Supplementary Materials

Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell type and phenotype associations.

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Supplementary Note

Supplementary Methods

Cohort descriptions and cohort-specific methods

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

Cardiovascular Health Study (CHS): The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four centers⁵ (NCT00005133 and NCT00149435). IRB approval was obtained at participating centers and written informed consent was obtained for all participants. 5,201 predominantly European ancestry persons were recruited in 1989-1990 from random samples of Medicare eligibility lists. An additional predominantly African-American cohort of 687 persons was subsequently enrolled in 1992-1993 for a total sample of 5,888. European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA available using the Illumina 370CNV BeadChip system (for European ancestry participants, in 2007) or the Illumina HumanOmni1-Quad_v1 BeadChip system (for African-American participants, in 2010). Additional genotypes were provided from the ITMAT-Broad-CARe (IBC) Illumina iSELECT chip (for European ancestry participants). Imputation was performed using 1000 Genomes³ Phase 1 v3 haplotypes and minimac⁴ (for European ancestry participants, 2012-11-16) or IMPUTE version 2.2.2 (for African-American participants). Logistic regression was performed in R, adjusting for age, sex, pack-years, current and ever smoking, CHS clinic (4 sites) and PCs 1-5.

COPDGene: Eligible subjects in COPDGene Study (NCT00608764, www.copdgene.org) were of non-Hispanic white (NHW) or African-American (AA) ancestry, aged 45-80 years old, with at least 10 packyears of smoking and no diagnosed lung disease other than COPD or asthma^{6,7 21,22}. IRB approval was obtained at all study centers, and all study participants provided written informed consent. Illumina (San Diego, CA) performed genotyping on the HumanOmniExpress array. Genotyping at the Z and S alleles was performed in all subjects. Subjects known or found to have severe alpha-1 antitrypsin deficiency were excluded. We performed imputation using MaCH^{8,9 10,11} and minimac^{4 4} (version 2012-10-09) and 1000 Genomes³ Phase I v3 European (EUR) and cosmopolitan reference panels, for whites and African-Americans, respectively. We removed variants with an r² value of \leq 0.3. We performed logistic regression on cases and controls defined based on pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of genetic ancestry, separately in non-Hispanic whites and African-Americans, using PLINK1.9¹⁰.

Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE; SCO104960, NCT00292552, www.eclipse-copd.com): Details of the ECLIPSE study and genome-wide association

analysis have been described previously¹². The ECLIPSE study was approved by the relevant ethics and review boards at the participating clinical centers. All participants provided written informed consent. Cases and controls were aged 40-75 with at least a 10 pack-year smoking history without other respiratory diseases. Genotyping was performed using the Illumina HumanHap 550 V3 (Illumina, San Diego, CA). Subjects and markers with a call rate of < 95% were excluded. Imputation was performed using MaCH^{8,9} and minimac⁴ (version 2012-10-09) and the 1000 Genomes³ Phase I v3 European (EUR) reference panel. Logistic regression was performed on cases and controls defined by pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of genetic ancestry using PLINK1.9¹⁰.

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

Genotyping was carried out using the Illumina Human1M-Duo BeadChip. Standard genotyping quality controls were performed independently in the Laval, UBC and Groningen cohorts. Genotypes were then imputed with the Michigan Imputation Server¹⁴ using the Haplotype Reference Consortium version 1 (HRC.r1-1) data as reference set. Variants with an r² value of ≤ 0.3 were removed from further analysis. Single-marker association tests were performed with PLINK v1.90^{10,11} adjusting for age, sex, smoking status, pack-years, ever smoking status, clinical center and genetic ancestry PC1 to PC10.

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

KARE: Details on the Korean Association Resource project (KARE) have been previously published^{17,18}. KARE was initiated in 2007 to undertake genome-wide analyses among 10,038 participants in the ruralbased Ansung and city-based Ansan South Korean cohorts. The study was approved at appropriate IRBs from participating institutions, and participants provided informed consent. KARE3 data were obtained from the third phenotype collection in 2008; lung function was collecting using the Vmax-2130 (Sensor Medics, Yorba Linda, CA, USA). Genotyping was performed using the Affymetrix Genome-Wide Human array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). We performed genotype imputation using IMPUTE2 and the 1000 Genomes³ Phase 3 cosmopolitan panel. Markers were converted to genotype from dosage with call rate \geq 95%, minor allele frequency \geq 1%, p for HWE \geq 1.0x10⁻⁵, imputation quality score \geq 0.9. Logistic regression, adjusting for age, sex, pack-years, principal components, current and ever smoking, was performed using PLINK¹⁹.

LifeLines: The LifeLines Cohort Study is a population-based cohort study established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy aging^{20–22}. Between 2006 and 2013, inhabitants of the northern part of The Netherlands and their families were invited to participate, thereby contributing to a three-generation design. Participants visited one of the LifeLines research sites for pre-bronchodilator spirometry following ATS guidelines. All participants signed an informed consent form before they received an invitation for the physical examination. The LifeLines Cohort Study is conducted according to the principles of the Declaration of Helsinki and in accordance with research code University Medical Center Groningen (UMCG), The Netherlands. The LifeLines study is approved by the medical ethical committee of the UMCG. Blood samples for a subset of individuals were genotyped using the Illumina CytoSNP-12v2 array. Independent Caucasian-ancestry samples (n = 13,436) have been imputed using the 1000 Genomes³ phase1 v3 reference panels. Genotypes were pre-phased using SHAPEIT2²³ and aligned to the reference panels using Genotype Harmonizer (www.molgenis.org/systemsgenetics) in order to resolve strand issues. The samples were imputed using minimac⁴ (version 2012-10-09), yielding 28,681,763 SNPs. Associations between genomic dosages with moderate/severe COPD were assessed with logistic regression models adjusted for age, smoking status (never/ever), current smoking (no/yes), pack years smoked and sex. All analysis were performed in software package PLINK version 1.07^{19,24}. Lovelace: The Lovelace Smokers Cohort (LSC) has been actively enrolling smokers from the Albuquerque, NM metropolitan area since 2001²⁵. All participants provided written informed consent, and the study was approved by the relevant IRB. Enrollment was restricted to current and former smokers age 40 to 74 years old with a minimum of 10 pack-years of smoking and no personal history of lung cancer. A detailed questionnaire written in English was used to collect information on demographics; medical, cigarette smoking, and exposure history; socioeconomic status; diet; and quality of life. Pulmonary function testing was performed at each visit. All participants signed a consent form, and the Western Institutional Review Board approved this project. The GWAS discovery set was comprised of 1200 Caucasian (self-reported) smokers. The HumanOmni2.5-4v1-H BeadChip (Illumina, San Diego, CA) was used to genotype 2,450,000 SNPs in 1200 Caucasian smokers from the LSC. After quality assessment, 1163 subjects with 1,599,980 SNPs remained in the genetic association analysis. Logistic regression was performed using PLINK on white subjects, adjusting for age, sex, pack-years, current and ever smoking, and ancestry.

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

provided informed consent and the protocols of MESA were approved by the IRBs of collaborating institutions and the National Heart, Lung and Blood Institute.

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

National Emphysema Treatment Trial (NETT; NCT00000606,

www.nhlbi.nih.gov/health/prof/lung/nett/) and Normative Aging Study (NAS): ³¹. NETT was a multicenter clinical trial to evaluate lung volume reduction surgery. All participants provided written informed consent, and the study was approved by the IRB at all participating institutions. Enrolled subjects had severe airflow obstruction by post-bronchodilator spirometry (FEV₁ < 45% predicted) and evidence of emphysema on computed tomography (CT) chest imaging; exclusion criteria included, but not limited to, history of recurrent infections with significant sputum production or bronchiectasis. A subset of 382 self-reported white subjects without severe alpha-1 antitrypsin deficiency were enrolled in the NETT Genetics Ancillary Study. The Normative Aging Study is a longitudinal study of healthy men established in 1963 aged 21 to 80 years from the greater Boston area, free of known chronic medical conditions. The study was conducted by the Veterans Administration (VA)³², and the local Institutional Review Board approved the study. Controls were of self-reported white ancestry and at least 10 packyears of cigarette smoking with no evidence of airflow limitaiton on spirometry on their most recent visit. Genotyping for NETT-NAS was performed using the Illumina Quad 610 array (Illumina, San Diego, CA)^{33,34}. Imputation was performed using MaCH^{8,9} and minimac⁴ (version 2012-10-09) and the 1000 Genomes Phase I v3 European (EUR) reference panel. Logistic regression was performed on cases and controls based on pre-bronchodilator spirometry, adjusting for age, sex, pack-years, current smoking, and principal components of ancestry using PLINK1.9^{10,11}.

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

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

determined using the ProbABEL³⁸ program according to an additive model, adjusting for age, sex, packyears, smoking status, and ancestry.

Subpopulations and intermediate outcome measures in COPD study (SPIROMICS; NCT01969344): Participants of the NHLBI SPIROMICS study were 40-80 years of age at baseline with a smoking history ≥20 pack-years. Recruitment included non-smokers, smokers without COPD, mild-moderate COPD, and severe COPD³⁹. All participants provided written informed consent and the Institutional Review Boards/Ethics Committees of all the cooperating institutions approved the study protocols. Genomewide genotyping was performed using the Illumina OmniExpress HumanExome BeadChip using standard techniques in the first 571 subjects with COPD and 175 smoking controls. Imputation was performed against 1000 Genomes reference panels using Impute-v2.30 using a quality cutoff of 0.9, and association analysis performed using PLINK adjusting for age, sex, pack-years, smoking status, and ancestry.

Studies with Custom Genotyping:

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

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

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

Genotyping in BECOPD, ICGN, and TCGS:

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

Ethical statements for ICGC studies

ICGC studies obtained IRB or other relevant ethical body approval as follows:

ARIC: IRB approval obtained from: Wake Forest Baptist Medical Center, Winston-Salem, NC; University of Mississippi Medical Center, Jackson, MS; University of Minnesota, Minneapolis, MN; Johns Hopkins University, Baltimore, MD

CHS: IRB approval obtained from: Sacramento County, Sacramento, CA - University of California, Davis; Washington County, Hagerstown, MD - Johns Hopkins University; Forsyth County, Winston-Salem, NC -Wake Forest University School of Medicine; Pittsburgh, PA - University of Pittsburgh

COPDGene: IRB approval obtained from: Ann Arbor VA; Baylor College of Medicine, Houston, TX; Brigham and Women's Hospital, Boston, MA; Columbia University, New York, NY; Duke University

Medical Center, Durham, NC; Fallon Clinic, Worcester, MA; Health Partners Research Foundation, Minneapolis, MN; Johns Hopkins University, Baltimore, MD; Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA; Michael E. DeBakey VAMC, Houston, TX; Minneapolis VA; Morehouse School of Medicine, Atlanta, GA; National Jewish Health, Denver; Temple University, Philadelphia, PA; University of Alabama, Birmingham, AL; University of California, San Diego, CA; University of Iowa, Iowa City; University of Michigan, Ann Arbor, MI; University of Minnesota, Minneapolis, MN; University of Pittsburgh, Pittsburgh, PA; University of Texas Health Science Center at San Antonio, San Antonio, TX

ECLIPSE: 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.

eQTL: 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.

FHS: IRB approval obtained from: Winston-Salem, NC--University of North Carolina; Minneapolis MN— University of Minnesota; Framingham, MA—Boston University; Salt Lake City, UT—University of Utah

KARE: The study was approved at appropriate IRBs from participating institutions and participants provided informed consent.

LifeLines: 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.

Lovelace: All participants signed a consent form, and the Western Institutional Review Board (Olympia, WA) approved this project.

MESA: IRB approval obtained from: National Heart, Lung and Blood Institute and Forsyth County, North Carolina: Wake Forest University School of Medicine; St. Paul, Minnesota: University of Minnesota; Chicago, Illinois: Northwestern University, University of Illinois, Loyola University; New York, New York: Columbia University, St. Francis Hospital; Baltimore, Maryland: Johns Hopkins University; Los Angeles, California: University of California, Los Angeles.

NETT/NAS: IRB approval obtained from: Baylor College of Medicine, Houston, TX; Brigham and Women's Hospital, Boston, MA; Cedars-Sinai Medical Center, Los Angeles, CA; Cleveland Clinic Foundation, Cleveland, OH; Columbia University, New York, NY; Duke University Medical Center, Durham, NC; Mayo Foundation, Rochester, MN; National Jewish Medical and Research Center, Denver, CO; Ohio State University, Columbus, OH; Saint Louis University, Saint Louis, MO; Temple University, Philadelphia, PA; University of California, San Diego, San Diego, CA; University of Maryland at Baltimore, Baltimore, MD; University of Michigan, Ann Arbor, MI; University of Pennsylvania, Philadelphia, PA; University of

Pittsburgh, Pittsburgh, PA; University of Washington, Seattle, WA; the Human Studies Subcommittee of the Department of Veterans Affairs Medical Center

GenKOLS: 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.

The Rotterdam Study: 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.

SPIROMICS: IRB approval obtained from: Columbia University; the University of California at Los Angeles; the University of California at San Francisco; the University of Michigan; the University of Utah; Wake Forest University

BEOCOPD: IRB approval obtained from: The Human Research Committees of Partners Health Care (Brigham and Women's Hospital and Massachusetts General Hospital) and the Brockton/West Roxbury VA Hospital

ICGN: The study was IRB approved at all relevant institutions and participants provided written informed consent.

TCGS: IRB approval obtained from: Institute of Tuberculosis and Lung Diseases in Warsaw; Brigham and Women's Hospital in Boston

UK Biobank

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

The UK Biobank is a resource with approximately 500,000 persons age 40-69 for whom extensive baseline questionnaire data, physiologic measures, and biologic specimens (urine and blood samples) have been obtained⁴⁷. The UK Biobank participants provided informed consent. The UK Biobank's Ethics and Governance Framework guides research ethics principles and polices, the adherence to which is overseen by the independent Ethics and Governance Council. Details of the derivation and quality control of spirometry, smoking, and case-control status were performed as described⁴⁸. Briefly, of 502,682 individuals in UK Biobank, 445,754 individuals had at least two measures of FEV1 and FVC and spirometry metrics, age, sex, height, and smoking. We used blow quality metrics from the Vitalograph spirometer and compared pre-defined measurements with the blow curve time series. We considered blows as 'acceptable' if their blow quality metrics were blank, ACCEPT, BELOW6SEC ACCEPT, or BELOW6SEC. We assessed back-extrapolated volumes derived from blow curve time series measurements as previously described⁴⁹ and excluded blows which their back-extrapolated volumes were greater than the larger of either 5% of FVC or 150 mL, leaving 776,927 blows from 387,277 participants. To confirm pre-defined FEV₁ and FVC, we independently derived FEV₁ and FVC from blow curve time series measurements. We further excluded blows which differences between pre-defined and newly derived FEV₁ and FVC were greater than 5%. Following above exclusion, 776,318 blows from 387,052 participants remained in the analysis. Additionally, we assessed if individuals' measures of FEV₁ and FVC were reproducible, allowing differences between the highest measure and others to be up to 250 mL. We defined COPD using modified GOLD criteria (as stated previously) based on highest values of reproducible measures of FEV₁ and FVC available in 324,299 individuals.

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

Sample-based genotyping quality control

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

SNP-based Genotyping quality control

Besides the QC steps described in Bycroft et al.⁵⁰, we filtered out: 1) variants with minor allele frequency lower than 1%; 2) variants with imputation quality lower than 0.5; 3) variants not included into the Haplotype Reference Consortium (HRC) imputation panel, as recommended by UK Biobank at the time of analysis. This left us with 7,810,596 variants.

Identification of individuals of European ancestry

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

Selecting individuals for genome-wide association analysis

We intersected the individuals passing spirometry QC and sample-based genotyping QC and selected individuals with European ancestry as described above. This left us 321,057 individuals in total. To identify individuals who were outliers in phenotype distribution, we plotted the distribution for each measure (FEV₁, FVC, and FEV₁/FVC) adjusting for sex, age, age², height, and smoking status (ever/never). We re-calculated phenotypic adjustment after excluding 10 European samples who were obvious outliers. As stated previously, we defined COPD using modified GOLD criteria for moderate to very severe airflow limitation⁵¹: FEV₁ less than 80% of predicted value and FEV₁/FVC less than 0.7. We excluded 59,358 individuals, who did not match the above criteria. To select completely unrelated individuals for genome-wide association analysis, we removed at least one individual from each related pair, giving preference to cases. Briefly, we created a graph from related pairs using genetic kinship information provided by UK Biobank. For each unconnected component, we removed control nodes (healthy individual), starting with the one with the highest degree. If all nodes were cases, we removed the one with the highest degree. We excluded additional 26,855 individuals based on kinship and further 34,035 individuals who had missing information on sex, ever smoking status, pack-years of

smoking, and age. We also excluded subjects who had withdrawn consent (updated as of May 2018). After excluding individuals, we were left with 200,792 individuals for genome-wide association analysis of COPD.

Sensitivity analyses for smoking, sex, and COPD phenotypic misclassification

To determine whether our results were driven by, or differed by, smoking status, we examined COPDassociated variants in relationship to ever-smoking status in UK Biobank. In addition, we separately examined these variants in ever- and never-smokers in UK Biobank. To test for sex-difference in genetic effects among our top variants, we performed a sex-stratified GWAS of COPD in UK Biobank and tested for differences between effects among males and females. For the latter we utilized the "difference test^{52,53}". In addition, we also included a variant-by-sex interaction term and tested this term. We defined significant effect differences by Bonferroni correction and further, we attempted to replicate all nominally significant variants (P for the difference test < 0.05) from our top SNPs in a meta-analysis of sex-stratified COPD association analyses in COPDGene NHW, COPDGene AA, ECLIPSE, and GenKOLS. We also investigated variants not our top variants but reaching genome-wide significance (P<5x10⁻⁸) only in one sex. We attempted to replicate these variants in the meta-analysis of COPD case-control cohorts as mentioned above. We used 5% Bonferroni corrected P value to determine significance in replication.

To simulate power for the difference test, we modified the power simulations in Winkler et al. ⁵² and made them applicable to a case-control dataset. We approximated the phenotypic variance attributable to the risk locus as in Peyrot et al.⁵⁴:

$$R_i^2 = 2pq(RR-1)^2/m^2$$

where m^2 is the mean liability of case subjects and depends on the prevalence of COPD, p is the risk allele frequency of variant i, q = 1 - p and RR is the relative risk, respectively. R_i can be derived from R_i^2 and the direction of the effect i.

The variance of a variant $i (se_i^2)$ is defined as

$$se_i^2 = \left[\left(1 - R_i^2 \right) \sigma_Y^2 \right] / (n_i \sigma_G^2)$$

Where n_i is sample size in stratum i.

Hence, we can derive the power of difference test as⁵²

$$\Phi\left(-z_{1-\frac{\alpha}{2}} - \sqrt{n_{1}}\frac{R_{1} - R_{2}}{\sqrt{1 - R_{1}^{2} + \frac{1}{f}(1 - R_{2}^{2})}}\right) + \Phi\left(-z_{1-\frac{\alpha}{2}} + \sqrt{n_{1}}\frac{R_{1} - R_{2}}{\sqrt{1 - R_{1}^{2} + \frac{1}{f}(1 - R_{2}^{2})}}\right)$$

As Φ denotes the cumulative standard normal distribution, z_q is the q-th quantile of Φ , α is the alpha level of the test, and $f = n_2/n_1$.

We performed an array of analyses to ascertain if a pre-bronchodilator spirometry definition of COPD (as opposed post-bronchodilator spirometry) and the inclusion of subjects with self-reported asthma subsequently impacted both effect size estimates and P values of genetic association. First, in the COPDGene study, we examined the difference in COPD diagnosis using pre- and post-bronchodilator spirometry. Then, we stratified individuals by self-reported asthma and compared the percent of

individuals in each stratum that were misclassified as having COPD based on a pre-bronchodilator spirometry definition of COPD. We also re-tested the association of COPD by excluding individuals in UK Biobank with self-reported asthma and the same control individuals as the primary analysis. Finally, in a subset of COPD case-control studies including COPDGene NHW and AA, ECLIPSE, and Norway/GenKOLS, we performed logistic regression (controlling for pack years, current smoking, sex, age, and PCs of genetic ancestry) and a meta-analysis to assess the relative COPD association effect sizes and P values of our top variants when using a pre- vs post-bronchodilator definition of COPD. For the comparison of effect sizes, we limited the variants being compared to those that were at least nominally significant (P < 0.05) in the meta-analysis of the COPD case-control studies.

Identification of cell types

Linkage equilibrium score regression (LDSC) requires specifically expressed gene sets to perform cell type-specific analysis⁵⁵. For two human datasets^{56,57}, we computed t-statistics for each cell type on gene expression data in Transcripts Per Kilobase Million (TPM) as described previously⁵⁵. We constructed gene sets for each cell type using genes in the top 10% of sorted t-statistics⁵⁵, and a control gene set (i.e., all genes available in a dataset). We annotated regions +/- 100-kb from each gene and computed LD scores as previously described⁵⁵. For two mouse datasets⁵⁸, we used pre-computed Wilcoxon or Welch P-values for each cell to select genes in the top 10%. We mapped gene identifiers from mouse to human using biomaRt⁵⁹.

We tested for enrichment of lung cell type in sets of genome-wide significant variants using SNPsea^{60,61}. Briefly, SNPsea performed three steps: identification of specifically expressed genes, assignment of gene in a locus, and significance testing. We first computed the Euclidean norm of gene expression values (TPM) in all cell types and divided expression values in each cell type using this value. The score was then converted to nonparametric percentiles. Second, we identified the most specifically expressed gene in a given locus by ranking the score. Finally, we then tested for significance using permutation using matched SNP sets.

Fine-mapping

We used biomaRt⁵⁹ to annotate variants in each credible set based on the Ensembl Variant Effect Predictor . We defined deleterious variants as those which resulted in non-synonymous, stop, or splice variants (terms: transcript_ablation, splice_acceptor_variant, splice_donor_variant, stop_gained, frameshift_variant, stop_lost, start_lost, transcript_amplification, inframe_insertion, inframe_deletion, missense_variant, and protein_altering_variant). Variants were annotated using Haploreg v4.1⁶² and SNPnexus⁶³.

Target gene identification

Rare coding variants

We performed single-variant analyses using Firth and efficient resampling methods (SKAT R package⁶⁴) for the COPDGene data (case-control) and generalized linear mixed models (GMMAT) for the BEOCOPD-ICGN data (using lung function) as previously published⁶⁵. Gene-based analyses were conducted using burden, SKAT, and SKAT-O tests with asymptotic and efficient resampling methods (SKAT package) combined with Fisher's method for the COPDGene data, and using SKAT-O tests (MONSTER) for the BEOCOPD-ICGN data. Two variant-filtering criteria were considered: deleterious variants (predicted by FATHMM) with minor allele frequency (MAF) < 0.01, and functional variants (moderate effect predicted by SNPEff) with MAF < 0.05. We also applied a gene-based segregation test (GESE) to the ultra-rare

(MAF < 0.1%) and loss-of-function variants in the BEOCOPD-ICGN data on the severe COPD affection status. In gene-based analyses, we combined results from all methods above and retained only most significant P values for each gene.

DEPICT

DEPICT utilizes pairwise gene correlation data from ~77,000 microarrays to create data-driven "reconstituted" gene sets from a backbone of curated data from GO, KEGG, REACTOME, protein-protein interaction data, and murine phenotypic gene sets. These "reconstituted" gene sets are used to prioritize genes at each GWAS loci based on the similarity each gene's "reconstituted" gene set memberships of genes at other GWAS loci⁶⁶.

Methylation quantitative trait loci (mQTL)

Of all genome-wide significant loci, we searched for overlapping methylation quantitative trait loci (mQTL) using previously published data⁶⁷. Briefly, lung tissues from 90 severe COPD cases (FEV₁ < 50% predicted) and 36 control subjects undergoing lung transplantation, lung volume reduction surgery, or lung nodule resection⁶⁸. All subjects were self-reported former smokers at least 1 month prior to the surgery. A cis-mQTL analysis was performed using the R/Bioconductor package Matrix eQTL (version 2.1.1)⁶⁹. We tested associations of each CpG site and genetic variants within 500 kb upstream and downstream (from the CpG site) using a linear regression model adjusting for age, sex, smoking packyears, two principal components of genetic ancestry, batch number, and principal components of methylation data as previous described⁶⁷. To determine whether these signals co-localized (rather than being related due to linkage disequilibrium), we performed colocalization analysis between our genomewide significant loci and mQTL using eCAVIAR⁷⁰ (eQTL and GWAS CAusal Variants Identification in Associated Regions). We tested variants that were significant in both datasets, P < 0.0027 in GWAS (equivalent to Z score > 3, as recommended by the author⁷⁰) and P < 3.2 x 10⁻⁶ in mQTL⁶⁷. We estimated the posterior probability of a variant being shared in both GWAS and mQTL, using a cut-off of 0.1 as previous demonstrated⁷⁰.

Drug repositioning using drug-gene expression signatures

We used a gene-based association method that utilizes GWAS summary statistics and gene expression reference databases to produce a gene list for drug-gene expression similarity analysis^{71,72}. In brief, we tested for associations of the genetic component of gene expression and COPD using gene expression data in a lung⁷³. This method gave us a rank gene list of up-regulated and down-regulated genes. We used the Query, an application in clue.io⁷⁴, to calculate connectivity score of our top 100 up-regulated and 100 down-regulated genes and drug-gene expression signatures. The connectivity score, ranging from -1 to 1, reflects the closeness between the expression profiles⁷⁵. A negative connectivity score means that our down-regulated genes are at the top of the reference profile⁷⁵. We included drug-gene expression signatures from 2,837 compounds in nine cell lines in the analysis⁷⁴. To find candidate drugs for repositioning, we used negative connectivity score less than -90% as the threshold⁷⁴, hypothesizing that a drug candidate need to produce an opposing or reverse expression signature induced by the disease.

Determining numbers and features of clusters

To determine phenotypic clustering, we identified the optimal number of clusters using the Calinski index^{76,77}. To identify features that independently predict cluster membership, we fitted a logistic

regression model via penalized maximum likelihood using the glmnet package⁷⁸. We determined optimal regularization parameters using 10-fold cross validation.

Relationship of genome-wide significant variants to smoking

To assess the effect of smoking, we tested association of 82 genetic variants and smoking status (everand never- smokers) in the UK Biobank. Of the 82 identified loci, three were associated with cigarette smoking after Bonferroni correction (P < 0.05/82) including the strongest association at the known 15q25 locus, but also *IER3* ($P = 9.2 \times 10^{-5}$) at 6p21 and *SPPL2C* ($P = 1.4 \times 10^{-4}$) at 17q21. To test if smoking status could have confounded the association of these variants and COPD, we re-performed the analysis of COPD stratifying by smoking status in the UK Biobank. The lead variants at these latter two loci were highly significant for COPD in never-smokers ($P = 6.7 \times 10^{-13}$ and 2.8×10^{-5} at *IER3* and *SPPL2C* loci, respectively). Seventy-eight of 82 genetic loci were nominally significant in never-smokers (P < 0.05) with the exception of four loci including *TESK2*, *RBMS3*, *RIN3*, and *CHRNA3* (**Supplementary Tables 14 and 15**).

Identification of sex-specific genetic effects

Of 82 genetic variants associated with COPD, we did not find significant evidence of difference in effect sizes of COPD among males and females after adjusting for multiple testing (**Supplementary Table 16**). The strongest evidence for different effect size was at *TGFB2* locus (rs3009947, beta_{males}=-0.06 and beta_{females}=-0.12, and P unadjusted =0.003). Twelfth of 82 COPD-associated variants were nominally significant for sex-difference (P<0.05); none of which was replicated in a meta-analysis of a subset of COPD case-control cohorts (**Supplementary Note** and **Supplementary Table 16**). Similarly, using a test for sex interactions, we did not identify any significant variants after correcting for multiple testing (top unadjusted P = 0.003, **Supplementary Table 16**). Power calculations indicate that we were well-powered to detect effect size different of > 0.04 for an allele frequency of ~0.27; for details, see the **Methods and Supplementary Figure 6**.

COPD misclassification sensitivity analyses

In 10,720 persons with both pre-bronchodilator and post-bronchodilator spirometry available in the COPDGene study, we defined ground truth for COPD status using post-bronchodilator spirometry. Using a pre-bronchodilator definition of COPD resulted in 113 out of 4,289 individuals (2.6%) without COPD being incorrectly assigned as a COPD cases and 18 out of 3,694 individuals (0.49%) with COPD being incorrectly assigned as controls (**Supplementary Table 17**). A self-reported doctor diagnosis of asthma had no significant impact on either the overall misclassification of individuals as being controls, COPD cases, or neither (16.6% without asthma and 18.3% with asthma, χ squared p value = 0.17); or specifically on the misclassification of individuals without COPD as having COPD (1.5% without asthma and 1.7% with asthma, χ squared p value = 0.77) when using pre-bronchodilator instead of postbronchodilator spirometry.

When comparing the relative effect size of our top 164 variants for a pre- versus post-bronchodilator definition of COPD in the subset of our COPD case-control cohorts (COPDGene, ECLIPSE, GenKOLS), 49 variants were at least nominally significant for association with COPD in the meta-analysis (**Supplementary Table 18**). For these 49 variants, the odds ratio obtained when using a pre- versus post-bronchodilator definition of COPD was very similar with Pearson correlation coefficient of 0.92 (p value < 1e-10). Generally, the post-bronchodilator COPD definition yielded larger effect sizes; however, the 95% confidence intervals for all estimates crossed the line of identity (**Supplementary Figure 7**).

We performed additional GWAS by excluding 6,717 self-reported asthma from 21,081 COPD cases in the UK Biobank. While the decreased sample size resulted in less significant associations, we observed highly concordant estimates of effect size between the analysis including and excluding asthma (**Supplementary Figure 8**). One outlier was the variant rs2070600 in *AGER*, which demonstrated a higher OR after excluding individuals with asthma. Association statistics for all genome-wide significant loci are shown in **Supplementary Tables 19 and 20**.

To estimate the effect of asthma inclusion in the overlapping loci analysis, we re-ran gwas-pw using statistics from GWAS of COPD including individuals with asthma. The analysis including asthmatic individuals identified 24 shared genome segments between COPD and asthma (posterior probability of shared association > 0.7). All segments identified in the analysis excluding asthmatics were also identified in this analysis, with the exception of the segment in chr12 (near *STAT6*) (posterior probability of 0.81 excluding asthma, 0.29 including asthma). Results of all loci (with and without exclusion of asthma cases) are shown in **Supplementary Table 21**.

In addition to individual loci effect, we re-estimated the genetic correlation between COPD and asthma using asthma-excluded statistics of COPD. The genetic correlation decreased but remained highly significant, from 0.42 (s.e.=0.04, p= 3.1×10^{-26}) to 0.26 (s.e.=0.05, p= 4.2×10^{-8}).

Functional consequences of fine-mapped variants

We explored functional consequence of variants with high posterior probability of association (PPA) from the fine-mapping analysis. We used various non-coding variation scoring systems to suggest variants' functional status. An intronic variant at *NPNT* (rs34712979) appeared to reside in regulatory regions for several cell types, including enhancers for fetal lung (**Supplementary Table 6**), and was predicted to be functional: CADD phred score =15.18 (among 15% most deleterious substitutions), FATHMM non-coding score=0.98 (predicted deleterious if >0.5), DeepSEA functional significance score=0.004 (a range of 0-1; lower scores mean higher likelihood of functional significance of the variant), FunSeq2 non-coding score=0.96 (a range of 0-1; higer scores mean more likely to be functional), ReMM score=0.95 (higher scores indicate more likely to be deleterious variants).

Genetic correlation of COPD and related traits

To gain further insight of genetic contribution of COPD and other traits, we estimated genetic correlation among traits using linkage disequilibrium score regression (LDSC) in LD hub^{79,80} (**Supplementary Table 22**). We again identified correlations between COPD and lung function (FEV₁ and FEV₁/FVC), asthma, height, and additionally identified correlation of COPD and lung cancer (r_g =0.18, P=0.003). However, we were not able to identify significant correlations with common COPD comorbidities, including bone mineral density, major depressive disorder, coronary artery disease, or type 2 diabetes mellitus. We found suggestive (P < 0.05) genetic correlation between COPD and hand grip, angina, weight, schizophrenia, and gastroesophageal reflux disease (**Supplementary Table 22**).

Identification of drug targets

The recent development of richer datasets of drug-induced gene expression signatures⁷⁴ and a statistical framework that utilizes genome-wide associations⁷¹ allow us to utilize genome-wide data for drug repositioning. This approach considers the similarity between disease and drug-induced gene expression signatures in an opposing pattern (i.e., use drug to reverse diseased gene expression signature). We approximated COPD gene expression patterns by calculating transcriptome-wide associations in lung

tissue from genetic predictors⁷². We calculated standardized connectivity scores⁷⁴ from drug-gene expression profiles across 2,837 compounds in nine cell lines including A594 and A555. We identified seven compounds with an opposing connectivity score >= 90%: leu-enkephalin (an opioid receptor agonist), huperizine-a (an acetylcholinesterase inhibitor), periplocymarin (an apoptosis stimulant), PAC-1 (a caspase activator), TER-14687 (an inhibitor of translocation of PKCq in T cells), vincristine (a tubulin inhibitor), and terreic-acid (a Bruton's tyrosine kinase (BTK) inhibitor).

Supplementary Information for Select Candidate Target Genes

* empirical pattern of gene expression in tissues from Human Protein Atlas⁸¹ (broad=expressed in multiple tissues, exclusive=expressed exclusively in lung, none=rarely expressed in lung).

Locus (SNP)	Genes	Expression*	Evidence
1p13.3	DENND2D	Broad	DENN domain containing 2D predominantly expresses in lymph node and appendix ⁸¹ . It is involved in Rab guanyl-nucleotide exchange factor activity ⁸² .
	CEPT1	Broad	Choline/ethanolamine phosphotransferase 1 encodes an enzyme which functions in the synthesis of choline- or ethanolamine- containing phospholipids ⁸³ .
	DRAM2	Broad	DNA damage regulated autophagy modulator 2 encodes the protein that binds microtubule-associated protein 1 light chain 3 and is required for autophagy ⁸⁴ . It is also associated with non-ST elevation myocardial infarction ⁸⁵ and retinal dystrophy ⁸⁶ .
	CHIA	Exclusive	Chitinase, acidic encodes a protein that degrades chitin ⁸³ . Its expression is specific to lung ^{81,87} . Genetic variants in or around this gene were associated with baseline FEV ₁ and rate of FEV ₁ decline ⁸⁸ , asthma ^{89–92} , acid mammalian chitinase activity ^{91,93} , and IgE ⁹⁰ although there were also some null results ⁹⁴ . The protein is involved in T helper-2 (Th2)- mediated diseases and protects pulmonary epithelial cells from growth factor withdrawal- and Fas ligand-induced apoptosis ⁹⁵ . It was induced via a Th2-specific, interleukin-13 (IL-13)-mediated pathway in epithelial cells and macrophages in an aeroallergen asthma model ⁹⁶ , and ADAM17/EGFR- dependent pathway ⁹⁷ .
	OVGP1	Broad	Oviductal glycoprotein 1 encodes an epithelial glycoprotein. It is secreted from non-ciliated oviductal epithelial cells and associates with ovulated oocytes, blastomeres, and spermatozoan acrosomal regions ⁸³ .
	WDR77	Broad	WD repeat domain 77 encodes an androgen receptor coactivator ⁸³ . It may be involved in the early stages of prostate cancer ⁸³ .
	ATP5F1 (ATP5PB)	Broad	ATP synthase peripheral stalk-membrane subunit b encodes a subunit of mitochondrial ATP synthase ⁸³ . Its hypomethylation was involved in drug resistance in chronic myeloid leukemia ⁹⁸ .
	FAM212B (INKA2)	Broad	Inka box actin regulator 2 is broadly expressed in multiple tissues including lung ⁸³ .
	PROK1	None	Prokineticin 1 induces proliferation, migration, and fenestration in capillary endothelial cells derived from endocrine glands ⁸³ . It is induced by hypoxia, and often is complementary to the expression of vascular endothelial

			growth factor (VEGF) ⁸³ . It was involved in angiogenesis in
	KCNCA	Prood	Cystic IIDrosis".
	KCNC4	Broau	encodes a protein that generates atvnical voltage-dependent
			transient current that may be important for neuronal
			excitability ⁸³ It was related to subacute by $noxia in$
			nulmonary arterial smooth muscle cells ¹⁰⁰
3p14.3	ABHD6	Broad	Abbydrolase domain containing 6 is involved in the control of
00-10	, 121, 120	Broad	macrophage activation and inflammation ¹⁰¹ .
	ARF4	Broad	ADP ribosvlation factor 4 encodes a protein that stimulates
			the ADP-ribosyltransferase activity of cholera toxin and plays
			a role in vesicular trafficking and as an activator of
			phospholipase D ⁸³ . It is involved in Golgi stress and
			susceptibility to pathogens ¹⁰² .
	IL17RD	Broad	Interleukin 17 receptor D encodes a membrane protein
			belonging to the interleukin-17 receptor (IL-17R) protein
			family ⁸³ . The gene product affects fibroblast growth factor
			signaling, inhibiting or stimulating growth through
			MAPK/ERK signaling ⁸³ . It also interacts with TNF receptor 2
			(TNFR2) to activate NF-κB ¹⁰³ .
	ARHGEF3	Broad	Rho guanine nucleotide exchange factor 3 encodes a protein
			that activates RHOA and RHOB, which have a role in bone
			cell biology ⁸³ . Its gene product also regulates a SPARC protein
			that participates in the assembly and turnover of the
			extracellular matrix ¹⁰⁴ . It also has a role in iron uptake ¹⁰⁵ .
			Genetic variants in or around this gene were associated with
			bone mineral density ⁸³ .
7p21.1	ITGB8	Broad	Integrin subunit beta 8 is a member of the integrin beta
			chain family and encodes a single-pass type I membrane
			protein that binds to an alpha subunit to form an integrin
			complex ³³ . The complexes mediate cell-cell and cell-
			extracellular matrix interactions and this complex plays a role
			In numan airway epitnelial proliferation ³³ and repair ⁴⁰³ . Its
			expression was increased in COPD ¹¹ ¹¹ . It is involved in
			dendritic cell trafficking, and airway inflammation and
			through an MMAD dependent nathway ¹¹⁰ and TCE P ^{107,111} . It is
			also regulated by SP2 AD 1 and the p29 pathway ¹¹²
	ABCB5	None	ATP hinding cassette subfamily B member 5 belongs to the
	10005	NUTC	ATP-hinding cassette (ABC) transporter superfamily of
			integral membrane proteins ¹¹³
	TMEM196	None	Transmembrane protein 196 is a novel functional tumor
			suppressor and is associated with lung cancer ¹¹⁴ .
11p15.2	BTBD10	Broad	The gene product of BTB domain containing 10 is an Akt
			activator ¹¹⁵ . This gene was associated with neurologic
			diseases ¹¹⁶ .

	PARVA	Broad	Parvin alpha encodes a member of the parvin family of actin- binding proteins ⁸³ . The encoded protein is part of the integrin-linked kinase signaling complex and plays a role in cell adhesion, motility and survival ⁸³ .
	MICALCL	Broad	MICAL C-terminal like gene product is predominantly expressed in skin, testis, and lung ⁸¹ .
15q25.2	ADAMTSL3	Broad	ADAMTS like 3 encodes a gene product that plays a role in cell-matrix interactions or in assembly of specific extracellular matrices ¹¹⁷ . It was associated with schizophrenia ¹¹⁸ and cardiac disorders in tetrasomy ¹¹⁹ .
	BNC1	None	Basonuclin 1 encodes a zinc finger protein that is present in the basal cell layer of the epidermis and in hair follicles, and in the germ cells of testis and ovary ^{83,120} . Its gene product modulates epithelial plasticity and TGF- β 1-induced loss of epithelial cell integrity ¹²¹ . It is a Pol I and Pol II transcription factor that is associated with epithelial expansion and proliferation ^{122,123} .
	BTBD1	Broad	BTB domain containing 1 encodes a protein that binds topoisomerase I. It is a transcription factor ¹²⁴ in the human histone deacetylase family ¹²⁵ . Its gene product is involved in mesenchymal ¹²⁶ and muscle cell differentiation ¹²⁷ .

Supplementary Figures

Supplementary Figure 1: Forest plots for 82 genome-wide significant associations Association statistics are based on the overall meta-analysis of COPD (35,735 cases and 222,076 controls). Error bars indicate 95% confidence interval.

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

1:17306029:A/C rs9435731

		0.50 0.71
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.85 [0.54 , 1.34]	
MESA AA	0.99 [0.62 , 1.58]	
KARE	1.11 [0.88 , 1.39]	
COPDGene AA	0.99 [0.83 , 1.17]	
CHS AA	0.89 [0.61 , 1.3]	
100	1.00 [0.79 , 1.40]	-
BS3	1 08 [0.79 1 46]	
RS2	0.9[0.64, 1.26]	
RS1	1 [0.74 . 1.35]	
Norway/GenKOLS	1.18 [0.99 . 1.4]	
NETT-NAS	0.95 [0.77 . 1.17]	
MESA Caucasian	1.06 [0.81 , 1.39]	
LifeLines	1.06 [0.92 , 1.22]	
FHS	0.95 [0.82 , 1.11]	
EQTL	1 [0.75 , 1.33]	
ECLIPSE	1.1 [0.85 , 1.43]	
COPDGene NHW	1.07 [0.98 , 1.16]	-
CHS EA	1.04 [0.9 , 1.2]	
ARIC	1.17 [1.05 , 1.3]	
UK Biobank	1.07 [1.04 , 1.09]	

0.71 Odds Ratio

1.5

Supplementary Figure 1-2: Forest plot for rs76841360 (PABPC4 locus at 1p34.3)

1:40060025:A/G rs76841360

		0.50 0.71 1.5 Odds Ratio
Overall	1.08 [1.05 , 1.1]	
KARE	0.93 [0.66 , 1.32]	
COPDGene AA	1.21 [0.91 , 1.59]	
	0.46[0.21,1.02]	<
SPIROMICS	1.25 [0.9 , 1.72]	$-\!\!\!-\!\!\!\!-\!\!\!\!-\!\!\!\!\rightarrow$
RS3	1.5 [1.06 , 2.12]	
RS2	0.97 [0.65 , 1.44]	
RS1	1.26 [0.91 , 1.76]	
Norway/GenKOLS	0.98 [0.8 , 1.21]	_
NETT-NAS	1.05 [0.82 , 1.35]	
MESA Caucasian	0.98 [0.72 , 1.34]	
LifeLines	1.12 [0.96 , 1.3]	
FHS	1.12[0.96,1.31]	
EQTL	0.86 [0.61 , 1.21]	
ECLIPSE	0.94 [0.7 , 1.28]	
COPDGene NHW	1.09 [0.98 , 1.21]	
CHS EA	1.04 [0.88 , 1.23]	
ARIC	1.15 [1.02 , 1.31]	
UK Biobank	1.07 [1.04 , 1.1]	

Supplementary Figure 1-3: Forest plot for rs4660861 (TESK2 locus at 1p34.1)

1:45946636:G/T rs4660861

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.85 [0.53 , 1.36]	
MESA AA	1.17 [0.81 , 1.69]	\longrightarrow
KARE	1.09 [0.88 , 1.35]	
COPDGene AA	1.02 [0.89 , 1.17]	
CHS AA	1.07 [0.77 , 1.49]	
RS3	0.96 [0.69 , 1.33]	
RS2	0.78 [0.56 , 1.09]	
RS1	0.97 [0.72 , 1.32]	
Norway/GenKOLS	1.12 [0.94 , 1.35]	
NETT-NAS	1.17 [0.94 , 1.46]	
MESA Caucasian	1.16 [0.89 , 1.51]	\rightarrow
LifeLines	1.04 [0.9 , 1.2]	
FHS	1.04 [0.89 , 1.21]	
EQTL	1.14 [0.85 , 1.52]	
ECLIPSE	0.87 [0.66 , 1.15]	
COPDGene NHW	1.12 [1.03 , 1.23]	- ■ -
CHS EA	1.2 [1.03 , 1.39]	
ARIC	1.05 [0.94 , 1.17]	
UK Biobank	1.05 [1.03 , 1.08]	

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

1:60913143:T/C rs72673419

		0.50 0.71 1.5 Odds Ratio
Overall	1.14 [1.09 , 1.19]	•
COPDGene AA	1.3 [1.04 , 1.61]	
CHS AA	1.25 [0.7 , 2.22]	\longrightarrow
SPIROMICS	2.06 [0.86 , 4.96]	
K53	1.24 [0.65 , 2.34]	
KS2	1 [0.44 , 2.31]	
RS1	0.95 [0.48 , 1.88]	
Norway/GenKOLS	0.92 [0.64 , 1.32]	
NETT-NAS	1.02 [0.6 , 1.73]	\longrightarrow
LifeLines	1.16 [0.86 , 1.58]	\longrightarrow
FHS	1.01 [0.71 , 1.43]	
EQTL	0.83 [0.43 , 1.6]	$\longleftrightarrow \blacksquare \longrightarrow$
ECLIPSE	1 [0.55 , 1.84]	\longrightarrow
COPDGene NHW	1.27 [1.01 , 1.59]	\longrightarrow
CHS EA	1.03 [0.7 , 1.53]	\longrightarrow
ARIC	1.41 [1.12 , 1.79]	
UK Biobank	1.13 [1.07 , 1.18]	

Supplementary Figure 1-5: Forest plot for rs629619 (DENND2D locus at 1p13.3)

1:111738108:T/C rs629619

		0.50 0.71 1.5 Odds Ratio
Overall	1.08 [1.06 , 1.11]	
MESA AA	1.14 [0.73 , 1.78]	_ >
COPDGene AA	1.07 [0.91 , 1.25]	
CHS AA	1.34 [0.88 , 2.03]	
RS3	1.24 [0.85 . 1.81]	_ >
RS2	1.53 [1.02 , 2.29]	>
RS1	0.82 [0.55 , 1.22]	
Norway/GenKOLS	1.07 [0.86 , 1.33]	=
NETT-NAS	1.15 [0.88 , 1.51]	$\longrightarrow \blacksquare \longrightarrow$
MESA Caucasian	1.17 [0.83 , 1.67]	\longrightarrow
LifeLines	1.01 [0.83 , 1.23]	_
FHS	1.42 [1.14 , 1.77]	
EQTL	0.76 [0.53 , 1.1]	_
ECLIPSE	1.09 [0.78 , 1.51]	\longrightarrow
COPDGene NHW	1.11 [0.99 , 1.24]	
CHS EA	1.06 [0.85 , 1.33]	_
ARIC	1.05 [0.91 , 1.21]	
UK Biobank	1.08 [1.05 , 1.11]	

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

1:218689155:C/T rs3009947

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.82 [0.52 , 1.28]	
MESA AA	1.38 [0.97 , 1.95]	
KARE	1.11 [0.86 , 1.43]	
COPDGene AA	0.93 [0.82 , 1.06]	
CHS AA	0.9[0.65,1.23]	
SPIROMICS	1.1 [0.86 , 1.41]	
RS3	1.03 [0.76 , 1.41]	
RS2	1.27 [0.9 , 1.78]	
RS1	1.23 [0.91 , 1.65]	
Norway/GenKOLS	1.07 [0.9 , 1.26]	
NETT-NAS	1.35 [1.1 , 1.67]	>
MESA Gaucasian	1.08 [0.83 , 1.41]	
	1 [0.86 , 1.15]	
FHS	0.97[0.85,1.1]	
EQIL	0.93[0.7,1.24]	
ECLIPSE	1.18[0.92,1.51]	
	1.17 [1.07 , 1.27]	
	1.22[1.00,1.4]	_
	1 22 [1 06 1 4]	
ARIC	1.03[0.92, 1.14]	
LIK Biobank	105[103 107]	

Supplementary Figure 1-7: Forest plot for rs11118406 (SLC30A10 locus at 1q41)

1:219924894:T/A rs11118406 UK Biobank 1.08 [1.05 , 1.1] ARIC 1.11 [0.99 , 1.25] 1.09 [0.93 , 1.28] CHS EA 1.09 [0.99 , 1.21] **COPDGene NHW** 1.36 [1.01 , 1.85] **ECLIPSE** EQTL 0.95 [0.69 , 1.31] FHS 1.01 [0.87 , 1.16] LifeLines 1.14 [0.98 , 1.34] 1.11 [0.83, 1.48] **MESA** Caucasian **NETT-NAS** 1.1 [0.86 , 1.39] Norway/GenKOLS 1.01 [0.83 , 1.22] RS1 1.09 [0.79 , 1.52] RS2 1.27 [0.88 , 1.85] \rightarrow RS3 0.99 [0.7 , 1.4] SPIROMICS 1.09 [0.82 , 1.44] 0.94 [0.68 , 1.29] CHS AA COPDGene AA 0.96 [0.84 , 1.09] KARE 1.14 [0.92 , 1.4] MESA AA 0.85 [0.59 , 1.22] MESA Hispanic 1.69 [1.07 , 2.68] 1.08 [1.05 , 1.1] Overall

0.50

0.71

Odds Ratio

1.5

Supplementary Figure 1-8: Forest plot for rs11579382 (CHRM3 locus at 1q43)

1:239901006:C/G rs11579382 UK Biobank 1.06 [1.03 , 1.08] ARIC 1.19 [1.07 , 1.33] 0.91 [0.79 , 1.05] CHS EA **COPDGene NHW** 1.03 [0.94 , 1.13] 0.98 [0.75 , 1.28] **ECLIPSE** EQTL 0.88 [0.66 , 1.17] FHS 1.09 [0.94 , 1.27] 1.08 [0.92 , 1.27] LifeLines 0.89 [0.69 , 1.15] **MESA** Caucasian 0.92 [0.75 , 1.14] **NETT-NAS** 1.12 [0.94 , 1.33] Norway/GenKOLS RS1 1.39 [1.02 , 1.89] RS2 0.81 [0.56 , 1.17] RS3 1.41 [1.03 , 1.92] 1.2 [0.85 , 1.69] CHS AA COPDGene AA 1.07 [0.92 , 1.24] KARE 1.3 [1.05 , 1.61] 1.08 [0.74 , 1.57] MESA AA MESA Hispanic 1.53 [0.98 , 2.38] 1.06 [1.04 , 1.08] Overall 0.50 0.71 1.5 Odds Ratio

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

2:9290357:T/C rs955277

		0.71 1.5 Odds Ratio
Overall	1.07 [1.05 , 1.09]	•
MESA Hispanic	1.39 [0.87 , 2.22]	
MESA AA	0.91 [0.63 , 1.31]	
KARE	0.85 [0.64 , 1.13]	
COPDGene AA	1.12 [0.97 , 1.29]	
CHS AA	1.23 [0.88 , 1.72]	_ >
RS3	1.46 [1.05 , 2.02]	
RS2	1.07 [0.75 , 1.52]	
RS1	0.83 [0.61 , 1.13]	
Norway/GenKOLS	1.11 [0.93 , 1.32]	
NETT-NAS	1.06 [0.85 , 1.31]	
MESA Caucasian	1.08 [0.84 , 1.39]	
LifeLines	0.98 [0.84 , 1.13]	
FHS	0.95 [0.83 , 1.08]	=
EQTL	1.07 [0.8 , 1.44]	
ECLIPSE	1.03 [0.79 , 1.35]	
COPDGene NHW	1.05 [0.96 , 1.15]	
CHS EA	1 [0.86 , 1.16]	
ARIC	1.05 [0.94 , 1.17]	
UK Biobank	1.08 [1.05 , 1.1]	

Supplementary Figure 1-10: Forest plot for rs10929386 (DDX1 locus at 2p24.3)

2:15906179:C/T rs10929386

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	•
MESA Hispanic	1.1 [0.69 , 1.75]	\longrightarrow
MESA AA	0.93 [0.65 , 1.34]	
COPDGene AA	1.11 [0.97 , 1.26]	
CHS AA	1.24 [0.91 , 1.7]	$-\!\!\!-\!\!\!-\!\!\!\!-\!\!\!\rightarrow$
RS3	1.24 [0.9 , 1.71]	
RS2	0.84 [0.6 , 1.2]	
RS1	0.89 [0.65 , 1.22]	
Norway/GenKOLS	1.04 [0.87 , 1.25]	
NETT-NAS	0.95 [0.76 , 1.18]	
MESA Caucasian	0.97 [0.75 , 1.27]	
LifeLines	1.23 [1.06 , 1.42]	
FHS	1.15 [0.99 , 1.33]	
ECLIPSE	1.2 [0.91 , 1.58]	\longrightarrow
COPDGene NHW	1.02 [0.94 , 1.12]	
CHS EA	1.11 [0.96 , 1.29]	
ARIC	1.04 [0.93 , 1.16]	
UK Biobank	1.06 [1.03 , 1.08]	

Supplementary Figure 1-11: Forest plot for rs12466981 (EML4 locus at 2p21)

2:42433247:C/T rs12466981

		0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.09]	
MESA AA	1.41 [0.79 , 2.53]	₽
KARE	1.14 [0.93 , 1.41]	
COPDGene AA	0.99 [0.81 , 1.22]	
CHS AA	1.09 [0.69 , 1.7]	\longrightarrow
RS3	0.94 [0.67 , 1.31]	
RS2	1.16 [0.79 , 1.72]	\longrightarrow
RS1	1.34 [0.93 , 1.94]	_ >
Norway/GenKOLS	1.16 [0.95 , 1.41]	
NETT-NAS	1.14 [0.9 , 1.45]	
MESA Caucasian	1.12[0.84,1.51]	\longrightarrow
LifeLines	1.05 [0.9 , 1.23]	
FHS	1.12 [0.97 , 1.29]	
EQTL	1.35 [1 , 1.83]	
ECLIPSE	1.07 [0.8 , 1.44]	
COPDGene NHW	1.09 [0.99 , 1.2]	
CHS EA	1.02 [0.86 , 1.2]	-
ARIC	1 [0.88 , 1.13]	
UK Biobank	1.06 [1.03 , 1.08]	

Supplementary Figure 1-12: Forest plot for rs72902175 (NR4A2 locus at 2q24.1)

2:157013035:T/C rs72902175



Supplementary Figure 1-13: Forest plot for rs2571445 (TNS1 locus at 2q35)

2:218683154:A/G rs2571445

		0.50 0.71 1.5 Odds Ratio
Overall	1.07 [1.05 . 1.09]	
MESA Hispanic	0.82 [0.5 , 1.34]	
MESA AA	1.23 [0.78 , 1.93]	\longrightarrow
COPDGene AA	0.97 [0.83 , 1.14]	
CHS AA	0.85 [0.59 , 1.23]	
SPIROMICS	1.08 [0.83 , 1.4]	
RS3	0.84 [0.61 , 1.16]	
RS2	1.45 [1.02 , 2.06]	
RS1	0.83 [0.6 , 1.15]	_
Norway/GenKOLS	1.06 [0.89 , 1.27]	
NETT-NAS	0.92[0.74,1.14]	_ _
MESA Caucasian	1.2 [0.93 , 1.57]	_ _>
LifeLines	1.19 [1.02 , 1.39]	
FHS	1.11 [0.96 , 1.29]	
ECLIPSE	1.11 [0.86 , 1.44]	
COPDGene NHW	1.07 [0.98 , 1.17]	
CHS EA	1.06 [0.91 , 1.22]	
ARIC	1.11 [0.99 , 1.24]	
UK Biobank	1.07 [1.05 , 1.1]	

Supplementary Figure 1-14: Forest plot for rs16825267 (PID1 locus at 2q36.3)

2:229569919:C/G rs16825267



Supplementary Figure 1-15: Forest plot for rs62191105 (*TWIST2* locus at 2q37.3)

2:239872704:C/T rs62191105

		0.71 1.5 Odds Ratio
Overall	1.09 [1.07 , 1.12]	\
COPDGene AA	1 [0.72 , 1.39]	
CHS AA	2.92 [1.14 , 7.46]	\longrightarrow
SPIROMICS	1.04 [0.76 , 1.42]	
RS3	0.93 [0.63 , 1.37]	
RS2	1.18 [0.76 , 1.82]	\longrightarrow
RS1	1.06 [0.74 , 1.52]	\longrightarrow
Norway/GenKOLS	1.22 [0.99 , 1.5]	\longrightarrow
NETT-NAS	1.12 [0.87 , 1.45]	
MESA Caucasian	1.18 [0.84 , 1.64]	\longrightarrow
LifeLines	1.18 [0.98 , 1.41]	
FHS	1.22 [1.01 , 1.47]	
ECLIPSE	1.2 [0.87 , 1.64]	\longrightarrow
COPDGene NHW	1.13 [1.02 , 1.26]	
CHS EA	1.01 [0.84 , 1.2]	
ARIC	0.92 [0.8 , 1.05]	
UK Biobank	1.09 [1.06 , 1.12]	
Supplementary Figure 1-16: Forest plot for rs2442776 (VGLL4 locus at 3p25.3)

3:11640601:G/A rs2442776

Overall	1.09 [1.06 , 1.12]	•
MESA Hispanic	0.75 [0.42 , 1.34]	<■
MESA AA	1.23 [0.82 , 1.83]	\longrightarrow
KARE	0.93 [0.75 , 1.14]	
COPDGene AA	1.21 [1.04 , 1.4]	
CHS AA	1.24 [0.87 , 1.78]	_ >
SPIROMICS	1.13 [0.77 , 1.64]	$\longrightarrow \blacksquare \longrightarrow$
RS3	1.14 [0.74 , 1.77]	\longrightarrow
RS2	0.92 [0.5 , 1.66]	
RS1	1.47 [0.98 , 2.21]	
Norway/GenKOLS	1.08 [0.84 , 1.38]	
NETT-NAS	0.99 [0.74 , 1.32]	
MESA Caucasian	1.2 [0.84 , 1.72]	
Lovelace	1.3 [0.95 , 1.78]	
LifeLines	0.99 [0.8 , 1.24]	
FHS	1.14 [0.93 , 1.38]	
EQTL	0.83 [0.55 , 1.25]	
ECLIPSE	0.94 [0.64 , 1.37]	_
COPDGene NHW	1.11 [0.98 , 1.26]	
CHS EA	1.35 [1.1 , 1.65]	
ARIC	0.96 [0.82 , 1.12]	
UK Biobank	1.09 [1.06 , 1.13]	

٢

0.50

0.71 Odds Ratio

1.5

Supplementary Figure 1-17: Forest plot for rs1529672 (RARB locus at 3p24.2)

3:25520582:C/A I	rs1529672
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	• ,•	0.50 0.71 1.5 Odds Ratio
Overall	1.09 [1.06 , 1.12]	•
TCGS-Korea	1.36 [0.79 , 2.34]	■>
MESA Hispanic	0.84 [0.49 , 1.45]	<
MESA AA	1.34 [0.85 , 2.12]	
COPDGene AA	1.06 [0.9 , 1.24]	
CHS AA	1.05 [0.7 , 1.56]	
	1.5 [1.03 , 2.16]	
TCGS-Poland	1.50[1,1.91] 1.5[1.02,0.46]	
SPIROMICS	1.42[0.92,2.2]	
RS2	1.05[1.05,2.05]	
	1.09[0.07, 1.37]	
NETT-NAS	1.12[0.04,1.49]	
	1 12 [0 84 1 40]	
LiteLines	1.14[0.94, 1.39]	
Lifel ince	1.10[0.90, 1.41]	
	1.45[1,2.12]	
EOCOPD/ICGN	1.08[0.9,1.3]	
ECLIPSE	1.12[0.8, 1.56]	\longrightarrow
	1.11 [0.99 , 1.25]	
CHS EA	1.38 [1.13 , 1.69]	
ARIC	1.3 [1.12 , 1.51]	\rightarrow
UK Biobank	1.06 [1.03 , 1.09]	
LUZ Disharah		

Supplementary Figure 1-18: Forest plot for rs13073544 (RBMS3 locus at 3p24.1)

3:29472412:C/G rs13073544

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.09]	
MESA AA	1.07 [0.66 , 1.73]	\longrightarrow
KARE	1.09 [0.77 , 1.54]	\longrightarrow
COPDGene AA	1.06 [0.89 , 1.26]	
CHS AA	1.34 [0.92 , 1.97]	
н53	0.84 [0.59 , 1.2]	
RS2	0.98[0.66, 1.45]	_
RSI	1.41 [1.02 , 1.95]	
Norway/GenkOLS	1.09[0.91, 1.3]	
NETT-NAS	1.04 [0.83 , 1.31]	
MESA Caucasian	1.37 [1.02 , 1.85]	B >
LifeLines	1.14 [0.98 , 1.34]	
FHS	1.15 [0.99 , 1.34]	
EQTL	0.97 [0.7 , 1.35]	
ECLIPSE	1.1 [0.83 , 1.46]	
COPDGene NHW	1.1 [1 , 1.22]	-
CHS EA	1.08 [0.92 , 1.27]	
ARIC	1.04 [0.92 , 1.17]	-
UK Biobank	1.06 [1.03 , 1.08]	

Supplementary Figure 1-19: Forest plot for rs17759204 (CACNA2D3 locus at 3p14.3)

3:55158224:G/A rs17759204

UK Biobank	1.07 [1.04 , 1.1]	
ARIC	1.15 [1.03 , 1.3]	
CHS EA	1 [0.85 , 1.17]	
COPDGene NHW	1.09 [0.99 , 1.2]	
ECLIPSE	1.08 [0.81 , 1.45]	
EQTL	0.95 [0.68 , 1.34]	
FHS	1 [0.87 , 1.15]	
LifeLines	1.18 [0.99 , 1.39]	
MESA Caucasian	1.04 [0.77 , 1.4]	
NETT-NAS	0.94 [0.74 , 1.19]	
Norway/GenKOLS	1.11 [0.92 , 1.35]	
RS1	1.07 [0.76 , 1.51]	
RS2	1.08 [0.75 , 1.58]	
RS3	0.97 [0.69 , 1.36]	
CHS AA	1.07 [0.7 , 1.64]	_ >
COPDGene AA	1.28 [1.06 , 1.55]	\rightarrow
KARE	1.35 [0.96 , 1.89]	
MESA AA	0.83 [0.48 , 1.43]	<
Overall	1.07 [1.05 , 1.1]	•
		0.50 0.71 1.5 Odds Ratio

40

Supplementary Figure 1-20: Forest plot for rs62259026 (SLMAP locus at 3p14.3)

3:57746515:C/T rs62259026

Overall	1.07 [1.04 , 1.09]	0.50 0.71 1.5 Odds Ratio
MESA Hispanic	1.13 [0.69 , 1.84]	\longrightarrow
MESA AA	1.14 [0.77 , 1.69]	_ >
KARE	1.03 [0.84 , 1.27]	
COPDGene AA	1.18 [1.03 , 1.36]	
CHS AA	1 [0.73 , 1.37]	=
RS3	1.37 [0.94 , 1.99]	
RS2	1.34 [0.88 , 2.04]	>
RS1	0.7 [0.49 , 0.99]	←
Norway/GenKOLS	1.13 [0.93 , 1.38]	
NETT-NAS	1.15 [0.88 , 1.49]	
MESA Caucasian	0.93 [0.69 , 1.27]	
LifeLines	1.04 [0.88 , 1.23]	
FHS	1.24 [1.06 , 1.44]	
EQTL	1.13 [0.8 , 1.6]	\longrightarrow
ECLIPSE	1.03 [0.75 , 1.4]	_
COPDGene NHW	1.09 [0.98 , 1.21]	
CHS EA	0.94 [0.8 , 1.12]	— —
ARIC	0.96 [0.85 , 1.09]	
UK Biobank	1.07 [1.04 , 1.09]	

Supplementary Figure 1-21: Forest plot for rs4093840 (ADCY5 locus at 3q21.1)

3:123077042:A/T rs4093840

Overall	1.06 [1.04 , 1.08]	0.50 0.71 1.5 Odds Ratio
	- · · ·	
MESA Hispanic	1.42 [0.91 , 2.21]	
MESA AA	1.08 [0.75 , 1.57]	>
COPDGene AA	1.03 [0.89 , 1.18]	
CHS AA	1.68 [1.17 , 2.41]	\rightarrow
RS3	1.09 [0.81 , 1.47]	
RS2	1.24 [0.89 , 1.72]	_ >
RS1	1.43 [1.05 , 1.94]	
Norway/GenKOLS	0.86 [0.72 , 1.03]	
NETT-NAS	1.01 [0.82 , 1.25]	e
MESA Caucasian	1.44 [1.1 , 1.89]	
LifeLines	1.02 [0.88 , 1.17]	
FHS	1.08 [0.95 , 1.23]	
EQTL	0.85 [0.63 , 1.15]	
ECLIPSE	0.75 [0.57 , 0.98]	_
COPDGene NHW	1.07 [0.98 , 1.17]	-
CHS EA	1.05 [0.91 , 1.21]	
ARIC	0.98 [0.88 , 1.09]	
UK Biobank	1.07 [1.05 , 1.09]	

Supplementary Figure 1-22: Forest plot for rs2955083 (EEFSEC locus at 3q21.3)

3:127961178:A/T rs2955083

		0.50 0.71 1.5 Odds Ratio
Overall	1.13 [1.1 , 1.17]	
MESA AA	0.83 [0.49 , 1.41]	← ■
COPDGene AA	1.21 [0.98 , 1.49]	
CHS AA	1.17 [0.69 , 1.98]	_ >
SPIROMICS	1.52 [1.06 , 2.18]	\longrightarrow
RS2	1.27 [0.72 , 2.25]	
RS1	1.64 [0.97 , 2.77]	\rightarrow
Norway/GenKOLS	1.21 [0.94 , 1.57]	\longrightarrow
NETT-NAS	1 [0.72 , 1.38]	
MESA Caucasian	1.17 [0.76 , 1.79]	_ >
LifeLines	1.15 [0.91 , 1.44]	
FHS	1.06 [0.86 , 1.31]	_
EQTL	1.09 [0.74 , 1.61]	_ >
ECLIPSE	1.44 [0.99 , 2.08]	
COPDGene NHW	1.35 [1.18 , 1.55]	
CHS EA	0.93 [0.74 , 1.16]	_
ARIC	1.2 [1.01 , 1.42]	
UK Biobank	1.11 [1.08 , 1.15]	

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

3:141147414:C/T rs7650602

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.96 [0.6 , 1.55]	\longrightarrow
MESA AA	1.04 [0.69 , 1.56]	\longrightarrow
KARE	0.96 [0.77 , 1.19]	
COPDGene AA	1.07 [0.93 , 1.23]	
CHS AA	0.79 [0.57 , 1.1]	
RS3	1.07 [0.78 , 1.48]	
RS2	1.05 [0.75 , 1.48]	
RS1	0.95 [0.7 , 1.3]	
Norway/GenKOLS	0.92 [0.77 , 1.09]	_ _
NETT-NAS	0.86 [0.69 , 1.08]	
MESA Caucasian	1.13 [0.86 , 1.48]	-
LifeLines	1.05 [0.91 , 1.21]	
FHS	1.13 [0.99 , 1.3]	
ECLIPSE	0.93 [0.71 , 1.22]	
COPDGene NHW	0.97 [0.89 , 1.06]	
CHS EA	1[0.86,1.17]	
ARIC	1.08 [0.97 , 1.21]	
UK Biobank	1.07 [1.04 , 1.09]	

Supplementary Figure 1-24: Forest plot for rs7642001 (*MECOM* locus at 3q26.2)

3:168746145:A/G rs7642001

Overall	1.08 [1.06 , 1.1]	
MESA Hispanic	1.52[0.92,2.51]	>
	0.9[0.72,1.11]	
	1.05[0.01, 1.20]	-
	0 01 [0 64 1 29]	
SPIROMICS	0.98 [0.75 , 1.27]	
RS3	1.5 [1.1 , 2.05]	
RS2	1.03 [0.73 , 1.43]	
RS1	0.86 [0.62 , 1.18]	
Norway/GenKOLS	1.14 [0.95 , 1.36]	
NETT-NAS	0.92 [0.75 , 1.14]	
MESA Caucasian	1.11 [0.86 , 1.45]	
LifeLines	1.21 [1.05 , 1.39]	
FHS	1.03 [0.89 , 1.19]	
EQTL	0.98 [0.73 , 1.32]	
ECLIPSE	1.19[0.91, 1.57]	_ >
COPDGene NHW	1.08 [0.99 , 1.18]	
CHS EA	1.08 [0.93 , 1.25]	
ARIC	1.06 [0.95 , 1.18]	
UK Biobank	1.08 [1.06 , 1.11]	

۲ 0.71

Odds Ratio

1.5

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

4:75673363:G/A rs4585380

		0.50 0.71 1.5 Odds Ratio
Overall	1.07 [1.05 , 1.09]	· · · · · · · · · · · · · · · · · · ·
MESA Hispanic	1.19[0.7,2.01]	\longrightarrow
MESA AA	0.99 [0.68 , 1.46]	
KARE	1.68 [0.67 , 4.17]	\longrightarrow
COPDGene AA	1.05 [0.91 , 1.21]	
CHS AA	0.97 [0.67 , 1.4]	
SPIROMICS	1.36 [1.04 , 1.79]	
RS3	0.71 [0.5 , 0.99]	
RS2	1.85 [1.19 , 2.88]	\longrightarrow
RS1	0.75 [0.54 , 1.05]	
Norway/GenKOLS	0.95 [0.77 , 1.16]	B
NETT-NAS	0.96 [0.75 , 1.23]	
MESA Caucasian	1.16 [0.87 , 1.56]	\longrightarrow
Lovelace	1.08 [0.82 , 1.42]	
LifeLines	1.19 [0.99 , 1.42]	
FHS	1.15 [0.99 , 1.34]	
EQTL	1.24 [0.91 , 1.7]	_ >
ECLIPSE	0.9 [0.66 , 1.22]	
COPDGene NHW	1.14 [1.03 , 1.26]	
CHS EA	1.13 [0.96 , 1.34]	
ARIC	0.92 [0.81 , 1.03]	
UK Biobank	1.07 [1.04 , 1.1]	

Supplementary Figure 1-26: Forest plot for rs7671261 (FAM13A locus at 4q22.1)

4:89883818:A/G rs7671261

		0.71 1.5 Odds Ratio
Overall	1.09 [1.07 , 1.11]	♦
TCGS-Korea	1.31 [0.77 , 2.23]	$ \longrightarrow $
MESA Hispanic	1.75 [1.09 , 2.8]	\longrightarrow
MESA AA	0.95 [0.65 , 1.39]	
KARE	1.25 [1.01 , 1.55]	\longrightarrow
COPDGene AA	1.05 [0.91 , 1.2]	
CHS AA	1.11 [0.8 , 1.55]	\longrightarrow
1000-Fulanu	1.10[0.92,1.5]	
JCCS Deland	1.22[0.94,1.37]	
	1.40 [1.00 , 2.02] 1.20 [0.04 - 1.57]	
	1.20 [0.00 , 1.72]	
RC1	1.20[1.00,1.31]	
Norway/GenKOIS	1.09 [1.12 , 1.70]	
MESA Caucacian		
l ifol inoc	1.02[0.09, 1.10]	
	1.23 [1.00 , 1.41] 1.11 [0.94 , 1.40]	
		>
	1.24 [1.13 , 1.35]	
	1.11[0.90,1.27]	
	1.04[0.94,1.16]	
	1.07 [1.05 , 1.09]	
LIK Biobank	107[105 100]	

Supplementary Figure 1-27: Forest plot for rs34712979 (NPNT locus at 4q24)

4:106819053:A/G I	rs34712979
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Overall	1.18 [1.16 , 1.21]	0.50 0.71 1.5 Odds Ratio
COPDGene AA	0.82 [0.5 , 1.36]	
CHS AA	1.15 [0.6 , 2.22]	_ >
RS3	1.34 [0.8 , 2.24]	€>
RS2	1.38 [0.81 , 2.34]	
RS1	0.95 [0.58 , 1.55]	\longrightarrow
Norway/GenKOLS	1.14 [0.87 , 1.49]	
NETT-NAS	0.99 [0.7 , 1.4]	
MESA Caucasian	1.39 [0.94 , 2.07]	
LifeLines	1.15 [0.84 , 1.59]	\longrightarrow
FHS	1.17 [0.89 , 1.53]	$-\!$
ECLIPSE	1.29 [0.85 , 1.95]	∎>
COPDGene NHW	1.27 [1.1 , 1.47]	-8-
CHS EA	1.25 [0.94 , 1.65]	$-\!\!-\!\!\!-\!\!\!\!-\!\!\!\!\rightarrow$
ARIC	1.11 [0.95 , 1.29]	
UK Biobank	1.19 [1.16 , 1.21]	

Supplementary Figure 1-28: Forest plot for rs13140176 (HHIP locus at 4q31.21)

4:145489098:A/G rs13140176 UK Biobank 1.17 [1.14 , 1.19] ARIC 1.13 [1.01 , 1.27] 1.12 [0.96 , 1.31] CHS EA 1.24 [1.13 , 1.36] **COPDGene NHW ECLIPSE** 1.42 [1.09 , 1.86] EOCOPD/ICGN 1.32 [1.15 , 1.51] FHS 1.11 [0.96 , 1.28] LifeLines 1.28 [1.09 , 1.5] **MESA** Caucasian 1.16 [0.87 , 1.53] **NETT-NAS** 1.53 [1.22 , 1.92] 1.26 [1.06 , 1.51] Norway/GenKOLS \rightarrow 1.28 [0.92 , 1.77] RS1 RS2 0.91 [0.65 , 1.28] RS3 1.67 [1.19 , 2.34] **TCGS-Poland** 1.37 [1.06 , 1.76] ₽ 1.31 [0.76 , 2.24] CHS AA 1.27 [1 , 1.61] COPDGene AA \rightarrow KARE 1.27 [1.01 , 1.6] 0.98 [0.59 , 1.63] MESA Hispanic **TCGS-Korea** 1.19 [0.69 , 2.05] 1.18 [1.16 , 1.2] Overall

0.50

0.71

Odds Ratio

1.5

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

5:52195033:A/G rs1551943

		0.50 0.71 1.5 Odds Ratio
Overall	1.08 [1.05 , 1.1]	4
COPDGene AA	0.8 [0.6 , 1.06]	
CHS AA	1 [0.52 , 1.94]	>
	0.02[0.07, 1.20]	
SPIROMICS	0.92 [0.67 , 1.25]	
RS3	1.12 [0.78 . 1.61]	$ \longrightarrow $
RS2	0.75 [0.49 , 1.15]	←
RS1	1.38 [1 , 1.92]	
Norway/GenKOLS	1.15 [0.94 , 1.4]	
NETT-NAS	1.2 [0.93 , 1.53]	$-\!\!\!-\!\!\!\!-\!\!\!\!-\!\!\!\!\rightarrow$
MESA Caucasian	0.87 [0.65 , 1.16]	_
Lovelace	1.08 [0.82 , 1.43]	
LifeLines	1.04 [0.87 , 1.23]	
FHS	1.35 [1.16 , 1.57]	
EQTL	0.91 [0.64 , 1.28]	
ECLIPSE	0.87 [0.64 , 1.18]	
COPDGene NHW	1.12 [1.01 , 1.24]	
CHS EA	1.17 [0.98 , 1.4]	
ARIC	1.13 [0.99 , 1.29]	
UK Biobank	1.07 [1.04 , 1.1]	

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

5:72144005:C/T rs34651

		0.50 0.71 1.5 Odds Ratio
Overall	1.11 [1.07 , 1.15]	
COPDGene AA	1.18 [0.76 , 1.84]	\longrightarrow
RS3	1.37 [0.79 , 2.37]	∎>
RS2	1.13 [0.59 , 2.17]	_ >
RS1	0.96 [0.53 , 1.73]	>
Norway/GenKOLS	1.58 [1.11 , 2.23]	\longrightarrow
NETT-NAS	0.88 [0.56 , 1.38]	
MESA Caucasian	1.05 [0.64 , 1.71]	$-\!\!-\!\!\!-\!\!\!\rightarrow$
LifeLines	0.98 [0.74 , 1.31]	
FHS	1.03 [0.77 , 1.38]	
EQTL	0.93 [0.51 , 1.71]	$ \longrightarrow $
ECLIPSE	1.33 [0.76 , 2.33]	
COPDGene NHW	1.2 [1 , 1.43]	
CHS EA	0.88 [0.66 , 1.18]	
ARIC	1.17 [0.96 , 1.42]	
UK Biobank	1.1 [1.06 , 1.15]	

Supplementary Figure 1-31: Forest plot for rs153916 (SPATA9 locus at 5q15)

5:95036700:T/C rs153916

MESA Hispanic 0.95 [0.61 , 1.47] TCGS-Korea 1.13 [0.6 , 2.15]	
MESA Hispanic 0.95 [0.61 , 1.47] TCGS-Korea 1.13 [0.6 , 2.15]	
MESA Hispanic 0.95 [0.61 , 1.47]	
	 ∎→ ∎→
MESA AA 1.14 [0.8 , 1.62] —	
KARE 1.25 [0.93 , 1.69]	
COPDGene AA 1.03 [0.9 , 1.18]	
CHS AA 0.81 [0.58 , 1.12]	
1.26 [0.97 , 1.63]	\rightarrow
SPIROWIDS 0.95 [0.73 , 1.23] — TCCS Baland 1.00 [0.07 , 1.00] —	
H53 1.14 [0.84 , 1.55] - CDIDOMICS 0.05 [0.70 , 1.00]	
HS2 1.14[0.81, 1.59] -	
RS1 1.44 [1.05 , 1.97]	
Norway/GenKOLS 0.98 [0.83 , 1.15] -	
NETT-NAS 0.96 [0.77 , 1.19] —	
MESA Caucasian 0.99 [0.77 , 1.28] —	-
LifeLines 0.98 [0.85 , 1.13]	
FHS 0.98 [0.85 , 1.11]	
EQTL 1.01 [0.76 , 1.33]	
EOCOPD/ICGN 1.1 [0.96 , 1.25]	
ECLIPSE 1.11 [0.86 , 1.43]	
COPDGene NHW 1.04 [0.95 , 1.14]	-
CHS EA 1.17 [1.02 , 1.35]	
ARIC 1.07 [0.96 , 1.19]	
UK Biobank 1.07 [1.04 , 1.09]	

Supplementary Figure 1-32: Forest plot for rs62375246 (HSPA4 locus at 5q31.1)

5:132439010:A/T rs62375246

Overall	1.06 [1.04 , 1.09]	0.50 0.71 1.5 Odds Ratio
MESA AA	0.8 [0.56 , 1.16]	
COPDGene AA	1.13 [0.98 , 1.31]	
CHS AA	0.85 [0.62 , 1.18]	
SPIROMICS	1.09 [0.81 , 1.46]	
RS3	1.23 [0.87 , 1.73]	$-\!\!\!-\!\!\!\!-\!\!\!\!-\!\!\!\!\rightarrow$
RS2	0.96 [0.67 , 1.38]	
RS1	1.38 [1 , 1.9]	
Norway/GenKOLS	0.99 [0.82 , 1.2]	
NETT-NAS	1.15 [0.9 , 1.47]	
MESA Caucasian	1.08 [0.8 , 1.45]	
LifeLines	0.96 [0.81 , 1.15]	
FHS	0.98 [0.83 , 1.16]	
EQTL	0.82 [0.6 , 1.13]	
ECLIPSE	1.04 [0.78 , 1.39]	
COPDGene NHW	0.99 [0.89 , 1.09]	
CHS EA	1.23 [1.04 , 1.45]	
ARIC	0.97 [0.86 , 1.09]	-
UK Biobank	1.08 [1.05 , 1.1]	

Supplementary Figure 1-33: Forest plot for rs10037493 (HTR4 locus at 5q32)

5:147854970:C/T rs10037493 UK Biobank 1.12 [1.1 , 1.14] ARIC 1.35 [1.21 , 1.51] 1.19 [1, 1.41] CHS EA **COPDGene NHW** 1.1 [1.01 , 1.2] 1.05 [0.79 , 1.39] ECLIPSE EOCOPD/ICGN 1.02 [0.89 , 1.16] EQTL 1.14 [0.86 , 1.53] FHS 1.2 [1.02 , 1.41] LifeLines 1.26 [1.07 , 1.49] Lovelace 1.33 [1.05 , 1.69] 1.24 [0.95 , 1.63] **MESA** Caucasian 1.05 [0.82 , 1.34] **NETT-NAS** Norway/GenKOLS 1.22 [1 , 1.49] RS1 1.71 [1.22 , 2.39] RS2 0.81 [0.55 , 1.19] RS3 0.92 [0.66 , 1.29] SPIROMICS 0.97 [0.75 , 1.26] TCGS-Poland 1.26 [0.98, 1.62] 1.2 [0.88 , 1.63] CHS AA **COPDGene AA** 1.03 [0.91 , 1.17] MESA AA 0.9 [0.62 , 1.29] MESA Hispanic 1.23 [0.78, 1.94] **TCGS-Korea** 1.38 [0.79, 2.4]

Overall

1.13 [1.1 , 1.15]



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

5:150595073:G/A rs979453

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.99 [0.6 , 1.64]	\longrightarrow
MESA AA	1.09 [0.72 , 1.64]	$ \longrightarrow $
COPDGene AA	1.05 [0.9 , 1.24]	
CHS AA	1.03 [0.7 , 1.51]	\longrightarrow
RS3	1.06 [0.77 , 1.47]	
RS2	1.14 [0.79 , 1.64]	
RS1	0.99 [0.72 , 1.36]	
Norway/GenKOLS	0.73 [0.61 , 0.88]	—
NETT-NAS	1.06 [0.85 , 1.32]	_
MESA Caucasian	1.04 [0.79 , 1.37]	
LifeLines	1.17 [1 , 1.36]	
FHS	1.16 [0.97 , 1.38]	
EQTL	0.9 [0.65 , 1.24]	
ECLIPSE	0.83 [0.64 , 1.09]	
COPDGene NHW	0.99[0.91,1.09]	-
CHS EA	0.93 [0.8 , 1.08]	
ARIC	1.09 [0.97 , 1.22]	
UK Biobank	1.07 [1.05 , 1.1]	

Supplementary Figure 1-35: Forest plot for rs10866659 (ADAM19 locus at 5q33.3)

5:156937043:G/A rs10866659 UK Biobank 1.09 [1.06 , 1.11] ARIC 1.23 [1.1 , 1.37] 1.08 [0.94 , 1.26] CHS EA 1.04 [0.95 , 1.14] **COPDGene NHW** 1.25 [0.95 , 1.64] **ECLIPSE** \rightarrow EQTL 0.96 [0.71 , 1.29] FHS 1.14 [0.99 , 1.32] LifeLines 0.96 [0.83 , 1.12] 1.22 [0.93 , 1.59] **MESA** Caucasian **NETT-NAS** 1.09 [0.87 , 1.36] Norway/GenKOLS 1.17 [0.98 , 1.41] RS1 0.69 [0.49 , 0.98] RS2 1.15 [0.81 , 1.63] RS3 1.37 [1, 1.88] SPIROMICS 1.23 [0.95 , 1.61] \rightarrow 0.87 [0.64 , 1.19] CHS AA 1.11 [0.97 , 1.27] COPDGene AA KARE 1.04 [0.79 , 1.35] MESA AA 1.1 [0.78, 1.56] MESA Hispanic 1.5 [0.95, 2.39] 1.09 [1.07 , 1.11] Overall 0.50 0.71 1.5 Odds Ratio

Supplementary Figure 1-36: Forest plot for rs12519165 (FGF18 locus at 5q35.1)

5:170901586:A/T rs12519165

Overall	1.07 [1.05 , 1.09]	0.50 0.71 1.5 Odds Ratio
MESA Hispanic	1.68 [0.96 , 2.95]	\rightarrow
MESA AA	1.01 [0.6 , 1.7]	\longrightarrow
COPDGene AA	1.1 [0.95 , 1.27]	
CHS AA	1.14 [0.8 , 1.63]	\longrightarrow
RS3	1.2 [0.79 , 1.84]	\longrightarrow
RS2	1.1 [0.71 , 1.69]	\longrightarrow
RS1	0.85 [0.57 , 1.28]	
Norway/GenKOLS	1.07 [0.86 , 1.33]	
NETT-NAS	1 [0.74 , 1.34]	
MESA Caucasian	1.13 [0.83 , 1.55]	\longrightarrow
LifeLines	1.17 [0.96 , 1.42]	
FHS	1.08 [0.85 , 1.36]	
ECLIPSE	0.88 [0.63 , 1.22]	
COPDGene NHW	1 [0.92 , 1.1]	-
CHS EA	0.97 [0.79 , 1.18]	
ARIC	0.92 [0.81 , 1.04]	
UK Biobank	1.08 [1.05 , 1.1]	

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

6:7211818:A/G rs1334576

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
TCGS-Korea	0.85 [0.52 , 1.38]	
MESA Hispanic	0.72 [0.46 , 1.12]	<
MESA AA	1.14 [0.8 , 1.63]	_ >
COPDGene AA	0.95 [0.83 , 1.09]	
CHS AA	0.95 [0.69 , 1.31]	
TCGS-Poland	0.85 [0.66 , 1.1]	
SPIROMICS	0.95 [0.73 , 1.22]	
RS3	1.22 [0.9 , 1.67]	\longrightarrow
RS2	0.91 [0.65 , 1.28]	
RS1	1.24 [0.93 , 1.66]	\longrightarrow
Norway/GenKOLS	1[0.84,1.18]	
NETT-NAS	0.93 [0.74 , 1.16]	
MESA Caucasian	0.9 [0.69 , 1.18]	
LifeLines	1[0.87,1.15]	
FHS	1.13 [0.99 , 1.28]	
EQTL	0.83 [0.62 , 1.09]	
EOCOPD/ICGN	1.09 [0.95 , 1.25]	
ECLIPSE	1.2 [0.92 , 1.57]	\longrightarrow
COPDGene NHW	1.08 [0.98 , 1.18]	
CHS EA	1.06 [0.92 , 1.22]	
ARIC	1 [0.89 , 1.11]	
UK Biobank	1.07 [1.05 , 1.09]	

Supplementary Figure 1-38: Forest plot for rs9350191 (ID4 locus at 6p22.3)

6:19842661:T/C rs9350191

		0.50 0.71 1.5 Odds Ratio
Overall	1.12 [1.09 , 1.15]	
COPDGene AA	1.27 [0.97 , 1.65]	_ >
CHS AA	0.95 [0.55 , 1.62]	>
RS3	1.58 [0.78 . 3.19]	>
RS2	1.76 [0.79 , 3.93]	
RS1	0.84 [0.46 , 1.55]	\leftarrow
Norway/GenKOLS	1.34 [0.97 , 1.85]	
NETT-NAS	1.06 [0.71 , 1.58]	
MESA Caucasian	0.99 [0.63 , 1.57]	
LifeLines	1.06 [0.86 , 1.3]	
ECLIPSE	0.84 [0.52 , 1.35]	
COPDGene NHW	1.18 [1.01 , 1.38]	
CHS EA	1.22 [0.84 , 1.78]	\longrightarrow
ARIC	1.1 [0.92 , 1.32]	_
UK Biobank	1.11 [1.08 , 1.15]	

Supplementary Figure 1-39: Forest plot for rs13198656 (PRL locus at 6p22.3)

6:22004909:T/C rs13198656

Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.74 [0.45 , 1.19]	<
MESA AA	0.95 [0.6 , 1.5]	
KARE	1.04 [0.81 , 1.33]	
COPDGene AA	0.97 [0.81 , 1.16]	
CHS AA	1.05 [0.7 , 1.58]	
SPIROMICS	1.13 [0.88 , 1.47]	
RS3	0.81 [0.59 , 1.1]	
RS2	0.98 [0.71 , 1.36]	
RS1	1.11 [0.82 , 1.5]	
Norway/GenKOLS	1.13 [0.95 , 1.34]	
NETT-NAS	0.83 [0.67 , 1.02]	
MESA Caucasian	1.21 [0.93 , 1.58]	_
LifeLines	1.08 [0.94 , 1.25]	_
FHS	1.1 [0.96 , 1.26]	_
EQTL	1.05 [0.79 , 1.4]	
ECLIPSE	1.12 [0.87 , 1.45]	
COPDGene NHW	1.1 [1.01 , 1.21]	-
CHS EA	0.98 [0.85 , 1.13]	
ARIC	1.1 [0.99 , 1.23]	-
UK Biobank	1.06 [1.04 , 1.09]	

 \rightarrow

 \geq

1.5

0.71 Odds Ratio

0.50

Supplementary Figure 1-40: Forest plot for rs2284174 (IER3 locus at 6p21.33)

6:30713580:C/T rs2284174



Supplementary Figure 1-41: Forest plot for rs2070600 (AGER locus at 6p21.32)

6:32151443:C/T rs2070600

UK Biobank	1.19 [1.14 , 1.25]	
ARIC	1.26 [0.98 , 1.63]	
CHS EA	1.07 [0.77 , 1.49]	_
COPDGene NHW	1.43 [1.16 , 1.76]	
ECLIPSE	1.52 [0.82 , 2.8]	>
EOCOPD/ICGN	1.16 [0.82 , 1.66]	_ _>
EQTL	1.07 [0.52 , 2.19]	_ >
FHS	1.17 [0.82 , 1.66]	
LifeLines	1.48 [0.95 , 2.3]	
NETT-NAS	1.46 [0.92 , 2.31]	
Norway/GenKOLS	0.91 [0.61 , 1.35]	
RS1	3.74 [0.28 , 49.18]	<>
RS2	0.79 [0.06 , 10.85]	$\langle \rangle$
RS3	14.51 [0.74 , 285.49]	>
SPIROMICS	1.45 [0.83 , 2.54]	
TCGS-Poland	0.85 [0.29 , 2.47]	$\longleftrightarrow \longrightarrow$
TCGS-Korea	1.32 [0.69 , 2.49]	●>
Overall	1.21 [1.15 , 1.26]	0.50 0.71 1.5
		Odas Ratio

Supplementary Figure 1-42: Forest plot for rs2806356 (ARMC2 locus at 6q21)

6:109266255:C/T rs2806356		
UK Biobank	1.1 [1.07 , 1.13]	
ARIC	1.11 [0.97 , 1.28]	
CHS EA	1.15 [0.96 , 1.38]	
COPDGene NHW	1.17 [1.05 , 1.31]	
ECLIPSE	0.82 [0.6 , 1.12]	
EOCOPD/ICGN	1.13 [0.95 , 1.33]	
EQTL	0.85 [0.6 , 1.22]	
FHS	0.95 [0.8 , 1.13]	
LifeLines	1.23 [1.03 , 1.47]	
MESA Caucasian	1.28 [0.92 , 1.77]	
NETT-NAS	1.16 [0.88 , 1.51]	
Norway/GenKOLS	1.35 [1.09 , 1.68]	
RS1	1 [0.68 , 1.47]	_
RS2	1.27 [0.84 , 1.94]	
RS3	0.93 [0.62 , 1.42]	
SPIROMICS	1.14 [0.81 , 1.58]	
TCGS-Poland	1.3 [0.93 , 1.84]	
CHS AA	1 35 [0 68 2 68]	_
COPDGene AA	0.92 [0.68 . 1.25]	
MESA Hispanic	1.43 [0.81 , 2.52]	
TCGS-Korea	22[11 439]	
	2.2[1.1, 7.00]	

Overall

1.1 [1.08 , 1.13]



Supplementary Figure 1-43: Forest plot for rs674621 (RFX6 locus at 6q22.1)

6:117257018:C/T rs674621

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	0.85 [0.51 , 1.41]	
MESA AA	1.07 [0.72 , 1.58]	
	1.13[0.92, 1.39]	
	1.05[0.91, 1.21]	
	1.22[0.89,1.68]	
		- ~
SPIROMICS	1.11 [0.84 , 1.46]	
RS3	0.89 [0.63 , 1.26]	
RS2	1.05 [0.73 , 1.49]	₽
RS1	1.25 [0.91 , 1.72]	\rightarrow
Norway/GenKOLS	1.2 [1.01 , 1.43]	
NETT-NAS	0.98 [0.78 , 1.22]	
MESA Caucasian	1.1 [0.83 , 1.46]	
LiteLines	1.11 [0.96 , 1.29]	
FHS	1.17 [1.01 , 1.34]	- ■
EQIL	0.82[0.6,1.11]	
EGLIPSE	1.12[0.84, 1.48]	
	1.07[0.97,1.18]	
	1.05[0.9,1.25]	
	105[00,122]	
	1[0.90, 1.12]	
LIK Biobank	106[103 108]	

1.5

Supplementary Figure 1-44: Forest plot for rs646695 (CITED2 locus at 6q24.1)

6:	140)280)398	:C/T	rs64669	5
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Overall	1.08 [1.05 , 1.1]	0.50 0.71 1.5 Odds Ratio
MESA Hispanic	0.85 [0.49 , 1.48]	←
MESA AA	1.6 [0.99 , 2.57]	
KARE	0.86 [0.69 , 1.07]	
COPDGene AA	1.06 [0.89 , 1.26]	
CHS AA	1.42 [0.94 , 2.14]	
SPIROMICS	1.24 [0.91 , 1.68]	_ >
RS3	0.85 [0.57 , 1.26]	
RS2	0.66 [0.42 , 1.03]	←
RS1	1.26 [0.9 , 1.74]	\longrightarrow
Norway/GenKOLS	1 [0.82 , 1.22]	_
NETT-NAS	1.29 [1.02 , 1.63]	\longrightarrow
MESA Caucasian	1.2 [0.9 , 1.6]	\longrightarrow
LifeLines	1.16 [0.98 , 1.38]	
FHS	0.98 [0.84 , 1.15]	
EQTL	0.98 [0.71 , 1.36]	
ECLIPSE	1.02 [0.77 , 1.37]	
COPDGene NHW	1.1 [1 , 1.22]	-
CHS EA	1.06 [0.9 , 1.24]	_ _
ARIC	1.15 [1.02 , 1.31]	
UK Biobank	1.07 [1.05 , 1.1]	

Supplementary Figure 1-45: Forest plot for rs9399401 (ADGRG6 locus at 6q24.1)

6:142668901:T/C rs9399401		
UK Biobank	1.16 [1.14 , 1.19]	
ARIC	1.16 [1.03 , 1.31]	
CHS EA	1.23 [1.05 , 1.44]	
COPDGene NHW	1.09 [0.99 , 1.2]	
ECLIPSE	0.96 [0.71 , 1.28]	
EOCOPD/ICGN	1.15 [0.99 , 1.34]	
EQTL	1.31 [0.95 , 1.8]	_
FHS	1.21 [1.03 , 1.42]	
LifeLines	1.14 [0.94 , 1.39]	_
MESA Caucasian	0.82 [0.61 , 1.1] 🛛 —	-
NETT-NAS	1.02 [0.81 , 1.29]	
Norway/GenKOLS	1.07 [0.88 , 1.3]	
RS1	1.32 [0.93 , 1.86]	_
RS2	1.24 [0.85 , 1.81]	
RS3	1.05 [0.74 , 1.49]	
SPIROMICS	1.04 [0.78 , 1.38]	
TCGS-Poland	1.12 [0.86 , 1.47]	
CHS AA	1.07 [0.75 , 1.51]	
COPDGene AA	1.2 [1.05 , 1.38]	
KARE	1.23 [0.98 , 1.56]	-
MESA AA	1.2 [0.84 , 1.72]	
MESA Hispanic	1.51 [0.93 , 2.46]	_
TCGS-Korea	2.04 [1.16 , 3.61]	
Overall	1.16 [1.13 , 1.18]	

_

0.71

Odds Ratio

─∎→ ∎→

 \rightarrow

 \rightarrow \rightarrow \rightarrow

1.5

—∎→ —∎— Supplementary Figure 1-46: Forest plot for rs798565 (AMZ1 locus at 7p22.3)

7:2752152:G/A rs798565

Overall	1.07 [1.04 , 1.09]	0.50 0.71 1.5 Odds Ratio
MESA Hispanic	0.93 [0.53 , 1.63]	\longrightarrow
MESA AA	1.46 [0.84 , 2.54]	
COPDGene AA	0.96 [0.78 , 1.19]	
CHS AA	0.83 [0.48 , 1.43]	← ■
nos	0.89 [0.62 , 1.26]	
RS2	0.87[0.52 1.21]	
RS1	0.94[0.67,1.43]	
Norway/GenKOLS	1 18 [0.97 1 45]	
NETT-NAS	0.91 [0.72 , 1.15]	
MESA Caucasian	1.02 [0.76 . 1.38]	
LifeLines	1.13 [0.95 . 1.34]	
FHS	0.95 [0.82 . 1.1]	
EQTL	1.02 [0.73 , 1.42]	
ECLIPSE	1.04 [0.78 , 1.4]	
COPDGene NHW	1.01 [0.91 , 1.11]	
CHS EA	1.03 [0.87 , 1.22]	
ARIC	0.92 [0.82 , 1.04]	
UK Biobank	1.09 [1.06 , 1.11]	

Supplementary Figure 1-47: Forest plot for rs2040732 (ITGB8 locus at 7p21.1)

7:20418134:C/T rs2040732

		0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	1.67 [0.99 , 2.81]	\rightarrow
MESA AA	1.13 [0.79 , 1.63]	\longrightarrow
KARE	1.14 [0.92 , 1.41]	
COPDGene AA	0.96 [0.84 , 1.1]	
CHS AA	0.95 [0.68 , 1.31]	
RS2	0.92 [0.66 , 1.29]	
RS1	0.86 [0.64 , 1.16]	
Norway/GenKOLS	1.21 [1.01 , 1.43]	
NETT-NAS	1.09 [0.88 , 1.35]	
MESA Caucasian	1.03 [0.8 , 1.34]	_
LifeLines	1.07 [0.92 , 1.23]	_
FHS	1.08 [0.95 , 1.22]	
EQTL	1.06 [0.8 , 1.41]	
ECLIPSE	0.9 [0.69 , 1.17]	
COPDGene NHW	0.97 [0.89 , 1.06]	
CHS EA	1.14 [0.99 , 1.32]	
ARIC	0.99 [0.89 , 1.1]	
UK Biobank	1.07 [1.05 , 1.09]	

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

7:99630342:C/T rs2897075

		0.71 1.5 Odds Ratio
Overall	1.07 [1.04 , 1.09]	•
MESA Hispanic	1.22 [0.77 , 1.92]	_ >
MESA AA	1.43 [0.87 , 2.35]	
KARE	1.19 [0.96 , 1.47]	
COPDGene AA	1 [0.82 , 1.22]	
CHS AA	1.43 [0.89 , 2.29]	
RS3	0.99 [0.72 , 1.36]	
RS2	1.04 [0.72 , 1.49]	_
RS1	0.99[0.71,1.38]	
Norway/GenKOLS	1.01 [0.84 , 1.21]	
NETT-NAS	1.16 [0.93 , 1.45]	
MESA Caucasian	1.08 [0.82 , 1.42]	
LifeLines	1.06 [0.92 , 1.23]	
FHS	1.14 [1 , 1.32]	
EQTL	1.26 [0.93 , 1.71]	\rightarrow
ECLIPSE	1.09 [0.84 , 1.42]	
COPDGene NHW	1.01 [0.93 , 1.11]	
CHS EA	1.02 [0.89 , 1.19]	
ARIC	1.14 [1.02 , 1.28]	
UK Biobank	1.06 [1.04 , 1.09]	

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

8:8697658:C/G rs9329170

Overall	1.1 [1.07 , 1.13]	0.50 0.71 1.5 Odds Ratio
	-	
MESA AA	1.02 [0.66 , 1.57]	>
COPDGene AA	1.14 [0.97 , 1.34]	
CHS AA	1.14 [0.78 , 1.67]	_ >
RS3	1.25 [0.79 , 1.99]	_ >
RS2	1.3 [0.8 , 2.11]	
RS1	0.91 [0.58 , 1.42]	
Norway/GenKOLS	1.33 [1.05 , 1.7]	
NETT-NAS	1.36 [1 , 1.87]	
MESA Caucasian	0.66 [0.46 , 0.95]	← ■
LifeLines	1.07 [0.86 , 1.33]	_
FHS	1.01 [0.83 , 1.23]	
EQTL	1.25 [0.81 , 1.94]	_ >
ECLIPSE	1.16 [0.82 , 1.65]	\longrightarrow
COPDGene NHW	1.05 [0.93 , 1.2]	
CHS EA	1.09 [0.88 , 1.36]	
ARIC	1.06 [0.91 , 1.23]	— — —
UK Biobank	1.1 [1.06 , 1.14]	

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

9:4143749:T/A rs10114763

Overall	1.07 [1.05 , 1.09]	· · · ·
MESA Hispanic	0.7 [0.44 , 1.1]	←
MESA AA	1.25 [0.88 , 1.78]	_ >
KARE	0.77 [0.56 , 1.07]	
COPDGene AA	1.14 [1 , 1.3]	
CHS AA	1.23 [0.9 , 1.68]	
SPIROMICS	1.09 [0.84 , 1.42]	
RS2	1.01 [0.73 , 1.39]	
RS1	1.2[0.89,1.62]	
Norway/GenKOLS	1.03 [0.86 , 1.23]	
NETT-NAS	1.16 [0.94 , 1.44]	
MESA Caucasian	1.25 [0.95 , 1.62]	
LifeLines	1.13 [0.98 , 1.29]	
FHS	1.12 [0.98 , 1.29]	
EQTL	0.84 [0.63 , 1.12]	
ECLIPSE	1.01 [0.77 , 1.32]	
COPDGene NHW	1.03 [0.94 , 1.12]	-
CHS EA	1 [0.87 , 1.16]	
ARIC	1.05 [0.94 , 1.17]	
UK Biobank	1.08 [1.05 , 1.1]	

0.71 Odds Ratio

1.5

0.50

71

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

9:23588684:T/C rs156394

		0.71 1.5 Odds Ratio
Overall	1.07 [1.05 , 1.09]	\
MESA Hispanic	1.8 [1.13 , 2.86]	\longrightarrow
MESA AA	1.44 [1 , 2.08]	
COPDGene AA	1 [0.83 , 1.19]	e
CHS AA	1.12 [0.8 , 1.57]	
100	1.04 [0.75 , 1.44]	
RS2	1.04[0.75, 1.44]	
RS2	14[099.2]	
RS1	1.53 [1.09 2.15]	>
Norway/GenKOLS	1.29 [1.07 . 1.56]	_ >
NETT-NAS	1.03 [0.82 , 1.3]	e
MESA Caucasian	1.01 [0.77 , 1.32]	_
LifeLines	0.99 [0.84 , 1.16]	
FHS	1.06 [0.91 , 1.25]	
ECLIPSE	1.02 [0.78 , 1.34]	
COPDGene NHW	1.09 [0.99 , 1.2]	
CHS EA	1.04 [0.9 , 1.21]	
ARIC	1[0.9,1.11]	
UK Biobank	1.07 [1.05 , 1.1]	
Supplementary Figure 1-52: Forest plot for rs7866939 (RASEF locus at 9q21.32)

9:85126163:C/T rs7866939

	1.00 [1.04 , 1.00]	0.50 0.71 1.5 Odds Ratio
Overall	106[104 108]	
TCGS-Korea	1.4 [0.86 , 2.27]	∎>
MESA Hispanic	1.33 [0.82 , 2.16]	
MESA AA	0.93 [0.63 , 1.36]	
COPDGene AA	1.02 [0.88 , 1.18]	
CHS AA	0.94 [0.67 , 1.32]	
TCGS-Poland	1.31 [1.03 , 1.68]	_ >
SPIROMICS	1.14 [0.86 , 1.5]	
RS3	0.81 [0.57 , 1.17]	_
RS2	1.32 [0.89 , 1.95]	
RS1	1.07 [0.75 , 1.52]	
Norway/GenKOLS	1.09 [0.89 , 1.33]	_
NETT-NAS	1 [0.78 , 1.27]	_
MESA Caucasian	1.07 [0.79 , 1.43]	
LifeLines	0.98 [0.83 , 1.16]	_
FHS	1.15 [0.96 , 1.38]	B
EOCOPD/ICGN	1.08 [0.94 , 1.24]	
ECLIPSE	1.15 [0.85 , 1.54]	
COPDGene NHW	1.1 [0.99 , 1.21]	
CHS EA	0.97 [0.82 , 1.15]	
ARIC	1.06 [0.94 , 1.2]	
UK Biobank	1.06 [1.03 , 1.08]	

Supplementary Figure 1-53: Forest plot for rs10760580 (COL15A1 locus at 9q22.33)

9:101661650:G/A rs10760580



Supplementary Figure 1-54: Forest plot for rs803923 (ASTN2 locus at 9q33.1)

9:119401650:A/G rs803923

Overall	1.06 [1.04 , 1.08]	· · · · · · · · · · · · · · · · · · ·
		4
MESA Hispanic	1.05 [0.68 , 1.63]	\longrightarrow
MESA AA	0.87 [0.6 , 1.25]	
KARE	1.03 [0.77 , 1.38]	
COPDGene AA	1.05 [0.91 , 1.2]	
CHS AA	1.34 [0.99 , 1.83]	
SPIROMICS	0.91 [0.7 , 1.18]	
RS3	0.93 [0.68 , 1.26]	
RS2	1.2 [0.84 , 1.72]	_ >
RS1	1.17 [0.86 , 1.6]	B >
Norway/GenKOLS	1.31 [1.1 , 1.55]	
NETT-NAS	1.07 [0.87 , 1.32]	
MESA Caucasian	1.28 [0.99 , 1.65]	
LifeLines	1.17 [1.02 , 1.34]	
FHS	1.1 [0.97 , 1.25]	
EQTL	1.1 [0.82 , 1.47]	
ECLIPSE	0.89 [0.68 , 1.16]	
COPDGene NHW	1.09 [1 , 1.19]	-
CHS EA	1.03 [0.89 , 1.18]	
ARIC	1.13 [1.01 , 1.25]	
UK Biobank	1.04 [1.02 , 1.07]	

0.50

0.71

Odds Ratio

1.5

Supplementary Figure 1-55: Forest plot for rs7068966 (CDC123 locus at 10p13)

10:12277992:C/T rs7068966 UK Biobank 1.11 [1.08 , 1.13] 1.08 [0.97 , 1.2] ARIC CHS EA 1.25 [1.09 , 1.44] **COPDGene NHW** 1.01 [0.92 , 1.1] **ECLIPSE** 0.88 [0.68 , 1.13] 1.08 [0.95 , 1.23] EOCOPD/ICGN 0.99 [0.75 , 1.31] EQTL 1.14 [1 , 1.3] FHS LifeLines 1.07 [0.93 , 1.24] 0.9 [0.7 , 1.15] **MESA** Caucasian 0.9 [0.72 , 1.12] **NETT-NAS** Norway/GenKOLS 1.15 [0.97 , 1.37] 1.16 [0.86 , 1.57] RS1 RS2 1.05 [0.74 , 1.48] RS3 0.97 [0.7 , 1.33] SPIROMICS 1.15 [0.9 , 1.49] 1.75 [1.35 , 2.28] **TCGS-Poland** 1.02 [0.71 , 1.47] CHS AA 1.18 [1.01 , 1.38] COPDGene AA 1 [0.66 , 1.51] MESA AA MESA Hispanic 1.26 [0.8 , 1.99] 1.13 [0.68 , 1.88] **TCGS-Korea** Overall 1.1 [1.08 , 1.12]

0.71

Odds Ratio

1.5

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

10:78318879:C/A rs2579762

	- · •	0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.09]	•
MESA Hispanic	0.97 [0.61 , 1.52]	
MESA AA	0.99 [0.62 , 1.6]	\longrightarrow
KARE	0.9 [0.72 , 1.12]	
COPDGene AA	0.92 [0.77 , 1.09]	
CHS AA	1.37 [0.9 , 2.1]	
RS3	0.95 [0.7 , 1.29]	
RS2	1.09 [0.79 , 1.51]	>
RS1	0.92 [0.68 , 1.24]	
Norway/GenKOLS	1.27 [1.07 , 1.51]	-
NETT-NAS	0.86 [0.7 , 1.06]	
MESA Caucasian	0.95 [0.73 , 1.23]	
LifeLines	1.26 [1.09 , 1.47]	
FHS	1.05 [0.92 , 1.2]	
EQTL	1.03 [0.78 , 1.37]	
ECLIPSE	0.99 [0.76 , 1.29]	
COPDGene NHW	1.01 [0.92 , 1.1]	
CHS EA	1.11 [0.96 , 1.28]	
ARIC	0.98 [0.89 , 1.1]	
UK Biobank	1.07 [1.05 , 1.1]	

Supplementary Figure 1-57: Forest plot for rs721917 (SFTPD locus at 10q22.3)

10:81706324:G/A rs721917 UK Biobank 1.05 [1.02 , 1.07] ARIC 1.03 [0.92 , 1.14] 1.1 [0.95 , 1.27] CHS EA **COPDGene NHW** 1.04 [0.95 , 1.13] 1.16 [0.89 , 1.51] ECLIPSE EOCOPD/ICGN 1.15 [1.01 , 1.32] EQTL 0.88 [0.67 , 1.16] FHS 1.03 [0.9 , 1.17] 1.24 [1.07 , 1.44] LifeLines 1.24 [0.95 , 1.62] **MESA** Caucasian 1.22 [0.98 , 1.51] **NETT-NAS** Norway/GenKOLS 1.15 [0.97 , 1.37] 1.08 [0.8 , 1.45] RS1 RS2 1.19 [0.85 , 1.67] 0.79 [0.58 , 1.08] RS3 SPIROMICS 1.17 [0.91, 1.5] 1.07 [0.83 , 1.37] **TCGS-Poland** CHS AA 1.26 [0.91, 1.76] **COPDGene AA** 1.14 [1, 1.29] KARE 0.9 [0.72 , 1.12] 0.99 [0.69 , 1.42] MESA AA 1.59 [0.99 , 2.55] MESA Hispanic 1.11 [0.67 , 1.82] **TCGS-Korea** Overall 1.06 [1.04 , 1.08]

0.50

0.71

Odds Ratio

1.5

Supplementary Figure 1-58: Forest plot for rs1570221 (STN1 locus at 10q24.33)

10:105656874:A/G rs1570221 UK Biobank 1.06 [1.03 , 1.08] ARIC 1.14 [1.02 , 1.27] 0.99 [0.86 , 1.15] CHS EA 1.13 [1.03 , 1.24] **COPDGene NHW** 1.17 [0.89 , 1.55] **ECLIPSE** EQTL 0.91 [0.68 , 1.21] FHS 1.15 [1 , 1.32] LifeLines 0.98 [0.85 , 1.13] 1.03 [0.8 , 1.34] **MESA** Caucasian **NETT-NAS** 1.15 [0.93 , 1.43] Norway/GenKOLS 0.94 [0.79 , 1.12] RS1 0.85 [0.62 , 1.16] 0.99 [0.7 , 1.41] RS2 RS3 1.19 [0.85 , 1.65] SPIROMICS 1.16 [0.89 , 1.53] 1.03 [0.66 , 1.58] CHS AA COPDGene AA 1.08 [0.9 , 1.29] KARE 1.04 [0.83 , 1.29] MESA AA 1.2 [0.74 , 1.97] 0.7 [0.44, 1.14] MESA Hispanic 1.06 [1.04 , 1.08] Overall

0.50

0.71

Odds Ratio

1.5

Supplementary Figure 1-59: Forest plot for rs4757118 (ARNTL locus at 11p15.2)

11:13171236:T/C rs4757118

		0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	•
MESA Hispanic	1.37 [0.89 , 2.11]	
MESA AA	1.25 [0.8 , 1.97]	
KARE	1 [0.81 , 1.22]	
COPDGene AA	1.17 [0.98 , 1.39]	
CHS AA	1.23 [0.83 , 1.83]	_ >
noo	0.90[0.72,1.33]	
RS3		
BS2	1 19 [0 85 1 66]	
RS1	0.93[0.7, 1.25]	
Norway/GenKOLS	1 12 [0 94 1 34]	
NETT-NAS	0.99[0.8, 1.22]	
MESA Caucasian		
LifeLines	0.99 [0.86 , 1.14]	
FHS	1.03 [0.89 . 1.19]	
EQTL	1.35 [1.01 , 1.81]	
ECLIPSE	1.13 [0.88 , 1.46]	
COPDGene NHW	0.96 [0.87 , 1.04]	
CHS EA	0.99 [0.85 , 1.14]	
ARIC	1.09 [0.98 , 1.22]	
UK Biobank	1.07 [1.04 , 1.09]	

Supplementary Figure 1-60: Forest plot for rs117261012 (PRSS23 locus at 11q14.2)

11:86444761:G/A rs117261012



Supplementary Figure 1-61: Forest plot for rs11049386 (CCDC91 locus at 12p11.22)

12:28320536:T/A rs11049386

Overall	1.06 [1.04 , 1.09]	0.50 0.71 1.5 Odds Ratio
	-	
KARE	1.78 [1.05 , 3.02]	$ \longrightarrow$
COPDGene AA	1.12 [0.84 , 1.51]	
CHS AA	1.15 [0.59 , 2.25]	_ >
RS3	1.1 [0.78 , 1.55]	\longrightarrow
RS2	0.94 [0.64 , 1.38]	
RS1	0.94 [0.68 , 1.32]	
Norway/GenKOLS	0.91 [0.75 , 1.11]	
NETT-NAS	0.98 [0.77 , 1.26]	
MESA Caucasian	1.15 [0.85 , 1.57]	\rightarrow
LifeLines	0.92 [0.79 , 1.07]	
FHS	1 [0.86 , 1.16]	
EQTL	1.2 [0.86 , 1.66]	
ECLIPSE	1.18 [0.88 , 1.59]	\rightarrow
COPDGene NHW	1.08 [0.98 , 1.2]	
CHS EA	1.06 [0.9 , 1.24]	
ARIC	1.01 [0.9 , 1.14]	
UK Biobank	1.07 [1.05 , 1.1]	

Supplementary Figure 1-62: Forest plot for rs7307510 (SNRPF locus at 12q23.1)

12:96237570:C/T rs7307510 UK Biobank 1.07 [1.04 , 1.1] 1.08 [0.94 , 1.23] ARIC CHS EA 1.07 [0.9 , 1.27] 1.02 [0.91 , 1.14] **COPDGene NHW** 1.17 [0.85 , 1.61] **ECLIPSE** 1.03 [0.88 , 1.22] EOCOPD/ICGN 1.25 [0.88 , 1.79] EQTL FHS 1.17 [0.99, 1.38] LifeLines 0.9 [0.76 , 1.07] 0.99 [0.72 , 1.35] **MESA** Caucasian 1.3 [1, 1.69] **NETT-NAS** Norway/GenKOLS 1.23 [0.97 , 1.56] 0.9 [0.63 , 1.28] RS1 RS2 1.29 [0.82 , 2.01] RS3 1.11 [0.74 , 1.66] SPIROMICS 1.18 [0.87 , 1.59] 1.06 [0.77 , 1.46] **TCGS-Poland** CHS AA 1.04 [0.73 , 1.47] 1.25 [1.07 , 1.45] **COPDGene AA** KARE 1.02 [0.75 , 1.39] MESA AA 1.11 [0.76 , 1.63] 0.83 [0.4 , 1.73] **TCGS-Korea**

Overall

1.08 [1.05 , 1.1]

0.50 0.71 1.5

Odds Ratio

Supplementary Figure 1-63: Forest plot for rs7958945 (MED13L locus at 12q24.21)

12:115947901:G/A rs7958945 UK Biobank 1.06 [1.04 , 1.09] ARIC 1.17 [1.04 , 1.3] 1.03 [0.89 , 1.2] CHS EA 1.06 [0.97 , 1.16] **COPDGene NHW** 0.82 [0.63 , 1.08] **ECLIPSE** 0.95 [0.7 , 1.29] EQTL FHS 0.9 [0.78 , 1.05] LifeLines 1.11 [0.95 , 1.29] 1.05 [0.81 , 1.36] Lovelace **MESA** Caucasian 1.24 [0.95 , 1.61] \rightarrow 0.98 [0.78 , 1.22] **NETT-NAS** 1.19 [0.99 , 1.44] Norway/GenKOLS RS1 0.79 [0.57 , 1.09] 0.9 [0.63 , 1.29] RS2 RS3 1 [0.72 , 1.4] SPIROMICS 1.11 [0.85 , 1.44] CHS AA 0.97 [0.69 , 1.35] 1.25 [1.08 , 1.44] COPDGene AA 1.2 [0.9 , 1.58] KARE MESA AA 1.11 [0.74 , 1.67] MESA Hispanic 0.74 [0.46 , 1.17] Overall 1.06 [1.04 , 1.09] 0.50 0.71 1.5

Odds Ratio

Supplementary Figure 1-64: Forest plot for rs9525927 (SERP2 locus at 13q14.11)

13:44842503:G/A rs9525927

		0.50 0.71 1.5 Odds Ratio
Overall	1.08 [1.05 , 1.1]	
MESA Hispanic	1.85 [1.1 , 3.09]	\longrightarrow
MESA AA	1.33 [0.84 , 2.12]	
	1.21 [0.98 , 1.5]	
	1.04 [0.88 , 1.24]	
	1.22[0.81, 1.83]	
SPIROMICS	0.92[0.67,1.27]	
RS3	1.01 [0.67 , 1.53]	>
RS2	0.94 [0.61 , 1.44]	
RS1	1.01 [0.69 , 1.5]	>
Norway/GenKOLS	0.92 [0.74 , 1.15]	_
NETT-NAS	1.07 [0.82 , 1.39]	_
MESA Caucasian	1.18 [0.85 , 1.64]	\longrightarrow
Lovelace	1.4 [1.05 , 1.87]	B >
LifeLines	1.31 [1.11 , 1.55]	
FHS	1.22 [1.04 , 1.44]	
EQTL	0.81 [0.56 , 1.16]	
ECLIPSE	1.01 [0.72 , 1.41]	
COPDGene NHW	1.08 [0.96 , 1.21]	
CHS EA	1.01 [0.84 , 1.22]	
ARIC	1.06 [0.92 , 1.21]	
UK Biobank	1.07 [1.04 , 1.1]	

Supplementary Figure 1-65: Forest plot for rs72699855 (RIN3 locus at 14q32.12)

14:93105953:G/C rs72699855



Supplementary Figure 1-66: Forest plot for rs72731149 (DTWD1 locus at 15q21.2)

15:49984710:G/C rs72731149 UK Biobank 1.12 [1.07 , 1.17] ARIC 0.96 [0.78 , 1.18] CHS EA 1.13 [0.85 , 1.51] **COPDGene NHW** 1.26 [1.06 , 1.49] 1.42 [0.88 , 2.29] ECLIPSE EQTL 1.31 [0.72, 2.36] -FHS 0.85 [0.64 , 1.13] 0.95 [0.68 , 1.32] LifeLines 1.62 [0.96 , 2.72] **MESA** Caucasian 1.44 [0.92 , 2.24] **NETT-NAS** Norway/GenKOLS 1.41 [0.99 , 1.99] 0.8 [0.46 , 1.39] RS1 RS2 1.06 [0.54 , 2.1] 0.97 [0.52 , 1.79] RS3 SPIROMICS 1.13 [0.7 , 1.84] 1.15 [0.79 , 1.67] CHS AA 1.06 [0.9 , 1.24] **COPDGene AA** 1.02 [0.8 , 1.29] KARE 1.76 [1.18 , 2.64] MESA AA 1.12 [1.08 , 1.16] Overall 0.50 0.71 1.5 Odds Ratio

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

Overall	1.13 [1.11 , 1.15]	♦
TCGS-Korea	1.38 [0.72 . 2.65]	
MESA Hispanic	1.12 [0.67 , 1.88]	_ >
MESA AA	1.1 [0.78 , 1.55]	>
KARE	1.17 [0.92 , 1.5]	>
COPDGene AA	1.32 [1.16 , 1.51]	→
CHS AA	1.1 [0.81 , 1.48]	
TCGS-Poland	1.26 [0.96 , 1.65]	_ _>
RS3	0.86 [0.62 , 1.2]	
RS2	1.14 [0.82 , 1.61]	_ >
RS1	1.4 [1.02 , 1.91]	
Norway/GenKOLS	0.95 [0.79 , 1.14]	
NETT-NAS	1.14 [0.92 , 1.42]	
MESA Caucasian	1.13 [0.86 , 1.49]	
LifeLines	1.15 [1 , 1.33]	
FHS	1.08 [0.95 , 1.24]	
EQTL	0.82 [0.62 , 1.1]	_
EOCOPD/ICGN	1.2 [1.04 , 1.38]	
ECLIPSE	1.11 [0.84 , 1.46]	
COPDGene NHW	1.12 [1.02 , 1.22]	
CHS EA	1.15 [0.99 , 1.33]	
ARIC	1.11 [0.99 , 1.24]	
UK Biobank	1.13 [1.1 , 1.15]	
15:71612514:G/T rs1441358		

1.5

0.71

Odds Ratio

Supplementary Figure 1-68: Forest plot for rs55676755 (CHRNA3 locus at 15q25.1)

15:78898932:G/C rs55676755 UK Biobank 1.08 [1.06 , 1.11] ARIC 1.19 [1.07 , 1.33] CHS EA 1.13 [0.98 , 1.31] **COPDGene NHW** 1.23 [1.13 , 1.35] ECLIPSE 1.25 [0.95 , 1.65] EOCOPD/ICGN 1.34 [1.17 , 1.53] -EQTL 0.88 [0.66 , 1.18] FHS 1.09 [0.94 , 1.26] LifeLines 1.15 [0.99 , 1.33] 1.04 [0.8 , 1.37] **MESA** Caucasian 1.58 [1.26 , 1.97] **NETT-NAS** Norway/GenKOLS 1.38 [1.15 , 1.65] 1.26 [0.91 , 1.74] RS1 RS2 0.73 [0.5 , 1.08] RS3 1.08 [0.79 , 1.49] SPIROMICS 1.43 [1.09 , 1.89] **TCGS-Poland** 1.91 [1.46 , 2.5] CHS AA 0.79 [0.51 , 1.24] COPDGene AA 1.34 [1.13 , 1.59] KARE 0.82 [0.41 , 1.62] MESA AA 1.1 [0.68, 1.76] 1.33 [0.77 , 2.29] MESA Hispanic **TCGS-Korea** 2.94 [0.57 , 15.3] Overall 1.11 [1.09 , 1.14] 0.50 0.71 1.5

Odds Ratio

Supplementary Figure 1-69: Forest plot for rs10152300 (ADAMTSL3 locus at 15q25.2)

15:84392907:G/A rs10152300

		0.50 0.71 1.5 Odds Ratio
Overall	1.08 [1.06 , 1.11]	•
KARE	1.67 [1.1 , 2.54]	\rightarrow
COPDGene AA	1.06 [0.81 , 1.39]	
CHS AA	1.36 [0.79 , 2.34]	
SPIROMICS	1.01 [0.74 , 1.38]	
KS3	1.16[0.79, 1.7]	
K52	1 [0.68 , 1.47]	
KS1	1.16 [0.82 , 1.64]	
Norway/GenKOLS	1.16 [0.95 , 1.43]	
NETT-NAS	1.03 [0.8 , 1.32]	
MESA Caucasian	0.82[0.6,1.12]	
LifeLines	1.07 [0.9 , 1.26]	
FHS	1.06 [0.9 , 1.24]	
EQTL	0.85[0.61,1.19]	
ECLIPSE	1.02 [0.76 , 1.37]	
COPDGene NHW	1.09 [0.98 , 1.21]	-
CHS EA	1.19 [1.01 , 1.41]	
ARIC	1.03 [0.91 , 1.17]	-
UK Biobank	1.09 [1.06 , 1.11]	

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

16:10709013:C/T rs56134392

C totali		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 . 1.08]	
MESA Hispanic	1.2 [0.74 , 1.93]	\longrightarrow
MESA AA	0.81 [0.54 , 1.22]	
COPDGene AA	1.08 [0.94 , 1.23]	
CHS AA	1.76 [1.24 , 2.49]	\rightarrow
RS3	1.3 [0.95 , 1.77]	
RS2	0.82 [0.57 , 1.18]	
RS1	0.98 [0.7 , 1.37]	
Norway/GenKOLS	1.17 [0.97 , 1.41]	
NETT-NAS	1.23 [0.98 , 1.54]	$-\!$
MESA Caucasian	0.87 [0.66 , 1.15]	
LifeLines	1.07 [0.92 , 1.25]	
FHS	0.97 [0.83 , 1.14]	
EQTL	0.86 [0.64 , 1.16]	_
ECLIPSE	0.94 [0.72 , 1.24]	
COPDGene NHW	1.04 [0.95 , 1.14]	-
CHS EA	1.1 [0.94 , 1.29]	
ARIC	1.1 [0.98 , 1.24]	-8-
UK Biobank	1.06 [1.03 , 1.08]	

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

16:58022625:G/A rs8044657

		0.50 0.71 1.5 Odds Ratio
Overall	1.11 [1.07 . 1.15]	•
MESA AA	1.34 [0.87 , 2.07]	
COPDGene AA	1.03 [0.9 , 1.19]	
CHS AA	0.98 [0.69 , 1.39]	
SPIROMICS	1.52 [1.02 , 2.27]	\longrightarrow
RS3	1.15 [0.65 , 2.01]	$\longrightarrow \blacksquare \rightarrow$
RS2	1.72 [0.85 , 3.5]	\longrightarrow
RS1	0.77 [0.46 , 1.29]	<■
Norway/GenKOLS	1[0.7,1.42]	
NETT-NAS	1.45 [0.99 , 2.14]	
MESA Caucasian	1.38 [0.85 , 2.23]	
LifeLines	1.34 [0.99 , 1.81]	
FHS	1.02 [0.73 , 1.42]	
EQTL	1.2 [0.7 , 2.05]	\longrightarrow
ECLIPSE	0.95 [0.59 , 1.55]	\longrightarrow
COPDGene NHW	1.14 [0.98 , 1.33]	
CHS EA	0.96 [0.75 , 1.22]	
ARIC	0.96 [0.79 , 1.18]	
UK Biobank	1.12 [1.07 , 1.16]	

Supplementary Figure 1-72: Forest plot for rs4888379 (CFDP1 locus at 16q23.1)

16:75340231:T/A rs4888379 UK Biobank 1.1 [1.08 , 1.13] ARIC 1.17 [1.05 , 1.3] CHS EA 0.99 [0.86 , 1.15] **COPDGene NHW** 1.07 [0.98, 1.17] ECLIPSE 0.95 [0.72 , 1.24] EOCOPD/ICGN 1.08 [0.94 , 1.23] EQTL 1.09 [0.81, 1.45] FHS 1.07 [0.94 , 1.21] 0.99 [0.86 , 1.14] LifeLines **MESA** Caucasian 1.16 [0.9 , 1.5] 1.18 [0.95 , 1.46] NETT-NAS Norway/GenKOLS 1.08 [0.91 , 1.28] 0.95 [0.7 , 1.29] RS1 1.03 [0.72 , 1.46] RS2 1.05 [0.77 , 1.44] RS3 1.19 [0.93 , 1.53] SPIROMICS **TCGS-Poland** 1.2 [0.94 , 1.53] CHS AA 1.06 [0.76, 1.48] **COPDGene AA** 1.23 [1.07 , 1.41] KARE 1.03 [0.84 , 1.27] 1.03 [0.7 , 1.52] MESA AA 1.22 [0.75 , 1.97] MESA Hispanic **TCGS-Korea** 0.66 [0.4 , 1.08]

Overall

1.1 [1.08 , 1.12]

0.50

0.71

Odds Ratio

1.5

Supplementary Figure 1-73: Forest plot for rs8080772 (EFCAB5 locus at 17q11.2)

17:28413129:T/C rs8080772

		0.50 0.71 1.5 Odds Ratio
Overall	1.06 [1.04 , 1.08]	
MESA Hispanic	1.03 [0.62 , 1.72]	\longrightarrow
MESA AA	0.92[0.51,1.68]	\longrightarrow
COPDGene AA	0.91 [0.72 , 1.14]	
CHS AA	0.79 [0.47 , 1.34]	
RS3	1.05 [0.76 , 1.46]	
RS2	1.12 [0.78 , 1.6]	
RS1	1.54 [1.09 , 2.17]	>
Norway/GenKOLS	1.04 [0.87 , 1.24]	
NETT-NAS	1.16 [0.93 , 1.45]	
MESA Caucasian	1.06 [0.8 , 1.39]	
LifeLines	1[0.86,1.16]	
FHS	1.09 [0.94 , 1.26]	
EQTL	1.22 [0.9 , 1.66]	
ECLIPSE	1.01 [0.77 , 1.33]	
COPDGene NHW	1.06 [0.97 , 1.17]	-
CHS EA	1.09 [0.94 , 1.28]	
ARIC	1.03 [0.92 , 1.15]	
UK Biobank	1.06 [1.04 , 1.09]	

Supplementary Figure 1-74: Forest plot for rs34727469 (RPL23 locus at 17q12)

17:36835079:T/C rs34727469



Supplementary Figure 1-75: Forest plot for rs62065216 (THRA locus at 17q21.1)

17:38218773:A/G rs62065216



Supplementary Figure 1-76: Forest plot for rs12373142 (SPPL2C locus at 17q21.31)

17:43924200:G/C rs12373142



Supplementary Figure 1-77: Forest plot for rs11655567 (SOX9 locus at 17q24.3)

17:69216687:C/T rs11655567 UK Biobank 1.06 [1.04 , 1.08] ARIC 1.15 [1.03 , 1.28] CHS EA 1.02 [0.88 , 1.17] 1.06 [0.97 , 1.15] **COPDGene NHW** 1.02 [0.79 , 1.32] **ECLIPSE** EQTL 0.87 [0.66 , 1.15] FHS 1.01 [0.89 , 1.15] LifeLines 1.11 [0.96 , 1.27] **MESA** Caucasian 1.16 [0.89 , 1.53] **NETT-NAS** 1.04 [0.85 , 1.28] Norway/GenKOLS 1.12 [0.95 , 1.34] RS1 1.23 [0.91 , 1.66] RS2 0.97 [0.7 , 1.33] RS3 1.37 [1.01 , 1.87] SPIROMICS 1.02 [0.79 , 1.32] CHS AA 0.89 [0.64 , 1.23] COPDGene AA 0.98 [0.85 , 1.13] KARE 1.15 [0.93 , 1.42] MESA AA 1.19 [0.8 , 1.79] MESA Hispanic 1.25 [0.8 , 1.96] 1.06 [1.04 , 1.08] Overall

0.71

Odds Ratio

1.5

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

18:8808464:C/T rs647097

		0.71 1.5 Odds Ratio
Overall	1.08 [1.05 , 1.1]	
MESA Hispanic	1.27 [0.78 , 2.07]	\longrightarrow
MESA AA	1.23 [0.85 , 1.78]	
COPDGene AA	1.09 [0.96 , 1.24]	
CHS AA	1.29 [0.94 , 1.78]	\longrightarrow
SPIROMICS	1.26 [0.93 , 1.7]	\longrightarrow
RS3	1.19 [0.85 , 1.66]	$ \longrightarrow $
RS2	1.24 [0.86 , 1.79]	>
RS1	1.17 [0.84 , 1.64]	_ >
Norway/GenKOLS	1.05 [0.87 , 1.27]	
NETT-NAS	1.04 [0.82 , 1.31]	
MESA Caucasian	1.38 [1.03 , 1.84]	\longrightarrow
LifeLines	1.01 [0.86 , 1.18]	_
FHS	1.01 [0.88 , 1.16]	
EQTL	0.94 [0.69 , 1.29]	
ECLIPSE	1.04 [0.78 , 1.38]	_
COPDGene NHW	1.07 [0.97 , 1.18]	
CHS EA	1.21 [1.03 , 1.41]	_
ARIC	1.12 [0.99 , 1.26]	
UK Biobank	1.07 [1.04 , 1.1]	

Supplementary Figure 1-79: Forest plot for rs72626215 (DMWD locus at 19q13.32)

19:46294136:G/A rs72626215



Supplementary Figure 1-80: Forest plot for rs2096468 (KCNE2 locus at 21q22.11)

21:35661745:A/C rs2096468

1.06 [1.04 , 1.08]	0.50 0.71 1.5 Odds Ratio
1.32 [0.84 , 2.06]	
1.11 [0.77 , 1.58]	\longrightarrow
1.27 [1.03 , 1.58]	\longrightarrow
1.03 [0.9 , 1.18]	
1.28 [0.93 , 1.77]	
1.15 [0.89 , 1.5]	
1.14 [0.84 , 1.56]	\longrightarrow
1.55 [1.1 , 2.18]	
1.28 [0.96 , 1.71]	
1.2 [1.01 , 1.42]	-
1.19 [0.97 , 1.47]	-
0.99 [0.77 , 1.29]	
1.04 [0.9 , 1.19]	
0.95 [0.84 , 1.07]	
0.76 [0.57 , 1.02]	
1.1 [0.84 , 1.43]	
1.08 [0.99 , 1.18]	-
1.09 [0.95 , 1.26]	
1.1 [0.99 , 1.23]	
1.05 [1.02 , 1.07]	
	1.05 [1.02 , 1.07] 1.1 [0.99 , 1.23] 1.09 [0.95 , 1.26] 1.08 [0.99 , 1.18] 1.1 [0.84 , 1.43] 0.76 [0.57 , 1.02] 0.95 [0.84 , 1.07] 1.04 [0.9 , 1.19] 0.99 [0.77 , 1.29] 1.19 [0.97 , 1.47] 1.2 [1.01 , 1.42] 1.28 [0.96 , 1.71] 1.55 [1.1 , 2.18] 1.14 [0.84 , 1.56] 1.15 [0.89 , 1.5] 1.28 [0.93 , 1.77] 1.03 [0.9 , 1.18] 1.27 [1.03 , 1.58] 1.11 [0.77 , 1.58] 1.32 [0.84 , 2.06] 1.06 [1.04 , 1.08]

Supplementary Figure 1-81: Forest plot for rs9617650 (MICAL3 locus at 22q11.21)

22:18488883:G/C rs9617650

Overall	1.08 [1.06 , 1.11]	0.50 0.71 1.5 Odds Ratio
MESA AA	1.2 [0.67 , 2.14]	\longrightarrow
COPDGene AA	1.17 [0.95 , 1.44]	
CHS AA	1.04 [0.62 , 1.74]	>
H23	0.98[0.61,1.59]	\longrightarrow
	1.30 [U.OZ , 2.20]	
RS2	1 36 [0.82 2 25]	
RS1	0.83[0.54 1.27]	
Norway/GenKOLS	1 16 [0 9 1 49]	
NETT-NAS	1.03 [0.75 . 1 41]	
MESA Caucasian	1.17 [0.81 . 1.7]	\longrightarrow
LifeLines	1.15 [0.92 , 1.43]	
FHS	1.23 [0.97 , 1.55]	
ECLIPSE	1.25 [0.86 , 1.81]	\longrightarrow
COPDGene NHW	1.04 [0.92 , 1.17]	
CHS EA	0.9 [0.73 , 1.12]	
ARIC	1.08 [0.93 , 1.25]	
UK Biobank	1.08 [1.05 , 1.11]	

Supplementary Figure 1-82: Forest plot for rs73158393 (SYN3 locus at 22q12.3)

22:33335386:C/G rs73158393

Overall	1.07 [1.05 , 1.09]	0.50 0.71 1.5 Odds Ratio
		4
MESA Hispanic	0.94 [0.53 , 1.66]	\longrightarrow
KARE	0.64 [0.34 , 1.17]	←-■
COPDGene AA	1.08 [0.8 , 1.44]	
CHS AA	3.67 [1.66 , 8.09]	\rightarrow
RS3	1.32 [0.91 . 1.93]	
RS2	1.07 [0.72 , 1.61]	
RS1	1.43 [0.99 , 2.07]	
Norway/GenKOLS	1.15 [0.94 , 1.4]	
NETT-NAS	1.47 [1.12 , 1.91]	
MESA Caucasian	0.91 [0.68 , 1.21]	
LifeLines	0.96 [0.81 , 1.13]	
FHS	0.98 [0.85 , 1.14]	
EQTL	1.22 [0.87 , 1.71]	_ >
ECLIPSE	1.06 [0.79 , 1.43]	
COPDGene NHW	1.08 [0.98 , 1.2]	
CHS EA	1.2 [1.01 , 1.42]	
ARIC	1.06 [0.93 , 1.19]	
UK Biobank	1.06 [1.04 , 1.09]	

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

Association statistics are based on the overall meta-analysis of COPD (35,735 cases and 222,076 controls). P values are two-sided based on Wald statistics without multiple comparison adjustment.



Supplementary Figure 2-1: Regional association plot for rs9435731 (MFAP2 locus at 1p36.13)

Supplementary Figure 2-2: Regional association plot for rs76841360 (PABPC4 locus at 1p34.3)





Supplementary Figure 2-3: Regional association plot for rs4660861 (TESK2 locus at 1p34.1)

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





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

Supplementary Figure 2-6: Regional association plot for rs3009947 (TGFB2 locus at 1q41)





Supplementary Figure 2-7: Regional association plot for rs11118406 (SLC30A10 locus at 1q41)

Supplementary Figure 2-8: Regional association plot for rs11579382 (CHRM3 locus at 1q43)




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

Supplementary Figure 2-10: Regional association plot for rs10929386 (DDX1 locus at 2p24.3)





Supplementary Figure 2-11: Regional association plot for rs12466981 (EML4 locus at 2p21)

Supplementary Figure 2-12: Regional association plot for rs72902175 (NR4A2 locus at 2q24.1)





Supplementary Figure 2-13: Regional association plot for rs2571445 (TNS1 locus at 2q35)

Supplementary Figure 2-14: Regional association plot for rs16825267 (PID1 locus at 2q36.3)





Supplementary Figure 2-15: Regional association plot for rs62191105 (TWIST2 locus at 2q37.3)

Supplementary Figure 2-16: Regional association plot for rs2442776 (VGLL4 locus at 3p25.3)





Supplementary Figure 2-17: Regional association plot for rs1529672 (RARB locus at 3p24.2)

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





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

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





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

Supplementary Figure 2-22: Regional association plot for rs2955083 (EEFSEC locus at 3q21.3)





Supplementary Figure 2-23: Regional association plot for rs7650602 (ZBTB38 locus at 3q23)

Supplementary Figure 2-24: Regional association plot for rs7642001 (MECOM locus at 3q26.2)





Supplementary Figure 2-25: Regional association plot for rs4585380 (BTC locus at 4q13.3)

Supplementary Figure 2-26: Regional association plot for rs7671261 (FAM13A locus at 4q22.1)





Supplementary Figure 2-27: Regional association plot for rs34712979 (NPNT locus at 4q24)

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





Supplementary Figure 2-29: Regional association plot for rs1551943 (ITGA1 locus at 5q11.2)

Supplementary Figure 2-30: Regional association plot for rs34651 (TNPO1 locus at 5q13.2)





Supplementary Figure 2-31: Regional association plot for rs153916 (SPATA9 locus at 5q15)

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





Supplementary Figure 2-33: Regional association plot for rs10037493 (HTR4 locus at 5q32)

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





Supplementary Figure 2-35: Regional association plot for rs10866659 (ADAM19 locus at 5q33.3)

Supplementary Figure 2-36: Regional association plot for rs12519165 (FGF18 locus at 5q35.1)





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

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





Supplementary Figure 2-39: Regional association plot for rs13198656 (PRL locus at 6p22.3)

Supplementary Figure 2-40: Regional association plot for rs2284174 (IER3 locus at 6p21.33)





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

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





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

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





Supplementary Figure 2-45: Regional association plot for rs9399401 (ADGRG6 locus at 6q24.1)

Supplementary Figure 2-46: Regional association plot for rs798565 (AMZ1 locus at 7p22.3)





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

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





Supplementary Figure 2-49: Regional association plot for rs9329170 (MFHAS1 locus at 8p23.1)

Supplementary Figure 2-50: Regional association plot for rs10114763 (GLIS3 locus at 9p24.2)





Supplementary Figure 2-51: Regional association plot for rs156394 (ELAVL2 locus at 9p21.3)

Supplementary Figure 2-52: Regional association plot for rs7866939 (RASEF locus at 9q21.32)





Supplementary Figure 2-53: Regional association plot for rs10760580 (COL15A1 locus at 9q22.33)

Supplementary Figure 2-54: Regional association plot for rs803923 (ASTN2 locus at 9q33.1)





Supplementary Figure 2-55: Regional association plot for rs7068966 (CDC123 locus at 10p13)

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





Supplementary Figure 2-57: Regional association plot for rs721917 (SFTPD locus at 10q22.3)

Supplementary Figure 2-58: Regional association plot for rs1570221 (STN1 locus at 10q24.33)





Supplementary Figure 2-59: Regional association plot for rs4757118 (ARNTL locus at 11p15.2)

Supplementary Figure 2-60: Regional association plot for rs117261012 (PRSS23 locus at 11q14.2)





Supplementary Figure 2-61: Regional association plot for rs11049386 (CCDC91 locus at 12p11.22)

Supplementary Figure 2-62: Regional association plot for rs7307510 (SNRPF locus at 12q23.1)





Supplementary Figure 2-63: Regional association plot for rs7958945 (MED13L locus at 12q24.21)

Supplementary Figure 2-64: Regional association plot for rs9525927 (SERP2 locus at 13q14.11)





Supplementary Figure 2-65: Regional association plot for rs72699855 (RIN3 locus at 14q32.12)

Supplementary Figure 2-66: Regional association plot for rs72731149 (DTWD1 locus at 15q21.2)





Supplementary Figure 2-67: Regional association plot for rs1441358 (THSD4 locus at 15q23)

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





Supplementary Figure 2-69: Regional association plot for rs10152300 (ADAMTSL3 locus at 15q25.2)

Supplementary Figure 2-70: Regional association plot for rs56134392 (TEKT5 locus at 16p13.13)





Supplementary Figure 2-71: Regional association plot for rs8044657 (TEPP locus at 16q21)

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





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

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





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

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





Supplementary Figure 2-77: Regional association plot for rs11655567 (SOX9 locus at 17q24.3)

Supplementary Figure 2-78: Regional association plot for rs647097 (MTCL1 locus at 18p11.22)





Supplementary Figure 2-79: Regional association plot for rs72626215 (DMWD locus at 19q13.32)

Supplementary Figure 2-80: Regional association plot for rs2096468 (KCNE2 locus at 21q22.11)




Supplementary Figure 2-81: Regional association plot for rs9617650 (MICAL3 locus at 22q11.21)

Supplementary Figure 2-82: Regional association plot for rs73158393 (SYN3 locus at 22q12.3)





Supplementary Figure 3: Distribution of number of variants in 99% credible sets

Number of variants in each credible set



Supplementary Figure 4: Heatmap of associations of phenotypes in COPDGene



Supplementary Figure 5: Associations of index variants and traits in NHGRI-EBI GWAS Catalog



Supplementary Figure 6: Power analysis for sex-difference analysis

The power analysis was based on the effective sample size of 104,119 (male) and 130,707 (female). X-axis and Y-axis represent effect sizes in males and females, respectively.

Supplementary Figure 7: Scatter plot of COPD odd ratio of nominally significant SNPs in meta-analysis of a subset of COPD case-control cohorts* using a pre- and post-bronchodilator definition of COPD

*COPD cohorts includes COPDGene AA, COPDGene NHW, ECLIPSE, and GenKOLS The meta-analysis of a subset of COPD case-control controls included: 666 cases and 1,298 controls in COPDGene AA, 2,442 cases and 1,663 controls in COPDGene NHW, 1,721 cases and 130 controls in ECLIPSE, and 827 cases and 600 controls in GenKOLS. Dots represent odds ratio (OR). Error bars indicate 95% confidence interval.



Variant OR for Pre- vs Post-BD Definition of COPD - nominally significant SNPs in COPD cohorts

Supplementary Figure 8: Comparison of odds ratios (OR) including and excluding individuals with asthma of 82 genome-wide significant variants

The association statistics are based on the analysis including (21,081 cases and 179,711 controls), excluding (14,364 cases and 179,711 controls) individuals with asthma. Dots represent odds ratio (OR). Error bars show 95% confidence interval for OR estimates.



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