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COPD-dependent effects of genetic variation in key inflammation pathway genes on lung cancer risk

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Abstract

Genome-Wide Association Studies (GWAS) have identified several loci contributing to lung cancer and COPD risk independently; however, inflammation-related pathways likely harbor additional lung cancer risk-associated variants in biologically relevant immune genes that differ dependent on COPD. We selected single nucleotide polymorphisms (SNPs) proximal to 2069 genes within 48 immune pathways. We modeled the contribution of these variants to lung cancer risk in a discovery sample of 1932 lung cancer cases and controls stratified by COPD status and validation sample of 953 cases and controls also stratified by COPD. There were 43 validated SNPs in those with COPD and 60 SNPs in those without COPD associated with lung cancer risk. Further, 29 of 43 and 28 of 60 SNPs demonstrated a statistically significant interaction with COPD in the pooled sample. These variants demonstrated tissue-dependent effects on proximal gene expression, enhanced network connectivity, and resided together in specific immune pathways. These results reveal that key inflammatory related genes and pathways, not found in prior GWAS, impact lung cancer risk in a COPD-dependent manner. Genetic variation identified in this study supplement prior lung cancer GWAS and serve as a foundation to further interrogate risk relationships in smoking and COPD populations.

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Introduction

Lung cancer is the leading cause of cancer death in the United States and the second most frequently occurring cancer type [1] Approximately 80–90% of lung cancer is attributable to smoking [2]. Rates of current smoking have declined by 8% from 1990–2014; however, lung cancer incidence during this period decreased by only 2.3% [3], and the large population of at-risk former smokers in the US remains a public health concern.

Tobacco smoke exposure is closely associated with the development of a spectrum of lung diseases including emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and lung cancer. Accumulating evidence suggests that prolonged exposure to cigarette smoke initiates lung and airway irritation giving rise to chronic inflammatory infiltration, closely linked to the remodeling of airway mucosa seen in airway obstruction as well as in the degradation of alveolar interstitium described in emphysema [4–6]. This chronic inflammatory state is believed to underlie the 2–3 fold increase of lung cancer risk in individuals with COPD [7,8].

Although smoking accounts for a majority of lung cancers, aggregation among families, occurrence in never smokers, and variability in risk among ever smokers suggests the existence of contributing genetic factors [9]. Lung cancer GWAS have identified several genotype-phenotype associations in regions such as 15q25.1 *(CHRNA5, CHRNA3),* 5p15.33 *(CLPTM1L, TERT)* and 6p21.33 *(BAG6/BAT3/MSH5)* that are consistent and reproducible across multiple populations [10–16]. This agnostic approach is useful for identifying novel genes and generating hypotheses about biological mechanisms previously unknown to be involved in lung cancer etiology. However, with genome-wide corrections for multiple testing, these studies restrict their reporting to the few top SNPs that pass stringent statistical thresholds, potentially excluding other significant SNPs with strong biological evidence supporting a role in lung cancer susceptibility. Therefore, the incorporation of knowledge on genes and pathways relevant to lung inflammation and tumorigenesis represents a complementary approach to generate novel hypotheses regarding the genetic contributors to risk and mechanistic differences in lung carcinogenesis.

We explored the contribution of genetic variation in immune pathways to lung cancer risk, separately by COPD status, in a discovery sample of 1008 cases and 924 controls and validated findings in an independent sample of 498 cases and 455 controls from the same population of inference. This was followed by evaluating whether the impact of each validated SNP was significantly heterogeneous among those with and without COPD as well as evaluating the functional and biological significance of the identified genetic variation.

Methods

Study Participants

The Wayne State University (WSU), McLaren Health Care (MHC) and Henry Ford Health System (HFHS) Institutional Review Boards approved the procedures used in collecting and processing participant information, and written informed consent was obtained from all subjects prior to participation. The INHALE study was initiated in 2012 and has been

previously described [17]. Briefly, lung cancer cases were enrolled at the Karmanos Cancer Center in Detroit or its network sites, or at HFHS in Detroit or its network sites, and volunteer controls were enrolled from the same geographic areas from which cases were drawn, preferentially matched to cases on smoking status (91.7% ever-smoking cases vs. 91.1% ever-smoking controls). Participants were 21–89 years of age, and were asked to complete an interview, low-dose chest CT scan and spirometry, and provide saliva, blood and tumor tissue samples. Further eligibility was restricted to those who carried health insurance (in the event medical follow-up was required based on a clinical finding on the CT or spirometry), and never had taken Amiodarone or been diagnosed with bronchiectasis or cystic fibrosis. Additionally, controls had never been diagnosed with lung cancer nor had surgical removal of any portion of either lung.

Data collection

Age, race, gender, history of COPD, family history of lung cancer and smoking history were collected in interviews. Pack years were calculated by multiplying the number of years smoked by the average number of cigarettes smoked per day divided by 20. Pulmonary function tests with spirometry were either performed by trained technicians in accordance with ATS guidelines [18] at the time of enrollment or spirometry results from pulmonary function tests (PFTs) were abstracted from medical records if completed within 6 months of the INHALE interview date. For analysis purposes, COPD was defined based on spirometry ($FEV_1/FVC < 0.70$); where FEV_1/FVC was missing (14%), self-reported history of COPD was used.

Genotyping and selection of immune system pathways

Genotyping was performed using the Illumina Multi-Ethnic GWAS/Exome Array (MEGA), which covers 1.7 million SNPs across the genome. The chip was designed to capture variation in ethnically diverse populations including Europeans, Asians, African Americans and Hispanics. The variants originate from sequencing discoveries, other GWAS panels, and published disease association studies. Immune system related genes and pathways were obtained from either the Reactome database or a published study of inflammation pathway genes and lung cancer risk [19,20]. The assembled immune system gene and pathway list contains manually curated, peer-reviewed pathway annotations cross-referenced with multiple databases including KEGG, Ensembl, and Uniprot by Reactome staff (Supplemental Table 1). Pathway annotations were included during the overrepresentation pathway analysis. MEGA SNP hg19 build 37 coordinates were cross-referenced with immune pathway gene locations according to the UCSC genome browser [21]. In addition to intragenic SNPs, SNPs within flanking, proximal regulatory regions were included if contained within +/− 2kB of the gene region based upon ENCODE proximal regulatory data [22, 23]. After removing invariant sites, there were 77,777 SNPs mapped to 2,015 immune pathway genes. SNPs were then filtered based on GenTrain score (<0.7), call rate <0.95 and inconsistent genotypes based on 19 CEPH sample replicates (99.88% concordance overall); 71,737 SNPs passed these quality control criteria. We required at least 15 minor allele carrier cases for each SNP evaluated (across discovery and validation samples) to avoid unstable effect estimates due to very rare SNPs. Thus, our analysis set consisted of 43,953 SNPs.

Statistical Analysis

The total number of INHALE participants with genotype data available was divided into a 'discovery' and 'validation' sample as follows: subjects were stratified by case-control status and randomly assigned to either the discovery or validation set by a ratio of 2:1. In this way the discovery set represented 2/3 of the total INHALE sample and the validation set represented the remaining 1/3 of the sample. There were no significant differences between the discovery and validation samples for any of the covariates used in this analysis (Supplemental Tables 2 and 3). Discovery and validation samples were further stratified by COPD status and analyzed separately.

We estimated African ancestry based on a panel of 128 ancestry informative markers (AIMs) described by Kosoy and colleagues [24]; 122 AIMs were genotyped and passed QC standards in the MEGA panel. Assuming Hardy-Weinberg Equilibrium, expected genotype relative frequencies were calculated for both European ('EUR') and African ('AFR') populations based on 1000 Genomes samples. For each of the three genotypes per AIM, the proportion of African ancestry was computed as $f(AFR_j)/(f(AFR_j)+f(EUR_j))$, where $f(AFR_j)$ is the expected frequency for genotype *j* in Africans and $f(EUR_j)$ is the expected frequency for genotype *j* in Europeans. Samples were then assigned a probability of African ancestry for each SNP corresponding to their observed genotype. These probabilities were summed and scaled for each individual to a standard uniform as $\frac{\sum_j(X_j - a_j)}{\sum_j(b_j - a_j)}$, where X_j the probability of African ancestry for the jth AIM, and a_j and b_j are the minimum and maximum possible probabilities for the jth AIM, respectively. This method of scoring ancestry was previously tested against principal component analysis (PCA) for correcting for population sub-structure and was found to perform similarly [24]. We verified these findings by conducting a PCA-based ancestry estimate with EIGENSTRAT using all 43,953 immune pathway-based SNPs and then comparing this estimate with African ancestry score. The top eigenvector explained ~74% of all variance explained by significant eigenvectors (n=19). African ancestry score and this top eigenvector were highly correlated (Spearman correlation: 0.832, $p = 1\times10^{-16}$)(Supplemental Figure S1).

In both the discovery and validation samples, logistic regression modeling was used to estimate individual SNP effects on lung cancer risk, separately among those with and without COPD, assuming an additive (per allele effect) genetic model. SNP effects were adjusted for age, gender, African ancestry score and pack years. Due to the exploratory nature of this study, we used a threshold of α=0.05 for carrying forward SNPs in either the COPD or no COPD discovery samples for testing in the respective validation sample. We assessed race-specific SNP effects by modeling each of the validated SNPs separately in whites and African Americans (also adjusting for ancestry score), combining the (COPD or no COPD) discovery and validation samples. We also used logistic regression modeling to determine whether the effects of any of the validated SNPs were statistically dependent on COPD in the pooled sample by incorporating an interaction term, the cross-product of SNP genotype (0, 1 or 2) and COPD status (0 or 1). For interaction modeling, we analyzed the combined sample of cases and controls with and without COPD. SNP effects on tissue-specific gene expression were modeled as *cis* expression quantitative trait loci (eQTL) as

described previously by the Genotype-Tissue Expression (GTEx) project version 7 [25]. Select GTEx tissues were evaluated for eQTL effects, lung and blood, to narrow the eQTL search to tissues directly involved in tobacco mediated lung injury. Multiple test corrections were computed for eQTL effects separately in each tissue. Network connectivity of genes was assessed using STRING as described previously [26]. Overrepresentation analysis was conducted using the hypergeometric distribution within the 48 immune pathways containing 2015 genes.

Data A vailability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Cohort description

A description of the INHALE case-control sample stratified by COPD is presented in Table 1. Lung cancer cases with COPD were more often white, ever smokers, and more likely to have a family history of lung cancer relative to controls with COPD. Cases in both strata (COPD versus no COPD) were more likely to be older and heavier smokers relative to controls, in addition to being diagnosed most often with adenocarcinoma and at later stages (stage III/IV, 72%). The total INHALE sample (N=2885) was subsequently split into a discovery (66%, n=1932/2885) and a validation (33%, n=953/2885) sample using random sampling. There were no significant differences between either cases in the discovery and validation samples or controls in the discovery and validation samples (Supplemental Tables 2 and 3).

Variant association testing

There were 43,953 immune-centric SNP association tests performed separately in samples with and without COPD (Supplementary Figures S2 and S3). SNP genotypes were modeled additively and adjusted for age, African ancestry, gender and pack years of smoking exposure. We carried forward 1,837 SNPs among cases and controls with COPD and 2,130 SNPs among cases and controls without COPD with a nominal p-value < 0.05 for evaluation in the validation sample. Upon testing these SNPs in the validation sample, 43 of 1,837 also met the α=0.05 threshold and were concordant in their direction of effect in the COPD validation sample (Supplemental Table 4). For cases and controls without COPD, 60 of 2,130 SNPs met these criteria in the validation sample (Supplemental Table 5). There were no validated SNPs in common to both strata.

To formally evaluate the context-dependency of validated SNPs in both the COPD and no COPD strata, we modeled interactions between COPD and each SNP in the pooled sample (discovery and validation samples combined). Interaction test results are presented in Table 2 for SNPs identified in individuals with COPD and Table 3 for SNPs identified in individuals without COPD. We considered an interaction test result of p<0.05 as sufficient evidence for context-dependency. We found significant COPD-dependent effects for 29 of 43 of the validated SNPs from the COPD stratum within 24 immune genes. Among the

validated SNPs in samples without COPD, 28 of 60 SNPs had a significant interaction with COPD within 26 immune pathway genes. Hence, out of 103 SNPs tested for context-dependency, 57 demonstrated significant COPD-dependent effects. We observed consistent context-dependent associations among these 57 SNPs when lung cancer cases were stratified by histology (adenocarcinoma and squamous cell carcinoma, Supplemental Tables 6 and 7).

Functional and biological significance

Considering our variant selection strategy, SNPs were selected for their proximity (±2kB) to immune pathway genes and each SNP was assigned to a specific gene. Through this gene assignment, we evaluated whether the genes represented by the 57 significant and context-dependent risk loci demonstrated functional or biological importance.

First, we interrogated the functional impact of risk notable SNPs on the expression of paired candidate genes using tissue-specific expression quantitative trait loci (eQTL) data from the GTEx consortium. We assessed eQTLs in two specimen types, lung tissue and whole blood leukocytes, to capture SNP functionality in the primary tissues relevant to lung inflammation (Table 4). Eleven risk significant and context-dependent SNP-gene pairs were significant eQTLs in lung, blood, or both tissues. Of variants notable for lung cancer risk with an interaction with COPD status (n=57), four SNPs demonstrated significant ($p < 0.05$) effects on paired candidate gene expression in lung tissue alone. Additionally, four SNPs demonstrated significant ($p < 0.05$) paired gene expression effects in whole blood leukocytes. Three SNP-gene pairs were significant in both tissues *(CD96, NRG1* and *UBE2O).*

As an alternative to functional characterization, we interrogated the biological significance of immunological genes implicated by context-dependent risk loci separately by COPD. First, we assessed the network connectivity of genes demonstrating context-dependent risk associations to determine whether these genes act in cohesive biological networks. Secondly, we assessed whether any of the immune pathways contained a greater number of loci-paired genes than we would expect by chance to identify the immunological pathways involved in lung cancer risk. To limit false positive results a significance threshold of α=0.01 was used. In COPD cases and controls, eight functional protein-protein network interactions were identified among candidate genes with significant and context dependent lung cancer risk associations (n=24), which was not statistically significant (p = 0.238; Supplemental Figure 4A). The 24 gene candidates in the COPD strata were also not significantly overrepresented at α=0.01 within any of the 48 immune pathways evaluated (Figure 1A). In individuals without COPD, candidate genes (n=26) contained 20 functional protein-network associations (Supplemental Figure 4B), more than expected by chance (p = 0.0002). Two immune pathways, *Fc-gamma receptor dependent phagocytosis (R-HSA-2029480) and DAP12 Interactions (R-HSA-2172127),* were significantly (p<0.01) overrepresented among these significant and context dependent lung cancer risk genes (Figure 1B).

These data demonstrate that immune-centric risk loci whose effects differ by COPD collectively reside within specific immune networks, and several directly regulate the expression of these network genes in tissues relevant to lung cancer.

Discussion

In this study we investigated the role of inflammation in lung cancer susceptibility, localized to biologically relevant immune pathways, to identify immune and inflammatory variants linked to lung cancer risk in individuals with and without COPD. Previous studies have implicated inflammation in the development of lung cancer independent of tobacco smoke exposure, and thus inflammation is thought to underlie the increased lung cancer susceptibility among those with COPD. However, prior scientific focus was limited to a narrower selection of inflammatory genes and processes [5, 27]. Such studies implicated genetic variation near and within inflammatory genes in lung cancer susceptibility [28, 29], either within known candidate genes identified *a posteriori* utilizing gene ontology searches and customized genotyping methodology [20, 30], or by extracting inflammatory relevant variants from GWAS [31]. We have complemented the efforts of previous studies, using an expanded inflammatory gene and pathway set paired with a high-density, multi-ethnic SNP array to determine which immune gene and pathway based loci confer lung cancer susceptibility in the presence and absence of COPD.

Few studies to-date assessed the role of genetic loci in lung cancer risk in individuals dual phenotyped for COPD. A study performed by Young and colleagues investigated the link between known lung cancer risk loci (n=11) and COPD in a smoking population of Caucasian New Zealanders [32]. They identified differential lung cancer risk effects in two variants that differed by COPD state and reported several other loci that may act as dual risk modifiers for lung cancer and COPD. Unfortunately, only a single inflammatory locus (rs2808630, *CRP*) was included in the study due to the limited scope of genotyping, and we were unable to validate any COPD dependent lung cancer risk associations within the *CRP* gene locus, which included rs2808630. Another such study conducted by Yang et al. investigated whether known *CHRNA3* lung cancer risk variants were also associated with COPD susceptibility and severity in a Chinese population of smokers, identifying a single significant association with potential mechanistic underpinnings [33]. They, however, did not investigate associations between inflammatory processes, COPD, and lung cancer susceptibility.

To expand upon these efforts, as well as to determine the COPD dependency of inflammatory gene and pathway variants in lung cancer risk, we conducted lung cancer association testing on 43,953 loci proximal (±2kB) to 2069 immune-centric genes in individuals separately by COPD status. We observed significant context-independent associations in the pooled discovery/validation samples for several genes *(APOB, PARK2,* and *PRKG1).* While SNPs in *PRKG1* were also validated in the context-dependent analyses, none of the 57 SNPs were in common to both strata (nor were they in LD with each other). However, we did find several correlations (D'>0.9) between SNPs that were identified in samples with COPD and those without COPD. LD was estimated using both D' and r^2 separately for white and African American samples; D' values were used to determine strong associations due to the presence of lower frequency SNPs in the MEGA panel and the sensitivity of r^2 to relative allele frequency differences between pairs of SNPs. Among white samples, three SNP pairs were in strong LD: rs2901600 in *DNM3* (COPD) and exm113346 in *SPTA1* (No COPD), rs10932427 in *ERBB4* (COPD) and rs3749096 in *EDAR* (No

COPD) and JHU_8.71282810 in *NCOA2* (COPD) and rs73241640 in *NRG1* (No COPD). No SNP pairs were in strong LD among African Americans. A lack of substantial overlapping loci/gene associations between the COPD stratums provides evidence that the genetic risk profiles for lung cancer greatly differ in individuals susceptible to COPD as opposed to individuals without COPD. As such, these findings align with prior work highlighting divergent inflammatory processes in smokers who are susceptible to COPD as opposed to smokers who are not [34]; and further, the divergent inflammatory processes likely contribute to the increased risk of lung carcinogenesis in individuals with COPD [35, 36].

Next, we interrogated the functional and biological significance of the immune-centric risk candidates, separately by COPD state. Functional analyses identified 19% (11/57) of the risk significant variants as significant *cis*-eQTLs in tissues of primary interest: lung and whole blood leukocyte tissues. This suggests that these variants may impart risk through modulating the expression patterns of lung and immunological tissues. Risk variants with no detectable eQTL signals may still play a role in regulating immunological gene expression in cases where lung inflammation is present; GTEx style studies in populations with active lung disease will be necessary to elucidate these effects.

Immune-centric gene candidates associated with lung cancer risk also demonstrated substantially more network connectivity in individuals without COPD (20 functional interactions) as opposed to individuals with COPD (8 functional interactions), despite the fact that approximately the same number of genes were represented in each stratum (24 in COPD versus 26 in no COPD). Immune-related risk signatures in smokers without COPD may reside in a narrow biological process whereas immune-related risk signatures in smokers with COPD reside across a more broad biological process. Moreover, pathway analysis revealed several pathways with an overrepresentation of risk candidates. Two classical innate immune activation schemes were represented; *DAP12 Interactions (R-HSA-2172127)* and *Fc-gamma receptor dependent phagocytosis (R-HSA-2029480).* Pathway involvement of the candidates was distinct between individuals with and without COPD, as no pathway was enriched in both stratums. These findings provide a biological context by which these variants may be contributing to differential lung cancer risk in individuals with and without COPD.

Due to known heterogeneity of minor allele relative frequencies between whites and African Americans, it is possible that race-specific effects exist among the 57 validated COPD-dependent SNPs. Indeed, six of 29 SNPs with risk effects in COPD (rs868936562, rs61505577, rs72969686, rs73783372, rs1074822 and rs61731180) and 4 of 28 SNPs in the no COPD stratum (rs867806199, rs114240594, rs4149646 and rs78466637) were restricted to either whites or African Americans, due to very low relative allele frequencies in the other race (i.e., no valid test). These variants could prove useful in understanding race related lung cancer susceptibility patterns. Conversely, the remaining variants represent a race-independent inflammatory relationship in lung cancer susceptibility in individuals with or without COPD. This set of variants could serve as useful risk stratification loci in admixed smoking populations. Furthermore, neither the race dependent or independent variants were shared between individuals with nor without COPD suggesting that the genetic risk profiles

in lung cancer differ greatly in individuals susceptible to COPD as opposed to individuals without COPD regardless of an individual's race.

The strengths of this study lie in the recruitment of a large set of racially diverse cases and controls with a well-defined COPD phenotype as well as the targeting of variation within genes directly involved in immune functions. This has allowed us to stratify the study population by COPD status to interrogate the contribution of immune-related variation to lung cancer susceptibility. There are, however, limitations to the approach we have taken. The requirement that participants carry a valid health insurance policy may limit generalizability to those who either can afford private insurance, have employer-provided benefits or qualify for Medicaid. In the state of Michigan, uninsured cancer patients can apply for Medicaid and therefore the most appropriate control group is one that is also insured. In addition, clinically actionable findings on CT could not be ignored based on ethical grounds; thus, insured participants had a mechanism through which findings could be acted upon. Another potential weakness of this study was the choice of a relatively loose significance threshold of $\alpha=0.05$ with no correction for multiple testing in the discovery phase of the analysis. Among the 43,953 SNPs, none were significant at a Bonferroni-corrected threshold ($p \leq 1.1 \times 10^{-6}$). However, we employed a stringent step-wise approach downstream to restrict our findings to the most consistent stratum-specific SNP effects. Likewise, the selection of the multi-ethnic genotyping array, while useful for a population containing Caucasians and African Americans, limited our ability to externally validate variant findings in prior lung cancer risk datasets, ultimately leading us to use an internal validation set.

Further research is necessary to determine the mechanistic link between risk-notable immune and inflammatory variants which differ by COPD states in at-risk populations. Moreover, the variants identified in this study will serve as a foundation to further interrogate the relationship of differential lung cancer risk profiling in individuals who have COPD as opposed to individuals who do not have COPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

COPD	chronic obstructive pulmonary disease
GWAS	genome-wide association study
SNP	single nucleotide polymorphism
MEGA	multi-ethnic genotyping array

GTEx	genotype-tissue expression project
PFT	pulmonary function test
eQTL	expression quantitative trait loci

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Impact

We evaluated the impact of genetic variation in immune and inflammatory genes and pathways on lung cancer in metropolitan Detroit lung cancer cases and controls with or without COPD. We demonstrate that variation in these genes and pathways impact lung cancer risk in a COPD dependent manner.

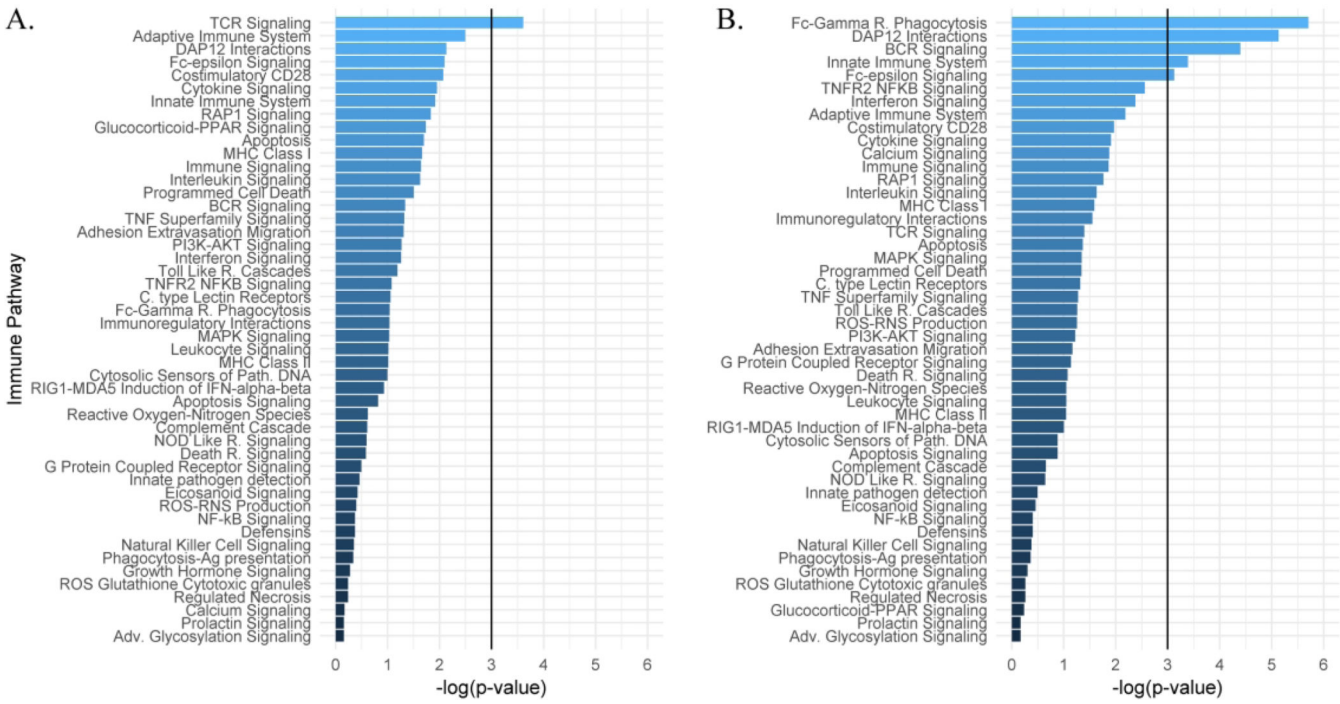

Figure 1. Pathway architecture of the significant risk candidates between COPD stratums.

Pathway analysis plots of the significant lung cancer risk and COPD interaction candidates within the designated immune pathways chosen for this study. Overrepresentation significance values are plotted on the x-axis for each pathway with a line designating the significance threshold. (A) Pathway significance values for candidates identified in individuals with COPD. (B) Pathway significance values for candidates identified in individuals without COPD.

Table 1.

Description of INHALE lung cancer case-control sample (N=2885), stratified by COPD status.

	COPD (n=1123/2885)			No COPD (n=1762/2885)		
Variable	**Lung Cancer Cases (n=677)**	**Controls (n=446)**	***p* value**	**Lung Cancer Cases (n=829)**	**Controls (n=933)**	***p* value**
Gender (n, %)						
Male	291 (43.0)	208 (46.6)	0.228	387 (46.7)	421 (45.1)	0.512
Female	386 (57.0)	238 (53.4)		442 (53.3)	512 (54.9)	
Race (n, %)						
White	435 (64.3)	240 (53.8)	0.001	545 (65.7)	573 (61.4)	0.060
African American	242 (35.7)	206 (46.2)		284 (34.3)	360 (38.6)	
Age (μ, SD)	64.6 (9.4)	62.5 (9.6)	<0.001	62.3 (11.1)	59.4 (9.3)	<0.001
<50	36 (5.3)	40 (9.0)	0.027	100 (12.1)	131 (14.0)	<0.001
51–59	174 (25.7)	127 (28.5)		234 (28.2)	353 (37.8)	
60–69	258 (38.1)	167 (37.4)		280 (33.8)	325 (34.8)	
70+	209 (30.9)	112 (25.1)		215 (25.9)	124 (13.3)	
Smoking status (n, %)						
Never	19 (2.8)	30 (6.7)	0.002	119 (14.4)	106 (11.4)	0.060
Ever	658 (97.2)	416 (93.3)		710 (85.6)	827 (88.6)	
Pack years (μ, SD) *	50.5 (29.9)	36.9 (27.2)	<0.001	41.2 (29.6)	30.4 (22.5)	<0.001
Family history of lung cancer						
No	500 (73.9)	384 (86.3)	<0.001	655 (79.1)	764 (81.9)	0.141
Yes	177 (26.1)	61 (13.7)		173 (20.9)	169 (18.1)	
Missing	0	1		1	0	
Histology						
Adenocarcinoma	330 (49.2)			511 (61.6)		
Squamous cell	173 (25.8)			139 (16.8)		
Small cell	105 (15.7)		---	105 (12.7)		---
other NSCLC	62 (9.3)			62 (7.5)		
unknown/missing	7			12		
Stage						
I	164 (24.6)			116 (14.3)		
II	67 (10.0)			70 (8.6)		
III	153 (22.9)		---	183 (22.5)		---
IV	283 (42.4)			443 (54.6)		
Missing	10			17		

* Reported as the mean and SD in smoking participants only

Table 2.

Tests of COPD x SNP interaction on lung cancer risk for the 43 validated SNPs in individuals with COPD

SNP	Gene	CHR	Position	COPD × SNP interaction *p* value	Pooled risk model results		
					OR*	95% CI	*p* value
rs2932538	MOV10	1	113216543	0.055	0.73	(0.59,0.91)	0.004
rs2901600	DNM3	1	171835654	**<0.001**	0.73	(0.61,0.87)	0.0005
rs693	APOB	2	21232195	0.680	0.83	(0.69,0.99)	0.0437
JHU_2.70774695	TGFA	2	70774696	**0.025**	4.34	(1.76,10.71)	0.0014
rs10932427	ERBB4	2	213073615	**0.012**	0.6	(0.44,0.81)	0.001
rs115435003	TRIP12	2	230629658	0.998	0.46	(0.23,0.94)	0.0325
rs546530	TRIP12	2	230752964	0.077	1.3	(1.09,1.56)	0.004
rs7570061	INPP5D	2	233977318	**0.005**	0.7	(0.57,0.86)	0.0006
rs79048756	CD96	3	111323053	**0.015**	0.41	(0.24,0.68)	0.0007
rs61505577	BMPR1B	4	95789665	**0.015**	2.48	(1.46,4.23)	0.0008
rs73836068	BMPR1B	4	95891132	0.057	1.87	(1.29,2.72)	0.001
JHU_6.117021274	KPNA5	6	117021275	**0.010**	0.4	(0.24,0.68)	0.0007
6:125369362-CT	RNF217	6	125369362	**0.022**	0.28	(0.11,0.7)	0.0062
rs73783372	PARK2	6	162155477	**0.015**	2.54	(1.52,4.25)	0.0004
JHU_7.54821275	SEC61G	7	54821276	0.070	4.37	(1.6,11.93)	0.004
JHU_7.139540808	TBXAS1	7	139540809	0.052	0.65	(0.48,0.88)	0.0053
JHU_8.71282810	NCOA2	8	71282811	**0.030**	0.24	(0.09,0.6)	0.0026
rs4745646	TJP2	9	71769323	**0.011**	1.52	(1.18,1.95)	0.001
rs688391	PRKCQ	10	6489652	0.312	1.34	(1.11,1.61)	0.0024
rs3793727	PRKCQ	10	6508377	**0.005**	1.56	(1.26,1.93)	<0.0001
rs658230	PRKCQ	10	6508563	**0.044**	1.39	(1.16,1.67)	0.0005
JHU_10.32320560	KIF5B	10	32320561	0.080	0.7	(0.55,0.88)	0.0021
rs12252698	PRKG1	10	53608098	**0.002**	0.69	(0.54,0.89)	0.0037
rs1937701	PRKG1	10	53608977	**0.009**	0.7	(0.57,0.86)	0.0007
JHU_10.75843193	VCL	10	75843194	**0.006**	0.44	(0.26,0.75)	0.0025
rs3127255	FBXW4	10	103370234	0.105	1.31	(1.07,1.6)	0.0086
rs666432	TRIM29	11	120003533	**0.003**	1.48	(1.14,1.93)	0.0037
rs4411364	TNFRSF19	13	24191374	**0.029**	1.43	(1.12,1.82)	0.0042
rs9510787	TNFRSF19	13	24205195	**0.034**	1.43	(1.12,1.82)	0.0042
rs1630	TNFRSF19	13	24249847	**0.010**	1.49	(1.22,1.82)	0.0001
rs17446928	FOXO1	13	41212225	**0.001**	0.39	(0.25,0.6)	<0.0001
rs76294435	PPP2R5C	14	102274571	0.077	0.4	(0.25,0.65)	0.0002
JHU_14.103934653	MARK3	14	103934654	0.099	0.73	(0.6,0.89)	0.0018
rs55986634	DAPK2	15	64275645	0.180	0.71	(0.58,0.88)	0.0018
rs75395345	PIAS1	15	68373718	0.993	1.26	(1,1.57)	0.0485
rs2071501	CSK	15	75095157	**0.033**	0.54	(0.37,0.79)	0.0015
JHU_16.4014963	ADCY9	16	4014964	**0.049**	1.46	(1.18,1.82)	0.0006

SNP	Gene	CHR	Position	COPD × SNP interaction *p* value	Pooled risk model results		
					OR*	95% CI	*p* value
rs933392	ADCY9	16	4032716	**0.036**	1.44	(1.16,1.79)	0.001
exm1358199	UBE2O	17	74387284	**0.023**	1.39	(1.14,1.69)	0.0012
JHU_18.49961949	DCC	18	49961950	**0.020**	0.68	(0.53,0.88)	0.0028
rs10414006	SPTBN4	19	41001921	**0.010**	0.62	(0.49,0.79)	0.0001
rs11879349	NLRP4	19	56364210	**0.041**	0.62	(0.47,0.82)	0.0008
exm2262720	PAK3	23	110379807	**0.034**	0.68	(0.52,0.88)	0.0033

* Logistic model adjusted for age, gender, African ancestry score and pack years

Table 3.

Tests of COPD x SNP interaction on lung cancer risk for the 60 validated SNPs in individuals without COPD

SNP	Gene	CHR	Position	COPD × SNP interaction *p* value	Pooled risk model results		
					OR*	95% CI	*p* value
exm69478	ASB17	1	76397972	0.156	1.29	(1.1,1.5)	0.0014
JHU_1.108497389	VAV3	1	108497390	**0.029**	0.72	(0.58,0.89)	0.0022
rs3754293	LAMTOR2	1	156024373	0.219	0.8	(0.69,0.93)	0.0028
exm113346	SPTA1	1	158645965	**<0.001**	6.46	(2.37,17.63)	0.0003
rs2230779	TRAF5	1	211533352	0.534	1.59	(1.18,2.14)	0.0024
rs10929693	ATP6V1C2	2	10863267	0.435	0.8	(0.69,0.93)	0.0032
exm175467	APOB	2	21225281	0.187	1.2	(1.02,1.43)	0.0316
newrs676210	APOB	2	21231524	0.183	1.21	(1.02,1.43)	0.0299
rs3749096	EDAR	2	109512428	**0.044**	1.34	(1.1,1.63)	0.0033
rs13418730	WIPF1	2	175540594	**0.048**	0.68	(0.52,0.89)	0.0046
rs7583875	AP1S3	2	224665694	0.062	0.8	(0.7,0.92)	0.0016
JHU_3.18396523	SATB1	3	18396524	0.127	0.35	(0.2,0.6)	0.0001
rs80069959	KCNH8	3	19223049	0.069	0.58	(0.4,0.84)	0.0040
JHU_3.119275362	CD80	3	119275363	**0.019**	0.53	(0.36,0.77)	0.0009
rs953239	TRPC1	3	142446205	**0.003**	1.23	(1.07,1.41)	0.0036
rs7623154	PIK3CA	3	178921158	**0.020**	1.25	(1.07,1.46)	0.0055
JHU_5.16912953	MYO10	5	16912954	**0.029**	2.24	(1.27,3.94)	0.0051
JHU_5.35873123	IL7R	5	35873124	0.187	0.6	(0.43,0.84)	0.0034
rs7726469	CAMK4	5	110586438	**0.020**	0.76	(0.65,0.9)	0.0015
rs12153148	KLHL3	5	136964764	0.066	0.74	(0.62,0.88)	0.0006
rs3777376	KLHL3	5	136965249	**0.042**	0.73	(0.61,0.87)	0.0005
rs7774142	LY86	6	6642058	**0.027**	1.3	(1.12,1.5)	0.0007
exm-rs3827784	LY86	6	6642405	**0.031**	1.31	(1.12,1.52)	0.0005
JHU_6.137043810	MAP3K5	6	137043811	**0.016**	2.19	(1.23,3.89)	0.0075
rs56247201	PARK2	6	162702092	0.191	0.5	(0.33,0.74)	0.0006
rs35537854	RPS6KA2	6	167072030	0.128	0.6	(0.42,0.85)	0.0041
JHU_7.30352063	ZNRF2	7	30352064	**0.001**	0.15	(0.04,0.53)	0.0033
JHU_7.30393775	ZNRF2	7	30393776	0.062	0.29	(0.14,0.62)	0.0014
exm689348	TNFRSF10A	8	23049292	0.298	0.75	(0.62,0.92)	0.0047
rs73241640	NRG1	8	31932616	**0.031**	0.39	(0.24,0.63)	0.0002
rs11776203	NRG1	8	32419119	**0.003**	0.76	(0.63,0.92)	0.0039
JHU_8.32431713	NRG1	8	32431714	0.446	0.42	(0.24,0.74)	0.0029
rs1014306	DAPK1	9	90157451	0.317	1.33	(1.14,1.54)	0.0002
rs12378686	DAPK1	9	90163570	0.547	1.3	(1.1,1.52)	0.0018
JHU_9.90198587	DAPK1	9	90198588	0.152	0.58	(0.4,0.82)	0.0024
rs10995319	PRKG1	10	52762887	0.125	1.32	(1.09,1.6)	0.0045
rs7904024	PRKG1	10	52841790	**0.022**	1.28	(1.11,1.48)	0.0007

SNP	Gene	CHR	Position	COPD × SNP interaction *p* value	Pooled risk model results		
					OR*	95% CI	*p* value
JHU_10.83841723	NRG3	10	83841724	0.415	2.87	(1.4,5.86)	0.0038
rs74153420	BMPR1A	10	88628433	0.287	2.4	(1.33,4.33)	0.0038
JHU_10.93222022	HECTD2	10	93222023	0.486	1.46	(1,2.11)	0.0481
JHU_10.123313013	FGFR2	10	123313014	**0.020**	1.49	(1.17,1.91)	0.0014
rs548142	DYNC2H1	11	103315520	**0.048**	0.75	(0.65,0.86)	0.0001
JHU_12.6438144	TNFRSF1A	12	6438145	**0.016**	1.83	(1.3,2.58)	0.0005
JHU_12.26512936	ITPR2	12	26512937	**0.011**	3.4	(1.48,7.86)	0.0041
rs61971164	STK24	13	99190397	0.072	0.73	(0.61,0.88)	0.0008
rs17565502	TNFSF13B	13	108954304	0.061	1.26	(1.08,1.47)	0.0039
JHU_14.23313974	MMP14	14	23313975	**0.011**	0.54	(0.35,0.82)	0.0038
rs78656887	PSMC1	14	90734095	**0.018**	0.48	(0.31,0.76)	0.0016
rs12441042	TLN2	15	62946064	0.085	0.79	(0.68,0.92)	0.0019
rs74318887	MEF2A	15	100229061	**0.027**	0.46	(0.29,0.74)	0.0012
rs76272325	PSMB6	17	4699845	0.172	0.5	(0.34,0.74)	0.0004
JHU_17.5413392	NLRP1	17	5413393	0.055	0.79	(0.68,0.93)	0.0033
JHU_17.40648111	ATP6V0A1	17	40648112	**0.003**	1.83	(1.33,2.51)	0.0002
rs12949223	CD300LD	17	72589264	0.246	1.24	(1.07,1.44)	0.0050
JHU_18.21773860	OSBPL1A	18	21773861	0.115	2.78	(1.49,5.17)	0.0012
rs11082490	SIGLEC15	18	43412628	**<0.001**	1.53	(1.27,1.84)	<0.0001
rs58993112	MALT1	18	56412784	0.159	1.35	(1.11,1.64)	0.0023
exm2253611	PDE4A	19	10546771	**0.029**	1.25	(1.08,1.45)	0.0027
rs9676881	KEAP1	19	10596780	**0.008**	1.32	(1.14,1.53)	0.0002
rs2898449	MX1	21	42814495	0.063	0.69	(0.54,0.87)	0.0020

*Logistic model adjusted for age, gender, African ancestry score and pack years

Table 4.

Significant eQTL and context-dependent lung cancer risk SNP-gene pairs in lung and whole blood leukocyte tissues

SNP	Gene	CHR	Position	COPD × SNP interaction *p* value	Lung cancer risk model *p* value	Lung eQTL *p* value	Lung eQTL FDR	Blood eQTL *p* value	Blood eQTL FDR
Significant eQTL SNP-gene pairs in individuals with COPD									
rs79048756	CD96	3	111323053	0.015	0.0007	3.7×10^{-4}	0.016	1.8×10^{-5}	6.6×10^{-4}
rs4745646	TJP2	9	71769323	0.011	0.0010	>0.05	-	7.2×10^{-4}	0.008
rs3793727	PRKCQ	10	6508377	0.005	0.0000	>0.05	-	0.007	0.049
rs666432	TRIM29	11	120003533	0.003	0.0037	0.036	0.25	>0.05	-
exm1358199	UBE2O	17	74387284	0.023	0.0012	4.6×10^{-6}	4.0×10^{-4}	<0.001	0.002
Significant eQTL SNP-gene pairs in individuals without COPD									
rs7623154	PIK3CA	3	178921158	0.020	0.0055	0.002	0.042	>0.05	-
rs953239	TRPC1	3	142446205	0.003	0.0036	0.002	0.042	>0.05	-
rs3777376	KLHL3	5	136965249	0.042	0.0005	>0.05	-	0.006	0.045
rs11776203	NRG1	8	32419119	0.003	0.0039	0.044	0.28	8.1×10^{-10}	6.0×10^{-8}
rs11082490	SIGLEC15	18	43412628	0.001	0.0000	>0.05	-	2.8×10^{-4}	0.003
rs9676881	KEAP1	19	10596780	0.008	0.0002	0.004	0.069	>0.05	-