New genetic signals for lung function highlight pathways and pleiotropy, and chronic obstructive pulmonary disease associations across multiple ancestries

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Abstract

Reduced lung function predicts mortality and is key to the diagnosis of COPD. In a genome-wide association study in 400,102 individuals of European ancestry, we define 279 lung function signals, 139 of which are new. In combination, these variants strongly predict COPD in independent patient populations. Furthermore, the combined effect of these variants showed generalisability across smokers and never-smokers, and across ancestral groups. We highlight biological pathways, known and potential drug targets for COPD and, in phenome-wide association studies, autoimmune-related and other pleiotropic effects of lung function associated variants. This new genetic evidence has potential to improve future preventive and therapeutic strategies for COPD.

Introduction

Impaired lung function is predictive of mortality[1] and is the key diagnostic criterion for chronic obstructive pulmonary disease (COPD). Globally, COPD accounted for 2.9 million deaths in 2016[2], being one of the key causes of both Years of Life Lost and Years Lived with Disability worldwide[3]. Determinants of maximally attained lung function and of lung function decline can influence the risk of developing COPD. Tobacco smoking is the single largest risk factor for COPD, although other environmental exposures and genetic makeup are important[4,5]. Genetic variants associated with lung function and COPD susceptibility can provide aetiological insights, assisting with risk prediction, as well as drug target identification and validation[6]. Whilst there has been considerable progress in identifying genetic markers associated with lung function and risk of COPD[4,7-19] seeking a high yield of associated genetic variants is key to progressing knowledge because: (i) implication of multiple molecules in each pathway will be needed to build an accurate picture of the pathways underpinning development of COPD; (ii) not all proteins identified will be druggable and; (iii) combining information across multiple variants can improve prediction of disease susceptibility.

Through new detailed quality control and analyses of spirometric measures of lung function in UK Biobank and expansion of the SpiroMeta Consortium, we undertook the largest genome-wide association study of lung function performed to date. Our study entailed a near seven-fold increase in sample size over previous studies of similar ancestry to address the following aims: (i) to generate a high yield of genetic markers associated with lung function; (ii) to confirm and fine-map previously reported lung function signals; (iii) to investigate the putative causal genes and biological pathways through which lung function associated variants act, and their wider pleiotropic effects on other traits; and (iv) to generate a weighted genetic risk score for lung function and test its association with COPD susceptibility in individuals of European and other ancestries.

Results

139 new signals for lung function

We increased the sample size available for the study of quantitative measures of lung function in UK Biobank by refining the quality control of spirometry based on recommendations of the UK Biobank Outcomes Adjudication Working Group (**Supplementary Note**). Genome-wide association analyses of forced expired volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC were then undertaken in 321,047 individuals in UK Biobank (**Supplementary Table 1**) and in 79,055 individuals from the SpiroMeta Consortium (**Supplementary Tables 2 and 3**). A linear mixed model approach implemented in BOLT-LMM[20] was used for UK Biobank to account for relatedness and fine-scale

population structure (**Online Methods**). A total of 19,871,028 autosomal variants imputed in both UK Biobank and SpiroMeta were analysed. Peak expiratory flow (PEF) was also analysed genome-wide in UK Biobank and up to 24,218 samples from SpiroMeta. GWAS results in UK Biobank were adjusted for the intercept of LD score regression[21], but SpiroMeta and the meta-analysis were not as intercepts were close to 1.00 (**Online Methods**). All individuals included in the genome-wide analyses were of European ancestry (**Supplementary Figure 1** and **Supplementary Note**).

To maximise statistical power for discovery of new (previously unreported) signals, whilst maintaining stringent significance thresholds to minimise reporting of false positives, we adopted a study design incorporating both two-stage and one-stage approaches (**Figure 1**). In the two-stage analysis, 99 new distinct signals, defined using conditional analyses[22], were associated with one or more traits at $P<5\times10^{-9}$ in UK Biobank and showed association ($P<10^{-3}$) with a consistent direction of effect in SpiroMeta ("Tier 1" signals, **Supplementary Figure 2; Supplementary Table 4**). In the one-stage analysis, we meta-analysed UK Biobank and SpiroMeta (up to 400,102 individuals) and 40 additional new distinct signals associated with one or more lung function traits reaching $P<5\times10^{-9}$ (see [23]) were identified (**Supplementary Figure 2, Supplementary Table 4**) that were also associated with $P<10^{-3}$ separately in UK Biobank and in SpiroMeta, with consistent direction of effect ("Tier 2" signals). An additional 323 autosomal signals were significantly associated with one or more lung function traits in the meta-analysis of UK Biobank and SpiroMeta ($P<5\times10^{-9}$) and reached $P<10^{-3}$ for association in only one of UK Biobank or SpiroMeta ("Tier 3" signals, **Supplementary Table 5**). Analysis of association of FEV_1, FVC and FEV_1/FVC with 240,417 chromosome X variants in 359,226 individuals (321,027 UK Biobank and 38,199 SpiroMeta[15]) gave an additional 5 Tier 3 signals. Only the 139 signals meeting Tier 1 and Tier 2 criteria were followed up further. The strength and direction of association of the sentinel variant (the variant in each signal with the lowest P value) for these 139 new signals across all 4 lung function traits are shown in **Figure 2**. Of the 139 signals, 131 were associated with at least two lung function traits at $P<10^{-3}$, eight signals were unique to FEV_1/FVC and no signals were unique to FEV_1, FVC or PEF at this threshold.

We assessed whether any of these 139 signals associated with lung function could be driven via an underlying association with smoking behaviour (**Online Methods**). Only rs193686 (in an intron of *MET*, **Supplementary Table 6**) was associated with smoking behaviour. Therefore, we tested for association between this variant and lung function in never smokers (n=173,658). Whilst rs193686 was associated with smoking initiation ($P=9.18\times10^{-6}$), the allele associated with smoking initiation was associated with increased lung function in never smokers (FEV_1/FVC $P=5.28\times10^{-10}$, **Supplementary Table 7**). Therefore, this signal was retained for further analysis.

A total of 279 signals of association for lung function

Of 157 previously published signals of association with lung function and COPD[3,6-18], 142 were associated at $P<10^{-5}$ in UK Biobank (**Online Methods, Supplementary Figure 3**, **Supplementary Table 8**). Two sentinel variants (rs1689510 and rs11134789) were associated with smoking initiation (**Supplementary Table 6**), but were also associated with lung function in never smokers (**Supplementary Table 7**). SNP rs17486278 at *CHRNA5* and rs11667314 near *CYP2A6* were each associated with cigarettes per day (**Supplementary Table 6**); neither were significantly associated with lung function among never smokers and so were excluded from further analysis. This brings the total number of distinct signals of association with lung function to 279 (**Supplementary Table 9**). None of these variants showed interaction with ever-smoking status ($P>1.8\times10^{-4}$, **Online Methods,**

Supplementary Table 7). Using the effect estimates, allele frequencies and assuming a total heritability of 40%[24,25] (**Online Methods**), we calculated that the 140 previously reported lung function signals showing association in this study (UK Biobank $P<10^{-5}$) explained 5.0%, 3.4%, 9.2% and 4.5% of the estimated heritability of FEV_1, FVC, FEV_1/FVC and PEF, respectively. The 139 new signals reported here, explain an additional 4.3%, 3.3%, 3.9% and 3.3% of the estimated heritability, respectively.

Identification of putative causal genes

Bayesian refinement was undertaken for each signal to identify the set of variants that were 99% likely to contain the underlying causal variant (assuming the causal variant has been analysed). The results from the meta-analysis of UK Biobank and SpiroMeta were used to define the 99% credible sets (**Online Methods**, **Supplementary Table 10, Supplementary File–Region Plots**).

To identify putative causal genes for each signal, we identified deleterious variants and variants associated with gene expression (eQTLs) or protein levels (pQTLs) within each 99% credible set for all new and previously reported signals outside the HLA region (**Online Methods**).

There were 25 SNPs, located in 22 unique genes, which were annotated as potentially deleterious (**Online Methods**, **Supplementary Table 11**). Amongst our new signals, there were 10 variants annotated as deleterious in 9 different genes: *DOCK9* (rs117633128), *CEP72* (rs12522955), *BCHE* (rs1799807), *DST* (rs11756977), *KIAA0753* (rs2304977, rs9889363), *LRRC45* (rs72861736), *BTC* (rs11938093), *C2orf54* (rs6709469) and *IER5L* (rs184457). Of these, the missense variant in *BCHE* (rs1799807) had the highest posterior probability (0.996) in its respective credible set, was low frequency (MAF=1.95%) and resulted in an amino acid change from aspartic acid (D) to glycine (G), known to affect the function of the encoded butyrylcholinesterase enzyme by altering substrate binding[26]. The two common missense variants in *KIAA0753* were within the credible set of new signal rs4796334. *KIAA0753*, *CEP72* and *LRRC45* all encode proteins with a role in ciliogenesis or cilia maintenance[27-31], and all are highly expressed in the airway epithelium[32].

Variants in the 99% credible sets were queried in three eQTL resources to identify associations with gene expression in lung[33-35] (sample size n=1,111; **Supplementary Table 12**), blood[36] (n=4,896) and a subset of GTEx[37] tissues (max n=388, **Online Methods**). The tissues included from GTEx were lung and blood, plus nine tissues known to contain smooth muscle (**Online Methods**). The latter were chosen based on previous reports of enrichment of lung function GWAS signals in smooth muscle-containing tissues[18,38]. We identified 88 genes, implicated by 58 of the 279 signals, for which the most significant SNP associated with expression of that gene in the respective eQTL resource was within one of the 99% credible sets (**Supplementary Table 13**).

We checked credible set variants for association with protein levels in a pQTL study[39] comprising SNP associations for 3,600 plasma proteins (**Online Methods**). We found 5 proteins with a sentinel pQTL contained within our lung function credible set: ECM1, THBS4, NPNT, C1QTNF5 and SCARF2 (**Supplementary Table 14**).

In total, 107 putative causal genes were identified (**Table 1**), amongst which, we highlight 75 for the first time as putative causal genes for lung function (43 implicated by a new signal and 32 newly implicated by a previous signal[18]).

Pathway analysis

We tested whether these 107 putative causal genes were enriched in gene sets and biological pathways (**Online Methods**), finding an enrichment of genes in elastic fibre and extracellular matrix organisation pathways, and a number of gene ontologies including gene sets relating to the cytoskeleton and processes involved in ciliogenesis (**Supplementary Table 15**). Whilst the enrichment in elastic fibre-related pathways is consistent with our previous study[18], enrichment in these pathways was further supported in this analysis by two new genes, *ITGAV* (at a new signal) and *GDF5* (a newly implicated gene for a previously reported signal), and by strengthened eQTL evidence for *TGFB2* and *MFAP2* at two previously reported signals. The presence of *TGFB2*, *GDF5* and *SMAD3* in our list of 107 genes resulted in enrichment of a TGF-β superfamily signalling pathway (TGF-Core) and related gene ontology terms (**Supplementary Table 15**).

Functional enrichment analyses

Using stratified LD-score regression,[40] we showed that FEV_1/FVC and FVC heritability is significantly enriched at variants overlapping histone marks that are specific to lung, foetal lung, and smooth muscle-containing (i.e. colon and stomach) cell lines. SNPs that overlap with H3K4me1 marks that are specific to foetal lung cells correspond to 6.99% of the input SNPs yet explain 57.09% ($P=2.85\times10^{-25}$) and 35.84% ($P=4.19\times10^{-21}$) of the SNP-chip heritability for FEV_1/FVC and FVC, respectively (**Supplementary Table 16**).

We also tested enrichment of (i) FEV_1/FVC and (ii) FVC SNPs at DNase I hypersensitive site (DHS) hotspots using GARFIELD[41] (**Online Methods**). For FEV_1/FVC results, we see significant enrichment across most cell lines with increased fold-enrichment in foetal and adult lung, foetal muscle and fibroblasts (**Supplementary Figure 4A**). For FVC, we see similar broad significant enrichment without evidence of increased enrichment in a subset of tissues (**Supplementary Figure 4B**). This suggests that SNPs influencing FVC may act via more complex and broader developmental pathways.

We used DeepSEA[42] to identify whether our signals were predicted to have a chromatin effect in lung-related cell lines. We identified 10 signals (including 5 new signals) for which the SNP with the largest posterior probability of being causal also had a significant predicted effect on a DHS in lung-related cells (**Supplementary Table 17**). This included a new signal near *SMURF2* (17q24.1, rs11653958).

Drug targets

All 107 putative causal genes were investigated for known gene-drug interactions[43] (**Supplementary Table 18**). We highlight two examples of new genetic signals implicating targets for drugs in development for indications other than COPD. One of our new signals is an eQTL for *ITGAV*. *ITGAV* encodes a component of the αvβ6 integrin heterodimer, which is inhibited by a monoclonal antibody in development for pulmonary fibrosis (NCT01371305) and for which the small molecule GSK3008348 (NCT03069989) is an antagonist[44]. Integrins have an emerging role as local activators of TGFβ and specifically the avb6 integrin heterodimer can activate latent-TGFβ[45]. In our study, the allele associated with reduced expression of *ITGAV* (**Supplementary Table 13**) was associated with increased lung function (**Supplementary Table 9**) suggesting that inhibitors of αvβ6 integrin might also have a beneficial effect in COPD. Another of our new signals is associated with expression of *TNFSF13* (synonym *APRIL*), a cytokine of the TNF ligand family. Atacicept blocks B cell stimulation by *TNFSF13* (as well as by BLyS) and reduced systemic lupus erythematosus disease activity in a recent

Phase IIb trial[46]. In our study, the allele associated with decreased expression of *TNFSF13* was associated with reduced FEV_1, indicating that vigilance for pulmonary consequences of atacicept may be warranted.

Genetic Risk Score: association with FEV_1/FVC and COPD in multiple ancestries

We constructed a genetic risk score (GRS) weighted by FEV_1/FVC effect sizes comprising all 279 sentinel variants, and tested for association with FEV_1/FVC and GOLD Stage 2-4 COPD (FEV_1/FVC<0.7 and FEV_1<80% predicted) in different ancestry groups in UK Biobank, and China Kadoorie Biobank (**Online Methods**, **Supplementary Table 19**). UK Biobank participants of non-European ancestry were not included in the discovery analyses. The GRS was associated with a significant decrease in lung function, and corresponding significant increase in COPD risk in each of the independent ancestry groups (**Figure 3a**).

We tested for a GRS interaction with smoking in European ancestry individuals in UK Biobank[47]. No statistical interaction was seen for FEV_1/FVC (interaction term -0.002 per SD change in GRS, 95% CI: [0.009, 0.005], P=0.532), whilst the findings for COPD were consistent with a slightly smaller effect of the GRS in ever-smokers (OR for ever-smoking-GRS interaction term per SD change in GRS 0.96, 95% CI: [0.92, 0.99], P=0.015).

The association of the GRS with COPD susceptibility was additionally tested in five independent COPD case-control studies (**Supplementary Table 20, Online Methods**). Similar effect size estimates were seen across each of the 5 European ancestry studies (**Figure 3b**); in the meta-analysis of these studies (n=6,979 cases and 3,915 controls), the odds ratio for COPD per standard deviation of the weighted GRS was 1.55 (95% CI: [1.48, 1.62]), $P=2.87\times10^{-75}$ (**Supplementary Table 21**). The GRS was also associated with COPD in individuals of African-American ancestry in COPDGene ($P=8.36\times10^{-7}$), albeit with a smaller effect size estimate, odds ratio=1.26 (95% CI: [1.15, 1.37]).

To aid clinical interpretation, we divided individuals in each of the five European ancestry COPD case-control studies into deciles, according to their value of the weighted GRS. The odds ratio for COPD in members of the highest GRS decile compared to the lowest GRS decile was 4.73 (95% CI: [3.79, 5.90]), $P=3.00\times10^{-43}$ (**Figure 3c**, **Supplementary Table 22**). We calculated the population attributable risk fraction (**Supplementary Note**) and estimated that the proportion of COPD cases attributable to risk scores above the first GRS decile was 54.6% (95% CI: [50.6%, 58.4%]).

Incorporation of the GRS into a risk model already comprising available clinical information (age, sex, height and pack-years of smoking in COPDGene non-Hispanic Whites) led to a statistically significant ($P=3.33\times10^{-10}$), yet modest, increase in the area under the curve, from 0.751 to 0.771 (**Supplementary Note**). Based on our estimated GRS relative risk and absolute risk estimates of COPD[48], one would expect the highest GRS risk decile group of smokers to have an absolute risk of developing COPD by approximately 70 years of age of 82.4%, versus 17.4% for the lowest GRS decile (**Supplementary Note**).

Pleiotropy and phenome-wide association studies

As phenome-wide association studies (PheWAS) can provide evidence mimicking pharmacological interventions of drug targets in humans and informing drug development[49], we undertook a PheWAS of 2,411 phenotypes in UK Biobank (**Online Methods, Figure 4, Supplementary Table 23**); 226 of the 279 sentinel variants were associated (FDR<1%) with one or more traits and diseases (excluding quantitative lung function traits). Eighty-five of the lung function signals were associated with

standing height. In order to investigate whether the genetic association signals for lung function were driven by incomplete adjustment for height, we tested for correlation of effects on lung function in UK Biobank and height in a meta-analysis of UK Biobank and the GIANT consortium for 246 of the 279 signals that had a proxy variant in GIANT[50]; there was no significant correlation (**Supplementary Figure 5**). Additionally, the PheWAS revealed associations with body composition measures such as fat free mass (54 SNPs) and hip circumference (40 SNPs), as well as muscle strength (32 SNPs, grip strength). One hundred and fourteen of the 279 SNPs were associated with several quantitative measures of blood count, including eosinophil counts and percentages (25 SNPs). Twenty-five of our SNPs were also associated with asthma including 12 SNPs associated both with asthma and eosinophil measures (**Supplementary Table 24)**. Eight of these SNPs were in LD (r^2>0.1) with a SNP reported for association with asthma in previously published genome-wide association studies. We compared our observed effect sizes with those estimated after exclusion of all self-reported asthma cases and observed similar estimates (**Supplementary Figure 6**) suggesting that the lung function associations we report are not driven by asthma.

We examined the specificity of genetic associations, given the potential for this to predict specificity of drug target modification, and found that 53 of the 279 signals were associated only with lung function and COPD-related traits. In contrast, three of our 279 signals were associated with over 100 traits across multiple categories – among these rs3844313, a known intergenic signal near *HLA-DQB1* was associated with 163 traits, and also had the strongest signal in the PheWAS, which was for association with intestinal malabsorption and coeliac disease.

In our 279-variant weighted GRS PheWAS analysis (**Supplementary Table 25**), we found association with respiratory traits including COPD, chronic bronchitis, emphysema, respiratory failure, corticosteroid use and both paediatric and adult-onset asthma (**Figure 5a**). The GRS was also associated with non-respiratory traits including coeliac disease, an intestinal autoimmune disorder (**Figure 5b**). These pleiotropic effects on risk of autoimmune diseases was further confirmed by analysis of previously reported GWAS (**Online Methods, Supplementary Table 26**) which showed overlapping single variant associations with Crohn's disease, ulcerative colitis, psoriasis, systemic lupus erythematosus, IgA nephropathy, pediatric autoimmune disease and type 1 diabetes.

Discussion

The large sample size of our study, achieved by our refinement of the spirometry in UK Biobank and inclusion of the substantially expanded SpiroMeta consortium data set, has doubled the yield of lung function signals to 279. Fine-mapping of all new and previously reported signals, together with gene and protein expression analyses with improved tissue specificity and stringency, has implicated new genes and pathways, highlighting the importance of cilia development, TGF-β signalling via SMAD3, and elastic fibres in the aetiology of airflow obstruction. Many of the genes and pathways reported here contain druggable targets; we highlight examples where the genetic variants mimicking therapeutic modulation of targets may have opposing effects on lung function. We have developed and applied the first weighted GRS for lung function and tested it in independent COPD case-control studies. Our GRS shows stronger association and larger effect size estimates than a previous GRS in European ancestry populations[18], as well as generalisability to other ancestry groups. We undertook the first comprehensive PheWAS for lung function signals, and report genetic variants with apparent specificity of effects and others with pleiotropic effects that might indicate shared biological pathways between different diseases.

For the first time in a GWAS of lung function, we report an enrichment of genes involved in ciliogenesis (including *KIAA0753*, *CDK2* and *CEP72*). Defects in primary cilia as a result of highly deleterious mutations in essential genes result in ciliopathies known to affect multiple organ systems. We found an enrichment of genes with a role in centriolar replication and duplication, core processes in primary and motile cilia formation. Mutations in *KIAA0753* cause the ciliopathies Joubert Syndrome and Orofaciodigital Syndrome[28]. Reduced airway motile cilia function impacting mucus clearance is a feature of COPD, but it has not been clear whether this is causal or the consequence of damage by external factors such as smoking or infection. Our findings suggest that impaired ciliary function might be a driver of the disease process. We have previously shown enrichment of rare variants in cilia-related genes in heavy smokers without airflow obstruction[51].

New signals, implicating *ITGAV* and *GDF5*, as well as stronger support for *TGFB2* and *MFAP2* as likely causal genes, provide new genetic support for the importance of elastic fibre pathways in lung function and COPD[18]. The elastic fibres of the extracellular matrix are known to be disrupted in COPD[52]. As the breakdown of elastic fibres by neutrophil elastase leads to emphysema in individuals with alpha$_1$-antitrypsin deficiency, we also assessed the association with the *SERPINA1* Z allele, which was not associated with FEV$_1$/FVC in our study (rs28929474, P=0.109 in UK Biobank).

Smoking and genetic risk both have important effects on lung function and COPD. For lung function, we found no interaction between smoking and individual variants, and for FEV$_1$/FVC no interaction between smoking status and the weighted GRS. However, for COPD a weak smoking-GRS interaction was observed. Whilst the weighted GRS showed a strong association with COPD susceptibility, and a high attributable risk, we do not claim that this would represent an appropriate method of screening for COPD risk. Importantly, our findings demonstrate the high absolute risk among genetically susceptible smokers (82.4% by approximately 70 years of age).

The unprecedented sample size of UK Biobank as a single cohort has revolutionised genetic studies. We used two complementary study designs to maximise sample size for discovery and ensure robustness of findings by requiring independent support for association. Furthermore, through additional analysis of the spirometry data in UK Biobank and substantial expansion of the SpiroMeta consortium, we have markedly increased samples sizes to almost seven times those included in previous studies. As no lower MAF threshold was applied in our analyses, an overall threshold of $P<5\times10^{-9}$, as recommended for re-sequencing analyses of European ancestry individuals[23], was applied. We identified the largest number of new signals in our more stringent two-stage design ("Tier 1", 99 new signals). Amongst the signals that we report as "Tier 3" (and did not include in further analyses), all reached $P<10^{-3}$ in UK Biobank and 183 met a less stringent threshold of P<0.05 in SpiroMeta. As the primary objective of our paper was to identify variants that were robustly associated with lung function and COPD; we did not include the Tier 3 signals in the downstream analyses. However, as a GRS based on fuller sets of variants are likely to add power for genetic prediction, we have made available our Tier 3 signals (and genome-wide findings) to the scientific community.

Our study is the first to investigate genome-wide associations with PEF. PEF is determined by various physiological factors including lung volume, large airway calibre, elasticity of the lung and expiratory muscle strength, is used for monitoring asthma, and was incorporated in a recently evaluated clinical score for diagnosing COPD and predicting acute exacerbations of COPD[53]. Overall, 133 of the 279 signals were also associated with PEF ($P<10^{-5}$) and for 15 signals (including 4 new signals), PEF was

the most significantly associated trait. Of note, a signal near *SLC26A9*, a known cystic fibrosis modifier gene[54], was highly significantly associated with PEF in UK Biobank ($P=3.97\times10^{-66}$) and nominally significant in SpiroMeta ($P=6.93\times10^{-3}$), with consistent direction of effect, but did not meet the Tier 2 criteria. This could reflect the limited power for PEF in SpiroMeta (up to 24,218 for PEF compared to 79,055 for the other traits).

Examining associations of a given genetic variant with a wide range of human phenotypes is a valuable tool in therapeutic target validation. As in our PheWAS, it can highlight variants which show associations with one or more respiratory traits that might be expected to demonstrate greater target specificity than variants associated with many traits. Additionally, in some instances, association with multiple traits may indicate the relevance of drug repurposing. Association of a given SNP with multiple traits does not necessarily imply shared aetiology, and further investigation is warranted. Our GRS PheWAS assesses broader genetic overlap between lung function and other traits and supports the evidence for some shared genetic determinants with autoimmune diseases.

Our study did not assess interaction of the signals with factors other than smoking, further studies might include assessments for interaction effects, for example, with sex, air pollution and dietary intake. We did not analyse variants on the sex chromosomes as those data were not available at the time of our study.

In summary, our study has doubled the number of signals for lung function and provides new understanding and resources of utility for the development of therapeutics. The 279-variant GRS we constructed was associated with a 4.73-fold increased relative risk of moderate-severe COPD between highest and lowest deciles, such that one would expect over 80% of smokers in the highest genetic risk decile to develop COPD. The GRS was also predictive of COPD across multiple ancestral groups. Our PheWAS highlights both expected and unexpected associations relevant to respiratory and other systemic diseases. Investigating the nature of the pleiotropic effects of some of these variants will be of benefit for drug target identification and validation.

Online Methods

Study Design Overview and rationale

For the two-stage approach, we firstly selected distinct signals of association (defined using conditional analyses) with one or more traits achieving $P<5\times10^{-9}$ in UK Biobank only (n up to 321,047). A threshold of $P<5\times10^{-9}$ was selected to maximise stringency of findings and to be consistent with currently recommended genome-wide significance thresholds for re-sequencing analyses of European ancestry individuals[23]. We then reported as new those signals which additionally met $P<10^{-3}$ in SpiroMeta (N effective>70% of n up to 79,055; see **Supplementary Note and Supplementary Figure 7** for power calculations), with consistent directions of effect and term them “Tier 1“ signals as they meet our highest level of stringency. Methods for conditional analyses and determining novelty are described below.

For the one-stage approach, we selected distinct signals of association (defined using conditional analyses) with one or more traits reaching $P<5\times10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta (n up to 400,102) and reported as new those which additionally met $P<10^{-3}$ in both UK Biobank and SpiroMeta with a consistent direction of effect. We term these signals “Tier 2“ as they meet our second-highest level of stringency.

All signals meeting either set of criteria described above, and that had not been previously published, were reported as new signals of association with lung function. Signals that reached $P<5\times10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta, had a consistent direction of effect in UK Biobank and SpiroMeta, but which did not reach $P<10^{-3}$ in both UK Biobank and SpiroMeta are presented as "Tier 3" and were not included in further analyses.

Data for chromosome X were available for 321,027 European individuals in UK Biobank and 38,199 individuals from SpiroMeta (1000 Genomes Project Phase 1 imputation).[55]

UK Biobank

The UK Biobank data resource is described elsewhere (http://www.ukbiobank.ac.uk). Individuals were selected for inclusion in this study if they met the following criteria: (i) had complete data for age, sex, height and smoking status; (ii) had spirometry meeting quality control requirements (based on analyses of acceptability, reproducibility and blow curve metrics; **Supplementary Note**); (iii) had genome-wide imputed genetic data and; (iv) were of European ancestry based on genetic data (**Supplementary Note**; **Supplementary Figure 1**). Genotyping was undertaken using the Affymetrix Axiom® UK BiLEVE and UK Biobank arrays[13]. Genotypes were imputed to the Haplotype Reference Consortium panel[56] (**Supplementary Note**), and retained if minor allele count≥3 and imputation quality (info)>0.5. A total of 321,047 individuals were included in this analysis (**Supplementary Table 1**).

Residuals from linear regression of each trait (FEV_1, FVC, FEV_1/FVC and PEF) against age, age^2, sex, height, smoking status (ever/never) and genotyping array were ranked and inverse-normal transformed to obtain adjusted, normally distributed Z-scores. These Z-scores were then used for genome-wide association testing under an additive genetic model using BOLT-LMM v2.3[20]. Principal components were not included as BOLT-LMM uses a linear mixed model to account for relatedness and fine-scale population structure.

Linkage disequilibrium (LD) score regression implemented in LDSC[21] was used to estimate inflation of test statistics due to confounding. Genomic control was applied, adjusting all test statistics by LD score regression intercepts: 1.12 for FEV_1, 1.14 for FVC, 1.19 for FEV_1/FVC and 1.13 for PEF (**Supplementary Figure 8**; **Supplementary Table 27**), acknowledging that this might be over-conservative for UK Biobank.

SpiroMeta consortium

The SpiroMeta consortium meta-analysis was comprised of a total of 79,055 individuals from 22 studies. Thirteen studies (n=21,436 individuals) were imputed to the 1000 Genomes Project Phase 1 reference panel[55] (B58C, BHS1&2, three Croatian studies [CROATIA-Korcula, CROATIA-Split and CROATIA-Vis], Health 2000, KORA F4, KORA S3, LBC1936, NSPHS, ORCADES, SAPALDIA and YFS) and 9 studies (n=61,682 individuals) were imputed to the Haplotype Reference Consortium (HRC) panel[57] (EPIC [obese cases and population-based studies], GS:SFHS, NFBC1966, NFBC1986, PIVUS, SHIP, SHIP-TREND, UKHLS and VIKING). See **Supplementary Tables 2** and **3** for the definitions of all abbreviations, study characteristics, details of genotyping platforms and imputation panels and methods). Measurements of spirometry for each study are described in the **Supplementary Note**.

In each study, linear regression models were fitted for each lung function trait (FEV_1, FEV_1/FVC, FVC and PEF, where available), with adjustment for age, age^2, sex and height. For studies with unrelated individuals, these models were fitted separately in ever smokers and never smokers, with additional

adjustment for principal components of ancestry. Studies with related individuals fitted mixed models in all individuals to account for relatedness, with ever smoking status as a covariate.

In all studies, rank-based inverse normal transformations were undertaken on the residuals, with these transformed residuals used as the phenotype for association testing under an additive genetic model (**Supplementary Table 3**).

In the study level results, variants were excluded if they had a very low minor allele count (MAC) (**Supplementary Table 3**) or imputation quality (info)<0.3. In studies with unrelated individuals, the ever and never smokers results were combined, using inverse variance weighted meta-analysis, to give an overall study result. Genomic control was then applied to all study level results, before combining results across all studies using inverse variance weighted meta-analysis. LD score regression intercepts for the meta-analysis were close to 1.00 (**Supplementary Figure 8**; **Supplementary Table 27**) and so genomic control was not applied.

Meta-analyses

A total of 19,871,028 variants (imputed or genotyped) in both UK Biobank and SpiroMeta were meta-analysed using inverse-variance weighted fixed effect meta-analysis, and no further genomic control was applied as LD score regression intercepts were close to 1.00 (**Supplementary Table 27**).

Selection of new signals using conditional analyses

All SNPs ±1Mb were extracted around each sentinel variant. GCTA[58] was then used to perform stepwise conditional analysis to select independently associated SNPs within each 2Mb region. LD was estimated for UK Biobank from the same individuals used in discovery, and for SpiroMeta, from an unrelated subset of 48,943 UK Biobank individuals[18]. Any secondary signals identified within each 2Mb region were required to meet Tier 1 or Tier 2 criteria (described above) after conditioning on the primary sentinel variant. A combined list of distinct lung function signals was then made across the 4 phenotypes, FEV_1, FVC, FEV_1/FVC and PEF as follows: where sentinel variants for 2 signals for different phenotypes were in high LD (r^2>0.5), we retained the most significant variant; where 2 signals were in moderate LD (0.1>r^2>0.5), we retained variants if, after conditional analysis, they still met the Tier 1 or Tier 2 threshold; for signals in low LD (r^2<0.1) we retained both variants. We then used the same criteria to identify a subset of new signals which were distinct from previously published independent signals (see below).

Assessment of previously reported lung function signals

We identified 184 autosomal signals from previous GWAS analyses of lung function and COPD[1,4-14]. After LD pruning (keeping only those signals with LD of r^2<0.1), we removed 24 non-independent SNPs, leaving 160 previously reported independent signals. Of 6 previously reported signals in the HLA region, we included only the 3 independent lung function HLA signals reported from conditional analysis using all imputed HLA genotypes[18]: *AGER* (rs2070600), *HLA-DQB1* (rs114544105) and near *ZNF184* (rs34864796) leaving 157 signals.

We confirmed association of previously reported signals in our data if they met any of three criteria: (i) the previously reported sentinel was associated ($P<10^{-5}$) with any lung function trait in UK Biobank; (ii) a proxy for the previously reported sentinel with r^2>0.5 was associated ($P<10^{-5}$) with any lung function trait in UK Biobank; (iii) a proxy for the previously reported sentinel with r^2>0.1 was associated with any lung function trait meeting tier 1 or tier 2 criteria (**Supplementary Figure 3**).

Effect on COPD susceptibility – genetic risk score in multiple ancestries

To test association of all lung function signals and COPD susceptibility, we constructed a 279-variant weighted GRS comprising the 139 novel and 140 previously reported signals; we used the previously reported sentinel SNP for published signals. Weights were derived using the FEV_1/FVC ratio decreasing (COPD risk *increasing*) alleles. For previously reported signals (n=140), results from the UK Biobank analysis were used to derive weights for the 94 signals that were not discovered using UK Biobank data and weights were taken from SpiroMeta for 46 signals where UK Biobank was included in the discovery of those signals. For novel signals identified in this study, weights were taken from SpiroMeta for two-stage (tier 1) signals (n=99), and the smallest absolute effect size from either of UK Biobank or SpiroMeta was used for one-stage (tier 2) signals (n=40) (**Supplementary Table 28**). This approach was taken in order to derive conservative weights for each variant, thus reducing the likelihood of bias by winner's curse. For the weighted GRS the number of risk alleles at each variant was multiplied by its weight.

The GRS was first calculated in unrelated individuals (KING kinship coefficient of<0.0884) within 6 ancestral groups of UK Biobank: Europeans, South Asians, Africans, Chinese, Mixed African and Europeans, and Mixed Other (total sample of unrelated individuals across six ancestries: 323,001) using PLINK. Weights and alleles were as described above. COPD was defined as FEV_1/FVC<0.7 and FEV_1<0.8 of the predicted value, i.e. GOLD stage 2-4 categorisation. Associations with the GRS were then tested using COPD (in ancestral groups with at least 100 COPD cases) and FEV_1/FVC as the outcomes.

In addition, we calculated the GRS in individuals from the China Kadoorie Biobank (CKB). Four of the 279 SNPs were not available in CKB (rs1800888, rs56196860, rs72724130 and rs77672322), and for 12 SNPs, proxies were used (minimum r^2=0.3). Analyses were undertaken in all COPD GOLD stage 2-4 cases (FEV_1/FVC<0.7 and FEV_1<0.8 of the predicted value, in 6,013 cases and 69,567 controls), against an unbiased set of population controls. The GRS was also tested for association with FEV_1/FVC in CKB (n=72,796).

Logistic regression of COPD case-control status with the GRS in UK Biobank and China Kadoorie Biobank assumed an additive genetic effect and was adjusted for age, age^2, sex, height, and smoking (**Supplementary Table 19**). Ten principal components were also included in UK Biobank analyses. In China Kadoorie Biobank, analyses were stratified by geographical regions and then meta-analysed using an inverse-variance fixed effect model. Linear models assessing the association with FEV_1/FVC were fitted using the same transformed outcome as in the main GWAS analysis.

We then tested association in 5 European ancestry COPD case-control studies: COPDGene (Non-Hispanic White Population) (3,068 cases and 2,110 controls), ECLIPSE (1,713 cases and 147 controls), GenKOLS (836 cases and 692 controls), NETT-NAS (374 cases and 429 controls) and SPIROMICS (988 cases and 537 controls) (**Supplementary Table 20**). In addition, we tested this GRS in the COPDGene African American population study (910 cases and 1,556 controls). Logistic regression models using COPD as outcome and the GRS as exposure were adjusted for age, age^2, sex, height, and principal components (**Supplementary Table 21, Supplementary Figure 9**). Single variant associations of the 279 SNPs with COPD are in **Supplementary Table 29.**

Next, we divided individuals in the external COPD case-control studies into deciles according to their values of the weighted GRS. This was undertaken separately by study group, and for each decile

logistic models were fitted, comparing the risk of COPD for members of each decile group compared to those in the lowest decile (i.e. those with lowest values of the weighted GRS). Covariates were as for the COPD analyses. Results were combined across European-ancestry study groups by fixed effect meta-analysis (**Supplementary Table 22**).

Effects on smoking behaviour

As our discovery GWAS in UK Biobank was adjusted for ever vs. never smoking status, and not for pack years of smoking (pack years information was missing for 32% of smokers), we evaluated whether any signals of association with lung function might be driven by an association with smoking behaviour by testing for association with smoking initiation (123,890 ever smokers vs. 151,706 never smokers) and cigarettes per day (n=80,015) in UK Biobank (full methods in **Supplementary Note**). We also tested for association with lung function in never smokers only (n=173,658). We excluded any signals associated with smoking behaviour (**Supplementary Table 6**), but not with lung function in never smokers.

Smoking interaction

For associated variants (new and previously reported), we repeated association testing for lung function separately in UK Biobank and SpiroMeta (up to 176,701 ever smokers and 197,999 never smokers), and tested for an interaction effect with smoking using the Welch test (**Supplementary Note**). A threshold of $P<1.79\times10^{-4}$ (Bonferroni corrected for 279 tests) indicated significance.

We further tested for interaction between the weighted GRS and smoking, within 303,619 unrelated individuals of European ancestry in UK Biobank, using COPD and FEV_1/FVC as outcomes (the FEV_1/FVC phenotype was pre-adjusted for age, age^2, sex, and height, and the residuals transformed as per the main GWAS analysis). For COPD (defined as $FEV_1/FVC<0.7$, and $FEV_1<80\%$ predicted) the following logistic model was fitted:

COPD ~ genotyping array + 10 principal components + age + age^2 + sex + height + smoking status + weighted risk score + (*smoking status* × *weighted risk score*)*.*

For FEV_1/FVC the following linear model was fitted:

FEV_1/FVC ~ genotyping array + 10 principal components + smoking status + weighted risk score + (smoking status x weighted risk score).

Proportion of variance explained

We calculated the proportion of variance explained by each of the previously reported (n=140) and new variants (n=139) associated with lung function using the formula:

$$\frac{\sum_{i=1}^{n} 2f_i(1-f_i)\beta_i^2}{V}$$

where n is the number of variants f_i and β_i are the frequency and effect estimate of the i'th variant, and V is the phenotypic variance (always 1 as our phenotypes were inverse-normal transformed). We used the same conservative effect estimates (β) as used to calculate GRS weights at the same set of 279 sentinel variants used for the GRS, which uses either UK Biobank or SpiroMeta effect estimates (described above). Our previously published estimate of proportion of variance explained[18] used effect estimates derived from UK Biobank. We assumed a heritability of 40%[24,25] to estimate the proportion of additive polygenic variance.

Fine-mapping

A Bayesian method[59] was used to fine-map lung-function-associated signals to the set of variants that were 99% likely to contain the underlying causal variant (assuming that the causal variant has been analysed). This was undertaken for new signals and for previously reported signals reaching $P<10^{-5}$ in UK Biobank. For the previously reported signals, the top sentinel variant from the current analysis in UK Biobank was used, instead of the previously reported variant. We used a value of 0.04 for the prior W in the approximate Bayes factor formula[60]. Effect sizes and standard errors for fine-mapping were obtained from an inverse variance weighted meta-analysis of UK Biobank and SpiroMeta (n up to 400,102). Signals in the HLA region were not included.

Implication of potentially causal genes

Annotation of deleterious variants

Variants in the 99% credible sets were checked for predicted functional effect if they were annotated as "exonic", "splicing", "ncRNA_exonic", "5'-UTR" or "3'-UTR" (untranslated region) by ANNOVAR[61]. We then used SIFT, PolyPhen-2 (implemented using the Ensembl GRCh37 Variant Effect Predictor, https://www.ensembl.org/vep, accessed 1 February 2018) and FATHMM[62] to annotate missense variants, and CADD (also implemented using VEP) to annotate non-coding variation. Variants were annotated as deleterious in our study if they were labelled 'deleterious' by SIFT, 'probably damaging' or 'possibly damaging' by PolyPhen-2, 'damaging' by FATHMM (specifying the 'Inherited disease' option of the coding variants methods, and setting the prediction algorithm to 'Unweighted') or had a CADD scaled score ≥ 20[4]. The union of the four methods was taken to establish the number of potentially deleterious variants and their unique genes.

Gene expression and protein levels

At 276 of 279 (3 HLA signals excluded) signals, the sentinel variant and 99% credible set[59] were used to query three eQTL resources: lung eQTL (n=1,111)[13], blood eQTL (n=4,896)[63] and GTEx (V7; with n up to 388 depending on tissue: Artery Aorta (n=267), Artery Coronary (n=152), Artery Tibial (n=388), Colon Sigmoid (n=203), Colon Transverse (n=246), Esophagus Gastroesophageal Junction (n=213), Esophagus Muscularis (n=335), Lung (n=383), Small Intestine Terminal Ileum (n=122), Stomach (n=237), and Whole Blood (n=369))[64], and one blood pQTL resource (n=3,301)[39].

A gene was classified as a 'putative causal gene' if the sentinel SNP or any SNP in the respective 99% credible set was associated with expression of this gene or its protein levels (FDR<5% for eQTL, $P<5.03\times10^{-8}$ [for 276 tests at 3,600 proteins] for pQTL) and if the GWAS sentinel SNP or any SNP in the respective 99% credible set was also the variant most strongly associated with expression of the respective gene or level of the respective protein (i.e. the sentinel eQTL/pQTL SNP) in one or more of the eQTL and pQTL data sets.

Pathway analysis

We tested for enrichment of genes identified via variant function annotation, gene expression or protein level analyses in pathway and gene set ontology databases using ConsensusPathDB.[65] Pathways or gene sets represented entirely by genes implicated by the same association signal were excluded. Gene sets and pathways with FDR<5% are reported.

Functional enrichment analyses

We carried out stratified LD score regression to identify significant enrichment of heritability at variants overlapping histone marks (e.g. H3K4me1, H3K4me3) that are specific to lung, foetal lung, and smooth muscle containing (i.e. colon, stomach) cell lines using methods specified by Finucane *et al*.[40]

We separately selected FEV_1/FVC and FVC associated SNPs passing two thresholds ($P<5\times10^{-5}$ and $P<5\times10^{-9}$ in the meta-analysis) as input to GARFIELD[41] to test for enrichment of our signals for 424 DHS hotspot annotations derived from 55 different tissues in the RoadMap Epigenomics project and the ENCODE projects.

Using DeepSEA[42], we analysed all SNPs in the 99% credible set for predicted chromatin effects. We reported effects for any chromatin effect and lung-related cell line that had an E-value<0.05 (i.e. the expected proportion of SNPs with a larger predicted effect based on empirical distributions of predicted effects for 1000 Genomes SNPs) and an absolute difference in probability of>0.1 (threshold for "high confidence") between the reference and alternative allele.

Drug targets

Genes identified as potentially causal using eQTL, pQTL or variant annotation were interrogated against the gene-drug interactions table of the Drug-Gene Interactions Database (DGIDB) (http://www.dgidb.org/data/), accessed 16th October 2017. Drugs were mapped to CHEMBL IDs (https://www.ebi.ac.uk/chembl/drug/indications), and indications (as MeSH headings) were added.

Phenome-wide association studies

To identify whether the 279 signals overlap with signals of association for other traits and diseases, the weighted GRS was calculated in up to 379,337 UK Biobank samples, and a phenome-wide association study (PheWAS) was performed, with the GRS as the exposure. Traits included UK Biobank baseline measures (from questionnaires and physical measures), self-reported medication usage, and operative procedures, as well as those captured in Office of Population Censuses and Surveys codes from the electronic health record. We also included self-reported disease variables and those from hospital episode statistics (ICD-10 codes truncated to three-character codes and combined in block and chapter groups), combining these where possible to maximise power. The GRS analysis included 2,453 traits, and the single-variant analysis contained 2,411 traits (traits with>200 cases were included for the single-variant PheWAS, whereas traits with>50 cases were included in the GRS PheWAS). Analyses were conducted in unrelated European-ancestry individuals (KING kinship coefficient <0.0442), and were adjusted for age, sex, genotyping array, and ten principal components. Logistic and linear models were fitted for binary and quantitative outcomes, respectively. False discovery rates were calculated on the basis of the number of traits in the GRS and single-variant PheWAS (2,453 or 2,411, respectively).

In addition, the sentinel variants and variants within the 99% credible sets were queried against the GWAS catalog[66] (https://www.ebi.ac.uk/gwas/, accessed 5th February 2018) and GRASP[67] (https://grasp.nhlbi.nih.gov/Overview.aspx, accessed 6th February 2018) for associations reported at $P<5\times10^{-8}$. Associations relating to methylation, expression, metabolite or protein levels, as well as lung function and COPD, were not included.

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SpiroMeta GWAS summary statistics, UK Biobank GWAS summary statistics and single-variant PheWAS results are available by request to the corresponding authors. UK Biobank GWAS summary statistics will also be available via UK Biobank (http://www.ukbiobank.ac.uk/). The newly derived spirometry quality control variables are available from UK Biobank.

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Figures and Figure Legends

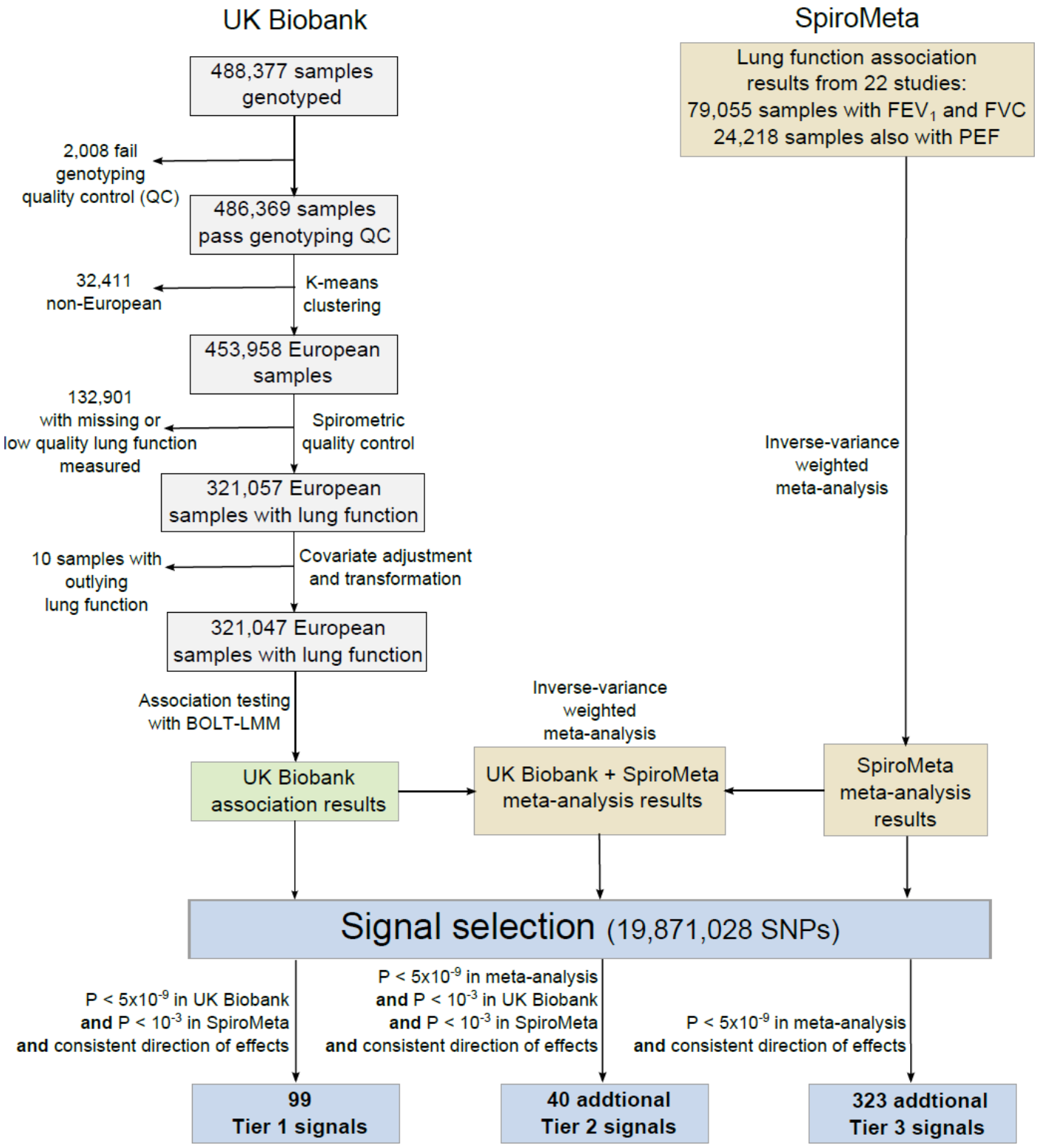


Figure 1: Study design

Tier 1 signals had $P<5\times10^{-9}$ in UK Biobank and $P<10^{-3}$ in SpiroMeta with consistent direction of effect. Tier 2 signals had $P<5\times10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta with $P<10^{-3}$ in UK Biobank and $P<10^{-3}$ in SpiroMeta with consistent directions of effect. Signals with $P<5\times10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta, and that had consistent directions of effect but did not meet $P<10^{-3}$ in both cohorts were reported as Tier 3.

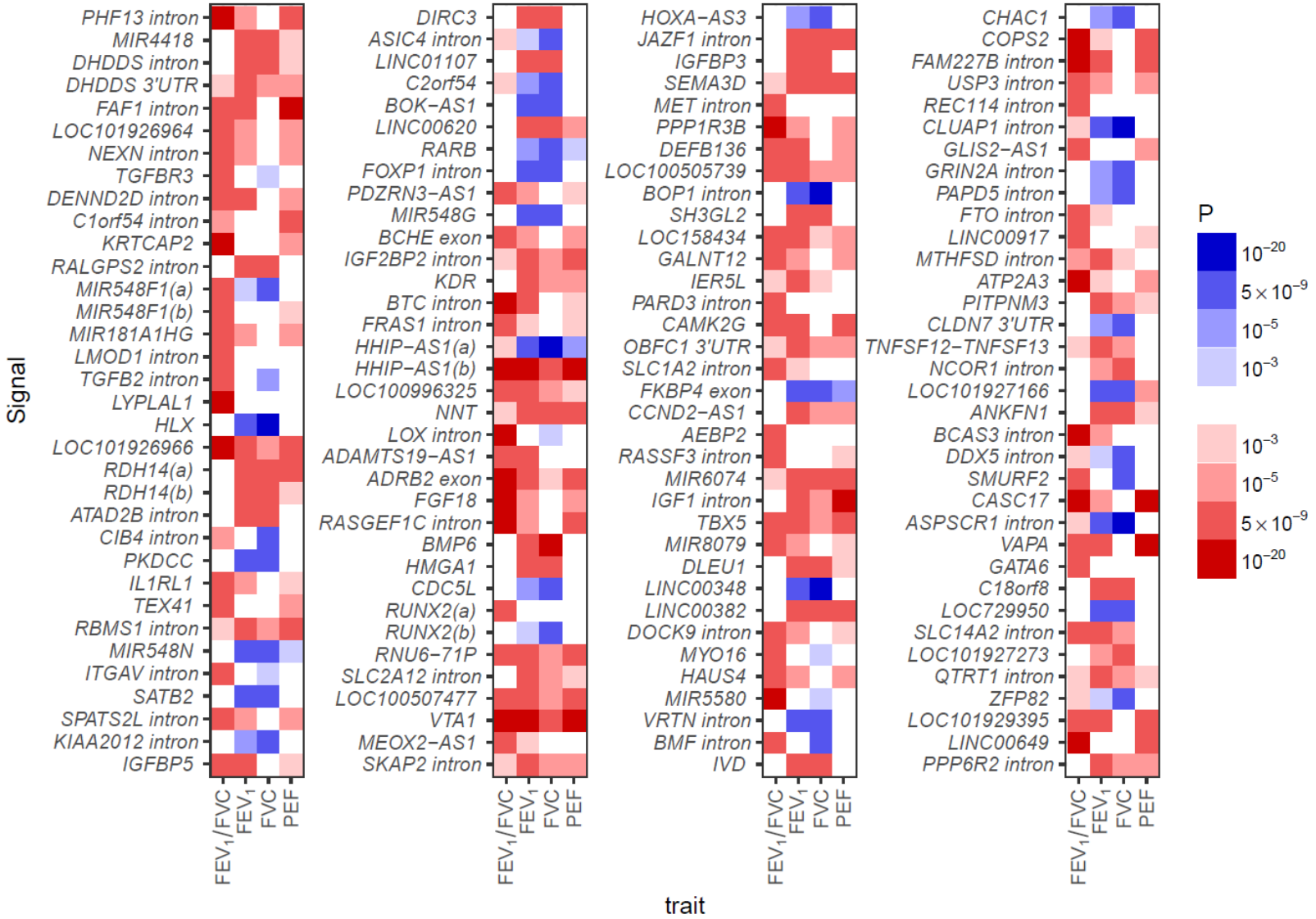


Figure 2: Strength and direction of association across four lung function traits for 139 novel signals: Signals are in chromosome and genomic position order from top to bottom then left to right. Red indicates a decrease in the lung function trait; blue indicates an increase. All effects are aligned to the allele associated with decreased FEV_1/FVC, hence the FEV_1/FVC column is only red or white. P-values are from the meta-analysis of UK Biobank and SpiroMeta (n=400,102). The scale points are thresholds

used for (i) confirmation in 2-stage analysis and 1-stage analysis ($P<10^{-3}$); (ii) confirmation of association of previous signals ($P<10^{-5}$); (iii) signal selection in 2-stage and 1-stage analysis ($P<5\times10^{-9}$); capped at ($P<10^{-20}$).

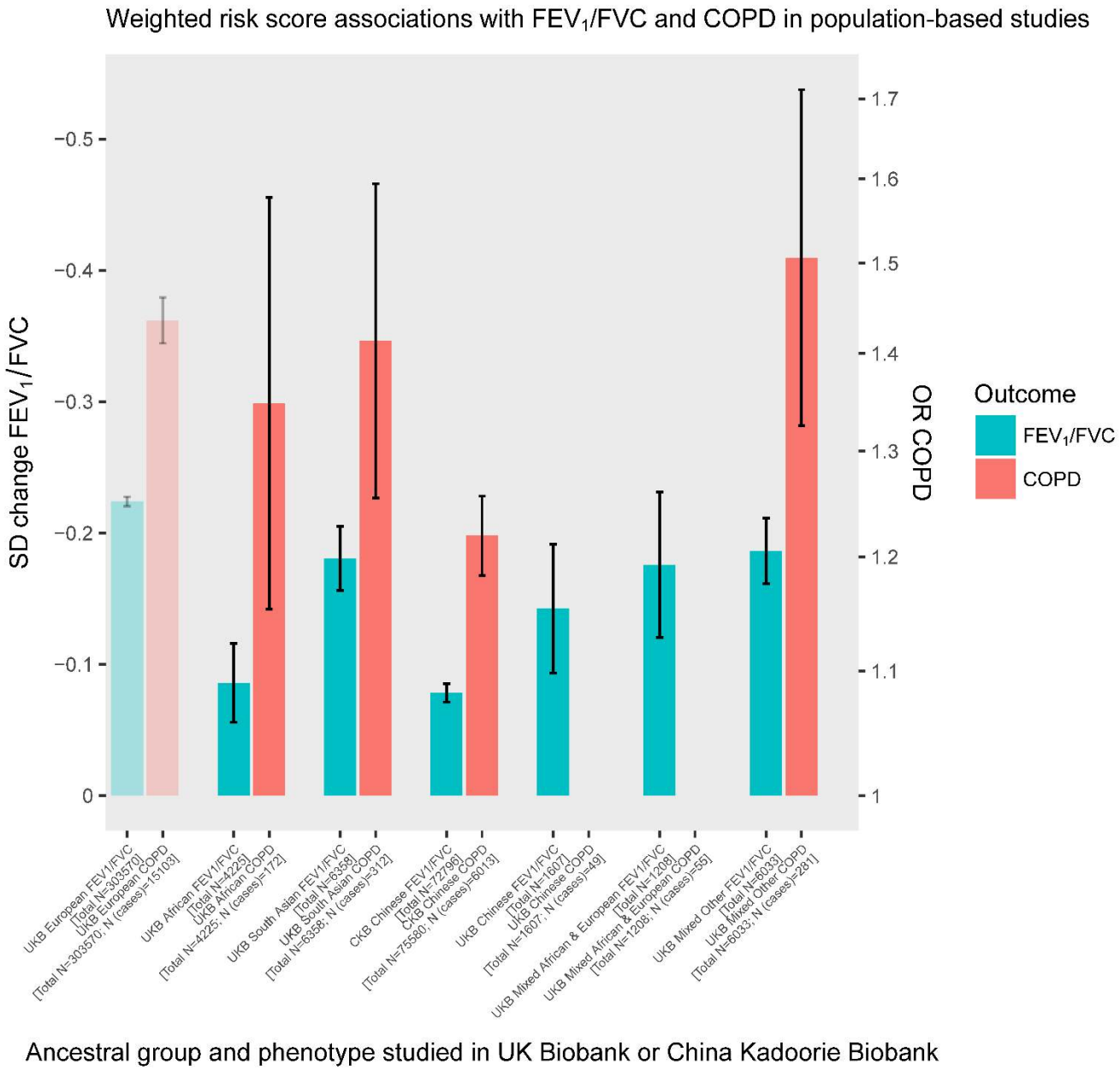
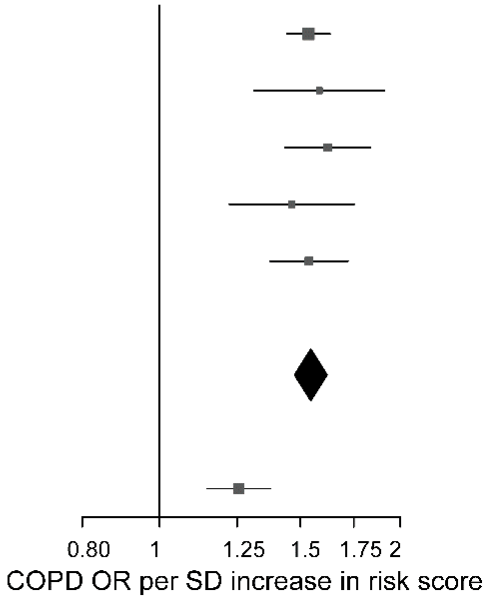


Figure 3: Association of weighted genetic risk score (GRS) with COPD and FEV_1/FVC.

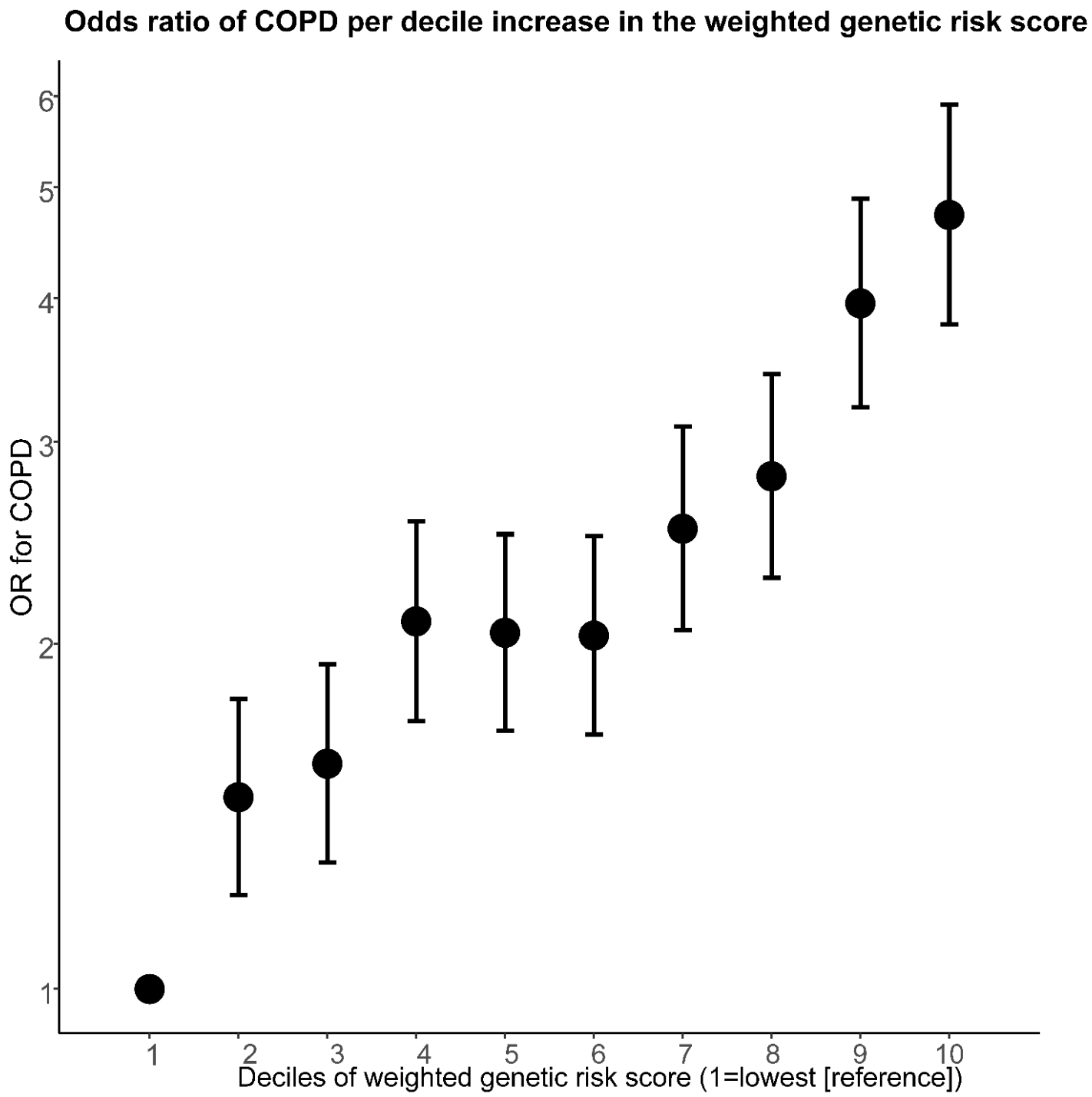
A. Association of the weighted genetic risk score (GRS) with FEV_1/FVC and COPD in UK Biobank and China Kadoorie Biobank (CKB). For means and standard deviations of the risk scores in each group, see **Supplementary Table 19.** The left-hand axis denotes change in standard deviation (SD) units of FEV_1/FVC per 1 SD increase in weighted GRS (blue bars). The right axis shows the translation of this effect to COPD in the same individuals, defined as FEV_1/FVC<0.7 and FEV_1<0.8 of the predicted value, i.e. GOLD stage 2-4 categorisation. Odds ratios (OR) for COPD (red bars) are given per 1 standard deviation (SD) increase in weighted GRS (OR for COPD shown only for ancestries in UK Biobank with>100 cases of COPD). Bars are labelled with ancestral groups, and the total sample size and number of COPD cases are given. The height of the bars represents the effect estimate, and the black whiskers represent 95% confidence intervals. Note some variants included in the GRS were discovered in UK Biobank individuals of European ancestry, and therefore the results for UKB Europeans (far left bars, greyed out) are shown for reference only. All other ancestral groups shown in the plot are independent to UK Biobank Europeans. There were 13 SNPs with MAF<0.1% in at least one ancestral group: 13/279 in Chinese (of which 4/13 were monomorphic). Two of the 13 SNPs that were monomorphic in Chinese people had MAF<0.1% in Africans.

Weighted risk score associations with COPD susceptibility in COPD case-control studies

Ancestry	Cohort	OR	95%LCI	95%UCI	P	Cases	Controls
European	COPDGene (EUR)	1.54	1.44	1.63	1.97×10^{-41}	3068	2110
	ECLIPSE	1.59	1.31	1.91	1.42×10^{-06}	1713	147
	GenKOLS	1.62	1.44	1.83	8.99×10^{-15}	836	692
	NETT−NAS	1.46	1.22	1.75	3.13×10^{-05}	374	429
	SPIROMICS	1.54	1.38	1.72	4.47×10^{-14}	988	537
	Meta−analysis	**1.55**	**1.48**	**1.62**	$\mathbf{1.48 \times 10^{-75}}$	**6979**	**3915**
African	COPDGene (AFR)	1.26	1.15	1.37	8.36×10^{-07}	910	1556



B. Odds ratio (OR) for COPD per 1 standard deviation (SD) increase in weighted genetic risk score in each of six study groups (COPDGene [Non-Hispanic White], COPDGene [African-American], ECLIPSE, GenKOLS, SPIROMICS, NETT-NAS). COPD was defined using GOLD 2-4 criteria. For means and standard deviations of the risk scores in each group see **Supplementary Table 21**. The vertical black line indicates the null effect (an OR of 1). The point estimate of each study is represented by a box proportional to the study's weight, with the lines representing the lower and upper bounds of the 95% confidence interval. A fixed effect meta-analysis of the five European-ancestry groups is denoted with a diamond, the width of which represents the 95% confidence interval for the estimate (I^2 statistic=0).



C. Odds ratios (OR) for COPD according to membership of deciles 2-10 of the weighted genetic risk score, with decile 1 as the reference group (the 10% of individuals with the lowest genetic risk score). Each point represents a meta-analysis of results for a given comparison (i.e. decile 2 vs reference, decile 3 vs reference … decile 10 versus reference) in five external European-ancestry study groups (COPDGene, ECLIPSE, GenKOLS, SPIROMICS, NETT-NAS). Deciles were calculated and models were run in each group separately. Points represent odds ratios, and error bars correspond to 95% confidence intervals (**Supplementary Table 22**).

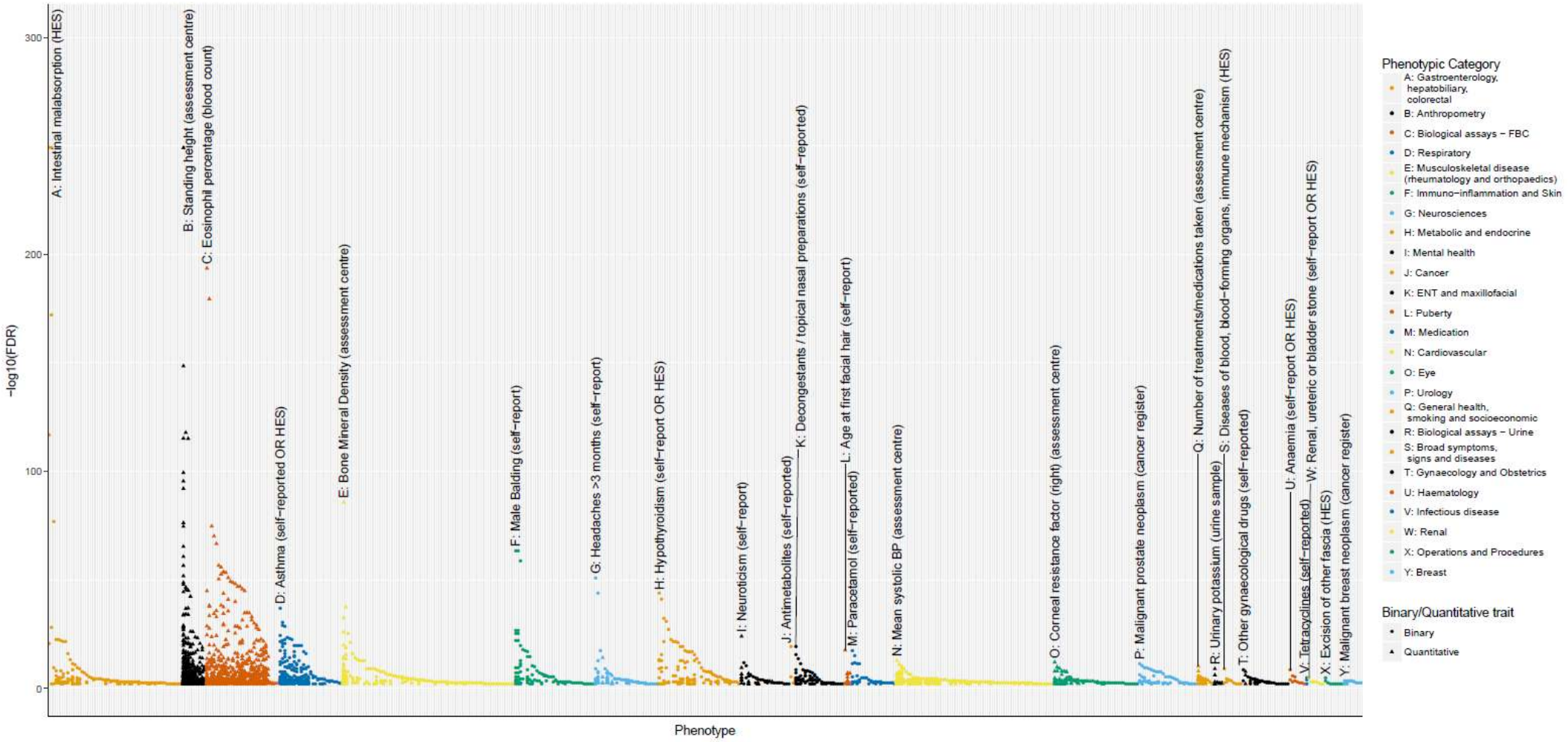


Figure 4: Individual PheWAS with 279 variants (traits passing FDR 1% threshold)

Separate association of 279 variants with 2,411 traits (FDR<1%) in UK Biobank (n up to 379,337). In each category, the trait with the strongest association, i.e. highest $-\log_{10}$(FDR), is shown first, followed by other traits in that category in descending order of $-\log_{10}$(FDR). Categories are colour-coded, and outcomes are denoted with a circular or triangular point, according to whether they were coded as binary or quantitative. The top association per-category is labelled with its rsID number, and a plain English label describing the trait. The letter at the beginning of each label allows easy cross-reference with the categories labelled in the legend. Zoomed in versions of each category with visible trait names and directionality are available in **Supplementary Figure 10**. These plots have signed $\log_{10}$(FDR) values, where a positive values indicates

that a positive SNP-trait association is concordant with the risk allele for reduced lung function (as measured by lower FEV_1/FVC). Tabulated results of all SNP-trait PheWAS associations associated at an FDR of<1% are available in **Supplementary Table 23**.

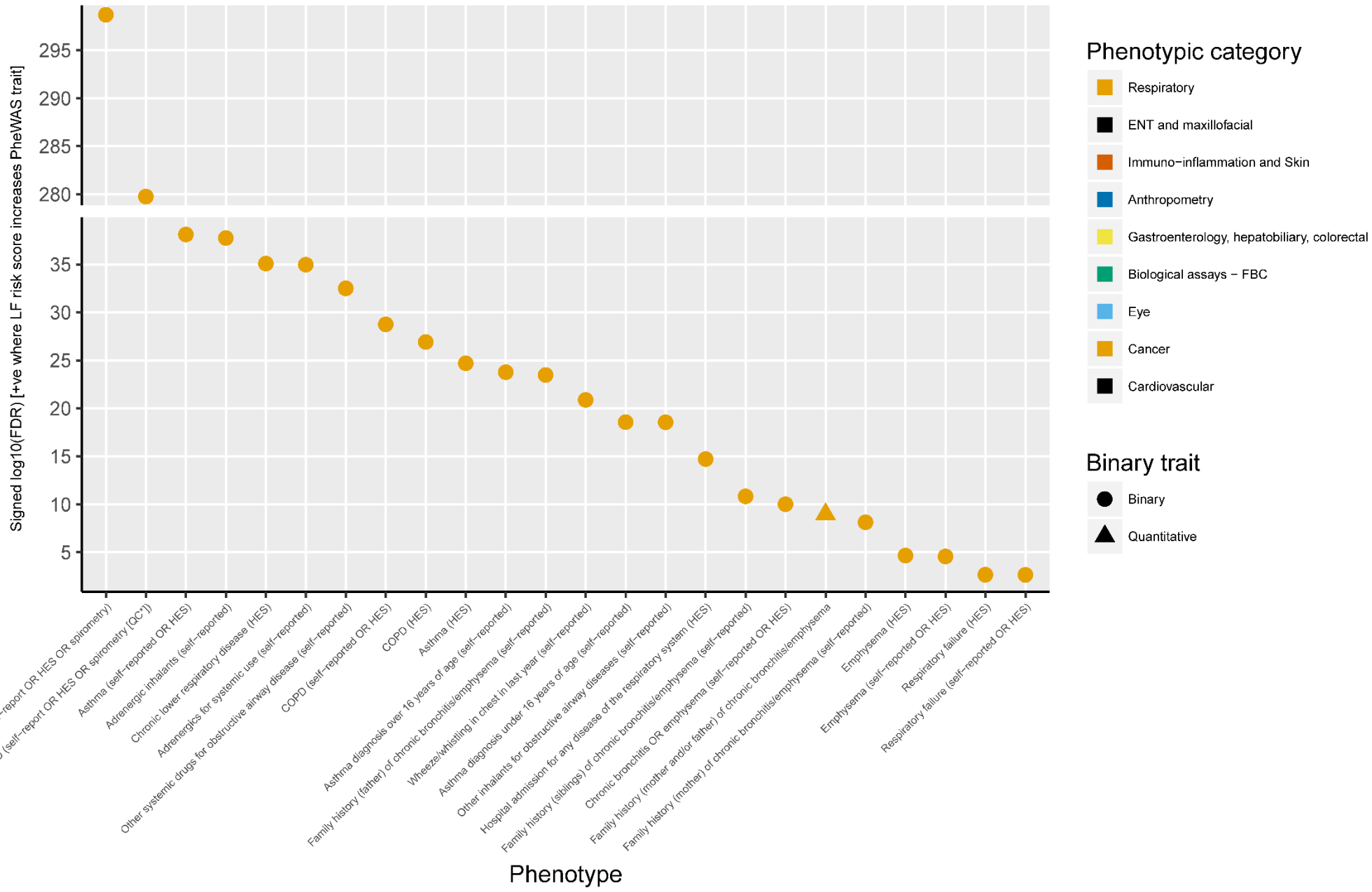
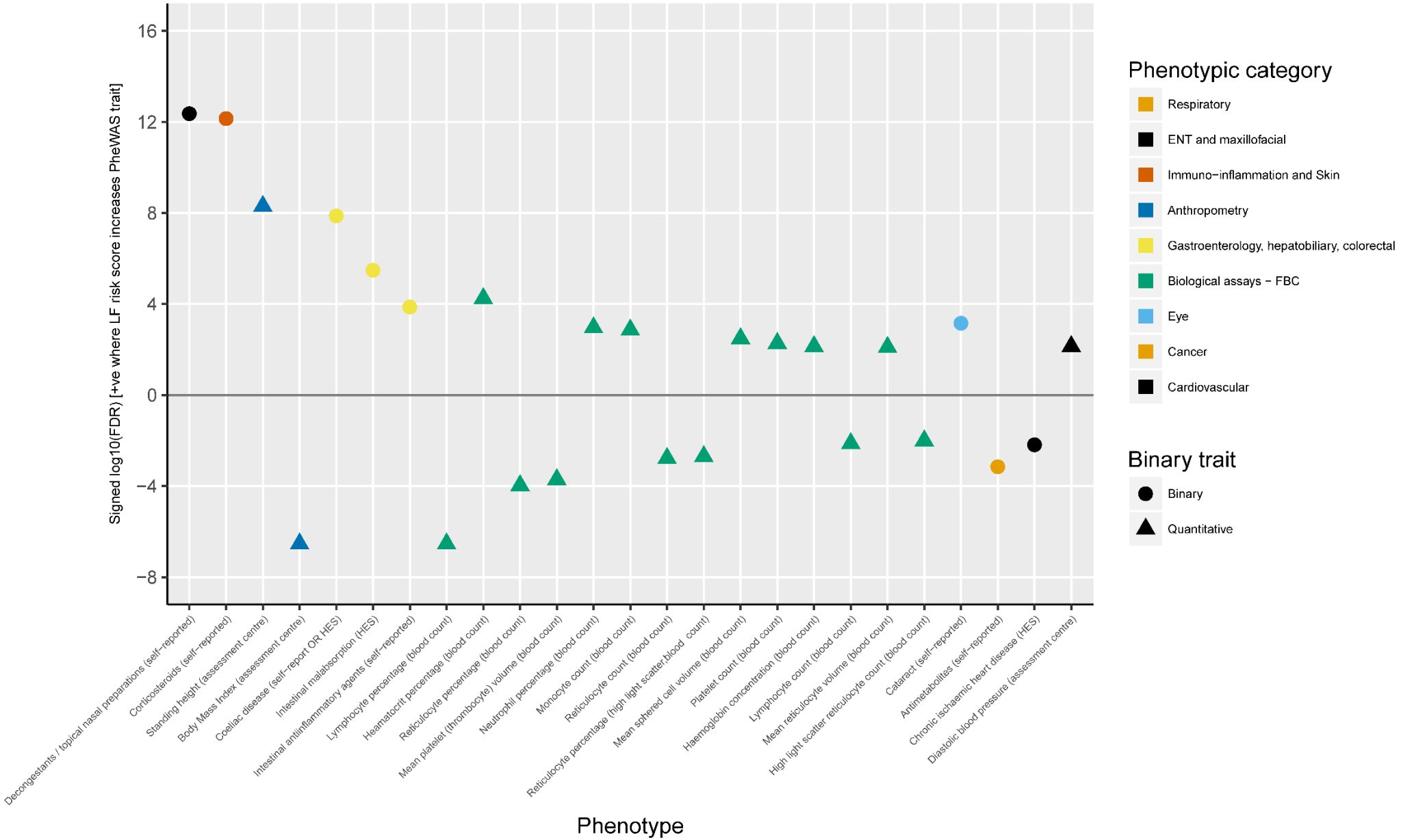

Signed log10(FDR) [+ve where LF risk score increases PheWAS trait]
295
290
285
280
35
30
25
20
15
10
5
COPD (self-report OR HES OR spirometry)
COPD (self-report OR HES OR spirometry (QC'ed))
Asthma (self-reported OR HES)
Adrenergic inhalants (self-reported)
Chronic lower respiratory disease (HES)
Adrenergics for systemic use (self-reported)
Other systemic drugs for obstructive airway disease (self-reported)
COPD (self-reported OR HES)
COPD (HES)
Asthma (HES)
Asthma diagnosis over 16 years of age (self-reported)
Family history (father) of chronic bronchitis/emphysema (self-reported)
Wheeze/whistling in chest in last year (self-reported)
Asthma diagnosis under 16 years of age (self-reported)
Other inhalants for obstructive airway diseases (self-reported)
Hospital admission for any disease of the respiratory system (HES)
Family history (siblings) of chronic bronchitis/emphysema (self-reported)
Chronic bronchitis OR emphysema (self-reported OR HES)
Family history (mother and/or father) of chronic bronchitis/emphysema
Family history (mother) of chronic bronchitis/emphysema (self-reported)
Emphysema (HES)
Emphysema (self-reported OR HES)
Respiratory failure (HES)
Respiratory failure (self-reported OR HES)
Phenotype
Phenotypic category
Respiratory
ENT and maxillofacial
Immuno-inflammation and Skin
Anthropometry
Gastroenterology, hepatobiliary, colorectal
Biological assays - FBC
Eye
Cancer
Cardiovascular
Binary trait
Binary
Quantitative

Figure 5: PheWAS with genetic risk score (traits passing FDR 1% threshold)

Association of 279 variant weighted genetic risk score with 2,453 traits (FDR<1%) in UK Biobank (n up to 379,337). In each panel, the category with the strongest association, i.e. highest $-\log_{10}$(FDR), is shown first, followed by all other associations in that category, ordered by descending order of $-\log_{10}$(FDR). Sample sizes varied across traits and are available in **Supplementary Table 25**, along with the full summary statistics for each association, plus details of categorisation and plain English labels for each trait. Trait categories are colour coded, and outcomes are denoted with a circular or triangular point, according to whether they were coded as binary or quantitative. The sign of the $\log_{10}$(FDR) value is positive where an increase in the risk score (i.e. greater risk of COPD, reduced lung function) is associated with a positive effect estimate for that trait. *QC refers to spirometry passing ERS/ATS criteria. HES=Hospital Episode Statistics.

A. Associations with respiratory traits.



B. Associations with all other traits. ENT=Ear, Nose and Throat; FBC=Full Blood Count.

Tables

Table 1: Genes implicated using gene expression data, protein level data and functional annotation

†Genes implicated by eQTL signals: Lung eQTL (n=1,111) and Blood eQTL (n=4,896) datasets and eleven GTEx (V7) tissues were screened: Artery Aorta (n=267), Artery Coronary (n=152), Artery Tibial (n=388), Colon Sigmoid (n=203), Colon Transverse (n=246), Esophagus Gastroesophageal Junction (n=213), Esophagus Muscularis (n=335), Lung (n=383), Small Intestine Terminal Ileum (n=122), Stomach (n=237), and Whole Blood (n=369); see **Supplementary Table 13** for direction of gene expression for the COPD risk (FEV_1/FVC reducing) allele.

‡Genes implicated by pQTL signals: pQLT look up in 3,600 plasma proteins (n up to 3,300).

*Genes implicated because they contain a deleterious variant (**Supplementary Table 11**).

"Other traits" column lists the other lung function traits for which the sentinel was associated at $P<5\times10^{-9}$ in the meta-analysis of UK Biobank and SpiroMeta.

In total, 107 putative causal genes were identified: 8 by both a deleterious variant and an eQTL signal (including *KIAA0753* implicated by two deleterious variants), 1 (*NPNT)* by both an eQTL and a pQTL signal, 1 (*SCARF2*) by both a deleterious variant and a pQTL signal, 13 by a deleterious variant only, 81 by an eQTL signal only and 3 by a pQTL signal only

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
DHDDS (intron)	FVC	FEV_1	Tier 2	rs9438626	1:26,775,367	G/C	*DHDDS*†
DHDDS (3'-UTR)	FEV_1		Tier 1	rs12096239	1:26,796,922	C/G	*HMGN2*†, *DHDDS*†
NEXN (intron)	FEV_1/FVC	FEV_1	Tier 1	rs9661687	1:78,387,270	T/C	*NEXN*†
DENND2D (intron)	FEV_1/FVC		Tier 1	rs9970286	1:111,737,398	G/A	*CEPT1*†, *CHI3L2*†, *DRAM2*†
C1orf54 (intron)	PEF	FVC	Tier 1	rs11205354	1:150,249,101	C/A	*MRPS21*†, *RPRD2*†, *ECM1*‡
KRTCAP2	FEV_1/FVC		Tier1	rs141942982	1: 155153537	T/C	*THBS4*‡
RALGPS2 (intron)	FEV_1		Tier 1	rs4651005	1:178,719,306	C/T	*ANGPTL1*†
LMOD1 (intron)	FEV_1/FVC	FEV_1	Tier 2	rs4309038	1:201,884,647	G/C	*SHISA4*†
ATAD2B (intron)	FVC	FEV_1	Tier 2	rs13009582	2:24,018,480	G/A	*UBXN2A*†
PKDCC	FVC		Tier 1	rs4952564	2:42,243,850	A/G	*PKDCC*†
ITGAV (intron)	FEV_1/FVC		Tier 1	rs2084448	2:187,530,520	C/T	*ITGAV*†
SPATS2L (intron)	FEV_1/FVC		Tier 2	rs985256	2:201,208,692	C/A	*SPATS2L*†
C2orf54	FVC	FEV_1	Tier 1	rs6437219	2:241,844,033	C/T	*C2orf54*†*
MIR548G	FVC		Tier 1	rs1610265	3:99,420,192	T/C	*FILIP1L*†
BCHE (exon)	FEV_1/FVC	FEV_1	Tier 1	rs1799807	3:165,548,529	C/T	*BCHE**
BTC (intron)	FEV_1/FVC	FEV_1/FVC	Tier 1	rs62316310	4:75,676,529	G/A	*BTC**
LOC100996325	FEV_1	FEV_1/FVC, PEF	Tier 1	rs11739847	5:609,661	A/G	*CEP72**
RNU6-71P	FEV_1	FVC, PEF	Tier 1	rs2894837	6:56,336,406	G/A	*DST**
JAZF1 (intron)	FEV_1		Tier 1	rs1513272	7:28,200,097	C/T	*JAZF1*†
MET (intron)	FEV_1/FVC		Tier 2	rs193686	7:116,431,427	T/C	*MET*†

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
IER5L	FEV_1		Tier 2	rs967497	9:131,943,843	G/A	*CRAT*†, *PPP2R4*†, *IER5L**
DOCK9	FEV_1/FVC		Tier 1	rs11620380	13:99,665,512	A/C	*DOCK9**
CHAC1	FVC		Tier 1	rs4924525	15:41,255,396	A/C	*INO80*†, *CHP1*†, *RAD51*†
ATP2A3	FEV_1/FVC		Tier 1	rs8082036	17:3,882,613	G/C	*ATP2A3*†
PITPNM3	FEV_1		Tier 2	rs4796334	17:6,469,793	A/G	*KIAA0753*†*, *TXNDC17*†, *PITPNM3*†
TNFSF12-TNFSF13	FEV_1		Tier 2	rs4968200	17:7,448,457	C/G	*TNFSF13*†, *SENP3*†
NCOR1 (intron)	FVC	FEV_1	Tier 2	rs34351630	17:16,030,520	C/T	*ADORA2B*†, *TTC19*†
ASPSCR1 (intron)	FVC	FEV_1	Tier 1	rs59606152	17:79,952,944	C/T	*LRRC45**
C18orf8	FVC		Tier 1	rs303752	18:21,074,255	A/G	*C18orf8*†
ZFP82	FVC	FVC, PEF	Tier 2	rs2967516	19:36,881,643	A/G	*ZFP14*†, *ZFP82*†
MFAP2	FEV_1/FVC	FEV_1, PEF	Previous	rs9435733	1:17,308,254	C/T	*MFAP2*†
LOC101929516	FEV_1/FVC		Previous	rs755249	1:39,995,074	T/C	*PABPC4*†
TGFB2	PEF	FEV_1/FVC	Previous	rs6604614	1:218,631,452	C/G	*TGFB2*†
TRAF3IP1	FEV_1	FVC, FEV_1/FVC, PEF	Previous	rs6710301	2:239,441,308	C/A	*ASB1**
SLMAP (intron)	FEV_1	FEV_1	Previous	rs6445932	3:57,879,611	T/G	*SLMAP*†
RSRC1 (intron)	FVC	FVC, FEV_1/FVC	Previous	rs12634907	3:158,226,886	G/A	*RSRC1*†
GSTCD (intron)	FEV_1	FEV_1, FVC, PEF	Previous	rs11722225	4:106,766,430	T/C	*INTS12*†
NPNT (intron)	FEV_1/FVC		Previous	rs34712979	4:106,819,053	A/G	*NPNT*†‡
AP3B1 (intron)	FVC		Previous	rs425102	5:77,396,400	G/T	*AP3B1*†
SPATA9	FEV_1/FVC		Previous	rs987068	5:95,025,146	C/G	*RHOBTB3*†
P4HA2-AS1	FVC	FEV_1, PEF	Previous	rs3843503	5:131,466,629	A/T	*SLC22A5*†, *P4HA2*†, *C1QTNF5*‡
CYFIP2 (intron)	FEV_1/FVC	FEV_1, PEF	Previous	rs11134766	5:156,908,317	T/C	*ADAM19*†
ADAM19 (intron)	FEV_1/FVC		Previous	rs11134789	5:156,944,199	A/C	*ADAM19*†*
DSP (intron)	FEV_1/FVC	FEV_1	Previous	rs2076295	6:7,563,232	T/G	*DSP*†
MIR588	FVC	FVC, PEF	Previous	rs6918725	6:126,990,392	T/G	*CENPW*†
GPR126 (exon)	FEV_1/FVC		Previous	rs17280293	6:142,688,969	A/G	*GPR126**
C1GALT1 (intron)	FEV_1/FVC	FEV_1	Previous	rs4318980	7:7,256,490	A/G	*C1GALT1*†
QSOX2 (3'-UTR)	FVC		Previous	rs7024579	9:139,100,413	T/C	*QSOX2*†
DNLZ (intron)	FVC	FEV_1, FVC, PEF	Previous	rs4073153	9:139,259,349	G/A	*SNAPC4*†, *CARD9*†, *INPP5E*†
CDC123 (intron)	FEV_1/FVC	FEV_1	Previous	rs7090277	10:12,278,021	T/A	*NUDT5*†
MYPN (intron)	FVC	FVC	Previous	rs10998018	10:69,962,954	A/G	*MYPN**
EML3 (intron)	FEV_1	FEV_1	Previous	rs71490394	11:62,370,155	G/A	*EEF1G*†, *ROM1*†*, *EML3*†*

Gene	Phenotype	Other traits	Novel Tier/ Previous	Sentinel SNP	Position (b37)	COPD risk/alt	Functionally implicated genes
ARHGEF17 (intron)	FEV_1/FVC		Previous	rs2027761	11:73,036,179	C/T	*FAM168A*†, *ARHGEF17*†*
RAB5B (intron)	FEV_1	PEF	Previous	rs1689510	12:56,396,768	C/G	*CDK2*†
LRP1 (intron)	FEV_1/FVC		Previous	rs11172113	12:57,527,283	T/C	*LRP1*†
FGD6 (intron)	FEV_1/FVC		Previous	rs113745635	12:95,554,771	T/C	*FGD6*†
RPAP1	FEV_1/FVC		Previous	rs2012453	15:41,840,238	G/A	*ITPKA*†, *LTK*†, *TYRO3*†, *RPAP1*†
AAGAB	FVC	FEV_1, PEF	Previous	rs12917612	15:67,491,274	A/C	*AAGAB*†, *SMAD3*†, *IQCH*†
THSD4 (intron)	FEV_1/FVC		Previous	rs1441358	15:71,612,514	G/T	*THSD4*†
IL27	FEV_1		Previous	rs12446589	16:28,870,962	A/G	*SBK1*†, *TUFM*†, *CCDC101*†, *SULT1A1*†, *SULT1A2*†*, *SH2B1*†, *NPIPL1*†, *CLN3*†, *ATXN2L*†, *EIF3C*†
MMP15 (intron)	FEV_1/FVC	PEF	Previous	rs11648508	16:58,063,513	G/T	*MMP15*†
SSH2 (intron)	FEV_1/FVC	FEV_1	Previous	rs2244592	17:28,072,327	A/G	*EFCAB5*†
FBXL20 (intron)	FVC	FVC, PEF	Previous	rs8069451	17:37,504,933	C/T	*CRKRS*†, *FBXL20*†
MAPT-AS1	FEV_1		Previous	rs79412431	17:43,940,021	A/G	*LRRC37A4*†, *MAPT**
TSEN54 (intron)	FEV_1	PEF	Previous	rs9892893	17:73,525,670	G/T	*CASKIN2*†, *TSEN54**
LTBP4 (exon)	FEV_1/FVC		Previous	rs34093919	19:41,117,300	G/A	*LTBP4**
ABHD12 (intron)	FEV_1	FEV_1, PEF	Previous	rs2236180	20:25,282,608	C/T	*PYGB*†*
UQCC1 (5'-UTR)	FVC	FEV_1	Previous	rs143384	20:34,025,756	G/A	*UQCC1*†, *GDF5*†
SLC2A4RG (intron)	FVC	FEV_1/FVC	Previous	rs4809221	20:62,372,706	A/G	*LIME1*†
SCARF2 (intron)	FEV_1	FEV_1	Previous	rs9610955	22:20,790,723	C/G	*SCARF2**‡