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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	All code for data processing and analysis, described in detail in the manuscript, is available through the following GitHub accounts: https://github.com/tborrman/liquid-chromatin-Hi-C https://github.com/tborrman/DpnII-seq https://github.com/dekkerlab/5C-CBFb-SMMHC-Inhib https://github.com/dekkerlab/cMapping https://github.com/dekkerlab/cworld-dekker https://github.com/hms-dbmi/hic-data-analysis-bootcamp https://github.com/mirnylab/cooltools/tree/master/cooltools Specific code usage: 5C data processing - https://github.com/dekkerlab/5C-CBFb-SMMHC-Inhib/blob/master/data_processing_steps.md - novocraft/V3.02.08 - https://github.com/dekkerlab/cMapping - cMapping/scripts/utilities/processFlowCell.pl - cMapping/scripts/utilities/combine5C.pl - https://github.com/dekkerlab/cworld-dekker - cworld-dekker/scripts/perl/column2matrix.pl - cworld-dekker/scripts/perl/subsetMatrix.pl - cworld-dekker/scripts/perl/singletonRemoval.pl - cworld-dekker/scripts/perl/anchorPurge.pl - cworld-dekker/scripts/perl/matrix2symmetrical.pl - cworld-dekker/scripts/perl/scaleMatrix.pl

- cworld-dekker/scripts/perl/binMatrix.pl
- cworld-dekker/scripts/perl/heatmap.pl
- https://github.com/blajoie/tab2hdf
- tab2hdf/scripts/tab2hdf.py
- https://github.com/blajoie/hdf2tab
- hdf2ab/scripts/hdf2tab.py
- https://github.com/dekkerlab/balance
- balance/scripts/balance.py

Hi-C data processing
- https://github.com/dekkerlab/cMapping
- python 2.7.9
- bowtie2 2.3.0
- numpy 1.13.3
- h5py 2.6.0
- cMapping/scripts/utilities/processFlowCell.pl
- cMapping/scripts/utilities/combineHiC.pl
- https://github.com/blajoie/tab2hdf
- tab2hdf/scripts/tab2hdf.py
- https://github.com/blajoie/hdf2tab
- hdf2ab/scripts/hdf2tab.py
- https://github.com/dekkerlab/balance
- balance/scripts/balance.py
- https://github.com/tborrman/liquid-chromatin-Hi-C
- liquid-chromatin-Hi-C/src/liquid_chromatin_HiC/filter_validpairs.py
- liquid-chromatin-Hi-C/src/liquid_chromatin_HiC/scale.py

A/B compartments
- https://github.com/dekkerlab/cworld-dekker
- cworld-dekker/scripts/perl/matrix2compartment.pl

LOS and half-life calculation
- https://github.com/tborrman/liquid-chromatin-Hi-C
- python 2.7.9
- R 4.0.0
- liquid-chromatin-Hi-C/src/liquid_chromatin_HiC/hdf2RangeCisPercent.py
- liquid-chromatin-Hi-C/src/scripts/LOS.R
- liquid-chromatin-Hi-C/src/scripts/make_LOS_table.R
- liquid-chromatin-Hi-C/src/scripts/get_half_life_exponential.R
- liquid-chromatin-Hi-C/src/scripts/get_halflife_residuals_moving_average.R

DpnII-seq data analysis
- https://github.com/tborrman/DpnII-seq
- python 2.7.9
- bowtie 1.0.0
- samtools 0.1.19
- bedtools 2.17.0
- r 3.4.3
- DpnII-seq/Snakefile

DpnII pre-digestion average fragment size analysis
- https://github.com/tborrman/liquid-chromatin-Hi-C
- R 4.0.0
- bowtie 1.0.0
- samtools 0.1.19
- bedtools 2.17.0
- liquid-chromatin-Hi-C/src/scripts/average_fragment_size.R

Sub nuclear structures
- https://github.com/tborrman/liquid-chromatin-Hi-C
- liquid-chromatin-Hi-C/src/liquid_chromatin_HiC/generate_feature_matrix_40kb.py
- liquid-chromatin-Hi-C/figures/figure5/RepliSeq_heatmap.R
- liquid-chromatin-Hi-C/figures/figure5/feature_halflife_heatmap.R

Gene expression
- https://github.com/tborrman/liquid-chromatin-Hi-C
- liquid-chromatin-Hi-C/src/liquid_chromatin_HiC/get_gene_positions.py
- liquid-chromatin-Hi-C/figures/figure5/subcompartment_halflife_FPKM_boxplot.R

Saddle plots
- https://github.com/hms-dbmi/hic-data-analysis-bootcamp/blob/master/notebooks/04_analysis_cooltools-eigenvector-saddle.ipynb
- https://github.com/open2c/cooltools

Scaling plot
- https://github.com/hms-dbmi/hic-data-analysis-bootcamp/blob/master/notebooks/02_analysis_scaling-curves.ipynb

- https://github.com/open2c/cooltools

Data
##
Databases
- Catalogue of Somatic Mutations In Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cell_lines/download)
- SNIPER subcomartments (Xiong and Ma, 2019)
- ENCODE datasets (Supplementary Table S4)
- NADs state track for the human embryonic fibroblast IMR90 cell line (Dillinger, Straub and Nemeth, 2017; PMID: 28575119)
- TSA-seq data: Nuclear Speckle, nuclear lamina, and PolII (Chen et al., 2018; PMID: 30154186)
- ENCODE RNA-seq (Accession ID: ENCFF782PCD)
- hg19 ensGene table from UCSC Table Browser
##

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All sequencing data have been submitted to a public data repository (GEO; accession number GSE134590).

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	All data was obtained for two independent biological replicates. Analysis of Hi-C statistics (Supplemental Table 3), Loss of structure and half-life calculations for the two replicates where concordant (Pearson Correlation r=0.78; Extended Data Figure 2E).
Data exclusions	No data were excluded from any analysis.
Replication	All results were observed in the two independent replicates, all effort to assess replication were successful.
Randomization	No analyses involved any randomization, as all statistical tests were based on normal distributions.
Blinding	No analyses involved blinding as no identifiable personal data was available for any samples or datapoints.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Lamin A antibody (ab 26300) Abcam;
CTCF antibody cell signaling (activeMotif 61311); SMC1 antibody (Bethyl Antibody A300-055A);
H3 antibody Abcam (ab1791).
Anti-Rabbit IgG, HRP-linked antibody #7074 Cell Signaling Technology. CST states the product is thoroughly validated.

Validation

Lamin A antibody (ab 26300) Abcam: knock-out validated (no reactivity with 76 Kda band when lamin A is knocked out). Abcam reports that the antibody cross-reacts with several smaller proteins. Dekker lab validated antibody for use in immunofluorescence by showing it stains nuclear periphery, and this staining disappears in mitosis.
CTCF antibody cell signaling (activeMotif 61311): Validation listed by the manufacturer: Western blot validated, showing a single band with the correct size. Chromatin Immunoprecipation DNA was sequenced and showed CTCF binding sites.
SMC1 antibody (Bethyl Antibody A300-055A): Validation listed by manufacturer: In Western blot a protein of the correct size is detected, with minor recognition of several smaller proteins. Dekker lab has validated this antibody for chromatin immunoprecipitation and found that this antibody identifies known cohesin binding sites that overlap CTCT sites as expected.
H3 antibody Abcam (ab1791): Validated by Abcam: website lists these validations: Western blot (correct size, competed with H3 peptide), by immunofluorescence (localized in nucleus), by cell fractionation (localized in nucleus). Also validated in Dekker lab by chromatin fractionation (associated with chromatin) and reactivity in Western blot with protein of correct size.
Anti-Rabbit IgG, HRP-linked antibody #7074 Cell Signaling Technology. CST states the product is thoroughly validated.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

K-562 (ATCC, CCL-243) , GM12878 (Coriell Institute)

Authentication

Karyotyping using Hi-C (K-562); cell morphology, and conformation of the beta-globin locus (GM12878, K-562).

Mycoplasma contamination

Cells were confirmed free of mycoplasm.

Commonly misidentified lines
(See ICLAC register)

None.