nature portfolio

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Last updated by author(s): *YYYY-MM-DD*

Reporting Summary

Nature Portfolio 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 Portfolio 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	n/a
Data analysis	n/a

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Provide your data availability statement here.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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	Technical Replicas
Data exclusions	N/A
Replication	3
Randomization	N/A
Blinding	N/A

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
☐	☐ Clinical data
☐	☐ Dual use research of concern
☐	☐ Plants

Methods

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

Antibodies

Antibodies used

Antibodies Source Catalog
53bp1 rb Bethyl labs A300-273A
53bp1 rb Novus NB100-304
BrdU rb abcam ab152095
CHD5 rb genetex GTX131065
CHD7 rb cell Signaling 6505s
CtIP ms Active Motif AB_2714164

CtIP rb Millipore MABE1060
CtIP ms Santa Cruz sc-271339
Flag ms Sigma F4042
Flag rb Cell Signaling CST2368
GAPDH ms GeneTex GTX627408
GAPDH rb Sigma G9545
GFP ms Santa Cruz sc-9996
GFP rb Abcam ab290
gH2AX ms Millipore 05-636
gH2AX ms Active Motif 39117, 39118
gH2AX rb cell signaling 2577.00
H3 rb Cell signaling 9715S
H3K36me1 rb abcam ab9048
H3K36me2 rb Abcam ab9049
H3K36me3 rb Diagenode c15410192
H4 rb abcam ab10158
H4K20me1 rb Sigma 07-1570
H4K20me2 rb Abcam ab9049
H4K20me3 rb Abcam ab9053
IgG ms Invitorgen 10400C
IgG rb Invitorgen 10500C
NSD1 rb Thermo/Invitrogen PA5-50857
NSD2 rb Active Motif 39879.00
NSD3 rb Abcam EPR25189-8
PAR ms Biotechne 4335-MC-100
PARP1 ms santa cruz sc-26349
PARP2 ms Santa Cruz sc-393343
pRPA s-4/8 rb Bethyl A300-245A
Rad51 rb Calbiochem PC130
RIF1 rb Bethyl labs A300-569A
RPA rb Cell Signaling 2267S
SETD2 rb Cell signaling 80290S
SETD3 rb St John's Laboratory STJ110374
SETD7 rb GeneTex GTX13731
T-RPA ms Santa Cruz sc-56594
Tubulin ms sigma T6074
KMT5A rb cell Signaling CST-2996
KMT5B rb abcam ab118569
KMT5C rb abcam ab267359

Validation

Antibodies Source Catalog Applications Dilutions *rb-Rabbit
53bp1 rb Bethyl labs A300-273A IF 1: 1000 (IF) *ms-mouse
53bp1 rb Novus NB100-304 WB, ChIP 1: 500 (WB), 1:50 ChIP
BrdU rb abcam ab152095 WB 1: 50 (IF)
CHD5 rb genetex GTX131065 IP, ChIP, WB, PLA 1:10 (ChIP), 1:250 (WB), 1:100 (PLA)
CHD7 rb cell Signaling 6505s WB 1: 500 (WB)
CtIP ms Active Motif AB_2714164 ChIP 1: 50 (ChIP)
CtIP rb Millipore MABE1060 IF, ChIP, WB 1: 50 (IF), 1:100(ChIP), 1:1000 (WB)
CtIP ms Santa Cruz sc-271339 WB 1: 50 (WB)
Flag ms Sigma F4042 IP, ChIP, WB 1: 500 (IP), 1:100(ChIP), 1:2000 (WB)
Flag rb Cell Signaling CST2368 IP, ChIP, WB 1: 500 (IP), 1:100(ChIP), 1:2000 (WB)
GAPDH ms GeneTex GTX627408 WB 1:1000 (WB)
GAPDH rb Sigma G9545 WB 1:1000 (WB)
GFP ms Santa Cruz sc-9996 WB 1:2000 (WB)
GFP rb Abcam ab290 IP, ChIP, WB 1: 500 (IP), 1:100(ChIP), 1:2000 (WB)
gH2AX ms Millipore 05-636 IF, PLA 1:1000 (IF), 1:400 (PLA)
gH2AX ms Active Motif 39117, 39118 ChIP 1:100 (ChIP)
gH2AX rb cell signaling 2577.00 IF, ChIP , PLA 1:500 (IF), 1:100 (ChIP), 1:100 (PLA)
H3 rb Cell signaling 9715S ChIP 1: 1000 (WB), 1:100(ChIP)
H3K36me1 rb abcam ab9048 ChIP 1: 1000 (WB), 1:100(ChIP)
H3K36me2 rb Abcam ab9049 ChIP 1: 1000 (WB), 1:100(ChIP)
H3K36me3 rb Diagenode c15410192 ChIP 1: 1000 (WB), 1:100(ChIP)
H4 rb abcam ab10158 ChIP 1: 1000 (WB), 1:100(ChIP)
H4K20me1 rb Sigma 07-1570 ChIP 1: 1000 (WB), 1:100(ChIP)
H4K20me2 rb Abcam ab9049 ChIP 1: 1000 (WB), 1:100(ChIP)
H4K20me3 rb Abcam ab9053 ChIP 1: 1000 (WB), 1:100(ChIP)
IgG ms Invitorgen 10400C IP, ChIP 1:100 (IP, ChIP)
IgG rb Invitorgen 10500C IP, ChIP 1:100 (IP, ChIP)
NSD1 rb Thermo/Invitrogen PA5-50857 ChIP 1:100(ChIP)

NSD2 rb Active Motif 39879.00 ChIP 1:100(ChIP)
NSD3 rb Abcam EPR25189-8 ChIP 1:100(ChIP)
PAR ms Biotechne 4335-MC-100 WB 1:250 (WB)
PARP1 ms santa cruz sc-26349 WB 1: 500 (WB)
PARP2 ms Santa Cruz sc-393343 WB 1: 50 (WB)
pRPA s-4/8 rb Bethyl A300-245A WB 1: 1000 (WB)
Rad51 rb Calbiochem PC130 IF 1: 1000 (IF)
RIF1 rb Bethyl labs A300-569A IF, ChIP 1: 1000 (IF), 1:50 (ChIP)
RPA rb Cell Signaling 2267S IF 1: 50 (IF)
SETD2 rb Cell signaling 80290S ChIP 1:100(ChIP), 1:50 (PLA)
SETD3 rb St John's Laboratory STJ110374 ChIP 1:100(ChIP)
SETD7 rb GeneTex GTX13731 ChIP 1:50(ChIP)
T-RPA ms Santa Cruz sc-56594 WB 1: 1000 (WB)
Tubulin ms sigma T6074 WB 1:2000 (WB)
KMT5A rb cell Signaling CST-2996 PLA 1:50 (PLA)
KMT5B rb abcam ab118569 ChIP, PLA 1:100(ChIP), 1:50 (PLA)
KMT5C rb abcam ab267359 PLA 1:50 (PLA)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	*State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.*
Authentication	Cell lines are purchased from ATCC or kind gift from collaborators
Mycoplasma contamination	All cell lines are regularly tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	n/a

Palaeontology and Archaeology

Specimen provenance	*Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*
Specimen deposition	*Indicate where the specimens have been deposited to permit free access by other researchers.*
Dating methods	*If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	n/a
Wild animals	n/a
Reporting on sex	n/a
Field-collected samples	n/a
Ethics oversight	n/a

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	n/a
Study protocol	n/a
Data collection	n/a
Outcomes	n/a

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	n/a
Files in database submission	n/a
Genome browser session (e.g. UCSC)	n/a

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*
Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*
Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Briefly, 50000 cells per ml U2OS cells were seeded in a 6-well plate treated with indicated siRNA for 48h. Post-transfection cells were washed twice with ice-cold PBS and fixed with 70% ethanol. Fixed cells were then treated with 50 µl of a 100 µg/ml stock of RNase inhibitor and 200 µl PI (from 50 µg/ml stock solution). Cells were then subjected to FACS to measure forward scatter (FS) and side scatter (SS) to identify single cells. The acquired population is then gated for cell cycle analysis using the Flow-Jo software.
Instrument	Cytotek Aurora
Software	Flow-Jo
Cell population abundance	Atleast, 50000 cells
Gating strategy	FS/SS, FS/RFP, RFP/GFP

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software

n/a

Normalization

n/a

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

n/a

Effect(s) tested

n/a

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

n/a

(See Eklund et al. 2016)

Correction

n/a

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis