Supplementary information, Fig.S1

a
CTCF HiChIP SC+DE

Read count per million

HiChIP
Hi-C

-10 kb   5' end   3' end   10 kb

b
CTCF HiChIP peaks

Percentage (%)

71.02%

All   CTCF peak+

c
Anchors of CTCF contacts

Percentage (%)

100%

All   CTCF peak+

d

A compartments
Others

Percentage (%)

CTCF peaks
(CTCF ChIP)

CTCF contacts
(CTCF HiChIP)

e

Manders overlap coefficient

***

H3K27ac   H3K9me3

CTCF

f

CTCF   H3K27ac   Merge

CTCF   H3K9me3   Merge

g

CTCF   H3K27ac   H3K9me3

-3k   3k

0   0.8   1.6

i
CTCF inter-A anchors

Percentage (%)

100%

All   CTCF peak+

h
CTCF contacts across all chromosomes

Chromosome   1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 X

SMC3 ChIP

CTCF ChIP

A/B

CTCF-enriched loci

CTCF HiChIP (hichipper)

CTCF HiChIP (ChIA-PET2)

j
CTCF-connected A compartments from CTCF HiChIP

Percentage (%)

78.7%

All   CTCF PLAC-seq

k
CTCF-connected A compartments from CTCF HiChIP

Percentage (%)

68.7%

All   CTCF ChIA-PET

l
Interactions from CTCF ChIA-PET data, 100 kb resolution

NB4 cell line

PAEC cell line

(Mb)   0 20 40 60 80 100   0 20 40 60 80 100   0 20 40 60 80 100 140   0 20 40 60 80 110

$-Log_{10}$ (p value)

50

0

Chr12   Chr15   Chr8   Chr10

m

Inter-compartment interaction alteration after CTCF depletion (*Nora et al, 2017* Hi-C data)

n

Inter-compartment interaction alteration after CTCF depletion (*Nora et al, 2020* Hi-C data)
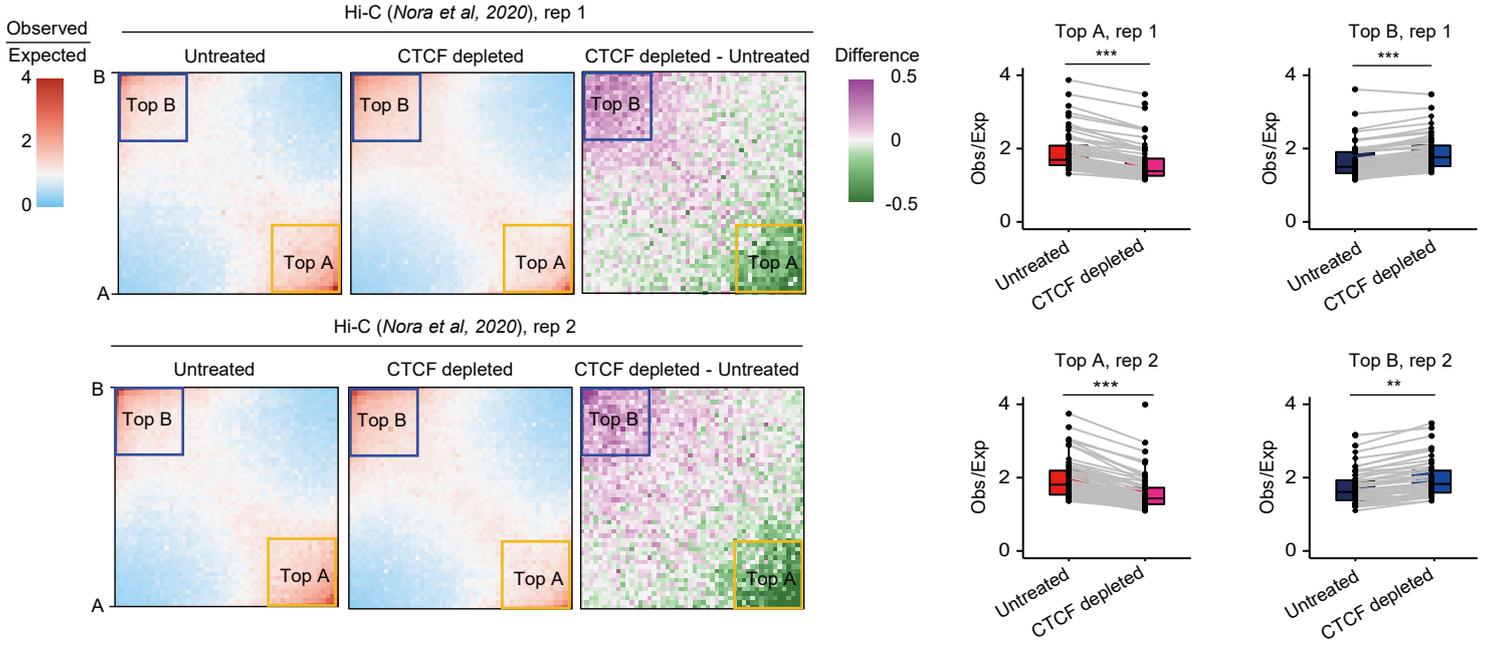
o

Distribution of common A compartment PC1 score after CTCF depletion (*Nora et al, 2017* Hi-C data)
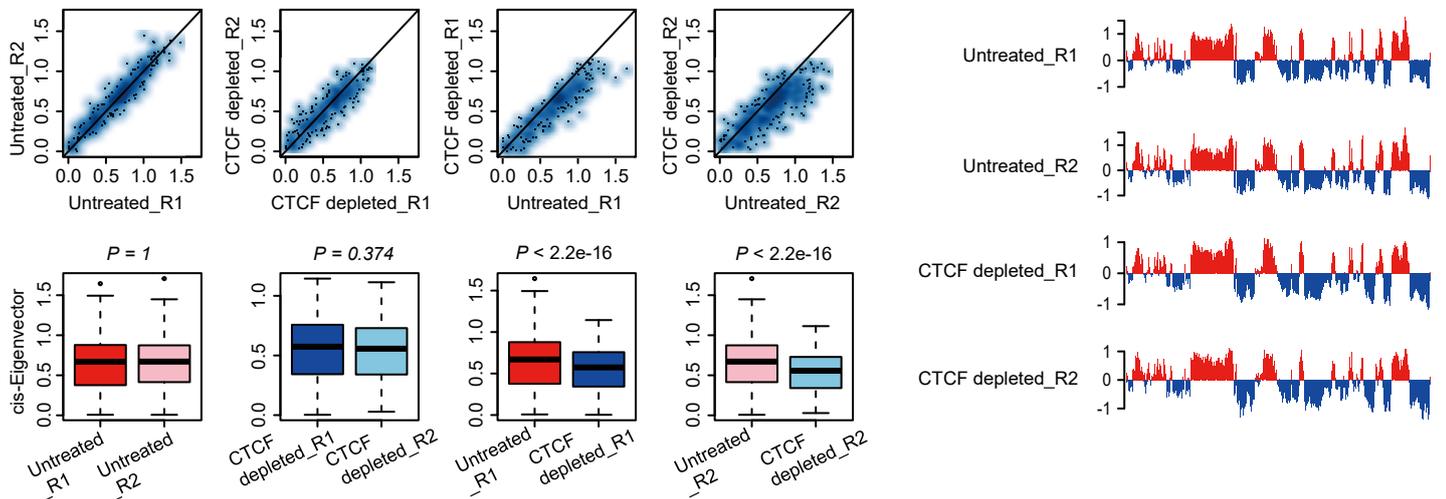
p

Distribution of common A compartment PC1 score after CTCF depletion
(*Nora et al, 2020* Hi-C data, public data processing pipeline)
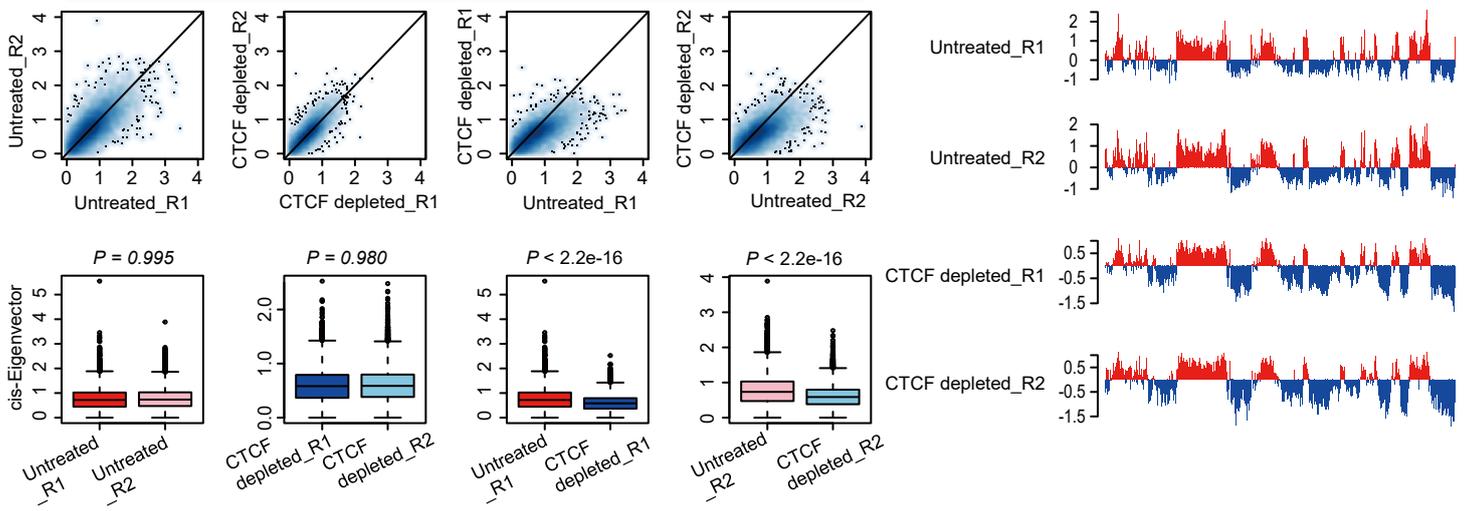
q

Inter-compartment interactions

Nora et al, 2017 Hi-C data   *Nora et al, 2020* Hi-C data
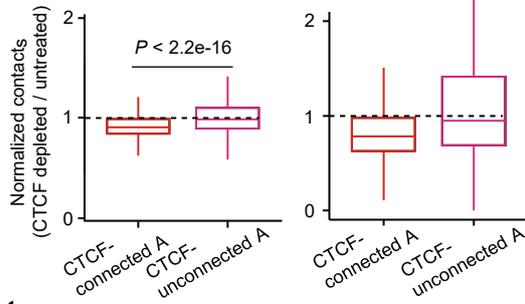
r

s
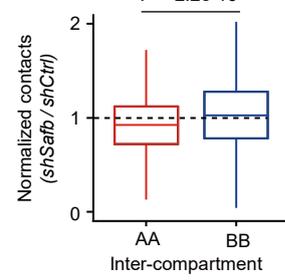
Inter-A compartment interactions
between CTCF-lacked loci
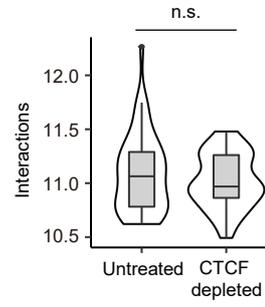
Inter-A compartment interactions
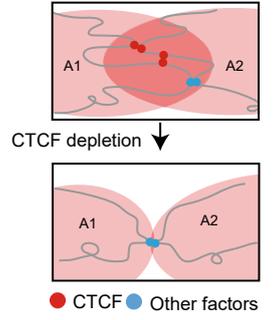
t
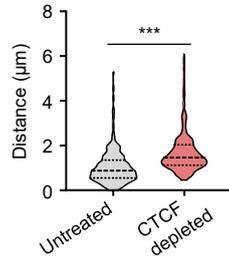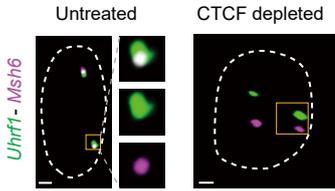
u
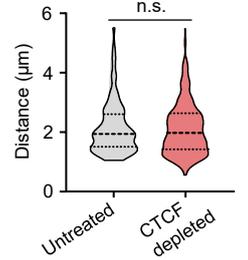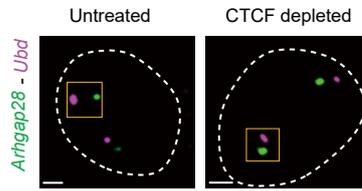
Supplementary information, Fig.S1 CTCF organizes inter-A compartment interactions. a Enrichment of self-ligation signal (Dangling ends (DE) and Self Circle (SC)) at CTCF narrow peaks from CTCF ChIP-seq data (GSE29218) compared with CTCF HiChIP. **b** Percentage of CTCF HiChIP peaks with CTCF ChIP-seq peaks (GSE29218). **c** Percentage of CTCF contact anchors with CTCF ChIP-seq peaks (GSE29218). **d** Percentage of CTCF peaks from ChIP-seq data (GSE29218) and CTCF contacts from HiChIP data involved in A compartments. **e** Boxplot showing the Manders overlap coefficient between CTCF and histone modifications. Welch's t-test; H3K27ac, n = 103 cells; H3K9me3, n = 112 cells; P = 1.884e-06. **f** Representative immunofluorescence images showing the co-localization between CTCF and H3K27ac (top), CTCF and H3K9me3 (bottom) in ESCs, scale bar denotes 2 μm. **g** Enrichment of H3K27ac (GSM851278) and H3K9me3 ChIP (GSM1003751) signal at CTCF ChIP-seq peaks (GSE29218). **h** CTCF contacts (CTCF HiChIP data) across all chromosomes. **i** Percentage of CTCF inter-A anchors with CTCF ChIP-seq peaks (GSE29218), the CTCF inter-A anchors were generated from CTCF HiChIP data. **j** Percentage of CTCF-connected A compartments (see methods) from CTCF HiChIP data that are also supported by CTCF PLAC-seq data (GSE119663). **k** Percentage of CTCF-connected A compartments from CTCF HiChIP data that are also supported by CTCF ChIA-PET data (GSM2645441). **l** CTCF ChIA-PET defined CTCF-connected regions in chr12, chr15 of NB4 (GSE137661) and in chr8, chr10 of PAEC (GSE139234). Black boxes denote the long-range interacted regions. **m** Saddle plots (left) and boxplots (right) showing the contact change between compartments with two replicates. Wilcoxon rank-sum test, Top A, rep 1: P = 6.066e-05; Top A, rep 2: P = 6.85e-06; Top B, rep 1: P = 0.1694; Top B, rep 2: P = 0.001268. Hi-C data were analyzed from the published literature of *Nora et al, 2017 (GSE98671).* **n** Saddle plots (left) and boxplots (right) showing the contact change between compartments with two replicates. Wilcoxon rank-sum test, Top A, rep 1: P = 5.921e-06; Top A, rep 2: P = 3.783e-08; Top

B, rep 1: P = 0.0006229; Top B, rep 2: P = 0.003635. Hi-C data were analyzed from the published literature of *Nora et al, 2020 (GSE156868)*. **o** Left: Scatter plots showing PC1 score of the common A compartments across the whole genome with two replicates. Right: PC1 score change of chromosome 17 before or after CTCF depletion with two replicates. Wilcoxon rank-sum test. Hi-C data from *Nora et al., 2017 (GSE98671)* were analyzed with our pipeline. **p** Left: Scatter plots showing PC1 score of the common A compartments across the whole genome with two replicates. Right: PC1 score change of chromosome 17 before and after CTCF depletion with two replicates, Wilcoxon rank-sum test; Hi-C data were analyzed with the pipeline from the published work *(GSE156868)*. **q** Boxplot showing the normalized contact change among CTCF-connected and CTCF-unconnected A compartments after CTCF depletion (CTCF depleted / untreated). Hi-C data are from *Nora et al., 2017* (left, *GSE98671*) *and Nora et al., 2020* (right, *GSE156868*). Wilcoxon rank-sum test. **r** Boxplot showing the normalized contacts among inter-A compartments after SAFB-deficiency (Hi-C data, GSE125037), Wilcoxon rank-sum test. **s** Left: Quantitation of aggregate peak analysis (APA) showing the genome-wide aggregate strength between CTCF-lacked loci (see methods) from different A compartments after CTCF depletion. Wilcoxon rank-sum test, P = 0.3565, Hi-C data are from *Nora et al., 2017 (GSE98671)*. Right: A model showing that CTCF mediates inter-A compartment interactions through CTCF-enriched loci, but the inter-A compartment interactions between CTCF-lacked loci also exist, which might be mediated by other factors. **t** The representative (left) images and quantification (right) of DNA FISH displaying distance change between *Uhrf1* (green) and *Msh6* (magenta) after CTCF depletion (Untreated: n = 205; CTCF depleted: n = 186; P = 1.906e-13; Welch's *t*-test), the two genes localized in CTCF-enriched loci, the scale bars denote 2 μm. **u** As a negative control, DNA FISH displaying the distance change between *Arhgap28* (green) and *Ubd* (magenta) after CTCF depletion, the two genes localize at different compartments, the scale bars denote 2 μm. Right: quantification of the

distance change between the two genes. Welch's *t*-test; Untreated: n = 183; CTCF depleted: n = 182; *P* = 0.825.