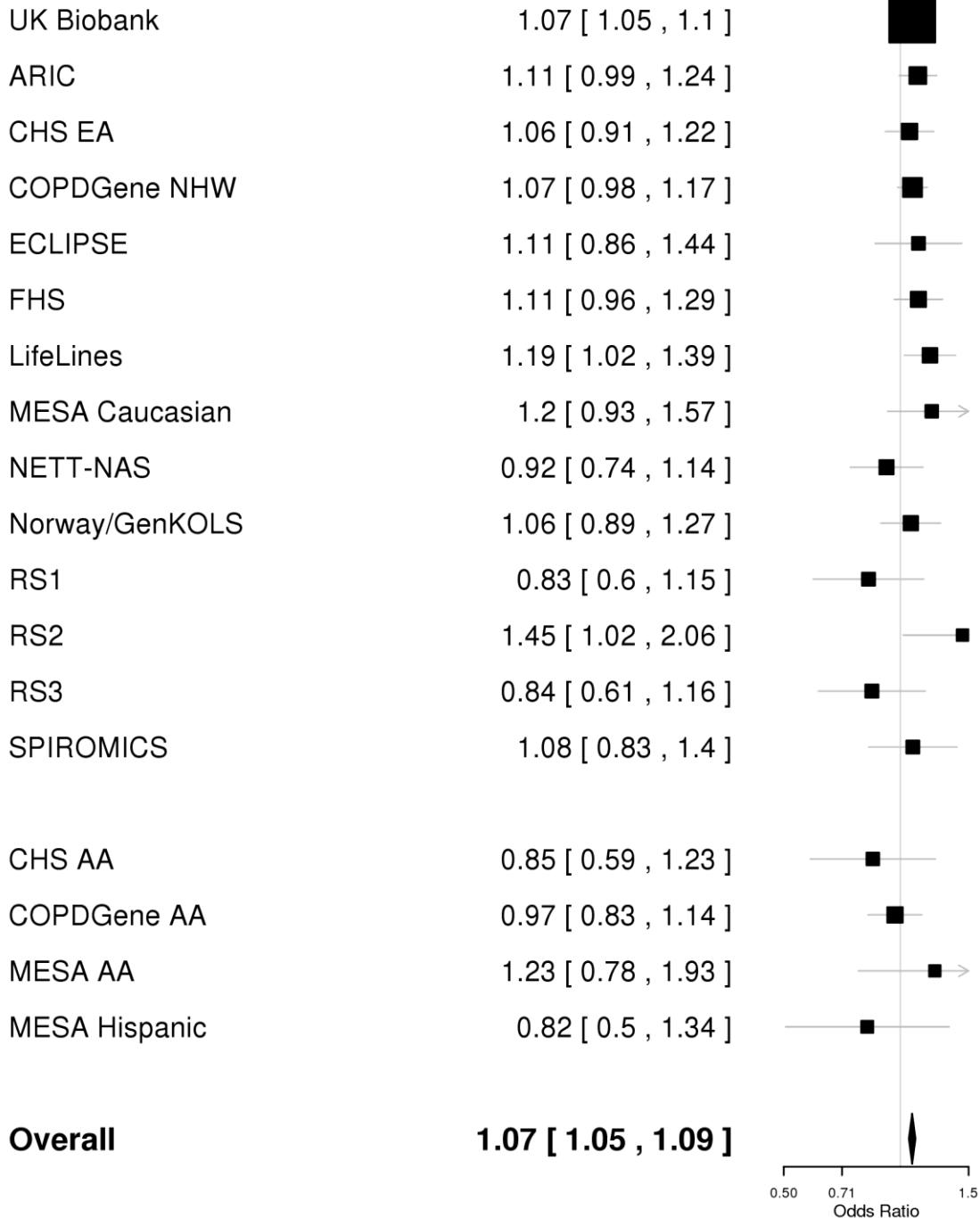
Supplementary Figure 1-8: Forest plot for rs11579382 (*CHRM3* locus at 1q43)**1:239901006:C/G rs11579382**

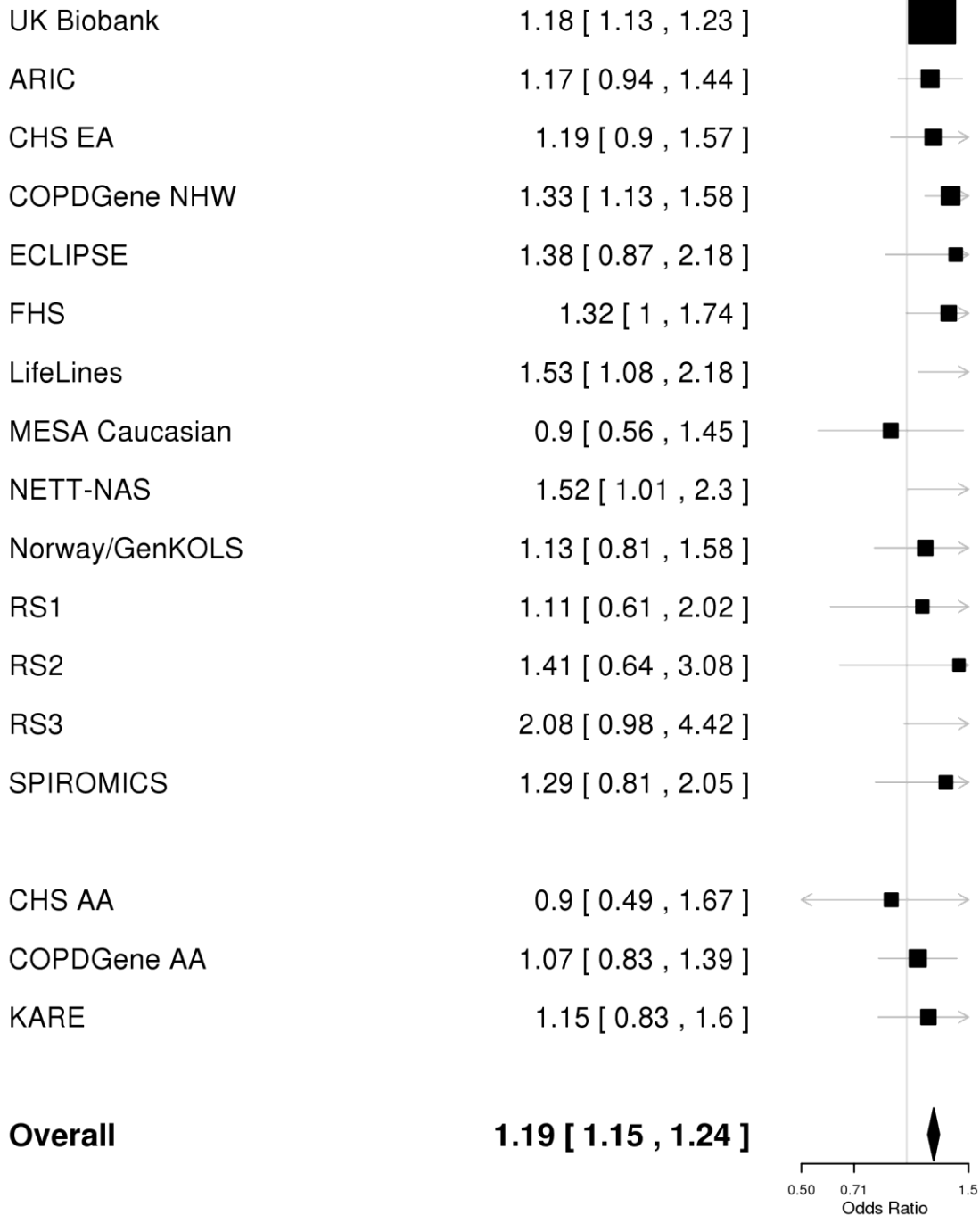
Supplementary Figure 1-9: Forest plot for rs955277 (ASAP2 locus at 2p25.1)

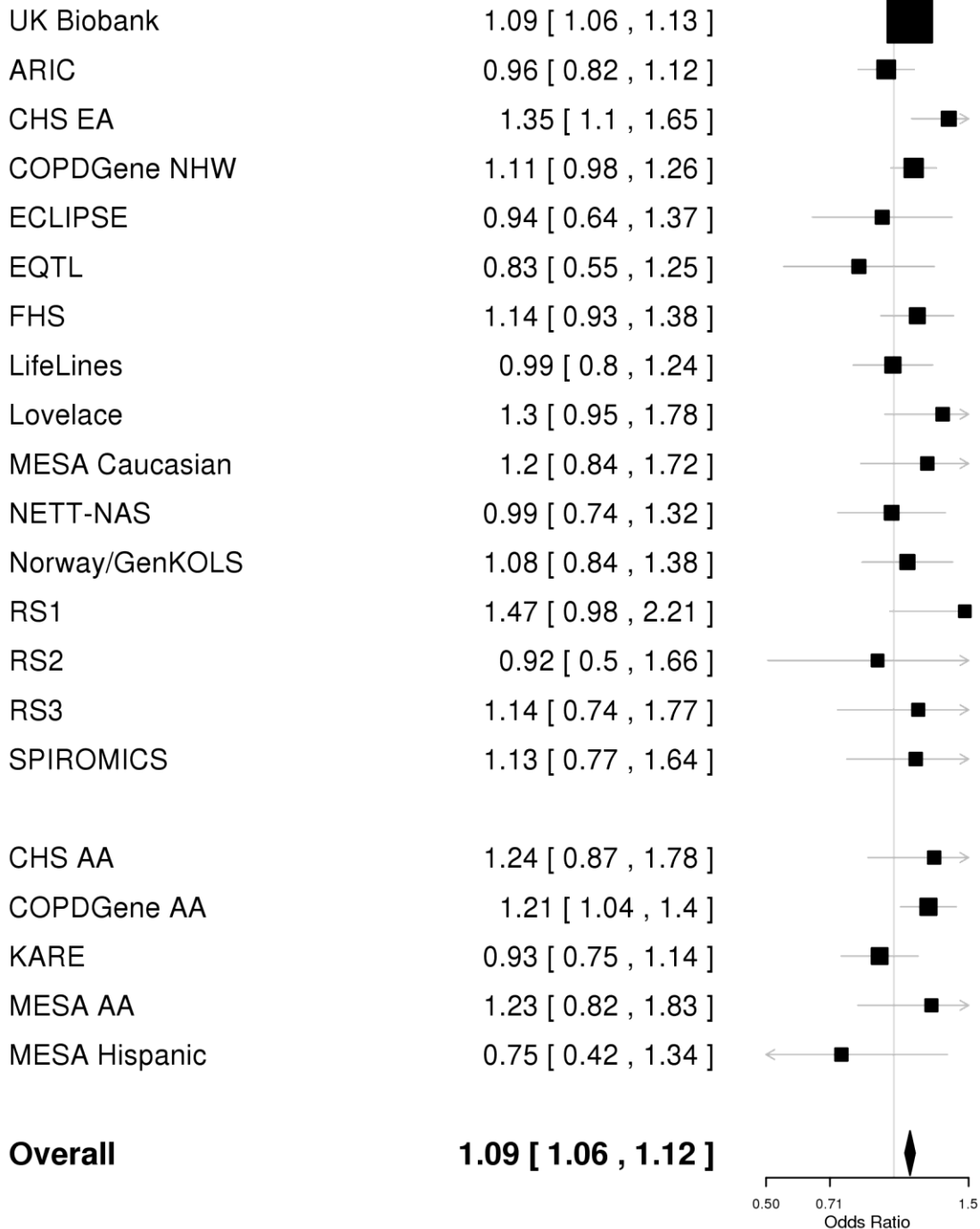
2:9290357:T/C rs955277

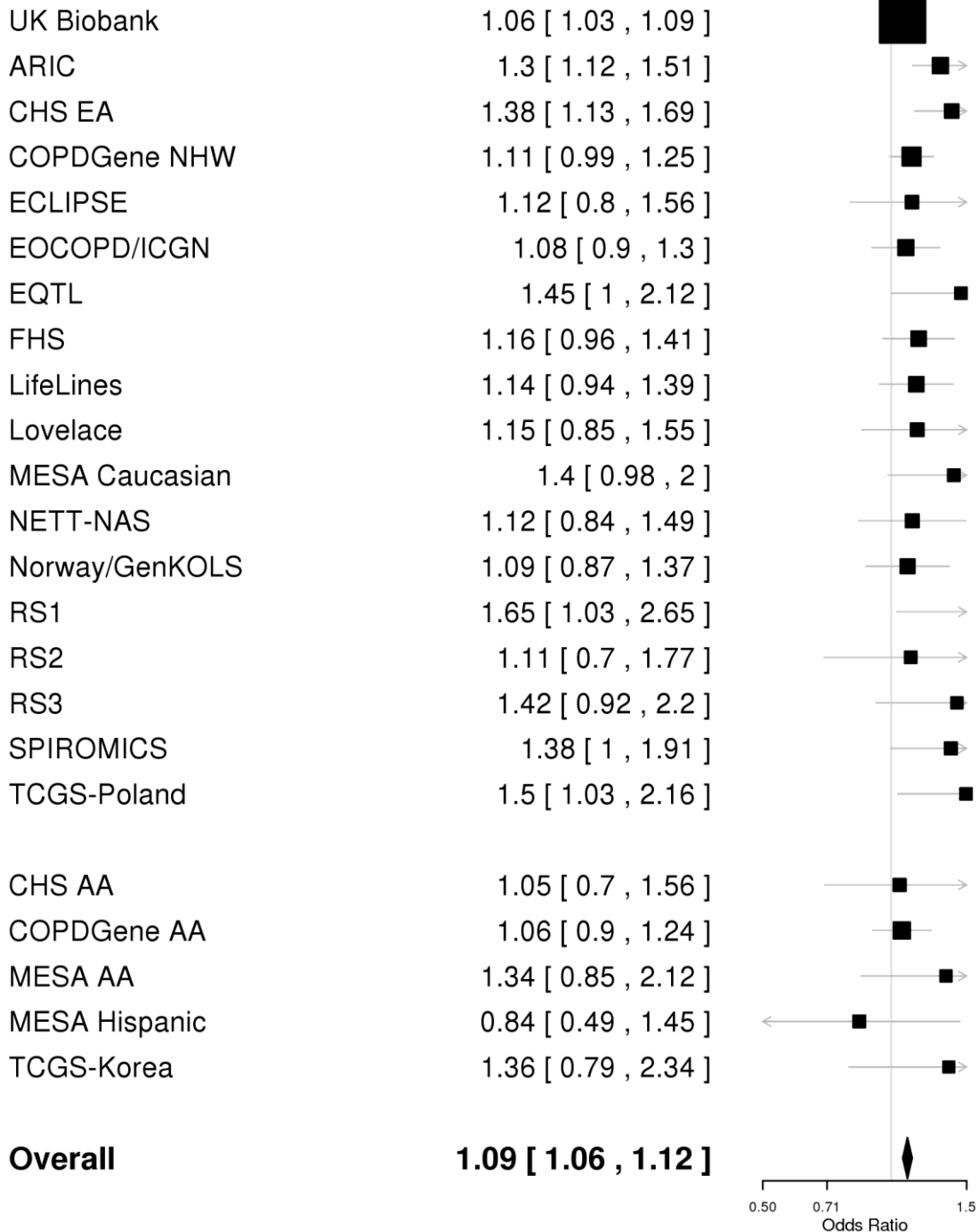
Supplementary Figure 1-10: Forest plot for rs10929386 (*DDX1* locus at 2p24.3)**2:15906179:C/T rs10929386**

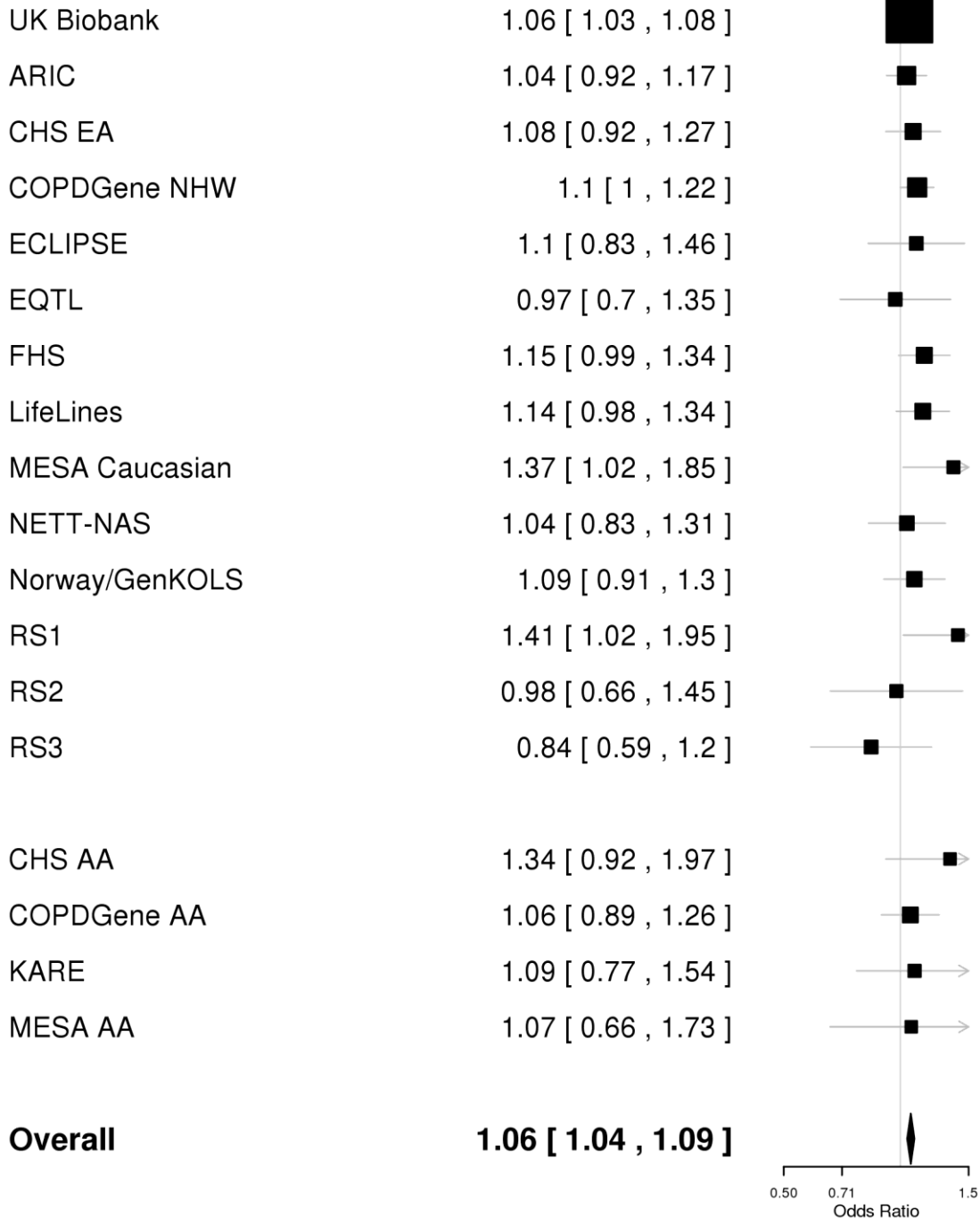
Supplementary Figure 1-12: Forest plot for rs72902175 (*NR4A2* locus at 2q24.1)**2:157013035:T/C rs72902175**

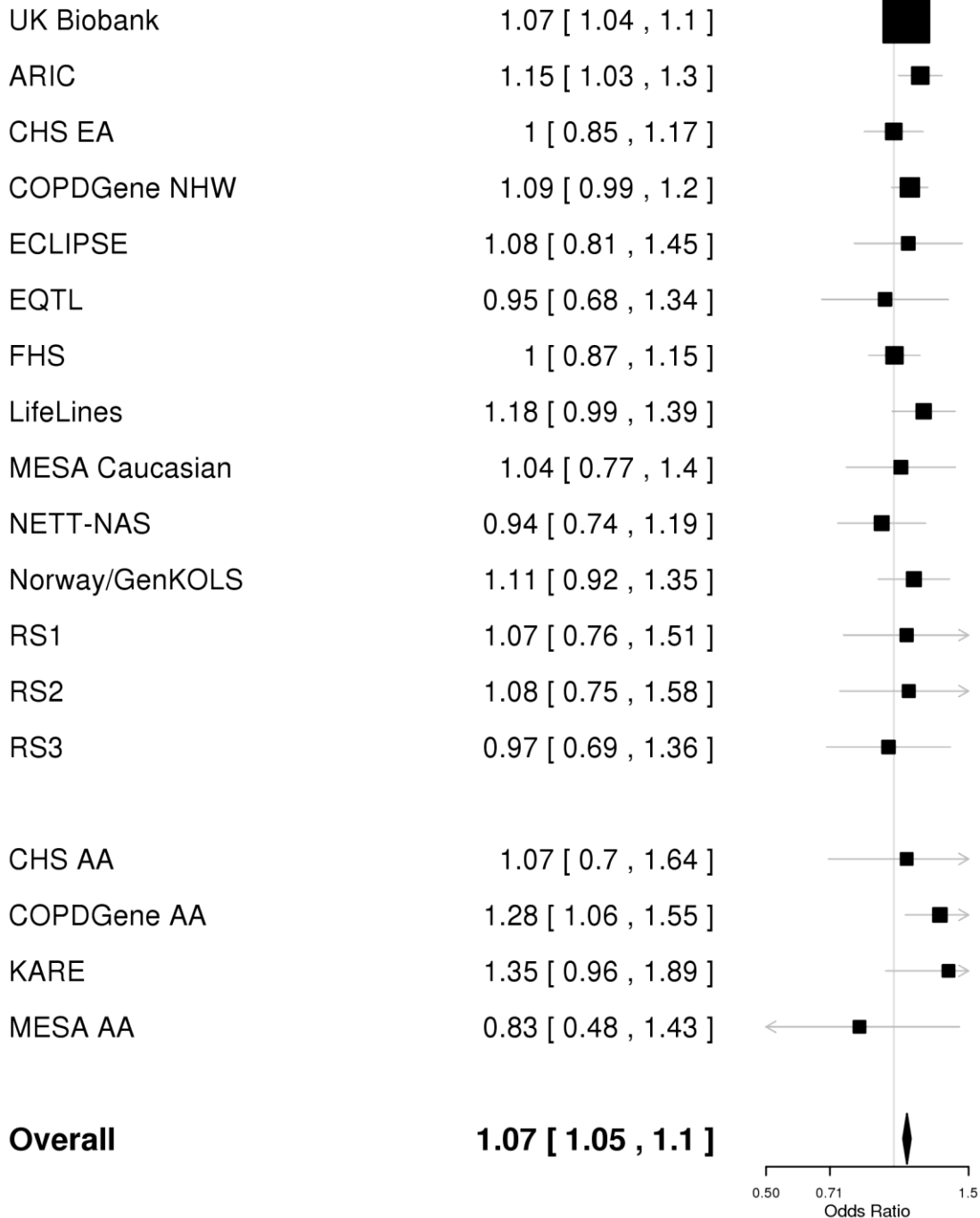
Supplementary Figure 1-13: Forest plot for rs2571445 (*TNS1* locus at 2q35)**2:218683154:A/G rs2571445**

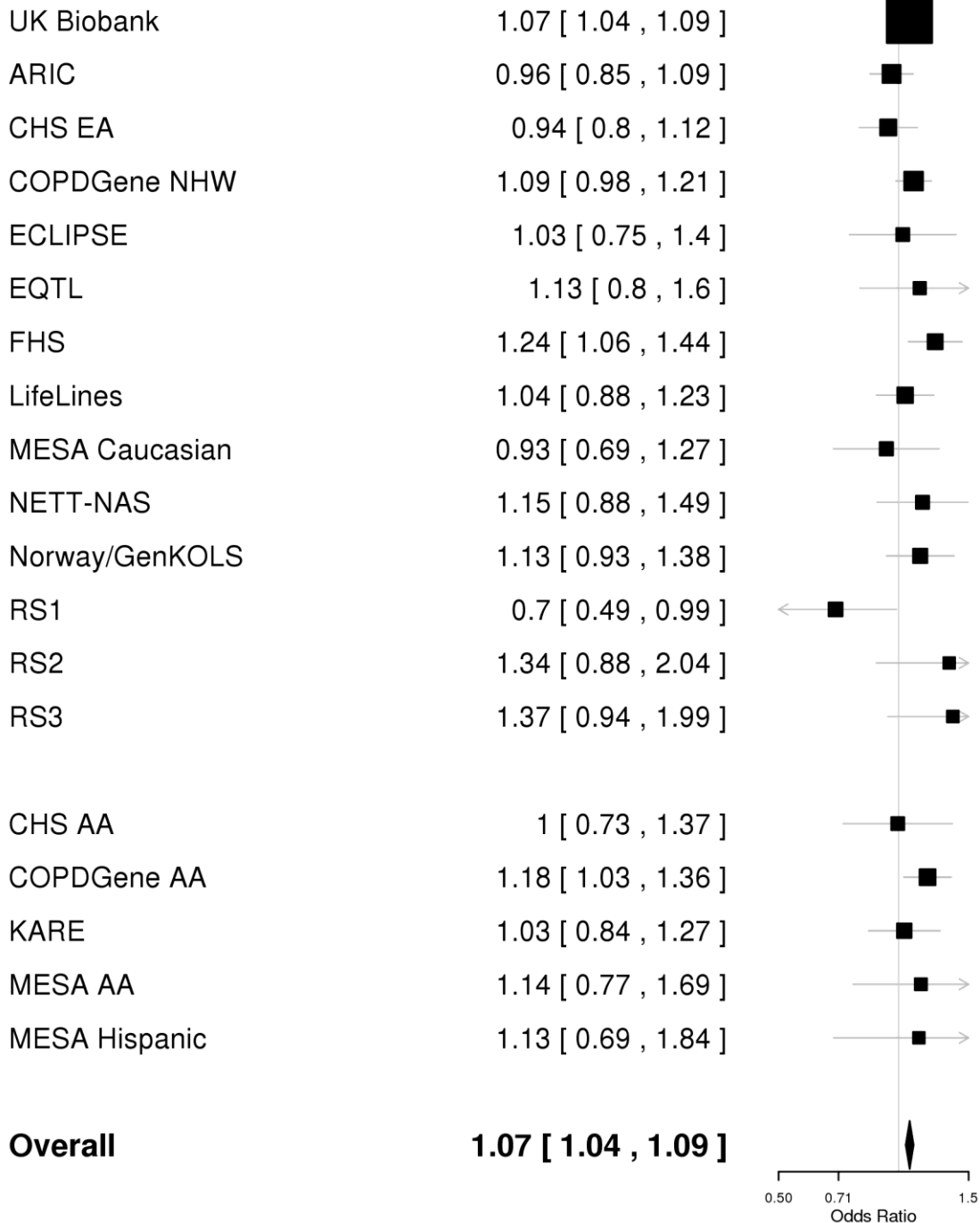
Supplementary Figure 1-14: Forest plot for rs16825267 (*PID1* locus at 2q36.3)**2:229569919:C/G rs16825267**

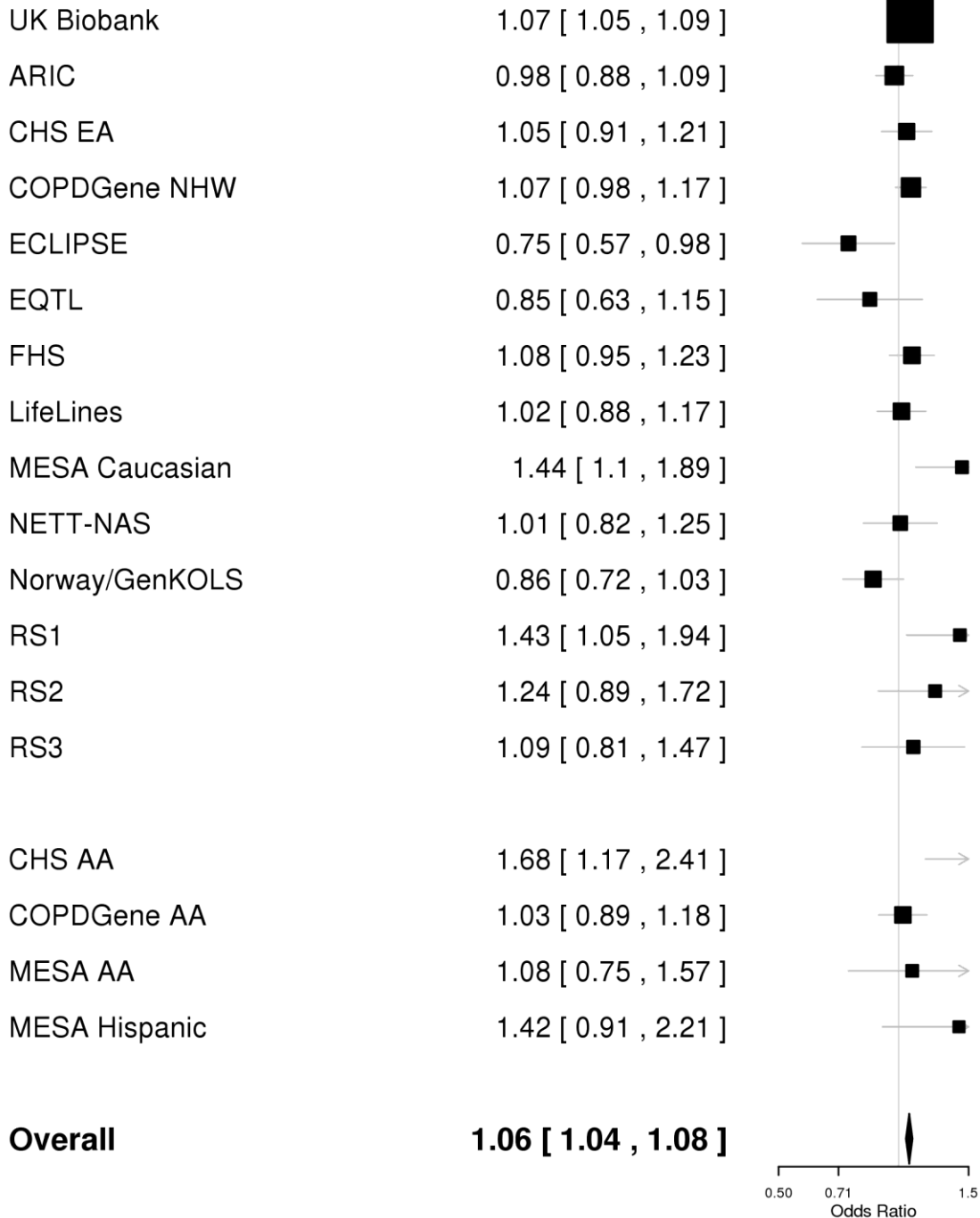
Supplementary Figure 1-16: Forest plot for rs2442776 (*VGLL4* locus at 3p25.3)**3:11640601:G/A rs2442776**

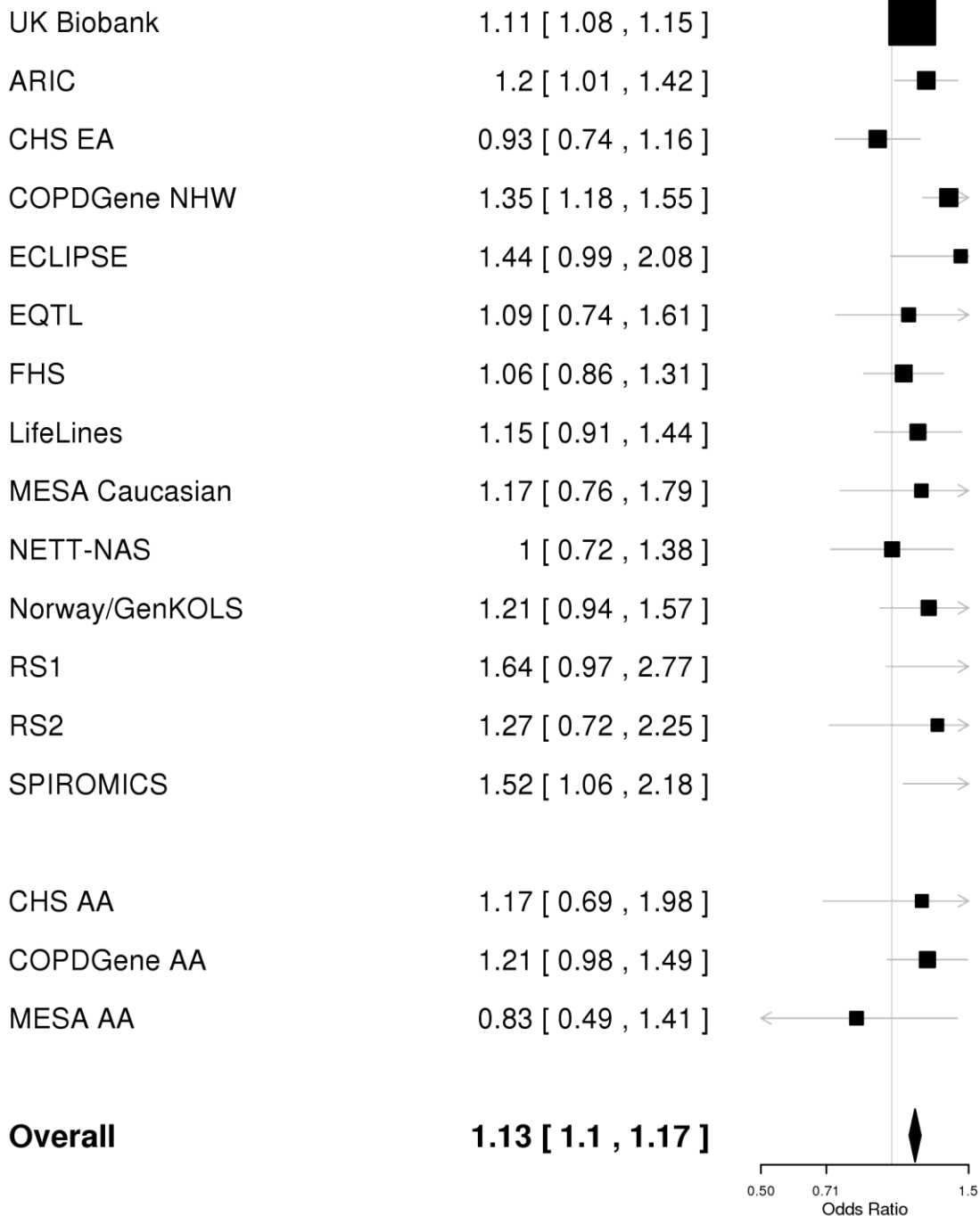
Supplementary Figure 1-17: Forest plot for rs1529672 (*RARB* locus at 3p24.2)**3:25520582:C/A rs1529672**

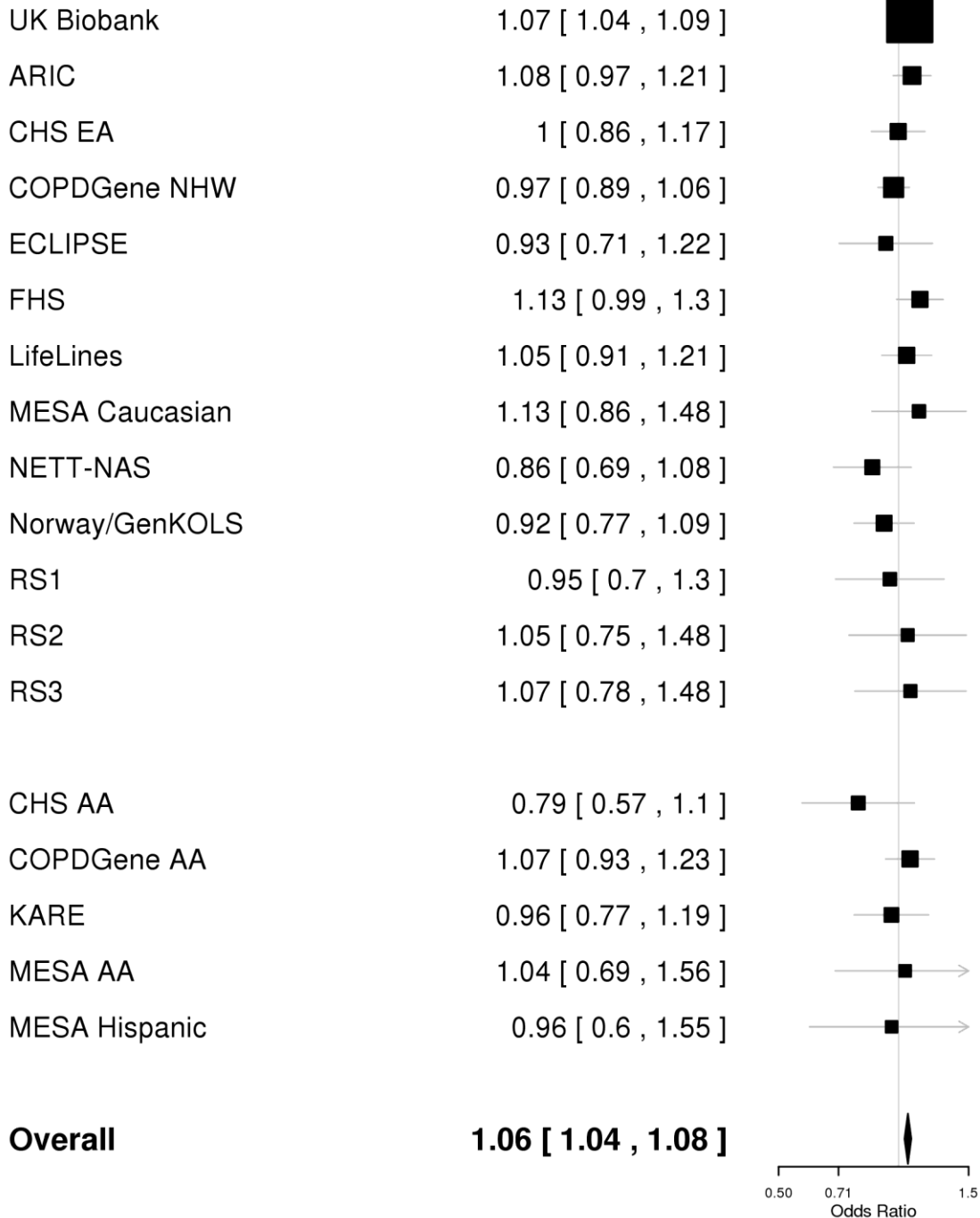
Supplementary Figure 1-18: Forest plot for rs13073544 (*RBMS3* locus at 3p24.1)**3:29472412:C/G rs13073544**

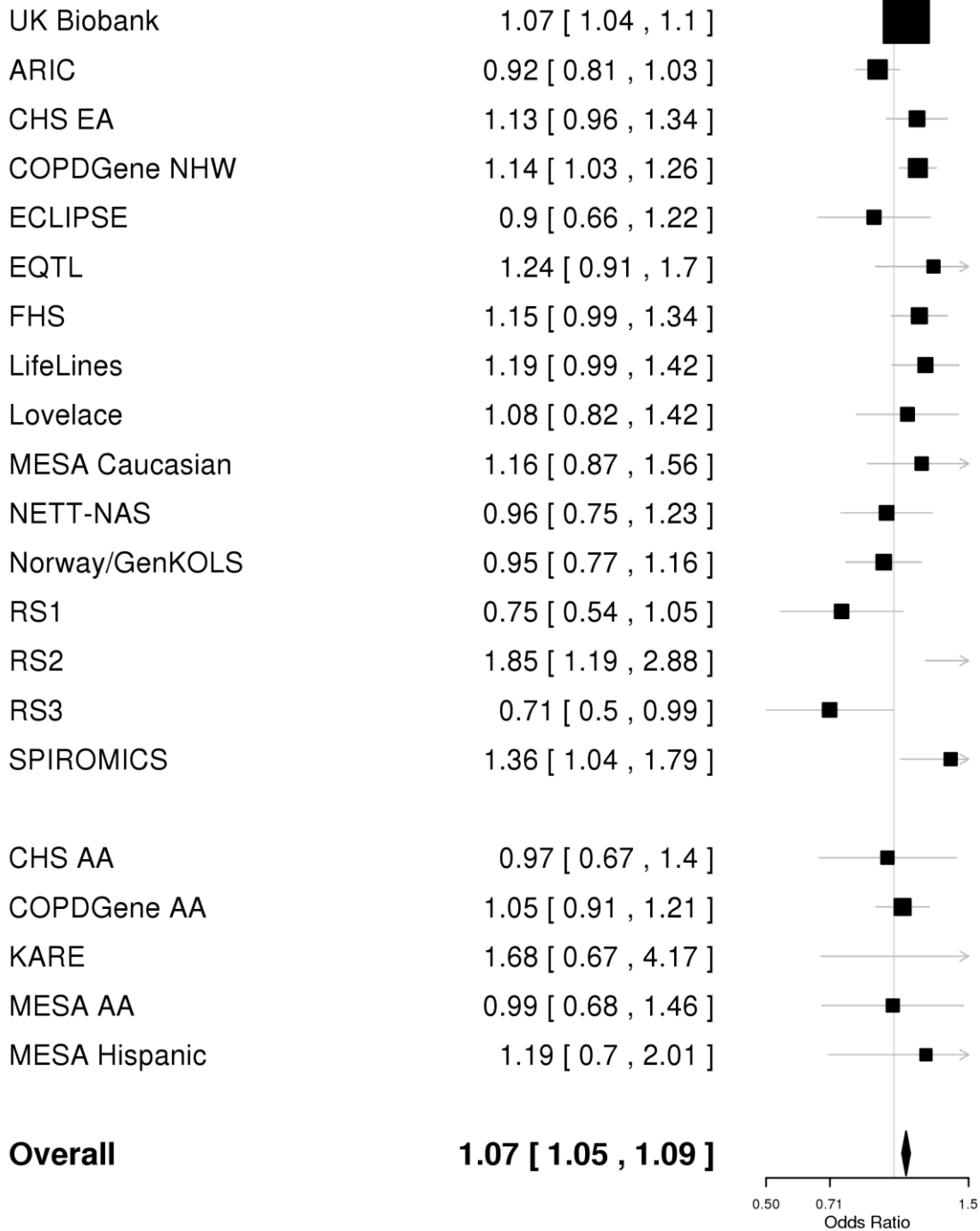
Supplementary Figure 1-19: Forest plot for rs17759204 (*CACNA2D3* locus at 3p14.3)**3:55158224:G/A rs17759204**

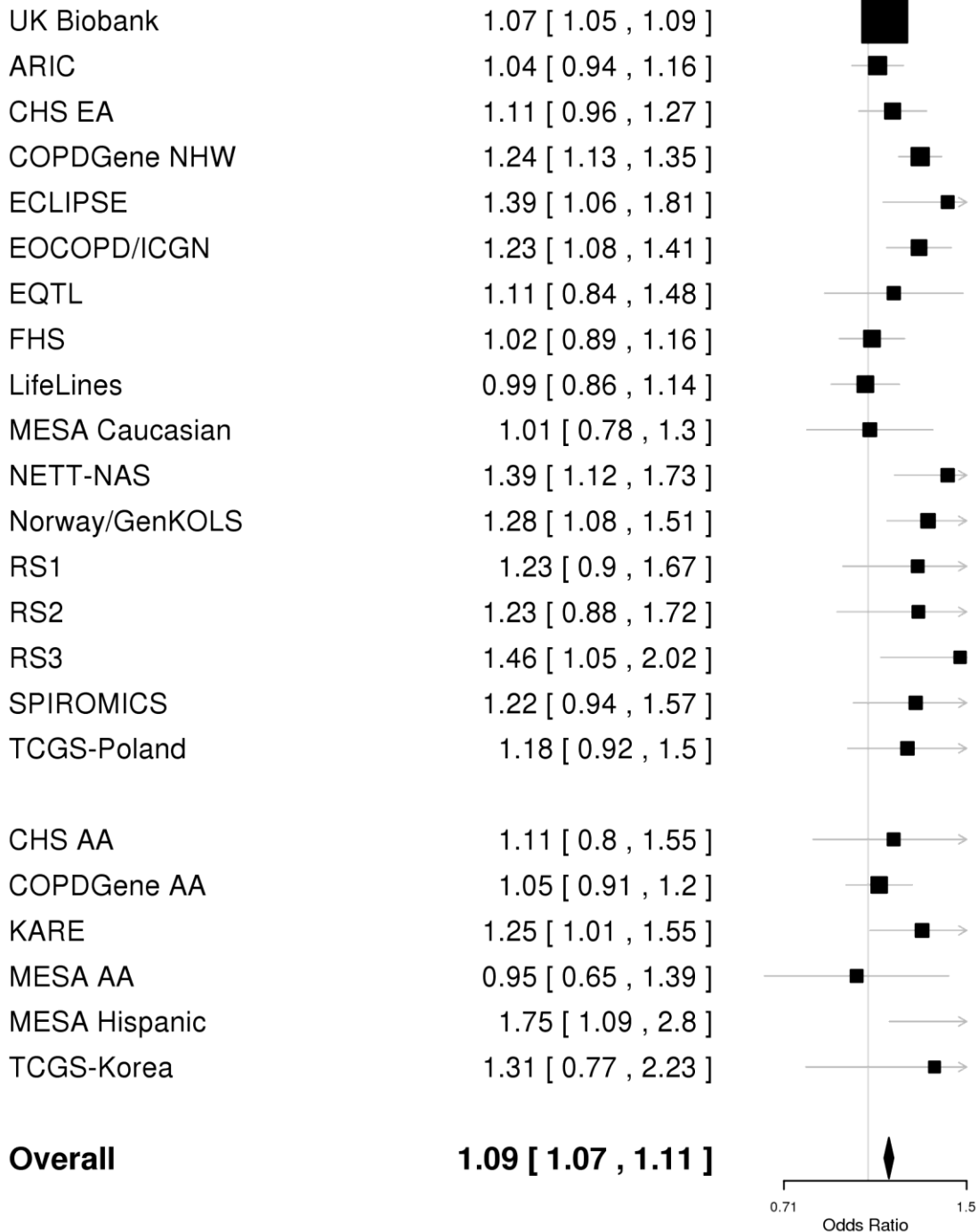
Supplementary Figure 1-20: Forest plot for rs62259026 (*SLMAP* locus at 3p14.3)**3:57746515:C/T rs62259026**

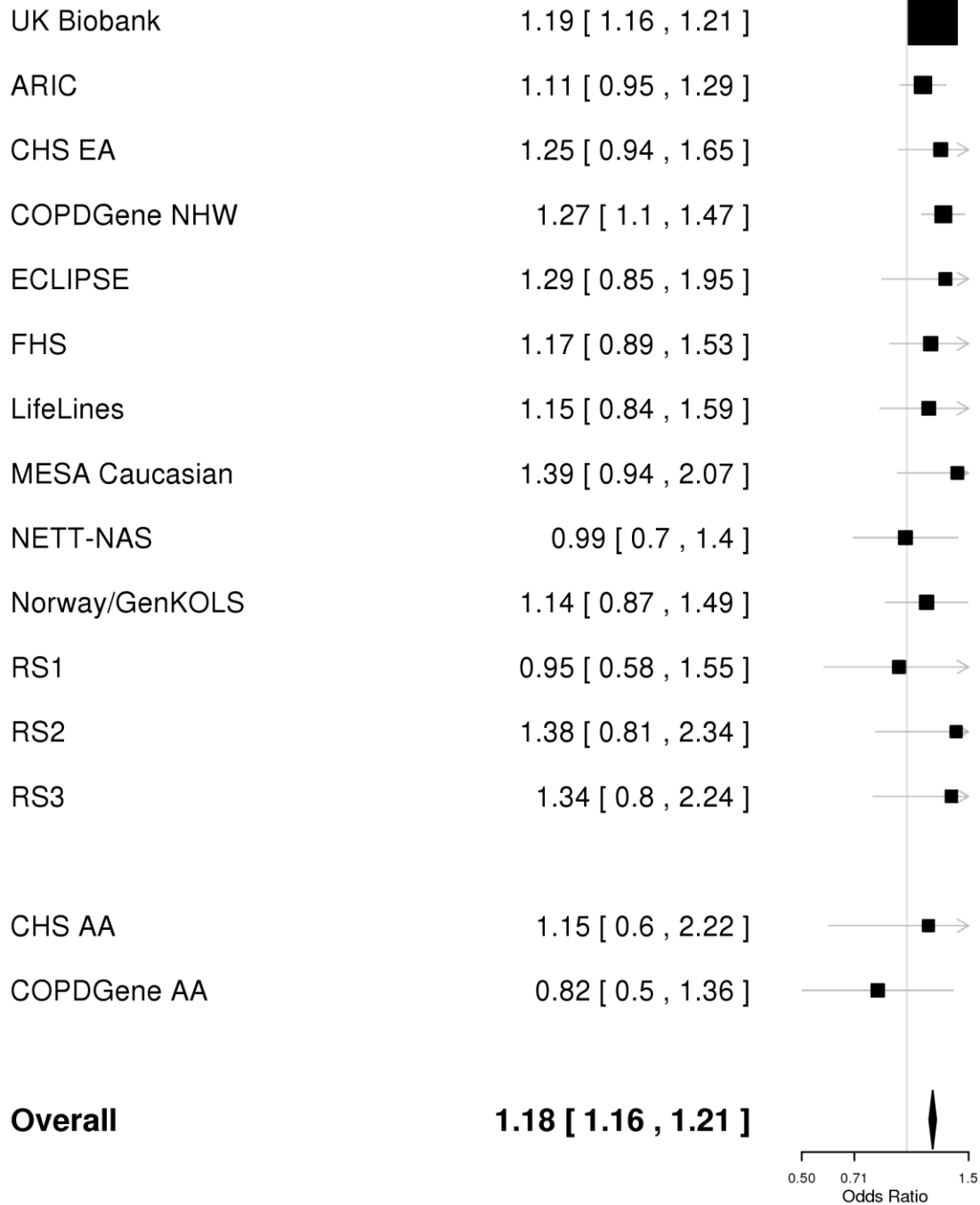
Supplementary Figure 1-21: Forest plot for rs4093840 (*ADCY5* locus at 3q21.1)**3:123077042:A/T rs4093840**

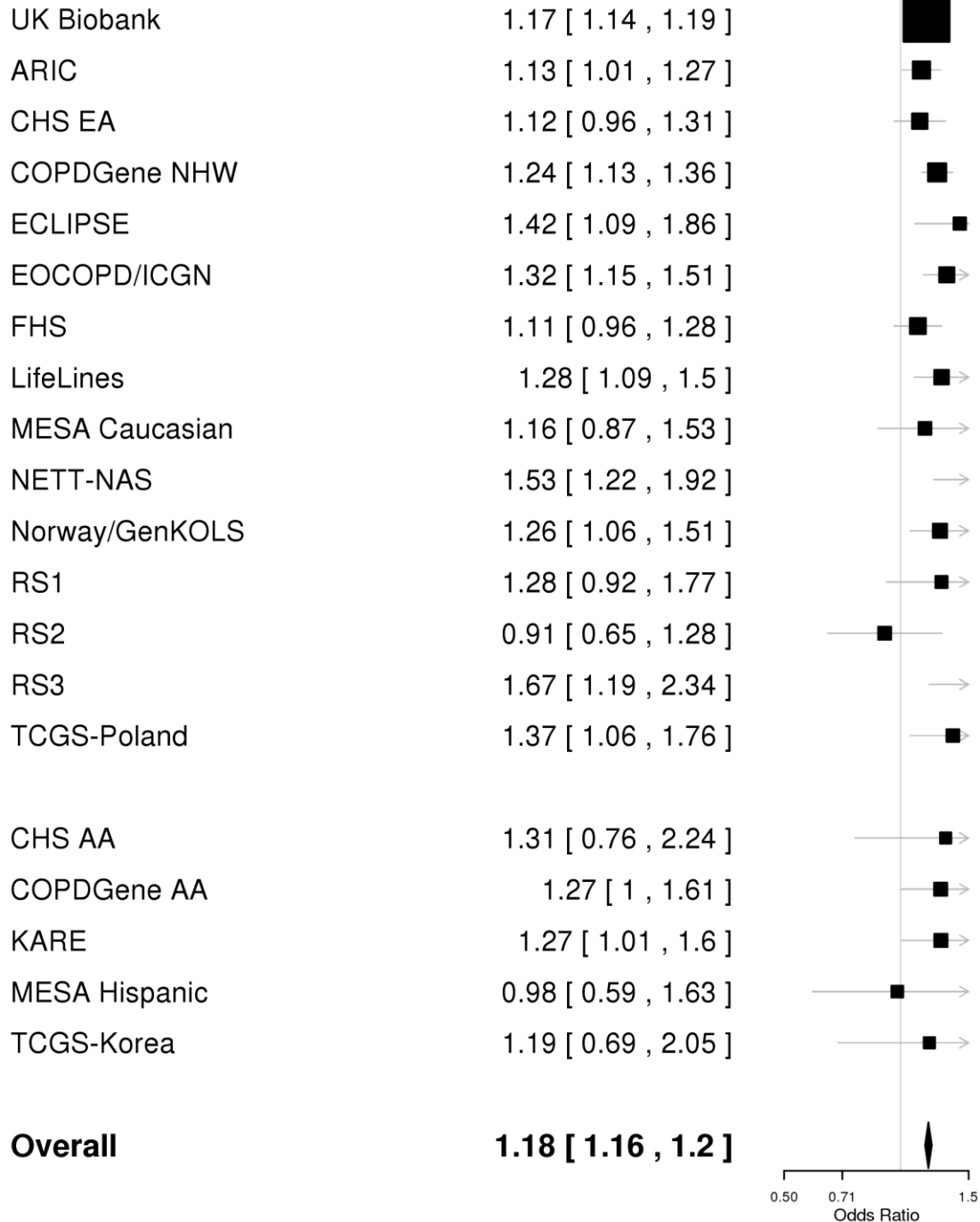
Supplementary Figure 1-22: Forest plot for rs2955083 (*EEFSEC* locus at 3q21.3)**3:127961178:A/T rs2955083**

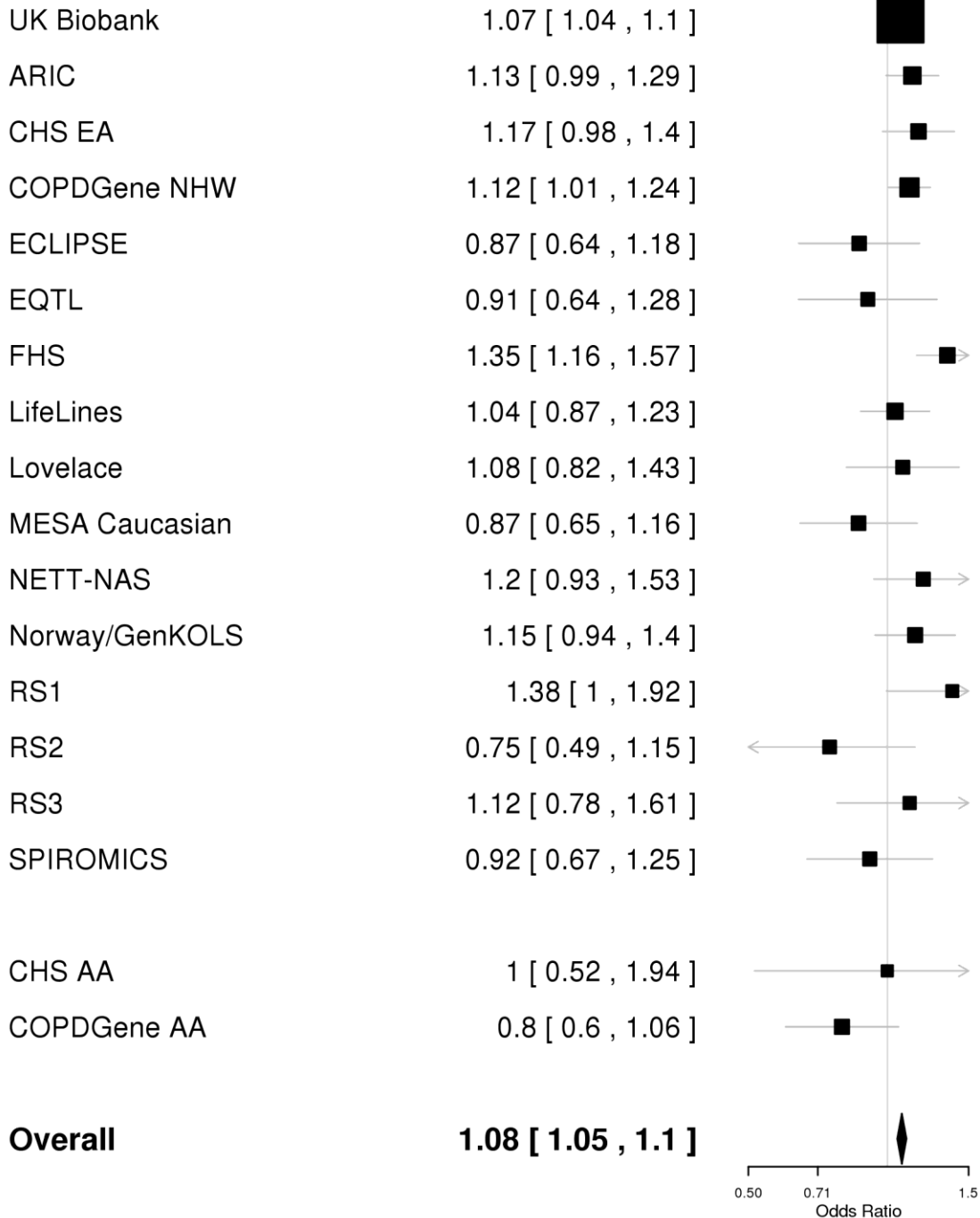
Supplementary Figure 1-23: Forest plot for rs7650602 (*ZBTB38* locus at 3q23)**3:141147414:C/T rs7650602**

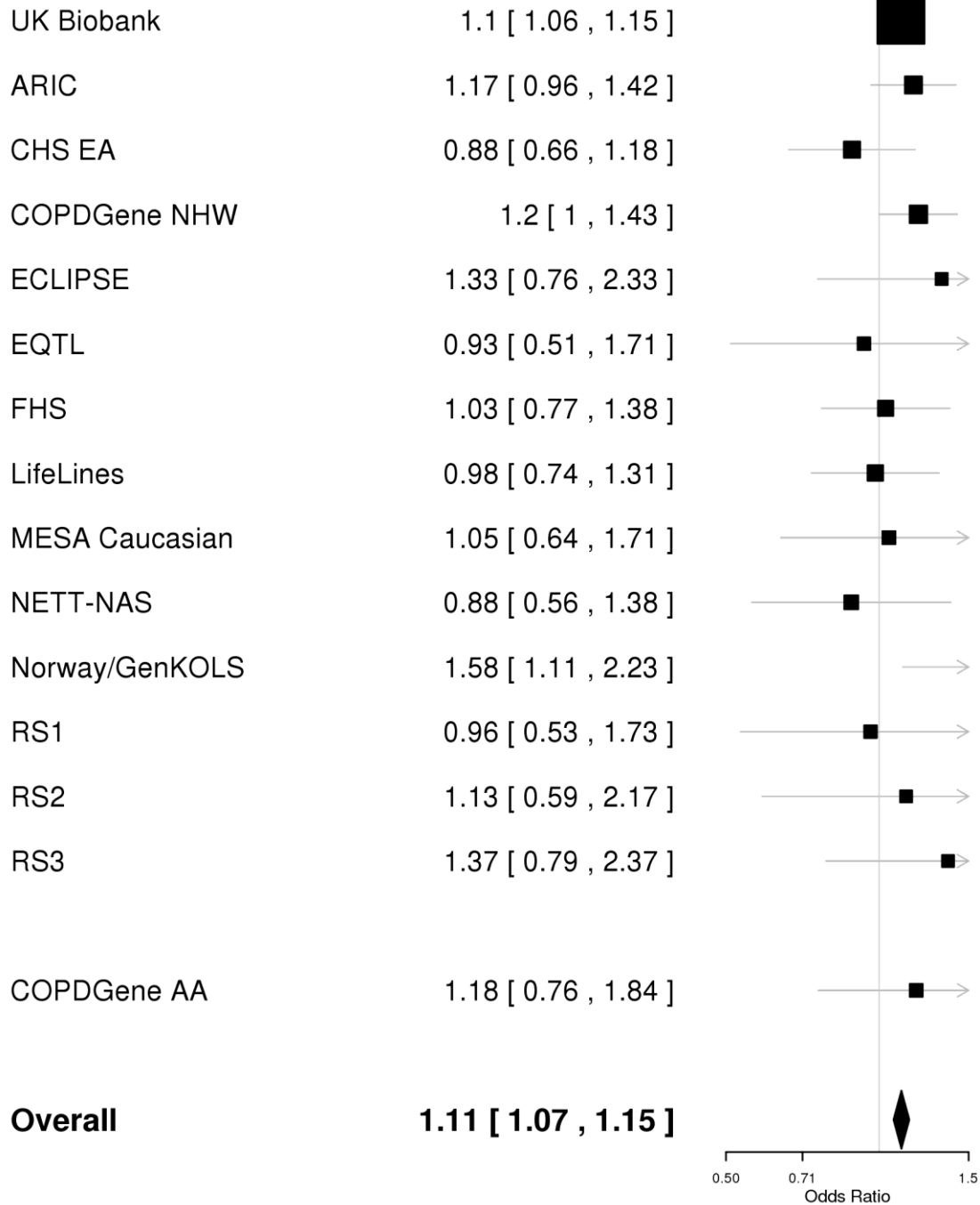
Supplementary Figure 1-25: Forest plot for rs4585380 (*BTC* locus at 4q13.3)**4:75673363:G/A rs4585380**

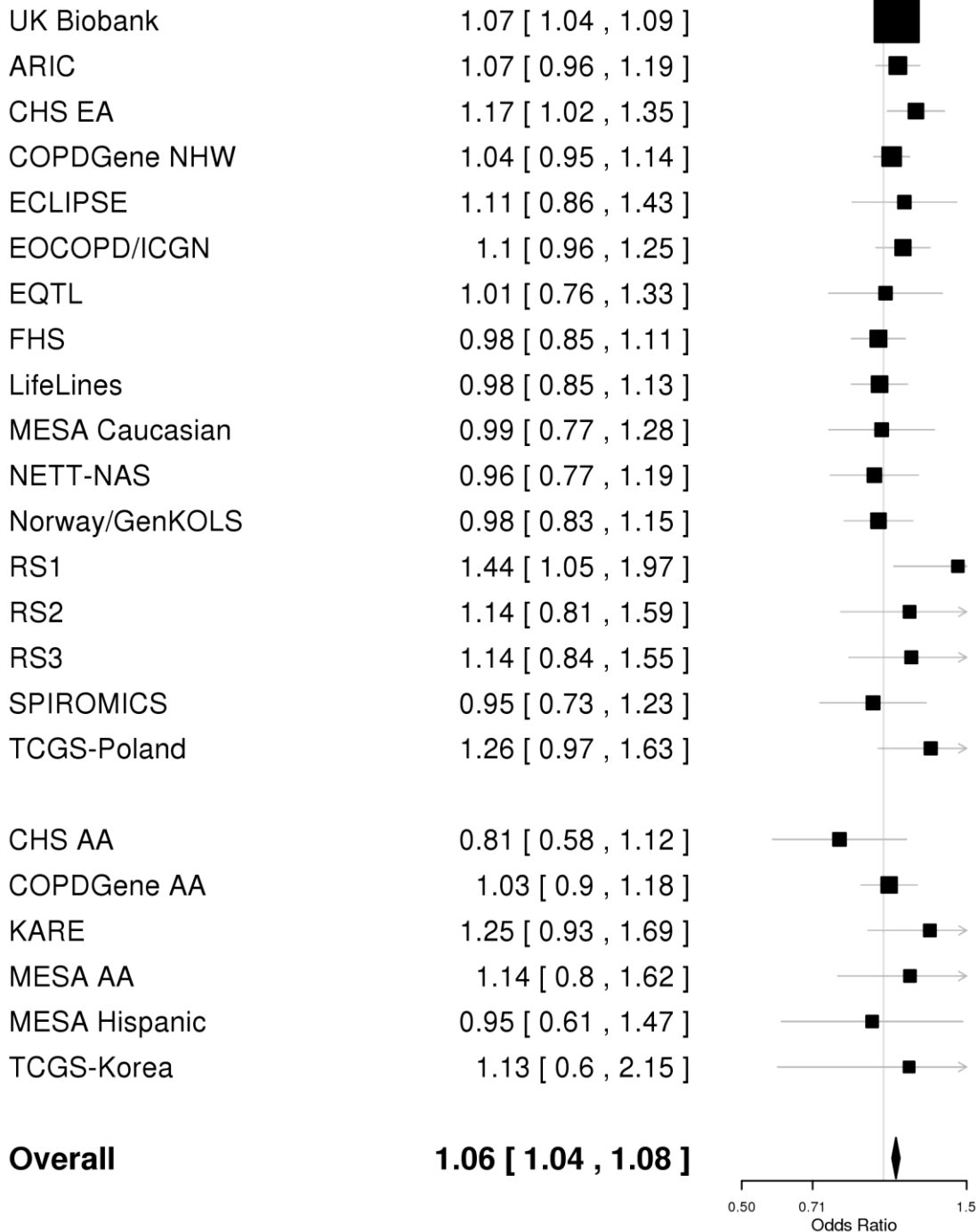
Supplementary Figure 1-26: Forest plot for rs7671261 (*FAM13A* locus at 4q22.1)**4:89883818:A/G rs7671261**

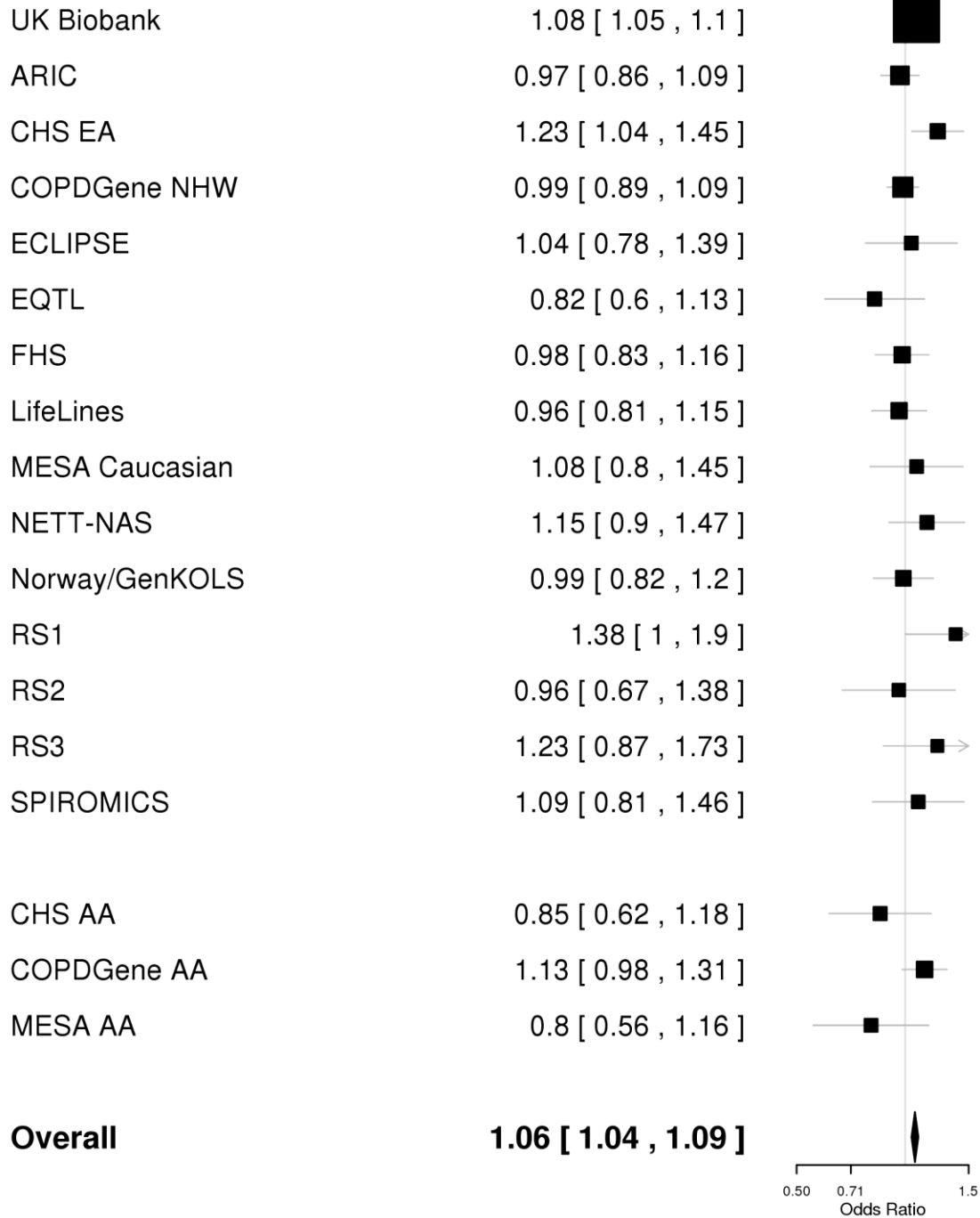
Supplementary Figure 1-27: Forest plot for rs34712979 (*NPNT* locus at 4q24)**4:106819053:A/G rs34712979**

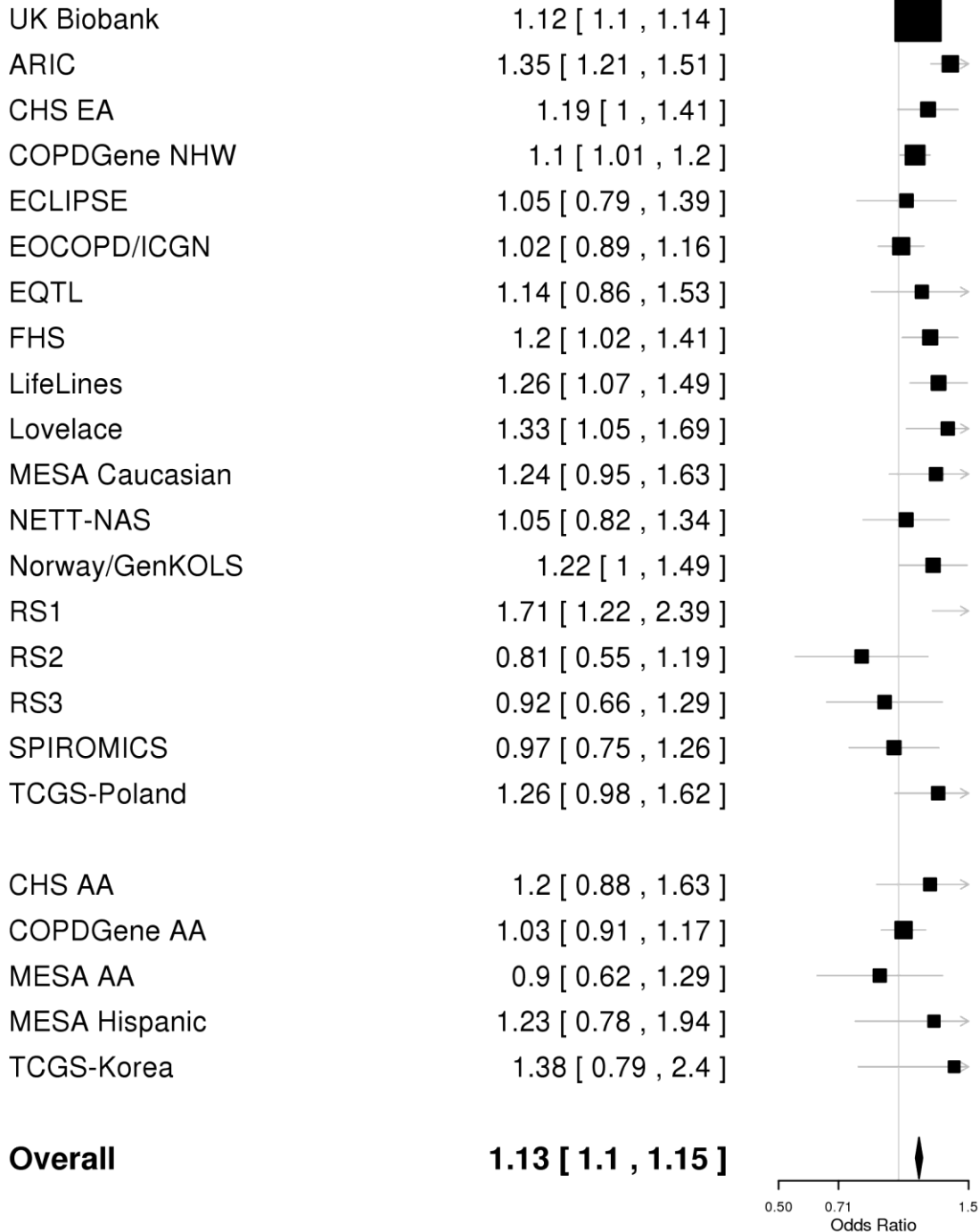
Supplementary Figure 1-28: Forest plot for rs13140176 (*HHIP* locus at 4q31.21)**4:145489098:A/G rs13140176**

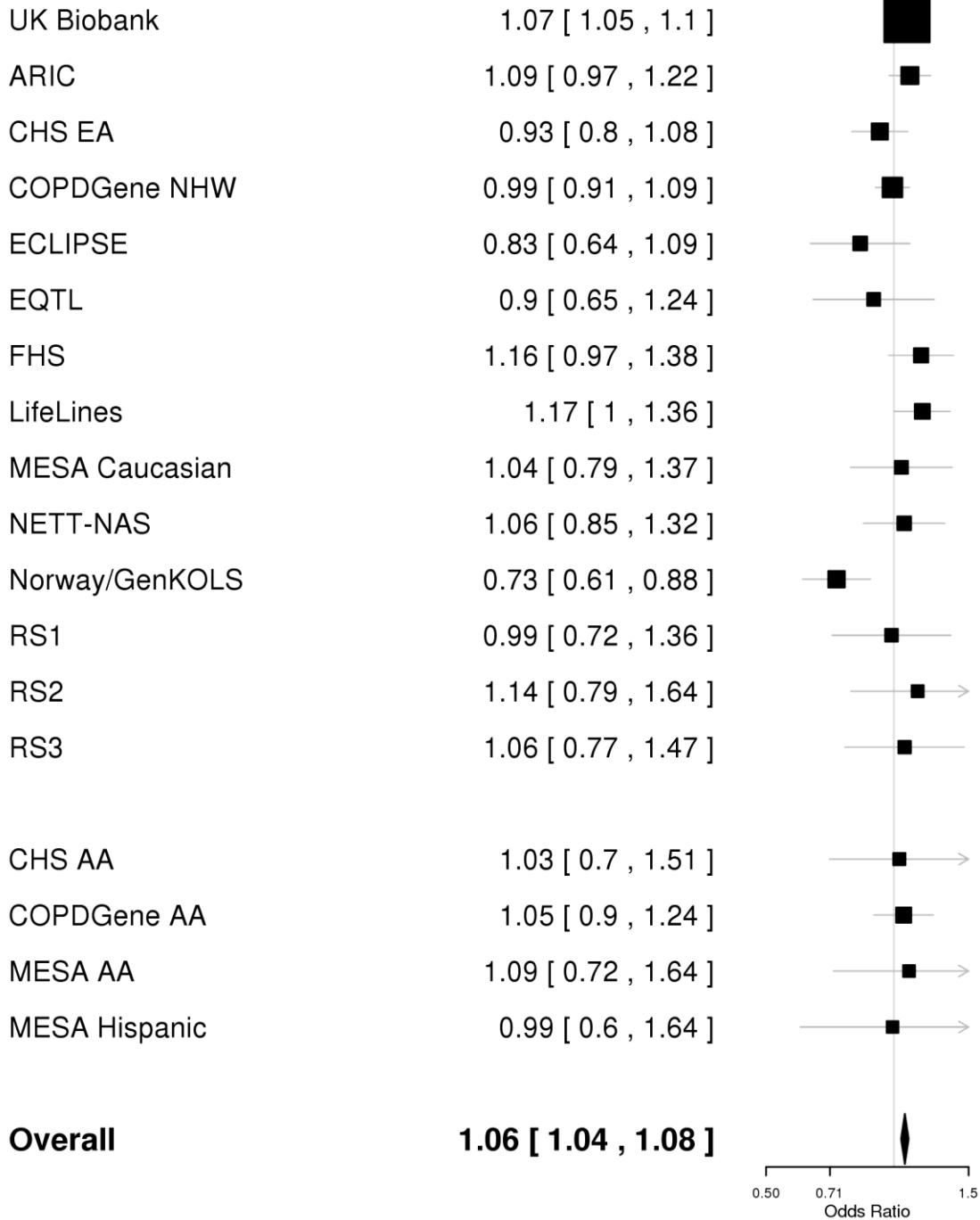
Supplementary Figure 1-29: Forest plot for rs1551943 (*ITGA1* locus at 5q11.2)**5:52195033:A/G rs1551943**

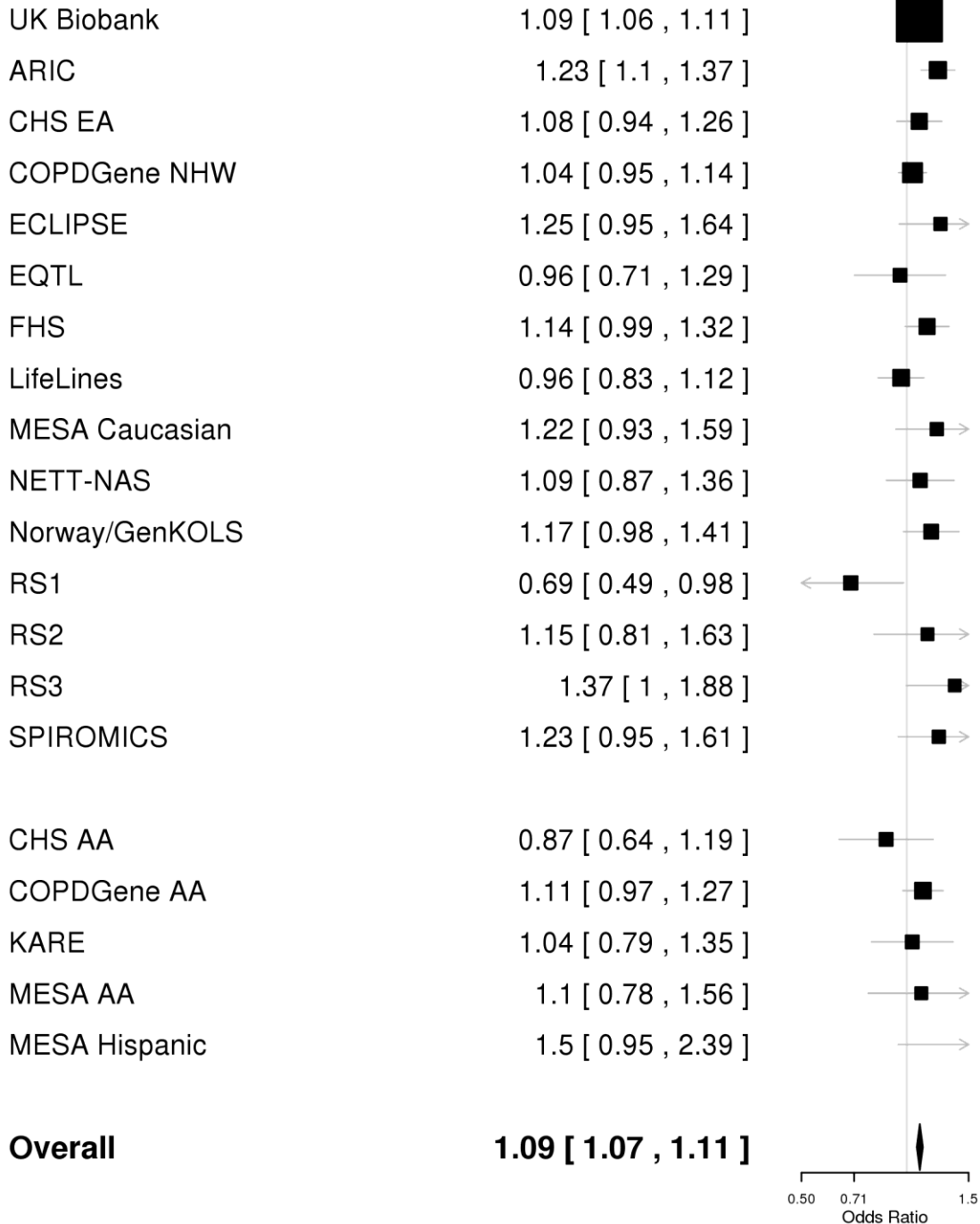
Supplementary Figure 1-30: Forest plot for rs34651 (*TNPO1* locus at 5q13.2)**5:72144005:C/T rs34651**

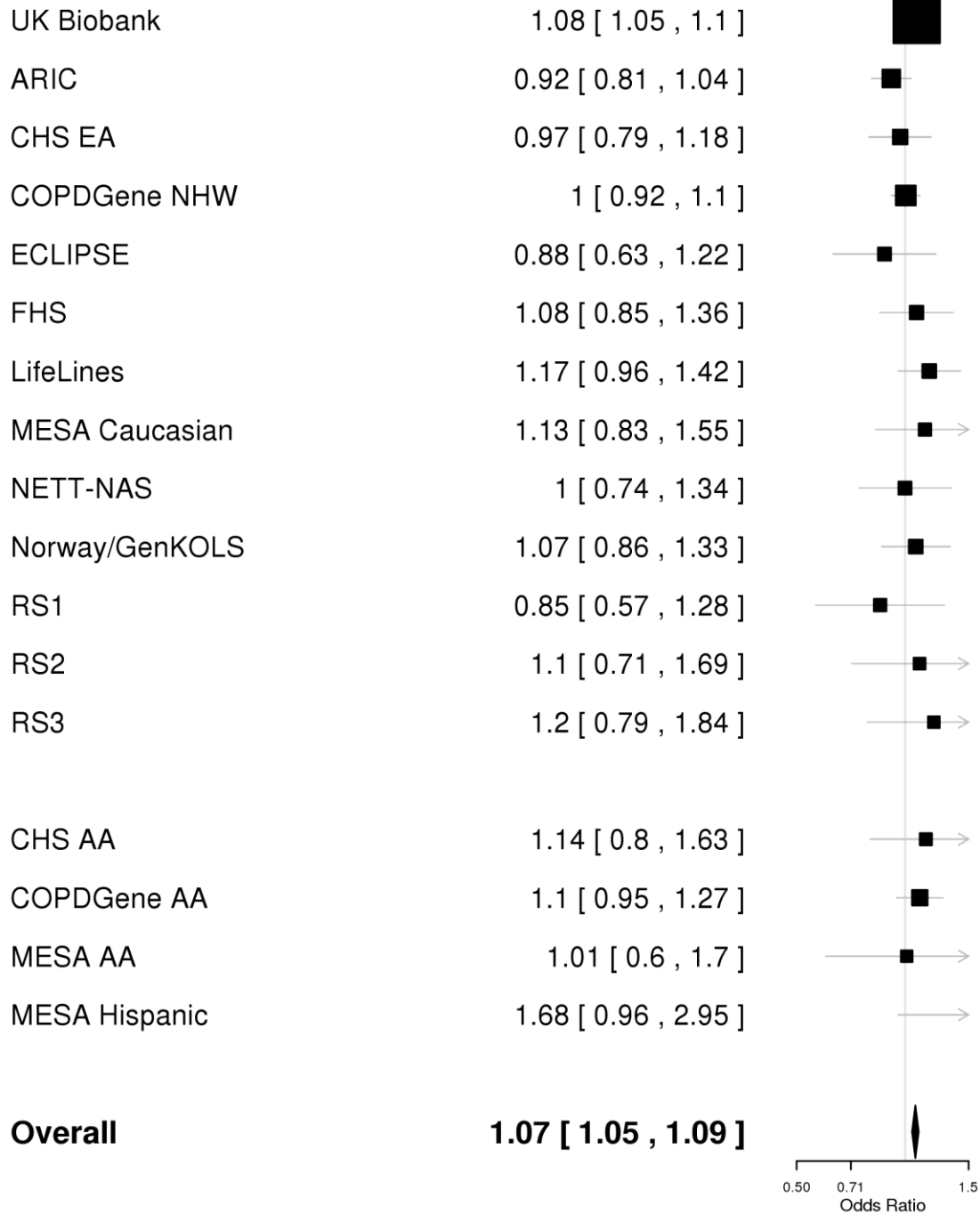
Supplementary Figure 1-31: Forest plot for rs153916 (*SPATA9* locus at 5q15)**5:95036700:T/C rs153916**

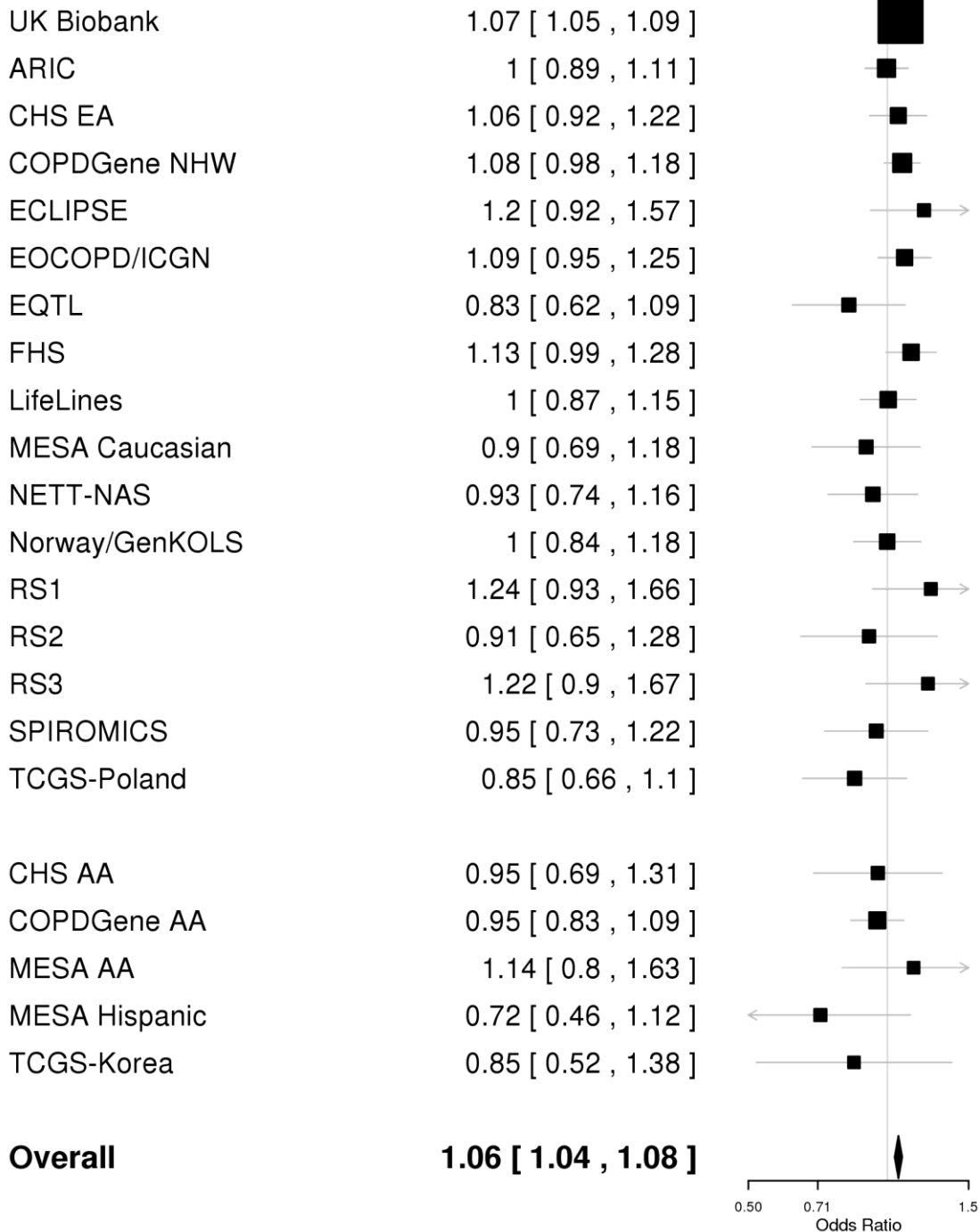
Supplementary Figure 1-32: Forest plot for rs62375246 (*HSPA4* locus at 5q31.1)**5:132439010:A/T rs62375246**

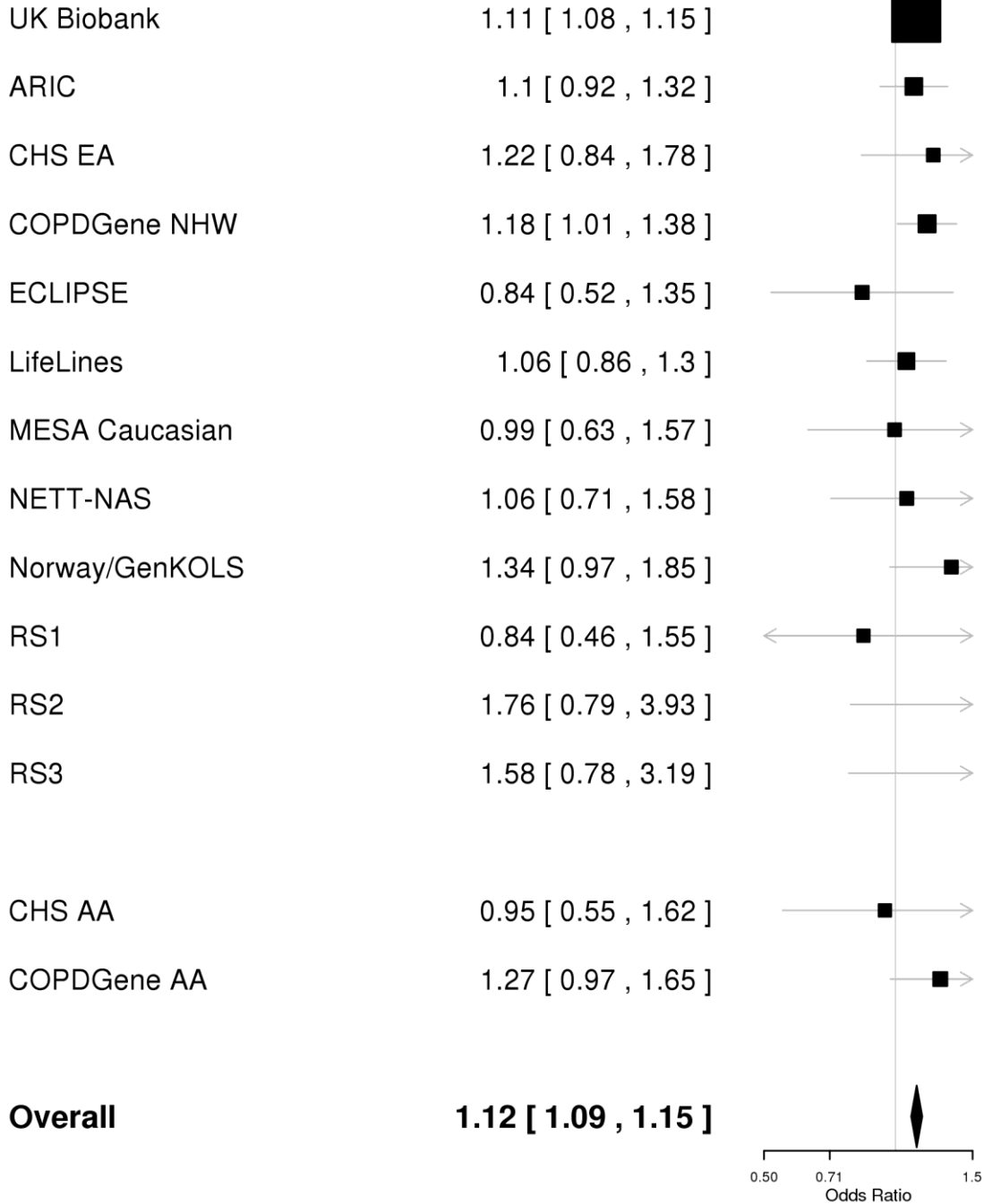
Supplementary Figure 1-33: Forest plot for rs10037493 (*HTR4* locus at 5q32)**5:147854970:C/T rs10037493**

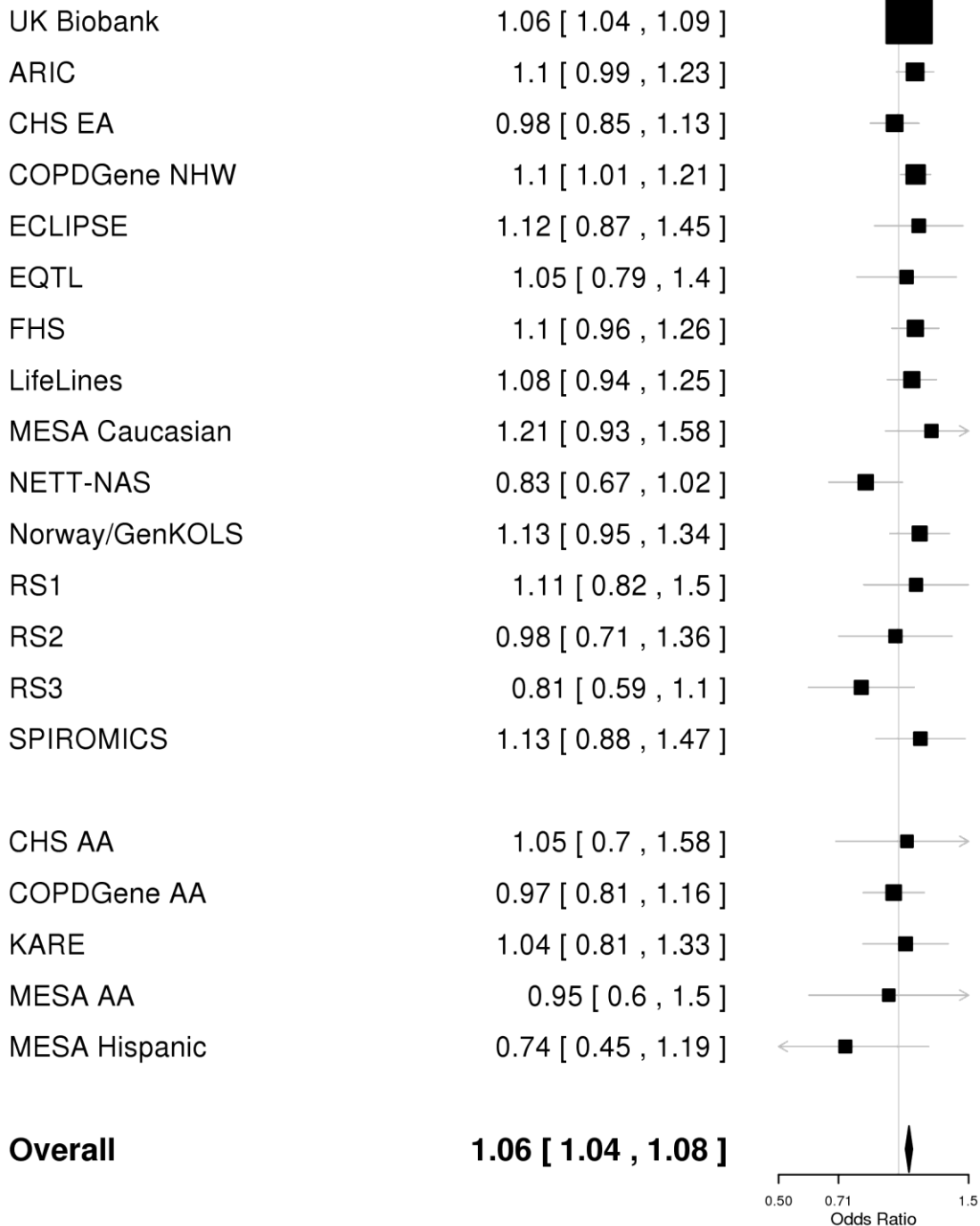
Supplementary Figure 1-34: Forest plot for rs979453 (*CCDC69* locus at 5q33.1)**5:150595073:G/A rs979453**

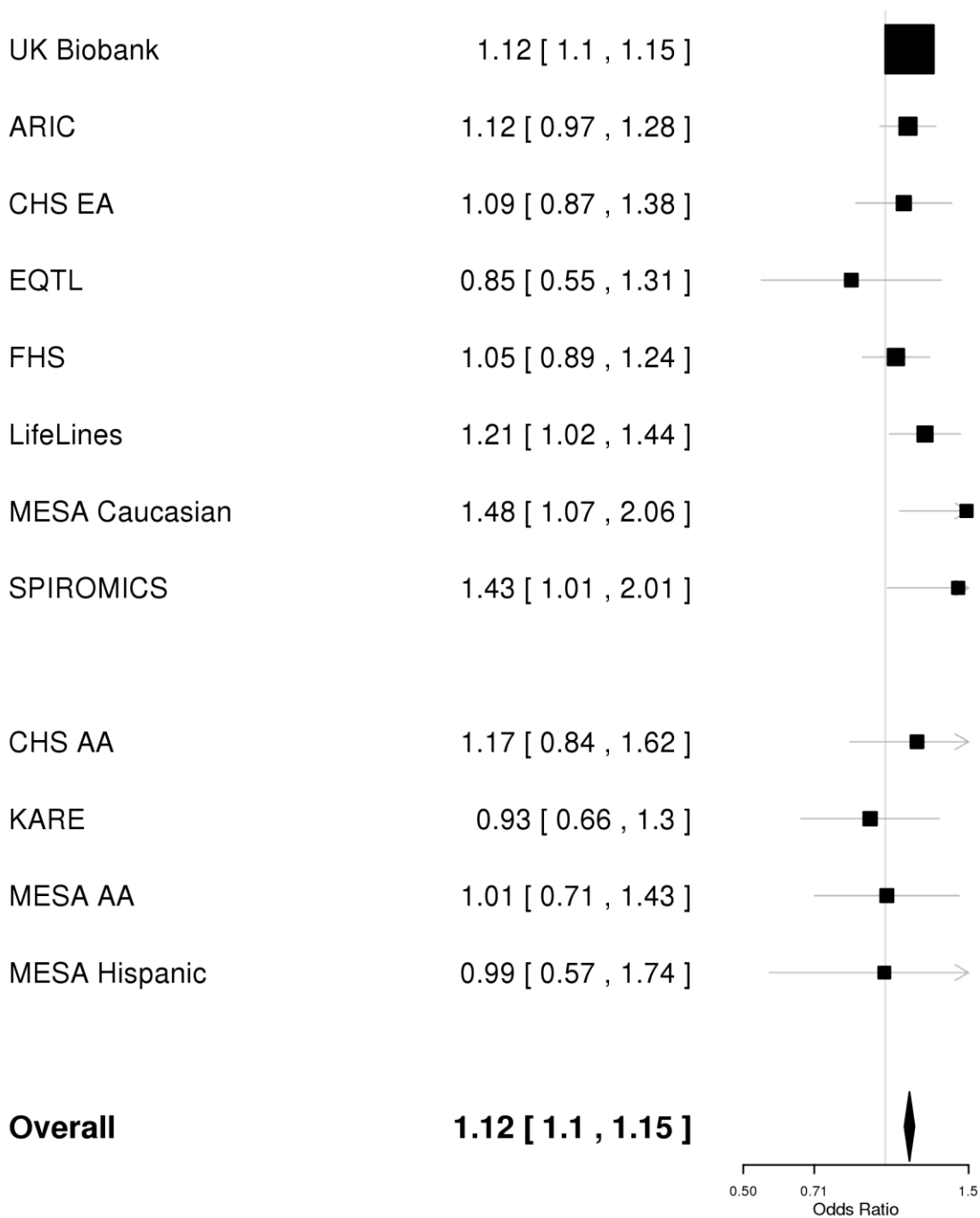
Supplementary Figure 1-35: Forest plot for rs10866659 (*ADAM19* locus at 5q33.3)**5:156937043:G/A rs10866659**

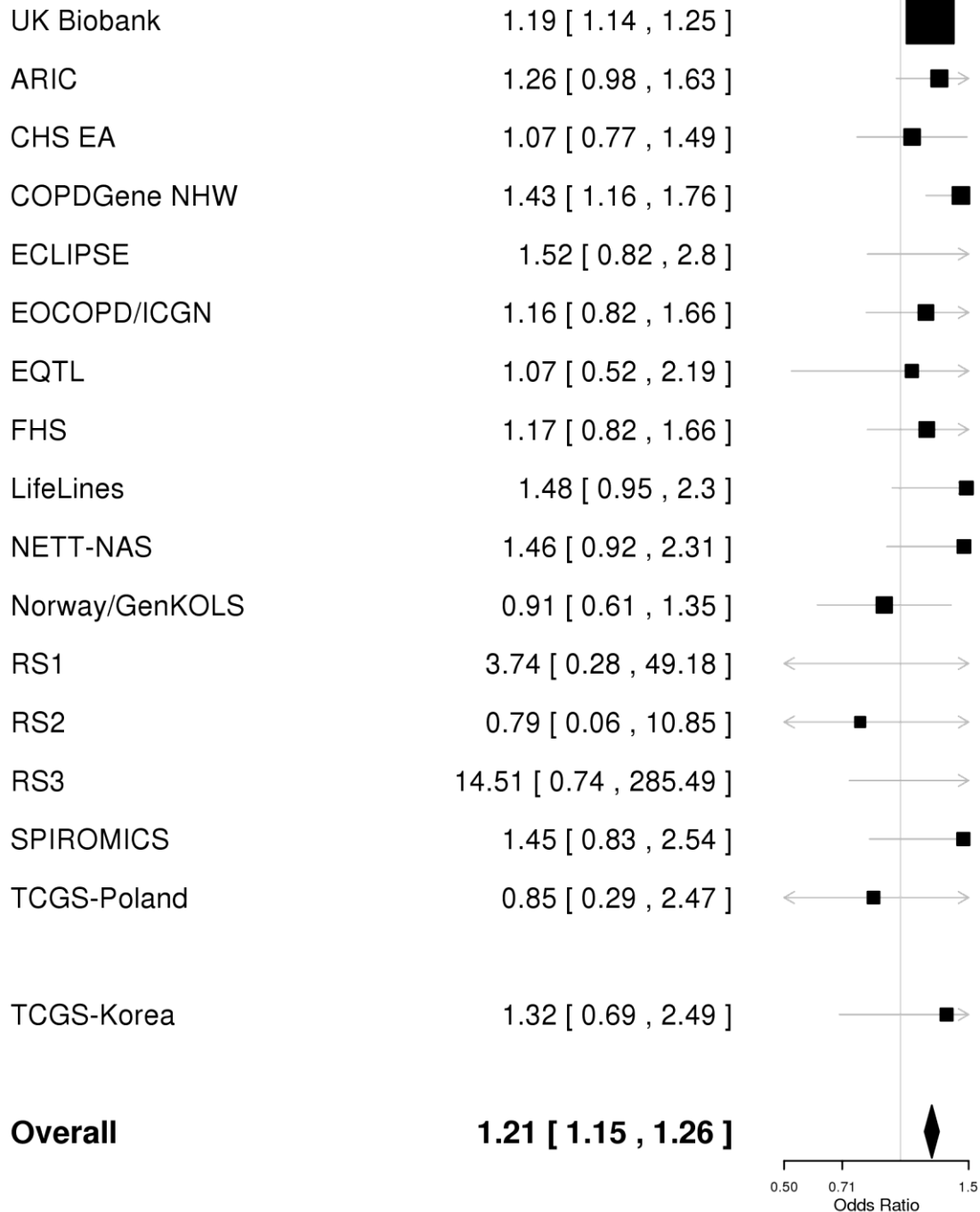
Supplementary Figure 1-36: Forest plot for rs12519165 (*FGF18* locus at 5q35.1)**5:170901586:A/T rs12519165**

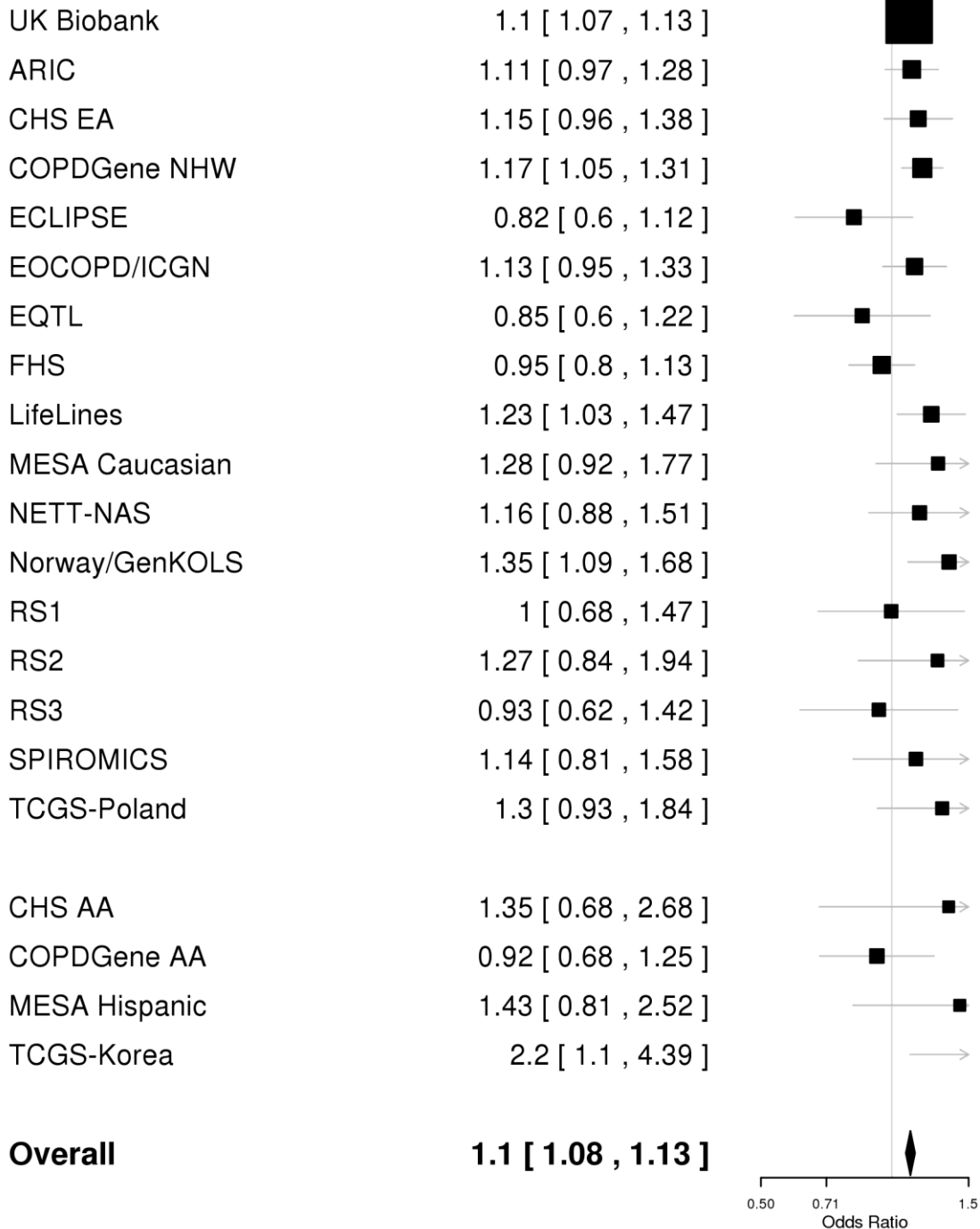
Supplementary Figure 1-37: Forest plot for rs1334576 (*RREB1* locus at 6p24.3)**6:7211818:A/G rs1334576**

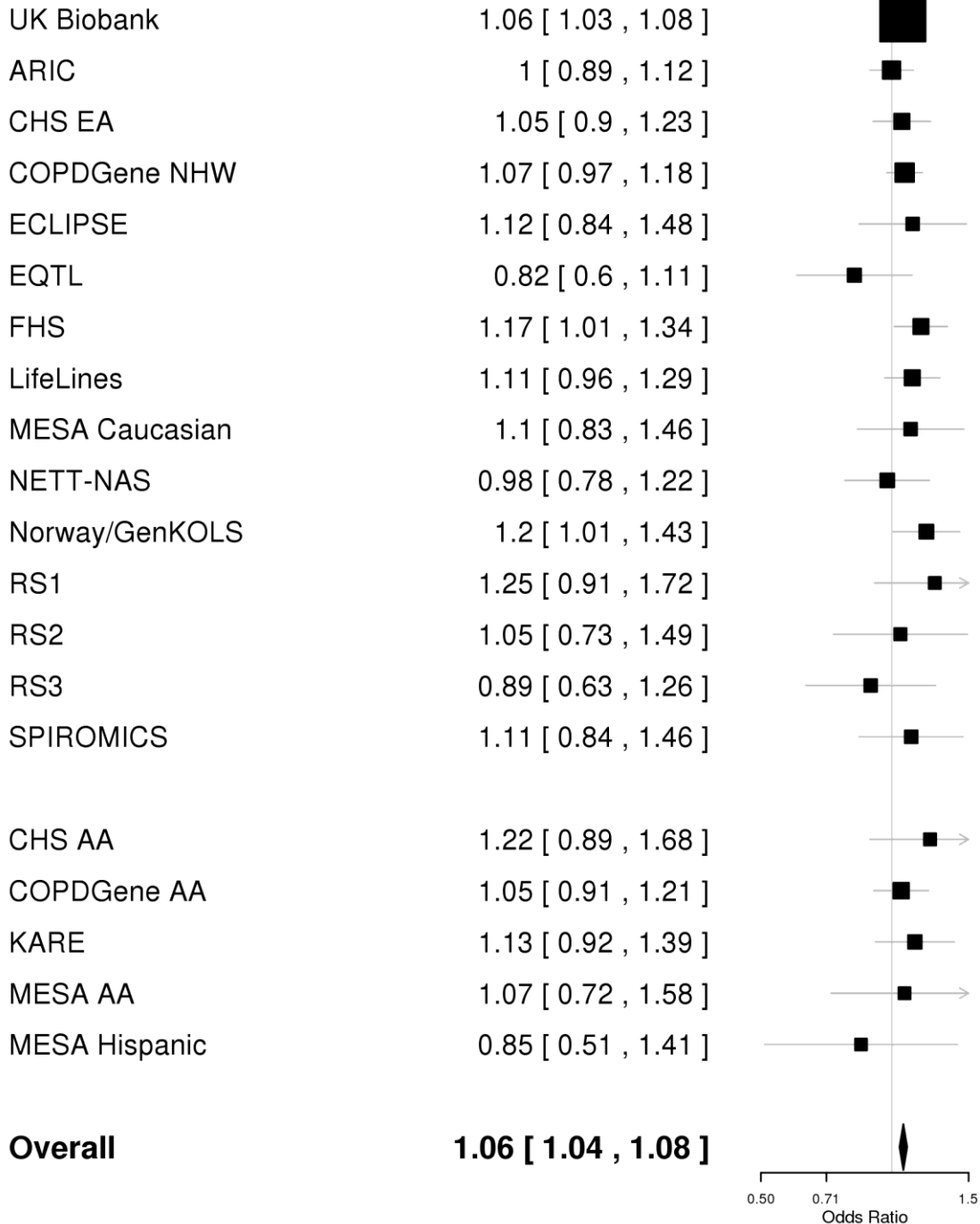
Supplementary Figure 1-38: Forest plot for rs9350191 (*ID4* locus at 6p22.3)**6:19842661:T/C rs9350191**

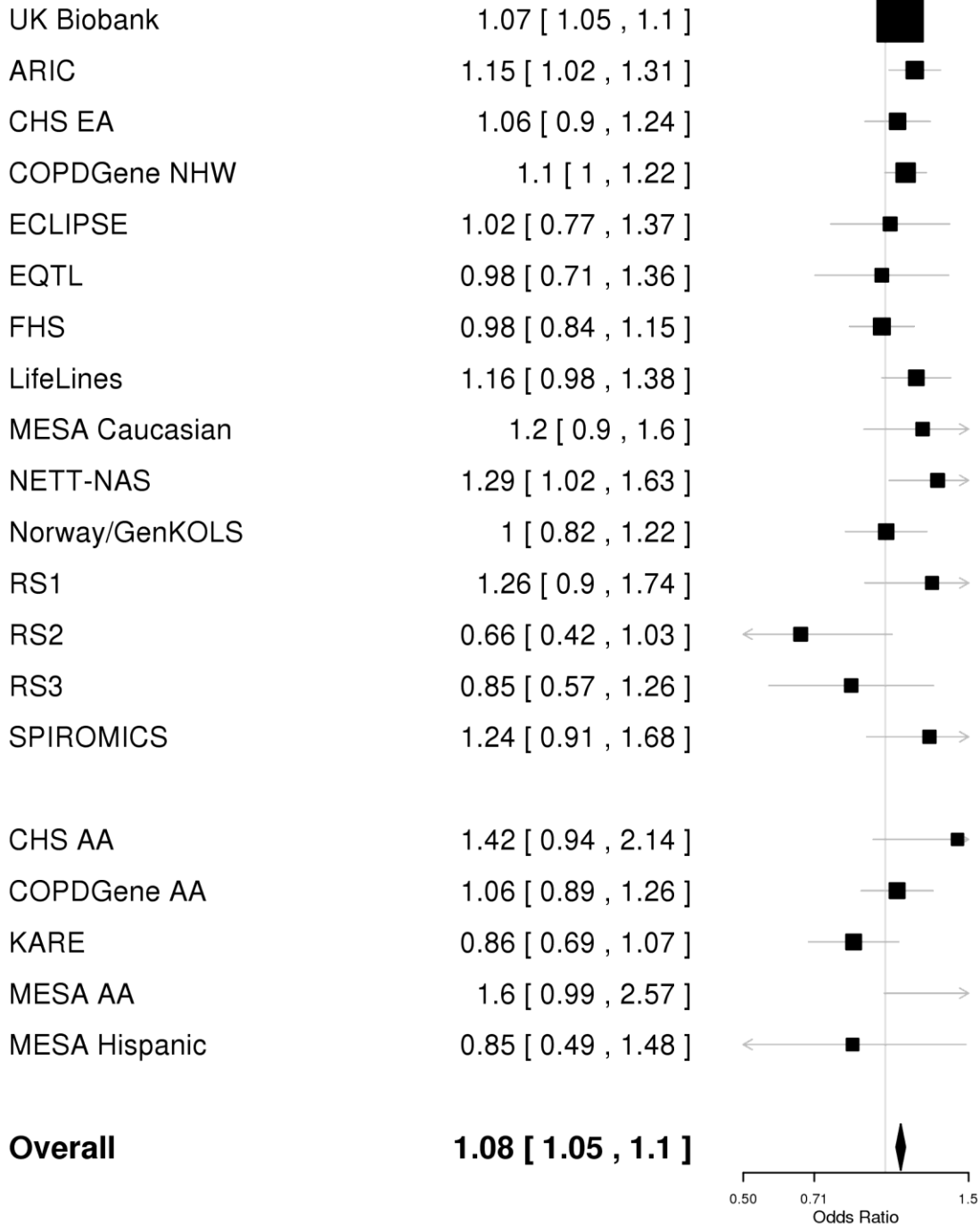
Supplementary Figure 1-39: Forest plot for rs13198656 (*PRL* locus at 6p22.3)**6:22004909:T/C rs13198656**

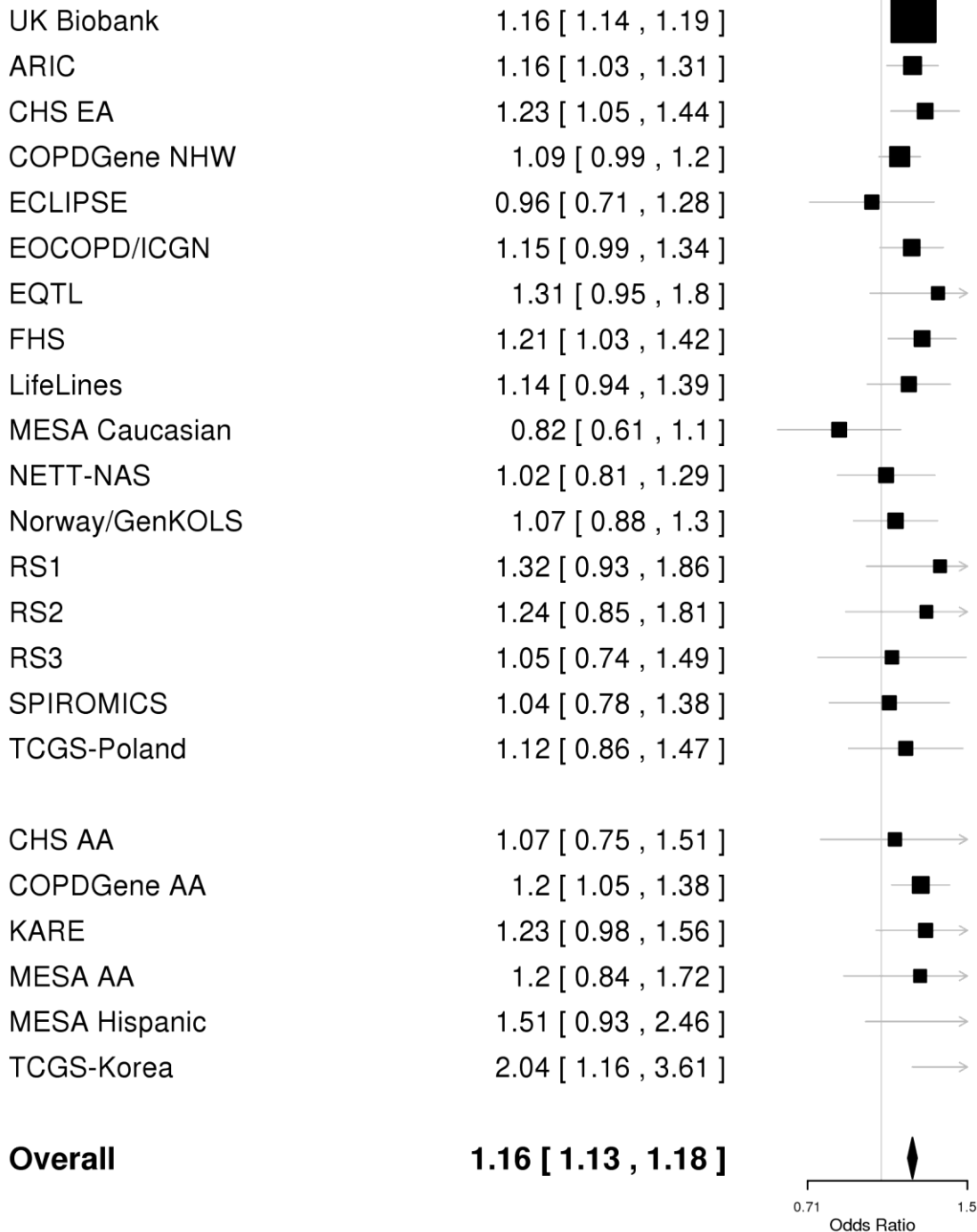
Supplementary Figure 1-40: Forest plot for rs2284174 (*IER3* locus at 6p21.33)**6:30713580:C/T rs2284174**

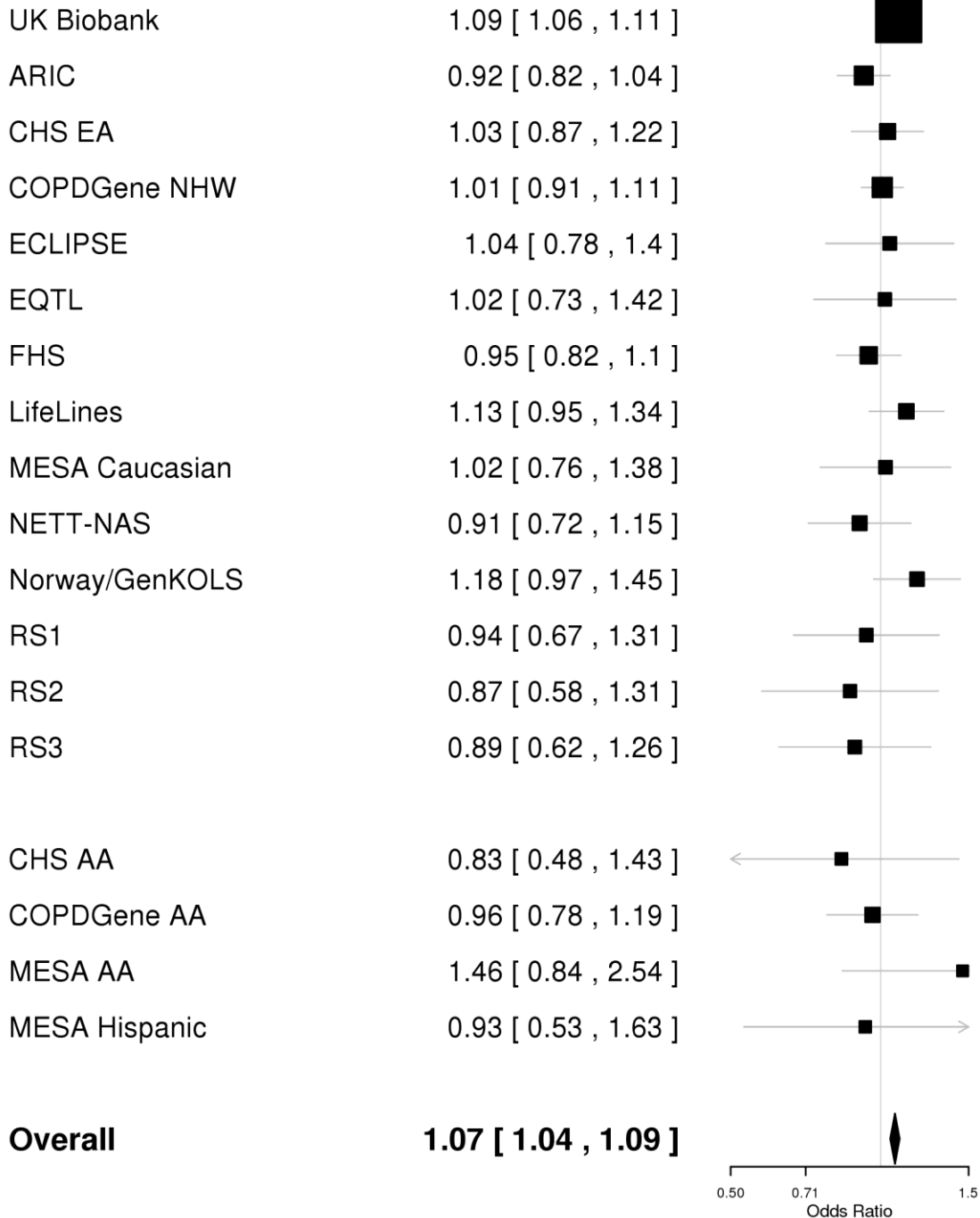
Supplementary Figure 1-41: Forest plot for rs2070600 (*AGER* locus at 6p21.32)**6:32151443:C/T rs2070600**

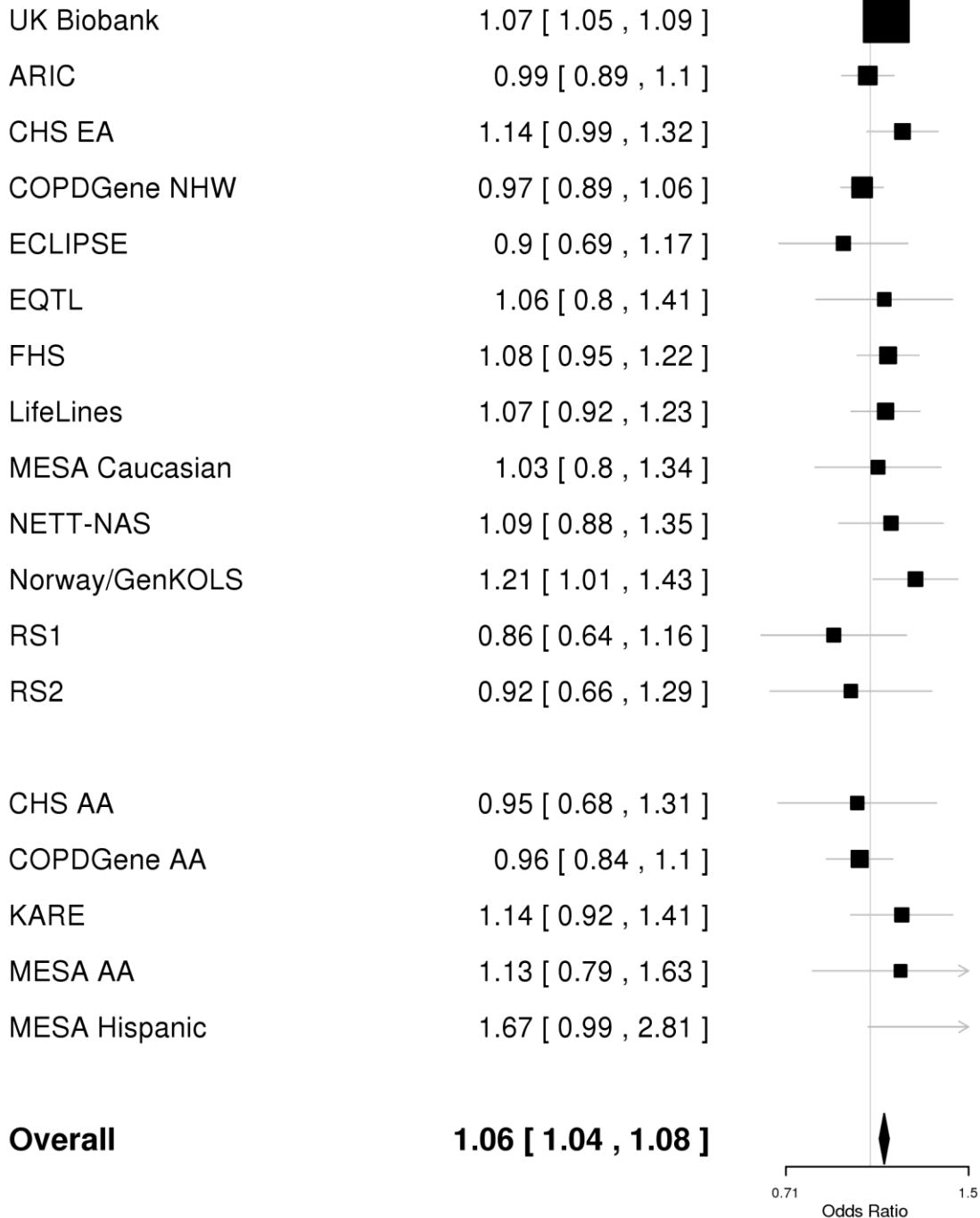
Supplementary Figure 1-42: Forest plot for rs2806356 (*ARMC2* locus at 6q21)**6:109266255:C/T rs2806356**

Supplementary Figure 1-43: Forest plot for rs674621 (*RFX6* locus at 6q22.1)**6:117257018:C/T rs674621**

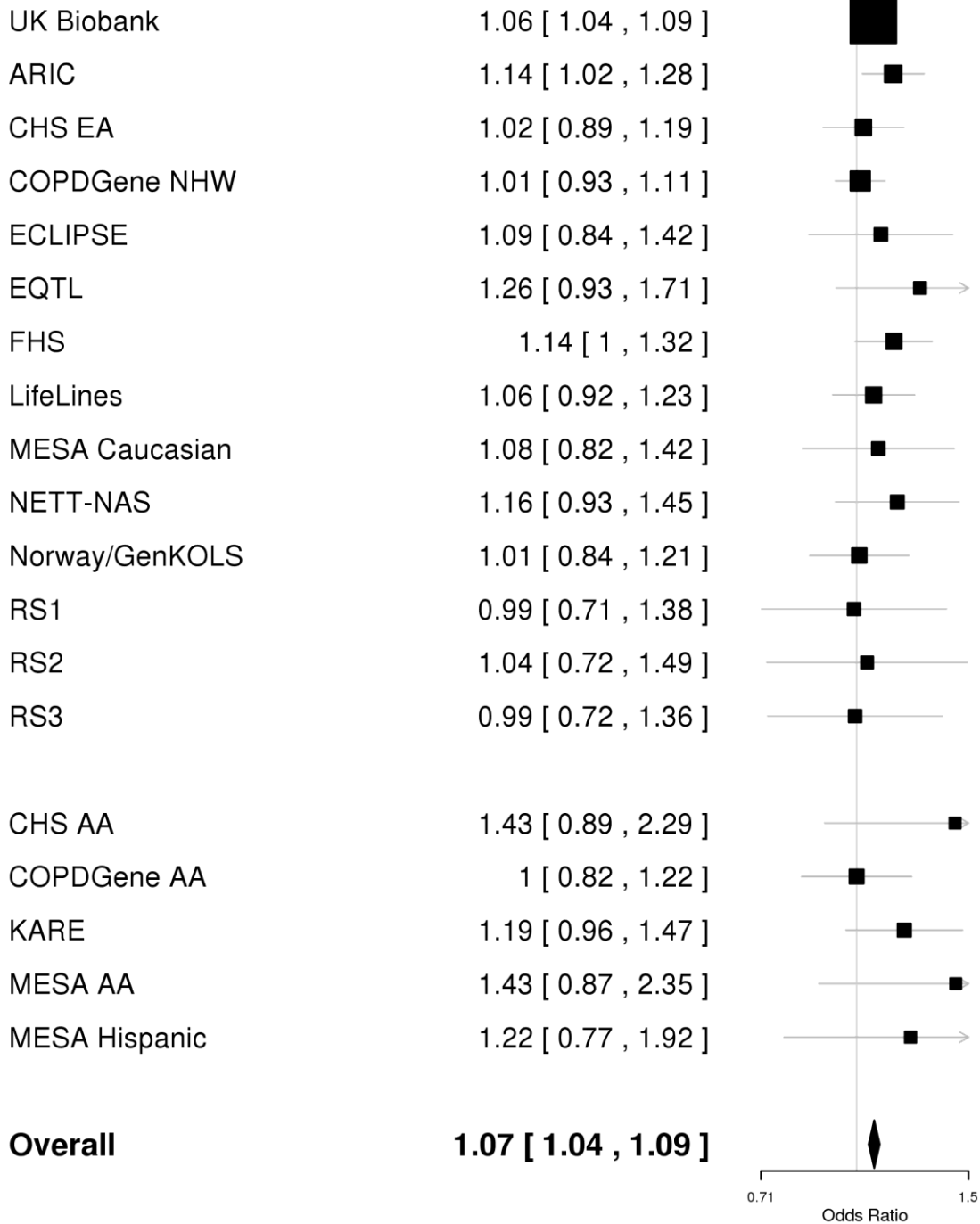
Supplementary Figure 1-44: Forest plot for rs646695 (*CITED2* locus at 6q24.1)**6:140280398:C/T rs646695**

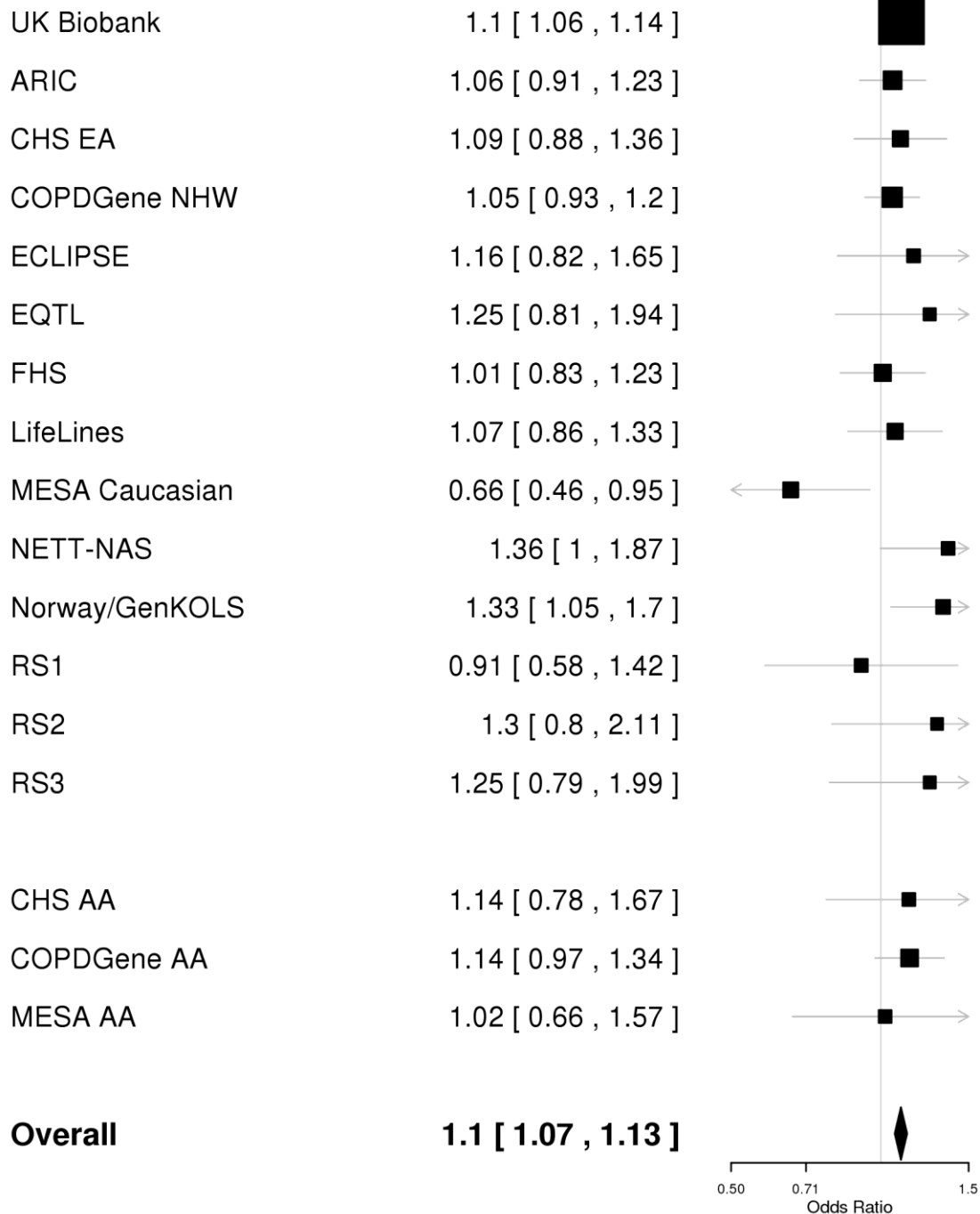
Supplementary Figure 1-45: Forest plot for rs9399401 (*ADGRG6* locus at 6q24.1)**6:142668901:T/C rs9399401**

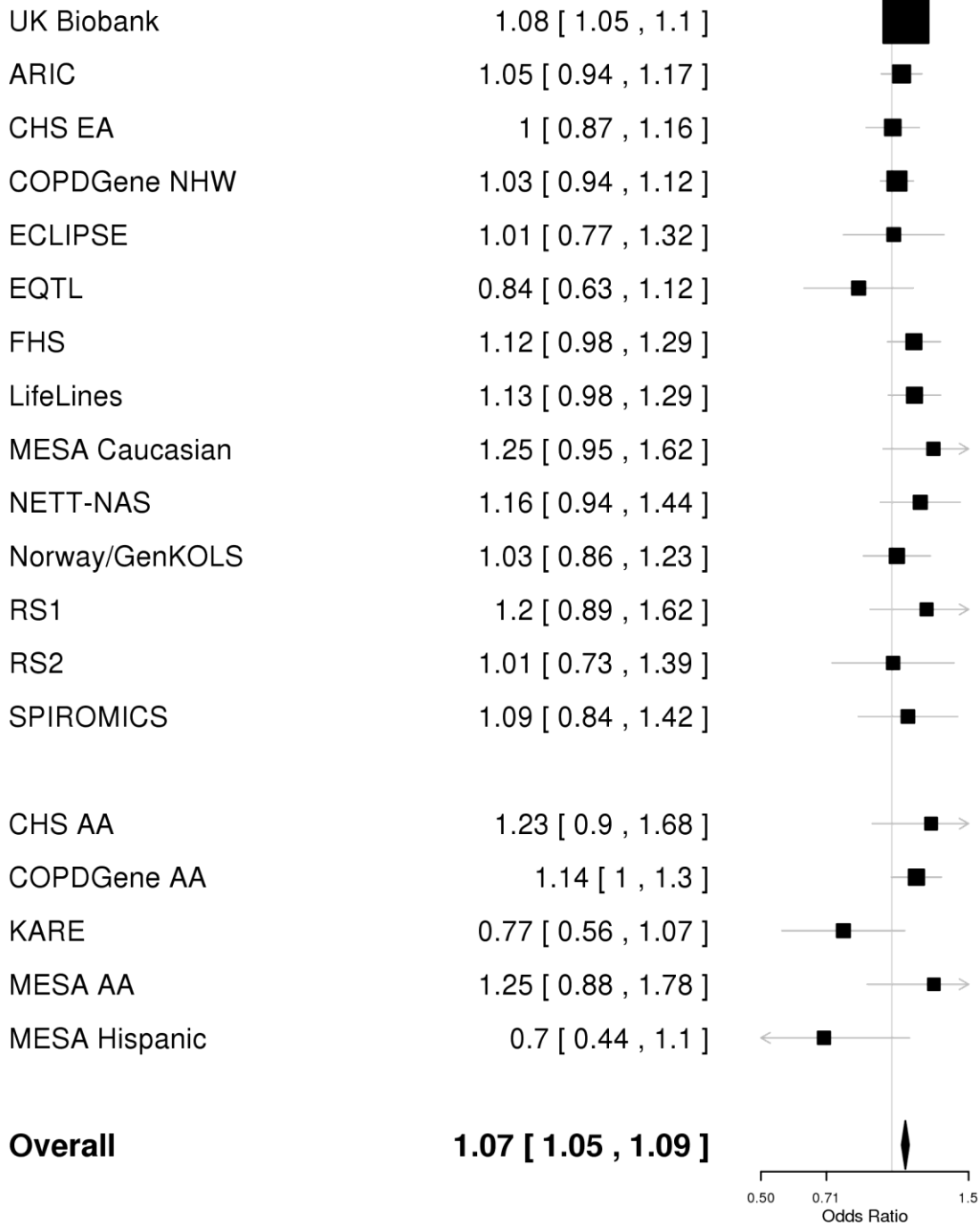
Supplementary Figure 1-46: Forest plot for rs798565 (*AMZ1* locus at 7p22.3)**7:2752152:G/A rs798565**

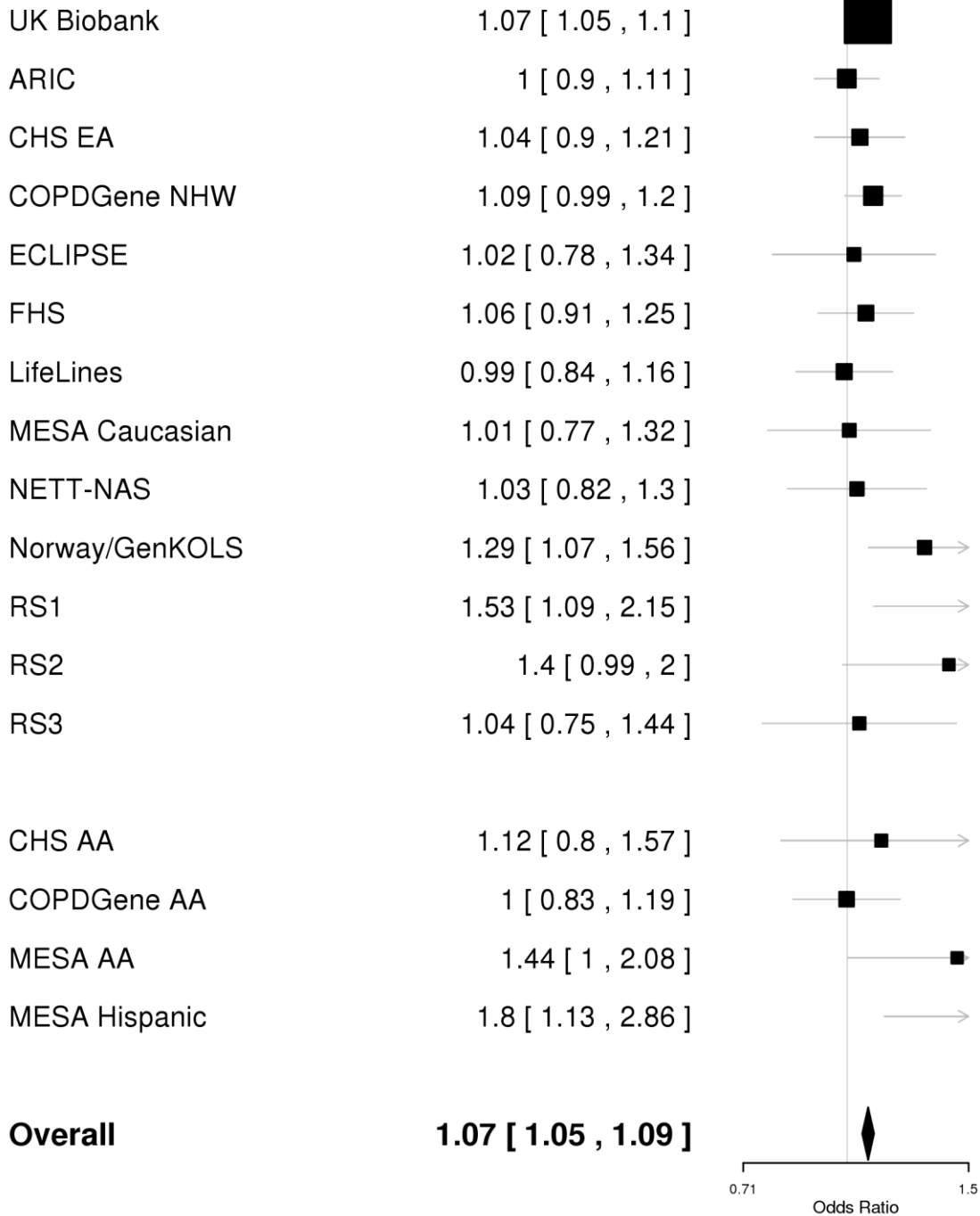
Supplementary Figure 1-47: Forest plot for rs2040732 (*ITGB8* locus at 7p21.1)**7:20418134:C/T rs2040732**

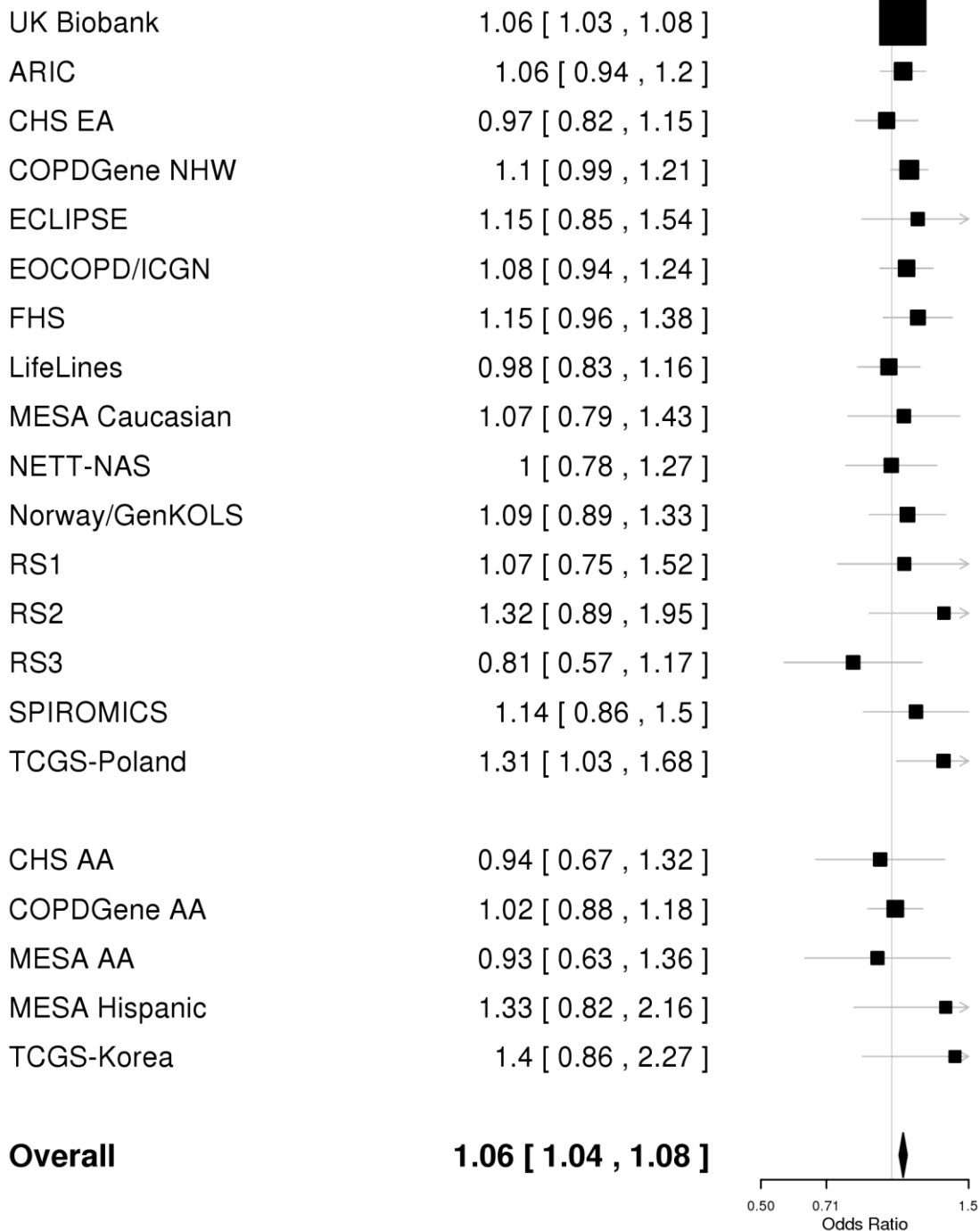
Supplementary Figure 1-48: Forest plot for rs2897075 (ZKSCAN1 locus at 7q22.1)

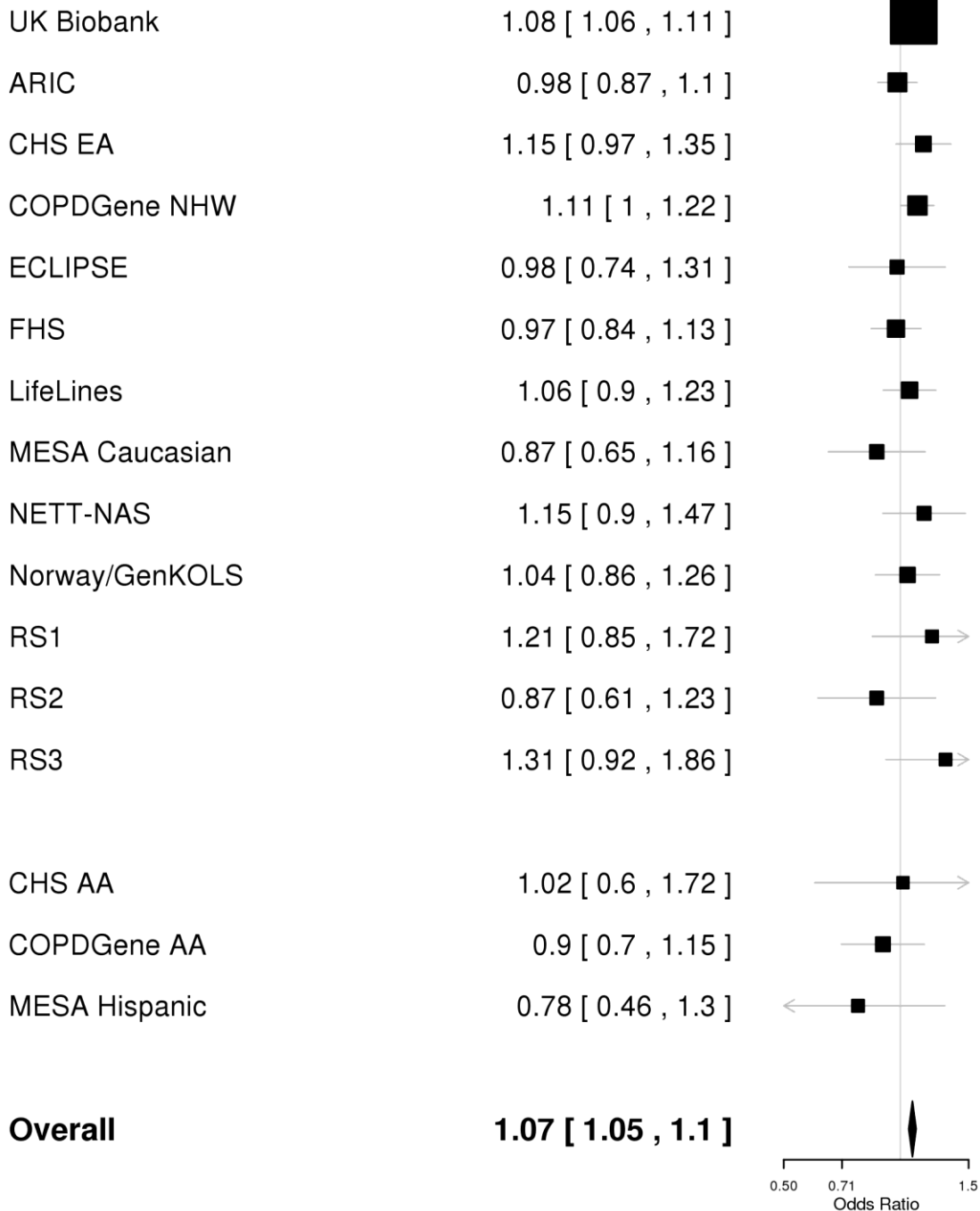
7:99630342:C/T rs2897075

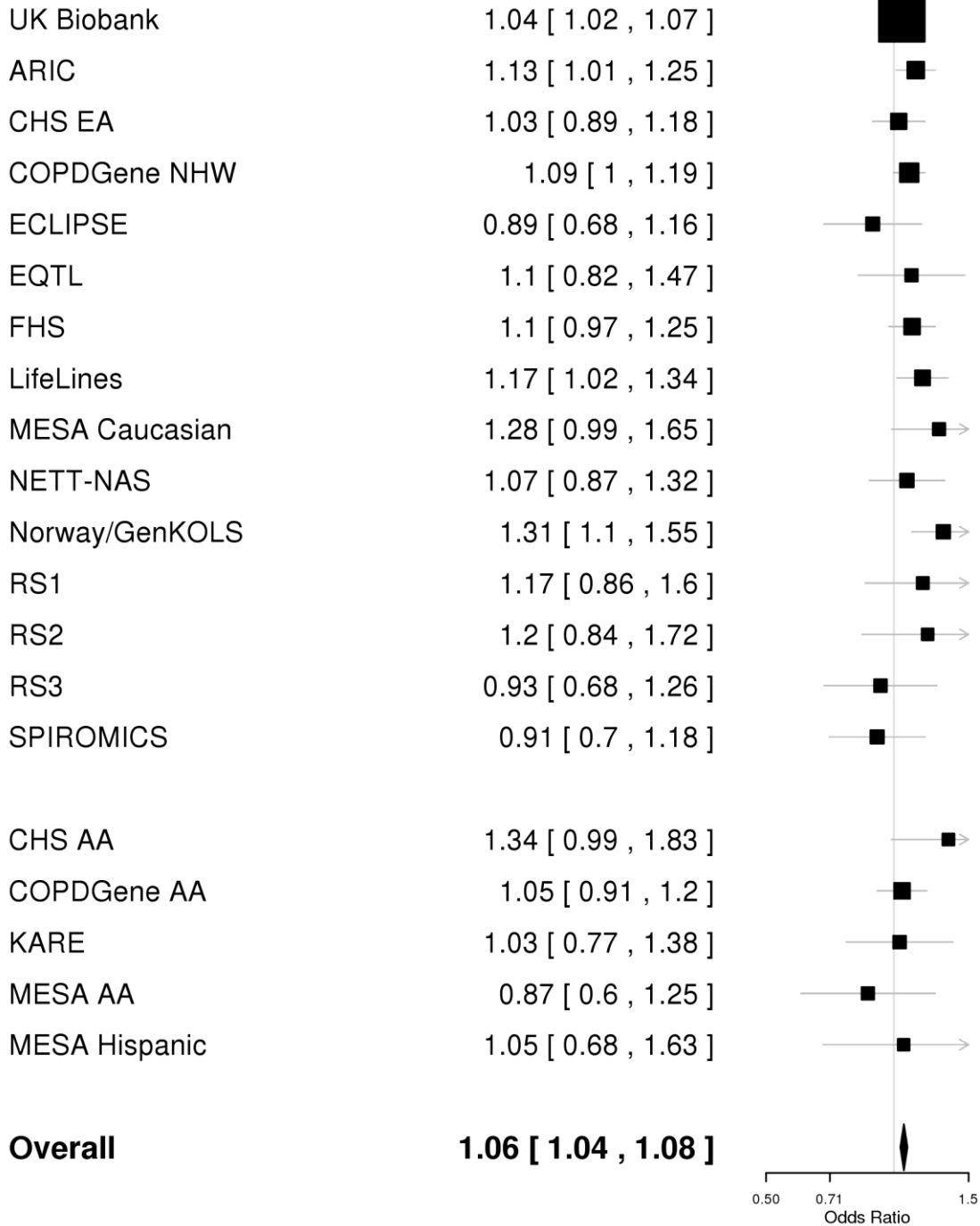
Supplementary Figure 1-49: Forest plot for rs9329170 (*MFHAS1* locus at 8p23.1)**8:8697658:C/G rs9329170**

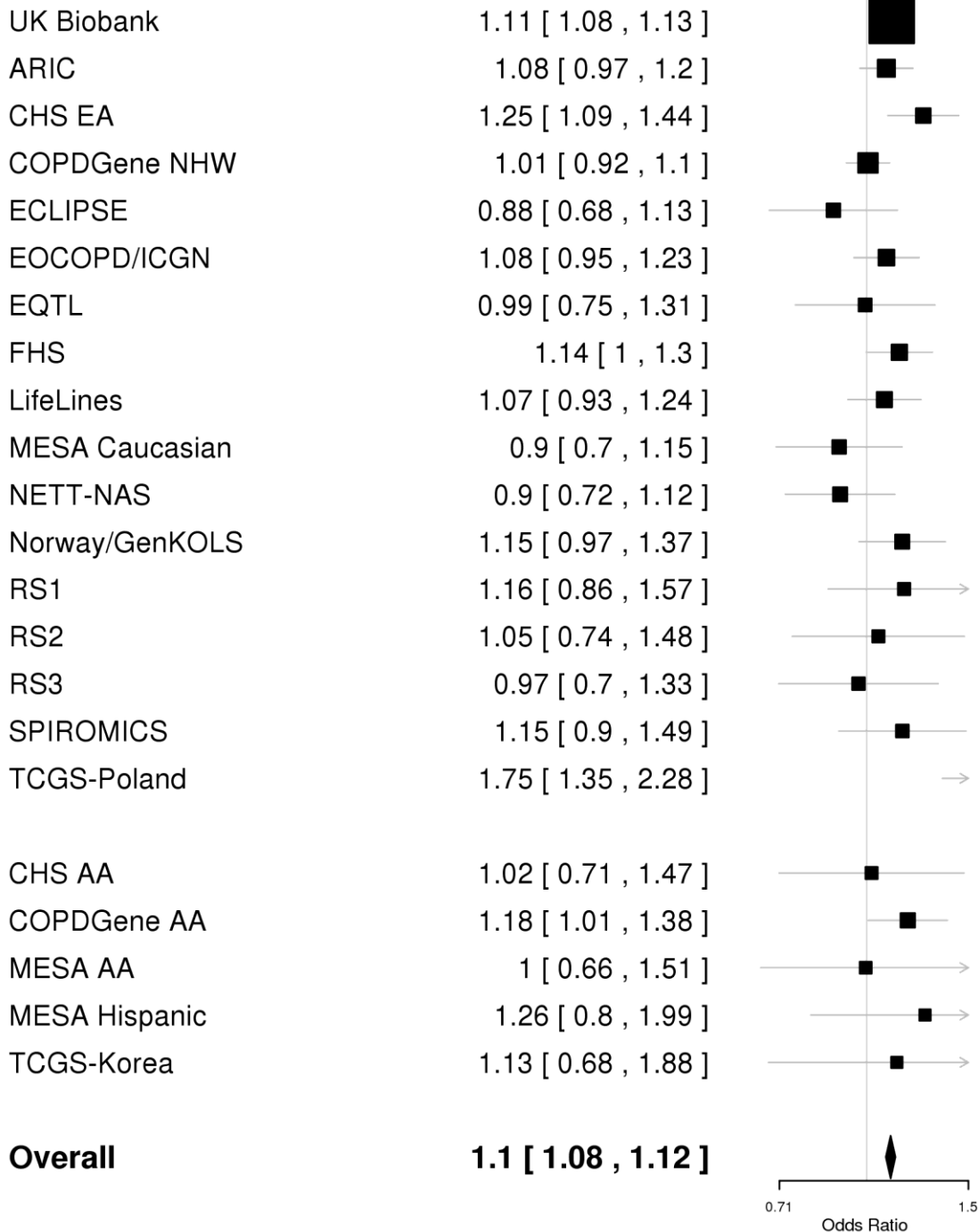
Supplementary Figure 1-50: Forest plot for rs10114763 (*GLIS3* locus at 9p24.2)**9:4143749:T/A rs10114763**

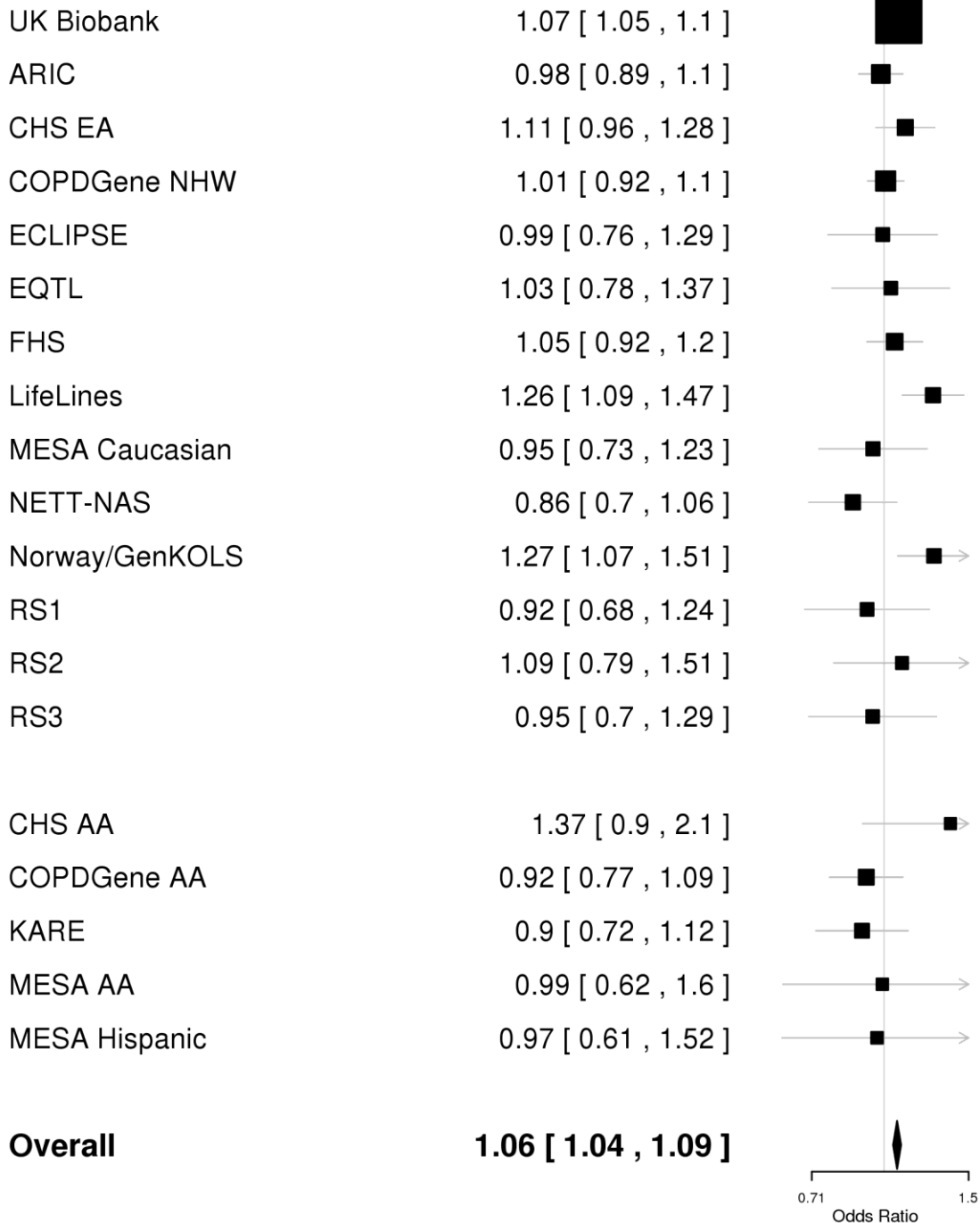
Supplementary Figure 1-51: Forest plot for rs156394 (*ELAVL2* locus at 9p21.3)**9:23588684:T/C rs156394**

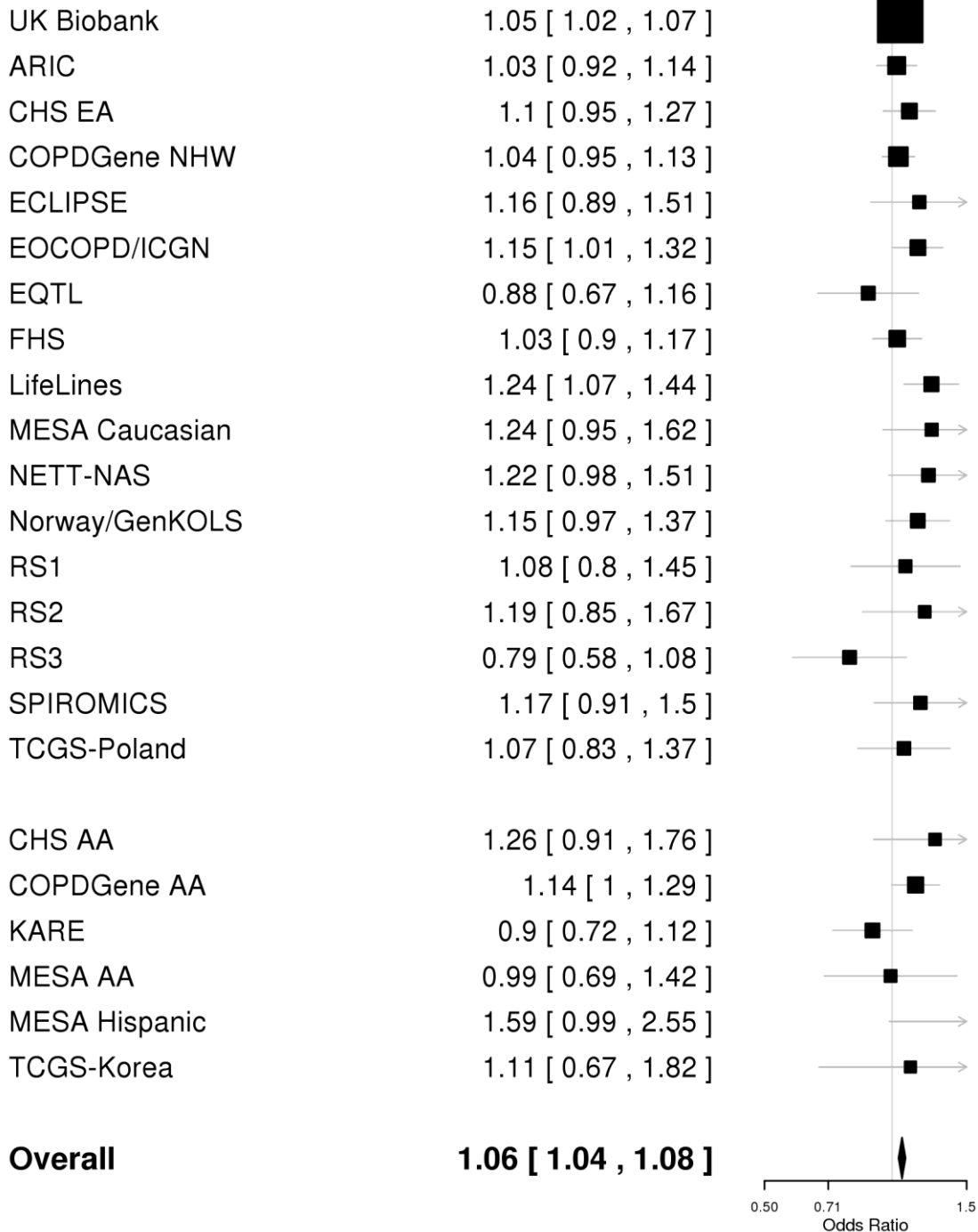
Supplementary Figure 1-52: Forest plot for rs7866939 (*RASEF* locus at 9q21.32)**9:85126163:C/T rs7866939**

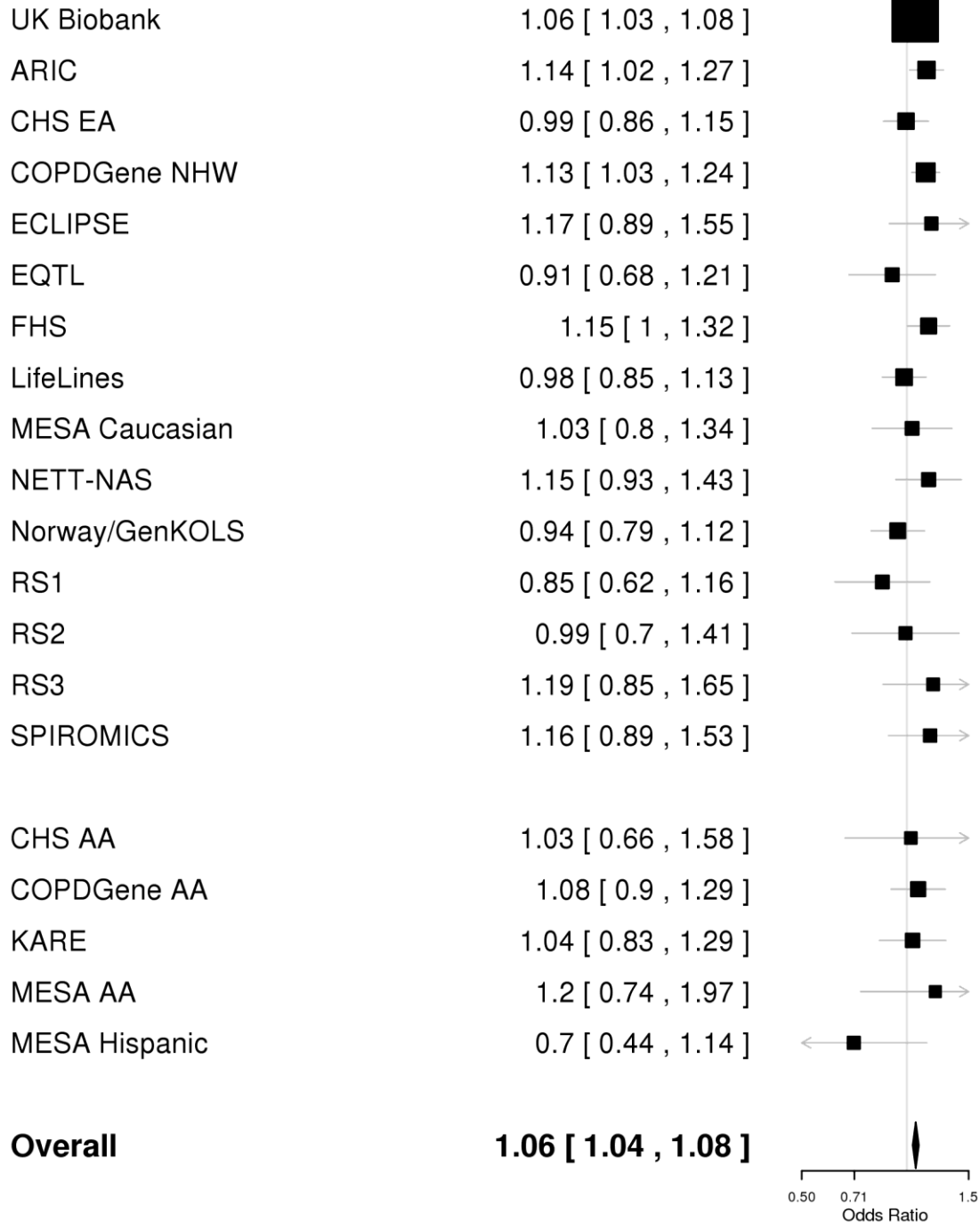
Supplementary Figure 1-53: Forest plot for rs10760580 (*COL15A1* locus at 9q22.33)**9:101661650:G/A rs10760580**

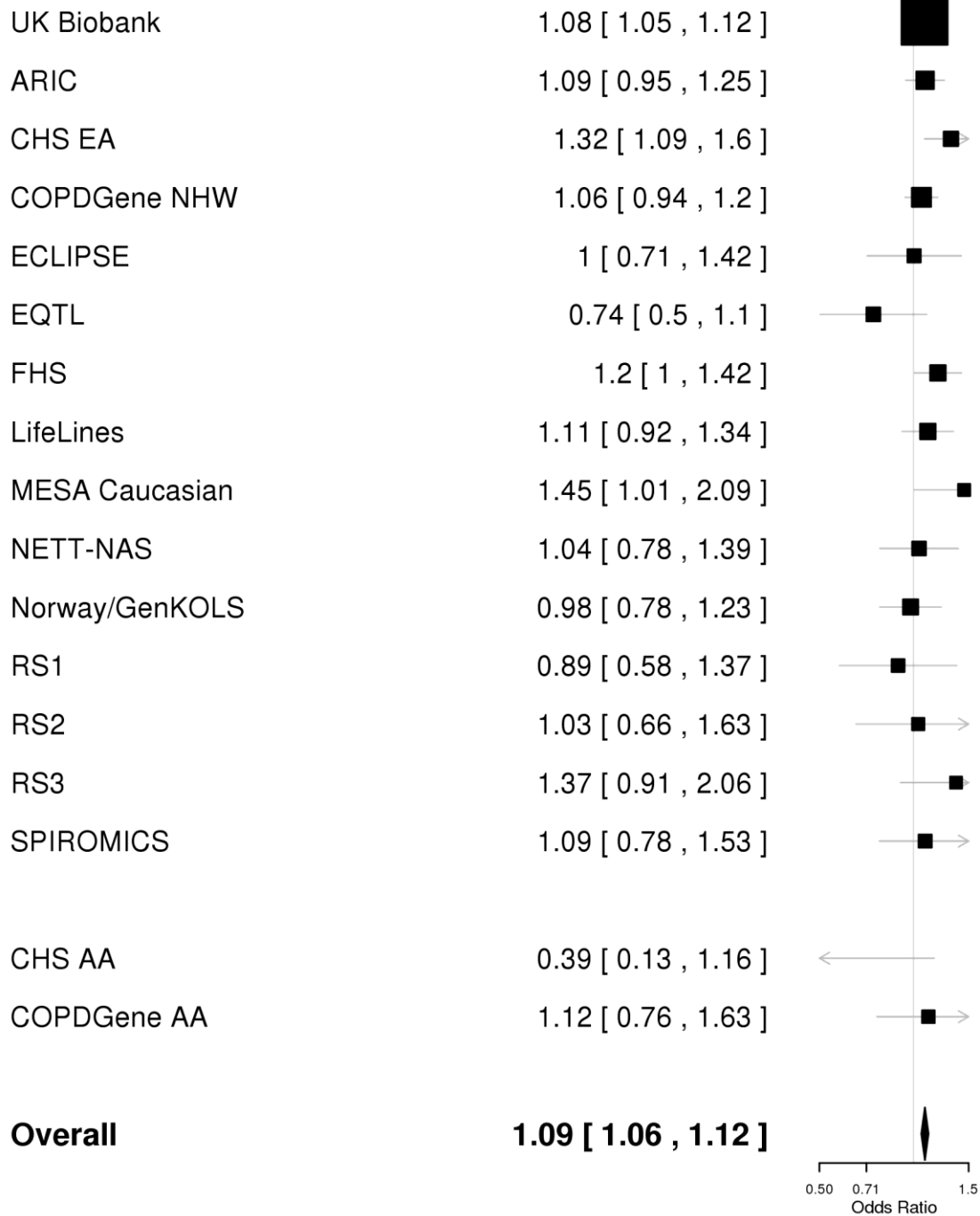
Supplementary Figure 1-54: Forest plot for rs803923 (*ASTN2* locus at 9q33.1)**9:119401650:A/G rs803923**

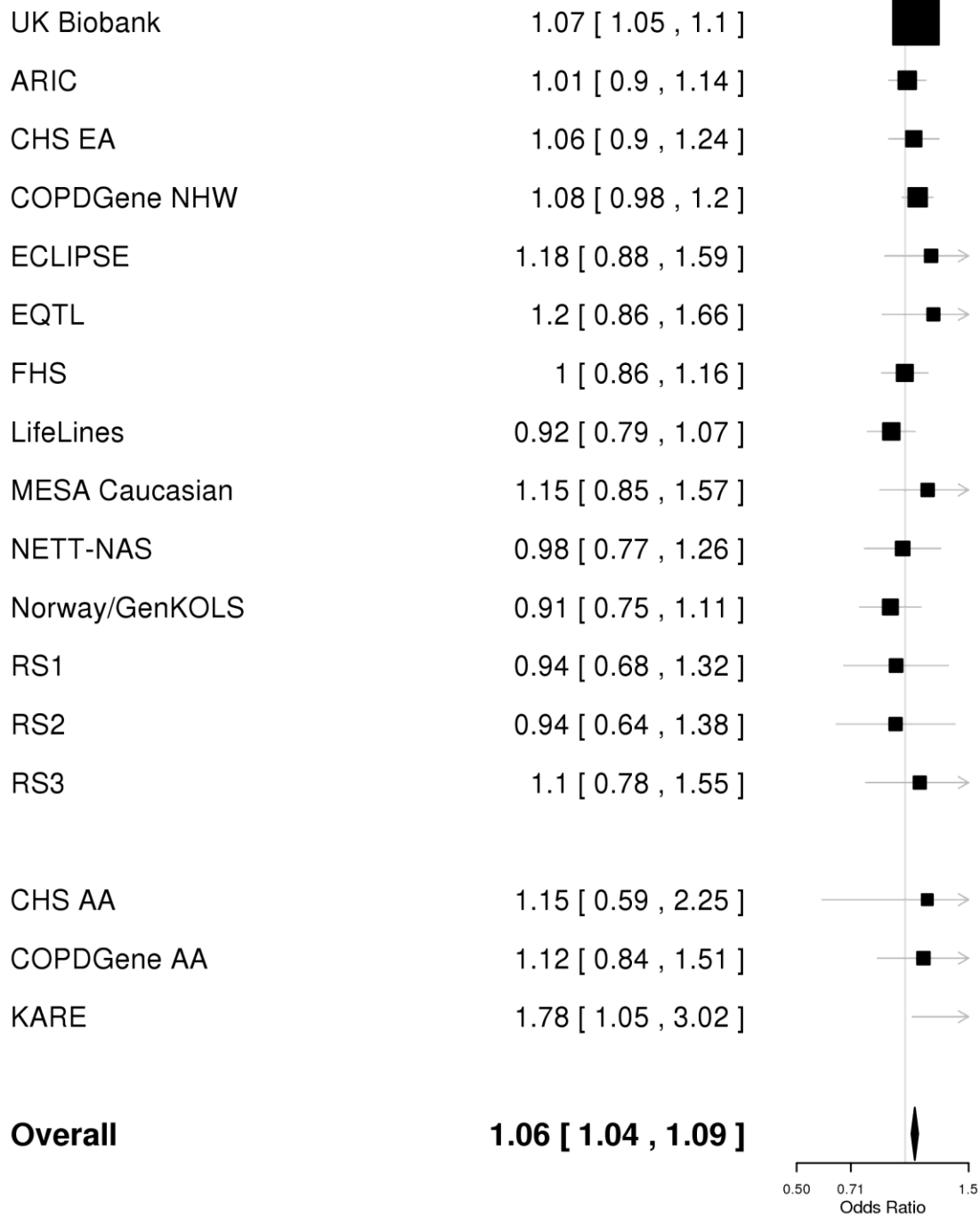
Supplementary Figure 1-55: Forest plot for rs7068966 (*CDC123* locus at 10p13)**10:12277992:C/T rs7068966**

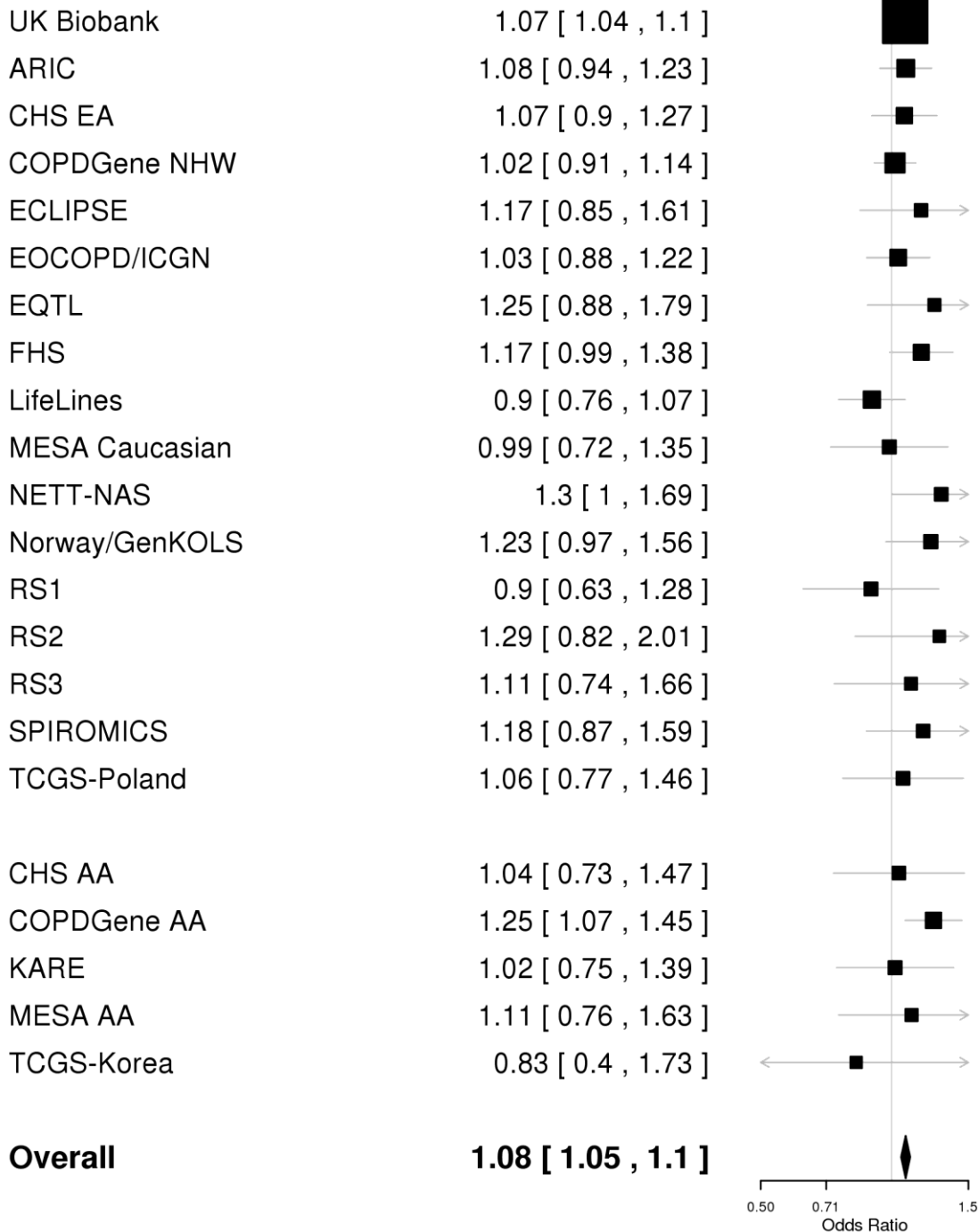
Supplementary Figure 1-56: Forest plot for rs2579762 (*LRMDA* locus at 10q22.3)**10:78318879:C/A rs2579762**

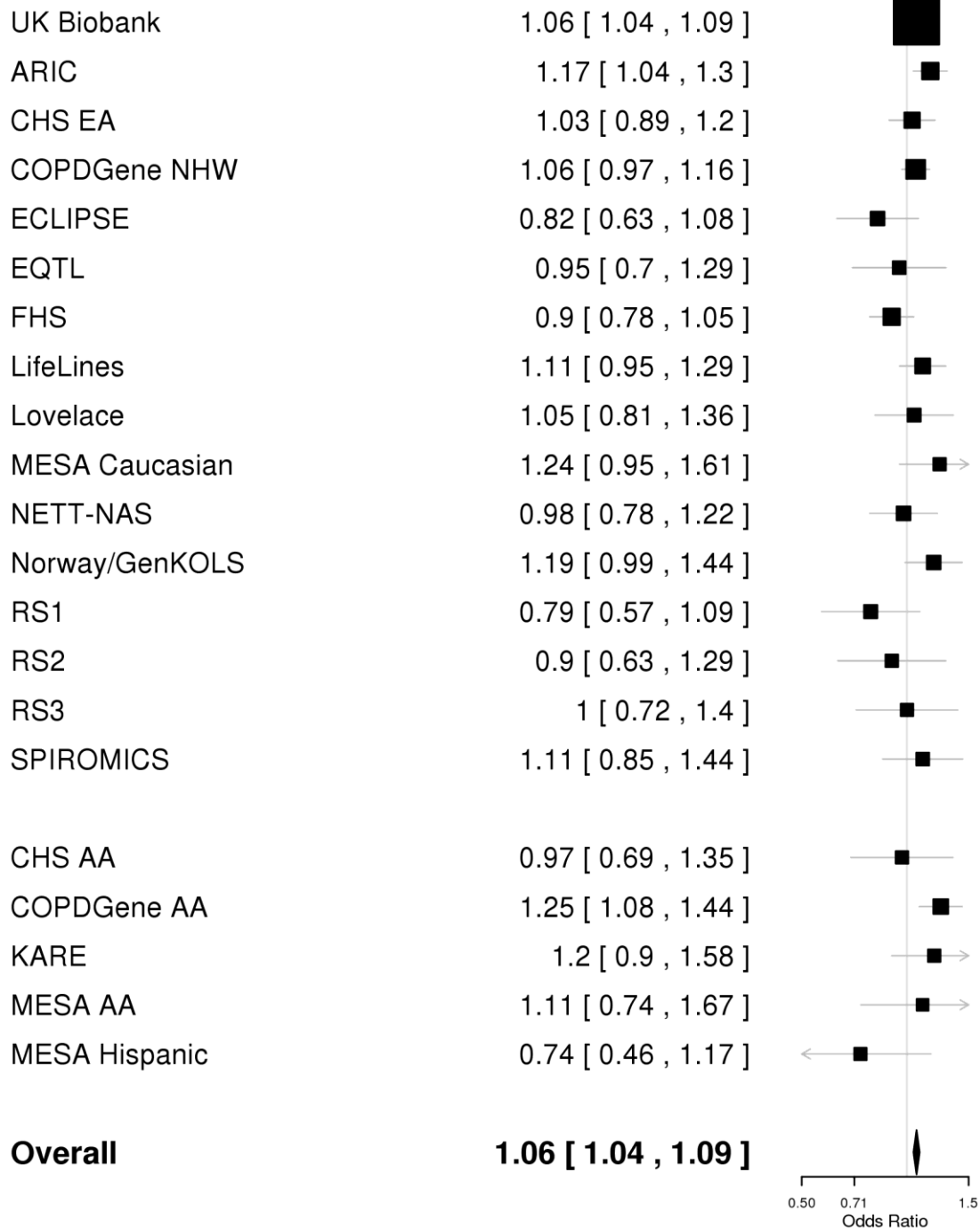
Supplementary Figure 1-57: Forest plot for rs721917 (*SFTPD* locus at 10q22.3)**10:81706324:G/A rs721917**

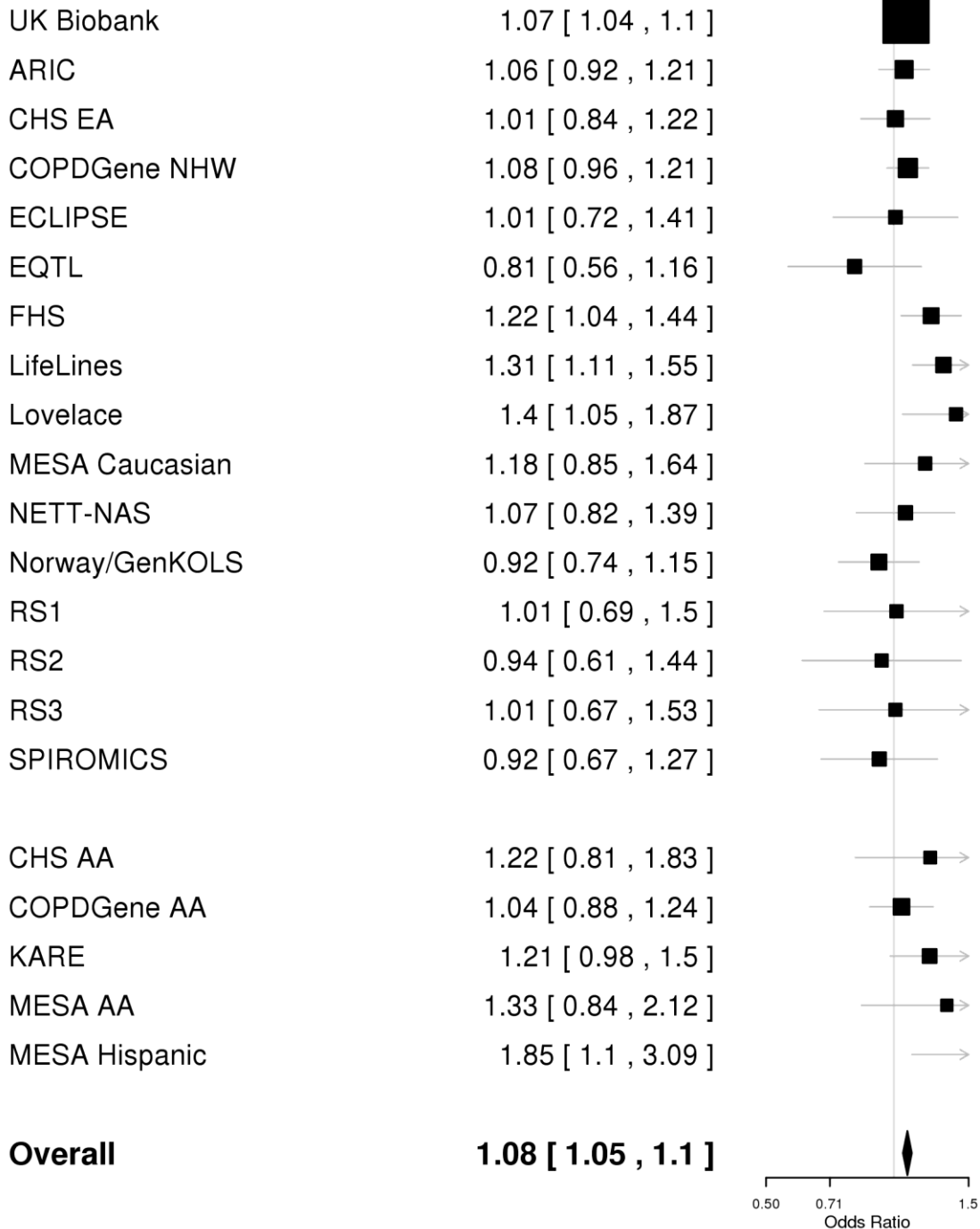
Supplementary Figure 1-58: Forest plot for rs1570221 (*STN1* locus at 10q24.33)**10:105656874:A/G rs1570221**

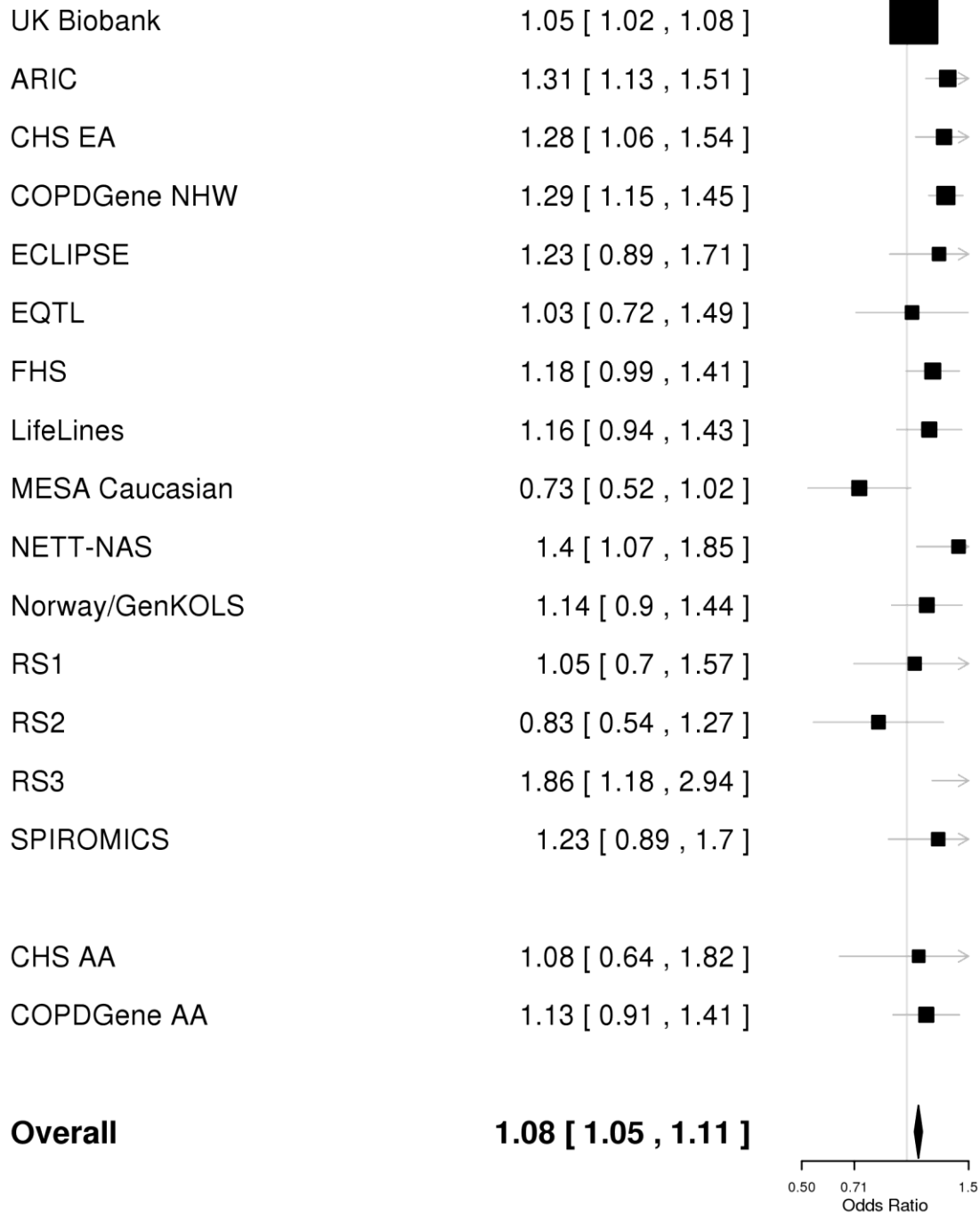
Supplementary Figure 1-60: Forest plot for rs117261012 (*PRSS23* locus at 11q14.2)**11:86444761:G/A rs117261012**

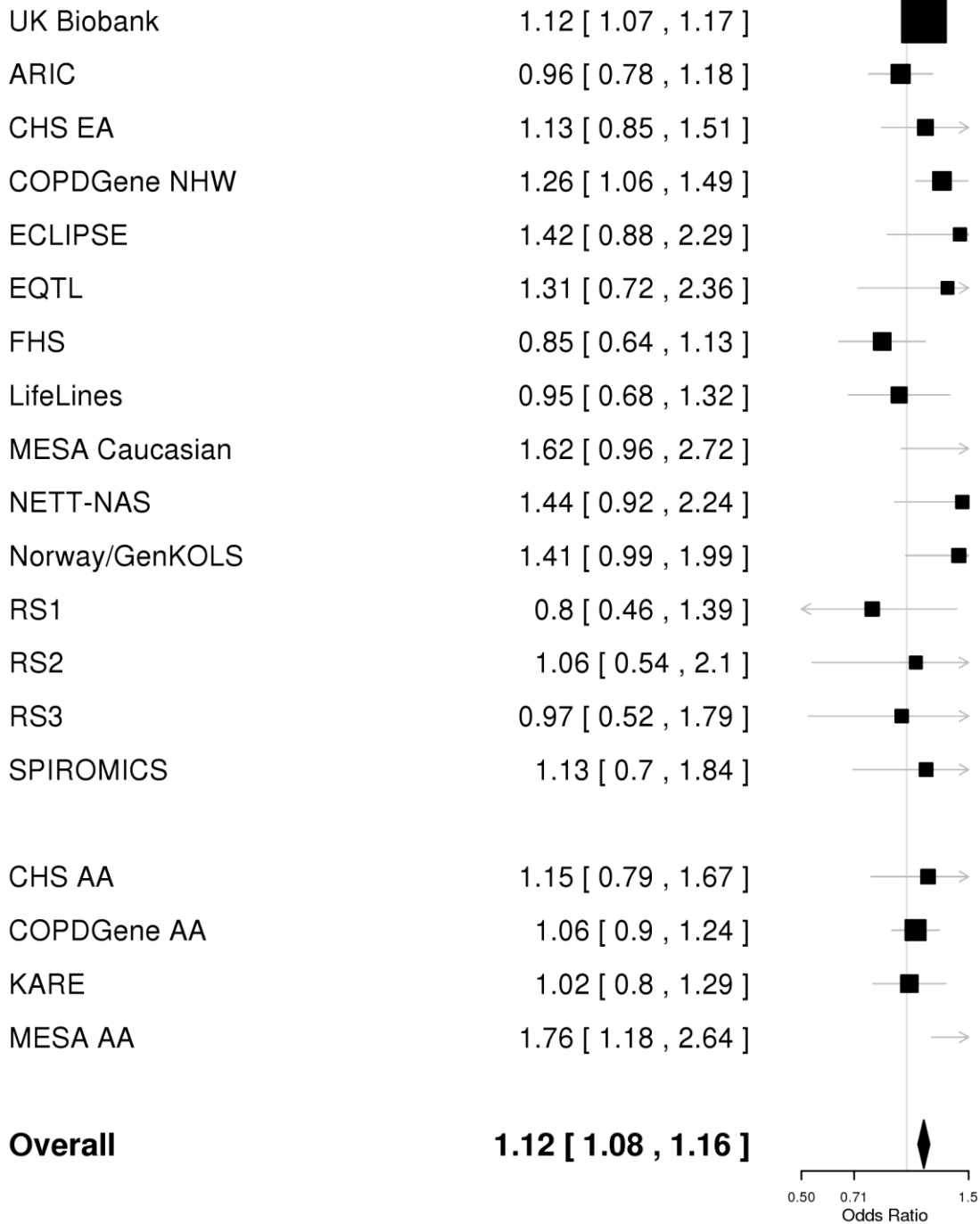
Supplementary Figure 1-61: Forest plot for rs11049386 (*CCDC91* locus at 12p11.22)**12:28320536:T/A rs11049386**

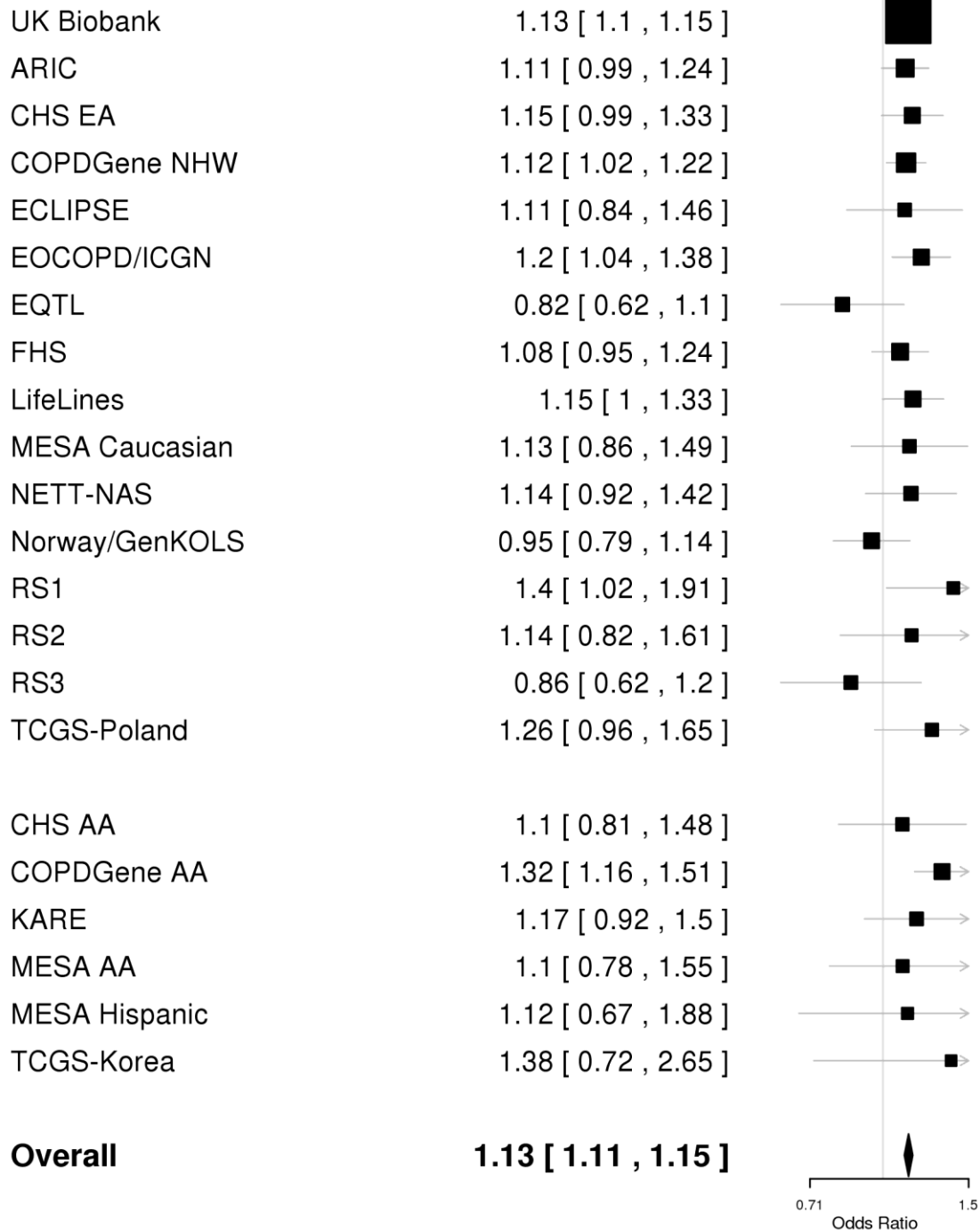
Supplementary Figure 1-62: Forest plot for rs7307510 (*SNRPF* locus at 12q23.1)**12:96237570:C/T rs7307510**

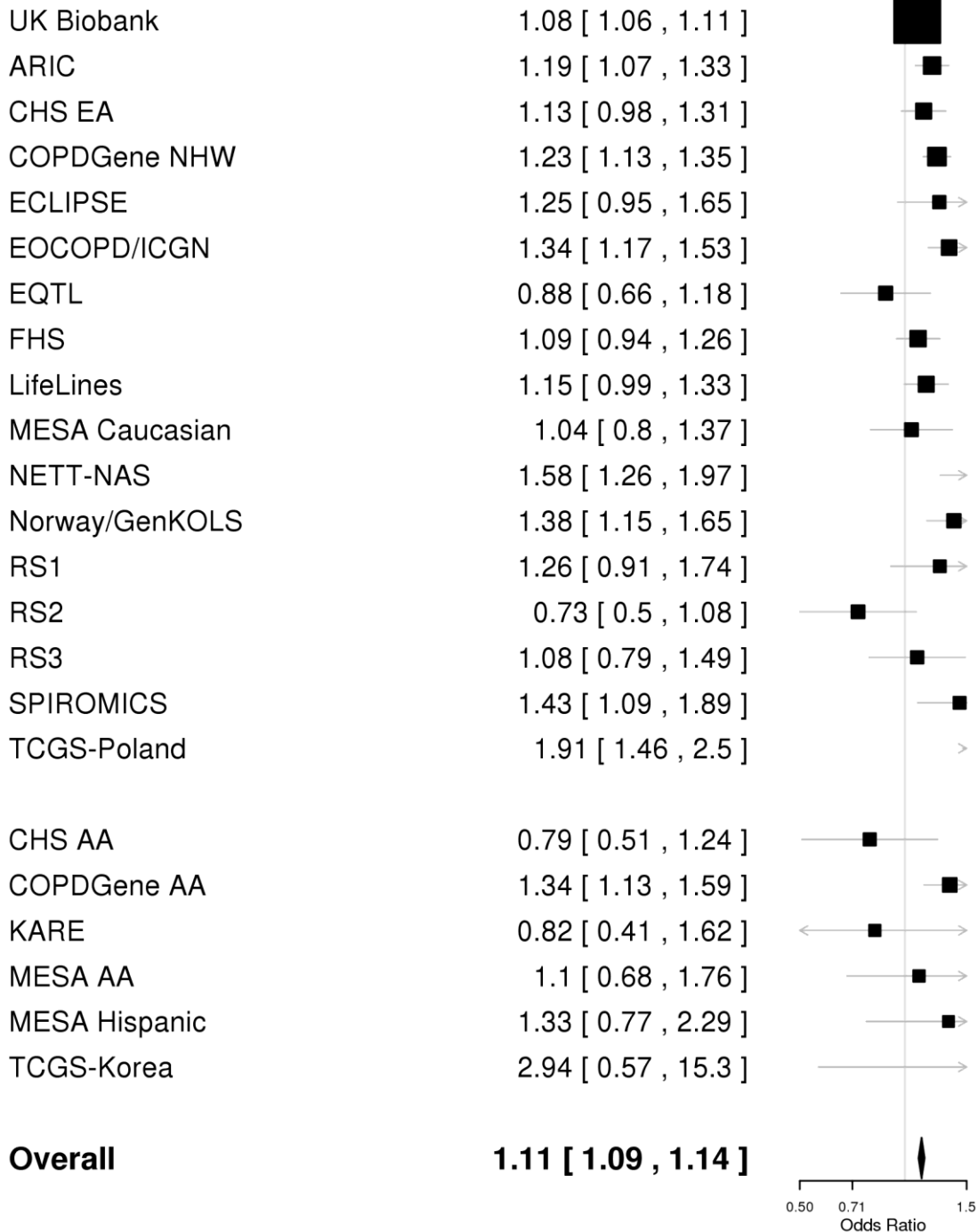
Supplementary Figure 1-63: Forest plot for rs7958945 (*MED13L* locus at 12q24.21)**12:115947901:G/A rs7958945**

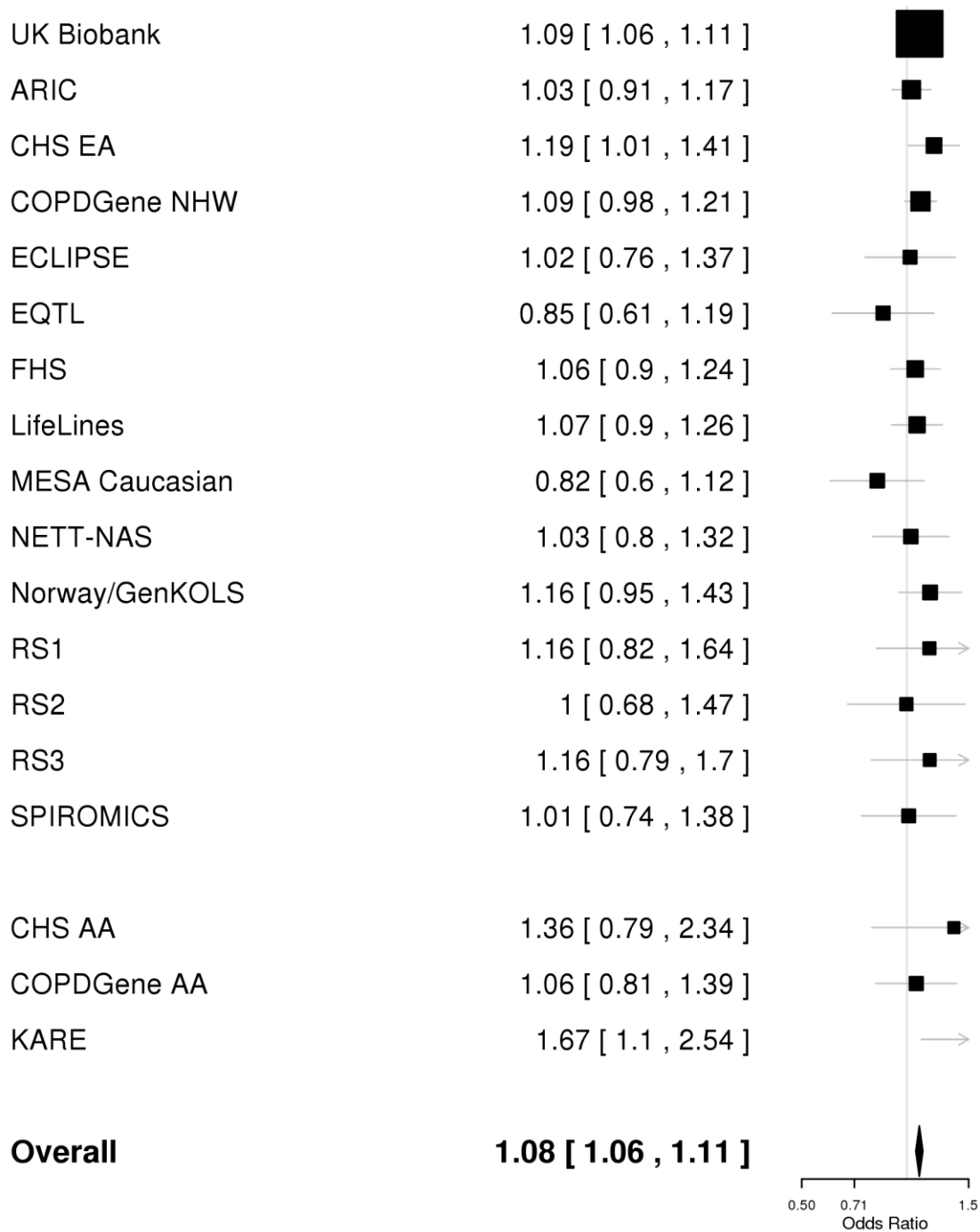
Supplementary Figure 1-64: Forest plot for rs9525927 (*SERP2* locus at 13q14.11)**13:44842503:G/A rs9525927**

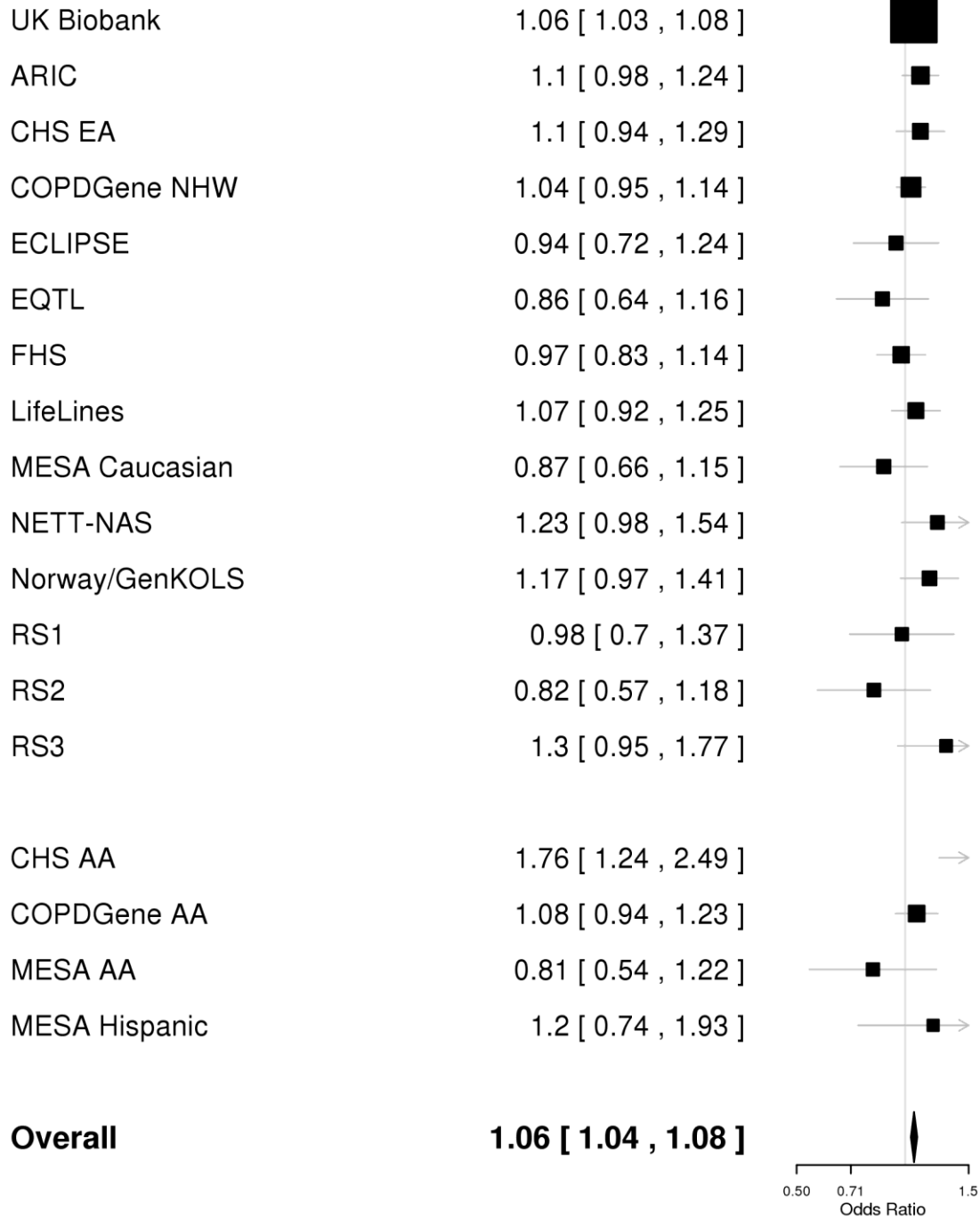
Supplementary Figure 1-65: Forest plot for rs72699855 (*RIN3* locus at 14q32.12)**14:93105953:G/C rs72699855**

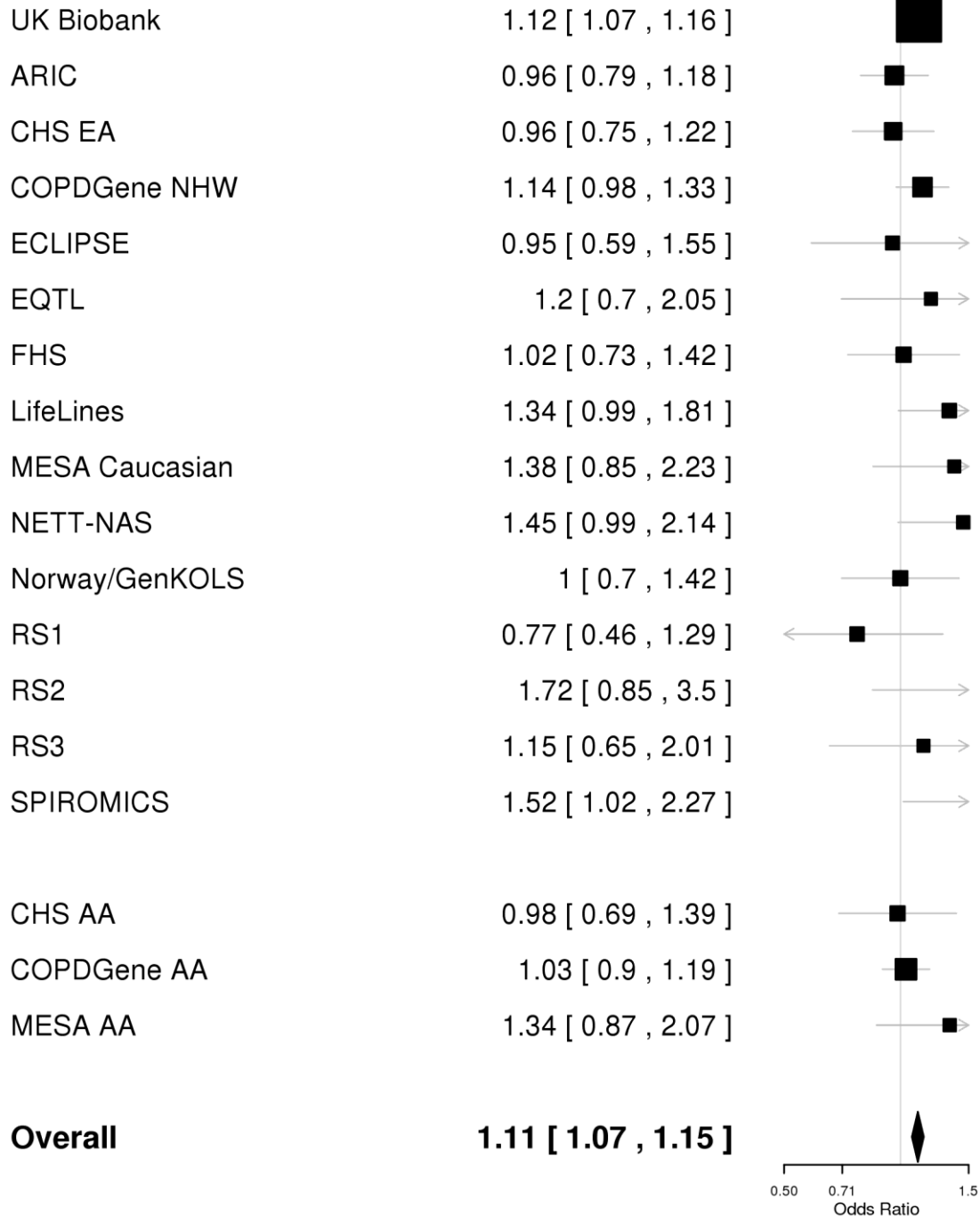
Supplementary Figure 1-66: Forest plot for rs72731149 (*DTWD1* locus at 15q21.2)**15:49984710:G/C rs72731149**

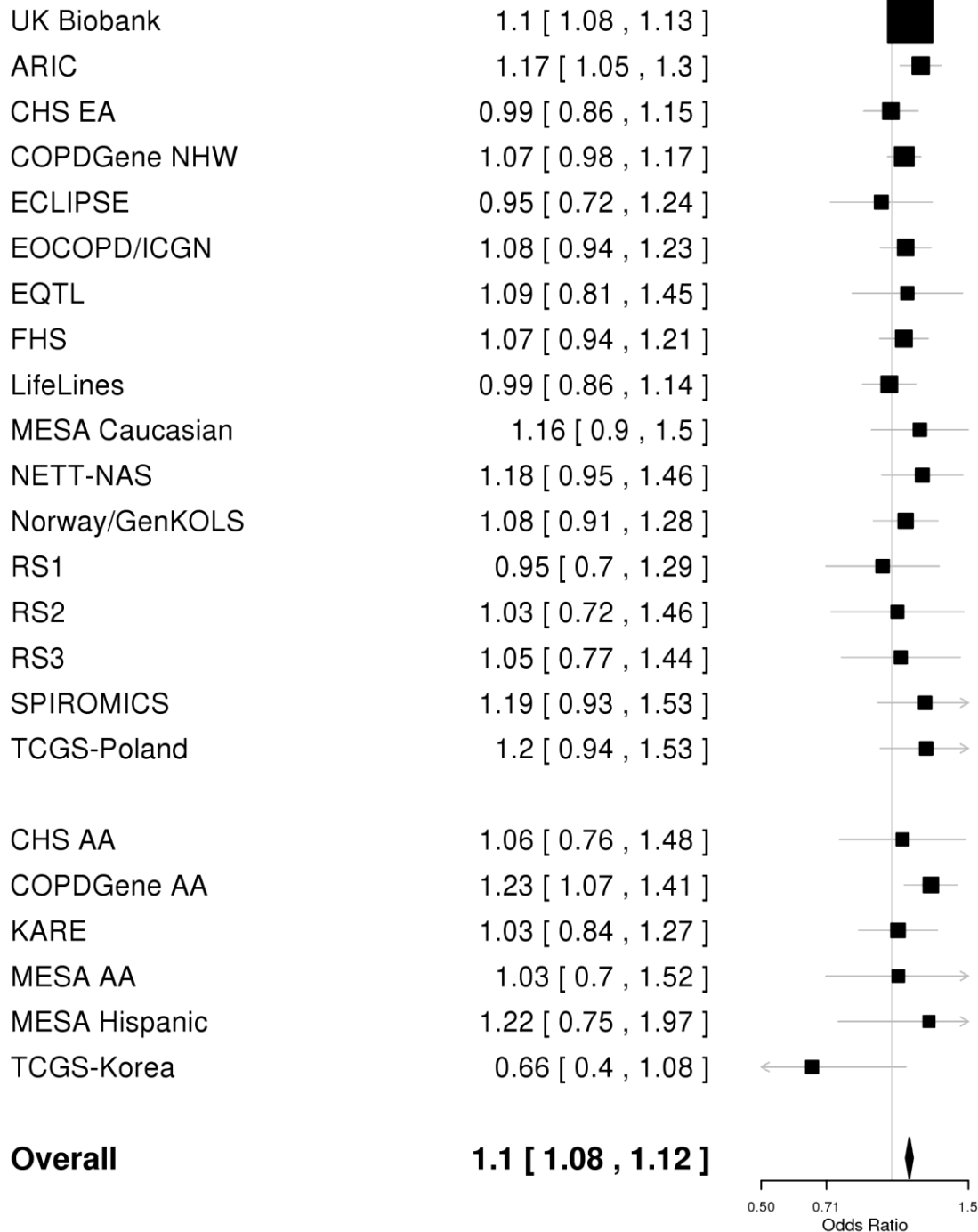
Supplementary Figure 1-67: Forest plot for rs1441358 (*THSD4* locus at 15q23)**15:71612514:G/T rs1441358**

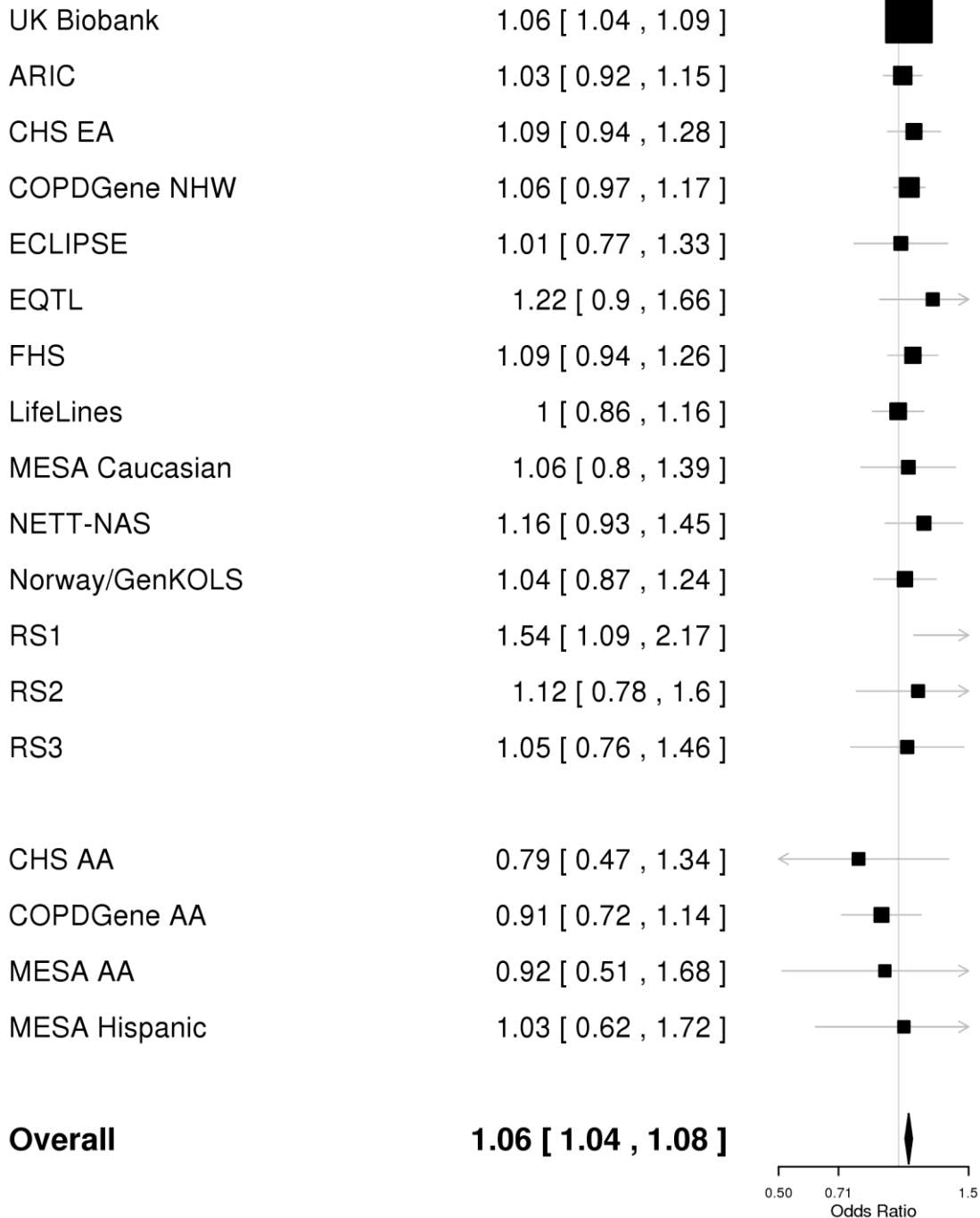
Supplementary Figure 1-68: Forest plot for rs55676755 (*CHRNA3* locus at 15q25.1)**15:78898932:G/C rs55676755**

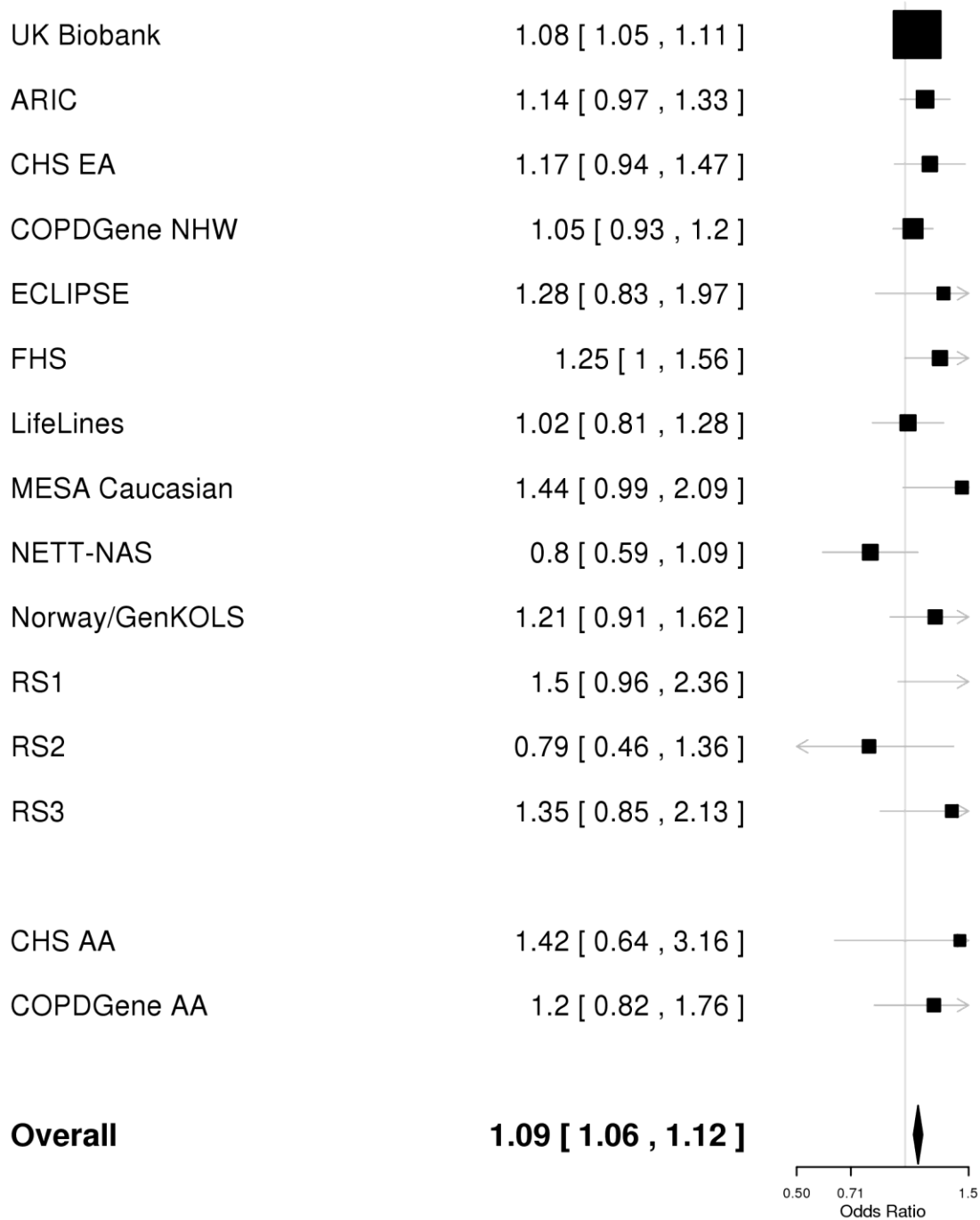
Supplementary Figure 1-69: Forest plot for rs10152300 (*ADAMTSL3* locus at 15q25.2)**15:84392907:G/A rs10152300**

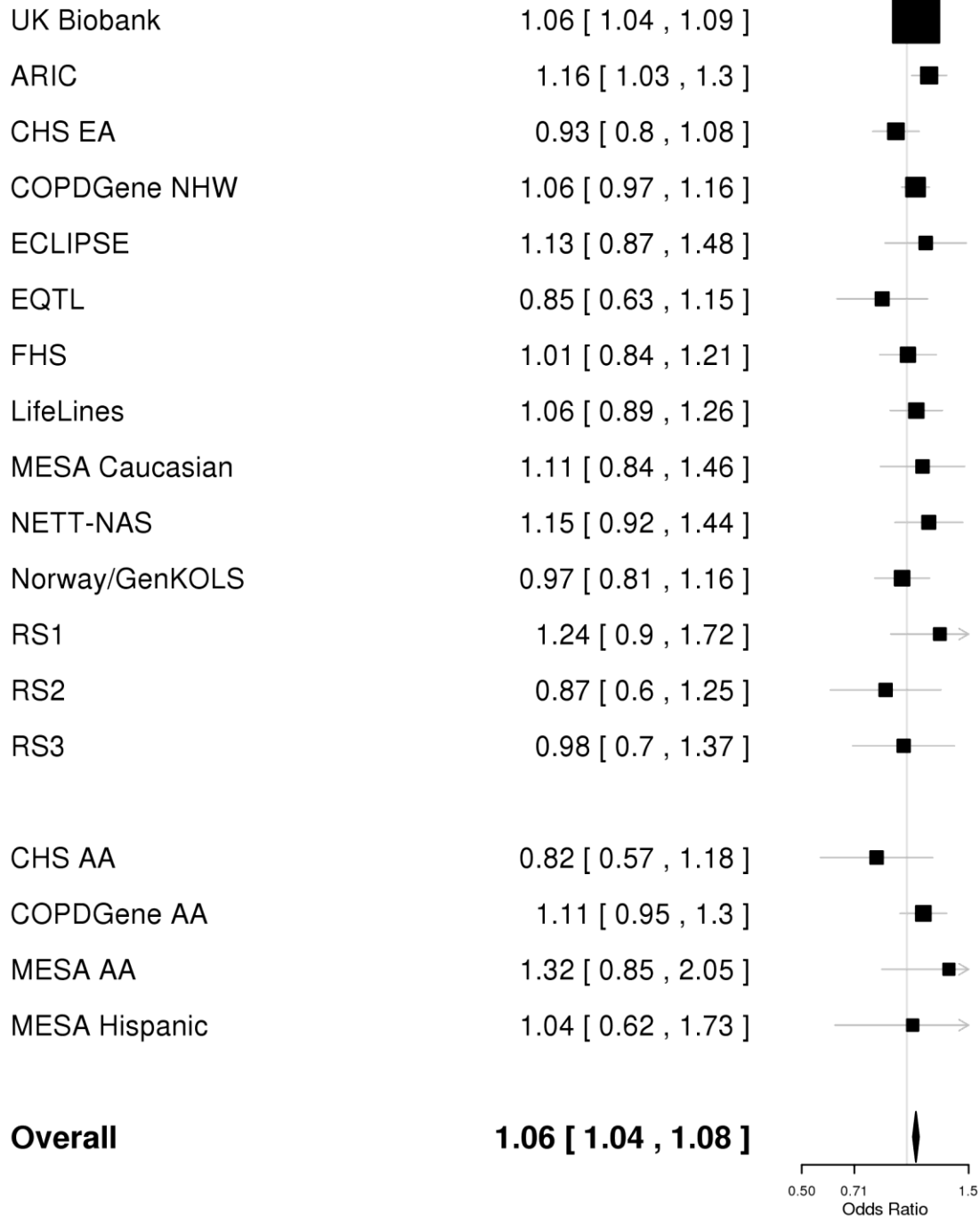
Supplementary Figure 1-70: Forest plot for rs56134392 (*TEKT5* locus at 16p13.13)**16:10709013:C/T rs56134392**

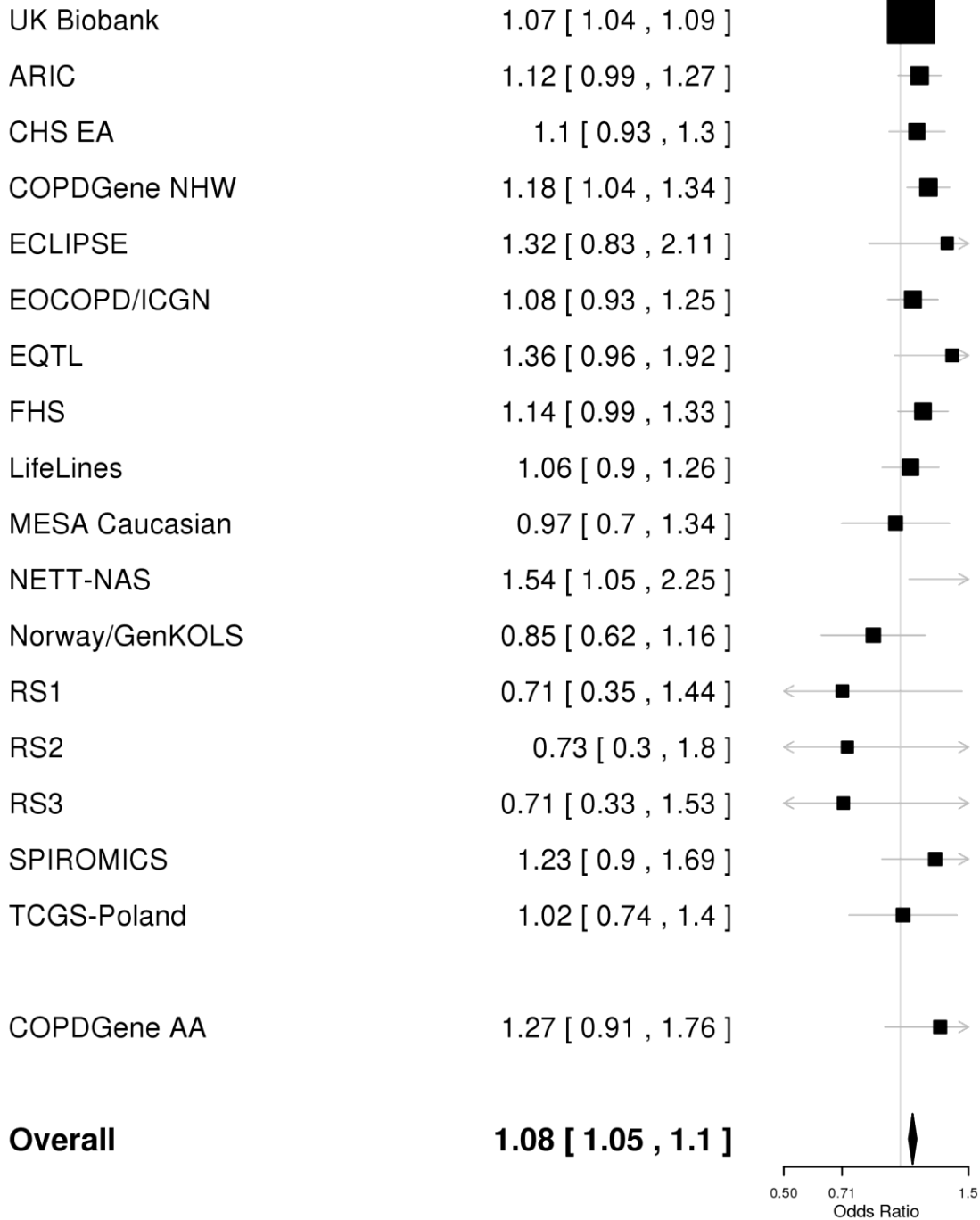
Supplementary Figure 1-71: Forest plot for rs8044657 (*TEPP* locus at 16q21)**16:58022625:G/A rs8044657**

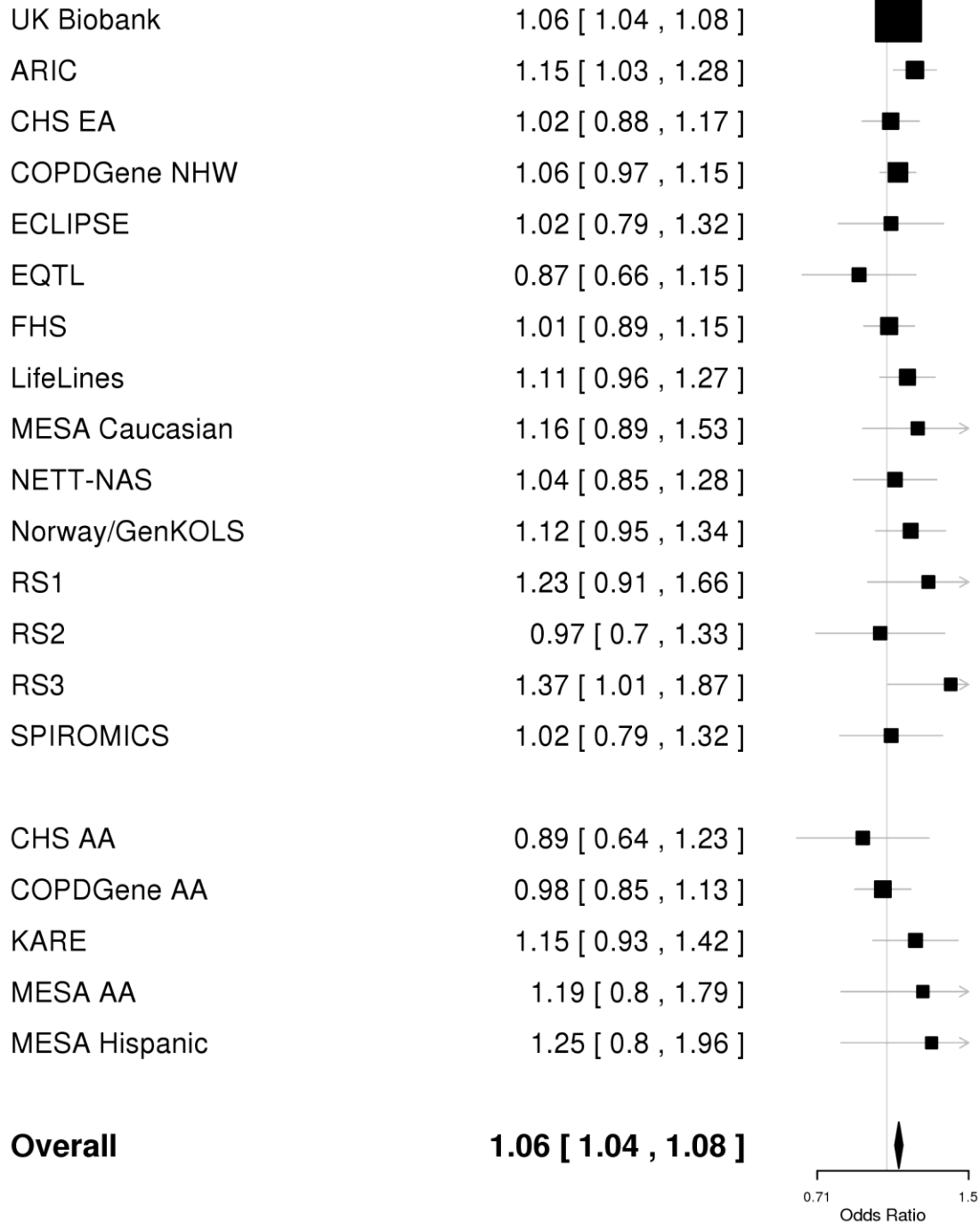
Supplementary Figure 1-72: Forest plot for rs4888379 (*CFDP1* locus at 16q23.1)**16:75340231:T/A rs4888379**

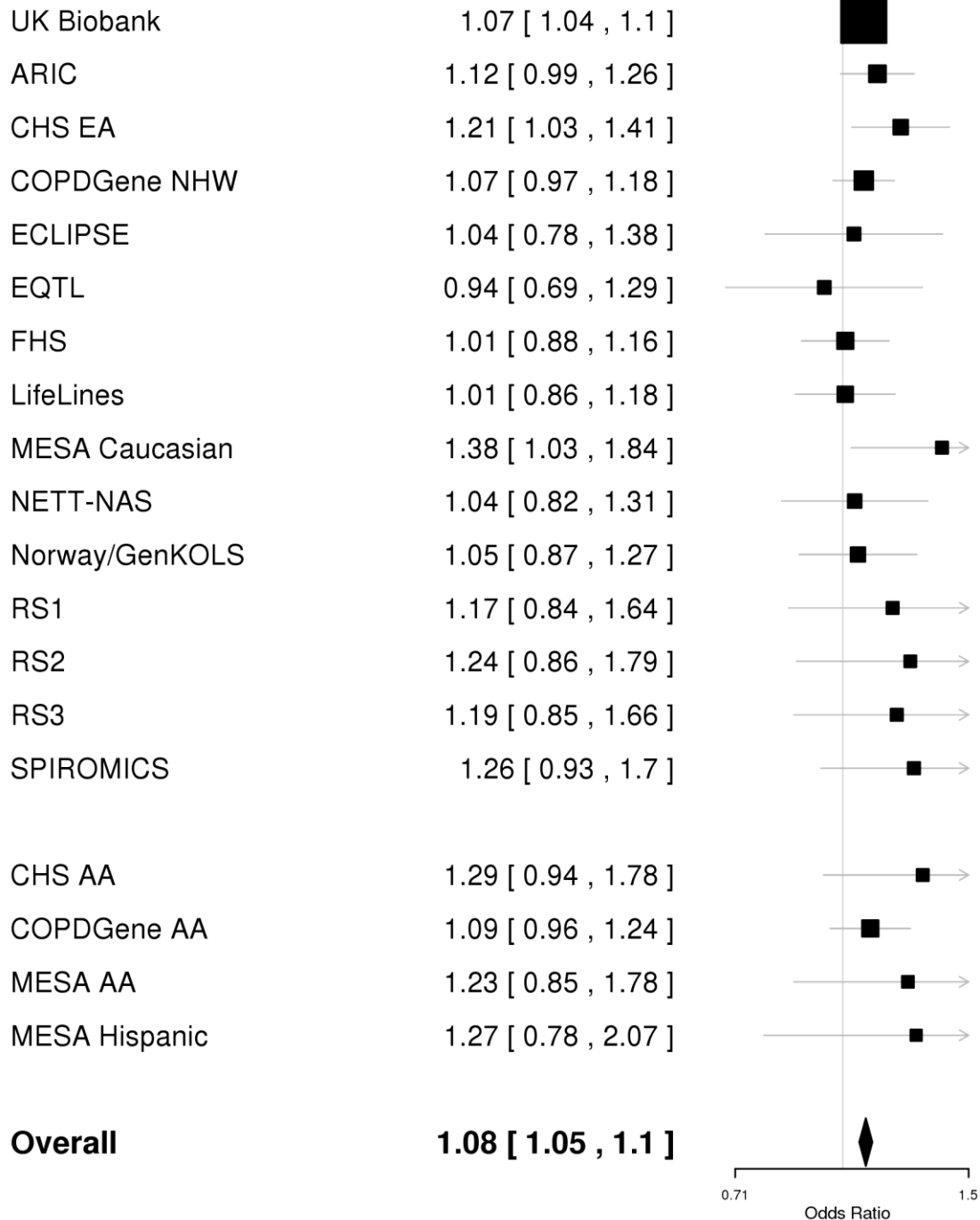
Supplementary Figure 1-73: Forest plot for rs8080772 (*EFCAB5* locus at 17q11.2)**17:28413129:T/C rs8080772**

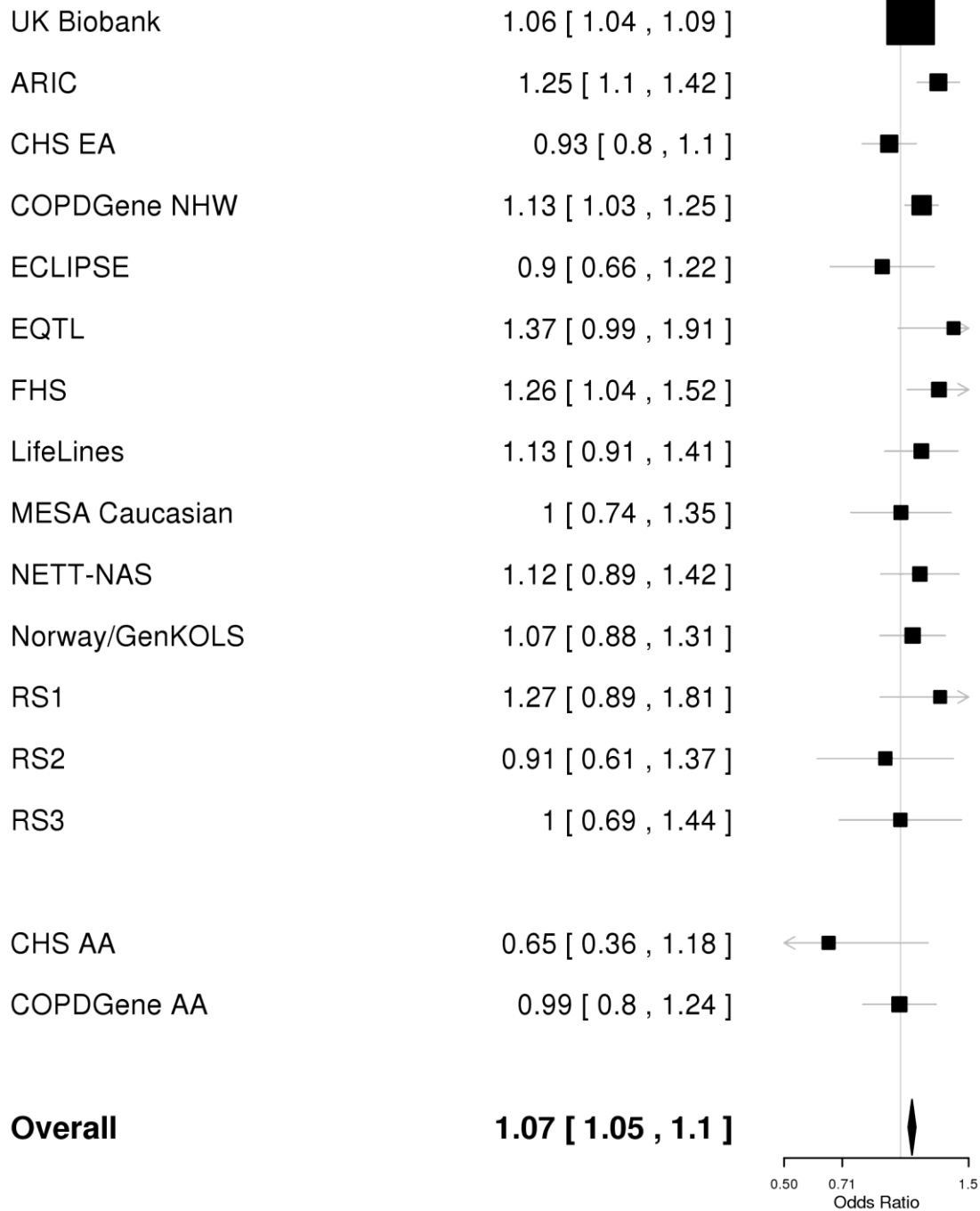
Supplementary Figure 1-74: Forest plot for rs34727469 (*RPL23* locus at 17q12)**17:36835079:T/C rs34727469**

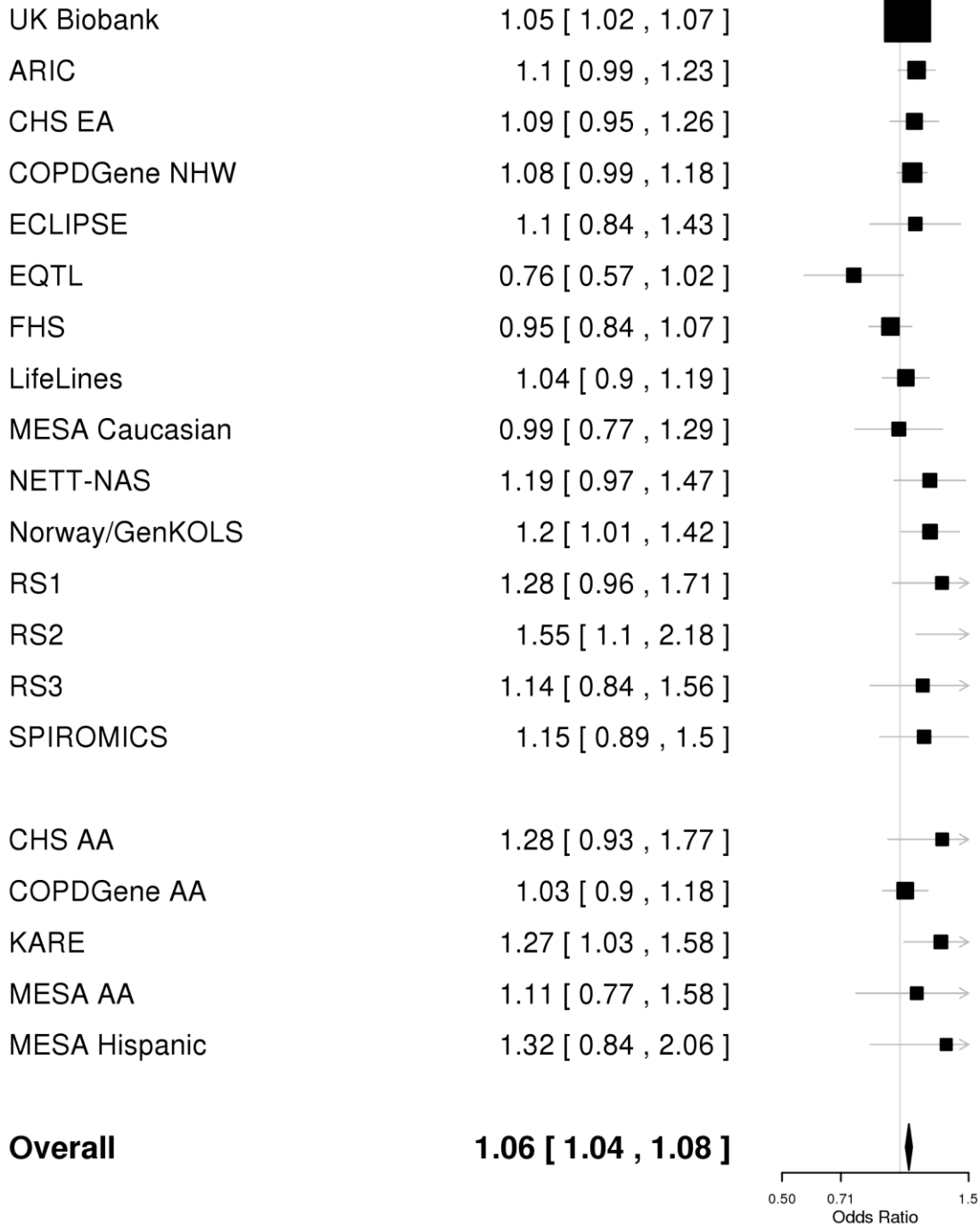
Supplementary Figure 1-75: Forest plot for rs62065216 (*THRA* locus at 17q21.1)**17:38218773:A/G rs62065216**

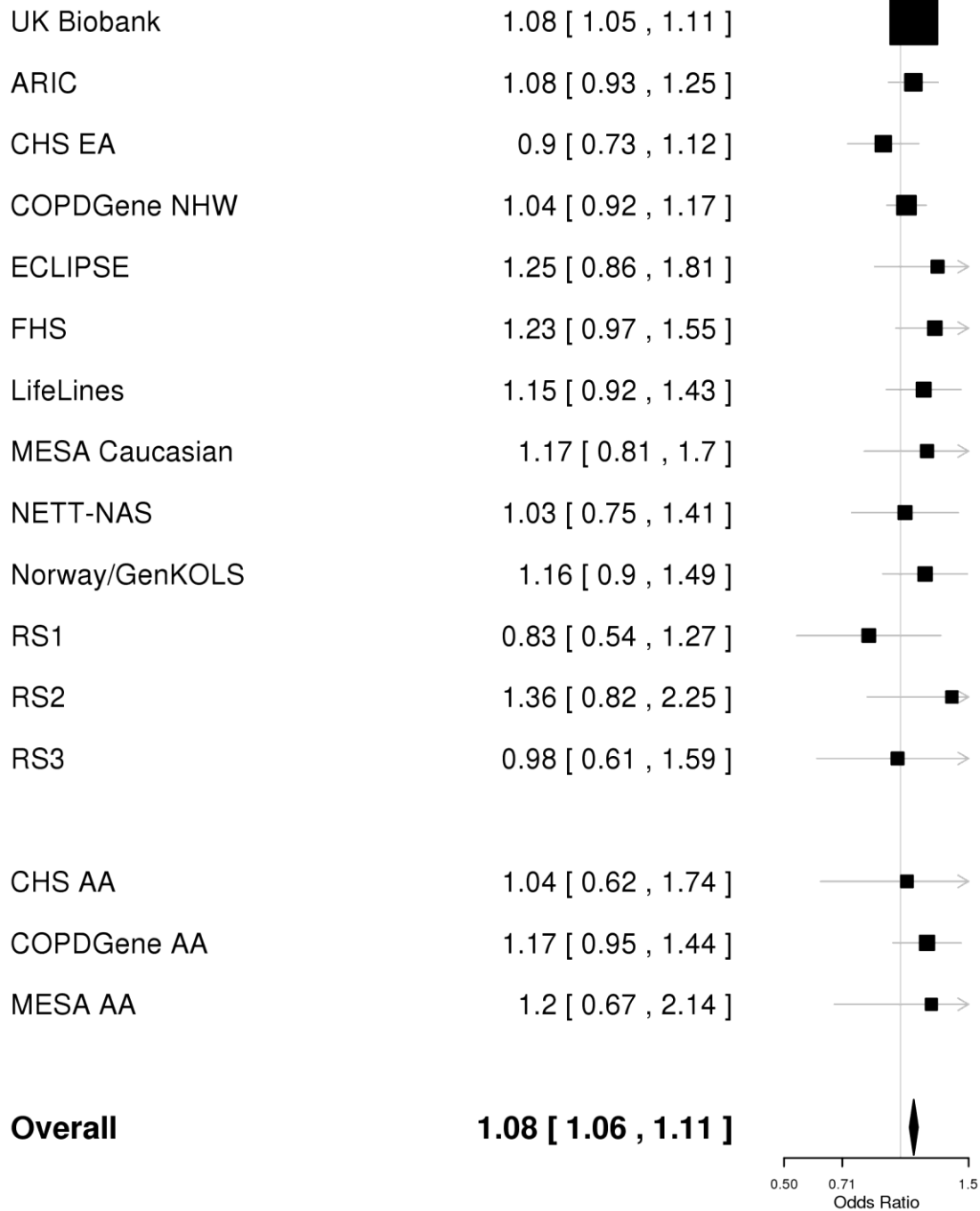
Supplementary Figure 1-76: Forest plot for rs12373142 (*SPPL2C* locus at 17q21.31)**17:43924200:G/C rs12373142**

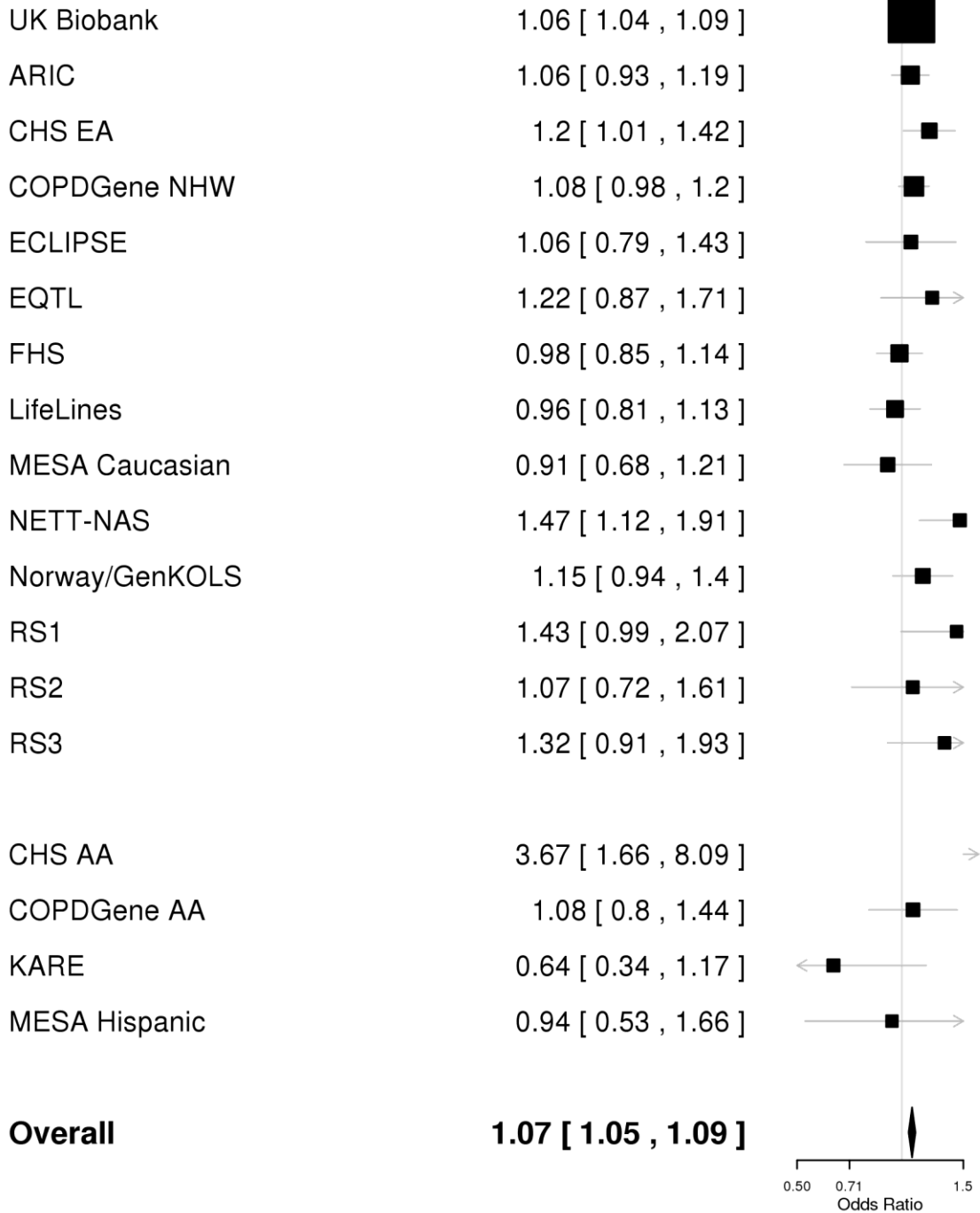
Supplementary Figure 1-77: Forest plot for rs11655567 (*SOX9* locus at 17q24.3)**17:69216687:C/T rs11655567**

Supplementary Figure 1-78: Forest plot for rs647097 (*MTCL1* locus at 18p11.22)**18:8808464:C/T rs647097**

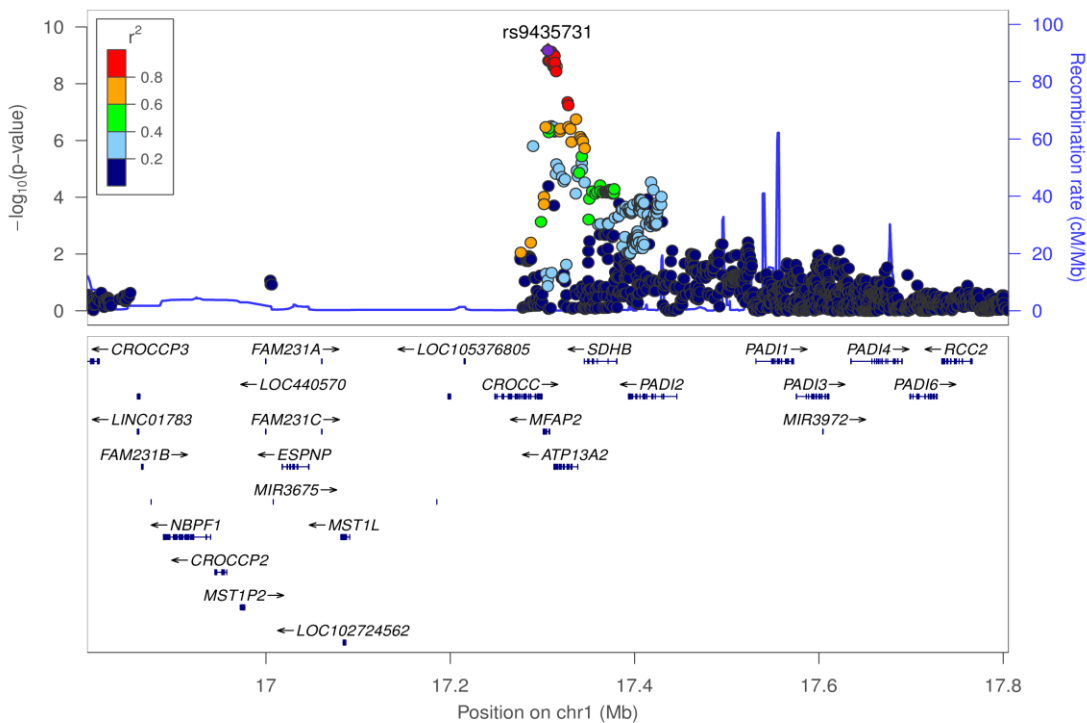
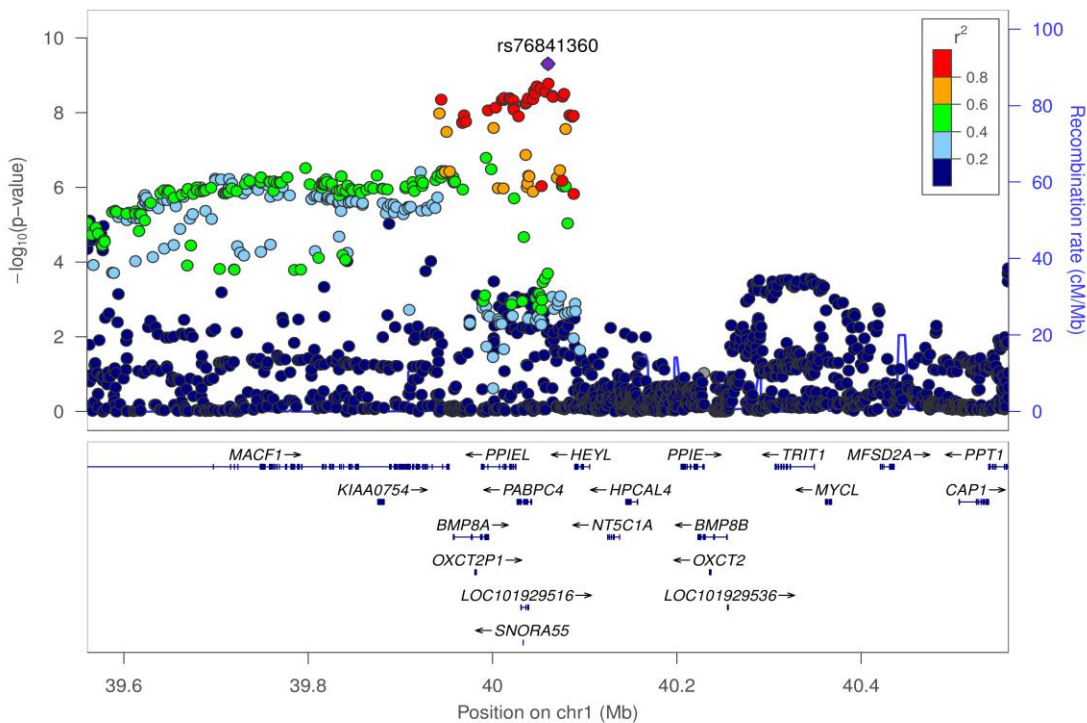
Supplementary Figure 1-79: Forest plot for rs72626215 (*DMWD* locus at 19q13.32)**19:46294136:G/A rs72626215**

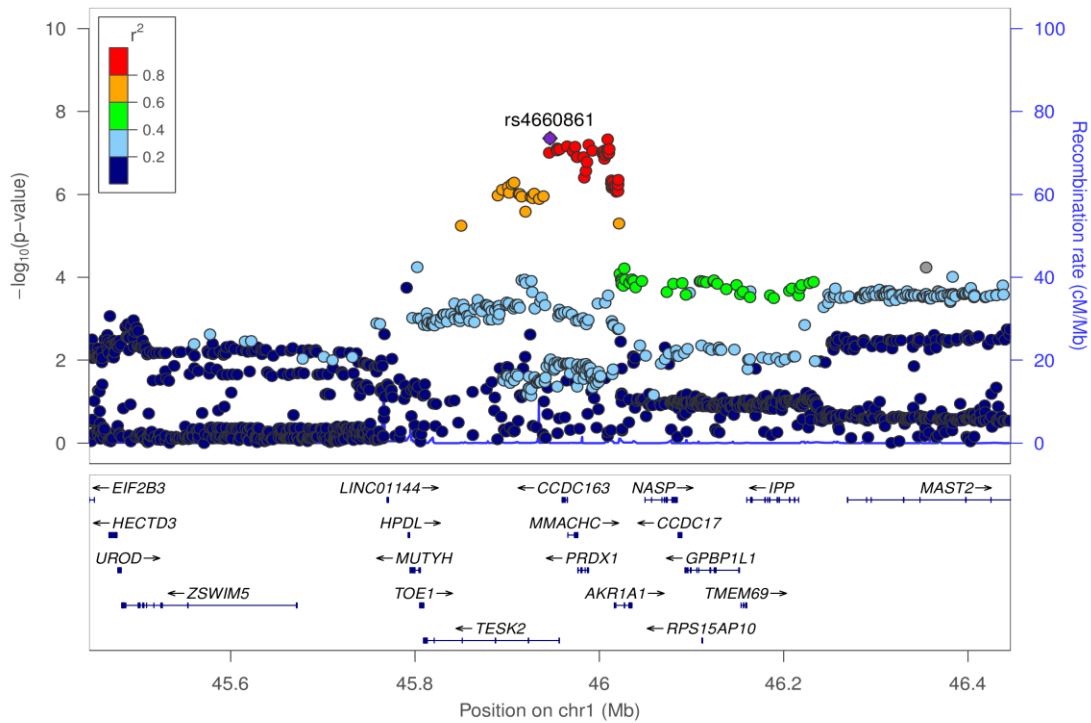
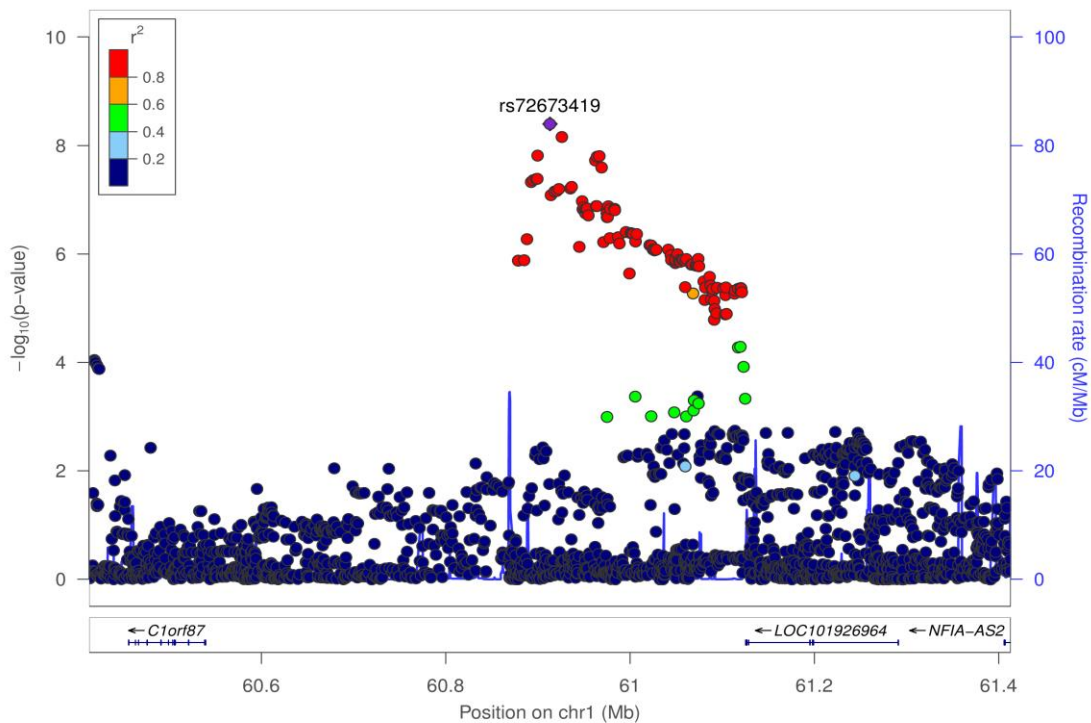
Supplementary Figure 1-80: Forest plot for rs2096468 (*KCNE2* locus at 21q22.11)**21:35661745:A/C rs2096468**

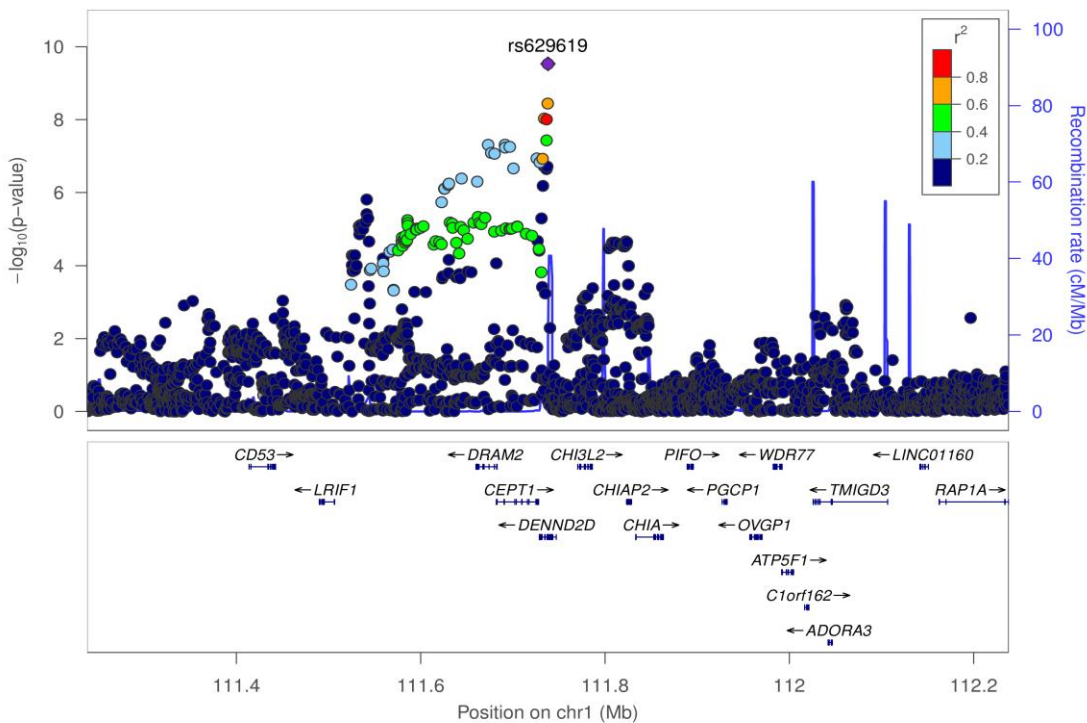
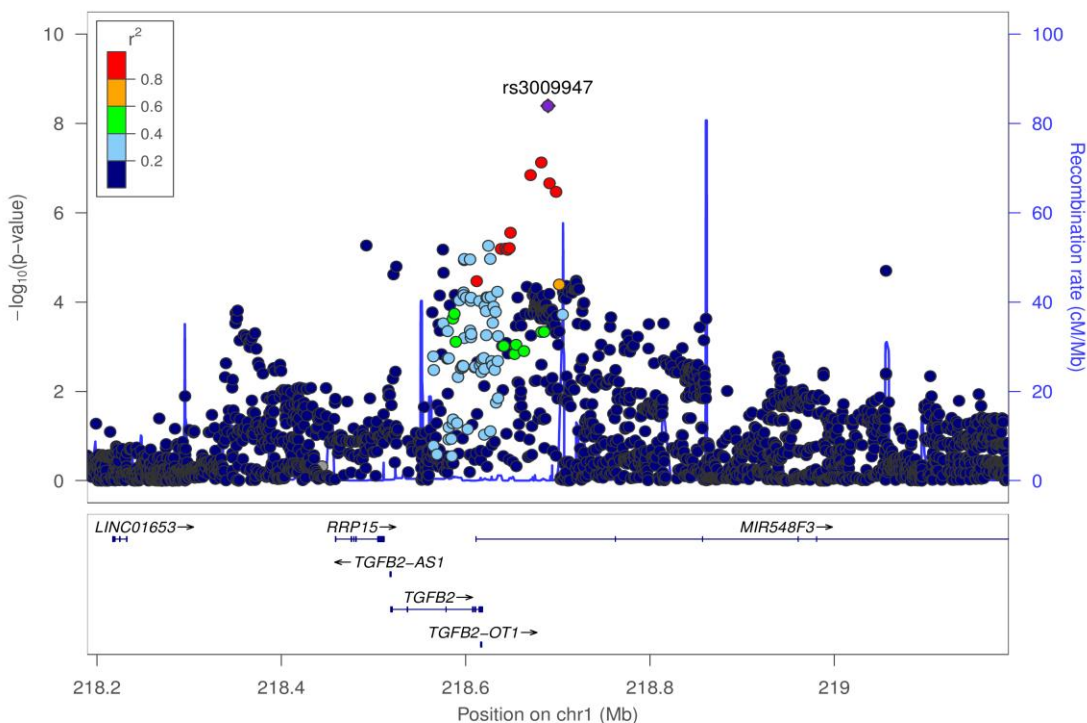
Supplementary Figure 1-81: Forest plot for rs9617650 (*MICAL3* locus at 22q11.21)**22:18488883:G/C rs9617650**

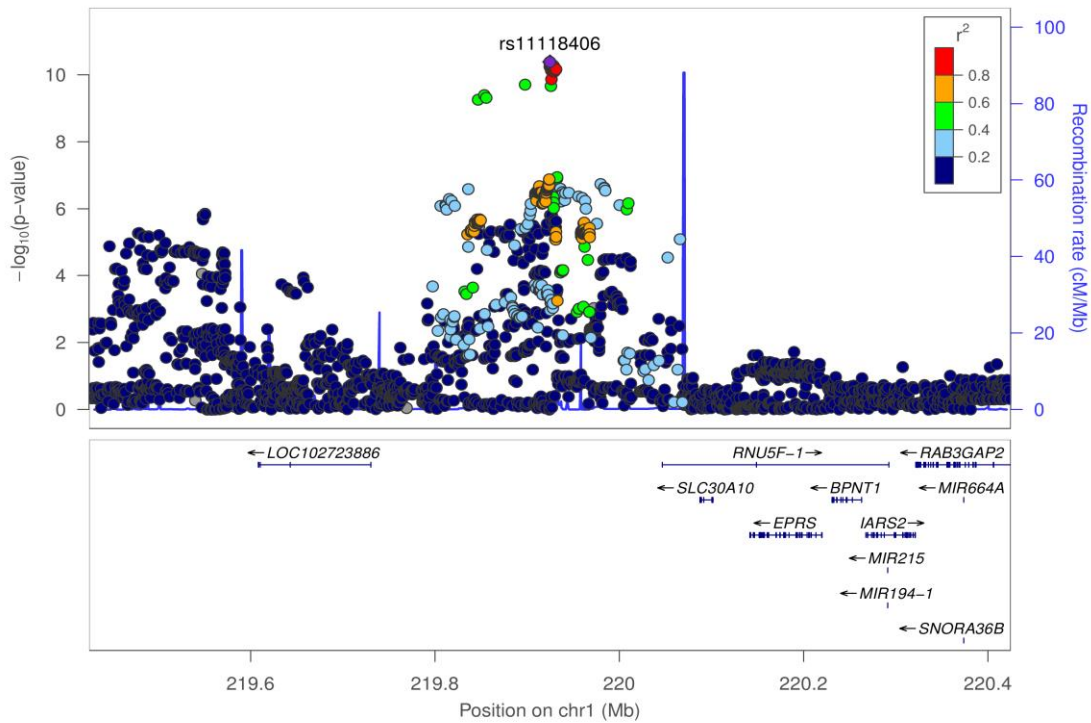
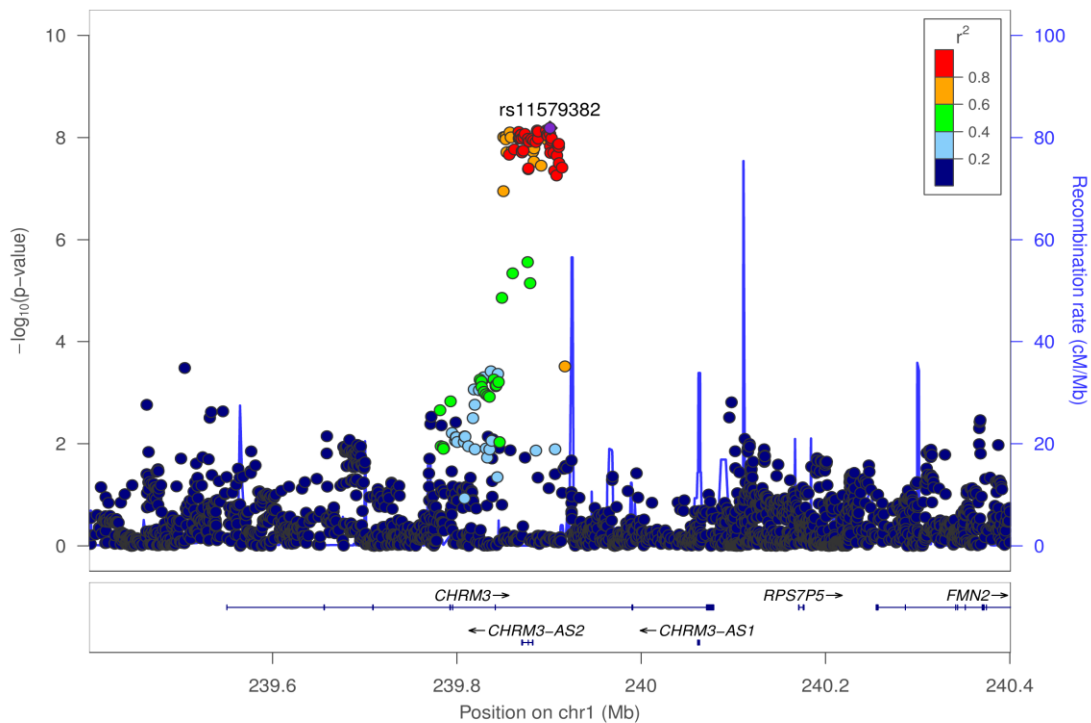
Supplementary Figure 1-82: Forest plot for rs73158393 (*SYN3* locus at 22q12.3)**22:33335386:C/G rs73158393**

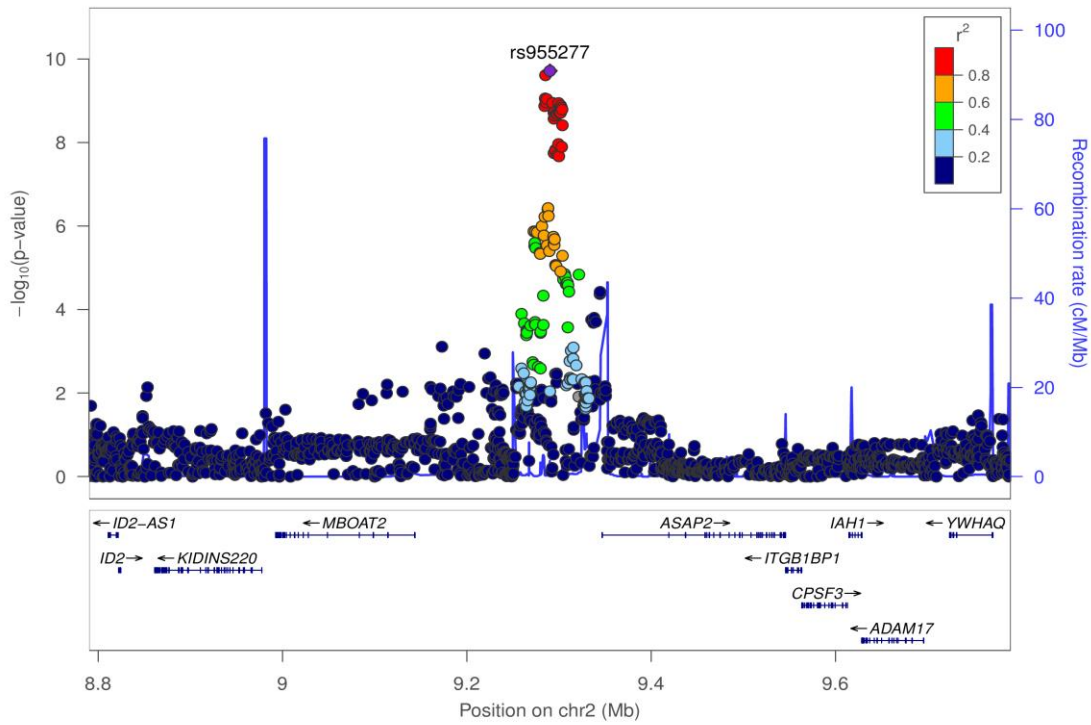
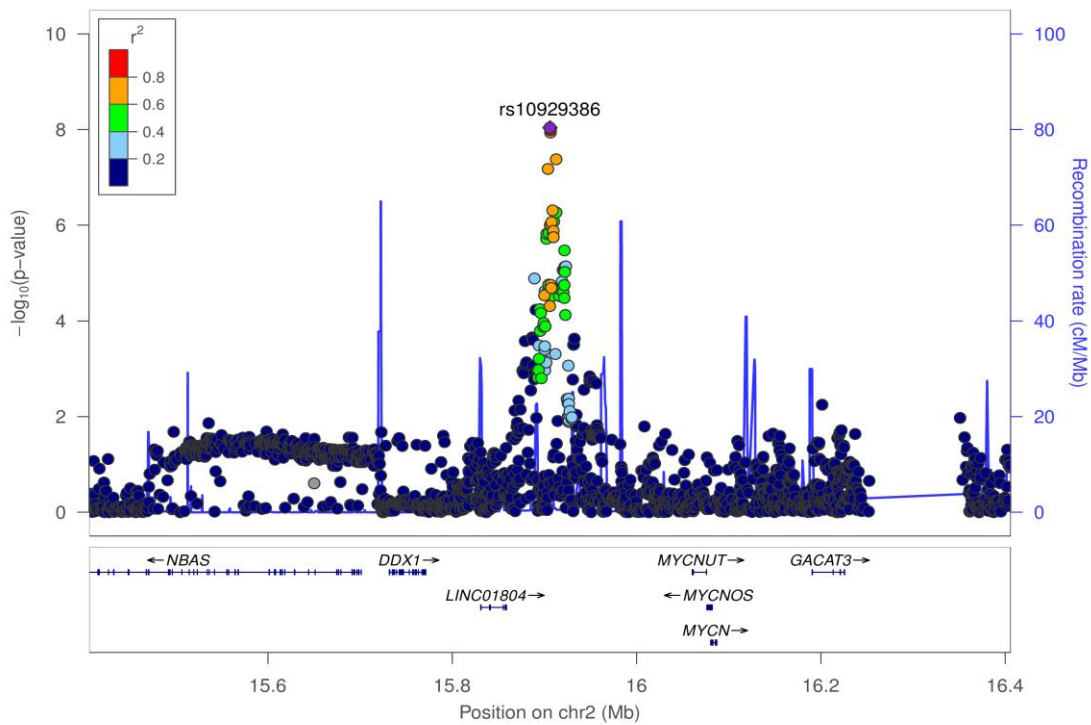
Supplementary Figure 2: Regional association plots for 82 genome-wide significant associations

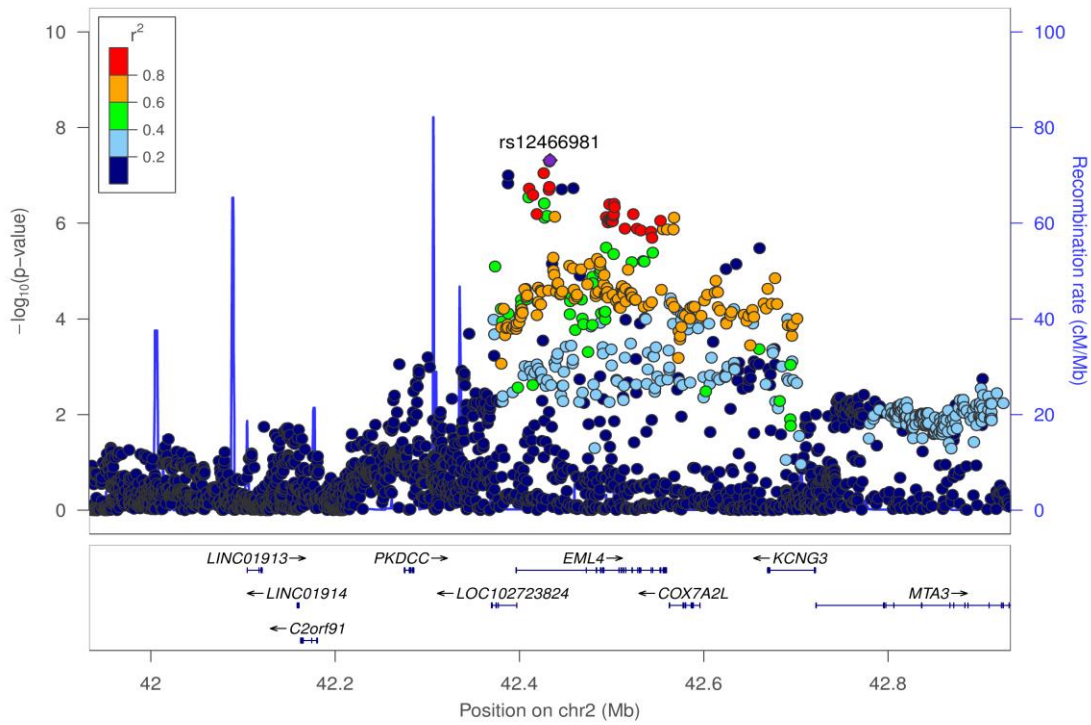
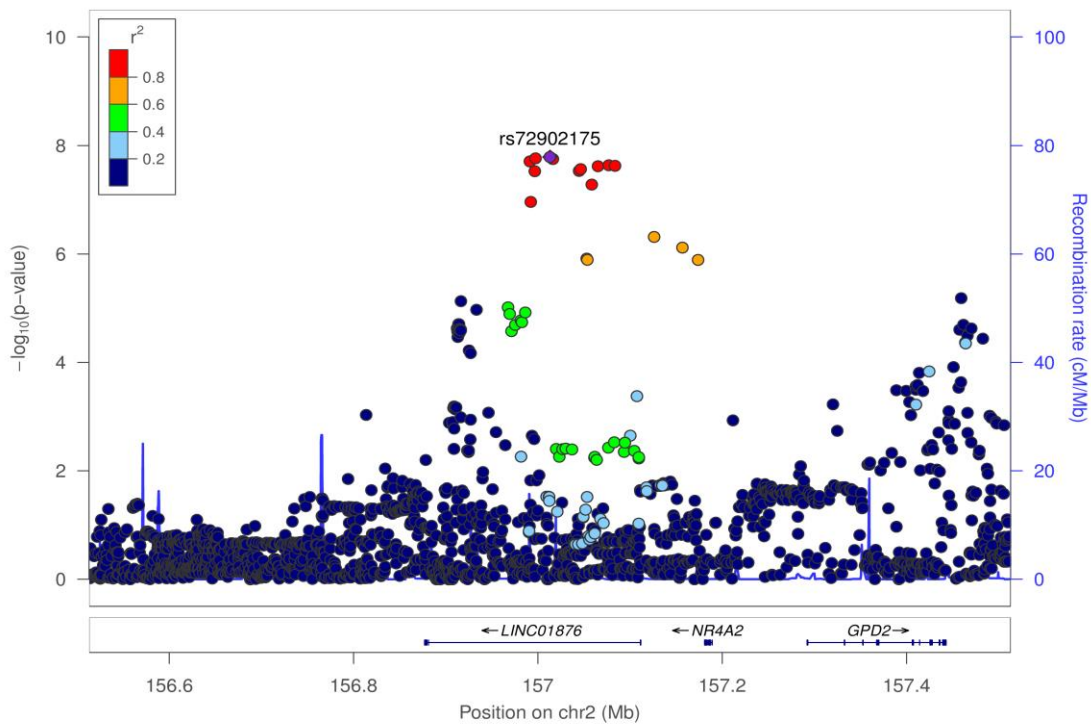
Supplementary Figure 2-1: Regional association plot for rs9435731 (*MFAP2* locus at 1p36.13)Supplementary Figure 2-2: Regional association plot for rs76841360 (*PABPC4* locus at 1p34.3)

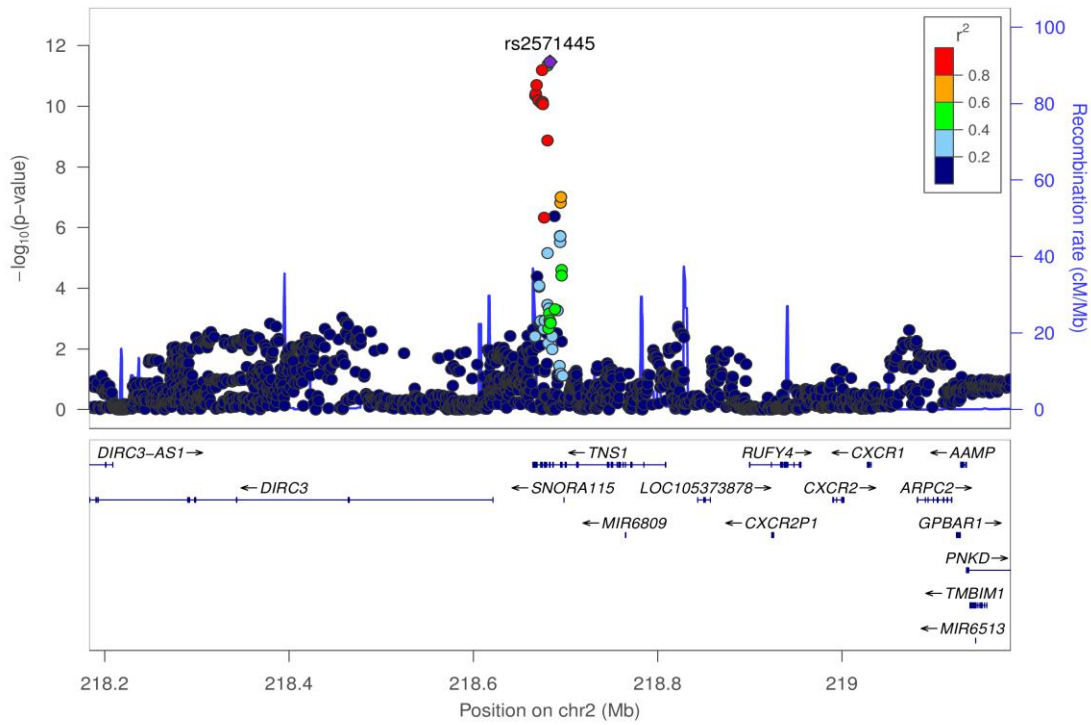
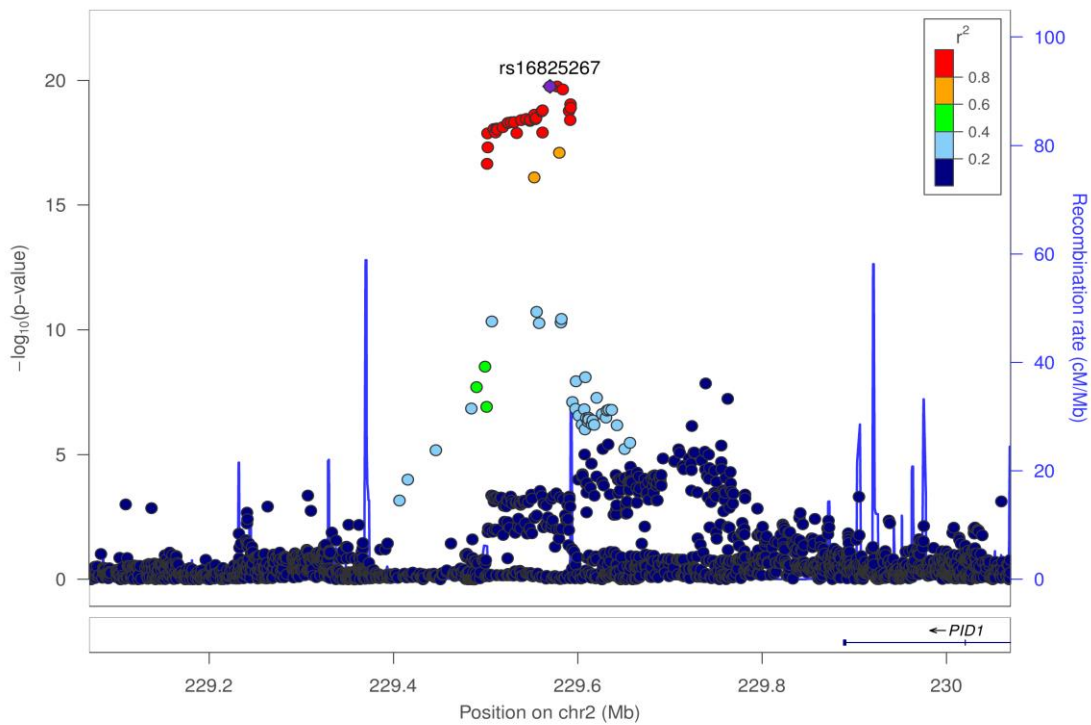
Supplementary Figure 2-3: Regional association plot for rs4660861 (*TESK2* locus at 1p34.1)Supplementary Figure 2-4: Regional association plot for rs72673419 (*C1orf87* locus at 1p32.1)

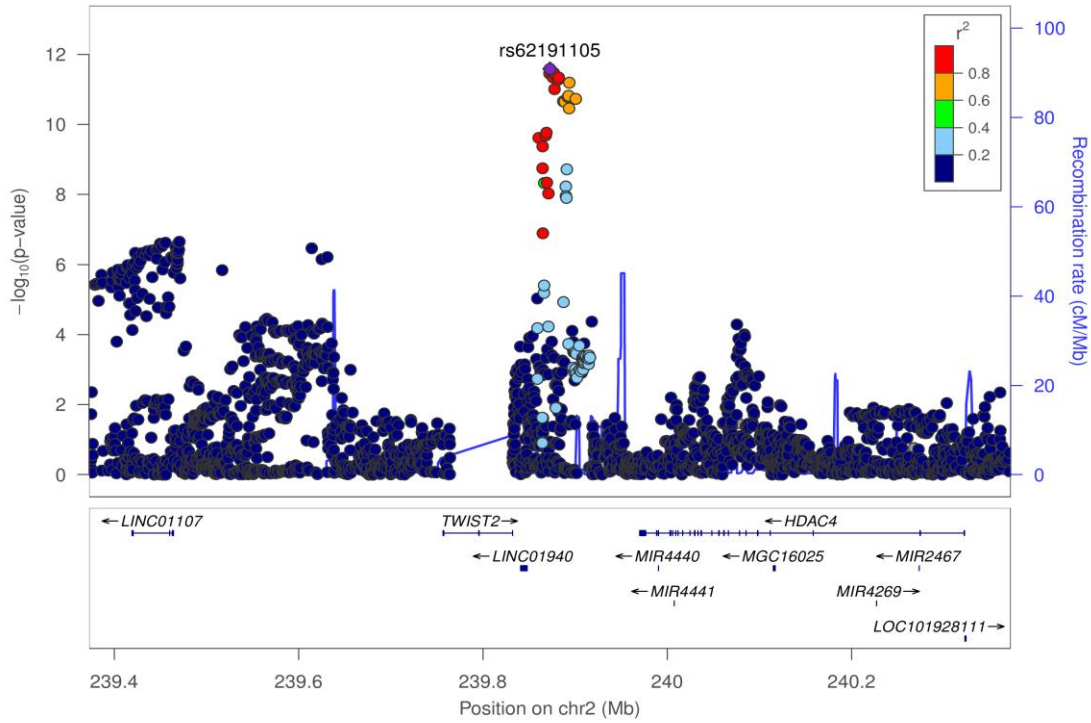
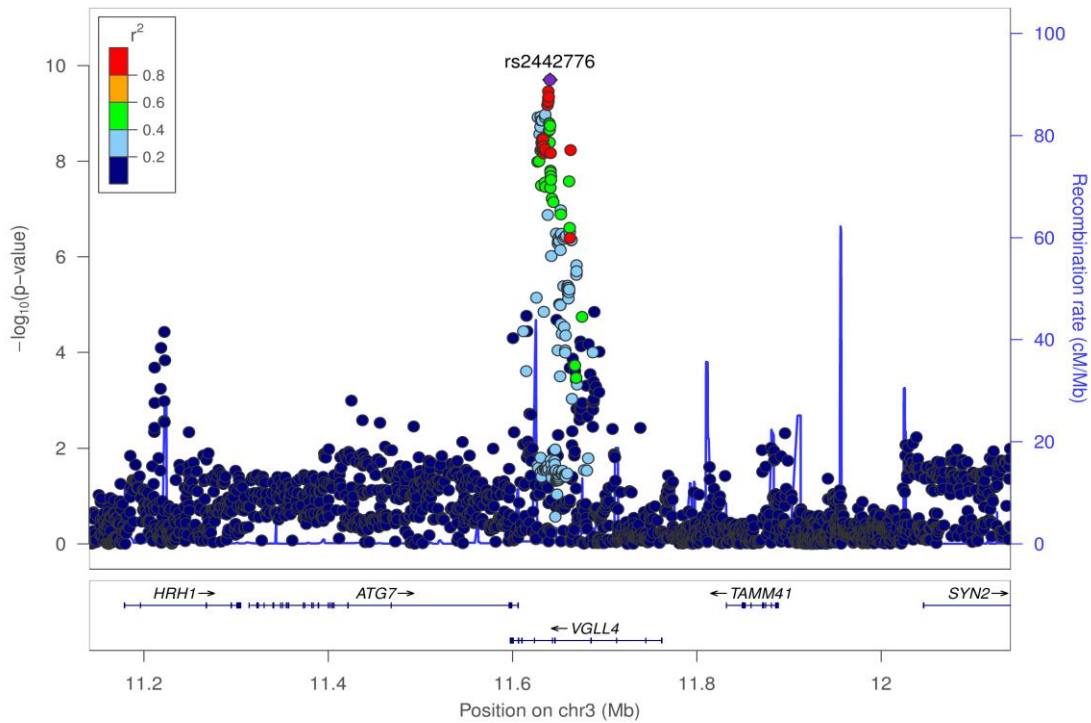
Supplementary Figure 2-5: Regional association plot for rs629619 (*DENND2D* locus at 1p13.3)Supplementary Figure 2-6: Regional association plot for rs3009947 (*TGFB2* locus at 1q41)

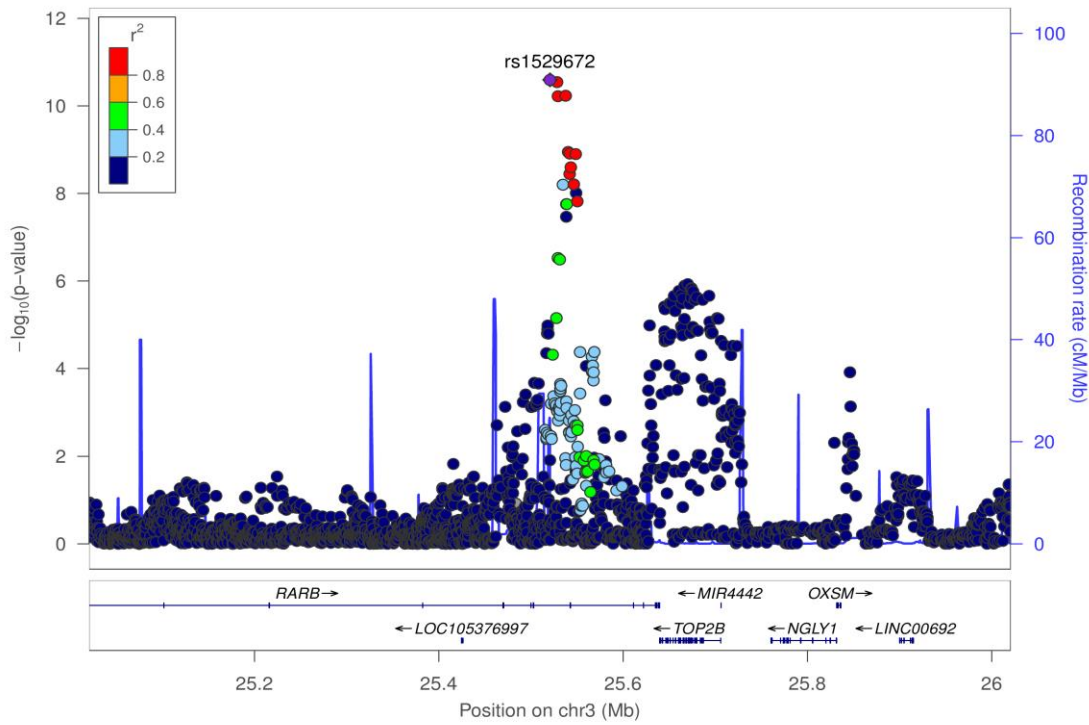
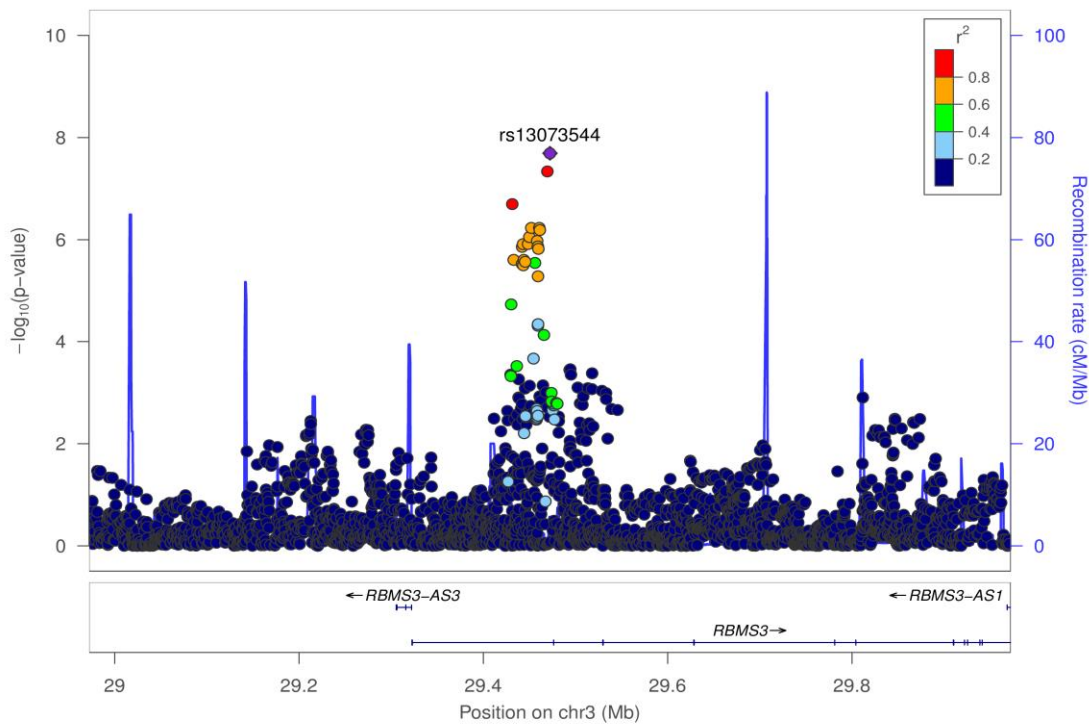
Supplementary Figure 2-7: Regional association plot for rs11118406 (*SLC30A10* locus at 1q41)Supplementary Figure 2-8: Regional association plot for rs11579382 (*CHRM3* locus at 1q43)

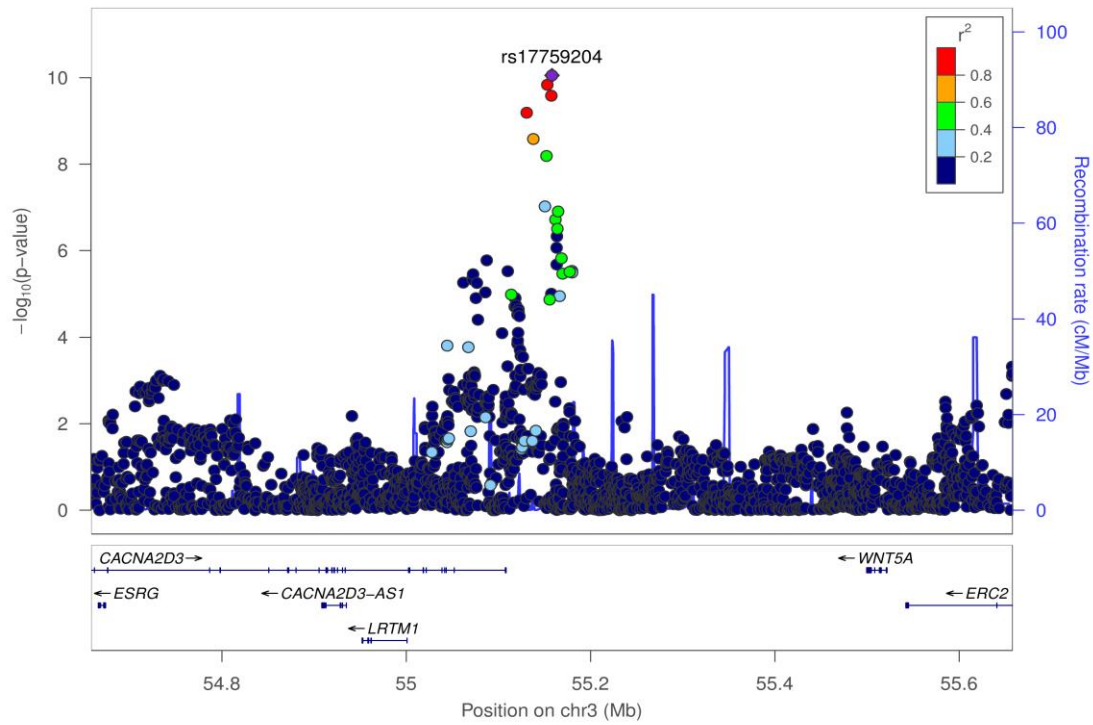
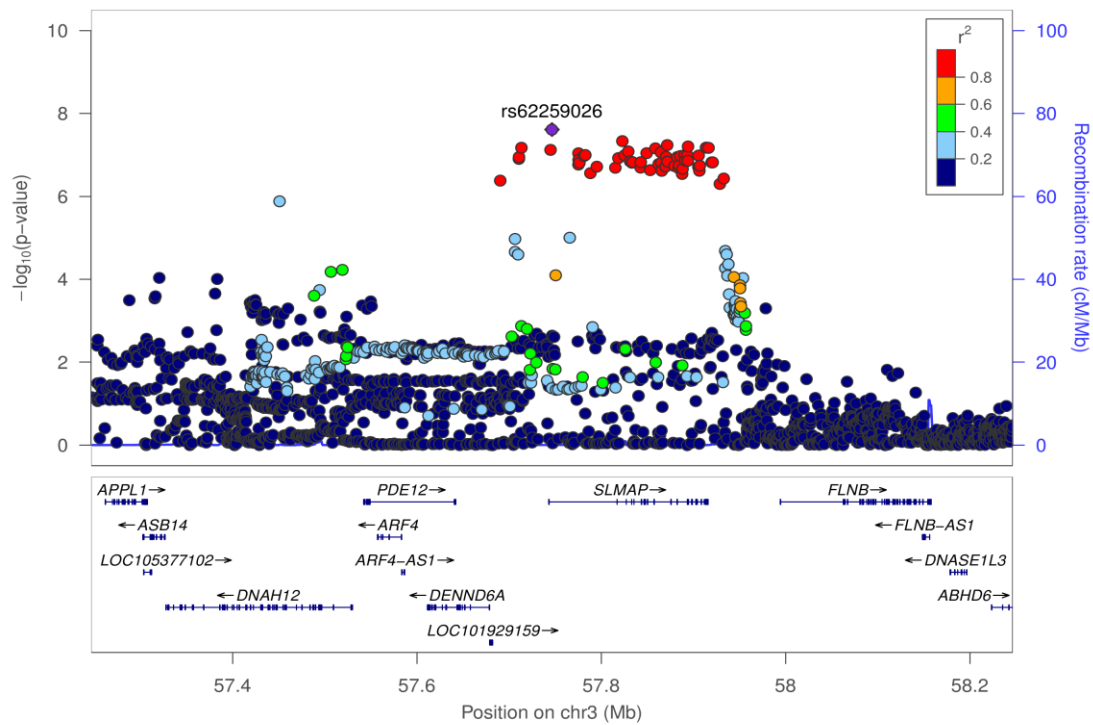
Supplementary Figure 2-9: Regional association plot for rs955277 (*ASAP2* locus at 2p25.1)Supplementary Figure 2-10: Regional association plot for rs10929386 (*DDX1* locus at 2p24.3)

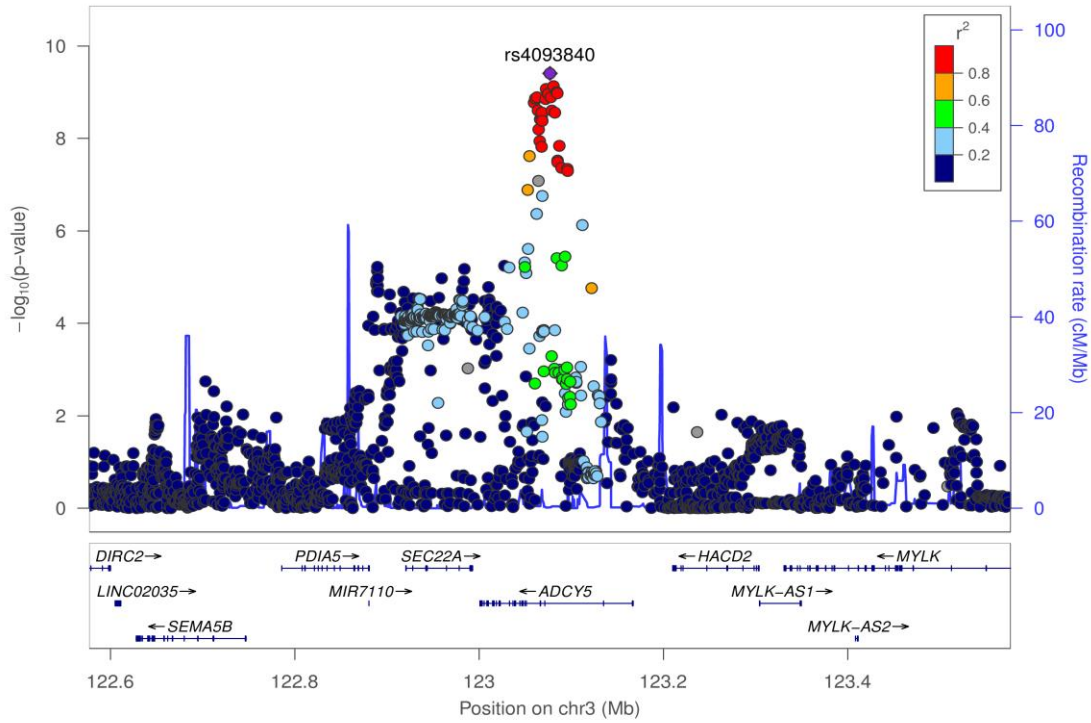
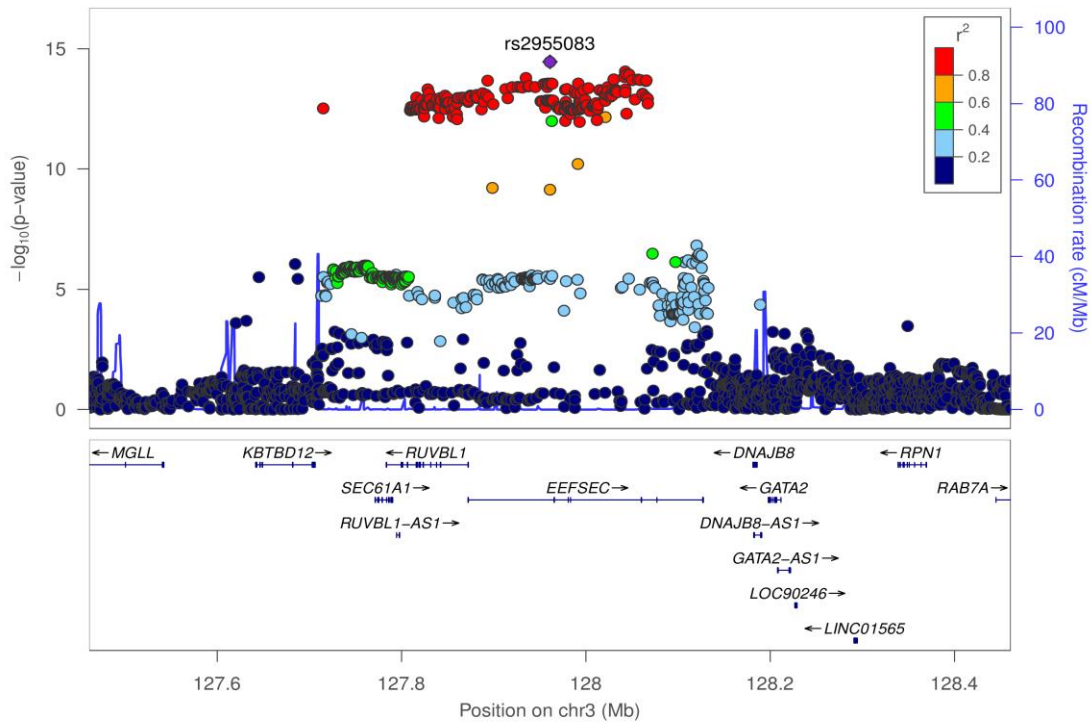
Supplementary Figure 2-11: Regional association plot for rs12466981 (*EML4* locus at 2p21)Supplementary Figure 2-12: Regional association plot for rs72902175 (*NR4A2* locus at 2q24.1)

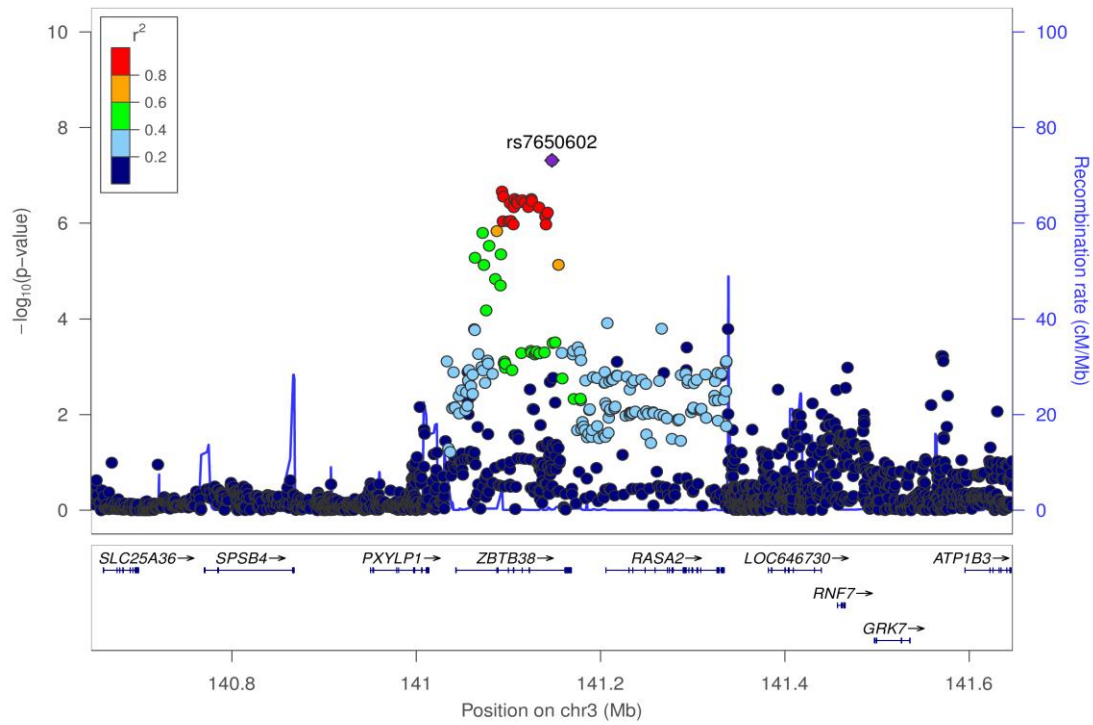
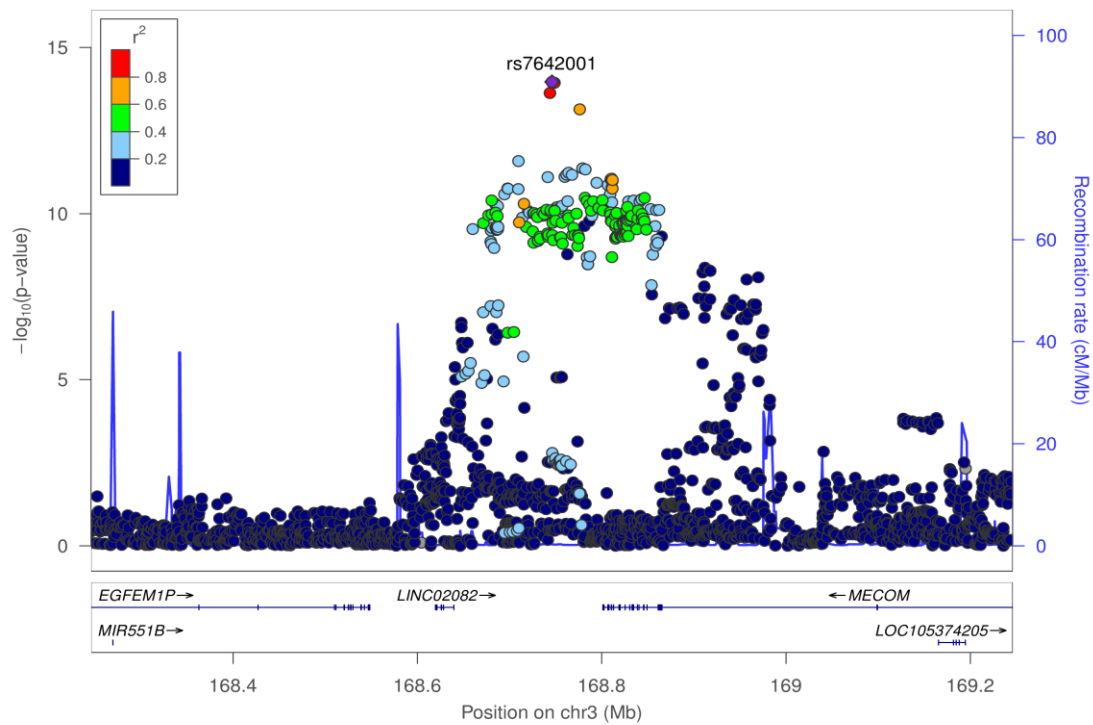
Supplementary Figure 2-13: Regional association plot for rs2571445 (*TNS1* locus at 2q35)Supplementary Figure 2-14: Regional association plot for rs16825267 (*PID1* locus at 2q36.3)

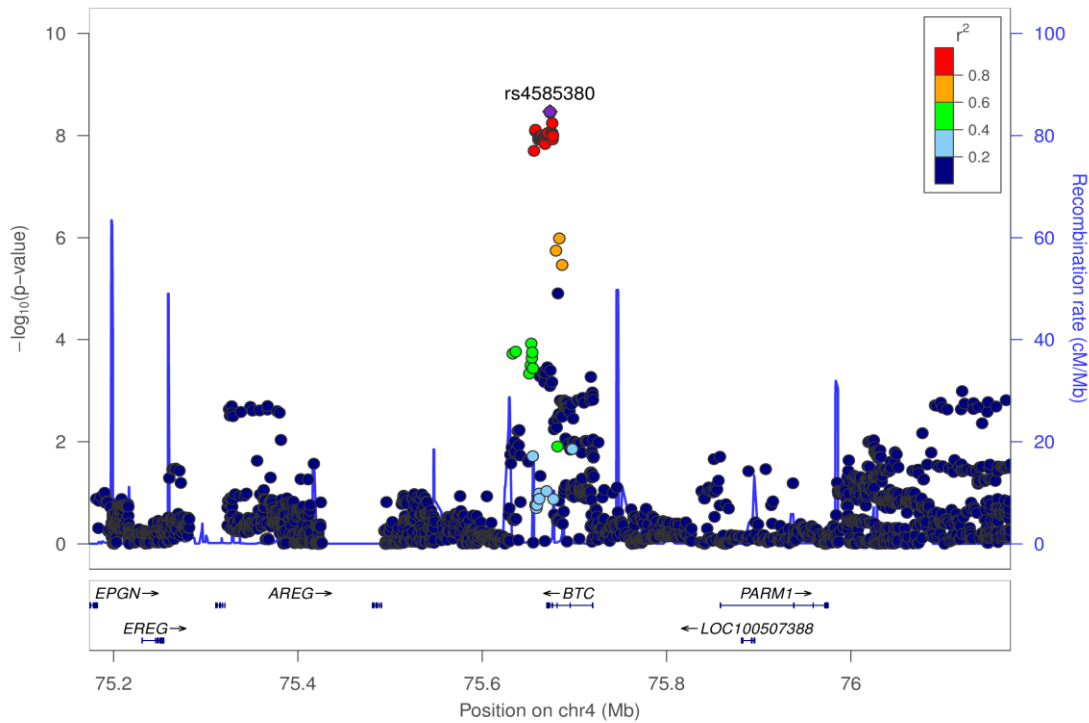
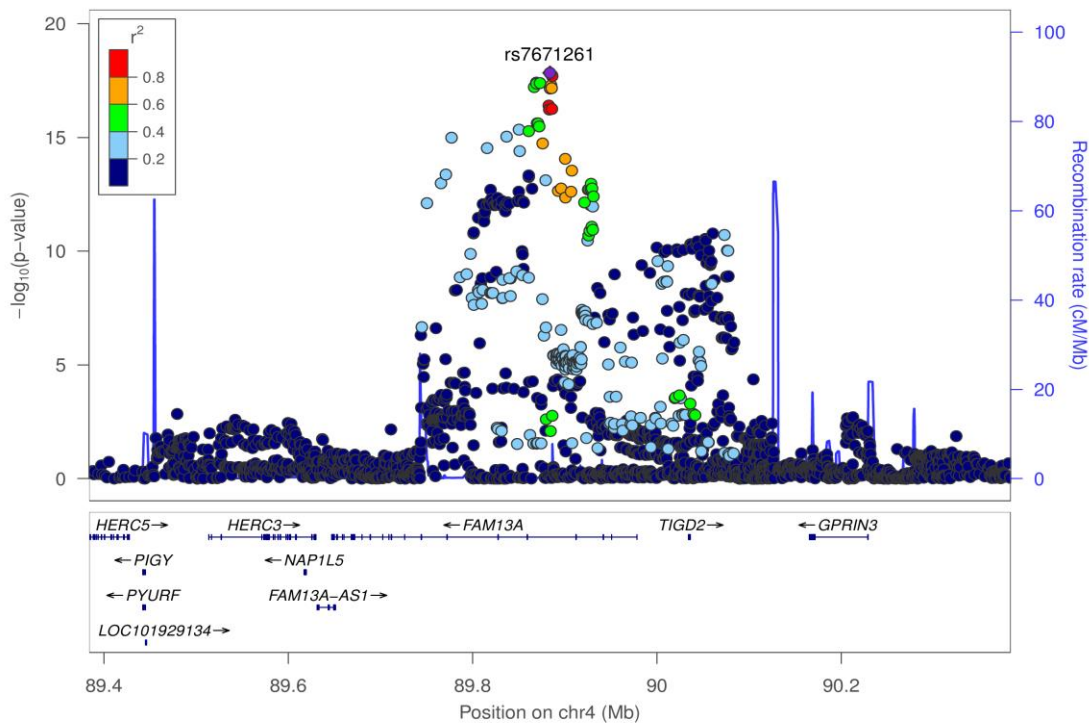
Supplementary Figure 2-15: Regional association plot for rs62191105 (*TWIST2* locus at 2q37.3)Supplementary Figure 2-16: Regional association plot for rs2442776 (*VGLL4* locus at 3p25.3)

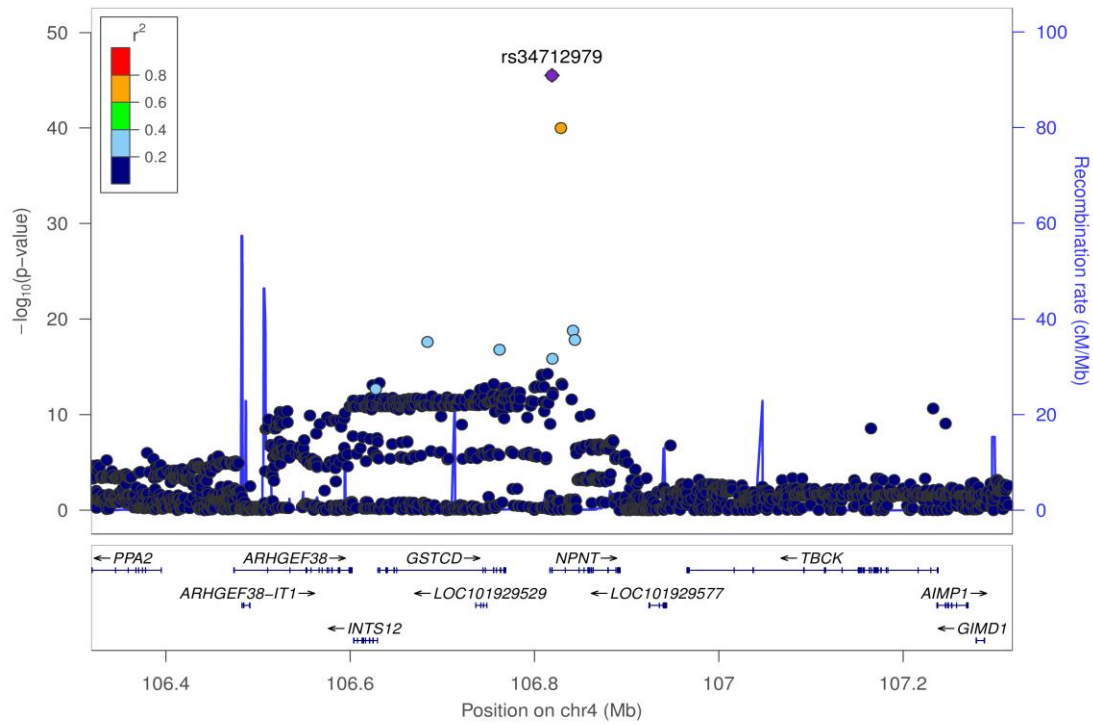
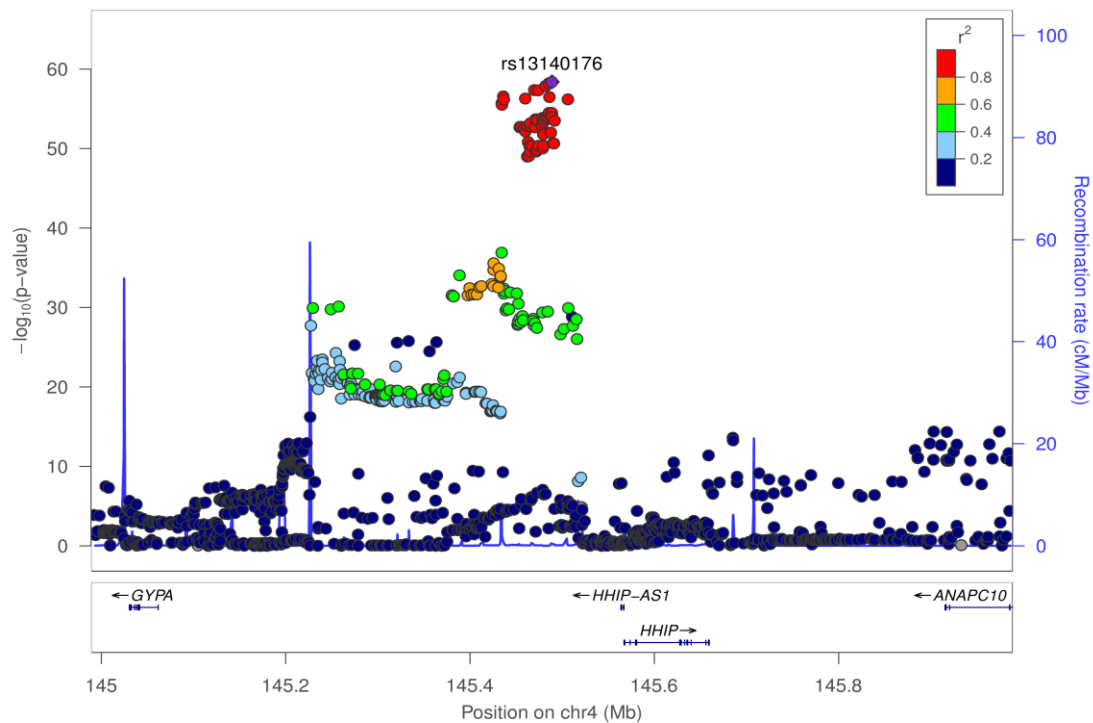
Supplementary Figure 2-17: Regional association plot for rs1529672 (*RARB* locus at 3p24.2)Supplementary Figure 2-18: Regional association plot for rs13073544 (*RBMS3* locus at 3p24.1)

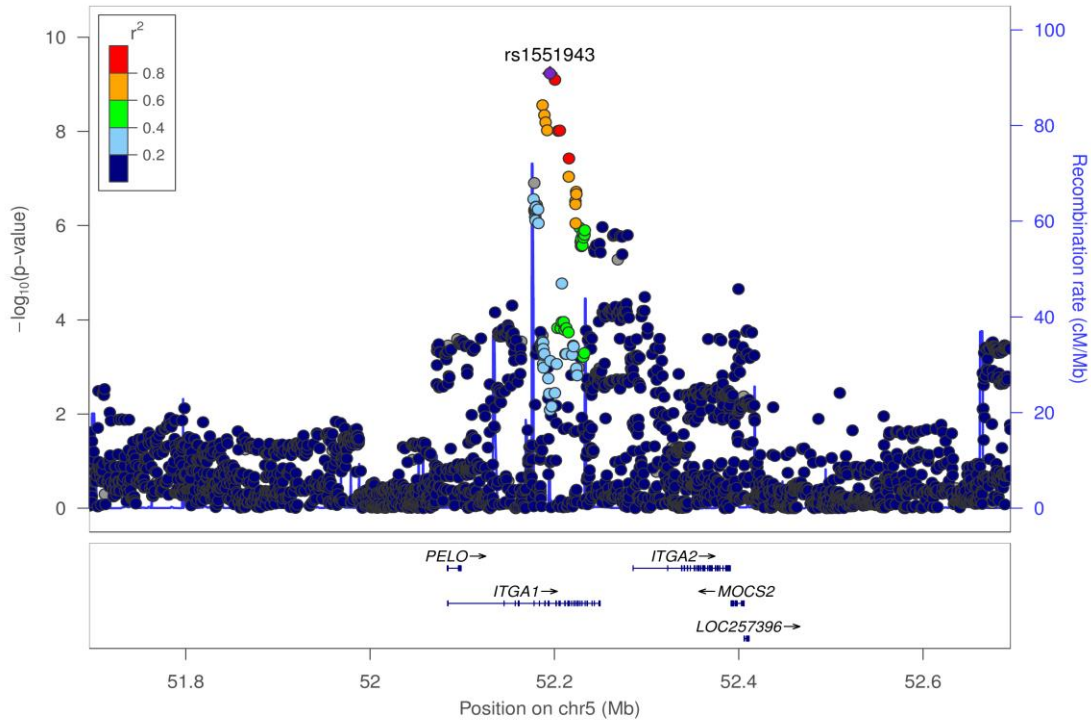
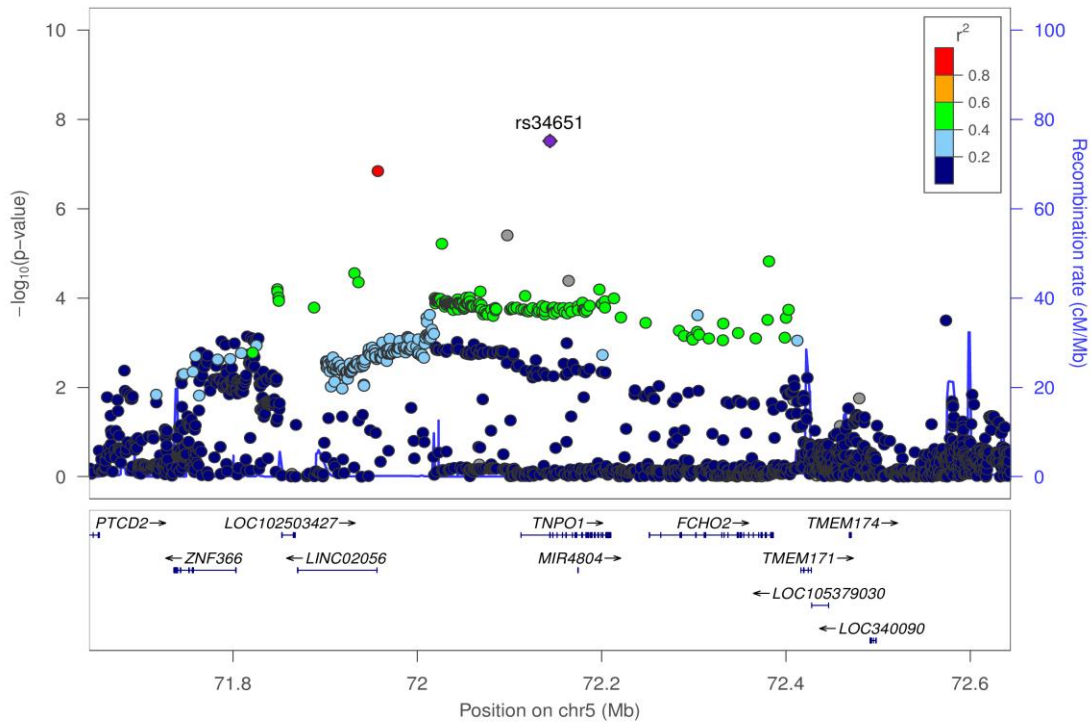
Supplementary Figure 2-19: Regional association plot for rs17759204 (*CACNA2D3* locus at 3p14.3)Supplementary Figure 2-20: Regional association plot for rs62259026 (*SLMAP* locus at 3p14.3)

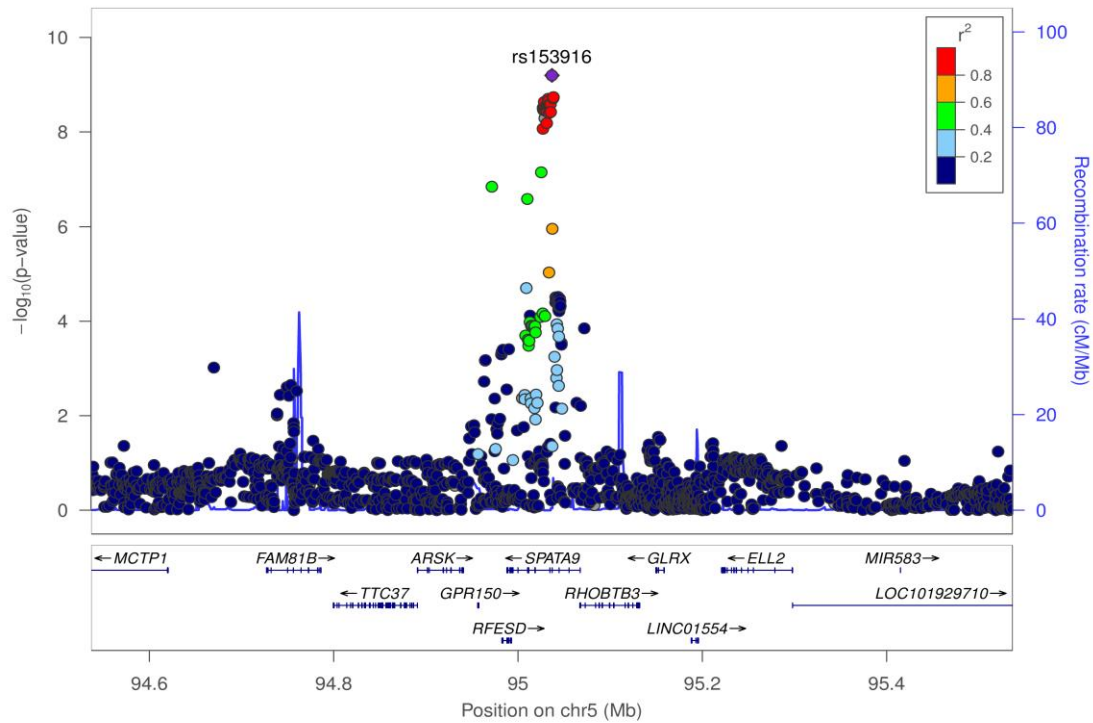
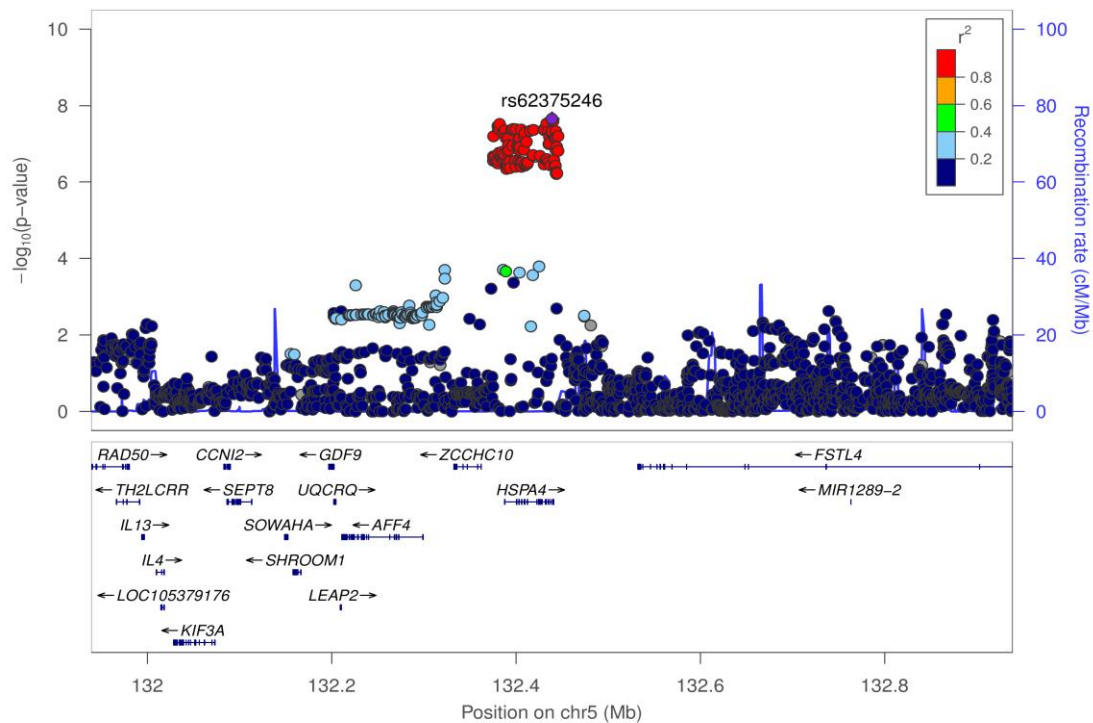
Supplementary Figure 2-21: Regional association plot for rs4093840 (*ADCY5* locus at 3q21.1)Supplementary Figure 2-22: Regional association plot for rs2955083 (*EEFSEC* locus at 3q21.3)

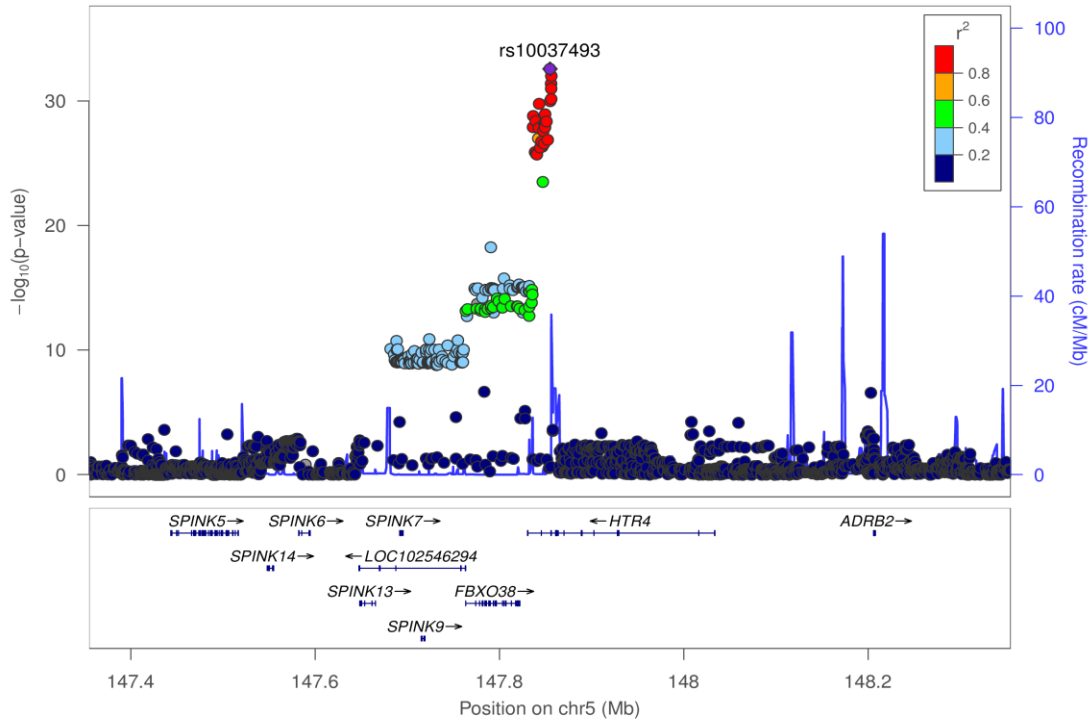
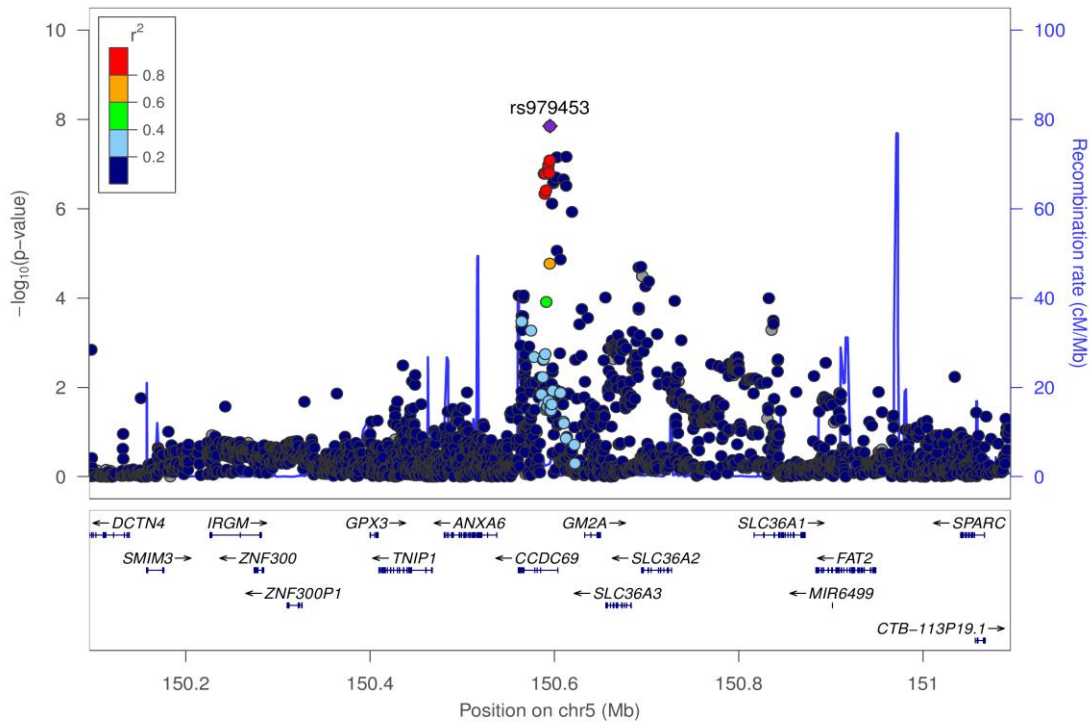
Supplementary Figure 2-23: Regional association plot for rs7650602 (*ZBTB38* locus at 3q23)Supplementary Figure 2-24: Regional association plot for rs7642001 (*MECOM* locus at 3q26.2)

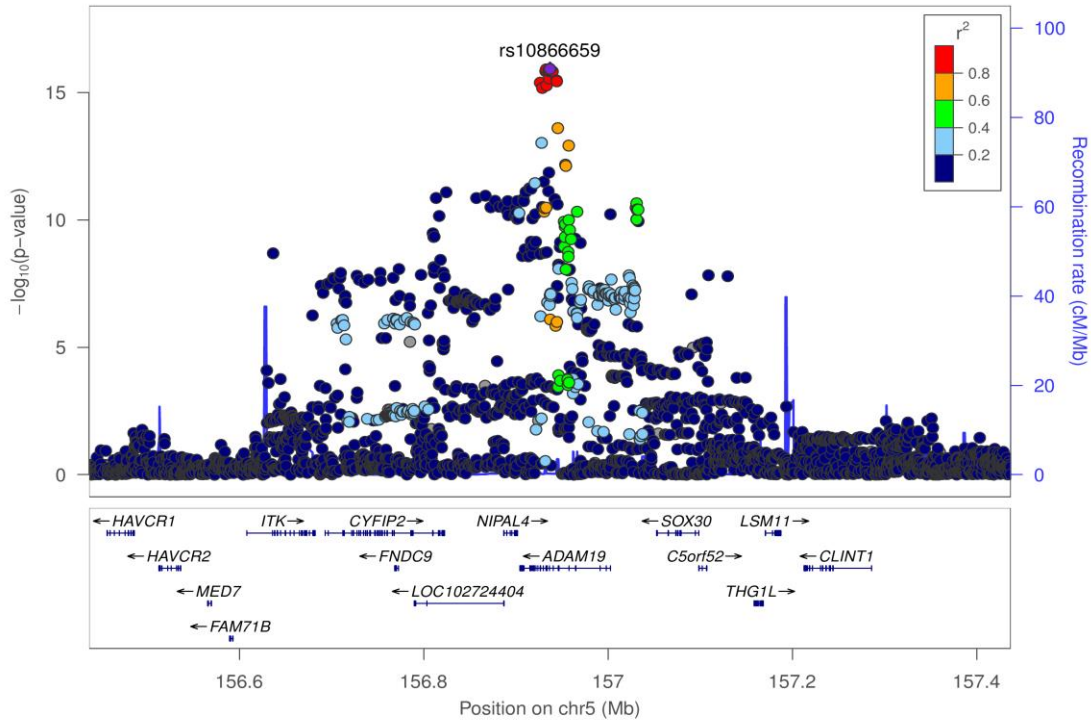
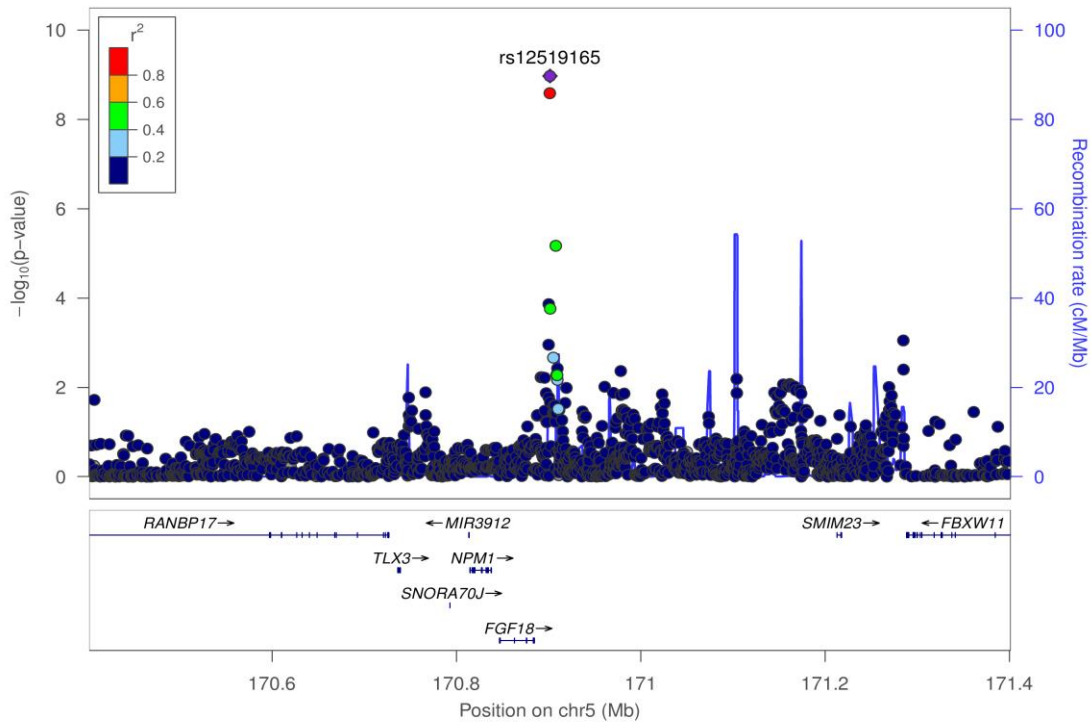
Supplementary Figure 2-25: Regional association plot for rs4585380 (*BTC* locus at 4q13.3)Supplementary Figure 2-26: Regional association plot for rs7671261 (*FAM13A* locus at 4q22.1)

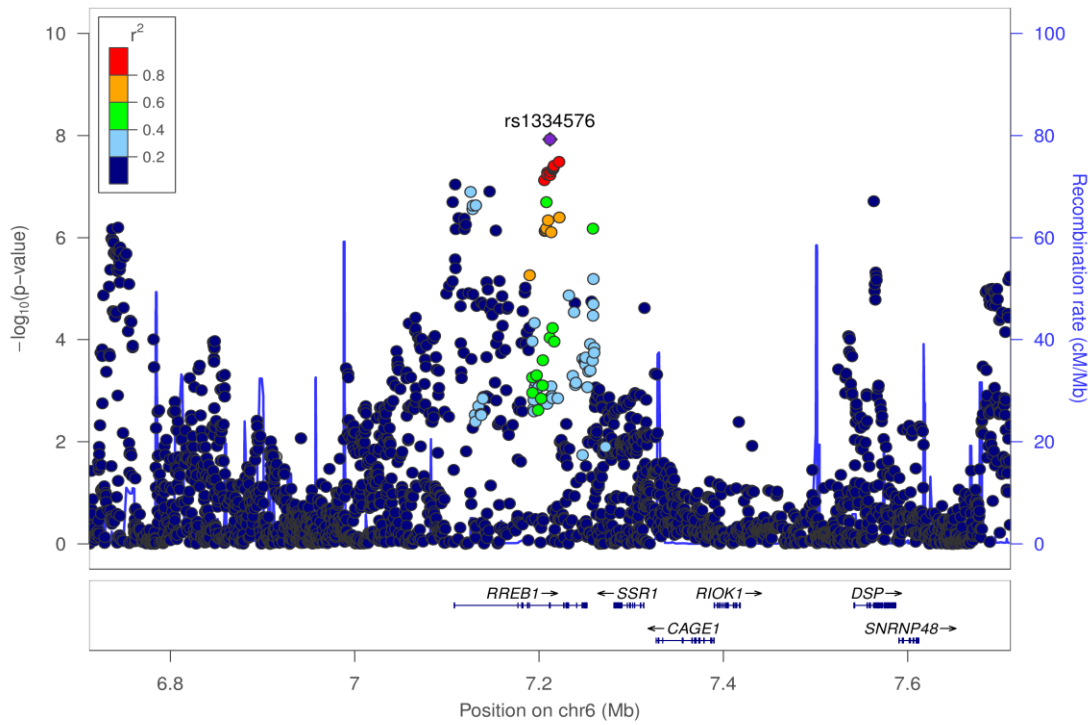
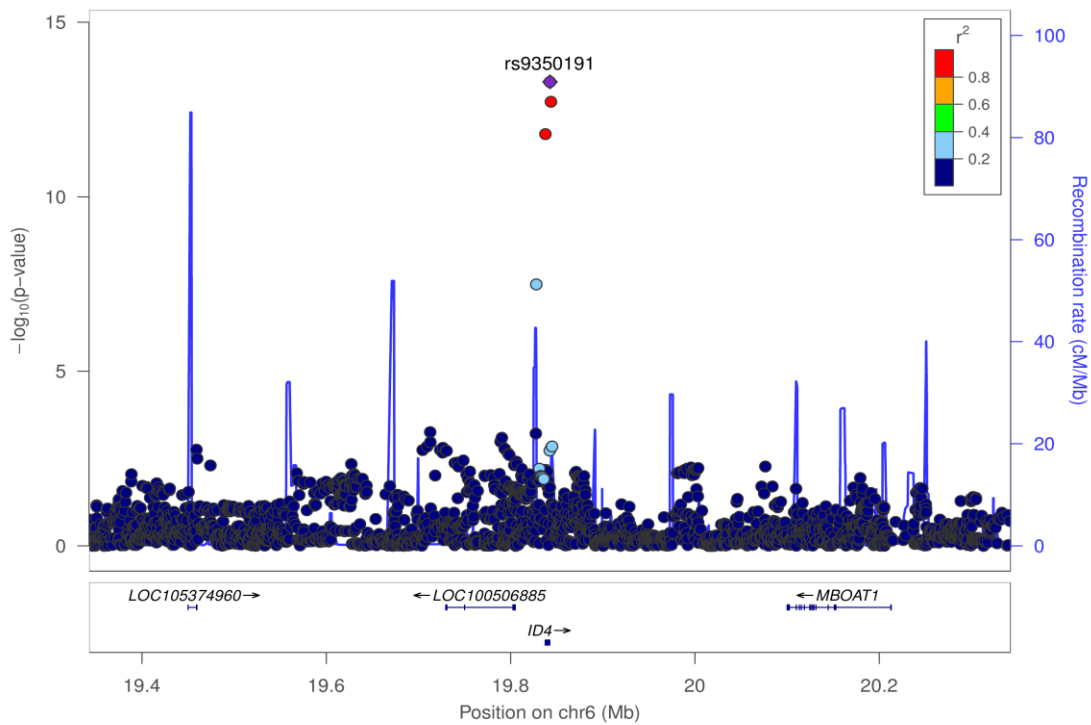
Supplementary Figure 2-27: Regional association plot for rs34712979 (*NPNT* locus at 4q24)Supplementary Figure 2-28: Regional association plot for rs13140176 (*HHIP* locus at 4q31.21)

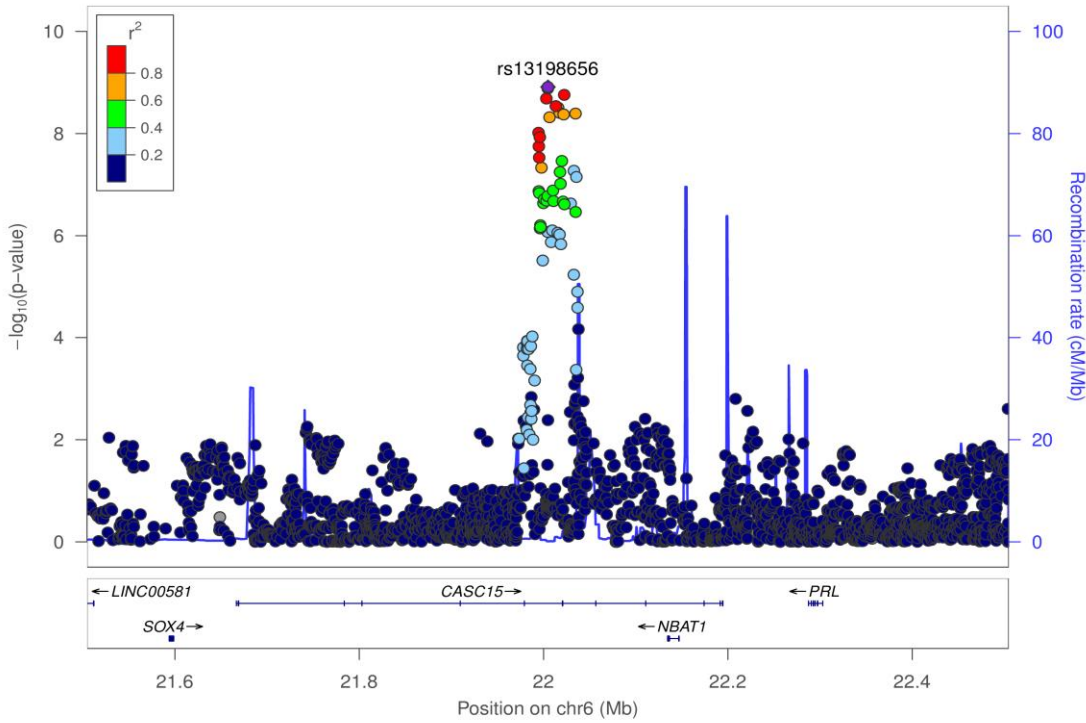
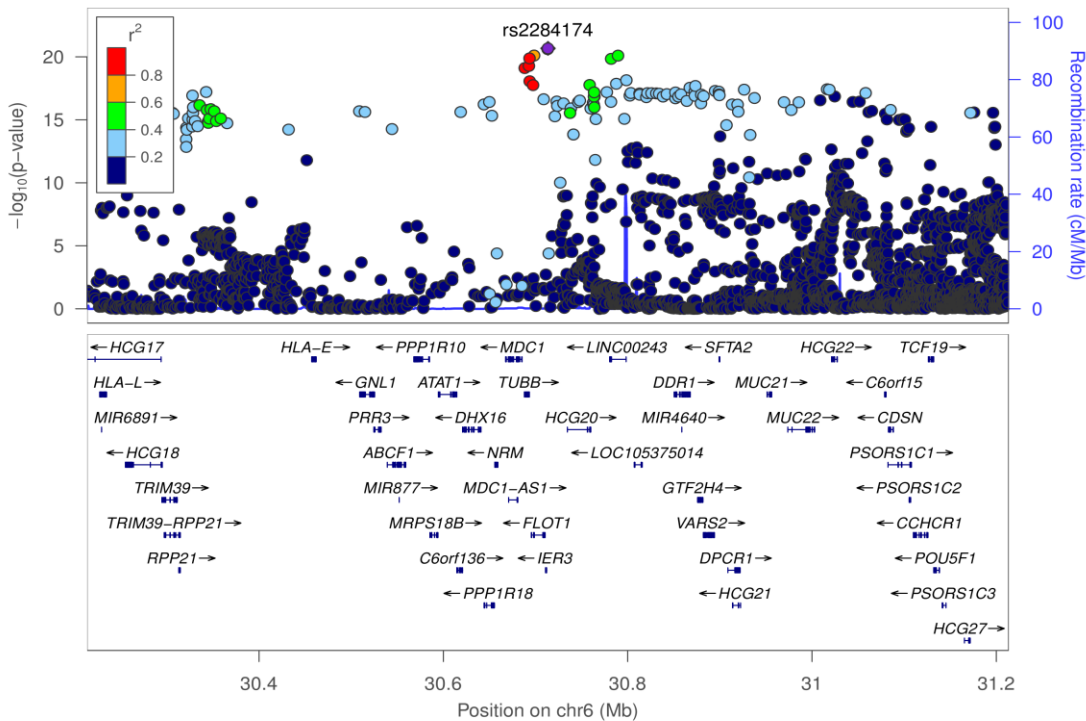
Supplementary Figure 2-29: Regional association plot for rs1551943 (*ITGA1* locus at 5q11.2)Supplementary Figure 2-30: Regional association plot for rs34651 (*TNPO1* locus at 5q13.2)

Supplementary Figure 2-31: Regional association plot for rs153916 (*SPATA9* locus at 5q15)Supplementary Figure 2-32: Regional association plot for rs62375246 (*HSPA4* locus at 5q31.1)

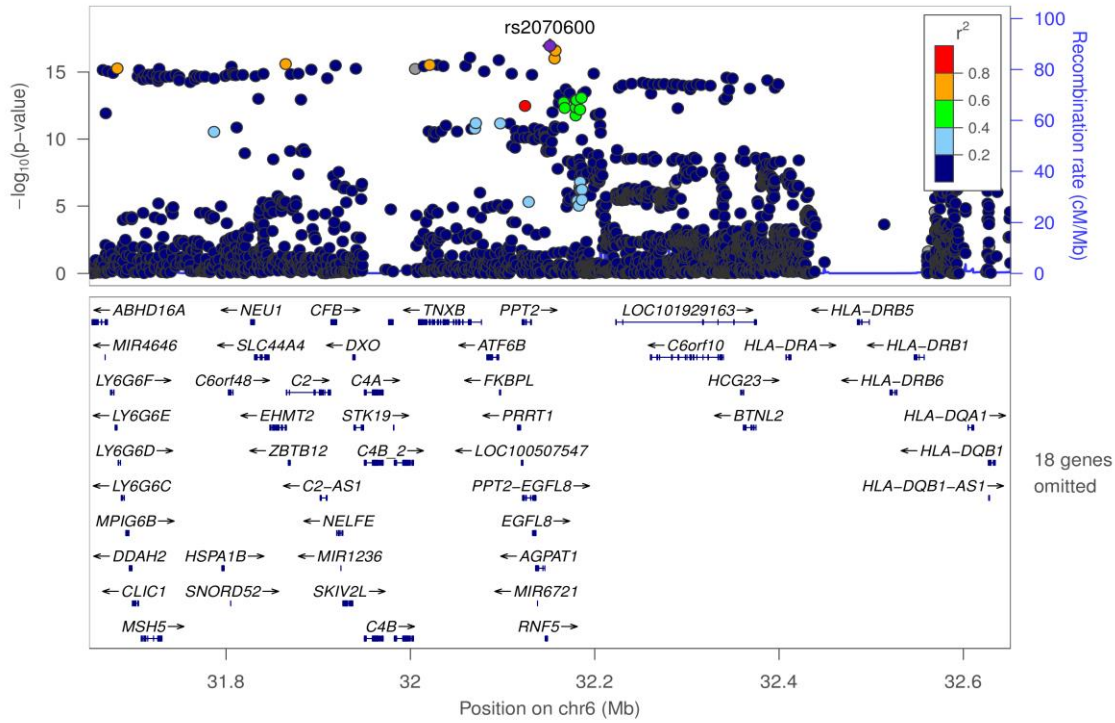
Supplementary Figure 2-33: Regional association plot for rs10037493 (*HTR4* locus at 5q32)Supplementary Figure 2-34: Regional association plot for rs979453 (*CCDC69* locus at 5q33.1)

Supplementary Figure 2-35: Regional association plot for rs10866659 (*ADAM19* locus at 5q33.3)Supplementary Figure 2-36: Regional association plot for rs12519165 (*FGF18* locus at 5q35.1)

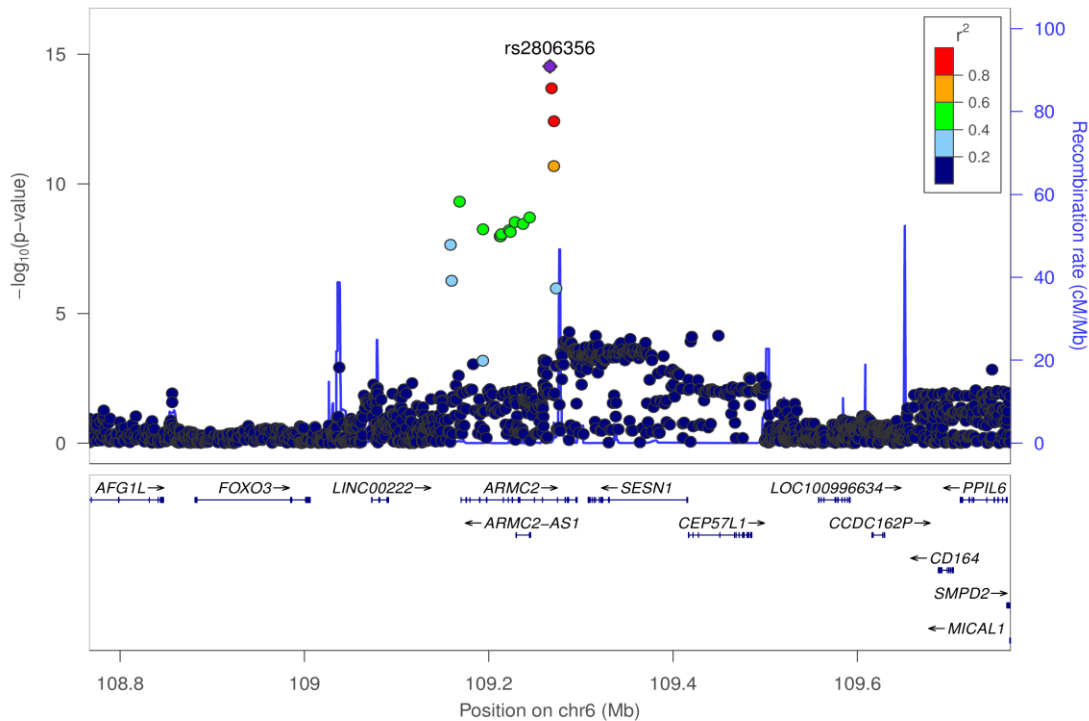
Supplementary Figure 2-37: Regional association plot for rs1334576 (*RREB1* locus at 6p24.3)Supplementary Figure 2-38: Regional association plot for rs9350191 (*ID4* locus at 6p22.3)

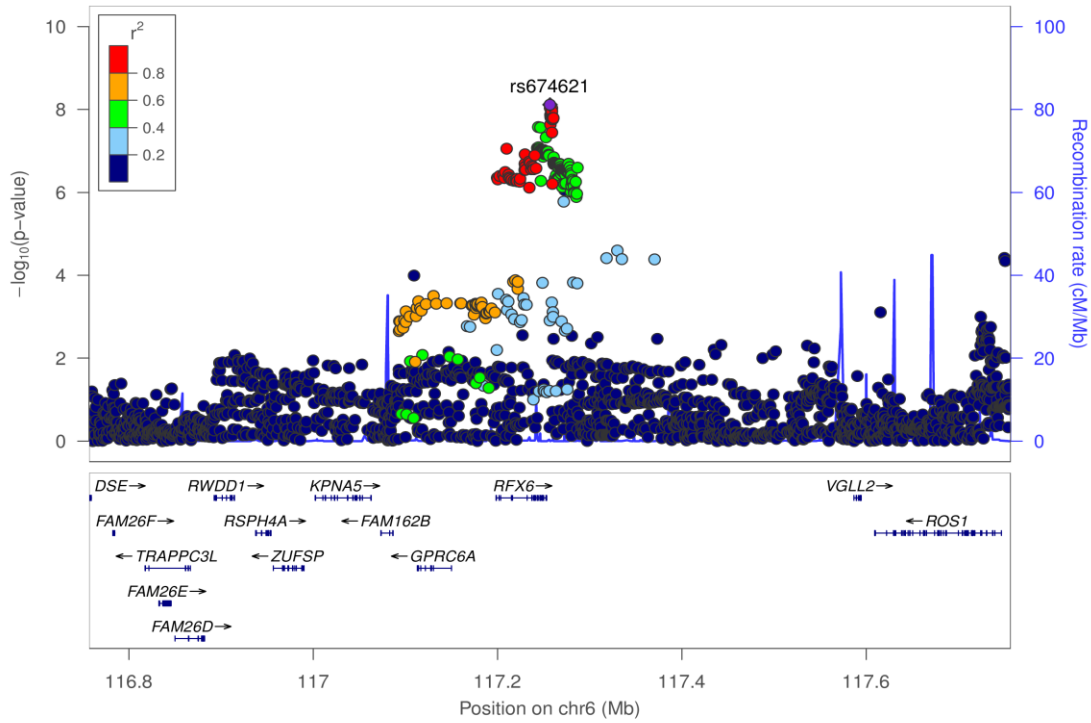
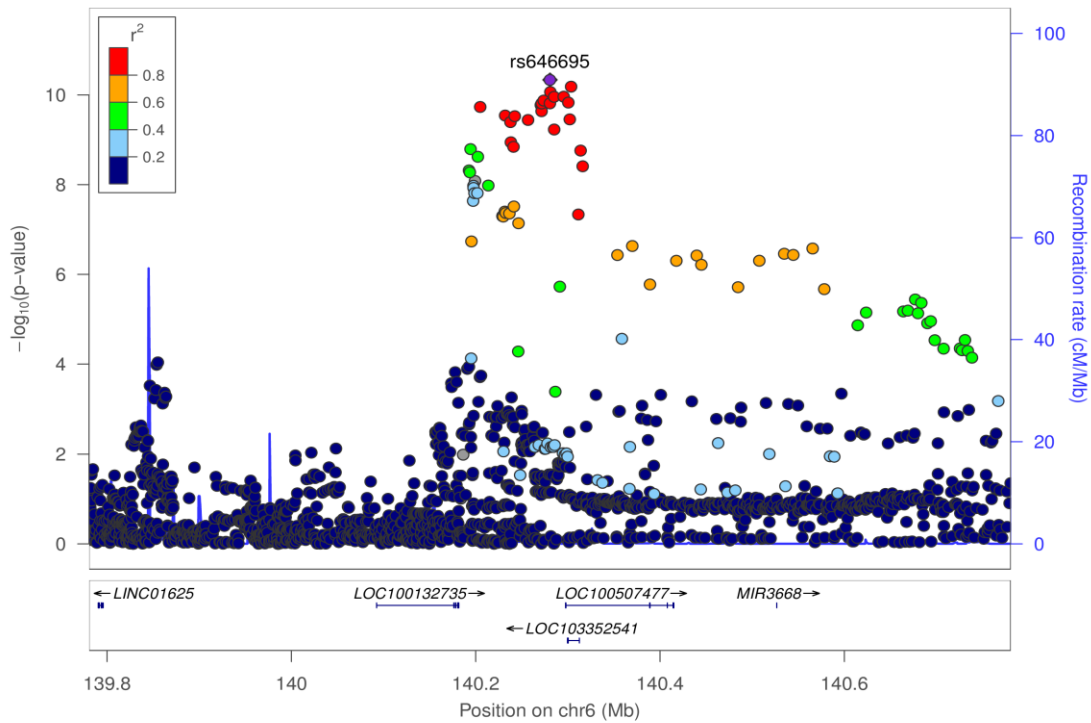
Supplementary Figure 2-39: Regional association plot for rs13198656 (*PRL* locus at 6p22.3)Supplementary Figure 2-40: Regional association plot for rs2284174 (*IER3* locus at 6p21.33)

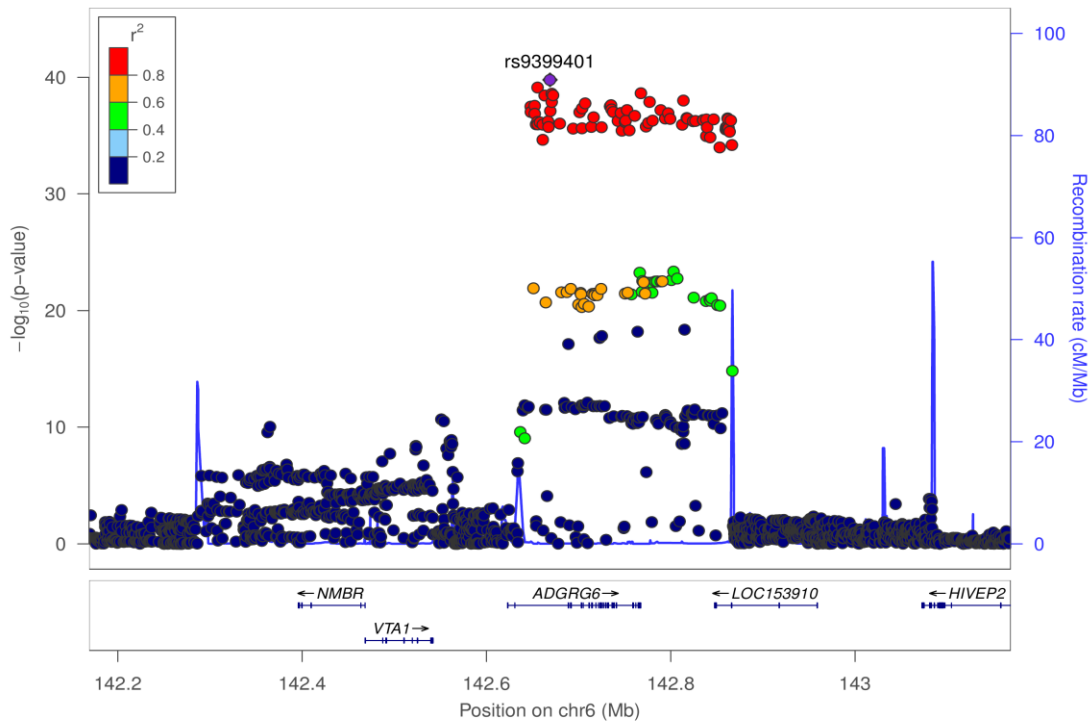
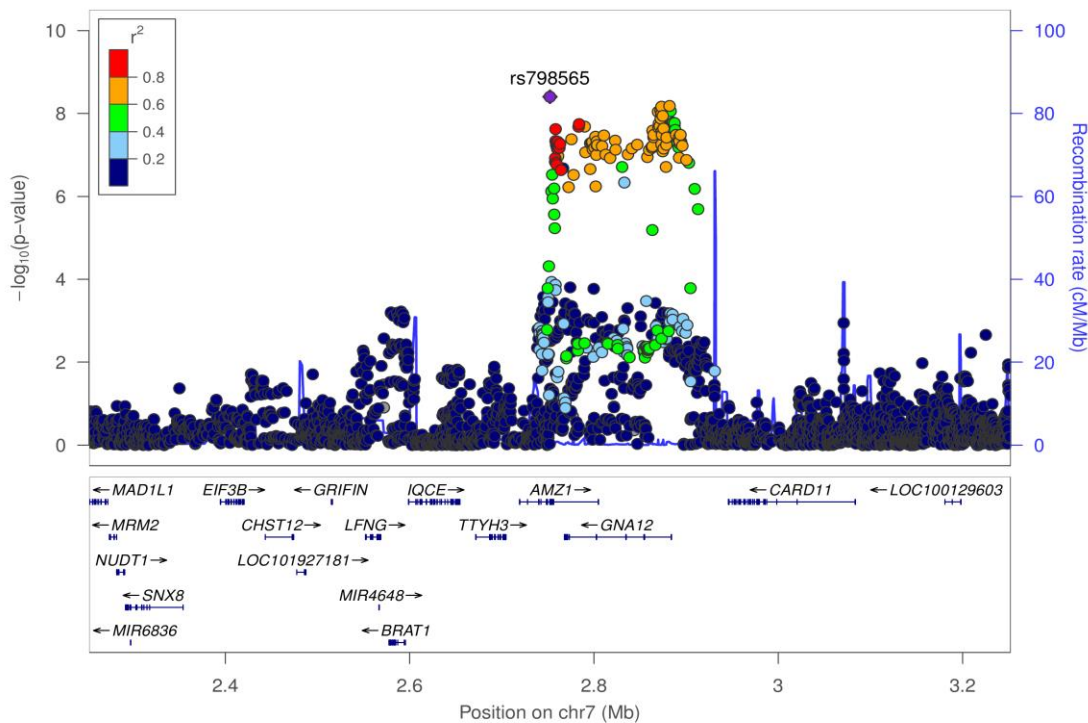
Supplementary Figure 2-41: Regional association plot for rs2070600 (AGER locus at 6p21.32)

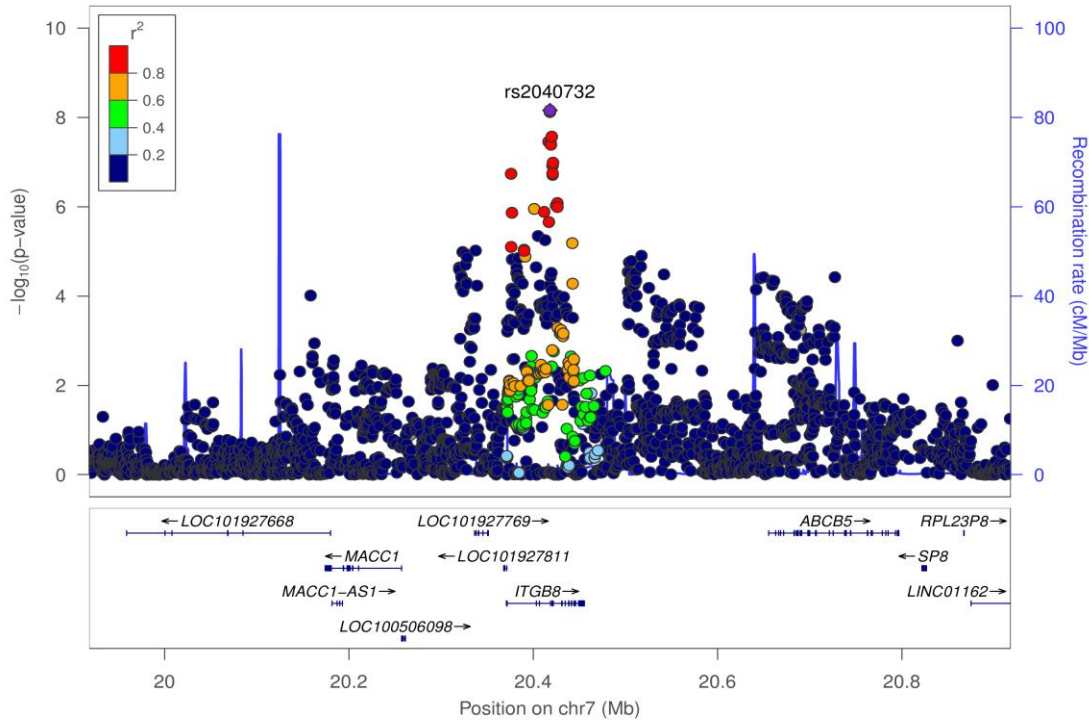
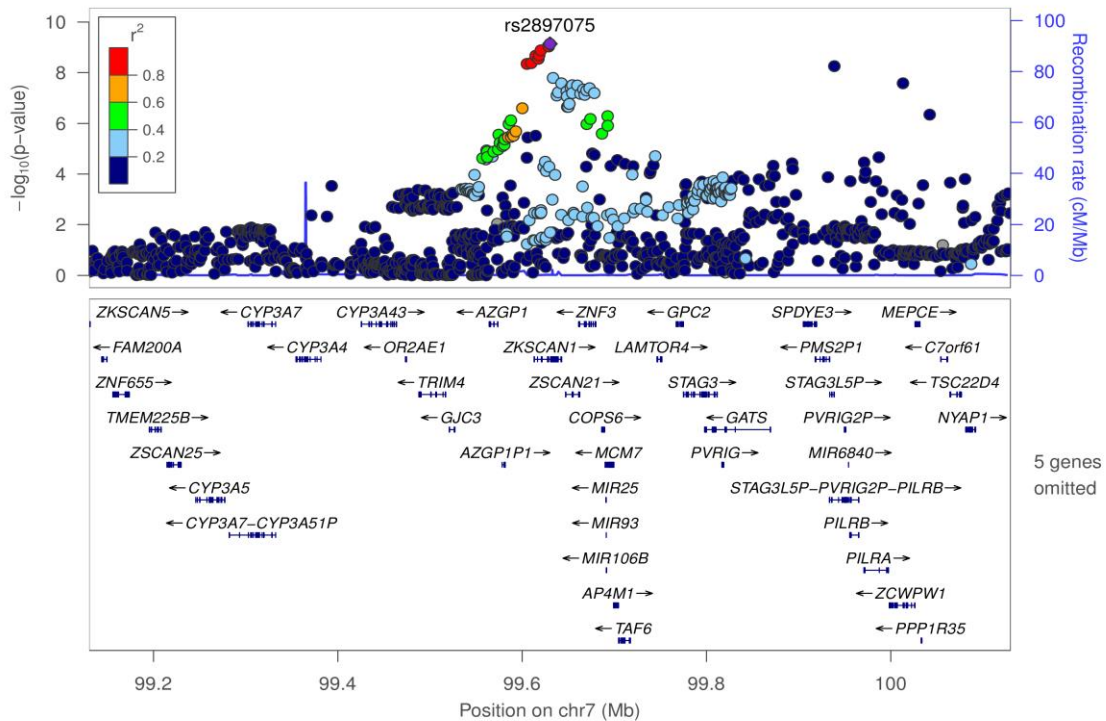


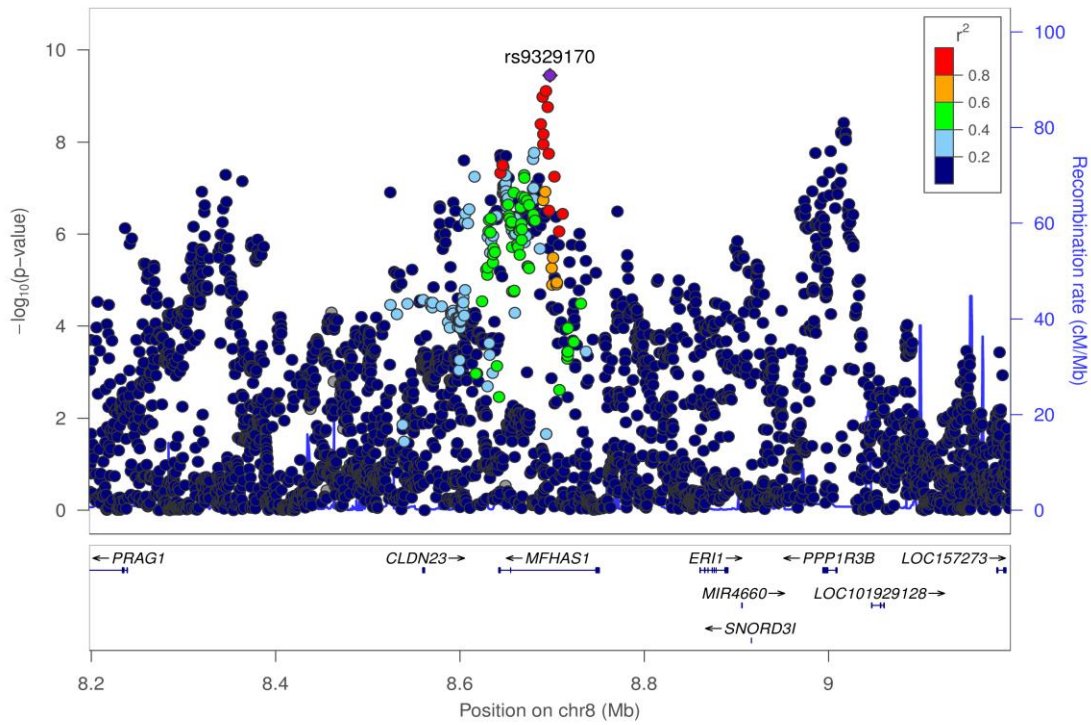
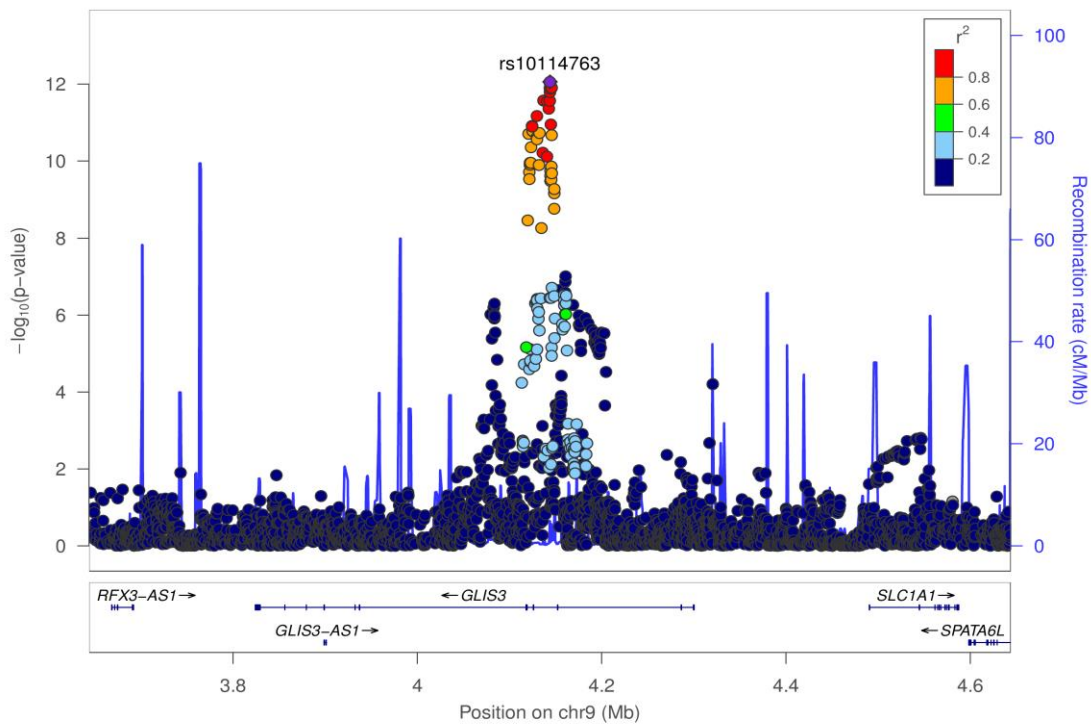
Supplementary Figure 2-42: Regional association plot for rs2806356 (ARMC2 locus at 6q21)

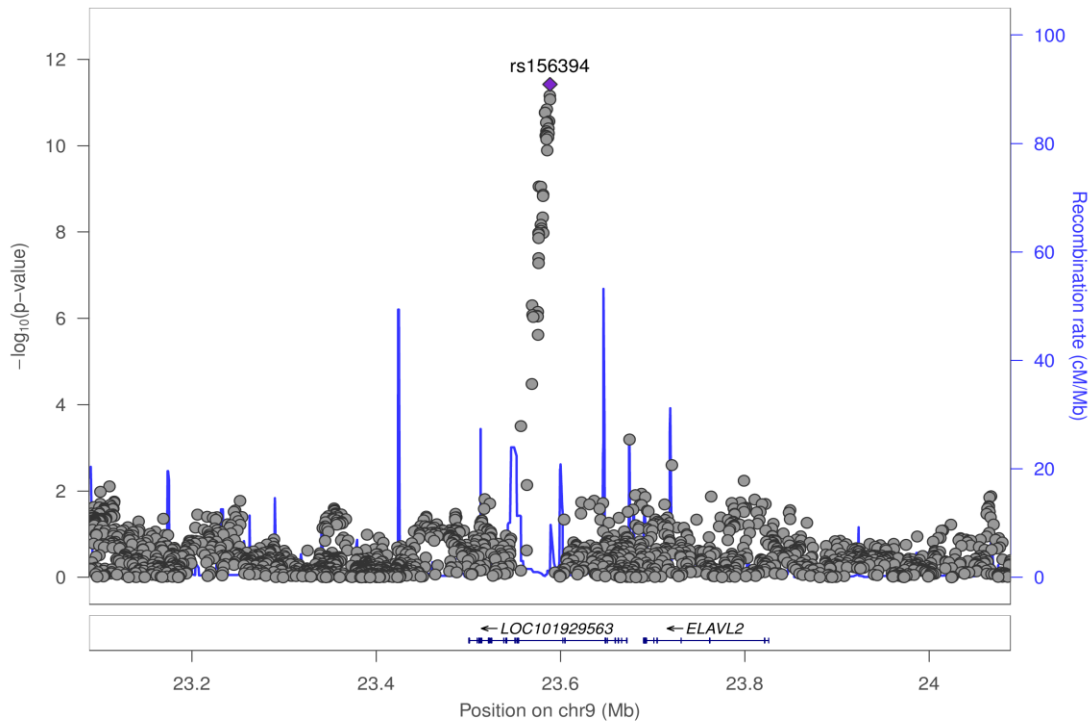
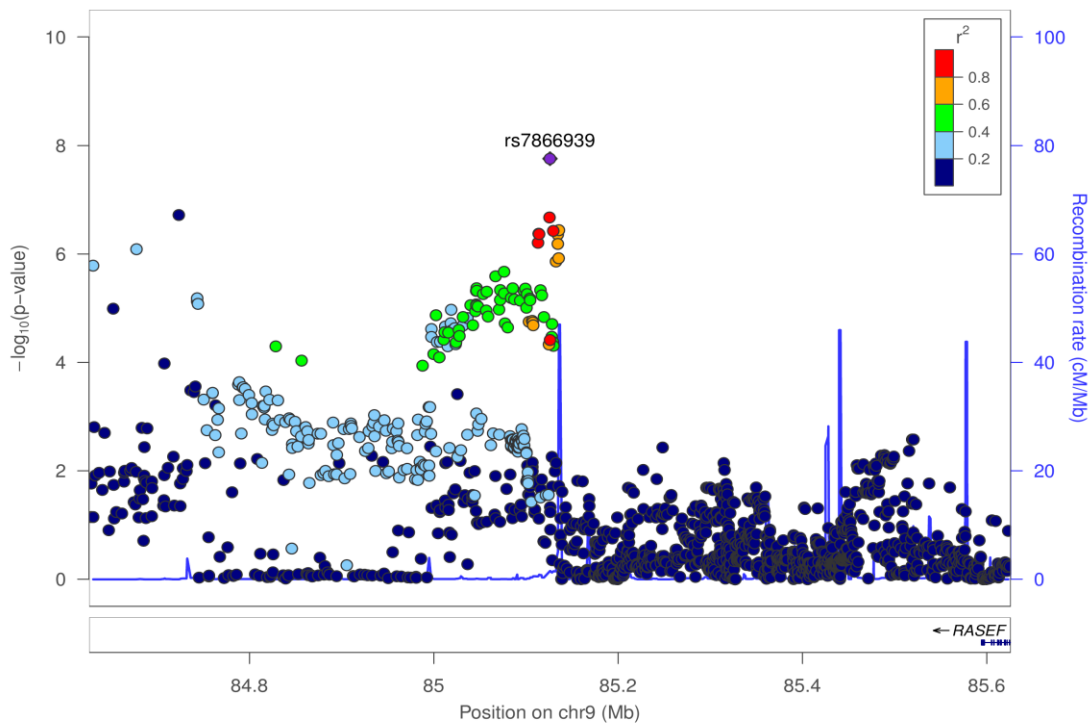


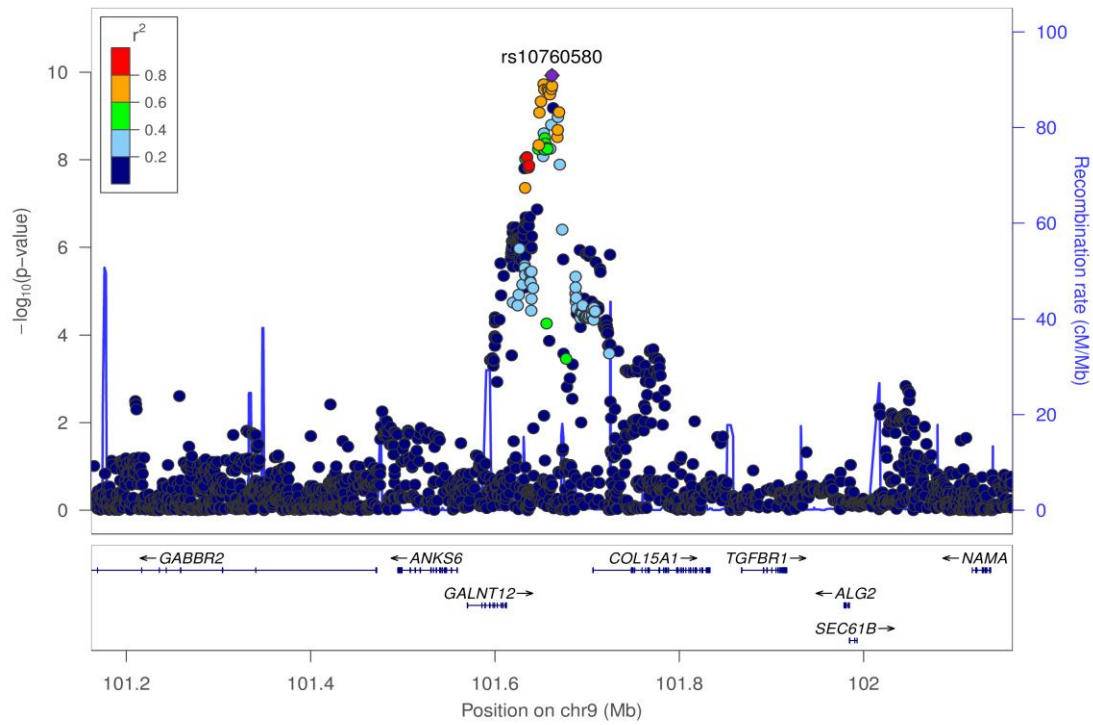
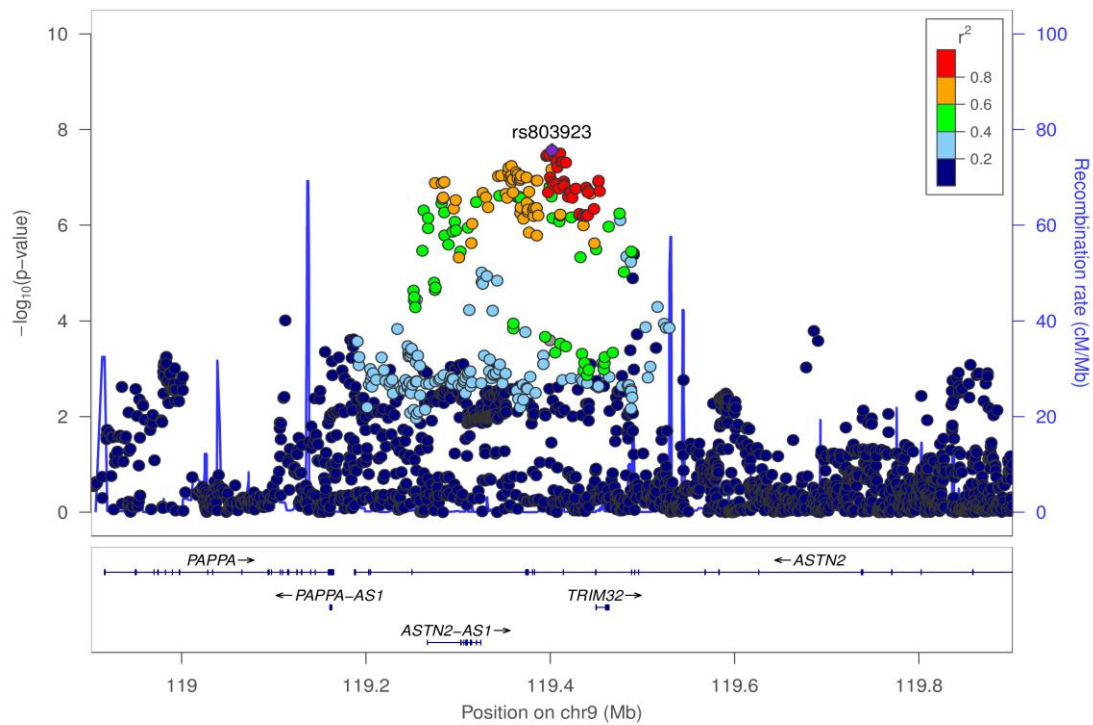
Supplementary Figure 2-43: Regional association plot for rs674621 (*RFX6* locus at 6q22.1)Supplementary Figure 2-44: Regional association plot for rs646695 (*CITED2* locus at 6q24.1)

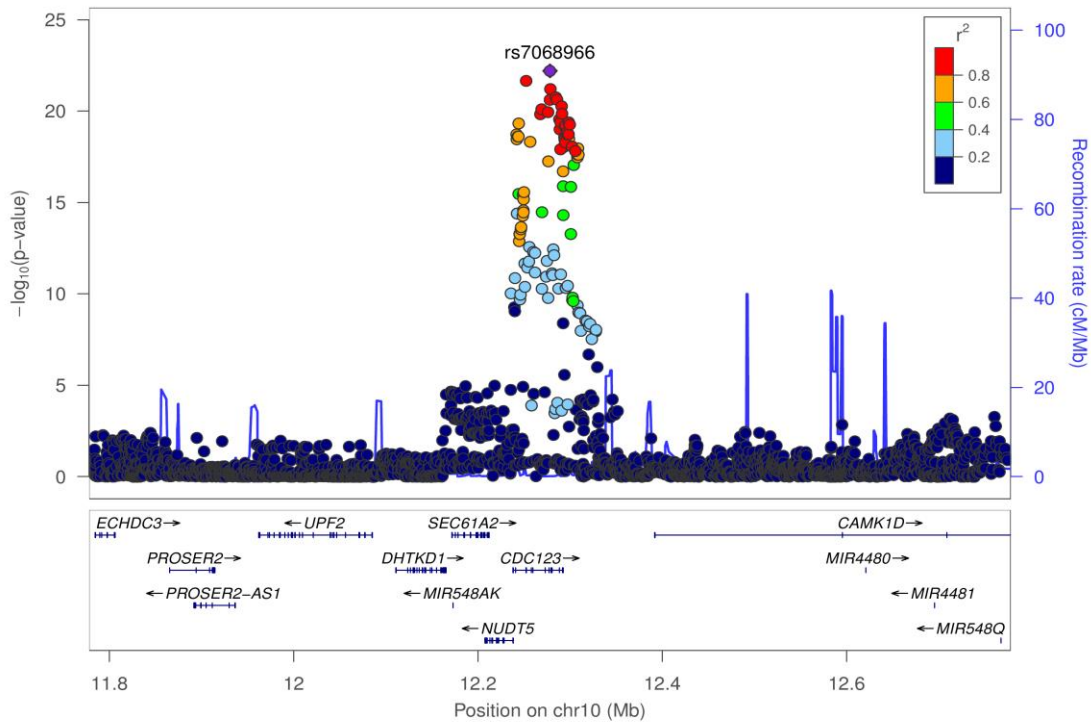
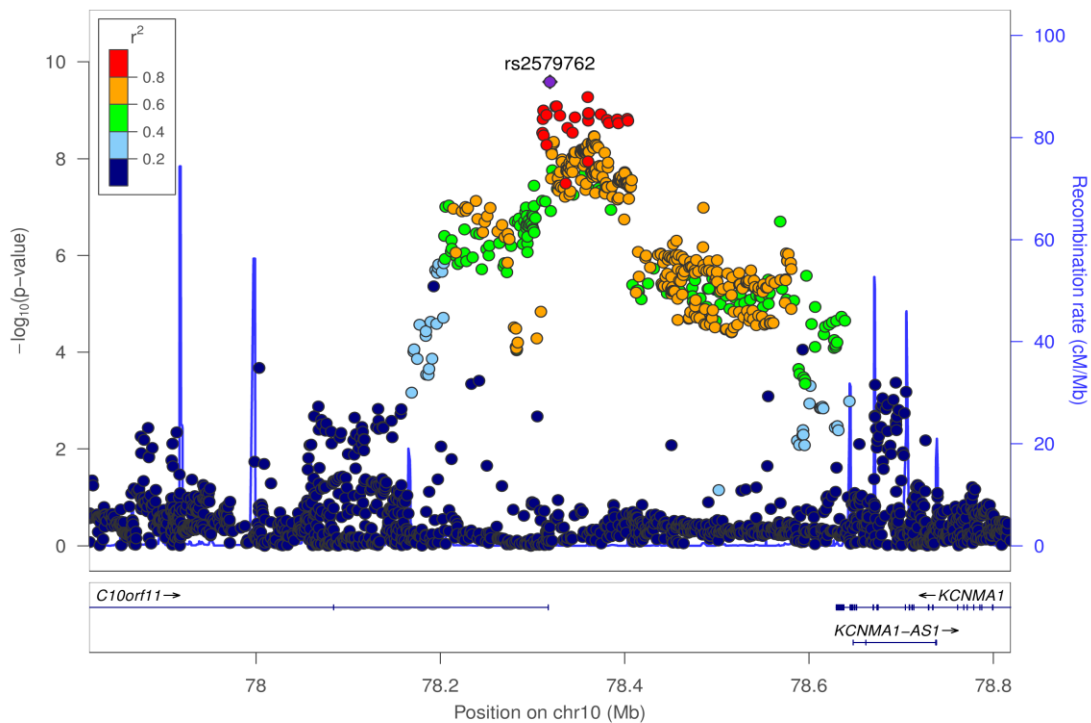
Supplementary Figure 2-45: Regional association plot for rs9399401 (*ADGRG6* locus at 6q24.1)Supplementary Figure 2-46: Regional association plot for rs798565 (*AMZ1* locus at 7p22.3)

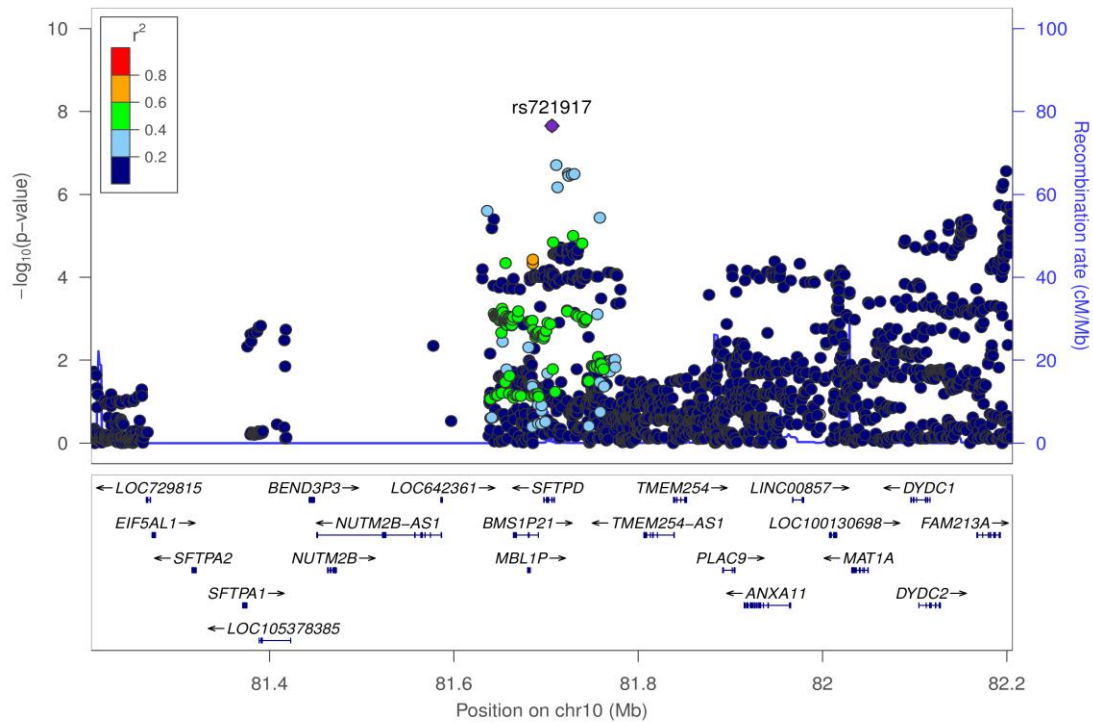
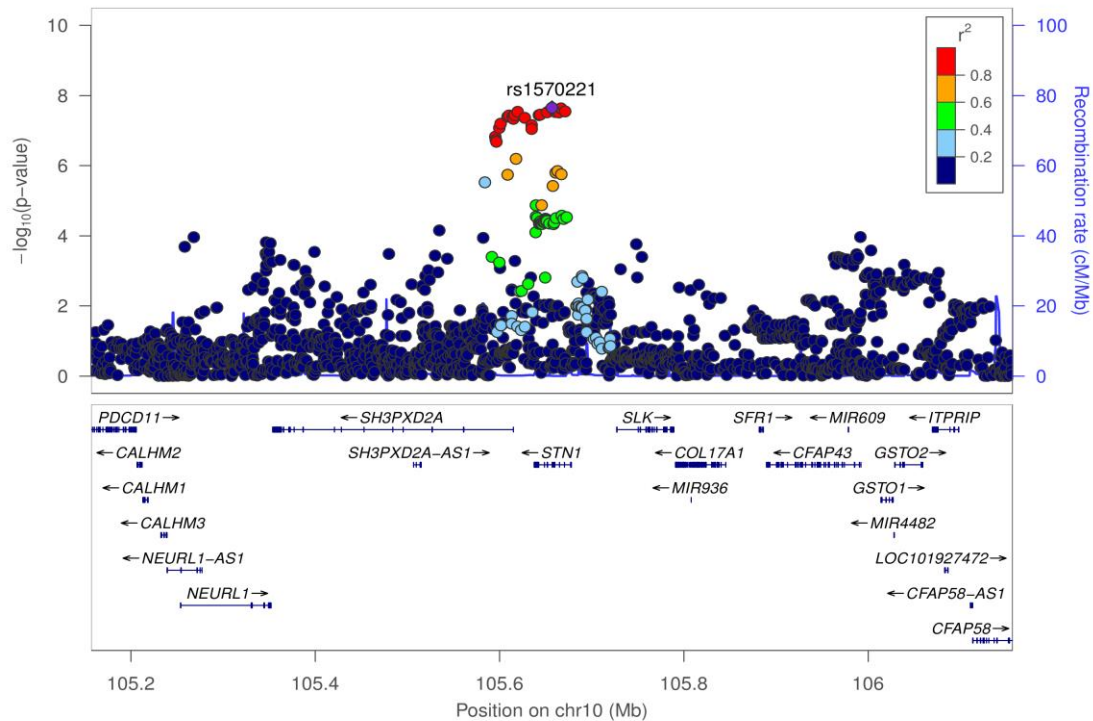
Supplementary Figure 2-47: Regional association plot for rs2040732 (*ITGB8* locus at 7p21.1)Supplementary Figure 2-48: Regional association plot for rs2897075 (*ZKSCAN1* locus at 7q22.1)

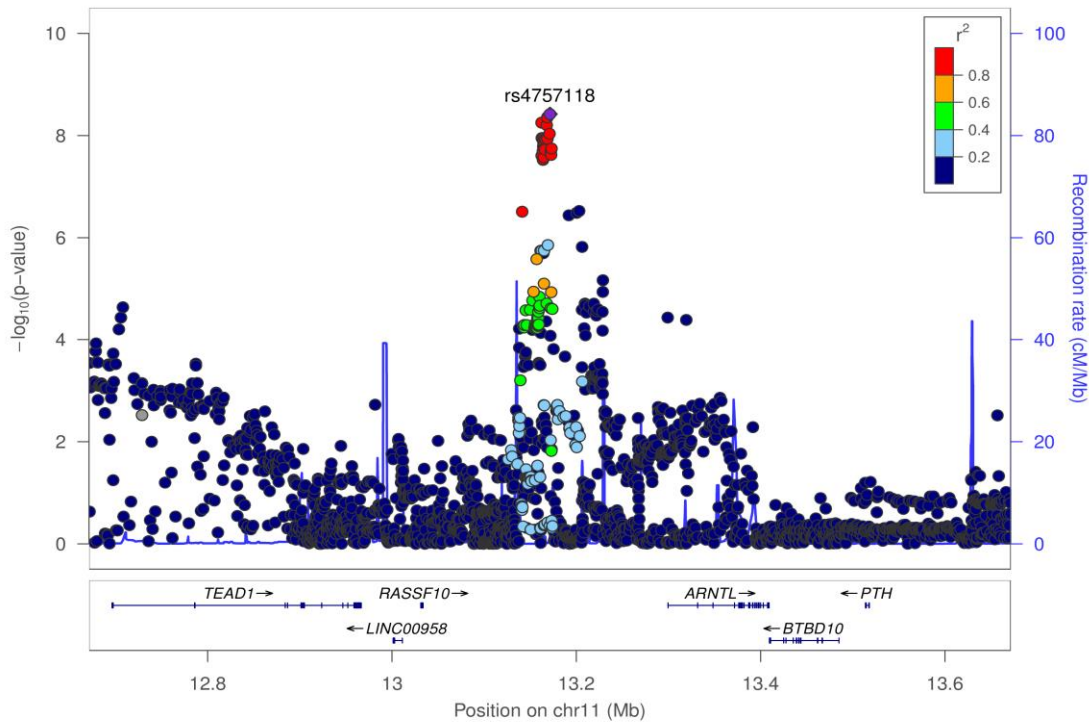
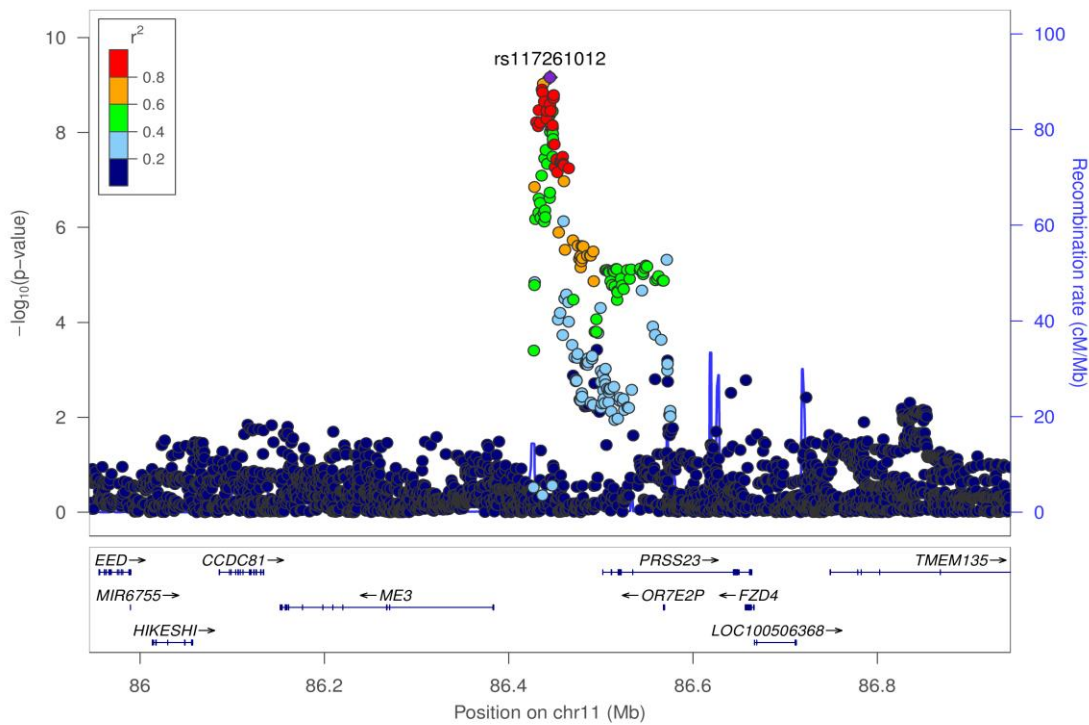
Supplementary Figure 2-49: Regional association plot for rs9329170 (*MFHAS1* locus at 8p23.1)Supplementary Figure 2-50: Regional association plot for rs10114763 (*GLIS3* locus at 9p24.2)

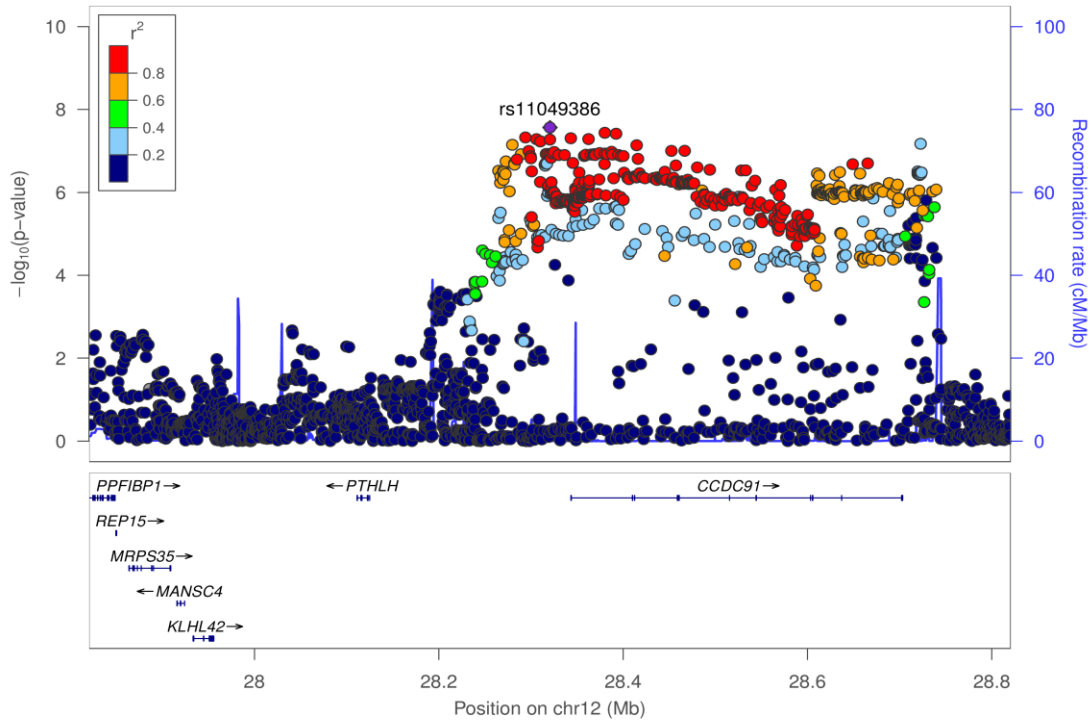
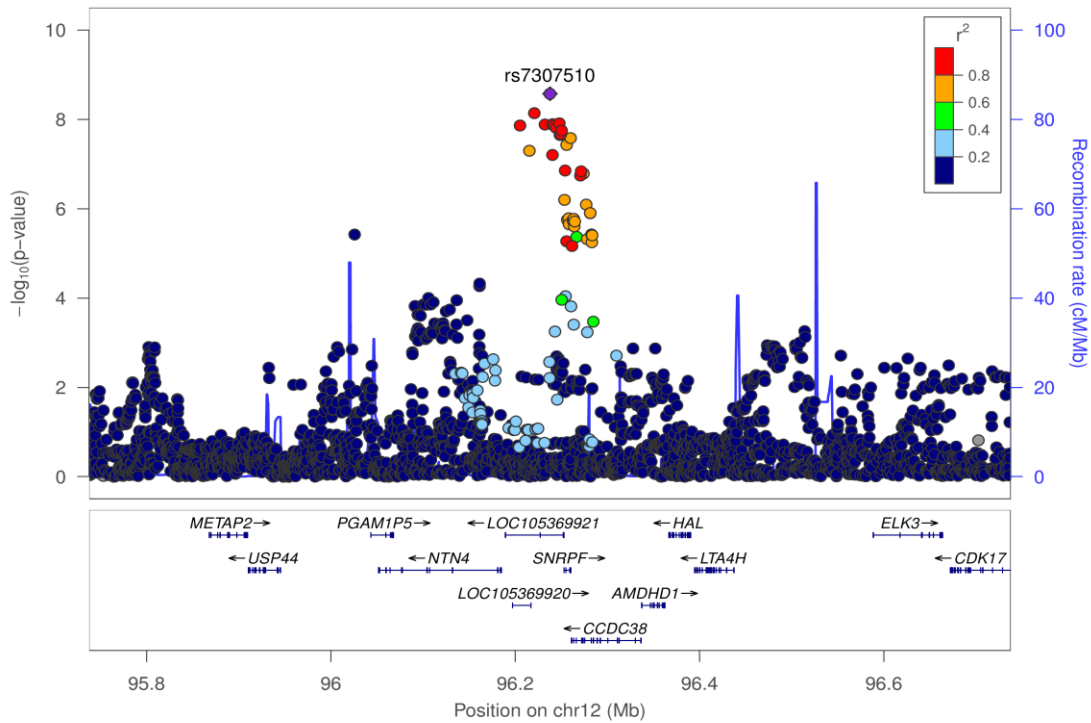
Supplementary Figure 2-51: Regional association plot for rs156394 (*ELAVL2* locus at 9p21.3)Supplementary Figure 2-52: Regional association plot for rs7866939 (*RASEF* locus at 9q21.32)

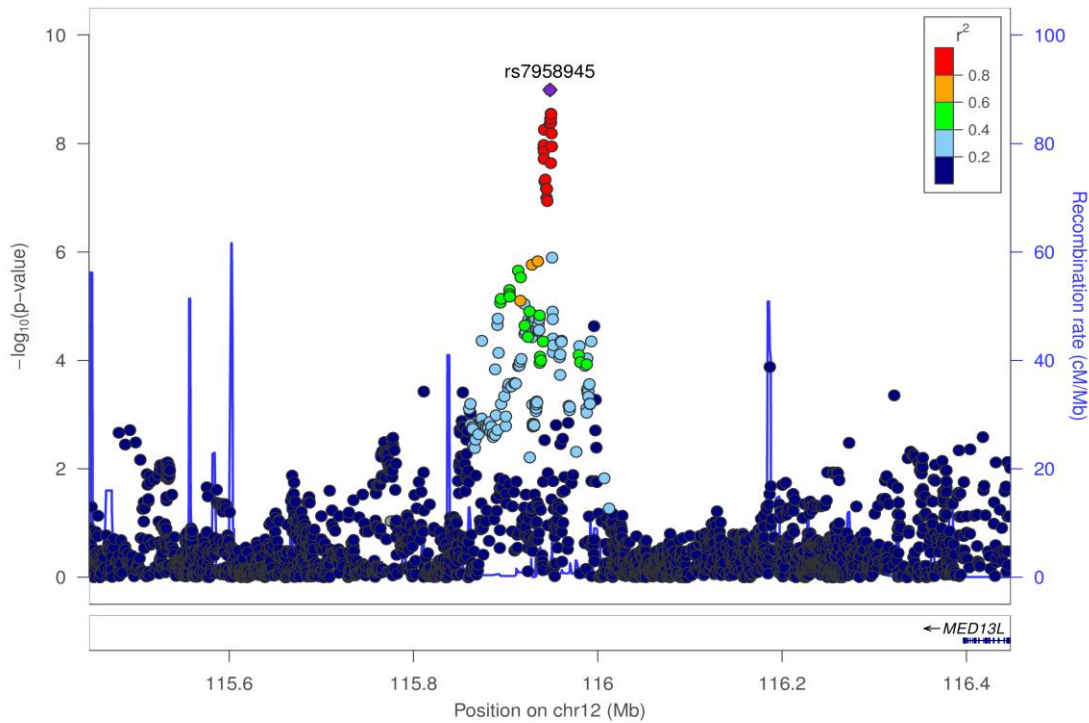
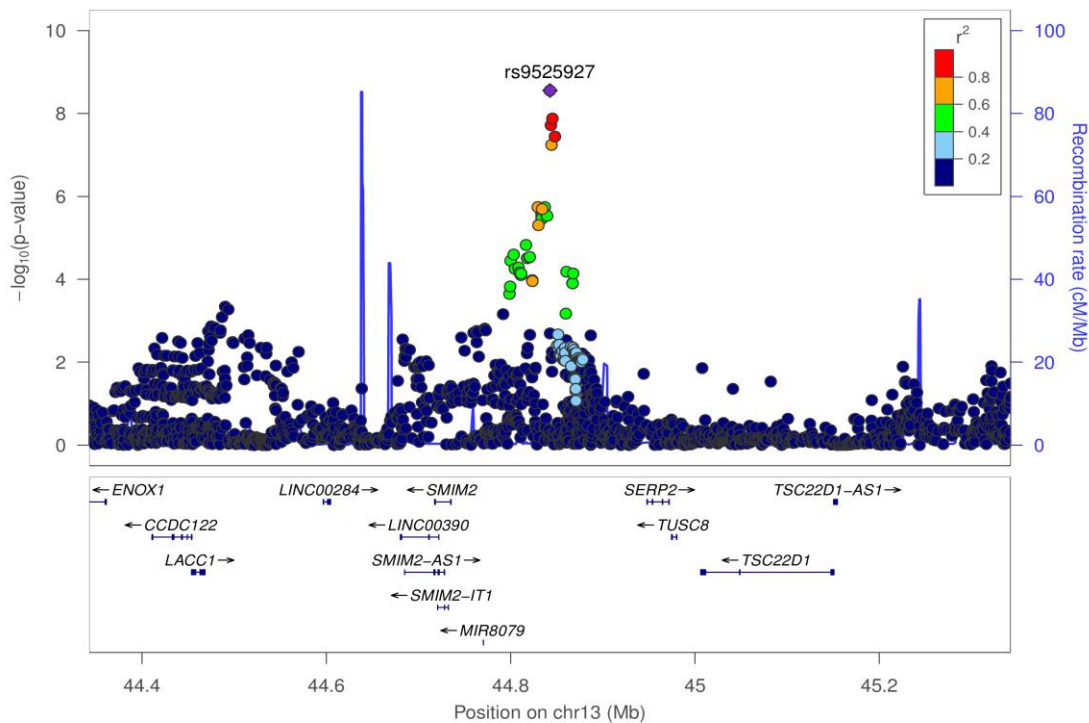
Supplementary Figure 2-53: Regional association plot for rs10760580 (*COL15A1* locus at 9q22.33)Supplementary Figure 2-54: Regional association plot for rs803923 (*ASTN2* locus at 9q33.1)

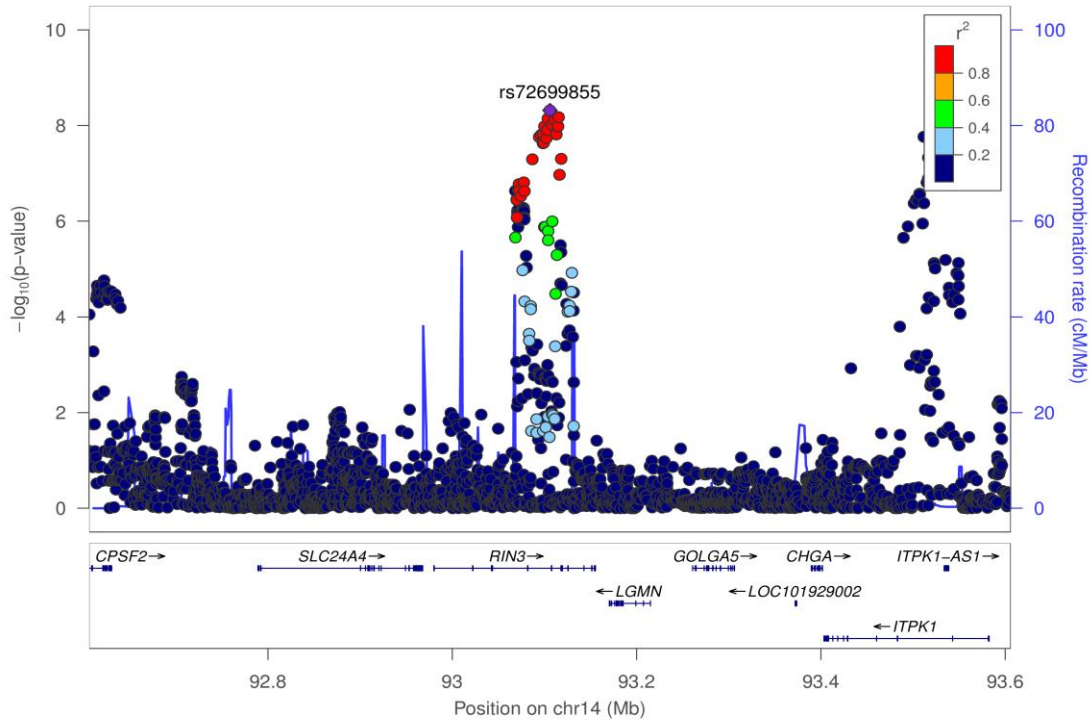
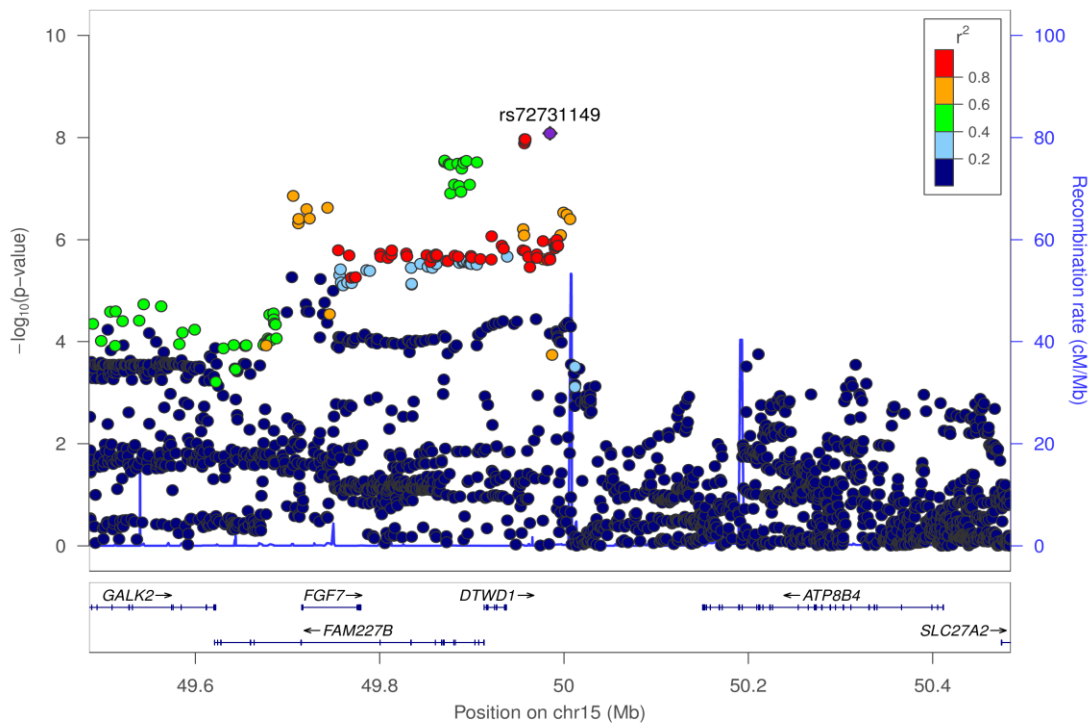
Supplementary Figure 2-55: Regional association plot for rs7068966 (*CDC123* locus at 10p13)Supplementary Figure 2-56: Regional association plot for rs2579762 (*LRMDA* locus at 10q22.3)

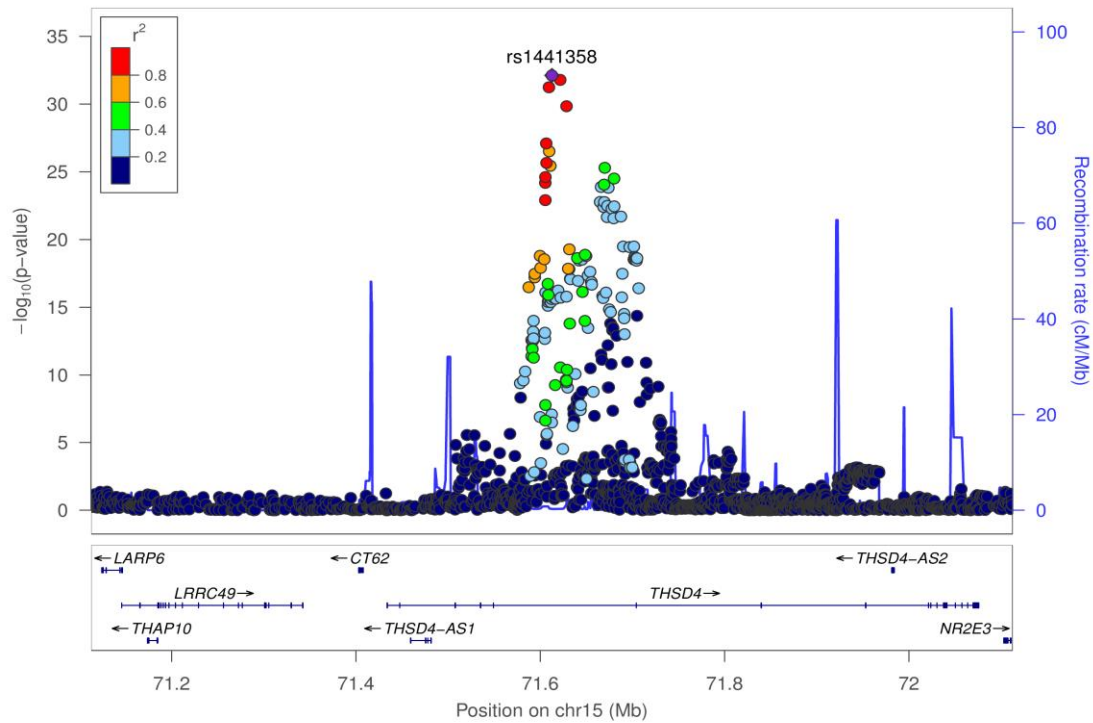
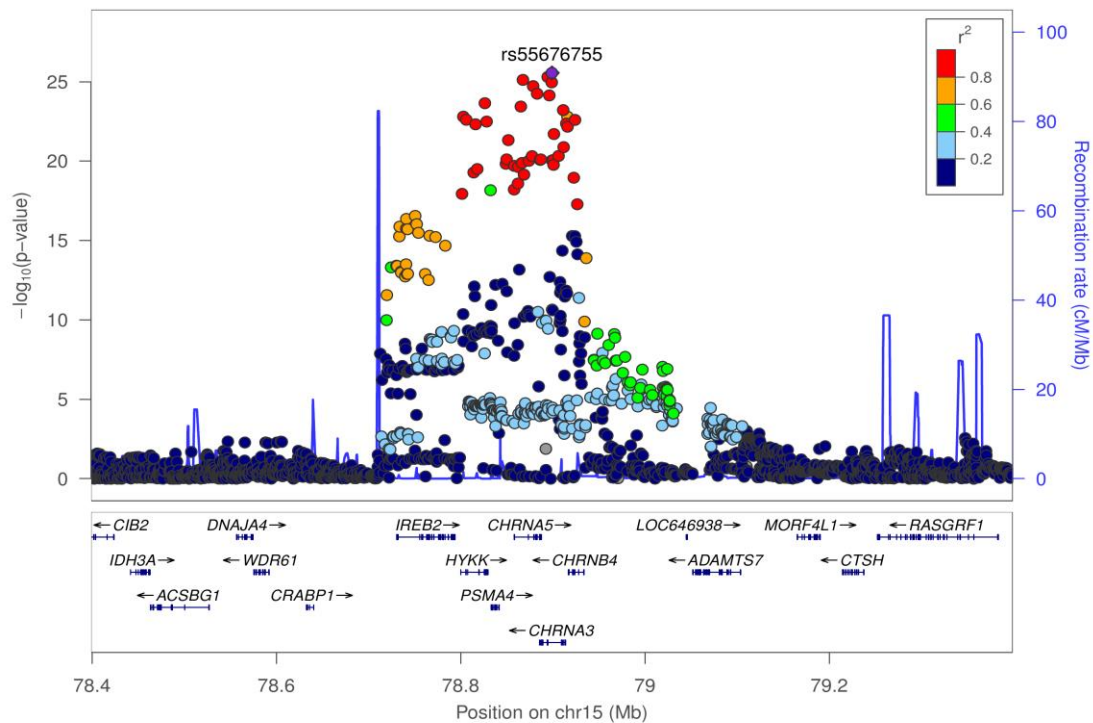
Supplementary Figure 2-57: Regional association plot for rs721917 (*SFTPD* locus at 10q22.3)Supplementary Figure 2-58: Regional association plot for rs1570221 (*STN1* locus at 10q24.33)

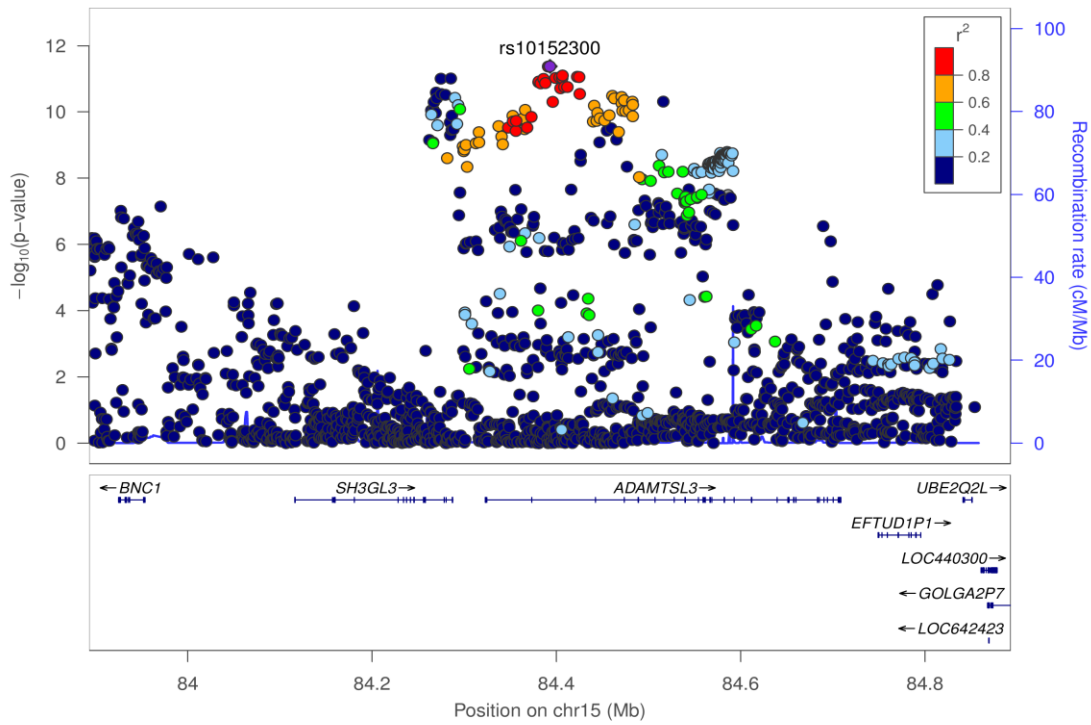
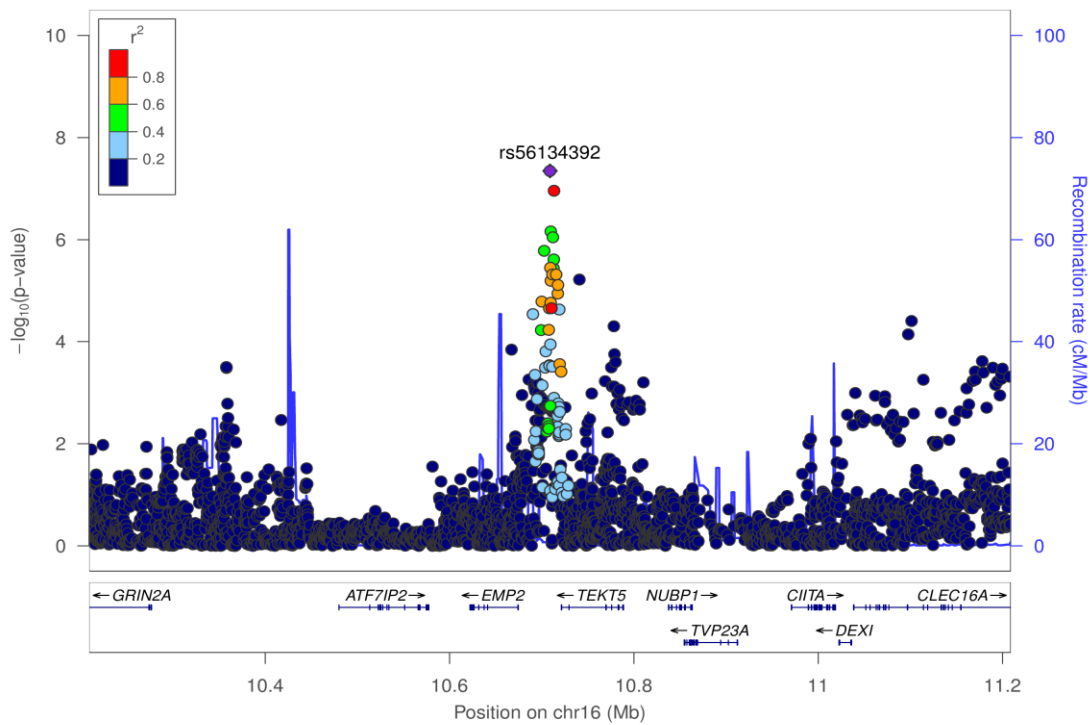
Supplementary Figure 2-59: Regional association plot for rs4757118 (*ARNTL* locus at 11p15.2)Supplementary Figure 2-60: Regional association plot for rs117261012 (*PRSS23* locus at 11q14.2)

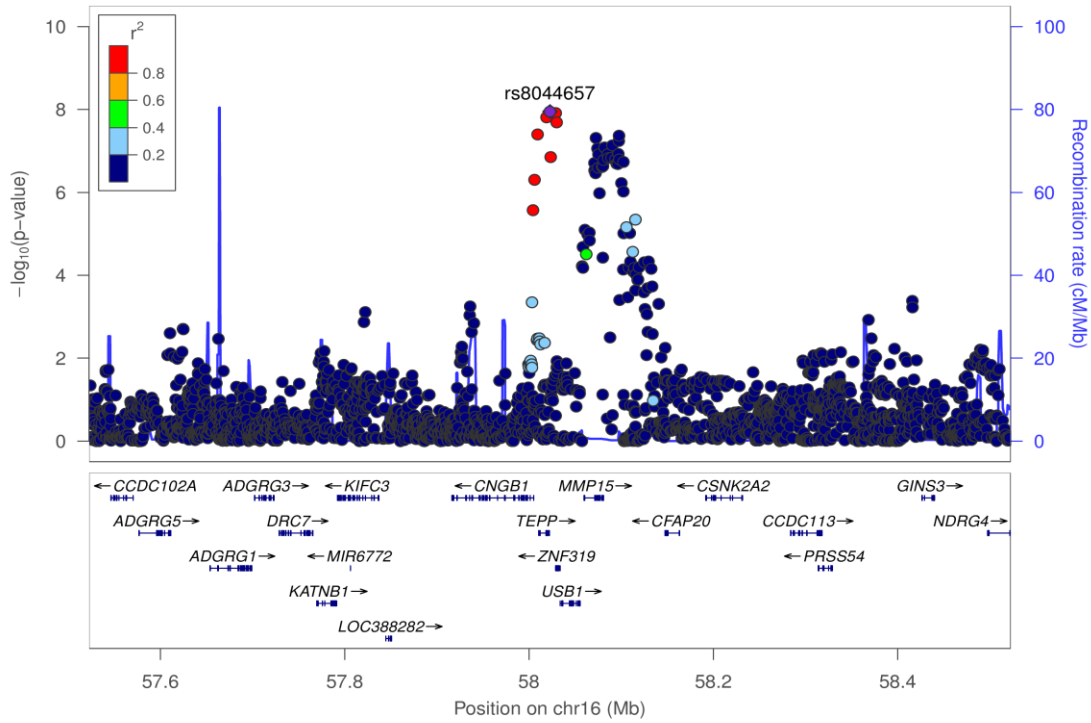
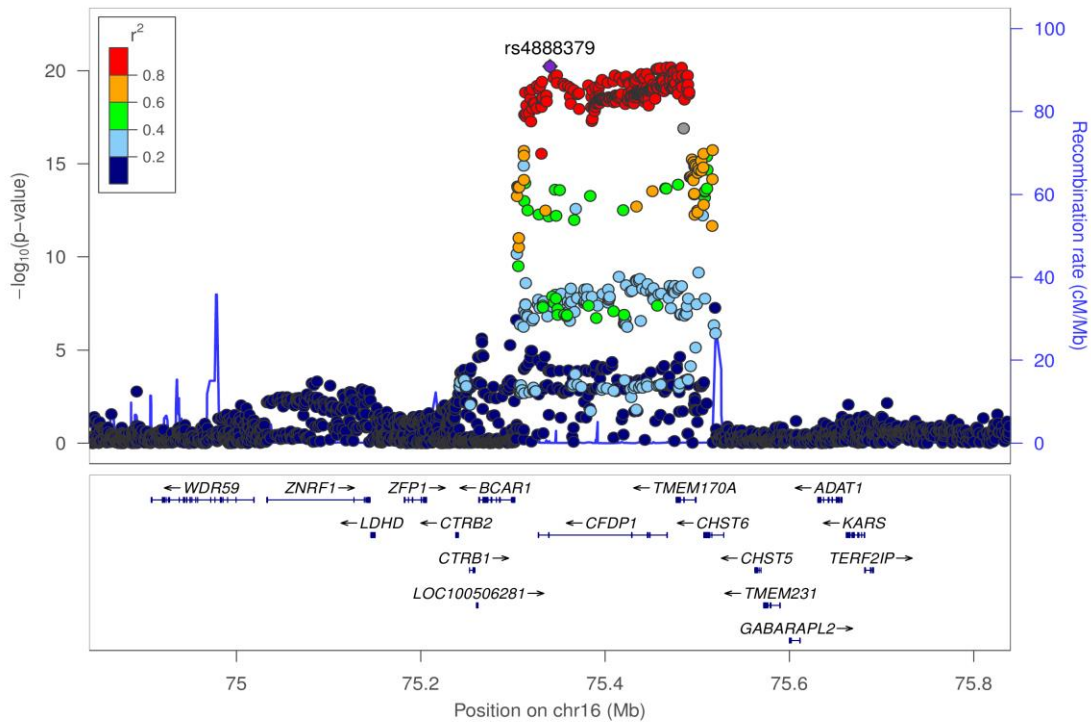
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Supplementary Figure 2-63: Regional association plot for rs7958945 (*MED13L* locus at 12q24.21)Supplementary Figure 2-64: Regional association plot for rs9525927 (*SERP2* locus at 13q14.11)

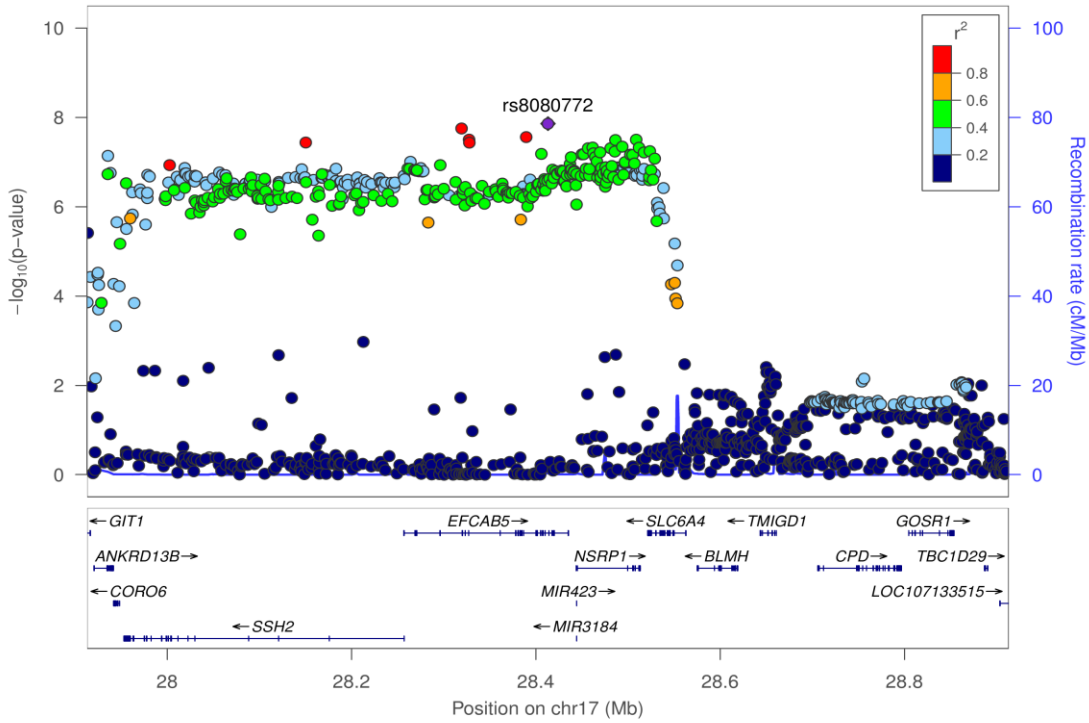
Supplementary Figure 2-65: Regional association plot for rs72699855 (*RIN3* locus at 14q32.12)Supplementary Figure 2-66: Regional association plot for rs72731149 (*DTWD1* locus at 15q21.2)

Supplementary Figure 2-67: Regional association plot for rs1441358 (*THSD4* locus at 15q23)Supplementary Figure 2-68: Regional association plot for rs55676755 (*CHRNA3* locus at 15q25.1)

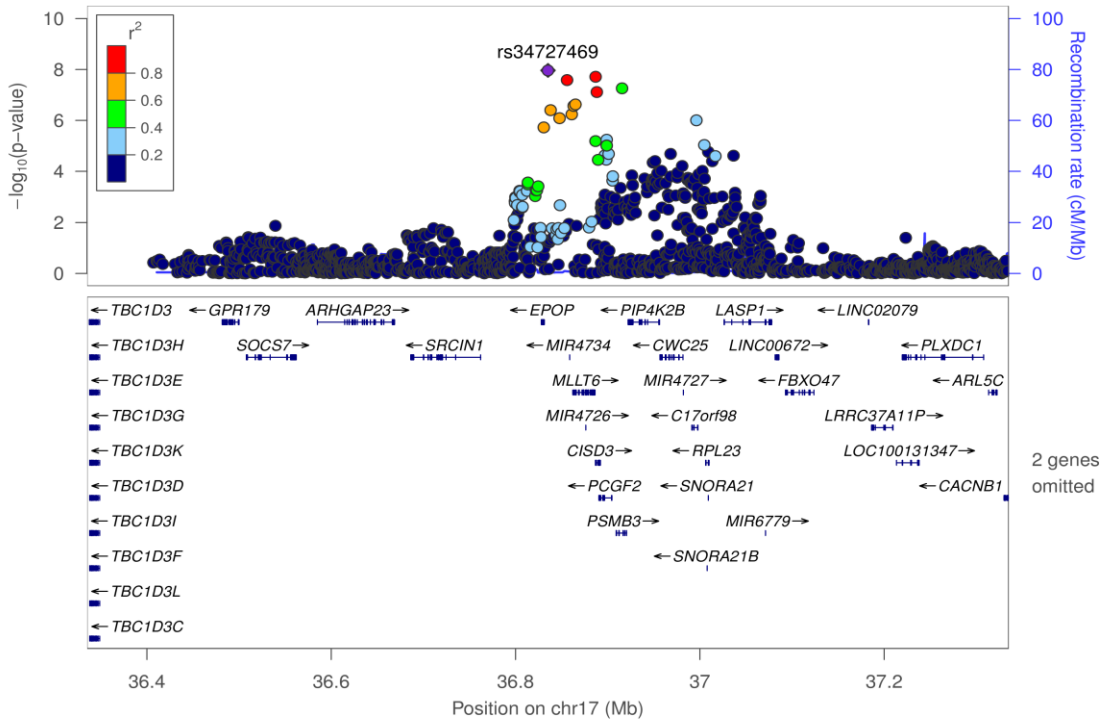
Supplementary Figure 2-69: Regional association plot for rs10152300 (*ADAMTSL3* locus at 15q25.2)Supplementary Figure 2-70: Regional association plot for rs56134392 (*TEKT5* locus at 16p13.13)

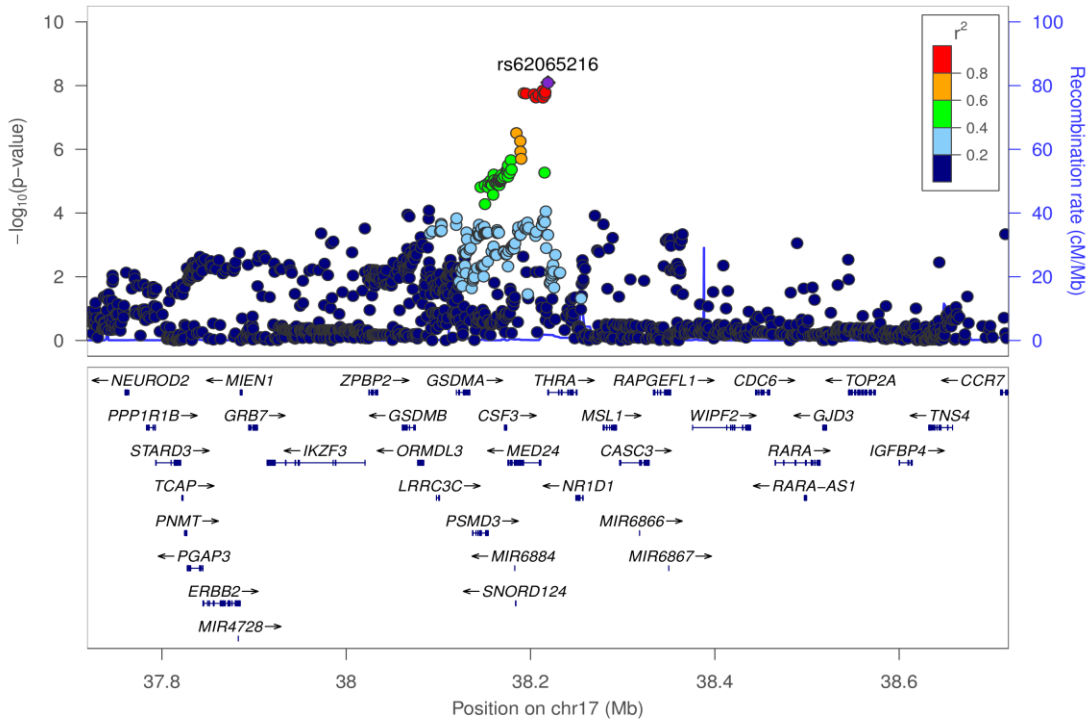
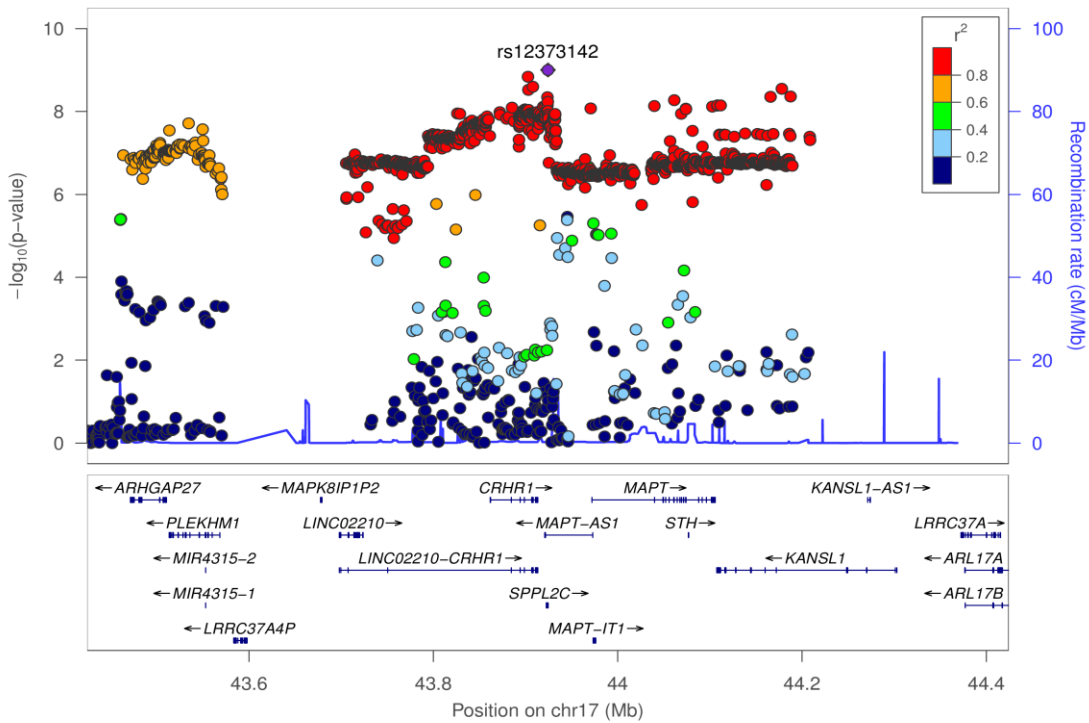
Supplementary Figure 2-71: Regional association plot for rs8044657 (*TEPP* locus at 16q21)Supplementary Figure 2-72: Regional association plot for rs4888379 (*CFDP1* locus at 16q23.1)

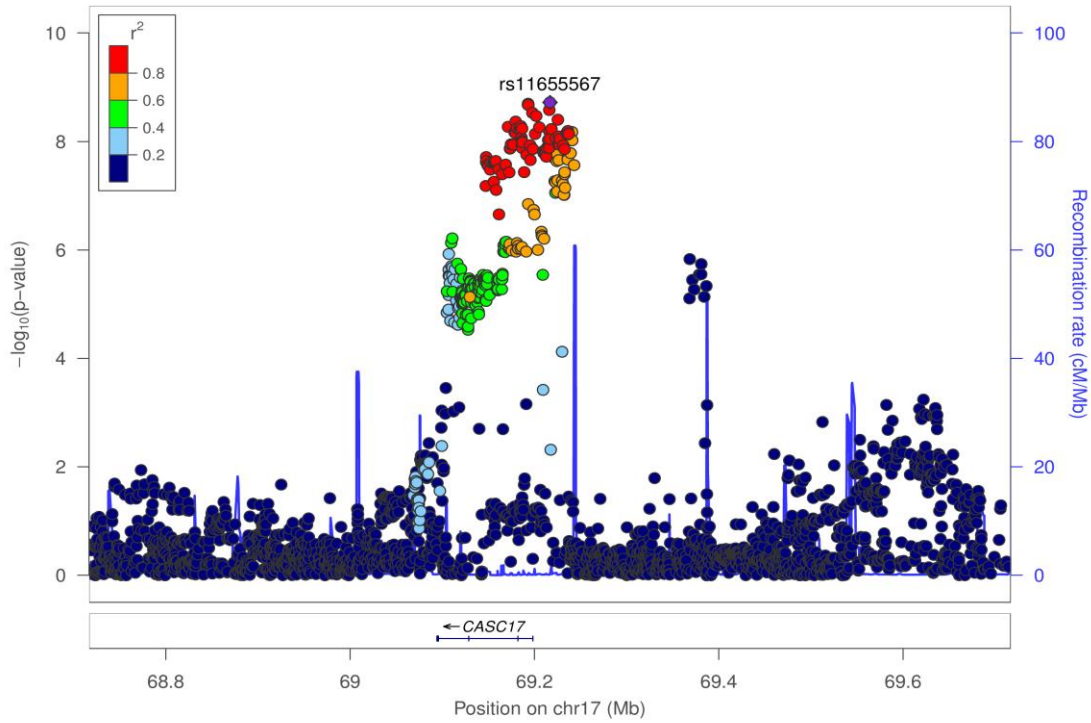
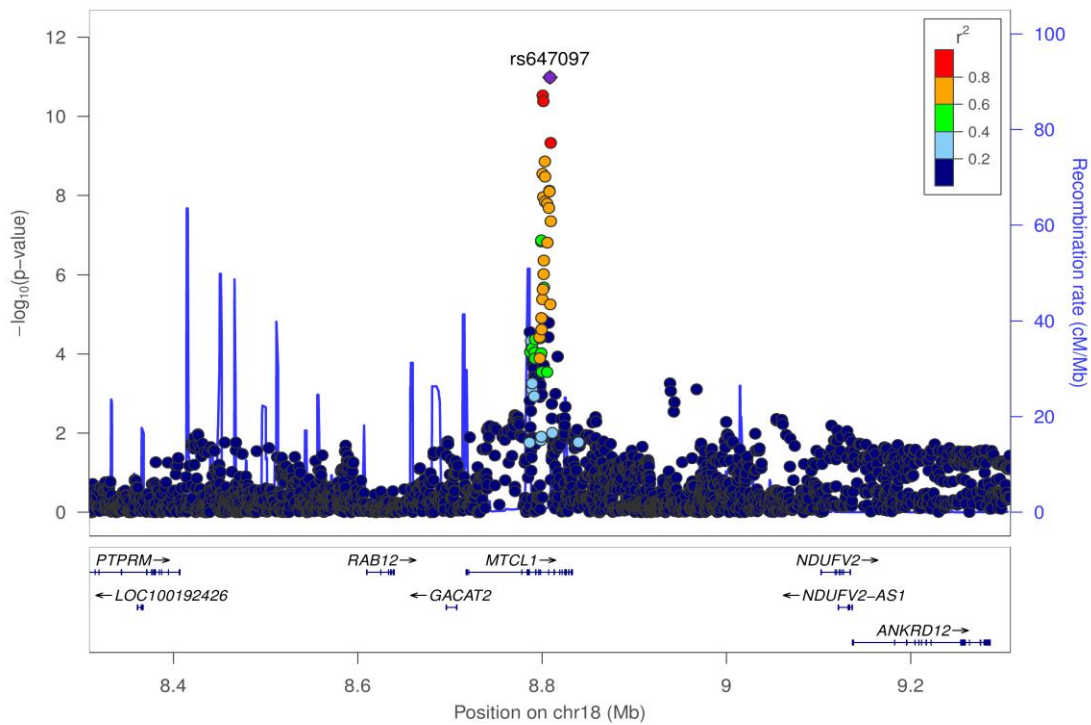
Supplementary Figure 2-73: Regional association plot for rs8080772 (*EFCAB5* locus at 17q11.2)

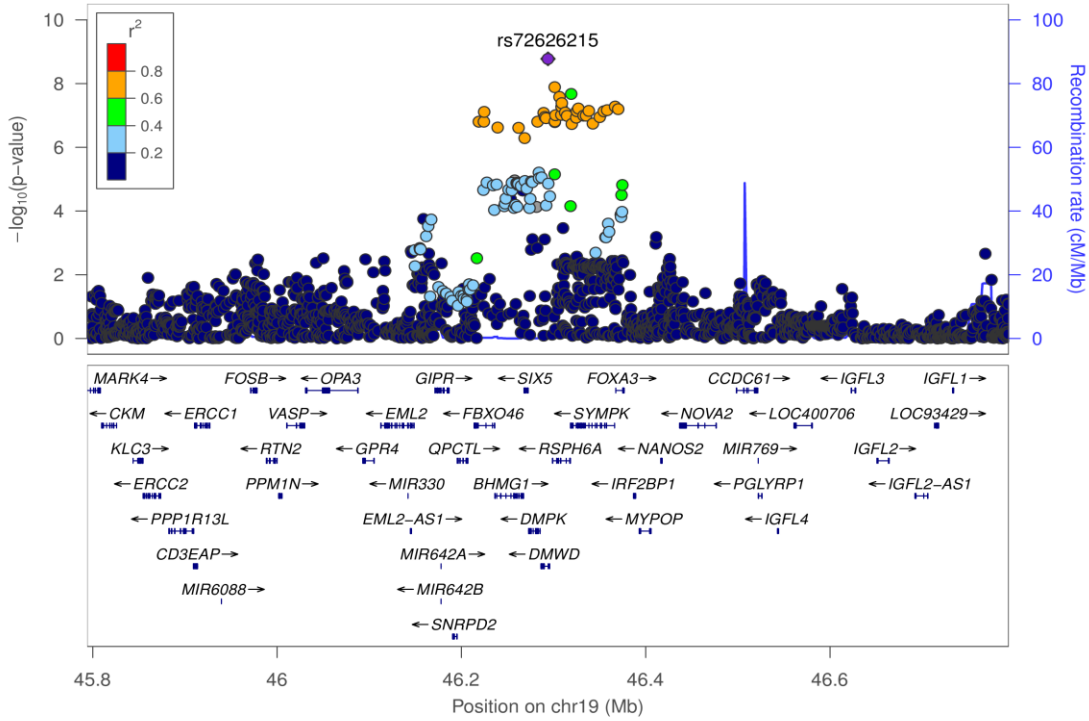
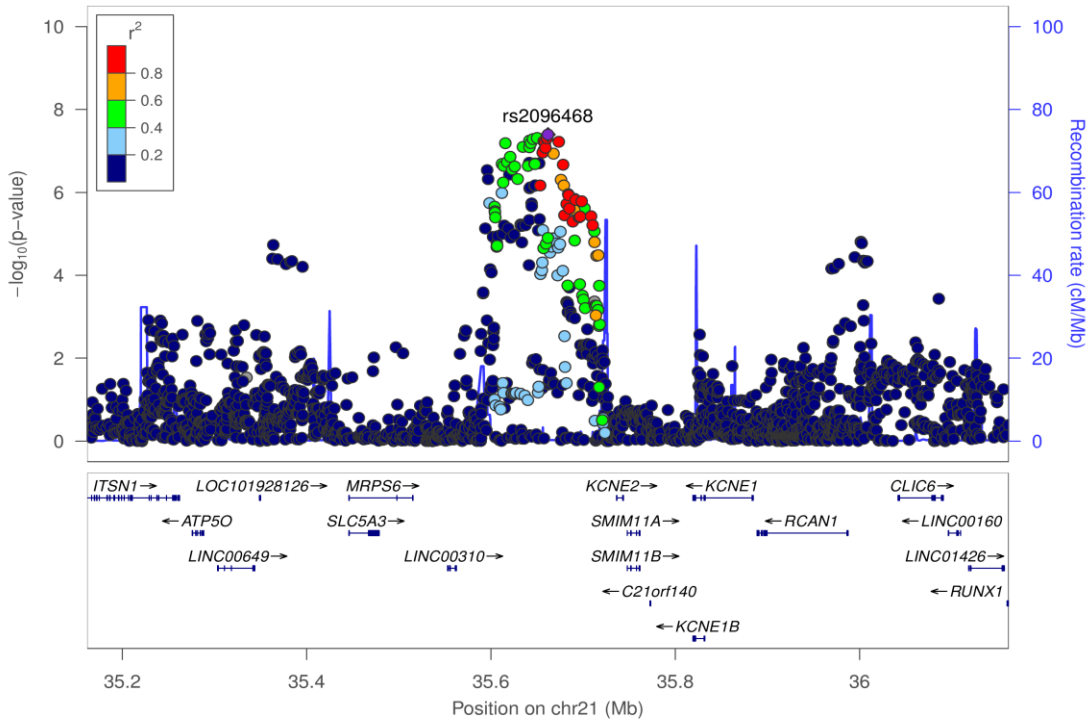


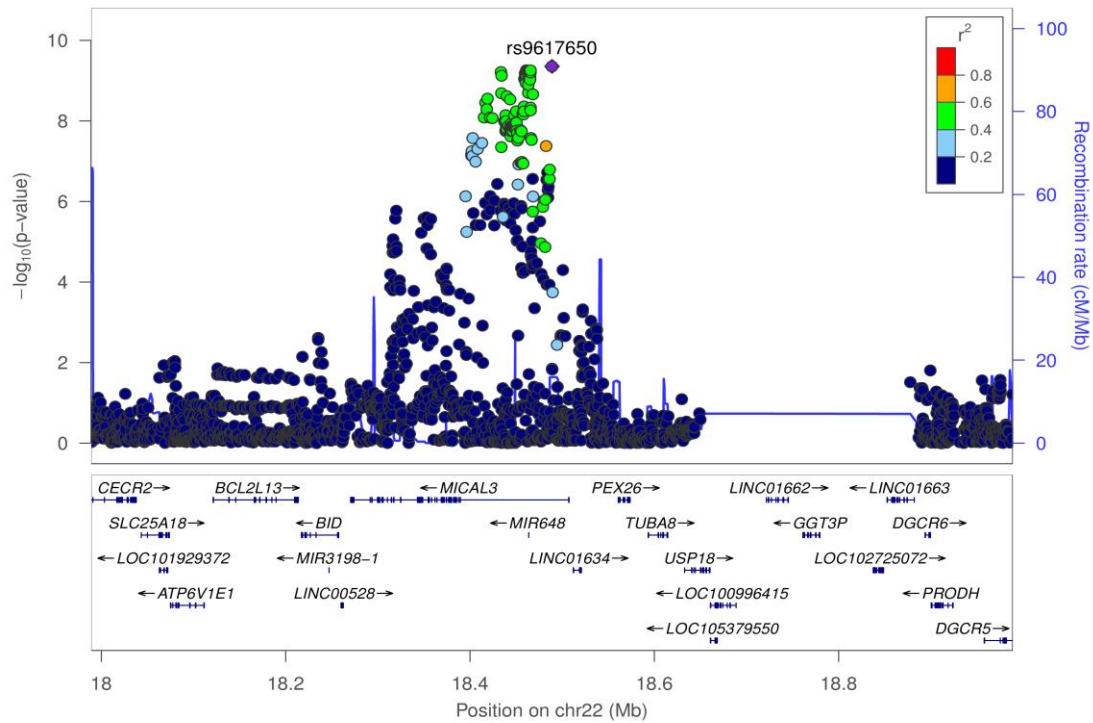
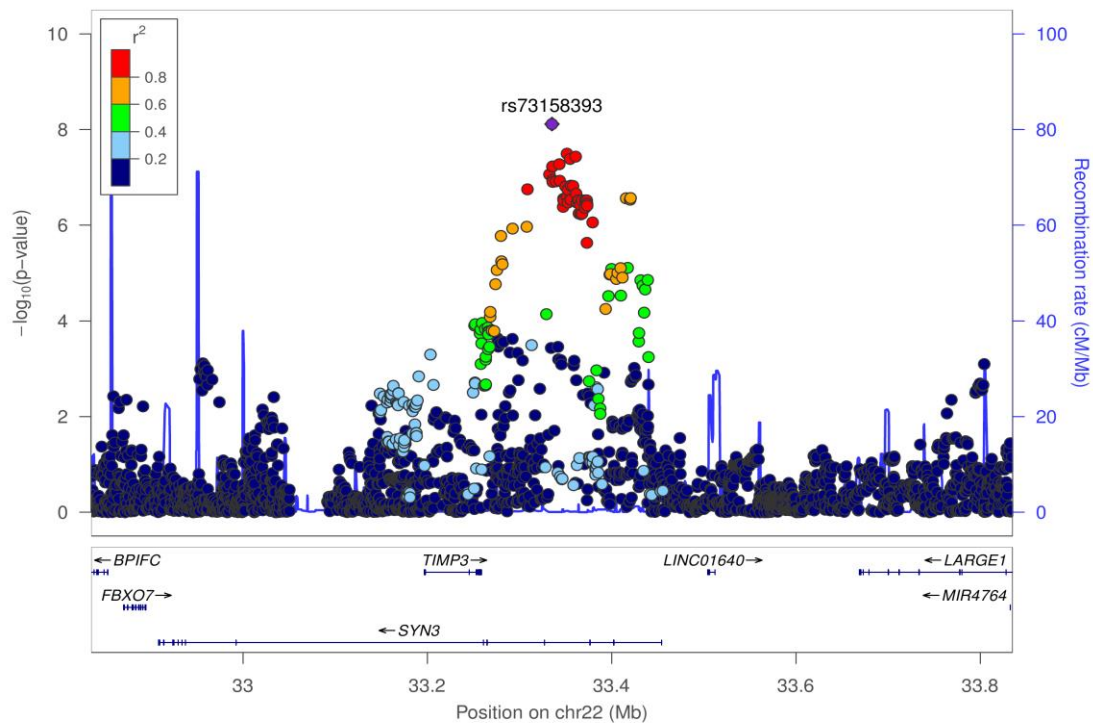
Supplementary Figure 2-74: Regional association plot for rs34727469 (*RPL23* locus at 17q12)



Supplementary Figure 2-75: Regional association plot for rs62065216 (*THRA* locus at 17q21.1)Supplementary Figure 2-76: Regional association plot for rs12373142 (*SPPL2C* locus at 17q21.31)

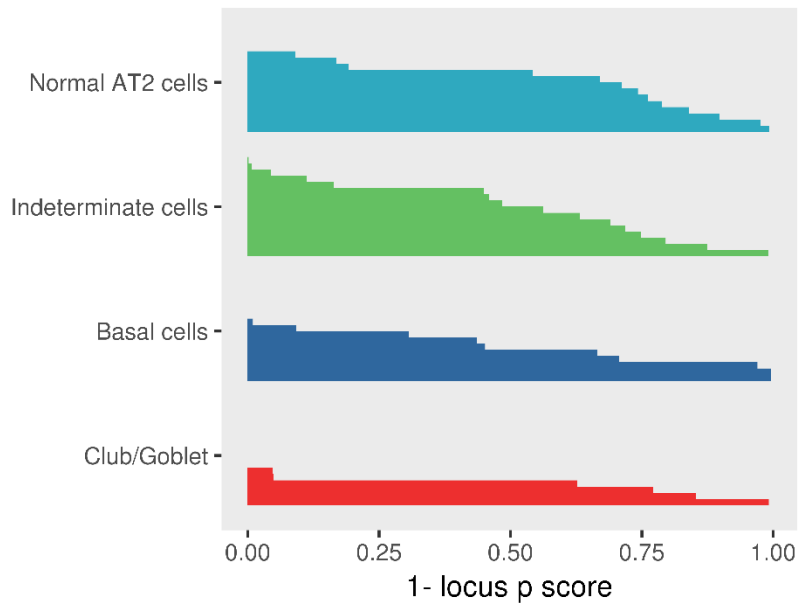
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Supplementary Figure 2-81: Regional association plot for rs9617650 (*MICAL3* locus at 22q11.21)Supplementary Figure 2-82: Regional association plot for rs73158393 (*SYN3* locus at 22q12.3)

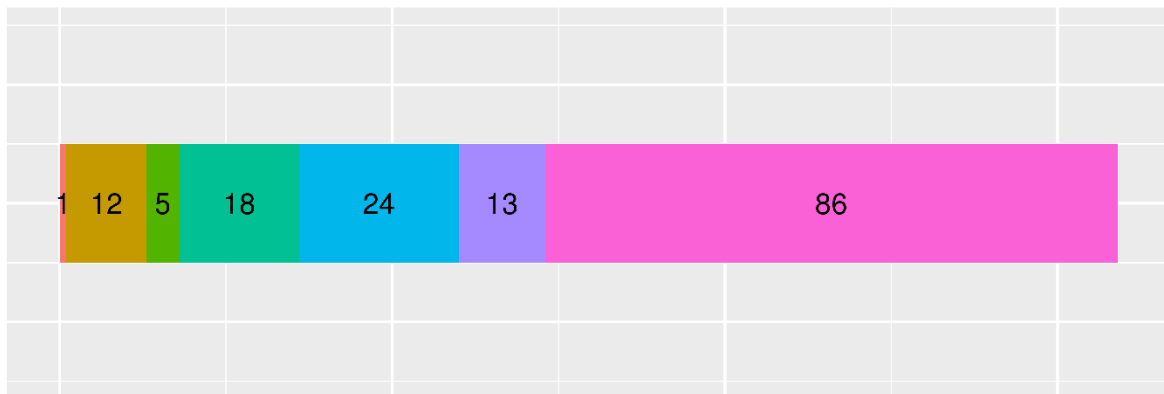
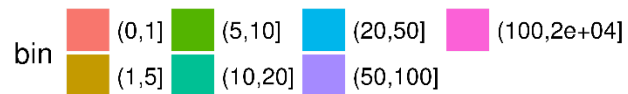
Supplementary Figure 3: Distribution of SNPSea gene enrichment in respiratory cell types

Locus p score is percentile of genes specifically expressed in each cell type (i.e., lower p score means higher specific expression). Determination of cell types was based on the prior study in pulmonary fibrosis patients and normal controls⁵⁴ (**Methods**).

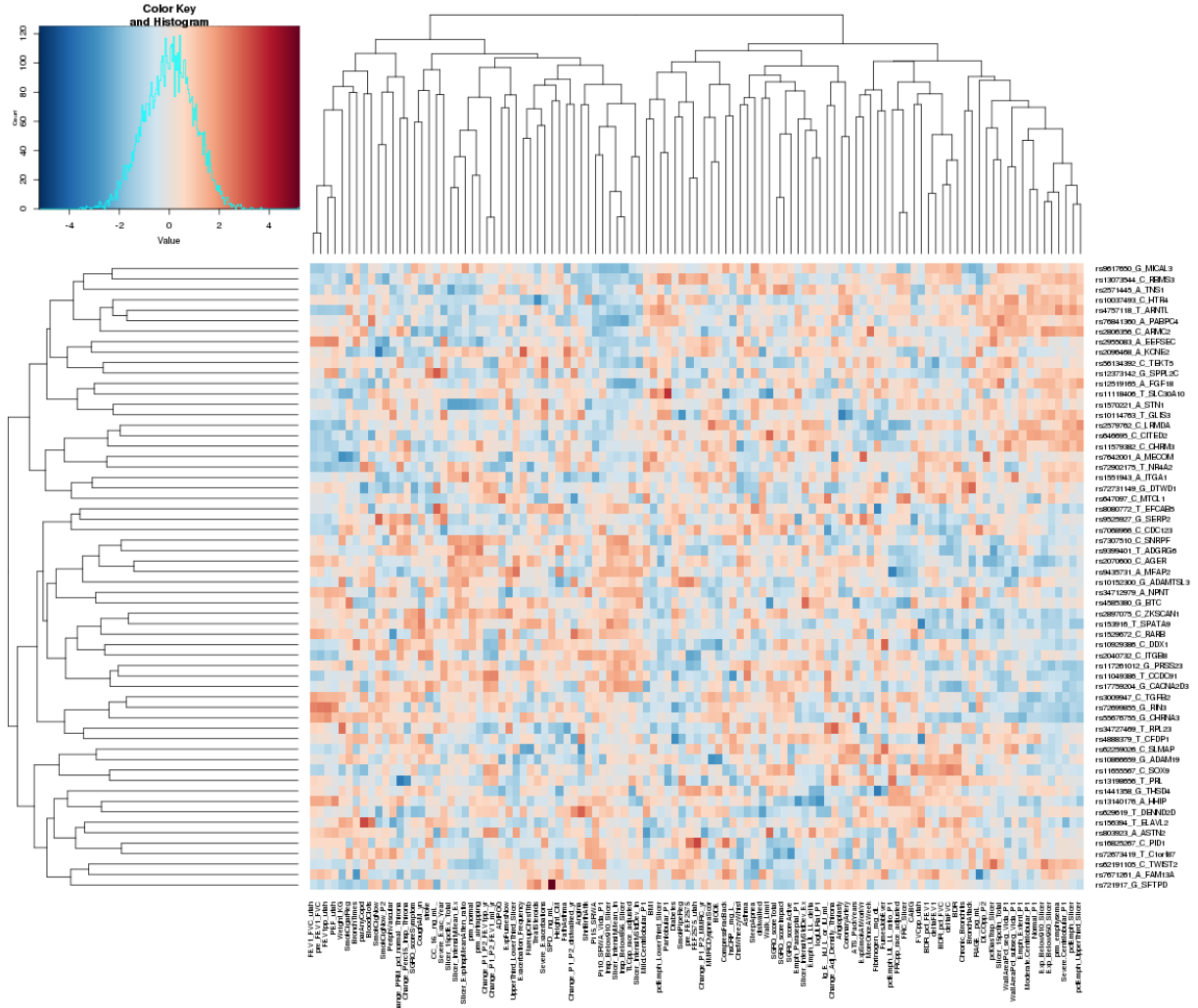


Supplementary Figure 4: Distribution of number of variants in 99% credible sets

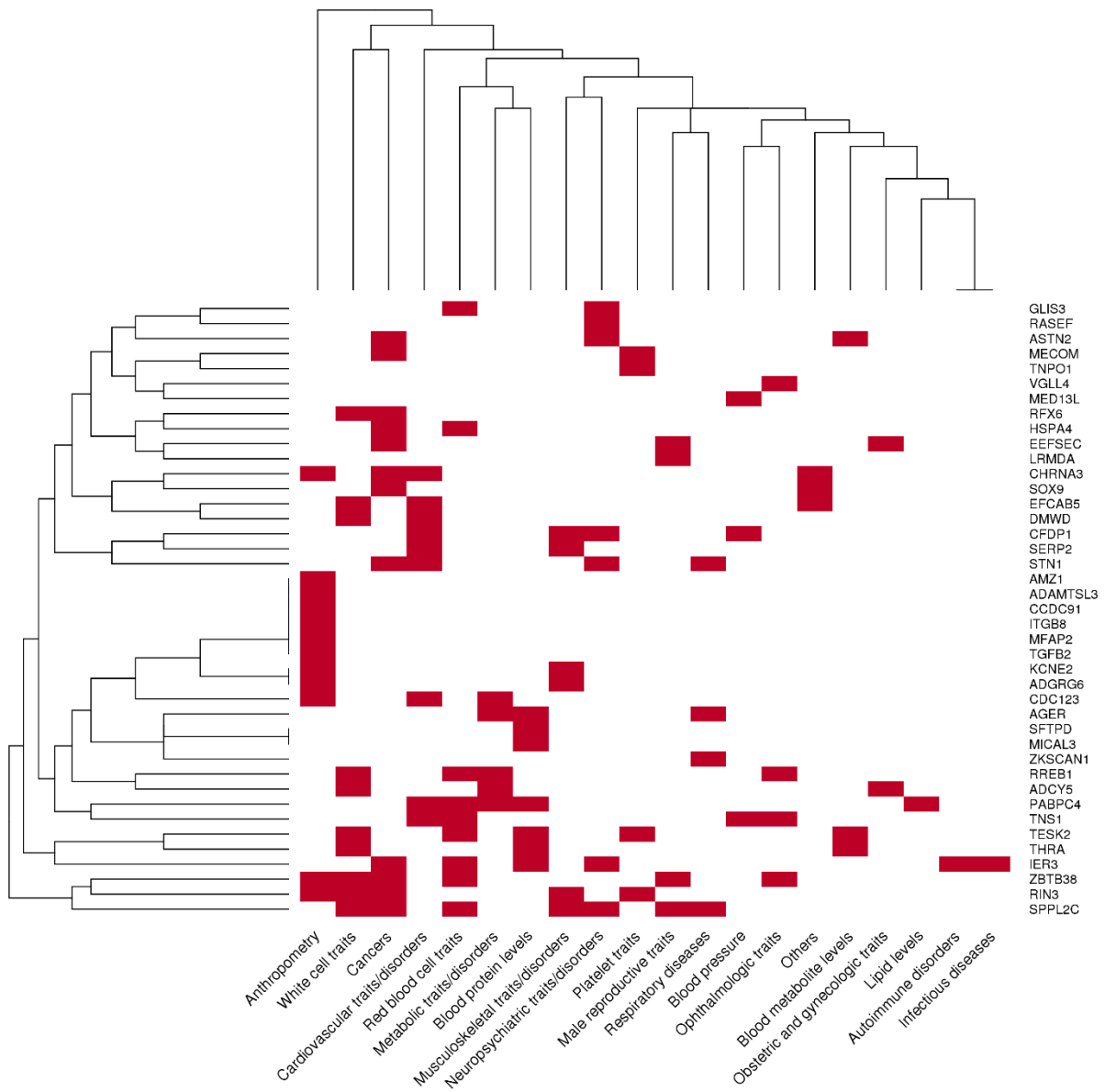
Number of variants in each credible set



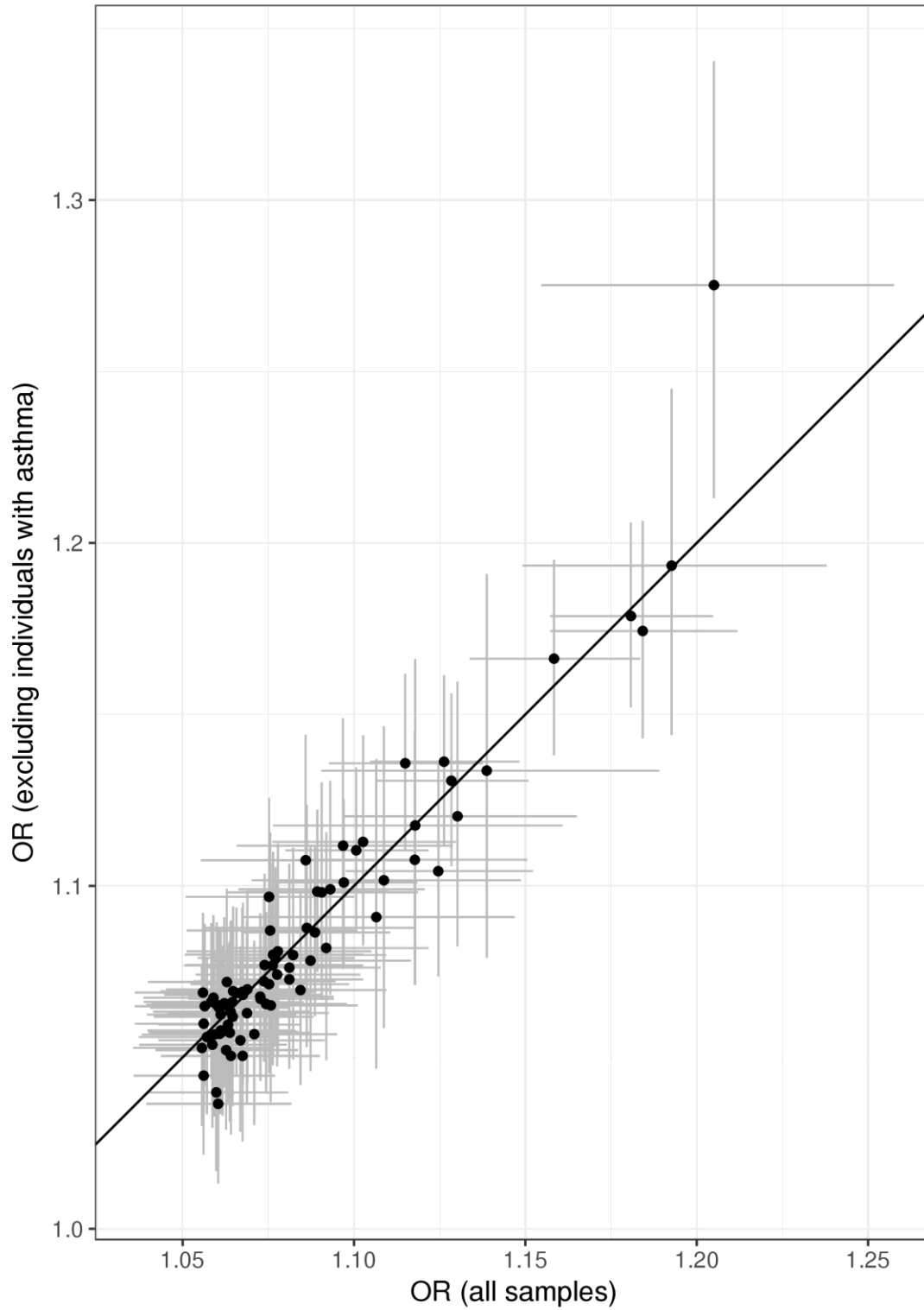
Supplementary Figure 5: Heatmap of associations of 82 index variants and phenotypes in COPDGen



Supplementary Figure 6: Associations of index variants and traits in NHGRI-EBI GWAS Catalog



Supplementary Figure 7: Comparison of odds ratios (OR) including and excluding individuals with asthma of 82 genome-wide significant variants
Error bars show 95% confidence interval for OR estimates.



Supplementary Tables

See the Excel file.

Supplementary Table 1 Cohort baseline characteristics in COPD cases and controls

Supplementary Table 2 Meta-analysis results showing 47 previously reported loci for COPD or lung function

Supplementary Table 3 Multiple independent associations within the same 2-Mb window identified using approximate conditional and joint analysis

Supplementary Table 4 Heritability enrichment in cell-type specific epigenomic mark from Roadmap Epigenomic Project

Supplementary Table 5 Genes specifically expressed in genome-wide significant loci

Supplementary Table 6 Functional annotation of variants with posterior probability of association greater than 0.6

Supplementary Table 7 Candidate target genes

Supplementary Table 8 Gene sets significantly enriched at FDR < 0.05 using DEPICT

Supplementary Table 9 Overlapping loci between COPD with asthma and pulmonary fibrosis

Supplementary Table 10 Lookup associations for quantitative computed tomography (QCT) features and cluster membership

Supplementary Table 11 Association results from GWAS catalog

Supplementary Table 12 Genetic correlation between COPD and other traits/diseases

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