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Supplemental information

Three-dimensional genome architecture coordinates key regulators of lineage specification in mammary epithelial cells

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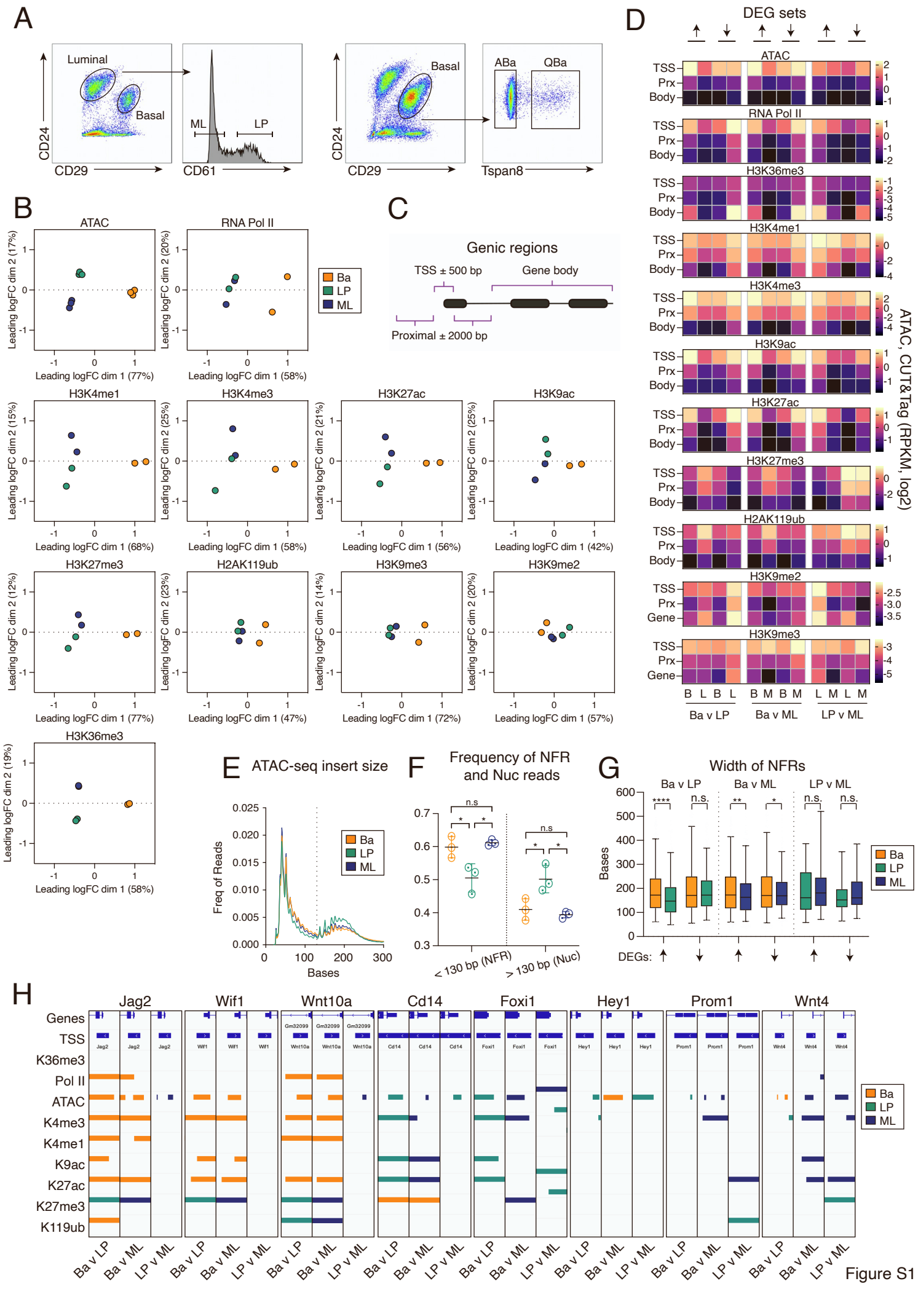

A
Luminal
Basal
CD24
CD29
ML
LP
CD61
Basal
ABa
QBa
Tspan8
B
ATAC
RNA Pol II
H3K4me1
H3K4me3
H3K27ac
H3K9ac
H3K27me3
H2AK119ub
H3K9me3
H3K9me2
H3K36me3
Leading logFC dim 1
Leading logFC dim 2
Ba
LP
ML
C
Genic regions
TSS ± 500 bp
Gene body
Proximal ± 2000 bp
D
DEG sets
ATAC
RNA Pol II
H3K36me3
H3K4me1
H3K4me3
H3K9ac
H3K27ac
H3K27me3
H2AK119ub
H3K9me2
H3K9me3
TSS
Prx
Body
Gene
B L B L
B M B M
L M L M
Ba v LP
Ba v ML
LP v ML
ATAC, CUT&Tag (RPKM, log2)
E
ATAC-seq insert size
Freq of Reads
Bases
F
Frequency of NFR and Nuc reads
n.s
< 130 bp (NFR)
> 130 bp (Nuc)
G
Width of NFRs
Ba v LP
Ba v ML
LP v ML
Bases
DEGs:
H
Jag2
Wif1
Wnt10a
Cd14
Foxi1
Hey1
Prom1
Wnt4
Genes
TSS
K36me3
Pol II
ATAC
K4me3
K4me1
K9ac
K27ac
K27me3
K119ub

Figure S1

Figure S1 (Related to Figure 1). **Patterns of histone modifications amongst the mammary epithelial populations. (A)** FACS purification strategy for mammary epithelial cells. Following gating for single, live cells by 7-AAD, lineage-positive ($CD31^+/CD45^+/TER\text{-}119^+$) cells were excluded and basal ($CD29^{hi}/CD24^+$), LP ($CD29^{lo}/CD24^+/CD61^+$) or ML/HS ($CD29^{lo}/CD24^+/CD61^-$) cells were sorted; alternatively, basal $Tspan8^+$ (QBa) or $Tspan8^-$ (ABa) cells were isolated. **(B)** Multi-dimensional scaling plots (MDS) of normalized, filtered and batch-corrected ATAC and CUT&Tag data. **(C)** Diagram depicting the genic regions to which CUT&Tag and ATAC reads were assigned. TSS region spans 1 kb in length; proximal refers to a 4 kb region lacking the TSS; the gene body is specific to each gene, but in all instances has reads mapping to the TSS and proximal regions subtracted. **(D)** Heatmap of ATAC-seq and CUT&Tag for DE genes. **(E)** ATAC-seq read length insert size, mapped as a frequency of the total reads from merged biological replicate libraries. Dotted line represents the 130 bp cutoff used to assign NFR and nucleosome-associated (Nuc) reads. **(F)** Frequency of ATAC-seq reads. **(G)** Boxplot showing the width of NFRs at the TSSs of DEGs, median, quartiles and 5^{th} and 95^{th} percentiles. Two-tailed t-tests with Welch's correction: n.s.= not significant, * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$. (H) Significant differential regions as determined by csaw (FDR < 0.05) in ATAC and CUT&Tag data of basal (Ba), LP and ML gene promoter regions. Color indicates the enrichment direction.

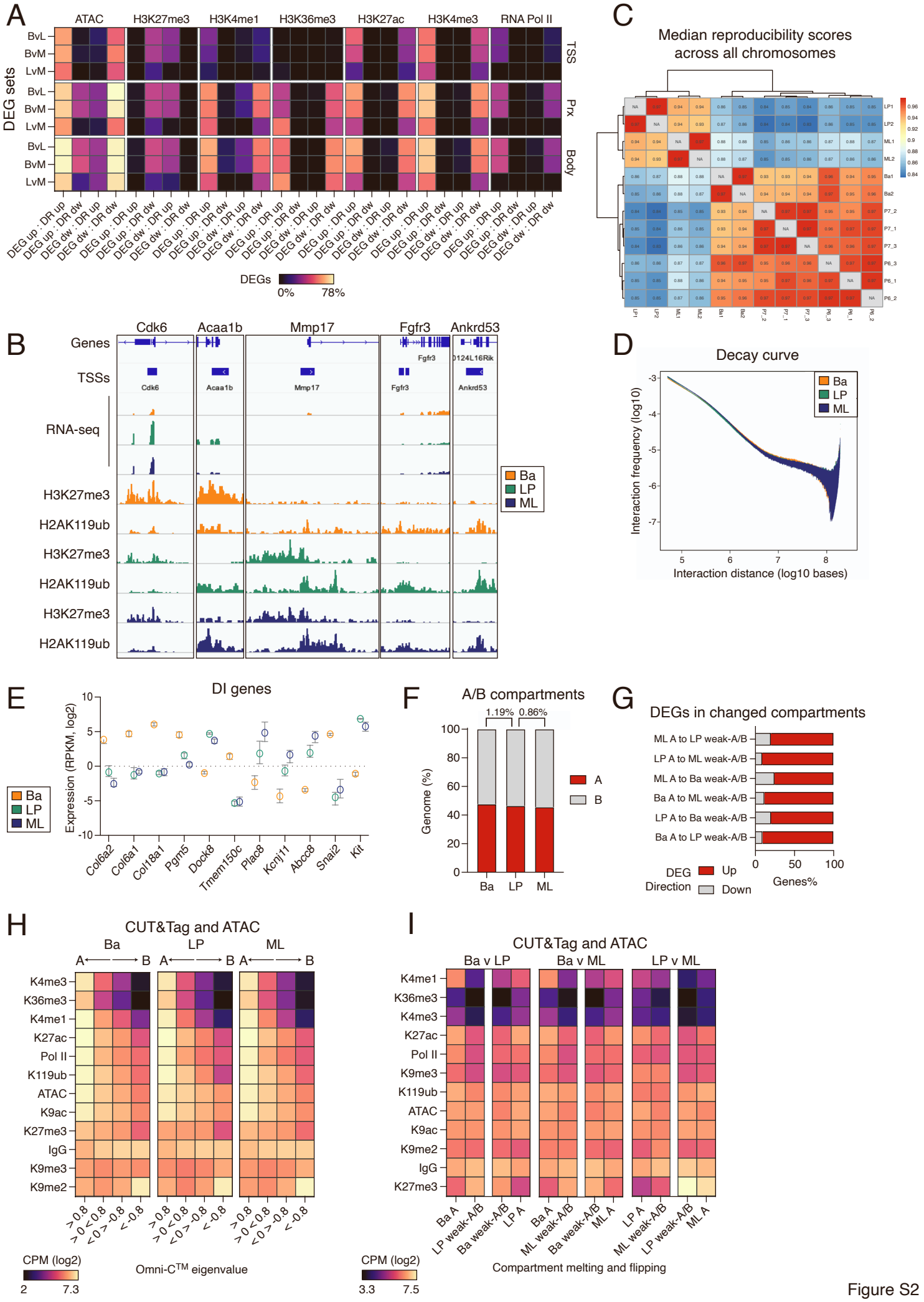

A
ATAC
H3K27me3
H3K4me1
H3K36me3
H3K27ac
H3K4me3
RNA Pol II
DEG sets
BvL
BvM
LvM
TSS
Prx
Body
DEG up : DR up
DEG up : DR dw
DEG dw : DR up
DEG dw : DR dw
DEGs
0%
78%
B
Genes
TSSs
RNA-seq
Cdk6
Acaa1b
Mmp17
Fgfr3
Ankrd53
H3K27me3
H2AK119ub
Ba
LP
ML
C
Median reproducibility scores
across all chromosomes
D
Decay curve
Interaction frequency (log10)
Interaction distance (log10 bases)
E
DI genes
Expression (RPKM, log2)
Col6a2
Col6a1
Col18a1
Pgm5
Dock8
Tmem150c
Plac8
Kcnj11
Abcc8
Snai2
Kit
F
A/B compartments
1.19%
0.86%
Genome (%)
A
B
G
DEGs in changed compartments
ML A to LP weak-A/B
LP A to ML weak-A/B
ML A to Ba weak-A/B
Ba A to ML weak-A/B
LP A to Ba weak-A/B
Ba A to LP weak-A/B
DEG Direction
Up
Down
Genes%
H
CUT&Tag and ATAC
K4me3
K36me3
K4me1
K27ac
Pol II
K119ub
ATAC
K9ac
K27me3
IgG
K9me3
K9me2
CPM (log2)
Omni-C™ eigenvalue
I
CUT&Tag and ATAC
Ba v LP
Ba v ML
LP v ML
K4me1
K36me3
K4me3
K27ac
Pol II
K9me3
K119ub
ATAC
K9ac
K9me2
IgG
K27me3
Compartment melting and flipping

Figure S2

Figure S2 (Related to Figure 1 and 2). **Analysis of histone modifications and chromatin compartments in the different mammary epithelial subsets. (A)** Heatmap of DEGs with an overlapping significant differential region (DR) in the TSS, TSS proximal (Prx) regions and gene-bodies (body) for pairwise comparisons. **(B)** Coverage track-plots of genes with divergent H3K27me3 and H2AK119ub profiles. **(C)** Heatmap of the median reproducibility scores from the Omni-C libraries at 50 kb resolution. Basal Tspan8^{+} and Tspan8^{-} cells are listed as P7 and P6, respectively. **(D)** Decay curves of Omni-C data of read-pair interactions as a function of the interaction distance, indicating typical interaction profiles. **(E)** Mean expression of genes located within DI loci. Error bars indicate the range of the biological replicates. **(F)** Genome determined as an A or B compartment, shown above is the percentage of change from basal to LP to ML cells. **(G)** DEGs whose expression is up or down as the compartment changes from A to weak-A/B, between pairwise comparisons. **(H)** Average CUT&Tag and ATAC reads in A (eigenvalues >0) and B (eigenvalues <0) compartments within each cell type. Reads are mapped to 100 kb genomic bins as counts per million (CPM). **(I)** Average CUT&Tag and ATAC reads in compartments that significantly change between pairwise comparisons of basal, LP and ML cells. CPM of reads to each 100 kb bin are indicated.

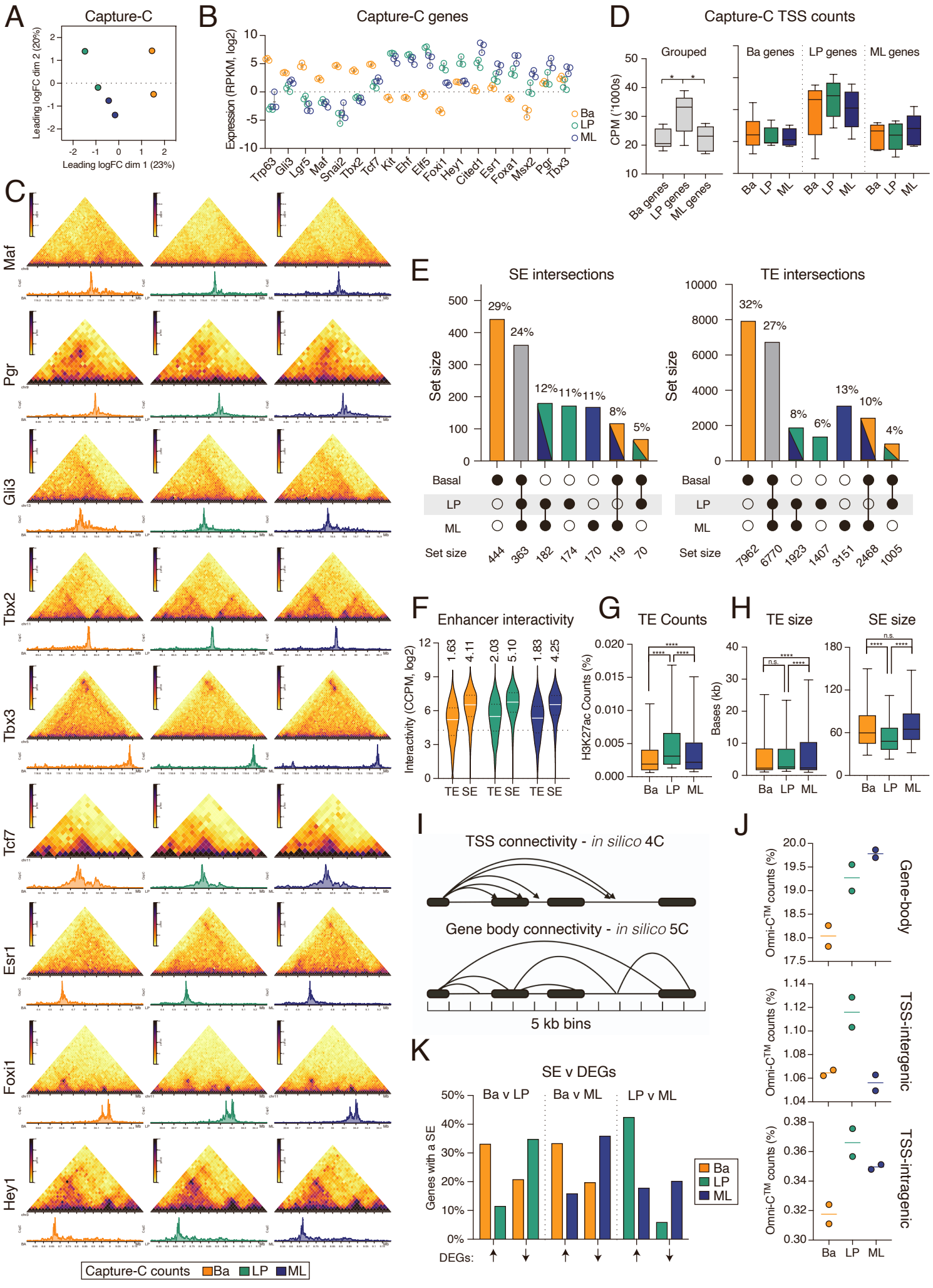

A
Capture-C
Leading logFC dim 2 (20%)
Leading logFC dim 1 (23%)
B
Capture-C genes
Expression (RPKM, log2)
Trp63 Gli3 Lgr5 Maf Snai2 Tbx2 Tcf7 Kit Ehf Elf5 Foxi1 Hey1 Cited1 Esr1 Foxa1 Msx2 Pgr Tbx3
Ba
LP
ML
D
Capture-C TSS counts
Grouped
CPM ('1000s)
Ba genes
LP genes
ML genes
Ba genes
LP genes
ML genes
C
Maf
Pgr
Gli3
Tbx2
Tbx3
Tcf7
Esr1
Foxi1
Hey1
Capture-C counts Ba LP ML
E
SE intersections
Set size
29%
24%
12%
11%
11%
8%
5%
Basal
LP
ML
Set size
444 363 182 174 170 119 70
TE intersections
Set size
32%
27%
8%
6%
13%
10%
4%
Basal
LP
ML
Set size
7962 6770 1923 1407 3151 2468 1005
F
Enhancer interactivity
Interactivity (CCPM, log2)
1.63 4.11 2.03 5.10 1.83 4.25
TE SE TE SE TE SE
G
TE Counts
H3K27ac Counts (%)
Ba LP ML
H
TE size
Bases (kb)
Ba LP ML
SE size
Ba LP ML
I
TSS connectivity - in silico 4C
Gene body connectivity - in silico 5C
5 kb bins
J
Omni-C™ counts (%)
Gene-body
Omni-C™ counts (%)
TSS-intergenic
Omni-C™ counts (%)
TSS-intragenic
Ba LP ML
K
SE v DEGs
Ba v LP
Ba v ML
LP v ML
Genes with a SE
Ba
LP
ML
DEGs:

Figure S3

Figure S3 (Related to Figure 3). **Identification of chromatin interactions involving key lineage-restricted genes and analysis of super-enhancers. (A)** MDS plot of the normalized and filtered Capture-C data from basal, LP and ML cells. **(B)** Expression of genes targeted with Capture-C. **(C)** Omni-C normalized contact matrices at 20 kb resolution and Capture-C CPM. Each capture site is associated with the major peak in the Capture-C tracks. **(D)** CPM of all Capture-C genes by gene group (basal, LP and ML) and lineage enrichment. **(E)** Upset plots of SEs and TEs showing shared (≥500 bp overlap) and unique regions for the cell types. **(F)** Interactivity from the Omni-C data as measured by FitHiChIP, shown as contact counts per million (CCPM) for TSS to TE or SEs. Highlighted above each plot is the fold-increase in CCPM over the expected background (dotted line). **(G)** H3K27ac counts of TEs, shown as a percentage of the merged biological replicate libraries. **(H)** Size of TEs and SEs. **(I)** Diagram depicting the Omni-C *in silico* 4C and 5C analyses used to connect the TSS or gene-body respectively with other interactions: only genes >100 kb were considered. **(J)** Omni-C library counts for the 5C and 4C analysis. The TSS analysis was split into TSS-to-intergenic or TSS-to-intragenic interactions. **(K)** DEGs that are connected to a SE. Genes were considered connected with a SE if they overlapped their gene-body or if their TSS interacted with a SE as detected by FitHiChIP through chromatin interactions or gene-body-overlap. *P < 0.05, ****P < 0.0001 (t-test with Welch's correction). Boxes shows median, quartiles and 5th and 95th percentiles.

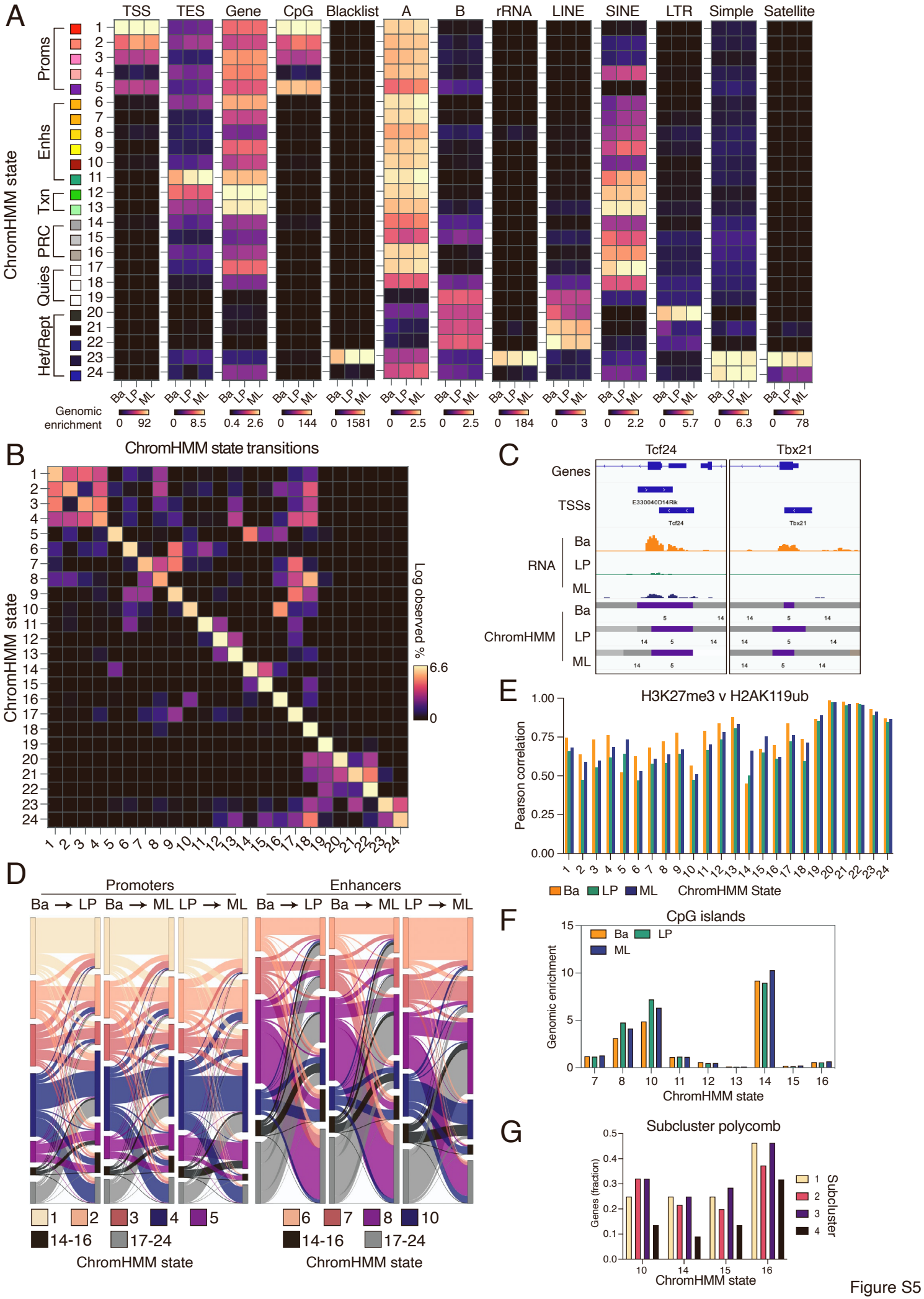

A
TSS
TES
Gene
CpG
Blacklist
A
B
rRNA
LINE
SINE
LTR
Simple
Satellite
ChromHMM state
Proms
Enhs
Txn
PRC
Quies
Het/Rept
Genomic enrichment
B
ChromHMM state transitions
ChromHMM state
Log observed %
C
Tcf24
Tbx21
Genes
TSSs
RNA
ChromHMM
D
Promoters
Enhancers
Ba → LP
Ba → ML
LP → ML
14-16
17-24
ChromHMM state
E
H3K27me3 v H2AK119ub
Pearson correlation
ChromHMM State
F
CpG islands
Genomic enrichment
G
Subcluster polycomb
Genes (fraction)
Subcluster

Figure S5

Figure S4 (Related to Figure 4**). Alternative use of transcription start sites associates with histone modification and chromatin looping. (A)** Expression and connectivity of differentially expressed TSSs between cell types. Expression values are Z-scored RNA-seq log2 RPKM, graphed as median and range. Connectivity values are Z-scored counts from *in silico* 4C analysis determining chromatin interactions between the TSSs and gene-bodies, graphed as mean and range. **(B)** Mean coverage (RPKM) of CUT&Tag and ATAC data across TSSs identified as either 'off' and 'on'. **(C)** Diagram depicting the analysis used to determine differentially expressed alternative transcriptional start sites (DEATSS) and differentially expressed transcriptional start sites (DETSS). **(D)** Coverage track-plots of expression (RPKM log2) for *Eya2* and *Lrrfip1* showing alternative TSSs, expression and H3K27ac (RPKM) for basal, LP and ML cells and known isoforms from RefSeq annotation.

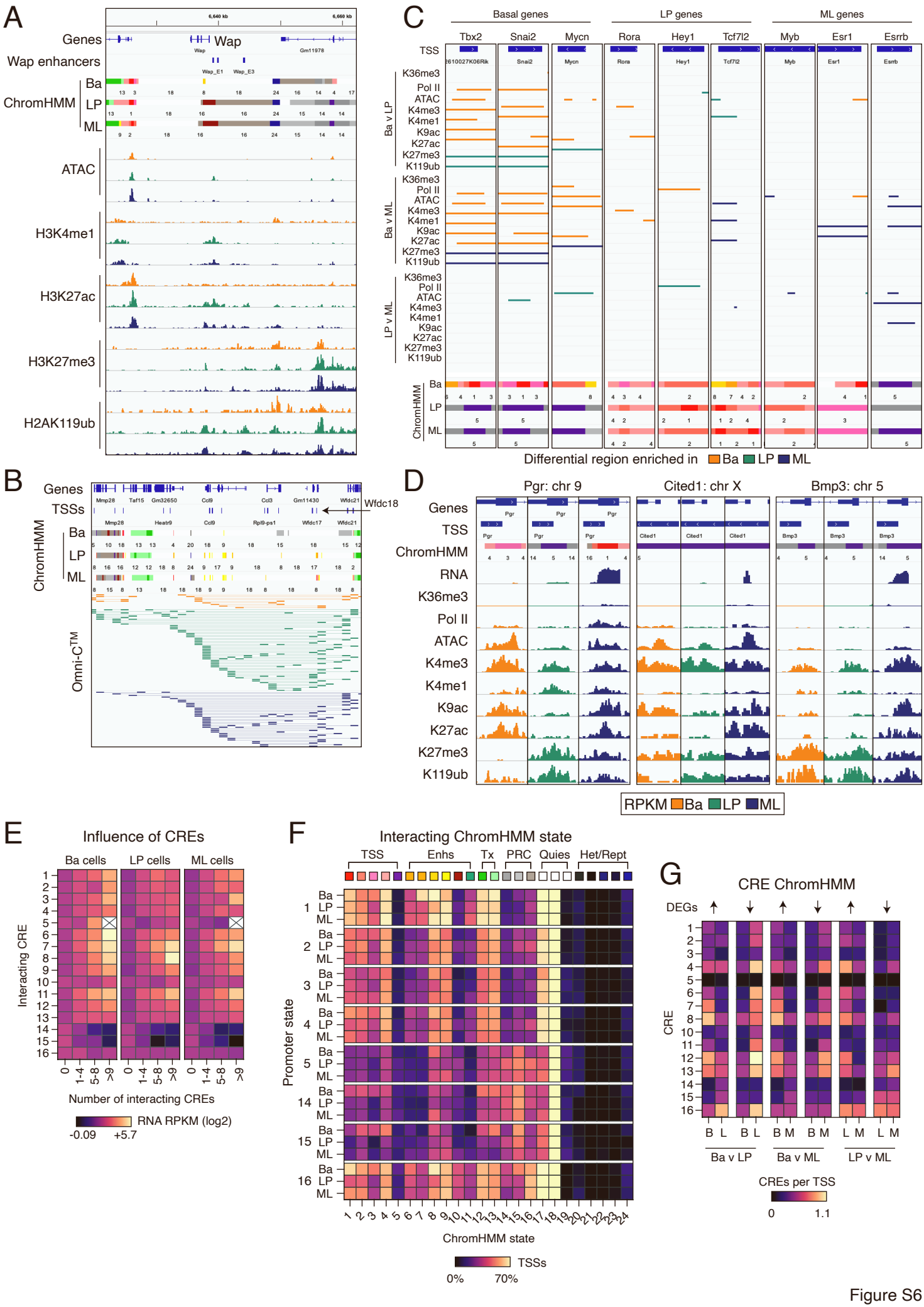
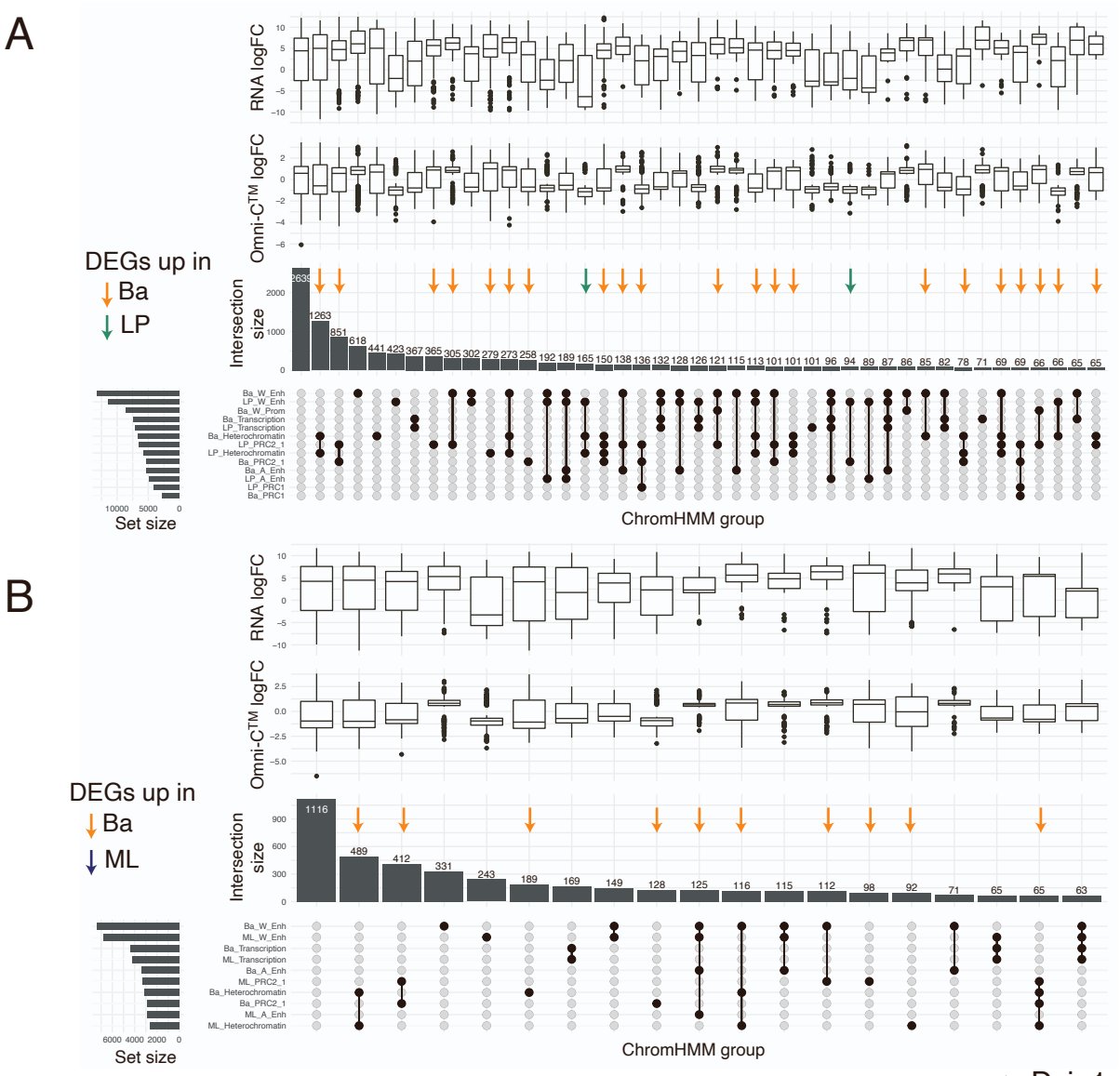

A
Genes
Wap enhancers
ChromHMM
Ba
LP
ML
ATAC
H3K4me1
H3K27ac
H3K27me3
H2AK119ub
Wap
Wap_E1
Wap_E3
B
Genes
TSSs
ChromHMM
Ba
LP
ML
Omni-C™
Wfdc18
C
Basal genes
LP genes
ML genes
Tbx2
Snai2
Mycn
Rora
Hey1
Tcf7l2
Myb
Esr1
Esrrb
TSS
Ba v LP
Ba v ML
LP v ML
K36me3
Pol II
ATAC
K4me3
K4me1
K9ac
K27ac
K27me3
K119ub
ChromHMM
Ba
LP
ML
Differential region enriched in Ba LP ML
D
Pgr: chr 9
Cited1: chr X
Bmp3: chr 5
Genes
TSS
ChromHMM
RNA
K36me3
Pol II
ATAC
K4me3
K4me1
K9ac
K27ac
K27me3
K119ub
RPKM Ba LP ML
E
Influence of CREs
Ba cells
LP cells
ML cells
Interacting CRE
Number of interacting CREs
RNA RPKM (log2)
-0.09
+5.7
F
Interacting ChromHMM state
TSS
Enhs
Tx
PRC
Quies
Het/Rept
Promoter state
ChromHMM state
TSSs
0%
70%
G
CRE ChromHMM
DEGs
CRE
B L B L B M B M L M L M
Ba v LP
Ba v ML
LP v ML
CREs per TSS
0
1.1

Figure S6

Figure S5 (Related to Figure 5**). Derivation of a chromatin model for the different mammary epithelial lineages. (A)** The enrichment of genomic features for the 24-state ChromHMM model. Shown are the enrichments in basal (Ba), LP and ML cells for TSS, transcriptional end sites (TES), gene-bodies (Gene), CpG islands, genome sequencing blacklisted sites (Blacklist), A and B chromatin compartments as determined by Omni-C and repeat element classes: ribosomal RNAs (rRNA)s, long-interspersed elements (LINE), short interspersed elements (SINE), long terminal repeats (LTR), simple repeats (Simple) and satellite regions (Satellite). **(B)** Transition frequencies between ChromHMM states. **(C)** Coverage track-plots for *Tcf24* and *Tbx21*. **(D)** Sankey transition plots showing the proportion of promoter and enhancer chromatin states that change between pairwise comparisons. States 14-16 were grouped as PRC and states 17-24 grouped as heterochromatin/silent. **(E)** Correlation of CUT&Tag H3K27me3 and H2AK119ub (RPKM, log2) across 24 ChromHMM state models in basal, LP and ML cells. **(F)** Genomic enrichment of CpG islands for different ChromHMM states. **(G)** Genes in scRNA-seq subclusters (Figure 5G) with an interacting polycomb state.


A
RNA logFC
Omni-C™ logFC
DEGs up in
Ba
LP
Intersection size
2639
1263
851
618
441
423
367
365
305
302
279
273
258
192
189
165
150
138
136
132
128
126
121
115
113
101
101
101
96
94
89
87
86
85
82
78
71
69
69
66
66
65
65
Ba_W_Enh
LP_W_Enh
Ba_W_Prom
Ba_Transcription
LP_Transcription
Ba_Heterochromatin
LP_PRC2_1
LP_Heterochromatin
Ba_PRC2_1
Ba_A_Enh
LP_A_Enh
LP_PRC1
Ba_PRC1
Set size
ChromHMM group
B
RNA logFC
Omni-C™ logFC
DEGs up in
Ba
ML
Intersection size
1116
489
412
331
243
189
169
149
128
125
116
115
112
98
92
71
65
65
63
Ba_W_Enh
ML_W_Enh
Ba_Transcription
ML_Transcription
Ba_A_Enh
ML_PRC2_1
Ba_Heterochromatin
Ba_PRC2_1
ML_A_Enh
ML_Heterochromatin
Set size
ChromHMM group

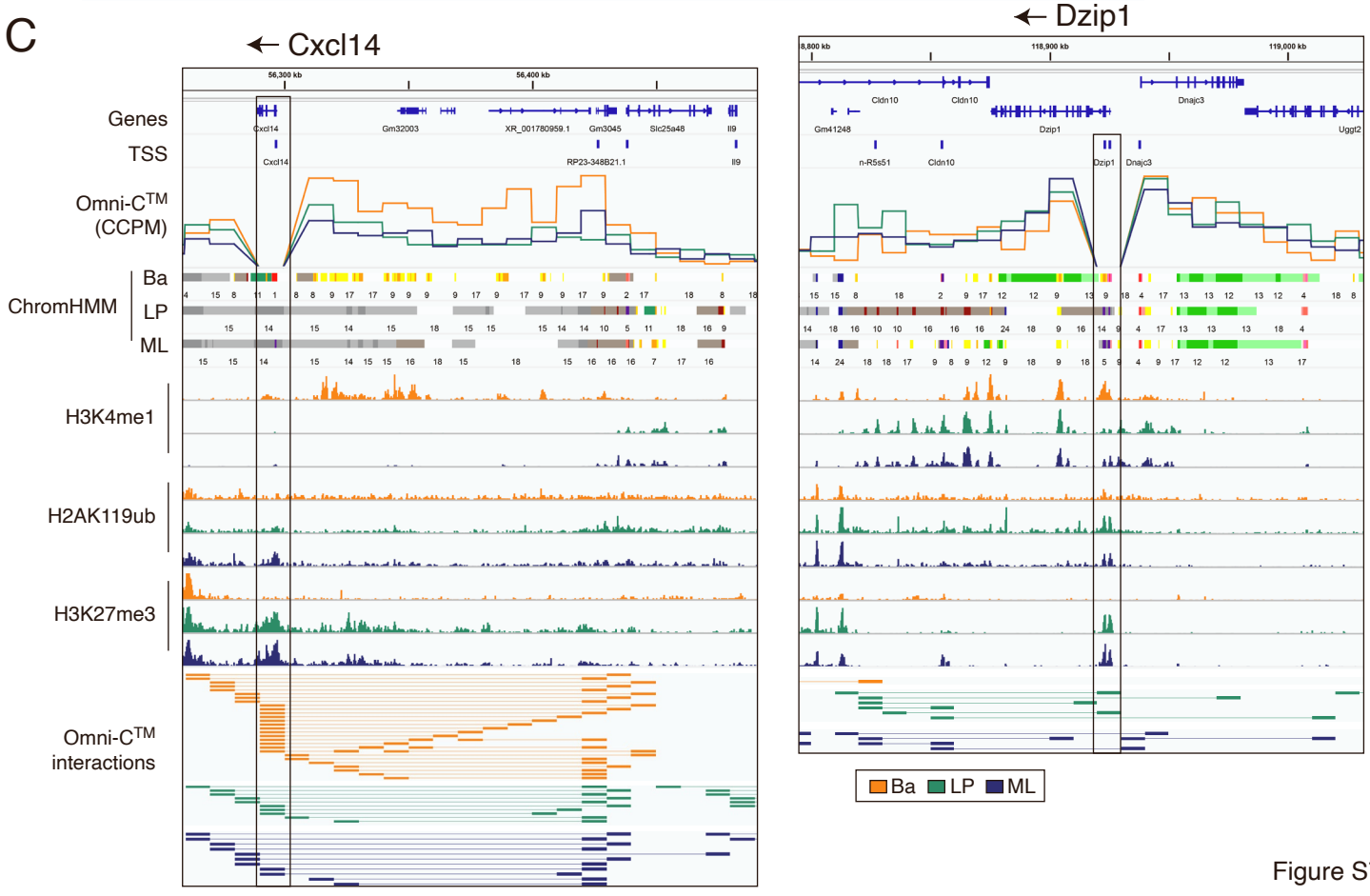
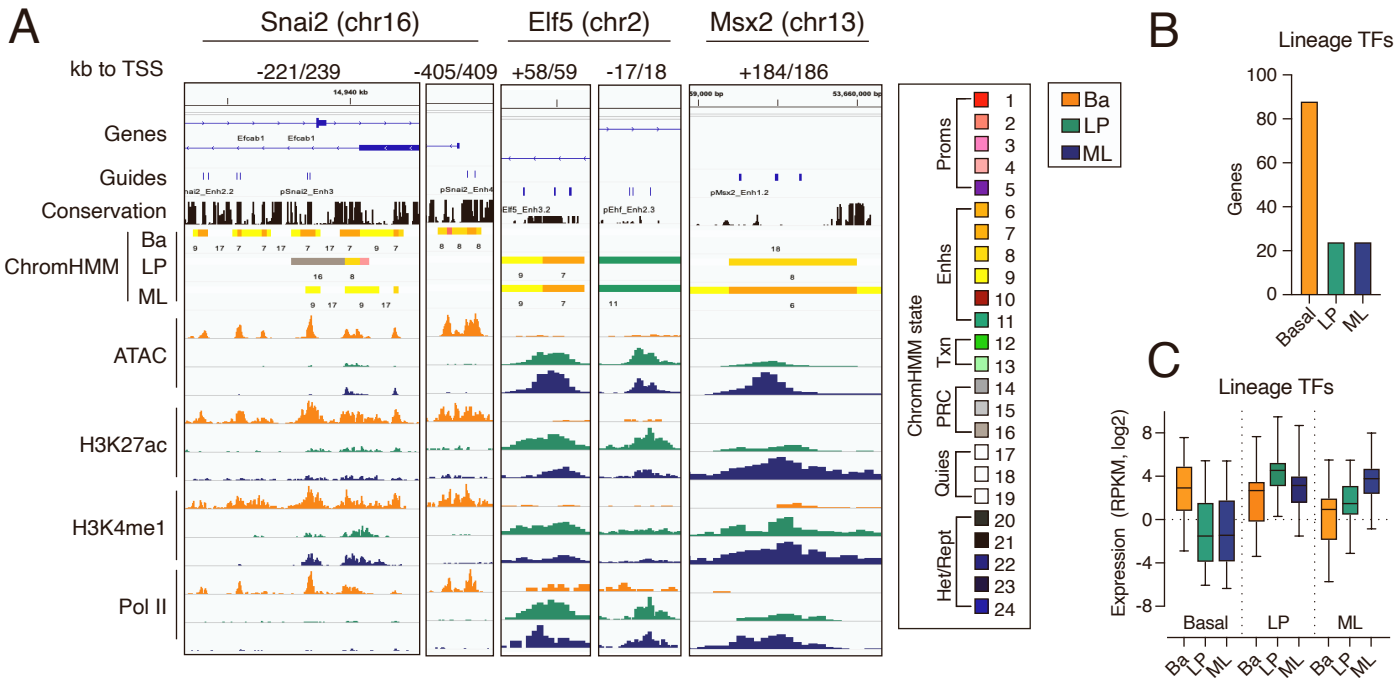
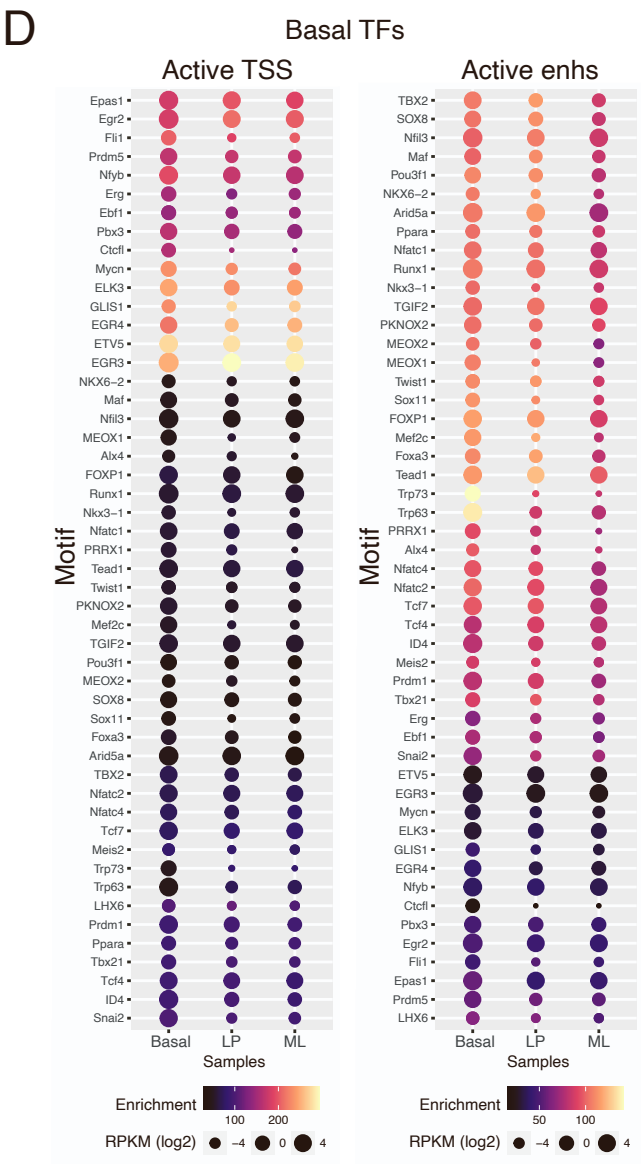
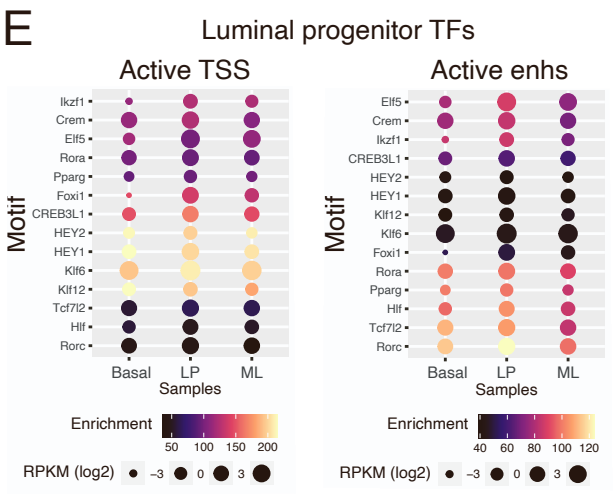

C
← Cxcl14
← Dzip1
Genes
TSS
Omni-C™ (CCPM)
ChromHMM
Ba
LP
ML
H3K4me1
H2AK119ub
H3K27me3
Omni-C™ interactions
56,300 kb
56,400 kb
Cxcl14
Gm32003
XR_001780959.1
Gm3045
Slc25a48
Il9
RP23-348B21.1
8,800 kb
118,900 kb
119,000 kb
Cldn10
Dnajc3
Gm41248
Dzip1
Uggt2
n-R5s51
Ba
LP
ML

Figure S7

Figure S6 (Related to Figure 5)**. The influence of promoter and distal CREs on lineage-restricted expression. (A)** Coverage track-plots of the *Wap* locus with the *Wap* enhancers identified by Shin et al. 2016.[1] **(B)** Coverage track-plot of the *Wfdc18* locus: shown are the genes, TSSs, ChromHMM states and Omni-C interactions as determined by FitHiChIP (FDR < 0.1). **(C)** Chromatin states of gene promoters, shown are the significant differential regions as determined by csaw (FDR < 0.05) in ATAC and CUT&Tag data of basal (Ba), LP and ML gene promoter regions (1 kb TSS region shown). Color indicates the enrichment direction in the comparison. Shown below are the ChromHMM states for Ba, LP and ML cells. **(D)** Coverage track-plots of ML gene promoters. Shown are CUT&Tag (RPKM), ATAC-seq (RPKM) and the ChromHMM states. Each TSS site is 1 kb for reference. **(E)** Heatmap of the average expression of genes with 0 or increasing numbers of interacting CREs in each population as determined by states showing overlapping interactions from the FitHiChIP analysis. **(F)** Heatmap of TSSs interacting with each chromatin state, as determined by overlapping with interactions from the FitHiChIP analysis. **(G)** Average number of CREs interacting with TSSs of DEGs from pairwise comparisons between basal, LP and ML cells.


A
Snai2 (chr16)
Elf5 (chr2)
Msx2 (chr13)
kb to TSS
-221/239
-405/409
+58/59
-17/18
+184/186
Genes
Guides
Conservation
ChromHMM
Ba
LP
ML
ATAC
H3K27ac
H3K4me1
Pol II
ChromHMM state
Proms
Enhs
Txn
PRC
Quies
Het/Rept
Ba
LP
ML
B
Lineage TFs
Genes
C
Lineage TFs
Expression (RPKM, log2)
Basal
LP
ML


D
Basal TFs
Active TSS
Active enhs
Motif
Epas1
Egr2
Fli1
Prdm5
Nfyb
Erg
Ebf1
Pbx3
Ctcfl
Mycn
ELK3
GLIS1
EGR4
ETV5
EGR3
NKX6–2
Maf
Nfil3
MEOX1
Alx4
FOXP1
Runx1
Nkx3–1
Nfatc1
PRRX1
Tead1
Twist1
PKNOX2
Mef2c
TGIF2
Pou3f1
MEOX2
SOX8
Sox11
Foxa3
Arid5a
TBX2
Nfatc2
Nfatc4
Tcf7
Meis2
Trp73
Trp63
LHX6
Prdm1
Ppara
Tbx21
Tcf4
ID4
Snai2
TBX2
SOX8
Nfil3
Maf
Pou3f1
NKX6–2
Arid5a
Ppara
Nfatc1
Runx1
Nkx3–1
TGIF2
PKNOX2
MEOX2
MEOX1
Twist1
Sox11
FOXP1
Mef2c
Foxa3
Tead1
Trp73
Trp63
PRRX1
Alx4
Nfatc4
Nfatc2
Tcf7
Tcf4
ID4
Meis2
Prdm1
Tbx21
Erg
Ebf1
Snai2
ETV5
EGR3
Mycn
ELK3
GLIS1
EGR4
Nfyb
Ctcfl
Pbx3
Egr2
Fli1
Epas1
Prdm5
LHX6
Basal
LP
ML
Samples
Enrichment
RPKM (log2)


E
Luminal progenitor TFs
Active TSS
Active enhs
Motif
Ikzf1
Crem
Elf5
Rora
Pparg
Foxi1
CREB3L1
HEY2
HEY1
Klf6
Klf12
Tcf7l2
Hlf
Rorc
Basal
LP
ML
Samples
Enrichment
RPKM (log2)

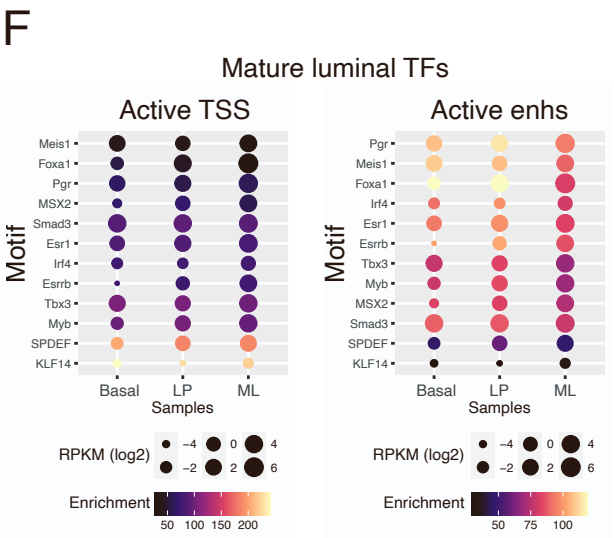

F
Mature luminal TFs
Active TSS
Active enhs
Motif
Meis1
Foxa1
Pgr
MSX2
Smad3
Esr1
Irf4
Esrrb
Tbx3
Myb
SPDEF
KLF14
Basal
LP
ML
Samples
RPKM (log2)
Enrichment

Figure S8

Figure S7 (Related to Figure 5) **Silencers primarily influence gene expression in luminal cells. (A and B)** Upset plot analysis of DEGs overlapping with DI regions between basal (Ba) and LP and basal and ML cells, respectively. Shown are the log fold-change expression (RPKM, log2) and log-FC chromatin interactivity (Omni-C) for basal versus LP and basal versus ML respectively, intersection size and ChromHMM combinations. ChromHMM states were summarized with state 1 = A_Prom, states 2-4 = W_Prom, states 5, 14 and 15 = PRC2_1, states 6 and 7 = A_Enh, states 8, 9 and 11 = W_Enh, states 10 and 16 = PRC1, states 12 and 13 = transcription, states 17-19 = silent chromatin and states 20-24 = heterochromatin. Arrows indicate the interactions that contain a repressive element (PRC1, PRC2 and or heterochromatin) and the color indicates the cell in which the DEG is more expressed. **(C)** Coverage track-plots for *Cxcl14* and *Dzip1*. Omni-C reads show regions connected to TSSs, whilst Omni-C interactions are those determined by FitHiChIP.

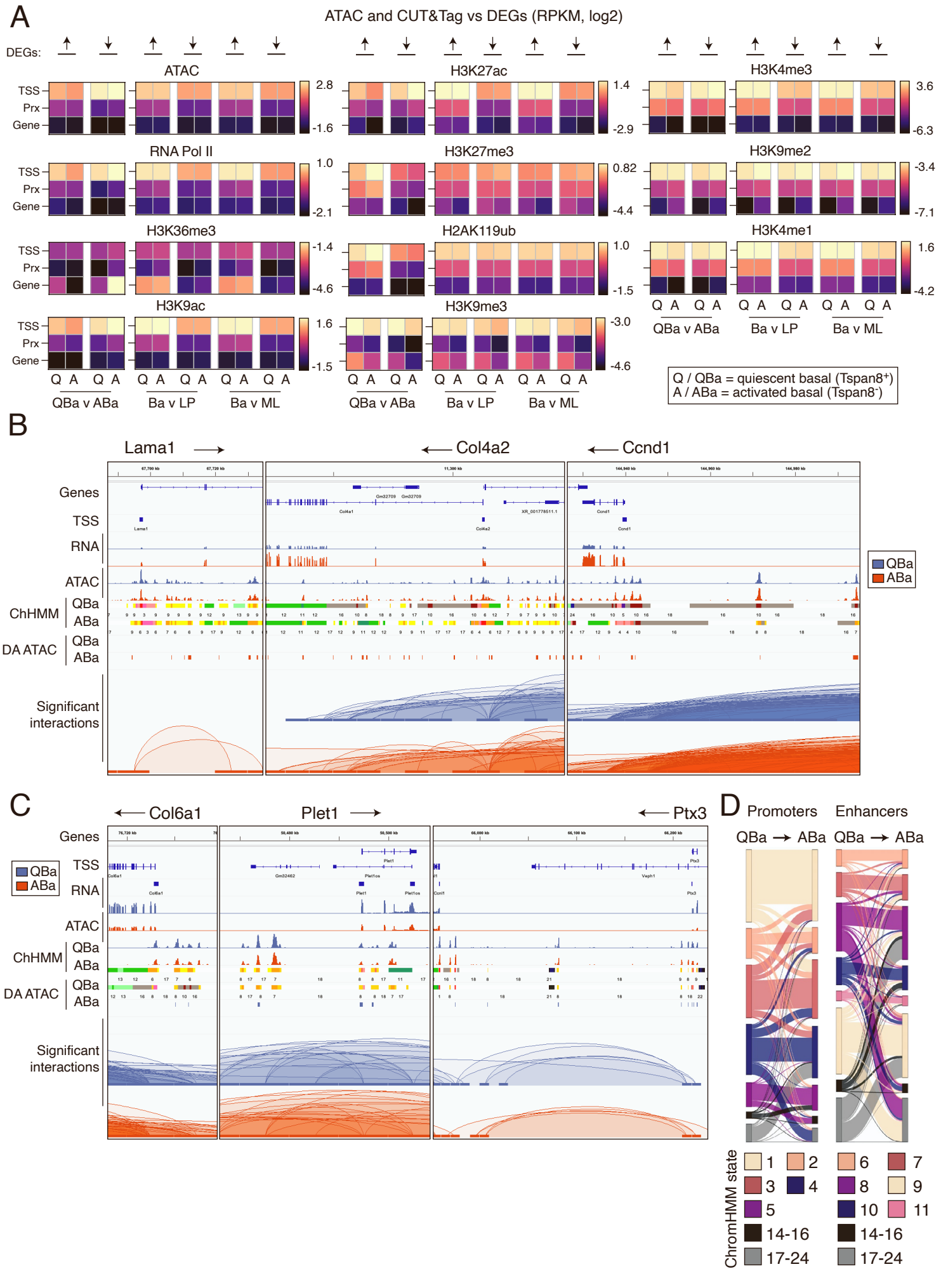

A
ATAC and CUT&Tag vs DEGs (RPKM, log2)
DEGs:
ATAC
H3K27ac
H3K4me3
RNA Pol II
H3K27me3
H3K9me2
H3K36me3
H2AK119ub
H3K4me1
H3K9ac
H3K9me3
TSS
Prx
Gene
Q A Q A
QBa v ABa
Ba v LP
Ba v ML
Q / QBa = quiescent basal (Tspan8+)
A / ABa = activated basal (Tspan8-)
B
Lama1
Col4a2
Ccnd1
Genes
TSS
RNA
ATAC
ChHMM
QBa
ABa
DA ATAC
Significant interactions
C
Col6a1
Plet1
Ptx3
D
Promoters
Enhancers
QBa → ABa
ChromHMM state
1
2
3
4
5
6
7
8
9
10
11
14-16
17-24

Figure S9

Figure S8 (Related to Figure 6**). Transcription factors display distinct chromatin binding patterns. (A)** Zoomed-in coverage track-plots from Figure 6A for the strongest enhancers of *Snai2*, *Elf5* and *Msx2*. From top to bottom, genes, short-guide-RNAs for CRISPR-activation, conservation across placental mammals, ChromHMM modeling, RPKM for ATAC and CUT&Tag. **(B)** Lineage-restricted TFs identified through signature profiling of basal (Ba, 88), LP (24) and ML (24) cells. **(C)** Gene expression of lineage-specific TFs. Boxes shows median, quartiles and 5th and 95th percentiles. **(D to F)** TOBIAS analysis of TF accessible motif enrichment (observed vs expected, log2, color chart) and TF RNA expression (circle size) for lineage-specific TFs, showing enrichment for active promoters (state 1) and distal active enhancers (state 7).

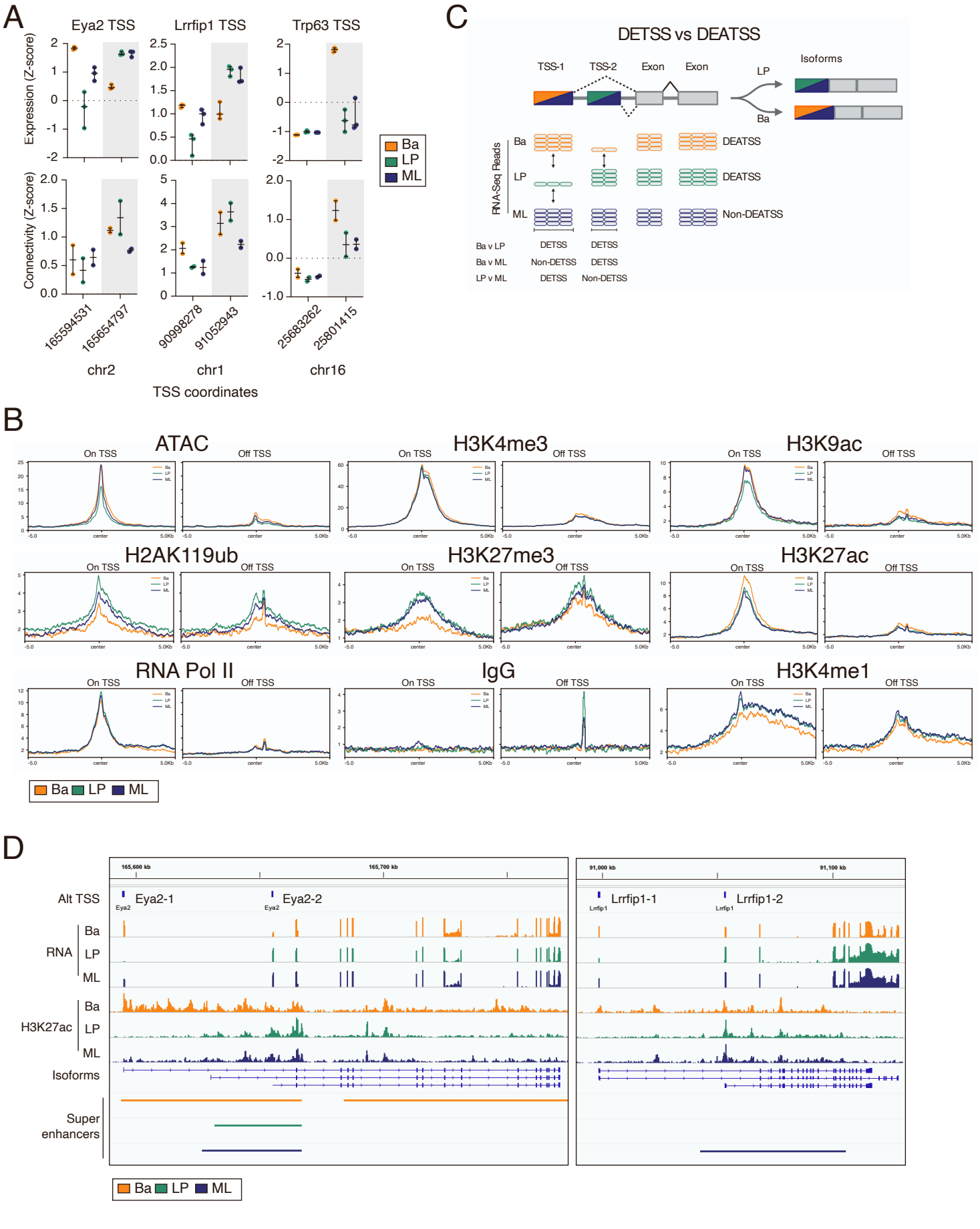

A
Eya2 TSS
Lrrfip1 TSS
Trp63 TSS
Expression (Z-score)
Connectivity (Z-score)
Ba
LP
ML
165594531
165654797
90998278
91052943
25683262
25801415
chr2
chr1
chr16
TSS coordinates
C
DETSS vs DEATSS
TSS-1
TSS-2
Exon
Exon
Isoforms
LP
Ba
RNA-Seq Reads
DEATSS
DEATSS
Non-DEATSS
Ba v LP
Ba v ML
LP v ML
DETSS
Non-DETSS
DETSS
DETSS
Non-DETSS
B
ATAC
H3K4me3
H3K9ac
H2AK119ub
H3K27me3
H3K27ac
RNA Pol II
IgG
H3K4me1
On TSS
Off TSS
Ba LP ML
D
Alt TSS
Eya2-1
Eya2-2
Lrrfip1-1
Lrrfip1-2
RNA
H3K27ac
Isoforms
Super enhancers
Ba LP ML

Figure S4

Figure S9 (Related to Figure 7)**. Histone modifications and chromatin looping events that define the basal compartment. (A)** Average RPKM for ATAC-seq and CUT&Tag across the TSS, proximal (Prx) and gene-body (Gene) regions for DEGs between QBa versus ABa, basal versus LP, and basal versus ML populations. **(B and C)** Coverage track-plots for genes enriched in active basal (ABa, Tspan8^{-}) and quiescent basal (QBa, Tspan8^{+}) cells, respectively. Shown are the genes, TSSs, expression (RPKM), ATAC-Seq (RPKM), ChromHMM, DA regions, and the interactions determined by FitHiChIP. **(D)** Sankey transition plots showing the proportion of promoter and enhancer chromatin states that change between QBa and ABa cells. States 14-16 were grouped as PRC and states 17-24 grouped H/S.

References

1. Shin, H.Y., Willi, M., HyunYoo, K., Zeng, X., Wang, C., Metser, G., and Hennighausen, L. (2016). Hierarchy within the mammary STAT5-driven Wap super-enhancer. Nature genetics *48*, 904-911. 10.1038/ng.3606.