A Systematic Analysis of Protein-altering Exonic Variants in Chronic Obstructive Pulmonary Disease

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Abstract

Genome-wide association studies (GWASs) have identified regions associated with chronic obstructive pulmonary disease (COPD). GWASs of other diseases have shown an approximately 10-fold overrepresentation of nonsynonymous variants, despite limited exonic coverage on genotyping arrays. We hypothesized that a large-scale analysis of coding variants could discover novel genetic associations with COPD, including rare variants with large effect sizes. We performed a meta-analysis of exome arrays from 218,399 controls and 33,851 moderate-to-severe COPD cases. All exome-wide significant associations were present in regions previously identified by GWAS. We did not identify any novel rare coding variants with large effect sizes. Within GWAS regions on chromosomes 5q, 6p, and 15q, four coding variants were conditionally significant ($p < 0.00015$) when adjusting for lead GWAS SNPs. A common *GSDMB* splice variant (rs11078928) previously associated with decreased risk for asthma, was nominally associated with decreased risk for COPD (MAF = 0.46, $p = 1.8 \times 10^{-4}$). Two stop variants in *CCHCR1*, a gene involved in regulating cell proliferation, were associated with COPD (both $p < 0.0001$). The *SERPINA1* Z allele was associated with a random effects odds ratio of 1.43 for COPD (95% CI: 1.17-1.74), though with marked heterogeneity across studies. Overall, COPD-associated exonic variants were identified in genes involved in DNA methylation, cell-matrix interactions, cell proliferation, and cell death. In conclusion, we performed the largest exome array meta-analysis of COPD to date and identified potential functional coding variants. Future studies are needed to identify rarer variants, and further define the role of coding variants in COPD pathogenesis.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation (1), and is one of the leading causes of morbidity and mortality worldwide (2). Genome-wide association studies (GWASs) have lent considerable insight into the genetic risk to COPD (3–7). Most GWAS variants are non-coding and are thought to affect COPD susceptibility through gene regulation (8). As such, identifying disease-causing variants in COPD GWAS regions remains challenging. While coding regions make up only about 1% of the genome, ~10% of GWAS signals in complex diseases are attributable to nonsynonymous variants (8). Specific rare coding variants may confer a particularly high risk for complex diseases such as COPD. For example, alpha-1 antitrypsin deficiency (AATD) is associated with a ~15-fold increased odds for emphysema (9) and is most commonly caused by homozygosity for the *SERPINA1* Z allele (rs28929474), which is a missense variant found in ~2-3% of the United States population (10). Exome sequencing of a French-Canadian family with early-onset emphysema identified a rare non-synonymous causal variant in protein tyrosine phosphatase non-receptor type 6 (*PTPN6*) (11). Germline mutations in telomerase genes have been observed in severe COPD cases (12). Thus, examining coding variants across the genome may identify important functional (protein-altering) variants associated with COPD.

Exome arrays were designed to allow genotyping of a large fraction of functional (nonsynonymous, splice, stop-gain) variants across the genome (13), and association analyses have been reported for COPD and lung function(14–16). However, several important questions regarding the utility of exome array studies in COPD remain unanswered. It is not known whether increasing sample size and power will identify novel rare coding variants that markedly increase COPD risk. There have since been several large-scale GWASs for lung function and COPD, yet GWASs have poor coverage of exonic variants and are not intended to identify rare coding variants; exome array results have not been directly compared to GWAS results, which may elucidate the functional variants being tagged by GWAS-identified SNPs. While the *SERPINA1* Z allele (rs28929474) is a known risk factor for COPD - even in heterozygous individuals (17) - the largest GWASs to date (3,4,6,7) did not identify an association of the *SERPINA1* Z allele with COPD or lung function; one reason for this result may be the smoking dependent effects of the Z allele and/or imputation inaccuracies, as the Z allele is not present on most genotyping arrays. However, the Z allele is present on exome arrays, allowing for direct assessment of the association of the Z allele with COPD risk. Further, many COPD case-control studies intentionally exclude ZZ individuals, which could introduce selection bias. A gene-by-environment interaction of cigarette smoking may be important for *SERPINA1* variants to contribute to COPD (18), which may affect the association of the Z allele on COPD in population-based cohorts (as opposed to COPD cohorts enriched for cigarette smoking).

We hypothesized that a larger exome array meta-analysis would provide increased power to detect rare and poorly imputed functional exonic variants associated with COPD and identify the most likely causal variants in previously-defined COPD GWAS regions. We also leveraged the exome array data to assess effect size heterogeneity of the Z allele across studies.

Methods

Study Cohorts

We included 12 cohorts in our analysis: ARIC (Atherosclerosis Risk in Communities) Study with African ancestry [Aa] and European ancestry [Ea] participants (19), CHS (Cardiovascular Health Study) including Ea and Aa participants(20), COPDGene (Genetic Epidemiology of COPD) with non-Hispanic white [NHW] and African-American [AA] participants (21), EOCOPD/ICGN (Boston Early-onset COPD Study (22,23) and International COPD Genetics Network (24)) studies, the FHS (Framingham Heart Study) (25–27), HABC (Health, Aging, and Body Composition) Study with Ea and Aa participants(28), KARE (Korean Association Resource) Study (29), MESA (Multi-Ethnic Study of Atherosclerosis) including non-Hispanic African-American, Chinese-American, Hispanic, and non-Hispanic White subpopulations (30,31), RS (Rotterdam Study) (32,33), TCGS (Transcontinental COPD Genetics Study) from Poland and South Korea (34), UK COPD Exome Chip Consortium (UKECC)(16), and UK Biobank (35). Moderate-to-severe COPD was primarily defined by pre-bronchodilator FEV₁/FVC ratio < 0.7 and FEV₁ < 80% predicted; post-bronchodilator measures were only performed in a minority of studies, and were used when available. Individual study details, including genotyping methods, are available in the Supplementary Materials.

Statistical Analyses

Genetic association analysis was performed for case-control moderate-to-severe COPD status using an additive genetic model adjusted for age, sex, cigarette smoking pack-years, and principal components of genetic ancestry. In the family-based studies including FHS and EOCOPD/ICGN, we utilized logistic regression with generalized estimating equations to adjust for familial clustering. Quality control on summary statistics from all cohorts was performed with EasyQC (36) to assure common variant names and reference strand across cohorts and minor allele count (MAC) > 10 within each cohort. In addition to these exome array results, we also included the subset of matching variants (MAC > 4) in a case-control association analysis of UK Biobank(4); models were adjusted for age, sex, pack-years of smoking, ever smoking (when available), and principal components of genetic ancestry.

We performed an inverse variance fixed effects meta-analysis of exome array results with METAL (37), and limited our analysis to putative functional (non-synonymous, stop, and splice) variants, which were annotated using wANNOVAR (38). Variants were considered for analysis if they were present in the UK Biobank and at least half of the other cohorts. Exome-wide significance was determined using Bonferroni adjustment ($p < 0.05/20,536$ variants $< 2.4\text{e-}6$). Replication of signals from previously reported exome array studies (14–16) was defined as a consistent direction of effect and exome-wide statistical significance. Plink v1.9(39) --clump was used to choose a single “index” variant from all variants with $R^2 \geq 0.2$ in each significantly associated genetic locus. We also performed a targeted analysis of splice and stop variants, considering p-values below a Bonferroni-adjusted threshold ($p < 0.05/\text{number-of-stop/splice-variants} < 0.05/257 < 0.00019$) to be nominally significant. We examined the relative association of exome-wide significant COPD variants with the spirometric parameters FEV₁ and FEV₁/FVC in the GWAS results from Shrine et al. (3). As genetic effects may vary with age, we examined whether age modifies the effect of exome-wide significant variants in the UK Biobank. Additionally, we evaluated the associated of alleles with age of COPD diagnosis in the COPDGene study. To examine the differential effects of associated variants based on smoking exposure, we performed stratified analyses in ever- versus never-smokers and heavy- (>20 pack-years) versus light- (≤ 20 pack-years) smokers in UK Biobank, and compared effect sizes between strata.

To determine whether the exome signals were novel, or accounted for by previously described associations, index exonic variants from each locus were compared to prior COPD and lung function GWAS results (3,4,6,7,26) and were considered distinctly associated if outside of a 2Mb window. For SNPs within this 2Mb window, we assessed linkage disequilibrium (LD) between exonic variants and prior GWAS variants by calculating an R^2 value using a reference panel of 10,000 randomly selected UK Biobank participants(4). To determine if exonic SNPs were distinct from previously described lead GWAS variants, we used results from GCTA-Conditional and joint (COJO) analyses (40) from a prior GWAS, as exome arrays do not assay genome-wide variants (4) (see Supplementary Materials).

To examine whether exonic SNPs explained the lead signal at previously reported GWAS loci, we examined whether the exonic variant was present within the 99% credible sets from a recent COPD GWAS (4), obtained using the method of Wakefield, *et al.* (41). We also evaluated predicted functional consequences of amino acid mutations using PolyPhen 2.0 and scaled CADD (Combined Annotation Dependent Depletion) scores (42,43). Briefly, CADD scores are based on a support vector machine model predicting the relative deleteriousness of a mutation within a dataset; scaling these scores on a rank order magnitude scale allows for external comparisons. For example, a scaled CADD score of 10 means the mutation is in the top 10% of deleterious mutations, a scaled CADD score of 20 means the mutation is in the top 1% of deleterious mutation, and so forth (42,43). To gain insight into potential biological pathways affected by exonic variants, we also queried gene names at genetics.opentargets.org, which reports relevant biological pathways based on the Reactome Database of Pathways(44,45). In addition, we performed expression and protein quantitative trait locus (eQTL and pQTL, respectively) look ups for COPD-associated exonic variants (see Supplementary Materials).

We also examined the association of the non-synonymous *SERPINA1* Z allele (rs28929474), the most common cause of alpha-1 antitrypsin deficiency, with COPD in our study. We performed meta-regression for COPD-associated variants and the Z allele, examining the heterogeneity of effect across cohorts by evaluating the contribution of FEV₁ % predicted and pack-years of smoking to individual COPD-associated variant effect sizes. Additional details can be found in the Supplementary Materials.

Results

Characteristics of cohorts

Characteristics of study participants in each cohort are shown in Table 1. In total, there were 218,399 controls and 33,851 moderate-to-severe COPD cases, which provided 99% power to detect variants with MAF of 0.01 and odds ratio of 1.3. (Table S1). The cohorts were diverse with respect to case ascertainment, sex distribution, cigarette smoking history, and ancestry. For example, COPDGene, BEOCOPD, ICGN, TCGS (Korea and Poland), and the UK COPD Exome Chip Consortium were COPD case-control studies and thus the participants were enriched for COPD cases, ever-smoking status, pack-years of smoking, and lower FEV₁ % predicted compared to individuals in the population-based cohorts. TCGS-Korea had the highest percentage of males (>95%) in both case and control participants, while the lowest proportion of males was observed amongst cases in BEOCOPD (39.9%) and controls (27.6%) in CHS Aa. Amongst COPD cases, there was a predominance of males, with 14 cohorts reporting over 55% of cases to be male. With respect to genetic ancestry, there were 7,493 African (including African-Americans), 236,312 European, 7,771 East Asian, and 674 Hispanic participants. Not surprisingly, with this sample size and the different cohort characteristics, all of the ANOVA or chi-squared P-values across were significant ($P < 1 \times 10^{-3}$).

Exome chip meta-analysis

An overview of the study design is shown in Figure 1. Exome arrays containing 109,036 non-synonymous, stop, and splice variants from ICGC (n=51,458) and UK Biobank (n= 200,792) were meta-analyzed; 20,536 variants were reported in UK Biobank and $\geq 50\%$ of the other studies. Distribution of variant allele frequencies are shown in Figure S1. Of these, 80 variants reached exome-wide Bonferroni-adjusted level of significance ($p < 2.4 \times 10^{-6}$) (Figure 2, Table S2). After clumping, these 80 variants were represented by 35 lead variants. All 35 lead variants were within 2 Mb of previously reported GWAS SNPs (Table 2). Eight of these variants met criteria (see Methods) for replication of exonic signals from prior exome array and genome-wide studies (Table S3). Twenty-one exonic variants were in low LD ($R^2 < 0.2$) with nearby GWAS variants.

Of the 35 exome-wide significant lead variants, we identified 4 novel conditionally significant exonic SNPs (Table 3), meaning that these SNPs were within 2Mb of COPD GWAS variants, though retained regional significance after conditioning on the lead COPD GWAS SNP using GCTA-COJO (Bonferroni p-value = 0.05/340 variants = 0.000147; see Methods). Seven of the 35 exonic variants were index variants, so conditional and joint analyses were not performed for these variants (rs721917, rs28929474, rs12373142, rs11205303, rs2571445, rs1800888, rs1334576) (4). The rs2454206 variant in *TET2* was significant after conditioning on the rs34712979 index variant, though this variant exists at a locus with two additional independent variants (rs2047409 and rs10516528)(5). We observed that the exonic rs2454206 variant association was no longer significant after conditioning on rs2047409 ($p=0.24$). In stepwise joint modeling considering these four *TET2* locus variants, only rs2454206 and rs34712979 were selected for the final model.

We also evaluated the 35 exome-wide significant lead variants in the 99% credible sets for the COPD GWAS loci from Sakornsakolpat et al. (4) (Table 4); 18 lead exonic variants were present in the 99% credible sets. Three variants had a posterior probability of association (PPA) $> 10\%$, and 10 variants were in the top 20% of their respective credible sets (Figure S2), suggesting these are more likely to be causal variants. Only rs1334576 in *RREB1* had a PPA $> 10\%$, ranked within the top 20% of its credible set, and was predicted to be damaging by PolyPhen and CADD. The remaining 17 top exonic variants (Table S4) were not present in their respective 99% credible set.

We also analyzed 257 stop or splice variants, of which 2 stop variants (rs3130453 and rs72856718) and 1 splice variant (rs11078928) reached Bonferroni-adjusted significance ($p < 0.00019$; see Methods) (Table S5). The stop variant rs3130453 (MAF=0.49) in the Coiled-Coil Alpha-Helical Rod Protein 1 (*CCHCR1*) gene was associated with an odds ratio of 1.04 [95% CI: 1.02-1.06, $p=1.3 \times 10^{-5}$] for COPD. The rs72856718 stop variant (MAF=0.09), also in the *CCHCR1* gene, was associated with an odds ratio of 1.08 [95% CI: 1.04-1.13, $p = 8.8 \times 10^{-5}$] for COPD. The splice variant, leading to an exon 6 deletion in *GSDMB*, had an odds ratio of 1.04 [95% CI: 1.02-1.06, $p = 1.8 \times 10^{-4}$] in association with COPD. Forest plots for all exome-wide significant, stop, and splice variants are shown in Figure S3. Reactome pathways for the genes associated with conditionally significant, stop, and splice variants are shown in Table S6. Twelve exonic variants (including stop/splice variants), many of which were highly correlated with each other (Figure 3), are located within the complex HLA region (hg19; chromosome 6:28477797-33448354).

Similar associations of variants in Table 2 were observed in a prior GWAS of FEV₁ and FEV₁/FVC, except that three variants (rs3885951, rs11078928, rs28929474) did not reach our level of exome-wide significance for either GWAS phenotype (Table S7). We also assessed for interactions of exome-wide significant variants in Table 2 with age in UK Biobank, and found no significant interactions (all $p < 0.05$). Furthermore, we evaluated whether each of these variants associated with earlier age of COPD diagnosis in the COPDGene cohort, and observed that the smoking behavior-associated rs16969968 SNP in *CHRNA5* was associated with earlier age of COPD diagnosis ($p = 0.001$, Figure S4). Comparing ever- to never- and heavy- to light-smokers, the effect sizes are generally similar between strata (Figure S5). The exceptions include rs1422795, rs2571446, and rs3829947 in ever- vs. never-smokers, and rs1422795 in heavy- versus light-smokers.

eQTL and pQTL analyses

The correlation between the 35 lead exonic variants and sentinel eQTL SNPs (i.e., the eQTL SNP with the lowest p-value of all eQTL SNPs assigned to an eGene) in which the LD R^2 is > 0.2 are shown in Table 5, and the full set of eQTL-regulated SNPs are shown in Table S8. Several exonic variants are associated with eQTL SNPs that regulate the same gene within lung tissue, including *FBXO38*, *ADGRG6*, *RREB1*, *C15orf40*, and *EFCAB5*. In pQTL analyses (46), 12 exonic variants were significantly associated with protein expression (Table 6).

SERPINA1 Z allele effects

The *SERPINA1* Z allele, rs28929474 was associated with a 1.18 odds ratio for COPD in fixed effects analysis ([95% CI: 1.10-1.26], $p=1.74e-6$) (Table S5). In the Z allele meta-analysis, there is evidence of heterogeneity ($I^2=0.6$) and the African Americans from the ARIC cohort exhibited an opposite direction of effect which was not statistically significant (Figure 4). Given the observed Z allele effect size heterogeneity, we performed a random effects meta-analysis, and the rs28929474 variant demonstrated association with a 1.43 odds ratio for COPD ([95% CI: 1.17-1.74], $p=0.0043$).

Meta-regression

For each exome-wide significant variant, we performed meta-regression to examine the cohort-specific effects of FEV₁ % predicted and pack-years of smoking; for the Z allele (rs28929474), we also examined the effects of inclusion of Z allele homozygotes on the reported variant effect sizes (Table S9). Mean differences in FEV₁ % predicted from individual cohorts did not account for the observed heterogeneity, nor did whether a study excluded Z allele homozygotes. Heterogeneity of effect sizes was at least partially attributable to mean differences in pack-years of smoking for several variants (rs12373142, rs1334576, rs16969968, rs2523989, rs3130453, rs7750641).

Discussion

In this study, we meta-analyzed exome array data from 33,851 moderate-to-severe COPD cases and 218,399 controls. We report 4 exonic variants on chromosomes 5q, 6p, and 15q, as well as 2 stop variants and 1 splice variant associated with COPD. We also examined the association of the *SERPINA1* Z allele (rs28929474) with COPD, and heterogeneity of effect sizes across cohorts. These results lend further insight into the potential pathogenesis of this disease and identify potential loci for laboratory-based validation.

Compared to prior studies, this exome array meta-analysis includes significantly more participants and extends prior findings by providing in-depth characterization of exonic variants. Using the criteria that exome-wide significance is reached, and the direction of effect and risk allele are the same in both the current and prior studies, 8 exonic variants from prior genome-wide and exome array studies were replicated (3,4,6,7,14–16,47). Of these, multiple lines of evidence suggest that rs1334576 in *RREB1* is likely a functional variant; *RREB1* is a zinc-finger transcription factor that binds to Ras-related elements in gene promoters, and has been implicated in cell differentiation (48–50). Smoking history was associated with the *CHRNA5* variant in meta-regression, which is not surprising given the well-established role of this locus in smoking behavior (51). This variant was also associated with early age of COPD diagnosis. Although we had adequate power to detect variants with a MAF of 0.01 with an effect size of 1.3 or greater, we did not identify any novel rare variants with large effect sizes. These data suggest that low frequency protein coding variants (down to 1%) with large effect sizes do not play a substantial role in COPD pathogenesis. However, this study was not powered to assess the impact of very rare variants (MAF < 0.01), nor the effects of low frequency and common protein coding variants on COPD subtypes.

While all variants were near previously identified COPD GWAS loci, applying a more relaxed multiple testing threshold (52,53) led to identification of four independently associated exonic variants that remained significant after conditioning on the lead nearby GWAS variant. The rs2287749 variant may be a causal variant based on conditional, credible set, and PolyPhen analyses, and is located within *ADAM19*, a metalloproteinase (55) involved in cell-matrix interactions and invadopodia formation in cancer cells (45) and previously implicated in COPD risk (4,54). Three independent variants have been previously reported at the *TET2* 4q24 locus (5). Conditional and joint analyses suggest that rs2047409 and rs34712979 account for the signal observed at this locus. *TET2* is involved in DNA demethylation and regulation of gene expression, and variants have been associated with extremes of FEV₁ (5), and linked to age-associated clonal hematopoiesis and self-reported COPD and/or asthma (56). Our results further highlight the importance of *TET2* in COPD risk. Two novel variants, rs4842860 and rs17361375, in *C15orf40* were identified. In eQTL analyses, the former SNP was correlated with eQTL SNP rs6603041 in both lung and blood. Neither variant was found in their respective 99% credible sets from a COPD GWAS. This finding might indicate that these variants are not causal or could indicate that this locus was not adequately characterized by GWAS. Deeper characterization of this locus could help clarify its role in COPD pathogenesis.

Examining only the most deleterious (stop and splice) variants, we identified three nominally-significant associations. We found two stop variants in the *CCHCR1* gene. *CCHCR1* has a role in regulating cell proliferation and differentiation, both of which are important in the pathogenesis of emphysema. The splice variant, rs11078928, encodes a polymorphism at a splice

acceptor site in *gasdermin-B* (*GSDMB*) on chromosome 17q21 (60). *GSDMB* is important in pyroptosis, a type of programmed cell death which releases inflammatory mediators. Pyroptosis is activated by caspase-mediated cleavage of the inhibitory C-terminus of gasdermin-B, releasing the functional N-terminus (61–63); The rs11078928 variant leads to a deletion of exon 6 in the N-terminus, rendering gasdermin-B unable to activate pyroptosis (60). The minor allele (C) has been associated with lower asthma risk (60), and was associated with lower COPD risk in our study. This finding is consistent with the notion that subpopulations of individuals have features of both asthma and COPD; indeed, childhood asthma is associated with lower lung function and increased risk for COPD in adulthood (64,65). Thus, *GSDMB* may contribute to the pathobiology of asthma-COPD overlap.

Prior investigations into the Z allele association with COPD have been conflicting. Many prior lung function and COPD genetic association studies (GWASs and exome-wide) have not reported associations with the *SERPINA1* Z allele (3–6,14–16). Yet, the Z allele has also been associated with severe COPD (66) and lung function (67) at genome-wide significance in cohorts enriched for COPD and heavy smoking, potentially with a gene-by-smoking interaction (68). We evaluated the effect of a directly genotyped (rather than imputed) Z allele and applied a random effects meta-analysis. The Z allele was associated with a 1.17–1.74 odds ratio for COPD.

We observed an asymmetric distribution of effect sizes and standard errors for the Z allele across cohorts, suggesting that there may be cohort-specific selection bias with regards to inclusion of individuals with the Z allele. The combination of the exclusion of homozygous Z allele individuals (PiZZ) from many COPD case-control studies and the inclusion of a large number of individuals with little to no smoking history in population-based cohorts likely diminished the power to detect an overall effect for Z allele. To explore this issue, we used meta-regression to assess the impact of intentional exclusion of ZZ individuals, lung function severity, and cigarette smoke exposure on Z allele effect size heterogeneity. None of these factors clearly explained the observed Z allele effect size heterogeneity across studies.

This study has several strengths and limitations. The primary strengths of this study are the large sample size, and the direct assessment of protein coding variant associations with COPD in the context of GWAS findings. We were not well-powered to detect variants with MAF < 0.01, so we are unable to assess the impact of very rare protein coding variants on COPD risk. Larger studies are needed to replicate our findings and assess the impact of very rare variants. Exome array data provide sparse coverage of variants across the genome, making colocalization analyses between COPD exonic variant associations and eQTLs or pQTLs impossible. However, we attempted to address this limitation by identifying eQTLs and pQTLs in highest LD with COPD exonic variants. Finally, we employed a limited set of bioinformatic prediction tools to identify functional variants, but the accuracy of such tools for predicting biologically important changes in protein structure and function is not clear (70). Laboratory-based validation is critical to understanding the causal influence of the exome array variants reported here.

In conclusion, we performed the largest exome array meta-analysis of moderate-to-severe COPD to date. We were unable to identify any protein-altering coding variants at exome-wide significance in regions not previously identified by GWAS. However, at previously-described GWAS loci, we report multiple coding variants associated with COPD, including 4 conditionally

significant nonsynonymous variants, two stop variants, and a splice variant. These variants exist in genes important in cell-matrix interactions, cell proliferation, DNA demethylation, regulation of proteases, and regulation of cell death. We further identify heterogeneity of effects of the *SERPINA1* Z allele across cohorts. Future studies will be needed to replicate and validate these identified exonic variants, identify rarer variants, and further describe the role of coding variants in COPD pathogenesis.

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Table legends

Table 1: Characteristics of cohorts in meta-analysis. In total, there were 218,399 controls and 33,851 moderate-to-severe COPD cases.

Table 2: Thirty-five lead exonic SNPs and nearby sentinel GWAS SNPs (within 2Mb). "*" = variant location within HLA region (hg19; chromosome 6: 28477797-33448354). "***" = $R^2 < 0.2$. Exonic variants were clumped prior to comparing to GWAS SNPs based on an $R^2 > 0.2$. References to GWAS variants are for the most recent publication.

Table 3: Conditionally significant exome array SNPs ($p < 0.000147$) within 2 Mb of GWAS SNPs identified in UK Biobank(4). Exonic variant effects were adjusted for the index SNPs indicated in the table. Chromosome positions based on build hg19. Note that the rs2454206 variant in *TET2* was significant after conditioning on the rs34712979 index variant, though this variant exists at a locus with two additional independent variants (rs2047409 and rs10516528)(5). We observed that the exonic rs2454206 variant was no longer significant after conditioning on rs2047409 ($p = 0.24$). Note that HLA imputation was not performed, so HLA region variants were not included in conditional and joint analyses.

Table 4: Exome array variants identified in 99% credible sets derived from UK Biobank(4) using the method by Wakefield et al.(41) and wANNOVAR functional annotations. PolyPhen and CADD were used to predict consequences of mutation. PPA = Posterior Probability of Association. CADD scores are based on a support vector machine model predicting the relative deleteriousness of a mutation within a dataset; scaling these scores on a rank order magnitude scale allows for external comparisons. For example, a scaled CADD score of 10 means the mutation is in the top 10% of deleterious mutations, a scaled CADD score of 20 means the mutation is in the top 1% of deleterious mutation, and so forth(42,43). Chromosome positions based on hg19. PPA = posterior probability of association. Percentile indicates the ranking of the exonic variant within the credible set of the GWAS index SNP.

Table 5: Exon SNPs and sentinel eQTL SNPs with $R^2 > 0.2$ and p-value (eQTL) $< 1e-8$. "*" indicates HLA region.

Table 6: Exonic genes associated with pQTL-regulated proteins at Bonferroni-corrected significance level ($p < 3.9e-7$). "*" indicates variant is in HLA region.

Figure legends

Figure 1: Overview of study design.

Figure 2: Manhattan plot of exome array variants. The horizontal red line indicates an exome-wide significance level of 2.4×10^{-6} . The exonic variants reaching exome-wide significance are annotated.

Figure 3: LD matrix (R^2) of exome array variants within the HLA region (hg19; 6:28477797-33448354).

Figure 4: Forest plot of the *SERPINA1* Z allele (rs28929474). The Z allele was associated with a 1.18 odds ratio for COPD in fixed effects analysis ([95% CI: 1.10-1.26], $p=1.74 \times 10^{-6}$), and 1.43 odds ratio for COPD in random effects analysis ([95% CI: 1.17-1.74], $p=0.0043$) ($I^2 = 0.60$). See Methods for cohort abbreviations.

Number of Variants

Exome Arrays in 218,339 controls and
33,851 cases

109,036
(nonsynonymous,
stop, splice)

Variants Reported in UK Biobank and
> 50% of ICGC cohorts

20,536

Select top COPD-associated exonic
variants at each locus and compare to
prior GWAS variants

35

Exonic variants significant after
conditioning on GWAS variant

4

rs1129740												1
rs7775397										1	0.88	
rs2070600									1	1	0.13	
rs3101017								1	1	0.82	0.76	
rs7750641							1	0.75	1	0.62	0.46	
rs72856718						1	1	1	1	1	0.69	
rs3130453					1	1	1	0.78	0.59	0.67	0.28	
rs2074506				1	0.3	0.61	1	1	0.69	0.84	0.07	
rs9262143			1	0.89	0.76	0.34	0.9	0.75	1	0.62	0.39	
rs929156		1	0.88	0.35	0.01	1	0.87	0.66	0.51	0.48	0.05	
rs2523989		1	0.48	0.91	0.34	0.67	0.02	0.8	0.67	1	0.54	0.28
rs3749971	1	0.89	0.72	0.84	0.61	0.73	0.06	0.79	0.62	1	0.56	0.41

Table 1: Characteristics of cohorts in meta-analysis. In total, there were 218,399 controls and 33,851 moderate-to-severe COPD cases.

<i>Cohort</i>	<i>n</i>		<i>Age in years (mean ± sd)</i>		<i>Males (%)</i>		<i>Pack Years of Smoking (mean ± sd)</i>		<i>FEV1 (% predicted)</i>	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
ARIC AA	289	2765	55.7 (5.84)	53.06 (5.73)	52.6	34.43	28.23 (29.4)	9.18 (16)	63.2 (13)	100.3 (12.5)
ARIC EA	1284	7405	56.33 (5.37)	53.73 (5.64)	56.15	44.09	37.73 (25.9)	11.83 (17.9)	65.5 (12.4)	100.7 (11)
BEOCPD	366	560	50.8 (8.2)	39.3 (12.2)	39.9	41.6	37.5 (16.5)	1.66 (14.2)	29.2 (22.6)	94.5 (8.5)
CHS AA	107	232	72.25 (4.91)	72.76 (5.25)	49.5	27.6	29.36 (24.4)	20.89 (20.4)	61.38 (13.4)	102.6 (15)
CHS EA	914	1690	73.51 (5.72)	71.87 (5.11)	60.2	32.3	44.59 (28.9)	25.77 (23.7)	59.97 (15.6)	99.49 (13.6)
COPDGene AA	796	1715	58.2 (6.6)	51.8 (3.8)	55.5	58.1	37.8 (13.8)	32.7 (11.1)	54 (13.1)	96.6 (9.4)
COPDGene NHW	2777	2507	65.2 (5.8)	59.3 (6.6)	55.7	49.4	49.8 (20.7)	35 (12)	50 (15.5)	95.5 (8.5)
FHS	625	4959	61.96 (12.1)	51.63 (13.2)	51.04	44.69	37.22 (24.2)	15.47 (16.9)	66.4 (11)	102 (12)
HABC AA	126	817	73.3 (2.84)	73.43 (2.91)	67.46	42.59	38.99 (24.8)	27.34 (23.5)	59.83 (13.6)	101.6 (20.5)
HABC EA	213	1259	73.53 (2.74)	73.75 (2.85)	56.34	52.9	49.71 (34.7)	33.36 (30.5)	62.79 (12.7)	97.7 (15.7)
ICGN	1769	696	59.4 (4.2)	54.9 (5.8)	58.6	48.3	45 (19.5)	25.1 (13.7)	39.2 (13.5)	97.5 (10.5)
KARE	106	6862	57.39 (8.14)	51.49 (8.64)	78.3	45.07	23.67 (25)	8.124 (14.7)	70.5 (8.6)	113.8 (16.3)
MESA Black	95	551	67.5 (8.95)	64.39 (9.39)	67.4	41.4	35 (25.5)	18.8 (17.8)	64.1 (13.9)	102.6 (14.4)
MESA Chinese	32	403	69.56 (9.09)	64.03 (9.34)	53.1	47.9	31.88 (21)	20.74 (18)	65.7 (13.4)	104.3 (14)
MESA Hispanic	61	613	67.74 (9.48)	62.82 (9.54)	63.9	43.2	33.73 (31.5)	15.82 (18)	65.3 (12.9)	100 (12.2)
MESA White	180	824	68.42 (8.87)	64.38 (9.61)	51.1	47	42.42 (33.2)	23.01 (22.7)	66.2 (12.1)	98.9 (11.7)
RS	60	415	80.1 (5.3)	79.6 (4.9)	70	52	30.3 (23.8)	14.3 (20.3)	66.5 (11.1)	111.6 (18.1)
TCGS Korea	149	219	69 (5)	53 (6)	99.3	96.8	40 (12)	25.5 (8.5)	33.2 (6.9)	93.6 (6.4)

TCGS Poland	304	307	62.2 (5.5)	58.3 (4.6)	70.1	67.4	40.3 (12.6)	32.3 (8.9)	28.7 (6.7)	102 (9)
UK Biobank	21081	179711	59.4 (7.3)	55.7 (8)	52	58	19.7 (23.9)	6.1 (12.5)	65.1 (11.8)	98.3 (11.4)
UK COPD Exome Chip Consortium	2517	3889	66.1 (7.74)	49 (6.08)	55.24	56.08	41.2 (24.4)	22.05 (15.6)	51.93 (10)	99.25 (10)

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Table 2: Thirty-five lead exonic SNPs and nearby sentinel GWAS SNPs (within 2Mb). "*" = variant location within HLA region (hg19; chromosome 6: 28477797-33448354). "***" = $R^2 < 0.2$. Exonic variants were clumped prior to comparing to GWAS SNPs based on an $R^2 > 0.2$. References to GWAS variants are for the most recent publication.

Exon rs no.	Chr	Position (hg19)	Risk allele	Other allele	Gene name	Risk allele frequency	OR (95% CI)	P	GWAS rs no.	GWAS closest gene	R2	source	trait
rs11205303	1	149906413	C	T	MTMR11	0.4	1.06 (1.03 - 1.08)	7.41E-08	rs11205354	Clorf54	0.0055**	Shrine 2019	PEF
rs2571445	2	218683154	A	G	TNSI	0.39	1.08 (1.05 - 1.1)	4.17E-13	rs2571445	TNSI	1	Shrine 2019	FEV1
rs11938093	4	75675841	A	T	BTC	0.74	1.07 (1.04 - 1.09)	4.44E-09	rs4585380	BTC	1	Sakornsakolpat 2019	moderate COPD
rs2454206	4	106196951	G	A	TET2	0.38	1.09 (1.05 - 1.09)	1.67E-10	rs10516526	GSTCD	0.011**	Wain 2017	FEV1
rs10043775	5	147805120	T	C	FBXO38	0.73	1.09 (1.06 - 1.11)	1.86E-13	rs10037493	HTR4	0.31	Sakornsakolpat 2019	moderate COPD
rs1800888	5	148206885	T	C	ADRB2	0.014	1.32 (1.22 - 1.42)	9.39E-13	rs1800888	ADRB2	1	Shrine 2019	FEV1
rs2287749	5	156918850	C	T	ADAM19	0.87	1.09 (1.06 - 1.12)	3.61E-09	rs72811310	ADAM19	0.8	Sakornsakolpat 2019	moderate COPD
rs1422795	5	156936364	C	T	ADAM19	0.35	1.08 (1.07 - 1.11)	1.94E-17	rs1990950	ADAM19	0.31	Wain 2017	FEV1/FVC
rs11740603	5	157098756	T	G	C5orf52	0.14	1.05 (1.05 - 1.11)	1.11E-07	rs1990950	ADAM19	0.029**	Wain 2017	FEV1/FVC
rs1334576	6	7211818	A	G	RREB1	0.42	1.07 (1.03 - 1.07)	5.11E-08	rs1334576	RREB1	1	Sakornsakolpat 2019	moderate COPD

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rs13195509	6	26463660	A	G	<i>BTN2A1</i>	0.12	1.11 (1.08 - 1.15)	2.53E-12	rs2070600	<i>AGER</i>	0.0023**	Shrine 2019	FEV1/FVC
rs61742093	6	27879982	G	A	<i>OR2B2</i>	0.11	1.11 (1.08 - 1.14)	5.98E-11	rs2070600	<i>AGER</i>	0.0026**	Shrine 2019	FEV1/FVC
rs2232423	6	28366151	G	A	<i>ZSCAN12</i>	0.11	1.11 (1.08 - 1.15)	1.96E-11	rs2070600	<i>AGER</i>	0.0023**	Shrine 2019	FEV1/FVC
rs3749971*	6	29342775	A	G	<i>OR12D3</i>	0.12	1.11 (1.08 - 1.14)	2.60E-11	rs2070600	<i>AGER</i>	0.003**	Shrine 2019	FEV1/FVC
rs2523989*	6	30078275	T	C	<i>TRIM31</i>	0.17	1.09 (1.06 - 1.12)	1.40E-10	rs2070600	<i>AGER</i>	0.0012**	Shrine 2019	FEV1/FVC
rs929156*	6	30139699	G	A	<i>TRIM15</i>	0.76	1.06 (1.04 - 1.09)	8.17E-08	rs2070600	<i>AGER</i>	0.044**	Shrine 2019	FEV1/FVC
rs9262143*	6	30652781	T	C	<i>PPP1R18</i>	0.14	1.11 (1.08 - 1.15)	9.98E-14	rs2070600	<i>AGER</i>	0.0044**	Shrine 2019	FEV1/FVC
rs2074506*	6	30890483	G	T	<i>VAR52</i>	0.65	1.06 (1.03 - 1.08)	2.79E-07	rs2070600	<i>AGER</i>	0.041**	Shrine 2019	FEV1/FVC
rs7750641*	6	31129310	T	C	<i>TCF19</i>	0.15	1.11 (1.08 - 1.14)	1.11E-12	rs2070600	<i>AGER</i>	0.0078**	Shrine 2019	FEV1/FVC
rs3101017*	6	31733466	C	T	<i>VWA7</i>	0.13	1.12 (1.09 - 1.15)	1.92E-14	rs2070600	<i>AGER</i>	0.0092**	Shrine 2019	FEV1/FVC
rs2070600*	6	32151443	C	T	<i>AGER</i>	0.94	1.19 (1.15 - 1.25)	1.31E-16	rs2070600	<i>AGER</i>	1	Shrine 2019	FEV1/FVC
rs7775397*	6	32261252	G	T	<i>C6orf10</i>	0.13	1.12 (1.08 - 1.15)	3.27E-13	rs2070600	<i>AGER</i>	0.011**	Shrine 2019	FEV1/FVC
rs1129740*	6	32609105	A	G	<i>HLA-DQA1</i>	0.59	1.07 (1.04 - 1.09)	9.84E-10	rs2070600	<i>AGER</i>	0.033**	Shrine 2019	FEV1/FVC
rs17280293	6	142688969	A	G	<i>ADGRG6</i>	0.97	1.32	8.13E-	rs17280293	<i>ADGRG6</i>	1	Shrine 2019	FEV1/FVC

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							(1.24 - 1.41)	18					
							1.14						
rs11155242	6	142691549	A	C	<i>ADGRG6</i>	0.81	(1.11 - 1.17)	5.98E-26	rs9399401	<i>ADGRG6</i>	0.62	Sakornsakolpat 2019	moderate COPD
							1.05						
rs721917	10	81706324	G	A	<i>SFTPD</i>	0.42	(1.03 - 1.07)	8.91E-08	rs721917	<i>SFTPD</i>	1	Shrine 2019	FEV1/FVC
							1.06						
rs11049488	12	28412372	G	A	<i>CCDC91</i>	0.7	(1.04 - 1.08)	4.67E-08	rs11049386	<i>PTHLH;CCDC91</i>	0.83	Sakornsakolpat 2019	moderate COPD
							1.05						
rs3829947	14	93118038	A	G	<i>RIN3</i>	0.45	(1.03 - 1.07)	5.35E-07	rs117068593	<i>RIN3</i>	0.18**	Wain 2017	FEV1
							1.09						
rs3885951	15	78825917	G	A	<i>HYKK</i>	0.096	(1.06 - 1.13)	4.71E-08	rs28534575	<i>CHRNA5</i>	0.026**	Sakornsakolpat 2019	moderate COPD
							1.11						
rs16969968	15	78882925	A	G	<i>CHRNA5</i>	0.33	(1.09 - 1.14)	5.03E-25	rs28534575	<i>CHRNA5</i>	0.14**	Sakornsakolpat 2019	moderate COPD
							1.05						
rs4842860	15	83680287	A	G	<i>C15orf40</i>	0.38	(1.03 - 1.07)	3.54E-07	rs7181169	<i>BTBD1</i>	0.44	Sakornsakolpat 2019	moderate COPD
							1.06						
rs17361375	15	83680329	G	A	<i>C15orf40</i>	0.79	(1.04 - 1.09)	3.72E-07	rs7181169	<i>BTBD1</i>	0.33	Sakornsakolpat 2019	moderate COPD
							1.07						
rs4842838	15	84582124	G	T	<i>ADAMTSL3</i>	0.47	(1.05 - 1.09)	2.92E-12	rs1896797	<i>SH3GL3</i>	0.28	Shrine 2019	FEV1/FVC
							1.05						
rs9897794	17	28296327	G	T	<i>EFCAB5</i>	0.48	(1.03 - 1.07)	1.51E-07	rs2244592	<i>SSH2</i>	0.71	Shrine 2019	FEV1/FVC
							1.08						
rs12373142	17	43924200	G	C	<i>SPPL2C</i>	0.22	(1.05 - 1.1)	1.80E-10	rs12373142	<i>SPPL2C</i>	1	Sakornsakolpat 2019	moderate COPD

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Table 3: Conditionally significant exome array SNPs ($p < 0.000147$) within 2 Mb of GWAS SNPs identified in UK Biobank(4). Exonic variant effects were adjusted for the index SNPs indicated in the table. Chromosome positions based on build hg19. Note that the rs2454206 variant in *TET2* was significant after conditioning on the rs34712979 index variant, though this variant exists at a locus with two additional independent variants (rs2047409 and rs10516528)(5). We observed that the exonic rs2454206 variant was no longer significant after conditioning on rs2047409 ($p = 0.24$). Note that HLA imputation was not performed, so HLA region variants were not included in conditional and joint analyses.

<i>Chr</i>	<i>GWAS Index SNP</i>	<i>Exonic SNP</i>	<i>Gene name</i>	<i>Exonic variant risk allele frequency</i>	<i>b</i>	<i>SE</i>	<i>P</i>	<i>b (Conditional)</i>	<i>SE (Conditional)</i>	<i>P (Conditional)</i>
5	rs10866659	rs2287749	<i>ADAM19</i>	0.9	0.089	0.014	1.00E-09	-0.057	0.014	4.30E-05
6	rs2284174	rs13195509	<i>BTN2A1</i>	0.069	0.12	0.015	7.80E-15	0.056	0.014	3.40E-05
15	rs10152300	rs17361375	<i>C15orf40</i>	0.81	0.058	0.012	1.60E-06	-0.051	0.012	2.20E-05
15	rs10152300	rs4842860	<i>C15orf40</i>	0.65	0.043	0.0099	1.60E-05	0.04	0.0099	5.20E-05

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Table 4: Exome array variants identified in 99% credible sets derived from UK Biobank(4) using the method by Wakefield et al.(41) and wANNOVAR functional annotations. PolyPhen and CADD were used to predict consequences of mutation. PPA = Posterior Probability of Association. CADD scores are based on a support vector machine model predicting the relative deleteriousness of a mutation within a dataset; scaling these scores on a rank order magnitude scale allows for external comparisons. For example, a scaled CADD score of 10 means the mutation is in the top 10% of deleterious mutations, a scaled CADD score of 20 means the mutation is in the top 1% of deleterious mutation, and so forth(42,43). Chromosome positions based on hg19. PPA = posterior probability of association. Percentile indicates the ranking of the exonic variant within the credible set of the GWAS index SNP. * *hg 19 position:effect allele:other allele*.

<i>Chr</i>	<i>Exonic SNP</i>	<i>Gene name</i>	<i>GWAS Index SNP for fine- mapping*</i>	<i>PPA</i>	<i>Rank</i>	<i>Percentile</i>	<i>Polyphen prediction</i>	<i>Polyphen rank score</i>	<i>Amino acid change</i>	<i>Scaled CADD</i>
2	rs2571445	<i>TNSI</i>	218683154:A:G	0.58	1	100	Benign	0.013	W1197R	5.551
4	rs11938093	<i>BTC</i>	75673363:G:A	0.032	4	93	Probably damaging	0.739	L124M	24.4
5	rs10043775	<i>FBXO38</i>	148059519:G:A	0.00031	356	91	Benign	0.013	S592P	12.25
5	rs10043775	<i>FBXO38</i>	148203236:T:C	4.70E-05	471	84	Benign	0.013	S592P	12.25
5	rs10043775	<i>FBXO38</i>	148611623:C:A	7.60E-05	368	85	Benign Possibly damaging	0.013	S592P	12.25
5	rs2287749	<i>ADAM19</i>	156948318:T:G	0.023	6	100	damaging	0.494	G660D	24.3
5	rs1422795	<i>ADAM19</i>	156937043:A:G	0.049	9	60	Benign Possibly damaging	0.391	S284G	14.33
5	rs11740603	<i>C5orf52</i>	156948318:T:G	1.00E-05	3708	6.2	Possibly damaging	0.451	R45L	24.2
5	rs11740603	<i>C5orf52</i>	157002695:C:T	1.20E-05	1110	59	Possibly damaging	0.451	R45L	24.2
6	rs1334576	<i>RREB1</i>	7211818:G:A	0.14	1	100	Possibly damaging	0.594	G195R	12.63
6	rs17280293	<i>ADGRG6</i>	142814991:C:T	0.024	5	0	Possibly damaging	0.493	S123G	24.7
10	rs721917	<i>SFTPD</i>	81706324:A:G	0.23	1	100	Benign	0.013	M31T	0.003

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12	rs11049488	<i>CCDC91</i>	28320536:T:A	0.0022	93	81	Benign	0.08	A36T	11.08
14	rs3829947	<i>RIN3</i>	92600798:G:T	5.20E-05	421	86	Benign	0.04	H215R	3.995
15	rs3885951	<i>HYKK</i>	78388464:C:T	6.60E-05	1189	67	Benign	0.104	K343E	18.98
15	rs3885951	<i>HYKK</i>	78923845:T:G	1.80E-05	944	66	Benign	0.104	K343E	18.98
15	rs16969968	<i>CHRNA5</i>	78898932:C:G	0.016	10	83	Benign	0.145	D398N	15.07
15	rs4842860	<i>C15orf40</i>	83693513:T:C	0.00088	70	78	Benign	0.013	C25R	0.029
15	rs17361375	<i>C15orf40</i>	83693513:T:C	0.00021	149	53	Benign	0.093	L11F	6.178
15	rs4842838	<i>ADAMTSL3</i>	84515943:C:G	3.30E-05	277	26	Benign	0.013	V661L	12.87
17	rs9897794	<i>EFCAB5</i>	28413129:T:C	0.0039	73	79	Benign	0.013	L237V	12.25
17	rs12373142	<i>SPPL2C</i>	43924200:C:G	0.03	1	100	Benign	0.139	P643R	0.117

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Table 5: Exon SNPs and sentinel eQTL SNPs with $R^2 > 0.2$ and p-value (eQTL) $< 1e-8$. "*" indicates HLA region.

<i>Chr</i>	<i>Exonic SNP</i>	<i>Gene name</i>	<i>eQTL rs no.</i>	<i>eQTL-regulated gene</i>	<i>Direction of effect</i>	<i>p-value</i>	<i>R2</i>	<i>Source</i>
5	rs10043775	<i>FBXO38</i>	rs6876982	FBXO38	+	2.00E-20	0.7	Hao et al. Lung cis-eQTL
6	rs11155242	<i>ADGRG6</i>	rs11155242	GPR126	-	5.20E-136	1	Vosa et al. cis-eQTL
6	rs13195509	<i>BTN2A1</i>	rs35304979	BTN3A2	+	3.10E-82	0.84	GTeX Lung
			rs3117425	BTN3A2	-	3.80E-45	0.59	Hao et al. Lung trans-eQTL
			rs149959	ZNF165	+	2.00E-09	0.27	Hao et al. Lung cis-eQTL
6	rs61742093	<i>OR2B2</i>	rs3117425	BTN3A2	-	3.80E-45	0.79	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.62	GTeX Lung
			rs149959	ZNF165	+	2.00E-09	0.32	Hao et al. Lung cis-eQTL
6	rs2232423	<i>ZSCAN12</i>	rs3117425	BTN3A2	-	3.80E-45	0.85	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.58	GTeX Lung
			rs149959	ZNF165	+	2.00E-09	0.31	Hao et al. Lung cis-eQTL
6	rs3749971*	<i>OR12D3</i>	rs3117425	BTN3A2	-	3.80E-45	0.92	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.5	GTeX Lung
			rs149959	ZNF165	+	2.00E-09	0.26	Hao et al. Lung cis-eQTL
6	rs2523989*	<i>TRIM31</i>	rs3117425	BTN3A2	-	3.80E-45	0.54	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.28	GTeX Lung
6	rs929156*	<i>TRIM15</i>	rs9261468	TRIM10	-	4.60E-11	0.89	Hao et al. Lung cis-eQTL
6	rs9262143*	<i>PPP1R18</i>	rs3117425	BTN3A2	-	3.80E-45	0.58	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.32	GTeX Lung
6	rs7750641*	<i>TCF19</i>	rs114810457	AGER	+	4.20E-82	0.29	Vosa et al. cis-eQTL
			rs3117425	BTN3A2	-	3.80E-45	0.41	Hao et al. Lung trans-eQTL
			rs35304979	BTN3A2	+	3.10E-82	0.22	GTeX Lung
6	rs3101017*	<i>VWA7</i>	rs114810457	AGER	+	4.20E-82	0.37	Vosa et al. cis-eQTL
			rs3117425	BTN3A2	-	3.80E-45	0.34	Hao et al. Lung trans-eQTL

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6	rs7775397*	<i>C6orf10</i>	rs114810457	AGER	+	4.20E-82	0.39	Vosa et al. cis-eQTL
			rs3117425	BTN3A2	-	3.80E-45	0.29	Hao et al. Lung trans-eQTL
6	rs1129740*	<i>HLA-DQA1</i>	rs9273500	HLA-DRA	-	2.60E-29	0.36	Vosa et al. cis-eQTL
6	rs1334576	<i>RREB1</i>	rs2714341	RREB1	-	1.20E-86	0.34	Vosa et al. cis-eQTL
15	rs16969968	<i>CHRNA5</i>	rs931794	PSMA4	+	5.60E-107	0.91	Vosa et al. cis-eQTL
			rs12591557	PSMA4	-	3.30E-20	0.37	Hao et al. Lung cis-eQTL
15	rs4842860	<i>C15orf40</i>	rs6603041	C15orf40	+	3.10E-110	0.64	Vosa et al. cis-eQTL
			rs6603041	C15orf40	+	9.70E-11	0.64	GTEx Lung
17	rs9897794	<i>EFCAB5</i>	rs7501472	CORO6	+	3.00E-61	0.78	Vosa et al. cis-eQTL
			rs4567782	EFCAB5	+	2.30E-09	0.97	Hao et al. Lung cis-eQTL
			rs3936006	EFCAB5	-	5.10E-74	0.93	Vosa et al. cis-eQTL

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Table 6: Exonic genes associated with pQTL-regulated proteins at Bonferroni-corrected significance level ($p < 3.9\text{e-}7$). "*" indicates variant is in HLA region.

<i>Marker</i>	<i>Exon rs no.</i>	<i>Exon HGNC Symbol</i>	<i>Effect</i>	<i>p-value</i>	<i>pQTL-regulated protein</i>
6:26463660	rs13195509	<i>BTN2A1</i>	0.3635	1.90E-10	MICB
6:27879982	rs61742093	<i>OR2B2</i>	-0.4214	1.40E-13	MICB
			-0.3019	2.20E-07	PDE4D
6:28366151	rs2232423	<i>ZSCAN12</i>	-0.4332	2.50E-14	MICB
			-0.333	8.40E-09	PDE4D
6:29342775	rs3749971	<i>OR12D3</i>	0.4299	1.20E-14	MICB
			0.3077	6.60E-08	PDE4D
6:30078275	rs2523989	<i>TRIM31</i>	0.2574	3.80E-07	GRIA4
			0.4292	1.80E-18	MICB
			0.2725	6.80E-08	PDE4D
6:31124849	rs3130453	<i>CCHCR1</i>	-0.2171	1.60E-08	PRSS3
6:31125257	rs72856718	<i>CCHCR1</i>	-0.7092	3.10E-22	CREB3L4
6:31129310	rs7750641	<i>TCF19</i>	0.3488	4.30E-11	C4A
			0.3216	1.50E-09	CD96
			0.4254	3.60E-16	GRIA4
			0.5975	3.30E-32	MICB
			0.4388	3.50E-17	PDE4D
6:31733466	rs3101017	<i>VWA7</i>	-0.4409	2.10E-15	C4A
			-0.4089	2.40E-13	CD96
			-0.305	8.50E-08	DEFB119
			-0.5098	1.70E-20	GRIA4
			-0.3301	5.70E-09	HLA-DQA2
			-0.3009	1.30E-07	IL21
			-0.6693	5.00E-36	MICB
			-0.5366	9.90E-23	PDE4D
			0.3086	5.50E-08	PRSS3
6:32151443	rs2070600	<i>AGER</i>	0.5749	8.40E-15	AGER
			0.5391	2.90E-13	PRSS3
			0.5014	1.90E-11	RACGAP1
6:32261252	rs7775397	<i>C6orf10</i>	-0.4155	1.70E-13	C4A
			-0.3764	3.20E-11	CD96
			-0.3222	1.90E-08	DEFB119
			-0.4735	2.20E-17	GRIA4
			-0.3798	2.10E-11	HLA-DQA2

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			-0.5861	1.00E-26	MICB
			-0.5085	5.10E-20	PDE4D
			0.315	3.90E-08	PRSS3
14:94844947	rs28929474	<i>SERPINA1</i>	-1.1964	1.20E-21	ACP2
			-0.7288	1.90E-08	DNAJB9
			-1.7387	8.60E-48	MRPL33
			-1.0455	1.40E-16	NCF2
			-1.0295	4.40E-16	PIM1
			-0.9825	1.10E-14	SNAP25
			-0.7328	1.60E-08	TXNDC5
			-0.7449	8.80E-09	WISP3
			-1.3836	3.20E-29	ZNF175