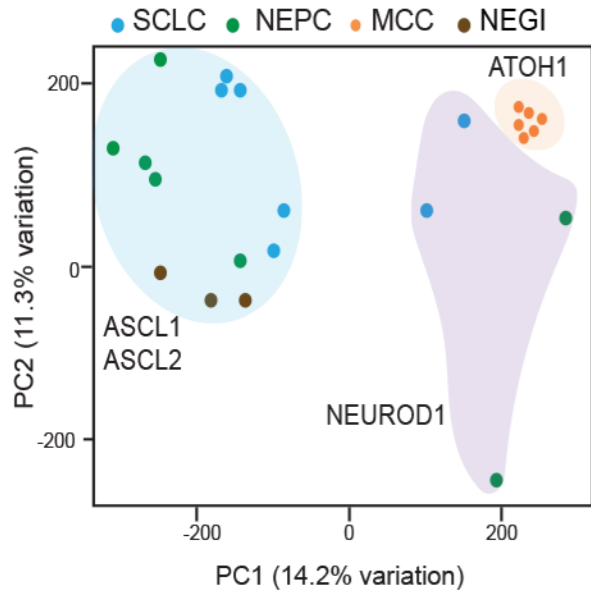
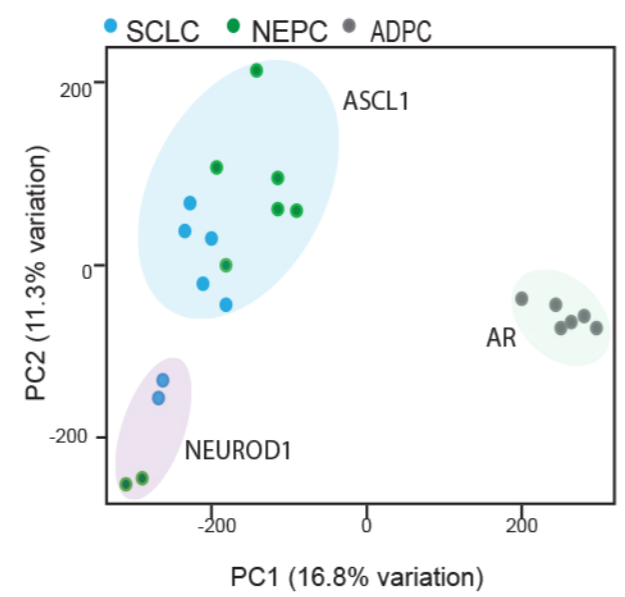


Supplemental Figure 1. NE carcinomas share a common chromatin state independent of their anatomical origin. (a) Correlation plots of the ATAC-seq signal for two LuCaP_49 replicates (Pearson's correlation $r = 0.9989$, left) and LuCaP_93 replicates (Pearson's correlation $r = 0.9988$, right). (b) PCA analysis of ATAC-seq data including neuroendocrine samples (MCC, NEPC, GINE, SCLC), ADPC LuCaPs and engineered prostate cells from a published study¹⁶. Those cells cover a spectrum of transdifferentiation from the basal prostate epithelium through intermediate stages toward a neuroendocrine phenotype with the alterations indicated in the legend. The final cell line samples ('PARCB', expressing dominant negative TP53 (TP53DN), myrAKT1, RB1-shRNA, c-MYC, and BCL2) cluster in close proximity to the NEPC, GINE and SCLC samples from our analysis. (c) Heatmap representation of the differential regions between ADs and NECs for the complete collection of NECs analyzed in our studies compared to the LuCaP ADPC and the TCGA primary prostate adenocarcinomas (PRAD). Each row is a peak location and each column is a sample. (d) Heatmap representation of the differential regions between ADs and NECs for the engineered cells from Park et al¹⁶. Each row is a peak location and each column is a sample. Shown above each column are the composite tag density plots for the AD sites (black) and NE sites (green). (e) Plot of patient RNA-seq data scored by NE (y-axis) and AD (x-axis) signatures derived from the ATAC-seq sites in Figure 1c. The left plot is data from Labreque et. al.¹⁷ the right plot is data from Beltran et. al³⁴. (f) UpSetR plot showing the intersections of ATAC-seq peaks containing the specified motifs and their intersection sizes.

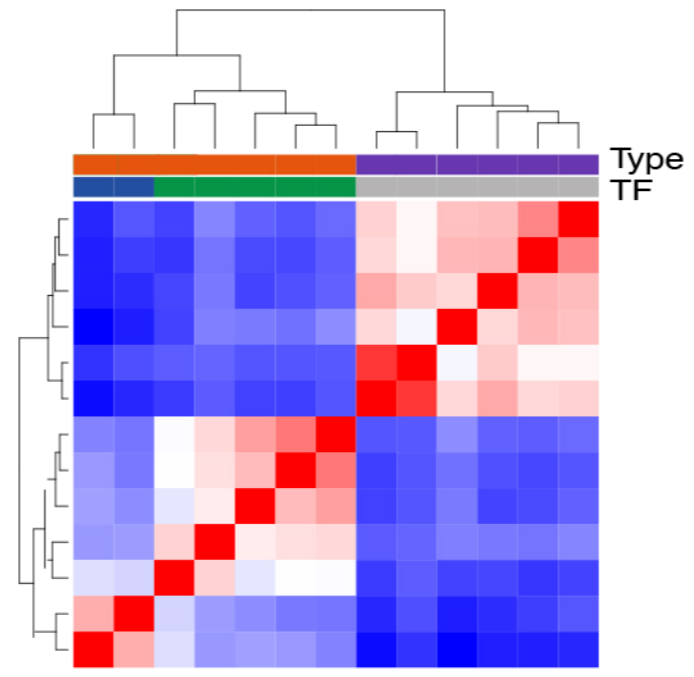
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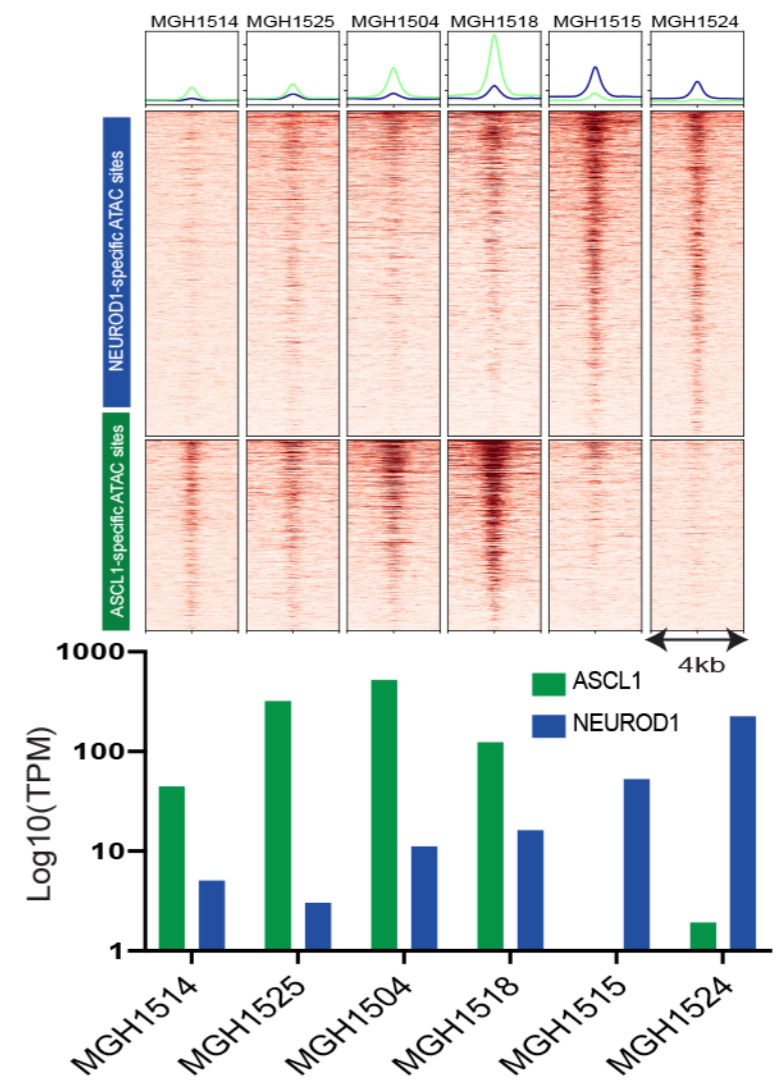
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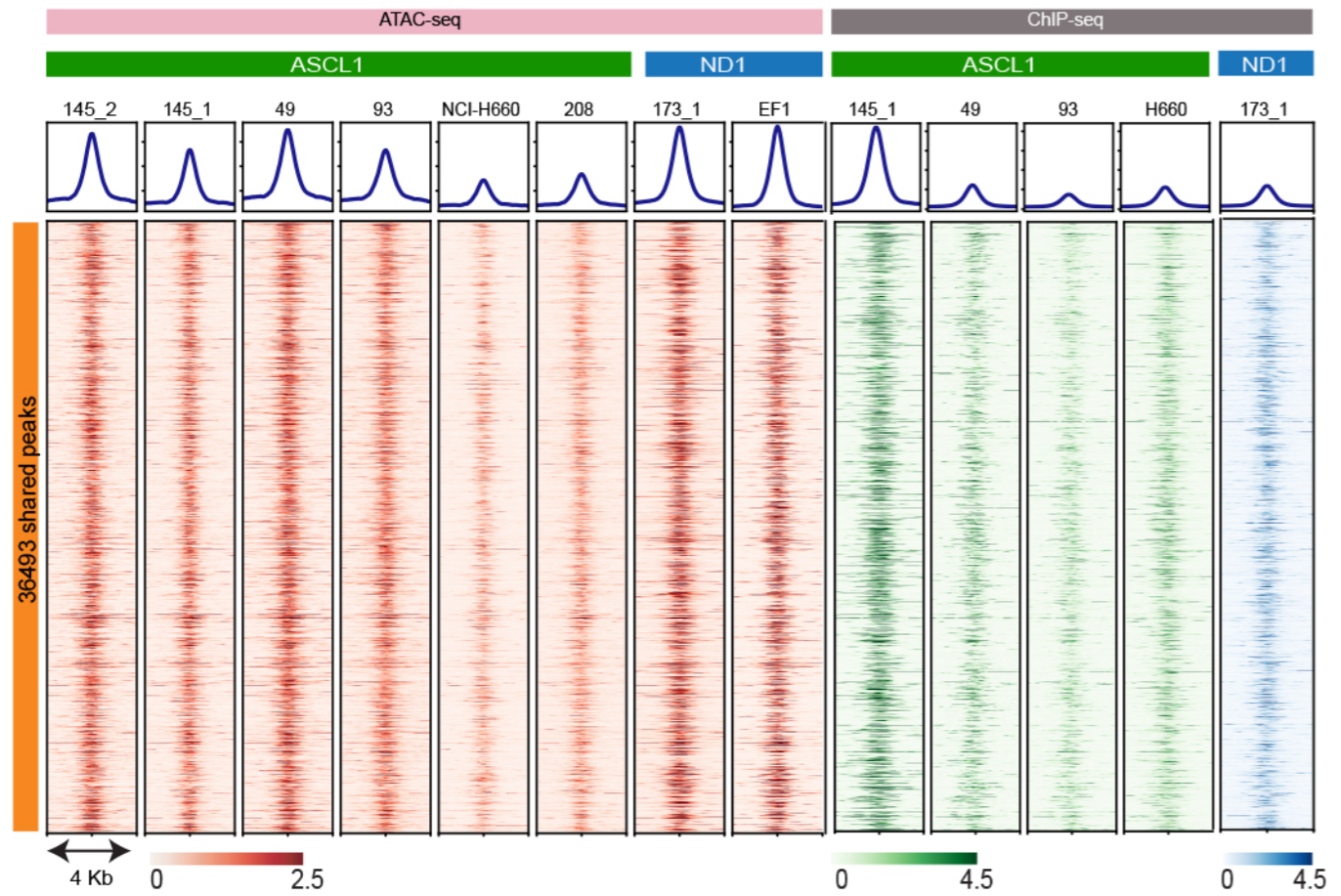
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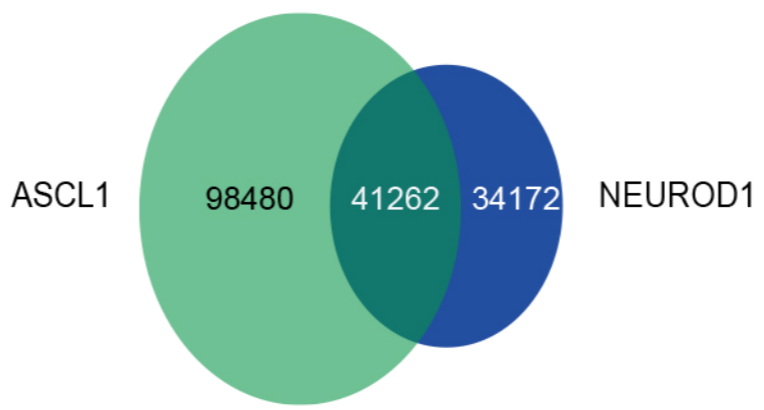
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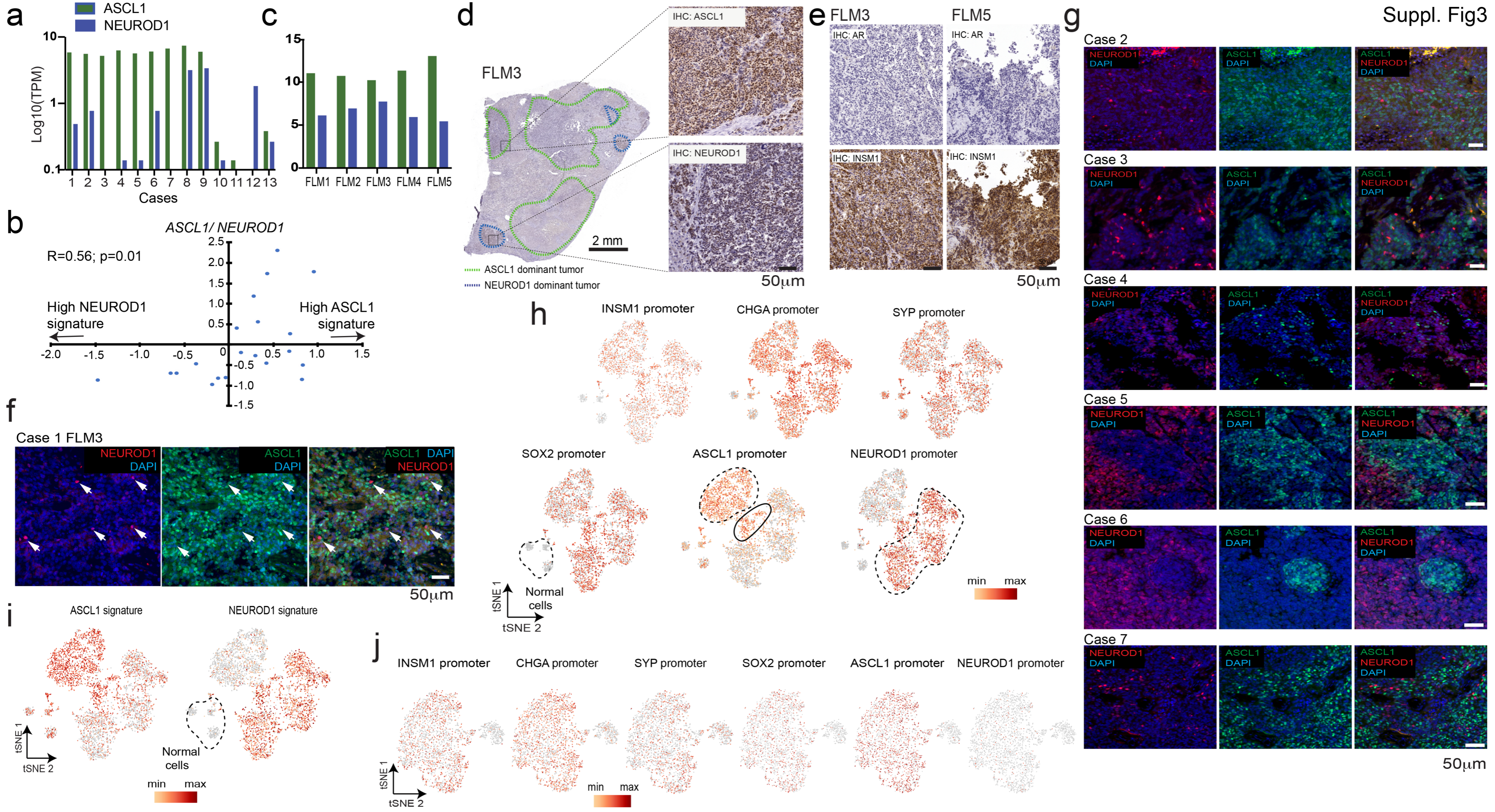
f



g



Supplemental Figure 2. NEPC shows tumor subtypes based on the differential expression of the transcription factors ASCL1 and NEUROD1. (a) PCA analysis of ATAC-seq data of NECs, samples are color coded by tumor type and clusters are highlighted based on the expression of the dominant bHLH TF in each sample. (b) PCA analysis of ATAC-seq data of SCLC, NEPC and ADPC, samples are color coded by tumor type and clusters are highlighted based on the expression of the dominant bHLH TF in each sample. (c) Hierarchical clustering of the pairwise Pearson's correlation of the RNA-seq signal across the NEPCs and ADPC. (d) Heatmap of the ATAC-seq signal in SCLCs at the ASCL1- and NEUROD1-specific DNA accessible regions identified in NEPC (on top) and corresponding expression of ASCL1 and NEUROD1 of the same SCLC tissues (bottom). (e) Heatmap of the ATAC-seq signal at the shared accessible regions in the ASCL1 and NEUROD1 NEPC subtypes (36493 peaks that are shared in at least four samples). Right side of the plot shows the ChIP-seq results for ASCL1 (green) and NEUROD1 (blue) for the indicated samples at the same sites. (f) Venn diagram representing the union of the ASCL1 binding sites obtained by ChIP-seq in PDXs (145.1, 93, 43 and H660) in red and the NEUROD1 bindings by ChIP-seq analysis in PDX 173.1 (in blue) (g) Top enriched consensus motifs identified in ASCL1 ChIP-seq (top) and NEUROD1 ChIP-seq data (bottom). Source data are provided as a Source Data file.



Supplemental Figure 3. Single cell analysis reveals that NEPC sub-types co-exist in

human metastasis and contribute to inter- and intra-tumoral heterogeneity. (a) Plot of

ASCL1 and NEUROD1 expression in NEPC tissues from a clinical cohort (Beltran et al. 2016).

(b) Scatter plot showing correlation between scores for gene expression signatures assessed

by GSVA analysis⁶⁰, and expression of *ASCL1* or *NEUROD1* for the clinical samples in the

Beltran and Labrecque cohorts. The resulting values show a spearman correlation of 0.57

($p=0.01$) indicating that the signatures are ranking the samples in accordance with the amount

of ASCL1 and NEUROD1 expressing cells. (c) Plot of ASCL1 and NEUROD1 expression in the

five fragments of liver metastases from case 1. (d) IHC analysis of a whole FLM3 section at low magnification showing distinct foci for ASCL1 expressing cells (circled in green) and NEUROD1

expressing cells (circled in blue). The right-hand side of the panel has high magnification

micrographs showing regions of ASCL1 positive (top) and NEUROD1 positive (bottom) tumor

cells. (e) Immunohistochemical analysis of AR (top) and INSM1 (bottom) of FLM3 and FLM5

tissues. (f) Representative immunofluorescence staining of FLM3 (case 1) for ASCL1 (green)

and NEUROD1 (red), white arrows are pointing at NEUROD1 expressing tumor cells showing

no ASCL1 expression. (g) Immunofluorescence staining of six additional NEPC metastatic

samples for ASCL1 (green), NEUROD1 (red) and nuclear staining DAPI (blue). Cases 2-5 are

patient samples, case 6 is an organoid model grown in vivo (PDOX) and case 7 is LuCaP 208.

(h) t-SNE analysis of the scATACseq data of FLM3, showing accessibility at the SOX2 promoter

(marking tumor cells) and accessibility at INSM1, CHGA and SYP promoters (NE markers).

ASCL1 (left) and NEUROD1 (right) open promoters mark ASCL1 and NEUROD1

subpopulations within the dashed lines. A small “mixed” cluster consists of cells that are open

for either ASCL1 or NEUROD1 but are intermixed (solid line). (i) t-SNE analysis of the scATAC-

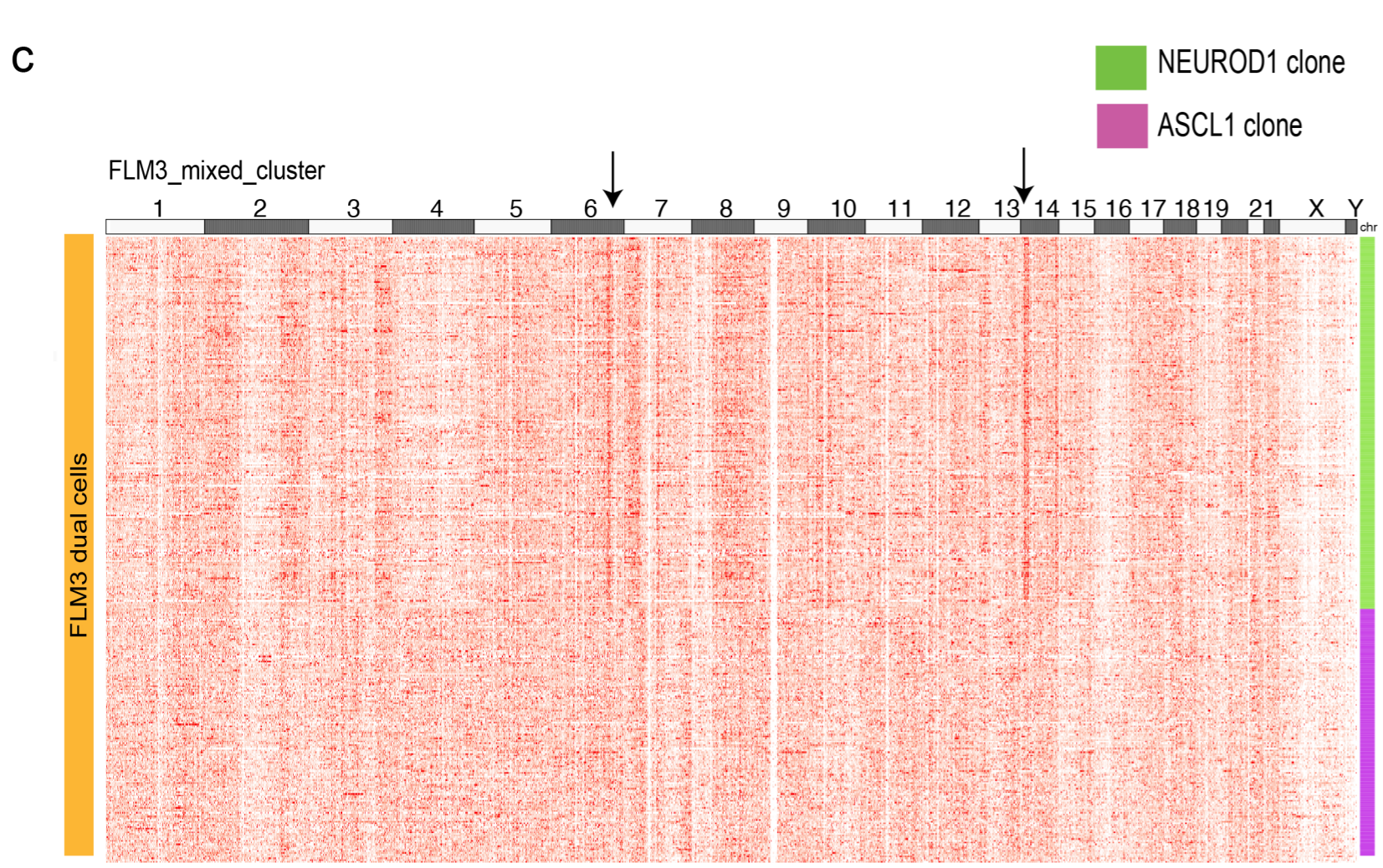
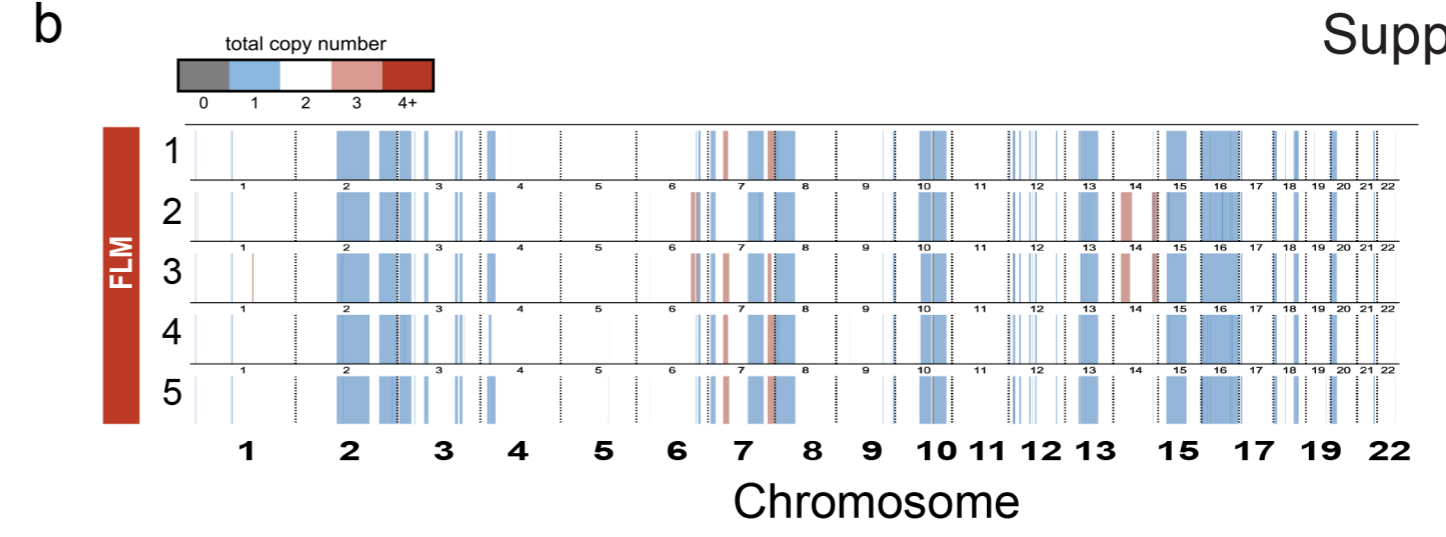
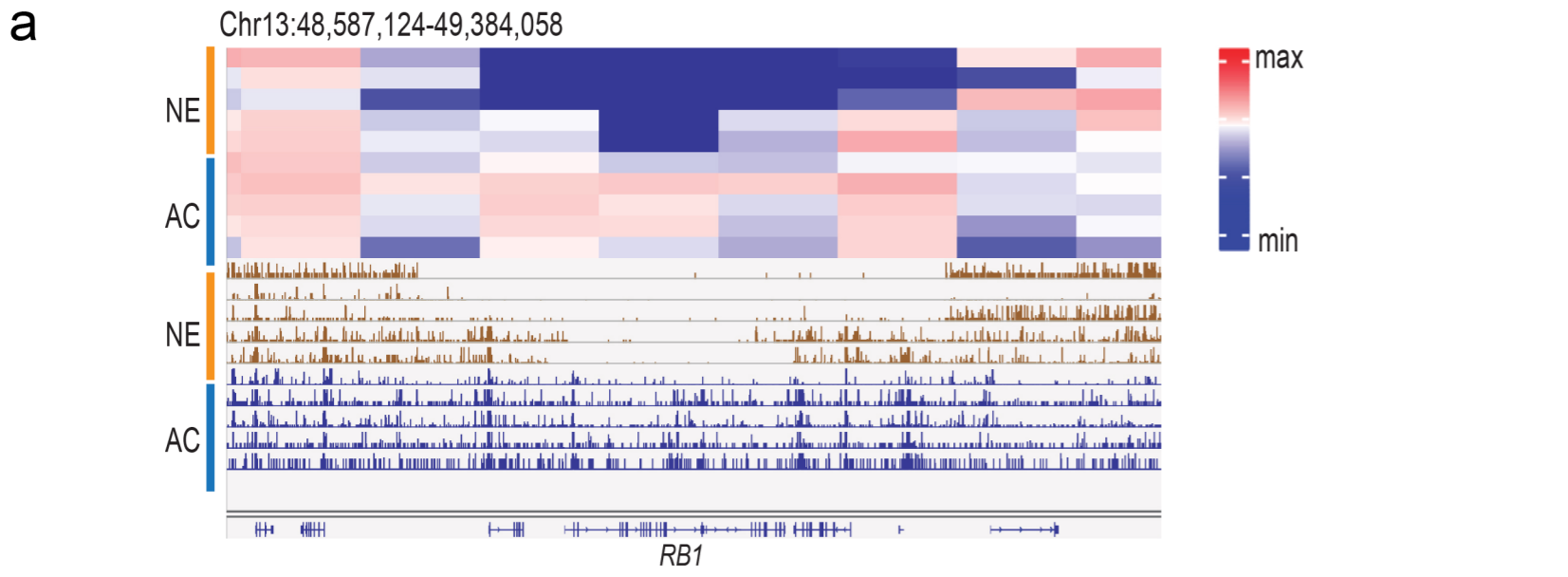
seq data of FLM3 showing accessibility at the top 30 differential ATAC-seq regions identified by

bulk analysis in ASCL1 (top) and NEUROD1 (bottom) subtypes. (j) t-SNE analysis of the

scATAC-seq data of FLM5, showing accessibility at the SOX2 promoter, accessibility at INSM1

(NE marker) and NEUROD1 (left) and ASCL1 (right) promoters marking NEUROD1 and ASCL1

subpopulations respectively. Source data are provided as a Source Data file.



Supplemental Figure 4. The NEPC sub-types are distinct clones. (a) Inference of CNV at RB1 locus from ATAC-seq bulk signal in NEPC and ADPC. (top) Heatmap representation of the inferred data and (bottom) IGV track of the actual ATAC-seq data at that locus. (b) Heatmap of the CNV alterations determined by WES across FLM3 (by clusters) and FLM5. (c) Heatmap of the single cell CNV analysis of the mixed cluster of ASCL1 and NEUROD1. Two dominant clusters are evident that are the same as the larger clusters of ASCL1 and NEUROD1 subclones. (d) UMAP of the single cell ATAC-seq data of FLM3 showing that all cells from the mixed cluster of Supp Fig. 3h resolve into either the ASCL1 and NEUROD1 cluster in this analysis. Source data are provided as a Source Data file.

Supplemental table 2. Motif analysis at NE-specific peaks

| Motif Name | Consensus | P-value | Log P-value | q-value (Benjamini) | # of Target Sequences with Motif(of 4540) | % of Target Sequences with Motif | # of Background Sequences with Motif(of 44756) | % of Background Sequences with Motif |
|--|------------------|-----------|-------------|---------------------|--|----------------------------------|---|--------------------------------------|
| Atoh1(bHLH)/Cerebellum-Atoh1-ChIP-Seq(GSE22111)/Homer | VNRVACGCTGGY | 1e-398 | -9.17E+02 | 0 | 2781 | 61.26% | 13641.7 | 30.48% |
| Ascl1(bHLH)/NeuralTubes-Ascl1-ChIP-Seq(GSE55840)/Homer | NNVVCAGCTGBN | 1e-384 | -8.85E+02 | 0 | 3364 | 74.10% | 19420.5 | 43.39% |
| NeuroD1(bHLH)/Islet-NeuroD1-ChIP-Seq(GSE30298)/Homer | GCCATCTGTT | 1e-363 | -8.38E+02 | 0 | 2308 | 50.84% | 10266.3 | 22.94% |
| NeuroG2(bHLH)/Fibroblast-NeuroG2-ChIP-Seq(GSE75910)/Homer | ACCATCTGTT | 1e-328 | -7.57E+02 | 0 | 3056 | 67.31% | 17367 | 38.80% |
| HEB(bHLH)/mES-Heb-ChIP-Seq(GSE53233)/Homer | VCAGCTGBNN | 1e-326 | -7.52E+02 | 0 | 3542 | 78.02% | 22448.3 | 50.16% |
| E2A(bHLH)/proBcell-E2A-ChIP-Seq(GSE21978)/Homer | DNRACAGCTGY | 1e-324 | -7.48E+02 | 0 | 3173 | 69.89% | 18591.1 | 41.54% |
| Olig2(bHLH)/Neuron-Olig2-ChIP-Seq(GSE30882)/Homer | RCCATMTGTT | 1.00E-291 | -6.71E+02 | 0 | 3228 | 71.10% | 19821.1 | 44.29% |
| Ptf1a(bHLH)/Panc1-Ptf1a-ChIP-Seq(GSE47459)/Homer | ACAGCTGTTN | 1.00E-290 | -6.69E+02 | 0 | 3899 | 85.88% | 27464 | 61.37% |
| MyoG(bHLH)/C2C12-MyoG-ChIP-Seq(GSE36024)/Homer | AACAGCTG | 1.00E-266 | -6.15E+02 | 0 | 2494 | 54.93% | 13402.9 | 29.95% |
| Tcf12(bHLH)/GM12878-Tcf12-ChIP-Seq(GSE32465)/Homer | VCAGCTGYTG | 1.00E-262 | -6.04E+02 | 0 | 2448 | 53.92% | 13095.1 | 29.26% |
| Tcf21(bHLH)/ArterySmoothMuscle-Tcf21-ChIP-Seq(GSE61369)/Homer | NAACAGCTGG | 1.00E-258 | -5.95E+02 | 0 | 2335 | 51.43% | 12205.7 | 27.27% |
| Myf5(bHLH)/GM-Myf5-ChIP-Seq(GSE24852)/Homer | BAACAGCTGT | 1.00E-240 | -5.55E+02 | 0 | 1900 | 41.85% | 9022.1 | 20.16% |
| Lhx1(bHLH)/Myotube-MyoD-ChIP-Seq(GSE21614)/Homer | RRCATGCTYTSY | 1.00E-242 | -4.89E+02 | 0 | 1986 | 43.74% | 10214.4 | 22.82% |
| Ap4(bHLH)/AML-Tfap4-ChIP-Seq(GSE45738)/Homer | NAHCAGCTGD | 1.00E-206 | -4.75E+02 | 0 | 2524 | 55.59% | 14927.7 | 33.35% |
| Lhx2(Homeobox)/HFS-Lhx2-ChIP-Seq(GSE48068)/Homer | TAATTAGN | 1.00E-178 | -4.11E+02 | 0 | 1694 | 37.31% | 8557.6 | 19.12% |
| Lhx1(Homeobox)/EmbryoCarcinoma-Lhx1-ChIP-Seq(GSE70957)/Homer | NNNYTAATTAR | 1.00E-169 | -3.90E+02 | 0 | 1715 | 37.78% | 8904 | 19.90% |
| Slug(Zf)/Mesoderm-Snai2-ChIP-Seq(GSE61475)/Homer | SNGCACCTGCHS | 1.00E-166 | -3.83E+02 | 0 | 1590 | 35.02% | 7995.8 | 17.87% |
| Lhx3(Homeobox)/Neuron-Lhx3-ChIP-Seq(GSE31456)/Homer | ADBTAATTAR | 1.00E-166 | -3.83E+02 | 0 | 2166 | 47.71% | 12695.4 | 28.37% |
| NF1(CTF)/LNCAP-NF1-ChIP-Seq(Unpublished)/Homer | CYTGCGABNSTGCCAR | 1.00E-162 | -3.75E+02 | 0 | 1214 | 26.74% | 5314.3 | 11.87% |
| E2A(bHLH)/near_PU.1/Bcell-PU.1-ChIP-Seq(GSE21512)/Homer | NVCACTGBN | 1.00E-148 | -3.43E+02 | 0 | 2676 | 58.94% | 17791.2 | 39.75% |
| Nkx6.1(Homeobox)/Islet-Nkx6.1-ChIP-Seq(GSE40975)/Homer | GKTAATGR | 1.00E-135 | -3.12E+02 | 0 | 2758 | 60.75% | 18977 | 42.40% |
| NF1-halfsite(CTF)/LNCAP-NF1-ChIP-Seq(Unpublished)/Homer | YTGCCAAAG | 1.00E-131 | -3.04E+02 | 0 | 2838 | 62.51% | 19872.4 | 44.40% |
| SCL(bHLH)/HPC7-Scl-ChIP-Seq(GSE13511)/Homer | AVCAGCTG | 1.00E-121 | -2.79E+02 | 0 | 4232 | 93.22% | 36268 | 81.04% |
| Tgif2(Homeobox)/mES-Tgif2-ChIP-Seq(GSE55404)/Homer | TGTCANVT | 1.00E-101 | -2.34E+02 | 0 | 3460 | 76.21% | 27394.9 | 61.21% |
| Tlx1(NR)/NPC-H3K4me1-ChIP-Seq(GSE16256)/Homer | CTGGCAGSCTGCCA | 1.00E-99 | -2.28E+02 | 0 | 1114 | 24.54% | 5775.3 | 12.90% |
| Isl1(Homeobox)/Neuron-Isl1-ChIP-Seq(GSE31456)/Homer | CTAATKGV | 1.00E-93 | -2.14E+02 | 0 | 2285 | 50.33% | 15853 | 35.42% |
| ZEB1(Zf)/PDAC-ZEB1-ChIP-Seq(GSE64557)/Homer | VCAGGTRDRY | 1.00E-92 | -2.12E+02 | 0 | 2701 | 59.49% | 19857.5 | 44.37% |
| Pit1+1bp(Homeobox)/GCrat-Pit1-ChIP-Seq(GSE58009)/Homer | ATGCATAATTCA | 1.00E-75 | -1.73E+02 | 0 | 587 | 12.93% | 2521.5 | 5.63% |
| Tbx5(T-box)/HL1-Tbx5 biotin-ChIP-Seq(GSE21529)/Homer | AGGTGTCA | 1.00E-74 | -1.72E+02 | 0 | 3473 | 76.50% | 28575.3 | 63.85% |
| Meis1(Homeobox)/MastCells-Meis1-ChIP-Seq(GSE48085)/Homer | VGCTGWCAVB | 1.00E-66 | -1.54E+02 | 0 | 2238 | 49.30% | 16415.6 | 36.68% |
| ZBTB18(Zf)/HEK293-ZBTB18.GFP-ChIP-Seq(GSE58341)/Homer | AACATCTGGGA | 1.00E-64 | -1.49E+02 | 0 | 1054 | 23.22% | 6173.1 | 13.79% |
| Tgif1(Homeobox)/mES-Tgif1-ChIP-Seq(GSE55404)/Homer | YTGWCADY | 1.00E-60 | -1.39E+02 | 0 | 3119 | 68.70% | 25409.9 | 56.78% |
| Sox6(HMG)/Myotubes-Sox6-ChIP-Seq(GSE32627)/Homer | CCATTGTNY | 1.00E-57 | -1.32E+02 | 0 | 1794 | 39.52% | 12720.4 | 28.42% |
| Pdx1(Homeobox)/Islet-Pdx1-ChIP-Seq(SRA008281)/Homer | YCATYAATCA | 1.00E-56 | -1.30E+02 | 0 | 1237 | 27.25% | 7919.4 | 17.70% |
| Nanog(Homeobox)/mES-Nanog-ChIP-Seq(GSE11724)/Homer | RGCCATTAAC | 1.00E-55 | -1.29E+02 | 0 | 3659 | 80.59% | 31453.8 | 70.28% |
| Sox3(HMG)/NPC-Sox3-ChIP-Seq(GSE33059)/Homer | CCWTTGTY | 1.00E-51 | -1.18E+02 | 0 | 1921 | 42.31% | 14152.9 | 31.62% |
| Bapx1(Homeobox)/VertebralCol-Bapx1-ChIP-Seq(GSE36672)/Homer | TTRAGTGSYK | 1.00E-50 | -1.16E+02 | 0 | 2356 | 51.89% | 18272.6 | 40.83% |
| Foxo1(Forkhead)/RAW-Foxo1-ChIP-Seq(Fan_et_al)/Homer | CTGTTTAC | 1.00E-48 | -1.11E+02 | 0 | 2159 | 47.56% | 16511.4 | 36.89% |
| Smad4(MAD)/ESC-SMAD4-ChIP-Seq(GSE29422)/Homer | VBSYGTCTGG | 1.00E-46 | -1.08E+02 | 0 | 2053 | 45.22% | 15572.2 | 34.79% |
| Sox2(HMG)/mES-Sox2-ChIP-Seq(GSE11431)/Homer | BCCATTGTTT | 1.00E-46 | -1.07E+02 | 0 | 1116 | 24.58% | 7264.3 | 16.23% |
| Nkx2.1(Homeobox)/LungAC-Nkx2.1-ChIP-Seq(GSE43252)/Homer | RSCACTYRAG | 1.00E-46 | -1.07E+02 | 0 | 2961 | 65.22% | 24486.1 | 54.71% |
| OCT-OCT-short(POU,Homeobox)/NPC-OCT6-ChIP-Seq(GSE43916)/Homer | ATGCATWATGCATRW | 1.00E-45 | -1.05E+02 | 0 | 889 | 19.58% | 5436.9 | 12.15% |
| AP-2gamma(AP2)/MCF7-TFAP2C-Bapx1-ChIP-Seq(GSE21234)/Homer | SCCTSAGGSCAW | 1.00E-43 | -1.01E+02 | 0 | 1859 | 40.95% | 13932.1 | 31.13% |
| Nkx2.2(Homeobox)/NPC-Nkx2.2-ChIP-Seq(GSE61673)/Homer | BTBRAGTGSN | 1.00E-43 | -1.01E+02 | 0 | 2343 | 51.61% | 18499.1 | 41.33% |
| EBF1(EBF)/Near-E2A-ChIP-Seq(GSE21512)/Homer | GTCCCCWGGGGA | 1.00E-43 | -9.99E+01 | 0 | 1934 | 42.60% | 14642.8 | 32.72% |
| Sox10(HMG)/SciaticNerve-Sox3-ChIP-Seq(GSE35132)/Homer | CCWTTGTYBY | 1.00E-42 | -9.84E+01 | 0 | 1834 | 40.40% | 13751.8 | 30.73% |
| Smad2(MAD)/ES-SMAD2-ChIP-Seq(GSE29422)/Homer | CTGTCTGG | 1.00E-42 | -9.72E+01 | 0 | 1977 | 43.55% | 15103 | 33.75% |
| Smad3(MAD)/NPC-Smad3-ChIP-Seq(GSE36673)/Homer | TWGTCTGV | 1.00E-41 | -9.62E+01 | 0 | 3041 | 66.98% | 25557.4 | 57.11% |
| Nkx2.5(Homeobox)/HL1-Nkx2.5 biotin-ChIP-Seq(GSE21529)/Homer | RSCACTYAA | 1.00E-41 | -9.51E+01 | 0 | 2515 | 55.40% | 20300.3 | 45.36% |
| AR-halfsite(NR)/LNCAP-AR-ChIP-Seq(GSE27824)/Homer | CCAGGAACAG | 1.00E-40 | -9.42E+01 | 0 | 3619 | 79.71% | 31749.7 | 70.94% |
| Sox4(HMG)/proB-Sox4-ChIP-Seq(GSE50066)/Homer | YCTTTGTTCC | 1.00E-40 | -9.41E+01 | 0 | 1086 | 23.92% | 7227.7 | 16.15% |
| OCT-OCT(POU,Homeobox,IR1)/NPC-Brn2-ChIP-Seq(GSE35496)/Homer | ATGAATWATTCATGA | 1.00E-40 | -9.28E+01 | 0 | 79 | 1.74% | 106.6 | 0.24% |
| Foxl2(Forkhead)/Ovary-Foxl2-ChIP-Seq(GSE60858)/Homer | WWTRTAAACAVG | 1.00E-39 | -8.99E+01 | 0 | 949 | 20.90% | 6154.1 | 13.75% |
| EBF1(EBF)/proBcell-EBF-ChIP-Seq(GSE21978)/Homer | DGTCCYRGGGA | 1.00E-38 | -8.96E+01 | 0 | 553 | 12.18% | 3031.5 | 6.77% |
| AP-2alpha(AP2)/Hela-AP2alpha-ChIP-Seq(GSE31477)/Homer | ATGCCCTGAGGC | 1.00E-37 | -8.61E+01 | 0 | 1526 | 33.61% | 11217.3 | 25.06% |
| Prop1(Homeobox)/GHF1-PROP1 biotin-ChIP-Seq(GSE77302)/Homer | NATAATBNAATTA | 1.00E-37 | -8.58E+01 | 0 | 733 | 16.15% | 4467.3 | 9.98% |
| Sox15(HMG)/CPA-Sox15-ChIP-Seq(GSE62909)/Homer | RAACAATGGN | 1.00E-37 | -8.56E+01 | 0 | 1263 | 27.82% | 8900 | 19.89% |
| Twist(bHLH)/HMLE-TWIST1-ChIP-Seq(Chang_et_al)/Homer | YCAKCTGNNCCAGN | 1.00E-36 | -8.51E+01 | 0 | 382 | 8.41% | 1847.6 | 4.13% |
| Six2(Homeobox)/NephronProgenitor-Six2-ChIP-Seq(GSE39837)/Homer | GWAAYHTGAKMC | 1.00E-34 | -7.93E+01 | 0 | 1130 | 24.89% | 7871.9 | 17.59% |
| FOXK1(Forkhead)/HEK293-FOXK1-ChIP-Seq(GSE51673)/Homer | NVWVTGTTTAC | 1.00E-34 | -7.92E+01 | 0 | 1153 | 25.40% | 8072.8 | 18.04% |
| Foxf1(Forkhead)/Lung-Foxf1-ChIP-Seq(GSE77951)/Homer | WWATRTAAACAN | 1.00E-33 | -7.73E+01 | 0 | 979 | 21.56% | 6622.5 | 14.80% |
| Rfx6(HTH)/Min6b1-Rfx6.HA-ChIP-Seq(GSE62844)/Homer | TGTTKCTAGCAACM | 1.00E-33 | -7.71E+01 | 0 | 1551 | 34.16% | 11644.4 | 26.02% |
| FOXA1(Forkhead)/LNCAP-FOXA1-ChIP-Seq(GSE27824)/Homer | WAAGTAAACA | 1.00E-33 | -7.67E+01 | 0 | 1244 | 27.40% | 8915.2 | 19.92% |
| Hoxc9(Homeobox)/Ain15-Hoxc9-ChIP-Seq(GSE21812)/Homer | GGCCATAAATCA | 1.00E-32 | -7.43E+01 | 0 | 644 | 14.19% | 3928.1 | 8.78% |
| Sox17(HMG)/Endoderm-Sox17-ChIP-Seq(GSE61475)/Homer | CCATTGTBY | 1.00E-32 | -7.41E+01 | 0 | 896 | 19.74% | 5983.1 | 13.37% |
| FoxEbox(Forkhead,bHLH)/Panc1-Foxa2-ChIP-Seq(GSE47459)/Homer | NNNVCTGWGYAACAA | 1.00E-31 | -7.25E+01 | 0 | 1245 | 27.42% | 9013 | 20.14% |
| RBPJ:Ebox(?,bHLH)/Panc1-Rbpj1-ChIP-Seq(GSE47459)/Homer | GGGARAARRGRMCAGN | 1.00E-31 | -7.21E+01 | 0 | 696 | 15.33% | 4375.2 | 9.78% |
| Nkx3.1(Homeobox)/LNCAP-Nkx3.1-ChIP-Seq(GSE28264)/Homer | AAGCACTTAA | 1.00E-30 | -6.99E+01 | 0 | 2371 | 52.22% | 19550.1 | 43.68% |
| Foxo3(Forkhead)/U2OS-Foxo3-ChIP-Seq(E-MTAB-2701)/Homer | DGTAACAACA | 1.00E-30 | -6.93E+01 | 0 | 859 | 18.95% | 5759.9 | 12.87% |
| Six1(Homeobox)/Myoblast-Six1-ChIP-Seq(GSE20150)/Homer | GKVTCADRTTWC | 1.00E-29 | -6.82E+01 | 0 | 371 | 8.17% | 1935.6 | 4.32% |
| Phox2a(Homeobox)/Neuron-Phox2a-ChIP-Seq(GSE31456)/Homer | YTAATYNRATTA | 1.00E-29 | -6.81E+01 | 0 | 486 | 10.70% | 2787.4 | 6.23% |
| Unknown(Homeobox)/Limb-p300-ChIP-Seq/Homer | SSCMATWAAA | 1.00E-29 | -6.78E+01 | 0 | 767 | 16.89% | 5024.5 | 11.23% |
| Barx1(Homeobox)/Stomach-Barx1.3xFlag-ChIP-Seq(GSE69483)/Homer | AAACMATTAN | 1.00E-29 | -6.75E+01 | 0 | 598 | 13.17% | 3664.3 | 8.19% |
| FOXA1(Forkhead)/MCF7-FOXA1-ChIP-Seq(GSE26831)/Homer | WAAGTAAACA | 1.00E-29 | -6.68E+01 | 0 | 1030 | 22.69% | 7259.6 | 16.22% |
| Eomes(T-box)/H9-Eomes-ChIP-Seq(GSE26097)/Homer | ATTAACACCT | 1.00E-28 | -6.61E+01 | 0 | 2277 | 50.15% | 18745.6 | 41.89% |
| HoxA9(Homeobox)/HSC-Hoxa9-ChIP-Seq(GSE33509)/Homer | GGCCATAAATCA | 1.00E-28 | -6.59E+01 | 0 | 807 | 17.78% | 5388.1 | 12.04% |

| | | | | | | | | |
|--|------------------|----------|-----------|---|------|--------|---------|--------|
| PRDM9(Zf)/Testis-DMC1-ChIP-Seq(GSE35498)/Homer | ADGGYAGYAGCATCT | 1.00E-28 | -6.56E+01 | 0 | 769 | 16.94% | 5078.7 | 11.35% |
| Pit1(Homeobox)/GCrat-Pit1-ChIP-Seq(GSE58009)/Homer | ATGMATATDC | 1.00E-28 | -6.49E+01 | 0 | 1073 | 23.63% | 7672.5 | 17.14% |
| Znf263(Zf)/K562-Znf263-ChIP-Seq(GSE31477)/Homer | CVGTSTCCCC | 1.00E-27 | -6.42E+01 | 0 | 2470 | 54.41% | 20682.3 | 46.21% |
| Zic3(Zf)/mES-Zic3-ChIP-Seq(GSE37889)/Homer | GGCCYCTGCTGGDH | 1.00E-27 | -6.28E+01 | 0 | 1197 | 26.37% | 8805 | 19.67% |
| Foxa2(Forkhead)/Liver-Foxa2-ChIP-Seq(GSE25694)/Homer | CYGTMTTACWYW | 1.00E-27 | -6.23E+01 | 0 | 920 | 20.26% | 6410 | 14.32% |
| HOXD13(Homeobox)/Chicken-Hoxd13-ChIP-Seq(GSE38910)/Homer | NCYAATAAAB | 1.00E-26 | -6.13E+01 | 0 | 1091 | 24.03% | 7907.2 | 17.67% |
| Oct6(POU,Homeobox)/NPC-Pou3f1-ChIP-Seq(GSE35496)/Homer | WATGCAAATGAG | 1.00E-26 | -6.12E+01 | 0 | 533 | 11.74% | 3245.5 | 7.25% |
| Unknown-ESC-element(?) /mES-Nanog-ChIP-Seq(GSE11724)/Homer | CACAGCAGGGGG | 1.00E-24 | -5.71E+01 | 0 | 1141 | 25.13% | 8445.8 | 18.87% |
| Tbr1(T-box)/Cortex-Tbr1-ChIP-Seq(GSE71384)/Homer | AAGGTGTAKA | 1.00E-24 | -5.65E+01 | 0 | 1566 | 34.49% | 12302.5 | 27.49% |
| NPAS2(bHLH)/Liver-NPAS2-ChIP-Seq(GSE39860)/Homer | KCCACGTGAC | 1.00E-23 | -5.51E+01 | 0 | 1416 | 31.19% | 10965.8 | 24.50% |
| Hoxb4(Homeobox)/ES-Hoxb4-ChIP-Seq(GSE34014)/Homer | TGATTRTGGCY | 1.00E-22 | -5.28E+01 | 0 | 296 | 6.52% | 1560.8 | 3.49% |
| FOXK2(Forkhead)/U2OS-FOXK2-ChIP-Seq(E-MTAB-2204)/Homer | SCHTGTTTACAT | 1.00E-22 | -5.25E+01 | 0 | 768 | 16.92% | 5317.8 | 11.88% |
| Pitx1(Homeobox)/Chicken-Pitx1-ChIP-Seq(GSE38910)/Homer | TAATCCCN | 1.00E-22 | -5.25E+01 | 0 | 3372 | 74.27% | 30210.4 | 67.50% |
| AMVB(HTH)/Testes-AMVB-ChIP-Seq(GSE44588)/Homer | TGGCAGTTGG | 1.00E-22 | -5.13E+01 | 0 | 1630 | 35.90% | 13044.7 | 29.15% |
| Zic(Zf)/Cerebellum-ZIC1.2-ChIP-Seq(GSE60731)/Homer | CCTGCTGAGH | 1.00E-21 | -5.01E+01 | 0 | 1294 | 28.50% | 9995 | 22.33% |
| FOXP1(Forkhead)/H9-FOXP1-ChIP-Seq(GSE31006)/Homer | NYTGTTTACTHN | 1.00E-21 | -4.98E+01 | 0 | 522 | 11.50% | 3335.5 | 7.45% |
| FOXM1(Forkhead)/MCF7-FOXM1-ChIP-Seq(GSE72977)/Homer | TRTTTACTHW | 1.00E-21 | -4.90E+01 | 0 | 1040 | 22.91% | 7751.5 | 17.32% |
| Pax8(Paired,Homeobox)/Thyroid-Pax8-ChIP-Seq(GSE26938)/Homer | GTCATGCHTGRCTGS | 1.00E-20 | -4.78E+01 | 0 | 618 | 13.61% | 4154.6 | 9.28% |
| Maz(Zf)/HepG2-Maz-ChIP-Seq(GSE31477)/Homer | GGGGGGGGG | 1.00E-20 | -4.76E+01 | 0 | 1681 | 37.03% | 13632 | 30.46% |
| Brn2(POU,Homeobox)/NPC-Brn2-ChIP-Seq(GSE35496)/Homer | ATGAATATTC | 1.00E-19 | -4.57E+01 | 0 | 165 | 3.63% | 725.5 | 1.62% |
| BMAL1(bHLH)/Liver-Bmal1-ChIP-Seq(GSE39860)/Homer | GNCACGTG | 1.00E-19 | -4.45E+01 | 0 | 1959 | 43.15% | 16367.2 | 36.57% |
| Sox9(HMG)/Limb-SOX9-ChIP-Seq(GSE73225)/Homer | AGGVNCCITTTG | 1.00E-19 | -4.41E+01 | 0 | 1088 | 23.96% | 8304.9 | 18.56% |
| Pitx1.Ebox(Homeobox,bHLH)/Hindlimb-Pitx1-ChIP-Seq(GSE41591)/Homer | YTAATRAWWCCAGA | 1.00E-18 | -4.35E+01 | 0 | 287 | 6.32% | 1601.3 | 3.58% |
| Rfx5(HTH)/GM12878-Rfx5-ChIP-Seq(GSE31477)/Homer | SCCTAGCAACAG | 1.00E-18 | -4.33E+01 | 0 | 445 | 9.80% | 2826.3 | 6.31% |
| Foxa3(Forkhead)/Liver-Foxa3-ChIP-Seq(GSE77670)/Homer | BSNTGTITACWYWG | 1.00E-18 | -4.32E+01 | 0 | 395 | 8.70% | 2431.2 | 5.43% |
| Brn1(POU,Homeobox)/NPC-Brn1-ChIP-Seq(GSE35496)/Homer | TATGCWAATBAV | 1.00E-18 | -4.27E+01 | 0 | 380 | 8.37% | 2321.6 | 5.19% |
| p63(p53)/Keratinocyte-p63-ChIP-Seq(GSE17611)/Homer | NNDRCATGYCYNRRCA | 1.00E-18 | -4.18E+01 | 0 | 536 | 11.81% | 3591.9 | 8.03% |
| ETS:E-box(ETS,bHLH)/HPC7-Sc1-ChIP-Seq(GSE22178)/Homer | AGGAARACAGCTG | 1.00E-17 | -4.02E+01 | 0 | 207 | 4.56% | 1059.8 | 2.37% |
| PAX5(Paired,Homeobox)/GM12878-PAX5-ChIP-Seq(GSE32465)/Homer | GCAGCAGCAGRTGACH | 1.00E-17 | -3.92E+01 | 0 | 582 | 12.82% | 4025.6 | 8.99% |
| CRX(Homeobox)/Retina-Crx-ChIP-Seq(GSE20012)/Homer | GCTAATCC | 1.00E-16 | -3.85E+01 | 0 | 2126 | 46.83% | 18188.7 | 40.64% |
| Tbet(T-box)/CD8-Tbet-ChIP-Seq(GSE33802)/Homer | AGGTGTGAAM | 1.00E-16 | -3.84E+01 | 0 | 1225 | 26.98% | 9708.3 | 21.69% |
| BMYB(HTH)/Hela-BMYB-ChIP-Seq(GSE27030)/Homer | NHAACBGYYV | 1.00E-16 | -3.83E+01 | 0 | 1502 | 33.08% | 12067.6 | 27.41% |
| NPAS(bHLH)/Liver-NPAS-ChIP-Seq(GSE39860)/Homer | NVCACGTG | 1.00E-16 | -3.70E+01 | 0 | 1733 | 38.17% | 14481.5 | 32.36% |
| PAX6(Paired,Homeobox)/Forebrain-Pax6-ChIP-Seq(GSE66961)/Homer | NGTGTCAVTSAAAGCG | 1.00E-16 | -3.69E+01 | 0 | 166 | 3.66% | 806.4 | 1.80% |
| CDX4(Homeobox)/ZebrafishEmbryos-Cdx4.Myc-ChIP-Seq(GSE48252)/Homer | NGYCATAAAWCH | 1.00E-15 | -3.63E+01 | 0 | 880 | 19.38% | 6669.2 | 14.90% |
| p73(p53)/Trachea-p73-ChIP-Seq(PRJA310161)/Homer | NRRCRAWGTCCDGRC | 1.00E-15 | -3.61E+01 | 0 | 112 | 2.47% | 459.9 | 1.03% |
| MYB(HTH)/ERMV-B-Myb-ChIP-Seq(GSE22095)/Homer | GGCVGTR | 1.00E-15 | -3.60E+01 | 0 | 1718 | 37.84% | 14377.9 | 32.13% |
| Cux2(Homeobox)/Liver-Cux2-ChIP-Seq(GSE35985)/Homer | HNRAATCAAT | 1.00E-15 | -3.59E+01 | 0 | 488 | 10.75% | 3311.8 | 7.40% |
| Tbx20(T-box)/Heart-Tbx20-ChIP-Seq(GSE29636)/Homer | GGTGYTGACAGS | 1.00E-15 | -3.56E+01 | 0 | 358 | 7.89% | 2261.4 | 5.05% |
| RFX(HTH)/K562-RFX3-ChIP-Seq(SRA012198)/Homer | CGTGTGCCATGGCAAC | 1.00E-15 | -3.54E+01 | 0 | 134 | 2.95% | 605.3 | 1.35% |
| ZNF416(Zf)/HEK293-ZNF416.GFP-ChIP-Seq(GSE58341)/Homer | WDNCTGGGCA | 1.00E-15 | -3.51E+01 | 0 | 1917 | 42.22% | 16307.5 | 36.44% |
| HOXA2(Homeobox)/mES-Hoxa2-ChIP-Seq(Donaldson_et_al.)/Homer | GYCATCMATCAT | 1.00E-14 | -3.40E+01 | 0 | 161 | 3.55% | 799.2 | 1.79% |
| Rfx1(HTH)/NPC-H3K4me1-ChIP-Seq(GSE16256)/Homer | RGTTGCCATGGCAA | 1.00E-14 | -3.32E+01 | 0 | 302 | 6.65% | 1858.1 | 4.15% |
| KLF14(Zf)/HEK293-KLF14.GFP-ChIP-Seq(GSE58341)/Homer | RGKGGGCGKGGC | 1.00E-13 | -3.21E+01 | 0 | 1950 | 42.95% | 16742.8 | 37.41% |
| p53(p53)/Saos-p53-ChIP-Seq(GSE15780)/Homer | RRCATGYCYRGRCATG | 1.00E-13 | -3.17E+01 | 0 | 162 | 3.57% | 829.2 | 1.85% |
| p53(p53)/Saos-p53-ChIP-Seq(Homer) | RRCATGYCYRGRCATG | 1.00E-13 | -3.17E+01 | 0 | 162 | 3.57% | 829.2 | 1.85% |
| X-box(HTH)/NPC-H3K4me1-ChIP-Seq(GSE16256)/Homer | GGTGTGCCATGGCAA | 1.00E-13 | -3.16E+01 | 0 | 174 | 3.83% | 917 | 2.05% |
| Sp5(Zf)/mES-Sp5.Flag-ChIP-Seq(GSE72989)/Homer | RGKGGGCGGAGC | 1.00E-13 | -3.15E+01 | 0 | 1188 | 26.17% | 9598.3 | 21.45% |
| Oct4(POU,Homeobox)/mES-Oct4-ChIP-Seq(GSE11431)/Homer | ATTGTGATAW | 1.00E-13 | -3.15E+01 | 0 | 512 | 11.28% | 3604.7 | 8.05% |
| HNF6(Homeobox)/Liver-Hnf6-ChIP-Seq(ERP000394)/Homer | NTATYGTACH | 1.00E-13 | -3.14E+01 | 0 | 565 | 12.44% | 4056.5 | 9.06% |
| Rfx2(HTH)/LoVo-RFX2-ChIP-Seq(GSE49402)/Homer | GTTGCCATGGCAACM | 1.00E-13 | -3.13E+01 | 0 | 149 | 3.28% | 743.1 | 1.66% |
| Mef2b(MADS)/HEK293-Mef2b.V5-ChIP-Seq(GSE67450)/Homer | GCTATTTTGGM | 1.00E-13 | -3.00E+01 | 0 | 841 | 18.52% | 6505.5 | 14.54% |
| Mef2c(MADS)/GM12878-Mef2c-ChIP-Seq(GSE32465)/Homer | DCYAAAAATAGM | 1.00E-12 | -2.88E+01 | 0 | 455 | 10.02% | 3184.8 | 7.12% |
| Tbox.Smud(T-box,MAD)/ESCd5-Smad2_3-ChIP-Seq(GSE29422)/Homer | AGGTGHCAGACA | 1.00E-12 | -2.87E+01 | 0 | 304 | 6.70% | 1946.2 | 4.35% |
| Otx2(Homeobox)/EpiLC-Otx2-ChIP-Seq(GSE56098)/Homer | NYTAATCYB | 1.00E-11 | -2.69E+01 | 0 | 791 | 17.42% | 6152 | 13.75% |
| ZNF467(Zf)/HEK293-ZNF467.GFP-ChIP-Seq(GSE58341)/Homer | TGGGGAGGGGCM | 1.00E-11 | -2.58E+01 | 0 | 1272 | 28.02% | 10586.3 | 23.65% |
| GSC(Homeobox)/FrogEmbryos-GSC-ChIP-Seq(DRA000576)/Homer | RGGATTAR | 1.00E-11 | -2.57E+01 | 0 | 1073 | 23.63% | 8748.4 | 19.55% |
| Cdx2(Homeobox)/mES-Cdx2-ChIP-Seq(GSE14586)/Homer | GYMATAAAA | 1.00E-11 | -2.55E+01 | 0 | 672 | 14.80% | 5141.2 | 11.49% |
| Hand2(bHLH)/Mesoderm-Hand2-ChIP-Seq(GSE61475)/Homer | TGACANRRCCAGRC | 1.00E-10 | -2.43E+01 | 0 | 697 | 15.35% | 5397.2 | 12.06% |
| MafA(bZIP)/Islet-MafA-ChIP-Seq(GSE30298)/Homer | TGCTGACTCA | 1.00E-10 | -2.42E+01 | 0 | 1036 | 22.82% | 8467.5 | 18.92% |
| Rbpj1(?) /Panc1-Rbpj1-ChIP-Seq(GSE47459)/Homer | HTTCCASG | 1.00E-10 | -2.39E+01 | 0 | 1748 | 38.50% | 15163.1 | 33.88% |
| PAX3:FKHR-fusion(Paired,Homeobox)/Rh4-PAX3:FKHR-ChIP-Seq(GSE22095)/Homer | ACCRTGACTAATTNN | 1.00E-10 | -2.32E+01 | 0 | 229 | 5.04% | 1445.3 | 3.23% |
| Tcf4(HMG)/Hct116-Tcf4-ChIP-Seq(SRA012054)/Homer | ASATCAAAGGVA | 1.00E-09 | -2.22E+01 | 0 | 506 | 11.15% | 3781.7 | 8.45% |
| HOXB13(Homeobox)/ProstateTumor-HOXB13-ChIP-Seq(GSE56288)/Homer | TTTTATKRRG | 1.00E-09 | -2.10E+01 | 0 | 988 | 21.76% | 8149.4 | 18.21% |
| HNF1b(Homeobox)/PDAC-HNF1B-ChIP-Seq(GSE64557)/Homer | GTTAATNATTA | 1.00E-08 | -2.06E+01 | 0 | 166 | 3.66% | 995 | 2.22% |
| OCT4-SOX2-TCF-NANOG(POU,Homeobox,HMG)/mES-Oct4-ChIP-Seq(GSE11431)/Homer | ATTTGCATAACAATG | 1.00E-08 | -2.04E+01 | 0 | 213 | 4.69% | 1365.9 | 3.05% |
| Foxh1(Forkhead)/hESC-FOXH1-ChIP-Seq(GSE29422)/Homer | NNTGTGGATTSS | 1.00E-08 | -1.97E+01 | 0 | 642 | 14.14% | 5058.8 | 11.30% |
| Mef2d(MADS)/Retina-Mef2d-ChIP-Seq(GSE61391)/Homer | GCTATTTTAGG | 1.00E-08 | -1.96E+01 | 0 | 215 | 4.74% | 1395.2 | 3.12% |
| Pbx3(Homeobox)/GM12878-PBX3-ChIP-Seq(GSE32465)/Homer | SCGTGCAMTCAN | 1.00E-08 | -1.92E+01 | 0 | 334 | 7.36% | 2386.4 | 5.33% |
| NFAT(RHD)/Jurkat-NFATC1-ChIP-Seq(Jolma_et_al.)/Homer | ATTTCCATT | 1.00E-08 | -1.90E+01 | 0 | 969 | 21.34% | 8056.8 | 18.00% |
| PBX3(Homeobox)/MCF7-PBX1-ChIP-Seq(GSE28007)/Homer | GSCTGCTACTCA | 1.00E-08 | -1.86E+01 | 0 | 136 | 3.00% | 794.8 | 1.78% |
| Brachyury(T-box)/Mesoendoderm-Brachyury-ChIP-exo(GSE54963)/Homer | ANNTMRCASBNNNGT | 1.00E-07 | -1.81E+01 | 0 | 323 | 7.11% | 2318.3 | 5.18% |
| Pax7(Paired,Homeobox)/Myoblast-Pax7-ChIP-Seq(GSE25064)/Homer | TAATCAATTA | 1.00E-07 | -1.80E+01 | 0 | 120 | 2.64% | 683.7 | 1.53% |
| ZNF415(Zf)/HEK293-ZNF415.GFP-ChIP-Seq(GSE58341)/Homer | GRTGMRRGAGCC | 1.00E-07 | -1.75E+01 | 0 | 795 | 17.51% | 6523.5 | 14.58% |
| ZNF189(Zf)/HEK293-ZNF189.GFP-ChIP-Seq(GSE58341)/Homer | TGGAACAGMA | 1.00E-07 | -1.75E+01 | 0 | 1010 | 22.25% | 8504 | 19.00% |
| HIF-1b(HLH)/T47D-HIF1b-ChIP-Seq(GSE59937)/Homer | RTACGTGC | 1.00E-07 | -1.74E+01 | 0 | 1053 | 23.19% | 8907.3 | 19.90% |
| TATA-Box(TBP)/Promoter/Homer | CCTTTTHAWAGSC | 1.00E-07 | -1.70E+01 | 0 | 1228 | 27.05% | 10566.3 | 23.61% |
| GATA3(Zf)/iTreg-Gata3-ChIP-Seq(GSE20898)/Homer | AGATAASR | 1.00E-07 | -1.67E+01 | 0 | 1328 | 29.25% | 11527.6 | 25.76% |
| Arnt:Ahr(bHLH)/MCF7-Arnt-ChIP-Seq(Lo_et_al.)/Homer | TBGCACGCAA | 1.00E-07 | -1.65E+01 | 0 | 662 | 14.58% | 5352.9 | 11.96% |
| PR(NR)/T47D-PR-ChIP-Seq(GSE31130)/Homer | VAGRACAKNCTGTBC | 1.00E-07 | -1.65E+01 | 0 | 2150 | 47.36% | 19449.9 | 43.46% |

Supplemental table 3. Characteristics of the ASCL1 and NEUROD1 ChIP-seq datasets

| Sample | ChIP-seq | Uniquely Mapped Reads (M) | Total_Peaks | DHS (per 5000 peaks) | FRiP |
|-------------|----------|---------------------------|-------------|----------------------|------|
| LuCaP49 | ASCL1 | 26.1 | 46859 | 4732 | 32.5 |
| LuCaP93 | ASCL1 | 25.9 | 49994 | 4664 | 21.1 |
| LuCaP145_1 | ASCL1 | 38.8 | 46303 | 4259 | 38.9 |
| H660 | ASCL1 | 25 | 61338 | 4869 | 34.4 |
| LuCaP173_p1 | NEUROD1 | 31.9 | 78124 | 4857 | 35.1 |
| LuCaP49 | H3K27ac | 94.7 | 27699 | 4690 | 9.2 |
| LuCaP93 | H3K27ac | 96.9 | 68618 | 4729 | 43.9 |
| LuCaP145_1 | H3K27ac | 74.3 | 69086 | 4665 | 48 |
| LuCaP145_2 | H3K27ac | 98.6 | 57843 | 4968 | 54.2 |
| LuCaP173_p1 | H3K27ac | 93.2 | 65495 | 4945 | 20.2 |
| EF-1 | H3K27ac | 101.2 | 68984 | 4969 | 44.8 |

DHS: DNase I hypersensitive site (per 5000 peaks)

FRiP: fraction of reads that fall into a peak