nature portfolio

Corresponding author(s): Alan R. Saltiel

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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	VersaMax Microplate Reader (96 well format, VERSA max), iTecan (v2.0), QuantStudio (v1.5.1), NanoDrop2000 (v1.3.1), LI-COR Odyssey XF Imager (2800), ZEISS LSM 880 with Airyscan (LSM T-PMT, ZEN Black v2.3 SP1), CHOPCHOP (v3)
Data analysis	Microsoft Excel for Microsoft 365 MSO (v2304), Image J Java (13.0.6 64-bit), GraphPad Prism (v10), Image Studio Lite (v5.x), ZEN Black (v2.3 SP1), ZEN Blue (v2.3)

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 within the article and its Supplementary Information. The Supplementary Information includes uncropped Western blot scans, genotyping primer sequences, qPCR primer sequences, shRNA oligo sequences, and sgRNA oligo sequences. Publicly available rare-variant

burden association results in humans (Table 2) were obtained from the GeneBass database (https://app.genebass.org). Mass spectrometry data from mouse liver tissues overexpressing RalA-WT, RalA-G23V or RalA-S28N have been deposited in Figshare under https://doi.org/10.6084/m9.figshare.32229999. Source data are provided with this paper.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	No statistical method was used to pre-determine sample size. Sample sizes were based on prior experience and availability of animals or cells, and are provided in the figure legends.
Data exclusions	Data were excluded only in cases of technical failure or loss of appropriate controls. No data were excluded arbitrarily.
Replication	All in vivo experiments were independently repeated with at least two biological cohorts. In vitro experiments were repeated at least twice with similar results. Replicate numbers are indicated in figure legends.
Randomization	Animals were randomly assigned to treatment or control groups. When applicable, mice were age and sex matched and randomized within the same housing cage to minimize cage effect.
Blinding	The researcher was blinded to the genotype during data collection. During data analysis, the researchers were not blinded to allocation since data comparison needs to be done between different genotypes or groups.

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

FLAG (Sigma, F3165), HA (C29F4)(Sigma, H3663; CST, 3724S), β-tubulin (Proteintech, 66240), GFP (B-2) (Santa Cruz Biotechnology, sc-9996), HSP90 (C45G5) (CST, 4877S), RalA (BD Biosciences, 610222), RalB (CST, 3523), RalA/B (Proteintech, 67094-1-Ig), RalGAPA1 (Thermo Fisher Scientific, PA5-68198), RalGAPA2 (Proteintech, 29843-1-AP), RalGAPB (Proteintech, 28330-1-AP), AKT (CST, 9272), phospho-AKT (Ser473) (CST, 9271), ERK1/2 (CST, 9102), phospho-ERK1/2 (CST, 9101), PCSK9 (Abcam, ab31762), LXRα (Abcam, ab41902), LRP1 EPR3724(Abcam, ab92544), nuclear SREBP2 1C6 (Santa Cruz Biotechnology, sc-13552), REPS1 D6F4 (CST, 6404), Transferrin Receptor H68.4 (Thermo Fisher Scientific, 136800), CTSA (Proteintech, 15020-1-A), SEC5 (Proteintech, 12751-1-AP), pan-RAS C-4 (Santa Cruz Biotechnology, sc-166691), RGL1 G-2 (Santa Cruz Biotechnology, sc-377170), RGL2 (Thermo Fisher Scientific, PA5-112690), RGL3 (Proteintech, 26626-1-AP), LDLR (R&D Systems, BAF2255), LAMP1 H4A3 (Santa Cruz Biotechnology, sc-20011), CD98 RL388 (BioLegend, 128202), ATPA1 EP1845Y (Abcam, ab76020), GAPDH 1E6D9 (Proteintech, 60004-1-Ig), Histone H3 (CST, 9715), KRAS F234 (Santa Cruz Biotechnology, sc-30), SNX17 (Proteintech, 10275-1-AP), RAB11A (Thermo Fisher Scientific, 71-5300) , P62 D5E2 (CST, 8025), EGFR D38B1 (CST, 4267), Donkey anti-Goat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488 (A-11055), Goat anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568 (A-11031), Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ Plus 647 (A32733), Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488 (A-11001), Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488 (A-11008), Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568 (A-11036), Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 647 (A-21244).

Validation

All antibodies were validated by manufacturer and confirmed with western blot or immunofluorescence staining.
FLAG: https://www.sigmaaldrich.com/US/en/product/sigma/f3165
HA: https://www.sigmaaldrich.com/US/en/product/sigma/h3663
HA: https://www.cellsignal.com/products/primary-antibodies/ha-tag-c29f4-rabbit-mab/3724
β-tubulin: https://www.ptglab.com/products/Tubulin-beta-Antibody-66240-1-Ig.htm
GFP: https://www.scbt.com/p/gfp-antibody-b-2
HSP90: https://www.cellsignal.com/products/primary-antibodies/hsp90-c45g5-rabbit-mab/4877
RalA: https://www.bdbiosciences.com/en-eu/products/reagents/microscopy-imaging-reagents/immunohistochemistry-reagents/purified-mouse-anti-ral-a.610222?tab=product_details
RalB: https://www.cellsignal.com/products/primary-antibodies/ralb-antibody/3523
RalA/B: https://www.ptglab.com/products/RALB-Antibody-67094-1-Ig.htm
RalGAPA1: https://www.thermofisher.com/antibody/product/RALGAPA1-Antibody-Polyclonal/PA5-68198
RalGAPA2: https://www.ptglab.com/products/C20orf74-Antibody-29843-1-AP.htm
RalGAPB: https://www.ptglab.com/products/RALGAPB-Antibody-28330-1-AP.htm
AKT: https://www.cellsignal.com/products/primary-antibodies/akt-antibody/9272
phospho-AKT (Ser473): https://www.cellsignal.com/products/primary-antibodies/phospho-akt-ser473-antibody/9271
ERK1/2: https://www.cellsignal.com/products/primary-antibodies/p44-42-mapk-erk1-2-antibody/9102
phospho-ERK1/2: https://www.cellsignal.com/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-antibody/9101
PCSK9: https://www.abcam.com/en-us/products/primary-antibodies/pcsk9-antibody-ab31762
LXRα: https://www.abcam.com/en-us/products/primary-antibodies/lxr-alpha-antibody-ppz0412-ab41902
LRP1: https://www.abcam.com/en-us/products/primary-antibodies/lrp1-antibody-epr3724-ab92544
nuclear SREBP2: https://www.scbt.com/p/srebp-2-antibody-1c6
REPS1: https://www.cellsignal.com/products/primary-antibodies/reps1-d6f4-rabbit-mab/6404
Transferrin Receptor: https://www.thermofisher.com/antibody/product/Transferrin-Receptor-Antibody-clone-H68-4-Monoclonal/13-6800
CTSA: https://www.ptglab.com/products/CTSA-Antibody-15020-1-AP.htm
pan-RAS: https://www.scbt.com/p/pan-ras-antibody-c-4
RGL1: https://www.scbt.com/p/rgl1-antibody-g-2
RGL2: https://www.thermofisher.com/antibody/product/RGL2-Antibody-Polyclonal/PA5-112690
RGL3: https://www.ptglab.com/products/RGL3-Antibody-26626-1-AP.htm
LDLR: https://www.rndsystems.com/products/mouse-ldlr-biotinylated-antibody_baf2255
LAMP1: https://www.scbt.com/p/lamp-1-antibody-h4a3
CD98: https://www.biolegend.com/en-us/products/purified-anti-mouse-cd98-4f2-antibody-4920
SEC5: https://www.ptglab.com/products/SEC5-Antibody-12751-1-AP.htm
ATPA1: https://www.abcam.com/en-us/products/primary-antibodies/sodium-potassium-atpase-antibody-ep1845y-plasma-membrane-loading-control-ab76020
GAPDH: https://www.ptglab.com/products/GAPDH-Antibody-60004-1-Ig.htm
Histone H3: https://www.cellsignal.com/products/primary-antibodies/histone-h3-antibody/9715
KRAS: https://www.scbt.com/p/k-ras-antibody-f234
SNX17: https://www.ptglab.com/products/SNX17-Antibody-10275-1-AP.htm
RAB11A: https://www.thermofisher.com/antibody/product/RAB11A-Antibody-Polyclonal/71-5300
P62: https://www.cellsignal.com/products/primary-antibodies/sqstm1-p62-d5e2-rabbit-monoclonal-antibody/8025
EGFR: https://www.cellsignal.com/products/antibody-conjugates/beta-catenin-l54e2-mouse-monoclonal-antibody-alexa-fluor-647-conjugate/4627
Donkey anti-Goat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: https://www.thermofisher.com/antibody/product/Donkey-anti-Goat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11055
Goat anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568: https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11031
Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ Plus 647: https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A32733
Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11001
Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11008

Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568: https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11036
Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 647 : https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21244

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293T, AML12, and HepG2 cells were obtained from the American Type Culture Collection. Primary hepatocytes were freshly isolated in our laboratory and used immediately for experiments.
Authentication	Commercial cell lines were validated by the American Type Culture Collection. All the cells were authenticated in the lab based on their morphology.
Mycoplasma contamination	Cell lines were tested and confirmed to be free of mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	All cell lines used in this study have been authenticated and are not listed among commonly misidentified cell lines.

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	Male and female mice on a C57BL/6 background were used in this study. For in vivo experiments, C57BL/6 mice were 1.5–7 months old. For primary hepatocyte isolation, mice were 2–4 months old. Male and female hepatocyte-specific RalGAPB knockout mice and RalGAPB^f/f littermate controls were used at 2–7 months of age for in vivo experiments and at 2–4 months of age for primary hepatocyte isolation. Male SpCas9 knockin mice were used at 1.5–7 months of age for in vivo experiments and at 2–4 months of age for primary hepatocyte isolation.
Wild animals	The study did not involve wild animals.
Reporting on sex	Both male and female mice were used in this study as indicated in the figure legends.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	Institutional Animal Care and Use Committee (IACUC) at the University of California San Diego approved and provided guidance on the study protocol.

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

Plants

Seed stocks	This study did not involve the use of any plants.
Novel plant genotypes	This study did not involve the use of any plants.
Authentication	This study did not involve the use of any plants.