Supplemental Data

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

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Supplemental Table 1. Immune system pathways utilized for genetic analysis of COPD-dependent lung cancer risk. Pathways and associated genes were annotated using the Reactome database.

Pathway	Sub-Pathway	# Genes	# SNPs
Adaptive Immunity		824	39227
	B-cell Receptor Signaling	233	13206
	T-cell Receptor Signaling	118	4118
	Costimulatory CD28 Family	69	2908
	Immunoregulatory Interactions	127	4710
	RAP1 Signaling	16	1589
	MHC Class I Family	368	14787
	MHC Class II Family	121	5133
Innate Immunity		790	43609
	Advanced Glycosylation Receptor Signaling	13	621
	Complement Cascade	84	4188
	C-type Lectin Receptors	124	4985
	Cytosolic Sensors of Pathogen DNA	67	2782
	DAP12 Interactions	376	24844
	Defensins	52	673
	Fc-epsilon Receptor Signaling	377	23564
	Fc-gamma Receptor Signaling	85	6496
	NOD-Like Receptor Signaling	51	2173
	RIG1-MDA5 Induction of IFN-alpha/beta	81	2728
	Innate Pathogen Detection	38	1632
	Toll-Like Receptor Cascades	151	7022
Cytokine Signaling		818	38457
	Interferon Signaling	202	8071
	Interleukin Signaling	430	23391
	Growth Hormone Signaling	24	1071
	Prolactin Signaling	15	650
	TNFR2-NFKB Signaling	97	2528
Programmed Cell Death		203	9173
	Apoptosis	166	7555
	Apoptosis Signaling	67	2819
	Death Receptor Signaling	51	2049
	Regulated Necrosis	21	599
Reactive Oxygen/Nitrogen Species		52	1966
	ROS Granules	20	704
	ROS/RNS Generation	34	1331
Immune Signaling		467	24782
	Calcium Signaling	14	1354
	G-protein Coupled Receptor Signaling	41	4334
	Eicosanoid Signaling	35	1554
	Glucocorticoid Receptor/Peroxisome Proliferator-Activated Receptor Signaling	18	955
	Leukocyte Signaling	111	5051
	Mitogen-Activated Protein Kinase Signaling	115	6404
	Natural Killer Cell Signaling	31	1075
	NF-KB Signaling	33	1327
	PI3K/AKT Signaling	35	1710
	TNF Family Signaling	35	1034
Adhesion/Extravasation/Migration		135	5313
Phagocytosis-Antigen Presentation		39	1299

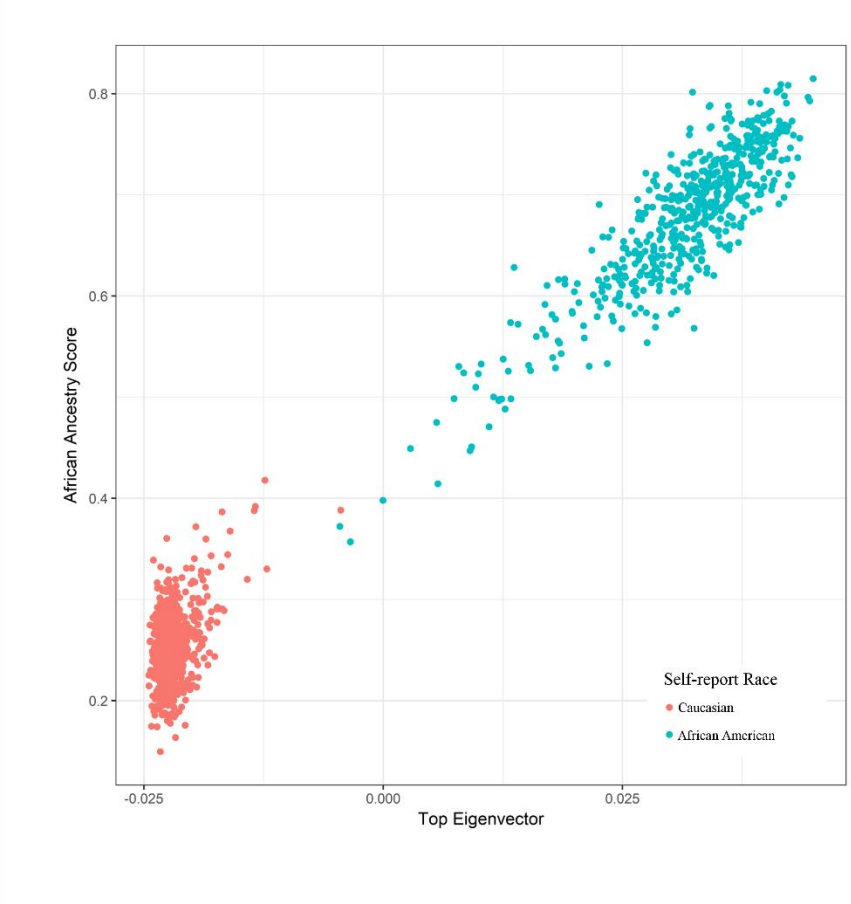
Supplemental Table 2. Comparison of lung cancer cases in test set with cases in validation set; samples were stratified by case-control status and randomly assigned to either test (2/3 of the total) or validation (1/3 of the total) sample.

Variable	Discovery (n=1008)	Validation (n=498)	Test of homogeneity
Gender (n, %)			
Male	455 (45.1)	223 (44.8)	0.895
Female	553 (54.9)	275 (55.2)	
Race (n, %)			
White	661 (65.6)	319 (64.1)	0.561
African American	347 (34.4)	179 (35.9)	
Age (mean, SD)	63.4 (10.5)	63.3 (10.2)	0.812
Smoking status (n, %)			
Never	88 (8.7)	50 (10.0)	0.407
Ever	920 (91.3)	448 (90.0)	
Pack years (smokers only) (mean, SD)	46.0 (29.8)	45.1 (30.7)	0.641
Family history of lung cancer			
No	770 (76.5)	385 (77.3)	0.715
Yes	237 (23.5)	113 (22.7)	
Missing	1	0	
History of COPD			
No	674 (69.4)	341 (71.0)	0.524
Yes	297 (30.6)	139 (29.0)	
Missing	37	18	
GOLD COPD (FEV_1/FVC < 70%)			
No	365 (49.3)	170 (47.0)	0.474
Yes	376 (50.7)	192 (53.0)	
Missing	267	96	
Histology			
Adenocarcinoma	574 (57.7)	266 (54.1)	0.183
Squamous cell	208 (20.9)	104 (21.1)	
Small cell	127 (12.8)	83 (16.9)	
other NSCLC	85 (8.6)	39 (7.9)	
unknown/missing	14	6	
Stage			
I	194 (19.6)	88 (18.0)	0.261
II	99 (10.0)	38 (7.8)	
III	229 (23.1)	108 (22.0)	
IV	469 (47.3)	256 (52.2)	
Missing	17	8	

Supplemental Table 3. Comparison of controls in test set with controls in validation set; samples were stratified by case-control status and randomly assigned to either test (2/3 of the total) or validation (1/3 of the total) sample.

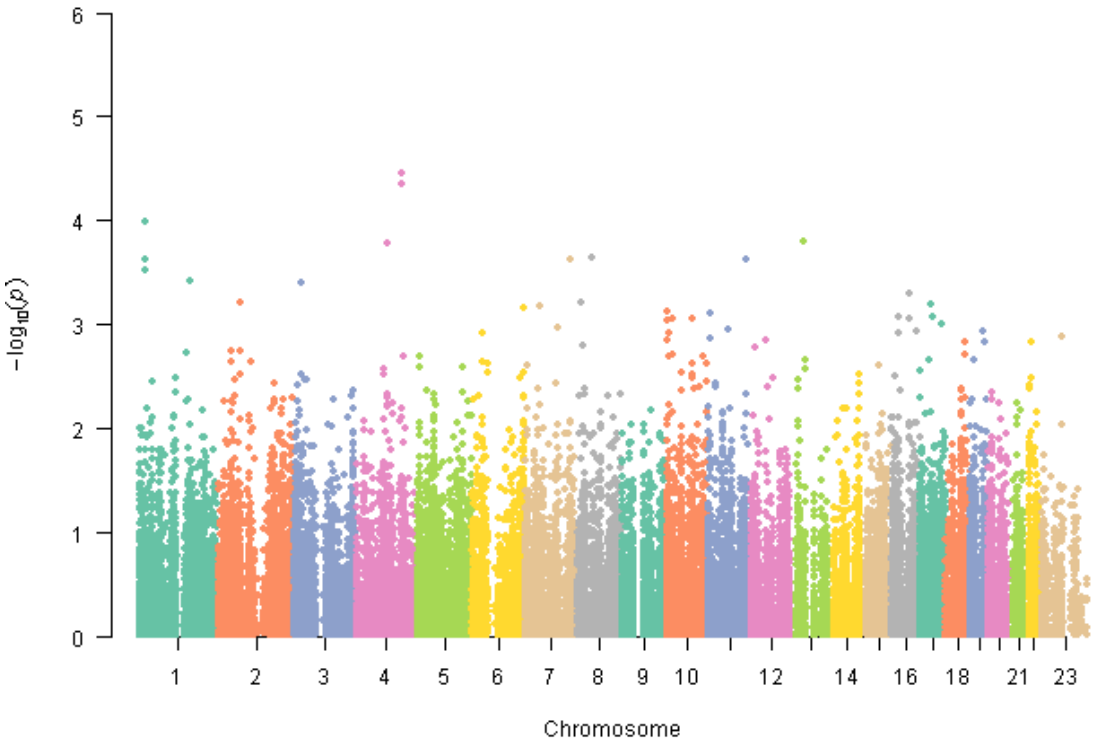
Variable	Test (n=924)	Validation (n=455)	Test of homogeneity
Gender (n, %)			
Male	415 (44.9)	214 (47.0)	0.458
Female	509 (55.1)	241 (53.0)	
Race (n, %)			
White	544 (58.9)	269 (59.1)	0.930
African American	380 (41.1)	186 (40.9)	
Age (mean, SD)	60.4 (9.5)	60.4 (9.5)	0.957
Smoking status (n, %)			
Never	87 (9.4)	49 (10.8)	0.428
Ever	837 (90.6)	406 (89.2)	
Pack years (smokers only) (mean, SD)	33.0 (25.2)	31.7 (22.6)	0.348
Family history of lung cancer			
No	774 (83.9)	374 (82.2)	0.437
Yes	149 (16.1)	81 (17.8)	
Missing	1	0	
History of COPD			
No	738 (80.0)	356 (78.2)	0.459
Yes	185 (20.0)	99 (21.8)	
Missing	1	0	
GOLD COPD ($FEV_1/FVC < 70\%$)			
No	615 (66.6)	317 (69.8)	0.223
Yes	309 (33.4)	137 (30.2)	
Missing	0	1	

Supplemental Figure 1: African Ancestry and principal component analysis for population stratification



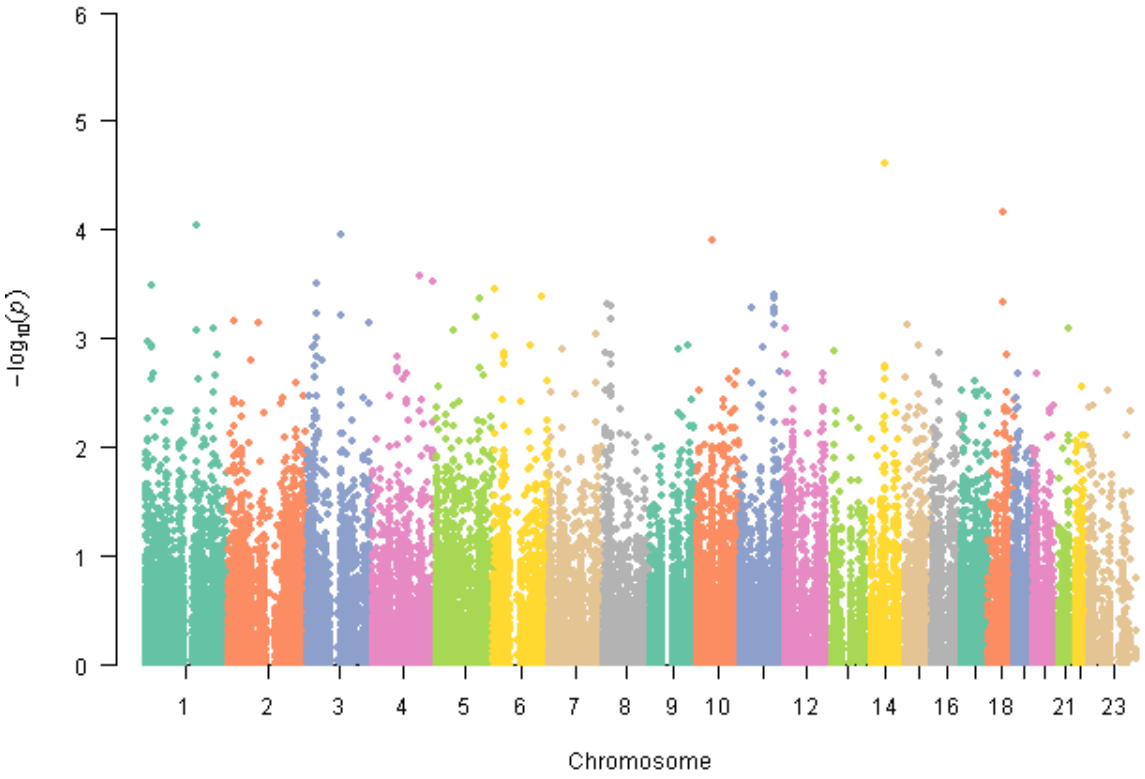
Legend: Comparison of the African ancestry score and top eigenvector for participants in the control group (n=1379). Dichotomous self-reported race is depicted in red (Caucasian) and blue (African American). EIGENSTRAT was used to conduct the principal component analysis. The top eigenvector explained ~74% of variance explained by significant eigenvectors (n=19). African ancestry score and the top eigenvector were highly correlated (Spearman correlation: 0.832, $p=1\times10^{-16}$).

Supplemental Figure 2: Manhattan plot of the discovery sample with COPD



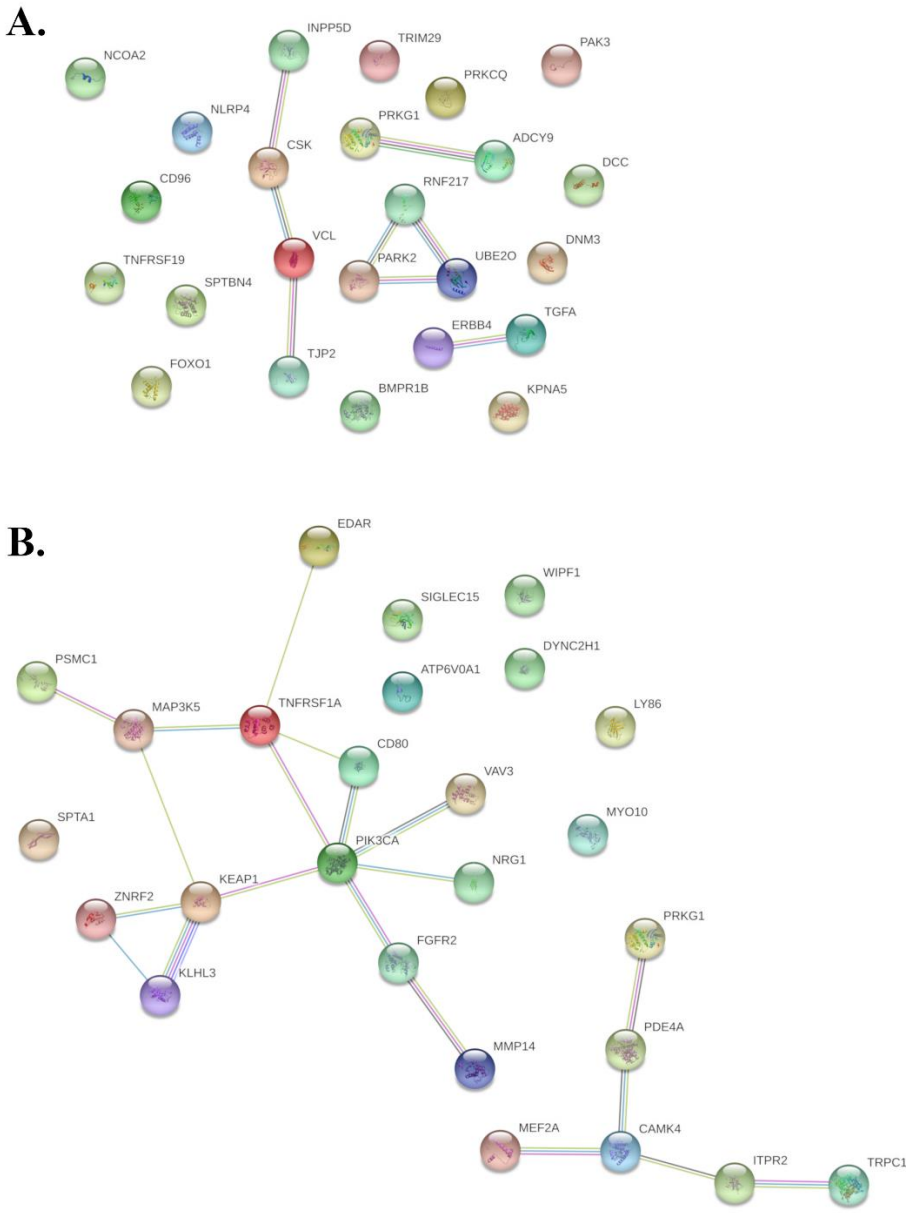
Legend: Manhattan plot of $-\log_{10}(p\text{-value})$ from 43,953 individual immune pathway SNP association test results with lung cancer risk among 760 discovery samples **with** COPD. SNPs were modeled additively, and effect estimates were adjusted for age, African ancestry score, gender and pack years.

Supplemental Figure 3: Manhattan plot of the discovery sample without COPD



Legend: Manhattan plot of $-\log_{10}(p\text{-value})$ from 43,953 individual immune pathway SNP association test results with lung cancer risk among 1172 discovery samples **without** COPD. SNPs were modeled additively, and effect estimates were adjusted for age, African ancestry score, gender and pack years.

Supplemental Figure 4. Protein-protein interaction plots of the significant lung cancer risk candidates between COPD stratums.



Legend: Protein-Protein Interaction plots of the significant gene candidates identified from the validated lung cancer risk model and COPD interaction model. Interaction data were derived from the STRING database and is based upon distinct levels of molecular evidence supporting illustrated protein associations. (A) Candidates identified in individuals with COPD. (B) Candidates identified in individuals without COPD.

Supplemental Table 4. Validated SNP-lung cancer associations among 1,123 lung cancer cases and controls with COPD

				Discovery Sample		Validation Sample	
Name	**Gene**	**CHR**	**Position**	**OR* (95% CI)**	**p value**	**OR* (95% CI)**	**p value**
rs2932538	MOV10	1	113216543	0.77 (0.59,1)	0.0489	0.64 (0.44,0.94)	0.0218
rs2901600	DNM3	1	171835654	0.79 (0.64,0.98)	0.0337	0.61 (0.44,0.84)	0.0028
exm175467	APOB	2	21225281	1.37 (1.03,1.82)	0.0291	1.83 (1.16,2.9)	0.0096
newrs676210	APOB	2	21231524	1.38 (1.04,1.83)	0.0253	1.83 (1.16,2.9)	0.0096
JHU_2.70774695	TGFA	2	70774696	2.89 (1.05,7.92)	0.0398	12.68 (1.56,103.06)	0.0175
rs10932427	ERBB4	2	213073615	0.66 (0.47,0.94)	0.0211	0.41 (0.21,0.8)	0.0088
rs546530	TRIP12	2	230752964	1.26 (1.01,1.57)	0.0436	1.38 (1.01,1.88)	0.0420
rs7570061	INPP5D	2	233977318	0.71 (0.55,0.92)	0.0091	0.66 (0.46,0.94)	0.0216
rs79048756	CD96	3	111323053	0.43 (0.23,0.81)	0.0091	0.35 (0.14,0.89)	0.0281
rs61505577	BMPR1B	4	95789665	2 (1.05,3.8)	0.0350	4.04 (1.55,10.56)	0.0044
rs73836068	BMPR1B	4	95891132	1.56 (1.01,2.42)	0.0456	3.1 (1.45,6.63)	0.0036
JHU_6.117021274	KPNA5	6	117021275	0.44 (0.24,0.82)	0.0103	0.31 (0.12,0.83)	0.0202
6:125369362-CT	RNF217	6	125369362	0.28 (0.09,0.91)	0.0345	0.21 (0.05,0.96)	0.0439
rs73783372	PARK2	6	162155477	2.43 (1.31,4.51)	0.0050	2.72 (1.09,6.79)	0.0319
JHU_7.54821275	SEC61G	7	54821276	3.72 (1.18,11.76)	0.0252	8.89 (1.03,76.48)	0.0466
JHU_7.139540808	TBXAS1	7	139540809	0.69 (0.48,1)	0.0482	0.54 (0.3,0.97)	0.0394
JHU_8.71282810	NCOA2	8	71282811	0.33 (0.11,0.94)	0.0382	0.08 (0.01,0.67)	0.0200
rs4745646	TJP2	9	71769323	1.49 (1.11,2.02)	0.0090	1.74 (1.1,2.74)	0.0174
rs688391	PRKCQ	10	6489652	1.3 (1.03,1.63)	0.0269	1.43 (1.02,2)	0.0381
rs3793727	PRKCQ	10	6508377	1.53 (1.18,1.99)	0.0014	1.56 (1.06,2.27)	0.0223
rs658230	PRKCQ	10	6508563	1.35 (1.08,1.69)	0.0093	1.46 (1.04,2.03)	0.0275
JHU_10.32320560	KIF5B	10	32320561	0.73 (0.55,0.97)	0.0323	0.63 (0.43,0.94)	0.0235
rs12252698	PRKG1	10	53608098	0.74 (0.55,1)	0.0490	0.6 (0.39,0.94)	0.0260
rs1937701	PRKG1	10	53608977	0.73 (0.57,0.95)	0.0168	0.68 (0.48,0.97)	0.0323
JHU_10.75843193	VCL	10	75843194	0.48 (0.24,0.93)	0.0301	0.37 (0.16,0.88)	0.0245
JHU_10.93222022	HECTD2	10	93222023	1.78 (1.01,3.14)	0.0457	2.5 (1.04,5.99)	0.0400
rs3127255	FBXW4	10	103370234	1.29 (1.01,1.65)	0.0434	1.49 (1.04,2.13)	0.0306
rs666432	TRIM29	11	120003533	1.41 (1.03,1.93)	0.0312	1.76 (1.05,2.96)	0.0323
rs4411364	TNFRSF19	13	24191374	1.38 (1.03,1.84)	0.0307	1.62 (1.02,2.58)	0.0423
rs9510787	TNFRSF19	13	24205195	1.38 (1.03,1.84)	0.0307	1.62 (1.02,2.58)	0.0423
rs1630	TNFRSF19	13	24249847	1.43 (1.13,1.82)	0.0033	1.61 (1.11,2.32)	0.0114
rs17446928	FOXO1	13	41212225	0.35 (0.2,0.6)	0.0002	0.46 (0.23,0.94)	0.0336
rs76294435	PPP2R5C	14	102274571	0.45 (0.25,0.8)	0.0063	0.3 (0.12,0.76)	0.0113
JHU_14.103934653	MARK3	14	103934654	0.75 (0.59,0.95)	0.0187	0.68 (0.48,0.96)	0.0268

rs55986634	DAPK2	15	64275645	0.77 (0.6,1)	0.0496	0.62 (0.42,0.9)	0.0114
rs2071501	CSK	15	75095157	0.58 (0.35,0.95)	0.0312	0.42 (0.23,0.78)	0.0058
JHU_16.4014963	ADCY9	16	4014964	1.36 (1.05,1.78)	0.0218	1.74 (1.18,2.55)	0.0049
rs933392	ADCY9	16	4032716	1.44 (1.1,1.88)	0.0077	1.49 (1.01,2.19)	0.0450
exm1358199	UBE2O	17	74387284	1.33 (1.05,1.69)	0.0184	1.58 (1.09,2.3)	0.0158
JHU_18.49961949	DCC	18	49961950	0.7 (0.52,0.95)	0.0207	0.63 (0.4,1)	0.0497
rs10414006	SPTBN4	19	41001921	0.63 (0.47,0.83)	0.0012	0.64 (0.42,0.98)	0.0397
rs11879349	NLRP4	19	56364210	0.65 (0.45,0.92)	0.0162	0.55 (0.34,0.88)	0.0134
exm2262720	PAK3	23	110379807	0.72 (0.52,0.99)	0.0443	0.57 (0.36,0.91)	0.0192

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

Supplemental Table 5. Validated SNP-lung cancer associations among 1,762 lung cancer cases and controls without COPD

				Discovery Sample		Validation Sample	
Name	**Gene**	**CHR**	**Position**	**OR* (95% CI)**	**p value**	**OR* (95% CI)**	**p value**
exm69478	ASB17	1	76397972	1.22 (1.01,1.47)	0.0395	1.45 (1.11,1.9)	0.0070
JHU_1.108497389	VAV3	1	108497390	0.77 (0.59,0.99)	0.0444	0.63 (0.44,0.92)	0.0170
rs3754293	LAMTOR2	1	156024373	0.83 (0.7,1)	0.0461	0.72 (0.55,0.93)	0.0136
exm113346	SPTA1	1	158645965	6.2 (1.7,22.6)	0.0057	6.69 (1.36,32.85)	0.0192
rs2230779	TRAF5	1	211533352	1.5 (1.04,2.17)	0.0304	1.76 (1.05,2.95)	0.0332
rs10929693	ATP6V1C2	2	10863267	0.82 (0.69,0.98)	0.0283	0.73 (0.56,0.96)	0.0240
rs693	APOB	2	21232195	0.82 (0.69,0.98)	0.0299	0.76 (0.59,0.98)	0.0366
rs3749096	EDAR	2	109512428	1.3 (1.02,1.66)	0.0341	1.45 (1.03,2.02)	0.0307
rs13418730	WIPF1	2	175540594	0.71 (0.51,0.98)	0.0392	0.62 (0.39,0.99)	0.0434
rs7583875	AP1S3	2	224665694	0.83 (0.7,0.98)	0.0273	0.76 (0.6,0.97)	0.0262
rs115435003	TRIP12	2	230629658	0.48 (0.25,0.93)	0.0300	0.34 (0.12,0.96)	0.0408
JHU_3.18396523	SATB1	3	18396524	0.33 (0.17,0.65)	0.0012	0.37 (0.14,0.97)	0.0429
rs80069959	KCNH8	3	19223049	0.6 (0.37,0.97)	0.0366	0.53 (0.29,0.98)	0.0431
JHU_3.119275362	CD80	3	119275363	0.56 (0.35,0.88)	0.0115	0.48 (0.25,0.91)	0.0258
rs953239	TRPC1	3	142446205	1.2 (1.01,1.43)	0.0351	1.29 (1.02,1.63)	0.0359
rs7623154	PIK3CA	3	178921158	1.22 (1.01,1.48)	0.0406	1.31 (1,1.72)	0.0490
JHU_5.16912953	MYO10	5	16912954	2.01 (1,4.02)	0.0486	2.82 (1.07,7.42)	0.0361
JHU_5.35873123	IL7R	5	35873124	0.64 (0.42,0.98)	0.0382	0.52 (0.29,0.95)	0.0320
rs7726469	CAMK4	5	110586438	0.79 (0.64,0.96)	0.0202	0.72 (0.53,0.96)	0.0248
rs12153148	KLHL3	5	136964764	0.74 (0.6,0.92)	0.0056	0.72 (0.53,0.98)	0.0374
rs3777376	KLHL3	5	136965249	0.75 (0.6,0.93)	0.0086	0.68 (0.49,0.94)	0.0206
rs7774142	LY86	6	6642058	1.27 (1.06,1.52)	0.0106	1.33 (1.03,1.73)	0.0308
exm-rs3827784	LY86	6	6642405	1.28 (1.07,1.54)	0.0075	1.34 (1.03,1.73)	0.0299
JHU_6.137043810	MAP3K5	6	137043811	1.97 (1,3.87)	0.0497	3.11 (1.03,9.32)	0.0433
rs56247201	PARK2	6	162702092	0.52 (0.31,0.85)	0.0091	0.47 (0.24,0.91)	0.0259
rs35537854	RPS6KA2	6	167072030	0.64 (0.41,0.99)	0.0445	0.56 (0.31,1)	0.0499
JHU_7.30352063	ZNRF2	7	30352064	0.19 (0.04,0.92)	0.0396	0.11 (0.01,0.9)	0.0398
JHU_7.30393775	ZNRF2	7	30393776	0.37 (0.15,0.89)	0.0263	0.17 (0.04,0.76)	0.0212
exm689348	TNFRSF10A	8	23049292	0.78 (0.61,0.99)	0.0413	0.69 (0.49,0.97)	0.0349
rs73241640	NRG1	8	31932616	0.46 (0.26,0.82)	0.0081	0.24 (0.09,0.67)	0.0061
rs11776203	NRG1	8	32419119	0.79 (0.63,0.99)	0.0410	0.71 (0.52,0.98)	0.0343
JHU_8.32431713	NRG1	8	32431714	0.47 (0.23,0.94)	0.0317	0.35 (0.13,0.94)	0.0375
rs1014306	DAPK1	9	90157451	1.35 (1.12,1.61)	0.0013	1.3 (1,1.69)	0.0495
rs12378686	DAPK1	9	90163570	1.28 (1.05,1.56)	0.0149	1.35 (1.01,1.8)	0.0450

JHU_9.90198587	DAPK1	9	90198588	0.6 (0.38,0.95)	0.0297	0.52 (0.29,0.91)	0.0226
rs10995319	PRKG1	10	52762887	1.27 (1.01,1.6)	0.0448	1.41 (1.01,1.97)	0.0466
rs7904024	PRKG1	10	52841790	1.26 (1.05,1.51)	0.0109	1.32 (1.04,1.68)	0.0221
JHU_10.83841723	NRG3	10	83841724	2.27 (1.03,5.03)	0.0432	10.12 (1.23,82.9)	0.0310
rs74153420	BMPR1A	10	88628433	2.12 (1.01,4.44)	0.0478	3.02 (1.14,8.01)	0.0265
JHU_10.123313013	FGFR2	10	123313014	1.36 (1.02,1.82)	0.0375	1.94 (1.21,3.09)	0.0058
rs548142	DYNC2H1	11	103315520	0.73 (0.61,0.87)	0.0006	0.77 (0.6,1)	0.0475
JHU_12.6438144	TNFRSF1A	12	6438145	1.66 (1.09,2.53)	0.0187	2.26 (1.24,4.1)	0.0076
JHU_12.26512936	ITPR2	12	26512937	2.95 (1.09,7.96)	0.0329	4.89 (1,23.86)	0.0497
rs61971164	STK24	13	99190397	0.73 (0.58,0.92)	0.0065	0.72 (0.52,0.99)	0.0433
rs17565502	TNFSF13B	13	108954304	1.21 (1,1.47)	0.0462	1.35 (1.03,1.76)	0.0270
JHU_14.23313974	MMP14	14	23313975	0.59 (0.34,1)	0.0484	0.43 (0.21,0.88)	0.0207
rs78656887	PSMC1	14	90734095	0.58 (0.35,0.96)	0.0347	0.24 (0.08,0.71)	0.0098
rs12441042	TLN2	15	62946064	0.82 (0.68,0.98)	0.0265	0.75 (0.58,0.97)	0.0266
rs75395345	PIAS1	15	68373718	1.25 (1.03,1.52)	0.0253	1.34 (1.02,1.77)	0.0363
rs74318887	MEF2A	15	100229061	0.47 (0.27,0.84)	0.0107	0.44 (0.2,0.99)	0.0483
rs76272325	PSMB6	17	4699845	0.54 (0.34,0.85)	0.0080	0.43 (0.21,0.88)	0.0209
JHU_17.5413392	NLRP1	17	5413393	0.82 (0.68,0.99)	0.0388	0.74 (0.56,0.97)	0.0291
JHU_17.40648111	ATP6V0A1	17	40648112	1.82 (1.24,2.67)	0.0024	1.8 (1.02,3.18)	0.0435
rs12949223	CD300LD	17	72589264	1.21 (1.01,1.46)	0.0433	1.3 (1,1.69)	0.0495
JHU_18.21773860	OSBPL1A	18	21773861	2.78 (1.26,6.14)	0.0117	2.73 (1.01,7.36)	0.0476
rs11082490	SIGLEC15	18	43412628	1.59 (1.27,2.01)	0.0001	1.42 (1.03,1.94)	0.0297
rs58993112	MALT1	18	56412784	1.31 (1.04,1.66)	0.0246	1.45 (1.03,2.05)	0.0336
exm2253611	PDE4A	19	10546771	1.23 (1.03,1.47)	0.0204	1.3 (1,1.69)	0.0478
rs9676881	KEAP1	19	10596780	1.32 (1.11,1.58)	0.0021	1.31 (1.01,1.71)	0.0413
rs2898449	MX1	21	42814495	0.72 (0.54,0.97)	0.0331	0.62 (0.41,0.94)	0.0231

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

Supplemental Table 6. Histology-specific effects of validated, consistent context dependent SNPs in cases and controls with COPD.

			Adenocarcinoma		Squamous cell	
Name	Gene	Chr	OR (95% CI)	p-val	OR (95% CI)	p-val
rs2901600	DNM3	1	0.77 (0.63,0.95)	0.0158	0.66 (0.50,0.87)	0.0029
JHU_2.70774695	TGFA	2	4.99 (1.93,12.90)	0.0009	5.63 (1.80,17.57)	0.0029
rs10932427	ERBB4	2	0.59 (0.40,0.85)	0.0049	0.62 (0.39,0.98)	0.0422
rs7570061	INPP5D	2	0.70 (0.55,0.89)	0.0033	0.69 (0.50,0.94)	0.0190
rs79048756	CD96	3	0.53 (0.29,0.95)	0.0336	0.21 (0.07,0.62)	0.0051
rs61505577	BMPR1B	4	2.32 (1.30,4.16)	0.0046	2.88 (1.35,6.10)	0.0059
JHU_6.117021274	KPNA5	6	0.46 (0.25,0.85)	0.0127	0.46 (0.20,1.08)	0.0743
6:125369362-CT	RNF217	6	0.30 (0.10,0.92)	0.0353	0.41 (0.11,1.54)	0.1860
rs73783372	PARK2	6	2.61 (1.48,4.61)	0.0009	2.40 (1.22,4.72)	0.0112
JHU_8.71282810	NCOA2	8	0.05 (0.01,0.47)	0.0088	0.58 (0.19,1.80)	0.3454
rs4745646	TJP2	9	1.58 (1.18,2.10)	0.0020	1.62 (1.13,2.31)	0.0081
rs3793727	PRKCQ	10	1.48 (1.17,1.89)	0.0013	1.54 (1.13,2.10)	0.0060
rs658230	PRKCQ	10	1.23 (1.00,1.53)	0.0543	1.47 (1.11,1.95)	0.0076
rs12252698	PRKG1	10	0.79 (0.59,1.05)	0.1041	0.60 (0.40,0.88)	0.0098
rs1937701	PRKG1	10	0.70 (0.55,0.90)	0.0046	0.58 (0.42,0.80)	0.0008
JHU_10.75843193	VCL	10	0.36 (0.18,0.71)	0.0030	0.60 (0.28,1.28)	0.1871
rs666432	TRIM29	11	1.60 (1.18,2.17)	0.0025	1.12 (0.75,1.69)	0.5681
rs4411364	TNFRSF19	13	1.40 (1.05,1.86)	0.0204	1.26 (0.87,1.83)	0.2129
rs9510787	TNFRSF19	13	1.40 (1.05,1.86)	0.0204	1.26 (0.87,1.83)	0.2129
rs1630	TNFRSF19	13	1.43 (1.13,1.80)	0.0026	1.61 (1.21,2.14)	0.0010
rs17446928	FOXO1	13	0.36 (0.21,0.63)	0.0003	0.52 (0.27,0.98)	0.0444
rs2071501	CSK	15	0.60 (0.38,0.94)	0.0255	0.38 (0.19,0.74)	0.0046
JHU_16.4014963	ADCY9	16	1.40 (1.09,1.79)	0.0079	1.53 (1.11,2.10)	0.0088
rs933392	ADCY9	16	1.28 (0.99,1.64)	0.0582	1.51 (1.10,2.08)	0.0118
exm1358199	UBE2O	17	1.24 (0.99,1.56)	0.0660	1.77 (1.32,2.38)	0.0001
JHU_18.49961949	DCC	18	0.72 (0.54,0.97)	0.0328	0.65 (0.44,0.96)	0.0302
rs10414006	SPTBN4	19	0.67 (0.51,0.88)	0.0040	0.59 (0.41,0.85)	0.0040
rs11879349	NLRP4	19	0.50 (0.35,0.71)	0.0001	0.72 (0.47,1.09)	0.1152
exm2262720	PAK3	23	0.75 (0.55,1.01)	0.0572	0.72 (0.49,1.04)	0.0766

Supplemental Table 7. Histology-specific effects of validated, consistent context dependent SNPs in cases and controls without COPD.

			Adenocarcinoma		Squamous cell	
Name	Gene	Chr	OR (95% CI)	p-val	OR (95% CI)	p-val
JHU_1.108497389	VAV3	1	0.68 (0.53,0.87)	0.0026	0.84 (0.56,1.25)	0.3903
exm113346	SPTA1	1	6.75 (2.34,19.46)	0.0004	9.72 (2.29,41.31)	0.0021
rs3749096	EDAR	2	1.16 (0.92,1.46)	0.2146	1.62 (1.12,2.35)	0.0101
rs13418730	WIPF1	2	0.71 (0.52,0.96)	0.0270	0.35 (0.17,0.72)	0.0042
JHU_3.119275362	CD80	3	0.58 (0.38,0.90)	0.0136	0.36 (0.15,0.89)	0.0264
rs953239	TRPC1	3	1.14 (0.98,1.33)	0.0975	1.39 (1.05,1.83)	0.0212
rs7623154	PIK3CA	3	1.30 (1.08,1.55)	0.0045	1.30 (0.96,1.75)	0.0859
JHU_5.16912953	MYO10	5	2.47 (1.33,4.57)	0.0040	2.60 (1.05,6.45)	0.0394
rs7726469	CAMK4	5	0.78 (0.64,0.94)	0.0105	0.72 (0.52,1.00)	0.0476
rs3777376	KLHL3	5	0.83 (0.68,1.01)	0.0614	0.60 (0.41,0.89)	0.0103
rs7774142	LY86	6	1.25 (1.06,1.48)	0.0086	1.37 (1.02,1.83)	0.0347
exm-rs3827784	LY86	6	1.25 (1.06,1.48)	0.0088	1.35 (1.01,1.81)	0.0454
JHU_6.137043810	MAP3K5	6	2.15 (1.13,4.08)	0.0189	2.69 (1.09,6.64)	0.0315
JHU_7.30352063	ZNRF2	7	0.09 (0.01,0.72)	0.0224	--	--
rs73241640	NRG1	8	0.26 (0.13,0.52)	0.0001	0.78 (0.33,1.84)	0.5725
rs11776203	NRG1	8	0.74 (0.60,0.92)	0.0063	0.92 (0.64,1.32)	0.6435
rs7904024	PRKG1	10	1.30 (1.10,1.53)	0.0019	1.18 (0.89,1.58)	0.2503
JHU_10.123313013	FGFR2	10	1.59 (1.21,2.09)	0.0010	1.49 (0.96,2.30)	0.0742
rs548142	DYNC2H1	11	0.76 (0.64,0.90)	0.0014	0.73 (0.55,0.97)	0.0317
JHU_12.6438144	TNFRSF1A	12	1.80 (1.23,2.63)	0.0024	1.55 (0.84,2.85)	0.1623
JHU_12.26512936	ITPR2	12	2.71 (1.06,6.93)	0.0369	1.77 (0.39,8.01)	0.4601
JHU_14.23313974	MMP14	14	0.61 (0.37,0.99)	0.0447	0.41 (0.17,1.00)	0.0501
rs78656887	PSMC1	14	0.60 (0.37,0.99)	0.0440	0.37 (0.14,1.01)	0.0524
rs74318887	MEF2A	15	0.48 (0.28,0.83)	0.0081	0.37 (0.14,1.00)	0.0511
JHU_17.40648111	ATP6V0A1	17	1.88 (1.32,2.67)	0.0005	1.57 (0.85,2.92)	0.1518
rs11082490	SIGLEC15	18	1.47 (1.20,1.81)	0.0003	1.81 (1.30,2.52)	0.0005
exm2253611	PDE4A	19	1.28 (1.08,1.51)	0.0037	1.25 (0.95,1.66)	0.1172
rs9676881	KEAP1	19	1.32 (1.12,1.56)	0.0009	1.24 (0.93,1.66)	0.1348