

Data Supplement for:

Twenty-two genetic loci in COPD overlap with population-based lung function and pulmonary fibrosis loci

Brian D. Hobbs^{1,2}, Kim de Jong^{3,4}, Maxime Lamontagne⁵, Yohan Bossé^{5,6}, Nick Shrine⁷, María Soler Artigas⁷, Victoria E. Jackson⁷, Louise V. Wain⁷, Ian P. Hall⁸, Annah B. Wyss⁹, Stephanie J. London⁹, Kari E. North¹⁰, Nora Franceschini¹⁰, David P. Strachan¹¹, Terri H. Beaty¹², John E. Hokanson¹³, James D. Crapo¹⁴, Peter J. Castaldi^{1,15}, Robert P. Chase¹, Traci M. Bartz^{16,17}, Susan R. Heckbert^{16,18,19}, Bruce M. Psaty^{16,19,20}, Sina A. Gharib²¹, Pieter Zanen²², Jan W. Lammers²³, Matthijs Oudkerk²⁴, H. J. Groen²⁵, Nick Locantore²⁶, Ruth Tal-Singer²⁶, Stephen I. Rennard^{27,28}, Wim Timens²⁹, Peter D. Paré³⁰, Jeanne C. Latourelle³¹, Josée Dupuis^{32,33}, George T. O'Connor^{33,34}, Jemma B. Wilk³³, Woo Jin Kim³⁵, Mi Kyeong Lee³⁵, Yeon-Mok Oh³⁶, Judith M. Vonk^{3,4}, Harry J. de Koning³⁷, Shuguang Leng³⁸, Steven A. Belinsky³⁸, Yohannes Tesfaigzi³⁸, Ani Manichaikul^{39,40}, Xin-Qun Wang⁴⁰, Stephen S. Rich^{39,40}, R Graham Barr⁴¹, David Sparrow⁴², Augusto L. Litonjua^{1,2}, Per Bakke⁴³, Amund Gulsvik⁴³, Lies Lahousse^{44,45}, Guy G. Brusselle^{44,45,46}, Bruno H. Stricker^{44,47,48,49}, André G. Uitterlinden^{44,48,49}, Elizabeth J. Ampleford⁵⁰, Eugene R. Bleecker⁵⁰, Prescott G. Woodruff⁵¹, Deborah A. Meyers⁵⁰, Dandi Qiao¹, David A. Lomas⁵², Jae-Joon Yim⁵³, Deog Kyeom Kim⁵⁴, Iwona Hawrylkiewicz⁵⁵, Pawel Sliwinski⁵⁵, Megan Hardin^{1,2}, Tasha E. Fingerlin^{56,57}, David A. Schwartz^{56,58,59}, Dirkje S. Postma^{4,25}, William MacNee⁶⁰, Martin D. Tobin^{7,61}, Edwin K. Silverman^{1,2}, H. Marika Boezen^{3,4}, *Michael H. Cho^{1,2}, COPD Gene Investigators, ECLIPSE Investigators, LifeLines Investigators, SPIROMICS Research Group, International COPD Genetics Network Investigators, UK BiLEVE Investigators, International COPD Genetics Consortium

1 Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA

2 Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA

3 University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, the Netherlands

4 University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands

5 Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada

6 Department of Molecular Medicine, Laval University, Québec, Canada

7 Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Leicester, UK

8 Division of Respiratory Medicine, Queen's Medical Centre, University of Nottingham, Nottingham, UK

9 Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA

10 Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

11 St George's, University of London, Cranmer Terrace, London SW17 0RE, UK

12 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

13 Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

14 National Jewish Health, Denver, CO, USA

15 Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA

16 Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA

17 Departments of Medicine and Biostatistics, University of Washington, Seattle, WA, USA

18 Department of Epidemiology, University of Washington, Seattle, WA, USA

19 Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA

20 Departments of Epidemiology, Medicine and Health Services, University of Washington, Seattle, WA, USA

21 Computational Medicine Core, Center for Lung Biology, UW Medicine Sleep Center, Department of Medicine, University of Washington, Seattle, WA, USA

22 University Medical Center Utrecht, Department of Pulmonary Diseases, Utrecht, the Netherlands

23 Department of Pulmonology, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands

24 Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

25 University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen, the Netherlands

26 GSK R&D, King of Prussia, PA, USA

27 Pulmonary, Critical Care, Sleep and Allergy Division, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA

28 Clinical Discovery Unit, AstraZeneca, Cambridge, UK

29 Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands

30 University of British Columbia Center for Heart Lung Innovation and Institute for Heart and Lung Health, St Paul's Hospital, Vancouver, British Columbia, Canada

31 Department of Neurology, Boston University School of Medicine, Boston, MA, USA

32 Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

33 The National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, MA, USA

34 Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

35 Department of Internal Medicine and Environmental Health Center, School of Medicine, Kangwon National University, Chuncheon, South Korea

36 Department of Pulmonary and Critical Care Medicine, and Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

37 Department of Public Health, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands

38 Lovelace Respiratory Research Institute, Albuquerque, NM, USA

39 Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA

40 Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA

41 Department of Medicine, College of Physicians and Surgeons and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

42 VA Boston Healthcare System and Department of Medicine, Boston University School of Medicine, Boston, MA, USA

43 Department of Clinical Science, University of Bergen, Bergen, Norway

44 Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

45 Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

46 Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

47 Netherlands Health Care Inspectorate, The Hague, the Netherlands

48 Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

49 Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA), Leiden, the Netherlands

50 Center for Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Winston Salem, NC, USA

51 Cardiovascular Research Institute and the Department of Medicine, Division of Pulmonary, Critical Care, Sleep, and Allergy, University of California at San Francisco, San Francisco, CA, USA

52 University College London, London, UK

53 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

54 Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, Seoul, South Korea
55 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
56 Center for Genes, Environment and Health, National Jewish Health, Denver, CO, USA
57 Department of Biostatistics and Informatics, University of Colorado Denver, Aurora, CO, USA
58 Department of Medicine, School of Medicine, University of Colorado Denver, Aurora, CO, USA
59 Department of Immunology, School of Medicine, University of Colorado Denver, Aurora, CO, USA
60 University of Edinburgh, Edinburgh, UK
61 National Institute for Health Research (NIHR) Leicester Respiratory Biomedical Research Unit, Glenfield Hospital, Leicester, UK

*Corresponding author:
Michael H. Cho (remhc@channing.harvard.edu)
tel: 617-525-0897
fax: 888-487-1078

Supplemental Methods:

Cohort descriptions and cohort-specific methods

ARIC: Atherosclerosis Risk in Communities (ARIC)¹ (NCT00005131), is a population based study of risk factors for atherosclerosis and its sequelae in adults from four U.S. field centers 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 made with a Collins Survey II water-seal spirometer (Collins Medical, Inc.) and Pulmo-Screen II software (PDS Healthcare Products, Inc.). Genotyping was done using the AffymetrixGeneChip SNP Array 6.0 and imputation was performed using IMPUTE2. Quality control steps for genotyping data included exclusions for call rate <95%, minor allele frequency <1%, HWE $P < 10^{-5}$, no chromosomal location, suspected first-degree relative of an included individual based on genotype data, or more than 8 standard deviations for any of the first ten principal components. The current analysis includes 7,224 Caucasian subjects with genotyping data, pulmonary function measures and complete covariate information. Imputation was performed using the 1000 Genomes² cosmopolitan reference panel, Phase I v3, using MaCH^{3,4}. Logistic regression was performed using ProbABEL⁵ v0.1-3.

B58C: The British 1958 birth cohort is a long-term follow-up of persons born in England, Scotland and Wales during one week in 1958. At age 44-45 years, cohort members were invited to participate in a biomedical examination in their home at which spirometry was performed in the standing position, without noseclips, using a Vitalograph Micro spirometer. Informed consent was obtained for all participants and ethical approval for the medical examination of the British 1958 Birth Cohort was obtained from the South-East Multicentre Research Ethics Committee (SE-MREC). Details of this fieldwork and the spirometric protocol have been published elsewhere^{6,7}. At the same examination, blood samples were collected with consent for DNA extraction and production

of immortalized cell lines. The resulting DNA collection has been widely used as a nationally representative reference set, including the Wellcome Trust Case-Control Consortium⁸, the Type 1 Diabetes Genetic Consortium⁹ and the GABRIEL asthma consortium¹⁰. Genotyping platform was performed using Illumina 550K/610K. Imputation was performed using the 1000 Genomes² March 2012, cosmopolitan reference panel and MaCH/minimac^{3,4,11}. ProbABEL⁵ 0.1-9 was used for analysis.

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 field centers¹² (NCT00005133 and NCT00149435). Local IRB approval was obtained at participating centers and written informed consent was obtained for all participants. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons were enrolled for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. 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. Imputation was performed using 1000 Genomes² Phase 1 v3 haplotypes and minimac¹¹ (2012-11-16). Logistic regression was performed in R, adjusting for CHS clinic (4 sites) and PCs 1-5.

COPD Pathology: Addressing Critical gaps, Early Treatment &

Diagnosis and Innovative Concepts (COPACETIC): The COPACETIC¹³ cohort includes Dutch (all Caucasian-ancestry) participants from the NELSON¹⁴ lung cancer screening trial recruited by the University Medical Centers of Groningen and Utrecht. The trials were approved by the Dutch Minister of Health and the ethics board at each participating centre. All participants gave written informed consent. All participants were substantial smokers (16.5 or more pack-years) aged between 50–75 years. Pre-bronchodilator pulmonary function tests were performed with standardized equipment according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines. All participants provided written informed consent. Blood samples were genotyped using the Illumina 610 Quad BeadChip. Genotype calling was done with the standard algorithm provided by Illumina and implemented in GenomeStudio software. Quality control was performed using PLINK¹⁵ software. Samples were excluded if more than 5% of genotype data was missing (n = 19), if samples were duplicated (n = 29), detected as an ethnic outlier (based on genetic distance derived from principal components c1 and c2; n = 49), derived from a relative of another participant (based on IBS estimation, $Phat > 0.5$, n = 13), or if the participant had a diagnosis of lung cancer (n = 16). Imputation was performed using the Impute2 pipeline developed by the GoNL - Impute team. In summary: The study data was lifted over from human genome build 36 to build 37 using PLINK and UCSC liftOver, followed by alignment to reference data and filtering on MAF larger than 1%, Hardy-Weinberg Equilibrium p-value of $1e-4$ and a call rate higher than 0.95. Afterwards the study data was pre-phased per chromosome using SHAPEIT2 v.2.644¹⁶. Finally the imputation over genome chunks of 5Mb was performed using IMPUTE2 2.3.0¹⁷. 1000 Genomes² phase1 integrated version 3 was used as reference panel. Associations between genomic dosages with moderate/severe COPD were assessed with logistic regression models adjusted for age, pack years smoked, and sex; current smoking status was not

available at the time of analysis. All analysis were performed in software package PLINK version 1.07^{15,18}.

COPDGene: Details of the COPDGene Study (NCT00608764, www.copdgene.org) have been described previously^{19,20}. Local IRB approval was obtained at all study centers and all study participants provided written informed consent. Eligible subjects were of non-Hispanic white or African-American ancestry, aged 45-80 years old, with a minimum of 10 pack-years of smoking and no lung disease (other than COPD or asthma). Genotyping was performed by Illumina (San Diego, CA) on the HumanOmniExpress array. Subjects were excluded for missingness, heterozygosity, chromosomal aberrations, gender check, population outliers, and cryptic relatedness. Genotyping at the Z and S alleles was performed in all subjects. Subjects known or found to have alpha-1 antitrypsin deficiency were excluded. Markers were excluded based on missingness, Hardy-Weinberg P-values, and low minor allele frequency. Imputation on the COPDGene cohorts was performed using MaCH^{3,4} and minimac¹¹ (version 2012-10-09). Reference panels for the non-Hispanic whites and African-Americans were the 1000 Genomes² Phase I v3 European (EUR) and cosmopolitan reference panels, respectively. Variants with an r^2 value of ≤ 0.3 were removed from further analysis. Logistic regression was performed on pre-bronchodilator spirometry defined cases and controls, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry, separately in non-Hispanic whites and African-Americans, using PLINK2^{21,22}.

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 previously²³. The ECLIPSE study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines, and was approved by the relevant ethics and review boards at the participating centers. All participants provided

written informed consent. ECLIPSE was an observational 3-year study of COPD. Both cases and controls were aged 40-75 with at least a 10 pack-year smoking history without other respiratory diseases; cases were post-bronchodilator GOLD²⁴ Grade 2 and above COPD, and controls had normal spirometry ($FEV_1 > 85\%$ predicted). Genotyping was performed using the Illumina HumanHap 550 V3 (Illumina, San Diego, CA). Subjects and markers with a call rate of $< 95\%$ were excluded. Population stratification exclusion and adjustment on self-reported white subjects was performed using EIGENSTRAT (EIGENSOFT Version 2.0)²⁵. Imputation was performed using MaCH^{3,4} and minimac¹¹ (version 2012-10-09) and the 1000 Genomes² Phase I v3 European (EUR) reference panel. Logistic regression was performed on pre-bronchodilator spirometry defined cases and controls, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry using PLINK2^{21,22}.

Expression Quantitative Trait Loci – Lung (eQTL): The lung eQTL study has been described previously²⁶. Briefly, patients who underwent lung 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. COPD diagnosis and severity were determined according to the

GOLD²⁴ recommendations. Patients whose lung function could have been influenced by lung diseases other than COPD and lung cancer were excluded. This includes patients with 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), lymphangiomyomatosis (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. Each genotyping set was filtered for low-quality loci with 10th percentile of Illumina GenCall score ≤ 0.1 , call rate $< 97\%$, Hardy-Weinberg equilibrium $P < 1 \times 10^{-7}$, and minor allele frequency (MAF) $< 1\%$. Samples were excluded after consideration for the 10th percentile of Illumina GenCall score ≤ 0.2 , genotype completion rate $< 90\%$, genotypic and phenotypic gender mismatch, unexpected duplicates and genetic relatedness, and genetic background outliers detected by STRUCTURE (k=4) with HapMap²⁷ subjects as internal controls. PC1 to PC10 were calculated with EIGENSOFT 4.2. Imputation was performed with SHAPEIT²⁸ (Shapeit.v1.ESHG.linux.x64) and IMPUTE2¹⁷ (impute_v2.2.2_x86_64_dynamic), and the reference set from the 1000 genomes² project (ALL_1000G_phasedintegrated_v3). Only SNPs that passed the cutoff $r^2 \geq 0.95$ were retained. Single-marker association tests were performed with PLINK v1.90^{21,22} adjusting for age, sex, smoking status, pack-years, ever smoking status, center and PC1 to PC10.

Framingham Heart Study (FHS; NCT00005121): Details on pulmonary function in the FHS have been previously published^{29,30}. The study was IRB-approved at the relevant institutions and all participants provided written informed consent. 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 the MaCH^{3,4} program for phasing. A total of 137,728 genotyped SNPs were removed based on the following filtering criteria: 22,018 SNPs for Hardy-Weinberg Equilibrium p-value of less than 1×10^{-6} , 48,285 SNPs for a call rate of less than 96.9%, 66,063 SNPs for a minor allele frequency of less than 0.01, 82 SNPs due to not mapping correctly from Build 36 to Build 37 locations, 428 SNPs missing a physical location, 25 SNPs for number of Mendelian errors greater than 1000, 786 SNPs due to not being on chromosomes 1-22 or X and 41 SNPs because they were duplicates. MaCH/minimac^{3,4,11} were used in this imputation to impute the FHS sample using the November 2010 release of the 1000 Genomes² multi-ethnic panel comprised of 1,092 samples. 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 principal component 1 (to adjust for population stratification).

KARE: Details on the Korean Association Resource project (KARE) have been previously published^{31,32}. KARE was initiated in 2007 to undertake genome-wide analyses analysis among 10,038 participants in the rural-based Ansong 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 collecting using a portable spirometer (Vmax-2130, Sensor Medics, Yorba Linda, CA, USA) according to standardized protocols of the American Thoracic Society (ATS). Genotyping was performed using the Affymetrix Genome-Wide Human array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). We performed imputation using IMPUTE2 and the 1000 Genomes² 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 was performed using PLINK¹⁸.

LifeLines: The LifeLines Cohort Study is a large population-based cohort study and biobank that was established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy aging³³⁻³⁵. 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 a physical examination, including 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 Genomes² phase1 v3 reference panels. Quality control of the data is based on SNP filtering on MAF above 0.001, HWE p -value $> 1 \times 10^{-4}$, call rate of 0.95 using PLINK¹⁵, and PCA to check for population outliers resulting in 268,407 SNPs and 13,436 samples kept for genome-wide association analysis. Before imputation, the genotypes were pre-phased using SHAPEIT2¹⁶ and aligned to the reference panels using Genotype Harmonizer (www.molgenis.org/systemsgenetics) in order to resolve strand issues. The samples were imputed using minimac¹¹ (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^{15,18}.

Lovelace: The LSC has been actively enrolling smokers from the Albuquerque, NM metropolitan area since 2001 and has been previously described³⁶. All participants provided written informed consent and the study was approved by the relevant IRB. Longitudinal studies to predict lung cancer and other chronic pulmonary diseases are conducted through assessing biomarkers present in sputum, blood, and urine samples. Enrollment was restricted to current and former smokers age 40 to 74 y 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. Sputum samples were collected by induction and stored in Saccomanno's fixative. 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 with methylation status of 12 tumor suppressor genes measured in sputum DNA samples.

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. We removed 37 subjects due to low call rate (< 95%, n = 7), low heterozygosity (n = 1), low Caucasian ancestry (< 85%, n = 2) and high relatedness with other samples (n = 27). Furthermore, SNPs were excluded if they had a call rate of < 90%, a minor allele frequency (MAF) < 0.008, or $P < 10^{-8}$ for Hardy-Weinberg equilibrium test, or were on Y or pseudo-autosomal region of X. The MAF cutoff is a technical one to identify at least 20 heterozygotes for accurate genotype clustering required by GenomeStudio. After quality assessment, 1163 subjects with 1,599,980 SNPs remained in the genetic association analysis. Logistic regression was performed using PLINK.

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 disease³⁷. Between 2000 and 2002, MESA recruited 6,814 men and women 45 to 84 years of age from Forsyth County, North Carolina; New York City; Baltimore; St. Paul, Minnesota; Chicago; and Los Angeles. 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 years³⁸. 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 Study, as previously described³⁹. 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 in the original MESA cohort, the MESA Family Study and the MESA Air Pollution Study who consented to genetic analyses were genotyped in 2009 using the Affymetrix Human SNP array 6.0. Genotype quality control for these data included filter on SNP level call rate < 95%, individual level call rate < 95%, heterozygosity > 53%, described previously⁴⁰. 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 Genomes² Phase 1 v3 March 2012 reference set. Logistic regression was performed using SNPTEST v2.4.0⁴¹.

National Emphysema Treatment Trial (NETT; NCT00000606,

www.nhlbi.nih.gov/health/prof/lung/nett/) and Normative Aging Study (NAS): Details of the National Emphysema Treatment Trial have been described previously⁴². 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 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 and conducted by the Veterans Administration (VA)⁴³. Participants provided written informed consent at each visit, and the VA Boston Healthcare System Institutional Review Board approved the study. Men aged 21 to 80 years from the greater Boston area, free of known chronic medical conditions, were enrolled. Smoking controls were of self-reported white ancestry and at least 10 pack-years of cigarette smoking with no evidence of airflow obstruction on spirometry on their most recent visit. Genotyping for NETT-NAS was performed using the Illumina Quad 610 array (Illumina, San Diego, CA), with quality control, population stratification adjustment, as described previously^{44,45}. Imputation was performed using MaCH^{3,4} and minimac¹¹ (version 2012-10-09) and the 1000 Genomes Phase I v3 European (EUR) reference panel. Logistic regression was performed on pre-bronchodilator spirometry defined cases and controls, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry using PLINK2^{21,22}.

GenKOLS (Norway): Details on the Norwegian GenKOLS (Genetics of Chronic Obstructive Lung Disease, GSK code RES11080) study have been described previously⁴⁶. Subjects with > 2.5 pack years of smoking history were recruited from Bergen, Norway; cases had post-bronchodilator

GOLD 2 or greater disease²⁴, while controls had normal spirometry; subjects with severe alpha-1 antitrypsin deficiency and other lung diseases (aside from asthma) were excluded. The study was performed in accordance with the ethical standards laid down in the Helsinki Declaration. The Regional Committee for Medical Research Ethics (REK Vest), the Norwegian Data Inspectorate and the Norwegian Department of Health approved the case-control study. A written informed consent was obtained from all participants. Genotyping was performed using Illumina HumanHap 550 arrays (Illumina, San Diego, CA), with quality control, population stratification adjustment as previously described. Imputation was performed using MaCH^{3,4} and minimac¹¹ (version 2012-10-09) and the 1000 Genomes² Phase I v3 European (EUR) reference panel. Logistic regression was performed on pre-bronchodilator spirometry defined cases and controls, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry using PLINK2^{21,22}.

The Rotterdam Study: The Rotterdam Study is a prospective population-based cohort study founded in 1990 in a suburb of Rotterdam, the Netherlands^{47,48}. 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 by trained paramedical personnel using the Master Screen® PFT Pro (CareFusion, San Diego, CA) according to the American Thoracic Society(ATS)/European Respiratory Society (ERS) guidelines.

A total of 6,318 subjects were genotyped in RS I, 2,516 in RS II and 3,540 subjects in RS III. Exclusions included a call rate < 98%, Hardy-Weinberg $P < 1 \times 10^{-6}$ and MAF < 0.01%. A total of 6,291 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 ProbABEL⁵ program according to an additive model.

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 COPD⁴⁹. All participants provided written informed consent and the Institutional Review Boards/Ethics Committees of all the cooperating institutions approved the study protocols. All SPIROMICS study participants have been comprehensively characterized with standardized comprehensive questionnaires (including clinical outcomes such as exacerbations requiring healthcare utilization, medication use, St. George's Respiratory Questionnaire [SGRQ], and BODE index), pre- and post-bronchodilator lung function, and CT scan imaging. Genome wide genotyping was performed using the Illumina OmniExpress HumanExome BeadChip using standard techniques in the first 571 subjects with COPD and 175 controls. Imputation was performed against 1000 Genomes reference panels using Impute-v2.30 using a quality cutoff of 0.9, and association analysis performed using PLINK.

Studies with Custom Genotyping:

Boston Early-Onset COPD Study (BEOCOPD; ClinicalTrials.gov: NCT01177618): Details of the BEOCOPD study have been described previously^{50,51}. IRB approval was obtained for the study and all participants provided written informed consent. BEOCOPD is an extended pedigree study constructed based on probands under 53 years of age with severe COPD (defined as forced expiratory volume in one second (FEV₁) < 40% predicted) and without severe alpha-1 antitrypsin deficiency. Given the small number of non-white subjects in this cohort, only white subjects were included in this analysis. Extended pedigrees from BEOCOPD, ICGN, TCGS-Poland, and TCGS-Korea

were genotyped together on the Illumina HumanExome v1.2 array with custom content (see below). Subject quality control included kinship via KING⁵² and kinship2⁵³, genotyping success rate, sex check, homozygosity, Mendelian errors. Markers were assessed for missingness, concordance between duplicate samples, and Hardy-Weinberg equilibrium. Assessment for population outliers and control for population stratification was performed using TRACE v1.0^{54,55} and HapMap population ²⁷ as the reference. Single-variant association analysis for pre-bronchodilator moderate-to-severe COPD, adjusting for age, pack-years, sex, and current and ever smoking, was performed in EOCOPD and ICGN 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/>)⁵⁶.

International COPD Genetics Network (ICGN): The ICGN has been described previously^{57,58}. ICGN recruited subjects ($FEV_1 < 60\%$ predicted and $FEV_1/FVC < 90\%$ predicted between ages 45-65) as probands and then enrolled available siblings and parents of the proband. The study was IRB approved at all relevant institutions and participants provided written informed consent. Given the small number of non-white subjects in this cohort, only white subjects were included in this analysis. Genotyping and analysis was performed as detailed above (in the **BEOCOPD** section).

Transcontinental COPD Genetics Study (TCGS) – Korea and Poland: TCGS has been described previously⁵⁹ and was 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 ($FEV_1 < 50\%$ predicted) and controls had normal spirometry. Subjects with other lung disease were excluded. TCGS-Poland enrolled white individuals, and TCGS-Korea enrolled Korean individuals. Details of genotyping are described

above (in the **BEOCOPD** section). We used PLINK2^{21,22} to perform logistic regression, adjusting for age, pack-years, sex, and current smoking status.

UK BiLEVE Cohort Information: UK BiLEVE is a subset of UK Biobank and is described in detail elsewhere⁶⁰. In brief, UK Biobank comprised 502,682 individuals of which 472,858 were of self-reported European ancestry and 275,939 had at least two measures of FEV₁ and FVC and passed ATS/ERS quality criteria⁶¹. Spirometry data was obtained using a Vitalograph Pneumotrac 6800 (Buckingham, UK); at least two measures were obtained. From these 275,939 individuals, 50,000 individuals were selected based on % predicted FEV₁ such that 10,000 individuals with low FEV₁, 10,000 individuals with near-average FEV₁, and 5,000 with high FEV₁ were selected from amongst never smokers (total n=105,272) and the same numbers from amongst the heavy smokers (total n=46,758). Equal numbers of males and females were selected and the number of individuals selected within each age-sex band was proportional to the number of individuals available for sampling for each band. Genotyping was undertaken using the Affymetrix Axiom UK BiLEVE array⁶⁰ and imputed to the 1000 Genomes Project² Phase 1 and UK10K⁶² combined panel. Of the 50,008 samples selected, 48,943 unrelated individuals passed all genotype and sample quality control steps and were used as the sampling frame for selection of samples included in the analysis described here. The UK Biobank received ethics approval from the National Health Service National Research Ethics Service (Ref 11/NW/0382). All participants provided written informed consent.

In UK BiLEVE, COPD status was defined based on spirometry with individuals with % predicted FEV₁<80% and FEV₁/FVC<0.7 (indicative of COPD GOLD stage 2 or worse) selected as COPD cases. COPD controls were individuals that did not meet the case criteria and were selected from the high % predicted FEV₁ group only (all had % predicted FEV₁>80%). Asthma was not an exclusion criterion for participation in the UK BiLEVE cohorts. Asthma cases in UK BiLEVE were defined as participants that either (i) answered “asthma” to a touchscreen question “Has a doctor

ever told you that you have had any of the following conditions? (You can select more than one answer) (Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy)", or (ii) reported asthma in verbal interview, as per any of the self-reported, non-cancer illness fields. Using this definition 3,862 asthma cases (including 1,803 never-smoker COPD cases, 284 never-smoker controls, 1,451 heavy smoker COPD cases, and 324 heavy smoker controls) were identified in the 19,246 Stage 2 samples. Analyses were carried out using the score test, implemented in SNPTEST v2.5b4 and assuming an additive genetic model of genotype dose. For never smokers, sex, age and the first 10 ancestry principal components were included as covariates. For heavy smokers, current smoking status and pack years were included as additional covariates.

Additional Supplemental Methods

Fine Mapping Analysis Methods

We attempted to determine, at each locus, whether we could identify a potentially causal variant. We performed these analyses using European ancestry subjects alone, and in all subjects with genome-wide data, and excluded variants that were not present in at least 80% of the full sample. We assumed a single causal variant at each locus, examined a +/- 250kb region around the top variant, and calculated approximate Bayes factors using the method of Wakefield⁶³ to determine the 95% credible set. While specific trans-ethnic mapping approaches^{64,65} can significantly assist in identifying causal loci, we found that the number of non-European samples in our study were likely insufficient to leverage these methods.

Functional Enrichment Analysis Methods

To identify enriched cell types for our COPD associations, we applied LD score regression to GenoSkyline⁶⁶ lung tissue annotations (the default LD score regression annotations collapse lung into the cardiovascular tissue type), as well as cell-type specific annotations from LD score regression⁶⁷. We also performed analysis using only the 22 genome-wide significant loci and tested for enrichment of imputed chromatin marks from ROADMAP using HaploReg 4.1⁶⁸. Further, we applied a more sophisticated analysis adjusting for local linkage disequilibrium patterns, GoShifter⁶⁹. Finally, we examined overlap with gene expression datasets using SNPsea⁷⁰.

Supplemental Pulmonary Fibrosis and COPD Overlap Methods

To further examine overlapping loci for COPD and pulmonary fibrosis, we combined summary statistics from our study and the pulmonary fibrosis GWAS by Fingerlin et al.^{71,72} using gwas-pw⁷³.

COPD Comorbidity Overlap Analysis Methods

We assessed the overlap between our results and two common COPD comorbidities, coronary artery disease and osteoporosis (through bone mineral density traits). We downloaded information on genome-wide significant ($P < 5 \times 10^{-8}$) associations with these comorbidities as reported in the NHGRI-EBI GWAS Catalog⁷⁴. We assessed the association statistics of these comorbid trait loci in our Stage 1 meta-analysis results.

Quantitative Imaging Overlap Analysis Methods

To explore the relationship between our top COPD-associated variants and imaging features of emphysema and airway thickness, we queried data from a GWAS of COPD quantitative imaging features⁷⁵. For each genome-wide significant COPD susceptibility locus in our overall meta-analysis, we assessed the corresponding quantitative imaging GWAS effect size, effect direction, and P value for association with the following quantitative imaging traits: %LAA-950 (percentage low attenuation area, using a threshold of -950 Hounsfield units); Perc15 (value of Hounsfield units at the 15th percentile of the density histogram); Pi10 (airway wall area: the value for a hypothetical 10-mm airway obtained by plotting a regression line of the square root of the airway wall area versus the airway internal perimeter); and WAP (percentage of the wall area compared to the total bronchial area).

Gene Set Enrichment Analysis Methods

As an attempt to minimize false positives in our gene set enrichment analysis, we divided the Stage 1 GWAS cohorts with full genome-wide data into two sets of roughly equal size. We then used i-GSEA4GWAS (<http://gsea4gwas.psych.ac.cn/>)⁷⁶ for each of the two GWAS data sets to assess enrichment of COPD GWAS loci in BioCarta (http://cgap.nci.nih.gov/Pathways/BioCarta_Pathways) and KEGG⁷⁷ pathways as well as gene ontology (GO) terms^{78,79}. We first evaluated GO terms and

pathways with a false-discovery rate (FDR) less than 5% in both analysis sets and then used a more stringent threshold of FDR < 1% to evaluate overlap of GO term and pathway enrichment in our two analysis sets.

Causal Gene Analysis Methods

For the genome-wide significant loci from the overall meta-analysis, we explored potential causative genes at each association locus using the PrixFixe method⁸⁰, assuming co-function of all significant loci. As required by the PrixFixe method, we assured our genome-wide significant loci were present in dbSNP v137⁸¹ and were represented HapMap²⁷ phase III data; for loci not meeting these requirements, proxy SNPs from HapMap phase III were selected based on strongest LD (r^2) with index SNP (see Supplemental Table S18 for details of the proxy variant used at each genome-wide significant locus).

Supplemental Results:

Fine Mapping Analysis Results

We examined 21 of our top 22 GWAS loci (excluding the HLA region) from the overall meta-analysis and identified a 95% credible set at each locus both in Europeans alone, and including all subjects. Results of these fine mapping analyses are presented in Table S20. For seven loci, the 95% credible set had 20 or fewer variants. In general, inclusion of additional, non-European samples reduced the number of variants in the credible set. We also examined association signals for these loci in the African-Americans (our largest non-European ethnicity). Five loci had a variant with $P < 0.001$ in LD ($r^2 > 0.2$ or $D' > 0.7$) with the lead variant in all subjects. Overall, these results suggest some loci for which a reasonable number of variants can be tested, and others for which functional annotation, sample size, and studies of other ethnicities could be most useful.

Lung eQTL Analysis Results

Genotypes and gene expression was available for 409 patients from Laval, 287 patients from the UBC, and 342 patients from Groningen. One hundred ten eQTL at 20 loci were nominally ($P < 0.05$) significant in the meta-analysis; 14 eQTL (P value $< 5.2 \times 10^{-8}$) involving 6 loci reached significance after Bonferroni correction. Supplemental Table S8 shows the most significant gene-SNP pairs at each locus. rs17486278 on chromosome 15 was also significantly associated with CHRNA5 and PSMA4 as previously reported⁸².

Functional Enrichment Analysis Results

The LD score regression functional enrichment analysis identified lung as the primary tissue (coefficient Z-score, 2.54), and fetal lung as the primary cell type (Z-score, 4.4). No inflammatory cell types were nominally significant (Z all < 1.75). In the ROADMAP⁶⁸ enrichment analysis, no individual cell was significant after correction for multiple testing, though we identified

nominal significance (P value, using GWAS background < 0.05) for A549 lung cancer, NHLF lung fibroblast, and primary helper and effector T cells from peripheral blood ($P > 0.01 < 0.05$). Using GoShifter⁶⁹ we identified nominal significance for fetal lung and IMR90 lung fibroblasts ($P = 0.006$ and 0.049 respectively); there was no evidence for immune cell enrichment. With the SNPsea⁷⁰ analysis, lung related cells ranked in the top annotations in both the Affymetrix (Lung, Trachea, Bronchial epithelial cells with unadjusted $0.02 > P > 0.03$) and FANTOM5 (lung, mesothelioma, and alveolar cell carcinoma $0.001 > P > 0.03$). In the Immgen dataset, our top enrichment was for lung dendritic cells ($P = 0.002$). No enrichment was seen for neutrophils, T-cells, and lung macrophages (P all > 0.09).

In summary, multiple analyses identified enrichment of lung cell types; in contrast, we were unable to find convincing and consistent evidence of enrichment for other cell types, including inflammatory cells. While this lack of enrichment could reflect a limited influence of genetically driven inflammatory factors contributing to COPD, this could also represent limitations in the power and assessment appropriate cell types in these datasets.

Supplemental Pulmonary Fibrosis and COPD Overlap Results

We found strong evidence for shared signals in the *FAM13A* and *DSP* regions (posterior probability of association > 0.99). We also identified three other regions with a posterior probability (PP) of > 0.4 . The first of these regions is near *MAPT* and *KANSL1*, in the chromosome 17 inversion region (PP 0.84). This region has been previously associated with the extremes of lung function⁶⁰. We noted two other regions with PP > 0.4 , both described as genome-wide significant in pulmonary fibrosis^{71,72}. These were 7q22 (PP of 0.59) and near *EHMT2* in the MHC (PP of 0.45). For both of these, the index SNP in pulmonary fibrosis had concordant direction of effect in COPD, though P-values were less significant ($P = 7.8 \times 10^{-3}$ and 5.4×10^{-2}).

COPD Comorbidity Overlap Analysis Results

We evaluated a total of 211 variants in 110 genomic regions in our assessment of overlap of COPD variants with previously reported genome-wide significant variants for coronary artery disease and bone mineral density. A Bonferroni-adjusted P-value for the lookup of 211 variants is $P < 2.4 \times 10^{-4}$. One coronary artery disease GWAS variant (rs3825807) at the 15q25.1 locus (near *ADAMTS7*) met this significance threshold for association with COPD. Of note, the 15q25 locus is associated with cigarette smoking, a shared risk factor for COPD and coronary disease. All 19 coronary artery disease and bone mineral density GWAS variants with at least nominally significant ($P < 0.05$) COPD association are reported in Supplemental Table S16.

Quantitative Imaging Overlap Analysis Results

We evaluated our 22 COPD susceptibility loci in a GWAS of COPD-related quantitative imaging phenotypes⁷⁵ to assess differential effects of our COPD susceptibility loci on emphysema and airway imaging phenotypes (Supplemental Table S17).

Gene Set Enrichment Analysis Results

To assess enrichment of our Stage 1 association analysis results in biologic pathways, we divided the Stage 1 analysis cohorts into discovery and validation sets of roughly equal size and analyzed each set using i-GSEA4GWAS (<http://gsea4gwas.psych.ac.cn/>)⁷⁶. We identified 32 GO terms and canonical pathways with significant enrichment (false discovery rate (FDR) $< 5\%$) in both sets. These enriched pathways related to cell homeostasis, cell differentiation, lymphoid organ and immune system development, biopeptide signaling and transcription factor complex activity. Using a more stringent FDR threshold of $< 1\%$, five pathways and GO terms overlapped between the discovery and validation analysis sets, including the T cell receptor pathway, sugar metabolism, ion and substrate channel activities, and response to organic substance stimulus.

Causal Gene Analysis Results

We used the PrixFixe method⁸⁰ to rank potential causal genes based on mutual function across all COPD genome-wide loci (Supplemental Table S19). In regions such as chr15q25.1, chr16p11.2, chr16q23.1, and chr19q13.2 with multiple genes in an LD window with our top COPD variant, the PrixFixe method did not rank the closest gene as the most likely causative gene based on mutual function of genes at all top COPD loci.

Supplemental Figures:

Figures S1a-v: Forest plots illustrate the association results at the individual cohort level in each stage of the analysis for each of the 22 genome-wide significant loci. For the Stage 1 analysis portion of the forest plots, the studies are grouped into studies containing individuals of European ancestry and studies containing individuals of non-European ancestry. The “Stage 1” odds ratio (OR) and 95% confidence interval (CI) represents a meta-analysis across the 26 Stage 1 analysis studies. The “Stage 2: BiLEVE” OR represents the meta-analysis of UK BiLEVE never smokers and heavy smokers. The “Overall” OR represents the cumulative meta-analysis across the Stage 1 results and the UK BiLEVE Stage 2 results. If the marker was not available in a specific cohort, the cohort is missing from the forest plot. Study abbreviations: ARIC = Atherosclerosis Risk in Communities, B58 = British 1958 Birth Cohort, CHS = Cardiovascular Health Study, COPACETIC = COPD Pathology: Addressing Critical gaps, Early Treatment & Diagnosis and Innovative Concepts, ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points, eQTL = Lung Expression Quantitative Trait Loci Study, FHS = Framingham Heart Study, KARE = Korean Association Resource project, MESA = Multi-Ethnic Study of Atherosclerosis, NETT-NAS = National Emphysema Treatment Trial / Normative Aging Study, RS = Rotterdam Study, SPIROMICS = Subpopulations and intermediate outcome measures in COPD study, EOCOPD = Boston Early-Onset COPD Study, ICGN = International COPD Genetics Network, TCGS = Transcontinental COPD Genetics Study, BiLEVE = UK Biobank Lung Exome Variant Evaluation; NHW = Non-Hispanic white, AA = African American, EA = European American.

Figure S1a: Forest plot for rs13141641 (*HHIP*)

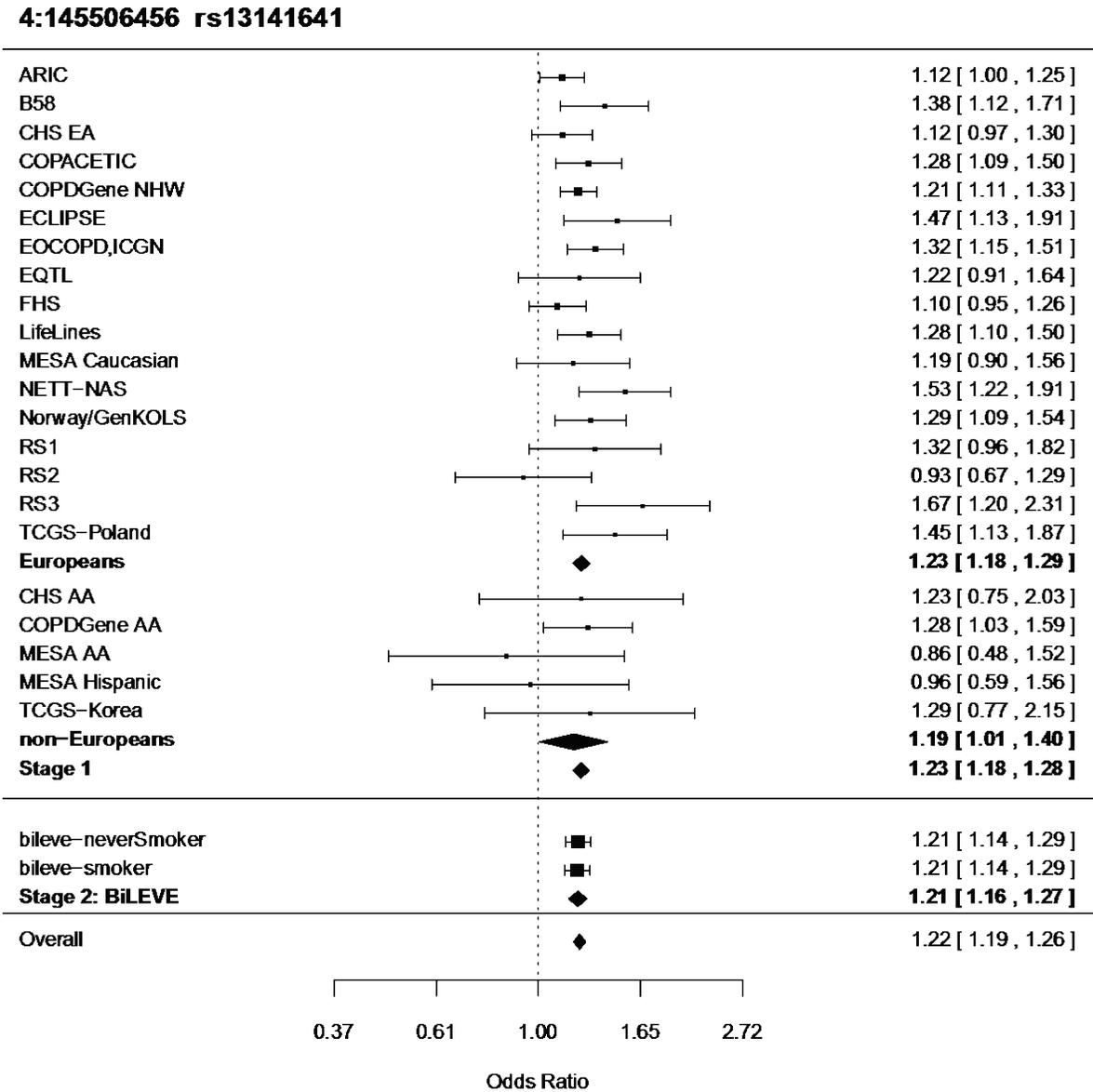


Figure S1b: Forest plot for rs17486278 (*CHRNA5*)

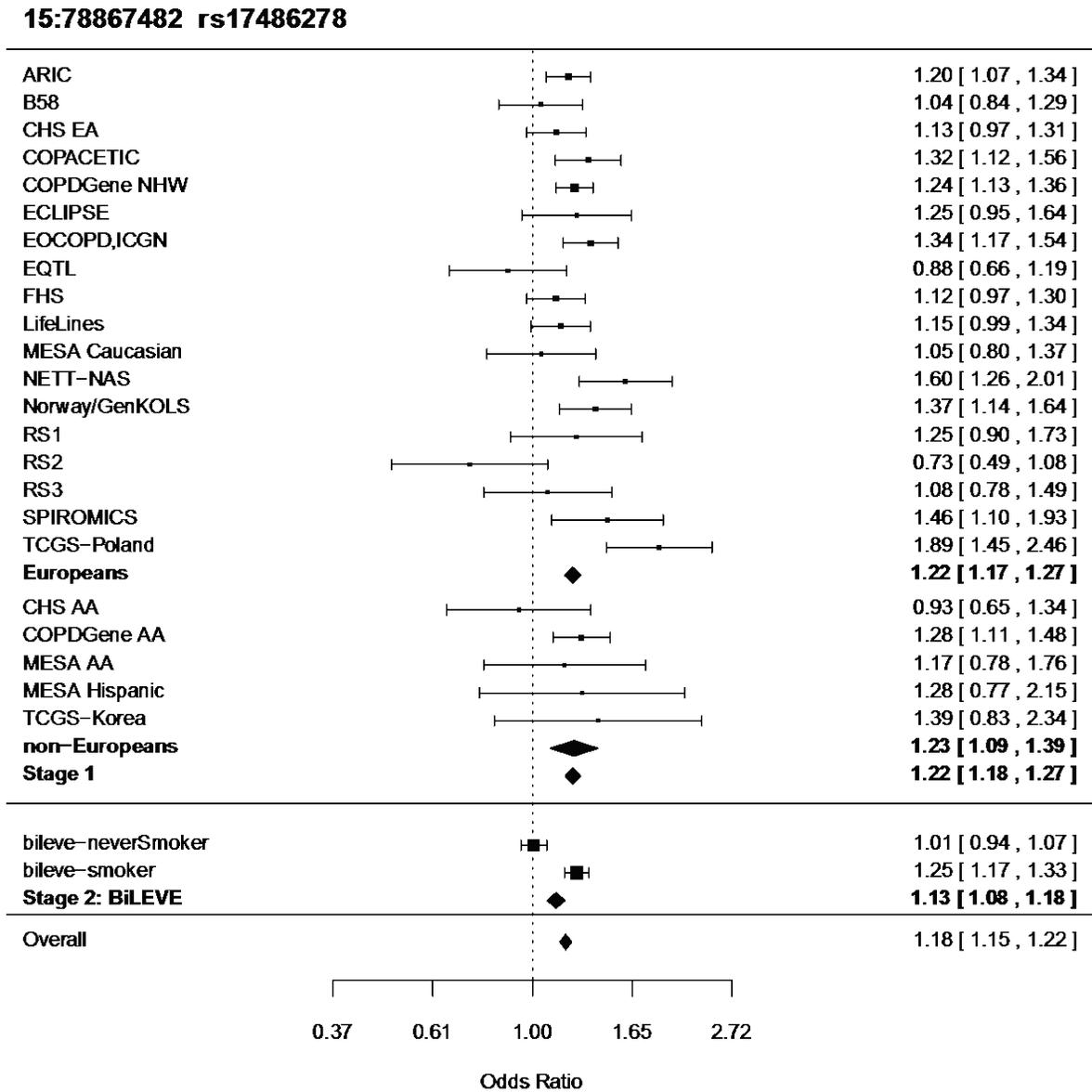


Figure S1c: Forest plot for rs7733088 (*HTR4*)

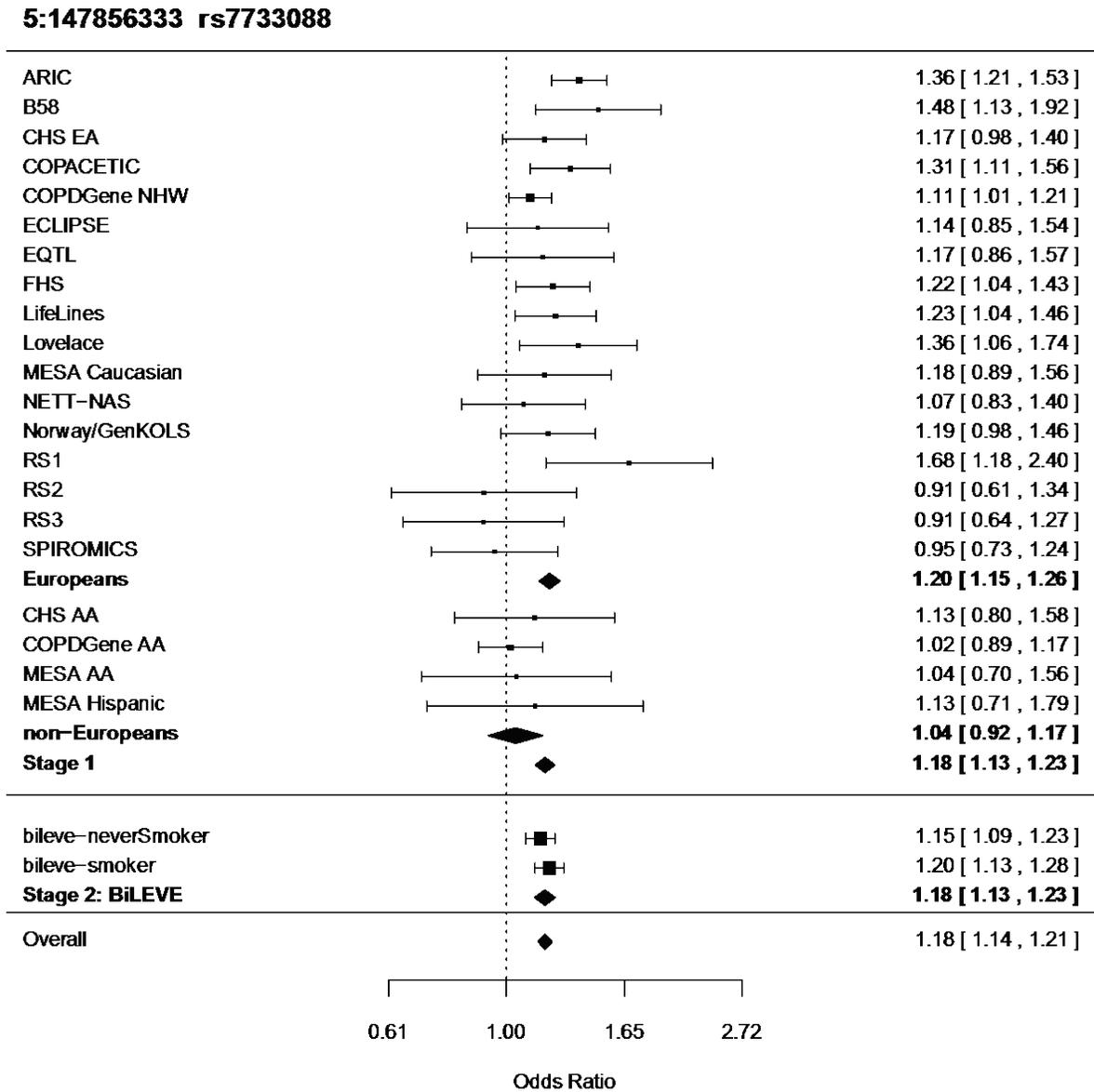


Figure S1d: Forest plot for rs9399401 (ADGRG6)

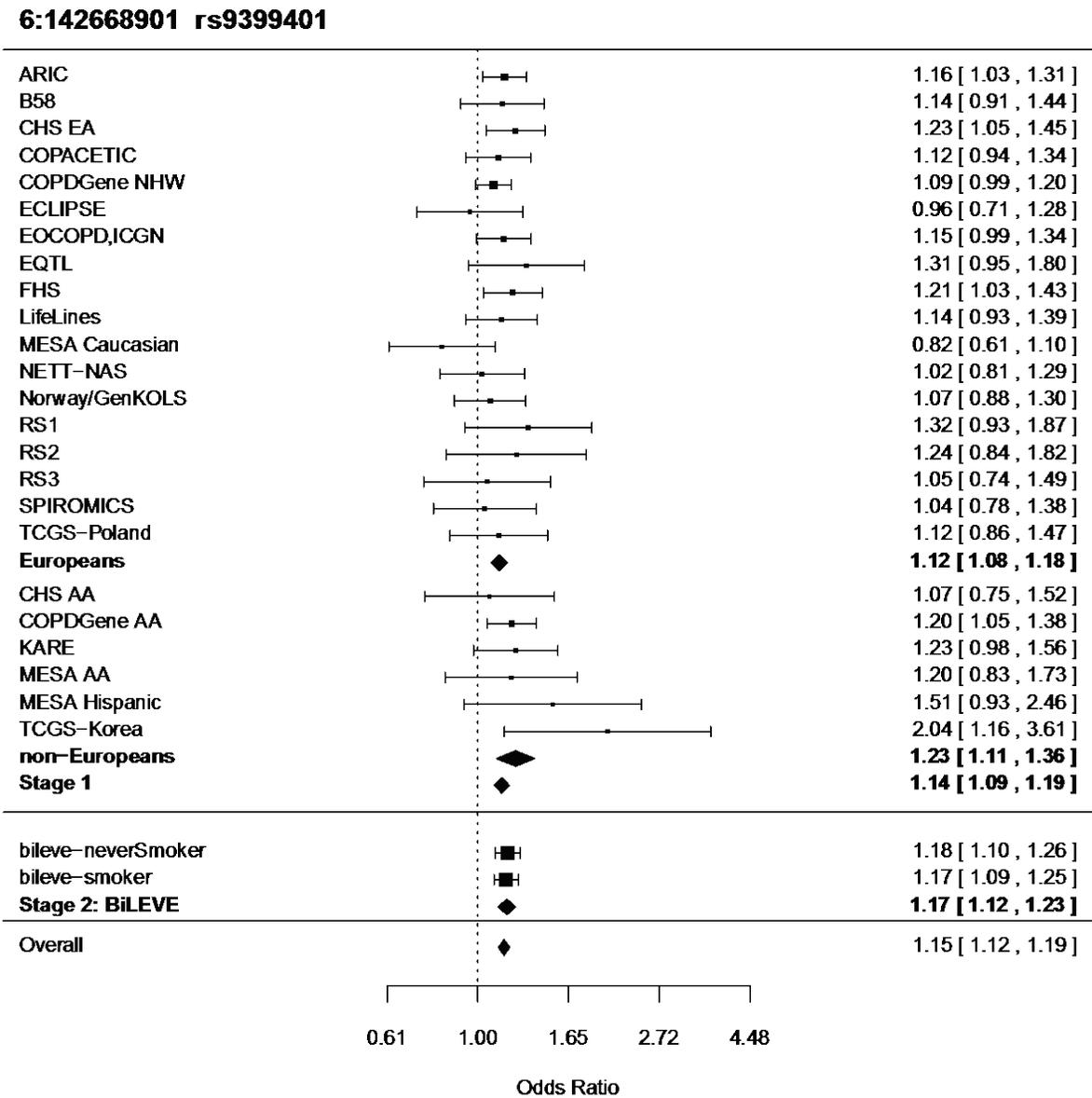


Figure S1e: Forest plot for rs1441358 (*THSD4*)

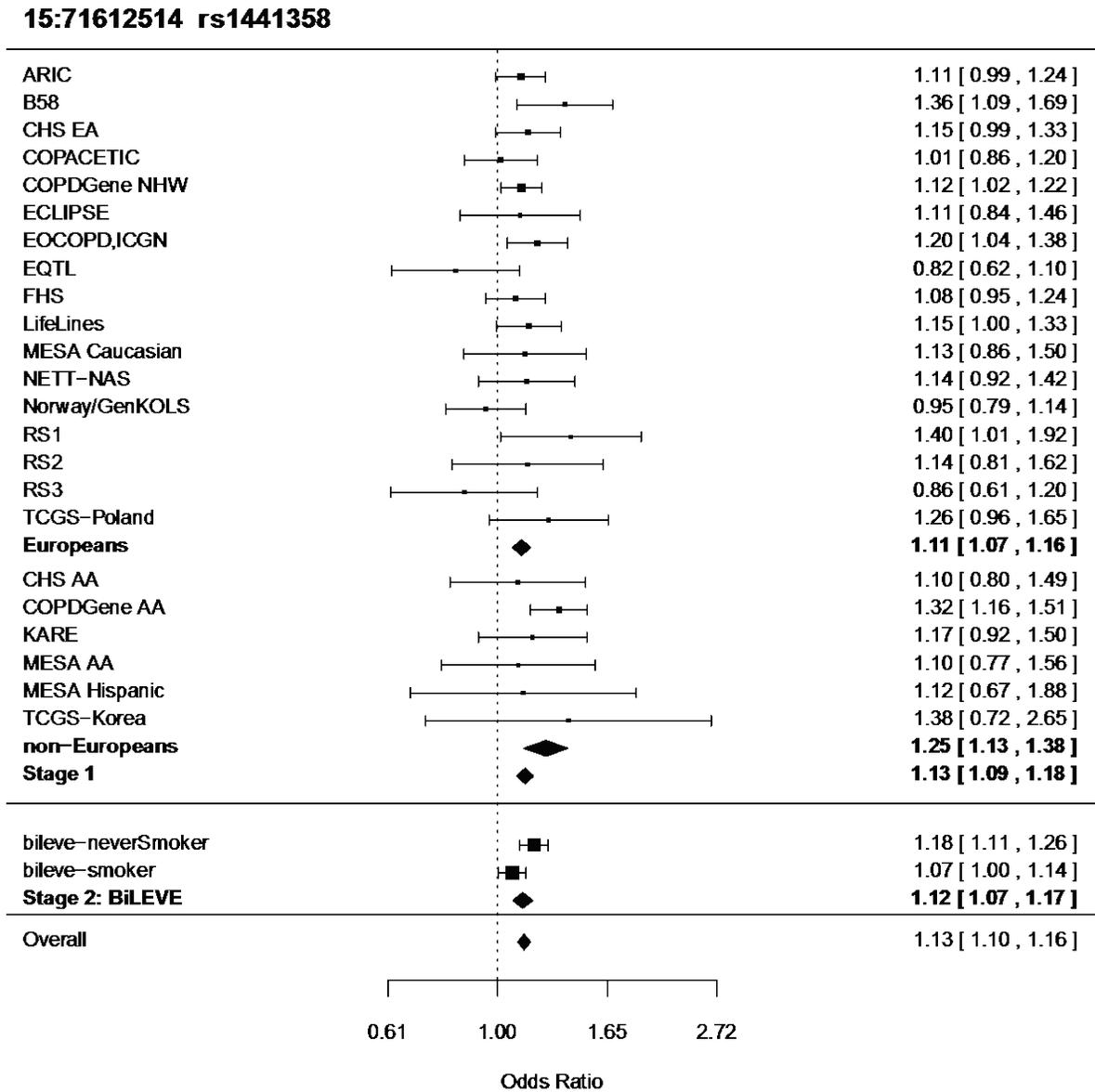


Figure S1f: Forest plot for rs6837671 (*FAM13A*)

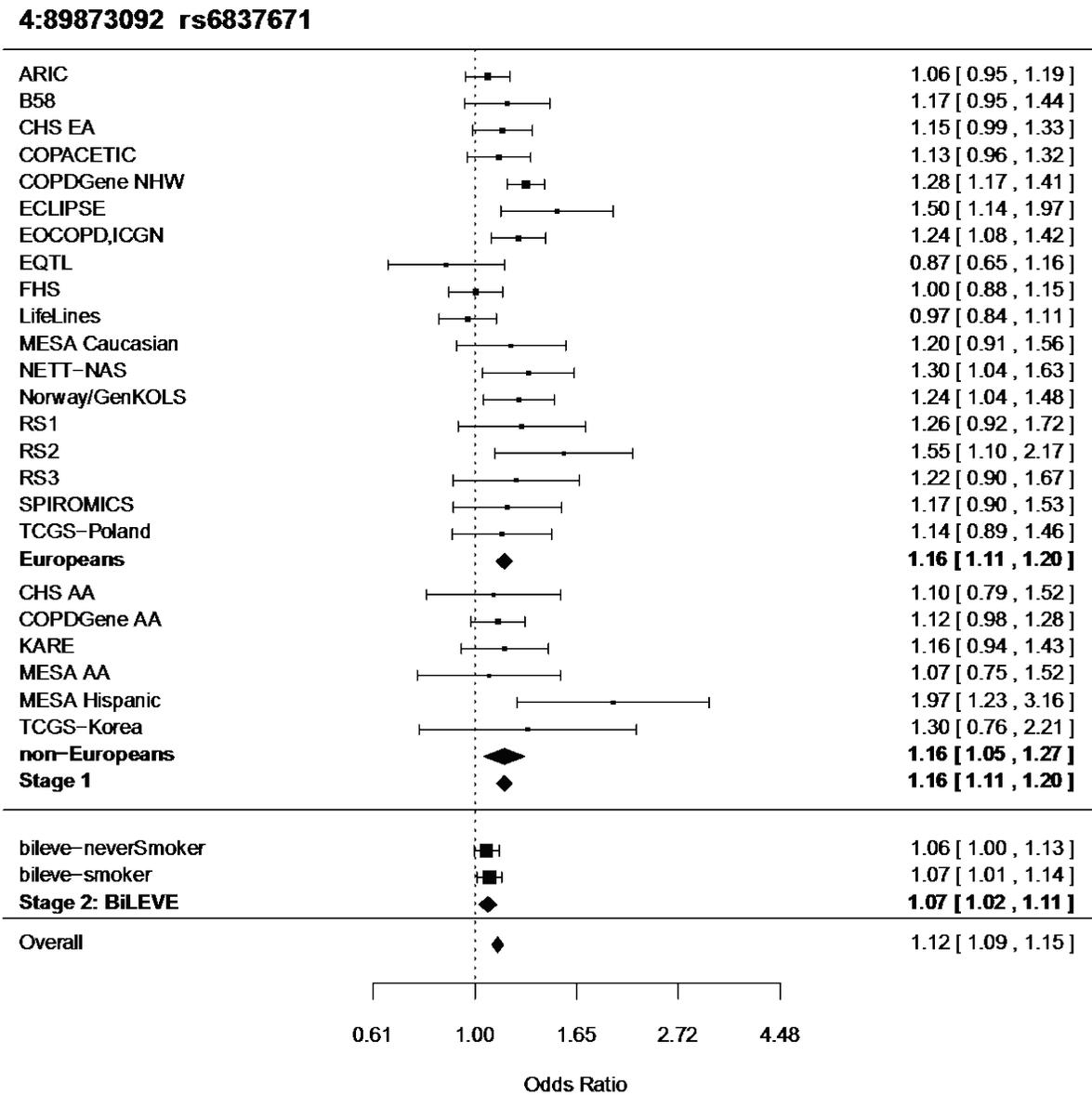


Figure S1g: Forest plot for rs11727735 (*GSTCD*)

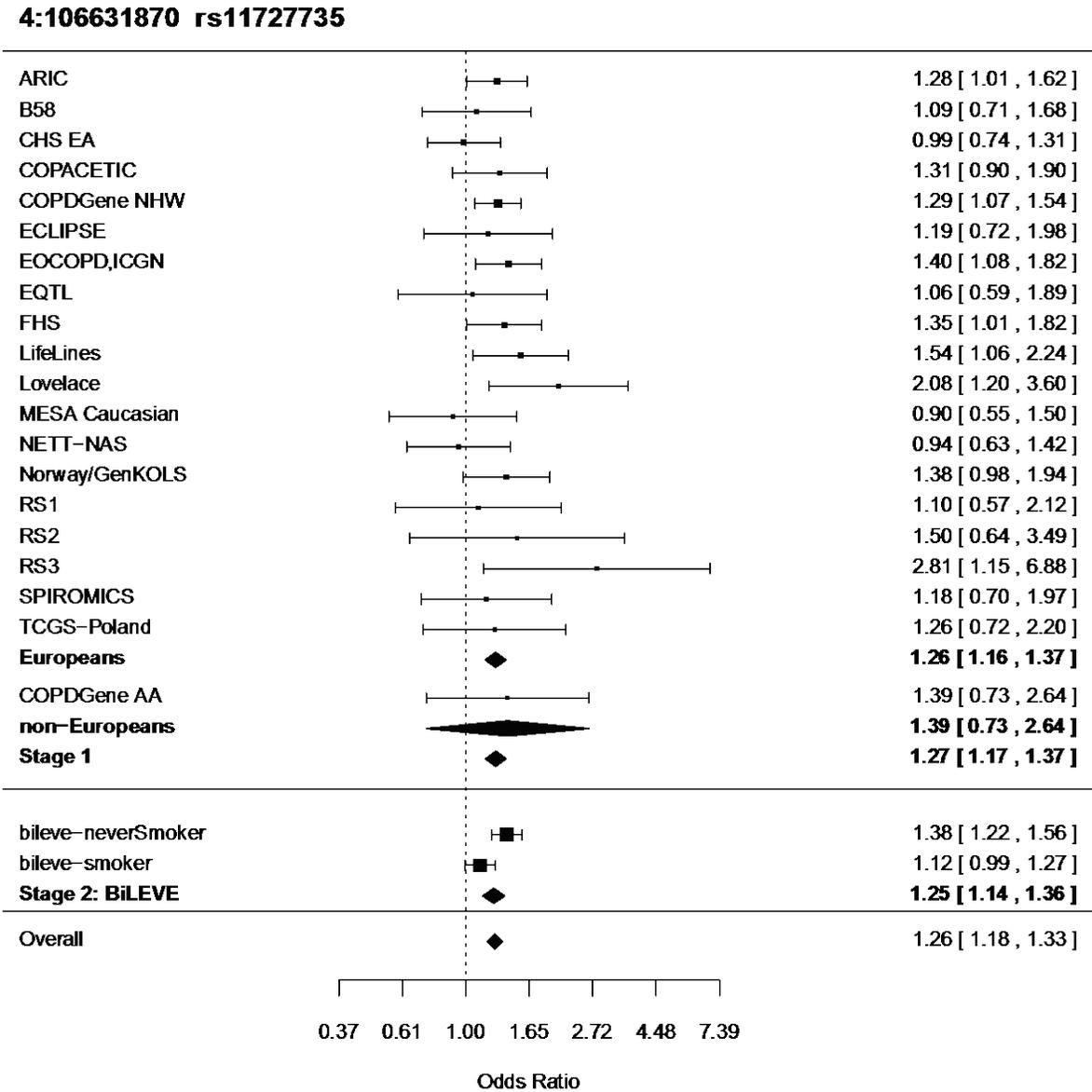


Figure S1h: Forest plot for rs754388 (*RIN3*)

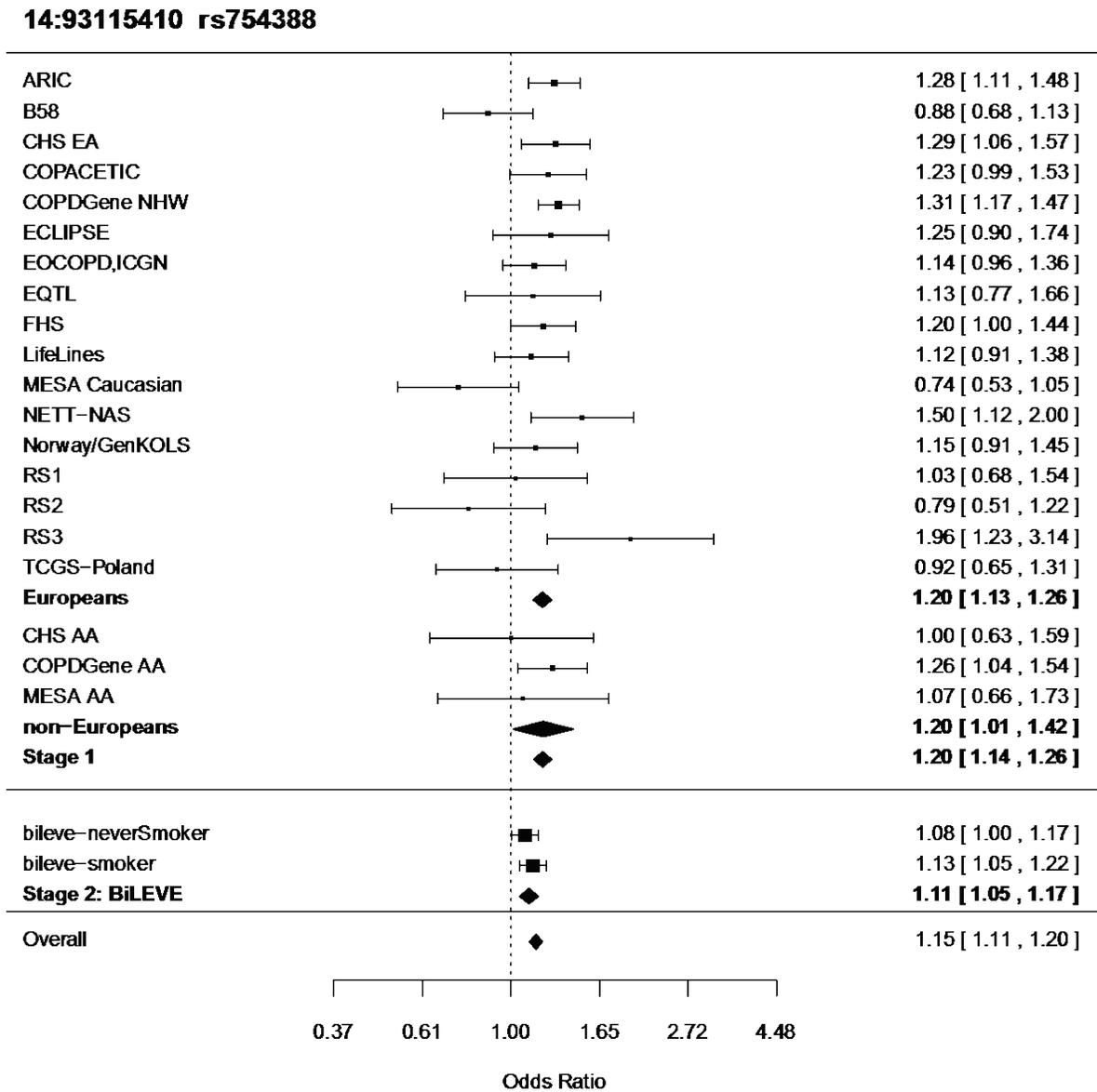


Figure S1i: Forest plot for rs113897301 (*ADAM19*)

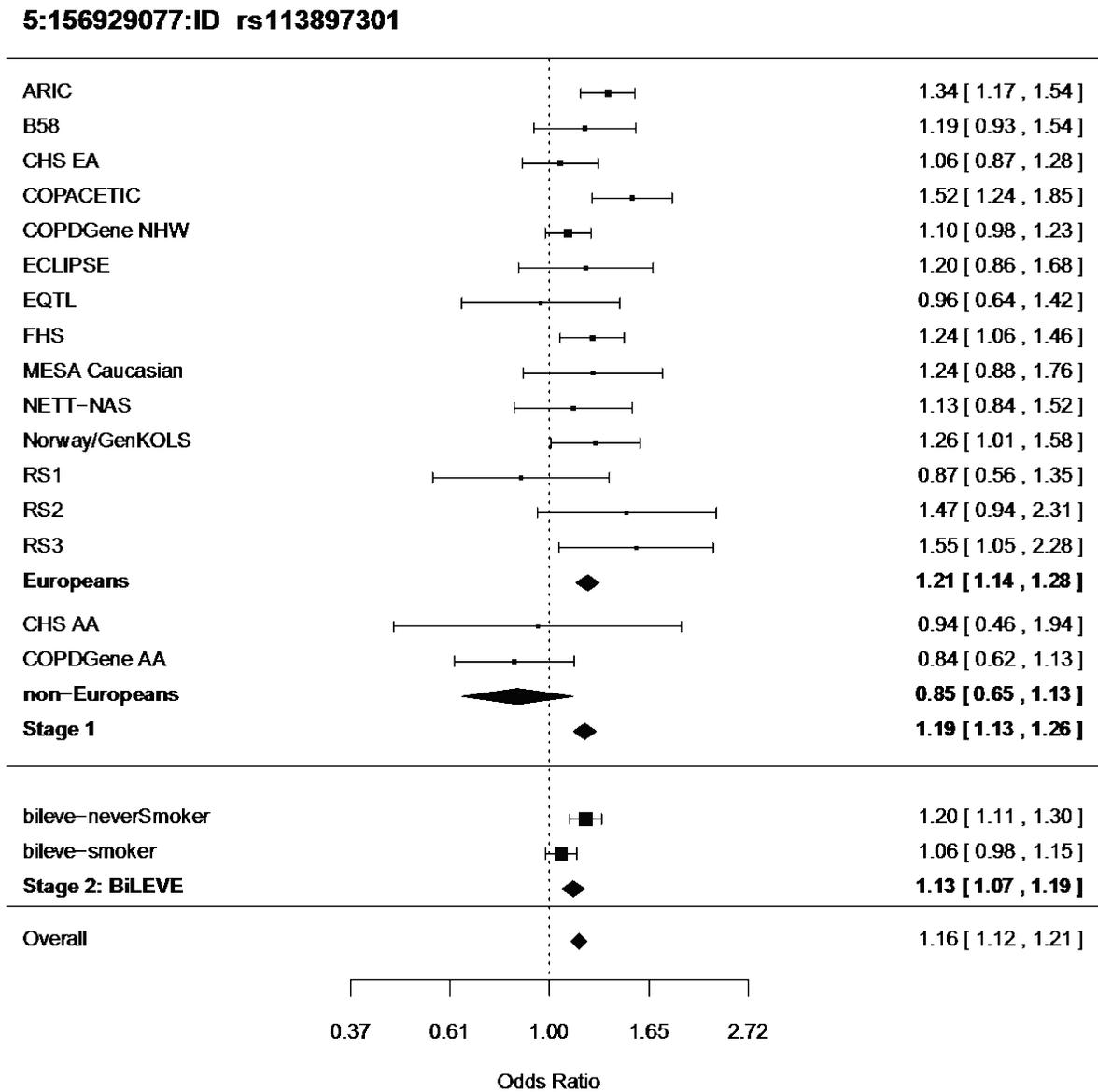


Figure S1j: Forest plot for rs2047409 (TET2)

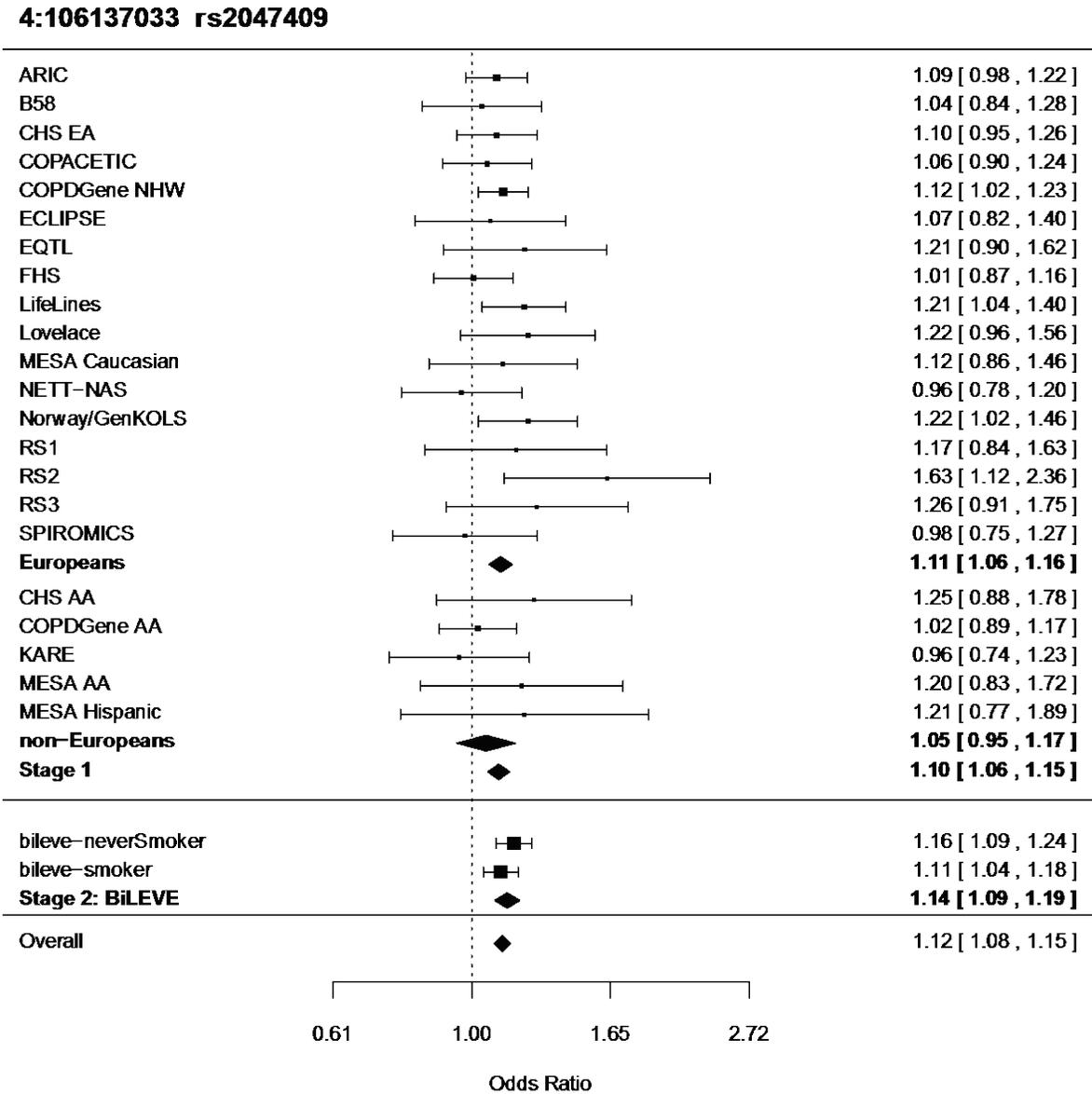


Figure S1k: Forest plot for rs2955083 (*EEFSEC*)

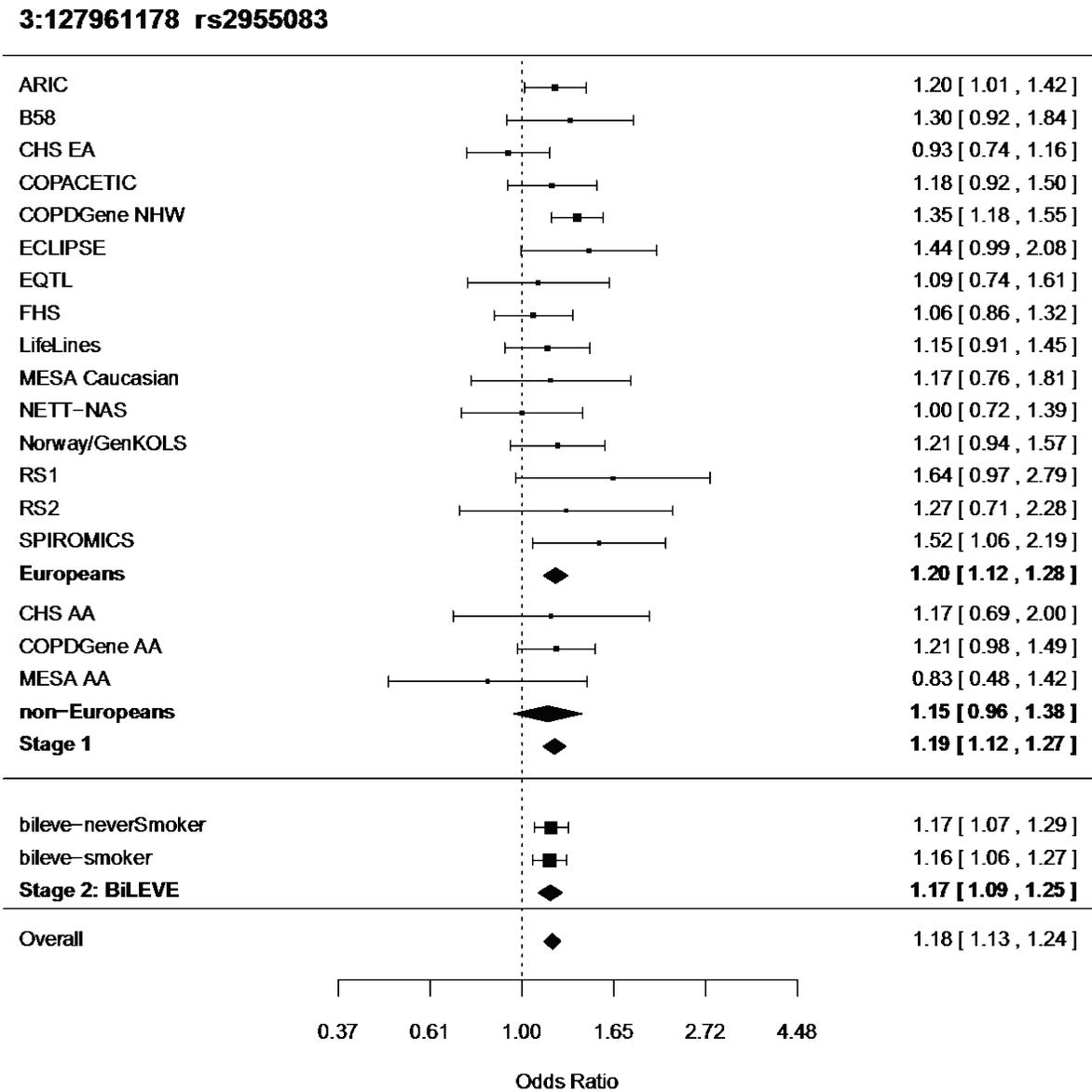


Figure S11: Forest plot for rs7186831 (*CFDP1*)

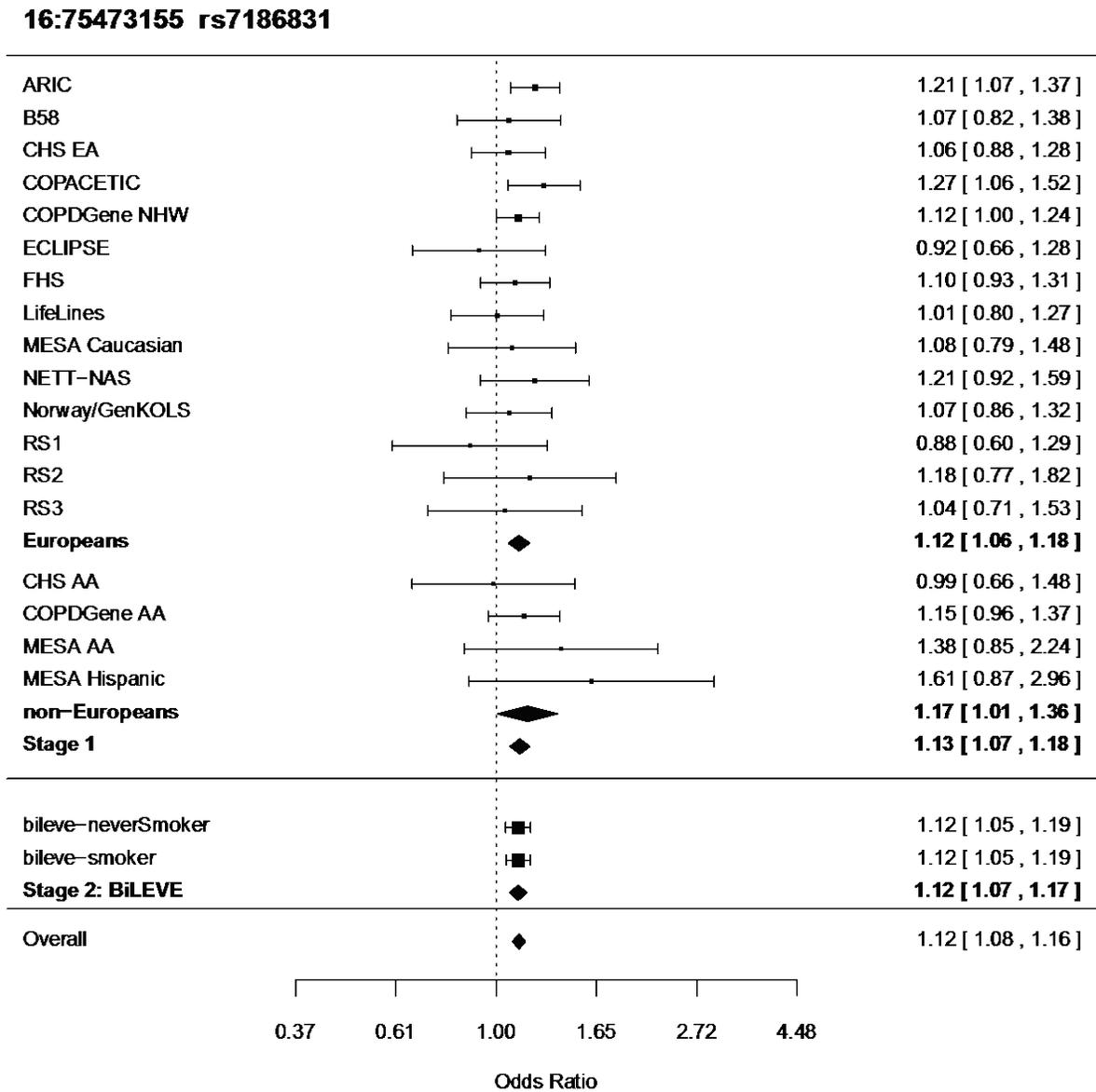


Figure S1m: Forest plot for rs10429950 (TGFB2)

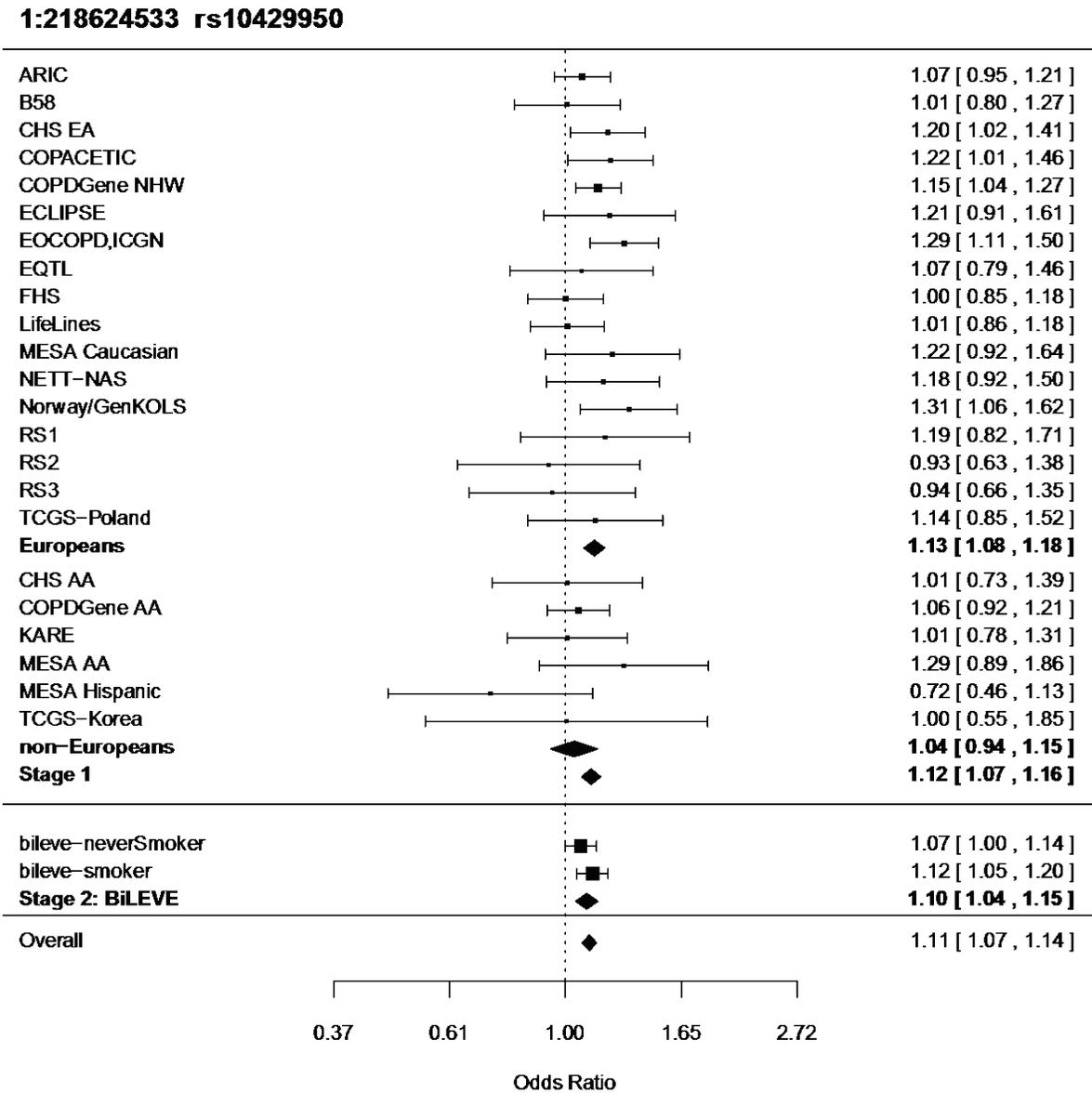


Figure S1n: Forest plot for rs2070600 (AGER)

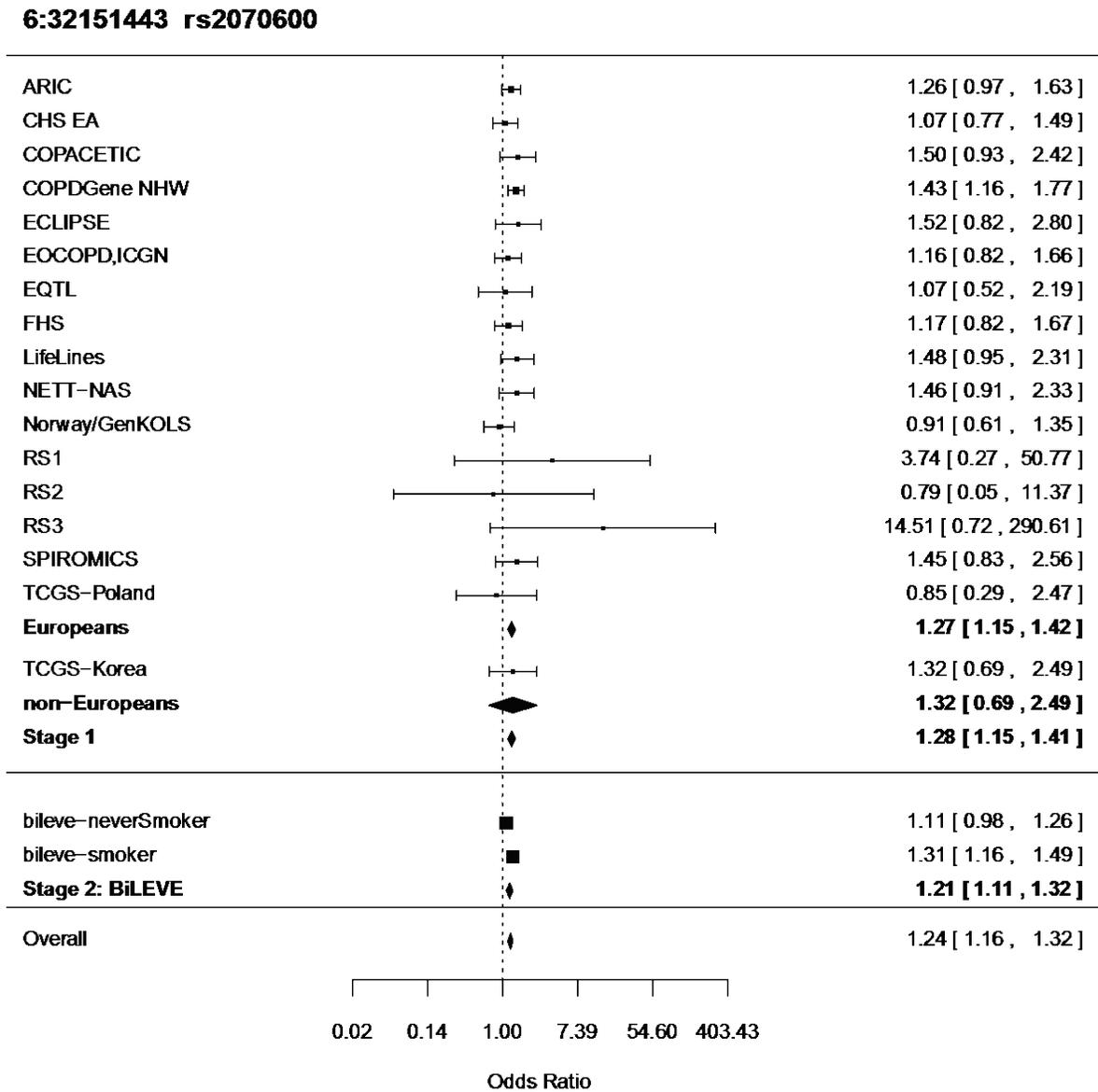


Figure S10: Forest plot for rs17707300 (*CCDC101*)

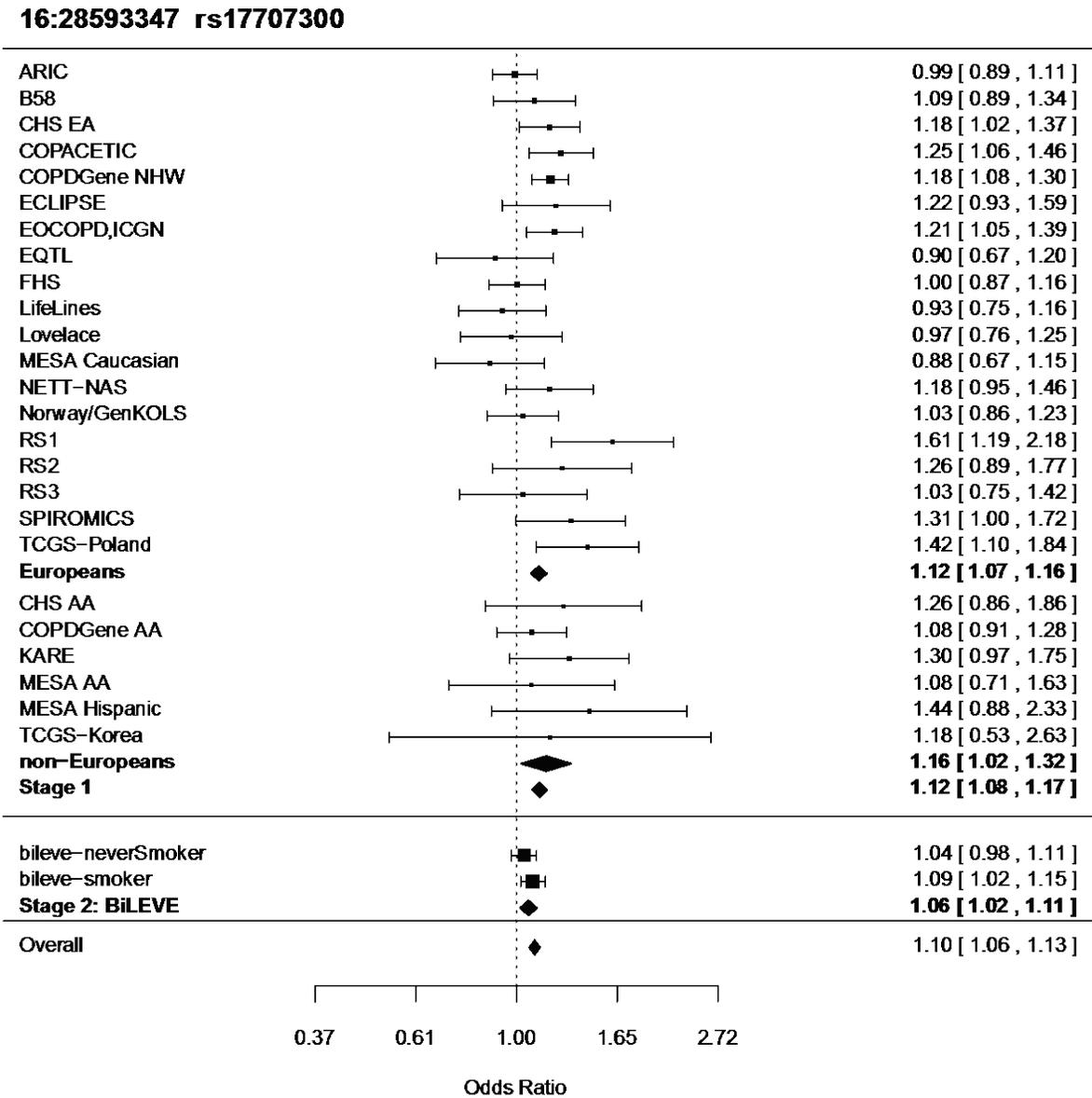


Figure S1p: Forest plot for rs2806356 (*ARMC2*)

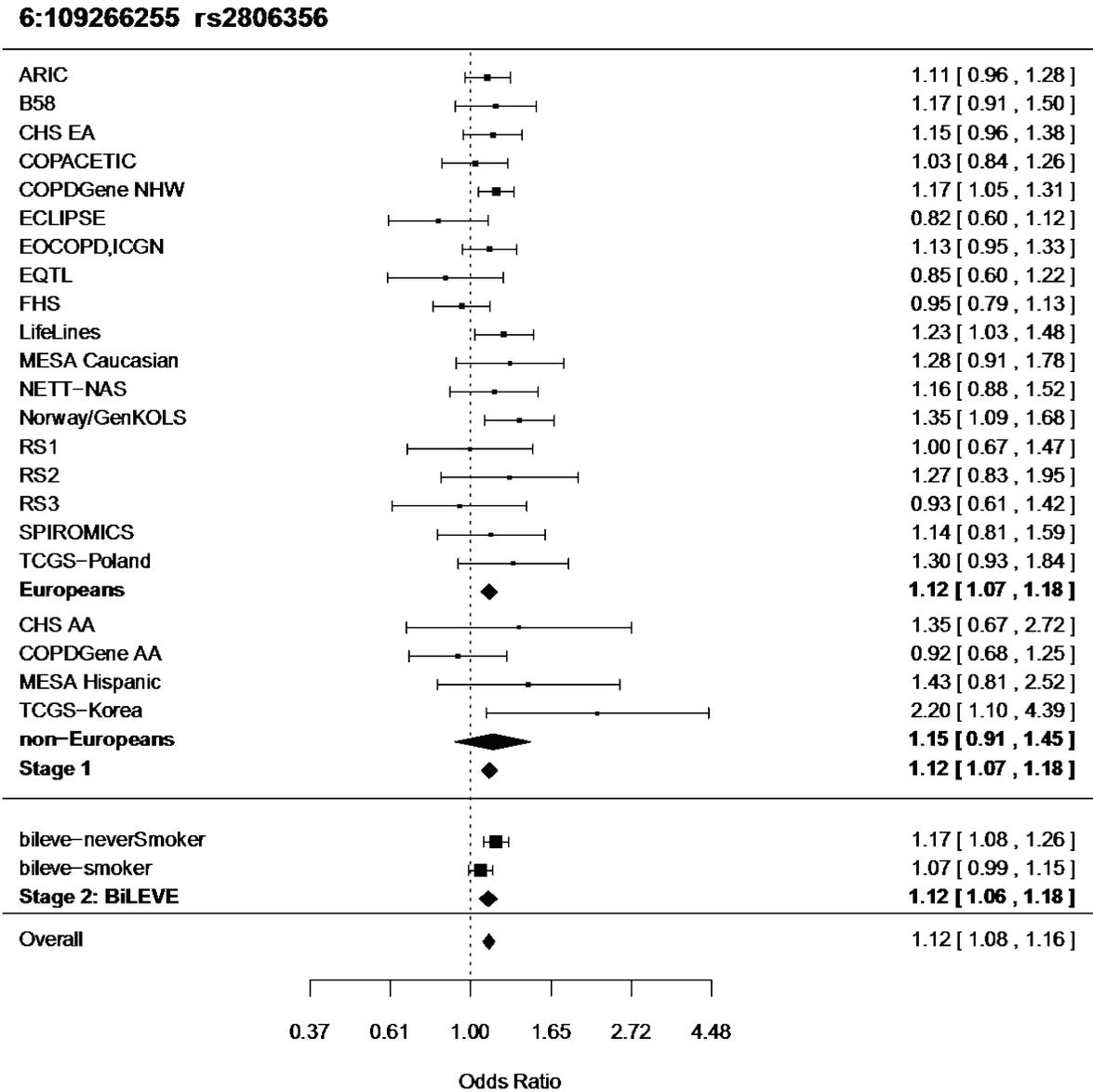


Figure S1q: Forest plot for rs16825267 (*PID1*)

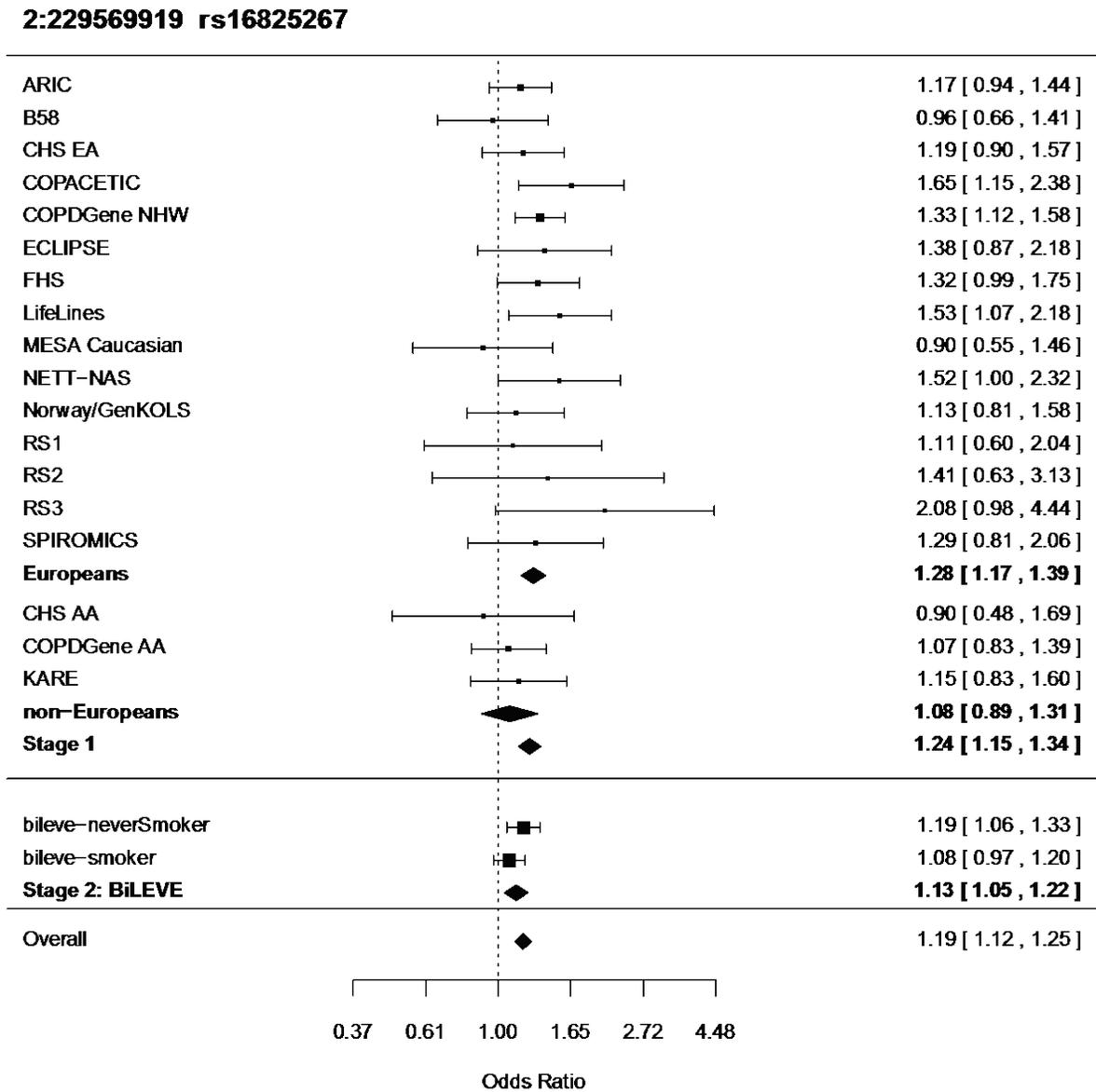


Figure S1r: Forest plot for rs2076295 (DSP)

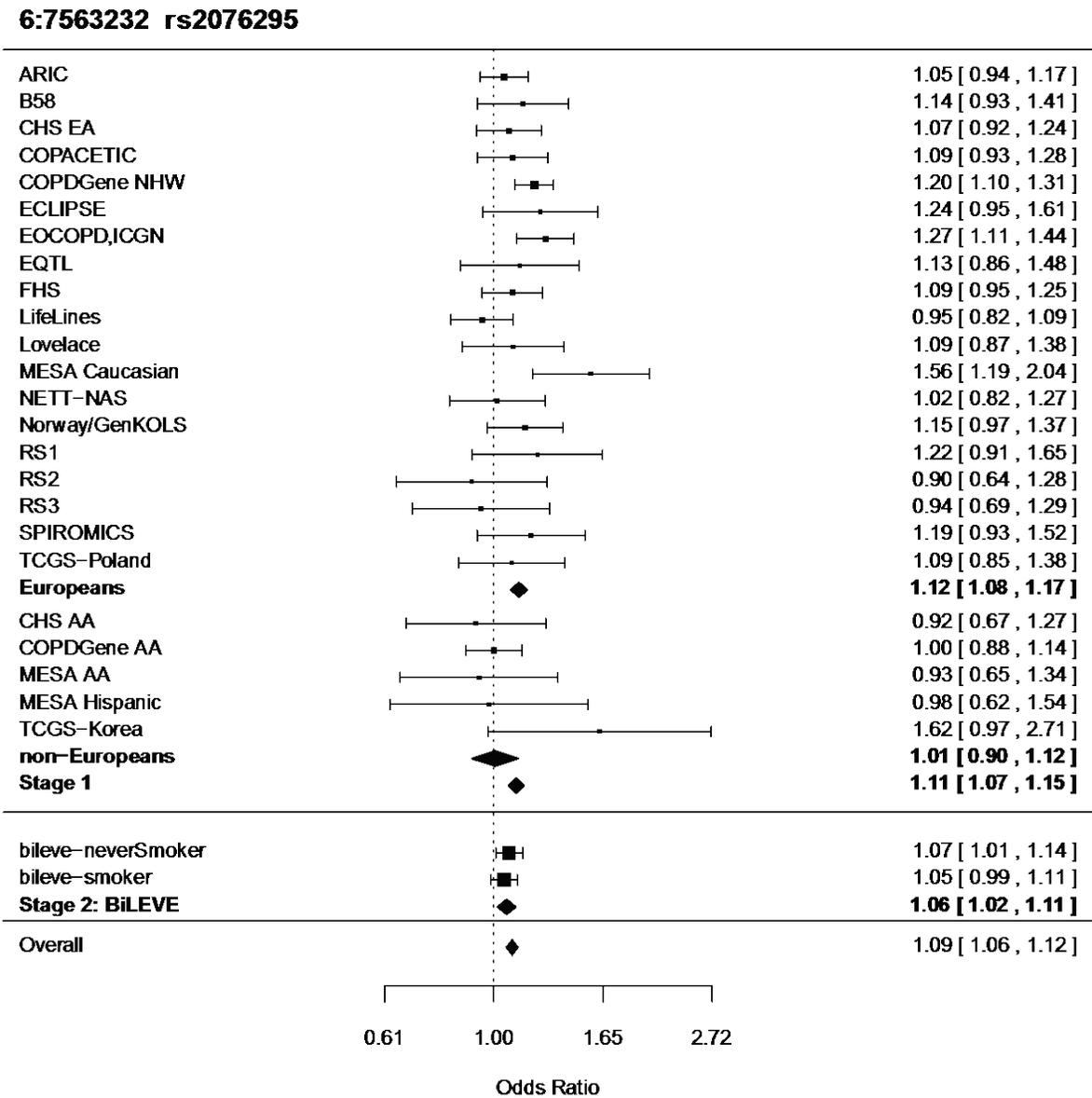


Figure S1s: Forest plot for rs647097 (*MTCL1*)

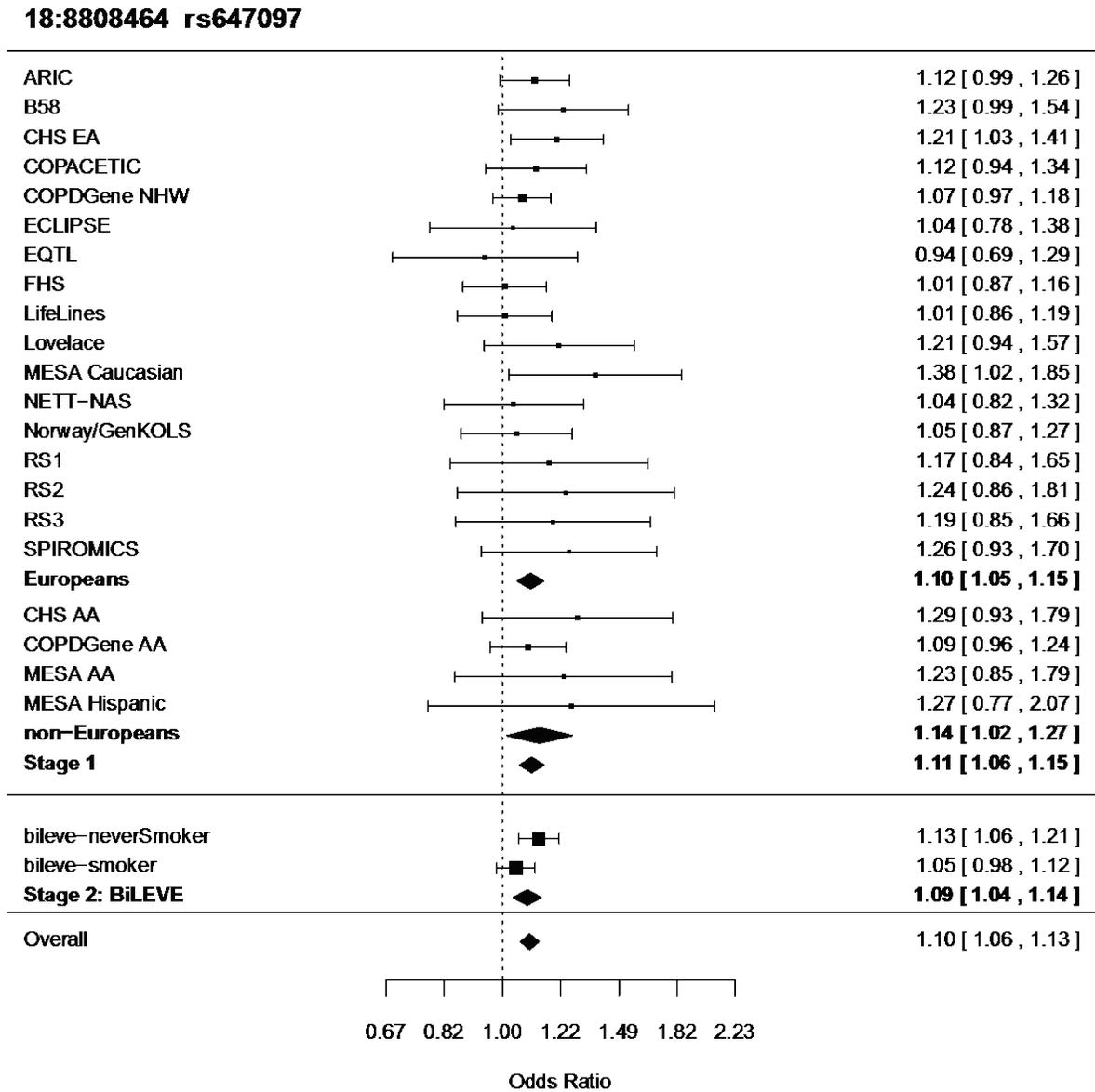


Figure S1t: Forest plot for rs1529672 (RARB)

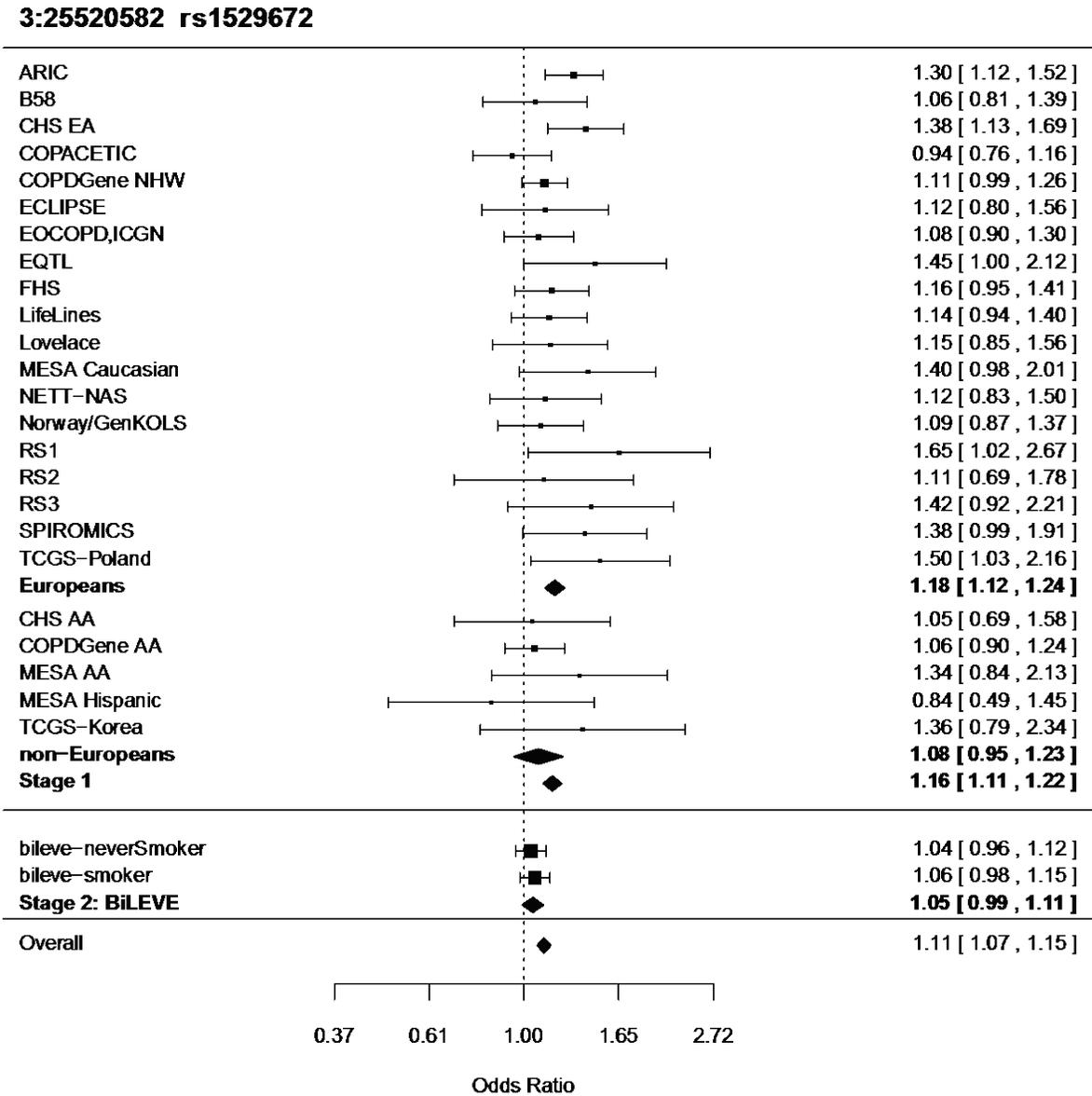


Figure S1u: Forest plot for rs721917 (*STFPD*)

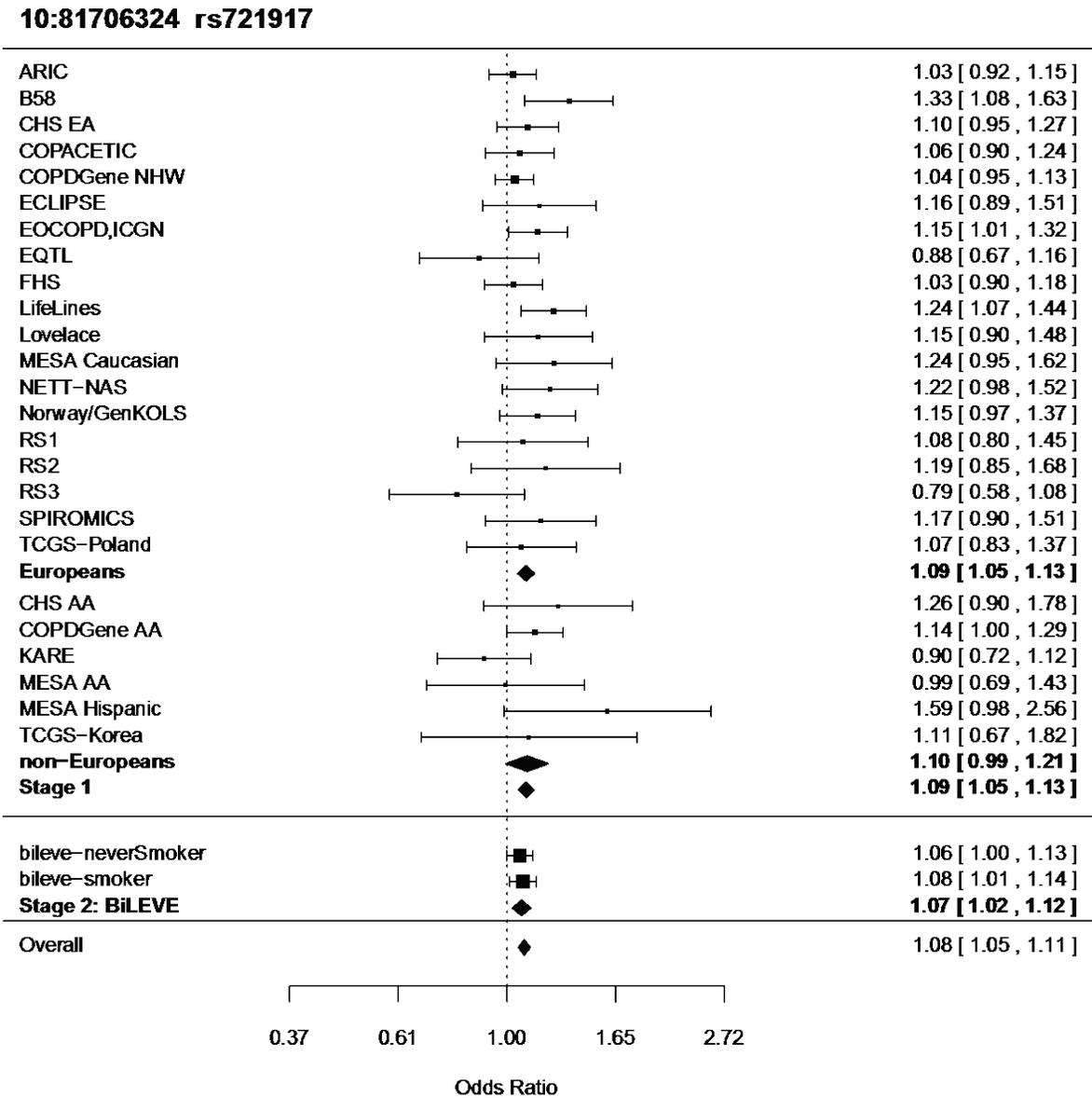


Figure S1v: Forest plot for rs12459249 (*CYP2A6*)

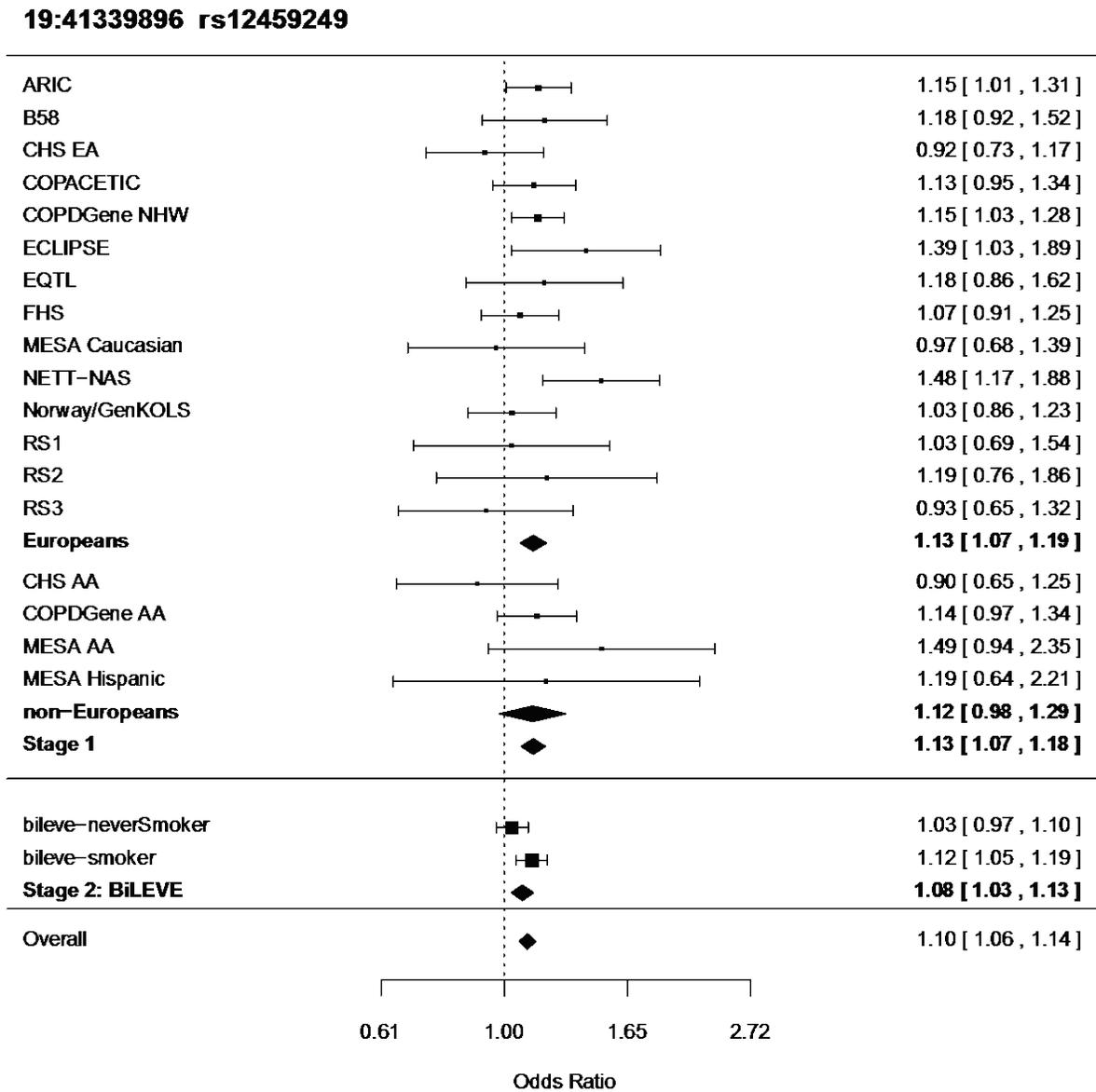


Figure S2a-v: LocusZoom⁸³ plots for each of the 22 genome-wide significant loci. The point size for each SNP is determined by the sample size for the SNP. The most significant variant in each plot as well as the largest points in each plot were tested in all available cohorts including UK BiLEVE. Smaller points indicate the variant was not tested in UK BiLEVE Stage 2 analysis and thus the $-\log_{10}$ P value is taken from the Stage 1 analysis.

Figure S2a: LocusZoom for rs13141641 (*HHIP*)

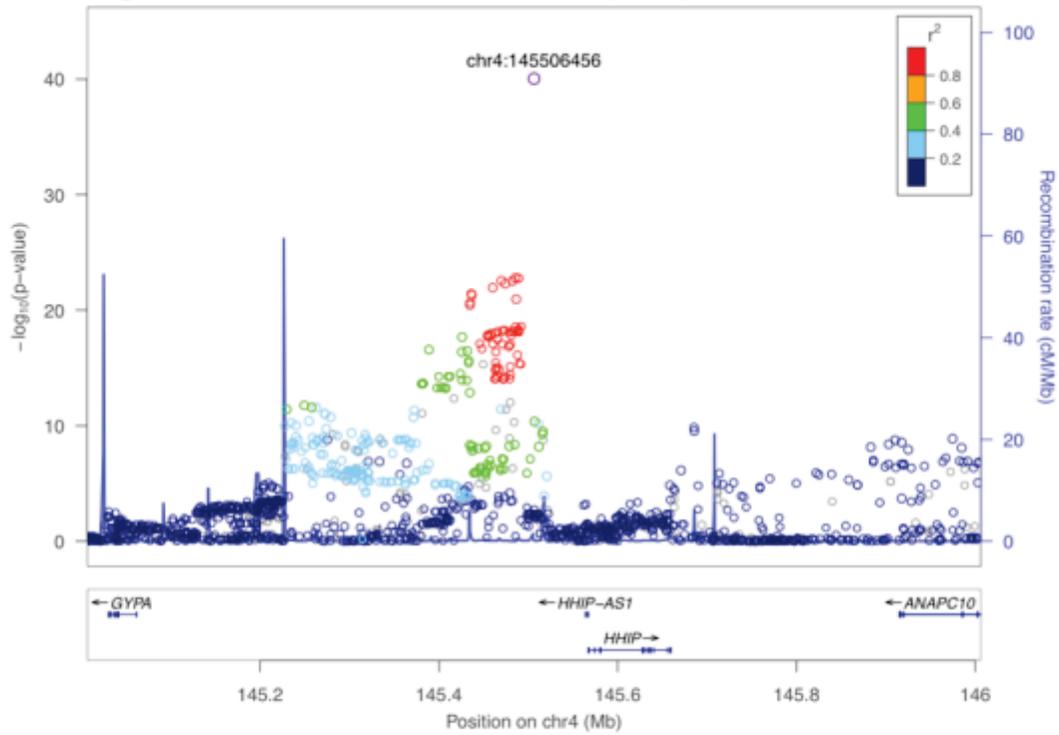


Figure S2b: LocusZoom for rs17486278 (*CHRNA5*)

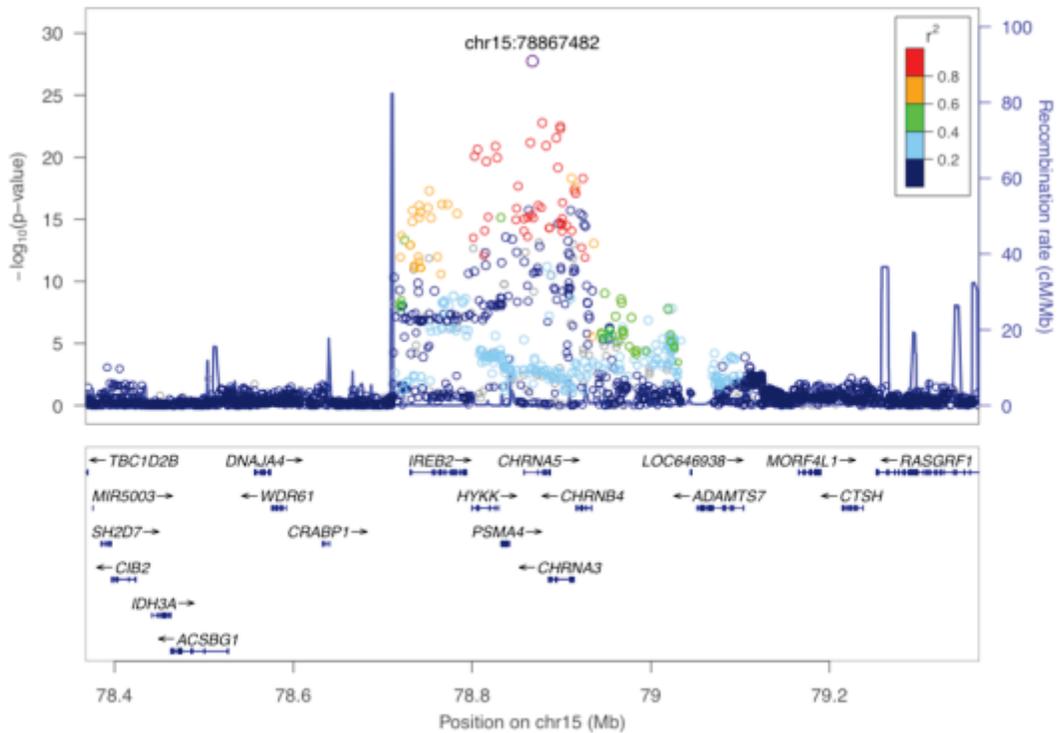


Figure S2c: LocusZoom for rs7733088 (*HTR4*)

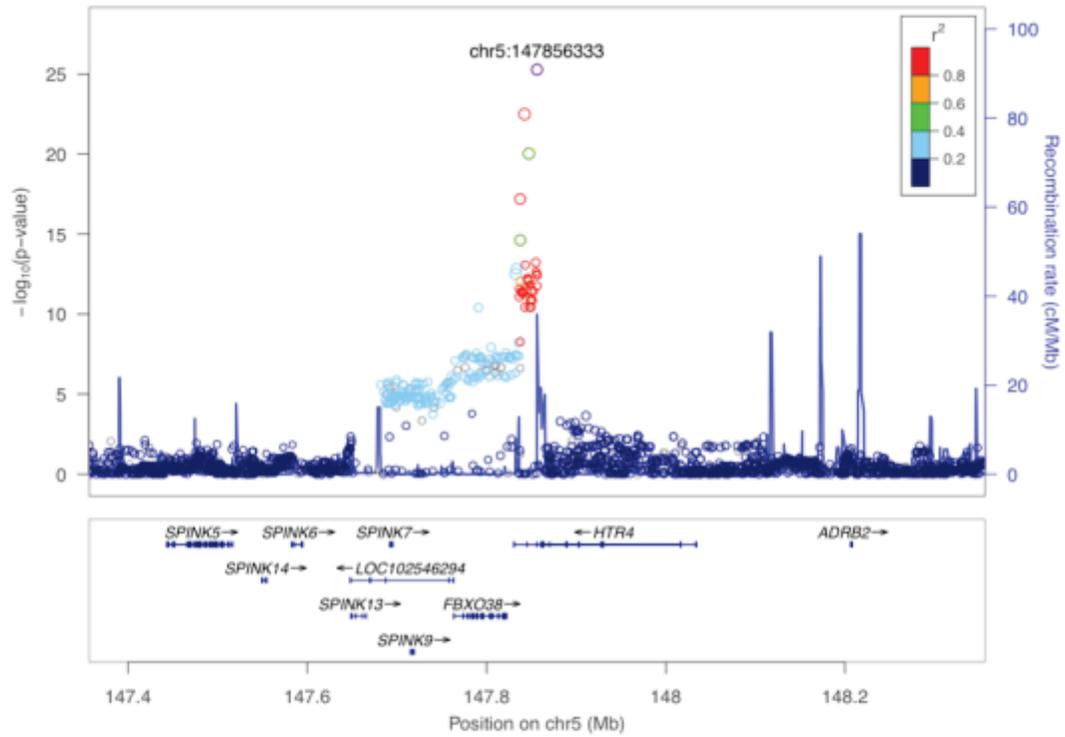


Figure S2d: LocusZoom for rs9399401 (*ADGRG6*)

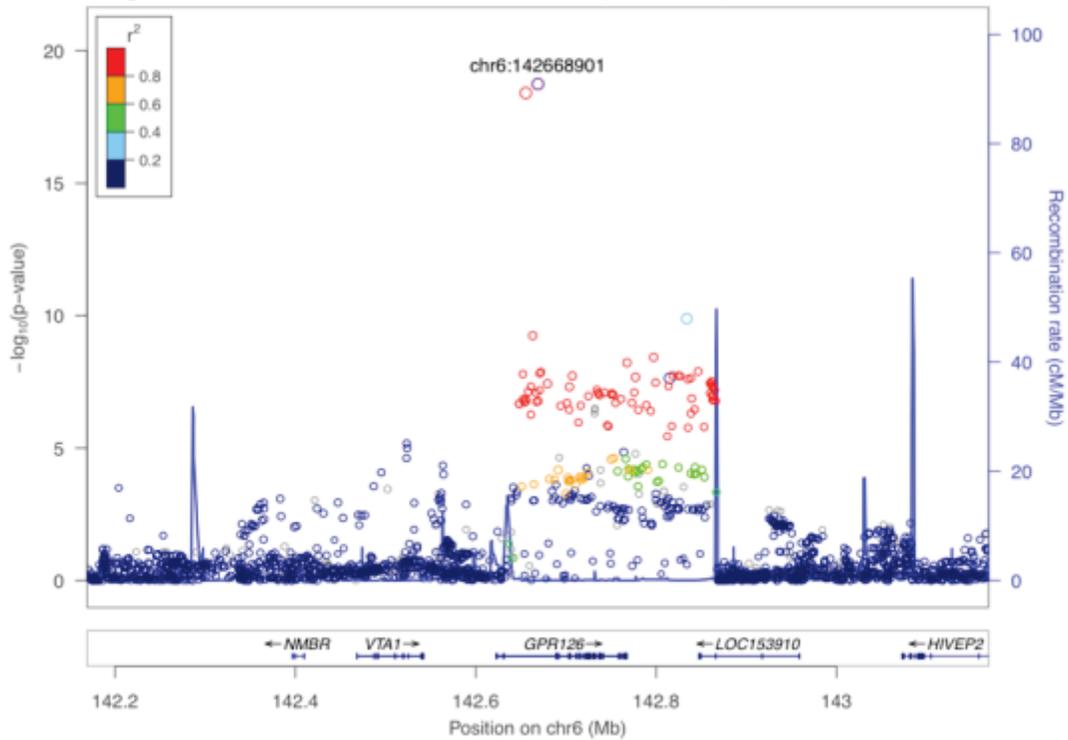


Figure S2e: LocusZoom for rs1441358 (*THSD4*)

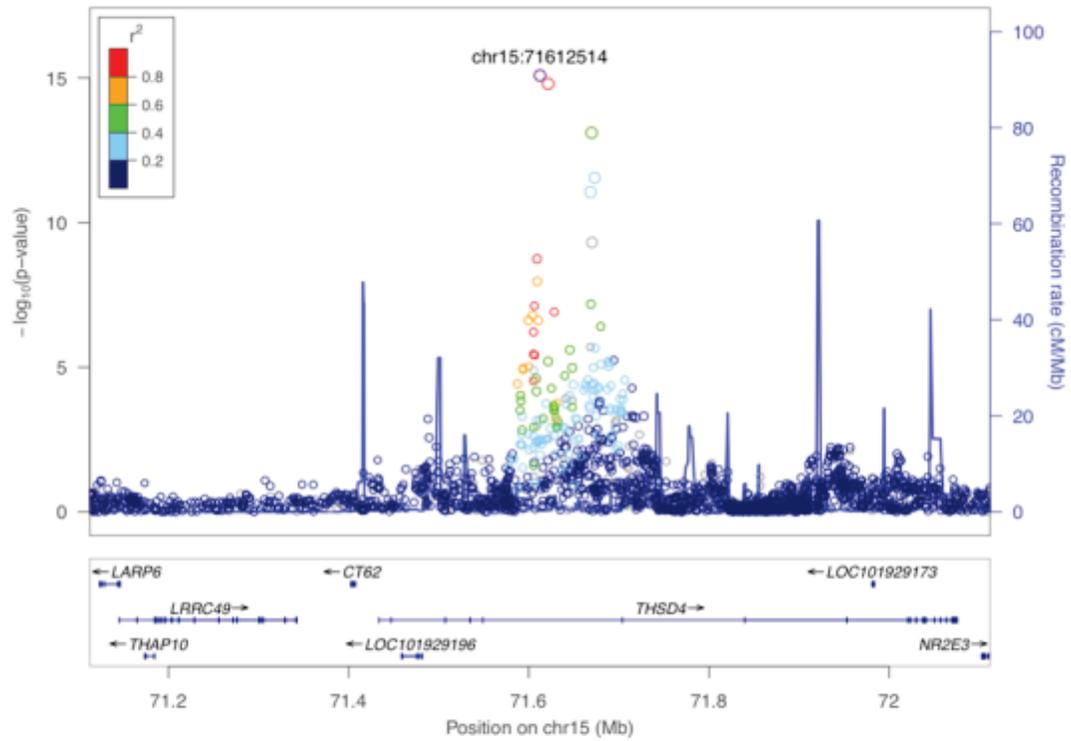


Figure S2f: LocusZoom for rs6837671 (*FAM13A*)

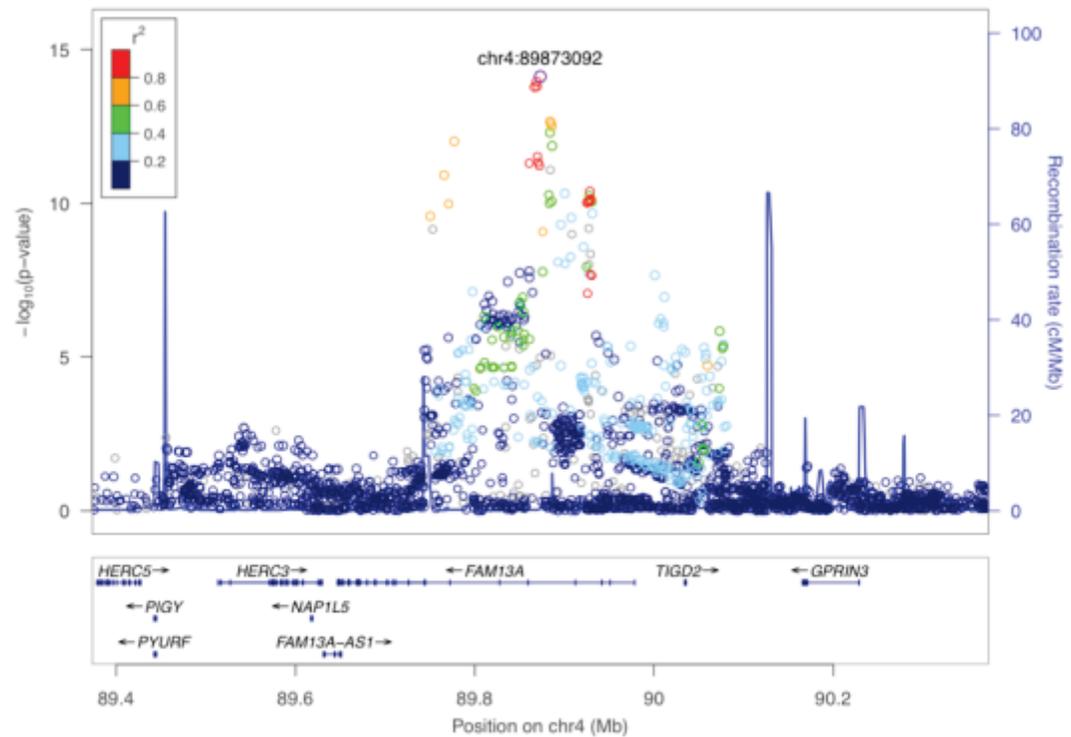


Figure S2g: LocusZoom for rs11727735 (*GSTCD*)

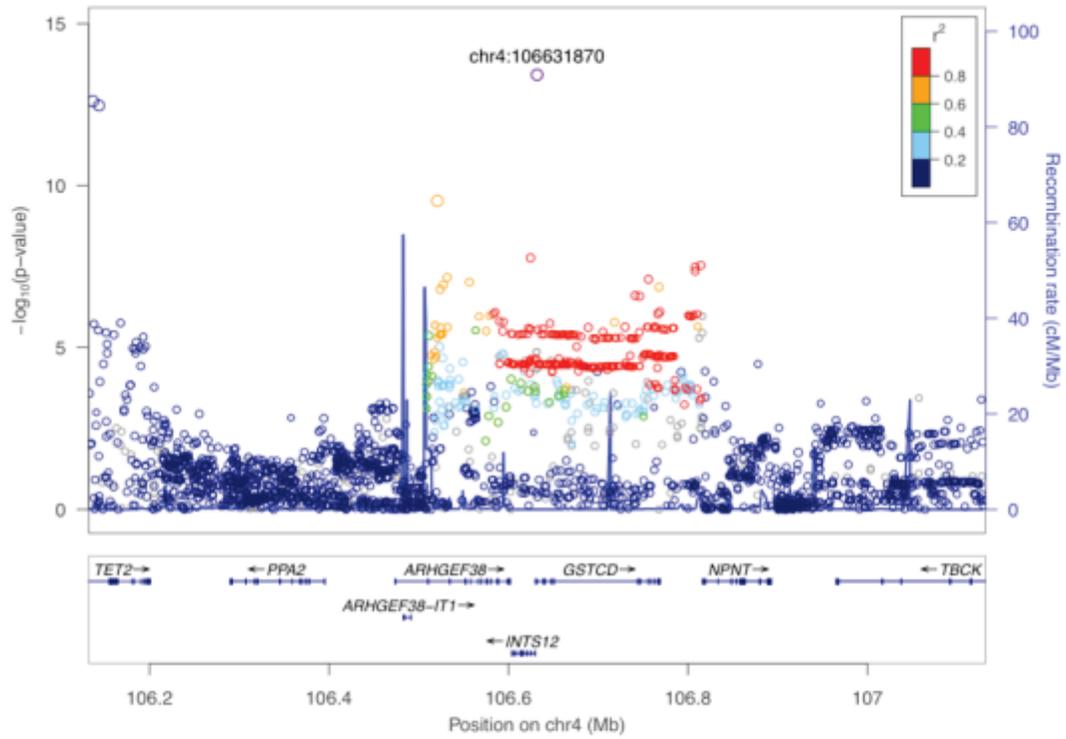


Figure S2h: LocusZoom for rs754388 (*RIN3*)

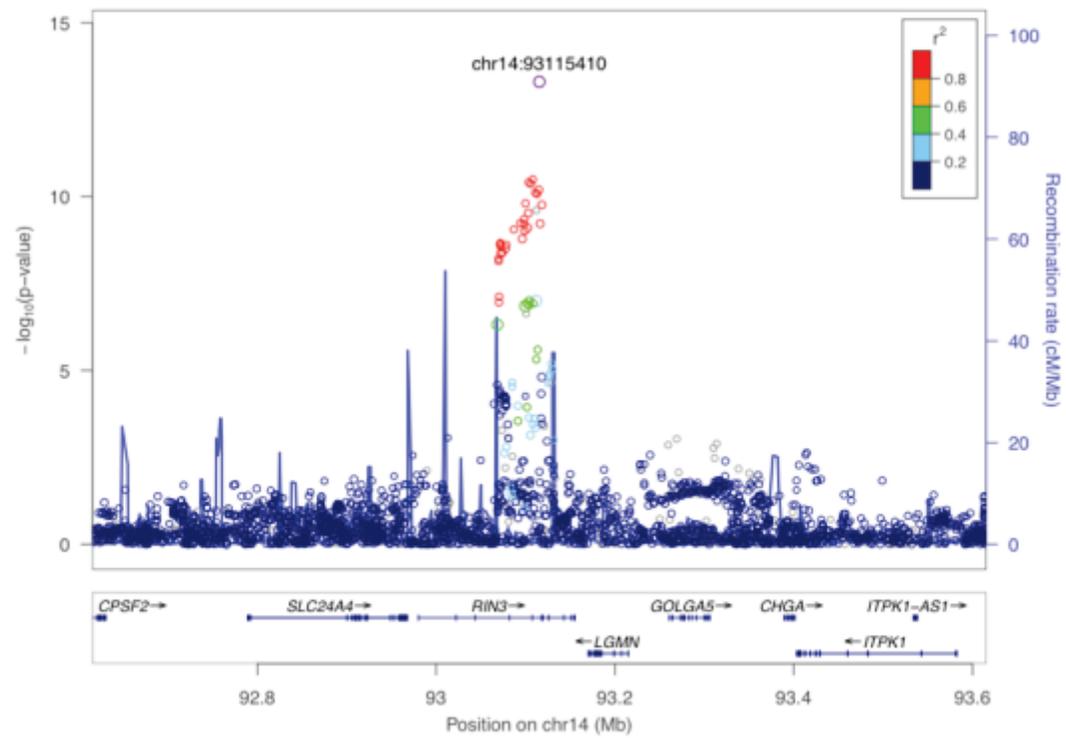


Figure S2i: LocusZoom for rs113897301 (ADAM19)

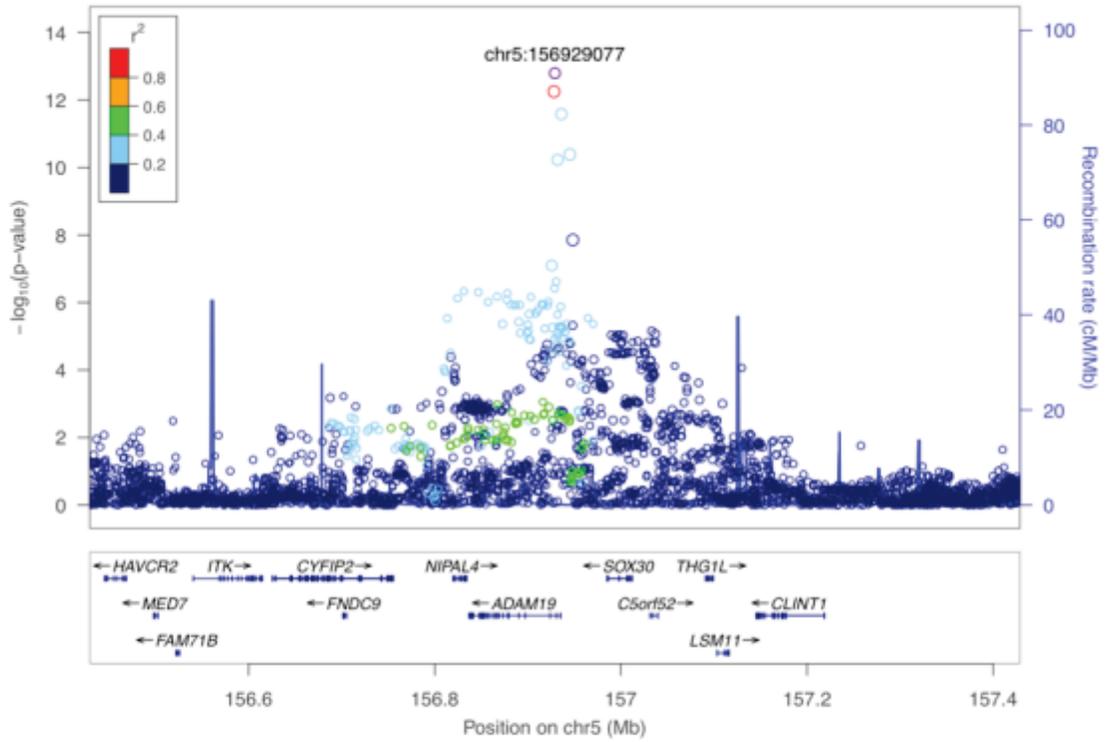


Figure S2j: LocusZoom for rs2047409 (TET2)

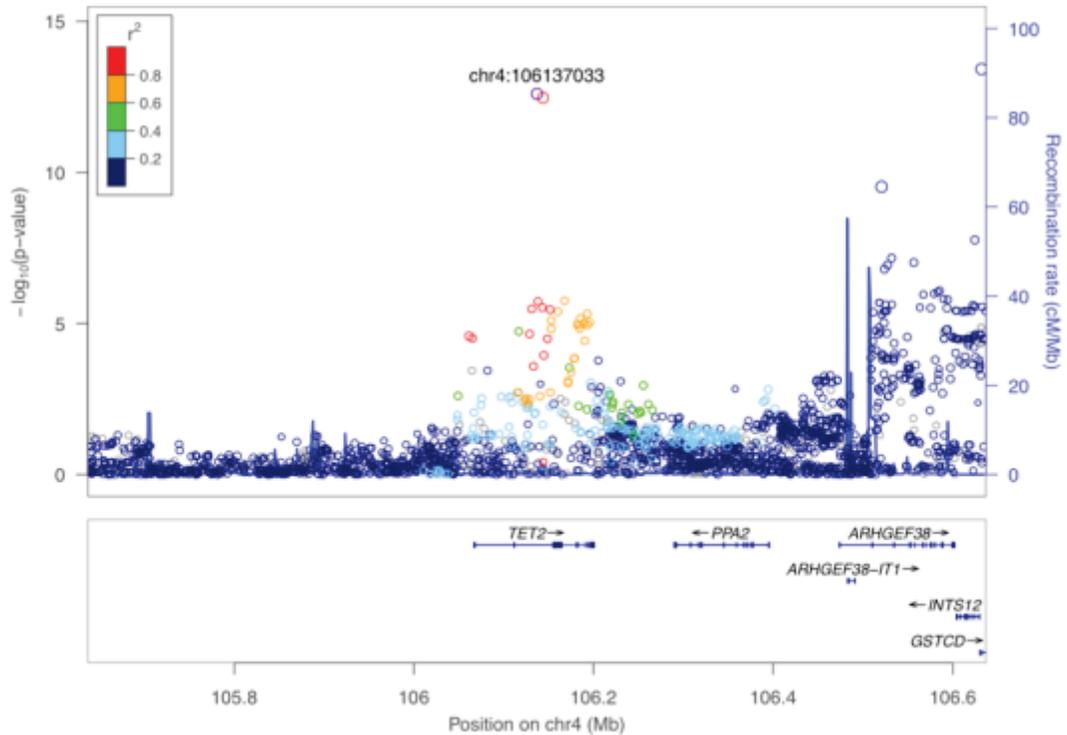


Figure S2k: LocusZoom for rs2955083 (*EEFSEC*)

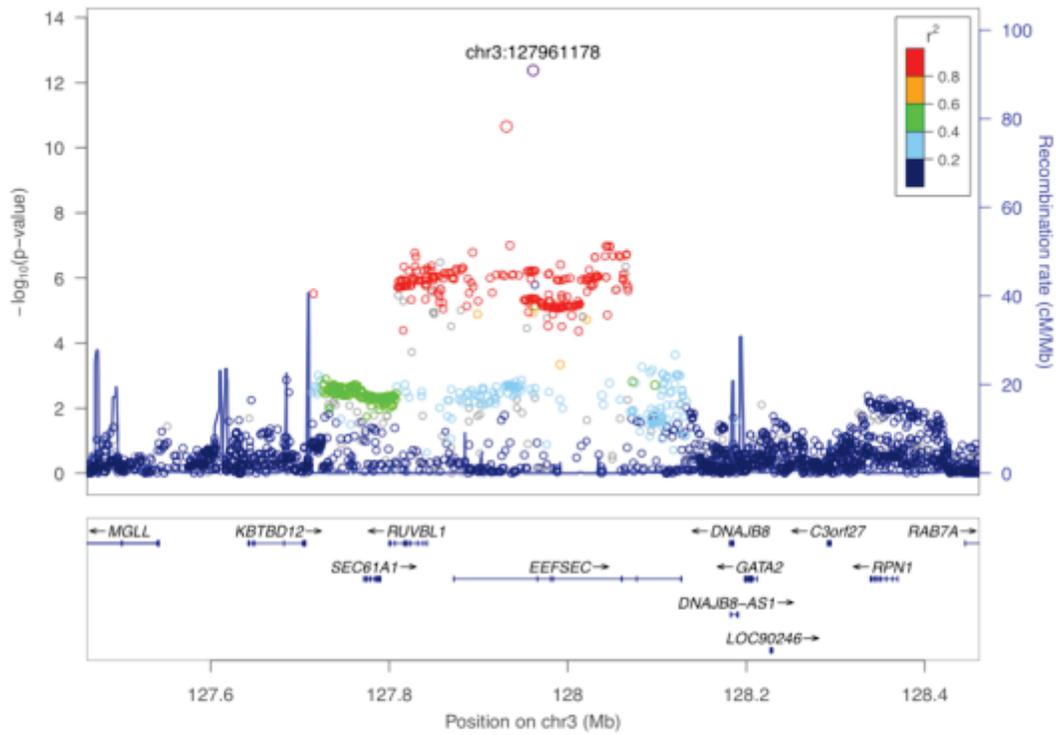


Figure S2l: LocusZoom for rs7186831 (*CFDP1*)

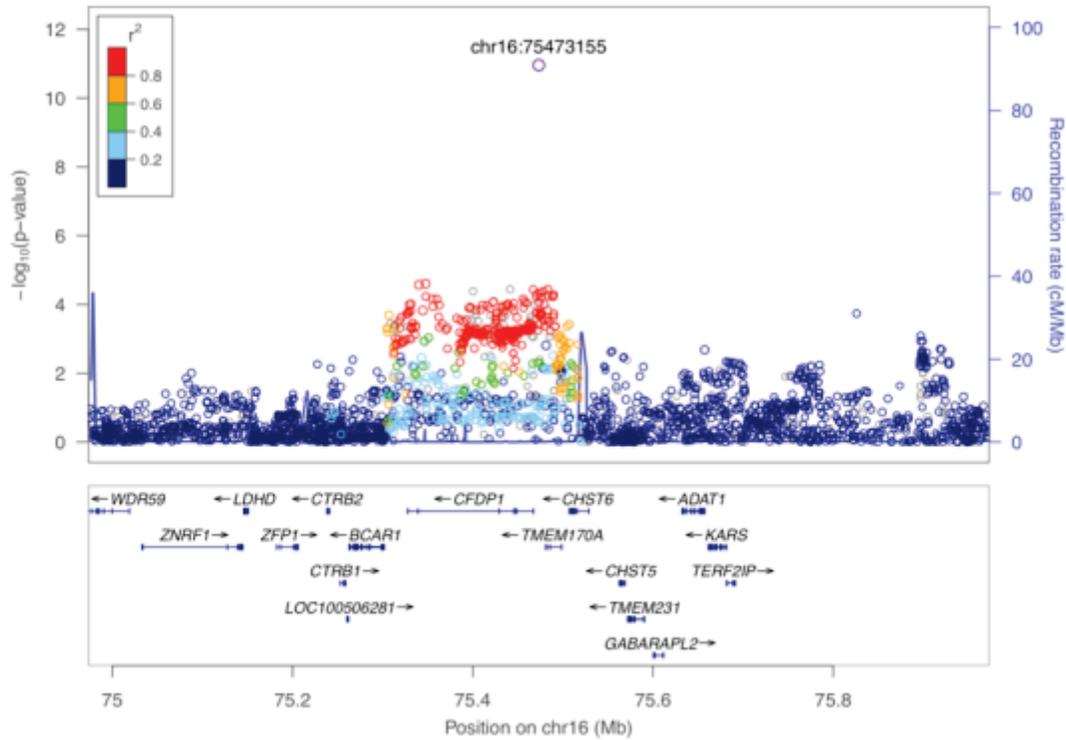


Figure S2m: LocusZoom for rs10429950 (*TGFB2*)

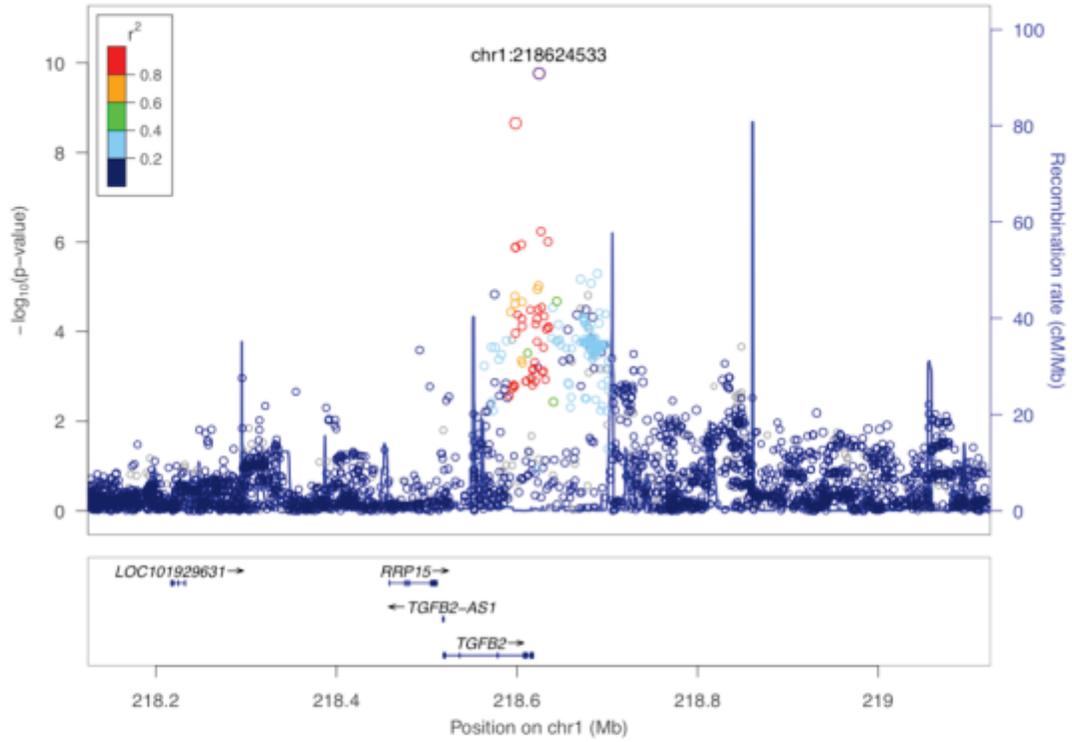


Figure S2n: LocusZoom for rs2070600 (*AGER*)

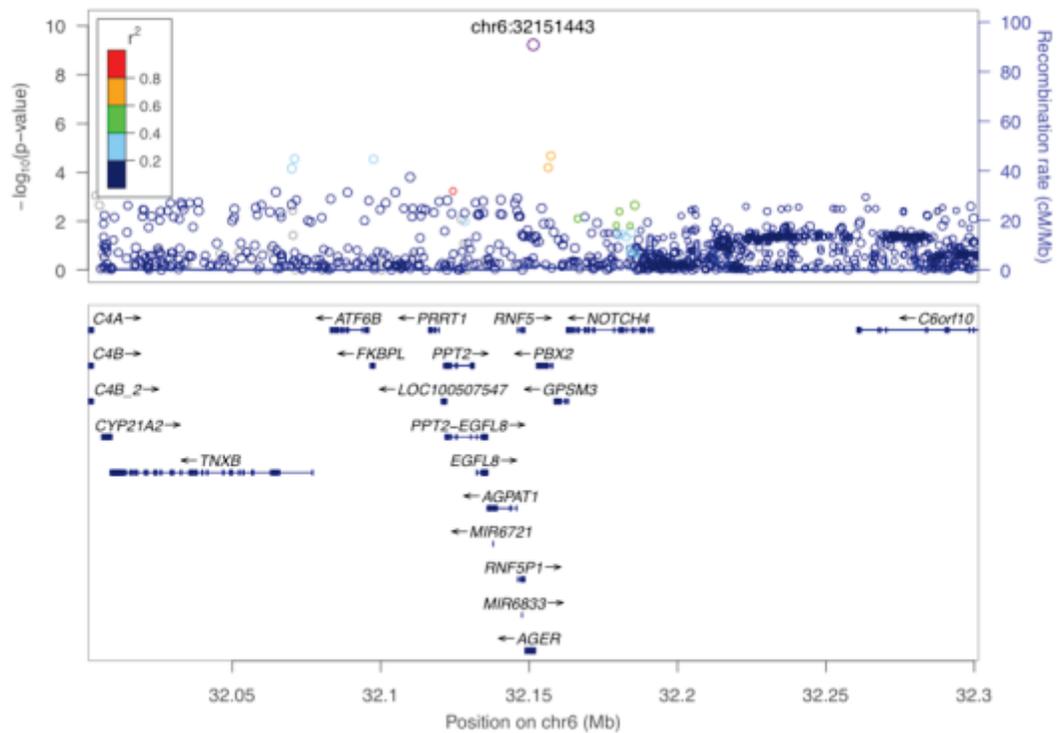


Figure S2o: LocusZoom for rs17707300 (*CCDC101*)

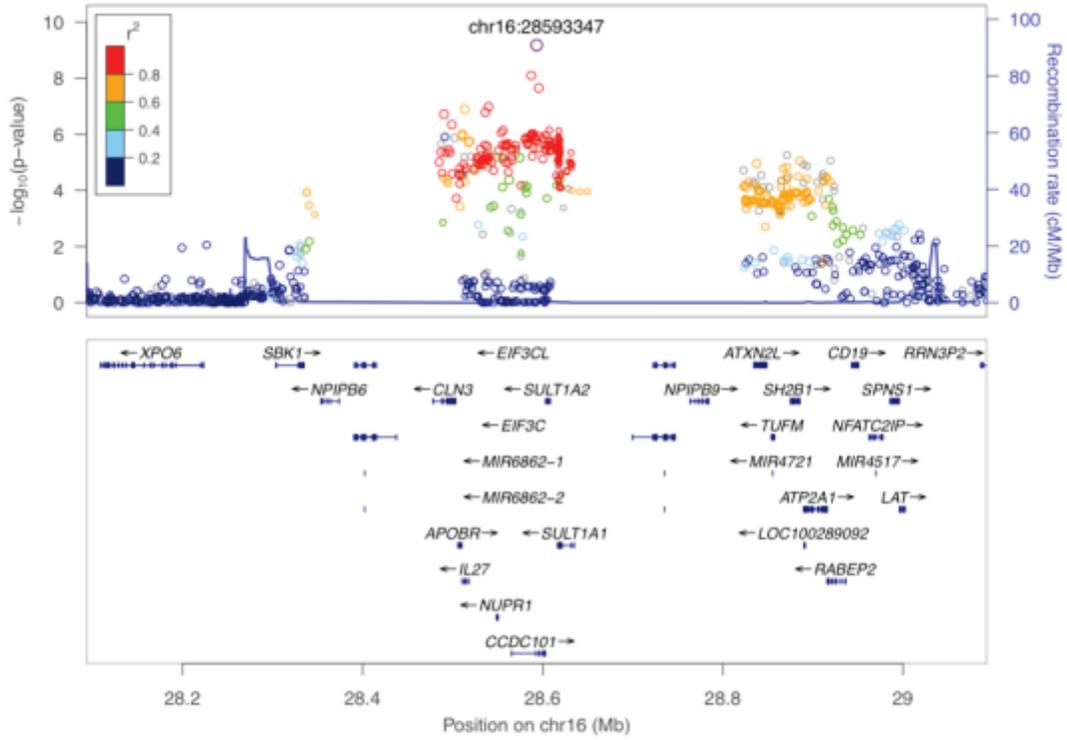


Figure S2p: LocusZoom for rs2806356 (*ARMC2*)

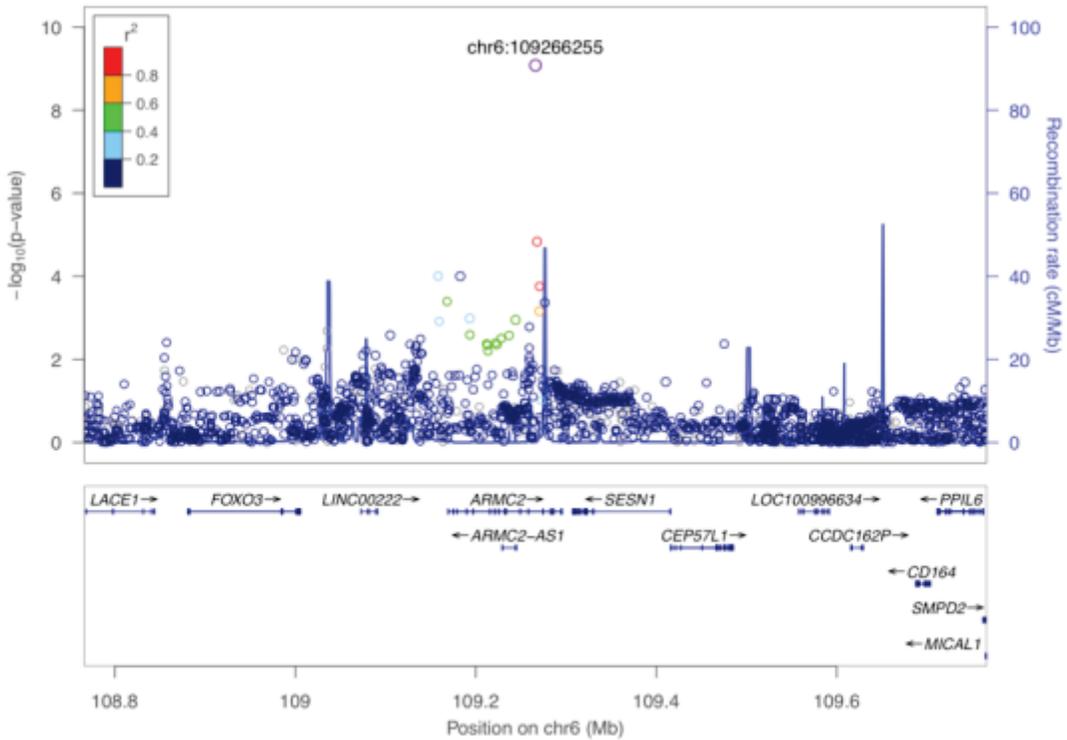


Figure S2q: LocusZoom for rs16825267 (*PID1*)

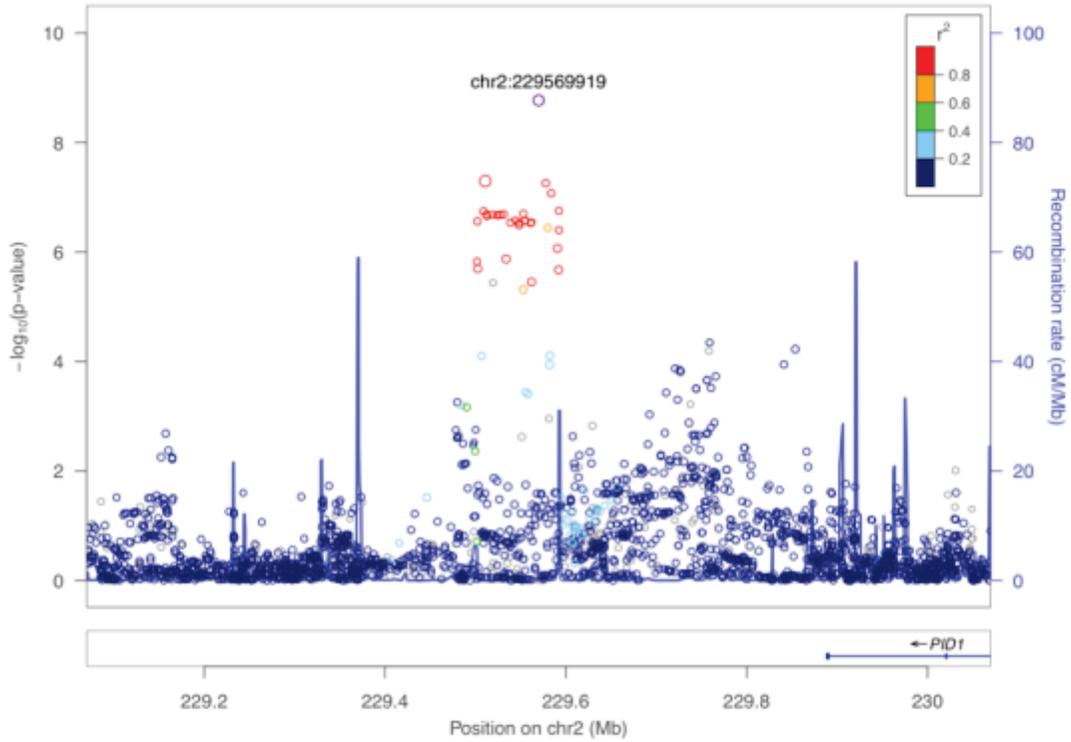


Figure S2r: LocusZoom for rs2076295 (*DSP*)

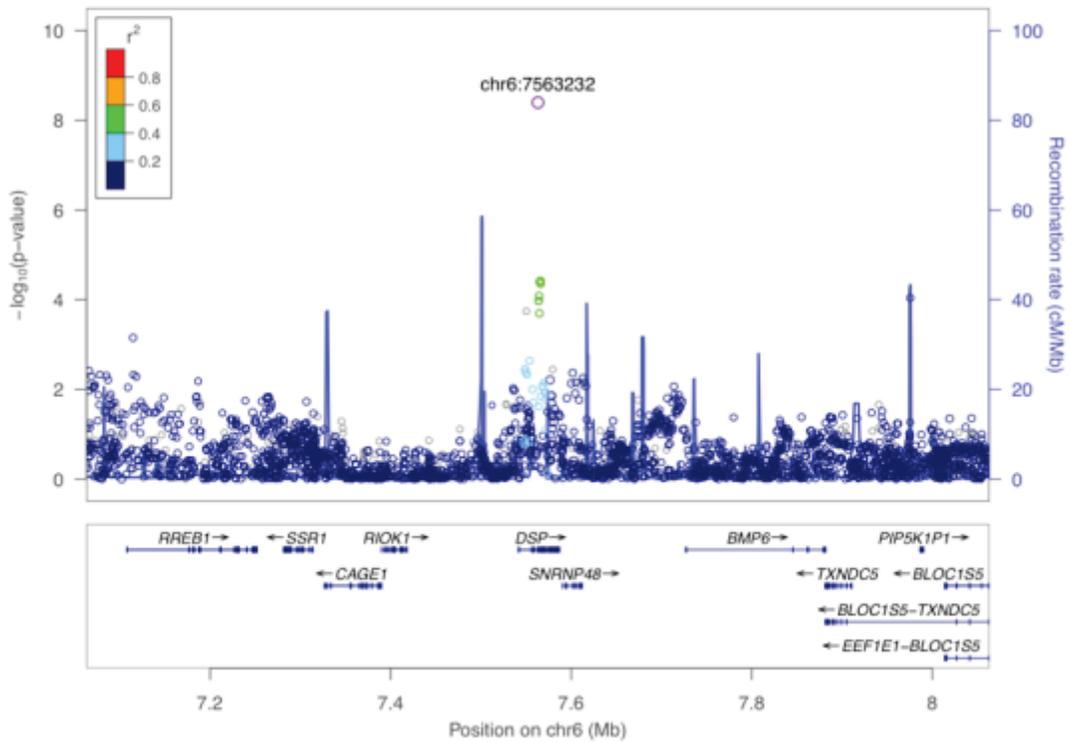


Figure S2s: LocusZoom for rs647097 (*MTCL1*)

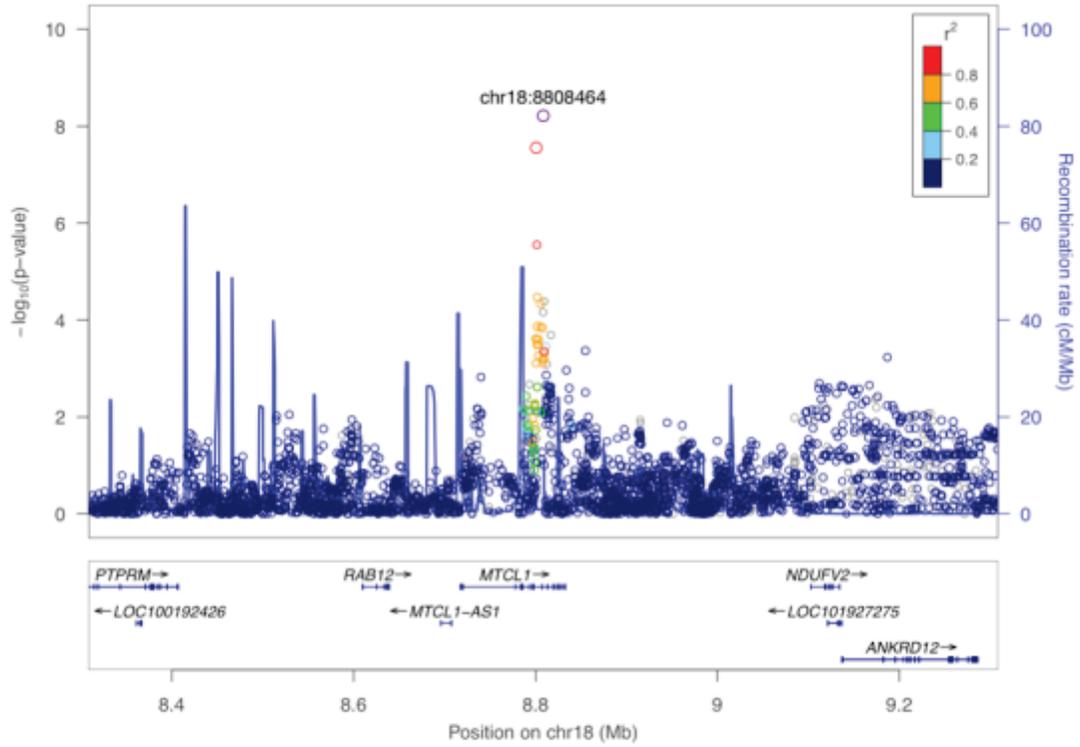


Figure S2t: LocusZoom for rs1529672 (*RARB*)

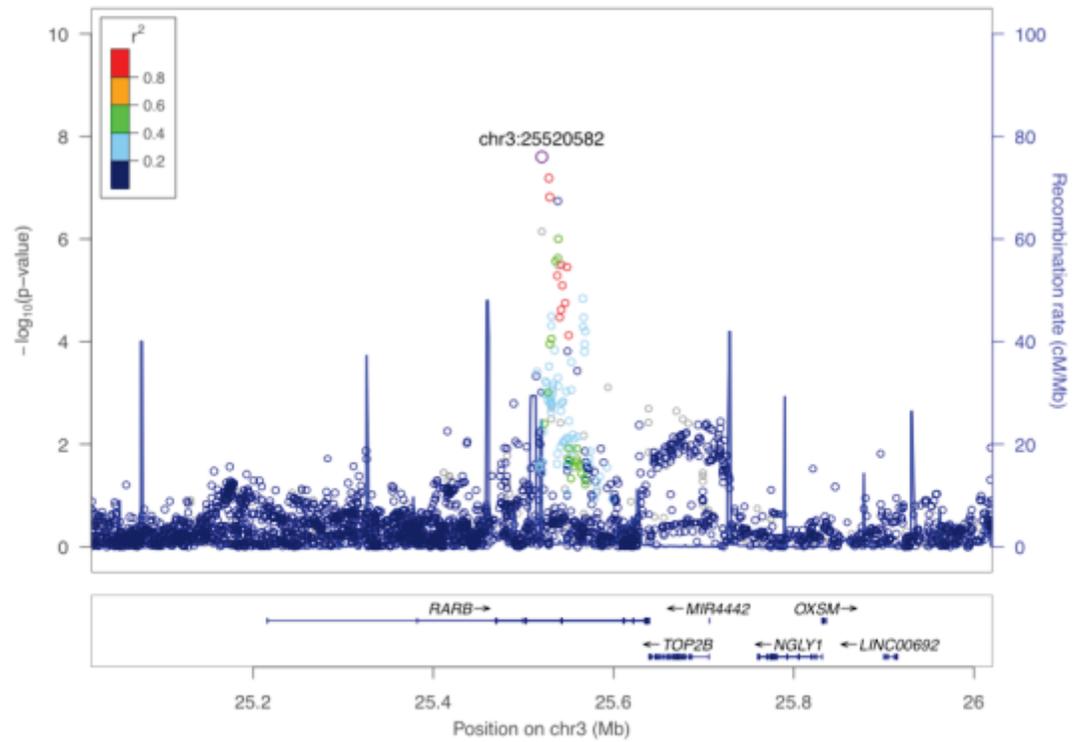


Figure S2u: LocusZoom for rs721917 (STFPD)

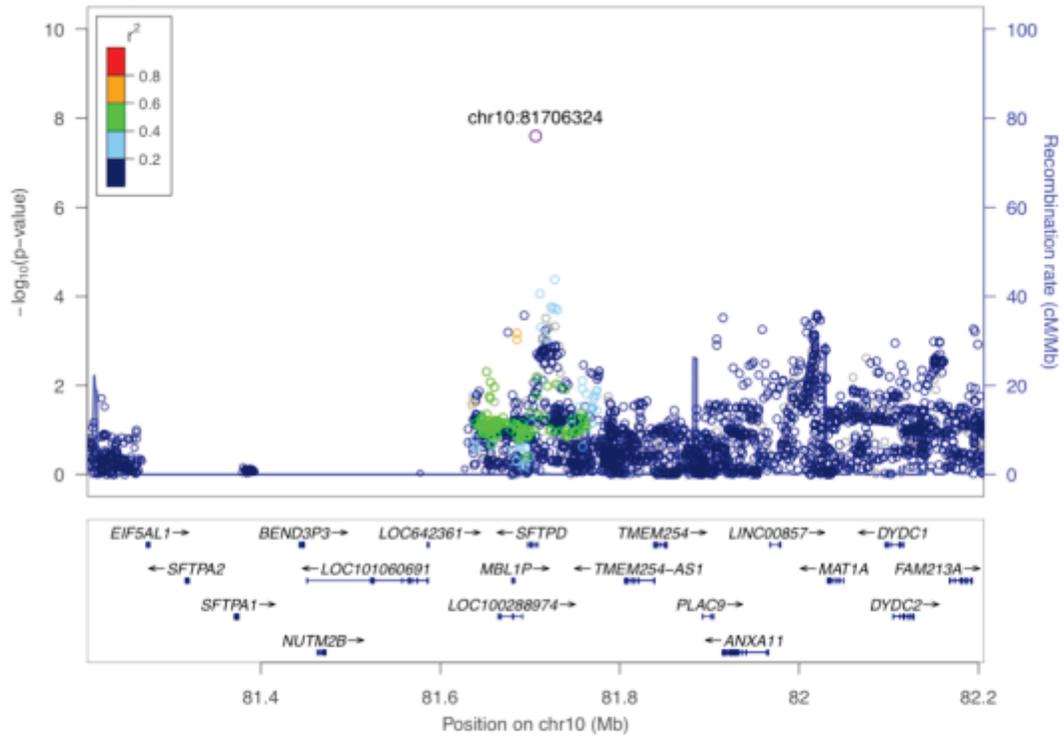


Figure S2v: LocusZoom for rs12459249 (CYP2A6)

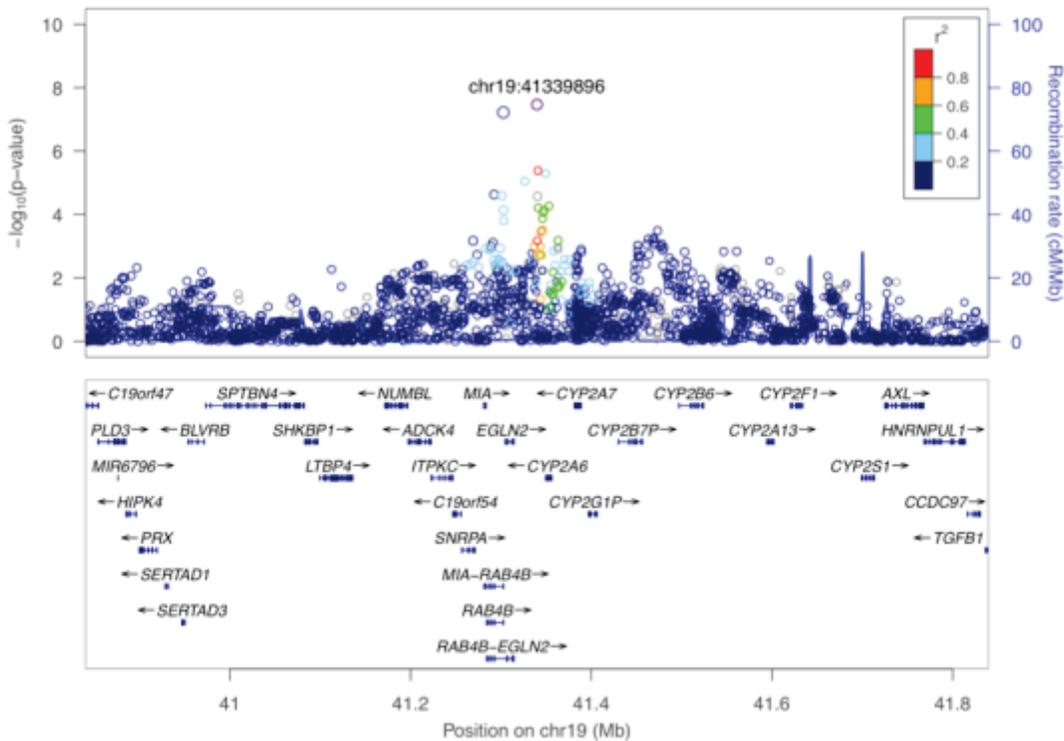


Figure S3a-e: LocusZoom⁸³ plots for the meta-analysis across the three Stage 1 cohorts of African Ancestry, including the Cardiovascular Health Study (CHS) African Americans (AA), COPDGene study AA, and the Multi-Ethnic Study of Atherosclerosis (MESA) AA. The regions shown (*HHIP*, *THSD4*, *CFDP1*, *ARMC2*, and *SFTPD*) contained at least one variant with an association $P < 0.001$ (with LD measured by $r^2 > 0.2$ or $D' > 0.7$ with the index SNP in the overall meta-analysis) in the meta-analysis across Stage 1 cohorts of African ancestry. The labeled variant is the top variant at the locus from the overall meta-analysis (all-ancestries) and the r^2 represents the African ancestry LD pattern relative to the top variant from the overall meta-analysis. Point size indicates the sample size for each variant in the meta-analysis of AA cohorts.

Figure S3a: LocusZoom for AA cohort meta-analysis for *HHIP* region

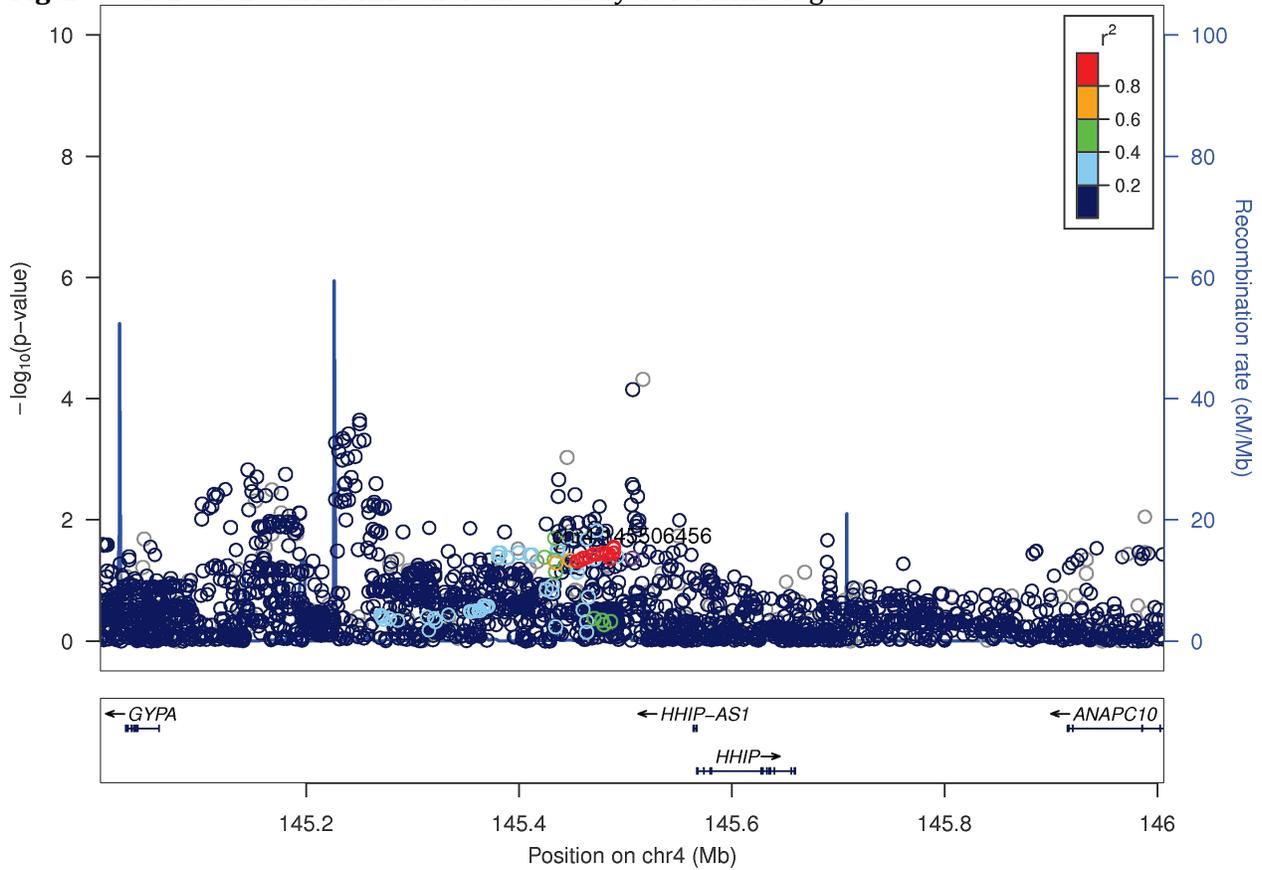


Figure S3b: LocusZoom for AA cohort meta-analysis for *THSD4* region

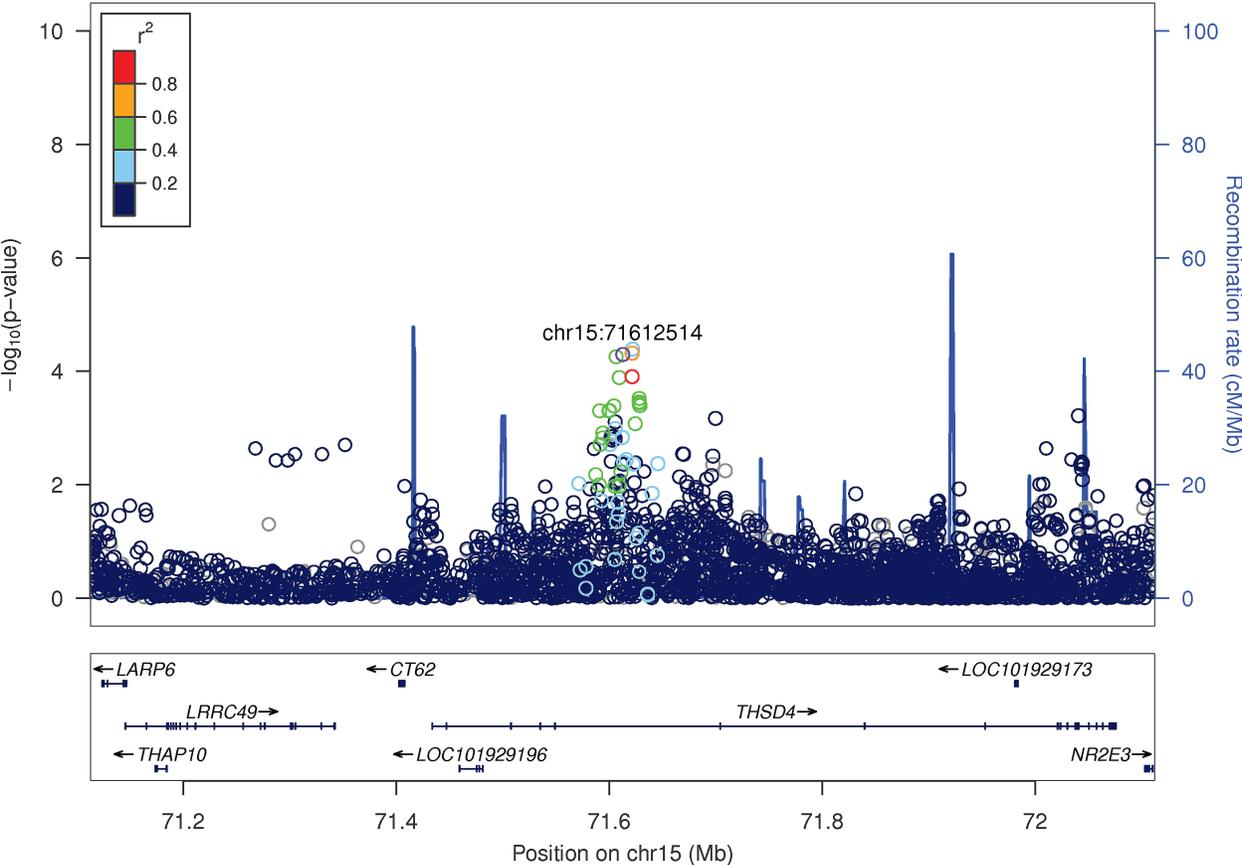


Figure S3c: LocusZoom for AA cohort meta-analysis for *CFDP1* region

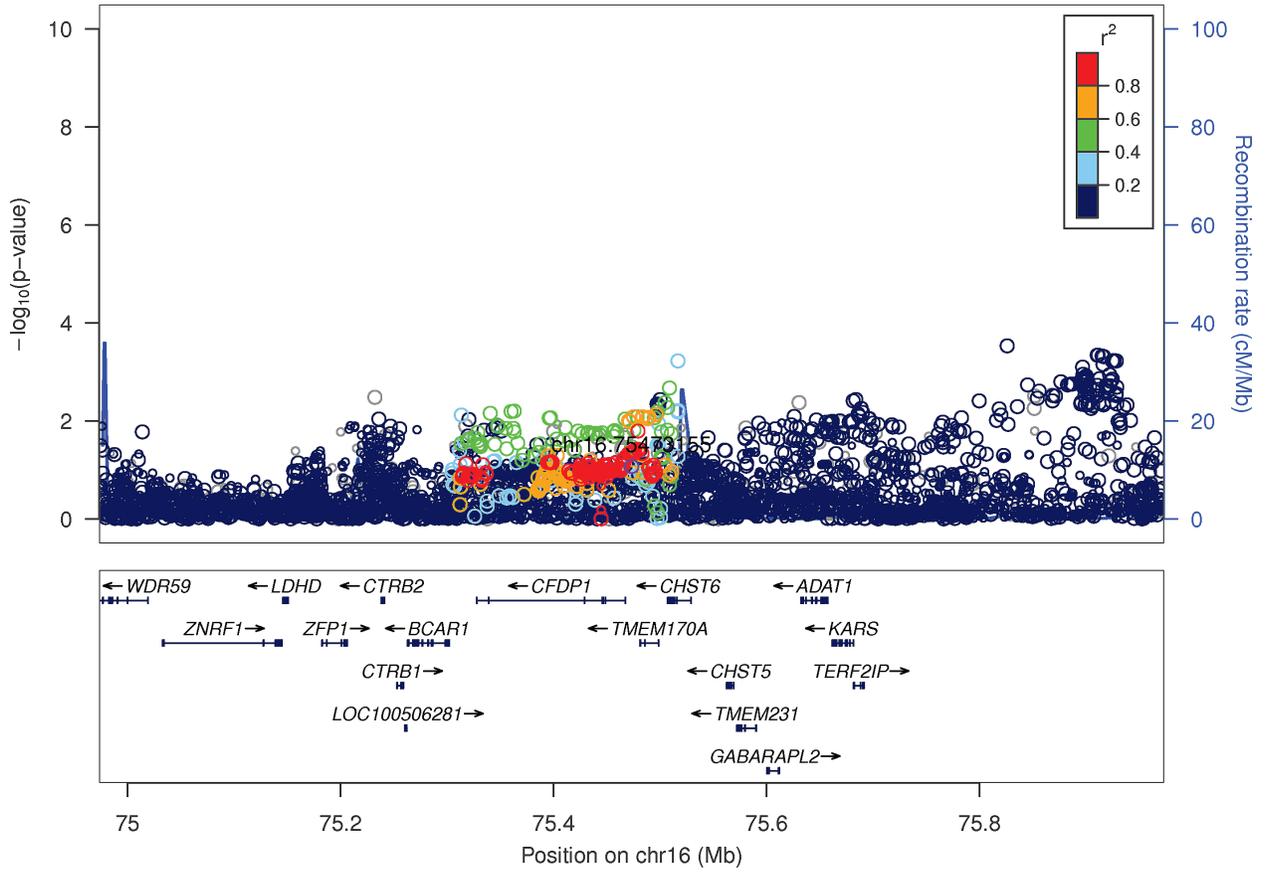


Figure S3d: LocusZoom for AA cohort meta-analysis for *ARMC2* region

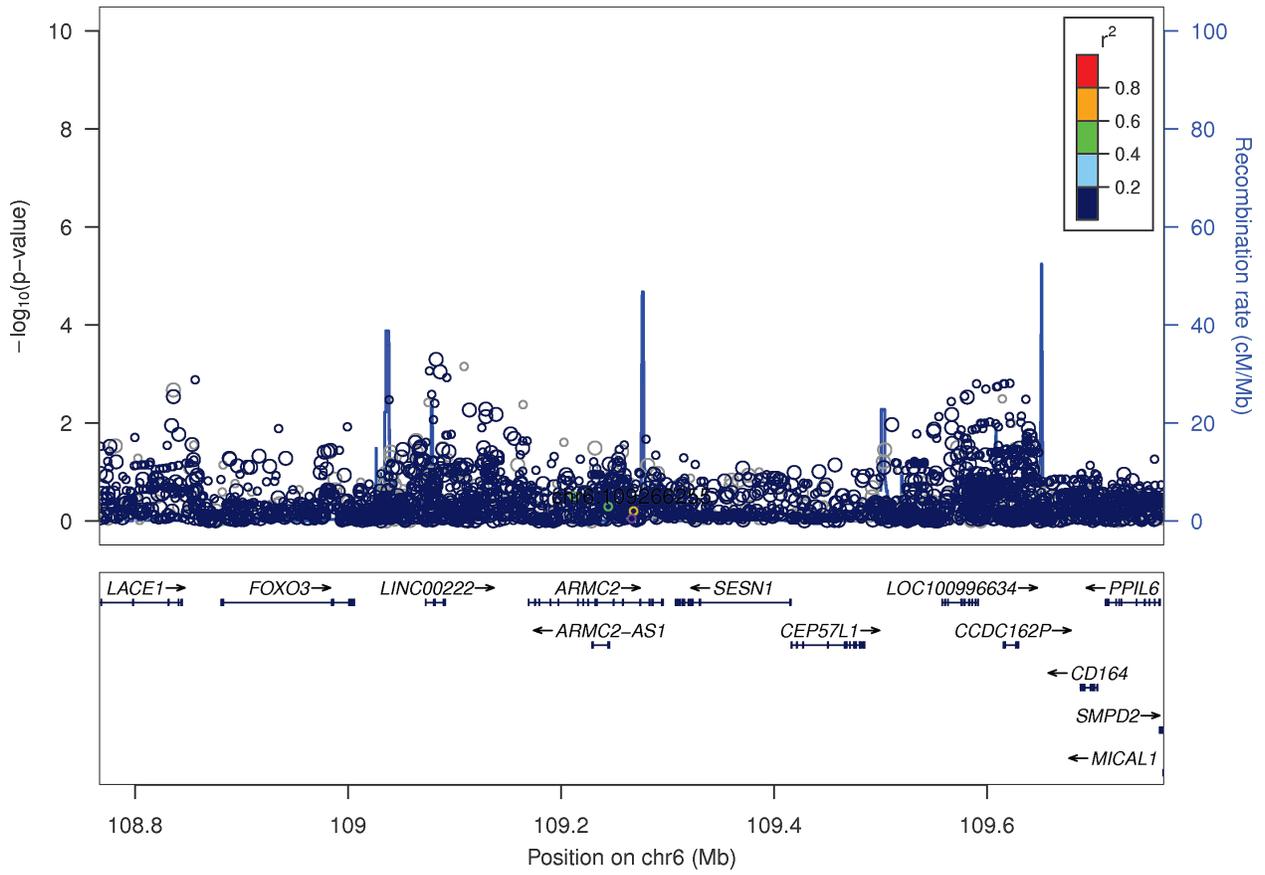


Figure S3e: LocusZoom for AA cohort meta-analysis for *SFTPD* region

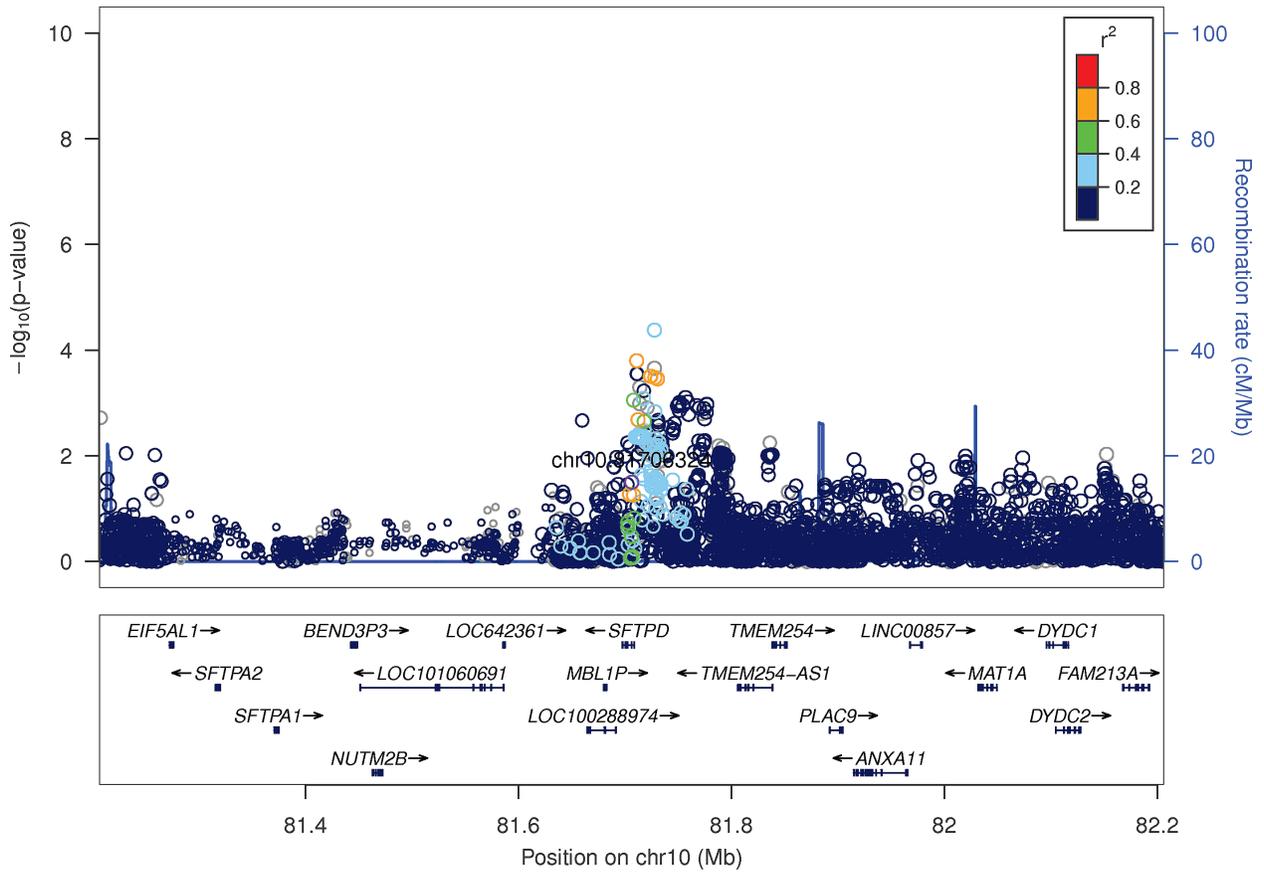


Figure S4: Comparison of effect size (beta) in the sensitivity analysis evaluating pre- and post-bronchodilator definitions of COPD for each of the 22 genome-wide significant loci.

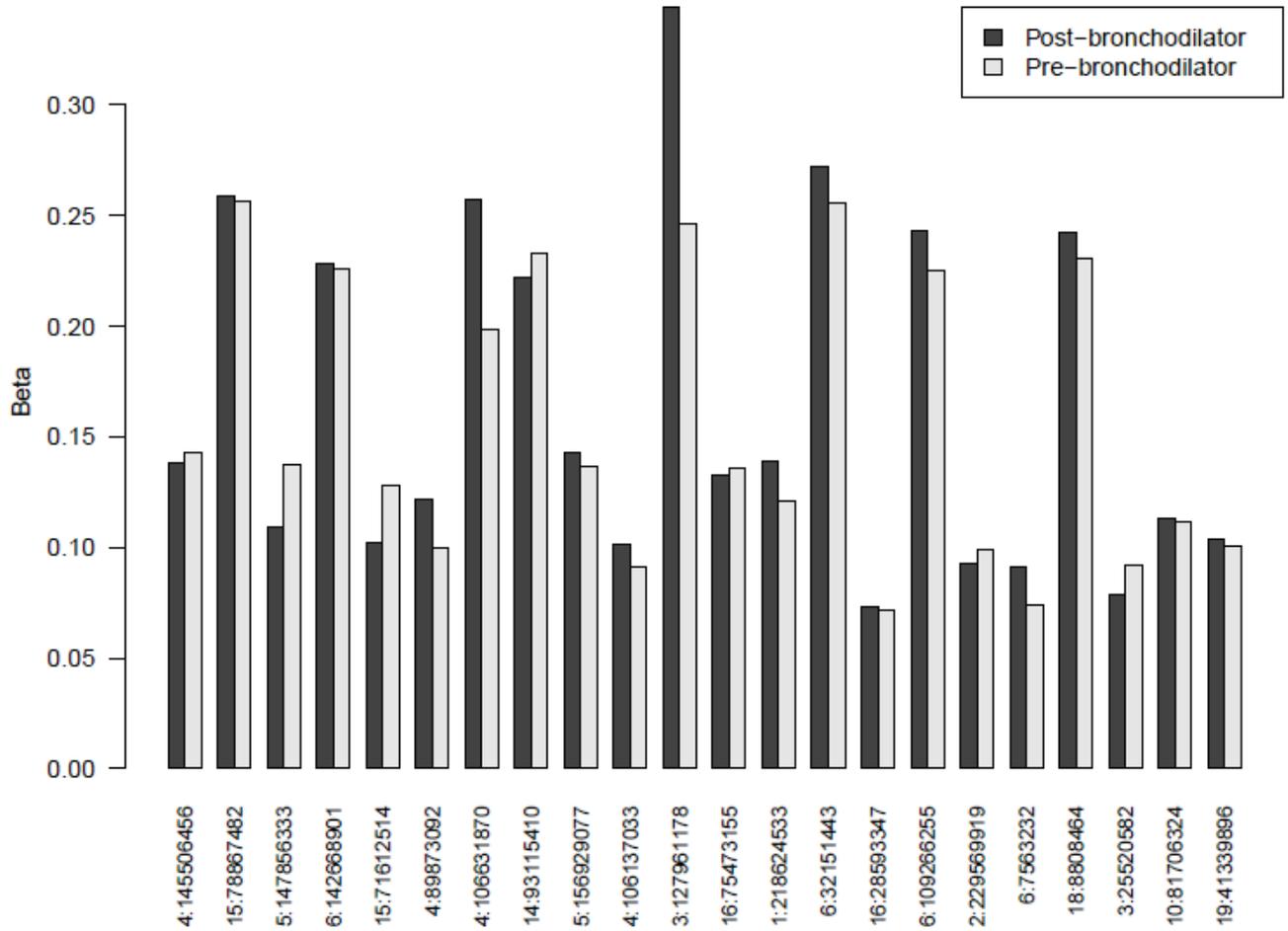


Figure S5: Comparison of $-\log_{10}P$ values in the sensitivity analysis evaluating pre- and post-bronchodilator definitions of COPD for each of the 22 genome-wide significant loci.

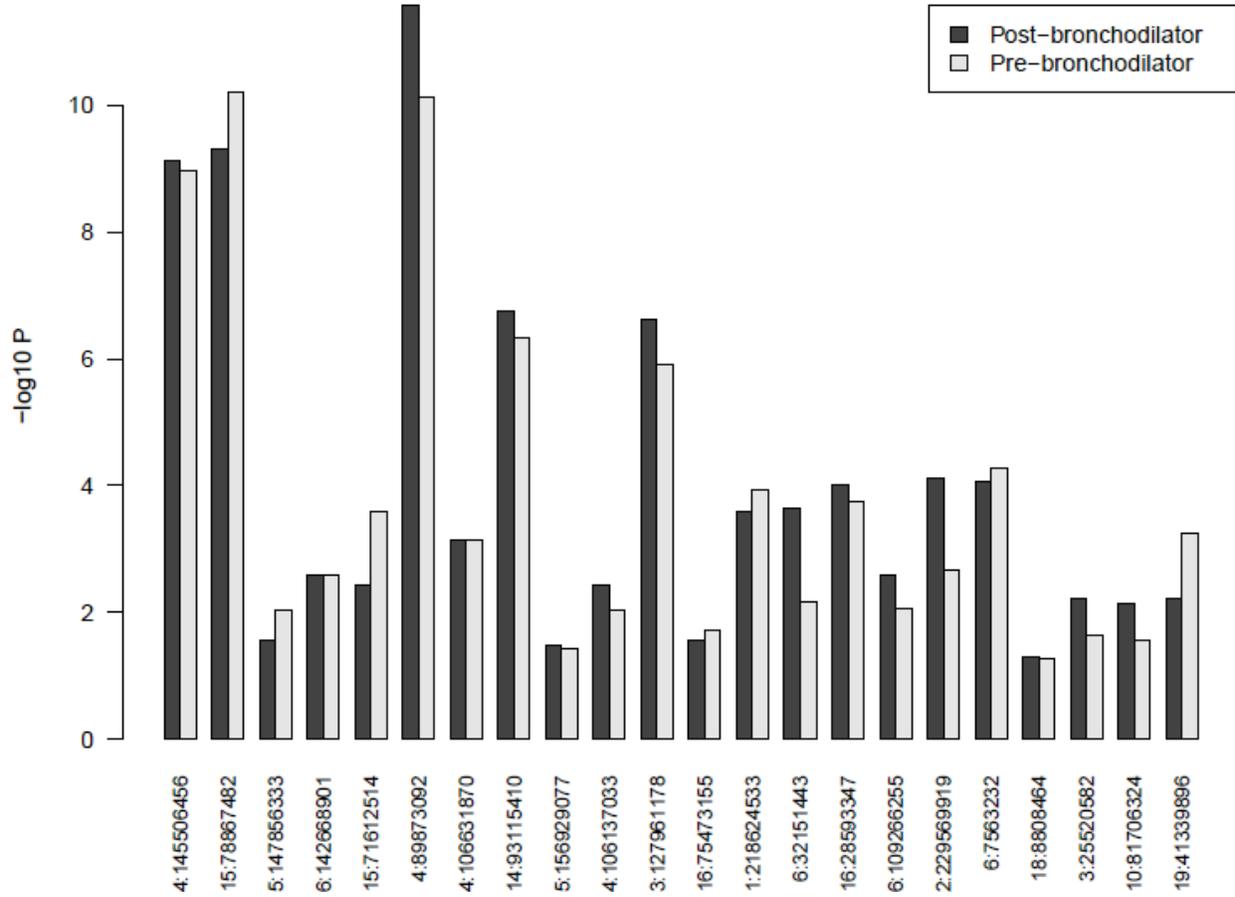
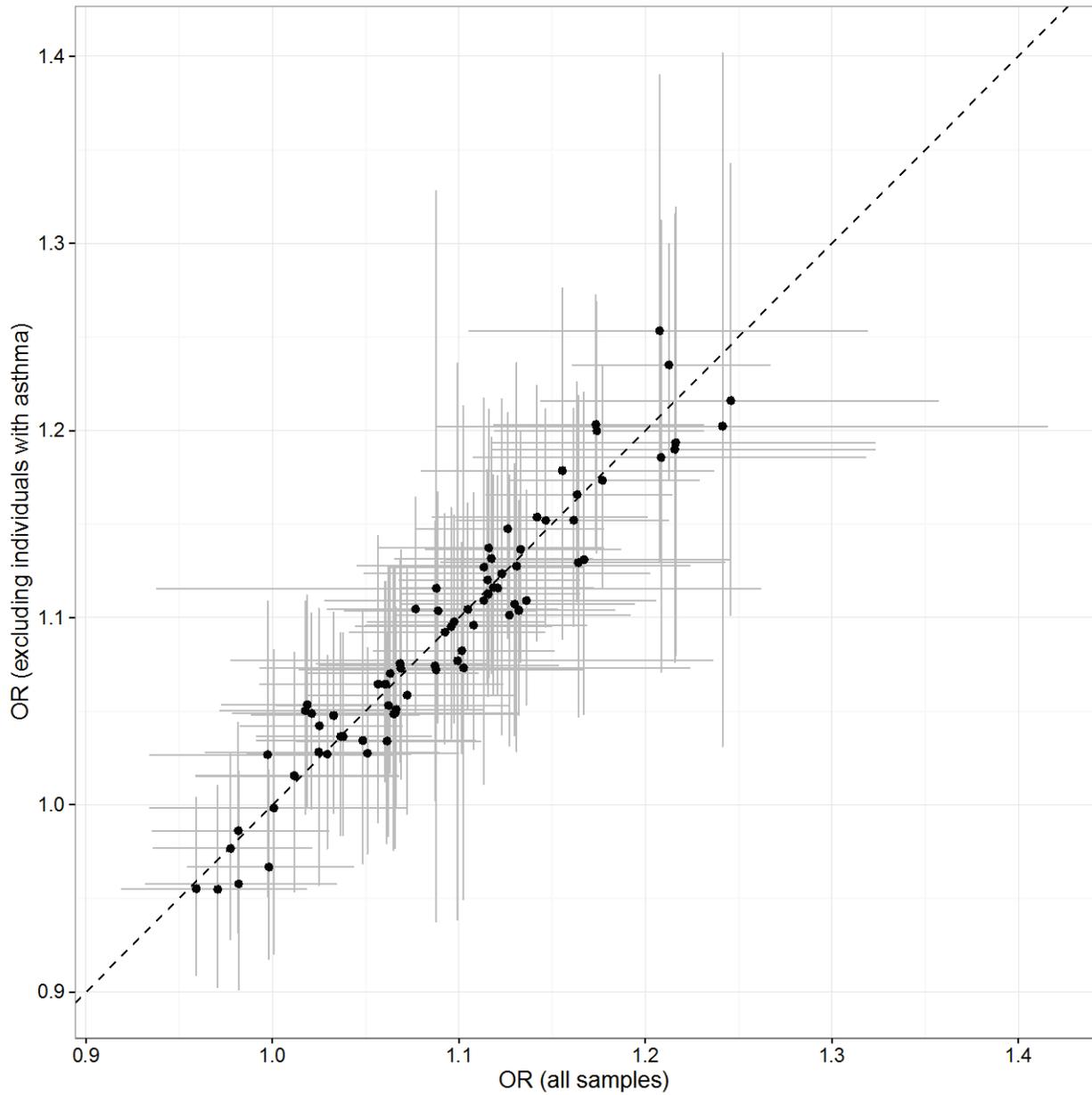


Figure S6: Comparison of odds ratios (OR), including and excluding individuals with a diagnosis of asthma, for each of 79 variants in the UK BiLEVE Stage 2 analysis.



Supplemental Tables:

Supplemental Table S1. Cohort baseline characteristics in COPD cases and controls.

Cohort	N		Age		% Female		% Ever smokers		Pack-years		FEV ₁ % predicted	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
ARIC	1060	6164	56.8 (5.4)	54.2 (5.6)	43.5	55.9	87.6	51.9	37.7 (25.7)	11.9 (17.9)	64.7 (12.5)	99.9 (11)
B58	205	3665	45 (0.3)	45 (0.3)	53.7	51.2	75	60.4	16.2 (14.2)	8.6 (11.4)	68.1 (9.5)	99.1 (11)
CHS EA	736	1586	73.1 (5.6)	71.7 (5)	44.6	71.4	72.7	40.2	31.4 (31.2)	10 (18.8)	59.8 (16.1)	100 (13.6)
COPACETIC	397	1906	61.9 (6.1)	59.7 (5.4)	2	1.6	100	100	45.6 (19.6)	38.9 (17.1)	65.3 (11.8)	106.9 (12.8)
COPDGene NHW	3068	2110	64.4 (8.3)	59.2 (8.6)	45.9	49.8	100	100	54.9 (27.1)	37.3 (20.1)	48.4 (18.5)	95.7 (10.7)
ECLIPSE	1741	149	63.6 (7.1)	57.3 (9.5)	33.1	42.8	100	100	50.4 (27.4)	30.9 (25.8)	43.3 (14.8)	105.2 (12.1)
EOCOPD *	394	495	53.6 (12.5)	40.5 (17.8)	60.2	57.2	88.3	63.3	39.8 (25.3)	10.4 (18.3)	38.4 (22.1)	97.2 (10.8)
ICGN *	1852	557	59 (7.1)	54.4 (8.9)	42.3	49.5	100	100	50.7 (28.2)	28.8 (20)	42.6 (18.1)	101.8 (13.9)
eQTL	252	224	64.6 (8.8)	61.5 (10.3)	38.9	50	98.4	86.2	52.6 (29.5)	38.6 (23.4)	61.1 (15.3)	97.7 (11.5)
FHS	701	5110	62.2 (11.8)	51.9 (13.3)	47.8	55	80.3	48.4	31.5 (27.6)	7.4 (14)	65.6 (11.9)	102.1 (11.9)
Lifelines	466	9863	53.9 (11.8)	47 (10.7)	48.9	59.9	77.9	54.4	17.2 (16.6)	6.4 (9.5)	70 (9.1)	105.1 (12)
Lovelace	259	641	64.9 (8.1)	54.4 (9.1)	78.7	81.3	100	100	52.7 (24.3)	36.6 (18.4)	61.5 (14.5)	100.1 (11.8)
MESA Caucasian	167	754	68.4 (8.9)	64.5 (9.7)	48.5	53.3	79.6	53.1	33.9 (34.2)	12.3 (20.4)	66 (12.4)	99 (11.7)
NETT-NAS	376	435	67.5 (5.8)	69.8 (7.5)	35.9	0	100	100	66.4 (30.7)	40.7 (27.8)	24.9 (6.6)	100 (13.2)
Norway/GenKOLS	846	695	65.5 (10.1)	55.4 (9.7)	41.7	50.2	100	100	31.9 (18.6)	19.4 (13.6)	46.4 (17)	92.6 (8.9)
RS1	112	815	79.5 (5)	78.5 (4.5)	38	60.5	83.9	61.8	28.6 (24.3)	12.3 (18)	64.5 (11.7)	113.4 (18)
RS2	94	811	73 (6)	71.6 (4.9)	44	55.6	90.4	61.3	33.4 (26.2)	12.1 (18.9)	64.2 (11.8)	108.6 (15.7)
RS3	106	1596	63 (6)	61.6 (5.4)	49	58.2	90.6	64	37.4 (28.2)	11.1 (16.4)	64.6 (12.7)	108.8 (14.3)
SPIROMICS	571	175	66.6 (7.6)	64.1 (9.2)	44.1	54	100	100	55.6 (24.2)	43.8 (23.8)	48.4 (18)	95.8 (10.8)
TCGS-Poland *	307	311	62.6 (7.4)	59.1 (7.2)	31.5	32.6	100	100	44.6 (22.5)	34.1 (15.1)	29.3 (9.6)	102.9 (12.6)
CHS AA	138	292	72.8 (5.2)	73 (5.3)	53.6	69.9	70.3	48.6	20.6 (25.1)	9.7 (17.1)	60.6 (14.2)	102.5 (14.6)
COPDGene AA	910	1556	58.6 (8.1)	52.8 (6)	46.8	43.8	100	100	42.7 (23.5)	36.1 (19.1)	51.2 (18.1)	97.2 (11.8)
KARE	199	6741	60.8 (8.4)	54.8 (8.6)	18	56	72.4	34.4	34.7 (20.1)	25.2 (17.9)	68 (9.5)	113.5 (15.2)
MESA AA	94	532	67.6 (9)	64.4 (9.4)	33	58.3	78.7	49.4	27.7 (26.7)	9.8 (16.2)	64.1 (13.9)	100.2 (14.5)
MESA Hispanic	52	548	68.4 (9.3)	63.3 (9.4)	32.7	55.8	71.2	41.8	25.4 (31.8)	6.9 (14.4)	65.1 (13.6)	100.4 (12.4)
TCGS-Korea *	153	205	68.5 (6.8)	52.8 (8.4)	1.6	3.4	100	100	44.3 (24.5)	27.6 (15)	34.8 (10.2)	95.5 (9.2)
UK BiLEVE Never Smokers	3737	4871	58.3 (7.7)	56.9 (7.9)	47.6	49.9	0	0	0	0	65.4 (11.4)	130.3 (8.3)
UK BiLEVE Heavy Smokers	5761	4877	59.3 (6.9)	56.9 (7.9)	45.5	49.8	100	100	41.6 (20.9)	29.8 (13.9)	61.2 (11.8)	118 (8.1)

Shaded studies have participants of European ancestry. All values represented as N, %, or mean (sd). ARIC = Atherosclerosis Risk in Communities, B58 = British 1958 Birth Cohort, CHS = Cardiovascular Health Study, COPACETIC = COPD Pathology: Addressing Critical gaps, Early Treatment & Diagnosis and Innovative Concepts, ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points, eQTL = Lung Expression Quantitative Trait Loci Study, FHS = Framingham Heart Study, KARE = Korean Association Resource project, MESA = Multi-Ethnic Study of Atherosclerosis, NETT-NAS = National Emphysema Treatment Trial / Normative Aging Study, RS = Rotterdam Study, SPIROMICS = Subpopulations and intermediate outcome measures in COPD study, EOCOPD = Boston Early-Onset COPD Study, ICGN = International COPD Genetics Network, TCGS = Transcontinental COPD Genetics Study, UK BiLEVE = UK Biobank Lung Exome Variant Evaluation; NHW = Non-Hispanic white, AA = African American, EA = European American. * Indicates the four studies with custom genotyping content (i.e. they did not have genome-wide data)

Supplemental Table S2. Ancestry and genomic control factor for each cohort in the Stage 1 meta-analysis.

Cohort	Ancestry	Effective Sample Size	Genomic Control Factor
ARIC	European	3617.9	1.026
B58	European	776.6	1.009
CHS EA	European	2010.8	1.016
COPACETIC	European	1314.3	1.013
COPDGene NHW	European	5000.8	1.017
ECLIPSE	European	549	1
EOCPD, ICGN *	European	2590.4	NA
EQTL	European	474.4	1.003
FHS	European	2465.7	1.035
Lifelines	European	1779.9	1.019
Lovelace	European	737.9	1.032
MESA Caucasian	European	546.9	1.03
NETT-NAS	European	806.7	1.038
Norway/GenKOLS	European	1526.2	1.009
RS1	European	393.9	1.025
RS2	European	336.9	1.036
RS3	European	397.6	1.012
SPIROMICS	European	535.8	1.017
TCGS-Poland *	European	618	NA
CHS AA	African American	374.8	1.044
COPDGene AA	African American	2296.8	1.009
KARE	Korean	773.2	1
MESA AA	African American	319.5	1.026
MESA Hispanic	Hispanic	190	1.006
TCGS-Korea *	Korean	350.4	NA

* These studies did not have genome-wide data available for analysis.

Supplemental Table S3. Full results table for all 79 variants submitted for testing in UK BiLEVE Stage 2 analysis. The top 22 variants with overall meta-analysis P value $< 5 \times 10^{-8}$ are shaded. Supplemental Table S3 is attached in Excel format “icgcSuppTableS3_fullStage2Testing.xlsx”.

Supplemental Table S4. Association of top 22 loci from meta-analysis of Stage 1 cohorts of European ancestry.

rsID	Closest Gene	Locus	Risk Allele	Alt Allele	Average Risk Allele Freq (Range)	Stage 1 OR (95% CI)	Stage 1 P Value
rs13141641	<i>HHIP</i>	4q31.21	T	C	0.594 (0.524-0.627)	1.229 (1.178-1.281)	4.05E-22
rs17486278	<i>CHRNA5</i>	15q25.1	C	A	0.358 (0.305-0.442)	1.231 (1.181-1.284)	3.04E-22
rs7733088	<i>HTR4</i>	5q32	G	A	0.602 (0.575-0.633)	1.193 (1.139-1.25)	8.30E-14
rs9399401	<i>ADGRG6</i>	6q24.1	T	C	0.724 (0.707-0.748)	1.124 (1.073-1.177)	6.13E-07
rs1441358	<i>THSD4</i>	15q23	G	T	0.333 (0.316-0.349)	1.106 (1.06-1.153)	3.30E-06
rs6837671	<i>FAM13A</i>	4q22.1	G	A	0.406 (0.364-0.454)	1.156 (1.11-1.204)	2.19E-12
rs11727735	<i>GSTCD</i>	4q24	A	G	0.936 (0.926-0.949)	1.271 (1.169-1.383)	2.14E-08
rs754388	<i>RIN3</i>	14q32.12	C	G	0.824 (0.812-0.851)	1.213 (1.148-1.281)	5.39E-12
rs113897301	<i>ADAM19</i>	5q33.3	AT	A	0.175 (0.15-0.187)	1.213 (1.154-1.271)	1.09E-10
rs2047409	<i>TET2</i>	4q24	A	G	0.617 (0.585-0.649)	1.112 (1.065-1.162)	1.45E-06
rs2955083	<i>EEFSEC</i>	3q21.3	A	T	0.881 (0.854-0.893)	1.197 (1.119-1.28)	1.58E-07
rs7186831	<i>CFDP1</i>	16q23.1	A	G	0.434 (0.417-0.452)	1.122 (1.063-1.185)	2.82E-05
rs10429950	<i>TGFB2</i>	1q41	T	C	0.733 (0.698-0.773)	1.138 (1.087-1.191)	4.14E-08
rs2070600	<i>AGER</i>	6p21.32	C	T	0.957 (0.945-0.987)	1.275 (1.149-1.415)	5.10E-06
rs17707300	<i>CCDC101</i>	16p11.2	C	T	0.374 (0.338-0.433)	1.119 (1.073-1.167)	1.19E-07
rs2806356	<i>ARMC2</i>	6q21	C	T	0.185 (0.158-0.198)	1.122 (1.065-1.181)	1.17E-05
rs16825267	<i>PID1</i>	2q36.3	C	G	0.929 (0.92-0.942)	1.294 (1.186-1.412)	7.19E-09
rs2076295	<i>DSP</i>	6p24.3	T	G	0.543 (0.442-0.581)	1.121 (1.077-1.166)	1.78E-08
rs647097	<i>MTCL1</i>	18p11.22	C	T	0.269 (0.259-0.297)	1.096 (1.046-1.148)	1.23E-04
rs1529672	<i>RARB</i>	3p24.2	C	A	0.834 (0.821-0.862)	1.181 (1.119-1.247)	1.80E-09
rs721917	<i>SFTPD</i>	10q22.3	G	A	0.425 (0.403-0.458)	1.083 (1.041-1.127)	8.85E-05
rs12459249	<i>CYP2A6</i>	19q13.2	C	T	0.664 (0.617-0.702)	1.124 (1.064-1.186)	2.81E-05

Supplemental Table S5. Association of top 22 loci from meta-analysis across the three Stage 1 cohorts of African ancestry.

rsID	Closest Gene	Locus	Risk Allele	Alt Allele	Average Risk Allele Freq	Stage 1 OR (95% CI)	Stage 1 P Value
rs13141641	<i>HHIP</i>	4q31.21	T	C	0.88	1.22 (1.01 - 1.47)	0.042
rs17486278	<i>CHRNA5</i>	15q25.1	C	A	0.29	1.22 (1.07 - 1.39)	2.2E-03
rs7733088	<i>HTR4</i>	5q32	G	A	0.67	1.03 (0.916 - 1.17)	0.59
rs9399401	<i>ADGRG6</i>	6q24.1	T	C	0.62	1.19 (1.05 - 1.34)	5.3E-03
rs1441358	<i>THSD4</i>	15q23	G	T	0.53	1.26 (1.13 - 1.42)	5.1E-05
rs6837671	<i>FAM13A</i>	4q22.1	G	A	0.58	1.11 (0.989 - 1.25)	0.075
rs11727735	<i>GSTCD</i>	4q24	A	G	---	---	---
rs754388	<i>RIN3</i>	14q32.12	C	G	0.86	1.2 (1.01 - 1.42)	0.036
rs113897301	<i>ADAM19</i>	5q33.3	AT	A	0.05	0.852 (0.645 - 1.13)	0.26
rs2047409	<i>TET2</i>	4q24	A	G	0.32	1.07 (0.944 - 1.2)	0.30
rs2955083	<i>EEFSEC</i>	3q21.3	A	T	0.88	1.15 (0.955 - 1.38)	0.14
rs7186831	<i>CFDP1</i>	16q23.1	A	G	0.23	1.15 (0.981 - 1.34)	0.086
rs10429950	<i>TGFB2</i>	1q41	T	C	0.64	1.07 (0.953 - 1.21)	0.25
rs2070600	<i>AGER</i>	6p21.32	C	T	---	---	---
rs17707300	<i>CCDC101</i>	16p11.2	C	T	0.16	1.1 (0.952 - 1.28)	0.19
rs2806356	<i>ARMC2</i>	6q21	C	T	0.053	0.981 (0.742 - 1.3)	0.89
rs16825267	<i>PID1</i>	2q36.3	C	G	0.93	1.05 (0.826 - 1.33)	0.70
rs2076295	<i>DSP</i>	6p24.3	T	G	0.49	0.984 (0.879 - 1.1)	0.78
rs647097	<i>MTCL1</i>	18p11.22	C	T	0.40	1.13 (1.01 - 1.27)	0.039
rs1529672	<i>RARB</i>	3p24.2	C	A	0.80	1.08 (0.938 - 1.24)	0.28
rs721917	<i>SFTPD</i>	10q22.3	G	A	0.41	1.13 (1.01 - 1.27)	0.031
rs12459249	<i>CYP2A6</i>	19q13.2	C	T	0.67	1.12 (0.976 - 1.29)	0.11

Supplemental Table S6. Summary of prior evidence for genome-wide association of our top 22 loci with either COPD or lung function. Novel loci have been highlighted with bold text.

ICGC Lead Variant	Closest Gene	Locus	Prior genome-wide COPD locus?	References for COPD association	Prior COPD SNP (LD with ICGC variant)	Consistent direction of effect?	Prior genome-wide lung function locus?	References for lung function association	Prior lung function SNP (LD with ICGC variant)	Consistent direction of effect?
rs13141641	<i>HHIP</i>	4q31.21	✓	Pillai et al. ⁸⁴ , Cho et al. ²⁰	rs1828591 (0.98), rs13141641 (same)	YES YES	✓	Wilk et al. ⁸⁵	rs13147758 (0.90)	YES
rs17486278	<i>CHRNA5</i>	15q25.1	✓	Pillai et al. ⁸⁴ , Cho et al. ²⁰	rs8034191 (0.90), rs12914385 (0.77)	YES YES				
rs7733088	<i>HTR4</i>	5q32	✓	Wilk et al. ³⁰	rs7733088 (same)	YES	✓	Hancock et al. ²⁹ , Repapi et al. ⁸⁶	rs11168048 (0.90), rs3995090 (0.98)	YES YES
rs9399401	<i>ADGRG6</i>	6q24.1					✓	Hancock et al. ²⁹	rs3817928 (0.62)	YES
rs1441358	<i>THSD4</i>	15q23					✓	Repapi et al. ⁸⁶	rs12899618 (0.29)	YES
rs6837671	<i>FAM13A</i>	4q22.1	✓	Cho et al. ⁴⁴	rs7671167 (0.64)	YES	✓	Hancock et al. ²⁹	rs2869967 (1)	YES
rs11727735	<i>GSTCD</i>	4q24	✓	Wain et al. ⁶⁰	rs10516528 (1)	YES	✓	Hancock et al. ²⁹ , Repapi et al. ⁸⁶	rs11097901 (1), rs10516526 (1)	YES YES
rs754388	<i>RIN3</i>	14q32.12	✓	Cho et al. ²⁰	rs754388 (same)	YES	✓	Soler Artigas et al. ⁸⁷	rs117068593 (0.96)	YES
rs113897301	<i>ADAM19</i>	5q33.3					✓	Hancock et al. ²⁹	rs2277027 (0.37)**	YES
rs2047409	<i>TET2</i>	4q24					✓	Wain et al. ⁶⁰	rs2047409 (same)	YES
rs2955083	<i>EEFSEC</i>	3q21.3								
rs7186831	<i>CFDP1</i>	16q23.1					✓	Soler Artigas et al. ⁸⁸	rs2865531 (0.96)	YES
rs10429950	<i>TGFB2</i>	1q41	✓	Cho et al. ²⁰	rs4846480 (1)	YES	✓	Soler Artigas et al. ⁸⁸	rs993925 (0.009)	NA (no LD)
rs2070600	<i>AGER</i>	6p21.32					✓	Hancock et al. ²⁹ , Repapi et al. ⁸⁶	rs2070600 (same)	YES
rs17707300	<i>CCDC101</i>	16p11.2	✓*	Hobbs et al. ⁵⁰	rs181206 (0.74)	YES				
rs2806356	<i>ARMC2</i>	6q21					✓	Soler Artigas et al. ⁸⁸	rs2798641 (1)	YES
rs16825267	<i>PID1</i>	2q36.3					✓	Hancock et al. ²⁹	rs1435867 (1)	YES
rs2076295	<i>DSP</i>	6p24.3								
rs647097	<i>MTCL1</i>	18p11.22								
rs1529672	<i>RARB</i>	3p24.2					✓	Soler Artigas et al. ⁸⁸	rs1529672 (same)	YES
rs721917	<i>SFTPD</i>	10q22.3								
rs12459249	<i>CYP2A6</i>	19q13.2	✓	Cho et al. ⁴⁵	rs7937 (0.24)	YES				

All linkage disequilibrium (LD) was calculated as r^2 in the 1000 genomes Phase 3 CEU unless otherwise noted. * locus was exome-wide significant. ** LD was calculated from COPD Gene non-Hispanic whites..

Supplemental Table S7. Details of the four novel COPD association loci.

Lead Novel SNP Chr:position (hg19) Cytogenetic band	Lead SNP and SNPs with $r^2 > 0.3$ (1000 Genomes CEU) gene annotations ⁸⁹	Details of genes annotated to lead SNPs and SNPs with $r^2 > 0.3$ with lead SNP	Regulatory information via lead SNP look-up in HaploReg v4.1 ^{68,90}	NHGRI-EBI GWAS catalog query for GWAS loci ($P < 5 \times 10^{-8}$) within ± 500 kb of lead SNP and with $r^2 > 0.3$ with lead SNP
rs2955083 3:127961178 3q21.3	rs2955083 (lead), <i>EEFSEC</i> intronic. rs11714256 ($r^2=0.37$), <i>RUVBL1</i> intronic. rs1042912 ($r^2=0.37$), <i>SEC61A1</i> , 3' UTR. rs17203687 ($r^2=0.31$), <i>KBTBD12</i> intronic.	<i>EEFSEC</i> codes for selenocysteine-specific elongation factor, is annotated to GTP and tRNA binding, and is a paralog to <i>TUFM</i> ⁹¹ . <i>RUVBL1</i> codes for RuvB-like 1 protein, which participates in ATPase and DNA helicase activity ⁹¹ . <i>SEC61A1</i> codes for protein transport protein Sec61 subunit alpha isoform 1, which is associated with membrane-bound ribosomes and is important to protein translocation ⁹² . <i>KBTBD12</i> codes for the Kelch repeat and BTB domain-containing protein 12, which is involved in protein ubiquitination ⁹¹ .	rs2955083 near <i>EEFSEC</i> and variants in high LD ($r^2 > 0.8$, 1000 genomes CEU) possess DNase hypersensitivity sites as well as promoter and enhancer site histone marks across nearly all indexed tissue types including lung, lung fibroblasts, fetal lung, and fetal lung fibroblasts. Additionally, 25 different regulatory motifs are altered by rs2955083 .	rs2687729 ($r^2=1.0$), menarche age at onset ⁹³ rs2999052 ($r^2=0.38$), hypospadias ⁹⁴ rs10934853 ($r^2=0.33$), prostate cancer ⁹⁵
rs2076295 6:7563232 6p24.3	rs2076295 (lead), <i>DSP</i> intronic. (No SNPs with $r^2 > 0.3$ in any additional genes)	<i>DSP</i> codes for desmoplakin, a major protein of desmosomes ⁹¹ , which is required for epidermal integrity ⁹⁶ . <i>DSP</i> mutations have been linked to several Mendelian syndromes involving palmoplantar keratoderma ⁹⁷ , left ventricular cardiomyopathy ⁹⁷ , familial arrhythmogenic right ventricular dysplasia ⁹⁸ , and lethal acantholytic epidermolysis bullosa ⁹⁹ . Further, our lead SNP in <i>DSP</i> has been previously associated with fibrotic idiopathic interstitial pneumonias in GWAS ⁷¹ ; however, the minor allele for rs2076295 has opposite direction of effect for pulmonary fibrosis and COPD risk.	rs2076295 reported to have DNase hypersensitivity sites and enhancer histone marks in blood and several solid organs; however, none in lung tissues	rs2076295 (lead), interstitial lung disease ^{71,100}
rs647097 18:8808464 18p11.22	rs647097 (lead), <i>MTCL1</i> intronic. (No SNPs with $r^2 > 0.3$ in any additional genes)	<i>MTCL1</i> codes for the microtubule cross-linking factor 1, important in epithelial-cell-specific microtubule stabilization and accumulation around the Golgi apparatus ^{101,102} .	rs647097 and variants in high LD ($r^2 > 0.8$ in 1000 genomes phase 1 CEU) have enhancer histone marks in fetal lung fibroblasts. Several regulatory motifs are altered by rs647097	None.
rs721917 10:81706324 10q22.3	rs721917 (lead), <i>SFTPD</i> non-synonymous (missense). (No SNPs with $r^2 > 0.3$ in any additional genes)	<i>SFTPD</i> codes for the pulmonary surfactant-associated protein D, which functions in lung innate immunity ⁹¹ . <i>Sftpd</i> (-/-) mice have been observed to have chronic inflammation, emphysema, and fibrosis ¹⁰³ . <i>SFTPD</i> variants have been examined in a COPD candidate gene study ¹⁰⁴ and SFTPD levels have been researched as a COPD biomarker ¹⁰⁵ .	rs721917 has enhancer histone marks in fetal lung tissue	rs1923539 ($r^2=0.38$), circulating surfactant protein D levels in COPD ¹⁰⁶

Supplemental Table S8. Full results ($P < 0.05$ in meta-analysis) for lung expression quantitative trait locus (eQTL) analysis. All cis- and trans- eQTL with $P < 0.05$ in meta-analysis are shown. eQTL associations meeting Bonferroni correction of $P < 5.2 \times 10^{-8}$ are highlighted. * refers to proxy variant. Supplemental Table S8 is attached in Excel format “icgcSuppTableS8_fullEqtlResults.xlsx”.

Supplemental Table 9a-b: Co-localization results. Probe = affymetrix probe ID, tile center given as chromosome position for hg19. ppH4 = posterior probability of co-localization of the GWAS and eQTL association. Results with posterior probability of co-localization > 0.6 are shown.

Supplemental Table 9a: Co-localization using the Lung eQTL data²⁶.

Probe	Gene	Tile center	ppH4
100149674_TGI_at	<i>RARB</i>	3:25520582	0.85
100139086_TGI_at	NA	4:145506456	0.95
100311674_TGI_at	<i>HHIP</i>	4:145506456	0.95
100133899_TGI_at	NA	4:145506456	0.94
100148028_TGI_at	<i>HHIP</i>	4:145506456	0.94
100312038_TGI_at	<i>FAM13A</i>	4:89873092	0.77
100313510_TGI_at	<i>AGER</i>	6:32151443	0.93
100131291_TGI_at	NA	6:7563232	0.99
100304914_TGI_at	<i>DSP</i>	6:7563232	0.99
100313405_TGI_at	<i>DSP</i>	6:7563232	0.99
100125626_TGI_at	<i>TGFB2</i>	1:218624533	0.62
100142979_TGI_at	<i>THSD4</i>	15:71612514	0.99
100308491_TGI_at	<i>THSD4</i>	15:71612514	0.99
100310339_TGI_at	<i>THSD4</i>	15:71612514	0.99
100130228_TGI_at	NA	15:71612514	0.68
100123649_TGI_at	<i>CHRNA3</i>	15:78867482	0.89
100129347_TGI_at	<i>SBK1</i>	16:28593347	0.79
100142003_TGI_at	<i>SPNS1</i>	16:28593347	0.67
100300284_TGI_at	<i>MTCL1</i>	18:8808464	0.76

Supplemental Table 9b: Co-localization using lung tissue from GTEx^{107, 107}

ensembleID	Gene	Tile center	ppH4
ENSG00000270720.1	<i>RP11-84C13.2</i>	4:89373092	0.75
ENSG00000135074.11	<i>ADAM19</i>	5:156429077	0.79
ENSG00000248544.2	<i>CTB-47B11.3</i>	5:156429077	0.67
ENSG00000176476.4	<i>SGF29</i>	16:28093347	0.89
ENSG00000178188.10	<i>SH2B1</i>	16:28093347	0.79
ENSG00000196502.7	<i>SULT1A1</i>	16:28093347	0.75
ENSG00000264455.1	<i>MIR4721</i>	16:28093347	0.7
ENSG00000168502.13	<i>MTCL1</i>	18:8308464	0.92

Supplemental Table S10. Sensitivity analysis results for COPD association of top 22 loci using Post- versus Pre-Bronchodilator Definitions of COPD in the COPDGene NHW and AA, ECLIPSE, NETT-NAS, and Norway/GenKOLS cohorts.

Location	rsID	Beta		P	
		Post-	Pre-	Post-	Pre-
4:145506456	rs13141641	0.23	0.23	7.80E-10	1.10E-09
15:78867482	rs17486278	0.22	0.23	5.10E-10	6.40E-11
5:147856333	rs7733088	0.08	0.09	0.027	0.0094
6:142668901	rs9399401	0.11	0.11	0.0026	0.0026
15:71612514	rs1441358	0.1	0.13	0.0037	0.00026
4:89873092	rs6837671	0.24	0.22	2.70E-12	7.40E-11
4:106631870	rs11727735	0.26	0.26	7.00E-04	0.00074
14:93115410	rs754388	0.24	0.23	1.80E-07	4.60E-07
5:156929077	rs113897301	0.1	0.1	0.032	0.037
4:106137033	rs2047409	0.1	0.09	0.0037	0.0091
3:127961178	rs2955083	0.27	0.26	2.40E-07	1.20E-06
16:75473155	rs7186831	0.09	0.1	0.027	0.019
1:218624533	rs10429950	0.14	0.14	0.00025	0.00012
6:32151443	rs2070600	0.34	0.25	0.00023	0.0068
16:28593347	rs17707300	0.14	0.14	1.00E-04	0.00018
6:109266255	rs2806356	0.14	0.12	0.0026	0.0087
2:229569919	rs16825267	0.26	0.2	7.50E-05	0.0022
6:7563232	rs2076295	0.13	0.14	8.40E-05	5.40E-05
18:8808464	rs647097	0.07	0.07	0.049	0.052
3:25520582	rs1529672	0.12	0.1	0.0059	0.023
10:81706324	rs721917	0.09	0.07	0.0072	0.028
19:41339896	rs12459249	0.11	0.14	0.0059	0.00055

Supplemental Table S11. Look-up of NHGRI-EBI GWAS Catalog asthma-associated trait genome-wide significant GWAS loci in our COPD association Stage 1 meta-analysis results. Only asthma-associated trait GWAS loci that were present in our Stage 1 analysis are reported. The asthma-associated traits in the NHGRI-EBI GWAS Catalog that were used in our look-up come from a number of GWAS studies.^{10,108-123} Supplemental Table S11 is attached in Excel format “icgcSuppTableS11_asthmaGwasCopdAssoc.xlsx”.

Supplemental Table S12. Association of top 22 COPD association loci from overall meta-analysis in the GABRIEL Consortium asthma GWAS¹⁰

Chr	SNP*	Asthma OR (Random Effects)	Asthma P Value (Random Effects)	Proxy SNP Used?	COPD Index SNP	LD (r ²) with COPD Index SNP
1	rs10429950	1.01	0.61	NO	--	--
3	rs1529672	1.03	0.27	NO	--	--
3	rs2811518	0.93	0.026	YES	rs2955083	1
4	rs2869967	1.02	0.44	YES	rs6837671	0.97
4	rs1391441	0.99	0.69	YES	rs2047409	0.90
4	rs11727735	0.96	0.26	NO	--	--
4	rs6817273	1.02	0.36	YES	rs13141641	0.93
5	rs3995090	0.98	0.29	YES	rs7733088	0.97
5	rs3734031	1.03	0.48	YES	rs56168343	0.56
6	rs2076295	1.00	0.86	NO	--	--
6	rs2070600	1.01	0.92	NO	--	--
6	rs2798641	1.03	0.18	YES	rs2806356	1
6	rs6570507	1.03	0.16	YES	rs9399401	0.96
10	rs721917	0.98	0.38	NO	--	--
14	rs11627032	1.03	0.26	YES	rs754388	0.63
15	rs6494904	1.00	0.84	YES	rs1441358	0.75
15	rs1051730	0.99	0.64	YES	rs17486278	0.93
16	rs4788073	1.00	0.92	YES	rs17707300	1
18	rs647097	1.04	0.13	NO	--	--
19	rs7251418	0.99	0.86	YES	rs12459249	0.88

*No proxy SNPs with r² > 0.5 could be found for top COPD SNPs rs7186831 (*CFDP1*) and rs16825267 (*PID1*)

Supplemental Table S13. Look-up of NHGRI-EBI GWAS Catalog “Nicotine Dependence” and “Smoking Behaviors” genome-wide significant GWAS loci in our COPD association Stage 1 meta-analysis results.

Chr	Position	SNP	Region	NHGRI-EBI Catalog Mapped Genes	Effect Allele	Average Effect Allele Freq	OR (COPD)	P value (COPD)
1	99445471	rs61784651	1p21.1	<i>LPPR5</i>	T	0.15	0.98	0.55
2	146316319	rs10193706	2q22.3	<i>TEX41 - PABPC1P2</i>	A	0.50	0.96	0.032
6	38901867	rs10807199	6p21.2	<i>DNAH8</i>	T	0.45	1.00	0.95
8	42546711	rs1451240	8p11.21	<i>SMIM19 - LOC105379396</i>	A	0.29	0.96	0.086
8	42550498	rs6474412	8p11.21	<i>SMIM19 - LOC105379396</i>	T	0.72	1.05	0.045
9	136478355	rs3025343	9q34.2	<i>FAM163B - DBH</i>	A	0.11	1.03	0.43
10	93348120	rs1329650	10q23.32	<i>HECTD2-AS1</i>	T	0.27	1.02	0.33
11	27679916	rs6265	11p14.1	<i>BDNF - BDNF-AS</i>	T	0.20	1.03	0.24
11	112861434	rs4466874	11q23.2	<i>NCAM1</i>	T	0.59	0.98	0.40
15	78851615	rs2036527	15q25.1	<i>PSMA4 - CHRNA5</i>	A	0.34	1.20	2.2E-18
15	78894339	rs1051730	15q25.1	<i>CHRNA3</i>	A	0.34	1.21	2.8E-22
19	41310571	rs3733829	19q13.2	<i>EGLN2 - RAB4B-EGLN2</i>	A	0.65	0.96	0.030
19	41363765	rs8102683	19q13.2	<i>CYP2A6 - CYP2A7</i>	T	0.25	0.95	0.017

Supplemental Table S14. Association of top 22 COPD loci from overall meta-analysis in the cigarettes per day (cig/day) GWAS by the Tobacco and Genetics Consortium¹²⁴

Chr	SNP	Effect Allele	Effect Allele Freq	Effect Size (cig/day)	Standard Error	P Value (Cig/day)	Proxy SNP Used?	COPD Index SNP	LD (r ²) with COPD Index SNP
1	rs10429950	T	0.72	-0.012	0.091	0.90	NO	--	--
2	rs16825267	C	0.93	-0.037	0.17	0.83	NO	--	--
3	rs1529672	A	0.17	0.0038	0.11	0.97	NO	--	--
3	rs2999073	C	0.88	-0.078	0.13	0.56	YES	rs2955083	1
4	rs2045517	T	0.40	-0.069	0.083	0.40	YES	rs6837671	0.97
4	rs2047409	A	0.62	-0.067	0.084	0.42	NO	--	--
4	rs11727735	A	0.93	0.12	0.16	0.48	NO	--	--
4	rs13141641	T	0.58	0.21	0.083	0.012	NO	--	--
5	rs7733088	A	0.38	0.034	0.094	0.72	NO	--	--
5	rs3734031	A	0.90	-0.098	0.13	0.46	YES	rs56168343	0.56
6	rs2076295	T	0.55	0.022	0.084	0.79	NO	--	--
6	rs2070600	T	0.04	0.069	0.21	0.74	NO	--	--
6	rs2806356	T	0.81	0.031	0.10	0.77	NO	--	--
6	rs9399401	T	0.70	0.077	0.089	0.39	NO	--	--
10	rs721917	A	0.58	-0.12	0.083	0.15	NO	--	--
14	rs754388	C	0.82	-0.14	0.12	0.23	NO	--	--
15	rs11853359	A	0.33	0.059	0.087	0.50	YES	rs1441358	0.98
15	rs17486278	A	0.65	-1.04	0.087	5.91E-33	NO	--	--
16	rs17707300	T	0.63	-0.030	0.085	0.72	NO	--	--
18	rs647097	T	0.74	-0.12	0.092	0.18	NO	--	--
19	rs7251418	A	0.28	-0.21	0.16	0.19	YES	rs12459249	0.88

Supplemental Table S15. Association of top 22 COPD loci from overall meta-analysis in the ever-smoking GWAS by the Tobacco and Genetics Consortium¹²⁴

Chr	SNP	Effect Allele	Effect Allele Freq	OR (Ever-Smoking)	P Value (Ever-Smoking)	Proxy SNP Used?	COPD Index SNP	LD (r ²) with COPD Index SNP
1	rs10429950	T	0.71	1.00	0.84	NO	--	--
2	rs16825267	C	0.89	0.97	0.24	NO	--	--
3	rs1529672	A	0.20	0.99	0.66	NO	--	--
3	rs2999073	C	0.84	1.03	0.18	YES	rs2955083	1
4	rs2045517	T	0.41	0.98	0.18	YES	rs6837671	0.97
4	rs2047409	A	0.61	1.02	0.058	NO	--	--
4	rs11727735	A	0.91	0.98	0.38	NO	--	--
4	rs13141641	T	0.57	1.00	0.89	NO	--	--
5	rs7733088	A	0.39	0.99	0.61	NO	--	--
5	rs3734031	A	0.87	0.96	0.024	YES	rs56168343	0.56
6	rs2076295	T	0.54	0.98	0.038	NO	--	--
6	rs2070600	T	0.07	1.02	0.42	NO	--	--
6	rs2806356	T	0.79	0.99	0.41	NO	--	--
6	rs9399401	T	0.69	1.00	0.72	NO	--	--
10	rs721917	A	0.57	1.00	0.68	NO	--	--
14	rs754388	C	0.79	1.01	0.74	NO	--	--
15	rs11853359	A	0.34	0.98	0.17	YES	rs1441358	0.98
15	rs17486278	A	0.65	1.00	0.94	NO	--	--
16	rs17707300	T	0.62	1.00	0.95	NO	--	--
18	rs647097	T	0.72	1.00	0.89	NO	--	--
19	rs7251418	A	0.28	1.02	0.38	YES	rs12459249	0.88

Supplemental Table S16. Look-up of NHGRI-EBI GWAS Catalog coronary artery disease and osteoporosis-related genome-wide significant GWAS loci¹²⁵⁻¹⁵⁴ in our COPD association Stage 1 meta-analysis results. Only comorbidity loci with COPD P value < 0.05 are reported.

SNP	Region	Trait	GWAS Reference PMID	Mapped Gene	Comorbid Trait Risk Allele	Freq of Comorbid Trait Risk Allele in COPD	COPD OR (95% CI) for Comorbid Trait Risk Allele	COPD Association P value
rs3825807	15q25.1	Coronary heart disease	21378990	<i>ADAMTS7</i>	A	0.576	0.927 (0.891 - 0.964)	1.5E-04
rs1994016	15q25.1	Coronary artery disease	21239051	<i>ADAMTS7</i>	C	0.608	0.93 (0.892 - 0.97)	6.9E-04
rs4380028	15q25.1	Coronary heart disease	21378988	<i>ADAMTS7 - TRK-CTT1-2</i>	C	0.605	0.94 (0.906 - 0.975)	0.0010
rs974819	11q22.3	Coronary heart disease	21378988	<i>LOC105369463 - LOC102723862</i>	T	0.332	0.938 (0.902 - 0.976)	0.0014
rs2128739	11q22.3	Coronary artery disease	26343387	<i>LOC105369463 - LOC102723862</i>	A	0.311	0.94 (0.901 - 0.98)	0.0037
rs13336428	16p13.3	Bone mineral density	22504420	<i>CLCN7 - PTX4</i>	A	0.447	0.942 (0.904 - 0.982)	0.0045
rs228769	17q21.31	Bone mineral density (hip)	19801982	<i>LOC105371789 - HDAC5</i>	G	0.261	0.938 (0.896 - 0.982)	0.0062
rs7932354	11p11.2	Bone mineral density (hip)	19801982	<i>ARHGAP1 - ZNF408</i>	T	0.345	1.06 (1.01 - 1.11)	0.0097
rs2519093	9q34.2	Coronary artery disease	26343387	<i>ABO</i>	T	0.192	1.06 (1.01 - 1.11)	0.018
rs56062135	15q22.33	Coronary artery disease	26343387	<i>SMAD3</i>	C	0.774	0.946 (0.901 - 0.992)	0.024
rs579459	9q34.2	Coronary heart disease	21378990	<i>ABO - SURF6</i>	C	0.215	1.05 (1.01 - 1.1)	0.028
rs10048146	16q24.1	Bone mineral density (spine)	19801982	<i>LOC105371390 - LOC105371391</i>	G	0.187	1.05 (1.01 - 1.11)	0.029
rs16921914	11p13	Bone mineral density (spine)	19801982	<i>DCDC5 - DCDC1</i>	A	0.279	1.05 (1 - 1.09)	0.030
rs964184	11q23.3	Coronary heart disease	21378990	<i>LOC105369514 - ZPR1</i>	G	0.152	0.945 (0.898 - 0.995)	0.032
rs6689306	1q21.3	Coronary artery disease	26343387	<i>IL6R</i>	A	0.412	0.958 (0.92 - 0.997)	0.034
rs736825	12q13.13	Bone mineral density	22504420	<i>HOXC5 - HOXC4 - HOXC6</i>	C	0.643	0.956 (0.917 - 0.997)	0.035
rs4468572	15q25.1	Coronary artery disease	26343387	<i>ADAMTS7 - TRK-CTT1-2</i>	C	0.566	0.958 (0.921 - 0.997)	0.036
rs344081	3q25.31	Bone mineral density	22504420	<i>LEKR1</i>	T	0.787	1.06 (1 - 1.12)	0.043
rs163879	11p14.1	Bone mineral density	22504420	<i>DCDC5</i>	T	0.651	0.96 (0.921 - 1)	0.048

Supplemental Table S17. Quantitative imaging GWAS results⁷⁵ for each of the 22 genome-wide significant loci from our COPD association overall meta-analysis.

rsID	Closest Gene	Locus	COPD Risk Allele	Emphysema				Airways			
				%LAA-950 Beta (95% CI)	%LAA-950 P Value	Perc15 Beta (95% CI)	Perc15 P Value	Pi10 Beta (95% CI)	Pi10 P Value	Wall Area Percent Beta (95% CI)	Wall Area Percent P Value
rs13141641	<i>HHIP</i>	4q31.21	T	0.12 (0.16, 0.091)	1.7E-12	-2.2 (-1.5, -2.9)	8.4E-10	-4e-04 (0.0033, -0.0041)	0.41	0.1 (0.19, 0.016)	0.027
rs17486278	<i>CHRNA5</i>	15q25.1	C	0.094 (0.13, 0.06)	4.9E-08	-1.4 (-0.75, -2.1)	4.4E-05	0.0031 (0.0066, -0.00043)	0.099	0.0036 (0.089, -0.082)	0.41
rs7733088	<i>HTR4</i>	5q32	G	0.022 (0.056, -0.011)	0.24	-0.5 (0.2, -1.2)	0.20	0.002 (0.0055, -0.0015)	9.5E-03	0.16 (0.24, 0.076)	2.7E-04
rs9399401	<i>ADGRG6</i>	6q24.1	T	0.065 (0.1, 0.031)	3.1E-04	-1.2 (-0.47, -1.9)	1.6E-03	-0.0013 (0.0024, -0.005)	0.27	0.021 (0.11, -0.067)	0.59
rs1441358	<i>THSD4</i>	15q23	G	0.05 (0.082, 0.017)	4.1E-03	-0.91 (-0.22, -1.6)	0.012	-1e-04 (0.0034, -0.0036)	0.96	0.043 (0.13, -0.041)	0.38
rs6837671	<i>FAM13A</i>	4q22.1	G	0.066 (0.098, 0.034)	8.4E-05	-1.2 (-0.55, -1.9)	1.6E-04	0.0036 (0.0071, 7.2e-05)	0.0525	0.13 (0.21, 0.05)	2.1E-03
rs11727735	<i>GSTCD</i>	4q24	A	0.036 (0.11, -0.036)	0.30	-0.67 (0.8, -2.1)	0.27	0.012 (0.019, 0.0038)	5.7E-03	0.39 (0.57, 0.21)	4.47E-05
rs754388	<i>RIN3</i>	14q32.12	C	0.093 (0.14, 0.05)	2.7E-05	-1.8 (-0.96, -2.7)	5.5E-05	0.0021 (0.0068, -0.0026)	0.45	0.11 (0.22, 0.0018)	0.040
rs2047409	<i>TET2</i>	5q33.3	A	0.034 (0.067, 0.0018)	0.012	-0.78 (-0.1, -1.5)	0.016	-3e-04 (0.0032, -0.0038)	0.92	0.058 (0.14, -0.026)	0.21
rs2955083	<i>EEFSEC</i>	4q24	A	0.058 (0.11, 0.0085)	0.029	-0.96 (0.075, -2)	0.087	0.0095 (0.015, 0.0042)	6.7E-04	0.093 (0.22, -0.033)	0.19
rs56168343*	<i>ADAM19</i>	3q21.3	T	0.052 (0.098, 0.007)	0.031	-1.3 (-0.38, -2.2)	7.7E-03	0.0022 (0.0073, -0.0029)	0.45	0.037 (0.15, -0.079)	0.60
rs7186831	<i>CFDP1</i>	16q23.1	A	0.0095 (0.049, -0.03)	0.45	-0.023 (0.8, -0.85)	0.98	0.0053 (0.0096, 0.00099)	0.020	0.14 (0.24, 0.036)	0.011
rs10429950	<i>TGFB2</i>	1q41	T	0.08 (0.11, 0.045)	1.1E-05	-1.3 (-0.6, -2.1)	4.9E-04	0 (0.0037, -0.0037)	0.99	0.084 (0.17, -0.0057)	0.087
rs2070600	<i>AGER</i>	6p21.32	C	0.24 (0.32, 0.15)	4.6E-09	-3.8 (-2, -5.5)	2.2E-06	-0.0036 (0.0058, -0.013)	0.53	0.073 (0.29, -0.15)	0.58
rs17707300	<i>CCDC101</i>	16p11.2	C	0.0051 (0.039, -0.029)	0.83	0.28 (0.98, -0.42)	0.49	0.0035 (0.0072, -0.00022)	0.085	0.055 (0.14, -0.032)	0.26
rs2806356	<i>ARMC2</i>	6q21	C	0.02 (0.064, -0.023)	0.42	-0.36 (0.54, -1.3)	0.49	0.0039 (0.0086, -8e-04)	0.13	0.19 (0.31, 0.082)	9.5E-04
rs16825267	<i>PID1</i>	2q36.3	C	0.082 (0.14, 0.019)	0.014	-1.7 (-0.38, -3)	0.015	-4e-04 (0.0063, -0.0071)	0.94	0.023 (0.18, -0.14)	0.83
rs2076295	<i>DSP</i>	6p24.3	T	0.031 (0.063, -0.00085)	0.014	-0.64 (0.014, -1.3)	0.066	-0.0012 (0.0021, -0.0045)	0.57	0.035 (0.12, -0.046)	0.46
rs647097	<i>MTCL1</i>	18p11.22	C	-0.001 (0.034, -0.036)	0.093	0.03 (0.75, -0.69)	0.32	0.0012 (0.0049, -0.0025)	0.59	0.077 (0.16, -0.011)	0.11
rs1529672	<i>RARB</i>	3p24.2	C	0.07 (0.11, 0.029)	8.4E-04	-1.7 (-0.81, -2.5)	2.0E-04	0.0012 (0.0057, -0.0033)	0.47	0.092 (0.2, -0.014)	0.11
rs721917	<i>SFTPD</i>	10q22.3	G	0.0099 (0.042, -0.022)	0.62	-0.085 (0.58, -0.75)	0.86	3e-04 (0.0036, -0.003)	0.71	0.07 (0.15, -0.012)	0.12
rs12459249	<i>CYP2A6</i>	19q13.2	C	0.073 (0.11, 0.035)	2.2E-04	-1.2 (-0.46, -2)	2.4E-03	8e-04 (0.0049, -0.0033)	0.78	0.08 (0.18, -0.016)	0.14

* The indel rs113897301 was not available in the quantitative imaging results, so rs56168343, the second most significant variant at the 3q21.3 locus, was used as a proxy.

Supplemental Table S18. For each of the 22 genome-wide significant loci, the highest LD (r^2) proxy SNP that was present in HapMap phase III was chosen as the input variant for the PrixFixe⁸⁰ method of gene prioritization.

Chr:position index variant	Chr:position HapMap III proxy variant	rsID HapMap III proxy variant	P value of proxy variant*	LD (r^2) between index and proxy
1:218624533	1:218624533	rs10429950	1.83E-07	1.00
2:229569919	2:229592304	rs3732192	1.78E-07	0.99
3:127961178	3:127991938	rs2811416	3.91E-07	1.00
3:25520582	3:25520582	rs1529672	2.37E-09	1.00
4:106137033	4:106131210	rs2007403	3.32E-06	1.00
4:106631870	4:106631870	rs11727735	1.55E-08	1.00
4:145506456	4:145474473	rs1489759	5.48E-15	0.92
4:89873092	4:89869332	rs2869967	1.55E-14	0.99
5:147856333	5:147856333	rs7733088	4.41E-14	1.00
5:156929077:ID	5:156932376	rs2277027	8.31E-06	0.37
6:109266255	6:109268050	rs2798641	1.46E-05	1.00
6:142668901	6:142670955	rs7756305	1.52E-08	1.00
6:32151443	6:32062687	rs2071293	4.12E-03	0.01
6:7563232	6:7563232	rs2076295	4.95E-08	1.00
10:81706324	10:81706324	rs721917	2.11E-06	1.00
14:93115410	14:93111120	rs11624512	7.76E-11	0.99
15:71612514	15:71612514	rs1441358	2.06E-10	1.00
15:78867482	15:78878541	rs951266	1.72E-23	0.99
16:28593347	16:28593347	rs17707300	6.25E-09	1.00
16:75473155	16:75479153	rs2161684	2.85E-04	0.62
18:8808464	18:8808464	rs647097	3.03E-06	1.00
19:41339896	19:41341589	rs7251418	1.93E-03	0.85

* The COPD association Stage 1 meta-analysis P value for the HapMap III compatible proxy variant.

Supplemental Table S19. Gene prioritization scores using PrixFixe⁸⁰ method of identifying co-functional genes across the genome-wide significant loci in our study.

Gene	Region	PrixFixe Score	Gene	Region	PrixFixe Score
<i>TGFB2</i>	chr1:q41	0.480	<i>CHRNA4</i>	chr15:q25.1	0.262
<i>RARB</i>	chr3:p24.2	0.188	<i>PSMA4</i>	chr15:q25.1	0.261
<i>RUVBL1</i>	chr3:q21.3	0.160	<i>CHRNA3</i>	chr15:q25.1	0.124
<i>EEFSEC</i>	chr3:q21.3	0.021	<i>CHRNA5</i>	chr15:q25.1	0.104
<i>FAM13A</i>	chr4:q22.1	0.164	<i>IREB2</i>	chr15:q25.1	0.057
<i>PPA2</i>	chr4:q24	0.179	<i>CLN3</i>	chr16:p11.2	0.333
<i>TET2</i>	chr4:q24	0.056	<i>NUPR1</i>	chr16:p11.2	0.157
<i>HHIP</i>	chr4:q31.21	0.184	<i>CCDC101</i>	chr16:p11.2	0.115
<i>HTR4</i>	chr5:q32	0.026	<i>IL27</i>	chr16:p11.2	0.111
<i>ADAM19</i>	chr5:q33.3	0.129	<i>APOBR</i>	chr16:p11.2	0.078
<i>CFB</i>	chr6:p21.32--p21.33	0.199	<i>SULT1A2</i>	chr16:p11.2	0.071
<i>TNXB</i>	chr6:p21.32--p21.33	0.187	<i>SULT1A1</i>	chr16:p11.2	0.070
<i>EGFL8</i>	chr6:p21.32--p21.33	0.111	<i>BCAR1</i>	chr16:q23.1	0.135
<i>C2</i>	chr6:p21.32--p21.33	0.083	<i>GABARAPL2</i>	chr16:q23.1	0.107
<i>SLC44A4</i>	chr6:p21.32--p21.33	0.052	<i>CFDP1</i>	chr16:q23.1	0.076
<i>EHMT2</i>	chr6:p21.32--p21.33	0.051	<i>CHST6</i>	chr16:q23.1	0.057
<i>RNF5</i>	chr6:p21.32--p21.33	0.022	<i>TMEM170A</i>	chr16:q23.1	0.053
<i>CYP21A2</i>	chr6:p21.32--p21.33	0.011	<i>CTRB2</i>	chr16:q23.1	0.047
<i>CYP21A1P</i>	chr6:p21.32--p21.33	0.009	<i>CCDC165</i>	chr18:p11.22	0.031
<i>LSM2</i>	chr6:p21.32--p21.33	0.008	<i>EGLN2</i>	chr19:q13.2	0.135
<i>RDBP</i>	chr6:p21.32--p21.33	0.006	<i>NUMBL</i>	chr19:q13.2	0.080
<i>DSP</i>	chr6:p24.3	0.259	<i>CYP2A6</i>	chr19:q13.2	0.067
<i>SNRNP48</i>	chr6:p24.3	0.007	<i>SNRPA</i>	chr19:q13.2	0.055
<i>GPR126</i>	chr6:q24.1--q24.2	0.053	<i>ADCK4</i>	chr19:q13.2	0.025
<i>SFTPD</i>	chr10:q22.3	0.321	<i>MIA</i>	chr19:q13.2	0.018
<i>C10orf57</i>	chr10:q22.3	0.073	<i>ITPKC</i>	chr19:q13.2	0.011
<i>RIN3</i>	chr14:q32.12	0.102	<i>CYP2G1P</i>	chr19:q13.2	0.002
<i>THSD4</i>	chr15:q23	0.164	<i>C19orf54</i>	chr19:q13.2	0.002

*The 2q36.2 locus (rs16825267; closest gene *PIDI*) is not present in PrixFixe's co-function networks, and is consequently not represented in the table.

**Genes with PrixFixe prioritization score of "0" are not shown. Thus, the 6q21 locus (rs2806356; closest genes *ARMC2*) is not represented in the table.

Supplemental Table S20: Results of fine-mapping analysis (see text). EUR = European ancestry only, All = all ethnicities with GWAS data, AA= African Americans.

rsID for index ICGC variant	Chr:Position for index ICGC variant	Number of variants in 95% credible set in +/- 250 kb region around index		Posterior probability of top-ranked variant in +/- 250 kb region around index		LD (r^2/D') with index variant for top AA variant in region
		EUR	All	EUR	All	
rs13141641	4:145506456	40	29	0.46	0.66	0.079/0.71
rs17486278	15:78867482	12	18	0.47	0.37	
rs7733088	5:147856333	20	19	0.2	0.36	
rs9399401	6:142668901	72	71	0.059	0.057	
rs1441358	15:71612514	64	37	0.28	0.44	0.34/0.93
rs6837671	4:89873092	14	9	0.34	0.85	
rs11727735	4:106631870	282	267	0.041	0.033	
rs754388	14:93115410	20	16	0.21	0.24	
rs113897301	5:156929077	2	1	0.91	0.99	
rs2047409	4:106137033	35	29	0.12	0.17	
rs2955083	3:127961178	196	192	0.032	0.043	
rs7186831	16:75473155	671	542	0.11	0.22	0.22/0.72
rs10429950	1:218624533	161	121	0.054	0.13	
rs17707300	16:28593347	113	97	0.04	0.11	
rs2806356	6:109266255	568	382	0.25	0.28	0.0073/1
rs16825267	2:229569919	29	29	0.1	0.11	
rs2076295	6:7563232	9	8	0.63	0.52	
rs647097	18:8808464	571	172	0.21	0.29	
rs1529672	3:25520582	10	10	0.7	0.61	
rs721917	10:81706324	1365	1193	0.16	0.15	0.42/0.93
rs12459249	19:41339896	142	22	0.23	0.52	

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COPDGene Investigators – Core Units

Administrative Core: James Crapo, MD (PI), Edwin Silverman, MD, PhD (PI), Barry Make, MD, Elizabeth Regan, MD, PhD

Genetic Analysis Core: Terri Beaty, PhD, Nan Laird, PhD, Christoph Lange, PhD, Michael Cho, MD, Stephanie Santorico, PhD, John Hokanson, MPH, PhD, Dawn DeMeo, MD, MPH, Nadia Hansel, MD, MPH, Craig Hersh, MD, MPH, Peter Castaldi, MD, MSc, Merry-Lynn McDonald, PhD, Emily Wan, MD, Megan Hardin, MD, Jacqueline Hetmanski, MS, Margaret Parker, PhD, Marilyn Foreman, MD, Brian Hobbs, MD, MMSc, Robert Busch, MD, MMSc, Adel El-Boueiz, MD, MMSc, Dandi Qiao, PhD, Elizabeth Regan, MD, Eitan Halper-Stromberg, Ferdouse Begum, Sungho Won, Sharon Lutz, PhD

Imaging Core: David A Lynch, MB, Harvey O Coxson, PhD, MeiLan K Han, MD, MS, MD, Eric A Hoffman, PhD, Stephen Humphries MS, Francine L Jacobson, MD, Philip F Judy, PhD, Ella A Kazerooni, MD, John D Newell, Jr., MD, Elizabeth Regan, MD, James C Ross, PhD, Raul San Jose Estepar, PhD, Berend C Stoel, PhD, Juerg Tschirren, PhD, Eva van Rikxoort, PhD, Bram van Ginneken, PhD, George Washko, MD, Carla G Wilson, MS, Mustafa Al Qaisi, MD, Teresa Gray, Alex Kluiber, Tanya Mann, Jered Sieren, Douglas Stinson, Joyce Schroeder, MD, Edwin Van Beek, MD, PhD

PFT QA Core, Salt Lake City, UT: Robert Jensen, PhD

Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO: Douglas Everett, PhD, Anna Faino, MS, Matt Strand, PhD, Carla Wilson, MS

Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO: John E. Hokanson, MPH, PhD, Gregory Kinney, MPH, PhD, Sharon Lutz, PhD, Kendra Young PhD, Katherine Pratte, MSPH, Lindsey Duca, MS

COPDGene Investigators – Clinical Centers

Ann Arbor VA: Jeffrey L. Curtis, MD, Carlos H. Martinez, MD, MPH, Perry G. Pernicano, MD

Baylor College of Medicine, Houston, TX: Nicola Hanaia, MD, MS, Philip Alapat, MD, Venkata Bandi, MD, Mustafa Atik, MD, Aladin Boriek, PhD, Kalpatha Guntupalli, MD, Elizabeth Guy, MD, Amit Parulekar, MD, Arun Nachiappan, MD

Brigham and Women's Hospital, Boston, MA: Dawn DeMeo, MD, MPH, Craig Hersh, MD, MPH, George Washko, MD, Francine Jacobson, MD, MPH

Columbia University, New York, NY: R. Graham Barr, MD, DrPH, Byron Thomashow, MD, John Austin, MD, Belinda D'Souza, MD, Gregory D.N. Pearson, MD, Anna Rozenshtein, MD, MPH, FACR

Duke University Medical Center, Durham, NC: Neil MacIntyre, Jr., MD, Lacey Washington, MD, H. Page McAdams, MD

Health Partners Research Foundation, Minneapolis, MN: Charlene McEvoy, MD, MPH, Joseph Tashjian, MD

Johns Hopkins University, Baltimore, MD: Robert Wise, MD, Nadia Hansel, MD, MPH, Robert Brown, MD, Karen Horton, MD, Nirupama Putcha, MD, MHS,

Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA: Richard Casaburi, PhD, MD, Alessandra Adami, PhD, Janos Porszasz, MD, PhD, Hans Fischer, MD, PhD, Matthew Budoff, MD, Harry Rossiter, PhD

Michael E. DeBakey VAMC, Houston, TX: Amir Sharafkhaneh, MD, PhD, Charlie Lan, DO

Minneapolis VA: Christine Wendt, MD, Brian Bell, MD

Morehouse School of Medicine, Atlanta, GA: Marilyn Foreman, MD, MS, Gloria Westney, MD, MS, Eugene Berkowitz, MD, PhD

National Jewish Health, Denver, CO: Russell Bowler, MD, PhD, David Lynch, MD

Reliant Medical Group, Worcester, MA: Richard Rosiello, MD, David Pace, MD

Temple University, Philadelphia, PA: Gerard Criner, MD, David Ciccolella, MD, Francis Cordova, MD, Chandra Dass, MD, Gilbert D'Alonzo, DO, Parag Desai, MD, Michael Jacobs, PharmD, Steven Kelsen, MD, PhD, Victor Kim, MD, A. James Mamary, MD, Nathaniel Marchetti, DO, Aditi Satti, MD, Kartik Shenoy, MD, Robert M. Steiner, MD, Alex Swift, MD, Irene Swift, MD, Maria Elena Vega-Sanchez, MD

University of Alabama, Birmingham, AL: Mark Dransfield, MD, William Bailey, MD, J. Michael Wells, MD, Surya Bhatt, MD, Hrudaya Nath, MD

University of California, San Diego, CA: Joe Ramsdell, MD, Paul Friedman, MD, Xavier Soler, MD, PhD, Andrew Yen, MD

University of Iowa, Iowa City, IA: Alejandro Comellas, MD, John Newell, Jr., MD, Brad Thompson, MD

University of Michigan, Ann Arbor, MI: MeiLan Han, MD, Ella Kazerooni, MD, Carlos Martinez, MD

University of Minnesota, Minneapolis, MN: Joanne Billings, MD, Tadashi Allen, MD

University of Pittsburgh, Pittsburgh, PA: Frank Scieurba, MD, Divay Chandra, MD, MSc, Joel Weissfeld, MD, MPH, Carl Fuhrman, MD, Jessica Bon, MD

University of Texas Health Science Center at San Antonio, San Antonio, TX: Antonio Anzueto, MD, Sandra Adams, MD, Diego Maselli-Caceres, MD, Mario E. Ruiz, MD

ECLIPSE Investigators — *Bulgaria:* Y. Ivanov, Pleven; K. Kostov, Sofia. *Canada:* J. Bourbeau, Montreal; M. Fitzgerald, Vancouver, BC; P. Hernandez, Halifax, NS; K. Killian, Hamilton, ON; R. Levy, Vancouver, BC; F. Maltais, Montreal; D. O'Donnell, Kingston, ON. *Czech Republic:* J. Krepelka, Prague. *Denmark:* J. Vestbo, Hvidovre. *The Netherlands:* E. Wouters, Horn-Maastricht. *New Zealand:* D. Quinn, Wellington. *Norway:* P. Bakke, Bergen. *Slovenia:* M. Kosnik, Golnik. *Spain:* A. Agusti, J. Sauleda, P. de Mallorca. *Ukraine:* Y. Feschenko, V. Gavrisyuk, L. Yashina, Kiev; N. Monogarova, Donetsk. *United Kingdom:* P. Calverley, Liverpool; D. Lomas, Cambridge; W. MacNee, Edinburgh; D. Singh, Manchester; J. Wedzicha, London. *United States:* A. Anzueto, San Antonio, TX; S. Braman, Providence, RI; R. Casaburi, Torrance CA; B. Celli, Boston; G. Giessel, Richmond, VA; M. Gotfried, Phoenix, AZ; G. Greenwald, Rancho Mirage, CA; N. Hanania, Houston; D. Mahler, Lebanon, NH; B. Make, Denver; S. Rennard, Omaha, NE; C. Rochester, New Haven, CT; P. Scanlon, Rochester, MN; D. Schuller, Omaha, NE; F. Scieurba, Pittsburgh; A. Sharafkhaneh, Houston; T. Siler, St. Charles, MO; E. Silverman, Boston; A. Wanner, Miami; R. Wise, Baltimore; R. ZuWallack, Hartford, CT.

ECLIPSE Steering Committee: H. Coxson (Canada), C. Crim (GlaxoSmithKline, USA), L. Edwards (GlaxoSmithKline, USA), D. Lomas (UK), W. MacNee (UK), E. Silverman (USA), R. Tal Singer (Co-chair, GlaxoSmithKline, USA), J. Vestbo (Co-chair, Denmark), J. Yates (GlaxoSmithKline, USA).

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