**Online Data Supplement to “Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis”**

\*Brian D. Hobbs1,2, \*Rachel K. Putman2, Tetsuro Araki3,4, Mizuki Nishino3,4, Gunnar Gudmundsson5, Vilmundur Gudnason6,7, Gudny Eiriksdottir7, Nuno Rodrigues Zilhao Nogueira7, Josée Dupuis8,9, Hanfei Xu8, George T. O’Connor9,10, Ani Manichaikul11,12 , Jennifer Nguyen11, Anna J. Podolanczuk13, Purnema Madahar13,Jerome I. Rotter14,15, David J. Lederer13,16, R. Graham Barr13,16, Stephen S. Rich11,12, Elizabeth J. Ampleford17, Victor E. Ortega17, Stephen P. Peters17, Wanda K. O’Neal18, John D. Newell Jr19,20, Eugene R. Bleecker21, Deborah A. Meyers21, Richard J. Allen22, Justin M. Oldham23, Shwu-Fan Ma24, Imre Noth24, R. Gisli Jenkins25, Toby M. Maher26,27, Richard B. Hubbard25,28, Louise V. Wain29, Tasha E. Fingerlin30,31, David A. Schwartz31,32,33 , George R. Washko2,4, Ivan O. Rosas2, Edwin K. Silverman1,2, Hiroto Hatabu3,4, \*Michael H. Cho1,2, \*Gary M. Hunninghake2,3, COPDGene Investigators, ECLIPSE Investigators, SPIROMICS Research Group, and UK ILD Consortium

1Channing Division of Network Medicine, Brigham and Women’s Hospital, Boston, MA, USA; 2Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Boston, MA, USA; 3Department of Radiology, Brigham and Women’s Hospital, Boston, MA, USA; 4Center for Pulmonary Functional Imaging, Brigham and Women’s Hospital, Boston, MA, USA; 5Dept of Respiratory Medicine, Landspital University Hospital, University of Iceland, Reykjavik, Iceland; 6Faculty of Medicine, University of Iceland, Reykjavik, Iceland; 7Icelandic Heart Association, Kopavogur, Iceland; 8Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; 9National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, MA, USA; 10Pulmonary Center, Department of Medicine, Boston University, Boston, MA, USA; 11Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA; 12Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA; 13Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA; 14Institute for Translational Genomics and Population Sciences and Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA; 15Division of Genomic Outcomes, Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA; 16Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA; 17 Department of Internal Medicine, Center for Precision Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA; 18Marsico Lung Institute, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; 19Division of Cardiovascular and Pulmonary Imaging, Department of Radiology, University of Iowa Carver College of Medicine, Iowa City, IA, USA; 20Department of Radiology, University of Washington, Seattle, WA, USA; 21Division of Genetics, Genomics and Precision Medicine, Department of Medicine, University of Arizona, Tucson, AZ, USA; 22Department of Health Sciences, University of Leicester, Leicester, UK; 23Department of Internal Medicine, University of California Davis, Davis, CA, USA; 24Divsion of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, VA, USA; 25NIHR Biomedical Research Centre, Respiratory Research Unit, School of Medicine, University of Nottingham, Nottingham, UK;26NIHR Respiratory Biomedical Research Unit, Royal Brompton Hospital, London, UK; 27Fibrosis Research Group, Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College, London, UK; 28Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK; 29National Institute for Health Research, Leicester Respiratory Biomedical Research Centre, Glenfield Hospital, Leicester, UK; 30Center for Genes, Environment and Health, National Jewish Health, Denver, CO, USA; 31Department of Biostatistics and Informatics, University of Colorado Denver, Aurora, CO, USA; 32Department of Medicine, School of Medicine, University of Colorado Denver, Aurora, CO, USA; 33Department of Immunology, School of Medicine, University of Colorado Denver, Aurora, CO, USA

\* These authors contributed equally to this work

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**COPDGene:**

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**COPDGene® Investigators – Core Units**

*Administrative Center*: James D. Crapo, MD (PI); Edwin K. Silverman, MD, PhD (PI); Barry J. Make, MD; Elizabeth A. Regan, MD, PhD

*Genetic Analysis Center*: Terri Beaty, PhD; Ferdouse Begum, PhD; Peter J. Castaldi, MD, MSc; Michael Cho, MD; Dawn L. DeMeo, MD, MPH; Adel R. Boueiz, MD; Marilyn G. Foreman, MD, MS; Eitan Halper-Stromberg; Lystra P. Hayden, MD, MMSc; Craig P. Hersh, MD, MPH; Jacqueline Hetmanski, MS, MPH; Brian D. Hobbs, MD; John E. Hokanson, MPH, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD; Merry-Lynn McDonald, PhD; Margaret M. Parker, PhD; Dandi Qiao, PhD; Elizabeth A. Regan, MD, PhD; Edwin K. Silverman, MD, PhD; Emily S. Wan, MD; Sungho Won, Ph.D.; Phuwanat Sakornsakolpat, M.D.; Dmitry Prokopenko, Ph.D.

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

*PFT QA Center, Salt Lake City, UT*: Robert Jensen, PhD

*Data Coordinating Center and Biostatistics*, *National Jewish Health, Denver, CO*: Douglas Everett, PhD; Jim Crooks, PhD; Camille Moore, PhD; Matt Strand, PhD; Carla G. Wilson, MS

*Epidemiology Core*, *University of Colorado Anschutz Medical Campus, Aurora, CO*: John E. Hokanson, MPH, PhD; John Hughes, PhD; Gregory Kinney, MPH, PhD; Sharon M. Lutz, PhD; Katherine Pratte, MSPH; Kendra A. Young, PhD

*Mortality Adjudication Core:* Surya Bhatt, MD; Jessica Bon, MD; MeiLan K. Han, MD, MS; Barry Make, MD; Carlos Martinez, MD, MS; Susan Murray, ScD; Elizabeth Regan, MD; Xavier Soler, MD; Carla G. Wilson, MS

*Biomarker Core*: Russell P. Bowler, MD, PhD; Katerina Kechris, PhD; Farnoush Banaei-Kashani, Ph.D

**COPDGene® Investigators – Clinical Centers**

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

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

*Brigham and Women’s Hospital, Boston, MA*: Dawn L. DeMeo, MD, MPH; Craig Hersh, MD, MPH; Francine L. Jacobson, MD, MPH; George Washko, MD

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

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

*HealthPartners Research Institute, Minneapolis, MN*: Charlene McEvoy, MD, MPH; Joseph Tashjian, MD

*Johns Hopkins University, Baltimore, MD*: Robert Wise, MD; Robert Brown, MD; Nadia N. Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS

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

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

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

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

*National Jewish Health, Denver, CO*: Russell Bowler, MD, PhD; David A. Lynch, MB

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

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

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

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

*University of Iowa, Iowa City, IA*: Alejandro P. Comellas, MD; Karin F. Hoth, PhD; John Newell, Jr., MD; Brad Thompson, MD

*University of Michigan, Ann Arbor, MI*: MeiLan K. Han, MD, MS; Ella Kazerooni, MD; Carlos H. Martinez, MD, MPH

*University of Minnesota, Minneapolis, MN*: Joanne Billings, MD; Abbie Begnaud, MD; Tadashi Allen, MD

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

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

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

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

**ECLIPSE Scientific Committee**: A. Agusti (Spain), P. Calverley (UK), B. Celli (USA), C. Crim (GlaxoSmithKline, USA), B. Miller (GlaxoSmithKline, USA), W. MacNee (Chair, UK), S. Rennard (USA), R. Tal-Singer (GlaxoSmithKline, USA), E. Wouters (The Netherlands), J. Yates (GlaxoSmithKline, USA).

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**United Kingdom Interstitial Lung Disease Consortium Investigators**

Helen L. Booth – Department of Thoracic Medicine, University College London Hospitals, London, UK; William A. Fahy – GlaxoSmithKline, Stevenage, UK; Ian P. Hall – Division of Respiratory Medicine, University of Nottingham, Nottingham, UK, National Institute for Health Research, Nottingham Biomedical Research Centre, Nottingham University Hospitals, Nottingham, UK; Simon P. Hart – Respiratory Research Group, Centre for Cardiovascular and Metabolic Research, The Hull York Medical School, Hull, UK; Mike R. Hill – Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK; Nik Hirani – MRC Centre for Inflammation Research at the University of Edinburgh, Edinburgh, UK; Richard B. Hubbard – Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK, National Institute for Health Research, Nottingham Biomedical Research Centre, Nottingham University Hospitals, Nottingham, UK; Toby M. Maher – NIHR Respiratory Biomedical Research Unit, Royal Brompton Hospital, London, UK, Fibrosis Research Group, Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College, London, UK; Robin J. McAnulty – UCL Respiratory Centre for Inflammation and Tissue Repair, University College London, London, UK; Ann B. Millar – Academic Respiratory Unit, School of Clinical Sciences, University of Bristol, Bristol, UK; Philip L. Molyneaux – NIHR Respiratory Biomedical Research Unit, Royal Brompton Hospital, London, UK, Fibrosis Research Group, Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College, London, UK; Vidyia Navaratnam – Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK; Eunice Oballa – GlaxoSmithKline, Stevenage, UK; Helen Parfrey – Respiratory Medicine, Papworth Hospital, Cambridge, UK; Gauri Saini – Respiratory Medicine, Nottingham University Hospitals Trust; Ian Sayers – Division of Respiratory Medicine, University of Nottingham, Nottingham, UK, National Institute for Health Research, Nottingham Biomedical Research Centre, Nottingham University Hospitals, Nottingham, UK; Martin D. Tobin – Department of Health Sciences, University of Leicester, Leicester, UK, National Institute for Health Research, Leicester Respiratory Biomedical Research Centre, Glenfield Hospital, Leicester, UK; Moira K.B. White – MRC Centre for Inflammation Research at the University of Edinburgh, Edinburgh, UK.

**METHODS**

**ILA Characterization**

In SPIROMICS interstitial lung abnormalities (ILA) were first scored as present or absent (Y/N). The following minimum criteria was used to classify the presence of ILA. Bilateral, non-dependent, peripheral (but not necessarily subpleural) ground glass and/or reticular opacities and/or honeycombing needed to be present. Peripheral opacities needed to be within 2 cm of the pleura. Non-dependent criteria were opacities present in the lateral or anterior segments of the lower lobes and/or opacities were present in the right middle, lingula, anterior/lateral or apical portions of the right upper lobe and left upper lobes. The distribution of the ILA was further classified as to upper/lower/diffuse in nature. The carina was used as the landmark to determine whether the opacities predominated in the upper lobes, *e.g.*, above the carina, lower lobes, below the carina, or diffuse, balanced between the carina. The presence of ground glass, reticular opacities, honeycombing and traction bronchiectasis were noted as important findings for ILA. The classification of subpleural predominant was made by limiting ILA subjects to those with visual evidence of bilateral, peripheral and/or subpleural, non-dependent, lower lobe, reticular opacities. In MESA the subpleural predominant classification was created by asking the radiologists characterizing the CT scans for ILA the following question, “Are the above findings predominantly subpleural?”.

**Genotyping and Imputation**

**AGES (Age, Gene/Environment, Susceptibility) Reykjavik Study**

Details of the AGES-Reykjavik Study have been previously described, including the assessment of ILA(1-3). Briefly, the AGES-Reykjavik study is a longitudinal birth cohort derived from the Reykjavik Study, which was established in 1967 and includes men and women that were born in Reykjavik, Iceland from 1907 to 1935 and are now followed by the Icelandic Heart Association. Genotyping was performed using Illumina 370CNV BeadChip array, genotype calling was performed using Illumina Bead Studio. Samples were excluded based on sample failure, genotype mismatch with reference panel and sex mismatch on genotypes (4, 5). Imputation was performed using MaCH (version 1.0.16), and the following QC filtering was applied at the variant level: call rate (<97%), Hardy Weinberg Equilibrium (p < 1 x 10-6, PLINK mishap haplotype-based test for non-random missing genotype data (p < 1 x 10-9), and mismatched positions between Illumina, dbSNP and/or HapMap (4, 5).

**COPDGene Study**

Details of the COPDGene Study (NCT00608764, www.copdgene.org) have been previously described, including description of the visual assessment of ILA(6-8). In brief, eligible subjects were of non-Hispanic white or African-American ancestry, aged 45-80 years old, with a minimum of 10 pack-years of smoking and no lung disease (other than COPD or asthma). Genotyping was performed by Illumina (San Diego, CA) on the HumanOmniExpress array. Subjects were excluded for missingness, heterozygosity, chromosomal aberrations, sex check, population outliers, and cryptic relatedness. 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. Markers were excluded based on missingness, Hardy-Weinberg P-values, and low minor allele frequency. Imputation on the COPDGene cohorts was performed via the Michigan Imputation Server using minimac3 with the Haplotype Reference Consortium (HRC v1.1) reference panel(9). Variants with an imputation accuracy r2 value of ≤ 0.5 were removed from further analysis.

**Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)**

Details of the ECLIPSE study (SCO104960, NCT00292552, www.eclipse-copd.com) including visual assessment of interstitial lung abnormalities and genome-wide association analysis have been described previously(1, 10, 11). In brief, ECLIPSE was an observational 3-year study of COPD. Genotyping was performed using the Illumina HumanHap 550 V3 (Illumina, San Diego, CA). Subjects and markers with a call rate of < 95% were excluded. Population stratification exclusion and adjustment on self-reported white subjects was performed using EIGENSTRAT (EIGENSOFT Version 2.0). Imputation was performed via the Michigan Imputation Server using minimac3 with the Haplotype Reference Consortium (HRC v1.1) reference panel(9). Variants with an imputation accuracy r2 value of ≤ 0.5 were removed from further analysis.

**The Framingham Heart Study (FHS; NCT00005121)**

Details of the FHS (NCT00005121, [www.framinghamheartstudy.org](http://www.framinghamheartstudy.org)) and on the visual assessment of ILA have been previously published(12). Briefly, the FHS began in 1948 and now includes three separate cohorts: the Original, the Offspring and the Generation 3 cohorts. The FHS is a longitudinal study originally designed to identify risk factors for cardiovascular disease(13). The study was approved by the Boston University Medical Campus IRB and all participants provided written informed consent. Data from the 8th exam cycle from the Offspring cohort and second exam cycle for the Generation 3 cohort were analyzed. Genotypes were from the Affymetrix 500K array supplemented by the Affymetrix MIPS 50K. From a total number of 546,344 genotyped SNPs with known physical location on the autosomes or the X chromosomes, 412,049 were used with the SHAPEIT program for phasing, using the duohmm option to take advantage of the familial information. Individuals with a call rate of < 95% were excluded. Additionally, markers were excluded based on missingness, Hardy-Weinberg P-values, and low minor allele frequency. Imputation to the Haplotype Reference Consortium using minimac3 was performed on the Michigan imputation server. We used the firth test implemented in the EPACTS software, adjusted for sex, age and pack years to assess association between genetic variants and ILA.

**Multi-Ethnic Study of Atherosclerosis (MESA)**

Details of the MESA study (NCT00005487, www.mesa-nhlbi.org) and ILA assessment have been previously reported(14-16). Briefly, MESA is a population-based longitudinal study of subclinical cardiovascular disease. Men and women ages 45-84 without cardiovascular disease were recruited from six US sites. Genotyping was performed on participants who consented using the Affymetrix Human SNP array 6.0. Genotype QC for these data included filter on SNP level call rate < 95%, individual level call rate < 95%, heterozygosity > 53%, described previously (17). 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 Non-Hispanic 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, the University of Michigan Imputation Server(9) was used to perform imputation for the MESA SHARe participants with the Haplotype Reference Consortium release 1 reference panel(9) for MESA Whites and cosmopolitan 1,000 Genomes Phase 3 for MESA African-Americans and Hispanics.

**SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS)**

Details of the SPIROMICS (NCT01969344, [www.spiromics.org](http://www.spiromics.org)) study have been previously published, methods for ILA assessment are detailed in the methods in this manuscript and supplement(18). Briefly, SPIROMICS recruited participants ages 40-80 years into strata including non-smokers with < 1 pack-year cigarette smoking history and those with a smoking history of ≥20 pack-years without COPD, mild-moderate COPD, and severe COPD. Genome wide genotyping was performed using the Illumina OmniExpress HumanExome BeadChip and BeadStudio (Illumina, Inc., San Diego, CA)(19, 20). For quality control subjects were removed if they had genotype call rates <95%, discrepant for genetic sex, failed the check for family relatedness, or were detected as an outlier. SNPs were removed if call rates <95%, inconsistent with Hardy-Weinberg Equilibrium (p<10-6), or minor allele frequency <0.01. Imputation was performed via the Michigan Imputation Server using minimac3 with the Haplotype Reference Consortium (HRC v1.1) reference panel(9).

**United Kingdom Interstitial Lung Disease Consortium, Idiopathic Pulmonary Fibrosis (IPF) Cohort**

The IPF GWAS comprised data from 3 studies as previously described(21-23) and totalling 2,668 IPF cases and 8,591 controls. All three studies were restricted to unrelated individuals of European ancestry and stringent quality control measures (such as removing individuals with poor call rates, heterozygosity outliers, duplicates, related individuals, ancestry outliers, and sex mismatches) were applied. All studies diagnosed IPF cases using American Thoracic Society and European Respiratory Society guidelines and had appropriate institutional review board or ethics approval. All three studies had been newly imputed using the Haplotype Reference Consortium (HRC v1.1) reference panel(9). Overlap of cases and controls between studies was assessed using KING v2.1.2 and duplicate individuals excluded.  Association testing for IPF susceptibility was undertaken assuming an additive genetic effect and adjusting for the first 10 principal components to account for fine-scale population structure. SNPTEST v2.5.2 was used for association testing. Variants with poor imputation quality (Rsq<0.5) or were in violation of Hardy-Weinberg Equilibrium (P<10-6) were excluded.

**Table E1.** Baseline characteristics of participants stratified by subpleural predominant interstitial lung abnormality (ILA) status.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | AGES-Reykjavik | | COPDGene Non-Hispanic Whites | | COPDGene African-Americans | | ECLIPSE | | Framingham Heart Study | | MESA  Non-Hispanic Whites | | SPIROMICS | |
| No ILA  (N=1785, 87%) | ILA  (N=260, 13%) | No ILA  (N=3771, 91%) | ILA  (N=363, 9%) | No ILA  (N=1717, 92%) | ILA  (N=154, 8%) | No ILA  (N=494, 79%) | ILA  (N=133, 21%) | No ILA  (N=530, 79%) | ILA  (N=138, 21%) | No ILA  (N=675, 90%) | ILA  (N=71, 10%) | No ILA  (N=450, 73%) | ILA  (N=168, 27%) |
| Age – yrs, mean (SD\*) | 76 (5) | 78 (5) | 61 (9) | 67 (8) | 54 (7) | 57 (8) | 62 (7) | 65 (7) | 58 (11) | 71 (11) | 69 (9) | 77 (8) | 65 (8) | 68 (7) |
| Sex – no. female (%) | 1078  (60) | 116  (45) | 1814  (48) | 151  (42) | 701  (41) | 85  (55) | 166  (34) | 33  (25) | 278 (53) | 67  (49) | 344  (51) | 36 (50) | 206 (46) | 76  (45) |
| Body Mass Index, mean (SD) | 27 (4) | 28 (5) | 29 (6) | 30 (6) | 29 (7) | 30 (7) | 27 (6) | 27 (5) | 28 (5) | 28 (5) | 28 (5) | 28 (4) | 27 (5) | 29 (5) |
| Pack-years Smoking, median (IQ†) | 2  (0, 26) | 21  (0, 50) | 40  (29, 56) | 47  (36, 65) | 34  (22, 46) | 36  (24, 47) | 45  (33, 62) | 43  (30, 60) | 0  (0,12) | 8  (0, 23) | 0  (0, 17) | 20  (7, 45) | 41  (30, 60) | 50  (38, 67) |
| Smoking Status – no. (%)  Current  Former  Never | 211  (12)  756  (42)  818  (46) | 39  (15)  155 (60)  66  (25) | 1426 (38)  2345 (62)  -- | 149  (41)  214  (59)  -- | 1377 (80)  340  (20)  -- | 122  (79)  32  (21)  -- | 189 (38)  305  (62)  -- | 53  (40)  80  (60)  -- | 33  (6)  238 (45)  259 (49) | 11  (8)  74  (54)  53  (38) | 43  (6)  322 (48)  210 (46) | 7 (10)  38 (53)  26 (37) | 126 (28)  294 (65)  30 (7) | 51  (30)  111 (66)  6 (4) |
| History of COPD‡ – no. (%) | -- | -- | 1527  (40) | 131  (36) | 380  (22) | 41  (27) | 494  (100) | 133  (100) | 46 (9) | 18 (13) | 129 (22) | 15 (25) | 290 (64) | 110 (66) |

\*SD is standard deviation

†IQ is interquartile interval

‡COPD is chronic obstructive pulmonary disease and defined as FEV1/FVC ratio < 70 on spirometry

Missing data: MESA Non-Hispanic Whites COPD status: ILA – 10; Framingham Heart Study Body Mass Index – 1; AGES-Reykjavik Body Mass Index – 1

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Chromosome | Position | rsID | Closest Gene | Risk Allele | Risk Allele Frequency | Odds Ratio  (95% CI\*) | P-Value |
| 11 | 1241221 | rs35705950 | *MUC5B* | T | 0.112 | 1.98  (1.75-2.24) | 4.45x10-27 |
| 6 | 87742637 | rs1324434 | *HTR1E* | G | 0.278 | 1.33  (1.21-1.46) | 7.60 x10-9 |
| 6 | 87741747 | rs7754449 | *HTR1E* | C | 0.278 | 1.33  (1.21-1.46) | 7.66 x10-9 |
| 6 | 87741484 | rs12214935 | *HTR1E* | T | 0.278 | 1.33  (1.21-1.46) | 7.68 x10-9 |
| 6 | 87748862 | rs9444461 | *HTR1E* | G | 0.315 | 1.33  (1.21-1.46) | 7.69 x10-9 |
| 6 | 87749643 | rs7738920 | *HTR1E* | C | 0.315 | 1.33  (1.21-1.46) | 7.70 x10-9 |
| 6 | 87742533 | rs12203383 | *HTR1E* | G | 0.278 | 1.33  (1.21-1.46) | 7.85 x10-9 |
| 6 | 87750366 | rs6454576 | *HTR1E* | T | 0.315 | 1.33  (1.21-1.46) | 8.0x10-9 |
| 6 | 87752321 | rs912535 | *HTR1E* | G | 0.316 | 1.33  (1.21-1.46) | 8.06 x10-9 |
| 6 | 87748686 | rs6916944 | *HTR1E* | C | 0.278 | 1.33  (1.21-1.46) | 8.11 x10-9 |
| 6 | 87737841 | rs7744971 | *HTR1E* | G | 0.278 | 1.33  (1.20-1.46) | 8.71 x10-9 |
| 6 | 87745338 | rs2325019 | *HTR1E* | C | 0.278 | 1.33  (1.20-1.46) | 9.23 x10-9 |
| 6 | 87749815 | rs7739124 | *HTR1E* | C | 0.330 | 1.31  (1.19-1.44) | 3.12 x10-9 |
| 3 | 106571023 | rs73199442 | *FCF1P3* | T | 0.060 | 1.68  (1.39-2.02) | 4.78 x10-9 |

**Table E2.** European ancestry only, genome wide significant variants associated with interstitial lung abnormalities (ILA)

\*CI is confidence interval

**Table E3.** European ancestry only, genome wide significant variants associated with subpleural predominant interstitial lung abnormalities (ILA)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Chromosome | Position | rsID | Closest Gene | Risk Allele | Risk Allele Frequency | Odds Ratio  (95% CI\*) | P-Value |
| 11 | 1241221 | rs35705950 | *MUC5B* | T | 0.110 | 2.23  (1.94-2.57) | 4.94x10-29 |
| 6 | 87752321 | rs912535 | *HTRE1* | G | 0.324 | 1.37  (1.23-1.52) | 4.46x10-9 |
| 6 | 87749643 | rs7738920 | *HTRE1* | C | 0.323 | 1.37  (1.23-1.52) | 6.54x10-9 |
| 6 | 87748862 | rs9444461 | *HTRE1* | G | 0.323 | 1.37  (1.23-1.52) | 6.56x10-9 |
| 6 | 87742637 | rs1324434 | *HTRE1* | G | 0.278 | 1.37  (1.23-1.52) | 6.92x10-9 |
| 6 | 87741747 | rs7754449 | *HTRE1* | C | 0.278 | 1.37  (1.23-1.52) | 6.97x10-9 |
| 6 | 87741484 | rs12214935 | *HTRE1* | T | 0.278 | 1.37  (1.23-1.52) | 6.99x10-9 |
| 6 | 87742533 | rs12203383 | *HTRE1* | G | 0.278 | 1.37  (1.23-1.52) | 7.08x10-9 |
| 6 | 87750366 | rs6454576 | *HTRE1* | T | 0.323 | 1.37  (1.23-1.52) | 7.18x10-9 |
| 6 | 87748686 | rs6916944 | *HTRE1* | C | 0.278 | 1.37  (1.23-1.52) | 7.31x10-9 |
| 6 | 87737841 | rs7744971 | *HTRE1* | G | 0.278 | 1.36  (1.23-1.52) | 7.96x10-9 |
| 6 | 87745338 | rs2325019 | *HTRE1* | C | 0.278 | 1.36  (1.23-1.52) | 8.16x10-9 |

\*CI is confidence interval

**Table E4.** Smoking status stratified meta-analysis of four top interstitial lung abnormality (ILA) and subpleural-predominant ILA in European-ancestry individuals from AGES, FHS, and MESA.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Phenotype | Chr\* | Position | rsid | Never Smokers | | Ever Smokers | |
| OR† (95% CI‡) | p | OR (95% CI) | p |
| ILA | 3 | 106571023 | rs73199442 | 1.47 (0.82-2.63) | 2.0 x10-1 | 1.81 (1.28-2.56) | 7.5 x10-4 |
| 5 | 62172476 | rs6886640 | 1.10 (0.82-1.47) | 5.2 x10-1 | 1.21 (0.99-1.47) | 6.2 x10-2 |
| 6 | 87737841 | rs7744971 | 0.84 (0.64-1.11) | 2.3 x10-1 | 1.23 (1.02-1.48) | 2.7 x10-2 |
| 11 | 1241221 | rs35705950 | 2.41 (1.69-3.42) | 9.8 x10-7 | 2.71 (2.09-3.53) | 9.6 x10-14 |
| Subpleural ILA | 3 | 106571023 | rs73199442 | 1.40 (0.74-2.63) | 3.0 x10-1 | 1.82 (1.25-2.65) | 1.8 x10-3 |
| 5 | 62172476 | rs6886640 | 1.07 (0.79-1.44) | 6.7 x10-1 | 1.19 (0.97-1.47) | 1.0 x10-3 |
| 6 | 87737841 | rs7744971 | 0.87 (0.65-1.17) | 3.6 x10-1 | 1.24 (1.02-1.51) | 3.4 x10-2 |
| 11 | 1241221 | rs35705950 | 2.82 (1.96-4.06) | 2.0 x10-8 | 2.96 (2.25-3.88) | 6.8 x10-15 |

\*Chr=chromosome

†OR=odds ratio

‡CI = confidence interval

**Table E5.** Association of genome-wide significant SNPs from prior idiopathic pulmonary fibrosis (IPF) GWAS with interstitial lung abnormalities (ILA).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Chromosome/  Location | rsID | IPF\* Risk Allele | Nearest Gene | Studies | IPF  Odds Ratio  (95% CI‡) | ILA† vs No ILA | | Subpleural ILA vs No ILA | |
| Odds Ratio  (95% CI) | P-Value | Odds Ratio  (95% CI) | P-Value |
| 3q26 | rs6793295 | C | *LRRC34* | Fingerlin, NG, 2013 | 1.30  (1.19, 1.42) | 1.06  (0.97, 1.15) | 0.20 | 1.12  (1.01, 1.24) | 0.025 |
| 4q22 | rs2609255 | G | *FAM13A* | Fingerlin, NG¶, 2013 | 1.29  (1.18, 1.42) | 1.18  (1.07, 1.29) | 4.5x10-4 | 1.22  (1.09, 1.35) | 3.2x10-4 |
| 5p15 | rs2736100 | A | *TERT* | Fingerlin, NG, 2013  Mushiroda, JMG‖, 2008 | 2.11  (1.61, 2.78) | 1.03  (0.95, 1.12) | 0.44 | 1.06  (0.96, 1.16) | 0.23 |
| 6p24 | rs2076295 | G | *DSP* | Fingerlin, NG, 2013  Allen, LRM§, 2017 | 1.44  (1.35, 1.54) | 1.14  (1.05, 1.23) | 1.0X10-3 | 1.18  (1.08, 1.29) | 3.0x10-4 |
| 7q22 | rs4727443 | C | *LOC100128334/*  *LOC105375423* | Fingerlin, NG, 2013 | 1.30  (1.19, 1.41) | 0.95  (0.87, 1.03) | 0.19 | 0.93  (0.84, 1.02) | 0.12 |
| 10q24 | rs11191865 | A | *STN1*  (a.k.a. *OBFC1*) | Fingerlin, NG, 2013 | 1.25  (1.15, 1.35) | 1.03  (0.95, 1.12) | 0.46 | 1.03  (0.94, 1.13) | 0.56 |
| 11p15 | rs35705950  rs5743890  rs5743894  rs7934606 | T  T  C  T | *MUC5B*  *TOLLIP*  *TOLLIP*  *MUC2* | Fingerlin, NG, 2013  Noth, LRM, 2013 | 2.43 (2.13, 2.77)  1.64(1.41, 1.92)  1.49 (1.33, 1.68)  1.52 (1.40, 1.65) | 1.97 (1.74, 2.22)  0.93 (0.82, 1.06)  1.14 (1.02, 1.28)  1.07 (0.98, 1.17) | 2.6x10-27  0.27  0.021  0.12 | 2.22 (1.93, 2.55)  0.97 (0.84, 1.12)  1.24 (1.10, 1.41)  1.12 (1.01, 1.24) | 1.6x10-29  0.71  5.5x10-4  0.026 |
| 13q34 | rs1278769 | G | *ATP11A* | Fingerlin, NG, 2013 | 1.27  (1.14, 1.39) | 1.04  (0.95, 1.15) | 0.37 | 1.04  (0.94, 1.16) | 0.45 |
| 15q15 | rs2034650 | A | *IVD* | Fingerlin, NG, 2013 | 1.30  (1.19, 1.41) | 1.08  (0.99, 1.17) | 0.072 | 1.15  (1.05, 1.26) | 2.8x10-3 |
| 15q25 | rs62025270 | A | *AKAP13* | Allen, LRM, 2017 | 1.27  (1.18, 1.37) | 1.09  (0.99, 1.20) | 0.086 | 1.07  (0.96, 1.20) | 0.23 |
| 17q21 | rs1981997  rs17690703 | G  C | *MAPT*  *MAPT-AS1* | Fingerlin, NG, 2013  Noth, LRM, 2013 | 1.41 (1.28, 1.56)  1.43 (1.27, 1.61) | 1.16 (1.03, 1.30)  1.20 (1.08, 1.34) | 0.011  1.1x10-3 | 1.19 (1.05, 1.36)  1.23 (1.09, 1.40) | 8.8x10-3  1.0x10-3 |
| 19p13 | rs12610495 | G | *DPP9* | Fingerlin, NG, 2013 | 1.29  (1.18, 1.41) | 1.14  (1.03, 1.26) | 0.010 | 1.23  (1.10, 1.37) | 2.3x10-4 |

\*IPF is idiopathic pulmonary fibrosis

†ILA is interstitial lung abnormalities

‡CI is confidence interval

¶NG is Nature Genetics

§LRM is Lancet Respiratory Medicine

**Table E6.** Replication of previously reported loci associated with high attenuation areas (HAA) in the MESA cohort\*.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Chromosome | hg19Position | rsID | Nearest Gene | ILA  OR†  (95% CI‡) | ILA  P-Value | Subpleural  OR (95% CI) | Subpleural  P-Value |
| 1 | 93408101 | rs114801796 | *DIPK1A*  (a.k.a*. FAM69A*) | 1.03  (0.59, 1.82) | 0.91 | 1.13  (0.61, 2.12) | 0.69 |
| 1 | 64724706 | rs138384996 | *UBE2U* | -- | -- | -- | -- |
| 1 | 8291827 | rs76164182 | *SLC45A1* | 1.06  (0.76, 1.49) | 0.72 | 0.99  (0.68, 1.45) | 0.98 |
| 2 | 127254486 | rs150536895 | *GYPC* | 1.33  (0.83, 2.12) | 0.23 | 1.54  (0.92, 2.58) | 0.10 |
| 3 | 103949823 | rs146792761 | *ALCAM* | 1.01  (0.42, 2.41) | 0.98 | 0.93  (0.33, 2.60) | 0.88 |
| 4 | 44775446 | rs6844387 | *GNPDA2* | 1.30  (1.00, 1.69) | 0.05 | 1.24  (0.86, 1.78) | 0.25 |
| 5 | 179742263 | rs190432524 | *GFPT2* | 1.15  (0.71, 1.85) | 0.58 | 1.11  (0.55, 2.23) | 0.78 |
| 6 | 36495778 | rs145855729 | *STK38* | 1.08  (0.78, 1.50) | 0.64 | 1.08  (0.70, 1.65) | 0.73 |
| 6 | 4148093 | rs2894439 | *FOXP4* | 1.11  (0.81, 1.53) | 0.52 | 1.43  (0.89, 2.30) | 0.14 |
| 8 | 32973995 | rs114571830 | *FUT10* | 0.92  (0.40, 2.11) | 0.84 | 0.48  (0.12, 1.93) | 0.30 |
| 8 | 71177444 | rs150377334 | *NCOA2* | 2.30  (0.71, 7.43) | 0.16 | 1.80  (0.38, 8.41) | 0.46 |
| 9 | 22790485 | rs7852363 | *FLJ35282* | 0.99  (0.89, 1.11) | 0.91 | 0.98  (0.86, 1.12) | 0.80 |
| 10 | 107354812 | rs74361312 | *SORCS3* | -- | -- | -- | -- |
| 10 | 3132994 | rs79441543 | *PFKP* | 1.2  (0.90, 1.68) | 0.20 | 0.98  (0.66, 1.46) | 0.92 |
| 12 | 124715694 | rs117323377 | *ZNF664*  *RFLNA*  *(a.k.a. FAM101A*) | 1.15  (0.88, 1.50) | 0.30 | 1.24  (0.92, 1.66) | 0.15 |
| 14 | 59455322 | rs141944608 | *DAAM1* | 1.27  (0.50, 3.27) | 0.62 | 1.56  (0.45, 5.41) | 0.49 |
| 14 | 55227152 | rs149416017 | *SAMD4A* | 1.05  (0.80, 1.39) | 0.72 | 1.12  (0.82, 1.52) | 0.48 |
| 14 | 37335713 | rs74315875 | *SLC25A21* | 0.92  (0.67, 1.26) | 0.61 | 0.94  (0.65, 1.35) | 0.74 |
| 16 | 88732573 | rs140142658 | *SNAI3-AS1* | 1.01  (0.74, 1.36) | 0.97 | 0.94  (0.66, 1.33) | 0.72 |
| 18 | 12955146 | rs182717611 | *SEH1L* | 1.38  (0.88, 2.17) | 0.16 | 1.38  (0.86, 2.23) | 0.19 |
| 21 | 24735151 | rs3079677 | *D21S2088E* | -- | -- | -- | -- |

\*MESA is the Multi-Ethnic Study of Atherosclerosis

†OR is odds ratio

‡CI is confidence interval

**Table E7.** Lookup of interstitial lung abnormalities (ILA) and subpleural predominant ILA genome wide significant SNPs for association with smoking behaviors from Liu et.al.(24)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Chr\* | Position | rsid | ILA Risk Allele | Smoking Initiation | | Smoking Cessation | | Cigarettes Per Day | | Smoking Start Age | |
| beta† | p | beta | p | beta | p | beta | p |
| 3 | 106571023 | rs73199442 | T | -5.1x10-3 | 0.37 | -7.3 x10-3 | 0.67 | -8.3 x10-3 | 0.16 | 1.9 x10-3 | 0.69 |
| 5 | 62172476 | rs6886640 | G | 3.1 x10-3 | 0.47 | -2.1 x10-3 | 0.89 | 1.0 x10-3 | 0.72 | -4.5 x10-3 | 0.13 |
| 6 | 87737841 | rs7744971 | G | -1.7 x10-3 | 0.50 | 3.7 x10-4 | 0.74 | 3.7 x10-4 | 0.95 | 5.2 x10-3 | 0.10 |
| 11 | 1241221 | rs35705950 | T | 2.0 x10-3 | 0.53 | 7.7 x10-3 | 0.29 | 5.0 x10-3 | 0.30 | -7.5 x10-3 | 0.13 |

\*Chr = chromosome

†beta represents the log odds for smoking initiation and smoking cessation

**Table E8.** Results of the assessment of overlap between the genome wide significant loci from reported in the smoking behavior GWAS from Liu et al.(24) and interstitial lung abnormalities (ILA) and subpleural predominant ILA.

See separately attached table in the excel spreadsheet.

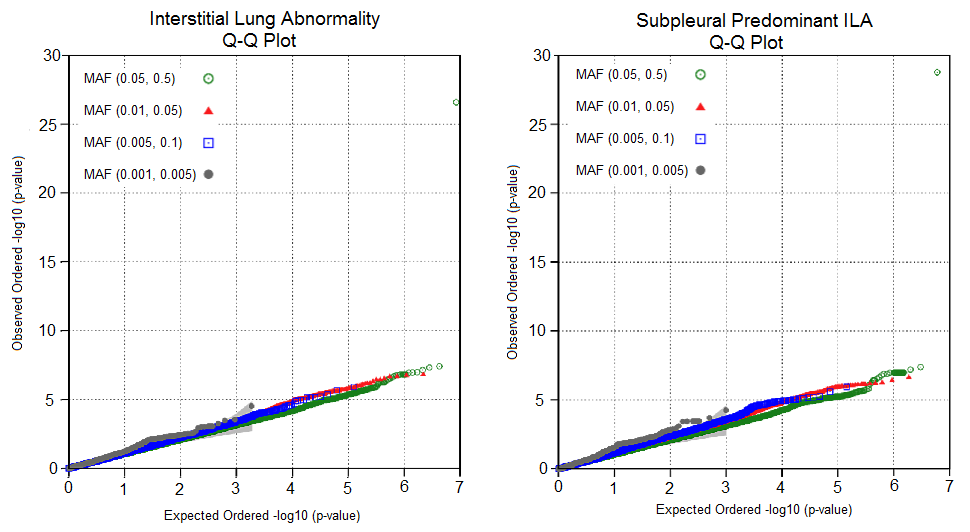
**Table E9.** Results of logistic regression adjusting for the *MUC5B* minor allele to assess for independence of the single nucleotide polymorphisms (SNPs) at the 11p15 locus.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ILA\* Phenotype | SNP† | Odds Ratio  (95% CI‡) | P-Value | Conditional  Odds Ratio  (95% CI) | P-Value |
| ILA | rs111521887 | 1.1  (0.93, 1.3) | 0.25 | 0.99  (0.82, 1.18) | 0.87 |
| ILA | rs5743890 | 0.95  (0.78, 1.14) | 0.57 | 0.99  (0.81, 1.2) | 0.92 |
| ILA | rs5743894 | 1.11  (0.94, 1.31) | 0.22 | 0.99  (0.83, 1.19) | 0.94 |
| ILA | rs7934606 | 1.06  (0.93, 1.2) | 0.36 | 1.01  (0.88, 1.15) | 0.91 |
| Subpleural Predominant | rs111521887 | 1.2  (0.99, 1.45) | 0.066 | 1.0  (0.81, 1.23) | 0.97 |
| Subpleural Predominant | rs5743890 | 0.83  (0.66, 1.05) | 0.12 | 0.9  (0.71, 1.14) | 0.39 |
| Subpleural Predominant | rs5743894 | 1.21  (1.0, 1.46) | 0.051 | 1.01  (0.82, 1.24) | 0.93 |
| Subpleural Predominant | rs7934606 | 1.11  (0.96, 1.29) | 0.17 | 1.02  (0.87, 1.19) | 0.82 |

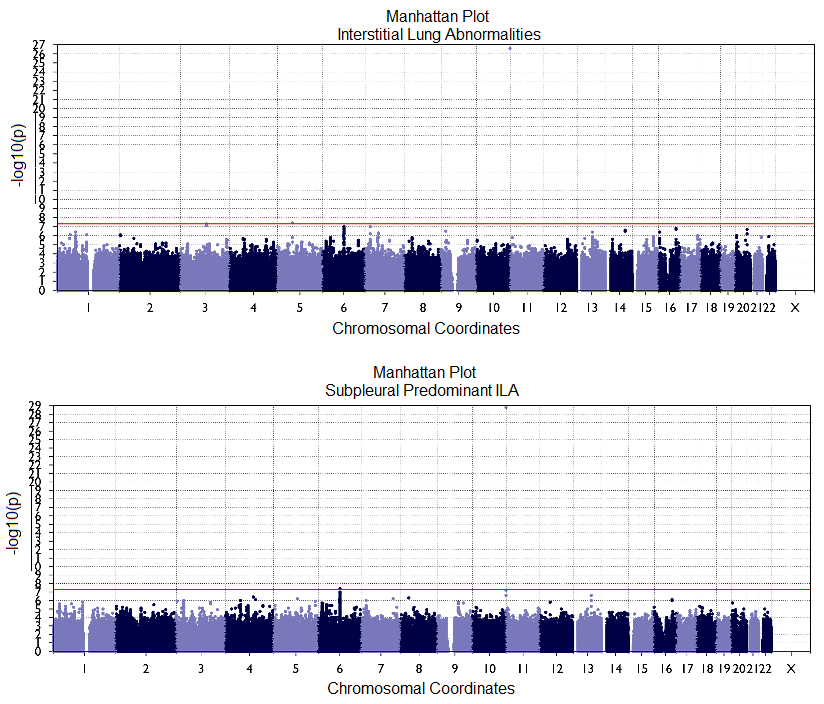
\*ILA is interstitial lung abnormality

†SNP is single nucleotide polymorphism

‡CI is confidence interval



**Figure E1.** Q-Q Plots for the overall meta-analysis of interstitial lung abnormalities (ILA) and subpleural predominant ILA.



**Figure E2.** Manhattan Plots for the overall meta-analysis of interstitial lung abnormalities (ILA) and subpleural predominant ILA.



**Figure E3.** Forest plots of smoking stratified (ever vs never smokers) of the genome wide significant SNPs in both interstitial lung abnormalities (ILA) and subpleural predominant ILA. Panel A are the results of the smoking stratified analysis in ILA at rs73199442 (*FCF1P3*). Panel B are the results of the smoking stratified analysis in ILA at rs6886640 (*IPO11*). Panel C are the results of the smoking stratified analysis in ILA at rs35705950 (*MUC5B*). Panel D are the results of the smoking stratified analysis in subpleural predominant ILA at rs7744971 (*HTRE1*). Panel E are the results of the smoking stratified analysis in subpleural predominant ILA at rs35705950 (*MUC5B*).

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