|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1**. Participant characteristics of lung cancer cases and controls in GWAS cohorts | | | | | | | | | | | | |  |  |  |  |  |  |  |  |  |  |  |
|  | 1st discovery cohort (n = 3900) | | | | |  |  |  | 2nd discovery cohort (n = 6573) | | | | |  |  |  | replication Cohort (n = 32465) | | | |  |  |  |
| Variants | Control  (n = 1977) | |  | Case  (n = 1923) | |  |  |  | Control  (n =3578) | |  | Case  (n = 2995) | |  |  |  | Control  (n = 14026) | |  | Case  (n = 18439) | |  |  |
|  | No. | % |  | No. | % |  | *P*-value |  | No. | % |  | No. | % |  | *P*-value |  | No. | % |  | No. | % |  | *P*-value |
| Age (years) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-64 | 502 | 25.4 |  | 420 | 21.8 |  | 0.009 |  | 2304 | 64.39 |  | 1825 | 60.9 |  | 0.004 |  | 8449 | 60.2 |  | 9513 | 51.6 |  | <0.0001 |
| >=65 | 1475 | 74.6 |  | 1503 | 78.2 |  |  |  | 1274 | 35.61 |  | 1170 | 39.1 |  |  |  | 5577 | 39.8 |  | 8926 | 48.4 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Gender |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Male | 1514 | 76.6 |  | 1520 | 79.0 |  | 0.06 |  | 2417 | 67.55 |  | 2093 | 69.9 |  | 0.04 |  | 8639 | 61.6 |  | 11495 | 62.3 |  | 0.37 |
| Female | 463 | 23.4 |  | 403 | 21.0 |  |  |  | 1161 | 32.45 |  | 902 | 30.1 |  |  |  | 5384 | 38.4 |  | 6941 | 37.6 |  |  |
| Omitted |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3 | 0.02 |  | 3 | 0.02 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Smoking Status |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Never | 633 | 32.0 |  | 138 | 7.1 |  | <0.0001 |  | 867 | 24.23 |  | 137 | 4.6 |  | <0.0001 |  | 4415 | 31.5 |  | 1800 | 9.8 |  | <0.0001 |
| Ever | 1339 | 67.7 |  | 1774 | 92.3 |  |  |  | 2702 | 75.52 |  | 2854 | 95.3 |  |  |  | 9930 | 66.5 |  | 16341 | 88.6 |  |  |
| Omitted | 5 | 0.3 |  | 11 | 0.6 |  |  |  | 9 | 0.25 |  | 4 | 0.1 |  |  |  | 281 | 2.0 |  | 298 | 1.6 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous |  |  |  | 488 | 25.4 |  |  |  |  |  |  | 307 | 10.3 |  |  |  |  |  |  | 4490 | 24.3 |  |  |
| Adenocarcinoma |  |  |  | 788 | 40.9 |  |  |  |  |  |  | 620 | 20.7 |  |  |  |  |  |  | 6819 | 37.0 |  |  |
| Other |  |  |  | 613 | 31.9 |  |  |  |  |  |  | 226 | 7.5 |  |  |  |  |  |  | 5487 | 29.8 |  |  |
| Omitted |  |  |  | 34 | 1.8 |  |  |  |  |  |  | 1842 | 61.5 |  |  |  |  |  |  | 1643 | 8.9 |  |  |

**Table 2.** Index SNPs in the chromosome 15q25.1 locus which were associated with lung cancer with P < 5.00E-8 in the 1st discovery cohort and in meta-analysis of the discovery cohorts

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Gene | Predicted function | A1 | A2 | 1st discovery cohort | |  | 2nd discovery cohort | |  | Meta-analysis of discovery cohorts | |  | replication cohort | |
|  |  |  |
| *P*-value | BONF\* |  | *P*-value | BONF\* |  | *P*-value | BONF\* |  | *P*-value | BONF\* |
| rs1051730 | CHRNA3 | coding | T | C | 2.28E-14 | 7.77E-11 |  | 3.03E-13 | 1.04E-09 |  | 1.64E-25 | 5.09E-20 |  | 3.11E-49 | 1.06E-45 |
| rs1996371 | CHRNB4 | intronic | G | A | 9.08E-12 | 3.10E-08 |  | 1.15E-05 | 3.93E-02 |  | 2.05E-14 | 6.36E-09 |  | 2.83E-24 | 9.65E-21 |
| rs6495314 | CHRNB4 | intronic | C | A | 1.47E-11 | 5.01E-08 |  | 7.29E-06 | 2.49E-02 |  | 1.47E-14 | 4.56E-09 |  | 8.54E-24 | 2.91E-20 |
| rs8034191 | HYKK | intronic | C | T | 3.05E-11 | 1.04E-07 |  | 8.98E-14 | 3.07E-10 |  | 2.40E-23 | 7.45E-18 |  | 2.12E-46 | 7.23E-43 |
| rs11638372 | CHRNB4 | intronic | T | C | 3.14E-10 | 1.07E-06 |  | 2.95E-05 | 1.01E-01 |  | 8.11E-13 | 2.52E-07 |  | 5.28E-24 | 1.80E-20 |
| rs2036534 | HYKK | 3downstream | C | T | 3.81E-10 | 1.30E-06 |  | 4.29E-06 | 1.47E-02 |  | 7.81E-14 | 2.42E-08 |  | 4.85E-32 | 1.65E-28 |
| rs4887077 | CHRNB4 | intronic | T | C | 4.16E-10 | 1.42E-06 |  | 2.39E-05 | 8.17E-02 |  | 7.72E-13 | 2.40E-07 |  | 2.23E-23 | 7.61E-20 |
| rs6495309 | CHRNB4 | 3downstream | T | C | 3.57E-08 | 1.22E-04 |  | 4.29E-06 | 1.47E-02 |  | 2.18E-12 | 6.76E-07 |  | 9.34E-29 | 3.19E-25 |

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

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3**. Pathways and GO terms in discovery and replication with threshold of FDR < 0.25 in both phase | | | |  |  | | |  | |  |  | |
|  |  | Meta-analysis of Discovery Cohorts | | | |  | | Replication Cohort | | | | |
| Source | Pathway/Gene set name | P-value | | | FDR |  | | P-value | | | FDR | |
| KEGG | neuroactive ligand receptor interaction | 0.001 | | | 0.006 |  | | 0.013 | | | 0.042 | |
| Reactome | neuronal system | 0.001 | | | 0.015 |  | | 0.014 | | | 0.082 | |
|  | transmission across chemical synapses | 0.003 | | | 0.023 |  | | 0.003 | | | 0.028 | |
| Gene Oncology | substrate specific channel activity | < 0.001 | | | 0.005 |  | | 0.002 | | | 0.004 | |
|  | ion channel activity | < 0.001 | | | 0.005 |  | | 0.002 | | | 0.004 | |
|  | substrate specific transporter activity | 0.001 | | | 0.006 |  | | 0.010 | | | 0.013 | |
|  | cation channel activity | 0.002 | | | 0.006 |  | | 0.002 | | | 0.008 | |
|  | ion transmembrane transporter activity | 0.002 | | | 0.006 |  | | 0.004 | | | 0.009 | |
|  | metal ion transmembrane transporter activity | 0.001 | | | 0.006 |  | | 0.002 | | | 0.003 | |
|  | transmembrane transporter activity | < 0.001 | | | 0.006 |  | | 0.007 | | | 0.012 | |
|  | gated channel activity | 0.002 | | | 0.006 |  | | 0.001 | | | 0.016 | |
|  | substrate specific transmembrane transporter activity | < 0.001 | | | 0.006 |  | | 0.006 | | | 0.012 | |
|  | cation transmembrane transporter activity | 0.001 | | | 0.006 |  | | 0.003 | | | 0.006 | |
|  | transmembrane receptor activity | 0.001 | | | 0.007 |  | | < 0.001 | | | 0.006 | |
|  | receptor activity | 0.017 | | | 0.021 |  | | 0.002 | | | 0.007 | |
|  | macromolecular complex | 0.001 | | | 0.008 |  | | 0.006 | | | 0.037 | |
|  | protein complex | 0.001 | | | 0.012 |  | | 0.006 | | | 0.080 | |
|  | intrinsic to membrane | 0.003 | | | 0.022 |  | | 0.002 | | | 0.025 | |
|  | intrinsic to plasma membrane | 0.004 | | | 0.024 |  | | 0.002 | | | 0.030 | |
|  | integral to membrane | 0.003 | | | 0.027 |  | | 0.002 | | | 0.027 | |
|  | membrane part | 0.005 | | | 0.028 |  | | 0.013 | | | 0.050 | |
|  | membrane | 0.006 | | | 0.032 |  | | 0.024 | | | 0.071 | |
|  | plasma membrane part | 0.009 | | | 0.032 |  | | 0.005 | | | 0.030 | |
|  | integral to plasma membrane | 0.003 | | | 0.035 |  | | 0.002 | | | 0.051 | |
|  | plasma membrane | 0.015 | | | 0.044 |  | | 0.034 | | | 0.085 | |

|  |
| --- |
| **Table 4**. Functional annotation of eQTL study results for our susceptibility GWAS GO terms with threshold of P value < 0.1 |

|  |  |
| --- | --- |
| GO Term | P-value |
| gated channel activity | 0.029 |
| ion channel activity | 0.071 |
| cation channel activity | 0.073 |
| substrate-specific channel activity | 0.08 |
| cation transmembrane transporter activity | 0.098 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 5**. Individual and combined effects of SNPs from our susceptibility pathways on lung cancer risk in the meta-analysis of Discovery Cohorts | | | | | | | | | | | | | |
|  |  | | Univariate analysis | | | | |  | Multivariate analysis\* | | | | |
|  |  | | OR | L95 | U95 | *P* | *P\_trend* |  | OR | L95 | U95 | *P* | *P\_trend* |
| CHRNA3 |  | |  |  |  |  |  |  |  |  |  |  |  |
| rs1051730 | 0 | | 1 |  |  |  | 1.29E-25 |  |  |  |  |  | 2.68E-24 |
|  | 1 | | 1.31 | 1.21 | 1.43 | 3.46E-10 |  |  | 1.32 | 1.21 | 1.44 | 1.23E-09 |  |
|  | 2 | | 1.86 | 1.65 | 2.09 | 8.80E-25 |  |  | 1.89 | 1.67 | 2.14 | 7.44E-24 |  |
| CHRNB4 |  | |  |  |  |  |  |  |  |  |  |  |  |
| rs6495309 | 0 | | 1 |  |  |  | 2.35E-12 |  |  |  |  |  | 4.56E-11 |
|  | 1 | | 1.22 | 1 | 1.5 | 0.05 |  |  | 1.21 | 0.98 | 1.49 | 0.08 |  |
|  | 2 | | 1.58 | 1.3 | 1.93 | 5.21E-06 |  |  | 1.56 | 1.27 | 1.91 | 2.67E-05 |  |
| KCNJ4 |  | |  |  |  |  |  |  |  |  |  |  |  |
| rs138396 | 0 | | 1 |  |  |  | 0.06 |  |  |  |  |  | 0.04 |
|  | 1 | | 1 | 0.91 | 1.09 | 0.94 |  |  | 1.01 | 0.92 | 1.1 | 0.89 |  |
|  | 2 | | 1.13 | 1.01 | 1.26 | 0.03 |  |  | 1.15 | 1.02 | 1.29 | 0.02 |  |
| SCN2B |  | |  |  |  |  |  |  |  |  |  |  |  |
| rs7944321 | 0 | | 1 |  |  |  | 0.07 |  |  |  |  |  | 0.14 |
|  | 1 | | 1.07 | 0.98 | 1.16 | 0.13 |  |  | 1.06 | 0.97 | 1.15 | 0.19 |  |
|  | 2 | | 1.12 | 0.94 | 1.34 | 0.22 |  |  | 1.09 | 0.91 | 1.32 | 0.35 |  |
| neuroactive ligand receptor interaction pathway | | | | | | | |  |  |  |  |  |  |
| (CHRNA3 rs1051730 and CHRNB4 rs6495309) | | | | | | | |  |  |  |  |  |  |
|  | 0-1 | 1 | |  |  |  | 2.80E-26 |  | 1 |  |  |  | 1.55E-24 |
|  | 2 | 1.32 | | 1.18 | 1.47 | 8.45E-07 |  |  | 1.32 | 1.18 | 1.48 | 1.82E-06 |  |
|  | 3 | 1.48 | | 1.32 | 1.65 | 4.94E-12 |  |  | 1.47 | 1.31 | 1.65 | 6.14E-11 |  |
|  | 4 | 2.04 | | 1.79 | 2.33 | 2.22E-26 |  |  | 2.07 | 1.8 | 2.38 | 4.99E-25 |  |
| gated channel activity term | | | | |  |  |  |  |  |  |  |  |  |
| (CHRNA3 rs1051730, CHRNB4 rs6495309,  KCNJ4 rs138396 and SCN2B rs7944321 ) | | | | | | | | | | | | | |
|  | 0-1 | 1 | |  |  |  | 4.39E-19 |  |  |  |  |  | 2.46E-18 |
|  | 2-3 | 1.29 | | 1.08 | 1.53 | 5.50E-03 |  |  | 1.3 | 1.08 | 1.56 | 5.50E-03 |  |
|  | 4-5 | 1.6 | | 1.34 | 1.9 | 1.84E-07 |  |  | 1.63 | 1.36 | 1.96 | 1.65E-07 |  |
|  | 6-8 | 2.15 | | 1.74 | 2.65 | 9.31E-13 |  |  | 2.17 | 1.74 | 2.7 | 4.01E-12 |  |
| \*Adjusted by age sex smoke status in the Logistic Model | | | | | | | |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 6**. Individual and combined effects of SNPs from our susceptibility pathways on lung cancer risk in Replication Cohort | | | | | | | | | | | | | |
|  |  | Univariate analysis | | | | | |  | Multivariate analysis\* | | | | |
|  |  | OR | L95 | U95 | *P* | | *P\_trend* |  | OR | L95 | U95 | *P* | *P\_trend* |
| CHRNA3 |  |  |  |  |  | |  |  |  |  |  |  |  |
| rs1051730 | 0 | 1 |  |  |  | | 1.70E-51 |  | 1 |  |  |  | 1.82E-44 |
|  | 1 | 1.28 | 1.22 | 1.34 | 3.43E-23 | |  |  | 1.27 | 1.21 | 1.33 | 2.62E-20 |  |
|  | 2 | 1.65 | 1.54 | 1.77 | 2.47E-46 | |  |  | 1.63 | 1.52 | 1.75 | 1.22E-40 |  |
| CHRNB4 |  |  |  |  |  | |  |  |  |  |  |  |  |
| rs6495309 | 0 | 1 |  |  |  | | 1.40E-29 |  | 1 |  |  |  | 1.55E-24 |
|  | 1 | 1.14 | 1.02 | 1.28 | 0.02 | |  |  | 1.12 | 1 | 1.26 | 0.05 |  |
|  | 2 | 1.46 | 1.31 | 1.63 | 1.32E-11 | |  |  | 1.42 | 1.27 | 1.6 | 2.13E-09 |  |
| KCNJ4 |  |  |  |  |  | |  |  |  |  |  |  |  |
| rs138396 | 0 | 1 |  |  |  | | 2.00E-04 |  | 1 |  |  |  | 5.00E-04 |
|  | 1 | 1.06 | 1.01 | 1.11 | 0.03 | |  |  | 1.05 | 1 | 1.11 | 0.08 |  |
|  | 2 | 1.13 | 1.06 | 1.21 | 2.00E-04 | |  |  | 1.13 | 1.06 | 1.21 | 4.00E-04 |  |
| SCN2B |  |  |  |  |  | |  |  |  |  |  |  |  |
| rs7944321 | 0 | 1 |  |  |  | | 8.90E-03 |  | 1 |  |  |  | 0.01 |
|  | 1 | 1.06 | 1.01 | 1.11 | 0.026 | |  |  | 1.05 | 1 | 1.11 | 0.04 |  |
|  | 2 | 1.1 | 0.99 | 1.22 | 0.083 | |  |  | 1.1 | 0.99 | 1.23 | 0.08 |  |
| neuroactive ligand receptor interaction pathway | | | | | |  |  |  |  |  |  |  |  |
| (CHRNA3 rs1051730 and CHRNB4 rs6495309) | | | | | | | |  |  |  |  |  |  |
|  | 0-1 | 1 |  |  |  | | 1.11E-58 |  | 1 |  |  |  | 4.80E-50 |
|  | 2 | 1.21 | 1.14 | 1.28 | 1.79E-09 | |  |  | 1.21 | 1.14 | 1.29 | 2.96E-09 |  |
|  | 3 | 1.44 | 1.36 | 1.54 | 1.44E-30 | |  |  | 1.42 | 1.33 | 1.52 | 2.43E-26 |  |
|  | 4 | 1.77 | 1.64 | 1.91 | 2.65E-49 | |  |  | 1.74 | 1.61 | 1.89 | 3.32E-43 |  |
| gated channel activity term | | |  |  |  | |  |  |  |  |  |  |  |
| (CHRNA3 rs1051730, CHRNB4 rs6495309,  KCNJ4 rs138396 and SCN2B rs7944321 ) | | | | | | | | | |  |  |  |  |
|  | 0-1 | 1 |  |  |  | | 3.36E-44 |  | 1 |  |  |  | 2.09E-37 |
|  | 2-3 | 1.18 | 1.07 | 1.3 | 8.00E-04 | |  |  | 1.15 | 1.04 | 1.28 | 5.40E-03 |  |
|  | 4-5 | 1.51 | 1.37 | 1.67 | 4.89E-17 | |  |  | 1.47 | 1.33 | 1.63 | 7.77E-14 |  |
|  | 6-8 | 1.79 | 1.59 | 2.02 | 2.84E-22 | |  |  | 1.72 | 1.52 | 1.95 | 8.27E-18 |  |
| \*Adjusted by age sex smoke status in the Logistic Model | | | | | | |  |  |  |  |  |  |  |