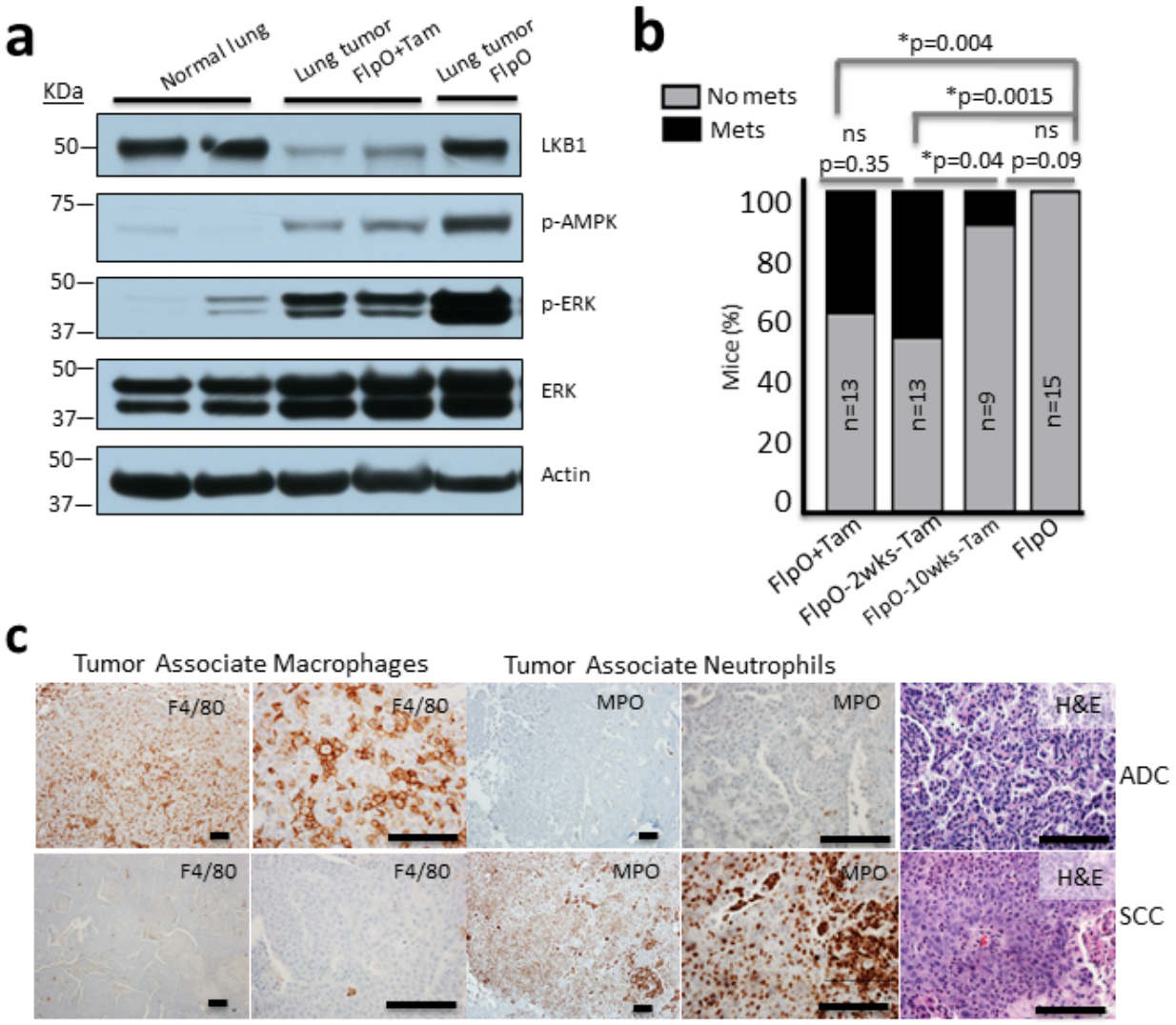
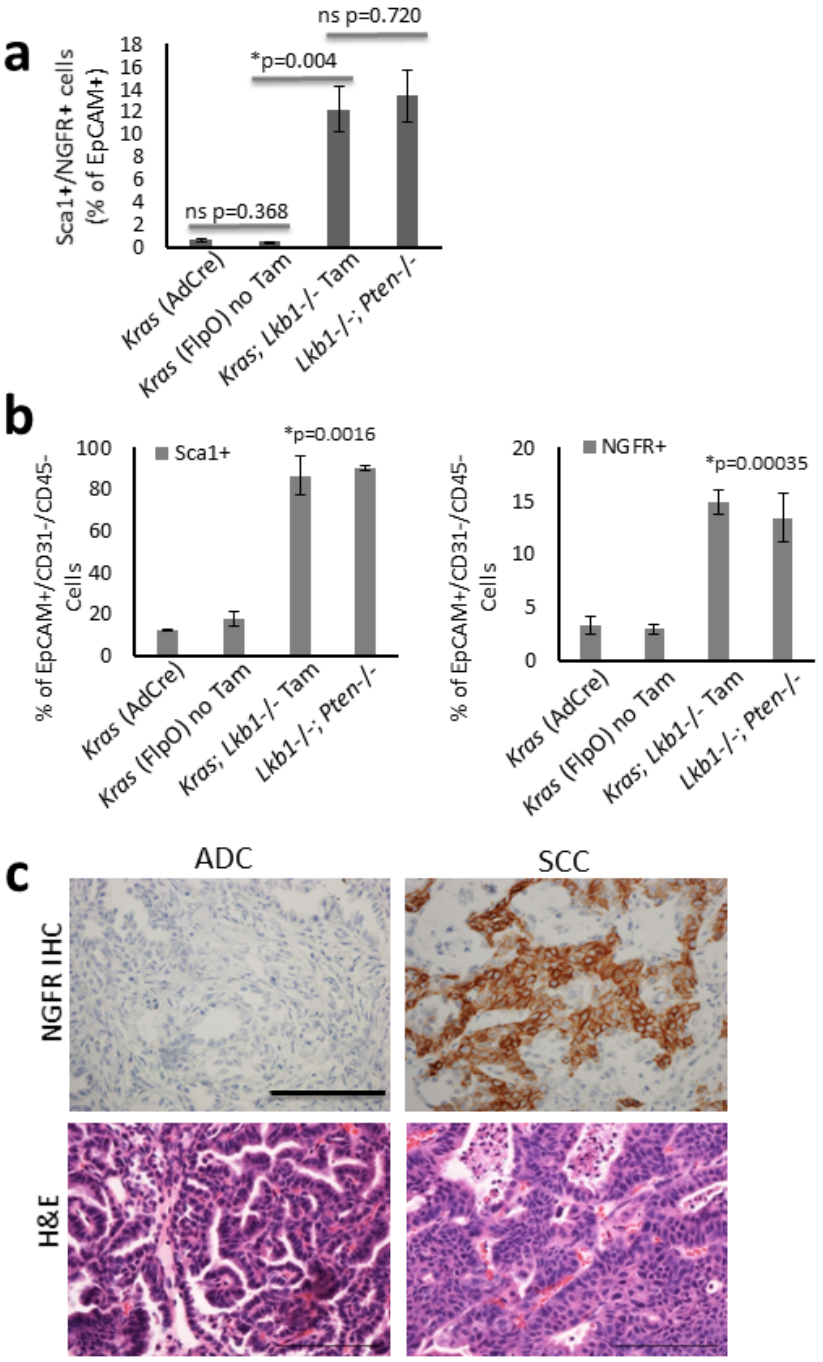


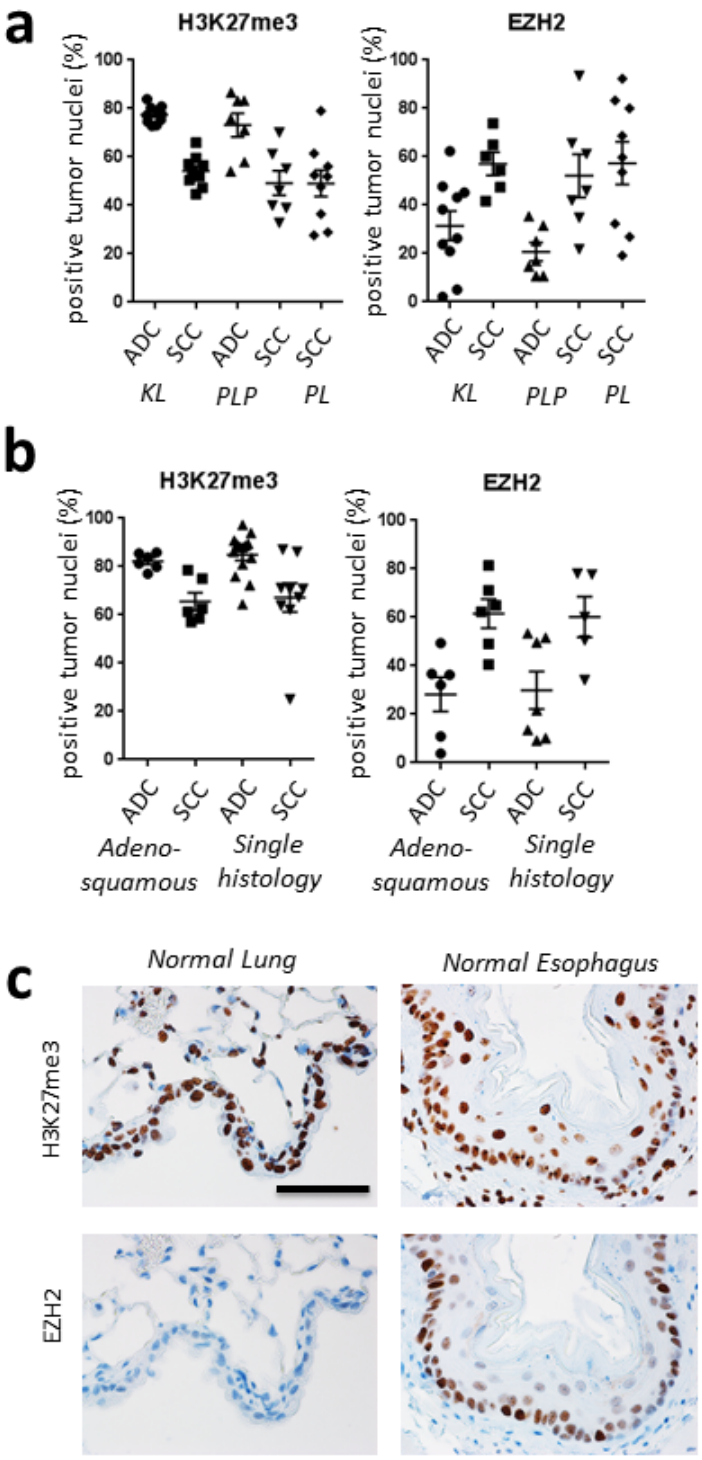

**Supplementary Figure 1: *Lkb1* deletion drives SCC transition and tumor progression in established KRAS tumors**

**a)** Western Blotting for LKB1, p-AMPK, p-ERK and total ERK in the indicated whole cell extracts. *Lkb1* deletion markedly decreases p-AMPK as expected. β-actin is the loading control. **b)** Incidence of metastasis within the cohorts as assessed by histologic examination of lymph nodes at endpoint, n and p values indicated on figure, p values represent Chi-squared test. **c)**



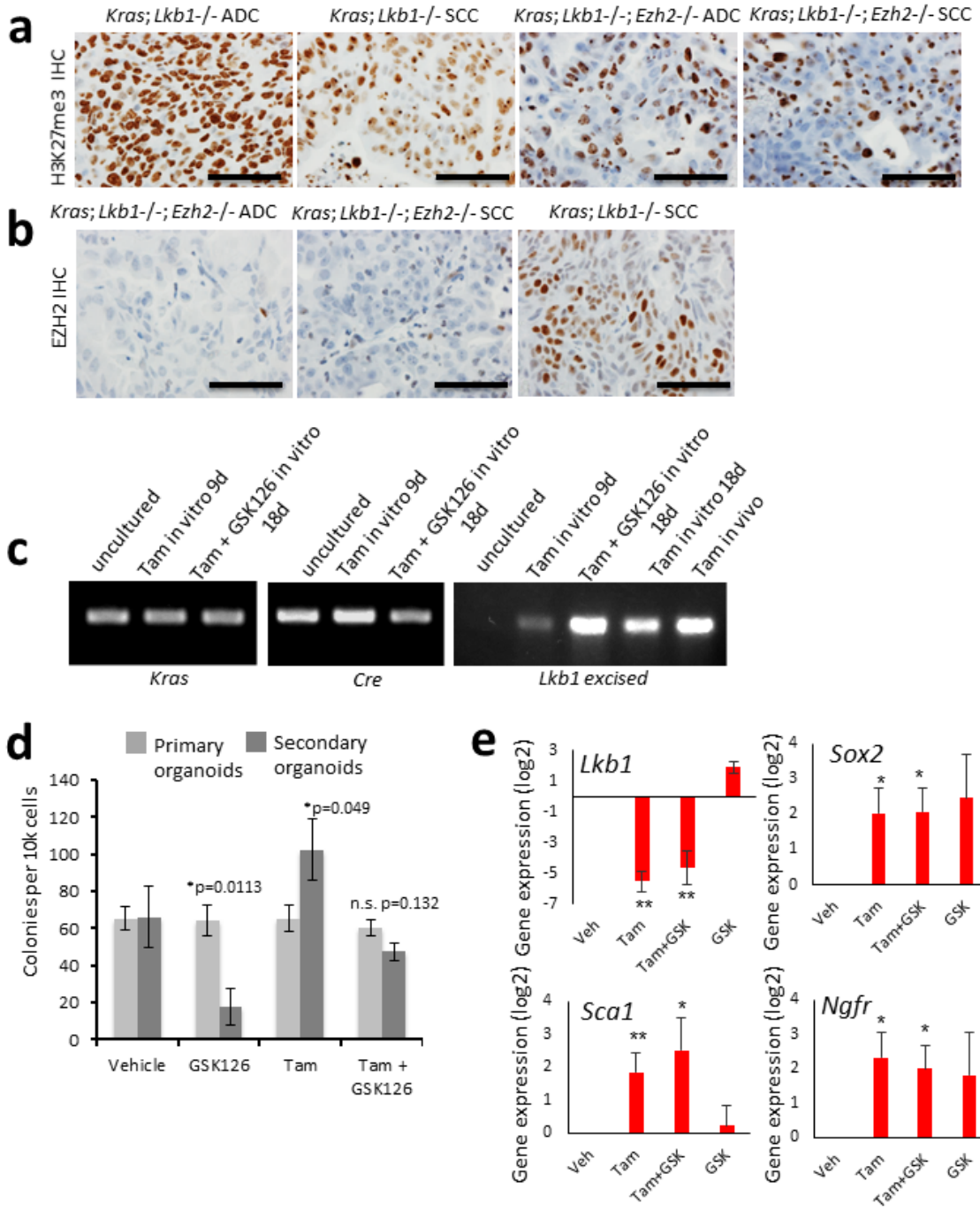

**Supplementary Figure 2: *Lkb1* deletion after transplant of KRAS adenocarcinoma cells drives SCC transition**

**a)** Flow cytometric analysis for average percentage of $NGFR^+/Sca1^+$ cells within the $DAPI^-/CD31^-/CD45^-/EpCAM^+$ of freshly dissociated tumors. Mean ± s.e.m. graphed, n=4 AdCre KRAS, n=3 no Tam, n=4 Tam, n=3 *Lkb1/Pten*, p values indicated on figure. **b)** Flow cytometric analysis for Sca1 and NGFR expression on the $DAPI^-/CD45^-/CD31^-/EpCAM^+$ cells of dissociated tumors from the indicated cohorts, mean ± s.e.m. graphed, n=4 AdCre KRAS, n=3 no Tam, n=4 Tam, n=3 *Lkb1/Pten*, p values for no Tam vs Tam comparison indicated on figure. **c)** Serial sections of hematoxylin and eosin staining of tumors paired with immunohistochemistry for NGFR, marking some epithelial cells in the post tamoxifen tumors, scale bar = 50μm.



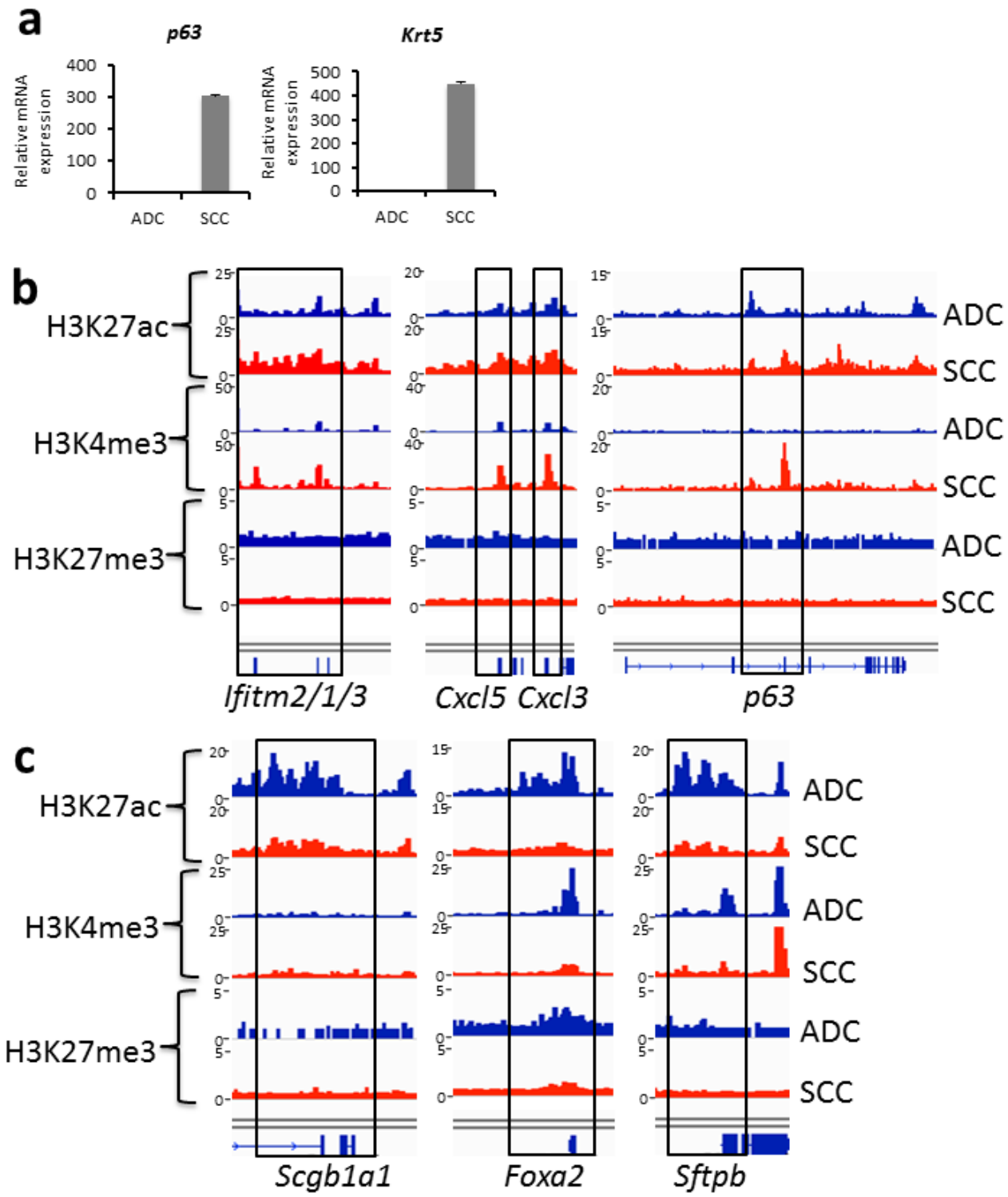

**Supplementary Figure 3: Loss of histone H3 lysine 27 trimethylation accompanies SCC transition**

**a+b)** More detailed graphical representation of the immunohistochemistry quantifications for EZH2 and H3K27me3 expression in the indicated tumor sections, **a)** murine tumors, **b)** human tumors. Mean ± s.e.m. graphed and each n can be observed on the graphs. **c)** Serial sections of immunohistochemistry for EZH2 and H3K27me3 in normal murine distal lung and esophagus, scale bar = 50μm.



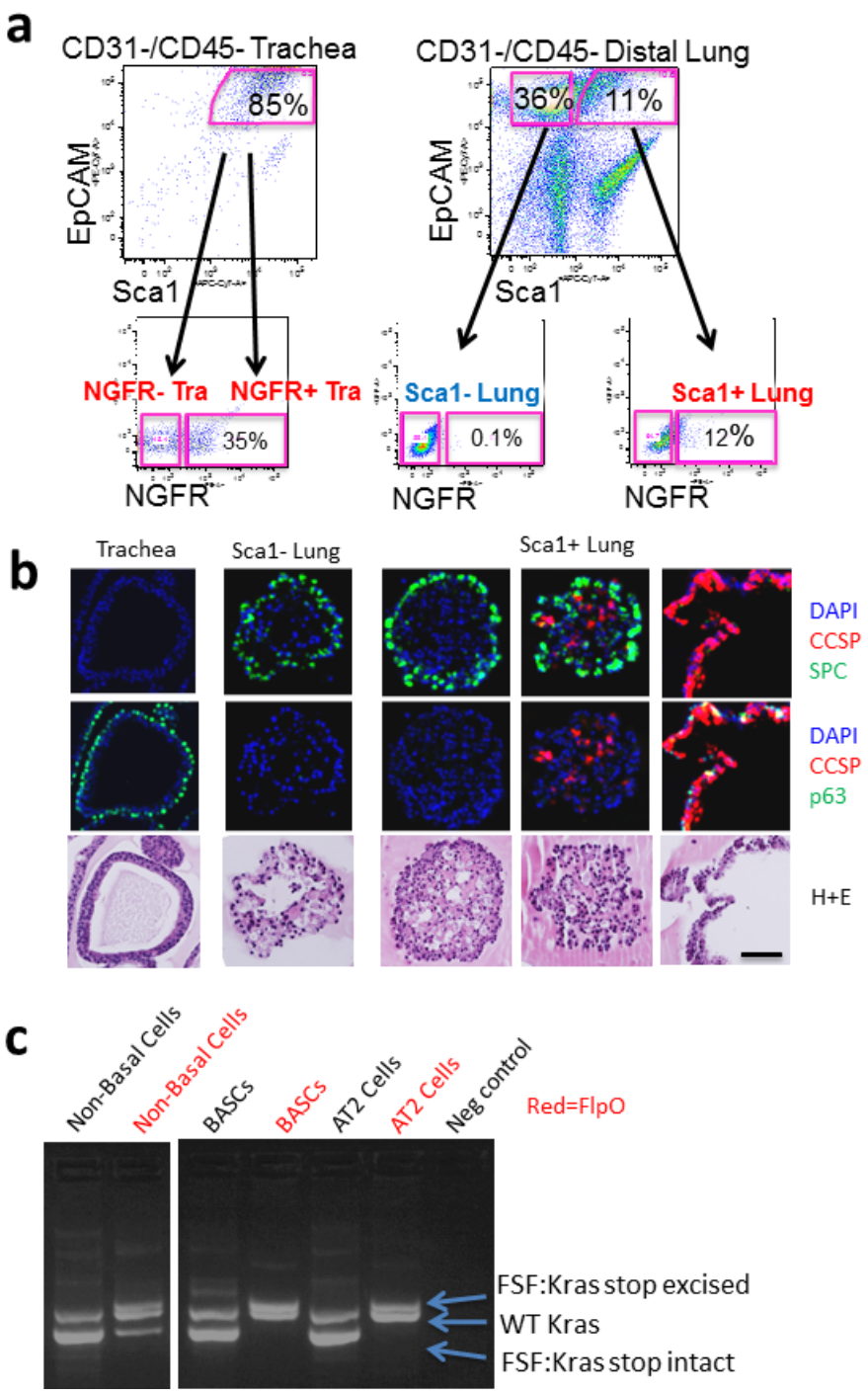

**Supplementary Figure 4: Deletion or inhibition of EZH2 potentiates SCC transition**

**a)** Immunohistochemistry for H3K27me3 in tumors of the indicated genotypes, scale bar = 50μm. **b)** Immunohistochemistry for EZH2 in tumors of the indicated genotypes, scale bar = 50μm. **c)** PCR for alleles from the 3D tumor organoid cultures with the indicated treatments, *Kras* and *Cre* shown as controls, the excised *Lkb1* band is only present with tamoxifen treatment. **d)** Average number of colonies per 10,000 cells plated in the 3D cultures in the indicated treatments, mean ± s.e.m. graphed, n=5 for primary cultures, n=3 for secondary cultures, p values indicated on figure. **e)** RT-qPCR for *Sox2*, *Sca1* and *Lkb1* in secondary tumor organoid 3D cultures treated with 100nM tamoxifen, 5μM of EZH2 inhibitor GSK126, or both for 18-24 days total, mean ± s.e.m. on $\log_2$ scale is graphed, ** indicates $p<0.01$, * indicates $p<0.05$, n=4 except for GSK, n=2.



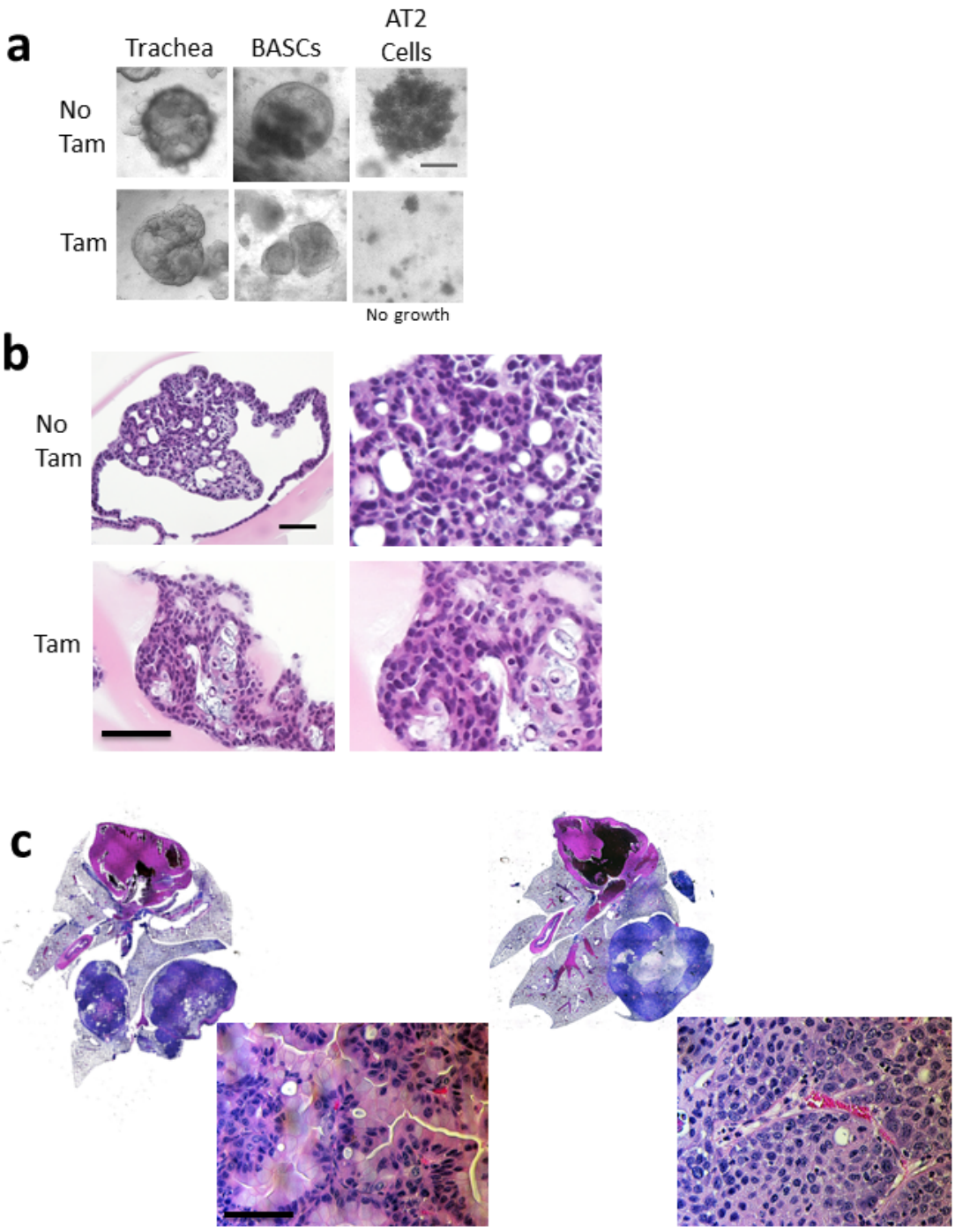

**Supplementary Figure 5: Chromatin landscapes of ADC and SCCs reveal de-repression of squamous genes**

**a)** RT-qPCR for expression the squamous genes *p63* and *Krt5* to confirm subtypes of tumors used for ChIP experiments. **b)** Genome browser snapshots of the squamous loci *Ifitm3, Cxcl3/5 and p63* with the indicated ChIP-sequencing peaks for H3K27ac, H3K27me3 and H3K4me3 in the ADC (blue) and SCC (red) KRAS/*Lkb1* tumor samples. **c)** Genome browser snapshots of the squamous loci *Scgb1a1*, *Foxa2* and *Sftpb* with the indicated ChIP-sequencing peaks for H3K27ac, H3K27me3 and H3K4me3 in the ADC (blue) and SCC (red) KRAS/*Lkb1* tumor samples.




**Supplementary Figure 6: KRAS activation is tolerated by Club Cell, BASC and AT2 Cell populations**

**a)** Flow cytometry scheme for isolating stem and progenitor populations. Basal cells are isolated from tracheal cell preparations by exclusion of CD31 and CD45, and gating on EpCAM+, Sca1+ and NGFR+ cells. Non-basal cells are EpCAM+ and Sca1+ but NGFR-. In the distal lung preparations, again CD31 and CD45 are excluded, prior to gating on EpCAM+ cells. Sca1- cells are enriched for AT2 cells, which are uniformly NGFR- in the normal mouse. BASCs are Sca1+ and some express NGFR. We used both NGFR+ and NGFR- BASCs for our experiments. **b)** Representative immunofluoresence for the cell lineage markers CCSP, SPC and p63 in indicated organoid cultures sections with hematoxylin and eosin staining below, scale bar = 50μm. **c)** PCR for *Kras* excision in organoid cultures derived from the indicated sorted lung cell populations.




**Supplementary Figure 7: *Lkb1* Deletion Drives Squamous Transition of Club Cell- and BASC-derived KRAS+ populations**

**a)** Representative brightfield images of KRAS+ colonies from the indicated cell types, scale bar = 100μm. **b)** Representative hematoxylin and eosin staining of sections from tracheal derived organoids treated with the indicated tamoxifen or not for 9 days, scale bar = 100μm. **c)** Whole lung histology, with representative images of magnified histology of the tumor from each lung, from BASC derived orthotopically transplanted KRAS/*Lkb1* cells, scale bar = 50μm.

## Supplementary Table 1: *Unique H3K27ac peaks in SCC samples*

***Unique somatic peaks associated with protein coding genes, top 185 of a possible 246 with Log2FC>2.5, p value<1E-10***

| LOG2FC | Negative LOG10 (p value) | Gene Name | Gene Description |
|---|---|---|---|
| 6.259 | 300.000 | Tmem45b | transmembrane protein 45b |
| 5.987 | 300.000 | Mroh5 | maestro heat-like repeat family member 5 |
| 5.985 | 275.755 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 5.704 | 71.065 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 5.496 | 25.304 | Chst9 | carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9 |
| 5.496 | 25.304 | Fut9 | fucosyltransferase 9 |
| 5.183 | 29.366 | Foxd4 | forkhead box D4 |
| 5.119 | 27.901 | Dgkg | diacylglycerol kinase, gamma |
| 5.099 | 44.700 | Slitrk6 | SLIT and NTRK-like family, member 6 |
| 5.086 | 27.316 | Tmprss11g | transmembrane protease, serine 11g |
| 5.018 | 25.854 | Barx2 | BarH-like homeobox 2 |
| 4.915 | 38.893 | Chst9 | carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9 |
| 4.841 | 36.578 | Fabp12 | fatty acid binding protein 12 |
| 4.716 | 20.612 | Chst9 | carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9 |
| 4.683 | 32.252 | Cpne8 | copine VIII |
| 4.671 | 25.993 | Ccdc91 | coiled-coil domain containing 91 |
| 4.603 | 24.552 | Car12 | carbonic anyhydrase 12 |
| 4.594 | 104.904 | Engase | endo-beta-N-acetylglucosaminidase |
| 4.588 | 18.584 | Sox2 | SRY (sex determining region Y)-box 2 |
| 4.415 | 26.237 | Gpr115 | G protein-coupled receptor 115 |
| 4.381 | 20.538 | A1bg | alpha-1-B glycoprotein |
| 4.335 | 29.096 | Tnc | tenascin C |
| 4.304 | 32.817 | Lbx1 | ladybird homeobox homolog 1 (Drosophila) |
| 4.273 | 40.836 | Pyroxd1 | pyridine nucleotide-disulphide oxidoreductase domain 1 |
| 4.262 | 49.142 | Ndfip2 | Nedd4 family interacting protein 2 |
| 4.210 | 22.261 | Hlf | hepatic leukemia factor |
| 4.179 | 78.192 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 4.174 | 21.414 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 4.098 | 20.287 | Tmprss11a | transmembrane protease, serine 11a |
| 4.074 | 89.946 | Ccdc91 | coiled-coil domain containing 91 |
| 4.053 | 95.768 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 4.035 | 15.713 | Mfsd10 | major facilitator superfamily domain containing 10 |
| 4.023 | 26.079 | Cpne8 | copine VIII |
| 3.890 | 26.490 | Tmprss11g | transmembrane protease, serine 11g |
| 3.800 | 24.287 | Pthlh | parathyroid hormone-like peptide |
| 3.796 | 18.456 | Irf5 | interferon regulatory factor 5 |
| 3.796 | 18.456 | Tmprss11g | transmembrane protease, serine 11g |
| 3.796 | 21.371 | Secisbp2 | SECIS binding protein 2 |
| 3.796 | 21.371 | Sord | sorbitol dehydrogenase |
| 3.713 | 14.714 | Marcks | myristoylated alanine rich protein kinase C substrate |
| 3.703 | 43.557 | Ehf | ets homologous factor |
| 3.699 | 38.259 | Six1 | sine oculis-related homeobox 1 |
| 3.686 | 58.643 | Phospho1 | phosphatase, orphan 1 |
| 3.679 | 61.023 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.658 | 82.717 | Helt | helt bHLH transcription factor |
| 3.652 | 28.958 | Prl2c5 | prolactin family 2, subfamily c, member 5 |
| 3.635 | 85.867 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.588 | 39.244 | Cdh6 | cadherin 6 |
| 3.564 | 12.796 | Sc5d | sterol-C5-desaturase (fungal ERG3, delta-5-desaturase) homolog (S. cerevisae) |
| 3.517 | 25.727 | Pthlh | parathyroid hormone-like peptide |
| 3.503 | 49.531 | S100a8 | S100 calcium binding protein A8 (calgranulin A) |
| 3.501 | 32.071 | Pyroxd1 | pyridine nucleotide-disulphide oxidoreductase domain 1 |
| 3.501 | 27.573 | Trp63 | transformation related protein 63 |
| 3.496 | 18.582 | Zfand2b | zinc finger, AN1 type domain 2B |
| 3.489 | 25.191 | Rps23 | ribosomal protein S23 |
| 3.452 | 15.932 | Frmd6 | FERM domain containing 6 |
| 3.450 | 13.820 | Capns2 | calpain, small subunit 2 |
| 3.437 | 44.498 | Ehf | ets homologous factor |
| 3.425 | 31.794 | Ppp1r3b | protein phosphatase 1, regulatory (inhibitor) subunit 3B |
| 3.418 | 41.852 | Olfr52 | olfactory receptor 52 |
| 3.398 | 37.089 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.366 | 14.595 | Rcn1 | reticulocalbin 1 |
| 3.352 | 12.479 | Amotl1 | angiomotin-like 1 |
| 3.342 | 16.180 | C9 | complement component 9 |
| 3.342 | 16.180 | Ccdc91 | coiled-coil domain containing 91 |
| 3.340 | 21.739 | Fbxl14 | F-box and leucine-rich repeat protein 14 |
| 3.332 | 31.012 | Gm5483 | predicted gene 5483 |
| 3.326 | 17.768 | Il1b | interleukin 1 beta |

| | | | |
|---|---|---|---|
| 3.305 | 37.649 | Gm5483 | predicted gene 5483 |
| 3.290 | 31.559 | Tnc | tenascin C |
| 3.281 | 18.833 | Qsox2 | quiescin Q6 sulfhydryl oxidase 2 |
| 3.276 | 22.281 | Cpeb2 | cytoplasmic polyadenylation element binding protein 2 |
| 3.275 | 13.534 | Rps23 | ribosomal protein S23 |
| 3.259 | 15.124 | Arhgap5 | Rho GTPase activating protein 5 |
| 3.259 | 15.124 | Gab1 | growth factor receptor bound protein 2-associated protein 1 |
| 3.248 | 23.614 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 3.248 | 23.614 | Ranbp6 | RAN binding protein 6 |
| 3.246 | 18.309 | Ipcef1 | interaction protein for cytohesin exchange factors 1 |
| 3.246 | 18.309 | Rbbp6 | retinoblastoma binding protein 6 |
| 3.217 | 14.336 | Chac1 | ChaC, cation transport regulator 1 |
| 3.217 | 14.336 | Entpd3 | ectonucleoside triphosphate diphosphohydrolase 3 |
| 3.217 | 14.336 | Perp | PERP, TP53 apoptosis effector |
| 3.203 | 47.308 | Vsnl1 | visinin-like 1 |
| 3.200 | 175.564 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 3.197 | 23.911 | Il1b | interleukin 1 beta |
| 3.191 | 40.144 | Il1r2 | interleukin 1 receptor, type II |
| 3.189 | 53.185 | Supt20 | suppressor of Ty 20 |
| 3.174 | 17.005 | Irf6 | interferon regulatory factor 6 |
| 3.166 | 263.729 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 3.165 | 48.704 | Cpeb2 | cytoplasmic polyadenylation element binding protein 2 |
| 3.164 | 32.722 | Trp63 | transformation related protein 63 |
| 3.160 | 21.537 | Oasl2 | 2'-5' oligoadenylate synthetase-like 2 |
| 3.160 | 21.537 | Pthlh | parathyroid hormone-like peptide |
| 3.119 | 19.166 | Irg1 | immunoresponsive gene 1 |
| 3.099 | 20.250 | Bcl2l15 | BCLl2-like 15 |
| 3.093 | 32.016 | Fam122a | family with sequence similarity 122, member A |
| 3.088 | 33.359 | Tas2r126 | taste receptor, type 2, member 126 |
| 3.069 | 60.172 | Cdca7 | cell division cycle associated 7 |
| 3.060 | 15.199 | Gzmk | granzyme K |
| 3.060 | 15.199 | Slamf6 | SLAM family member 6 |
| 3.059 | 23.768 | Oacyl | O-acyltransferase like |
| 3.055 | 29.399 | Slco1a6 | solute carrier organic anion transporter family, member 1a6 |
| 3.053 | 74.967 | Upp1 | uridine phosphorylase 1 |
| 3.052 | 18.140 | Rps27a | ribosomal protein S27A |
| 3.036 | 16.286 | Tmppe | transmembrane protein with metallophosphoesterase domain |
| 3.032 | 23.260 | Tbc1d8 | TBC1 domain family, member 8 |
| 3.021 | 51.760 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.019 | 50.415 | Ptpn22 | protein tyrosine phosphatase, non-receptor type 22 (lymphoid) |
| 3.018 | 25.695 | Il1b | interleukin 1 beta |
| 3.018 | 17.375 | 1810011O10Rik | RIKEN cDNA 1810011O10 gene |
| 3.013 | 59.582 | S100a8 | S100 calcium binding protein A8 (calgranulin A) |
| 3.011 | 96.166 | Ccdc91 | coiled-coil domain containing 91 |
| 2.983 | 32.758 | Zfyve26 | zinc finger, FYVE domain containing 26 |
| 2.972 | 23.088 | Krt5 | keratin 5 |
| 2.970 | 17.959 | Dgkh | diacylglycerol kinase, eta |
| 2.963 | 26.873 | Iyd | iodotyrosine deiodinase |
| 2.962 | 28.219 | Ccpg1 | cell cycle progression 1 |
| 2.961 | 15.269 | Syt6 | synaptotagmin VI |
| 2.952 | 68.786 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 2.948 | 35.292 | Mmp25 | matrix metallopeptidase 25 |
| 2.940 | 25.026 | Marcks | myristoylated alanine rich protein kinase C substrate |
| 2.932 | 74.870 | Klhl6 | kelch-like 6 |
| 2.923 | 89.032 | Tas2r143 | taste receptor, type 2, member 143 |
| 2.902 | 16.701 | Grhl1 | grainyhead-like 1 (Drosophila) |
| 2.897 | 17.797 | Tbcd | tubulin-specific chaperone d |
| 2.893 | 18.893 | Meis2 | Meis homeobox 2 |
| 2.890 | 20.238 | Cxcl2 | chemokine (C-X-C motif) ligand 2 |
| 2.890 | 75.192 | Il1r2 | interleukin 1 receptor, type II |
| 2.880 | 113.658 | Bcl2l15 | BCLl2-like 15 |
| 2.876 | 171.180 | Zfp715 | zinc finger protein 715 |
| 2.868 | 31.460 | Musk | muscle, skeletal, receptor tyrosine kinase |
| 2.864 | 34.754 | Cpeb2 | cytoplasmic polyadenylation element binding protein 2 |
| 2.861 | 18.395 | Ehf | ets homologous factor |
| 2.861 | 18.395 | Gm17455 | predicted gene, 17455 |
| 2.845 | 24.981 | Eea1 | early endosome antigen 1 |
| 2.843 | 92.263 | Il1b | interleukin 1 beta |
| 2.842 | 13.510 | Jazf1 | JAZF zinc finger 1 |
| 2.836 | 28.029 | Pvrl1 | poliovirus receptor-related 1 |
| 2.835 | 14.606 | Gxylt1 | glucoside xylosyltransferase 1 |
| 2.824 | 144.041 | Ifitm3 | interferon induced transmembrane protein 3 |
| 2.824 | 45.610 | Kdm2a | lysine (K)-specific demethylase 2A |
| 2.814 | 27.538 | Oasl2 | 2'-5' oligoadenylate synthetase-like 2 |
| 2.786 | 34.251 | Pdzd2 | PDZ domain containing 2 |
| 2.785 | 38.404 | Rassf6 | Ras association (RalGDS/AF-6) domain family member 6 |
| 2.784 | 21.307 | Cdca7 | cell division cycle associated 7 |
| 2.778 | 24.359 | Marcks | myristoylated alanine rich protein kinase C substrate |

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|---|---|---|---|
| 2.777 | 39.260 | Trp63 | transformation related protein 63 |
| 2.776 | 117.930 | Arhgap5 | Rho GTPase activating protein 5 |
| 2.764 | 16.666 | Acot1 | acyl-CoA thioesterase 1 |
| 2.761 | 30.223 | Atf1 | activating transcription factor 1 |
| 2.760 | 11.419 | Serpinb10 | serine (or cysteine) peptidase inhibitor, clade B (ovalbumin), member 10 |
| 2.757 | 20.574 | Zfp715 | zinc finger protein 715 |
| 2.749 | 32.792 | Cxcl5 | chemokine (C-X-C motif) ligand 5 |
| 2.745 | 22.528 | Fam122a | family with sequence similarity 122, member A |

## Supplementary Table 2: *Unique H3K4me3 peaks in SCC samples*

***Unique somatic peaks associated with protein coding genes, top 185 with an additional 1 selected locus, of a possible 584 with Log2FC>1.4, p value<1E-10***

| LOG2FC | Negative LOG10 (p value) | Gene Name | Gene Description |
|---|---|---|---|
| 6.947 | 72.129 | Tmprss11b | transmembrane protease, serine 11B |
| 6.101 | 207.438 | Frmd6 | FERM domain containing 6 |
| 5.849 | 110.129 | Ccdc91 | coiled-coil domain containing 91 |
| 5.760 | 74.011 | Cfap20 | cilia and flagella associated protein 20 |
| 5.412 | 56.966 | Tmprss11g | transmembrane protease, serine 11g |
| 5.171 | 157.277 | Krt17 | keratin 17 |
| 5.108 | 53.837 | Ppbp | pro-platelet basic protein |
| 4.986 | 33.237 | Dsc2 | desmocollin 2 |
| 4.790 | 35.134 | Ptprm | protein tyrosine phosphatase, receptor type, M |
| 4.786 | 189.576 | Slitrk6 | SLIT and NTRK-like family, member 6 |
| 4.781 | 68.456 | Foxd4 | forkhead box D4 |
| 4.774 | 28.015 | Jazf1 | JAZF zinc finger 1 |
| 4.738 | 117.737 | Dst | dystonin |
| 4.542 | 89.523 | Fat2 | FAT tumor suppressor homolog 2 (Drosophila) |
| 4.523 | 50.179 | Trp73 | transformation related protein 73 |
| 4.476 | 58.742 | Tmprss11g | transmembrane protease, serine 11g |
| 4.452 | 307.626 | Trp63 | transformation related protein 63 |
| 4.372 | 87.353 | Arhgef16 | Rho guanine nucleotide exchange factor (GEF) 16 |
| 4.371 | 39.651 | Arhgap30 | Rho GTPase activating protein 30 |
| 4.271 | 45.129 | Pkp1 | plakophilin 1 |
| 4.201 | 38.587 | Pthlh | parathyroid hormone-like peptide |
| 4.164 | 25.424 | Rad51b | RAD51 homolog B |
| 4.134 | 28.595 | Slc35c1 | solute carrier family 35, member C1 |
| 4.130 | 315.651 | Krt5 | keratin 5 |
| 4.112 | 69.998 | Ccdc91 | coiled-coil domain containing 91 |
| 4.098 | 141.072 | Pthlh | parathyroid hormone-like peptide |
| 3.974 | 21.504 | Aqp4 | aquaporin 4 |
| 3.880 | 47.999 | Amotl1 | angiomotin-like 1 |
| 3.842 | 34.410 | Il1b | interleukin 1 beta |
| 3.793 | 96.179 | Pex10 | peroxisomal biogenesis factor 10 |
| 3.786 | 253.246 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 3.769 | 187.113 | Grik3 | glutamate receptor, ionotropic, kainate 3 |
| 3.705 | 80.920 | Spsb1 | splA/ryanodine receptor domain and SOCS box containing 1 |
| 3.685 | 27.394 | Tmprss11b | transmembrane protease, serine 11B |
| 3.620 | 62.555 | Adcyap1 | adenylate cyclase activating polypeptide 1 |
| 3.615 | 47.730 | Padi3 | peptidyl arginine deiminase, type III |
| 3.611 | 125.555 | Mrgpra2a | MAS-related GPR, member A2A |
| 3.605 | 30.257 | Tmpo | thymopoietin |
| 3.605 | 156.522 | Irg1 | immunoresponsive gene 1 |
| 3.596 | 78.156 | D1Ertd622e | DNA segment, Chr 1, ERATO Doi 622, expressed |
| 3.590 | 27.608 | Sord | sorbitol dehydrogenase |
| 3.564 | 43.203 | Dcaf4 | DDB1 and CUL4 associated factor 4 |
| 3.557 | 140.324 | Chst11 | carbohydrate sulfotransferase 11 |
| 3.547 | 33.408 | Cdk5rap1 | CDK5 regulatory subunit associated protein 1 |
| 3.525 | 52.978 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.519 | 97.433 | Clca5 | chloride channel calcium activated 5 |
| 3.503 | 45.299 | Krt6b | keratin 6B |
| 3.494 | 125.745 | Mrgpra2b | MAS-related GPR, member A2B |
| 3.481 | 33.653 | Bnc1 | basonuclin 1 |
| 3.464 | 164.921 | Dsg3 | desmoglein 3 |
| 3.424 | 89.236 | Cxcr2 | chemokine (C-X-C motif) receptor 2 |
| 3.420 | 213.146 | Spatc1 | spermatogenesis and centriole associated 1 |
| 3.415 | 59.854 | S100a7a | S100 calcium binding protein A7A |
| 3.408 | 245.205 | Nlrp12 | NLR family, pyrin domain containing 12 |
| 3.402 | 63.300 | S100a8 | S100 calcium binding protein A8 (calgranulin A) |
| 3.383 | 28.619 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 3.378 | 24.649 | Tcerg1 | transcription elongation regulator 1 (CA150) |
| 3.372 | 49.807 | Galm | galactose mutarotase |
| 3.352 | 224.445 | Amer2 | APC membrane recruitment 2 |
| 3.350 | 33.392 | Prickle2 | prickle homolog 2 (Drosophila) |

| | | | |
|---|---|---|---|
| 3.346 | 122.696 | Galnt6 | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 |
| 3.334 | 232.194 | Krt85 | keratin 85 |
| 3.334 | 32.868 | Gm884 | predicted gene 884 |
| 3.321 | 28.895 | Nlrp12 | NLR family, pyrin domain containing 12 |
| 3.320 | 95.441 | Retnlg | resistin like gamma |
| 3.301 | 30.226 | Amer2 | APC membrane recruitment 2 |
| 3.280 | 63.405 | Serpinb10 | serine (or cysteine) peptidase inhibitor, clade B (ovalbumin), member 10 |
| 3.268 | 53.866 | Ltf | lactotransferrin |
| 3.239 | 286.676 | S100a8 | S100 calcium binding protein A8 (calgranulin A) |
| 3.235 | 87.925 | Sik1 | salt inducible kinase 1 |
| 3.235 | 87.925 | Stfa2l1 | stefin A2 like 1 |
| 3.235 | 55.506 | Asb7 | ankyrin repeat and SOCS box-containing 7 |
| 3.218 | 210.553 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 3.218 | 22.833 | Dusp6 | dual specificity phosphatase 6 |
| 3.217 | 51.278 | Pola2 | polymerase (DNA directed), alpha 2 |
| 3.217 | 51.278 | Rassf6 | Ras association (RalGDS/AF-6) domain family member 6 |
| 3.208 | 112.205 | Fabp5 | fatty acid binding protein 5, epidermal |
| 3.178 | 23.652 | Prps1l1 | phosphoribosyl pyrophosphate synthetase 1-like 1 |
| 3.169 | 44.166 | Tmprss13 | transmembrane protease, serine 13 |
| 3.140 | 30.610 | Cxcr1 | chemokine (C-X-C motif) receptor 1 |
| 3.138 | 19.682 | Ptgdr | prostaglandin D receptor |
| 3.137 | 41.286 | Ltf | lactotransferrin |
| 3.132 | 31.695 | AF251705 | cDNA sequence AF251705 |
| 3.113 | 49.344 | Lin28a | lin-28 homolog A (C. elegans) |
| 3.100 | 23.447 | Sgms2 | sphingomyelin synthase 2 |
| 3.093 | 72.120 | Dmxl2 | Dmx-like 2 |
| 3.092 | 42.440 | Arfgef1 | ADP-ribosylation factor guanine nucleotide-exchange factor 1(brefeldin A-inhibited) |
| 3.091 | 24.534 | Pvrl1 | poliovirus receptor-related 1 |
| 3.090 | 37.900 | Klhdc4 | kelch domain containing 4 |
| 3.076 | 51.850 | Pdzd2 | PDZ domain containing 2 |
| 3.062 | 30.997 | Fbln1 | fibulin 1 |
| 3.053 | 28.055 | Dmkn | dermokine |
| 3.050 | 63.195 | Asb7 | ankyrin repeat and SOCS box-containing 7 |
| 3.040 | 33.179 | Tmprss11e | transmembrane protease, serine 11e |
| 3.040 | 26.202 | Tnfrsf1a | tumor necrosis factor receptor superfamily, member 1a |
| 3.026 | 115.669 | Asprv1 | aspartic peptidase, retroviral-like 1 |
| 3.001 | 96.509 | Hcar2 | hydroxycarboxylic acid receptor 2 |
| 2.985 | 48.656 | Dapl1 | death associated protein-like 1 |
| 2.983 | 57.826 | Dgat2 | diacylglycerol O-acyltransferase 2 |
| 2.980 | 123.616 | Slfn4 | schlafen 4 |
| 2.973 | 55.979 | Trak1 | trafficking protein, kinesin binding 1 |
| 2.953 | 36.888 | Hist2h2aa2 | histone cluster 2, H2aa2 |
| 2.949 | 32.850 | Dmxl2 | Dmx-like 2 |
| 2.943 | 177.304 | Wfdc21 | WAP four-disulfide core domain 21 |
| 2.941 | 19.894 | Sfn | stratifin |
| 2.932 | 147.702 | Il1f9 | interleukin 1 family, member 9 |
| 2.932 | 51.042 | Gda | guanine deaminase |
| 2.924 | 68.142 | Hsd17b2 | hydroxysteroid (17-beta) dehydrogenase 2 |
| 2.906 | 25.372 | Ly6c2 | lymphocyte antigen 6 complex, locus C2 |
| 2.904 | 46.012 | Dennd4a | DENN/MADD domain containing 4A |
| 2.892 | 18.893 | Bmp2k | BMP2 inducible kinase |
| 2.880 | 73.354 | Styxl1 | serine/threonine/tyrosine interacting-like 1 |
| 2.867 | 186.070 | Il1b | interleukin 1 beta |
| 2.836 | 16.801 | Plekhs1 | pleckstrin homology domain containing, family S member 1 |
| 2.832 | 101.420 | Cd177 | CD177 antigen |
| 2.823 | 43.412 | Pvrl1 | poliovirus receptor-related 1 |
| 2.814 | 49.517 | BC117090 | cDNA sequence BC1179090 |
| 2.807 | 61.363 | Eef1a1 | eukaryotic translation elongation factor 1 alpha 1 |
| 2.790 | 22.406 | Gadd45b | growth arrest and DNA-damage-inducible 45 beta |
| 2.787 | 179.485 | Trim30b | tripartite motif-containing 30B |
| 2.780 | 117.316 | Fam167a | family with sequence similarity 167, member A |
| 2.779 | 31.809 | BC100530 | cDNA sequence BC100530 |
| 2.773 | 70.778 | Tnfsf14 | tumor necrosis factor (ligand) superfamily, member 14 |
| 2.770 | 28.268 | Ppp1r42 | protein phosphatase 1, regulatory subunit 42 |
| 2.769 | 99.002 | Tarm1 | T cell-interacting, activating receptor on myeloid cells 1 |
| 2.768 | 35.719 | Ear10 | eosinophil-associated, ribonuclease A family, member 10 |
| 2.759 | 48.795 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 2.759 | 48.795 | Pcsk9 | proprotein convertase subtilisin/kexin type 9 |
| 2.756 | 175.633 | Eea1 | early endosome antigen 1 |
| 2.754 | 235.515 | C1qtnf9 | C1q and tumor necrosis factor related protein 9 |
| 2.748 | 72.139 | Cep19 | centrosomal protein 19 |
| 2.738 | 20.330 | Angpt2 | angiopoietin 2 |
| 2.731 | 23.142 | Psca | prostate stem cell antigen |
| 2.728 | 89.644 | Meis2 | Meis homeobox 2 |
| 2.719 | 21.800 | Coq7 | demethyl-Q 7 |
| 2.718 | 80.613 | Mmp8 | matrix metallopeptidase 8 |
| 2.716 | 130.265 | Chil1 | chitinase-like 1 |
| 2.708 | 52.252 | Marcks | myristoylated alanine rich protein kinase C substrate |

| | | | |
|---|---|---|---|
| 2.699 | 57.643 | Txnl4b | thioredoxin-like 4B |
| 2.693 | 35.873 | Stfa2 | stefin A2 |
| 2.690 | 65.613 | Gm5483 | predicted gene 5483 |
| 2.679 | 27.564 | Dusp6 | dual specificity phosphatase 6 |
| 2.673 | 70.290 | Syk | spleen tyrosine kinase |
| 2.660 | 144.920 | LOC100038947 | signal-regulatory protein beta 1-like |
| 2.654 | 41.789 | Srgn | serglycin |
| 2.650 | 57.355 | Syne1 | spectrin repeat containing, nuclear envelope 1 |
| 2.636 | 16.439 | Tmpo | thymopoietin |
| 2.635 | 39.117 | Ofcc1 | orofacial cleft 1 candidate 1 |
| 2.619 | 47.243 | Rnf149 | ring finger protein 149 |
| 2.616 | 33.868 | Rnf157 | ring finger protein 157 |
| 2.615 | 19.636 | Trem1 | triggering receptor expressed on myeloid cells 1 |
| 2.606 | 143.525 | Pitx1 | paired-like homeodomain transcription factor 1 |
| 2.604 | 87.911 | Arhgap32 | Rho GTPase activating protein 32 |
| 2.599 | 234.960 | Gda | guanine deaminase |
| 2.595 | 26.901 | Pgbd5 | piggyBac transposable element derived 5 |
| 2.593 | 19.160 | Pde6h | phosphodiesterase 6H, cGMP-specific, cone, gamma |
| 2.588 | 20.643 | B430306N03Rik | RIKEN cDNA B430306N03 gene |
| 2.584 | 22.363 | Atl2 | atlastin GTPase 2 |
| 2.577 | 101.440 | Vsnl1 | visinin-like 1 |
| 2.566 | 209.788 | Adam8 | a disintegrin and metallopeptidase domain 8 |
| 2.564 | 23.612 | Zfp715 | zinc finger protein 715 |
| 2.560 | 208.154 | Clec4e | C-type lectin domain family 4, member e |
| 2.552 | 229.681 | Il1b | interleukin 1 beta |
| 2.552 | 32.371 | Atxn7l3b | ataxin 7-like 3B |
| 2.551 | 42.228 | Eps8l3 | EPS8-like 3 |
| 2.549 | 28.069 | Pak1 | p21 protein (Cdc42/Rac)-activated kinase 1 |
| 2.548 | 26.348 | Erg | avian erythroblastosis virus E-26 (v-ets) oncogene related |
| 2.534 | 43.015 | Furin | furin (paired basic amino acid cleaving enzyme) |
| 2.534 | 168.924 | Ifitm1 | interferon induced transmembrane protein 1 |
| 2.527 | 253.776 | Mefv | Mediterranean fever |
| 2.526 | 19.465 | Pgs1 | phosphatidylglycerophosphate synthase 1 |
| 2.525 | 146.954 | Trem1 | triggering receptor expressed on myeloid cells 1 |
| 2.522 | 102.658 | Hdac4 | histone deacetylase 4 |
| 2.518 | 39.108 | 2010002M12Rik | RIKEN cDNA 2010002M12 gene |
| 2.513 | 41.224 | Rybp | RING1 and YY1 binding protein |
| 2.510 | 86.943 | Shisa5 | shisa homolog 5 (Xenopus laevis) |
| 2.507 | 53.596 | Fam134b | family with sequence similarity 134, member B |
| 2.507 | 92.038 | Slc22a20 | solute carrier family 22 (organic anion transporter), member 20 |
| 2.504 | 64.249 | Hk3 | hexokinase 3 |
| 2.497 | 139.982 | Lmnb1 | lamin B1 |
| 2.497 | 128.237 | Gcnt1 | glucosaminyl (N-acetyl) transferase 1, core 2 |
| 2.495 | 98.560 | Cd300ld | CD300 molecule-like family member d |
| 2.493 | 27.925 | Notch2 | notch 2 |
| 1.479 | 97.208 | Sox2 | SRY (sex determining region Y)-box 2 |

## Supplementary Table 3: *Unique H3K27ac peaks in ADC samples*

***Unique somatic peaks associated with protein coding genes, top 185 and an additional 2 selected loci, of a possible 1820 with Log2FC>2.5, p value<1E-10***

| LOG2FC | Negative LOG10 (p value) | Gene Name | Gene Description |
|---|---|---|---|
| -7.845 | 51.798 | Cobl | cordon-bleu WH2 repeat |
| -7.533 | 41.356 | Tmem121 | transmembrane protein 121 |
| -7.260 | 33.913 | Rdh14 | retinol dehydrogenase 14 (all-trans and 9-cis) |
| -6.938 | 26.786 | Ppp3cc | protein phosphatase 3, catalytic subunit, gamma isoform |
| -6.923 | 26.489 | Hecw1 | HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1 |
| -6.892 | 25.896 | Gm8369 | predicted gene 8369 |
| -6.861 | 25.304 | Tmem121 | transmembrane protein 121 |
| -6.675 | 22.049 | 1700071K01Rik | RIKEN cDNA 1700071K01 gene |
| -6.543 | 19.982 | 1110059E24Rik | RIKEN cDNA 1110059E24 gene |
| -6.523 | 19.687 | Fut8 | fucosyltransferase 8 |
| -6.462 | 18.802 | Crb2 | crumbs homolog 2 (Drosophila) |
| -6.440 | 18.507 | Kcnk1 | potassium channel, subfamily K, member 1 |
| -6.419 | 18.213 | Phtf2 | putative homeodomain transcription factor 2 |
| -6.397 | 17.918 | Gm8369 | predicted gene 8369 |
| -6.353 | 17.330 | Fgfr1 | fibroblast growth factor receptor 1 |
| -6.330 | 17.036 | Usp12 | ubiquitin specific peptidase 12 |
| -6.284 | 16.448 | Socs1 | suppressor of cytokine signaling 1 |
| -6.211 | 15.567 | Sall4 | sal-like 4 (Drosophila) |
| -6.186 | 15.273 | Grap2 | GRB2-related adaptor protein 2 |
| -6.160 | 14.980 | Spry4 | sprouty homolog 4 (Drosophila) |

| | | | |
|---|---|---|---|
| -6.108 | 14.394 | Epha4 | Eph receptor A4 |
| -6.108 | 14.394 | Ets1 | E26 avian leukemia oncogene 1, 5' domain |
| -6.108 | 14.394 | Tmem123 | transmembrane protein 123 |
| -6.081 | 14.101 | Tmem121 | transmembrane protein 121 |
| -6.053 | 13.808 | Plekhh2 | pleckstrin homology domain containing, family H (with MyTH4 domain) member 2 |
| -6.025 | 13.516 | Luzp2 | leucine zipper protein 2 |
| -6.025 | 13.516 | Sult5a1 | sulfotransferase family 5A, member 1 |
| -5.997 | 13.224 | Cr2 | complement receptor 2 |
| -5.997 | 13.224 | Usp15 | ubiquitin specific peptidase 15 |
| -5.997 | 13.224 | Zfp703 | zinc finger protein 703 |
| -5.968 | 12.931 | Gm5082 | predicted gene 5082 |
| -5.968 | 12.931 | Sh2d2a | SH2 domain protein 2A |
| -5.968 | 12.931 | Tsen2 | tRNA splicing endonuclease 2 homolog (S. cerevisiae) |
| -5.947 | 30.246 | Olfr164 | olfactory receptor 164 |
| -5.938 | 12.639 | F2rl1 | coagulation factor II (thrombin) receptor-like 1 |
| -5.938 | 12.639 | Isca2 | iron-sulfur cluster assembly 2 homolog (S. cerevisiae) |
| -5.938 | 12.639 | Lingo2 | leucine rich repeat and Ig domain containing 2 |
| -5.938 | 12.639 | Npy | neuropeptide Y |
| -5.877 | 12.056 | Palld | palladin, cytoskeletal associated protein |
| -5.877 | 12.056 | Zfp354b | zinc finger protein 354B |
| -5.845 | 11.765 | Anp32a | acidic (leucine-rich) nuclear phosphoprotein 32 family, member A |
| -5.845 | 11.765 | Cystm1 | cysteine-rich transmembrane module containing 1 |
| -5.845 | 11.765 | Osbpl6 | oxysterol binding protein-like 6 |
| -5.845 | 11.765 | Slc2a7 | solute carrier family 2 (facilitated glucose transporter), member 7 |
| -5.845 | 11.765 | Zswim6 | zinc finger SWIM-type containing 6 |
| -5.841 | 27.901 | Nol11 | nucleolar protein 11 |
| -5.812 | 11.474 | Ddx10 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 10 |
| -5.812 | 11.474 | Maf | avian musculoaponeurotic fibrosarcoma (v-maf) AS42 oncogene homolog |
| -5.779 | 11.183 | Lyzl1 | lysozyme-like 1 |
| -5.779 | 11.183 | Sorbs1 | sorbin and SH3 domain containing 1 |
| -5.779 | 11.183 | Tex36 | testis expressed 36 |
| -5.772 | 81.638 | Onecut2 | one cut domain, family member 2 |
| -5.745 | 10.892 | Dad1 | defender against cell death 1 |
| -5.745 | 10.892 | Etaa1 | Ewing tumor-associated antigen 1 |
| -5.745 | 10.892 | Pde6a | phosphodiesterase 6A, cGMP-specific, rod, alpha |
| -5.745 | 10.892 | Zfp618 | zinc finger protein 618 |
| -5.741 | 25.854 | Onecut3 | one cut domain, family member 3 |
| -5.711 | 10.602 | Abca5 | ATP-binding cassette, sub-family A (ABC1), member 5 |
| -5.711 | 10.602 | Ift122 | intraflagellar transport 122 |
| -5.711 | 10.602 | Tekt2 | tektin 2 |
| -5.697 | 24.978 | Sh2d1b1 | SH2 domain protein 1B1 |
| -5.675 | 10.311 | Bend5 | BEN domain containing 5 |
| -5.675 | 10.311 | Spdef | SAM pointed domain containing ets transcription factor |
| -5.638 | 10.021 | B3gnt7 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7 |
| -5.638 | 10.021 | Gas2 | growth arrest specific 2 |
| -5.638 | 10.021 | Ptx3 | pentraxin related gene |
| -5.638 | 10.021 | Slc19a3 | solute carrier family 19, member 3 |
| -5.599 | 38.484 | Cryl1 | crystallin, lambda 1 |
| -5.552 | 53.161 | Ptprn2 | protein tyrosine phosphatase, receptor type, N polypeptide 2 |
| -5.549 | 37.025 | Haao | 3-hydroxyanthranilate 3,4-dioxygenase |
| -5.549 | 37.025 | Wfs1 | Wolfram syndrome 1 homolog (human) |
| -5.536 | 22.064 | Med13l | mediator complex subunit 13-like |
| -5.484 | 21.192 | Otol1 | otolin 1 homolog (zebrafish) |
| -5.431 | 20.322 | Pla2r1 | phospholipase A2 receptor 1 |
| -5.421 | 33.528 | Car8 | carbonic anhydrase 8 |
| -5.375 | 19.452 | Gldc | glycine decarboxylase |
| -5.356 | 19.163 | Tox3 | TOX high mobility group box family member 3 |
| -5.336 | 18.873 | Mettl15 | methyltransferase like 15 |
| -5.316 | 30.912 | Ntm | neurotrimin |
| -5.304 | 30.622 | Col6a2 | collagen, type VI, alpha 2 |
| -5.267 | 55.150 | Camk1g | calcium/calmodulin-dependent protein kinase I gamma |
| -5.234 | 53.705 | Mcpt8 | mast cell protease 8 |
| -5.204 | 28.304 | Lax1 | lymphocyte transmembrane adaptor 1 |
| -5.171 | 16.564 | Ets1 | E26 avian leukemia oncogene 1, 5' domain |
| -5.171 | 16.564 | Nrsn1 | neurensin 1 |
| -5.157 | 50.531 | Alpi | alkaline phosphatase, intestinal |
| -5.151 | 27.148 | Gcnt4 | glucosaminyl (N-acetyl) transferase 4, core 2 (beta-1,6-N-acetylglucosaminyltransferase) |
| -5.137 | 26.859 | Matn1 | matrilin 1, cartilage matrix protein |
| -5.127 | 15.989 | 4921539E11Rik | RIKEN cDNA 4921539E11 gene |
| -5.127 | 15.989 | 4930523C07Rik | RIKEN cDNA 4930523C07 gene |
| -5.127 | 15.989 | Dennd5b | DENN/MADD domain containing 5B |
| -5.127 | 15.989 | Golt1a | golgi transport 1 homolog A (S. cerevisiae) |
| -5.127 | 15.989 | Ostf1 | osteoclast stimulating factor 1 |
| -5.127 | 15.989 | Tprg | transformation related protein 63 regulated |
| -5.104 | 15.702 | Lpp | LIM domain containing preferred translocation partner in lipoma |
| -5.081 | 15.415 | Pax5 | paired box 5 |
| -5.057 | 15.128 | Scml4 | sex comb on midleg-like 4 (Drosophila) |

| | | | |
|---|---|---|---|
| -5.057 | 15.128 | Snx29 | sorting nexin 29 |
| -5.034 | 14.841 | Cd209d | CD209d antigen |
| -5.034 | 14.841 | Tgfbr2 | transforming growth factor, beta receptor II |
| -5.024 | 24.552 | Mei4 | meiosis-specific, MEI4 homolog (S. cerevisiae) |
| -5.009 | 24.265 | Cdk5rap2 | CDK5 regulatory subunit associated protein 2 |
| -4.985 | 14.268 | Plac9a | placenta specific 9a |
| -4.977 | 33.980 | Snx10 | sorting nexin 10 |
| -4.960 | 13.983 | Satb2 | special AT-rich sequence binding protein 2 |
| -4.960 | 13.983 | St8sia3 | ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 3 |
| -4.960 | 13.983 | Tmem121 | transmembrane protein 121 |
| -4.960 | 13.983 | Zfpm1 | zinc finger protein, multitype 1 |
| -4.949 | 23.115 | Proser2 | proline and serine rich 2 |
| -4.938 | 53.629 | Camk2n1 | calcium/calmodulin-dependent protein kinase II inhibitor 1 |
| -4.933 | 22.828 | Xylt1 | xylosyltransferase 1 |
| -4.917 | 22.541 | Acnat2 | acyl-coenzyme A amino acid N-acyltransferase 2 |
| -4.917 | 22.541 | Fam83d | family with sequence similarity 83, member D |
| -4.908 | 13.412 | Clvs2 | clavesin 2 |
| -4.908 | 13.412 | Nrip1 | nuclear receptor interacting protein 1 |
| -4.908 | 13.412 | Ralyl | RALY RNA binding protein-like |
| -4.908 | 13.412 | Shh | sonic hedgehog |
| -4.901 | 22.254 | Serpind1 | serine (or cysteine) peptidase inhibitor, clade D, member 1 |
| -4.900 | 31.965 | R3hdml | R3H domain containing-like |
| -4.885 | 21.968 | Smad2 | SMAD family member 2 |
| -4.872 | 40.203 | Rph3a | rabphilin 3A |
| -4.856 | 50.189 | Rasgrp1 | RAS guanyl releasing protein 1 |
| -4.852 | 21.395 | Fam19a5 | family with sequence similarity 19, member A5 |
| -4.852 | 21.395 | Mboat2 | membrane bound O-acyltransferase domain containing 2 |
| -4.846 | 39.347 | Atp8b1 | ATPase, class I, type 8B, member 1 |
| -4.837 | 39.062 | Ppie | peptidylprolyl isomerase E (cyclophilin E) |
| -4.836 | 21.109 | Onecut3 | one cut domain, family member 3 |
| -4.827 | 12.557 | Filip1l | filamin A interacting protein 1-like |
| -4.827 | 12.557 | Mpg | N-methylpurine-DNA glycosylase |
| -4.217 | 12.633 | Foxa2 | forkhead box A2 |
| -4.217 | 12.633 | Foxo1 | forkhead box O1 |

## Supplementary Table 4: *Unique H3K4me3 peaks in ADC samples*

***Unique somatic peaks associated with protein coding genes, top 185 and an additional 2 selected loci, of a possible 2506 with Log2FC>1.4, p value<1E-10***

| LOG2FC | Negative LOG10 (p value) | Gene Name | Gene Description |
|---|---|---|---|
| -6.340 | 31.535 | Adck3 | aarF domain containing kinase 3 |
| -5.599 | 18.213 | Slc12a7 | solute carrier family 12, member 7 |
| -5.520 | 54.038 | Paqr5 | progestin and adipoQ receptor family member V |
| -5.464 | 16.448 | Tnfsf8 | tumor necrosis factor (ligand) superfamily, member 8 |
| -5.391 | 15.567 | Klra17 | killer cell lectin-like receptor, subfamily A, member 17 |
| -5.261 | 14.101 | Elavl4 | ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D) |
| -5.261 | 14.101 | Map3k7 | mitogen-activated protein kinase kinase kinase 7 |
| -5.057 | 12.056 | Nfatc3 | nuclear factor of activated T cells, cytoplasmic, calcineurin dependent 3 |
| -4.961 | 22.254 | Faim3 | Fas apoptotic inhibitory molecule 3 |
| -4.896 | 21.109 | Mylk | myosin, light polypeptide kinase |
| -4.855 | 10.311 | Pydc3 | pyrin domain containing 3 |
| -4.791 | 19.397 | Sh2d1b1 | SH2 domain protein 1B1 |
| -4.773 | 19.112 | Tank | TRAF family member-associated Nf-kappa B activator |
| -4.755 | 18.827 | Sec16b | SEC16 homolog B (S. cerevisiae) |
| -4.703 | 58.728 | Mcpt1 | mast cell protease 1 |
| -4.662 | 8.865 | Cadm4 | cell adhesion molecule 4 |
| -4.659 | 17.408 | Scara5 | scavenger receptor class A, member 5 (putative) |
| -4.621 | 8.577 | Nt5c1a | 5'-nucleotidase, cytosolic IA |
| -4.619 | 16.842 | Tmem54 | transmembrane protein 54 |
| -4.564 | 61.328 | Rpia | ribose 5-phosphate isomerase A |
| -4.536 | 15.713 | Ankrd1 | ankyrin repeat domain 1 (cardiac muscle) |
| -4.536 | 15.713 | Ubtd2 | ubiquitin domain containing 2 |
| -4.533 | 8.001 | Agpat4 | 1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta) |
| -4.470 | 14.869 | Pax5 | paired box 5 |
| -4.424 | 14.308 | Klra18 | killer cell lectin-like receptor, subfamily A, member 18 |
| -4.386 | 69.408 | Myof | myoferlin |
| -4.380 | 76.874 | Ctse | cathepsin E |
| -4.355 | 21.414 | Msln | mesothelin |
| -4.289 | 26.916 | Olfr164 | olfactory receptor 164 |
| -4.285 | 55.596 | Ly86 | lymphocyte antigen 86 |
| -4.278 | 100.790 | R3hdml | R3H domain containing-like |

| | | | |
|---|---|---|---|
| -4.277 | 12.633 | Ptprg | protein tyrosine phosphatase, receptor type, G |
| -4.273 | 55.039 | Gimap3 | GTPase, IMAP family member 3 |
| -4.253 | 32.724 | Ldlrad4 | low density lipoprotein receptor class A domain containing 4 |
| -4.251 | 12.355 | Anks4b | ankyrin repeat and sterile alpha motif domain containing 4B |
| -4.224 | 12.078 | Mecom | MDS1 and EVI1 complex locus |
| -4.224 | 82.210 | Thpo | thrombopoietin |
| -4.224 | 31.892 | Slamf6 | SLAM family member 6 |
| -4.197 | 11.801 | Ano1 | anoctamin 1, calcium activated chloride channel |
| -4.197 | 11.801 | Gpr132 | G protein-coupled receptor 132 |
| -4.185 | 38.132 | Resp18 | regulated endocrine-specific protein 18 |
| -4.170 | 11.525 | Cd2 | CD2 antigen |
| -4.168 | 37.576 | Gimap7 | GTPase, IMAP family member 7 |
| -4.151 | 18.044 | Msx1 | msh homeobox 1 |
| -4.133 | 17.765 | C530008M17Rik | RIKEN cDNA C530008M17 gene |
| -4.115 | 35.910 | Cd19 | CD19 antigen |
| -4.106 | 23.025 | Onecut2 | one cut domain, family member 2 |
| -4.076 | 16.929 | Ccr7 | chemokine (C-C motif) receptor 7 |
| -4.074 | 72.214 | A430107P09Rik | RIKEN cDNA A430107P09 gene |
| -4.057 | 16.651 | Gna14 | guanine nucleotide binding protein, alpha 14 |
| -4.017 | 16.096 | Apitd1 | apoptosis-inducing, TAF9-like domain 1 |
| -4.013 | 32.869 | Gpr18 | G protein-coupled receptor 18 |
| -3.997 | 15.819 | Dnajc22 | DnaJ (Hsp40) homolog, subfamily C, member 22 |
| -3.993 | 9.877 | Camk2n1 | calcium/calmodulin-dependent protein kinase II inhibitor 1 |
| -3.993 | 9.877 | Commd8 | COMM domain containing 8 |
| -3.993 | 9.877 | Ippk | inositol 1,3,4,5,6-pentakisphosphate 2-kinase |
| -3.993 | 9.877 | S1pr1 | sphingosine-1-phosphate receptor 1 |
| -3.976 | 20.547 | Sncb | synuclein, beta |
| -3.974 | 37.053 | Prss2 | protease, serine 2 |
| -3.961 | 9.604 | Itgae | integrin alpha E, epithelial-associated |
| -3.950 | 41.523 | Mzb1 | marginal zone B and B1 cell-specific protein 1 |
| -3.935 | 14.990 | Clu | clusterin |
| -3.934 | 24.746 | Tff1 | trefoil factor 1 |
| -3.929 | 9.332 | Atp8b1 | ATPase, class I, type 8B, member 1 |
| -3.929 | 9.332 | Gpr133 | G protein-coupled receptor 133 |
| -3.896 | 9.061 | Gprin1 | G protein-regulated inducer of neurite outgrowth 1 |
| -3.896 | 9.061 | Lrrc66 | leucine rich repeat containing 66 |
| -3.873 | 109.291 | Smpd3 | sphingomyelin phosphodiesterase 3, neutral |
| -3.862 | 8.790 | Galnt5 | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 5 |
| -3.862 | 8.790 | Rapgef6 | Rap guanine nucleotide exchange factor (GEF) 6 |
| -3.862 | 8.790 | Ybx3 | Y box protein 3 |
| -3.847 | 13.890 | Sned1 | sushi, nidogen and EGF-like domains 1 |
| -3.832 | 18.092 | Rbfox1 | RNA binding protein, fox-1 homolog (C. elegans) 1 |
| -3.827 | 8.520 | Thbs1 | thrombospondin 1 |
| -3.825 | 13.616 | Gcm2 | glial cells missing homolog 2 (Drosophila) |
| -3.792 | 21.769 | Cd83 | CD83 antigen |
| -3.764 | 154.940 | Sall4 | sal-like 4 (Drosophila) |
| -3.764 | 17.009 | Ccr6 | chemokine (C-C motif) receptor 6 |
| -3.759 | 54.695 | Cd2 | CD2 antigen |
| -3.754 | 12.796 | Ptp4a3 | protein tyrosine phosphatase 4a3 |
| -3.728 | 16.469 | Ano1 | anoctamin 1, calcium activated chloride channel |
| -3.722 | 20.427 | Clstn3 | calsyntenin 3 |
| -3.722 | 20.427 | Ttc30a1 | tetratricopeptide repeat domain 30A1 |
| -3.655 | 11.710 | Gabrp | gamma-aminobutyric acid (GABA) A receptor, pi |
| -3.655 | 11.710 | Gramd4 | GRAM domain containing 4 |
| -3.655 | 11.710 | Slc38a8 | solute carrier family 38, member 8 |
| -3.629 | 11.439 | Txndc5 | thioredoxin domain containing 5 |
| -3.618 | 18.562 | Vmn2r11 | vomeronasal 2, receptor 11 |
| -3.609 | 30.473 | Muc5b | mucin 5, subtype B, tracheobronchial |
| -3.609 | 42.916 | Trpa1 | transient receptor potential cation channel, subfamily A, member 1 |
| -3.608 | 55.627 | Cxcr5 | chemokine (C-X-C motif) receptor 5 |
| -3.602 | 11.170 | Adcy7 | adenylate cyclase 7 |
| -3.602 | 11.170 | Insc | inscuteable homolog (Drosophila) |
| -3.600 | 30.208 | Kcnip1 | Kv channel-interacting protein 1 |
| -3.596 | 14.595 | Abcc4 | ATP-binding cassette, sub-family C (CFTR/MRP), member 4 |
| -3.591 | 22.542 | Ptpn14 | protein tyrosine phosphatase, non-receptor type 14 |
| -3.578 | 46.364 | Ptprt | protein tyrosine phosphatase, receptor type, T |
| -3.575 | 10.901 | Il2rb | interleukin 2 receptor, beta chain |
| -3.556 | 14.063 | Il21r | interleukin 21 receptor |
| -3.542 | 28.619 | Thpo | thrombopoietin |
| -3.539 | 17.241 | Hira | histone cell cycle regulation defective homolog A (S. cerevisiae) |
| -3.535 | 13.798 | Pbx1 | pre B cell leukemia homeobox 1 |
| -3.522 | 28.092 | Olfr164 | olfactory receptor 164 |
| -3.520 | 10.364 | Bai1 | brain-specific angiogenesis inhibitor 1 |
| -3.520 | 10.364 | Rpia | ribose 5-phosphate isomerase A |
| -3.515 | 13.534 | Onecut2 | one cut domain, family member 2 |
| -3.513 | 24.385 | St8sia3 | ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 3 |
| -3.491 | 10.097 | Camk2d | calcium/calmodulin-dependent protein kinase II, delta |

| | | | |
|---|---|---|---|
| -3.467 | 48.740 | Aff3 | AF4/FMR2 family, member 3 |
| -3.450 | 12.743 | Cd247 | CD247 antigen |
| -3.442 | 40.797 | Spdef | SAM pointed domain containing ets transcription factor |
| -3.432 | 69.389 | Lgals6 | lectin, galactose binding, soluble 6 |
| -3.432 | 9.564 | Cd5 | CD5 antigen |
| -3.432 | 9.564 | Duxbl3 | double homeobox B-like 3 |
| -3.426 | 46.902 | Ern2 | endoplasmic reticulum (ER) to nucleus signalling 2 |
| -3.406 | 49.305 | Klra18 | killer cell lectin-like receptor, subfamily A, member 18 |
| -3.404 | 15.149 | Nol11 | nucleolar protein 11 |
| -3.399 | 42.406 | Capzb | capping protein (actin filament) muscle Z-line, beta |
| -3.399 | 42.406 | Rgs10 | regulator of G-protein signalling 10 |
| -3.376 | 24.429 | Spp2 | secreted phosphoprotein 2 |
| -3.371 | 9.035 | Gm8369 | predicted gene 8369 |
| -3.371 | 9.035 | Nrarp | Notch-regulated ankyrin repeat protein |
| -3.371 | 9.035 | Sulf1 | sulfatase 1 |
| -3.371 | 9.035 | Wwc1 | WW, C2 and coiled-coil domain containing 1 |
| -3.369 | 18.309 | Nfasc | neurofascin |
| -3.360 | 57.542 | Pld4 | phospholipase D family, member 4 |
| -3.355 | 20.977 | Elfn2 | leucine rich repeat and fibronectin type III, extracellular 2 |
| -3.354 | 18.047 | Cgrrf1 | cell growth regulator with ring finger domain 1 |
| -3.354 | 18.047 | Sh2d1b2 | SH2 domain protein 1B2 |
| -3.352 | 40.578 | Gm14461 | predicted gene 14461 |
| -3.349 | 14.372 | Ankdd1b | ankyrin repeat and death domain containing 1B |
| -3.349 | 14.372 | Trim44 | tripartite motif-containing 44 |
| -3.339 | 8.771 | Ptprn | protein tyrosine phosphatase, receptor type, N |
| -3.337 | 11.437 | Skor2 | SKI family transcriptional corepressor 2 |
| -3.328 | 5.353 | Rnf19b | ring finger protein 19B |
| -3.326 | 52.529 | Acan | aggrecan |
| -3.320 | 23.135 | Cd79a | CD79A antigen (immunoglobulin-associated alpha) |
| -3.313 | 11.178 | Eid1 | EP300 interacting inhibitor of differentiation 1 |
| -3.312 | 13.857 | Trim58 | tripartite motif-containing 58 |
| -3.307 | 8.508 | Bsg | basigin |
| -3.307 | 8.508 | Cd22 | CD22 antigen |
| -3.307 | 8.508 | Postn | periostin, osteoblast specific factor |
| -3.305 | 35.825 | Dock8 | dedicator of cytokinesis 8 |
| -3.302 | 19.940 | Siglec1 | sialic acid binding Ig-like lectin 1, sialoadhesin |
| -3.289 | 10.919 | Stk32b | serine/threonine kinase 32B |
| -3.285 | 40.918 | AI607873 | expressed sequence AI607873 |
| -3.278 | 95.042 | Clu | clusterin |
| -3.274 | 8.246 | Prss2 | protease, serine 2 |
| -3.260 | 16.487 | Sla2 | Src-like-adaptor 2 |
| -3.258 | 52.102 | Lhx8 | LIM homeobox protein 8 |
| -3.240 | 7.985 | Adtrp | androgen dependent TFPI regulating protein |
| -3.240 | 7.985 | Anp32a | acidic (leucine-rich) nuclear phosphoprotein 32 family, member A |
| -3.240 | 7.985 | Sall4 | sal-like 4 (Drosophila) |
| -3.239 | 10.404 | Plet1 | placenta expressed transcript 1 |
| -3.239 | 10.404 | Susd2 | sushi domain containing 2 |
| -3.220 | 18.396 | Btbd11 | BTB (POZ) domain containing 11 |
| -3.213 | 12.580 | Slc45a3 | solute carrier family 45, member 3 |
| -3.213 | 10.148 | Akap13 | A kinase (PRKA) anchor protein 13 |
| -3.213 | 10.148 | Efna5 | ephrin A5 |
| -3.213 | 10.148 | Foxp1 | forkhead box P1 |
| -3.213 | 10.148 | Tox | thymocyte selection-associated high mobility group box |
| -3.210 | 44.166 | Kng2 | kininogen 2 |
| -3.205 | 7.725 | Ikzf3 | IKAROS family zinc finger 3 |
| -2.372 | 140.221 | Sftpb | surfactant associated protein B |
| -2.077 | 61.328 | Foxa2 | forkhead box A2 |

## Supplementary Table 5: *ROSE algorithm on H3K27ac peaks in SCC samples*

***top 200 somatic super-enhancers associated with protein coding genes, and microRNA 21a***

| Ranking | Gene Name | Gene Description |
|---|---|---|
| 1 | Tomm20 | translocase of outer mitochondrial membrane 20 homolog (yeast) |
| 2 | Mir21a | microRNA 21a |
| 3 | Ergic1 | endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1 |
| 4 | Mcl1 | myeloid cell leukemia sequence 1 |
| 5 | Ifitm3 | interferon induced transmembrane protein 3 |
| 6 | 1600014C10Rik | RIKEN cDNA 1600014C10 gene |
| 7 | Zfp217 | zinc finger protein 217 |
| 8 | Socs3 | suppressor of cytokine signaling 3 |
| 9 | Bcl2l1 | BCL2-like 1 |
| 10 | Furin | furin (paired basic amino acid cleaving enzyme) |
| 11 | Myh9 | myosin, heavy polypeptide 9, non-muscle |
| 12 | Ier5 | immediate early response 5 |
| 13 | E030018B13Rik | RIKEN cDNA E030018B13 gene |

| | | |
|---|---|---|
| 14 | Pxn | paxillin |
| 15 | Irf2bp2 | interferon regulatory factor 2 binding protein 2 |
| 16 | Lrp1 | low density lipoprotein receptor-related protein 1 |
| 17 | Mbp | myelin basic protein |
| 18 | Ccdc12 | coiled-coil domain containing 12 |
| 19 | Ptpn1 | protein tyrosine phosphatase, non-receptor type 1 |
| 20 | Sik1 | salt inducible kinase 1 |
| 21 | Tatdn2 | TatD DNase domain containing 2 |
| 22 | Irf1 | interferon regulatory factor 1 |
| 23 | Rara | retinoic acid receptor, alpha |
| 24 | Sorl1 | sortilin-related receptor, LDLR class A repeats-containing |
| 25 | Lyst | lysosomal trafficking regulator |
| 26 | Cap1 | CAP, adenylate cyclase-associated protein 1 (yeast) |
| 27 | Gsr | glutathione reductase |
| 28 | Cd14 | CD14 antigen |
| 29 | Spatc1 | spermatogenesis and centriole associated 1 |
| 30 | Rin3 | Ras and Rab interactor 3 |
| 31 | Ly6e | lymphocyte antigen 6 complex, locus E |
| 32 | Aff1 | AF4/FMR2 family, member 1 |
| 33 | Iqgap1 | IQ motif containing GTPase activating protein 1 |
| 34 | Incenp | inner centromere protein |
| 35 | Tgfbr1 | transforming growth factor, beta receptor I |
| 36 | S100a9 | S100 calcium binding protein A9 (calgranulin B) |
| 37 | Btg2 | B cell translocation gene 2, anti-proliferative |
| 38 | Pfkfb3 | 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 |
| 39 | Trim8 | tripartite motif-containing 8 |
| 40 | Fam49b | family with sequence similarity 49, member B |
| 41 | Tspan14 | tetraspanin 14 |
| 42 | Cxcr2 | chemokine (C-X-C motif) receptor 2 |
| 43 | Ptpn22 | protein tyrosine phosphatase, non-receptor type 22 (lymphoid) |
| 44 | Zmiz1 | zinc finger, MIZ-type containing 1 |
| 45 | Irf2bpl | interferon regulatory factor 2 binding protein-like |
| 46 | Fgr | Gardner-Rasheed feline sarcoma viral (Fgr) oncogene homolog |
| 47 | Actb | actin, beta |
| 48 | Rassf6 | Ras association (RalGDS/AF-6) domain family member 6 |
| 49 | Midn | midnolin |
| 50 | Csf3r | colony stimulating factor 3 receptor (granulocyte) |
| 51 | Ndst1 | N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1 |
| 52 | Asprv1 | aspartic peptidase, retroviral-like 1 |
| 53 | Irf2bpl | interferon regulatory factor 2 binding protein-like |
| 54 | Bcl3 | B cell leukemia/lymphoma 3 |
| 55 | Junb | jun B proto-oncogene |
| 56 | Litaf | LPS-induced TN factor |
| 57 | Cflar | CASP8 and FADD-like apoptosis regulator |
| 58 | Osgin1 | oxidative stress induced growth inhibitor 1 |
| 59 | Clvs1 | clavesin 1 |
| 60 | Slfn2 | schlafen 2 |
| 61 | Fbxl5 | F-box and leucine-rich repeat protein 5 |
| 62 | Cmip | c-Maf inducing protein |
| 63 | Pstpip1 | proline-serine-threonine phosphatase-interacting protein 1 |
| 64 | Mknk2 | MAP kinase-interacting serine/threonine kinase 2 |
| 65 | Rassf3 | Ras association (RalGDS/AF-6) domain family member 3 |
| 66 | Eea1 | early endosome antigen 1 |
| 67 | Sgms1 | sphingomyelin synthase 1 |
| 68 | Actn1 | actinin, alpha 1 |
| 69 | Tgm2 | transglutaminase 2, C polypeptide |
| 70 | Ubxn11 | UBX domain protein 11 |
| 71 | Hist1h3e | histone cluster 1, H3e |
| 72 | Fkbp8 | FK506 binding protein 8 |
| 73 | Ifnar2 | interferon (alpha and beta) receptor 2 |
| 74 | Il4ra | interleukin 4 receptor, alpha |
| 75 | Zfp608 | zinc finger protein 608 |
| 76 | Ninj2 | ninjurin 2 |
| 77 | Spi1 | spleen focus forming virus (SFFV) proviral integration oncogene |
| 78 | Krt80 | keratin 80 |
| 79 | Il1r2 | interleukin 1 receptor, type II |
| 80 | Vps54 | vacuolar protein sorting 54 (yeast) |
| 81 | Cd44 | CD44 antigen |
| 82 | Ptpn6 | protein tyrosine phosphatase, non-receptor type 6 |
| 83 | Adam19 | a disintegrin and metallopeptidase domain 19 (meltrin beta) |
| 84 | Hic1 | hypermethylated in cancer 1 |
| 85 | Tnrc18 | trinucleotide repeat containing 18 |
| 86 | Atf1 | activating transcription factor 1 |
| 87 | Pim1 | proviral integration site 1 |
| 88 | Tbl1xr1 | transducin (beta)-like 1X-linked receptor 1 |
| 89 | Plekha2 | pleckstrin homology domain-containing, family A (phosphoinositide binding specific) member 2 |
| 90 | Ifngr1 | interferon gamma receptor 1 |
| 91 | Xbp1 | X-box binding protein 1 |

| | | |
|---|---|---|
| 92 | Cxcl1 | chemokine (C-X-C motif) ligand 1 |
| 93 | S100a3 | S100 calcium binding protein A3 |
| 94 | Armc12 | armadillo repeat containing 12 |
| 95 | Hif1a | hypoxia inducible factor 1, alpha subunit |
| 96 | Lasp1 | LIM and SH3 protein 1 |
| 97 | Irf2bp2 | interferon regulatory factor 2 binding protein 2 |
| 98 | Pf4 | platelet factor 4 |
| 99 | Nek6 | NIMA (never in mitosis gene a)-related expressed kinase 6 |
| 100 | Zfp36 | zinc finger protein 36 |
| 101 | Cd9 | CD9 antigen |
| 102 | Rab7 | RAB7, member RAS oncogene family |
| 103 | Ndufs8 | NADH dehydrogenase (ubiquinone) Fe-S protein 8 |
| 104 | Gnai2 | guanine nucleotide binding protein (G protein), alpha inhibiting 2 |
| 105 | Cyth4 | cytohesin 4 |
| 106 | Rhof | ras homolog gene family, member f |
| 107 | Coro2a | coronin, actin binding protein 2A |
| 108 | Dnajb12 | DnaJ (Hsp40) homolog, subfamily B, member 12 |
| 109 | Fos | FBJ osteosarcoma oncogene |
| 110 | Itgb2 | integrin beta 2 |
| 111 | Msl1 | male-specific lethal 1 homolog (Drosophila) |
| 112 | Snx29 | sorting nexin 29 |
| 113 | Notch1 | notch 1 |
| 114 | Rab31 | RAB31, member RAS oncogene family |
| 115 | C1qtnf9 | C1q and tumor necrosis factor related protein 9 |
| 116 | Jun | jun proto-oncogene |
| 117 | Ctsd | cathepsin D |
| 118 | 1110007C09Rik | RIKEN cDNA 1110007C09 gene |
| 119 | Fosl2 | fos-like antigen 2 |
| 120 | 2810408A11Rik | RIKEN cDNA 2810408A11 gene |
| 121 | Wasf2 | WAS protein family, member 2 |
| 122 | Cdkn2aipnl | CDKN2A interacting protein N-terminal like |
| 123 | Inpp5d | inositol polyphosphate-5-phosphatase D |
| 124 | Phlda1 | pleckstrin homology-like domain, family A, member 1 |
| 125 | Cubn | cubilin (intrinsic factor-cobalamin receptor) |
| 126 | Alcam | activated leukocyte cell adhesion molecule |
| 127 | Tfeb | transcription factor EB |
| 128 | Tpm1 | tropomyosin 1, alpha |
| 129 | Sh3bp2 | SH3-domain binding protein 2 |
| 130 | Tctex1d4 | Tctex1 domain containing 4 |
| 131 | C5ar2 | complement component 5a receptor 2 |
| 132 | Fcgr3 | Fc receptor, IgG, low affinity III |
| 133 | Ly6e | lymphocyte antigen 6 complex, locus E |
| 134 | Bcl6 | B cell leukemia/lymphoma 6 |
| 135 | Ccdc80 | coiled-coil domain containing 80 |
| 136 | Cux1 | cut-like homeobox 1 |
| 137 | Cxcr4 | chemokine (C-X-C motif) receptor 4 |
| 138 | N4bp1 | NEDD4 binding protein 1 |
| 139 | Zfhx3 | zinc finger homeobox 3 |
| 140 | Lcp1 | lymphocyte cytosolic protein 1 |
| 141 | Tmem140 | transmembrane protein 140 |
| 142 | Kdm6b | KDM1 lysine (K)-specific demethylase 6B |
| 143 | Tgif1 | TGFB-induced factor homeobox 1 |
| 144 | Nfkbia | nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha |
| 145 | Cotl1 | coactosin-like 1 (Dictyostelium) |
| 146 | Entpd1 | ectonucleoside triphosphate diphosphohydrolase 1 |
| 147 | Swap70 | SWA-70 protein |
| 148 | Hnrnpl | heterogeneous nuclear ribonucleoprotein L |
| 149 | Rreb1 | ras responsive element binding protein 1 |
| 150 | Dhrs3 | dehydrogenase/reductase (SDR family) member 3 |
| 151 | Tbc1d14 | TBC1 domain family, member 14 |
| 152 | Ccdc91 | coiled-coil domain containing 91 |
| 153 | Sgms1 | sphingomyelin synthase 1 |
| 154 | Runx1 | runt related transcription factor 1 |
| 155 | Rbm47 | RNA binding motif protein 47 |
| 156 | Csf1 | colony stimulating factor 1 (macrophage) |
| 157 | Prss22 | protease, serine 22 |
| 158 | Klhl6 | kelch-like 6 |
| 159 | Fpr1 | formyl peptide receptor 1 |
| 160 | Osbpl9 | oxysterol binding protein-like 9 |
| 161 | Akap13 | A kinase (PRKA) anchor protein 13 |
| 162 | Klf3 | Kruppel-like factor 3 (basic) |
| 163 | Lipc | lipase, hepatic |
| 164 | Pla2g7 | phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma) |
| 165 | Chd2 | chromodomain helicase DNA binding protein 2 |
| 166 | Smad7 | SMAD family member 7 |
| 167 | Agps | alkylglycerone phosphate synthase |
| 168 | Cdt1 | chromatin licensing and DNA replication factor 1 |
| 169 | Pigx | phosphatidylinositol glycan anchor biosynthesis, class X |

| | | |
|---|---|---|
| 170 | Amer2 | APC membrane recruitment 2 |
| 171 | Zbtb42 | zinc finger and BTB domain containing 42 |
| 172 | Fam129b | family with sequence similarity 129, member B |
| 173 | Egln3 | egl-9 family hypoxia-inducible factor 3 |
| 174 | Tle3 | transducin-like enhancer of split 3, homolog of Drosophila E(spl) |
| 175 | Pacsin2 | protein kinase C and casein kinase substrate in neurons 2 |
| 176 | Tpst2 | protein-tyrosine sulfotransferase 2 |
| 177 | Ly6a | lymphocyte antigen 6 complex, locus A |
| 178 | Fli1 | Friend leukemia integration 1 |
| 179 | Ubc | ubiquitin C |
| 180 | Pde4b | phosphodiesterase 4B, cAMP specific |
| 181 | 6430531B16Rik | RIKEN cDNA 6430531B16 gene |
| 182 | Klhdc8a | kelch domain containing 8A |
| 183 | Rin3 | Ras and Rab interactor 3 |
| 184 | Ier3 | immediate early response 3 |
| 185 | Zfp541 | zinc finger protein 541 |
| 186 | Ankrd11 | ankyrin repeat domain 11 |
| 187 | Tnfrsf26 | tumor necrosis factor receptor superfamily, member 26 |
| 188 | Erg | avian erythroblastosis virus E-26 (v-ets) oncogene related |
| 189 | Vps37b | vacuolar protein sorting 37B (yeast) |
| 190 | Ptma | prothymosin alpha |
| 191 | Lrrfip1 | leucine rich repeat (in FLII) interacting protein 1 |
| 192 | Tnfrsf1b | tumor necrosis factor receptor superfamily, member 1b |
| 193 | Zfp608 | zinc finger protein 608 |
| 194 | Zfp503 | zinc finger protein 503 |
| 195 | Rhob | ras homolog gene family, member B |
| 196 | Slc16a11 | solute carrier family 16 (monocarboxylic acid transporters), member 11 |
| 197 | Dusp6 | dual specificity phosphatase 6 |
| 198 | Dhrs3 | dehydrogenase/reductase (SDR family) member 3 |
| 199 | Tnfaip2 | tumor necrosis factor, alpha-induced protein 2 |
| 200 | Pagr1a | PAXIP1 associated glutamate rich protein 1A |

## Supplementary Table 6: *ROSE algorithm on H3K27ac peaks in ADC samples*

***top 200 somatic super-enhancers associated with protein coding genes, and microRNA 21a***

| Ranking | Gene Name | Gene Description |
|---|---|---|
| 1 | Irf2bp2 | interferon regulatory factor 2 binding protein 2 |
| 2 | Mir21a | microRNA 21a |
| 3 | Sik1 | salt inducible kinase 1 |
| 4 | Rad51b | RAD51 homolog B |
| 5 | Myh9 | myosin, heavy polypeptide 9, non-muscle |
| 6 | Ddit4 | DNA-damage-inducible transcript 4 |
| 7 | Mcl1 | myeloid cell leukemia sequence 1 |
| 8 | Ergic1 | endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1 |
| 9 | Socs3 | suppressor of cytokine signaling 3 |
| 10 | Abhd2 | abhydrolase domain containing 2 |
| 11 | Ly6e | lymphocyte antigen 6 complex, locus E |
| 12 | Sgms1 | sphingomyelin synthase 1 |
| 13 | Dhrs3 | dehydrogenase/reductase (SDR family) member 3 |
| 14 | Zmiz1 | zinc finger, MIZ-type containing 1 |
| 15 | Carns1 | carnosine synthase 1 |
| 16 | Bcl2l1 | BCL2-like 1 |
| 17 | Trim8 | tripartite motif-containing 8 |
| 18 | Smad3 | SMAD family member 3 |
| 19 | Cblc | Casitas B-lineage lymphoma c |
| 20 | Irf2 | interferon regulatory factor 2 |
| 21 | Capzb | capping protein (actin filament) muscle Z-line, beta |
| 22 | Irf2bpl | interferon regulatory factor 2 binding protein-like |
| 23 | E030018B13Rik | RIKEN cDNA E030018B13 gene |
| 24 | Lta | lymphotoxin A |
| 25 | Sdc1 | syndecan 1 |
| 26 | Ski | ski sarcoma viral oncogene homolog (avian) |
| 27 | Hyal3 | hyaluronoglucosaminidase 3 |
| 28 | Dusp7 | dual specificity phosphatase 7 |
| 29 | Il4ra | interleukin 4 receptor, alpha |
| 30 | Zfp217 | zinc finger protein 217 |
| 31 | Htra4 | HtrA serine peptidase 4 |
| 32 | Pmepa1 | prostate transmembrane protein, androgen induced 1 |
| 33 | Kxd1 | KxDL motif containing 1 |
| 34 | Tpm1 | tropomyosin 1, alpha |
| 35 | Cebpa | CCAAT/enhancer binding protein (C/EBP), alpha |
| 36 | Pgpep1 | pyroglutamyl-peptidase I |

| | | |
|---|---|---|
| 37 | Actn1 | actinin, alpha 1 |
| 38 | St3gal1 | ST3 beta-galactoside alpha-2,3-sialyltransferase 1 |
| 39 | Plekhf1 | pleckstrin homology domain containing, family F (with FYVE domain) member 1 |
| 40 | Synpo | synaptopodin |
| 41 | Phlda1 | pleckstrin homology-like domain, family A, member 1 |
| 42 | Ier5 | immediate early response 5 |
| 43 | Sema4b | sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B |
| 44 | Zmynd8 | zinc finger, MYND-type containing 8 |
| 45 | Crebzf | CREB/ATF bZIP transcription factor |
| 46 | Smad7 | SMAD family member 7 |
| 47 | Ndst1 | N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1 |
| 48 | Tspan14 | tetraspanin 14 |
| 49 | Slc34a3 | solute carrier family 34 (sodium phosphate), member 3 |
| 50 | Furin | furin (paired basic amino acid cleaving enzyme) |
| 51 | Btg2 | B cell translocation gene 2, anti-proliferative |
| 52 | Ccdc12 | coiled-coil domain containing 12 |
| 53 | Fam129b | family with sequence similarity 129, member B |
| 54 | Rgs3 | regulator of G-protein signaling 3 |
| 55 | Plekhg2 | pleckstrin homology domain containing, family G (with RhoGef domain) member 2 |
| 56 | Tnfrsf1b | tumor necrosis factor receptor superfamily, member 1b |
| 57 | Adssl1 | adenylosuccinate synthetase like 1 |
| 58 | Ctsd | cathepsin D |
| 59 | Shb | src homology 2 domain-containing transforming protein B |
| 60 | Pxn | paxillin |
| 61 | Syngr2 | synaptogyrin 2 |
| 62 | Wasf2 | WAS protein family, member 2 |
| 63 | Sftpb | surfactant associated protein B |
| 64 | Col4a2 | collagen, type IV, alpha 2 |
| 65 | 1600014C23Rik | RIKEN cDNA 1600014C23 gene |
| 66 | Elk3 | ELK3, member of ETS oncogene family |
| 67 | Hif1a | hypoxia inducible factor 1, alpha subunit |
| 68 | Vgll4 | vestigial like 4 (Drosophila) |
| 69 | Sipa1l3 | signal-induced proliferation-associated 1 like 3 |
| 70 | Lipc | lipase, hepatic |
| 71 | Tgif1 | TGFB-induced factor homeobox 1 |
| 72 | Tnrc18 | trinucleotide repeat containing 18 |
| 73 | Ak2 | adenylate kinase 2 |
| 74 | Rac2 | RAS-related C3 botulinum substrate 2 |
| 75 | Ech1 | enoyl coenzyme A hydratase 1, peroxisomal |
| 76 | Myo1e | myosin IE |
| 77 | Ptpn1 | protein tyrosine phosphatase, non-receptor type 1 |
| 78 | Coro2a | coronin, actin binding protein 2A |
| 79 | Tmem107 | transmembrane protein 107 |
| 80 | Bcar3 | breast cancer anti-estrogen resistance 3 |
| 81 | Zfp36l1 | zinc finger protein 36, C3H type-like 1 |
| 82 | Pim1 | proviral integration site 1 |
| 83 | Junb | jun B proto-oncogene |
| 84 | Src | Rous sarcoma oncogene |
| 85 | Actb | actin, beta |
| 86 | B3gnt7 | UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7 |
| 87 | Rara | retinoic acid receptor, alpha |
| 88 | Tatdn2 | TatD DNase domain containing 2 |
| 89 | Fth1 | ferritin heavy chain 1 |
| 90 | Baiap2 | brain-specific angiogenesis inhibitor 1-associated protein 2 |
| 91 | Epha2 | Eph receptor A2 |
| 92 | Iqgap1 | IQ motif containing GTPase activating protein 1 |
| 93 | Krt8 | keratin 8 |
| 94 | Midn | midnolin |
| 95 | Pwwp2b | PWWP domain containing 2B |
| 96 | Mex3a | mex3 homolog A (C. elegans) |
| 97 | Sbno2 | strawberry notch homolog 2 (Drosophila) |
| 98 | Ccr7 | chemokine (C-C motif) receptor 7 |
| 99 | S100a4 | S100 calcium binding protein A4 |
| 100 | Laptm4a | lysosomal-associated protein transmembrane 4A |
| 101 | Fcgr2b | Fc receptor, IgG, low affinity IIb |
| 102 | Foxp1 | forkhead box P1 |
| 103 | Fos | FBJ osteosarcoma oncogene |
| 104 | Cerk | ceramide kinase |
| 105 | Setd1b | SET domain containing 1B |
| 106 | Asprv1 | aspartic peptidase, retroviral-like 1 |
| 107 | Myof | myoferlin |
| 108 | Mknk2 | MAP kinase-interacting serine/threonine kinase 2 |
| 109 | Actn4 | actinin alpha 4 |
| 110 | Rassf2 | Ras association (RalGDS/AF-6) domain family member 2 |
| 111 | Ninj2 | ninjurin 2 |

| | | |
|---|---|---|
| 112 | Ddx47 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 47 |
| 113 | Hes1 | hairy and enhancer of split 1 (Drosophila) |
| 114 | D8Ertd82e | DNA segment, Chr 8, ERATO Doi 82, expressed |
| 115 | Pdlim2 | PDZ and LIM domain 2 |
| 116 | Nr1d1 | nuclear receptor subfamily 1, group D, member 1 |
| 117 | Rreb1 | ras responsive element binding protein 1 |
| 118 | Sep9 | septin 9 |
| 119 | Lrp1 | low density lipoprotein receptor-related protein 1 |
| 120 | Fam49b | family with sequence similarity 49, member B |
| 121 | Pacsin2 | protein kinase C and casein kinase substrate in neurons 2 |
| 122 | Cdkn2b | cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) |
| 123 | Mbp | myelin basic protein |
| 124 | Cyth1 | cytohesin 1 |
| 125 | Hspa8 | heat shock protein 8 |
| 126 | Itpk1 | inositol 1,3,4-triphosphate 5/6 kinase |
| 127 | Ly86 | lymphocyte antigen 86 |
| 128 | Scgb1a1 | secretoglobin, family 1A, member 1 (uteroglobin) |
| 129 | Mpv17l2 | MPV17 mitochondrial membrane protein-like 2 |
| 130 | Ypel3 | yippee-like 3 (Drosophila) |
| 131 | Mpeg1 | macrophage expressed gene 1 |
| 132 | Dusp6 | dual specificity phosphatase 6 |
| 133 | Notch2 | notch 2 |
| 134 | Plau | plasminogen activator, urokinase |
| 135 | Irf2bpl | interferon regulatory factor 2 binding protein-like |
| 136 | Lama5 | laminin, alpha 5 |
| 137 | Piezo1 | piezo-type mechanosensitive ion channel component 1 |
| 138 | Fam53b | family with sequence similarity 53, member B |
| 139 | Ttc7 | tetratricopeptide repeat domain 7 |
| 140 | E230025N22Rik | Riken cDNA E230025N22 gene |
| 141 | Lrrfip1 | leucine rich repeat (in FLII) interacting protein 1 |
| 142 | Hnrnpa3 | heterogeneous nuclear ribonucleoprotein A3 |
| 143 | Gsr | glutathione reductase |
| 144 | Ldlrap1 | low density lipoprotein receptor adaptor protein 1 |
| 145 | Ppard | peroxisome proliferator activator receptor delta |
| 146 | S1pr2 | sphingosine-1-phosphate receptor 2 |
| 147 | Nek6 | NIMA (never in mitosis gene a)-related expressed kinase 6 |
| 148 | Armc12 | armadillo repeat containing 12 |
| 149 | Hfe | hemochromatosis |
| 150 | Adamts4 | a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 4 |
| 151 | Elmsan1 | ELM2 and Myb/SANT-like domain containing 1 |
| 152 | Ctsc | cathepsin C |
| 153 | Spag7 | sperm associated antigen 7 |
| 154 | Gpr146 | G protein-coupled receptor 146 |
| 155 | Lasp1 | LIM and SH3 protein 1 |
| 156 | Clic1 | chloride intracellular channel 1 |
| 157 | Gltscr1 | glioma tumor suppressor candidate region gene 1 |
| 158 | Aff1 | AF4/FMR2 family, member 1 |
| 159 | Rbm47 | RNA binding motif protein 47 |
| 160 | Pnrc2 | proline-rich nuclear receptor coactivator 2 |
| 161 | Zc3h4 | zinc finger CCCH-type containing 4 |
| 162 | Dok1 | docking protein 1 |
| 163 | Hpcal1 | hippocalcin-like 1 |
| 164 | Rassf3 | Ras association (RalGDS/AF-6) domain family member 3 |
| 165 | Bcl9l | B cell CLL/lymphoma 9-like |
| 166 | Spns2 | spinster homolog 2 |
| 167 | Myzap | myocardial zonula adherens protein |
| 168 | Ier5l | immediate early response 5-like |
| 169 | Pkig | protein kinase inhibitor, gamma |
| 170 | Vamp5 | vesicle-associated membrane protein 5 |
| 171 | Scd2 | stearoyl-Coenzyme A desaturase 2 |
| 172 | C1qtnf9 | C1q and tumor necrosis factor related protein 9 |
| 173 | Plac8 | placenta-specific 8 |
| 174 | Litaf | LPS-induced TN factor |
| 175 | Ifi47 | interferon gamma inducible protein 47 |
| 176 | Ccdc19 | coiled-coil domain containing 19 |
| 177 | Snai1 | snail family zinc finger 1 |
| 178 | Tgfbr2 | transforming growth factor, beta receptor II |
| 179 | Nfkbia | nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha |
| 180 | Mgat5 | mannoside acetylglucosaminyltransferase 5 |
| 181 | Cflar | CASP8 and FADD-like apoptosis regulator |
| 182 | Cmip | c-Maf inducing protein |
| 183 | Polr2e | polymerase (RNA) II (DNA directed) polypeptide E |
| 184 | Rasa3 | RAS p21 protein activator 3 |
| 185 | Tgm2 | transglutaminase 2, C polypeptide |
| 186 | BC051665 | cDNA sequence BC051665 |
| 187 | Synj2 | synaptojanin 2 |

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|---|---|---|
| 188 | Pnpla2 | patatin-like phospholipase domain containing 2 |
| 189 | Metrnl | meteorin, glial cell differentiation regulator-like |
| 190 | Sdc4 | syndecan 4 |
| 191 | Igfbp7 | insulin-like growth factor binding protein 7 |
| 192 | Mrpl52 | mitochondrial ribosomal protein L52 |
| 193 | Bahcc1 | BAH domain and coiled-coil containing 1 |
| 194 | St6gal1 | beta galactoside alpha 2,6 sialyltransferase 1 |
| 195 | Slc9a3r1 | solute carrier family 9 (sodium/hydrogen exchanger), member 3 regulator 1 |
| 196 | Elmo3 | engulfment and cell motility 3 |
| 197 | Herpud1 | homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1 |
| 198 | Adam19 | a disintegrin and metallopeptidase domain 19 (meltrin beta) |
| 199 | Dyrk3 | dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 3 |
| 200 | Sh3bp4 | SH3-domain binding protein 4 |