nature portfolio

Corresponding author(s): *Double-anonymous peer review submissions: write DAPR and your manuscript number here instead of author names.*

Last updated by author(s): *YYYY-MM-DD*

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 comercial, open source used
Data analysis	limma package (v.3.44.3); getSnpBeta function from minfi; ChAMP (v.2.16.2); software R (v.4.0.2); beta2m function of the lumi package (v.2.40.0); gsameth function from the missMethyl package (v.1.22.0)

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

statement included

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	In this study, we reported the biological sex of participants using the terms "male" and "female," although the table in the manuscript uses the term "gender." We acknowledge that sex refers to biological differences, while gender encompasses socially constructed roles and identities. The term "gender" in the table should be interpreted as sex in this context, as no information on participants' gender identity was collected or analyzed. This distinction will be clarified to align with current reporting guidelines and promote accurate and inclusive scientific communication.
Reporting on race, ethnicity, or other socially relevant groupings	No data on race, ethnicity, or other socially relevant groupings were collected or analyzed in this study, as these variables were not relevant to the study design or research objectives.
Population characteristics	Population characteristics reported in this study include age and SDHB mutation status. Age at diagnosis was recorded for all participants and is presented in Table 1. In addition, individuals were stratified based on the presence or absence of pathogenic variants in the SDHB gene, a clinically relevant biomarker associated with disease aggressiveness in pheochromocytomas and paragangliomas.
Recruitment	Tumor tissue samples were collected from 37 patients diagnosed with PPGL between 2003 and 2019 at six clinical centers in Spain and the USA. Participating institutions included Hospital Universitario Central de Asturias (Spain), Mayo Clinic (USA), Hospital Universitario de Bellvitge (Spain), Hospital Provincial de Castellón (Spain), Hospital Universitario La Fe (Spain), and Complejo Universitario de Navarra (Spain).
Ethics oversight	Informed consent was obtained from all participants, and the study was approved by the Ethics Committee of the Hospital Universitario Central de Asturias. All procedures were conducted in accordance with institutional guidelines and the principles of the Declaration of Helsinki.

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	This study includes 37 patients with pheochromocytomas and paragangliomas (PPGLs), a rare group of neuroendocrine tumors. Within this inherently limited patient population, only a subset carries pathogenic SDHB mutations and an even smaller proportion presents with metastatic disease (fewer than 20%). Given these constraints, we assembled the largest and most representative cohort available across multiple clinical centers, aiming to ensure the biological and clinical relevance of our findings. While the sample size limits the power for broad statistical generalization, the study is designed as an exploratory investigation to uncover meaningful molecular patterns in this rare disease context. These findings may guide future studies with larger or prospective cohorts.
Data exclusions	No data were excluded from the analyses. All samples that met the inclusion criteria and passed quality control were retained for downstream analysis.
Replication	Cell-based stdies were replicated
Randomization	Randomization was not applicable in this study, as the research was designed to investigate specific molecular features in a defined subgroup of patients with pheochromocytomas and paragangliomas, particularly those carrying SDHB mutations. The inclusion of cases was intentional and based on clinical and genetic characteristics relevant to the study objectives, rather than random allocation.
Blinding	Analyses of epigenetic data were performed with blinding to clinical and genetic information to reduce bias in data interpretation. Other aspects of the study, such as sample selection, were not blinded due to the observational and retrospective nature of the research.

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: anti-SDHB antibody (Sigma-Aldrich Cat# HPA002868, RRID:AB_1079889); Anti-β-actin (Sigma-Aldrich, Cat# A1978, RRID:AB_476692)

Validation: externaly validated (comercial)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): Primary human cells were derived from fresh tumor tissues obtained from patients undergoing surgical resection of pheochromocytomas or paragangliomas (PPGLs) at the Hospital Universitario Central de Asturias (Spain) with appropriate informed consent and institutional ethical approval (Research Ethics Committee on Medicinal Products of the Principality of Asturias; Code 2020.547; Oviedo, Spain).

Authentication: As these are primary, patient-derived cells and not established or commercially available cell lines, standard authentication methods such as STR profiling were not applicable. Tumor origin and histopathological diagnosis were confirmed by a certified pathologist. In select cases, tumor genotype (e.g., SDHx mutation status) was confirmed by genetic testing.

As these are primary, patient-derived cells and not established or commercially available cell lines, standard authentication methods such as STR profiling were not applicable. Tumor origin and histopathological diagnosis were confirmed by a certified pathologist. In select cases, tumor genotype (e.g., SDHx mutation status) was confirmed by genetic testing.

Mycoplasma contamination: All primary cultures were routinely tested for mycoplasma contamination using PCR-based assay and were confirmed to be negative.

Commonly misidentified lines (See ICLAC register): Not applicable. The study did not use any established cell lines listed in the ICLAC register of misidentified cell lines.

Palaeontology and Archaeology

Specimen provenance: NA

Specimen deposition: NA

Dating methods: NA

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight: NA

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: NA

Wild animals: NA

Reporting on sex: NA

Field-collected samples	NA
Ethics oversight	NA

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 ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NA
Study protocol	NA
Data collection	NA
Outcomes	NA

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	NA
Novel plant genotypes	NA
Authentication	NA

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.*	NA
Files in database submission	NA
Genome browser session (e.g. UCSC)	NA

Methodology

Replicates	NA
Sequencing depth	NA
Antibodies	NA
Peak calling parameters	NA
Data quality	NA
Software	NA

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	NA
Instrument	NA
Software	NA
Cell population abundance	NA
Gating strategy	NA

☐ 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	NA
Design specifications	NA
Behavioral performance measures	NA

Acquisition

Imaging type(s) NA

Field strength NA

Sequence & imaging parameters NA

Area of acquisition NA

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software NA

Normalization NA

Normalization template NA

Noise and artifact removal NA

Volume censoring NA

Statistical modeling & inference

Model type and settings NA

Effect(s) tested NA

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

Statistic type for inference NA

(See Eklund et al. 2016)

Correction NA

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 NA

Graph analysis NA

Multivariate modeling and predictive analysis NA