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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	bcl2fastq 2.18.0.12
Data analysis	bowtie2 2.3.4.1; samtools 1.7; bedtools 2.26 ; R 4.0.2; ; analysis code available at https://github.com/nirfriedman/cfChIP-seq.git

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

Provide your data availability statement here.

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	n/a
Data exclusions	In all experiments, cfChIP-seq samples were removed from consideration if they did not meet pre-established QC standard: the number of unique aligned reads was below 200K or the %signal was below 20%. Exceptions to this rule in samples where %signal * unique reads > 200K.
Replication	We performed biological and technical repeats. Please see discussion of reproducibility in Supplementary Note for full set of results. All replication attempts were reported.
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
☒	☐ 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

IgG - Cell signalling #2729S
H3K4Me1 - Diagenode #C15410194
H3K4Me2 - Diagenode #C15410035
H3K4Me3 - Diagenode #C15410003
H3K36Me3 - Diagenode #C15410192

Validation

IgG - Cell signalling #2729S was validated as a negative control for ChIP by the manufacturer, and showed extremely low signal compared to anti H3, Rbp1 CTD, or anti H3K9me2.

Anti H3K4me3 C15410003 from Diagenode was shown by the manufacturer to be highly specific in ChIP-qPCR and ChIP-seq in HeLa cells by showing high ChIP signal at promoters of highly expressed genes such as EIF4A2 and GAPDH and a very low signal at promoters of inactive genes such as MYOD1. Specificity was also demonstrated by testing against IgG background. https://www.diagenode.com/en/p/h3k4me3-polyclonal-antibody-premium-50-ug-50-ul

Anti H3K36me3 C15410192 from Diagenode was shown by the manufacturer to be highly specific in ChIP-qPCR and ChIP-seq in HeLa cells by showing high ChIP signal at coding regions of actively transcribed genes as a positive control compared to promoter regions and coding regions of inactive genes as a negative control. Specificity was also demonstrated by testing against IgG background. https://www.diagenode.com/en/p/h3k36me3-polyclonal-antibody-premium-50-mg-42-ml

Anti H3K4me1 C15410194 from Diagenode was shown by the manufacturer to be highly specific in ChIP-qPCR and ChIP-seq in K562 cells by showing high ChIP signal at positive regions surrounding the ACTB and GAS2L1 genes and negative controls at the promoters of promoters of EIF4A2 and GAPDH genes. Specificity was also demonstrated by testing against IgG background. https://www.diagenode.com/en/p/h3k4me1-polyclonal-antibody-premium-50-mg-54-ml

Anti H3K4me2 from Diagenode was tested in ChIP-qPCR and ChIP-seq on HeLaS3 chromatin by the manufacturer. The antibody shows high signal at regions surrounding the promoters of highly transcribed genes as positive control and low signal at promoter centers. Specificity was also demonstrated by testing against IgG background. https://www.diagenode.com/en/p/h3k4me2-polyclonal-antibody-classic-50-mg-42-ml

Human research participants

Policy information about studies involving human research participants

Population characteristics	See Supplemental Table 3 for all details
Recruitment	Self reported subjects were recruited through a call within our institute. Patients were recruited through the physician treating them
Ethics oversight	The study was approved by the Ethics Committees of the Hebrew University-Hadassah Medical Center of Jerusalem. Informed consent was obtained from all subjects or their legal guardians before blood sampling.

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

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.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	FASTQ and BAM files for all the cfChIP-seq samples performed in this study.
Genome browser session (e.g. UCSC)	https://genome.ucsc.edu/s/nirfriedman/cfChIP-seq

Methodology

Replicates	We performed several biological and technical repeats on healthy samples. Full details on these are Table S1
Sequencing depth	We aimed for 5-10M reads/sample. In some cases the numbers were much larger (difference in library size). Table S1 lists sequencing statistics for each sample, including estimate of sequencing capture rates.
Antibodies	See antibodies above
Peak calling parameters	no peak calling - we used quantative read counting in pre-defined regions. See Methods and Supplemental Note for details.
Data quality	See Supplemental Note
Software	See Supplemental Note and https://github.com/nirfriedman/cfChIP-seq.git