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	No software or code was used for data collection.
Data analysis	bcl2fastq v2.19.0 (https://support.illumina.com/sequencing/sequencing_software/bcl2fastq-conversion-software.html) BWA MEM v0.7.15 (https://github.com/lh3/bwa) DeepVariant v0.10 (https://github.com/google/deepvariant) GLnexus v1.4.3 (https://github.com/dnanexus-rnd/GLnexus) PLINK 1.9 (https://www.cog-genomics.org/plink2/) Variant Effect Predictor (VEP) v100.4 (https://github.com/Ensembl/ensembl-vep/) REGENIE v3.4 or older (https://github.com/rgcgithub/regenie/) SuSiE v0.12.35 (https://github.com/stephenslab/susieR) STAR v2.5.3a (https://github.com/alexdobin/STAR) Picard v2.9.0 (https://github.com/broadinstitute/picard) RNA-SeQC v1.1.9 (https://github.com/getzlab/rnaseqc) COLOC v5.2.3 (https://github.com/chr1swallace/coloc) DEPICT v1 (https://github.com/perslab/depict) DESeq2 v1.34.0 (https://www.bioconductor.org/packages/release/bioc/html/DESeq2.html) PEAR v0.9.8 (https://cme.h-its.org/exelixis/web/software/pear/doc.html) Bowtie2 v2.5.4 (https://github.com/benlangmead/bowtie2) Prism v10 (https://www.graphpad.com) Illumina BCL Convert v4.3.6 (https://www.10xgenomics.com) FastQC v0.12.1 (www.bioinformatics.babraham.ac.uk/projects/fastqc)

10X Genomics Cell Ranger v7 (https://www.10xgenomics.com/support/software/cell-ranger/latest?gad_source=1)
ArrayStudio v12.5 (https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-omicsoft-suite/)
Scrublet v0.2.3 (https://github.com/swolock/scrublet)
Scanpy v1.9.1 (https://scanpy.scverse.org/en/stable/)
Harmonypy v0.0.10 (https://github.com/slowkow/harmonypy/releases/tag/v0.0.10)
Freestyle software v1.8.65.0 (https://www.thermofisher.com/)
The custom perl script used for the characterization of barcoded samples in the mouse experiments is available for download at: https://rgc-community.regeneron.com/.

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

Summary association statistics for the TG-HDL genome-wide discovery analysis are available at https://rgc-community.regeneron.com/. All other association results are reported in the manuscript and its associated Supplementary Materials. Data from the MCPS are available to bona fide researchers. For more details, the study's Data and Sample Sharing policy is available (in English or Spanish) at https://www.ctsu.ox.ac.uk/research/mcps. Study data can be examined through the study's Data Showcase at https://datashare.ndph.ox.ac.uk/mexico/ and MCPS ancestry-specific allele frequencies are available at https://rgc-mcps.regeneron.com. Data from the BELIEVE study are available on reasonable request to the Data Access Committee. Further information on the application process can be found on the BELIEVE study website https://www.believestudy-bangladesh.org/accessing-believe-data/. UKB genotypic and phenotypic data are available to approved investigators via the UK Biobank study (www.ukbiobank.ac.uk/). Additional information about how to access the data are available at https://www.ukbiobank.ac.uk/use-our-data/. GHS data are available to qualified academic noncommercial researchers for reproducibility of data, results and conclusions of the manuscript through the portal at https://regeneron.envisionpharma.com/vt_regeneron/ under a data access agreement. For UCLA-ATLAS (ATLAS) cohort, due to privacy regulations, individual-level data cannot be published. Comprehensive processed data and summary statistics are available in the supplementary tables or through the UCLA-ATLAS browser (atlas-phewas.mednet.ucla.edu). For PMBB, BioMe, DBS, MAYO-RGC and CCPM, academic, non-commercial researchers interested in reproducing the results reported in this manuscript may request access to data via a data access agreement by reaching out to the associated biobank at the following links: PMBB, https://pmbb.med.upenn.edu/contact.php; BioMe, https://mountsinaimillion.org/en/contact; DBS, Contact: JONATHAN.COHEN@UTSOUTHWESTERN.EDU; MAYO-RGC, https://www.mayo.edu/research/centers-programs/mayo-clinic-biobank/for-researchers; CCPM, https://medschool.cuanschutz.edu/cobiobank/contact-us. MDCS data may be available to qualified academic non-commercial researchers to reproduce results reported in this manuscript through the portal at https://www.malmo-kohorter.lu.se/malmo-cohorts, following the principles outlined in this policy https://www.malmo-kohorter.lu.se/sites/malmo-kohorter.lu.se/files/mdcs_mpp_mos_request_form_vermar20.doc. Indiana-CLDB data can be made available for those requesting via Indiana Biobank's data request process. Application is reviewed by three members of the Indiana Biobank's Scientific Review Committee and if approved, made available on a secure-enclave for analysis. South Asia Biobank data may be accessible to researchers upon request to the data access committee. Contact forms and emails are provided on the Global Health Research Unit (GHRU) on Diabetes and Cardiovascular Disease in South Asia website (www.ghru-southasia.org).

Raw values for all experimental data are provided in the Source Data file. RNA-sequencing data have been deposited at Gene Expression Omnibus (GEO) with accession number GSE330407.

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	Biologic sex phenotype was derived from genetic data and included as covariate as described in the methods section.
Reporting on race, ethnicity, or other socially relevant groupings	Ancestry estimation was derived from genetic data and reported in descriptive statistics of Supplementary Table S1.
Population characteristics	Population characteristics were provided in Supplementary Table S1.
Recruitment	Our study included participants from both population-based and health-system based cohorts and are described in the methods section with relevant references for additional details on recruitment.
Ethics oversight	All studies received approval from the relevant ethics committees, and participants gave their informed consent to take part in the research. More details are provided in the references for respective cohorts in the Methods section.

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	-Human studies: Sample size was determined by the maximal set of participants in each cohort with genotypic and phenotypic data after quality control. -Animal Studies: Sample size was chosen based on previous experience with similar experiments, experimental feasibility, availability of samples and N necessary to obtain definitive, significant results. No statistical methods were used to predetermine sample sizes. The sample size information of experiments has been provided in each figure legend.
Data exclusions	-Human Studies: Exclusions within each cohort were done based on missing genotypic and phenotypic data. Also filtering based on established quality control protocols was done. -Animal Studies: No data were excluded from the analysis.
Replication	-Human Studies: No replication analyses were performed. -Animal Studies: All experiments with AAV8-gRNAs (Flcn/Fnip1/Fnip2) on high fat diets for up to 13 weeks, studies in primary human hepatocytes (Fnip1) and studies with AAV-shRNAs (Hpn) were independently performed at least twice on cohorts from independent litters. All attempts at replication were successful. Studies with long-term (30 weeks) inhibition of Flcn/Fnip1/Fnip2, as well as studies on chow, at thermoneutrality or using GalNac-conjugated siRNAs were performed once, but yielded results that were similar to the AAV8-gRNA studies on high fat diets. In some studies, independent methods were used to analyze samples and verify results (e.g. DNA editing, mRNA and protein analysis to confirm gene perturbation).
Randomization	-Animal Studies: For all animal studies, mice were allocated into experimental groups based on matching body weight, body composition and lipid levels. The goal was to balance weight, body composition and lipid levels at baseline (similar values between groups), to allow for evaluation of treatment efficacy following intervention. -Cell culture studies: cells were randomly assigned to experimental groups.
Blinding	-Animal Studies: Investigators were blinded to group allocation during serum chemistry analysis, liver lipid analysis, protein analysis and DNA editing analysis. Blinding was not possible during the in-live part of the mouse studies due to the need to treat mice with different reagents according to experimental designs. In cell culture studies, blinding was not relevant, as the groups needed to be allocated to appropriate experimental and control 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	FNIP1 (clone E9Y5U) Rabbit Monoclonal Antibody #36892, Cell Signaling Technologies HSP90 (clone C45G5) Rabbit Monoclonal Antibody #4877 , Cell Signaling Technologies
Validation	The manufacturer provides validation data on the website, evaluating FNIP1 antibody by Western Blot in human cell lines that express or do not express human FNIP1. From the website: "Western Blot analysis of extracts from various cell lines using FNIP1 (E9Y5U) Rabbit mAb or anti-Actinin (D6F6) XP Rabbit mAb #6487. Negative expression of FNIP1 protein in U-937 cells is consistent with the predicted expression pattern." (https://www.cellsignal.com/products/primary-antibodies/fnip1-e9y5u-rabbit-monoclonal-antibody/36892) The HSP90 antibody has been extensively used in publications, with the manufacturer website listing 686 citations (https://www.cellsignal.com/products/primary-antibodies/hsp90-c45g5-rabbit-monoclonal-antibody/4877)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Cryopreserved Primary Human Hepatocytes from ThermoFisher (Catalog # HMCPTS): Donor HU8450-Male, 16yo, Caucasian
Authentication	Cells were assessed for Phase I enzyme activities, transporter activity and bile canaliculi formation by the manufacturer
Mycoplasma contamination	Cells were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

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	The studies involved C57BL/6NTac (WT) mice from Taconic, and Cas9-Ready (ver. 2.5, ID #2673) mice, expressing Cas9 transgene under the CAG promoter (previously reported in Smagris et. al., PLoS Genetics 2024 PMID: 38437227). Mice were between 6-11 weeks old at the beginning of the studies. Mice were housed on a 12h light/dark cycle at 22 ± 1°C or 30°C (for experiments at thermoneutral conditions), at humidity-controlled conditions (30-70% humidity), in static cages (≤5/cage) with free access to food and water.
Wild animals	The study did not involve wild animals.
Reporting on sex	The metabolic studies involved male mice only, which historically have shown more robust metabolic disease phenotypes than females.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	All animal procedures were conducted in compliance with protocols approved by the Regeneron Pharmaceuticals Institutional Animal Care and Use Committee.

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

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.*