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	The custom computational analysis pipeline consists of three modules: (i) A bioinformatics pipeline for single-cell mutation calling and genotyping, available at https://github.com/haochenz96/TapVarCallSmk or 10.5281/zenodo.17309019. (ii) Copy number clone calling pipeline, Tapestri-CN, available at https://github.com/haochenz96/tap_cn_calling or 10.5281/zenodo.17309013. (iii) The fast-ConDoR pipeline for phylogenetic analysis, available at https://github.com/Bolladeen/full-ConDoR or 10.5281/zenodo.17309066.
Data analysis	The downstream analyses to reproduce Figures in the manuscript are available at: https://github.com/haochenz96/Tapestri_main_manuscript_analysis or 10.5281/zenodo.17309023.

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

Processed H5 files required for replicating relevant analysis using provided scripts (detailed in below section) are published on Zenodo: https://doi.org/10.5281/zenodo.17155593.
Raw BAM files are deposited to European Genomephenome Archive (EGA) under Study ID EGAS50000001351. Readers interested in gaining access through EGA need to contact the data access committee (DAC) of this dataset and start an application. The DAC will try to respond within two weeks but may take longer in special conditions. The MSKCC MDP DAA, to be provided by the DAC and include guidelines and restrictions on data usage, must be signed. Once the application is approved, an EGA account will be provided for data access. The time length of access to the data will be determined by the DAC on a case-by-case basis. Further information about EGA can be found at https://ega-archive.org and "The European Genomephenome Archive of human data consented for biomedical research" (http://www.nature.com/ng/journal/v47/n7/full/ng.3312.html). Other data may be made available upon reasonable 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	Sex breakdown is as follows: male = 14, female = 10. No sex-based analysis was done as that was deemed irrelevant.
Reporting on race, ethnicity, or other socially relevant groupings	Socially-relevant grouping was not applicable in this study. The race breakdown is as follows: white = 16, white spanish/hispanic/latino not otherwise specified (NOS) = 4, black = 1, native American/American Indian/Alaska = 1. 2 patients preferred not to answer. The imbalanced racial composition might confound this study as pancreatic cancers in different populations might be subject to different oncogenic mutational process and thus different genomic features. This could not be well accounted for because we only had access to patients treated at Memorial Sloan Kettering Cancer Center in New York, USA.
Population characteristics	Age at diagnosis statistics of this cohort of N=24 are: mean = 64.74 years, standard deviation = 12.21 years. 6 patients had germline BRCA2 mutations. These patients were intentionally included as their genomic evolution is of high clinical relevance; the proportion in the cohort (25%) is higher than that of the general pancreatic cancer population (~5%, according to Park et al., JAMA 2021). 8 patients' samples in the resected tissue biobank program were treatment naive; 11 patients' samples in the autopsy program were post-treatment; the other 6 patients had longitudinal samples before and after treatment.
Recruitment	Patients treated at Memorial Sloan Kettering Cancer Center were given the option to participate in the relevant research programs (resected tissue biobanking, Last Wish Program and Tracking of Pancreatic Cancer Regression and Resistence) and elected to donate their tissues with written consent.
Ethics oversight	Use of human samples in this study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center (under protocols #06-107, #15-021, #15-149).

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	The total cohort size (N=24) was as big as we could achieve given the economic cost and logistical complexity of conducting the deep single-cell DNA sequencing analysis on primary human patient samples.
Data exclusions	No patient was excluded from this study.
Replication	Replication was not applicable due to the use of human patient samples. Technical replication was done at each step: single-nucleus DNA sequencing and downstream analyses.
Randomization	Not applicable.

Blinding	Not applicable.

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

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.*