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	RNA-Seq data and ChIP-Seq data was generated by Novogene (UK) and provided for download as tar-compressed fastq.gz files.
Data analysis	RNA-Seq Salmon (v1.10.1) was used to quantify transcript count from RNA-Seq. A full decoy index was generated using whole genome and transcript sequences obtained from GENCODE genes database, with the hg38 (release 43) and mm39 (release 32) genomes, respectively. Trimmed fastq files were processed using Salmon (v1.10.1) with the following parameters: gcbias, writeUnmappedNames. GenomicFeatures(v1.46.5) was used to generate transcript-to-gene objects in R, using GTF files obtained from the GENECODE gene database. Salmon quantification file was subsequently analysed using DESeq2 (v1.34.0). Briefly, tximport (v1.22.0) was used to import Salmon quantification files into R. DESeqDataSetFromTximport was used to process transcript count. As the human cell lines were inherently different in genome, this difference was factored in when using DESeq2 in our comparison between DMSO and ponatinib treatment. In DESeqDataSetFromTximport(), the following parameter was used in the "design" option: ~condition+cell_line. For all other analyses with DESeq2, ~condition was used in the "design" option. Subsequently, genes with low transcript counts below 5 were filtered out from the analysis using rowSums(counts()) >= 5. DESeq() and results() were used to determine differentially expressed genes (DEGs). Data generated by results() were filtered for DEGs with a p-adjusted value < 0.05 and a log2 fold change > 1 or < -1. To generate DEG expression heatmaps, rlog() transformation, followed by assay()[DEG,] (where DEG is a vector of DEGs) generated a matrix. The matrix was used to plot a heatmap with pheatmap (v1.0.12), where the scale="row" option was added. For principal component analysis (PCA) plots, plotPCA() was used with intgroup = c("Treatment") option. ChIP-Seq Trimmed fastq files were aligned to the human genome, hg38, using bowtie2 (v2.4.4), using the additional parameter: --no-unal. SAM files

generated by bowtie2 were converted to BAM format using samtools (v1.14) view -S -b. Bam files were processed using samtools fixmate m, samtools sort -o, samtools markdup -r, samtools collate -o, samtools sort -o again.

To generate a file for visualisation on a genome browser, the final bam files were processed by deeptools (v3.5.1) suite. To generate bigwig files, bamCoverage was used with the following parameters: --normalizeUsing RPKM, --extendReads, --effectiveGenomeSize 2913022398 (for hg38), or 2654621783 (for mm39).

To determine peak enrichment across the genome, macs2 (v2.2.7.1) callpeak was used, with an IgG ChIP used as the input control. The following parameters were used: -q 0.05, B, - SPMR, --broad (only for H3K27ac ChIP), and -g hs (for hg38) or mm (for mm39).

To determine reads within specific region, the Homer (v4.11) package suite was used. The Homer suit was used to create tag directories using makeTagDirectory, with the added parameter: - keepAll.

PCHi-C

Libraries were processed in the same method as previously described11. Raw fastq data was processed by HiCUP (v0.7.3) with the following parameters set in the configuration file: bowtie2, longest di-tag length: 850, shortest di-tag length: 100. The intermediate file generated by HiCUP was further processed in R using CHiCAGO (v1.18.0) and processed as described in Freire-Pritchett et al12 to generate interaction files and scores. Interaction files generated by CHiCAGO was visualised on the WashU epigenome browser https://epigenomegateway.wustl.edu/browser/. The makePeakMatrix.R pipeline was used to generate a matrix file of all interactions in all PCHi-C samples.

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

Raw and processed data generated here can be found at Gene Expression Omnibus (GEO) under accession numbers GSE279589, GSE279594, GSE279643, GSE279644.

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	Information on sex or gender was not used in this study.
Reporting on race, ethnicity, or other socially relevant groupings	n.a.
Population characteristics	n.a.
Recruitment	Leukaemia patients that provided leukemia cells for this study were patients of the Hammersmith Hospital associated with Imperial College London. All patients gave specific informed consent for the use of surplus tissue. All samples were pseudo-anonymised on receipt and given a study ID.
Ethics oversight	Human leukaemia samples used in this research project were deposited into, stored in and subsequently retrieved from the Imperial College Healthcare Tissue Bank (ICHTB). ICHTB is approved by NRES to release human material for research (12/WA/0196). A sub collection dedicated to this project was initiated (MEC_AR_16_030) and access to this sub collection for this project was granted. Healthy BM samples were provided as cryopreserved samples by The John Goldman Centre for Cellular Therapy of Hammersmith Hospital and collected under respective licenses. All patients gave specific informed consent for the use of surplus tissue. All samples were pseudo-anonymised on receipt and given a study ID.

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	0

Data exclusions	0
Replication	0
Randomization	0
Blinding	0

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[ ]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[ ]	[ ] Clinical data
[ ]	[ ] Dual use research of concern
[ ]	[ ] Plants

Methods

n/a	Involved in the study
[ ]	[x] ChIP-seq
[ ]	[x] Flow cytometry
[ ]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used	Flow cytometry: Anti-CD10 (BioLegend, cl.HI10A), anti-CD19 (BioLegend, cl.HIB19), anti-CD179a (VpreB, BioLegend), anti-IgL (BioLegend). Western blot: Anti-phospho-CRKL (#3181), anti-H3K27ac (#4353), anti-Histone 3 (#9715), anti-Lamin B1 (#12586), anti-beta-Tubulin (#2128), anti-HA-tag (#3724), and anti-STAT5 (i.e., pan-STAT5A/B #94205), anti-STAT3 (#12640), anti-STAT6 (#5397), anti-P300 (#86377), anti-ETV5 (#16274). ChIP-Seq: anti-Histone H3 (acetyl K27) antibody – ChIP Grade (ab4729) (Abcam) and polyclonal rabbit IgG (isotype control) (sc2027).
Validation	*Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	All cell lines used were from DSMZ. Murine cells were from C57Bl/6 and TRP53BP1-/- mice as indicated and exclusively female. Gender information from leukemia cells from patients was not obtained.
Authentication	None of the cell lines was further authenticated.
Mycoplasma contamination	Cell lines were routinely tested for being negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

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	C57Bl/6 and Trp53bp1-/-
Wild animals	*Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Reporting on sex	mice were exclusively female
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	Experiments using murine cells were performed in agreement with ASPA guidelines and regulations and protocols approved by Home Office UK.

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 ICMJEguidelines for publication of clinical research and a completedCONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

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

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

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.

Raw and processed data generated here can be found at Gene Expression Omnibus (GEO) under accession numbers GSE279589, GSE279594, GSE279643, GSE279644.

Files in database submission

Provide a list of all files available in the database submission.

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

For murine experiments n=3 replicates were performed, for PCA analysis of different B-ALLs n=1 for each cell line/sample was performed. For functional experiments in Figure 5, n=2 experiments were performed for each.

Sequencing depth

20 million reads per sample

Antibodies

ChIP-Seq for H3K27ac was done as described in Boulianne et al5 using anti-Histone H3 (acetyl K27) antibody – ChIP Grade (ab4729) (Abcam) and polyclonal rabbit IgG (isotype control) (sc2027) (Santa Cruz Biotechnologies).

Peak calling parameters

To determine peak enrichment across the genome, macs2 (v2.2.7.1) callpeak was used, with an IgG ChIP used as the input control. The following parameters were used: -q 0.05, B, - SPMR, --broad (only for H3K27ac ChIP), and -g hs (for hg38) or mm (for mm39).

Data quality

Quality of raw sequencing reads was assessed using FastQC.

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	For processing of primary B-ALL samples, whole blood, bone marrow or leukapheresis from these patients was separated by density gradient using centrifugation according to the manufacturer's protocol to retrieve mononuclear cells. Purity of samples was checked by flow cytometry. For healthy controls, cryopreserved cells were thawed, sorted by flow cytometry using anti-human CD10 and CD19 antibodies. Cell lines were washed by PBS and stained for analysis by flow cytometry.
Instrument	BD LSRFortessa
Software	FLowjo
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	Cells were gate on live cells by FSC/SSC and gated on clear subpopulations defined by the antibodies used.

☒ 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	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
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

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

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

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

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

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.