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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 our Editorial Policies 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	SDS-PAGE and DNA gel images were acquired using an ImageQuant LAS-4000 imager (GE Healthcare Life Sciences) or a Typhoon FLA 9500 biomolecular imager (GE Healthcare Life Sciences). Quantitative PCR data was collected using a ViiA 7 Real-Time PCR System (Applied Biosystems).
Data analysis	SDS-PAGE and DNA gels were analyzed using Image Studio Lite (Li-Cor, v5.2). Custom Python (2.7.10) scripts were used for analysis of nucleosome thermal stability and remodeling and are available at https://github.com/jdbagert/oncohistonelibrary. Plots and data visualization were performed with Python (2.7.10) and the Matplotlib library (2.2.3). Crystal structure visualizations were performed with UCSF Chimera (v. 1.13.1). Mononucleosome barcode reads were analyzed using a custom R script (Dann et al., 2017). Quantification of RNA transcripts was performed with the k-mer counting software Salmon (Patro et al., 2017). Quantification of RNA transcripts was performed with the k-mer counting software Salmon, and a reference genome produced using Illumina's iGenomes UCSC mm10 package. Expression levels were estimated by counting reads with featureCounts (v1.4.4) using default settings. The gene symbol-summarized read counts were normalized using the variance stabilized transformation technique (VST), and expression levels clustered using Euclidean distance and hierarchical clustering with the Ward variance minimization algorithm to produce heatmaps. Differentially expressed genes were identified using the DESeq Package. Gene ontology (GO) analysis was performed with DAVID and top GO and KEGG pathway terms were plotted against their Benjamini FDR values on a logarithmic scale.

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 and 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

RNA-seq raw data discussed in this publication have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE146959. All other data are included within this paper, Extended Data, and Supplementary Information files.

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 sample sizes used are listed in the manuscript. No sample-size calculations were used to determine sample size. Sample sizes were chosen according to community standards, balancing statistical power and experimental burden, and were sufficient for statistical analysis of the quantitative biochemical and biophysical data presented.
Data exclusions	No data were excluded.
Replication	All attempts to replicate biochemical and biophysical experiments were successful, and representative data are presented in the manuscript. RNA-seq and barcoded nucleosome library experiments were performed once with n=3-4 (as described in the manuscript).
Randomization	Randomization was not performed, as the experiments performed were not deemed to be at risk for bias associated with the order of analysis.
Blinding	The authors were not blind to the experiments carried out in the study, as the experiments performed were not deemed to be at risk for experimenter bias.

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 and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	Mouse Alexa Fluor 488 anti-HA antibody (BioLegend, Cat#901509) Purified anti-HA.11 Epitope Tag Antibody (BioLegend, Cat#901501) Histone H2B (D2H6) Rabbit mAb (Cell Signaling Technology, Cat#12364) Goat Anti-Rabbit IgG-HRP Conjugate (Bio-Rad, Cat#1706515) Mouse IgG HRP Linked Whole Ab (GE Healthcare Life Sciences, Cat#NA931)
Validation	Mouse Alexa Fluor 488 anti-HA antibody (https://www.biolegend.com/en-us/products/alexa-fluor-488-anti-ha-11-epitope-tag-

antibody-10993)
Purified anti-HA.11 Epitope Tag Antibody (https://www.biolegend.com/en-us/products/purified-anti-ha-11-epitope-tag-antibody-11374)
Histone H2B (D2H6) Rabbit mAb (https://www.cellsignal.com/products/primary-antibodies/histone-h2b-d2h6-rabbit-mab/12364)
Goat Anti-Rabbit IgG-HRP Conjugate (https://www.bio-rad.com/en-us/sku/1706515-goat-anti-rabbit-igg-h-l-hrp-conjugate?ID=1706515)
Mouse IgG HRP Linked Whole Ab (https://www.sigmaaldrich.com/catalog/product/sigma/gena9311ml?lang=en&region=US)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T (ATCC, CRL-11268) C3H10T1/2 (ATCC, CCL-226) Sf9 (Gibco, 11496015)
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	The cell lines used in this study tested negatived for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None used