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	No custom software or code were used for data collection
Data analysis	The open-source software, tools, and packages used for data analysis in this study, as well as the version of each program, were ImageJ (v2.1.0), R (v3.5.3 and v3.6.1), FASTQC (v0.11.9), HISAT2 (v2.1.0), featureCounts (v2.0.1), Bowtie2 (v2.3), snpEff (v5.1), Mutect2 (v4.0), picard (v2.2), cellranger (v6.1.2), Seurat R package (v3.0.1), DESeq2 (Bioconductor v3.10), minfi (Bioconductor v3.10), ConsensusClusterPlus (Bioconductor v3.10), Heatmap.2 R package (gplots v3.13), and ggplot2 (v3.3.6). No custom software, tools, or packages were used.

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

Human tumor DNA methylation (n=119), RNA sequencing (n=41), whole exome sequencing (n=34), or single-cell RNA sequencing data (n=6) reported in this

manuscript will be deposited in the NCBI Gene Expression Omnibus. Cell line RNA-sequencing (n=6), selumetinib-treated cell line RNA-sequencing (n=10), CRISPRi NF2-deficient cell line RNA-sequencing (n=4), or single-cell RNA sequencing of mouse xenograft data (n=5) reported in this manuscript will similarly be deposited in the NCBI Gene Expression Omnibus. Additional RNA-sequencing and H3K27 trimethylation ChIP sequencing data from previously reported PRC2-intact or PRC2-deficient neurofibroma cell lines is available under GSE 118185 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE118185) or GSE118183 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE118183), respectively19. The publicly available GRCh37 (hg19, https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.13/) and GRCm38 datasets (mm10, https://www.ncbi.nlm.nih.gov/assembly/GCF_000001635.20/) were used in this study.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	n/a
Population characteristics	n/a
Recruitment	As part of routine clinical practice at UCSF, all patients included in this study signed an informed consent waiver to contribute de-identified data to scientific research projects.
Ethics oversight	UCSF Institutional Review Board (13-12587, 17-22324, 17-23196, 18-24633)

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	No sample size calculation was performed given the rarity of these tumors - all retrospectively identified patient samples meeting diagnostic criteria were included in this study.
Data exclusions	No data was excluded
Replication	Attempts at replication were succcessful
Randomization	Retrospective study, randomized not performed
Blinding	All molecular or genomic analyses were performed blinded to the clinical data of samples.

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

Methods

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

Antibodies

Antibodies used	IHC: H3K27me3 (Cell Signaling Technology, #9733, clone C36B11, 1:50 dilution), SOX10 (Cell Marque, #383R-1, clone EP268, 1:50 dilution), S100B (Ventana, #760-2523, 1:2 dilution), or p53 (Dako, #GA61661-2, clone DO-7, 1:50 dilution). IB: pERK (Cell Signaling Technologies, #4370, 1:1,000 dilution), beta tubulin (Developmental Hybridoma Studies Bank, #E7, 1:10,000 dilution), pAkt (Cell Signaling Technologies, #4060, 1:1,000 dilution), pMEK (Cell Signaling Technologies, #9121, 1:1,000 dilution), pPAK (Cell Signaling Technologies, #2601, 1:1,000 dilution), Caspase-3 (Cell Signaling Technologies, #9662, 1:1,000 dilution), Caspase-7 (Cell Signaling Technologies, #9492, 1:1,000 dilution), or NF2 (Abcam, #ab88957, clone AF1G4, 1:2,000 dilution).
Validation	Antibodies validated by manufacturers for all reagents and in CRISPRi cell lines where relevant.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Cell lines were obtained from the Neurofibromatosis Therapeutic Acceleration Program or American Type Culture Collection
Authentication	Cell lines were verified by next generation sequencing as noted in the manuscript
Mycoplasma contamination	All cell lines were tested for mycoplasma and found negative. Our research group carries out mycoplasma testing once per month on all active cell lines.
Commonly misidentified lines (See ICLAC register)	None

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	NU/NU mice (Harlan Sprague Dawley)
Wild animals	n/a
Reporting on sex	Only female recipient mice were used for subcutaneous xenograft experiments in accordance with institutional practice
Field-collected samples	n/a
Ethics oversight	UCSF Institutional Animal Care and Use Committee (IACUC, AN174769)

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