nature portfolio

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Last updated by author(s): Oct 31, 2025

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	FACS: GFP⁺ cell isolation using BD FACSAria Soap. Short-read WGS: NovaSeq X (Macrogen Inc.). Long-read sequencing: PromethION P2 Solo sequencer. Capture sequencing: HiSeq X (Macrogen Inc., standard procedure). Amplicon sequencing: MiSeq (Illumina). ELISA: Serum TTR levels measured on SYNERGY LX multi-mode reader (Bio Tek). Imaging: Fluorescence images acquired using BZ-X700 microscope (Keyence). Western blot/Aggregation assay: Images captured using iBright CL 1500 (Thermo Fisher Scientific). Cytokine analysis: DISCOVERY WORKBENCH 4.0 (Meso Scale Discovery). Proteomics (LC-MS/MS): Orbitrap Eclipse Tribrid MS with FAIMS Pro interface, connected to Vanquish Neo UHPLC system (Thermo Fisher Scientific).
Data analysis	FACS: Flowjo (version 10.10.0, BD Biosciences). CRISPR editing analysis: CRISPResso2 (http://crispresso.pinellolab.partners.org/). Image analysis: BZ-X Analyzer software (Keyence). Western blot densitometry: iBright CL 1500 software (Thermo Fisher Scientific). Cytokine data analysis: DISCOVERY WORKBENCH 4.0 (Meso Scale Discovery). Proteomics data analysis: Proteome Discoverer Software v2.5 (Thermo Fisher Scientific). Statistical analysis: GraphPad Prism 10 software (GraphPad, San Diego, CA, USA).

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 data that support the findings of this study are available from the corresponding author upon reasonable request. Whole-genome sequencing (WGS), capture, and amplicon sequencing data generated in this study have been deposited in the DNA Data Bank of Japan (DDBJ) Sequence Read Archive (DRA) under BioProject accession PRJDB37936 and are publicly accessible. All other data supporting the findings of this study are available within the paper and its Supplementary Information 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	This study did not involve human participants, their data, or biological materials.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable.
Population characteristics	Not applicable.
Recruitment	Not applicable.
Ethics oversight	Not applicable.

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 sizes are reported in the figure legends and were chosen based on previous similar studies.
Data exclusions	No data were excluded from the analyses.
Replication	All experiments were independently replicated at least three times with consistent results.
Randomization	Animals were randomly assigned to treatment and control groups.
Blinding	Investigators were blinded to group allocation during data collection and analysis.

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

All antibodies used in this study are described below with details on host species, supplier, catalog number, dilution, and validation.Immunohistochemistry (IHC):Paraffin-embedded liver sections (4 µm thick) were stained with rabbit polyclonal anti-mouse transthyretin (mTtr) antibody (1:250, LS-C407961, LSBio, Zürich, Switzerland).Frozen liver sections (4 µm thick) were stained with rabbit polyclonal anti-mTtr antibody (1:250, LS-C407961, LSBio), rabbit polyclonal anti-TTR antibody (1:1,000, 201630-T10, Sino Biological, Peking, China), and mouse monoclonal anti-CD68 antibody (1:50, ab53444, Abcam, Cambridge, UK).Western blotting (WB):Caspase-3 (Cas3) was detected with rat polyclonal anti-Cas3 antibody (1:1,000, C4U Corporation), followed by goat anti-rat IgG, HRP-linked antibody (1:2,000, #7077, Cell Signaling Technology, Danvers, MA, USA).α-Tubulin was detected using rabbit monoclonal α-Tubulin antibody (1:2,000, #2144, Cell Signaling Technology), followed by goat anti-rabbit IgG, HRP-linked antibody (1:2,000, #7074, Cell Signaling Technology).

Validation

Validation of all primary antibodies was confirmed by the manufacturers and supported by experimental results described in the Methods section ("Immunohistochemistry" and "Western blotting").The anti-mTtr (LS-C407961, LSBio) and anti-TTR (201630-T10, Sino Biological) antibodies produced specific cytoplasmic staining in hepatocytes consistent with the known localization of transthyretin, in agreement with previous reports and manufacturer datasheets.The anti-CD68 antibody (ab53444, Abcam) selectively labeled macrophages in hepatic tissue, consistent with the manufacturer's validation data.The anti-Cas3 antibody (C4U Corporation) yielded a single band at the expected molecular weight in Western blotting, and recombinant Cas3 protein was used as a positive control to confirm antibody specificity.The α-Tubulin antibody (#2144, Cell Signaling) produced a single band corresponding to the expected molecular weight, as validated by the manufacturer.All antibodies showed staining or banding patterns consistent with the expected expression profiles in mouse liver samples.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

HepG2 (human hepatocellular carcinoma, RCB1886) and Hepa1-6 (mouse hepatoma, RCB1638) cell lines were obtained from the RIKEN Cell Bank (Tsukuba, Japan).

Authentication

Both HepG2 and Hepa1-6 cell lines were authenticated by the RIKEN Cell Bank using short tandem repeat (STR) profiling prior to distribution. No additional authentication was performed by the authors after purchase.

Mycoplasma contamination

All cell lines were tested for mycoplasma contamination by PCR-based assay and confirmed to be negative before use.

Commonly misidentified lines
(See ICLAC register)

None of the cell lines used in this study are listed as commonly misidentified cell lines in the ICLAC register.

Palaeontology and Archaeology

Specimen provenance

Not applicable.

Specimen deposition

Indicate where the specimens have been deposited to permit free access by other researchers.

Dating methods

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

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

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	Species and strain information Male Jcl:ICR mice (CLEA Japan, Shizuoka, Japan) and TtrhV30orf/hV30orf mice (Transgenic Inc., Kobe, Japan) were used for all experiments. All animals were maintained under specific pathogen-free (SPF) conditions. Experiments were performed using mice aged 4 weeks to 10 months. Housing conditions All mice were housed in standard cages under a 12-hour light/dark cycle (lights on from 07:00 to 19:00) at a constant temperature of 22 ± 2 °C and relative humidity of 40–60%. Animals were provided with standard rodent chow and water ad libitum.
Wild animals	Not applicable.
Reporting on sex	Only male mice were used because serum TTR concentrations were consistently lower in females, which could introduce variability in data interpretation. Using male mice ensured consistency across experimental groups.
Field-collected samples	Not applicable.
Ethics oversight	All animal care and experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Tokyo (IACUC Approval Number: A21-57).

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Not applicable.
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks: Not applicable.

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.*

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication.
Not applicable.

Files in database submission: *Provide a list of all files available in the database submission.*

Genome browser session
(e.g. UCSC)
Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates: *Describe the experimental replicates, specifying number, type and replicate agreement.*

Sequencing depth: *Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*

Antibodies: *Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*

Peak calling parameters: *Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*

Data quality: *Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*

Software: *Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cells were detached using trypsin-EDTA solution (32777-44, Nacalai Tesque), passed through a 35-µm Cell Strainer to obtain a single-cell suspension, and sorted based on GFP fluorescence. Non-transfected Hepa1-6 cells were used to define background fluorescence levels.
Instrument	BD FACSAria (BD Biosciences, Franklin Lakes, NJ, USA).
Software	BD FACSDiva software for acquisition and initial gating; plots generated and analyzed using FlowJo (version 10.10.0; BD Biosciences).
Cell population abundance	EGFP-positive cells obtained after transfection with pCas3 or px458 plasmids were sorted and analyzed. Percentages are not reported.
Gating strategy	Cells were gated based on forward and side scatter to exclude debris and doublets, followed by GFP fluorescence gating. A representative figure of the gating strategy is provided in the Supplementary Information.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	Not applicable.
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
Normalization template	*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.