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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	All confocal images were acquired on a Zeiss LSM900. The oxygen consumption rate (OCR) of cells was measured over time using Seahorse XF Analyzer. Sequencing was performed on the Illumina platform.
Data analysis	For single-cell analysis,library demultiplexing was conducted using the BMC/BCC pipelines v1.8 (BioMicroCenter Software,https://openwetware.org/wiki/BioMicroCenter:Software), and Fast-q reads were aligned to the human genome using Cell Ranger version 6.1.2 (lOx Genomics). Batch effects were corrected using Harmony (https://github.com/immunogenomics/harmony). Molecular dynamics simulations employed PyMOL v2.0, CHARMM-GUI (https://charmm-gui.org/), GROMACS 2022.3, and VMD v1.94 software. LC-MS analysis was performed with Lipidsearch © software (version 4.2.27) and Compound Discoverer 3.2 (CD, Thermo Fisher Scientific). OCRs were computed in the XFe Assay Version (2.6.3.5) software. Electrophysiological recordings and data analysis were conducted using GraphPad Prism 10 software suites. Custom pipelines and analysis scripts were developed in Python version 3.8.13 and R version 4.2.3. The following Python packages (algorithms) were used for analysis : Scikit-learn v1.6.1 (GaussianMixture), Statsmodels v0.14.4 (mixedlm), Scanpy v1.10.3, Umap-learn v0.5.7, GSEAPY v1.1.5, Numpy v1.24.3 (Kernighan-Lin), NetworkX v3.2.1 (spring_layout), AICSImageIO v4.14.0. The following R packages (algorithms) were used for analysis: edgeR v4.4.0, Limma v3.62.1 (voom, lmFit, eBayes, topTable), fGSEA v1.32.2. Additional software packages used were METIS https://github.com/KarypisLab/METIS, Trim Galore v0.6.10, STAR aligner v2.5.2b, featureCounts v2.0.1.

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 postmortem human data and associated ROSMAP metadata can be accessed through the Synapse AD Knowledge Portal at https://adknowledgeportal.synapse.org/. These data are subject to controlled access in compliance with human privacy regulations. To access the data, a data use certificate (DUC) must be obtained. This requirement ensures the anonymity of ROSMAP study participants. A DUC can be obtained by following the instructions on https://help.adknowledgeportal.org/apd/Data-Use-Certificates.2623373330.html. Expected turnaround is within one week of DUC submission. Once approved, data may be downloaded and accessed for one year. Data generated or used for data analysis in this study are available here: Primary post-mortem human multi-omics dataset: https://www.synapse.org/#!Synapse:syn53461705. Processed post-mortem human multi-omics data: https://singlecell.broadinstitute.org/. Bulk mRNA-seq fastq files and count matrices: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE299277. LC-MS data: https://datadryad.org/dataset/doi:10.5061/dryad.zcrjdfnn5; imaging data: https://datadryad.org/dataset/doi:10.5061/dryad.zcrjdfnn5; postmortem human PFC proteomic data: https://www.synapse.org/#!Synapse:syn2 1449368, Reference 1: Cell type specific marker genes for human brain: https://datadryad.org/dataset/doi:10.5061/dryad.zcrjdfnn5, Reference 2: Cell type specific marker genes for human brain: https://datadryad.org/dataset/doi:10.5061/dryad.zcrjdfnn5, Gene Ontology Biological Process 2023 : https://maayanlab.cloud/Enrichr/#libraries, NeuN+/- bulk RNA-sequencing from post- mortem human brain: https://datadryad.org/dataset/doi:10.5061/dryad.zcrjdfnn5, WikiPathways 2019 Human: https://maayanlab.cloud/Enrichr/#libraries, snRNAseq from postmortem human PFC from p.Ala1527Gly variant-carriers and controls: https://www.synapse.org/#!Synapse:syn5 2293417, Human MioCarta3.0: https://www.broadinstitute.org/mitocarta NA/mitocarta30-inventory-mammalian-mitochondrial-proteins-and-pathways, Human prefrontal cortex layer markers based transcriptomics on dissected layers: https://www.nature.com/articles/nn.4548#article-info, Human dorsolateral prefrontal cortex spatial transcriptomics markers : https://www.nature.com/articles/s41593- 020-00787-0#article-info, human genome GRCh38: https://ftp.ebi.ac.uk/pub/databases/gencode/Gencode_human/release_47/GRCh38.primary_assembly.genome.fa.gz

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	Biological sex was self-reported as part of the ROSMAP study. Individual-level meta data can be accessed through the Synapse AD Knowledge Portal (syn53461705). These data are subject to controlled access in compliance with human privacy regulations. Biological sex was balanced across genotypes of interest to avoid confounding and was included in statistical models where indicated in the methods. Analyses were not stratified by sex due to sample size.
Reporting on race, ethnicity, or other socially relevant groupings	No socially constructed or socially relevant categorization variables were used in this manuscript.
Population characteristics	Postmortem PFC samples used in this study from the 12 ABCA7 LoF variant carriers and 24 ABCA7 PTC non-carrier controls were matched based on a number of potentially confounding variables, including AD pathology (78% AD Reagan positive), age at death (mean 88 years, SD 6 years), post-mortem intervals (mean 7.5 hours, SD 5.5 hours), sex (55% female), APOE genotype (25% APOE4 positive), and cognition. See Extended Figures and Supplementary Text for the specific distributions.
Recruitment	No donors were specifically recruited for this manuscript; the tissue had previously been obtained from participants in the Religious Order Study.
Ethics oversight	The Religious Orders Study and Rush Memory and Aging Project were approved by an IRB of Rush University Medical Center.

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 calculations were performed to determine sample size. For the snRNA-seq cohort, sample size was constrained by the availability of human postmortem tissue and the rarity of ABCA7 LoF variants in the population (minor allele frequency« 1%). In iPSC experiments, sample sizes varied due to data exclusions and the feasibility of repeating experiments across multiple differentiation batches, based on cell availability. Typically, cells derived from at least four wells were used per condition per experiment.

Data exclusions	Low-quality snRNA-seq libraries were excluded, and the exclusion criteria are described in the "Cell filtering metrics" and "Individual-level filtering" sections of the supplementary materials in the manuscript. Low-quality confocal image segmentations were excluded blinded to condition, as detailed in the "Confocal Image Quantification" section. For oxygen consumption rate analyses, curves were visually inspected in a blinded manner to exclude wells that did not respond to drug injections, as described in the "Seahorse metabolic assays and OCR analysis" section.
Replication	All snRNAseq was performed once. Bulk mRNAseq of WT vs p.Try622* vs p.Glu50fs*3 lines was performed once. Bulk RNAseq for p.Tyr622* line -/+ CDP-choline was performed twice with consistent results. Lipidomic LC-MS analysis of WT vs p.Tyr622* lines was performed once. Lipidomic LC-MS analysis of p.Glu50fs*3 was performed three times. Data were consistent between the first two runs; detection sensitivity for the third run was too low to allow comparison with the first two runs. Lipidomic LC-MS analysis of the p.Tyr622* line + CDP-choline was performed twice with similar results. All metabolomic LC-MS analysis was performed once. TMRM staining of the WT and p.Tyr622* lines -/+ CDP-choline was performed twice with similar results. The MitoHealth assay was performed three times with similar results on WT, p.Tyr622*, and p.Glu50fs*3 lines and twice with similar results on the p.Tyr622* line -/+ CDP-choline. The CellRox assay was performed once on p.Tyr622* line -/+ CDP-choline. The amyloid ELISA on 5-6 months old p.Tyr622* spheroids vs WT spheroids was performed twice with similar results. The amyloid ELISA on 5-6 months old p.Tyr622* spheroids -/+ CDP-choline was performed once. The amyloid ELISA on the WT and p.Tyr622* lines was successfully performed once. The Seahorse assay was successfully performed twice with similar results on WT, p.Tyr622*, and p.Glu50fs* lines and once on the p.Tyr622* line -/+ CDP-choline. All electrophysiology experiments were performed once.
Randomization	The study participants were allocated into groups (control vs. LoF) based on ABCA7 genotype. All available LoF subjects were included. Control subjects were selected to match LoF subjects as closely as possible based on AD pathology, age at death, post-mortem intervals, sex, APOE genotype, and cognition. For the ABCA7 p.Ala1527Gly analysis, all available subjects who did not have an ABCA7 LoF and who were not part of the previous control group were included. These subjects were then split into two groups based on their ABCA7 p.1527 status. Clinical covariates were not explicitly matched between the two groups, but included in the statistical model. For cell culture experiments, otherwise isogenic cells were grouped based on their ABCA7 mutation status. CDP-choline treatment allocation was random.
Blinding	Investigators were blinded to sample groups for the single-cell data collection. For cell culture experiments, differences in the growth rates between the WT and LoF lines precluded investigator blinding. All imaging was performed with consistent imaging and analysis settings within a given experiment, ie, across all conditions tested. Investigators were blinded to groups when excluding images based on poor cell qualities or mask assignment and when excluding wells from Seahorse analysis based on poor assay quality. Settings for the subsequent data analysis were predetermined independent of sample identity and then algorithmically, ie, without any manual decision points, applied equally across all 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	NEUN (Synaptic Systems, 266004), TUJ1 (Biolegend, MNS-435P), SM312 (Biolegend, 837904), MAP2 (Biolegend, 822501)
Validation	Each antibody was verified by the respective manufacturer for its suitability for human species and for use in immunohistochemistry applications.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Human iPSC lines used in this study were generated by the Picower Institute for Learning and Memory iPSC core. The initial parental cell line (AG09173) was obtained from the Coriell Institute. HEK293T cells (ATCC #CRL-3216) were sourced from ATCC.
Authentication	IPSC lines are confirmed by cell marker staining, RNA-sequencing and karyotyping. No further authentication of HEK293T cells was performed.
Mycoplasma contamination	All cell lines used here tested negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

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.*