nature portfolio

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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	Flow cytometry data using the Flow-Jo (v.10) analysis software.
Data analysis	R (v3.6.1 and v4.3.2), https://cran.r-project.org; GCTA (v1.93.2), https://cnsgenomics.com/software/gcta; LocusZoom (v1.3), https://genome.sph.umich.edu/wiki/LocusZoom_Standalone; HOMER http://homer.ucsd.edu/homer; DeepTools https://deeptools.readthedocs.io/en/latest/; Cutadapt https://cutadapt.readthedocs.io/en/stable/; rmDup https://legacy.ibp.ucla.edu/research/xiao/Software_files/ASARP/doc/rmDup.html; Bowtie2 https://bowtie-bio.sourceforge.net/bowtie2/index.shtml; GraphPad Prism 10, https://www.graphpad.com/; Bioconductor packages (edgeR, Limma R) https://www.bioconductor.org/.

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

The raw datasets generated in this study have been deposited in the Gene Expression Omnibus (GEO): RNA-seq (under accession code GSE299089), CRISPR screening (GSE299544) and CUT&Tag (GSE299545). Summary statistics from FinnGen GWAS used in this study are available from https://www.finngen.fi/en/access_results (DF9 - May 11, 2023).

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	Findings do not apply to one sex only.
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	We performed the CRISPR screen in triplicate. We also performed all of the validation experiments with at least 3 replicates.
Data exclusions	We did not exclude data from these studies.
Replication	All experiments were performed at least in triplicate as stated in the figure legends and in the methods section.
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: IL-1β (BioLegend, 508208), anti-H3K27Ac (Active Motif, 91193).

Validation: We did not perform additional validation of the antibodies beyond what the vendors provided. IL-1β was among the top CRISPR hits screen providing confidence on the specificity of the antibody.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): U937 cells were purchased from American Type Culture Collection (CRL-1593.2). Sex: male.
Jurkat cells were purchased from American Type Culture Collection (TIB-152). Sex: male.
Primary human CD14+ monocytes were purchased from BioIVt.

Authentication: We confirmed the identity of the U937 and Jurkat cells internally using STR profiling and externally using IDEXX BioAnalytics.

Mycoplasma contamination: Our cell lines are tested monthly for mycoplasma contamination at IDEXX BioAnalytics. All cell lines tested negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register): No commonly misidentified cell lines were used in the study.

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.

https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE299545
token: qpulywgoppyxjcz

Files in database submission

GSE299545_WT0R1-K27_bowtie2.scaled240731.bedgraph.gz
GSE299545_WT0R2-K27_bowtie2.scaled240731.bedgraph.gz
GSE299545_WT16R1-K27_bowtie2.scaled240731.bedgraph.gz
GSE299545_WT16R2-K27_bowtie2.scaled240731.bedgraph.gz
GSE299545_TNRC18KO0R1-K27_bowtie2.scaled240731.bedgraph.gz
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GSE299545_TNRC18KO16R2-K27_bowtie2.scaled240731.bedgraph.gz

GSM9040655 U937 cells, WT, H3K27ac, 0 hr rep1
GSM9040656 U937 cells, WT, H3K27ac, 0 hr rep2
GSM9040657 U937 cells, WT, H3K27ac, 16 hr rep1
GSM9040658 U937 cells, WT, H3K27ac, 16 hr rep2
GSM9040659 U937 cells, TNRC18 KO, H3K27ac, 0 hr rep1
GSM9040660 U937 cells, TNRC18 KO, H3K27ac, 0 hr rep2
GSM9040661 U937 cells, TNRC18 KO, H3K27ac, 16 hr rep1
GSM9040662 U937 cells, TNRC18 KO, H3K27ac, 16 hr rep2

Genome browser session
(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

CUT & Tag experiments were performed on two biological replicates per condition using the CUT & Tag-IT Assay Kit (Active Motif, 53172) following manufacturers recommendation.

Sequencing depth

We obtained greater than 20 million reads for each of our Cut and Tag samples.

Antibodies

anti-H3K27Ac (Active Motif, 91193).

Peak calling parameters

Peaks were defined by using the HOMER command (findPeaks - style histone) and we selected peaks that were observed in both replicates.

Data quality

HOMER requires the tag density at peaks to be 4-fold greater than in the surrounding 10 kb region and assumes the local density of tags follows a Poisson distribution which it uses to estimate the expected peak numbers. Using the expected distribution of peaks, HOMER calculates the expected number of false positives in the data set for each tag threshold, setting the threshold that beats the desired False Discovery Rate <0.001. Therefore, we ensure that only the sharp peaks with low local background are called and considered for downstream analyses and the Pearson correlation between replicates were >0.9.

Software

Preprocessed reads were aligned to human genome (hg38) using Bowtie2 and Drosophila genome (spike in control) to generate the normalization factor. Bedtools were used to sort and index, HOMER was used to generate tag directories and define peaks, and bedgraph was used to generate files for visualization.

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

Cells were harvested and washed twice with FACS buffer (PBS + 1% FBS), incubated with IC Fix buffer (eBioscience, Cat #88-8824-00) in dark for 30 minutes at room temperature, washed twice with FACS buffer, resuspended in 1X Permeabilization buffer (eBioscience, Cat #88-8824-00) for 10 minutes and washed twice with 1X perm buffer. Cells were then resuspended in 100 mL/well of FC-block (BioLegend, 422302) (1:100 in Perm buffer) for 15 minutes at room temperature in the dark. Without washing, directly add 100 L/well of IL-1β (BioLegend, 508208) at 2X (1:50 in perm buffer) to the FC-block currently in well (1:100 final dilution) and incubate at RT for 15 minutes in the dark.

Instrument

BD LSR Fortessa Cell Analyzer.

Software

Flow-Jo (v.10).

Cell population abundance

We collected 10,000 events and ended up with 6500-7200 cells after going through the FSC/SSC, single cell gating strategy.

Gating strategy

Cells were gated on FSC/SCC, single cell, and then positive for Alexa Fluor® 647 IL1b.

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