Identification of susceptibility pathways for the role of chromosome 15q25.1 in modifying lung cancer risk

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Supplementary table 1. Participant characteristics for the eQTL study

Variants	All participants (n = 420)	
	No.	%
Age (years)	63.4± 10.0	
Gender		
Male	235	55.95
Female	185	44.05
Smoking Status		
Never	37	8.81
Ever	383	91.19
Histology		
Squamous	240	57.14
Adenocarcinoma	108	25.72
Other	72	17.14

Supplementary table 2. Pathways and GO terms in sensitivity analysis for pathway enrichment with threshold of FDR < 0.25 in either phase of discovery and replication

		Enrichment with actual P values of the candidate SNPs alone				Enrichment with using the observed P values of the candidate SNPs and setting the P values of the index SNPs to 0.01			
		Meta-analysis of Discovery Cohorts		Replication Cohort		Meta-analysis of Discovery		Replication Cohort	
Source	Pathway/Gene set name	P-value	FDR	P-value	FDR	P-value	FDR	P-value	FDR
KEGG	neuroactive ligand receptor interaction					0.004	0.024		
Reactome	neuronal system					0.004	0.09		
	transmission across chemical synapses					0.018	0.086		
	immune system	0.021	0.1245			0.044	0.139		
	transmembrane transport of small molecules	0.016	0.214			0.017	0.111		
	gpcr downstream signaling							0.039	0.217
Gene Oncology	substrate specific channel activity					0.002	0.025	0.004	0.017
	ion channel activity					0.002	0.025	0.004	0.017
	gated channel activity					0.016	0.024	0.003	0.052
	cation channel activity					0.009	0.022	0.003	0.032
	ion transmembrane transporter activity					0.005	0.019	0.024	0.057
	metal ion transmembrane transporter activity					0.003	0.019	0.007	0.023
	transmembrane transporter activity					0.002	0.012	0.04	0.071
	substrate specific transmembrane transporter activity					0.002	0.015	0.036	0.073
	cation transmembrane transporter activity					0.004	0.013	0.014	0.041
	transmembrane receptor activity			0.022	0.24	0.01	0.022	0.002	0.021
	receptor activity					0.042	0.075	0.01	0.038
	protein complex					0.003	0.058	0.046	0.191
	intrinsic to membrane	0.045	0.184			0.018	0.087	0.039	0.227
	membrane part					0.019	0.064	0.042	0.196
	substrate specific transporter activity					0.004	0.012		
	macromolecular complex					0.003	0.039		
	intrinsic to plasma membrane					0.014	0.073		
	integral to membrane	0.037	0.1904			0.013	0.098		
	membrane					0.02	0.081		
	plasma membrane part					0.024	0.083		
	integral to plasma membrane					0.009	0.07		

	intracellular organelle part	0.042	0.227			0.038	0.082		
	organelle part	0.042	0.227			0.038	0.082		
	phosphotransferase activity alcohol group as acceptor			0.036	0.19			0.049	0.072
	protein kinase activity							0.033	0.068
canonical pathways	mark signaling pathway			0.042	0.08			0.03	0.07

Supplementary table 3. Pathways and GO terms in discovery and replication with threshold of P value < 0.05 in both phase using GSA-SNP2

	Pathway/Gene set name	Meta-analysis of Discovery Cohorts p-value	Replication Cohort p-value
KEGG	neuroactive ligand receptor interaction	4.71E-06	5.11E-08
Reactome	neurotransmitter receptor binding and downstream transmission in the postsynaptic cell	1.51E-05	4.39E-11
	transmission across chemical synapses	3.45E-04	8.87E-09
	adaptive immune system	3.92E-02	4.08E-03
	l1cam interactions	4.82E-02	1.59E-02
Gene Oncology	substrate specific transporter activity	1.36E-06	1.11E-04
	transmembrane transporter activity	3.12E-06	6.17E-05
	cation transmembrane transporter activity	3.13E-06	4.22E-07
	substrate specific transmembrane transporter activity	5.77E-06	1.15E-05
	ion transmembrane transporter activity	1.21E-05	3.16E-06
	cation channel activity	2.23E-05	4.94E-10
	metal ion transmembrane transporter activity	4.15E-05	8.36E-09
	ion channel activity	7.26E-05	6.28E-10
	substrate specific channel activity	7.26E-05	6.28E-10
	gated channel activity	1.46E-04	1.13E-10
	transmembrane receptor activity	2.78E-03	1.31E-07
	receptor activity	1.11E-02	1.50E-06
	voltage gated cation channel activity	2.74E-02	9.57E-04
	voltage gated channel activity	2.74E-02	9.57E-04
	receptor complex	6.35E-04	5.32E-11
	integral to membrane	1.22E-03	1.85E-03
	integral to plasma membrane	1.45E-03	7.55E-04
	intrinsic to membrane	1.57E-03	1.88E-03
	intrinsic to plasma membrane	1.95E-03	7.90E-04
	membrane part	2.17E-03	6.56E-03
	plasma membrane part	3.35E-03	5.74E-04
	protein complex	9.28E-03	2.13E-04
	macromolecular complex	1.90E-02	1.36E-03
	plasma membrane	2.36E-02	3.65E-03
	membrane	2.51E-02	1.54E-02

Supplementary table 4. Functional annotation of eQTL study results for our susceptibility GWAS GO terms

		Analysis with genes in chromosome 15q25.1 and its related genes	Analysis with the related genes alone
Category	GO Term	*P* -value	*P* -value
GO:0022836	gated channel activity	0.029	0.088
GO:0005216	ion channel activity	0.071	0.17
GO:0005261	cation channel activity	0.073	0.2
GO:0022838	substrate-specific channel activity	0.08	0.186
GO:0008324	cation transmembrane transporter activity	0.098	0.199
GO:0015075	ion transmembrane transporter activity	0.128	0.229
GO:0022891	substrate-specific transmembrane transporter activity	0.221	0.348
GO:0022857	transmembrane transporter activity	0.282	0.42
GO:0005886	plasma membrane	0.354	0.391
GO:0022892	substrate-specific transporter activity	0.37	0.514
GO:0046873	metal ion transmembrane transporter activity	0.371	0.358
GO:0005887	integral to plasma membrane	0.59	0.708
GO:0031226	intrinsic to plasma membrane	0.636	0.747
GO:0004888	transmembrane signaling receptor activity	0.676	0.798
GO:0044459	plasma membrane part	0.695	0.77
GO:0004872	receptor activity	0.775	0.862
GO:0031224	intrinsic to membrane	0.852	0.872
GO:0016020	membrane	0.865	0.866
GO:0016021	integral to membrane	0.876	0.895
GO:0044425	membrane part	0.961	0.967

Supplementary table 5. Index SNPs in the chromosome 15q25.1 locus which were associated with lung cancer among smokers

SNP	Gene	Predicted function	Position	A1	A2	1st discovery cohort			2nd discovery cohort			Meta-analysis of Discovery Cohorts			Replication Cohort		
						P -value	OR	BONF*	*P* -value	OR	BONF*	*P* -value	OR	BONF*	*P* -value	OR	BONF*
rs1051730	CHRNA3	coding	76681394	T	C	3.10E-14	1.49	1.06E-10	1.19E-11	1.31	4.04E-08	2.05E-23	1.37	6.36E-18	2.71E-52	1.34	9.24E-49
rs8034191	HYKK	intronic	76593078	C	T	2.29E-11	1.42	7.79E-08	1.60E-11	1.30	5.46E-08	5.32E-21	1.34	1.65E-15	3.99E-51	1.33	1.36E-47
rs1996371	CHRNB4	intronic	76743861	G	A	3.34E-11	1.41	1.14E-07	2.96E-04	1.15	1.00E+00	6.77E-12	1.24	2.10E-06	3.12E-24	1.21	1.06E-20
rs6495314	CHRNB4	intronic	76747584	C	A	7.40E-11	1.40	2.52E-07	1.73E-04	1.16	1.00E+00	5.05E-12	1.24	1.57E-06	1.69E-23	1.21	5.76E-20
rs11638372	CHRNB4	intronic	76770614	T	C	8.48E-10	1.37	2.89E-06	4.10E-04	1.15	1.00E+00	8.37E-11	1.22	2.60E-05	3.28E-23	1.20	1.12E-19
rs4887077	CHRNB4	intronic	76765419	T	C	1.15E-09	1.37	3.92E-06	3.97E-04	1.15	5.90E-01	9.96E-11	1.22	3.09E-05	2.93E-23	1.20	9.99E-20
rs2036534	HYKK	3downstream	76614003	C	T	2.02E-09	0.69	6.90E-06	1.22E-04	0.83	4.15E-01	2.46E-11	0.78	7.63E-06	1.69E-33	0.76	5.76E-30
rs6495309	CHRNB4	3downstream	76702300	T	C	3.74E-08	0.71	1.27E-04	3.66E-05	0.82	1.25E-01	3.55E-11	0.78	1.10E-05	5.72E-29	0.78	1.95E-25

**P* -value was adjusted for multiple comparisons using Bonferroni correction.

Supplementary Table 6. Pathways and GO terms for smoking-related lung cancer in the discovery and replication cohorts with threshold of FDR < 0.25

		Meta-analysis of Discovery Cohorts		Replication Cohort	
Source	Pathway/Gene set name	P-value	FDR	P-value	FDR
Kegg	neuroactive ligand receptor interaction	0.004	0.017	< 0.001	0.003
Gene Oncology	receptor activity	0.009	0.078	< 0.001	0.019
	substrate-specific channel activity	0.009	0.098	0.002	0.012
	metal ion transmembrane transporter activity	0.022	0.103	0.002	0.018
	cation transmembrane transporter activity	0.033	0.119	0.005	0.011
	ion channel activity	0.008	0.122	0.002	0.01
	transmembrane transporter activity	0.035	0.133	0.006	0.022
	transmembrane receptor activity	0.001	0.144	0.002	0.015
	cation channel activity	0.006	0.146	0.002	0.011