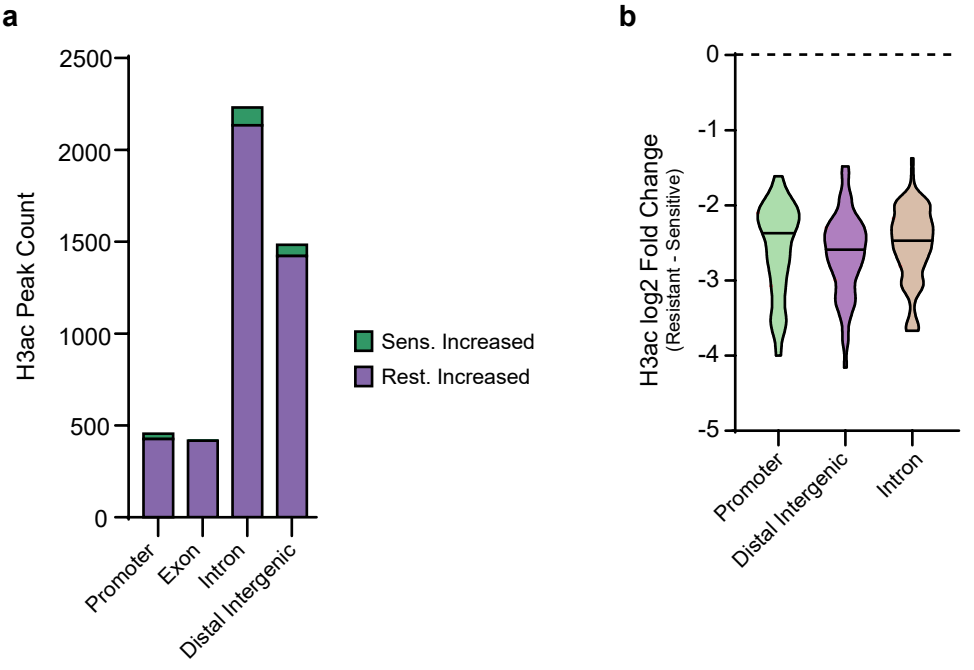
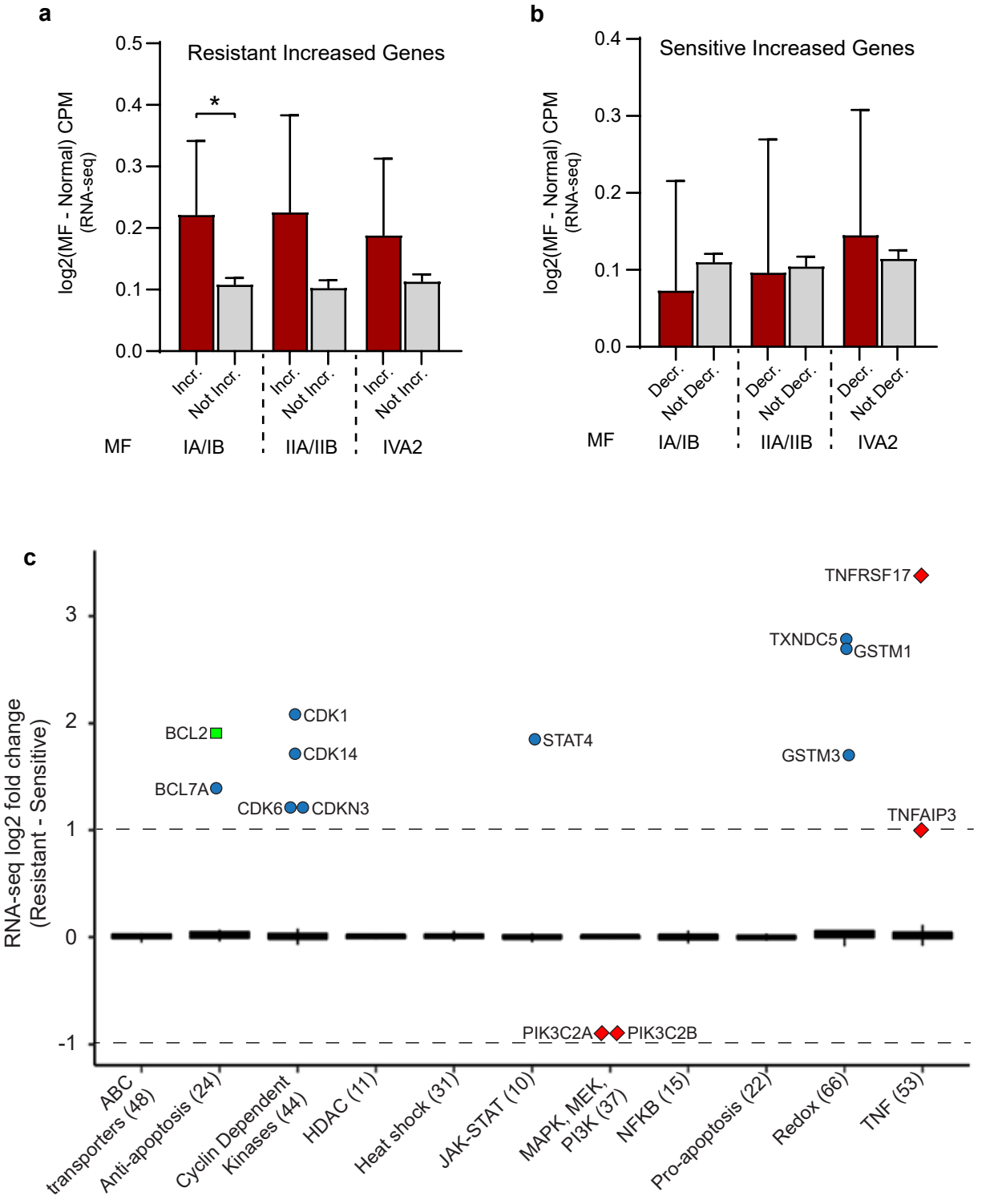
Supplementary Material

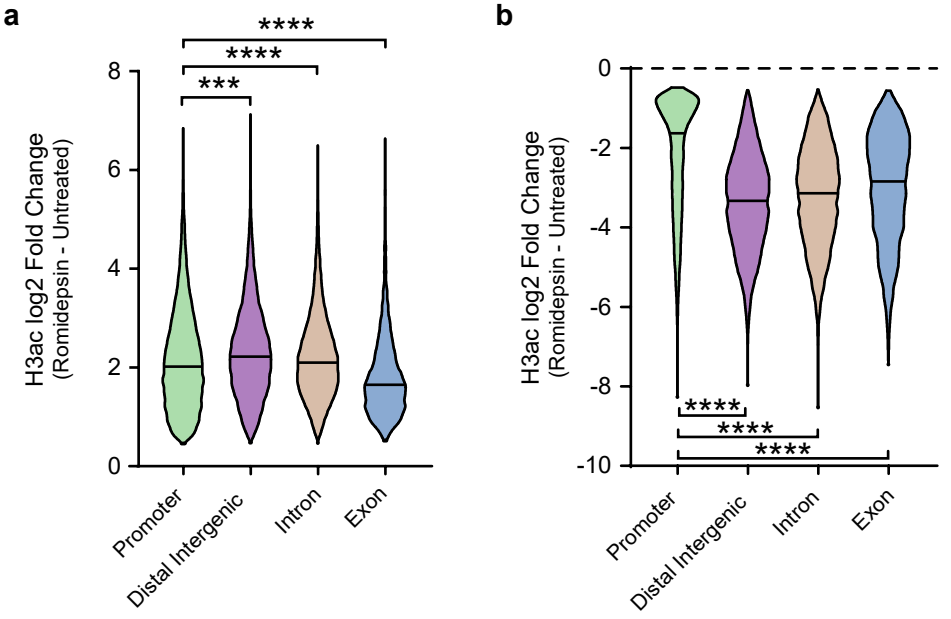
Supplemental Figure 1



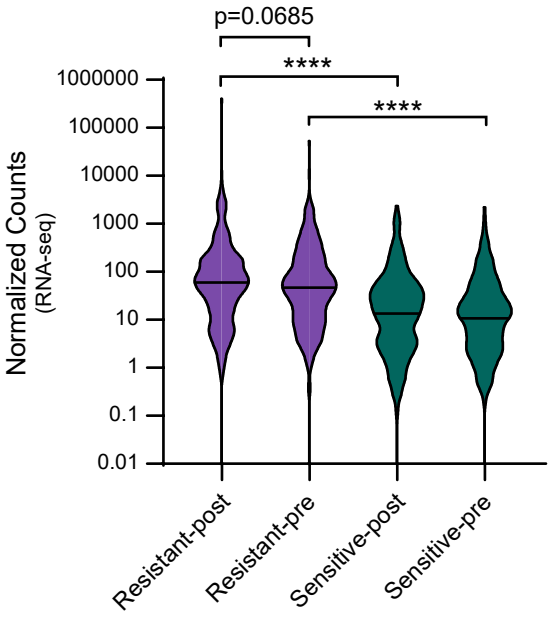
Supplemental Figure 2



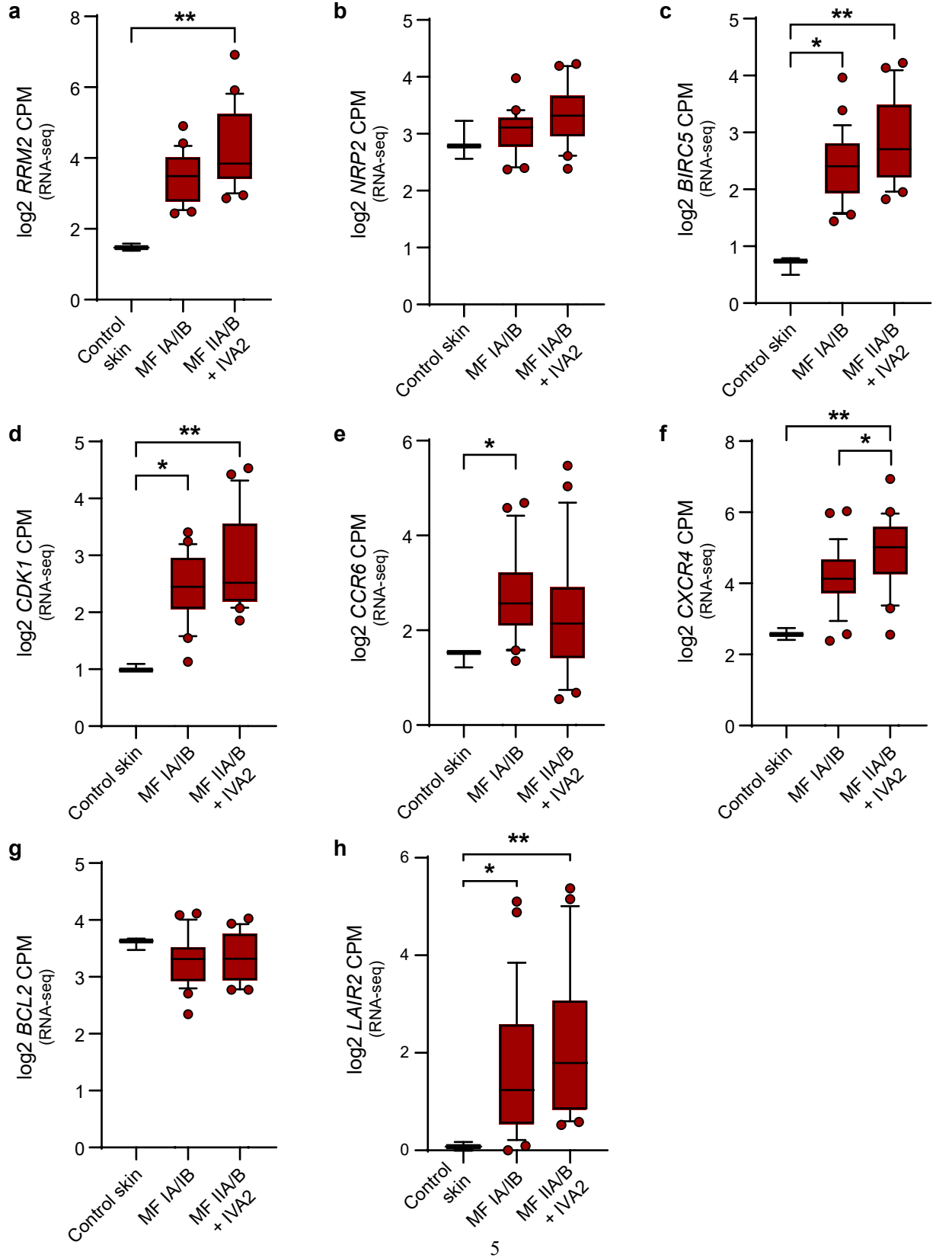
Supplemental Figure 3



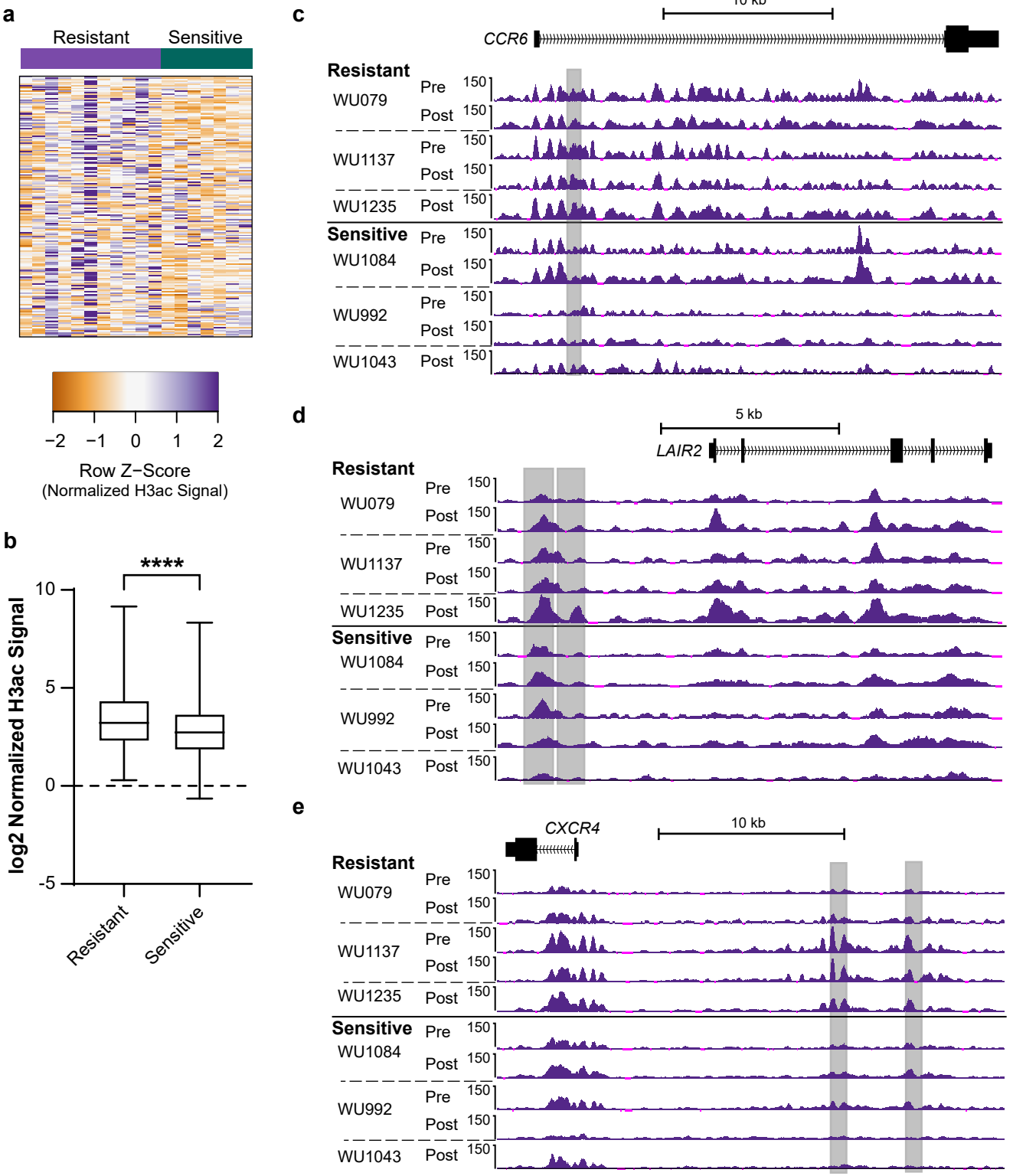
Supplemental Figure 4



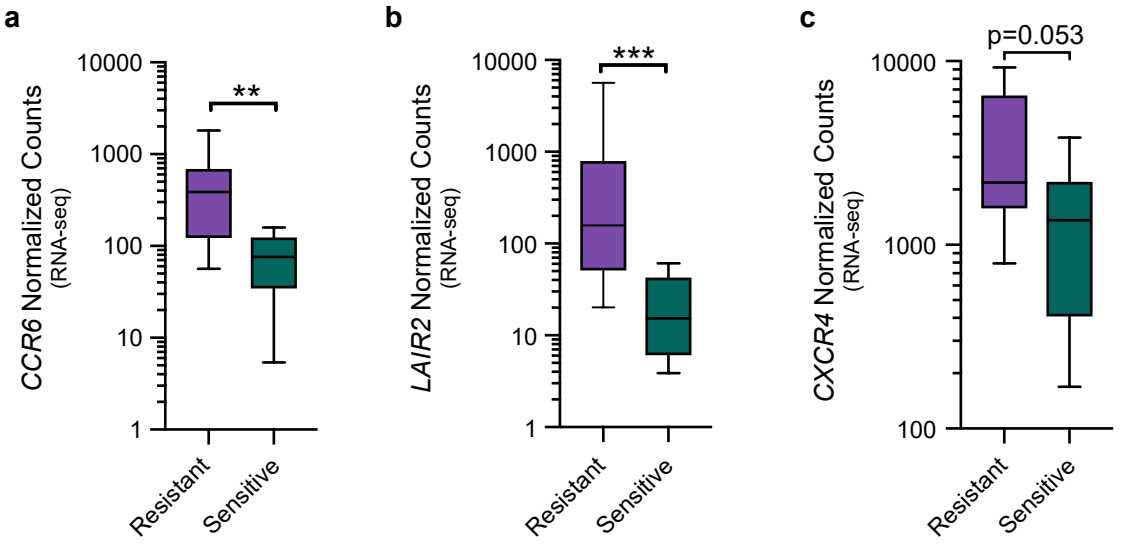
Supplemental Figure 5



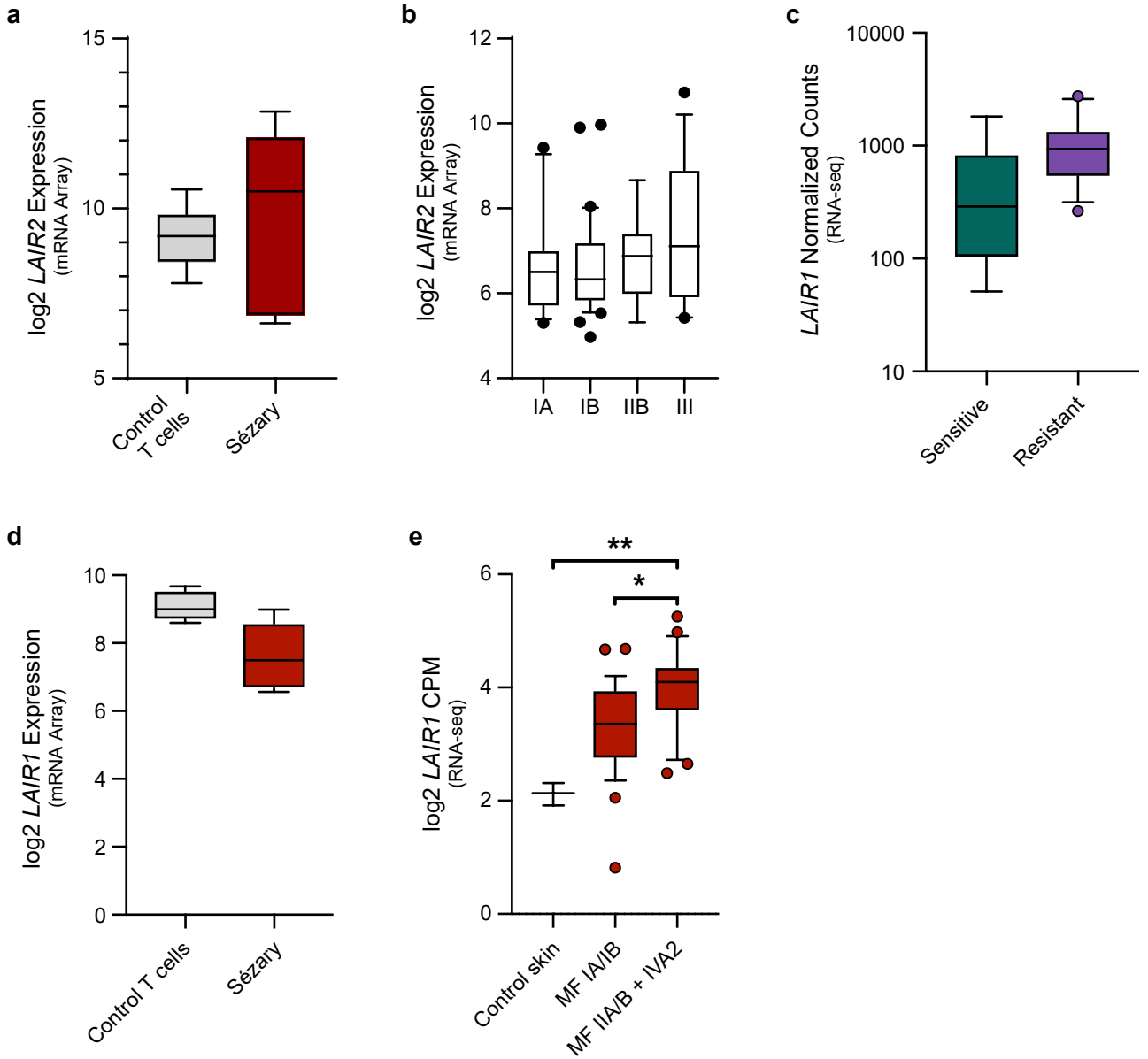
Supplemental Figure 6



Supplemental Figure 7



Supplemental Figure 8



Supplemental Figure 9

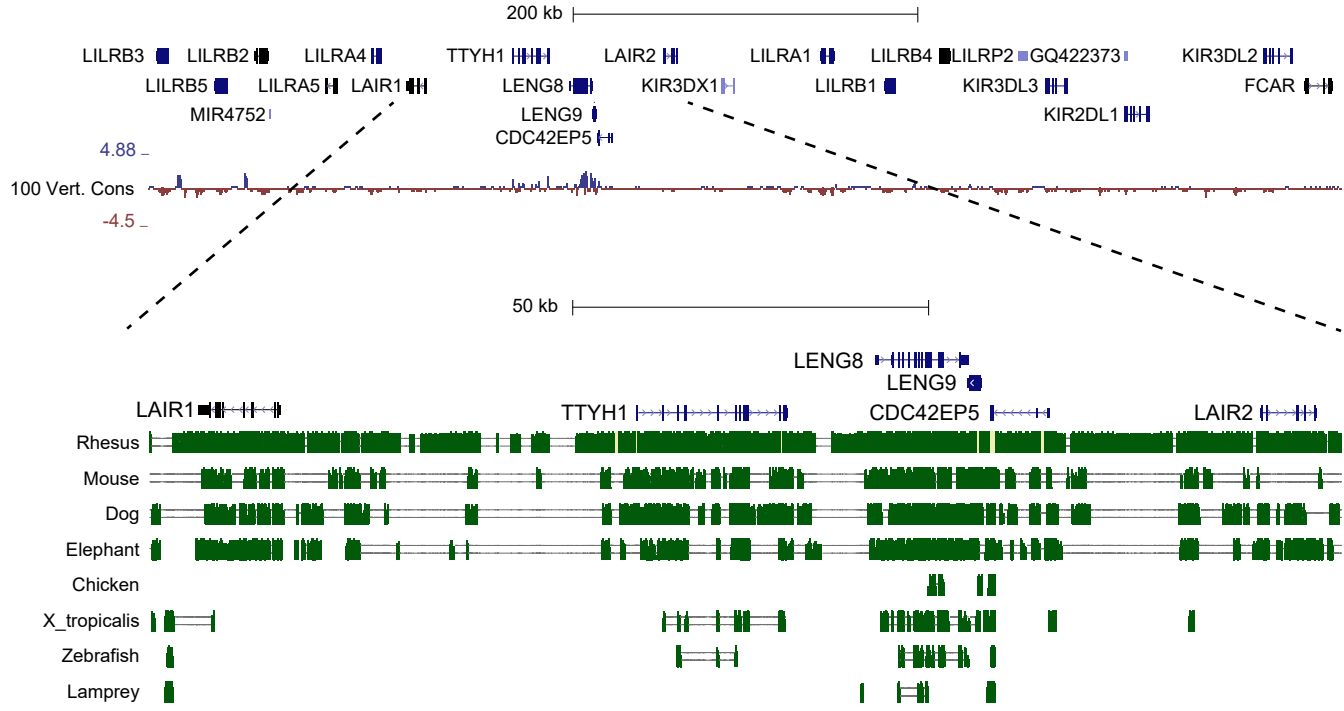


Figure S1. Epigenome-wide profiling of MF/SS identifies hyperacetylation of genes and regulatory elements in HDACi-responsive tumors compared to resistant. a) Number of differentially acetylated H3ac peaks categorized by functional genomic region. **b)** Violin plot showing differences in log2 fold changes for H3ac peaks enriched in sensitive samples categorized by functional genomic region. Exon peaks were excluded from the plot due to their low number (n=6).

Figure S2. Expression of HDACi-associated resistant vs sensitive genes is also altered in an independent MF dataset and most genes with significant expression changes in HDACi resistance pathways have not been previously reported. a) Bar plot comparing RNA-seq log2 fold changes of MF to normal T cells from Querfeld et al 2018 for genes with increased expression (Incr.) to unchanged/decreased genes (Not Incr.) in WUSM Resistant samples. Data is grouped by MF stage. (Mann-Whitney test; *, $P \leq 0{\cdot}05$; mean with 95% confidence interval shown). **b)** Bar plot as in **a**, but for genes with increased expression (Incr.) to unchanged/decreased genes (Not Incr.) in WUSM Sensitive samples. **c)** Box plot shows expression fold change (Resistant vs Sensitive, RNAseq) of genes in pathways reportedly associated with HDACi resistance (Robey et al., Mol Pharm 2011; Lee et al., Adv. Cancer Res 2012). (#) = Total number of genes in each group. Dashed lines mark log2 fold change ≥ 1 and ≤ -1. Labeled data points indicate gene with expression difference and adjusted p value $\leq 0{\cdot}05$. Blue circles - genes not previously associated with HDACi resistance; green square - previously associated with HDACi resistance; red diamond - previously reported but fold change in opposite direction.

Figure S3. Acetylation fold changes correspond to expression fold changes in HDACi-treated control T cells. a) Violin plot showing differences in log2 fold changes for H3ac peaks enriched in Romidepsin-treated samples categorized by functional genomic region (Kruskal-Wallis test; ***, $P \leq 0{\cdot}001$; ****, $P \leq 0{\cdot}0001$). **b)** Violin plot showing differences in log2 fold changes for H3ac peaks enriched in untreated samples categorized by functional genomic region (Kruskal-Wallis test; ***, $P \leq 0{\cdot}001$; ****, $P \leq 0{\cdot}0001$).

Figure S4. Expression of resistance-associated genes are increased in resistant samples both before and after HDACi treatment. mRNA expression of resistance-associated genes (n=357) in paired pre and one week post treatment samples for both Resistant (n=2) and Sensitive (n=2) patients (Mann-Whitney test; *, $P \leq 0{\cdot}05$; **, $P \leq 0{\cdot}01$; ***, $P \leq 0{\cdot}001$; ****, $P \leq 0{\cdot}0001$).

Figure S5. Expression of resistance-associated genes in external dataset. a) *RRM2*, **b)** *NRP2*, **c)** *BIRC5*, **d)** *CDK1*, **e)** *CCR6*, **f)** *CXCR4*, **g)** *BCL2*, and **h)** *LAIR2* mRNA expression in control skin and primary mycosis fungoides samples (RNAseq; Querfeld et al., 2018; Kruskal-Wallis test; *, $P \leq 0{\cdot}05$; **, $P \leq 0{\cdot}01$). Mean with 10-90th percentile shown.

Figure S6. Enhancer regions near putative HDACi resistance genes have higher acetylation in HDACi-resistant samples. a) Heatmap of H3ac peaks (n=181) associated with *LAIR2*, *CXCR4*, and *CCR6* in HDACi-Resistant and Sensitive groups. **b)** Log2 normalized H3ac signal for enhancer regions shown in (A) for HDACi-resistant and sensitive samples (Mann-Whitney test; ****, $P \leq 0{\cdot}0001$). **c)** UCSC genome browser snapshot showing the *CCR6* locus with additional representative Resistant and Sensitive samples, as in 4A. **d)** UCSC genome browser snapshot showing the *LAIR2* locus with additional representative Resistant and Sensitive samples, as in 4C. **e)** UCSC genome browser snapshot showing the *CXCR4* locus with additional representative Resistant and Sensitive samples, as in 4E. All signal tracks are normalized to reads per kilobase per million mapped reads (RPKM). Regions confirmed to have enhancer activity by luciferase reporter are highlighted.

Figure S7. Expression of resistance-associated genes with validated enhancer elements. Boxplots show expression of indicated genes (RNAseq) in Resistant and Sensitive groups (Wald test – DESeq2; **, $P \leq 0{\cdot}01$; ***, $P \leq 0{\cdot}001$). Mean with 5-95th percentile shown.

Figure S8. *LAIR1* mRNA expression is not consistently altered in MF/SS. a) *LAIR2* mRNA expression in control T cells (n=9) and primary Sèzary samples (n=6) (mRNA microarray; Wang et al., 2011). **b)** *LAIR2* mRNA expression in primary stage IA (n=13), IB (n=30), IIB (n=8), and III (n=12) MF samples (mRNA microarray; Shin et al., 2007). **c)** *LAIR1* mRNA expression in CD4+ T cells purified from Sensitive and Resistant MF/SS samples (WUSM, RNAseq). **d)** *LAIR1* mRNA expression in control T cells and primary SS samples (microarray; Mann-Whitney test; Wang et al., 2011). **e)** *LAIR1* mRNA expression in control skin (n=3) and primary MF biopsies (IA/IB n=28; IIA/B + IVA2 n=21) (RNAseq; Querfeld et al., 2018; Kruskall-Wallis test; **, $P \leq 0{\cdot}01$; ***, $P \leq 0{\cdot}001$). Mean with 10-90th percentile shown.

Figure S9. *LAIR2* lies within a cluster of polymorphic leukocyte receptor genes. Genome browser diagram of the locus with genes and vertebrate conservation tracks. *LAIR1* and *LAIR2* lie within the leukocyte receptor complex (LRC), a gene cluster on chromosome 19q13·4 that is rich in leukocyte immunoglobulin-like receptor (LIR) and Killer cell immunoglobulin-like receptors (KIRs).