

SUPPLEMENTARY INFORMATION

Disease specific epigenetic deregulation of enhancers, transposons and polycomb targets in acute promyelocytic leukemia

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Supplementary figures

Fig. S1. **a** Density plot of gene expression levels in APL and AML patient samples as defined as high (RPKM >2), and low (RPKM < 0.01) expression. **b** Functional genomic annotation enrichment using publicly available data for the 15 chromatin states in the AML patient group. **c** Heatmap of Jaccard index of chromatin states between APL and AML. **d** Enrichment of ATRA responsive genes in the 15 APL chromatin states. TSS regions are defined as TSS $\pm$ 500bp, OverlapEnrichment of ATRA responsive genes (UP/DOWN regulated in ATRA treatment vs. control in NB4 cells).

Fig. S2. Unsupervised consensus clustering (from k=2 to k=5) based on the top 2000 most variable histone profiles within each chromatin state

Fig. S3. Unsupervised consensus clustering (from k=2 to k=5) based on 2000-4000 most variable histone profiles within each chromatin state showing no significant improvement compared to the top 2000 most variable histone profiles as shown in Supplementary Fig. 2.

Fig. S4. **a** Heat map of correlations of unsupervised clustering using the top 2000 most variable features of H3K27ac profiles within E2_EnhA chromatin state in APL and AML samples. **b** Genomic annotation of PML-RARA target sites. **c** Heat map of H3K27ac in AML-specific enhancers in APL and AML samples. **d** GO biological process enrichment of genes correlating to APL specific enhancers (Pearson correlation *p*-value below 0.01, correlation above 0.7). **e** The HALLMARK, KEGG and REACTOME enrichment of genes correlating to APL specific enhancers. **f** Bar plot of percentage of enhancer associated genes in differential expression analysis (LFC: log2FoldChange, green for not significant, blue for LFC < 1, purple for LFC $\geq$ 1). **g** The heatmap showing the log2FoldChange in expression (by RNA-seq) of genes associated to APL enhancers in APL vs. AML patient samples and in NB4 cells exposed to ATRA vs. control RNA-seq. **h** Bar plot of the number of genes associated with APL specific and PML-RARA bound enhancers differential expressed in ATRA treatment NB4 cells from GSE131325.

Fig. S5. **a** Scatter plot of *INSR* expression during normal hematopoietic differentiation (GSE42519), t-test performed for comparing early and late promyelocytes with hematopoietic stem cells. **b** Scatter plot of *INSR* expression in NB4 cells exposed to ATRA or DMSO during different time points (GSE131325). *p*.adj=0.0003, log2FoldChange = -1.5. **c**

INSR expression in NB4 cells exposed to ATRA or DMSO in this study. **d** Bar plot of the number of genes associated with APL specific and PML-RARA bound super-enhancers differential expressed in ATRA treatment NB4 cells from GSE131325. **e** IGV track of *S100P* showing APL specific super enhancers, APL-specific enhancers, PML-RARA binding sites, H3K27ac profile in APL, H3K27ac profile in AML, H3K4me3 profile in APL, H3K4me3 profile in AML, RNAPOLII loops by ChIA-PET in U937 cells (without PML-RARA expression), RNAPOLII loops by ChIA-PET in U937+ZnSO₄ cells (with PML-RARA expression). **f** and **g** Relative expression of *S100P* (**f**) and *LINC02481* (**g**) in APL and AML patient cells and normal CD34⁺ bone marrow cells. **h** IGV track of zoomed region at chr17 (data displayed as described above for panel **d**). **i** Box plot of *ZNF385C* in APL and AML patient cells and normal CD34⁺ bone marrow cells.

Fig. S6. a Bar plot showing gains and losses of H3K9me3 in heterochromatin-related chromatin states E10_Het, E11_HetRep, E12_HetLADS and E14_HetLADS, including AML vs NBM. **b** Bar plot showing the distribution of transposable element families that overlaps with gain and loss of H3K9me3. **c** Expression heatmap of genes associated with significant gain (right) and loss (left) H3K9me3 modification within the E14_HetLADS state. **d** Bar plot of the number of genes with gained H3K27me3 differential expressed in ATRA treatment NB4 cells from GSE131325.

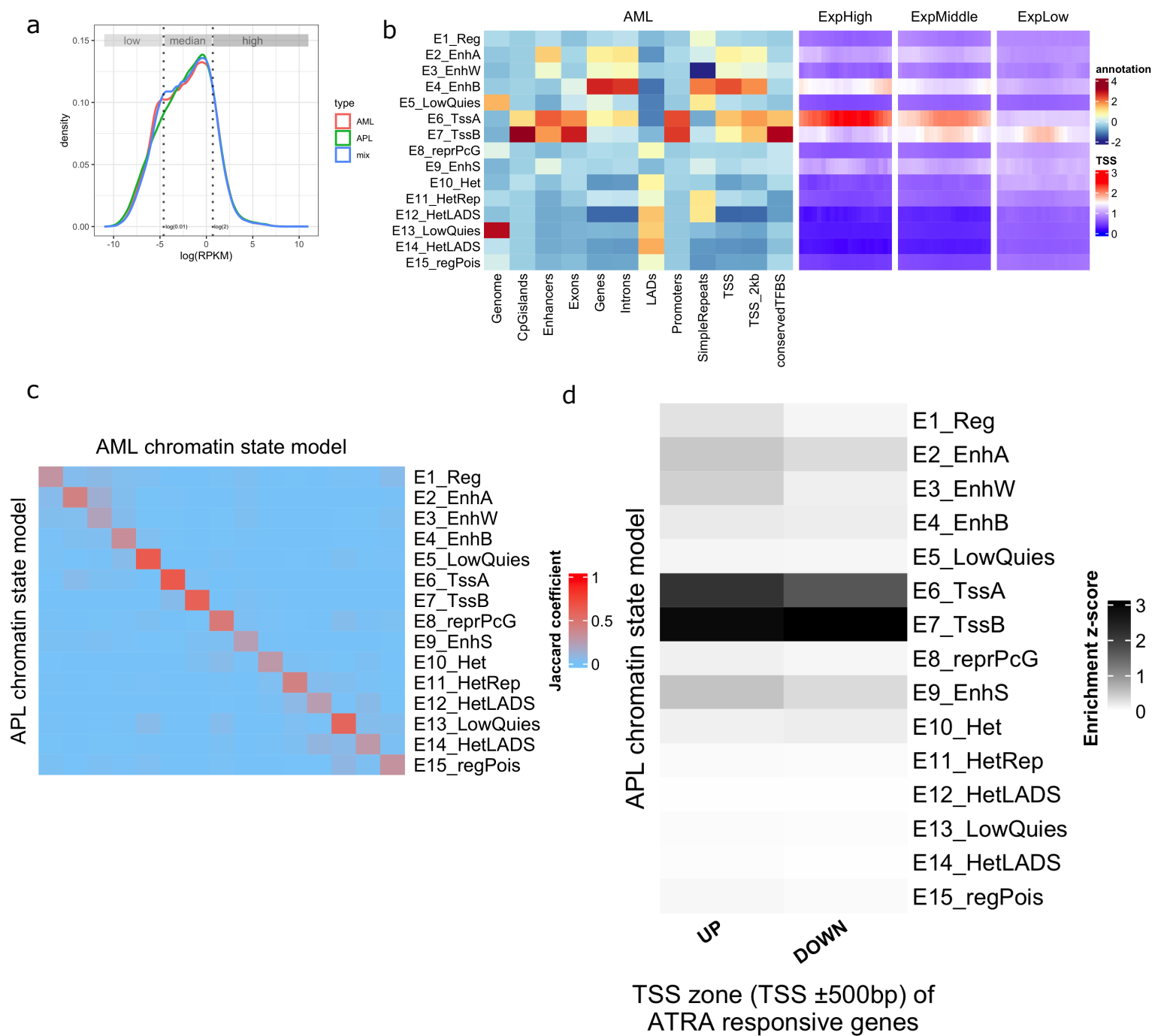


Fig. S1

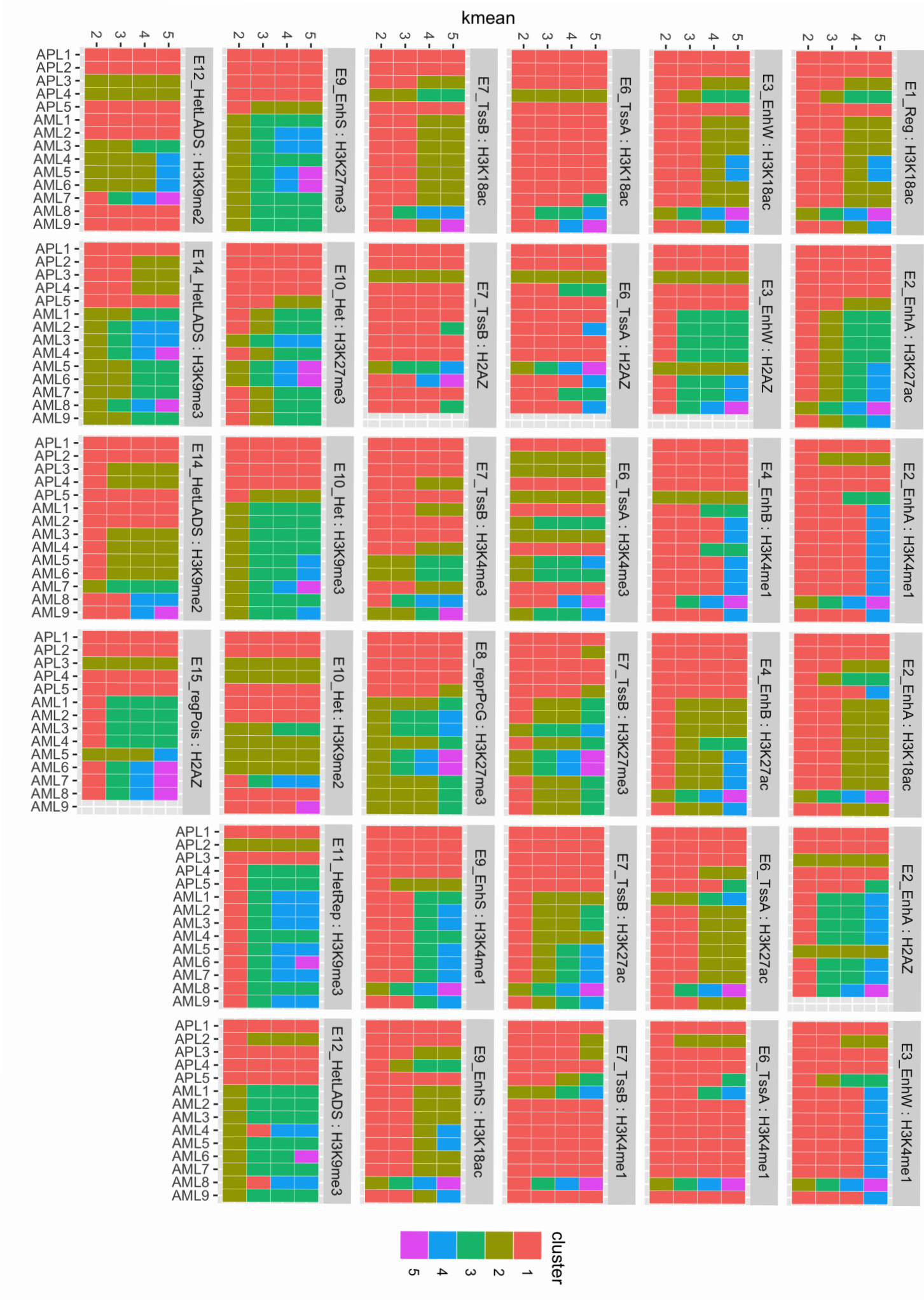


Fig. S2

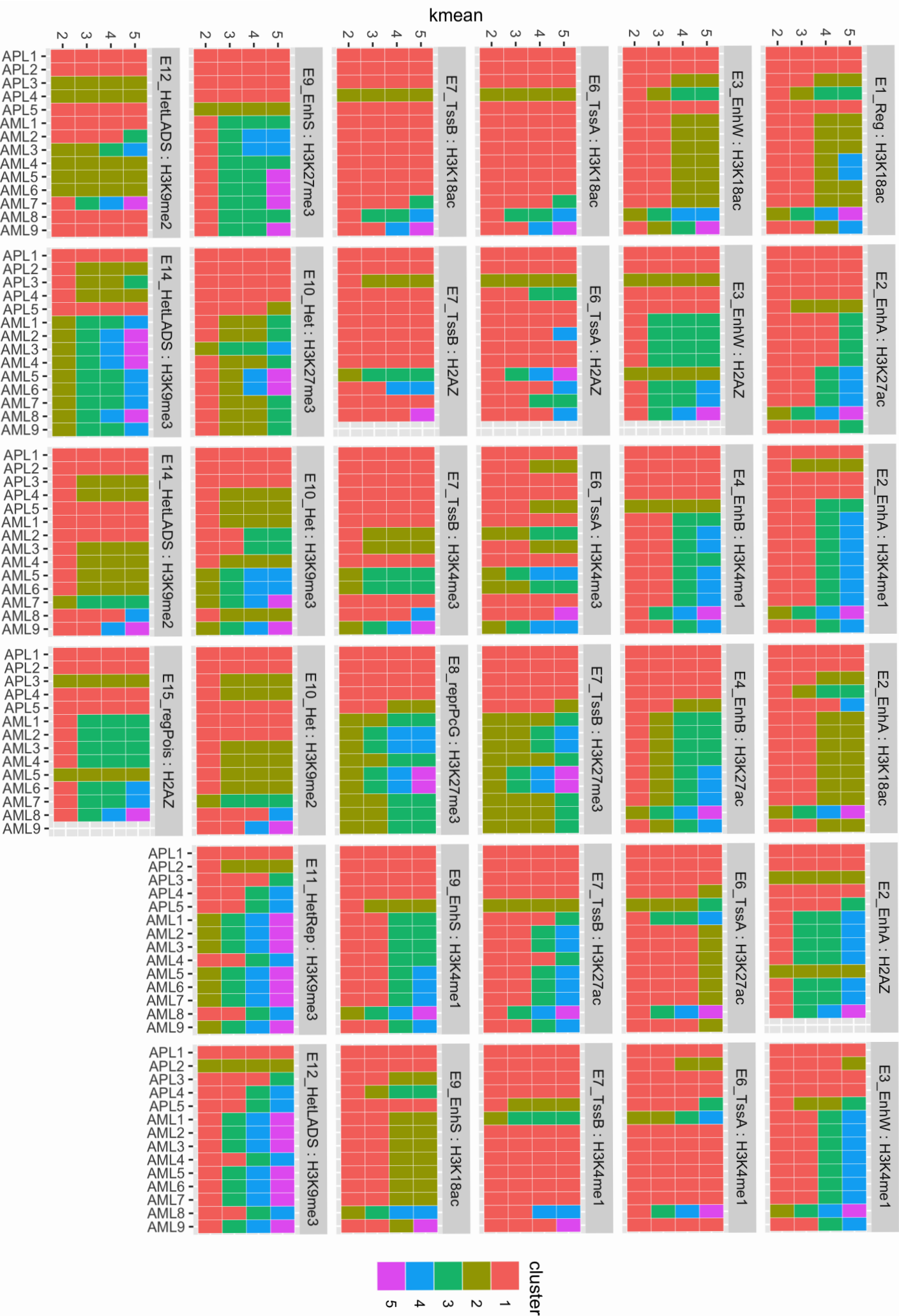


Fig. S3

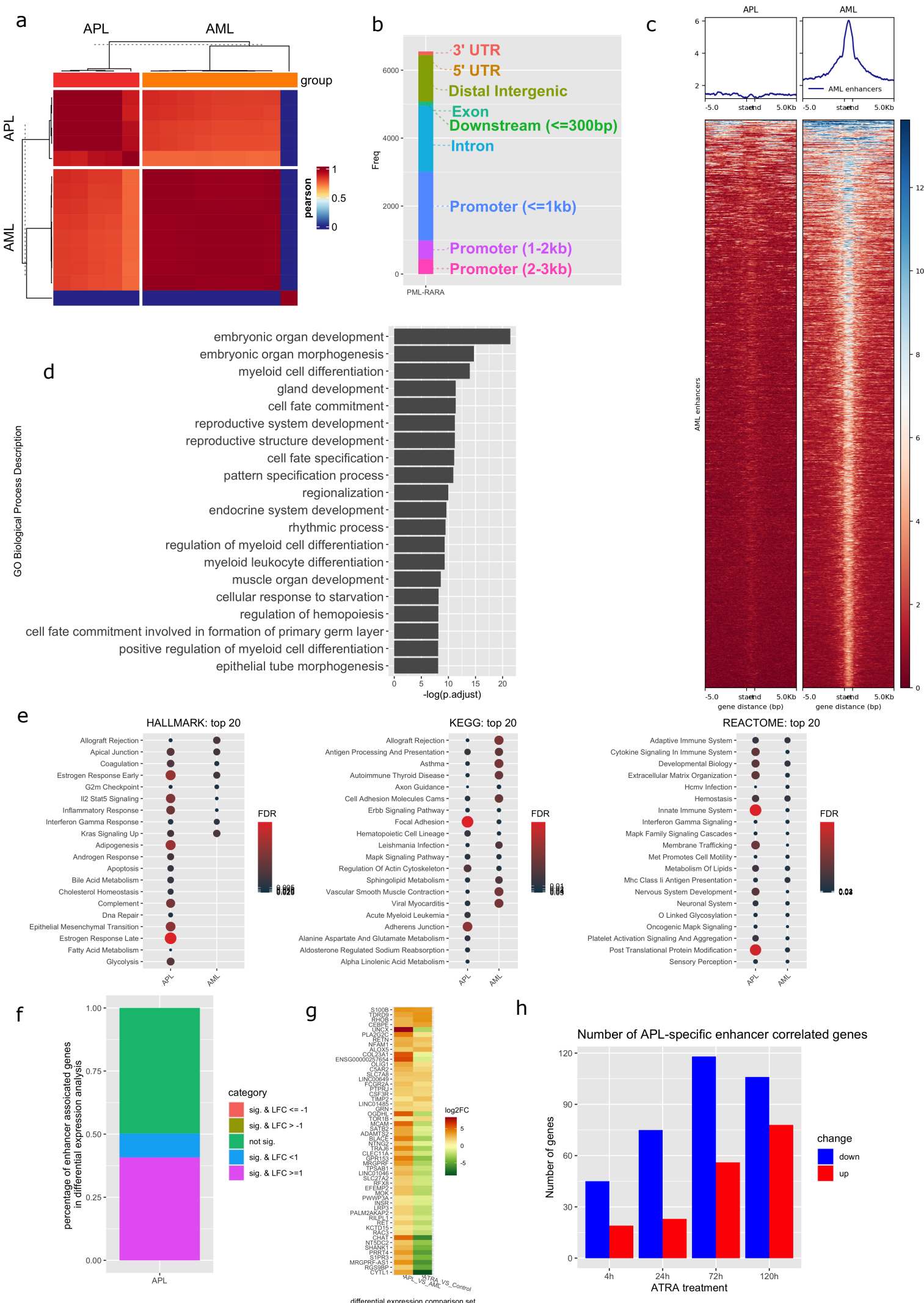


Fig. S4

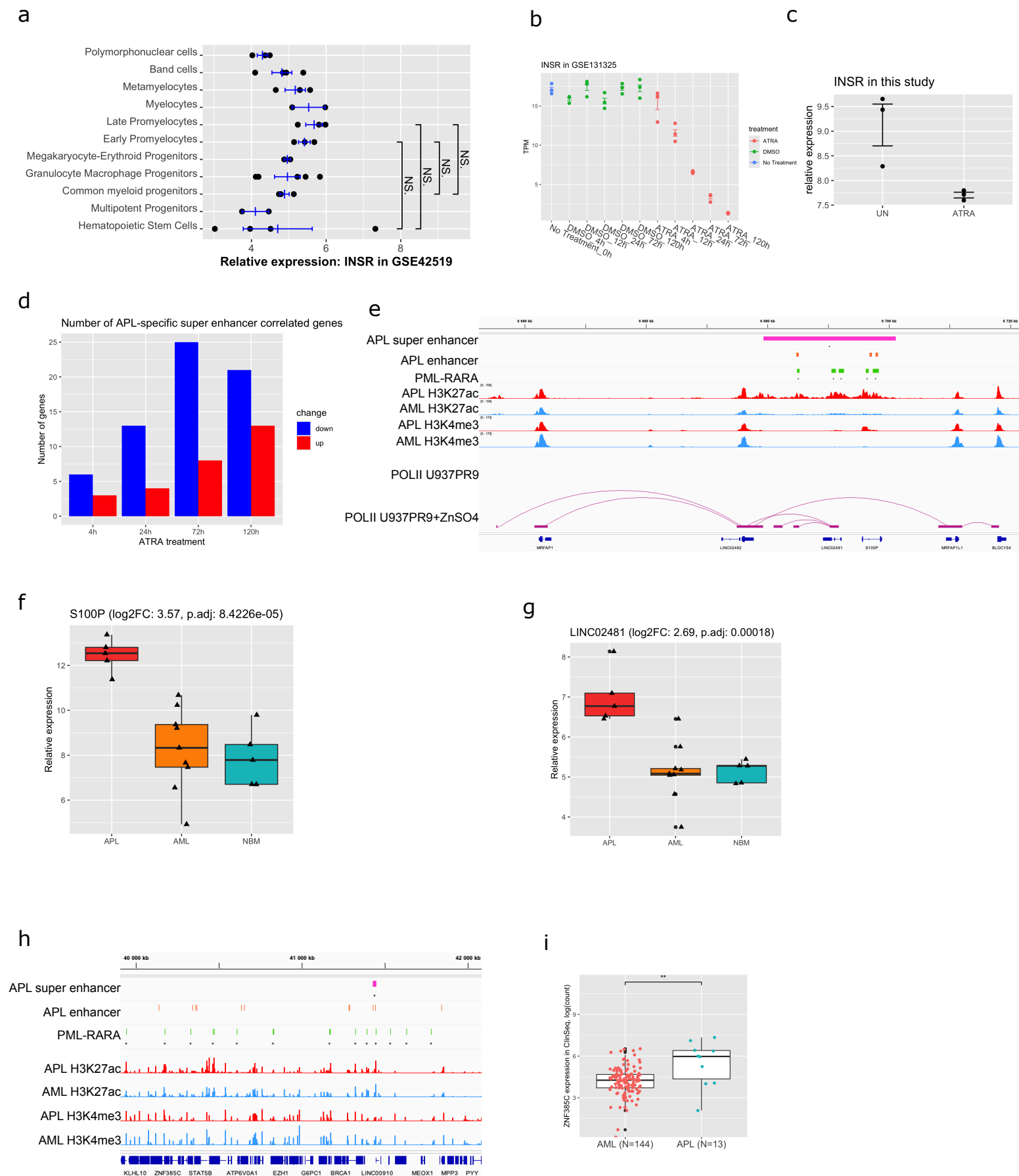


Fig. S5

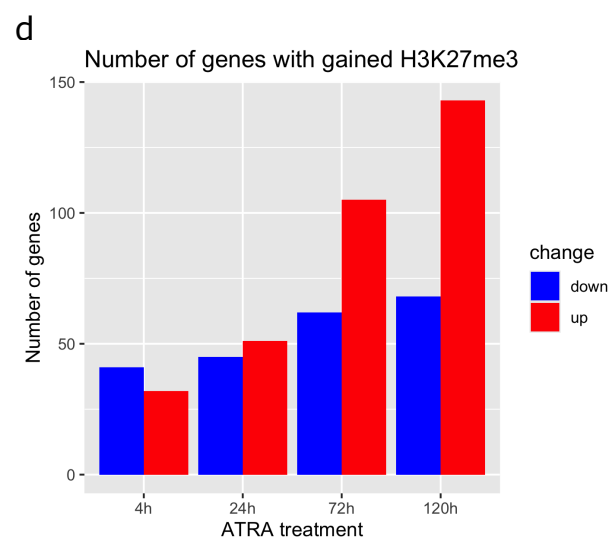
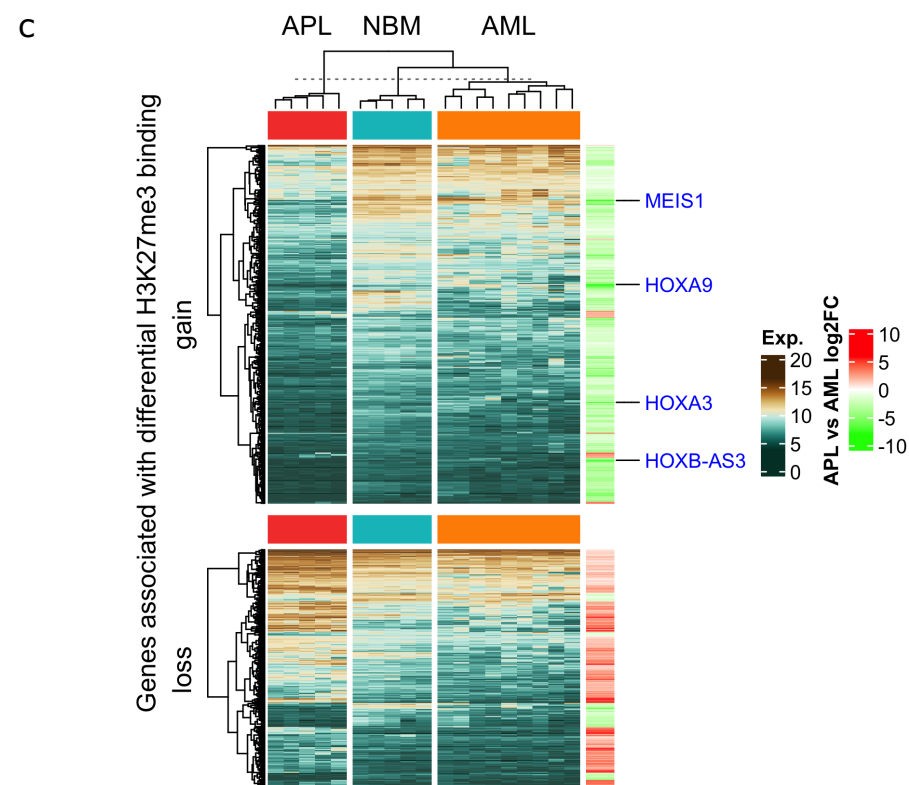
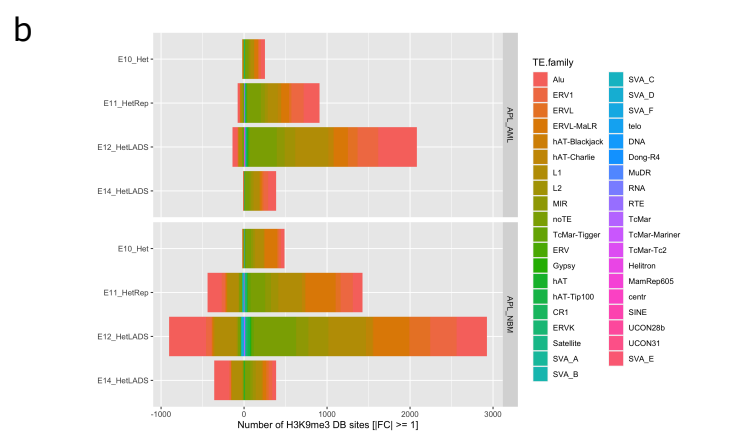
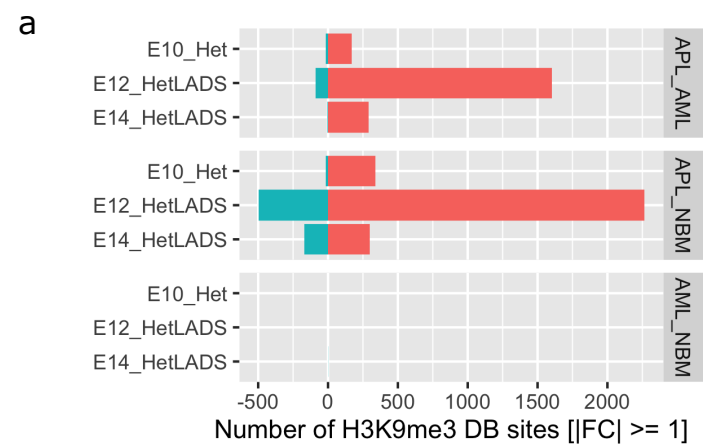


Fig. S6