

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
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size (<i>n</i>) 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 checked="" type="checkbox"/>	<input 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 checked="" type="checkbox"/>	<input type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 checked="" type="checkbox"/>	<input type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), 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	Confocal images were acquired with Zeiss Zen software (v2.6). Bioenergetic experiments were generated using Seahorse Wave Desktop Software v2.6.1 (Agilent) and Cytation 5 (BioTek Instrument). Western blot membranes were visualized using iBright Analysis software (v1.8.1). qRT-PCR data was acquired with QuantStudio Real-Time PCR software (v1.3). Confocal images were acquired on Zeiss LSM780 or Zeiss LSM800 confocal microscopes. Cell sorting was performed with BD Aria Fusion. Metabolomics raw data were processed in Bruker Compass TargetAnalysis (v3.1). MEA data were acquired with Multi Channels Systems (v2.0.11.0). Electron microscopy: MAPS software package (v3.27).
Data analysis	Image analysis: Fiji Image J (v2.14.0); Statistics: Prism (v10); Bioenergetic experiments: Agilent Seahorse Wave Desktop Software v2.6.1; General expression data analysis: ThermoFisher Cloud (web-based analysis platform), Qiagen GeneGlobe (web-based analysis platform); Metabolomics data analysis: Bruker Compass DataAnalysis (4.1). MEA data analysis: Multi Channel Analyzer (Multi Channel Systems, v 2.0.6.0).

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](#)

All data supporting the findings of this study are available from the corresponding author upon request. All data presented in the manuscript are provided as source data files.

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 type="checkbox"/>	<input checked="" 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

anti-APOE (Millipore, #AB947)
 anti-ATP5F1 (Proteintech, #68304-1-Ig)
 anti-CPT1A (8F6AE9) (Abcam, #ab128568)
 anti-FABP6 (Proteintech, #13781-1-AP)
 anti-FABP7 (Sigma-Aldrich, #ABN14)
 anti-GAPDH (Millipore, #374)
 anti-GFAP (Abcam, #ab53554)
 anti-MAP2 (Synaptic Systems, #188 004)
 anti-MFN1 (3F11C11) (Proteintech, # 66776-1-Ig)
 anti-MFN2 (7H42L13) (Invitrogen, #702768)
 anti-MTCO1 (1D6E1A8) (Invitrogen, #459600)
 anti-NANOG (R&D Systems, #AF1997)
 anti-OCT4 (clone 3A2A20) (StemCell, #60093)
 anti-S100 (DAKO, #GA504)
 anti-sortilin (for IF: R&D #AF3154, for WB: BD Biosciences #612101)
 anti-SOX2 (clone 245610, #MAB2018)
 anti-SSEA4 (MC813-70) (Abcam, #16287)
 Total OXPHOS Human WB antibody cocktail (Abcam, #ab110411)
 Total OXPHOS Rodent WB antibody cocktail (Abcam, #STN-19467)

Validation

anti-APOE (Millipore, #AB947): https://www.merckmillipore.com/DK/en/product/Anti-Apolipoprotein-E-Antibody,MM_NF-AB947
 anti-ATP5F1 (Proteintech, #68304-1-Ig): <https://www.ptglab.com/products/ATP5F1-Antibody-68304-1-Ig.htm>
 anti-CPT1A (8F6AE9) (Abcam, #ab128568): <https://www.abcam.com/products/primary-antibodies/cpt1a-antibody-8f6ae9-ab128568.html>
 anti-FABP3 (Proteintech, #10676-1-AP): <https://www.ptglab.com/products/FABP3-Antibody-10676-1-AP.htm>
 anti-FABP5 (BioVendor, #RD181060100): <https://www.biovendor.com/epidermal-fatty-acid-binding-protein-human-rabbit-polyclonal-antibody>
 anti-FABP6 (Proteintech, #13781-1-AP): <https://www.ptglab.com/products/FABP6-Antibody-13781-1-AP.htm>
 anti-FABP7 (Sigma-Aldrich, #ABN14): https://www.merckmillipore.com/DK/en/product/Anti-Brain-lipid-binding-protein-Antibody,MM_NF-ABN14
 anti-GAPDH (Millipore, #MAB374): https://www.merckmillipore.com/DK/en/product/Anti-Glyceraldehyde-3-Phosphate-Dehydrogenase-Antibody-clone-6C5,MM_NF-MAB374
 anti-GFAP (Abcam, #ab53554): <https://www.abcam.com/products/primary-antibodies/gfap-antibody-ab53554.html>
 anti-MAP2 (Synaptic Systems, #188 004): <https://www.sysy.com/product/188004#list>
 anti-MFN1 (3F11C11) (Proteintech, # 66776-1-Ig): <https://www.ptglab.com/products/MFN1-Antibody-66776-1-Ig.htm>
 anti-MFN2 (7H42L13) (Invitrogen, #702768): <https://www.thermofisher.com/antibody/product/MFN2-Antibody-clone-7H42L13-Recombinant-Monoclonal/702768>
 anti-MTCO1 (1D6E1A8) (Invitrogen, #459600): <https://www.thermofisher.com/antibody/product/MTCO1-Antibody-clone-1D6E1A8-Monoclonal/459600>
 anti-NANOG (R&D Systems, #AF1997): https://www.rndsystems.com/products/human-nanog-antibody_af1997
 anti-OCT4 (clone 3A2A20) (StemCell, #60093): <https://www.stemcell.com/products/anti-human-oct4-oct3-antibody-clone-3a2a20.html>
 anti-S100 (DAKO, #GA504): <https://www.agilent.com/en/product/immunohistochemistry/antibodies-controls/primary-antibodies/s100-%28dako-omnis%29-76198>

 anti-sortilin antibodies were additionally validated in this study by gene knockdown in mice model and in hiPSCs (for IF: https://www.rndsystems.com/products/human-sortilin-antibody_af3154, for WB: <https://www.bdbiosciences.com/ko-kr/products/reagents/western-blotting-and-molecular-reagents/western-blot-reagents/purified-mouse-anti-neurotensin-receptor-3.612101>)

 anti-SOX2 (clone 245610, #MAB2018): https://www.rndsystems.com/products/human-mouse-rat-sox2-antibody-245610_mab2018
 anti-SSEA4 (Abcam, #16287): <https://www.abcam.com/en-an/products/primary-antibodies/ssea4-antibody-mc813-70-ab16287>
 Total OXPHOS Human WB antibody cocktail (Abcam, #ab110411): <https://www.abcam.com/products/panels/total-oxphos-human-wb-antibody-cocktail-ab110411.html>
 Total OXPHOS Rodent WB antibody cocktail (Abcam, #STN-19467): antibody under this catalog number was discontinued (available as Abcam #ab110413)
 anti-VIM (clone V9) (DAKO, #M0725): <https://www.agilent.com/cs/library/packageinsert/public/103621002.PDF>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	Human induced human pluripotent stem cell lines (BIHi005-A (https://hpscereg.eu/cell-line/BIHi005-A), WTSli009-A (https://hpscereg.eu/cell-line/WTSli009-A) and BIHi043(MDCI-053-A-49; https://hpscereg.eu/cell-line/HMGUi001-A)) were obtained from the MDC Technology Platform Pluripotent Stem Cells (in-house) or the Wellcome Trust Sanger Institute.
Authentication	Cell lines were quality-controlled for genome stability and pluripotency, and verified for APOE and SORT1 genotypes as described in method section.
Mycoplasma contamination	All cell lines were routinely tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No such line lines were used in this study.

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	All animal procedures were conducted in accordance to local ethics committees approval (X9017/17). Experiments were conducted in male 12-weeks old mice on an inbred C57Bl6/J background. The animals were kept on normal chow (4.5% crude fat, 39% carbohydrates).
Wild animals	No wild animals were used in the study.
Reporting on sex	Studies were conducted in male and female mice.
Field-collected samples	No samples collected from the field were used in the study.
Ethics oversight	All animal procedures were conducted in accordance with local ethics committees approval (X9017/17) and overseen by institutional animal welfare officers.

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

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.