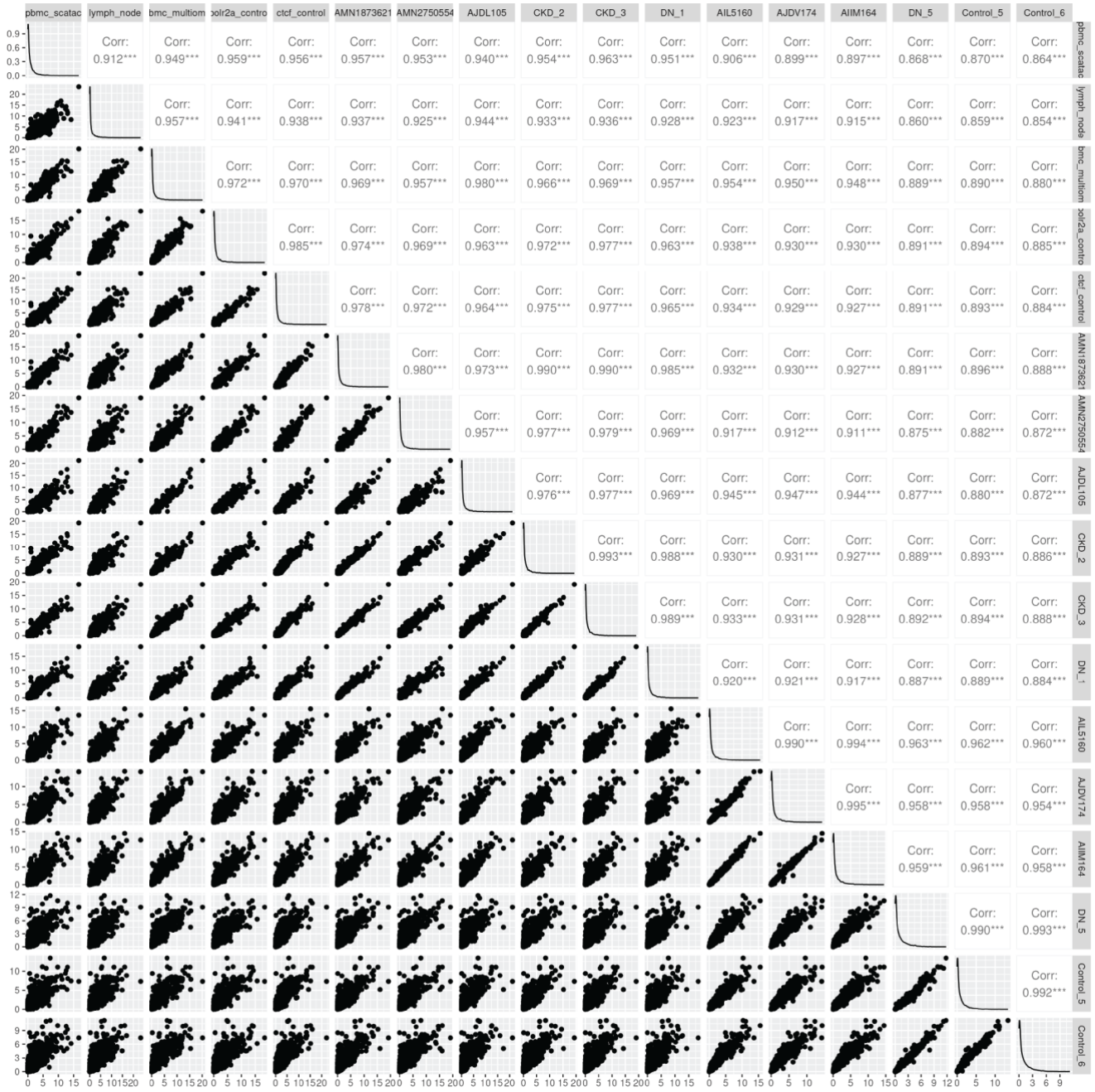
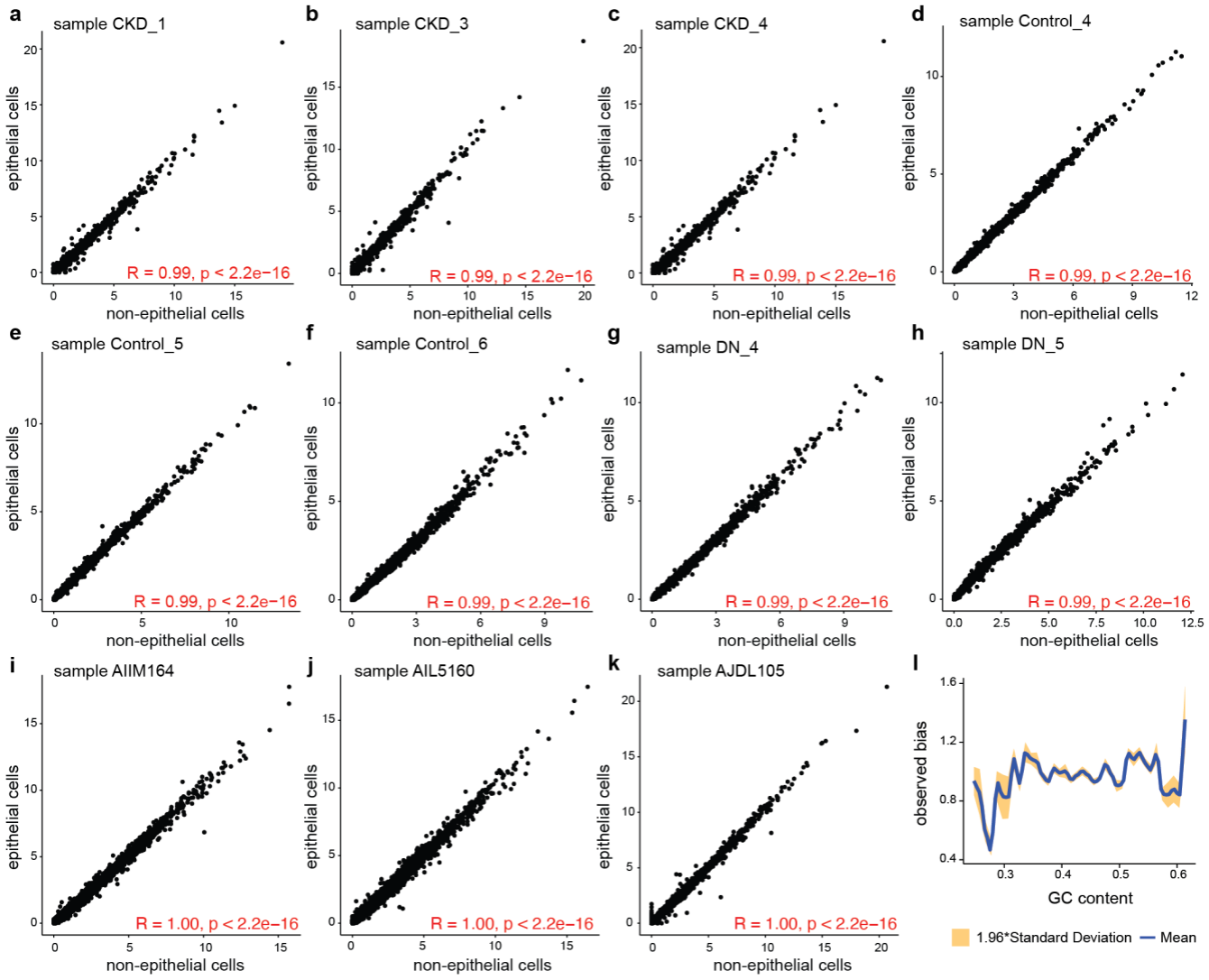
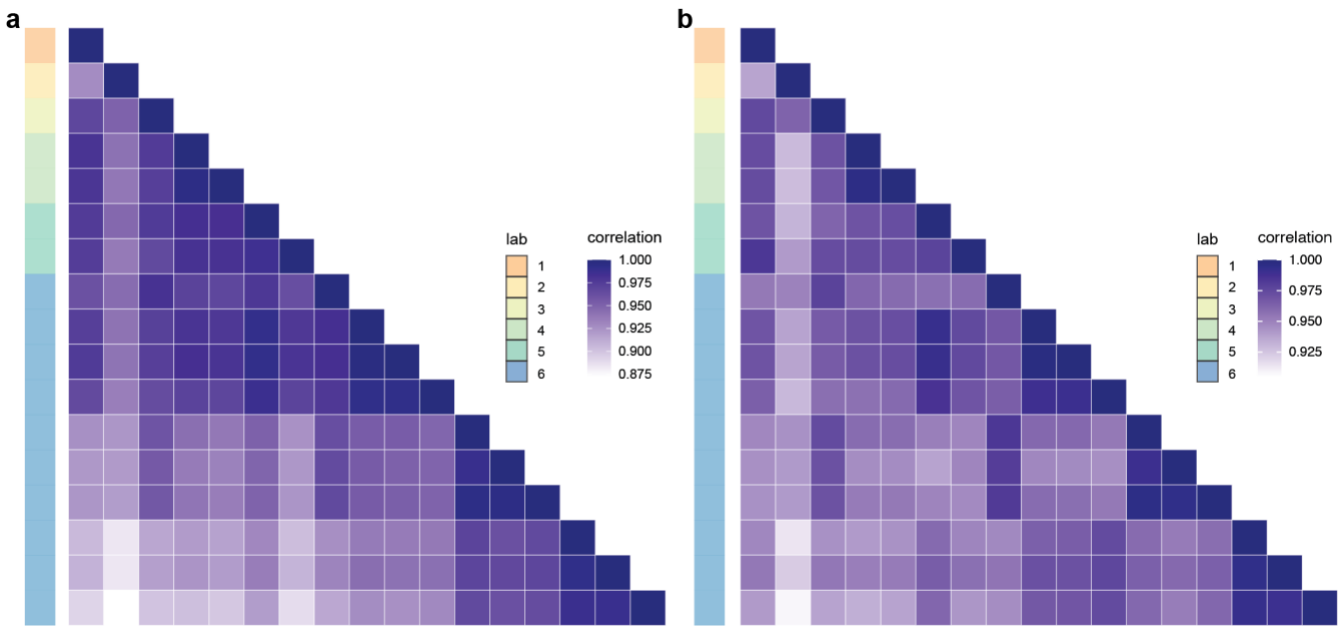


Supplementary Figure 1:
Scatter plots of observed Tn5 bias in mitochondria regions.



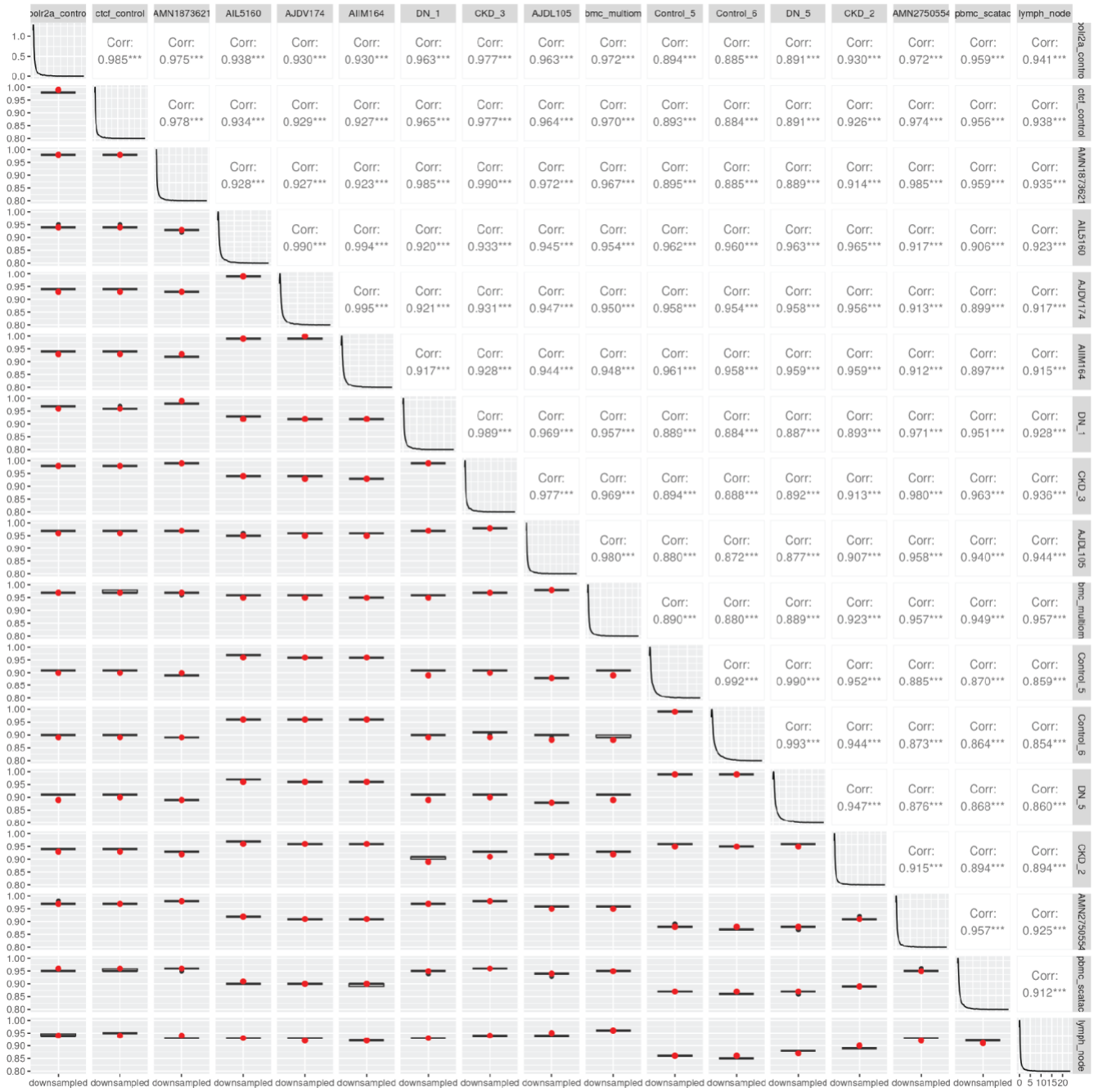
Supplementary Figure 2:

a-k: Scatter plots of observed Tn5 bias across different cell types within the same sample. n = 16000, pvalues and correlations from Pearson correlation tests. **l**, relationship between GC content and observed bias.



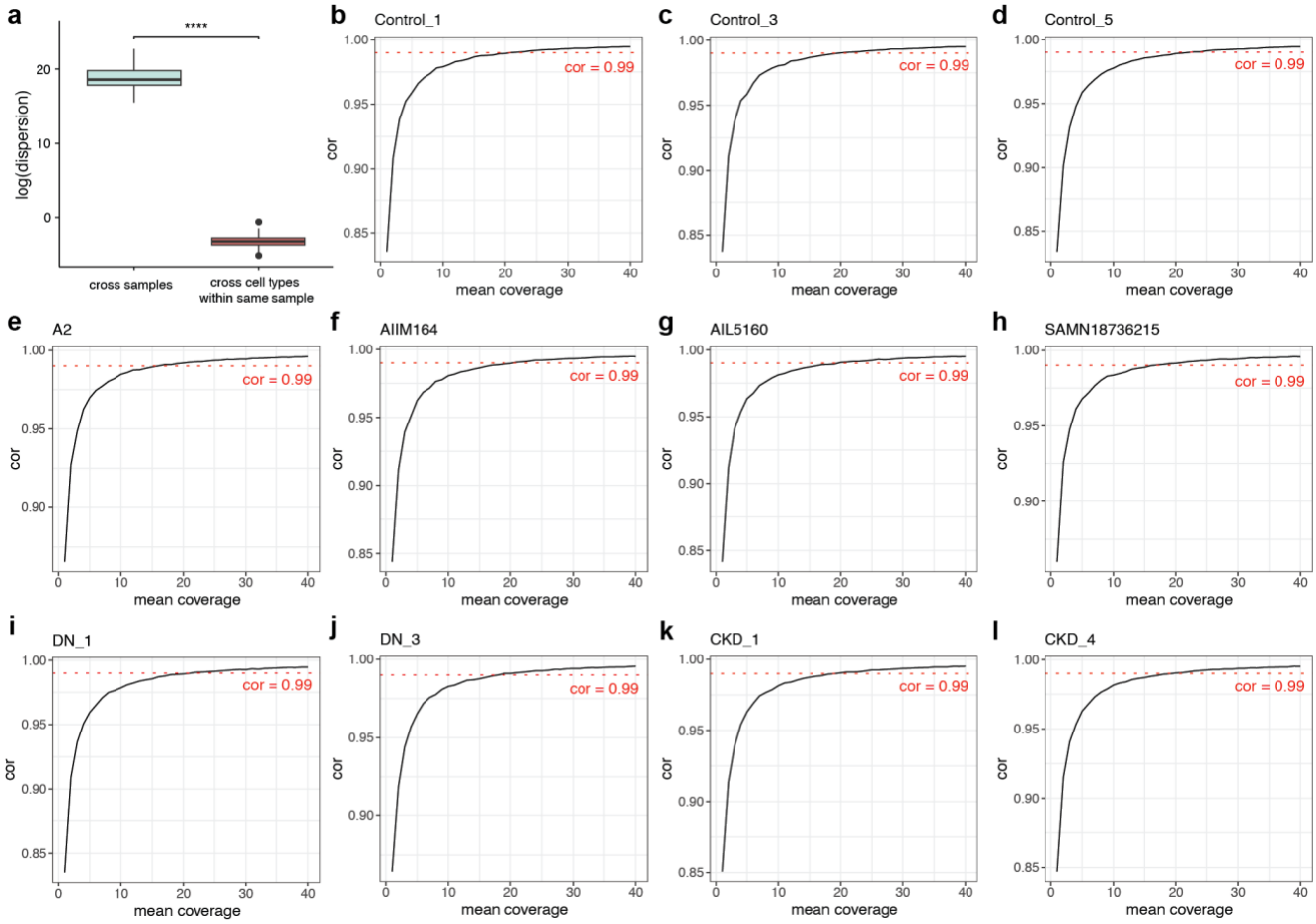
Supplementary Figure 3:

Correlations of observed Tn5 insertions (left) and kmer bias (k = 5) (right) in mitochondrial DNA regions between samples reveal sample-to-sample variations; the same color in the color bar indicates the samples are from the same lab.



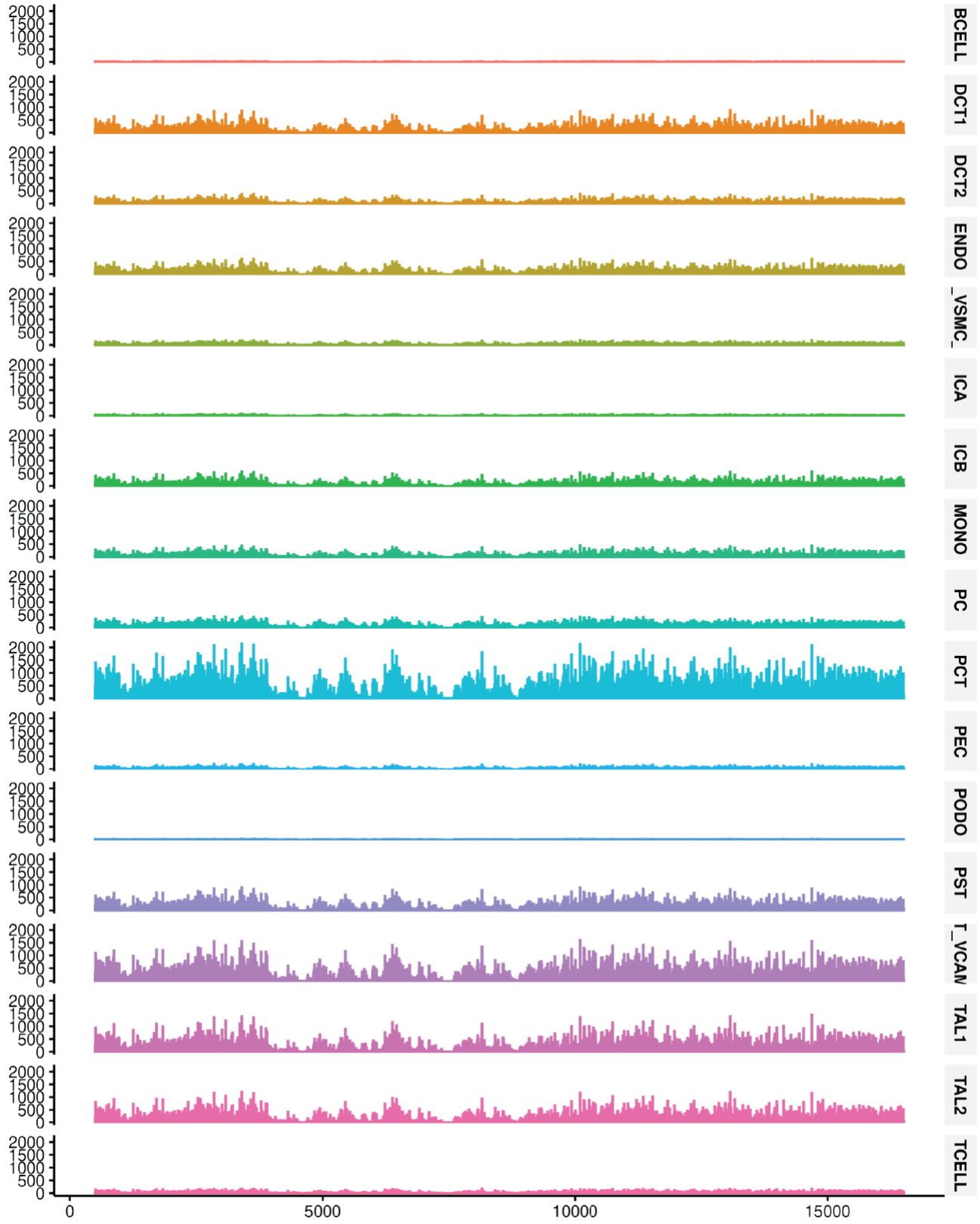
Supplementary Figure 4:

Boxplot shows the distribution of 50 correlation values of observed Tn5 bias after coverage equalization via binomial downsampling. Red dot represents the correlation between samples without downsampling.

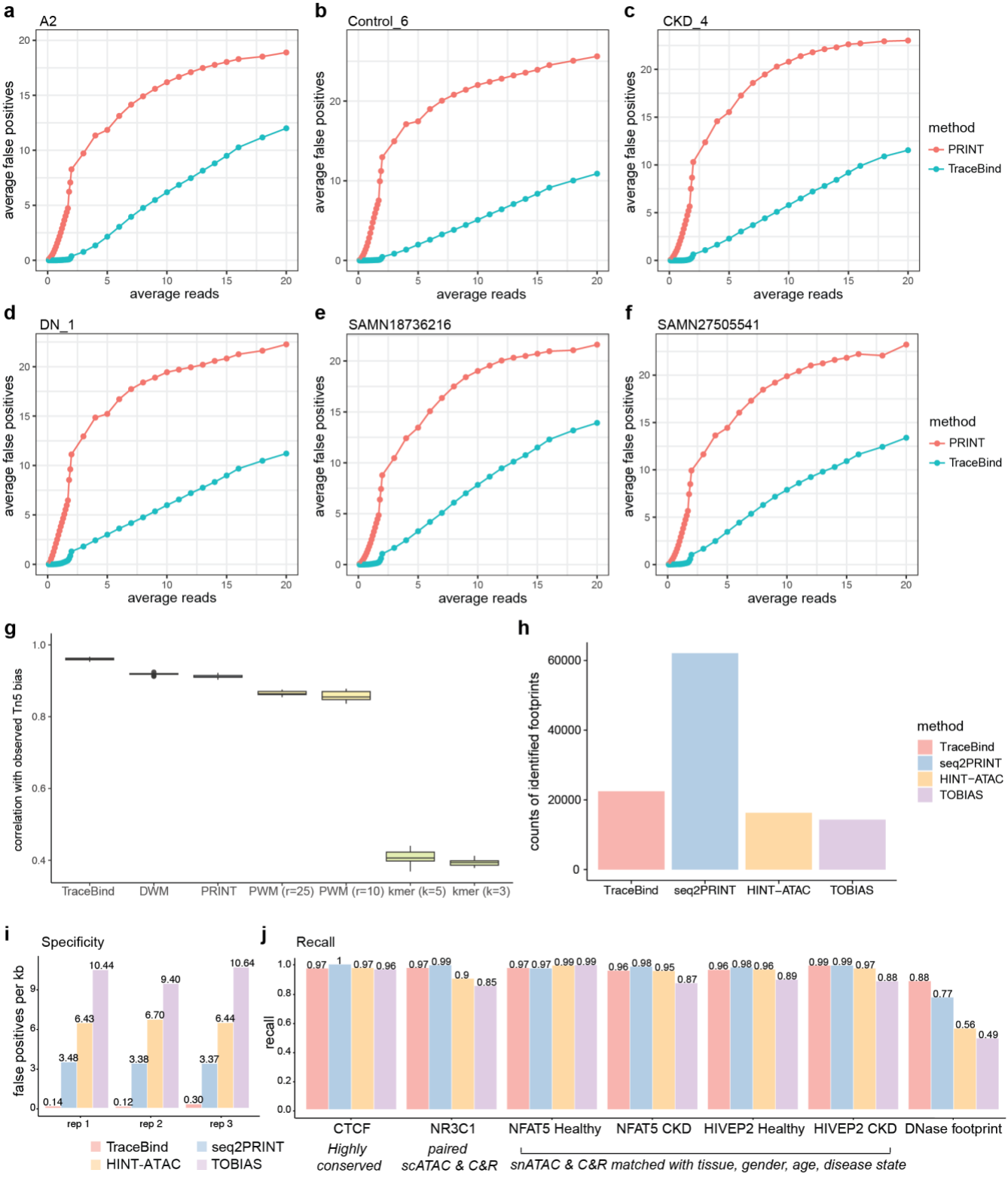


Supplementary Figure 5:

a: Estimated dispersion in negative binomial model for Tn5 insertions per base in mitochondria DNA region, using observed Tn5 bias for another sample (cross samples), and sample-level observed Tn5 bias for different cell types within the sample (within samples) ($n_{cross\_samples} = 561$, $n_{within\_samples} = 734$). Centre lines, median; boxes, interquartile range (IQR); whiskers, 5th and 95th percentiles (of estimated dispersions). **b-l:** Power analysis showing the correlation between downsampled mitochondrial reads and raw reads across different mean coverage levels in the downsampled samples.


2000
1500
1000
500
0
BCELL
DCT1
DCT2
ENDO
VSMC
ICA
ICB
MONO
PC
PCT
PEC
PODO
PST
T_VCAM
TAL1
TAL2
TCELL
0
5000
10000
15000

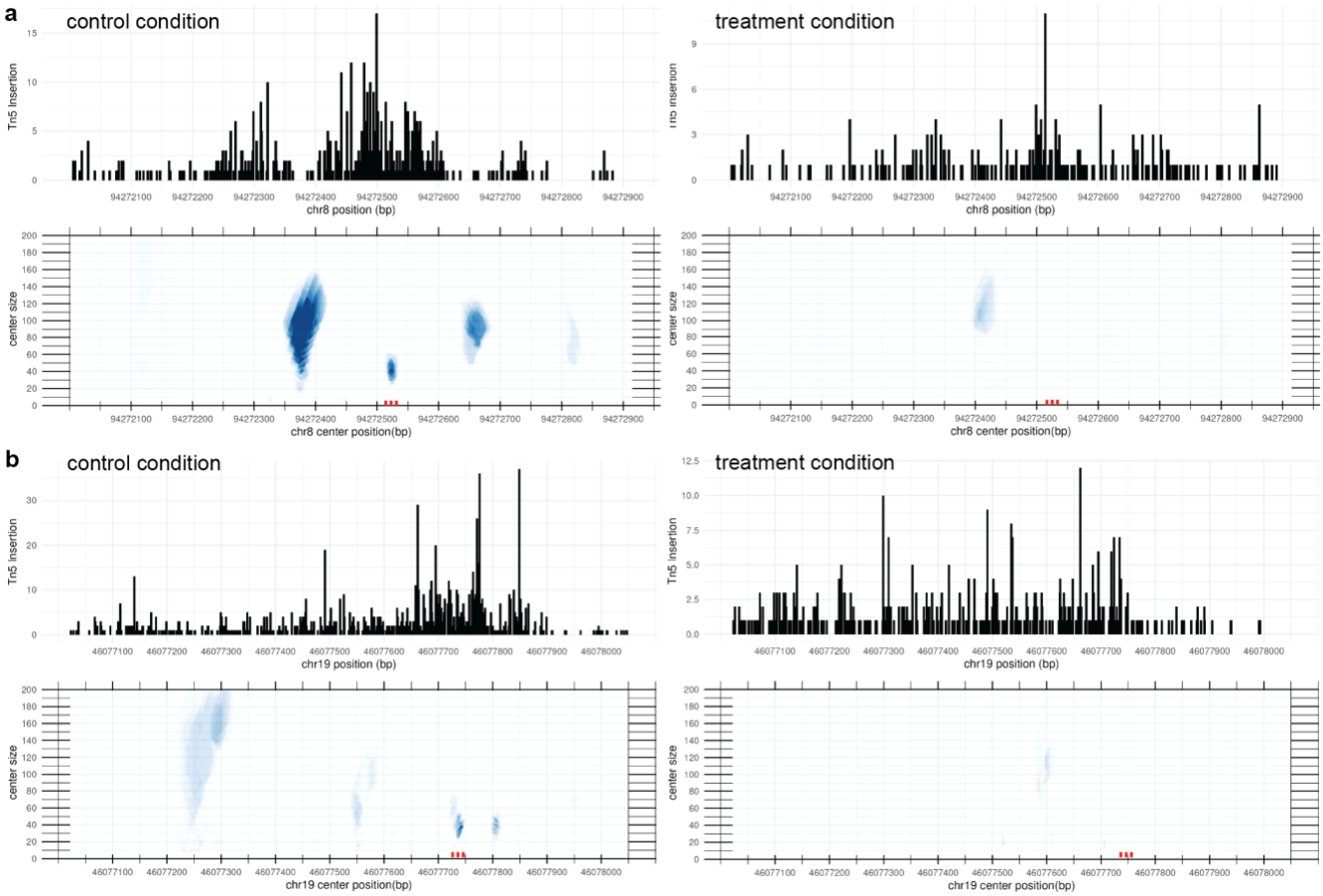
Supplementary Figure 6:
For the sample with the highest number of cells, raw Tn5 insertion counts per base pair were measured across cell types in mitochondrial regions, showing that the coverage is relatively low for some cell types.



Supplementary Figure 7:

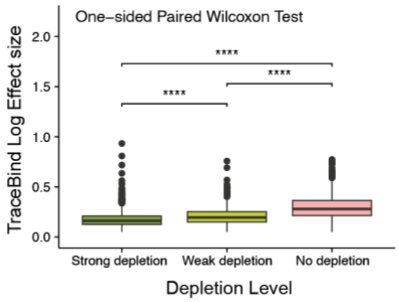
a-f: The comparison of average number of false positives in mitochondria test region using different Tn5 bias. **g,** The correlation of predicted and observed Tn5 bias for each method ($n_{sample} = 41$). **h,** The

counts of identified footprints by different methods with DNase footprints as ground truth. **i,** The false positive rates of different methods. **j**, The recalled by different methods with ChIP/CUT&RUN (C&R) as ground truth.

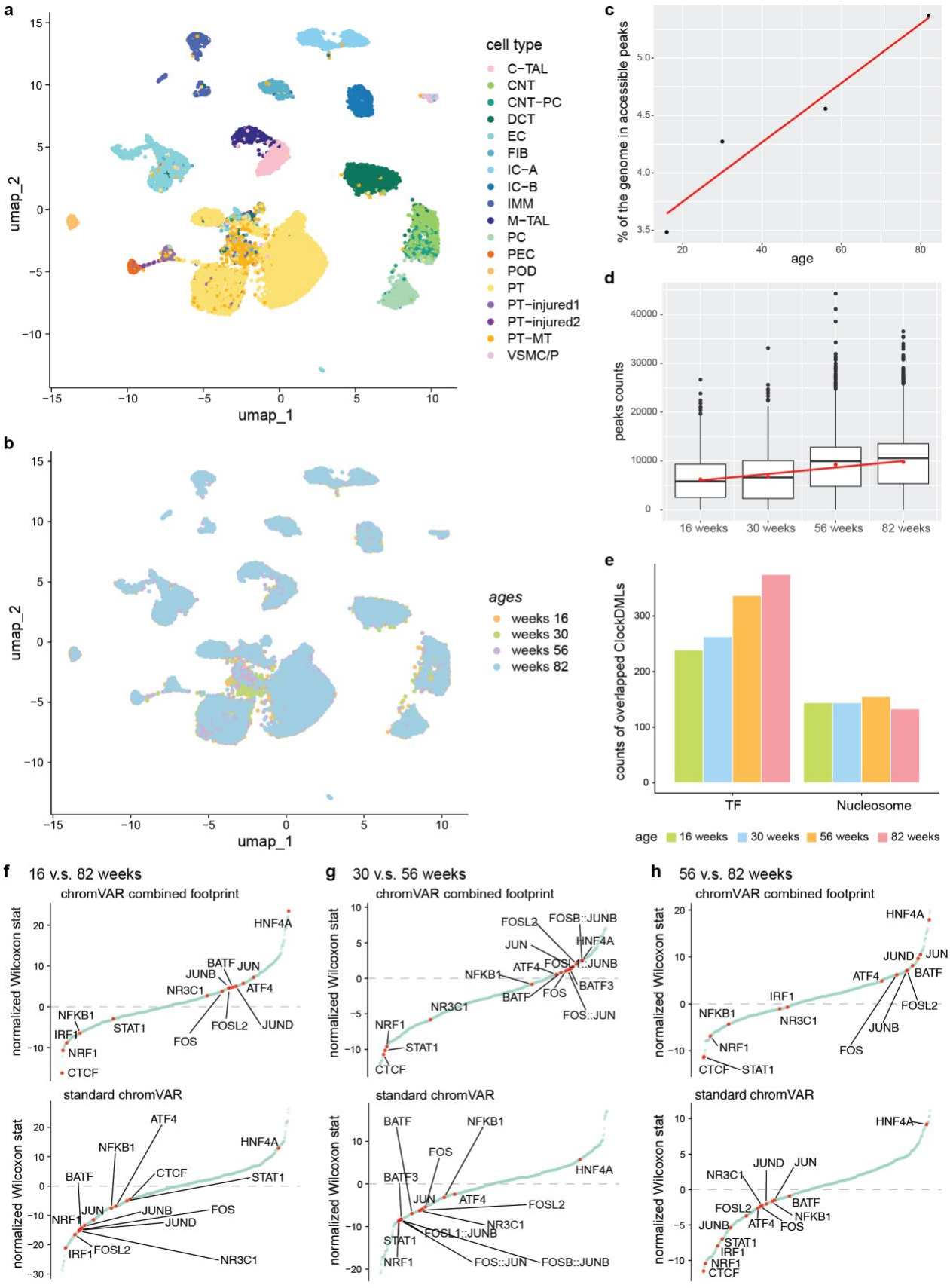


Supplementary Figure 8:

Example regions showing predicted footprints at CTCF motif sites bound in the control but not in the treatment condition. Red dotted lines indicate CTCF motif positions. P values are derived from TraceBind multiscale test.



Supplementary Figure 9:
Log effect sizes of predicted overlapped nucleosomes across different depletion levels of nucleosomes nucleosomes (n = 2,185 footprints, defined as regions with width ≥ 120 base pairs). **** indicates statistical significance from two-sided Wilcoxon Rank Sum test after multiple test adjustments (p value ≤ 2.22×10^{-16}) comparing enrichment changes in different groups.


a
umap_2
umap_1
cell type
C−TAL
CNT
CNT−PC
DCT
EC
FIB
IC−A
IC−B
IMM
M−TAL
PC
PEC
POD
PT
PT−injured1
PT−injured2
PT−MT
VSMC/P
b
umap_2
umap_1
ages
weeks 16
weeks 30
weeks 56
weeks 82
c
% of the genome in accessible peaks
age
d
peaks counts
16 weeks
30 weeks
56 weeks
82 weeks
e
counts of overlapped ClockDMLs
TF
Nucleosome
age
16 weeks
30 weeks
56 weeks
82 weeks
f
16 v.s. 82 weeks
chromVAR combined footprint
normalized Wilcoxon stat
HNF4A
BATF
JUN
JUNB
NR3C1
ATF4
NFKB1
STAT1
IRF1
FOSL2
JUND
FOS
NRF1
CTCF
standard chromVAR
normalized Wilcoxon stat
ATF4
NFKB1
HNF4A
BATF
CTCF
STAT1
JUN
JUNB
FOS
NRF1
JUND
IRF1
FOSL2
NR3C1
g
30 v.s. 56 weeks
chromVAR combined footprint
normalized Wilcoxon stat
FOSL2
FOSB::JUNB
JUN
HNF4A
ATF4
FOSL1::JUNB
NFKB1
BATF3
BATF
FOS
NR3C1
FOS::JUN
NRF1
STAT1
CTCF
standard chromVAR
normalized Wilcoxon stat
BATF
NFKB1
FOS
BATF3
HNF4A
JUN
ATF4
FOSL2
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STAT1
NRF1
FOS::JUN
FOSB::JUNB
h
56 v.s. 82 weeks
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normalized Wilcoxon stat
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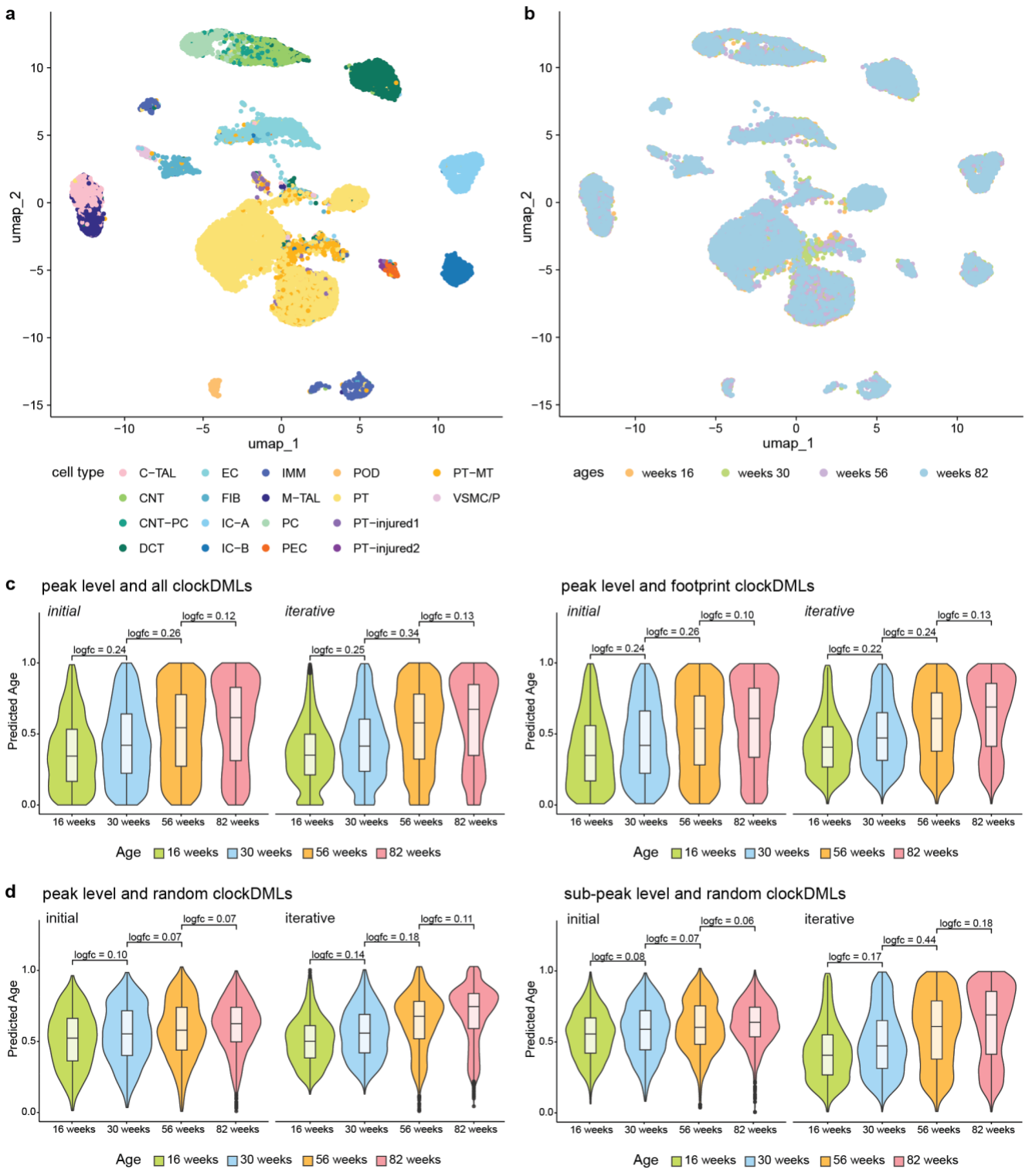
JUND
JUN
ATF4
BATF
IRF1
FOSL2
NFKB1
NR3C1
JUNB
NRF1
FOS
CTCF
STAT1
standard chromVAR
normalized Wilcoxon stat
HNF4A
JUND
JUN
NR3C1
BATF
FOSL2
NFKB1
JUNB
ATF4
FOS
STAT1
IRF1
NRF1
CTCF

Supplementary Figure 10:

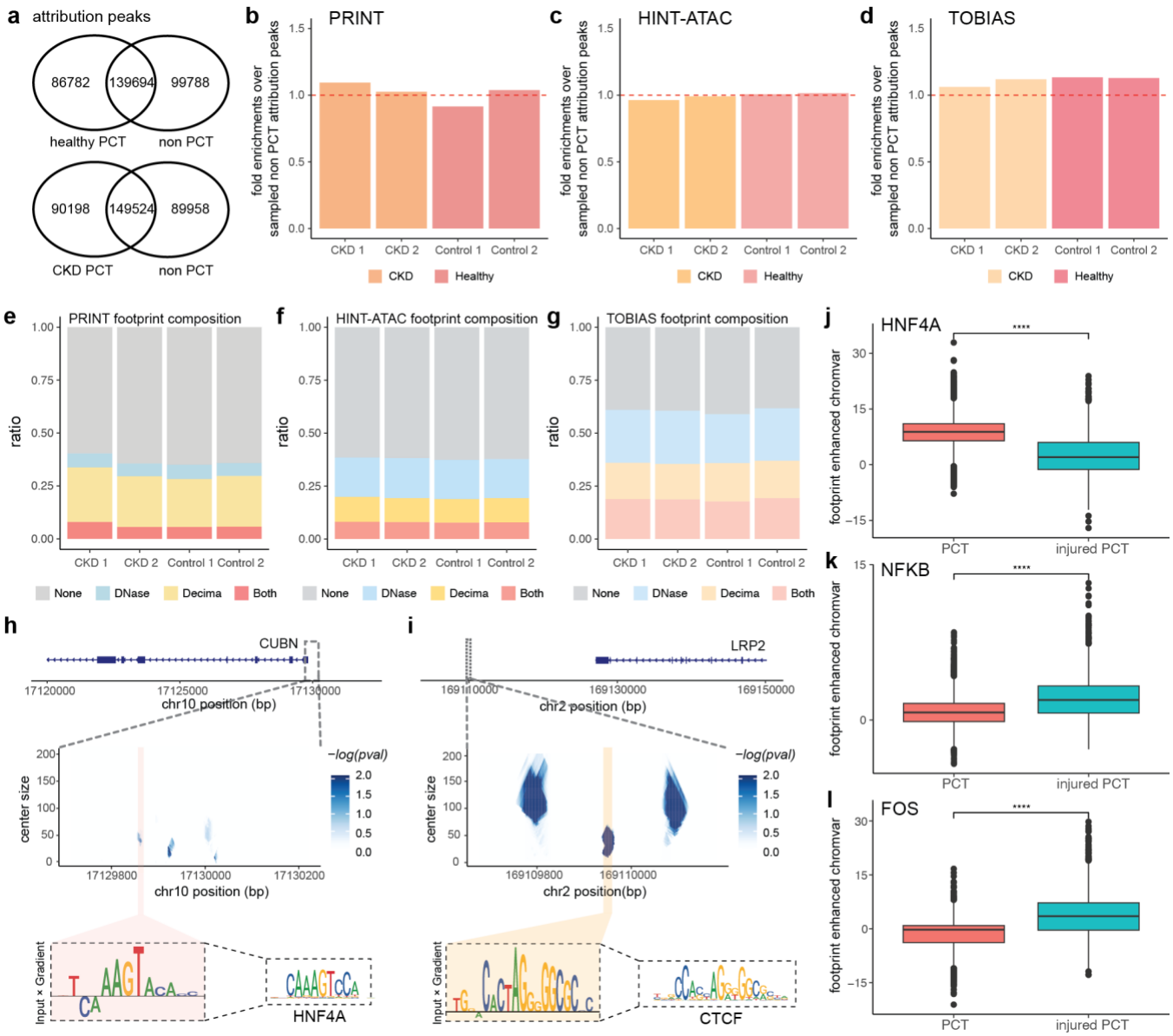
a, b: visualizations of scATAC data based on peak level colored by cell types and samples (after integration) (n = 1,225 cells at 16 weeks; n = 1,516 cells at 32 weeks; n = 2,506 cells at 56 weeks; n = 2,747 cells at 82 weeks). **c, d**, percentage of genome covered by accessible regions (peaks) and the number of peaks per cell across different age groups (n = 1,225 cells at 16 weeks; n = 1,516 cells at 32 weeks; n = 2,506 cells at 56 weeks; n = 2,747 cells at 82 weeks). **e**, Numbers of footprints overlapping with age-associated hypomethylation sites. **f**, Comparison of transcription factor (TF) activity scores across different age groups using standard chromVAR and footprint-informed chromVAR. Positive normalized Wilcoxon statistics means higher activities in older groups.



Supplementary Figure 11:

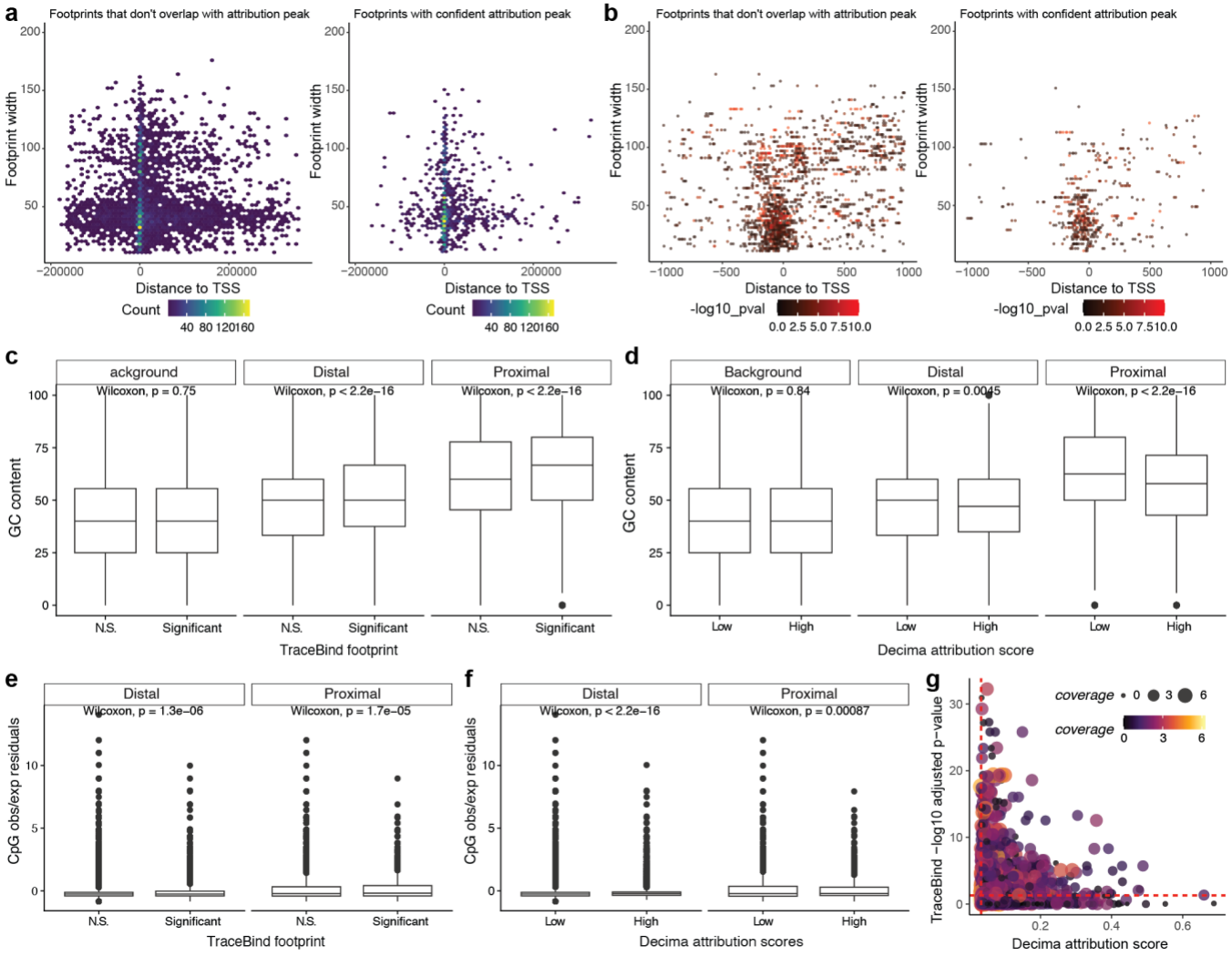
a, b: visualizations of scATAC data based on sub-peak level split by TraceBind footprints, colored by cell types and samples (after integration) level (n = 1,225 cells at 16 weeks; n = 1,516 cells at 32 weeks; n = 2,506 cells at 56 weeks; n = 2,747 cells at 82 weeks). Centre lines, median; boxes, interquartile

range (IQR); whiskers, 5th and 95th percentiles (of predicted cells ages). **c, d**: Epitrace results using different sets of age-associated differentially methylated loci (ClockDMLs) and peak resolution levels.



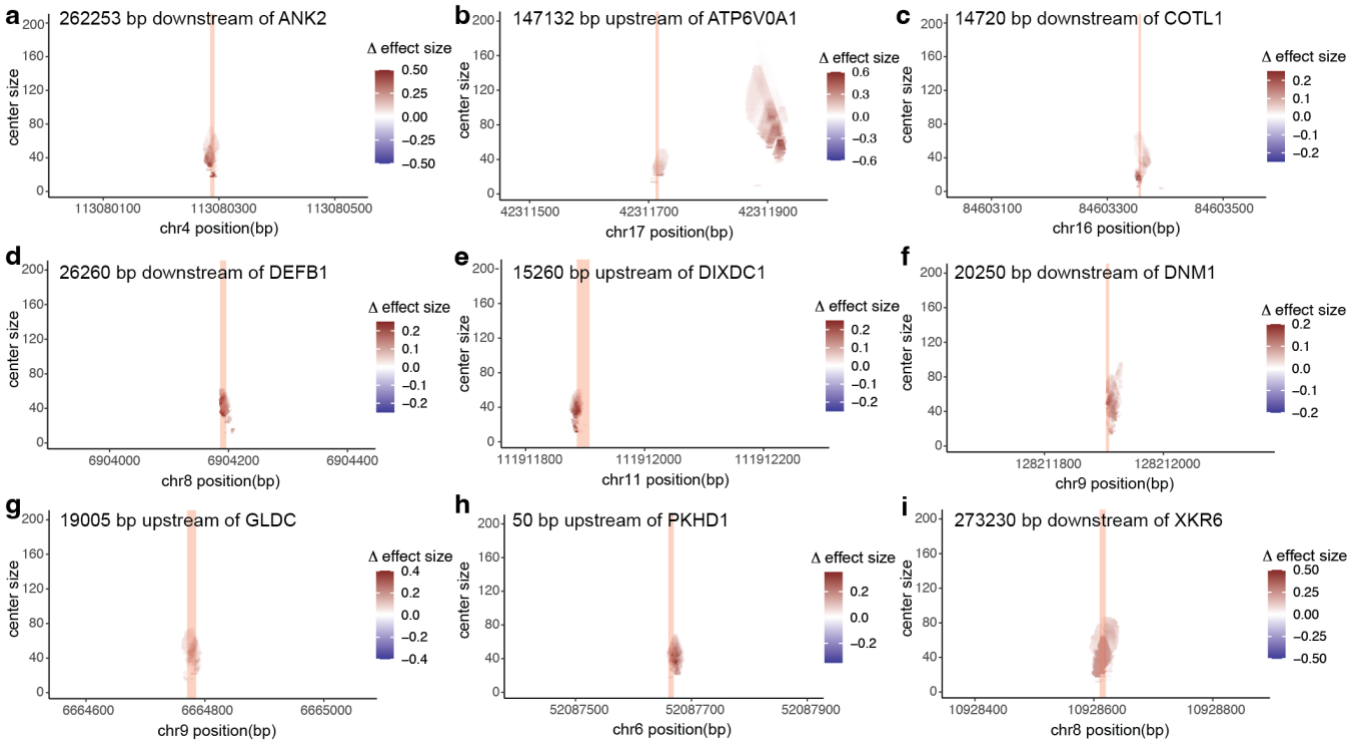
Supplementary Figure 12:

a, Number of attribution peaks identified by Decima near PCT differentially expressed genes in PCT and non PCT cell types. **b-d,** Enrichment changes over randomly sampled non attribution peaks for other methods. **e-g,** the composition of footprint for different methods. **h-i**, Motif overlapped with Decima and footprint other samples, p-values derived from TraceBind multiscale test. **j-l,** footprint-enhanced chromVar score for HNF4A and FOS in PCT and injured PCT (n_{PCT} = 1519, $n_{injured}$ = 803). **** indicates statistical significance from two-sided Wilcoxon Rank Sum test after multiple test adjustments (p value ≤ 2.22×10^{-16}). Centre lines, median; boxes, interquartile range (IQR); whiskers, 5th and 95th percentiles (chromVar scores)



Supplementary Figure 13:

a, Distribution of TraceBind footprint widths and their distance to the transcription start site (TSS) for footprints that do not overlap with/without high-scoring Decima attribution peaks. **b**, In promoter-proximal regions, distribution of TraceBind footprint widths and their distance to the TSS for footprints that overlap with/without high-scoring Decima attribution peaks. **c-d,** Distributions of GC content across different genomic contexts, stratified by non-significant versus significant footprints and by low versus high Decima attribution scores. P-values are derived from two-sided Wilcoxon Rank Sum test after multiple test adjustments. Centre lines, median; boxes, interquartile range (IQR); whiskers, 5th and 95th percentiles (of GC contents). **e-f**, Distributions of CpG observed/expected ratios (controlled for GC content) across different genomic contexts, stratified by non-significant versus significant footprints and by low versus high Decima attribution scores. P-values are derived from two-sided Wilcoxon Rank Sum test after multiple test adjustments. Centre lines, median; boxes, interquartile range (IQR); whiskers, 5th and 95th percentiles (of CpG observed/expected ratios). **g**, Relationship between TraceBind −log10 adjusted p-value and local coverage within high-scoring Decima attribution.



Supplementary Figure 14:

a-i: Key disease loci that show differential footprint binding (upregulated in injured PCT cells) and differential decima attribution peaks, with color box representing decima differential peaks that overlap with AP-1 motif. sites. P-values are derived from TraceBind multiscale test.