**Supplemental Table 1.** List of the 121 Known Susceptibility Loci from Published GWAS Studies of LC, COPD, SM and PF Levels (as of December 2016, Supplemental Table 1) [1-32](#_ENREF_1).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Loci**(n = 121) | **Start** | **End** | **Known Association** (LC, COPD, SM and PF) |  **Gene** (n = 260) |
| 1p22.3  | 87595448 | 87634887 | LC  | *AK002179, LOC339524* |
| 1p31.1 | 78413590 | 78444777 | LC | *FUBP* |
| 1p32.3  | 53708040 | 53905693 | SM, COPD  | *LRP8, SLC25A3P1, FLJ40434* |
| 1p35.2  | 29563027 | 31196432 | SM  | *PTPRU, MATN1* |
| 1p36.13 | 17300998 | 17308081 | PF  | *MFAP2*  |
| 1q21.3  | 154377668 | 154441926 | PF  | *IL6R*  |
| 1q23.2  | 159682078 | 159786047 | LC  | *DUSP23, FCRL6, CRP, CRPP1* |
| 1q32.1  | 203148058 | 203155922 | PF  | *CHI3L1*  |
| 1q41  | 218518675 | 219386207 | COPD, PF  | *TGFB2, LYPLAL1*  |
| 1q44  | 244515936 | 244552388 | SM  | *C1orf100* |
| 2p13.3  | 69172363 | 69208112 | LC  | *GKN1, GKN2* |
| 2p16.3  | 48010220 | 48034092 | SM  | *MSH6* |
| 2p21  | 46926348 | 47168994 | SM, COPD  | *SOCS5, MCFD2* |
| 2p24.3  | 15731744 | 15771235 | PF  | *DDX1, RPLP1P5*  |
| 2q13  | 113670547 | 113676458 | PF  | *IL37, HMGN2P23* |
| 2q21.1  | 129274863 | 130697790 | SM, COPD  | *ISCA1P, RPL22P7* |
| 2q23.3  | 152214105 | 152333860 | LC  | *TNFAIP6, RIF1* |
| 2q35  | 218664511 | 218808796 | PF  | *TNS1*  |
| 2q36.3  | 227700670 | 230136057 | COPD, PF  | *RHBDD1, PID1*  |
| 2q37.3  | 239335625 | 240322643 |  PF  | *ASB1, HDAC4, FLJ43879*  |
| 3p22.3  | 32859509 | 32933771 |  PF  | *TRIM71*  |
| 3p24  | 25469833 | 30032809 | LC, COPD, PF  | *RARB, RBMS3*  |
| 3q13.13 | 107241782 | 111371206 | COPD, SM  | *PVRL3, CD96, BBX, ZBED2* |
| 3q24  | 143692166 | 143711210 | LC, SM  | *C3orf58, GM2AP1* |
| 3q26.2  | 168801286 | 168864093 | PF  | *MECOM (EVI1)*  |
| 3q28  | 189349215 | 190369308 | LC, SM  | *TP63, P3H2, IL1RAP* |
| 3q29  | 194789012 | 194991895 | LC  | *C3orf21, XXYLT1* |
| 4p16.1 | 9783257 | 9785633 | LC | *DRD5* |
| 4q22.1  | 89647104 | 89978346 | COPD, PF  | *FAM13A*  |
| 4q24  | 106067841 | 106892828 | COPD, PF  | *INTS12, NPNT, FLJ20184, GSTCD, TET2, RPL6P14*  |
| 4q25  | 107842958 | 107957453 | PF  | *DKK2, RAC1P5*  |
| 4q27  | 122589151 | 122618147 | COPD, SM  | *ANXA5* |
| 4q31 | 145030455 | 145659881 | COPD, PF  | *HHIP, GYPA, KRT18P51, AS1* |
| 5p15.33 | 304290 | 1445543 | LC, SM, PF  | *TERT, CLPTM1L, AHRR, SLC6A3, MIR4457* |
| 5q11.2  | 52084135 | 52249485 | PF  | *ITGA1*  |
| 5q14.3  | 90664540 | 90679149 | SM  | *LOC133789, ARRDC3, AS1, RAB5CP2* |
| 5q15  | 94994019 | 95132071 | PF  | *SPATA9, RHOBTB3*  |
| 5q32  | 145969067 | 148016624 | LC, COPD, PF  | *PPP2R2B, STK32A, DPYSL3, HTR4* |
| 5q33.2  | 155753766 | 156185070 | SM  | *PPIGP1, SGCD* |
| 5q33.3  | 156904311 | 157002831 | COPD, PF  | *ADAM19*  |
| 6p21.2  | 39760772 | 39872653 | PF  | *DAAM2*  |
| 6p21.33 | 31465854 | 33548070 | LC, SM, COPD, PF  | *BTNL2, BAT3, APOM, BAG6, HLA II, MSH5, MICB, LTB, NCR3, AGER,* *PPT2, DQB1, DRA, DRB9/5, AIF1, ZBTB9, BAK1* |
| 6p22.1  | 28317690 | 29365448 | LC, SM | *OR12D2/3, ZKSCAN3, ZNF323, TRNAA, UGC, NOP56P1, RPL13P* |
| 6p22.3  | 21666674 | 22194616 | PF  | *AK026189, LINC00340*  |
| 6p25.1  | 4706392 | 4955778 | SM  | *CDYL* |
| 6q21  | 109169618 | 109295675 | COPD, PF  | *ARMC2*  |
| 6q22.1  | 117609529 | 117891020 | LC, SM  | *ROS1, DCBLD1* |
| 6q23-27 | 153332031 | 153452389 | LC  | *RGS17* |
| 6q24.1  | 142623055 | 142767403 | PF  | *GPR126, ADGRG6*  |
| 6q25.1  | 150464187 | 150571528 | PF  | *PPP1R14C*  |
| 6q27 | 167343003 | 167370077 | LC | *RNASET2* |
| 7p14.3  | 31792631 | 32110980 | SM  | *PDE1C, SLC25A5P5* |
| 7q21.3  | 94023872 | 94060544 | PF  | *COL1A2* |
| 7q31.1  | 108110865 | 109600270 | SM  | *C7orf66, LOC154907, PNPLA8, THAP5, DNAJB9, EIF3IP1* |
| 7q31.31 | 117864711 | 120390387 | SM  | *ANKRD7, KCND2* |
| 7q33  | 137982806 | 138127685 | PF  | *RPS17P12, IMPDH1P3* |
| 8p11.21 | 42552561 | 42623929 | SM  | *CHRNB3, CHRNA6, C8orf40* |
| 8p12 | 31497267 | 32622558 | LC | *NRG1* |
| 8p21.1 | 27317277 | 27402439 | LC | *EPHX2, CHRNA2* |
| 8p22  | 15397595 | 15624158 | PF  | *TUSC3*  |
| 8q11.21 | 50824596 | 51705427 | PF  | *SNTG1*  |
| 9p21.2  | 25676386 | 26892826 | SM  | *TUSC1, CAAP1* |
| 9p21.3 | 21802634 | 21865969 | LC | *MTAP* |
| 9q22.32 | 98205263 | 98270322 | PF  | *PTCH1, LOC100507346*  |
| 9q31.1 | 107543283 | 108159628 | LC | *ABCA1, SLC44A1* |
| 9q34.2  | 136443536 | 136524466 | SM  | *FAM163B, DBH* |
| 10p13  | 12237960 | 12292589 | PF  | *CDC123*  |
| 10p14  | 8096666 | 8117164 | LC  | *GATA3* |
| 10p15.1 | 3818187 | 3827473 | LC  | *KLF6 (BCD1)* |
| 10q22.1 | 73724119 | 73848790 | SM  | *CHST3, SPOCK2* |
| 10q22.3 | 77542518 | 78317126 | COPD, PF  | *C10orf11, ATP5G1P8, SFTPD*  |
| 10q23.31 | 90694830 | 96088148 | LC, COPD, SM | *ACTA2, PLCE1, LOC100188947* |
| 10q24.2 | 99624756 | 99790585 | LC | *CRTAC1* |
| 10q24.3 | 105637317 | 105678045 | LC | *OBFC1* |
| 10q25  | 106034886 | 114578504 | LC, SM, PF  | *GSTO2, VTI1A* |
| 11p13  | 34903842 | 34937939 | PF  | *APIP, EH, NDUFB8P3* |
| 11p14.1 | 27676441 | 27681196 | SM  | *BDNF, AS* |
| 11q12.1 | 57228009 | 57283192 | LC | *RTN4RL2, SLC43A1* |
| 11q23.3 | 118064441 | 118123083 | LC | *MPZL3, AMICA1* |
| 12p11.2 | 32260184 | 32531141 | PF  | *BICD1*  |
| 12p12.3 | 19592607 | 19675173 | PF  | *AEBP2, RPL34P25 , TCP1P3*  |
| 12p13.33 | 1021254 | 1605099 | LC  | *RAD52, ERC1, HTR1DP1* |
| 12q13.3 | 57522281 | 57607125 | PF  | *LRP1*  |
| 12q21.2 | 77415025 | 78606792 | SM  | *E2F7, NAV3* |
| 12q23.1 | 96260825 | 96336428 | PF  | *CCDC38*  |
| 13q12.12 | 24144508 | 24463587 | LC  | *MIPEP, TNFRSF19, MTCO3P2* |
| 13q13.1 | 32889616 | 32973809 | LC | *BRCA2* |
| 13q14  | 51286758 | 51417885 | PF  | *DLEU7*  |
| 13q31.3 | 92050934 | 93519487 | LC  | *GPC5* |
| 14q22.1 | 52471519 | 52535946 | PF  | *NID2*  |
| 14q23.1 | 58030639 | 58618847 | PF  | *SLC35F4, C14orf37, UBA52P3* |
| 14q24.2 | 70510933 | 70655787 | PF  | *SLC8A3*  |
| 15q11.2 | 25068793 | 25223729 | PF  | *SNRPN*  |
| 15q12  | 26788693 | 27018223 | SM  | *LOC503519, MRPS18CP5, GABRB3* |
| 15q15.2 | 43524792 | 43559055 | LC  | *TGM5* |
| 15q21.1 | 47476402 | 48066420 | LC | *SEMA6D, SECISBP2L* |
| 15q23  | 70340129 | 72075722 | COPD, PF  | *THSD4, TLE3, UACA*  |
| 15q25.1 | 78730517 | 78933587 | LC, COPD, SM, PF  | *CHRNA3/5, PSMA4, CHRNB4, AGPHD1, IREB2* |
| 15q26.1 | 92937139 | 93199031 | PF  | *FLJ32831, C15orf32, FAM174B, ST8SIA2* |
| 16p13.3 | 8619501 | 8622226 | SM  | *RPS26P51, TMEM114* |
| 16q12  | 53737874 | 54148379 | PF  | *FTO* |
| 16q13  | 58059281 | 58080804 | PF  | *MMP15*  |
| 16q21  | 58059281 | 62070739 | PF  | *CDH8, RPS15AP34, MMP15*  |
| 16q23.1 | 75327607 | 79246564 | COPD, PF  | *WWOX, CFDP1*  |
| 17p12  | 15207128 | 15370925 | PF  | *CDRT4, TEKT3, RPL9P2* |
| 17p13.2 | 6944948 | 6947242 | LC  | *SLC16A11, P53* |
| 17q12  | 34340095 | 34398841 | PF  | *CCL23/18* |
| 17q24.2 | 65373396 | 65980494 | LC, PF  | *BPTF, PITPNC1* |
| 18p11.3 | 6941742 | 7117813 | LC  | *LAMA1* |
| 18q11.2 | 20715726 | 20840434 | SM  | *CABLES1* |
| 18q12.1 | 65373396 | 65693379 | PF  | *PITPNC1* |
| 19p12  | 20011721 | 20046382 | SM  | *ZNF505/93* |
| 19q13.2 | 41281281 | 41388657 | LC, COPD, SM, PF  | *RAB4B/D, EGLN2, MIA, CYP2A6/7* |
| 20q13.2 | 52769987 | 52790516 | LC  | *CYP24A1* |
| 20q13.33 | 62289162 | 62327606 | LC | *RTEL1* |
| 21q22.11 | 35552977 | 35743440 | PF  | *KCNE2, LINC00310* |
| 21q22.13 | 37757688 | 37789125 | PF  | *CHAF1B, PSMD4P1* |
| 21q22.3 | 46494492 | 46646478 | PF  | *ADARB1*  |
| 22q12.1 | 29083730 | 29137822 | LC | *CHEK2* |
| 22q12.2 | 30279157 | 30426857 | LC  | *MTMR3* |
| Xq23  | 115301957 | 115306225 | PF  | *AGTR2*  |

**Abbreviations:** LC, lung cancer; COPD, chronic obstructive pulmonary disease; SM, smoking behavior; PF, pulmonary function.

**Supplemental Table 2.** Characteristics of the Multiple-Candidates-Carriers in the Discovery

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subject** | **Age, y** | **Sex** | **Smoking PY** | **Histology** |  **Candidate SNVs \*** |
| **Cases (n = 13)** | mean 65 | 69% M | mean 41 | 69% Adenocarcinoma |  |
| F1 (familial) | 70 | F | 15 | Other | *RTEL1* Gln397Glu *- BDNF* Thr2Ile |
| F2 (familial) | 58 | M | 45 | Adenocarcinoma | *LAMA1* Gly1227Arg *- BRCA2* Tyr42Cys |
| S1 (sporadic) | 65 | M | 50 | Adenocarcinoma | ***BRD9* Splice acceptor** - *SNTG1* Splice donor |
| S2 (sporadic) | 58 | M | 0 | Adenocarcinoma | *IFIT3* Leu390Arg – *DZIP3* Gly67Cys  |
| S3 (sporadic) | 80 | F | 31 | Squamous | *SNTG1* Splice donor - *DZIP3* Pro990Leu - *DAAM2* Arg172His |
| S4 (sporadic) | 61 | M | 50 | Adenocarcinoma | ***ZNF93* Gly337Glu** - ***BRD9* Splice acceptor** |
| S5 (sporadic) | 53 | F | 81 | Adenocarcinoma | *DRD5* Cys335X *- SAPCD1* Gln76X  |
| S6 (sporadic) | 68 | M | 35 | Other | *SNTG1* Val121Leu - *SLC12A7* Splice donor  |
| S7 (sporadic) | 57 | M | 88 | Adenocarcinoma | *IFIT3* Leu390Arg - *CCDC147* Arg696Cys |
| S8 (sporadic) | 60 | M | 30 | Adenocarcinoma | ***ZNF93* Gly337Glu** - Lys388Asn - *DPPA2* Ala157Ser - *RTEL1* Gln397Glu |
| S9 (sporadic) | 55 | M | 45 | Adenocarcinoma | ***ZNF93* Gly337Glu** - Lys388Asn |
| S10 (sporadic)  | 85 | M | 45 | Squamous | ***ZNF93* Gly337Glu** - Lys388Asn |
| S11 (sporadic) | 69 | F | 15 | Adenocarcinoma | *CEP55* Glu321Lys - *ITPRIP* Asp236Tyr |
| **Controls (n = 8)** | mean 64 | 63% M | mean 55 |  |  |
| C1  | 65 | M | 74 | - | *DAAM2* Arg172His - *DUSP23* Cys95Ser  |
| C2  | 61 | M | 45 | - | ***DAAM2* Asp762Gly** - *COL4A3* Pro1109Ser  |
| C3  | 58 | M | 76 | - | ***DAAM2* Asp762Gly** - *ZCWPW2* Asn23Ser  |
| C4  | 62 | F | 67 | - | *DAAM2* Pro555Leu - *DRD5* Met75Thr |
| C5  | 65 | F | 45 | - | ***DAAM2* Asp762Gly** - *PLCE1* Thr467Ile - *ADAMTS18* Arg1053Trp |
| C6  | 58 | F | 53 | - | ***DAAM2* Asp762Gly** *- BRCA2* Tyr42Cys |
| C7  | 80 | M | 45 | - | *COL4A3* Pro1109Ser- *RTEL1* Met652Thr |
| C8  | 59 | M | 41 | - | *ADAMTS18* Arg1053Trp - *CCDC113* Lys100Asn |

Abbreviations: LC, lung cancer; SNVs, Single nucleotide variants; F, female; M, male; PY, pack-years.

\* The top validated candidates are bolded.

**Reference for Supplemental Table 1**

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