

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](#).

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

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|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A description of all covariates tested |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | 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

For data collection we used Excel (V2016 and V2000, Microsoft, Redmont, WA), DatLab Software V6 and 7 (Oroboros Instruments, Innsbruck Austria), PROSize (Advanced Analytical Technologies, Ames, IA), Ion Torrent Suit (Life Technologies, Waltham, MA) and Illumina HiSeq 2500 Instrument Software (Illumina, San Diego, CA).

Data analysis

Data analyses were performed utilizing commercially or publicly available software. Software tools, including versions, references and links are provided in the Methods section.

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. 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

Data that support the findings of this study are available within the article and its supplementary files or from the authors upon reasonable request. Supplementary Information provides Supplementary Tables and Figures, Supplementary Data 1 provides a list of mtDNA Heteroplasmies, the Source Data File provides data sets underlying Fig. 2-8 and Supplementary Fig. 1-4 and 6-8. The Supplementary Software iSee Package for 3D visualization of Complex I mutations is provided for download or online access at [<https://github.com/genepi/mt-c1>]. DNA and RNA sequence data sets have been deposited in EGA (European Genome-Phenome Archive [www.ega-archive.org]) under the following accession numbers: EGAD00001005931 (RNAseq data set, [<https://ega-archive.org/datasets//EGAD00001005931>]) and EGAD00001005945 (mtDNA data set, [<https://ega-archive.org/datasets//EGAD00001005945>]). Prostate cancer gene expression datasets with survival information were accessed at the Cancer Genome Atlas (TCGA) Data Portal ([<https://cancergenome.nih.gov/>]): TCGA-PRAD ([<https://portal.gdc.cancer.gov/projects/TCGA-PRAD>]) and the Gene Expression Omnibus portal ([<https://www.ncbi.nlm.nih.gov/geo/>]): GSE16560 ([<https://www.ncbi.nlm.nih.gov/geo/acc/GSE16560>]).

www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE16560)), GSE40272 ([https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE40272]), GSE70768 ([https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE70768]) and GSE70769 ([https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE70769]). Protein structure data were accessed at the Protein Data Base (PDB, [https://www.rcsb.org/]: 4HE8 ([https://www.rcsb.org/structure/4HE8]), 4HEA ([https://www.rcsb.org/structure/4HEA]), 5STD ([https://www.rcsb.org/structure/5STD]), 5XTC ([https://www.rcsb.org/structure/5XTC])).

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	50 paired malignant/nonmalignant tissue samples
Data exclusions	no data were excluded
Replication	Measurement of split tissue samples in HRR analysis, 3 NGS runs for mtDNA samples, paired-end NGS for RNA samples, 3-6 biological replicates for cell line HRR analysis.
Randomization	No randomization. Groups according to clinical parameters (tumor grading, patients age, PSA and free serum levels, respirometry pattern, presence/absence of mutations, gene expression signature)
Blinding	No 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 type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data

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	anti-p63 (4A4) Mouse Monoclonal Primary Antibody, Roche, #05867061001 Monoclonal Rabbit Anti-Human P504S (AMACR) Clone 13H4, #M3616, DAKO-Agilent anti-VADC1 (D73D12, Cell Signaling Technologies, Leiden, The Netherlands; 1:400, anti-SDHA (D6J9M, Cell Signaling Technologies; 1:400) anti-NDUFS4 (EP7832, Abcam, Cambridge, UK; 1:200)
Validation	IHC antibodies used in routine and/or validated by provider. Antibodies used in previous studies (doi: 10.1038/pcan.2013.4, 10.1155/2018/1347174)

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	LNCaP and PC3 prostate cancer and benign prostate epithelial RWPE1 cell lines were purchased from the American Type Culture Collection (ATCC; Rockville, MD). DuCaP prostate cancer cells were obtained from Radboud University, Nijmegen, The Netherlands. The human telomerase reverse transcriptase-immortalized benign prostate epithelial cell line EP156T was established by hTERT overexpression (doi: 10.1158/0008-5472.CAN-05-2183).
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Authentication	Short tandem repeat analysis using the AmpFISTR® SGM Plus® PCR amplification kit (Applied Biosystems, Waltham, MA)
Mycoplasma contamination	Regular testing, Venor GeM-qEP PCR based assay, BioProducts, #11-9025
Commonly misidentified lines (See ICLAC register)	Not included

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Prostate cancer patients undergoing radical prostatectomy as a first line treatment. Patients received standard of care radical prostatectomies for treatment of prostate cancer.
Recruitment	University Hospital for Urology, Medical University of Innsbruck
Ethics oversight	Ethics Committee of the Medical University Innsbruck

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	Study with tissue samples of patients who received standard of care radical prostatectomy, no clinical trial
Study protocol	Patients underwent standard-of-care radical prostatectomy. Tissue samples for the study were afterwards excised from the radical prostatectomy specimens by a certified uropathologist.
Data collection	Tissue Archive Database of Prostate Cancer Biobank (Departments of Urology and Pathology, Medical University Innsbruck)
Outcomes	PSA serum level, tumor histopathology