**Table S1. Patients’ detail of RNA sequencing**

T: Primary tumor; N: Regional lymph node

|  |  |  |  |
| --- | --- | --- | --- |
| **Patients' id** | **1** | **2** | **3** |
| **Age at diagnosis** | 64 | 56 | 31 |
| **Gender** | Male | Female | Male |
| **Primary location** | Root of tongue | Ventrum of tongue | Gum |
| **tumor stage** | I | II | I |
| **T stage** | T2 | T1 | T3 |
| **N stage** | N1 | N0 | N0 |
| **Histologic grade** | G1 | G2 | G1 |
| **Radiation** | No | No | No |
| **Recurrence** | No | Yes | No |
| **Follow-up time** | 9 months | 8 months | 11 months |
| **Cigerate** | Yes | No | No |
| **Alcohol consumption** | Yes | No | No |
| **Survival state** | Alive | Alive | Alive |

**Table S2. Patients’ characteristics in the tissue microarray chips**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | | **No. cases** |
| **Age** |  |  |
|  | >60ys | 51 |
|  | ≤60ys | 20 |
| **Gender** |  |  |
|  | Male | 29 |
|  | Female | 42 |
| **Tumor stage** | |  |
|  | Adjacent tissue | 10 |
|  | Well | 33 |
|  | Moderate | 23 |
|  | Poor | 5 |
| **Primary location** | |  |
|  | tongue | 20 |
|  | Bucca | 20 |
|  | Lip | 4 |
|  | Palate | 9 |
|  | Oral cavity | 1 |
|  | Gum | 7 |

**Table S3. Details of the 4 selected patients in immunohistological staining**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Tissue type** | **Gender** | **Age** | **Tumor stage** | | **Tumor size** | **Location** | **T**  **stage** | **N**  **stage** |
| Tumor | Female | 76 | | I | 2\*1 cm | Dorsum of tongue | T1 | N0 |
| Tumor | Male | 59 | | II | 5.5\*4\*4 cm | Dorsum of tongue | T3 | N0 |
| Tumor | Female | 53 | | III | 1.8\*1.3\*0.7 cm | Ventrum of tongue | T1 | N0 |
| Adjacent | Male | 80 | |  |  | tongue |  |  |

**Table S4. 229 DEGs according to RNA sequencing**

|  |  |  |  |
| --- | --- | --- | --- |
| **DEGs** | **Log2(fold change)** | **P-value** | **FDR** |
| CRISP3 | -9.769350 | 2.52E-37 | 8.39E-33 |
| MMP7 | 10.387680 | 5.56E-30 | 9.27E-26 |
| IGHV3-21 | 6.992692 | 1.46E-21 | 1.62E-17 |
| TMPRSS11B | -5.296710 | 8.49E-18 | 7.07E-14 |
| ENDOU | -5.308590 | 2.59E-17 | 1.72E-13 |
| MAL | -4.716870 | 5.88E-14 | 3.26E-10 |
| KRT78 | -4.798150 | 9.81E-14 | 4.67E-10 |
| BARX2 | -4.230360 | 1.10E-12 | 4.60E-09 |
| OTOP3 | -5.484780 | 1.79E-11 | 6.64E-08 |
| IGLV2-14 | 7.701678 | 3.62E-11 | 1.21E-07 |
| HMGCS2 | -10.360700 | 4.08E-11 | 1.24E-07 |
| CWH43 | -4.310420 | 3.11E-10 | 8.63E-07 |
| CRNN | -5.247760 | 5.95E-10 | 1.42E-06 |
| MMP9 | 4.370365 | 5.69E-10 | 1.42E-06 |
| NMU | -3.998550 | 7.22E-10 | 1.60E-06 |
| TGM3 | -4.247180 | 1.51E-09 | 3.14E-06 |
| SLC27A6 | -5.093410 | 2.86E-09 | 5.60E-06 |
| PAX9 | -3.413950 | 4.37E-09 | 8.09E-06 |
| CYSRT1 | -3.288640 | 6.95E-09 | 1.22E-05 |
| SCEL | -3.208250 | 1.03E-08 | 1.71E-05 |
| LAMB4 | -4.771660 | 1.45E-08 | 2.30E-05 |
| SLCO1B3 | 8.098291 | 1.69E-08 | 2.56E-05 |
| ADAM12 | 6.384544 | 1.83E-08 | 2.65E-05 |
| CYP3A5 | -4.457590 | 2.13E-08 | 2.95E-05 |
| PLAU | 3.177674 | 2.64E-08 | 3.52E-05 |
| C2orf54 | -3.198000 | 2.88E-08 | 3.57E-05 |
| SAMD5 | -3.666750 | 2.90E-08 | 3.57E-05 |
| MMP1 | 7.293344 | 4.48E-08 | 5.33E-05 |
| ADAMTS2 | 3.205386 | 4.65E-08 | 5.34E-05 |
| DEGS2 | -3.969630 | 5.11E-08 | 5.68E-05 |
| HMGA2 | 5.394417 | 5.87E-08 | 6.26E-05 |
| SLURP1 | -3.875930 | 6.02E-08 | 6.26E-05 |
| EPGN | -3.284080 | 7.04E-08 | 7.10E-05 |
| ADAMDEC1 | 6.605911 | 7.58E-08 | 7.43E-05 |
| SPINK5 | -4.089790 | 8.55E-08 | 8.13E-05 |
| MUC21 | -5.859920 | 9.57E-08 | 8.61E-05 |
| RHCG | -4.905900 | 9.45E-08 | 8.61E-05 |
| RAET1E | -3.627930 | 1.05E-07 | 9.16E-05 |
| GREM1 | 3.327055 | 1.08E-07 | 9.19E-05 |
| C1QTNF6 | 3.611950 | 1.20E-07 | 0.000100 |
| GBP6 | -2.992770 | 1.40E-07 | 0.000114 |
| AIF1L | -3.013300 | 1.51E-07 | 0.000120 |
| LAMP5 | 3.964079 | 1.58E-07 | 0.000122 |
| CCL11 | 5.256163 | 1.87E-07 | 0.000142 |
| BBOX1 | -3.466980 | 2.45E-07 | 0.000178 |
| CLIC3 | -2.861980 | 2.50E-07 | 0.000178 |
| SOX11 | 7.345734 | 2.40E-07 | 0.000178 |
| TUBB3 | 3.382867 | 2.74E-07 | 0.000190 |
| VSIG10L | -2.954030 | 2.91E-07 | 0.000198 |
| IGHG1 | 6.326588 | 3.63E-07 | 0.000242 |
| SLITRK5 | -5.630450 | 3.79E-07 | 0.000248 |
| IL1RN | -3.022290 | 4.31E-07 | 0.000276 |
| MMP12 | 5.500682 | 5.23E-07 | 0.000325 |
| SLC25A21 | -3.727060 | 5.27E-07 | 0.000325 |
| ENSG00000229732.1 | -3.517020 | 6.56E-07 | 0.000397 |
| SPINK7 | -4.078330 | 6.80E-07 | 0.000405 |
| TGM1 | -3.132470 | 8.57E-07 | 0.000501 |
| TFAP2B | -6.206250 | 9.86E-07 | 0.000564 |
| TTYH3 | 2.727757 | 1.00E-06 | 0.000564 |
| ZBED2 | -2.884110 | 1.44E-06 | 0.000786 |
| ZNF469 | 3.987272 | 1.43E-06 | 0.000786 |
| GREM2 | -3.517580 | 1.54E-06 | 0.000814 |
| SBSN | -2.884350 | 1.54E-06 | 0.000814 |
| CST1 | 10.341230 | 1.61E-06 | 0.000838 |
| FAM3B | -3.276440 | 1.65E-06 | 0.000846 |
| DSG1 | -2.565780 | 1.73E-06 | 0.000873 |
| HAS3 | 3.030086 | 2.14E-06 | 0.001047 |
| NFE2L3 | 3.239792 | 2.11E-06 | 0.001047 |
| CNTFR | -3.106340 | 2.18E-06 | 0.001052 |
| EXPH5 | -3.074080 | 2.21E-06 | 0.001052 |
| EMP1 | -3.374840 | 2.28E-06 | 0.001070 |
| PTK6 | -3.038920 | 2.32E-06 | 0.001071 |
| ACPP | -2.978030 | 2.46E-06 | 0.001119 |
| SPRR2A | -3.222580 | 2.49E-06 | 0.001119 |
| THY1 | 2.616886 | 2.55E-06 | 0.001132 |
| NCCRP1 | -2.569470 | 2.86E-06 | 0.001253 |
| DUOX1 | -2.554370 | 3.35E-06 | 0.001448 |
| MARCKSL1 | 2.659274 | 3.48E-06 | 0.001486 |
| PPEF1 | 6.987485 | 3.67E-06 | 0.001546 |
| C1orf116 | -2.536470 | 4.07E-06 | 0.001696 |
| ACER1 | -4.005330 | 4.21E-06 | 0.001731 |
| FAM25A | -4.314070 | 4.47E-06 | 0.001817 |
| CNFN | -2.472400 | 5.25E-06 | 0.002062 |
| HOXC9 | 7.273947 | 5.26E-06 | 0.002062 |
| KRT84 | -10.206800 | 5.14E-06 | 0.002062 |
| ADAMTS14 | 5.767747 | 6.78E-06 | 0.002625 |
| SERPINH1 | 2.478165 | 6.90E-06 | 0.002641 |
| KRT4 | -6.268510 | 7.32E-06 | 0.002760 |
| RPLP0P2 | 5.899106 | 7.38E-06 | 0.002760 |
| FAIM2 | -3.317680 | 7.99E-06 | 0.002956 |
| LINC00675 | -4.340230 | 8.63E-06 | 0.003159 |
| KRT36 | -9.838880 | 8.92E-06 | 0.003230 |
| CYP4F29P | -4.796560 | 1.04E-05 | 0.003709 |
| PPL | -2.888640 | 1.05E-05 | 0.003727 |
| IGLV6-57 | 7.967626 | 1.09E-05 | 0.003831 |
| ATP6V0A4 | -3.320100 | 1.15E-05 | 0.003935 |
| MFAP2 | 2.686261 | 1.14E-05 | 0.003935 |
| MAOB | -2.732070 | 1.26E-05 | 0.004297 |
| PLEKHG4B | 4.482171 | 1.39E-05 | 0.004666 |
| KRTAP13-2 | -9.953400 | 1.41E-05 | 0.004698 |
| CLEC3B | -2.391280 | 1.66E-05 | 0.005479 |
| SDR16C5 | -2.483070 | 1.69E-05 | 0.005503 |
| COL4A6 | 3.146229 | 1.75E-05 | 0.005667 |
| AQP3 | -2.361550 | 1.83E-05 | 0.005796 |
| PLA2G7 | 4.620354 | 1.82E-05 | 0.005796 |
| CPXM1 | 2.803459 | 2.16E-05 | 0.006790 |
| EPHX2 | -2.705660 | 2.39E-05 | 0.007452 |
| ALS2CL | -2.393330 | 2.43E-05 | 0.007461 |
| FCGR3A | 2.999325 | 2.44E-05 | 0.007461 |
| HCG22 | -4.868080 | 2.47E-05 | 0.007474 |
| ENSG00000259807.1 | 6.226989 | 2.53E-05 | 0.007531 |
| SLAMF8 | 3.301359 | 2.53E-05 | 0.007531 |
| MYEOV | -3.614810 | 2.61E-05 | 0.007695 |
| MYBL2 | 2.614425 | 2.76E-05 | 0.007991 |
| TIMP1 | 2.268462 | 2.75E-05 | 0.007991 |
| ENSG00000250103.1 | -6.983870 | 2.86E-05 | 0.008215 |
| INHBA | 4.312152 | 2.98E-05 | 0.008490 |
| EVA1A | 3.914609 | 3.09E-05 | 0.008587 |
| MSC | 2.664587 | 3.09E-05 | 0.008587 |
| MT4 | -5.459870 | 3.09E-05 | 0.008587 |
| FAM3D | -3.356120 | 3.17E-05 | 0.008659 |
| PRSS3 | -2.655060 | 3.15E-05 | 0.008659 |
| ENSG00000261327.3 | 4.763542 | 3.21E-05 | 0.008686 |
| CAB39L | -2.687380 | 3.30E-05 | 0.008878 |
| EPS8L1 | -2.274000 | 3.35E-05 | 0.008939 |
| C9orf152 | -5.967880 | 3.41E-05 | 0.009020 |
| S100A14 | -3.025200 | 3.46E-05 | 0.009076 |
| LINC01395 | -5.456510 | 3.66E-05 | 0.009531 |
| CHL1 | -2.791850 | 3.78E-05 | 0.009755 |
| COL10A1 | 7.893234 | 4.08E-05 | 0.010446 |
| LRFN2 | -5.832520 | 4.48E-05 | 0.011393 |
| MMP11 | 7.450353 | 4.78E-05 | 0.012056 |
| CYP3A4 | -6.311650 | 4.91E-05 | 0.012243 |
| HOXD13 | 5.935897 | 4.92E-05 | 0.012243 |
| A2ML1 | -2.420340 | 5.13E-05 | 0.012647 |
| KLHL6 | 2.769694 | 5.38E-05 | 0.013179 |
| TNFSF4 | 3.527421 | 5.67E-05 | 0.013795 |
| TJP3 | -2.680610 | 5.84E-05 | 0.013994 |
| ZNF185 | -2.111460 | 5.83E-05 | 0.013994 |
| GRHL1 | -2.235780 | 6.10E-05 | 0.014521 |
| IL18 | -2.333840 | 6.32E-05 | 0.014831 |
| OTOP2 | -4.300960 | 6.30E-05 | 0.014831 |
| IGFL1 | -2.292260 | 6.50E-05 | 0.015132 |
| GSTM5 | -2.734410 | 6.58E-05 | 0.015212 |
| MGLL | -2.144820 | 6.76E-05 | 0.015523 |
| C1QTNF7 | -2.893420 | 6.93E-05 | 0.015822 |
| BICDL2 | -2.280860 | 7.02E-05 | 0.015918 |
| SH3BGRL2 | -2.244830 | 7.47E-05 | 0.016820 |
| COL5A3 | 2.203929 | 7.77E-05 | 0.017257 |
| VWA2 | -3.386810 | 7.74E-05 | 0.017257 |
| CRCT1 | -3.855530 | 7.95E-05 | 0.017430 |
| MPZ | -2.535560 | 7.90E-05 | 0.017430 |
| DUOXA1 | -2.276700 | 8.74E-05 | 0.019030 |
| BNIPL | -2.216050 | 9.29E-05 | 0.019830 |
| CTHRC1 | 4.213538 | 9.22E-05 | 0.019830 |
| P3H1 | 2.301112 | 9.26E-05 | 0.019830 |
| ADH7 | -2.196770 | 9.42E-05 | 0.019986 |
| DPT | -2.185840 | 9.52E-05 | 0.020079 |
| MFAP4 | -2.154510 | 9.85E-05 | 0.020627 |
| TACSTD2 | -2.286470 | 0.000100 | 0.020890 |
| LOXL2 | 2.759751 | 0.000101 | 0.020933 |
| EMILIN1 | 2.139058 | 0.000102 | 0.020945 |
| MDK | 2.175780 | 0.000103 | 0.020977 |
| TMEM132A | 2.233427 | 0.000104 | 0.021076 |
| CA9 | 7.208159 | 0.000105 | 0.021180 |
| VAV3 | -2.377450 | 0.000109 | 0.021889 |
| MICAL2 | 2.990489 | 0.000112 | 0.022333 |
| IVL | -2.040230 | 0.000118 | 0.023405 |
| TREM2 | 4.099469 | 0.000119 | 0.023405 |
| SCARA5 | -2.469860 | 0.000120 | 0.023597 |
| AIM1L | -2.125060 | 0.000125 | 0.024368 |
| UHRF1 | 2.414327 | 0.000127 | 0.024576 |
| P2RY2 | -2.222180 | 0.000129 | 0.024780 |
| IGLV1-51 | 9.217503 | 0.000131 | 0.025089 |
| DBNDD1 | -2.540960 | 0.000133 | 0.025379 |
| PXDN | 2.812818 | 0.000135 | 0.025492 |
| MXD1 | -2.271850 | 0.000136 | 0.025614 |
| ATP6V1C2 | -2.785720 | 0.000141 | 0.026300 |
| ZNF750 | -2.041840 | 0.000143 | 0.026680 |
| COL3A1 | 3.032294 | 0.000146 | 0.026974 |
| ENSG00000260402.1 | -4.523620 | 0.000147 | 0.026974 |
| KRTAP3-3 | -7.511100 | 0.000149 | 0.027326 |
| IFI30 | 3.409240 | 0.000152 | 0.027698 |
| MYZAP | -2.991500 | 0.000155 | 0.028024 |
| C4orf48 | 2.543381 | 0.000163 | 0.029011 |
| FSCN1 | 2.057363 | 0.000162 | 0.029011 |
| NHLH2 | -4.067410 | 0.000162 | 0.029011 |
| NKX2-3 | -4.196430 | 0.000165 | 0.029285 |
| TPPP3 | -2.228060 | 0.000166 | 0.029334 |
| TNC | 2.036516 | 0.000170 | 0.029767 |
| NRG2 | -3.401150 | 0.000172 | 0.030011 |
| MMP13 | 11.210940 | 0.000182 | 0.031621 |
| HOXB9 | 5.697134 | 0.000183 | 0.031638 |
| GDF10 | -2.401410 | 0.000187 | 0.032036 |
| PITX1 | -2.121090 | 0.000189 | 0.032217 |
| SPOCD1 | 5.767881 | 0.000195 | 0.033109 |
| IGHV5-51 | 6.488617 | 0.000202 | 0.034125 |
| CSTA | -2.585370 | 0.000207 | 0.034397 |
| ENSG00000233850.1 | -4.330840 | 0.000206 | 0.034397 |
| KRTAP13-1 | -9.167600 | 0.000205 | 0.034397 |
| C6orf132 | -1.972110 | 0.000209 | 0.034533 |
| IGHV3-33 | 5.043637 | 0.000209 | 0.034533 |
| CPZ | 2.639445 | 0.000213 | 0.034827 |
| GPRIN1 | 3.062115 | 0.000213 | 0.034827 |
| CYP4F12 | -2.590860 | 0.000217 | 0.035041 |
| FGFBP1 | -1.958570 | 0.000216 | 0.035041 |
| SPRR3 | -3.323040 | 0.000221 | 0.035596 |
| LAMC2 | 3.498799 | 0.000226 | 0.035999 |
| PCDH20 | -3.958690 | 0.000226 | 0.035999 |
| PMEPA1 | 2.051444 | 0.000227 | 0.035999 |
| WNK4 | -5.471970 | 0.000235 | 0.037108 |
| SCG2 | 4.219755 | 0.000239 | 0.037499 |
| ENSG00000261068.1 | -2.771960 | 0.000240 | 0.037563 |
| CLDN17 | -4.441320 | 0.000243 | 0.037774 |
| EVPL | -2.460860 | 0.000257 | 0.039778 |
| ENSG00000184324.11 | 8.235196 | 0.000258 | 0.039800 |
| LOC100128770 | -2.815900 | 0.000260 | 0.039958 |
| PAQR5 | -2.671770 | 0.000263 | 0.039958 |
| TMEM154 | -2.115940 | 0.000262 | 0.039958 |
| PITX2 | -2.063240 | 0.000290 | 0.043863 |
| IL11 | 4.497916 | 0.000295 | 0.044409 |
| HOXB7 | 4.028861 | 0.000299 | 0.044822 |
| HOXA10-AS | 5.487574 | 0.000314 | 0.046971 |
| DCSTAMP | 6.620736 | 0.000319 | 0.047512 |
| ENSG00000231062.1 | -4.543220 | 0.000327 | 0.047734 |
| GYS2 | -6.744740 | 0.000327 | 0.047734 |
| MIR133A1HG | -3.393880 | 0.000328 | 0.047734 |
| SOCS1 | 2.358373 | 0.000326 | 0.047734 |
| TTC9 | -2.023650 | 0.000326 | 0.047734 |

**Table S5. The first 100 GO enrichment results of the DEGs in BP, CC and MF**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene counts** | **P-value** | **FDR** | **Term** |
| **GO-BP** |  |  |  |
| 155 | 2.71E-34 | 7.72E-31 | Single-Organism Process |
| 163 | 2.35E-32 | 3.35E-29 | Cellular Process |
| 143 | 6.76E-31 | 6.43E-28 | Single-Organism Cellular Process |
| 107 | 1.33E-28 | 9.51E-26 | Multicellular Organismal Process |
| 99 | 1.91E-28 | 1.09E-25 | Single-Multicellular Organism Process |
| 93 | 2.84E-27 | 1.35E-24 | Anatomical Structure Development |
| 54 | 5.26E-26 | 2.15E-23 | Tissue Development |
| 94 | 9.67E-26 | 3.24E-23 | Developmental Process |
| 86 | 1.02E-25 | 3.24E-23 | Multicellular Organism Development |
| 92 | 6.74E-25 | 1.92E-22 | Single-Organism Developmental Process |
| 78 | 9.93E-24 | 2.58E-21 | System Development |
| 26 | 4.07E-22 | 9.61E-20 | Extracellular Matrix Organization |
| 26 | 4.37E-22 | 9.61E-20 | Extracellular Structure Organization |
| 64 | 1.59E-21 | 3.25E-19 | Animal Organ Development |
| 23 | 3.23E-21 | 6.16E-19 | Skin Development |
| 125 | 5.38E-21 | 9.60E-19 | Biological Regulation |
| 23 | 2.68E-19 | 4.49E-17 | Epidermis Development |
| 118 | 3.16E-19 | 5.01E-17 | Regulation of Biological Process |
| 112 | 8.58E-18 | 1.29E-15 | Regulation of Cellular Process |
| 18 | 2.95E-17 | 4.21E-15 | Epidermal Cell Differentiation |
| 16 | 6.67E-17 | 8.67E-15 | Keratinocyte Differentiation |
| 34 | 6.68E-17 | 8.67E-15 | Epithelium Development |
| 15 | 2.75E-16 | 3.41E-14 | Collagen Metabolic Process |
| 96 | 3.34E-16 | 3.98E-14 | Response to Stimulus |
| 60 | 3.76E-16 | 4.29E-14 | Cell Differentiation |
| 15 | 4.98E-16 | 5.47E-14 | Multicellular Organismal Macromolecule Metabolic Process |
| 15 | 2.09E-15 | 2.21E-13 | Multicellular Organism Metabolic Process |
| 109 | 2.25E-15 | 2.29E-13 | Organic Substance Metabolic Process |
| 111 | 3.21E-15 | 3.16E-13 | Metabolic Process |
| 61 | 4.69E-15 | 4.46E-13 | Cellular Developmental Process |
| 71 | 6.89E-15 | 6.34E-13 | Positive Regulation of Biological Process |
| 12 | 1.36E-14 | 1.21E-12 | Collagen Catabolic Process |
| 61 | 1.95E-14 | 1.69E-12 | Single-Organism Metabolic Process |
| 12 | 2.93E-14 | 2.46E-12 | Multicellular Organism Catabolic Process |
| 47 | 5.07E-14 | 4.14E-12 | Anatomical Structure Morphogenesis |
| 64 | 2.38E-13 | 1.89E-11 | Positive Regulation of Cellular Process |
| 59 | 4.32E-13 | 3.33E-11 | Response to Chemical |
| 22 | 5.81E-13 | 4.36E-11 | Epithelial Cell Differentiation |
| 33 | 2.06E-12 | 1.51E-10 | Cell Adhesion |
| 33 | 2.34E-12 | 1.67E-10 | Biological Adhesion |
| 9 | 3.20E-12 | 2.23E-10 | Collagen Fibril Organization |
| 99 | 3.84E-12 | 2.61E-10 | Primary Metabolic Process |
| 38 | 4.04E-12 | 2.69E-10 | Cell Proliferation |
| 61 | 4.46E-12 | 2.89E-10 | Negative Regulation of Biological Process |
| 58 | 6.94E-12 | 4.40E-10 | Negative Regulation of Cellular Process |
| 19 | 3.19E-11 | 1.98E-09 | Skeletal System Development |
| 43 | 3.26E-11 | 1.98E-09 | Cellular Response to Chemical Stimulus |
| 32 | 3.97E-11 | 2.36E-09 | Regulation of Cell Proliferation |
| 89 | 6.58E-11 | 3.83E-09 | Macromolecule Metabolic Process |
| 9 | 6.92E-11 | 3.95E-09 | Peptide Cross-Linking |
| 75 | 9.55E-11 | 5.35E-09 | Cellular Response to Stimulus |
| 44 | 1.21E-10 | 6.66E-09 | Response to Organic Substance |
| 25 | 1.32E-10 | 7.12E-09 | Organ Morphogenesis |
| 95 | 1.95E-10 | 1.03E-08 | Cellular Metabolic Process |
| 41 | 3.98E-10 | 2.07E-08 | Cell Surface Receptor Signaling Pathway |
| 8 | 8.37E-10 | 4.27E-08 | Keratinization |
| 22 | 1.23E-09 | 6.17E-08 | Positive Regulation of Cell Proliferation |
| 9 | 2.44E-09 | 1.20E-07 | Extracellular Matrix Disassembly |
| 47 | 6.05E-09 | 2.93E-07 | Regulation of Response to Stimulus |
| 25 | 7.04E-09 | 3.35E-07 | Cell Migration |
| 26 | 9.48E-09 | 4.36E-07 | Cell Motility |
| 26 | 9.48E-09 | 4.36E-07 | Localization of Cell |
| 38 | 1.44E-08 | 6.55E-07 | Regulation of Multicellular Organismal Process |
| 64 | 1.89E-08 | 8.42E-07 | Single Organism Signaling |
| 64 | 1.96E-08 | 8.61E-07 | Signaling |
| 64 | 2.26E-08 | 9.60E-07 | Cell Communication |
| 17 | 2.26E-08 | 9.60E-07 | Tube Development |
| 28 | 2.31E-08 | 9.60E-07 | Response to Endogenous Stimulus |
| 63 | 2.32E-08 | 9.60E-07 | Cellular Component Organization |
| 33 | 3.58E-08 | 1.46E-06 | Response to ExteRNAl Stimulus |
| 27 | 3.74E-08 | 1.50E-06 | Locomotion |
| 17 | 4.51E-08 | 1.79E-06 | Tissue Morphogenesis |
| 63 | 5.92E-08 | 2.32E-06 | Cellular Component Organization orBiogenesis |
| 57 | 6.79E-08 | 2.62E-06 | Protein Metabolic Process |
| 35 | 8.50E-08 | 3.24E-06 | Immune System Process |
| 16 | 9.56E-08 | 3.59E-06 | Embryonic Morphogenesis |
| 37 | 9.89E-08 | 3.67E-06 | Regulation of Signal Transduction |
| 19 | 1.05E-07 | 3.83E-06 | Single-Organism Catabolic Process |
| 20 | 1.09E-07 | 3.92E-06 | Response to Lipid |
| 59 | 1.38E-07 | 4.92E-06 | Localization |
| 39 | 1.57E-07 | 5.54E-06 | Regulation of Cell Communication |
| 32 | 1.84E-07 | 6.40E-06 | Cellular Response to Organic Substance |
| 39 | 2.42E-07 | 8.34E-06 | Regulation of Signaling |
| 12 | 4.55E-07 | 1.55E-05 | Tube Morphogenesis |
| 38 | 4.68E-07 | 1.57E-05 | Positive Regulation of Metabolic Process |
| 57 | 6.03E-07 | 2.00E-05 | Signal Transduction |
| 27 | 6.55E-07 | 2.15E-05 | Movement of Cell orSubcellular Component |
| 36 | 6.69E-07 | 2.17E-05 | Positive Regulation of Cellular Metabolic Process |
| 10 | 7.69E-07 | 2.47E-05 | Connective Tissue Development |
| 26 | 7.83E-07 | 2.48E-05 | Positive Regulation of Gene Expression |
| 9 | 8.22E-07 | 2.58E-05 | Cartilage Development |
| 14 | 8.97E-07 | 2.78E-05 | Morphogenesis of An Epithelium |
| 19 | 9.83E-07 | 3.02E-05 | Embryo Development |
| 21 | 1.00E-06 | 3.05E-05 | Anatomical Structure Formation Involved In Morphogenesis |
| 25 | 1.28E-06 | 3.83E-05 | Proteolysis |
| 59 | 1.47E-06 | 4.37E-05 | Regulation of Metabolic Process |
| 20 | 1.62E-06 | 4.76E-05 | Secretion |
| 21 | 1.74E-06 | 5.08E-05 | Cellular Response to Endogenous Stimulus |
| 42 | 1.90E-06 | 5.48E-05 | Response to Stress |
| 13 | 2.33E-06 | 6.66E-05 | Regulation of Hormone Levels |
| **GO-CC** |  |  |  |
| 112 | 9.18E-50 | 2.52E-47 | Extracellular Region |
| 101 | 3.26E-46 | 4.46E-44 | Extracellular Region Part |
| 67 | 1.48E-26 | 1.08E-24 | Extracellular Exosome |
| 67 | 1.93E-26 | 1.08E-24 | Extracellular Vesicle |
| 67 | 1.96E-26 | 1.08E-24 | Extracellular Organelle |
| 28 | 1.47E-23 | 6.72E-22 | Proteinaceous Extracellular Matrix |
| 29 | 9.57E-23 | 3.58E-21 | Extracellular Matrix |
| 70 | 1.05E-22 | 3.58E-21 | Membrane-Bounded Vesicle |
| 44 | 5.41E-22 | 1.65E-20 | Extracellular Space |
| 70 | 8.08E-22 | 2.21E-20 | Vesicle |
| 153 | 1.49E-21 | 3.71E-20 | Cell |
| 152 | 4.79E-21 | 1.09E-19 | Cell Part |
| 129 | 6.27E-18 | 1.32E-16 | Organelle |
| 123 | 1.39E-17 | 2.72E-16 | Membrane-Bounded Organelle |
| 73 | 1.83E-16 | 3.35E-15 | Cell Periphery |
| 128 | 2.40E-14 | 4.12E-13 | Intracellular |
| 68 | 3.53E-14 | 5.69E-13 | Plasma Membrane |
| 125 | 6.83E-14 | 1.04E-12 | Intracellular Part |
| 94 | 7.16E-13 | 1.03E-11 | Membrane |
| 9 | 1.44E-11 | 1.97E-10 | Cornified Envelope |
| 100 | 7.31E-11 | 9.54E-10 | Cytoplasm |
| 11 | 1.96E-10 | 2.45E-09 | Extracellular Matrix Component |
| 68 | 1.07E-08 | 1.27E-07 | Membrane Part |
| 8 | 4.87E-08 | 5.56E-07 | Collagen Trimer |
| 20 | 2.11E-07 | 2.31E-06 | Plasma Membrane Region |
| 56 | 4.61E-07 | 4.86E-06 | Intrinsic Component of Membrane |
| 55 | 5.17E-07 | 5.25E-06 | Integral Component of Membrane |
| 7 | 1.13E-06 | 1.10E-05 | Basement Membrane |
| 11 | 5.40E-06 | 5.10E-05 | Apical Part of Cell |
| 93 | 5.71E-06 | 5.21E-05 | Intracellular Organelle |
| 19 | 1.73E-05 | 0.000153 | Cell Junction |
| 19 | 1.90E-05 | 0.000162 | Endoplasmic Reticulum Part |
| 23 | 2.45E-05 | 0.000203 | Endoplasmic Reticulum |
| 9 | 3.47E-05 | 0.000273 | Apical Plasma Membrane |
| 30 | 3.49E-05 | 0.000273 | Plasma Membrane Part |
| 66 | 7.13E-05 | 0.000542 | Cytoplasmic Part |
| 7 | 0.00017 | 0.001261 | Basolateral Plasma Membrane |
| 37 | 0.000248 | 0.001792 | Endomembrane System |
| 9 | 0.000263 | 0.00185 | Cell-Cell Junction |
| 7 | 0.000347 | 0.002336 | Intermediate Filament Cytoskeleton |
| 3 | 0.000349 | 0.002336 | Complex of Collagen Trimers |
| 80 | 0.000361 | 0.002356 | Intracellular Membrane-Bounded Organelle |
| 3 | 0.000437 | 0.002784 | Desmosome |
| 6 | 0.000728 | 0.004535 | Intermediate Filament |
| 6 | 0.000849 | 0.00517 | Endoplasmic Reticulum Lumen |
| 2 | 0.001784 | 0.010628 | Microfibril |
| 2 | 0.002443 | 0.013945 | Banded Collagen Fibril |
| 2 | 0.002443 | 0.013945 | Fibrillar Collagen Trimer |
| 60 | 0.002669 | 0.014628 | Intracellular Organelle Part |
| 13 | 0.002669 | 0.014628 | Endoplasmic Reticulum Membrane |
| 6 | 0.003027 | 0.016263 | Extrinsic Component of Membrane |
| 13 | 0.003186 | 0.016539 | Nuclear Outer Membrane-Endoplasmic Reticulum Membrane Network |
| 2 | 0.003199 | 0.016539 | Fibril |
| 60 | 0.004442 | 0.022539 | Organelle Part |
| 8 | 0.005112 | 0.025468 | Anchoring Junction |
| 6 | 0.005514 | 0.026977 | Cell Projection Membrane |
| 10 | 0.006242 | 0.030004 | Cell Surface |
| 8 | 0.007117 | 0.033051 | Lysosome |
| 8 | 0.007117 | 0.033051 | Lytic Vacuole |
| 2 | 0.007751 | 0.035396 | Proton-Transporting V-Type Atpase Complex |
| 4 | 0.008151 | 0.036614 | Growth Cone |
| 4 | 0.009135 | 0.040369 | Site of Polarized Growth |
| 5 | 0.00982 | 0.042652 | Cell Cortex |
| 9 | 0.010118 | 0.042652 | Polymeric Cytoskeletal Fiber |
| 9 | 0.010118 | 0.042652 | Supramolecular Fiber |
| 4 | 0.010637 | 0.044158 | Ruffle |
| 13 | 0.010866 | 0.044439 | Vacuole |
| 4 | 0.011326 | 0.045638 | Cytoplasmic Side of Plasma Membrane |
| 6 | 0.013147 | 0.052206 | Secretory Granule |
| 3 | 0.014645 | 0.057325 | Keratin Filament |
| 4 | 0.014923 | 0.057589 | Cytoplasmic Side of Membrane |
| 3 | 0.018102 | 0.068888 | Extrinsic Component of Cytoplasmic Side of Plasma Membrane |
| 3 | 0.019986 | 0.074713 | Endoplasmic Reticulum-Golgi Intermediate Compartment |
| 5 | 0.020178 | 0.074713 | Cytoplasmic Region |
| 15 | 0.02157 | 0.078803 | Integral Component of Plasma Membrane |
| 3 | 0.023007 | 0.082945 | Bicellular Tight Junction |
| 3 | 0.024605 | 0.086639 | Occluding Junction |
| 6 | 0.024664 | 0.086639 | Side of Membrane |
| 15 | 0.028369 | 0.098395 | Intrinsic Component of Plasma Membrane |
| 2 | 0.02903 | 0.099427 | Proton-Transporting Two-Sector Atpase Complex |
| 2 | 0.030111 | 0.100615 | Chloride Channel Complex |
| 2 | 0.030111 | 0.100615 | Lateral Plasma Membrane |
| 3 | 0.032835 | 0.108395 | Apical Junction Complex |
| 8 | 0.033586 | 0.109554 | Vacuolar Part |
| 3 | 0.03608 | 0.11509 | Leading Edge Membrane |
| 1 | 0.036543 | 0.11509 | Collagen Type Iv Trimer |
| 1 | 0.036543 | 0.11509 | Vacuolar Proton-Transporting V-Type Atpase, V0 Domain |
| 7 | 0.039698 | 0.120139 | Vacuolar Membrane |
| 6 | 0.040466 | 0.120139 | Secretory Vesicle |
| 2 | 0.040531 | 0.120139 | Cortical Actin Cytoskeleton |
| 3 | 0.040889 | 0.120139 | Extrinsic Component of Plasma Membrane |
| 5 | 0.041502 | 0.120139 | Cell Leading Edge |
| 1 | 0.041654 | 0.120139 | Network-Forming Collagen Trimer |
| 1 | 0.041654 | 0.120139 | Collagen Network |
| 1 | 0.041654 | 0.120139 | Growth Cone Membrane |
| 1 | 0.046738 | 0.129355 | Smad Protein Complex |
| 1 | 0.046738 | 0.129355 | Intercellular Canaliculus |
| 1 | 0.046738 | 0.129355 | Basement Membrane Collagen Trimer |
| 1 | 0.046738 | 0.129355 | Laminin Complex |
| 2 | 0.048121 | 0.131852 | Endoplasmic Reticulum-Golgi Intermediate Compartment Membrane |
| **GO-MF** |  |  |  |
| 150 | 4.84E-26 | 2.27E-23 | Binding |
| 118 | 7.69E-19 | 1.80E-16 | Protein Binding |
| 33 | 4.03E-12 | 6.30E-10 | Receptor Binding |
| 14 | 4.14E-11 | 4.86E-09 | Cytokine Activity |
| 21 | 5.75E-10 | 5.39E-08 | Structural Molecule Activity |
| 10 | 1.08E-09 | 8.43E-08 | Metalloendopeptidase Activity |
| 11 | 8.49E-09 | 5.69E-07 | Metallopeptidase Activity |
| 11 | 2.58E-08 | 1.48E-06 | Serine-Type Peptidase Activity |
| 11 | 2.83E-08 | 1.48E-06 | Serine Hydrolase Activity |
| 26 | 3.83E-08 | 1.79E-06 | Transition Metal Ion Binding |
| 48 | 1.36E-07 | 5.79E-06 | Cation Binding |
| 47 | 2.65E-07 | 1.04E-05 | Metal Ion Binding |
| 48 | 3.92E-07 | 1.35E-05 | Ion Binding |
| 13 | 4.04E-07 | 1.35E-05 | Endopeptidase Activity |
| 9 | 8.97E-07 | 2.64E-05 | Serine-Type Endopeptidase Activity |
| 20 | 9.00E-07 | 2.64E-05 | Sequence-Specific DNA Binding |
| 15 | 1.14E-06 | 3.15E-05 | Peptidase Activity, Acting on L-Amino Acid Peptides |
| 16 | 1.26E-06 | 3.28E-05 | Sequence-Specific Double-Stranded DNA Binding |
| 15 | 1.69E-06 | 4.02E-05 | Peptidase Activity |
| 11 | 1.71E-06 | 4.02E-05 | Transcriptional Activator Activity, RNA Polymerase II Transcription Regulatory Region Sequence-Specific Binding |
| 15 | 2.01E-06 | 4.49E-05 | RNA Polymerase II Transcription Factor Activity, Sequence-Specific DNA Binding |
| 11 | 2.42E-06 | 5.16E-05 | Transcription Factor Activity, RNA Polymerase II Core Promoter Proximal Region Sequence-Specific Binding |
| 9 | 2.59E-06 | 5.28E-05 | Peptidase Regulator Activity |
| 8 | 3.37E-06 | 6.45E-05 | Growth Factor Activity |
| 15 | 3.44E-06 | 6.45E-05 | Transcription Regulatory Region Sequence-Specific DNA Binding |
| 8 | 3.85E-06 | 6.94E-05 | Endopeptidase Inhibitor Activity |
| 16 | 4.59E-06 | 7.97E-05 | Double-Stranded DNA Binding |
| 8 | 4.97E-06 | 8.33E-05 | Endopeptidase Regulator Activity |
| 8 | 5.40E-06 | 8.61E-05 | Peptidase Inhibitor Activity |
| 9 | 5.50E-06 | 8.61E-05 | Transcriptional Activator Activity, RNA Polymerase II Core Promoter Proximal Region Sequence-Specific Binding |
| 15 | 6.22E-06 | 9.41E-05 | Calcium Ion Binding |
| 16 | 9.98E-06 | 0.000146 | Transcription Regulatory Region DNA Binding |
| 16 | 1.04E-05 | 0.000146 | Regulatory Region DNA Binding |
| 16 | 1.06E-05 | 0.000146 | Regulatory Region Nucleic Acid Binding |
| 20 | 1.32E-05 | 0.000176 | Macromolecular Complex Binding |
| 21 | 1.35E-05 | 0.000176 | Molecular Function Regulator |
| 19 | 1.65E-05 | 0.000209 | Zinc Ion Binding |
| 8 | 1.80E-05 | 0.000213 | Glycosaminoglycan Binding |
| 53 | 1.81E-05 | 0.000213 | Catalytic Activity |
| 13 | 1.81E-05 | 0.000213 | RNA Polymerase II Regulatory Region Sequence-Specific DNA Binding |
| 13 | 1.95E-05 | 0.000223 | RNA Polymerase II Regulatory Region DNA Binding |
| 7 | 2.32E-05 | 0.000253 | Oxidoreductase Activity, Acting on Paired Donors, With Incorporation or Reduction of Molecular Oxygen |
| 9 | 2.32E-05 | 0.000253 | Cytokine Receptor Binding |
| 7 | 2.83E-05 | 0.000301 | Heparin Binding |
| 5 | 3.66E-05 | 0.000376 | Collagen Binding |
| 14 | 3.69E-05 | 0.000376 | Oxidoreductase Activity |
| 3 | 4.05E-05 | 0.000404 | Receptor Antagonist Activity |
| 3 | 6.39E-05 | 0.000624 | Receptor Inhibitor Activity |
| 14 | 6.92E-05 | 0.000662 | Protein Complex Binding |
| 5 | 7.39E-05 | 0.000693 | Extracellular Matrix Structural Constituent |
| 18 | 0.000108 | 0.00099 | Identical Protein Binding |
| 4 | 0.000135 | 0.001219 | Receptor Regulator Activity |
| 5 | 0.000174 | 0.001536 | Cytokine Binding |
| 9 | 0.000201 | 0.001748 | Enzyme Inhibitor Activity |
| 6 | 0.000239 | 0.001949 | Iron Ion Binding |
| 4 | 0.000244 | 0.001949 | Transcriptional Activator Activity, RNA Polymerase II Transcription Factor Binding |
| 4 | 0.000244 | 0.001949 | Transcriptional Repressor Activity, RNA Polymerase II Activating Transcription Factor Binding |
| 17 | 0.000247 | 0.001949 | Nucleic Acid Binding Transcription Factor Activity |
| 17 | 0.000247 | 0.001949 | Transcription Factor Activity, Sequence-Specific DNA Binding |
| 7 | 0.000249 | 0.001949 | Sulfur Compound Binding |
| 3 | 0.000349 | 0.002687 | Aromatase Activity |
| 26 | 0.000468 | 0.00354 | Hydrolase Activity |
| 3 | 0.000485 | 0.003614 | Oxidoreductase Activity, Acting on Paired Donors, With Incorporation orReduction of Molecular Oxygen, Reduced Flavin orFlavoprotein as One Donor, And Incorporation of One Atom of Oxygen |
| 5 | 0.000647 | 0.004739 | Heme Binding |
| 14 | 0.000684 | 0.004935 | Enzyme Regulator Activity |
| 5 | 0.000718 | 0.005099 | Growth Factor Receptor Binding |
| 2 | 0.000768 | 0.005373 | Interleukin-1 Binding |
| 5 | 0.000876 | 0.006045 | Tetrapyrrole Binding |
| 8 | 0.000894 | 0.006075 | Core Promoter Proximal Region Sequence-Specific DNA Binding |
| 4 | 0.00093 | 0.006215 | Rho Guanyl-Nucleotide Exchange Factor Activity |
| 8 | 0.000941 | 0.006215 | Core Promoter Proximal Region DNA Binding |
| 3 | 0.001168 | 0.007606 | RNA Polymerase II Transcription Coactivator Activity |
| 2 | 0.001225 | 0.007871 | Structural Constituent of Epidermis |
| 3 | 0.001351 | 0.008565 | Oxidoreductase Activity, Acting on Paired Donors, With Incorporation orReduction of Molecular Oxygen, Nad(P)H as One Donor, And Incorporation of One Atom of Oxygen |
| 4 | 0.001376 | 0.008606 | Transcriptional Repressor Activity, RNA Polymerase II Transcription Factor Binding |
| 2 | 0.001492 | 0.009208 | Protein-Glutamine Gamma-Glutamyltransferase Activity |
| 4 | 0.00168 | 0.010231 | Serine-Type Endopeptidase Inhibitor Activity |
| 5 | 0.001784 | 0.010592 | Protein Binding, Bridging |
| 2 | 0.001784 | 0.010592 | Bmp Binding |
| 4 | 0.001813 | 0.01063 | Monooxygenase Activity |
| 3 | 0.002134 | 0.012355 | Scavenger Receptor Activity |
| 5 | 0.002315 | 0.013239 | Transcriptional Repressor Activity, RNA Polymerase II Transcription Regulatory Region Sequence-Specific Binding |
| 2 | 0.002443 | 0.013804 | toxic Substance Binding |
| 4 | 0.002681 | 0.014967 | Transcriptional Repressor Activity, RNA Polymerase II Core Promoter Proximal Region Sequence-Specific Binding |
| 5 | 0.002749 | 0.01517 | Binding, Bridging |
| 2 | 0.002809 | 0.015281 | Rac Guanyl-Nucleotide Exchange Factor Activity |
| 3 | 0.002835 | 0.015281 | Oxygen Binding |
| 7 | 0.002876 | 0.015326 | RNA Polymerase II Core Promoter Proximal Region Sequence-Specific DNA Binding |
| 8 | 0.003011 | 0.015867 | Chromatin Binding |
| 2 | 0.003613 | 0.018828 | Oxidoreductase Activity, Acting on The Ch-Nh2 Group of Donors, Oxygen as Acceptor |
| 3 | 0.003662 | 0.018873 | Cysteine-Type Endopeptidase Inhibitor Activity |
| 9 | 0.004542 | 0.023157 | Transcription Factor Activity, Transcription Factor Binding |
| 9 | 0.004743 | 0.023918 | Transcription Factor Activity, Protein Binding |
| 2 | 0.004995 | 0.024922 | Retinol Dehydrogenase Activity |
| 4 | 0.005053 | 0.024947 | Growth Factor Binding |
| 2 | 0.005502 | 0.026878 | Oxidoreductase Activity, Acting on The Ch-Nh2 Group of Donors |
| 3 | 0.005959 | 0.028811 | Cargo Receptor Activity |
| 4 | 0.006399 | 0.030623 | Transcription Factor Activity, RNA Polymerase II Transcription Factor Binding |
| 2 | 0.007156 | 0.033899 | Transferase Activity, Transferring Amino-Acyl Groups |
| 3 | 0.007504 | 0.035193 | Smad Binding |

**Table S6. KEGG enrichment analysis results of the DEGs**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene**  **counts** | **P-Value** | **FDR** | **Terms** |
| 5 | 4.79E-05 | 0.005747 | Drug metabolism - cytochrome P450 |
| 5 | 0.000157 | 0.006615 | Protein digestion and absorption |
| 5 | 0.000165 | 0.006615 | Rheumatoid arthritis |
| 4 | 0.000508 | 0.015231 | Retinol metabolism |
| 4 | 0.000769 | 0.018455 | Metabolism of xenobiotics by cytochrome P450 |
| 4 | 0.001163 | 0.019932 | ECM-receptor interaction |
| 4 | 0.001163 | 0.019932 | Chemical carcinogenesis |
| 4 | 0.002338 | 0.03507 | Amoebiasis |
| 6 | 0.003378 | 0.045037 | Cytokine-cytokine receptor interaction |
| 4 | 0.004149 | 0.049782 | Leukocyte transendothelial migration |