

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	The idat files resulting from the iScan were used for all analyses. Initially, a quality filter was applied using the SeSaMe package (1.12.9) function "sesameQC".
Data analysis	All data analyses were performed in R (4.1.1). Plots were generated by ComplexHeatmap, umap, circlize, ggplot2 and ggalluvial. Significantly different CpG sites were determined by limma (v3.58.1). The CpG sites located in the promoter region of a gene were determined using https://github.com/zhou-lab/KYCG_knowledgebase_MM285 and then displayed as a heatmap with ComplexHeatmap (v2.18.0). The Epidish package (2.10.0) and PRmeth (https://doi.org/10.1186/s12859-022-04893-7) were used for deconvolution approaches. Pre-processing of human reference samples was done with minfi (1.40.0). For gene expression array data, the DESeq2 package (v1.46.0) and the EnhancedVolcano package (v1.24.0) were used. For mouse-human matching, we trained a random forest classifier using the randomForest package (v4.7-1.2). Data was visualized using IGV, Adobe Illustrator (28.5), UMAP (umap, v0.2.10.0) and Affinity Designer. No custom code or software has been generated within this article.

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](#)

All data necessary for the conclusions of the study are provided with the article. All mouse DNA methylation data employed in this project can be found under GEO (GSE275151). Human rhabdoid tumor DNA methylation data has been downloaded from GSE123601, GSE109381 and GSE228091. Transcriptomic data of different mouse models were downloaded from GSE188654, GSE103348, GSE112699, GSE120344, GSE107263, GSE155471, GSE65888, GSE62625, GSE24628, GSE50824 and GSE2426. Source data underlying all graphical representations used in the figures are provided as Supplementary Tables. Plasmids and engraftable tumor cells of novel models for pHGG will be shared with the scientific community upon request.

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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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](https://www.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

Data exclusions

Replication

Randomization

Blinding

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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used

GFAP GA5 1:200 MAB3402 Sigma/Merck
 Olig2 1:100 ABE1024 Merck
 CD20 E3N7O 1:100 70168 Cell Signaling
 CD3 SP7 1:75 ab16669 abcam
 Iba-1 1:500 019-19741 WAKO
 anti-HA Tag (C29F4) Lot: 11 1:1000 3724S Cell Signaling
 CD19 BUV395 1D3 1:300 563557 BD
 LIVE/DEAD™ Blue 1:500 L34961 ThermoFisher
 CD11b BUV805 M1/70 1:500 568345 BD
 Siglec H Pacific Blue 551 1:100 129609 BioLegend
 Ly6C BV510 HK1.4 1:500 128033 BioLegend
 NK1.1 BV785 PK136 1:400 108749 BioLegend
 TCR β FITC H57-597 1:500 109205 BioLegend
 Ly6G PerCP-Cy5.5 1A8 1:500 127615 BioLegend
 CD127 PE eBioSB/199 1:50 12-1273-82 eBioscience
 CD335 (NKp46) PE/Dazzle™ 594 29A1.4 1:300 137629 BioLegend
 CD4 PE-Cy7 GK1.5 1:500 15-0041 eBioscience
 CD25 APC PC61 1:200 102012 BioLegend
 CD8 Alexa Fluor 700 53-6.7 1:500 56-0081-82 ebioscience
 CD45 APC efluor780 30-F11 1:200 56-0451 ebioscience

Validation

https://www.cellsignal.com/products/primary-antibodies/ha-tag-c29f4-rabbit-mab/3724?srsltid=AfmBOopbrFOvwDuHuqqezF7Dwli92-vCBoZ97Se_KF83VLauH3c99816

https://www.sigmaaldrich.com/DE/de/product/mm/mab3402?mmredirect=1&utm_source=google&utm_medium=cpc&utm_id=12478270955&utm_campaign=%7Bcampaignname%7D&utm_content=119588671918&utm_term=&gad_source=1&gad_campaignid=12478270955&gclid=Cj0KCQjwndHEBhDVARIsAGhOg3BmZC6QAO61rxPQEj2ODF7mDBIn48vmrmLr0wdvDB8I37kSkqWltcYaAlMaEALw_wcB

https://www.sigmaaldrich.com/DE/de/product/mm/abe1024?utm_source=google&utm_medium=cpc&utm_id=12478270955&utm_campaign=%7Bcampaignname%7D&utm_content=119588671918&utm_term=&gad_source=1&gad_campaignid=12478270955&gclid=Cj0KCQjwndHEBhDVARIsAGhOg3BHVZmnmAF175AjbKzb3mkUD3-X_DDutR9uBrf_R0lQBaoJktB6nJcaAgjxEALw_wcB

https://www.cellsignal.com/products/primary-antibodies/cd20-e3n7o-xp-rabbit-mab/70168?srsltid=AfmBOoq8YeVRXqwr2NQ7CDbU5aLYf5qL19StmZ_9zrmUa5-4ZiTrBorT

https://www.abcam.com/en-us/products/primary-antibodies/cd3-epsilon-antibody-sp7-ab16669?srsltid=AfmBOoo3_ymCTWJWHwEs1vhqqmpsQcldZHppnRy_V2TkhHmPOYS5QIFL

<https://labchem-wako.fujifilm.com/us/product/detail/W01W0101-1974.html>

https://www.bdbiosciences.com/en-pl/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/buv395-rat-anti-mouse-cd19.563557?tab=product_details

<https://www.fishersci.de/shop/products/live-dead-fixable-blue-dead-cell-stain-kit-uv-excitation-3/15582241?srsltid=AfmBOoqB8-RJ8RrXcKNwtzjUmIQIMPBcP9sJjcgwrfnK7H5KnW208vY4>

https://www.bdbiosciences.com/en-dk/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/buv805-rat-anti-cd11b.568345?tab=product_details

<https://www.biolegend.com/de-de/products/pacific-blue-anti-mouse-siglec-h-antibody-6904>

<https://www.biolegend.com/de-de/products/brilliant-violet-510-anti-mouse-ly-6c-antibody-8726>

<https://www.biolegend.com/de-de/products/brilliant-violet-785-anti-mouse-nk-1-1-antibody-10367>

<https://www.biolegend.com/de-de/products/fitc-anti-mouse-tcr-beta-chain-antibody-270>

<https://www.thermofisher.com/antibody/product/CD45-Antibody-clone-30-F11-Monoclonal/56-0451-82>
<https://www.thermofisher.com/antibody/product/CD8a-Antibody-clone-53-6-7-Monoclonal/56-0081-82>
<https://www.biolegend.com/de-de/products/apc-anti-mouse-cd25-antibody-420?GroupID=BLG10428>
<https://www.thermofisher.com/antibody/product/CD4-Antibody-clone-GK1-5-Monoclonal/15-0041-82>
<https://www.biolegend.com/en-gb/products/pe-dazzle-594-anti-mouse-cd335-nkp46-antibody-13172?GroupID=BLG8849>
https://www.antibodyregistry.org/AB_953562
<https://www.biolegend.com/de-de/products/percp-cyanine5-5-anti-mouse-ly-6g-antibody-6116>

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	Mus musculus, NSG, CD1 and C57BL/6, up to 1.5 years, depending on the model and animal permit of the research institute
Wild animals	Study did not involve wild animals.
Reporting on sex	Sex has not been considered in this study.
Field-collected samples	Study did not involve samples collected in the field.
Ethics oversight	All animal protocols for model generation, including allografts, were approved by the relevant authority (Regierungspräsidium Karlsruhe) under registration numbers G-168/17 and G-265/21, or by the state of Hamburg (Reference N2019/99), respectively.

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

Plants

Seed stocks	The study does not comprise plants.
Novel plant genotypes	The study does not comprise plants.
Authentication	The study does not comprise plants.-