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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	Odyssey Infrared Imaging system (LI-COR, ver 3.0.16), VICTOR Nivo Multimode Plate Reader (PerkinElmer),
Data analysis	Excel (Microsoft), Prism 9 (GraphPad), ImageJ (NIH), Morpheus, https://software.broadinstitute.org/morpheus, Proteome Discoverer (ThermoScientific, version 1.3), Mascot algorithm (Matrix Science, version 2.6.0)

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

The mass spectrometry proteomics data in Figure 3 have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD043192 and are publicly available as of the date of publication. This paper does not report any codes. Full results of the discovery, replication, and HexCer analysis of lipidomics are provided in the Supplementary Data 1, 2 and 3, respectively. Source data are provided in Supplementary Data 4.

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	Sample size were determined based on previous studies using Tmem106b-/- mice (Klein et al., 2017, Perez-Canamas et al 2020, Zhou et al. 2020).
Data exclusions	No data were excluded from the analyses.
Replication	Two independent lipidomic analyses (discovery and replication analyses) consistently showed a decrease in HexCer and sulfatide in Tmem106b-/- mice. The results of mass spectormetric analysis were validated using the co-IP experiment. At least three independent experiments were performed in the co-IP experiments. GALC activity assay was performed using two different assays (using MUGAL and HMGal).
Randomization	Animals were grouped based on their genotype.
Blinding	All lipidomic analyses were performed by investigators who were blinded to the genotypes. Investigators were also blinded to the genotypes in HMGal-GALC activity assay. Investigators were not blinded during the mass spectrometric analysis, co-IP assays and MUGAL-GALC activity assay.

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

Rabbit anti-TMEM106B (Abcam #ab140185),
Rabbit anti-TMEM106B (E7H7Z)(Cell Signaling Technology #93334),
Rabbit anti-Myc Tag (71D10) (Cell Signaling Technology #2278),
Mouse anti-Myc Tag (9B11) (Cell Signaling Technology #2276),
Mouse anti-GFP (B-2) (Santa Cruz, #c-9996),
Mouse anti-RFP (RF5R) (ThermoFisher Scientific #MA5-15257),
Mouse anti-beta-actin (8H10D10) (Cell Signaling Technology #3700),
Mouse anti-beta-tubulin (D3U1W) (Cell Signaling Technology #86298),
Chicken anti-mouse GALC antibody (homemade, CL1021AP),
Mouse anti-GAPDH (Proteintech #60004-1-Ig),
Rabbit anti-LAMP1 (Cell Signaling Technology #9091),
Alexa Fluor 488 donkey anti-mouse IgG (H+L) (Invitrogen #A21202),
Alexa Fluor 568 donkey anti-rabbit IgG (H+L) (Invitrogen #A10042),
Donkey IRDye 680LT anti-Mouse (LI-COR 926-68022),
Donkey IRDye 680LT anti-Rabbit (LI-COR 926-68023),
Donkey IRDye 800CW anti-Mouse (LI-COR 926-32212),
Donkey IRDye 800CW anti-Rabbit (LI-COR 926-32213)

Validation

The antibodies used in this study are all commercially available (except for anti-GALC antibody CL1021AP) and have been commonly used in previous studies. The validation materials can be also found on the companies' website. Chicken anti-GALC antibody (CL1021AP) was validated in previous studies (Lee et al.(2010) J. Neurosci., 30, 5489-5497; Potter et al. (2013) HMG, 19, 3397-3414) and in the present study using GALC KO twitcher mice.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	293T/17; Embryonic Kidney: Human (ATCC, CRL-11268)
Authentication	The cell line used was not authenticated.
Mycoplasma contamination	The cell line used tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	n/a

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	TMEM106B-deficient mice on C57BL/6 background were described previously (Klein et al. 2017). This Tmem106b−/− line was generated by LacZ gene trap strategy and expresses 5 to 10% residual full-length TMEM106B protein (Zhou et al. 2020; Perez-Canamas et al. 2020). Lipidomic analyses were performed using 12-month-old TMEM106B-deficient mice and wild-type (WT) littermates.
Wild animals	This study did not involve wild animals.
Reporting on sex	Both male and female were used in this study. In Fig. 1 and 3, 3 males and 3 females were used. In Fig. 2, 5 males and 2 females were used. In Fig. 4, 2 males and 4 females were used. Similar results were obtained from male and female.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All protocols were approved by Yale Institutional Animal Care and Use Committee (IACUC).

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