**Supplementary tables**

Table S1. Paired primers of 14 significantly differentiated SNVs for sequenom massarray genotyping from whole exome sequencing results

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TERM | SNP\_ID | 2nd-PCRP | 1st-PCRP | AMP\_LEN | UEP\_DIR | UEP\_MASS | UEP\_SEQ | EXT1\_CALL | EXT1\_MASS | EXT1\_SEQ | EXT2\_CALL | EXT2\_MASS | EXT2\_SEQ | |
| iPLEX | **rs4926472** | ACGTTGGATGATGAGCACTCGCCTCACAAC | ACGTTGGATGTGGTCAGAAGGCCGTACCCA | 130 | F | 4553 | ATGTTCCCCGGAAGC | C | 4800.2 | ATGTTCCCCGGAAGCC | T | 4880.1 | | ATGTTCCCCGGAAGCT |
| iPLEX | **rs1034268** | ACGTTGGATGGACGTGTTGCTTTTTTAGGG | ACGTTGGATGAAGCCCCCCAAAAAACCATC | 122 | F | 7722.1 | GAAGAATTCATCATCAGGTAGTAAA | A | 7993.3 | GAAGAATTCATCATCAGGTAGTAAAA | G | 8009.3 | | GAAGAATTCATCATCAGGTAGTAAAG |
| iPLEX | **rs10783071** | ACGTTGGATGAACGCGCCTGGCCAAATATG | ACGTTGGATGTTTCAACGTCCTGTGGATGC | 167 | R | 6416.2 | AAGACATACATACAGGCAACT | C | 6703.4 | AAGACATACATACAGGCAACTG | A | 6743.3 | | AAGACATACATACAGGCAACTT |
| iPLEX | **rs10747493** | ACGTTGGATGCATGGTTAAGAGATAATATG | ACGTTGGATGAAGCATTACCTGTGTGACGC | 132 | F | 7137.7 | GAAAATGAAGAATGAATGCATAC | C | 7384.9 | GAAAATGAAGAATGAATGCATACC | T | 7464.8 | | GAAAATGAAGAATGAATGCATACT |
| iPLEX | **rs2275558** | ACGTTGGATGTGTCTCCAATGTCCTGCTTC | ACGTTGGATGGCTGATGCATTCCCATGCTG | 139 | R | 5589.6 | GCAAGTGCTGGGACAGGC | G | 5836.8 | GCAAGTGCTGGGACAGGCC | A | 5916.7 | | GCAAGTGCTGGGACAGGCT |
| iPLEX | rs10913157 | ACGTTGGATGGTGGTGGAAAAGAGGATAGC | ACGTTGGATGTAGCTCTATACTGGGAAGCG | 105 | F | 5541.6 | cAACTGAATGGACAGCAG | A | 5812.8 | cAACTGAATGGACAGCAGA | G | 5828.8 | | cAACTGAATGGACAGCAGG |
| iPLEX | rs20558 | ACGTTGGATGTCTCTGTCTTCCTGCCTTAG | ACGTTGGATGCGTGAGGCAAACATTCACAC | 124 | F | 5154.4 | AGCCTGCAATTGCAATC | C | 5401.6 | AGCCTGCAATTGCAATCC | T | 5481.5 | | AGCCTGCAATTGCAATCT |
| iPLEX | rs2274064 | ACGTTGGATGGCAGAAGCTATATGAGCCAG | ACGTTGGATGCCTTGCCTAGGTAATCCTTC | 121 | R | 5162.4 | ccTGATCCCTGTGGGCA | T | 5433.6 | ccTGATCCCTGTGGGCAA | C | 5449.6 | | ccTGATCCCTGTGGGCAG |
| iPLEX | rs9425343 | ACGTTGGATGTGAAGAACAACCATCCTCTG | ACGTTGGATGCAGAAGACTCTTGATCAACC | 121 | R | 8118.3 | gggcCAGAATCAGAGTGGTGAACAGA | C | 8405.5 | gggcCAGAATCAGAGTGGTGAACAGAG | A | 8445.4 | | gggcCAGAATCAGAGTGGTGAACAGAT |
| iPLEX | rs12120084 | ACGTTGGATGAAGGTGTACCAAAGCGTGTC | ACGTTGGATGTCACACCCACTGAATCCTAC | 112 | R | 5331.5 | cccCTCCATGGCTCATCC | G | 5578.7 | cccCTCCATGGCTCATCCC | C | 5618.7 | | cccCTCCATGGCTCATCCG |
| iPLEX | **rs2802808** | ACGTTGGATGACCGATGCTACTGCCATTGC | ACGTTGGATGTGGTTGTAGTAGTTGTGGCG | 135 | F | 4441.9 | CGCACCTACCACCAT | C | 4689.1 | CGCACCTACCACCATC | G | 4729.1 | | CGCACCTACCACCATG |
| iPLEX | **rs2275531** | ACGTTGGATGGAGACACCAGTACTTGATGC | ACGTTGGATGTTCCAGAGTCCACGATTCCC | 139 | F | 5205.4 | tgGCACGGCCACAGAGC | C | 5452.6 | tgGCACGGCCACAGAGCC | T | 5532.5 | | tgGCACGGCCACAGAGCT |
| iPLEX | **rs78622116** | ACGTTGGATGGCTCTGAGGAAAGTACTAGG | ACGTTGGATGACTCTGATACTCTGGGAGTC | 119 | R | 6247.1 | GGCGACTGTGATCAGGAAGG | T | 6518.3 | GGCGACTGTGATCAGGAAGGA | C | 6534.3 | | GGCGACTGTGATCAGGAAGGG |
| iPLEX | rs143981271 | ACGTTGGATGACTCTGATACTCTGGGAGTC | ACGTTGGATGGCTCTGAGGAAAGTACTAGG | 119 | F | 4832.2 | TTCCTGATCACAGTCG | C | 5079.3 | TTCCTGATCACAGTCGC | T | 5159.3 | | TTCCTGATCACAGTCGT |

Table S2. Results of clinical relevance by damaging or probably damaging prediction.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | **Group** | type | Chr | fisher P | mut | Func | Gene | Func | ExAC\_EAS | gnomAD\_exome\_EAS | gnomAD\_genome\_EAS |
| rs77618489 | **high** | SNP | chr4 | 0.0108359 | T/A | exonic | SLC9B1 | stop\_gained | . | 5.96E-05 | 0.0057 |
| rs3927729 | **likeyhigh** | SNP | chr1 | 0.0054775 | C/T | exonic | NOTCH2NL | missense\_variant | 0.4439 | 0.4326 | 0.3506 |
| rs774477802 | **likeyhigh** | InDel | chr11 | 0.0325077 | AGG/A | exonic | MUC6 | frameshift\_variant | 0.0168 | 0.0004 | 0.1399 |
| rs10778257 | **likeyhigh** | SNP | chr12 | 0.0108359 | T/G | exonic | C12orf42 | missense\_variant | 0.531 | 0.4915 | 0.4888 |
| rs545833279 | **likeyhigh** | SNP | chr14 | 0.0197666 | G/C | exonic | AHNAK2 | missense\_variant | 0.0541 | 0.0014 | 0.036 |
| rs879577127 | **likeyhigh** | InDel | chr19 | 0.0325077 | CACCACCCTTACCCAAGGAGGCA/C | exonic | ZNF77 | frameshift\_truncation&splice\_donor\_variant | . | 0.0749 | 0.1716 |
| rs4579578 | **likeyhigh** | SNP | chr9 | 0.0484098 | G/T | exonic | HMCN2 | missense\_variant | . | . | 0.5807 |
| rs2275156 | **likeyhigh** | SNP | chr9 | 0.0197666 | T/G | exonic | MAMDC4 | missense\_variant | 0.8838 | 0.8834 | 0.881 |

Table S3. Top 100 of 4797 significantly differentiated SNVs between cases and controls (P < 0.05)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mut\_type | Chr | Start | End | Share\_num | Mut | Func | Gene | SNV | Fisher P |
| InDel | chr15 | 52681573 | 52681573 | 2/9 | GA/G | intronic | MYO5A | rs67583538 | 1.08E-05 |
| SNP | chr3 | 1.89E+08 | 1.89E+08 | 9/9 | A/T | UTR5 | TP63 | rs28673064 | 1.08E-05 |
| SNP | chr11 | 64110348 | 64110348 | 9/9 | T/G | intronic | CCDC88B | rs11602301 | 2.17E-05 |
| InDel | chr22 | 36744887 | 36744887 | 9/9 | GC/G | intronic | MYH9 | rs548467551 | 2.17E-05 |
| InDel | chr21 | 44118958 | 44118958 | 1/9 | AT/A | intronic | PDE9A | rs371074544 | 3.25E-05 |
| InDel | chr3 | 51422766 | 51422766 | 1/9 | G/GGAGGAT | exonic | MANF | rs782725256 | 3.25E-05 |
| InDel | chr4 | 84234190 | 84234190 | 1/9 | A/AG | intronic | HPSE | rs376213212 | 3.25E-05 |
| SNP | chr1 | 2.47E+08 | 2.47E+08 | 9/9 | T/A | intronic | TFB2M | rs3124131 | 5.41E-05 |
| InDel | chr16 | 84224967 | 84224967 | 1/9 | G/GGCCCGC | exonic | ADAD2 | rs554488585 | 5.41E-05 |
| InDel | chr2 | 37447473 | 37447473 | 1/9 | AT/A | intronic | CEBPZ | . | 5.41E-05 |
| SNP | chr6 | 39832363 | 39832363 | 1/9 | C/A | intronic | DAAM2 | rs2504094 | 5.41E-05 |
| InDel | chr16 | 71805160 | 71805160 | 1/9 | TG/T | intronic | AP1G1 | rs111908998 | 6.50E-05 |
| SNP | chr11 | 1016776 | 1016776 | 1/9 | C/G | exonic | MUC6 | rs33988517 | 0.000119076 |
| InDel | chr12 | 9313518 | 9313518 | 1/9 | AT/A | intronic | PZP | rs200870789 | 0.000119076 |
| SNP | chr14 | 79276733 | 79276733 | 9/9 | C/A | intronic | NRXN3 | rs4133797 | 0.000119076 |
| InDel | chr15 | 69715488 | 69715488 | 1/9 | TC/T | intronic | KIF23 | rs199725995 | 0.000119076 |
| InDel | chr16 | 88762943 | 88762943 | 1/9 | TA/T | UTR3 | RNF166 | rs781077044 | 0.000119076 |
| SNP | chr19 | 3193146 | 3193146 | 9/9 | C/G | intronic | NCLN | rs496342 | 0.000119076 |
| InDel | chr19 | 17894075 | 17894075 | 1/9 | TC/T | intronic | FCHO1 | rs367923594 | 0.000119076 |
| SNP | chr3 | 42202061 | 42202061 | 9/9 | G/T | intronic | TRAK1 | rs4974003 | 0.000119076 |
| SNP | chr3 | 1.7E+08 | 1.7E+08 | 9/9 | T/A | upstream | LRRIQ4 | rs7628572 | 0.000119076 |
| SNP | chr4 | 39187522 | 39187522 | 9/9 | G/T | intronic | WDR19 | rs6839511 | 0.000119076 |
| SNP | chr4 | 1.69E+08 | 1.69E+08 | 9/9 | A/G | intronic | DDX60L | rs6840397 | 0.000119076 |
| InDel | chr4 | 1.7E+08 | 1.7E+08 | 1/9 | T/TA | intronic | NEK1 | rs141863651 | 0.000119076 |
| InDel | chr6 | 17102600 | 17102600 | 1/9 | A/ACAG | intronic | STMND1 | . | 0.000119076 |
| SNP | chr6 | 36944495 | 36944495 | 9/9 | A/G | intronic | MTCH1 | rs708007 | 0.000119076 |
| InDel | chr4 | 1.7E+08 | 1.7E+08 | 1/9 | TG/T | intronic | NEK1 | rs370525243 | 0.000184026 |
| SNP | chr1 | 86046561 | 86046561 | 9/9 | C/A | UTR5 | CYR61 | rs2297140 | 0.000216502 |
| SNP | chr6 | 90432584 | 90432584 | 9/9 | A/T | intronic | MDN1 | rs2016744 | 0.000227327 |
| InDel | chr20 | 18446024 | 18446024 | 1/9 | C/CTA | splicing | DZANK1 | rs771701870 | 0.000238152 |
| InDel | chr18 | 51880587 | 51880587 | 2/9 | AT/A | intronic | STARD6 | rs141426557 | 0.000324753 |
| SNP | chr1 | 2.38E+08 | 2.38E+08 | 8/9 | T/C | intronic | RYR2 | rs571092 | 0.000335578 |
| InDel | chr11 | 639374 | 639374 | 1/9 | GC/G | intronic | DRD4 | rs745361642 | 0.000411353 |
| InDel | chr2 | 1.29E+08 | 1.29E+08 | 1/9 | GA/G | intronic | POLR2D | rs34858843 | 0.000411353 |
| SNP | chr4 | 54876132 | 54876132 | 9/9 | C/A | UTR3 | CHIC2 | rs4437313 | 0.000411353 |
| SNP | chr3 | 1.83E+08 | 1.83E+08 | 7/9 | G/A | exonic | YEATS2 | rs262993 | 0.000443829 |
| InDel | chr3 | 1.83E+08 | 1.83E+08 | 7/9 | ATGT/A | intronic | YEATS2 | rs375913473 | 0.000443829 |
| SNP | chr10 | 11784978 | 11784978 | 9/9 | C/T | intronic | ECHDC3 | rs7076220 | 0.000508779 |
| SNP | chr10 | 11805354 | 11805354 | 9/9 | A/G | exonic | ECHDC3 | rs12258196 | 0.000508779 |
| SNP | chr10 | 11805357 | 11805357 | 9/9 | G/A | exonic | ECHDC3 | rs10906011 | 0.000508779 |
| InDel | chr17 | 4725799 | 4725799 | 1/9 | AG/A | intronic | PLD2 | rs368510753 | 0.000508779 |
| InDel | chr2 | 44101537 | 44101537 | 8/9 | A/AT | intronic | ABCG8 | rs138296512 | 0.000552079 |
| SNP | chr3 | 1.84E+08 | 1.84E+08 | 6/9 | T/C | ncRNA\_exonic | YEATS2-AS1 | rs263031 | 0.000552079 |
| SNP | chr6 | 71547371 | 71547371 | 8/9 | C/T | intronic | SMAP1 | rs12199707 | 0.000552079 |
| SNP | chr11 | 13399791 | 13399791 | 8/9 | A/G | intronic | ARNTL | rs10832030 | 0.000703631 |
| InDel | chr20 | 43374840 | 43374840 | 9/9 | GC/G | ncRNA\_exonic | KCNK15-AS1 | rs3834659 | 0.000703631 |
| InDel | chr5 | 42718427 | 42718427 | 1/9 | G/GT | intronic | GHR | rs3834253 | 0.000703631 |
| SNP | chr1 | 1.12E+08 | 1.12E+08 | 8/10 | T/C | intronic | DRAM2 | rs325917 | 0.000714456 |
| SNP | chr4 | 2341194 | 2341194 | 9/9 | T/C | exonic | ZFYVE28 | rs2071680 | 0.000714456 |
| SNP | chr9 | 1.33E+08 | 1.33E+08 | 9/9 | A/T | intronic | ASS1 | rs543048 | 0.000714456 |
| SNP | chr13 | 32348859 | 32348859 | 4/9 | T/C | intronic | RXFP2 | rs9549049 | 0.000714456 |
| SNP | chr14 | 90738567 | 90738567 | 7/9 | A/G | intronic | PSMC1 | rs4904667 | 0.000714456 |
| SNP | chr15 | 62945250 | 62945250 | 9/9 | G/A | intronic | TLN2 | rs12916083 | 0.000714456 |
| SNP | chr16 | 71419595 | 71419595 | 7/9 | A/G | intronic | CALB2 | rs4327058 | 0.000714456 |
| SNP | chr2 | 2.16E+08 | 2.16E+08 | 1/9 | C/T | UTR5 | ATIC | rs28366034 | 0.000714456 |
| SNP | chr2 | 2.16E+08 | 2.16E+08 | 1/9 | C/T | UTR5 | ATIC | rs28366035 | 0.000714456 |
| SNP | chr21 | 19770734 | 19770734 | 9/9 | G/C | intronic | TMPRSS15 | rs2824805 | 0.000714456 |
| SNP | chr22 | 26897773 | 26897773 | 8/10 | A/G | intronic | TFIP11 | rs4289294 | 0.000714456 |
| SNP | chr3 | 1.91E+08 | 1.91E+08 | 9/9 | A/T | intronic | GMNC | rs1393055 | 0.000714456 |
| SNP | chr4 | 5693112 | 5693112 | 7/9 | C/T | intronic | EVC2 | rs35705473 | 0.000714456 |
| SNP | chr4 | 1.86E+08 | 1.86E+08 | 9/9 | G/A | exonic | PDLIM3 | rs4635850 | 0.000714456 |
| SNP | chr4 | 1.86E+08 | 1.86E+08 | 9/9 | G/A | intronic | PDLIM3 | rs10866276 | 0.000714456 |
| SNP | chr6 | 36949527 | 36949527 | 9/9 | C/T | intronic | MTCH1 | rs2293390 | 0.000714456 |
| InDel | chr6 | 1.1E+08 | 1.1E+08 | 3/9 | C/CT | intronic | FIG4 | rs11459279 | 0.000714456 |
| SNP | chr21 | 43557698 | 43557698 | 2/9 | A/C | exonic | UMODL1 | rs3819142 | 0.000757756 |
| InDel | chr22 | 45813434 | 45813434 | 7/9 | AT/A | intronic | RIBC2 | rs11320557 | 0.000757756 |
| SNP | chr22 | 45821887 | 45821887 | 7/9 | G/A | exonic | RIBC2 | rs1022477 | 0.000757756 |
| SNP | chr22 | 45822161 | 45822161 | 7/9 | C/G | intronic | RIBC2 | rs5765345 | 0.000757756 |
| SNP | chr22 | 45826880 | 45826880 | 7/9 | G/A | exonic | RIBC2 | rs2072770 | 0.000757756 |
| SNP | chr22 | 45827020 | 45827020 | 7/9 | G/A | intronic | RIBC2 | rs5765352 | 0.000757756 |
| InDel | chr8 | 6264359 | 6264401 | 2/9 | CCTCCCCCGCTGCCTGTCCCACCAAAACCCCCTGCTCCTGCTCT/C | intronic | MCPH1 | rs755701501 | 0.000801057 |
| SNP | chr2 | 1.8E+08 | 1.8E+08 | 7/9 | C/T | intronic | ZNF385B | rs12623873 | 0.000822707 |
| SNP | chr2 | 1.8E+08 | 1.8E+08 | 7/9 | G/A | intronic | ZNF385B | rs2271760 | 0.000822707 |
| SNP | chr21 | 45742115 | 45742115 | 2/9 | G/A | intronic | PFKL | rs2277808 | 0.000822707 |
| SNP | chr21 | 45735995 | 45735995 | 2/9 | T/C | intronic | PFKL | rs2847231 | 0.001017558 |
| SNP | chr1 | 1.12E+08 | 1.12E+08 | 1/9 | G/A | intronic | CEPT1 | rs2243393 | 0.001093334 |
| SNP | chr1 | 1.2E+08 | 1.2E+08 | 4/9 | A/T | intronic | PHGDH | rs627070 | 0.001093334 |
| InDel | chr1 | 2.32E+08 | 2.32E+08 | 1/9 | AT/A | intronic | EGLN1 | rs371204614 | 0.001093334 |
| InDel | chr11 | 1.02E+08 | 1.02E+08 | 1/9 | A/AT | intronic | BIRC3 | rs762000514 | 0.001093334 |
| SNP | chr16 | 21161552 | 21161552 | 8/9 | T/A | intronic | DNAH3 | rs11074486 | 0.001093334 |
| SNP | chr16 | 58549341 | 58549341 | 8/9 | G/T | upstream | SETD6 | rs3809594 | 0.001093334 |
| SNP | chr19 | 7153011 | 7153011 | 8/9 | A/C | intronic | INSR | rs72996158 | 0.001093334 |
| SNP | chr19 | 59010819 | 59010819 | 8/9 | G/T | intronic | SLC27A5 | rs2278497 | 0.001093334 |
| InDel | chr2 | 29152376 | 29152376 | 1/9 | TA/T | intronic | WDR43 | rs373812740 | 0.001093334 |
| SNP | chr2 | 95488938 | 95488938 | 8/9 | C/A | ncRNA\_intronic | ANKRD20A8P | rs201145481 | 0.001093334 |
| InDel | chr2 | 1.19E+08 | 1.19E+08 | 9/9 | A/ATAAAG | intronic | DDX18 | rs112417042 | 0.001093334 |
| InDel | chr2 | 1.8E+08 | 1.8E+08 | 9/9 | TG/T | UTR3 | ZNF385B | rs397986825 | 0.001093334 |
| SNP | chr3 | 10089497 | 10089497 | 8/9 | C/T | intronic | FANCD2 | rs114101942 | 0.001093334 |
| SNP | chr3 | 10089499 | 10089499 | 8/9 | A/G | intronic | FANCD2 | rs200073821 | 0.001093334 |
| SNP | chr3 | 10089509 | 10089509 | 8/9 | A/G | intronic | FANCD2 | rs77520528 | 0.001093334 |
| SNP | chr3 | 56026034 | 56026034 | 1/9 | C/G | intronic | ERC2 | rs4974160 | 0.001093334 |
| InDel | chr4 | 1E+08 | 1E+08 | 8/9 | T/TGG | upstream | ADH5;LOC100507053 | rs11434442 | 0.001093334 |
| SNP | chr6 | 1.7E+08 | 1.7E+08 | 7/9 | A/T | intronic | ERMARD | rs6459658 | 0.001093334 |
| SNP | chr1 | 2.38E+08 | 2.38E+08 | 9/9 | T/C | intronic | RYR2 | rs571026 | 0.001309836 |
| SNP | chr12 | 10251287 | 10251287 | 7/9 | C/T | intronic | CLEC1A | rs6488257 | 0.001309836 |
| InDel | chr12 | 11327283 | 11327283 | 9/9 | GT/G | UTR3 | SMIM10L1 | rs568269643 | 0.001309836 |
| SNP | chr15 | 90191827 | 90191827 | 9/9 | T/C | exonic | KIF7 | rs8037349 | 0.001309836 |
| SNP | chr15 | 90195765 | 90195765 | 9/9 | A/G | intronic | KIF7 | rs11630003 | 0.001309836 |
| SNP | chr15 | 90195766 | 90195766 | 9/9 | A/G | intronic | KIF7 | rs11630004 | 0.001309836 |
| SNP | chr15 | 90195967 | 90195967 | 9/9 | C/G | exonic | KIF7 | rs8179066 | 0.001309836 |
| SNP | chr17 | 37316988 | 37316988 | 7/9 | T/C | exonic | ARL5C | rs16522 | 0.001309836 |
| SNP | chr17 | 37319029 | 37319029 | 7/9 | T/G | exonic | ARL5C | rs544198 | 0.001309836 |
| SNP | chr17 | 37319065 | 37319065 | 7/9 | C/T | exonic | ARL5C | rs657672 | 0.001309836 |

Table S4. A total of 467 exonic missense SNVs were annotated on 330 genes (P < 0.05).

|  |
| --- |
| TMEM201, HNRNPCL2, EMC1, AKR7A3, SRSF4, ZMYND12, KLF17, CCDC17, IPP, MAST2, LOC110117498, NEXN, BRDT, NBPF8, PDE4DIP, NOTCH2NL, NBPF10, NBPF26, OR6K3, IGSF9, PBX1, PRRC2C, QSOX1, CACNA1E, LAMC1, NCF2, EDEM3, SWT1, KIF14, NFASC, SRGAP2, IL24, PIGR, CR1, EPHX1, OR2T35, ACP1, TPO, TAF1B, CLHC1, PROKR1, HK2, POLR1A, PROM2, FAM178B, VWA3B, RFX8, GLI2, POTEF, TTN, MFSD6, DNAH7, KIAA2012, CTLA4, TNS1, HJURP, TRPM8, GPR35, PASK, GAL3ST2, MALRD1, PIP4K2A, ANKRD30A, C10orf71, PCDH15, NPFFR1, OPN4, FFAR4, RRP12, MMS19, HPSE2, NRAP, VWA2, PSMD13, MUC6, SYT8, SLC22A18AS, OR52I2, OR51A7, OR51B2, OR52H1, OR56A3, FAM160A2, SWAP70, APIP, PDHX, AGBL2, NUP160, PTPRJ, OR4B1, OR4X1, TRIM49B, FAM86C1, ALG9, DLAT, OR6T1, OR10G4, OR10G9, OR10G8, OR10G7, TIRAP, FOXM1, CLEC4C, CLEC4D, CLEC1A, SMCO2, MUC19, BCDIN3D, KRT72, CALCOCO1, OR6C68, MON2, HELB, C12orf42, SVOP, ACACB, OAS1, RASAL1, HCAR3, STARD13, NUFIP1, RCBTB1, UTP14C, CARS2, UPF3A, OR10G2, MRPL52, KIAA0391, RALGAPA1, TXNDC16, KCNH5, FAM161B, TSHR, NRDE2, AHNAK2, GOLGA6L2, ZFYVE19, SHF, HDC, MEGF11, NOX5, GOLGA6L3, ACAN, TICRR, KIF7, ADAMTS17, RGS11, PIGQ, WDR90, RHOT2, CACNA1H, TPSG1, TRAP1, TFAP4, C16orf71, CIITA, ABCC6, CLEC19A, PDILT, ACSM5, DRC7, PRSS54, CES4A, MARVELD3, NECAB2, ATP2C2, MC1R, C17orf97, SMG6, GGT6, CYB5D1, DNAH9, SPECC1, CCT6B, SLFN12, SLFN12L, ARL5C, SLC4A1, ABCA6, ABCA10, OTOP2, MRPS7, USP36, AATK, B3GNTL1, SMCHD1, SLC35G4, SLC14A1, ELOA2, ALPK2, SERPINB8, ABCA7, C19orf35, ZNF77, CACTIN, EBI3, ZNRF4, CATSPERD, PRR22, DUS3L, KRI1, DOCK6, CCDC105, OR10H3, ZNF99, LSR, THAP8, CYP2A7, CYP2B6, ZNF45, PPFIA3, DKKL1, KLK1, FPR1, VN1R2, LILRA6;LILRB3, NLRP4, ZSCAN5B, TMC2, ADRA1D, MCM8, BMP2, DZANK1, IFNAR2, UMODL1, LOC102724428, LSS, C21orf58, PIWIL3, MYO18B, HPS4, THOC5, SEC14L2, SLC16A8, FAM109B, CYP2D6, PRR5, RIBC2, TTLL8, PRRT3, TATDN2, KAT2B, ACAA1, ACKR2, FAM198A, LRIG1, EPHA3, OR5H2, CD200R1, POLQ, ALDH1L1, GATA2, PLXND1, FNDC3B, YEATS2, HTR3C, PIGZ, CRIPAK, EVC2, CPZ, ATP10D, REST, ART3, FRAS1, FAT4, MAP9, WDR17, NEIL3, DNAH5, ANKRD31, LOX, GRAMD2B, ALDH7A1, CSF2, PCDH12, SH3RF2, FBXO38, GM2A, FAT2, RARS, CDHR2, FOXQ1, ATXN1, DNAH8, CRISP3, KIAA1586, TBX18, FHL5, VNN1, T, WDR27, ERMARD, FBXL18, USP42, GRID2IP, THSD7A, ABCB5, DNAH11, FAM221A, PHTF2, LRRD1, PPP1R9A, MUC12, MUC17, LAMB1, FAM131B, PTPRN2, DLC1, SLC18A1, CHRNA2, ADGRA2, POU5F1B, ANKRD18A, SMC5, PCSK5, DAPK1, SPATA31E1, FBP2, COL27A1, HMCN2, LAMC3, QSOX2, MAMDC4, KIAA1210, MAGEC3, SLITRK2, TMEM257 SIK1,PIK3R3, NBPF9 |

Table S5. Gene ontology and pathway analysis results of 330 genes of 467 significant exonic missense variants (P < 0.05)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Category | Term |  | Count | % | PValue | Genes |
| GOTERM\_BP\_DIRECT | GO:0050911 | detection of chemical stimulus involved in sensory perception of smell | 18 | 5.487805 | 5.91E-04 | OR52I2, OR52H1, OR5H2, OR10H3, OR10G2, OR6K3, OR51B2, OR10G4, OR2T35, OR6T1, OR4X1, OR6C68, OR10G8, OR10G7, OR56A3, OR10G9, OR51A7, OR4B1 |
| GOTERM\_BP\_DIRECT | GO:0007186 | G-protein coupled receptor signaling pathway | 27 | 8.231707 | 0.003108029 | OR52H1, OR6K3, OR51B2, FPR1, ADRA1D, OR2T35, PROKR1, HCAR3, ADGRA2, FFAR4, OR6C68, OR4B1, OR52I2, OR5H2, OR10G2, GPR35, OR10G4, TSHR, OR4X1, VN1R2, ACKR2, OR10G8, RGS11, OR10G7, OR56A3, OR10G9, OR51A7 |
| GOTERM\_BP\_DIRECT | GO:0032870 | cellular response to hormone stimulus | 5 | 1.52439 | 0.005957428 | LOC102724428, NPFFR1, FFAR4, SIK1, CACNA1H |
| GOTERM\_BP\_DIRECT | GO:0048739 | cardiac muscle fiber development | 3 | 0.914634 | 0.006863152 | MYO18B, NEXN, TTN |
| GOTERM\_BP\_DIRECT | GO:0034446 | substrate adhesion-dependent cell spreading | 4 | 1.219512 | 0.023362785 | KIF14, LAMB1, LAMC1, SRGAP2 |
| GOTERM\_BP\_DIRECT | GO:0007507 | heart development | 8 | 2.439024 | 0.02969776 | ACAN, BMP2, DNAH11, LOX, DNAH5, GATA2, PCSK5, GLI2 |
| GOTERM\_BP\_DIRECT | GO:0045454 | cell redox homeostasis | 5 | 1.52439 | 0.036316354 | NCF2, QSOX1, PDILT, QSOX2, TXNDC16 |
| GOTERM\_BP\_DIRECT | GO:0007018 | microtubule-based movement | 5 | 1.52439 | 0.042500735 | DNAH8, DNAH5, KIF14, DNAH9, KIF7 |
| GOTERM\_BP\_DIRECT | GO:0010868 | negative regulation of triglyceride biosynthetic process | 2 | 0.609756 | 0.047814476 | LOC102724428, SIK1 |
| GOTERM\_BP\_DIRECT | GO:0006090 | pyruvate metabolic process | 3 | 0.914634 | 0.048813301 | PDHX, SLC16A8, DLAT |
| GOTERM\_CC\_DIRECT | GO:0016021 | integral component of membrane | 114 | 34.7561 | 1.67E-04 | SLC4A1, TXNDC16, SMCHD1, CYP2D6, ADGRA2, SMCO2, THSD7A, MALRD1, IFNAR2, ALG9, KCNH5, FNDC3B, OR6T1, ABCA10, CLEC4C, CLEC4D, TMEM257, OR4X1, EPHA3, CHRNA2, OR6K3, OR51B2, ABCB5, FPR1, PCDH15, PCDH12, ART3, IGSF9, CACNA1H, SEC14L2, TPO, TRPM8, PROM2, SLC14A1, OPN4, PRRT3, GGT6, PTPRN2, OR5H2, ABCA6, MUC17, EPHX1, ABCA7, SYT8, MC1R, VNN1, FAT2, NOX5, FAT4, OR51A7, PHTF2, MEGF11, CRISP3, PIGQ, PIGZ, AATK, ADRA1D, PTPRJ, PCSK5, MFSD6, CLEC1A, ERMARD, MUC12, FFAR4, CTLA4, RRP12, GAL3ST2, ACP1, SLC18A1, SLFN12L, MAMDC4, OR52I2, CR1, SVOP, SLC35G4, GPR35, ABCC6, HTR3C, NBPF10, LSR, TMC2, CYP2A7, CD200R1, VN1R2, OR56A3, LILRA6, OR52H1, OR10H3, ATP10D, ATP2C2, OR2T35, TMEM201, ZNRF4, SLITRK2, EMC1, MARVELD3, LRIG1, OR6C68, SPATA31E1, OR4B1, EVC2, WDR17, MON2, OR10G2, OR10G4, LILRB3, OTOP2, TSHR, NFASC, FRAS1, OR10G8, OR10G7, OR10G9, UMODL1 |
| GOTERM\_CC\_DIRECT | GO:0005604 | basement membrane | 7 | 2.134146 | 0.001828222 | ACAN, FRAS1, LAMC3, HMCN2, VWA2, LAMB1, LAMC1 |
| GOTERM\_CC\_DIRECT | GO:0005887 | integral component of plasma membrane | 36 | 10.97561 | 0.008834411 | PIGR, NPFFR1, PLXND1, OR10H3, ABCB5, FPR1, ADRA1D, PTPRJ, SLC4A1, PCDH12, ATP2C2, ART3, PROKR1, HCAR3, TPO, CLEC1A, MUC12, FFAR4, CTLA4, SLC16A8, SLC18A1, PROM2, IFNAR2, SLC14A1, OPN4, CR1, PTPRN2, KCNH5, TPSG1, GPR35, LILRB3, TSHR, OR6T1, MC1R, ACKR2, EPHA3 |
| GOTERM\_CC\_DIRECT | GO:0005796 | Golgi lumen | 6 | 1.829268 | 0.020415235 | ACAN, MUC17, MUC19, MUC12, PCSK5, MUC6 |
| GOTERM\_CC\_DIRECT | GO:0030018 | Z disc | 6 | 1.829268 | 0.044003989 | AHNAK2, MYO18B, NEXN, SLC4A1, FBP2, TTN |
| GOTERM\_CC\_DIRECT | GO:0005886 | plasma membrane | 81 | 24.69512 | 0.044219458 | PIGR, NPFFR1, HPSE2, PLXND1, MAST2, KIF14, ADRA1D, PTPRJ, SLC4A1, ADGRA2, FFAR4, PIP4K2A, CTLA4, SLC16A8, THSD7A, QSOX2, IFNAR2, OR52I2, CR1, KCNH5, DAPK1, SWAP70, ABCC6, HTR3C, LSR, TIRAP, OR6T1, CLEC4C, CD200R1, CLEC4D, CATSPERD, OR4X1, VN1R2, OR56A3, EPHA3, OR52H1, CHRNA2, OR10H3, OR6K3, OR51B2, EBI3, ABCB5, ATP10D, FPR1, PCDH15, RASAL1, PCDH12, CACNA1E, OR2T35, IGSF9, PROKR1, HCAR3, TPO, RHOT2, OR6C68, TRPM8, SRGAP2, OR4B1, SLC14A1, OPN4, OR5H2, OR10G2, OR10G4, AHNAK2, UPF3A, ABCA7, SYT8, TSHR, NFASC, FRAS1, VNN1, MC1R, FAT2, CRIPAK, ACKR2, OR10G8, FAT4, RGS11, OR10G7, OR10G9, OR51A7 |
| GOTERM\_CC\_DIRECT | GO:0005606 | laminin-1 complex | 2 | 0.609756 | 0.048101701 | LAMB1, LAMC1 |
| GOTERM\_CC\_DIRECT | GO:0043259 | laminin-10 complex | 2 | 0.609756 | 0.048101701 | LAMB1, LAMC1 |
| GOTERM\_CC\_DIRECT | GO:0030286 | dynein complex | 3 | 0.914634 | 0.049357106 | DNAH11, DNAH8, DNAH9 |
| GOTERM\_MF\_DIRECT | GO:0005524 | ATP binding | 44 | 13.41463 | 1.34E-04 | CIITA, DNAH7, MCM8, DNAH8, MAST2, DNAH5, ABCB5, ATP10D, KIF14, AATK, ACSM5, SMC5, DNAH9, ATP2C2, ACACB, HK2, CCT6B, TTN, SMCHD1, HELB, RARS, NLRP4, MYO18B, PIP4K2A, SLFN12L, TRAP1, POLQ, DNAH11, DAPK1, ABCA6, SWAP70, ABCC6, ABCA7, PASK, KIF7, SLFN12, LOC102724428, ABCA10, OAS1, SIK1, ALPK2, CARS2, EPHA3, TTLL8 |
| GOTERM\_MF\_DIRECT | GO:0004930 | G-protein coupled receptor activity | 25 | 7.621951 | 5.19E-04 | OR52H1, NPFFR1, OR6K3, OR10H3, OR51B2, OR2T35, PROKR1, HCAR3, ADGRA2, FFAR4, OR6C68, OR4B1, OR52I2, OPN4, OR5H2, OR10G2, GPR35, OR10G4, OR6T1, OR4X1, OR10G8, OR10G7, OR56A3, OR10G9, OR51A7 |
| GOTERM\_MF\_DIRECT | GO:0004984 | olfactory receptor activity | 18 | 5.487805 | 6.56E-04 | OR52I2, OR52H1, OR5H2, OR10H3, OR10G2, OR6K3, OR51B2, OR10G4, OR2T35, OR6T1, OR4X1, OR6C68, OR10G8, OR10G7, OR56A3, OR10G9, OR51A7, OR4B1 |
| GOTERM\_MF\_DIRECT | GO:0016887 | ATPase activity | 11 | 3.353659 | 7.85E-04 | ABCA10, DNAH11, DNAH7, ABCA6, DNAH8, DNAH5, ABCB5, KIF14, DNAH9, ABCA7, KIF7 |
| GOTERM\_MF\_DIRECT | GO:0003777 | microtubule motor activity | 7 | 2.134146 | 0.001836703 | DNAH11, DNAH7, DNAH8, DNAH5, KIF14, DNAH9, KIF7 |
| GOTERM\_MF\_DIRECT | GO:0042626 | ATPase activity, coupled to transmembrane movement of substances | 5 | 1.52439 | 0.005395999 | ABCA10, ABCA6, ABCC6, ABCB5, ABCA7 |
| GOTERM\_MF\_DIRECT | GO:0005509 | calcium ion binding | 21 | 6.402439 | 0.012329941 | EDEM3, NECAB2, DNAH7, SWAP70, NOTCH2NL, PCDH15, PCDH12, SYT8, CACNA1E, TTN, NBPF26, ACAN, TPO, RHOT2, CDHR2, HMCN2, FAT2, VWA2, NOX5, FAT4, UMODL1 |
| GOTERM\_MF\_DIRECT | GO:0005201 | extracellular matrix structural constituent | 5 | 1.52439 | 0.022887006 | ACAN, COL27A1, LAMB1, LAMC1, MUC6 |
| GOTERM\_MF\_DIRECT | GO:0016712 | oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen | 3 | 0.914634 | 0.023654058 | CYP2A7, CYP2B6, CYP2D6 |
| GOTERM\_MF\_DIRECT | GO:0008392 | arachidonic acid epoxygenase activity | 3 | 0.914634 | 0.023654058 | CYP2A7, CYP2B6, CYP2D6 |
| GOTERM\_MF\_DIRECT | GO:0000026 | alpha-1,2-mannosyltransferase activity | 2 | 0.609756 | 0.031966896 | ALG9, PIGZ |
| GOTERM\_MF\_DIRECT | GO:0016971 | flavin-linked sulfhydryl oxidase activity | 2 | 0.609756 | 0.047566458 | QSOX1, QSOX2 |
| GOTERM\_MF\_DIRECT | GO:0003756 | protein disulfide isomerase activity | 3 | 0.914634 | 0.048353748 | QSOX1, PDILT, QSOX2 |
| KEGG\_PATHWAY | hsa04740 | Olfactory transduction | 17 | 5.182927 | 7.47E-04 | OR52I2, OR52H1, OR5H2, OR10H3, OR10G2, OR6K3, OR51B2, OR10G4, OR6T1, OR4X1, OR6C68, OR10G8, OR10G7, OR56A3, OR10G9, OR51A7, OR4B1 |
| KEGG\_PATHWAY | hsa02010 | ABC transporters | 5 | 1.52439 | 0.005651833 | ABCA10, ABCA6, ABCC6, ABCB5, ABCA7 |
| KEGG\_PATHWAY | hsa05146 | Amoebiasis | 6 | 1.829268 | 0.029908774 | COL27A1, CSF2, LAMC3, PIK3R3, LAMB1, LAMC1 |

**Table S6.** Information of 14 significant SNVs for genotyping from WES.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNV** | **Gene** | **Chr** | **Position** | **Mut** | **Shared** | **Func** | **Mut\_type** | **P** |
| **rs4926472** | **TMEM201** | **chr1** | **9670834** | **C/T** | **9** | **exonic** | **missense** | **0.03227** |
| **rs1034268** | **ZMYND12** | **chr1** | **42898843** | **A/G** | **9** | **exonic** | **missense** | **0.007751** |
| **rs10783071** | **BRDT** | **chr1** | **92428495** | **C/A** | **8** | **exonic** | **missense** | **0.024768** |
| **rs10747493** | **BRDT** | **chr1** | **92457843** | **C/T** | **8** | **exonic** | **missense** | **0.024768** |
| **rs2275558** | **PBX1** | **chr1** | **164529120** | **G/A** | **8** | **exonic** | **missense** | **0.01522** |
| rs10913157 | PRRC2C | chr1 | 171486912 | G/A | 8 | exonic | **missense** | 0.019767 |
| rs20558 | LAMC1 | chr1 | 183094547 | T/C | 8 | exonic | missense | 0.038862 |
| rs2274064 | NCF2 | chr1 | 183542387 | T/C | 9 | exonic | **missense** | 0.045292 |
| rs9425343 | EDEM3 | chr1 | 184663537 | A/C | 9 | exonic | **missense** | 0.002587 |
| rs12120084 | KIF14 | chr1 | 200522566 | G/C | 8 | exonic | missense | 0.022495 |
| **rs2802808** | **NFASC** | **chr1** | **204966428** | **C/G** | **8** | **exonic** | **missense** | **0.009375** |
| **rs2275531** | **PIGR** | **chr1** | **207109116** | **C/T** | **9** | **exonic** | **missense** | **0.010836** |
| **rs78622116** | **OR2T35** | **chr1** | **248801592** | **C/T** | **9** | **exonic** | **missense** | **0.021791** |
| rs143981271 | OR2T35 | chr1 | 248801611 | C/T | 9 | exonic | missense | 0.010479 |

Table S7. Shesis results of genotypes and alleles of the 8 significant SNVs for validation.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNV | P | FDR | OR [95% CI] | Allele frequency | | P | FDR | Genotype frequency |  |  | Call rate | HWE-P |
| rs4926472 | 0.323 | 0.518 | 0.777 [0.471~1.282] | C | T | 0.267 | 0.51 | C/T | T/T | C/C | 0.95 | 0.829 |
| Case |  |  |  | 47(0.33) | 95(0.669) |  |  | 37(0.521) | 29(0.408) | 5(0.07) |  |  |
| Control |  |  |  | 49(0.388) | 77(0.611) |  |  | 29(0.46) | 24(0.38) | 10(0.158) |  |  |
| rs1034268 | 0.242 | 0.485 | 0.745 [0.455~1.221] | G | A | 0.443 | 0.51 | G/G | A/A | G/A | 0.957 | 1 |
| Case |  |  |  | 93(0.654) | 49(0.345) |  |  | 30(0.422) | 8(0.112) | 33(0.464) |  |  |
| Control |  |  |  | 75(0.585) | 53(0.414) |  |  | 23(0.359) | 12(0.187) | 29(0.453) |  |  |
| rs10783071 | 0.926 | 0.926 | 1.023 [0.625~1.672] | C | A | 0.447 | 0.51 | C/C | C/A | A/A | 0.95 | 1 |
| Case |  |  |  | 56(0.394) | 86(0.605) |  |  | 9(0.126) | 38(0.535) | 24(0.338) |  |  |
| Control |  |  |  | 49(0.388) | 77(0.611) |  |  | 11(0.174) | 27(0.428) | 25(0.396) |  |  |
| rs10747493 | 0.645 | 0.737 | 0.891 [0.545~1.454] | C | T | 0.377 | 0.51 | C/C | C/T | T/T | 0.943 | 1 |
| Case |  |  |  | 55(0.392) | 85(0.607) |  |  | 9(0.128) | 37(0.528) | 24(0.342) |  |  |
| Control |  |  |  | 53(0.42) | 73(0.579) |  |  | 13(0.206) | 27(0.428) | 23(0.365) |  |  |
| rs2275558 | 0.636 | 0.737 | 1.128 [0.683~1.86] | G | A | 0.822 | 0.822 | G/A | A/A | G/G | 0.95 | 1 |
| Case |  |  |  | 52(0.371) | 88(0.628) |  |  | 34(0.485) | 27(0.385) | 9(0.128) |  |  |
| Control |  |  |  | 44(0.343) | 84(0.656) |  |  | 28(0.437) | 28(0.437) | 8(0.125) |  |  |
| rs2802808 | **0.009** | **0.039** | 1.889 [1.162~3.072] | C | G | **0.027** | 0.073 | C/C | C/G | G/G | 0.95 | 1 |
| Case |  |  |  | 61(0.429) | 81(0.57) |  |  | 12(0.169) | 37(0.521) | 22(0.309) |  |  |
| Control |  |  |  | 74(0.587) | 52(0.412) |  |  | 23(0.365) | 28(0.444) | 12(0.19) |  |  |
| rs2275531 | **0.009** | **0.039** | 2.002 [1.178~3.404] | C | T | **0.013** | 0.069 | C/C | T/T | C/T | 0.978 | 0.721 |
| Case |  |  |  | 90(0.633) | 52(0.366) |  |  | 28(0.394) | 9(0.126) | 34(0.478) |  |  |
| Control |  |  |  | 104(0.776) | 30(0.223) |  |  | 43(0.641) | 6(0.089) | 18(0.268) |  |  |
| rs78622116 | **0.022** | **0.048** | NA [NA~NA] | T | C | **0.023** | 0.069 | T/T | C/T |  | 0.964 | 0.999 |
| Case |  |  |  | 142(1) | 0(0) |  |  | Case 71(1) |  |  |  |  |
| Control |  |  |  | 125(0.961) | 5(0.038) |  |  | 60(0.923) | 5(0.076) |  |  |  |

Table S8. Gene interaction results of 8 SNVs for validation.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP set |  | Nonmissing | Case Interaction | Control Interaction | diff | p | Holm | SidakSS | SidakSD | FDR\_BH | FDR\_BY |
| rs4926472 | rs2275558 | 133 | -0.071 | -0.011 | -0.059 | **0.037** | 1 | 0.658 | 0.645 | 0.429 | 1 |
| rs10783071 | rs2802808 | 134 | -0.007 | -0.064 | 0.056 | **0.004** | 0.132 | 0.124 | 0.124 | 0.132 | 0.519 |