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Reporting Summary

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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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 Image: Apero/Leica Biosystems ScanScope FL, CODEX Instrument Manager (CIM) v1.29.

Data analysis Statistical analyses were all performed using R Statistical Software version 4.5.0 and GraphPad Prism v9.3. Functional profiling: GraphPad Prism v9.3. Imaging: HALO v3.1, CODEX Processor v1.7.0.6, QuPath v0.5.1, GraphPad Prism v9.3, R 4.5, and Python 3.8. Custom Python script for cell annotation that we have made publicly available (<https://github.com/Powers-Brissova-Research-Group/pediatric-pancreas-image-analysis>).

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](#)

Imaging data is available via Pancreatlas (RRID:SCR_018567; <https://pancreatlas.org>).

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

Donor demographic information is detailed in Figure 1, Figure S1, and Table S1. Information about biological sex came from the medical record. Where appropriate, data are analyzed based on sex.

Reporting on race, ethnicity, or other socially relevant groupings

Donor demographic information is detailed in Figure 1, Figure S1, and Table S1. Information about race or ethnicity came from the medical record. Where appropriate, data are analyzed based on race or ethnicity.

Population characteristics

De-identified donor information is detailed in Table S1.

Recruitment

Pancreata from organ donors without diabetes were obtained through partnerships of islet isolation centers with the International Institute for Advancement of Medicine (IIAM), National Disease Research Interchange (NDRI), and local organ procurement organizations. De-identified donor information is detailed in Figure 1, Figure S1, and Table S1.

Ethics oversight

The Institutional Review Boards at the Vanderbilt University Medical Center and University of Florida declared that studies on de-identified human pancreatic specimens do not qualify as human subject research

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

Sample sizes for multivariable analyses and developmental groups were driven by availability of organs and tissue that met predefined collection criteria. This study's sample size is largest of its kind including analysis of 123 pediatric pancreas donors (36 neonatal, 36 infancy, 51 childhood) and islets from 14 adult donors used for comparison in functional studies. Accounting of donor information and the number and specific donors used for each analysis included in the manuscript is detailed in Table S1.

Data exclusions

Imaging: tissue and islet areas were annotated by hand to exclude out-of-focus regions and poor tissue quality (see more details in Methods section of manuscript)

Replication

We validated the robustness of our findings through the use of a large donor cohort.

Randomization

De-identified medical histories included information on human tissue specimens based on age, sex, BMI, race/ethnicity, islet isolation site and islet processing parameters. Detailed information, including sample types and experimental usage for each donor is available in Table S1. See also Results and Methods.

Blinding

Data were generated using quantitative methods that were applied uniformly to all samples regardless of group assignment. In cases where experimenter input was required (e.g., algorithm tuning for image analysis), sample group assignment was hidden in effort to mitigate any experimental bias.

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

Primary antibodies used in multiplex antibody-based imaging (see Table S2A) included: ACTA2 (Rabbit, Cell Signaling, 50513SF, RRID:AB_2924256, 1:600), ARX (Sheep, R&D, AF7068, RRID:AB_10973178, 1:200), ATP1A1 (Rabbit, Cell Signaling, 99935SF, RRID:AB_2798866, 1:200), CD11c (Mouse, Akoya Biosciences, 4350012, RRID:AB_2895050, 1:100), CD14 (Mouse, BioLegend, 325602, RRID:AB_830675, 1:100), CD163 (Mouse, BioLegend, 333602, RRID:AB_1088991, 1:200), CD19 (Mouse, Akoya, 4550099, RRID:AB_2924255, 1:100), CD206 (Mouse, BioLegend, 321102, RRID:AB_571923, 1:200), CD3 (Mouse, Akoya Biosciences, 4350008, RRID:AB_2895047, 1:100), CD31 (Mouse, Akoya Biosciences, 4250009, RRID:AB_2895051, 1:400), CD34 (Mouse, BioLegend, 343602, RRID:AB_1732014, 1:200), CD39L3 (Mouse, N/A, RRID:AB_2752250, 1:100), CD4 (Mouse, Akoya Biosciences, 4350010, RRID:AB_2895048, 1:100), CD45 (Mouse, Akoya Biosciences, 4150003, RRID:AB_2895052, 1:200), CD8 (Mouse, Akoya Biosciences, 4150004, RRID:AB_2895049, 1:100), CHGA (Mouse, Novus, NBP2-34674, RRID:AB_2864388, 1:400), COL-IV (Rabbit, Abcam, ab226485, RRID:AB_2801511, 1:50), COL1A1 (Mouse, Abcam, ab6308, RRID:AB_305411, 1:200), COL4A1 (Rabbit, Abcam, ab6586, RRID:AB_305584, 1:100), CPEP (Mouse, ThermoFisher, MA1-19159, RRID:AB_1073884, 1:200), GCG (Mouse, Abcam, ab10988, RRID:AB_297642, 1:200), GHRL (Rat, R&D, MAB8200, RRID:AB_2637039, 1:400), HLA-DR (Mouse, BioLegend, 307602, RRID:AB_314684, 1:300), IBA1 (Rabbit, Abcam, ab221790, RRID:AB_2924254, 1:200), ISL1 (Mouse, BD, 562546, RRID:AB_11154228, 1:100), Ki67 (Mouse, Akoya Biosciences, 4250019, RRID:AB_2895046, 1:600), KRT (Mouse, Akoya Biosciences, 4150020, RRID:AB_2924252, 1:500), KRT19 (Rabbit, Abcam, ab195872, RRID:AB_2924252, 1:400), LAMA2 (Rabbit, Abcam, ab238458, RRID:AB_2924253, 1:200), MCAM (Mouse, BioLegend, 361002, RRID:AB_2562883, 1:150), NCAM1 (Mouse, BioLegend, 304602, RRID:AB_314444, 1:250), NEUROD1 (Mouse, BD, 563000, RRID:AB_2737942, 1:100), NKX2-2 (Mouse, DSHB, 74.5A5, RRID:AB_531794, 1:200), PAX6 (Rabbit, BioLegend, 901301, RRID:AB_2565003, 1:200), PDX1 (Rabbit, Cell Signaling, 5679S (custom), RRID:AB_10706174, 1:100), PPY (Mouse, R&D, MAB62971, RRID:AB_11127208, 1:600), pS6-235 (Rabbit, Cell Signaling, 81736SF, RRID:AB_2938546, 1:300), pS6-240 (Rabbit, Cell Signaling, 35708SF, RRID:AB_2938547, 1:300), SST (Mouse, Novus, NBP2-37447, RRID:AB_2890053, 1:600), SYP (Rabbit, Cell Signaling, 25056SF, RRID:AB_2924257, 1:300), TUBB3 (Mouse, BioLegend, 801201, RRID:AB_2313773, 1:150).

Primary antibodies used for immunohistochemistry imaging (see Table S4A) included: CPEP (Rat, DSHB, GN-ID4, RRID_AB_2255626, 1:100), CD31 (Mouse, BD Biosciences, 550389, RRID_AB_2252087, 1:100), COL4A1 (Rabbit, Abcam, ab6586, RRID_AB_305584, 1:1000), GHRL (Mouse, Abcam, ab57222, RRID_AB_941760, 1:5000), GHRL (Rat, R&D Systems, MAB8200, RRID_AB_2637039, 1:1000), GCG (Mouse, Abcam, ab10988, RRID_AB_297642, 1:500), GCG (Rabbit, Cell Signaling, 2760s, RRID_AB_659831, 1:10k), GCG (Guinea pig, Linco (Millipore), 4031, RRID_AB_433707, 1:1k-10k), GCG (Rabbit, Linco (Millipore), 4030, RRID_AB_1977523, 1:1000), GP2 (Mouse, MBL International, D277-3, RRID_AB_10598500, 1:250), GP2 (Mouse, P. Streeter, N/A, 1:100), INS (Guinea pig, Abcam, ab7842, RRID_AB_306130, 1:1000), INS (Guinea pig, Cell Marque, 273A-14, RRID_AB_1158520, 1:100-500), INS (Guinea pig, Dako (Agilent), A0564, RRID_AB_10013624, 1:1000), INS (Guinea pig, Linco (Millipore), 4010, RRID_AB_1587205, 1:1000), INS (Goat, Santa Cruz, sc7839, RRID_AB_2296108, 1:100), Ki67 (Rabbit, Abcam, ab15580, RRID_AB_443209, 1:5000), NKX6.1 (Rabbit, BCBC (P. Serup), AB1069, N/A, 1:1000-2000), NKX6.1 (Mouse, DSHB, F55A12, RRID_AB_532379), PPY (Rabbit, Bachem, T-4088, RRID_AB_518533, 1:1000), PPY (Mouse, R&D Systems, MAB62971, RRID_AB_11127208, 1:100), PAX6 (Rabbit, BioLegend, 901302, RRID_AB_2565003, 1:2000), PAX6 (Rabbit, Covance, PRB-278P, RRID_AB_291612, 1:200), PTF1A (Goat, C. Wright, N/A, 1:500), SST (Sheep, American Research Products, 13-2366, RRID_AB_1542966, 1:500), SST (Goat, Santa Cruz, sc7819, RRID_AB_2302603, 1:500-1000), SYN1/2, Rabbit, Synaptic Systems, 106002, RRID_AB_887804, 1:200).

Secondary antibodies were purchased from Jackson ImmunoResearch (see Table S4B): Goat IgG-Cy5 (Donkey, 705-175-147, 1:200), Goat IgG-Cy2 (Donkey, 705-225-147, 1:500), Goat IgG-Cy3 (Donkey, 705-165-147, 1:500), Guinea pig IgG-AlexaFluor 488 (Donkey, 706-545-148, 1:500), Guinea pig IgG-AlexaFluor 647 (Donkey, 706-605-148, 1:200), Guinea pig IgG-Cy2 (Donkey, 706-225-148, 1:500), Guinea pig IgG-Cy3 (Donkey, 706-165-148, 1:500), Guinea pig IgG-Cy5 (Donkey, 706-175-148, 1:200), Mouse IgG-Cy2 (Donkey, 715-225-150, 1:500), Mouse IgG-Cy3 (Donkey, 715-165-150, 1:500), Mouse IgG-Cy5 (Donkey, 715-175-150, 1:200), Rabbit IgG-AlexaFluor 488 (Donkey, 711-545-152, 1:500), Rabbit IgG-Cy2 (Donkey, 711-225-152, 1:500), Rabbit IgG-Cy3 (Donkey, 711-165-152, 1:500), Rabbit IgG-Cy5 (Donkey, 711-175-152, 1:200), Rat IgG-AlexaFluor 488 (Donkey, 712-545-153, 1:500), Rat IgG-Cy2 (Donkey, 712-225-153, 1:500), Rat IgG-Cy3 (Donkey, 712-165-153, 1:500), Rat IgG-Cy5 (Donkey, 712-175-153, 1:200), Sheep IgG-Cy2 (Donkey, 713-225-147, 1:500), Sheep IgG-Cy3 (Donkey, 713-165-147, 1:500), Sheep IgG-Cy5 (Donkey, 713-175-147, 1:200).

Validation

Antibodies used in this study are commercially available and validated (see Methods and Supplemental Tables listed above for manufacturer information).

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 *Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*

Study protocol *Note where the full trial protocol can be accessed OR if not available, explain why.*

Data collection *Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*

Outcomes *Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

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, mosaicism, off-target gene editing) were examined.*