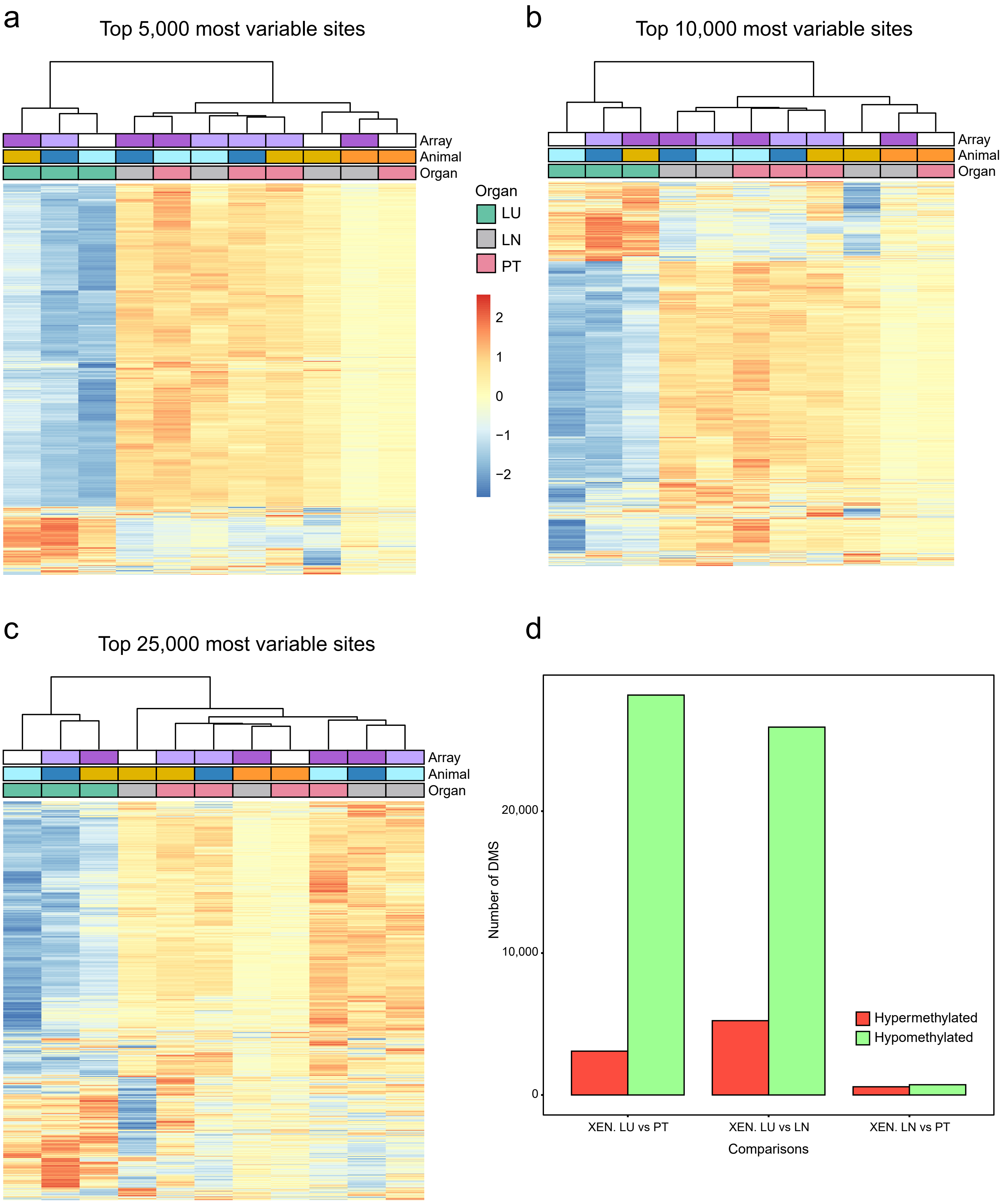
Supplementary Figure 1



a Top 5,000 most variable sites

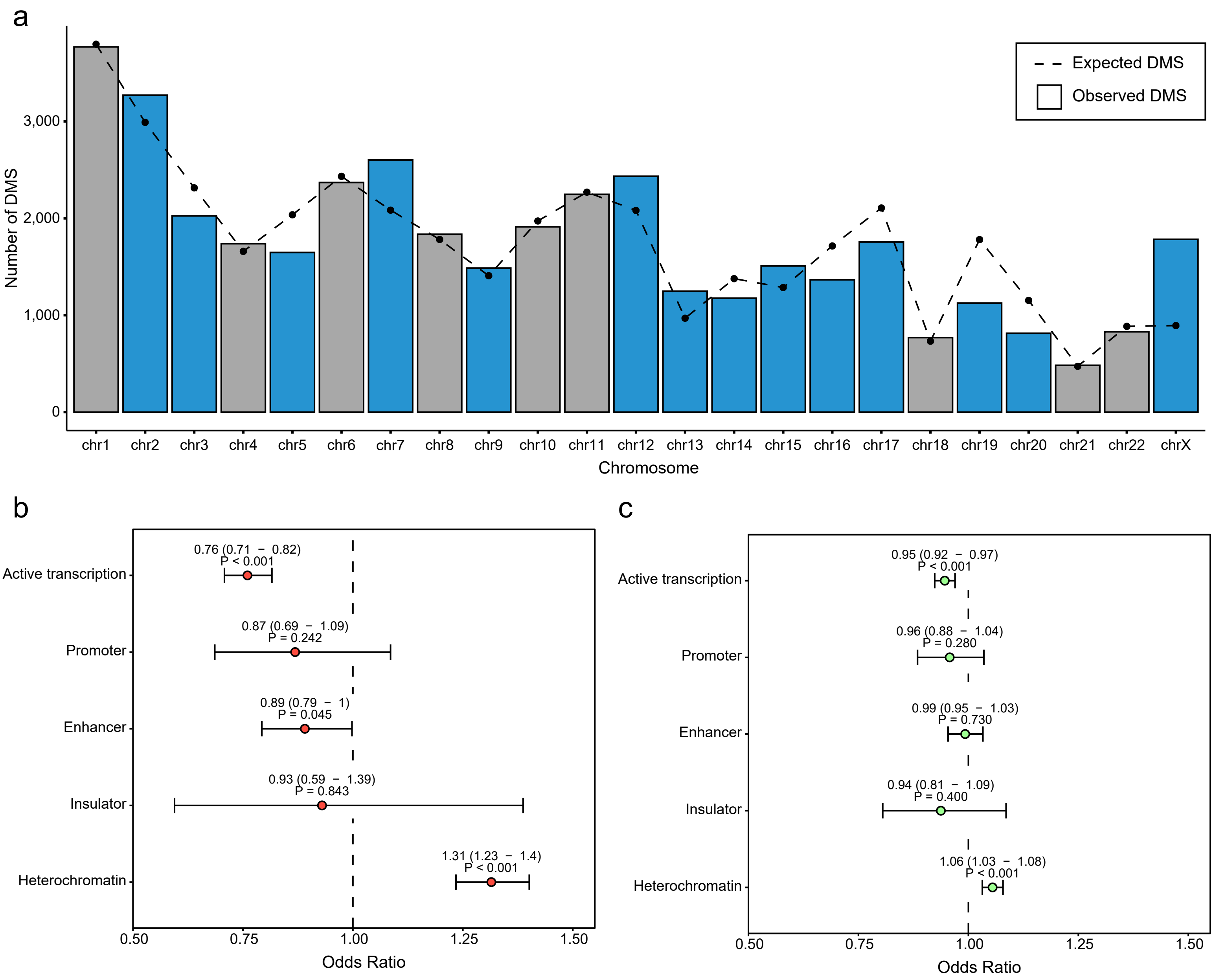
b Top 10,000 most variable sites

c Top 25,000 most variable sites

d

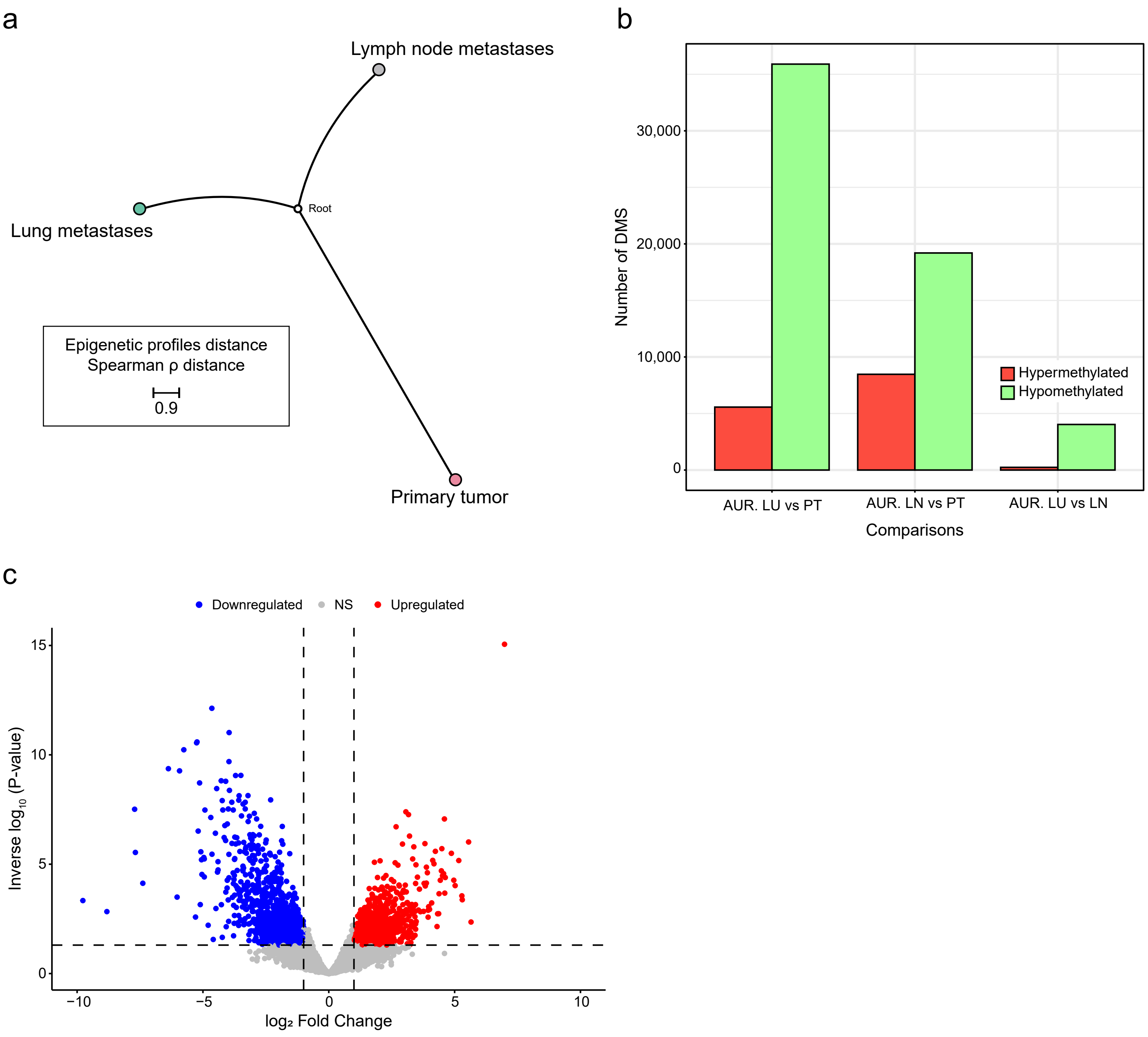
Supplementary Figure 1. The epigenomic landscape of TNBC lung metastases, lymph node metastases, and primary tumors in the XEN model. a) Heatmap of the 5,000, **b)** 10,000, **c)** and 25,000 most variable sites. **d)** Barplot displaying the number of DMS between XEN comparisons (LU vs. PT; LU vs. LN; LN vs PT). Hypomethylated events are in green, and hypermethylated in red.

Supplementary Figure 2



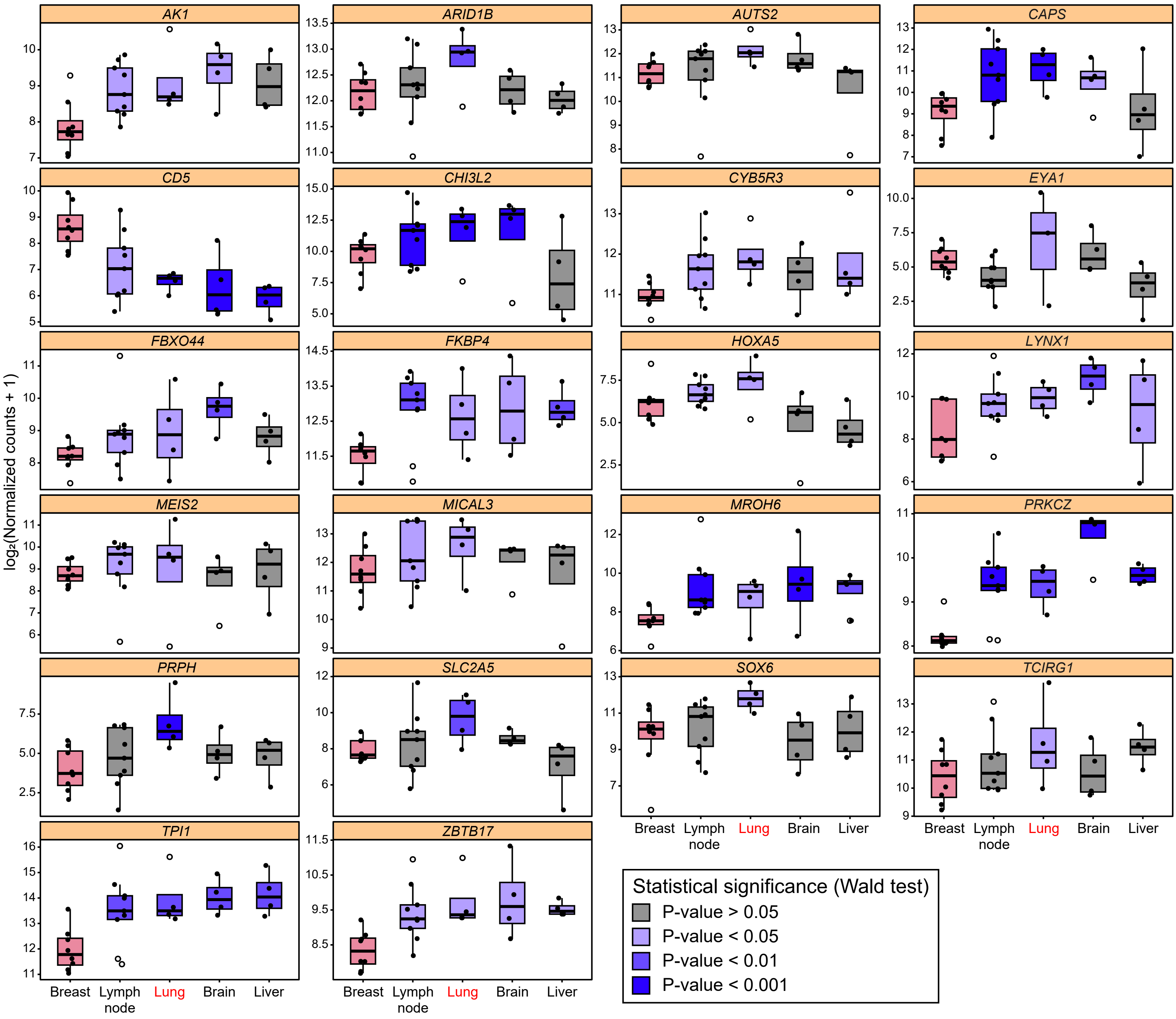
Supplementary Figure 2: Chromatin states and DNA methylation overlap between TNBC lung metastases and lymph node and primary tumors. a) Number of DMS per-chromosome expected and observed in TNBC lung metastases compared to lymph node and primary tumors. Gray bars indicate non-significant differences, while blue bars represent those chromosomes with significant enrichment or depletion (P-adjusted < 0.05). **b)** Forest plot displaying the odds ratio with 95% confidence intervals for hypermethylated and **c)** hypomethylated DMS across different chromatin states.

Supplementary Figure 3



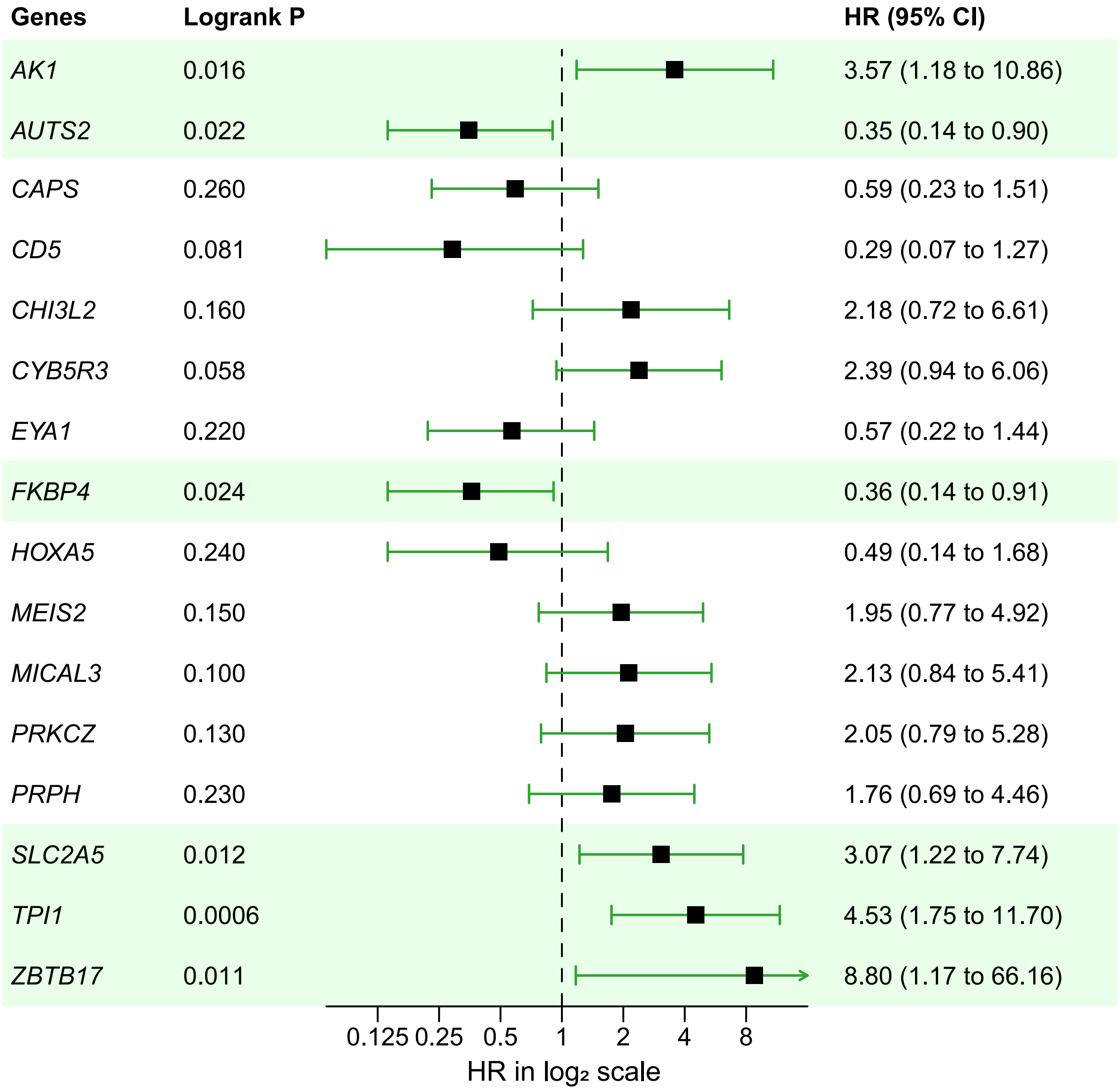
Supplementary Figure 3. DNA methylation and gene expression differences between TNBC lung and lymph node metastases and primary tumors from the AURORA US cohort. a) A phylogenetic tree representing DNAm-based Spearman ρ distance between TNBC tumors from different sites. **b)** Barplot displaying the number of DMS between AUR comparisons. Hypomethylated events are shown in green, and hypermethylated events are shown in red. **c)** Volcano plot represents the $\log_2$ fold change of gene expression (x-axis) and the inverse $\log_{10}$ P-value (y-axis) comparison between lung metastases and primary tumors from the AUR cohort. 1,146 genes were downregulated (blue) and 1,220 were upregulated (red).

Supplementary Figure 4



Supplementary Figure 4: Boxplots showing expression patterns of epigenetically regulated genes in TNBC metastases across different tissue sites from the AURORA US cohort. Statistical significance was determined with the DESeq2 Wald test, with gradient purple shades indicating $P < 0.05$, $P < 0.01$, and $P < 0.001$.

Supplementary Figure 5



Genes	**Logrank P**	**HR (95% CI)**
AK1	0.016	3.57 (1.18 to 10.86)
AUTS2	0.022	0.35 (0.14 to 0.90)
CAPS	0.260	0.59 (0.23 to 1.51)
CD5	0.081	0.29 (0.07 to 1.27)
CHI3L2	0.160	2.18 (0.72 to 6.61)
CYB5R3	0.058	2.39 (0.94 to 6.06)
EYA1	0.220	0.57 (0.22 to 1.44)
FKBP4	0.024	0.36 (0.14 to 0.91)
HOXA5	0.240	0.49 (0.14 to 1.68)
MEIS2	0.150	1.95 (0.77 to 4.92)
MICAL3	0.100	2.13 (0.84 to 5.41)
PRKCZ	0.130	2.05 (0.79 to 5.28)
PRPH	0.230	1.76 (0.69 to 4.46)
SLC2A5	0.012	3.07 (1.22 to 7.74)
TPI1	0.0006	4.53 (1.75 to 11.70)
ZBTB17	0.011	8.80 (1.17 to 66.16)

Supplementary Figure 5. Prognostic impact of epigenetically regulated genes identified from the comparison between lung metastases and primary TNBC tumors. Forest plot showing the association between gene expression and LMFS in TNBC primary tumors. It includes HR and 95% CI estimated from the associated unadjusted Cox proportional hazards model and the log-rank test P-value. Genes highlighted in green indicate statistically significant associations.