Supplemental Information

Lineage-specific and shared cytokine-sensing genes respond differentially to the master regulator STAT5

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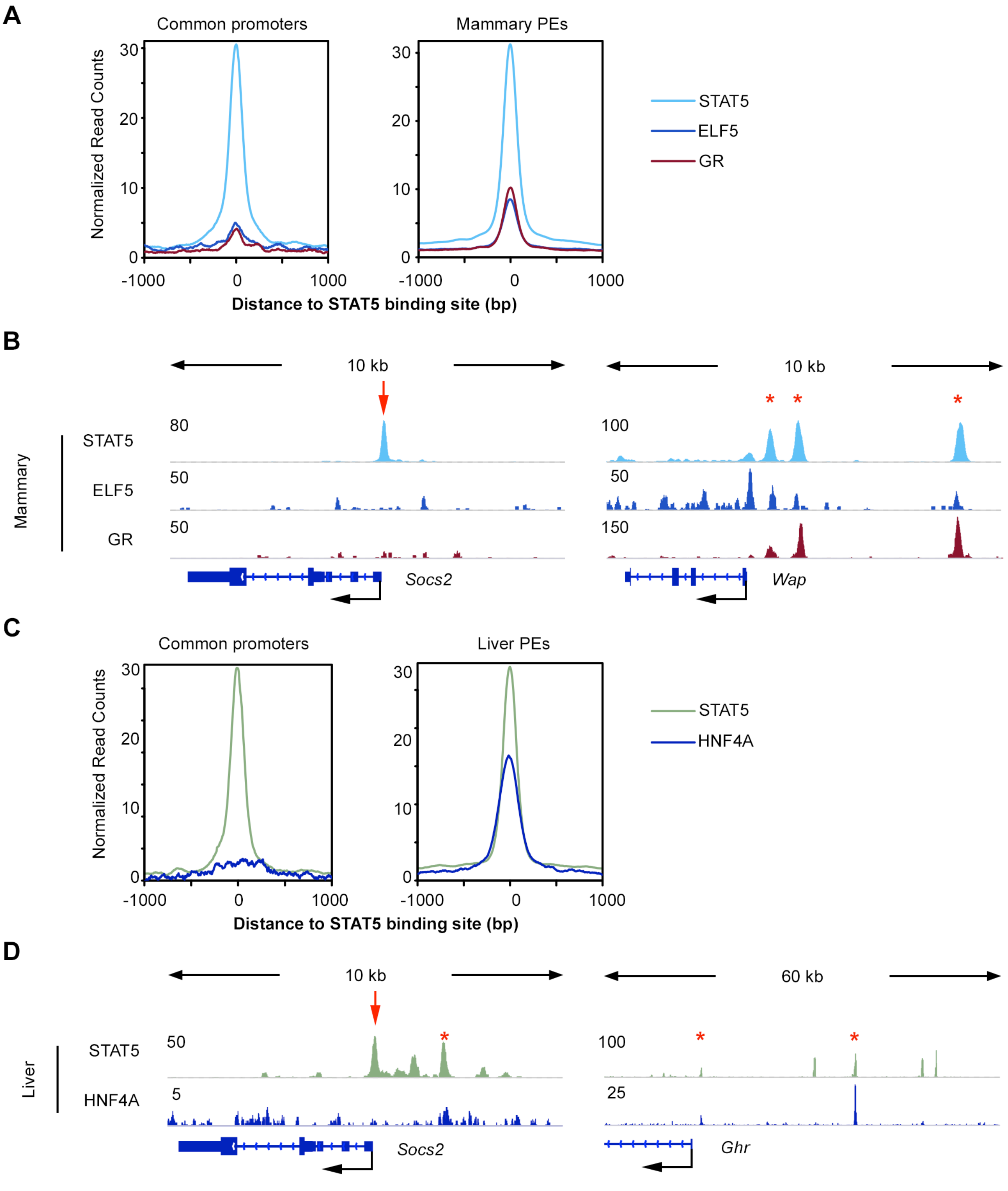

Figure S1. STAT5 co-localizes with lineage-specific factors on putative enhancers but not common promoters, Related to Figure 1

STAT5 co-localizes with ELF5 and GR on mammary specific putative enhancers (PEs) (A-B) and HNF4A on liver specific PEs (C-D).

(A) Average profiles of STAT5, ELF5 and GR binding around the center of STAT5 binding common promoters and PEs in mammary gland.

(B) ChIP-seq binding profiles of STAT5, ELF5 and GR in mammary gland. Red arrow and asterisks indicate common promoters and putative enhancers respectively.

(C) Average profiles of STAT5 and HNF4A binding around the center of STAT5 binding common promoters and putative enhancers in liver.

(D) ChIP-seq binding profiles of STAT5 and HNF4A in liver. Red arrow and asterisks indicate common promoters and putative enhancers respectively.

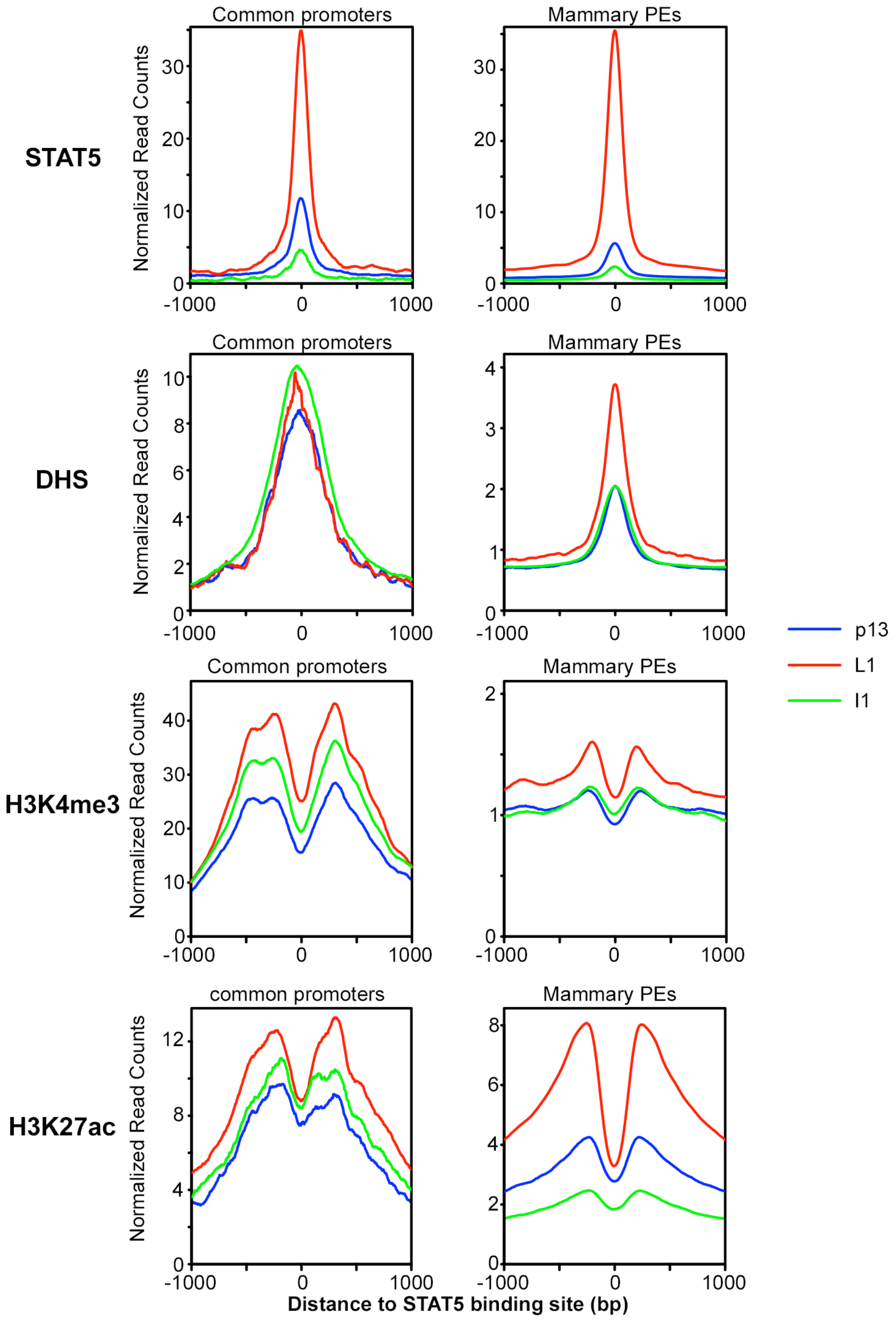

Figure S2. Chromatin accessibility and histone markers coordinate with STAT5 binding on mammary specific putative enhancers but not common promoters, Related to Figure 2.

Average profiles of STAT5 binding, DHS (DNaseI hypersensitive sites) and indicated histone markers around the center of STAT5 binding common promoters and putative enhancers (PEs) in mammary gland at P13, L1 and I1. STAT5 binding coordinated with PRL level on both groups of elements. Chromatin accessibility and the level of active marker H3K27ac are correlated with STAT5 binding on putative enhancers. DNase-seq signaling, H3K4me3 and H3K27ac levels on common promoters persists regardless of STAT5 binding level.

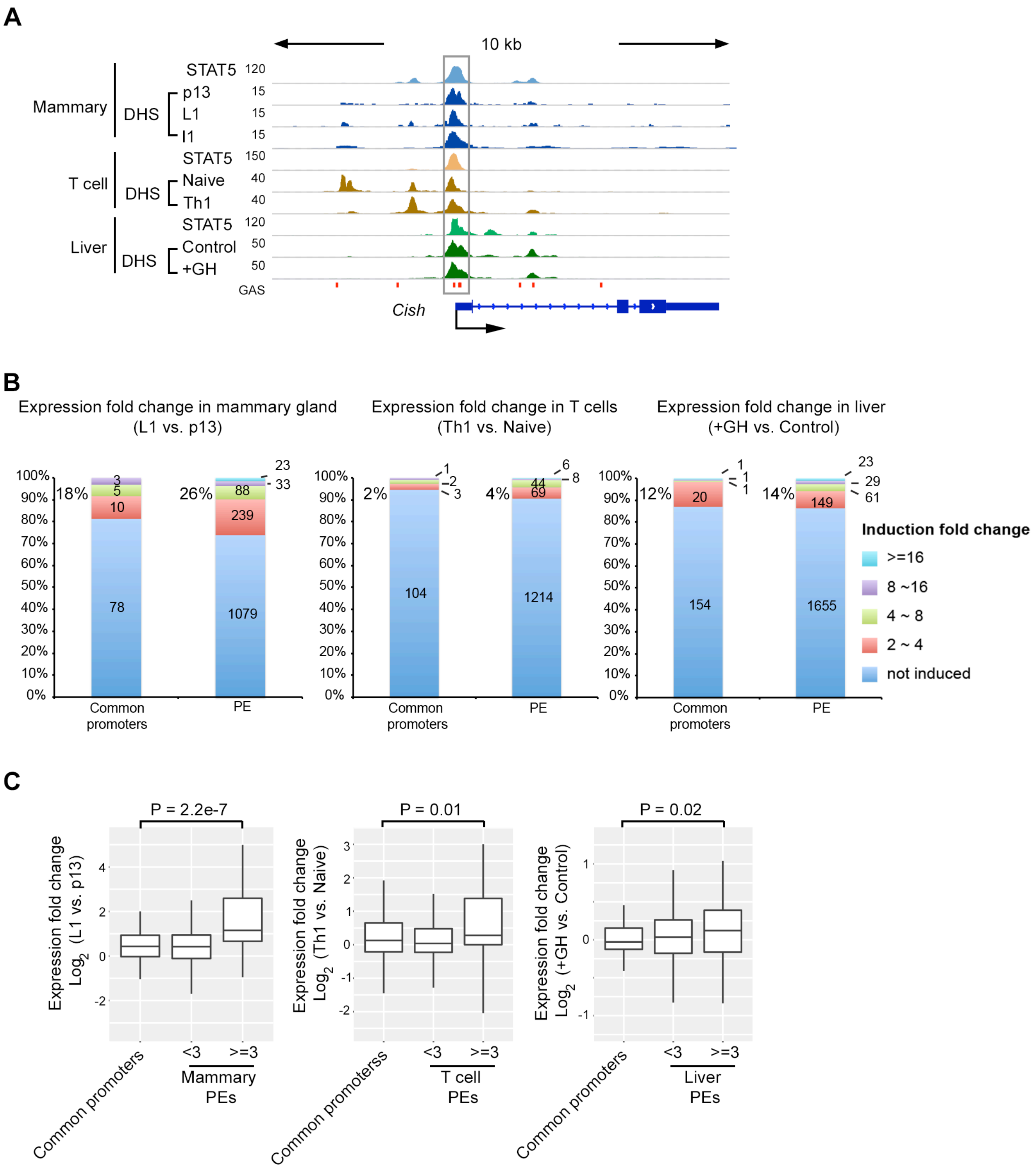

Figure S3. Genes enclosed lineage-specific STAT5 binding putative enhancers are induced at a significantly greater extent comparing to those with common promoters upon cytokine level increase, Related to Figure 2.

(A) Representative gene locus enclosed a common promoter (*Cish* locus). ChIP-seq of STAT5 and DNase-seq binding profiles (reads per 10 million) are shown. STAT5 binding is highlighted.

(B) Genes enclosed common promoters and lineage-specific putative enhancers (PEs) were grouped by differential induction levels upon cytokine level increase in mammary gland (left), T cells (middle) and liver (right). Bar plots depict the percentages of each group in common promoter-genes and PE-genes. The percentage of genes showing over 2-fold induction is indicated. The number of genes in each category is also shown.

(C) Genes enclosed multiple lineage-specific putative enhancers (PEs) are induced at a significantly higher level than those with common promoters. Genes enclosed putative enhancers are grouped by the number of enclosing enhancers. Box plots indicate the gene expression change of genes enclosed indicated STAT5 binding elements. P values of *wilcox* tests are shown on top.

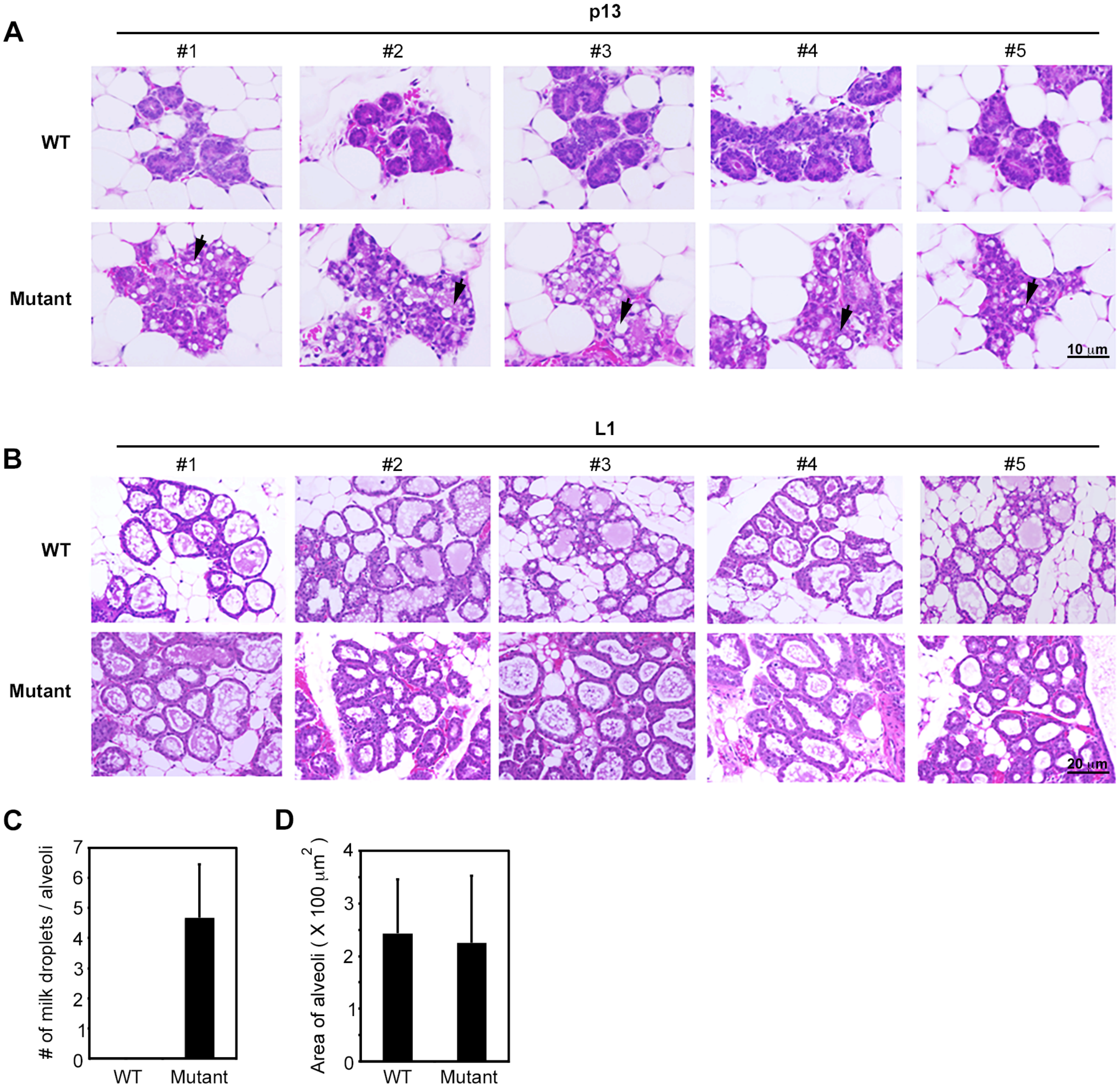

Figure S4. Mammary gland is precociously differentiated in *Socs2-Δs* mutant, Related to Figure 4.

(A-B) Pictures of H&E staining mammary sections from 5 individual mice in each group are shown. Precociously developed alveoli containing milk droplets were observed in mutant mammary glands at p13 (black arrows).

(C) Bar plot shows the average number of milk droplets observed in each p13 alveoli. The number was calculated from 100 alveoli of each group.

(D) Bar plot shows the average size of alveoli observed in L1 mammary gland. 40 alveoli from each group were measured.

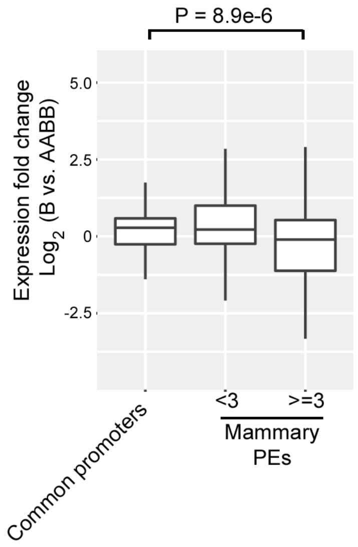

Figure S5. Genes enclosed multiple mammary specific STAT5 binding putative enhancers are down-regulated at a greater level comparing to those with common promoters in STAT5 deficient mice, Related to Figure 6.

Genes enclosed putative enhancers are grouped by the number of enclosing putative enhancers (PEs). Box plot depicts gene expression change of indicated group of genes between wild-type (AABB) and Stat5a$^{-/-}$;Stat5b$^{+/-}$ (B) mammary gland at L1. P value of *wilcox* test is shown on top.

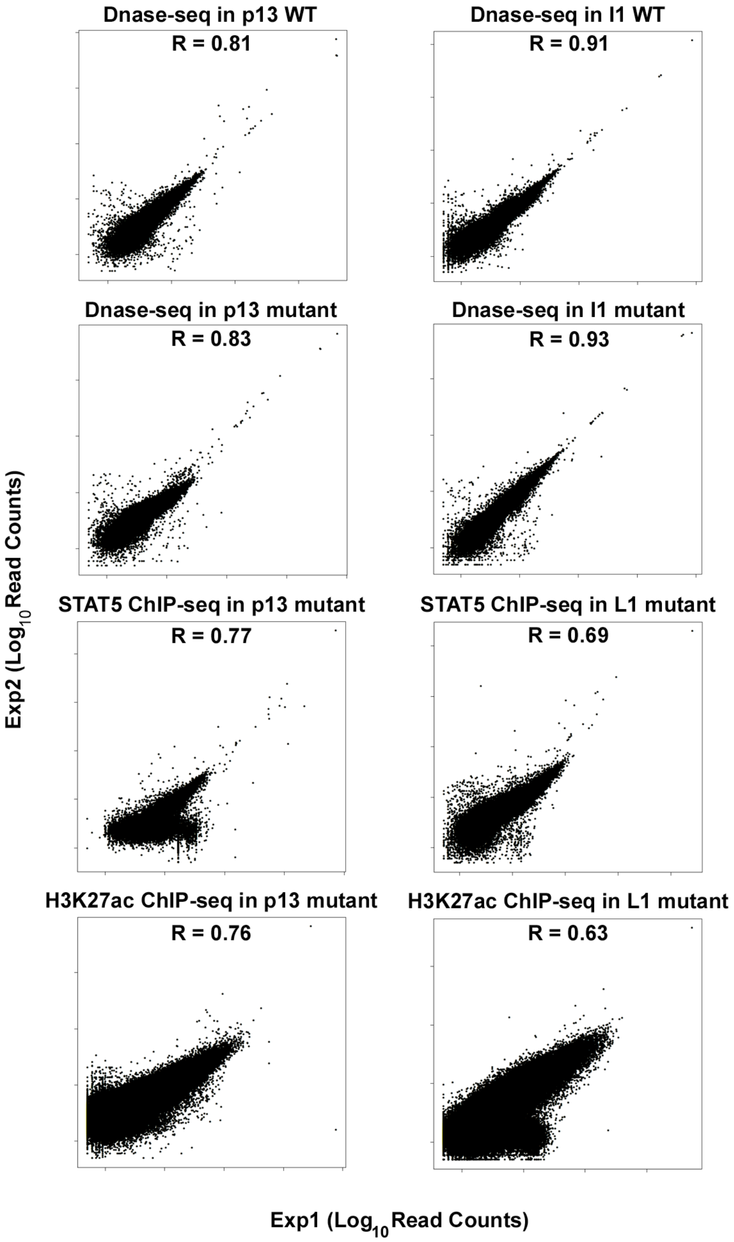

Figure S6. Spearman correlation of ChIP-seq and DNase-seq experiments, Related to Experimental Procedures.

Scatter plots depict the read counts from biological replicates of ChIP-seq or DNase-seq experiments. The R values of *Spearman* correlation are shown on top.

Table S1, related to Figure 1. Common and tissue-specific STAT5 binding sites.

Table S2, related to Figure 1. Motifs enriched in STAT5 binding common promoters.

Table S3, related to Figure 2. STAT5-bound common promoters and lineage-specific putative enhancers.

Table S4, related to Figure 2. FPKM of genes associated with STAT5-bound common promoters and putative enhancers in mammary gland, liver and T cells.

Table S5, related to Figure 4. FPKM of deregulated genes in *Socs2-Δs* mutant p13 mammary gland.

Table S6, related to Figure 6. Expression of genes associated with STAT5-bound common promoters and potential enhancers in WT and STAT5 deficient L1 mammary gland.