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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	GraphPad Prism7, Microsoft Office Excel 2010, BWAv0.5.9, MATLAB (version 8.5, release R2015a), BD FACSDiva 6, FlowJo7.5.5, Xcalibur 2.1, Tune Plus 2.7
Data analysis	GESS1.2, R/Bioconductor3.2.2, Metascape 3.0, GenomeAnalysisTK-1.6-11, bwa Version:0.5.4 (R1273), Picard-tools-1.69, Samtools 0.1.17, Variant Effect Predictor (VEP) 2.7, MOLSOFT ICM, Spotfire 6.5.3, Mascot v2.5.1, Transproteomic pipeline (TPP) v3.3sqall, Pipeline Pilot 8.5.0.200, R 3.1.2

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 upon request. 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

The microarray data was deposited in GEO (GSE115690). The GEO dataset will be released upon publication. Other datasets that were generated during the current study are provided as supplemental material or
are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample size calculation was performed. Given resource constraints experiments were designed to support parametric analysis. Triplicates were used for the majority of studies unless otherwise indicated.
Data exclusions	No data excluded from analysis
Replication	Experiments were independently replicated at least twice and in majority of cases >2 times. All data was reproducible in the independent experiments
Randomization	Randomization is not relevant to these studies as experiments were performed using human cancer cell lines that were grown as a pool and then separated into individual tubes or wells on the day of the experiment.
Blinding	Blinding not relevant to these studies. Control groups were used and compared to experimental groups. Work described in this manuscript is exploratory research and experiments will not influence design of clinical trials.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	No restrictions upon reasonable request

Antibodies

Antibodies used	Details on antibodies used in studies including source, catalog number and dilutions are indicated in Supplementary Table 6

Validation	The ICD3 and SLC39A7/ZIP7 antibody was validated using recombinant protein and cell lines with presence or absence of the protein. In addition the SLC39A7 antibody was validated by genetic knockdown of the target using siRNA reagents. All other antibodies are widely used in the literature and the commercial company's spec sheet describes their validation.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HPB-ALL DSMZ ACC483 TALL-1 DSMZ ACC521 RPMI-8402 DSMZ ACC290 PF382 DSMZ ACC38 Loucy DSMZ ACC394 SUP-T1 DSMZ ACC140 SUP-T11 DSMZ ACC605 P12-Ichikawa DSMZ ACC34 MT-3 DSMZ ACC403 HSC-3 JCRB 0623 C33a ATCC HTB-31 L cells G. Weinmaster (UCLA) SN3T9 G. Weinmaster (UCLA) U2OS ATCC HTB-96
Authentication	All cell lines in the manuscript were authenticated by single-nucleotide polymorphism (SNP) fingerprinting
Mycoplasma contamination	All cell lines were tested for mycoplasma and confirmed negative
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in these studies.

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	Notch1 Cell surface staining: HPB-ALL cells were diluted to 1x106 cells/mL in FACS Buffer (PBS/0.1%BSA/0.01%NaN3). 2.5x105 cells/well were added to each well of a 96 well plate and centrifuged at 1500 rpm for 5 min at 4°C before removing the supernatant. Anti-Notch1 APC antibody or Mouse IgG Isotype Control labeled with APC (R&D) was added to the cell pellets, 10uL in 100 uL of FACS buffer and incubated for 1 hour at 4°C. The cells were washed and pelleted 2 times with 100 uL FACS Buffer. Finally, cells were resuspended in 200 uL FACS buffer and fluorescence values were measured with a BD FACSCanto II (BD Biosciences). Apoptosis: 0.1x106 cells were treated with compounds for 72hrs as indicated in the figures. Cell were washed with 1x PBS and resuspended in 1x Annexin binding buffer (10mM HEPES, 140mM NaCl, 2.5 mM CaCl2) containing 5uL FITC-AnnexinV (ThermoFisher) and 1 u g/mL PI. The mixture was incubated at room temperature for 10 minutes in the dark and then fluorescence values were measured with a BD FACSCanto II (BD Biosciences).
Instrument	FACSCantoII
Software	FlowJo10 (TreeStar), BDFACS Diva Software
Cell population abundance	10,000 total cellular events were collected for each sample after single cell gating (FSC vs SSC)
Gating strategy	For Notch 1 cell surface staining: Single cells were gated based on FSC vs SSC properties. Histograms were generated and gates were drawn with values above the isotype control indicating staining of Notch1 on the cell surface. Apoptosis: Cells were initially gated using forward and side scatter properties to isolate single cells. Scatter plots of AnnexinV staining vs PI staining were gated into quadrants. AnnexinV and PI negative were assigned as the viable cell population. AnnexinV and PI positive are cells undergoing apoptosis. PI positive and Annexin negative constitute dead cells and PI negative and AnnexinV positive is labeled as cell debris or early apoptotic. Figure exemplifying gating strategy is provided as supplementary figure 15

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