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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	Primer3 (0.4.0), LiCor Odyssey (xx.xx), Axograph (1.7.6)
Data analysis	Please see more full description in the Methods section, but briefly, HISAT2 (2.0.4) was used for read alignment and featureCounts tool (1.5.0) was used for gene-level quantification. We used the R package DESeq2 (1.26.0) for raw gene counts to determine differentially expressed genes by Tcf4 genotype. We found enriched gene pathway in GO databases with the R-package clusterProfiler (3.6.0). Cell type specific analyses were performed with the CSEA tool (pSI package 1.1). Independent validation of CSEA analysis took RNA-seq raw gene counts from purified cell types of mouse brain from Zhang et al. (2014) and the CIBERSORT (v1.03) online tool. R code used to analyze data in this study and the analyzed data are available at www.github.com/LieberInstitute/PTHS_mouse.

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

RNA-seq data from cortex and whole-brain of TCF4 mutant mice are available at www.github.com/LieberInstitute/PTHS_mouse. Intermediary files or analyses generated with our RNA-seq processing pipeline are available upon request from authors. R code used to analyze data in this study and analszed data are available at www.github.com/LieberInstitute/PTHS_mouse

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	For mega-analysis sample size was viewed sufficiently powered based on preliminary differential expression analyses on just our contributing dataset of 23 mice (1 of 5 mouse models in the paper). For biological validation experiments, N was based on previously published datasets (Olmos-Serano et al., 2015)
Data exclusions	None of the samples were excluded from analysis.
Replication	We compared the replicability of differentially expressed genes across the five independent datasets used for the discovery analysis. We also compared our results to independent mouse models of ASD. These data can be found in Figure 1, where replication between all 5 Tcf4 mouse models are shown.
Randomization	We used all animals born following crossing of a Tcf4 heterozygous male with a wild-type female, which provided a natural randomization of the outcome of interest. We used both males and female offsprings.
Blinding	Investigators were blinded to the genotypes of the animals until RNA-seq data were generated, and were blinded for all biological validation experiments. This is described in additional detail in the Methods section.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

NG2 ab5320 1:1000 Millipore Rabbit
CC-1 OP80-100UG Lot: 29138611:500 Calbiochem Mouse
PDGFRa 558774 Lot:8332502 Clone: APA5 1:500 BD Pharmagen Rat
CNPase MAB326 Lot : 2922433 1:500 Millipore Mouse
MBP Sc-271524 Lot: A2017 1:500 Santa Cruz Mous
Olig2 AB9610 Lot: 3259538 1:500 Millipore Rabbit
MBP MCA4095 Lot: 1:100 Bio Rad Rat
MOG MA5680 Lot:3215487 Clone 8-18C5 1:500 Millipore Mouse
anti-ITF2 Lot: F0910 (N-16) (1:500, Santa Cruz)
anti-GAPDH Lot: GR285925-2 (1:1000, Abcam)
Mouse anti-MOG, (abcam, 1:500
Donkey anti-Rat A21208 (1:1000) Life Technologies 488
Donkey anti-Rabbit A10042 (1:1000) Life Technologies 568
Goat anti Mouse A21050 (1:1000) Life Technologies 633
Goat anti Rat A21094 (1:1000) Life Technologies 633
Donkey anti Mouse 925-68072 (1:5000 LICOR 680)
Donkey anti Mouse 925-32212 (1:5000 LICOR 800)
Donkey anti Rabbit 926-68073 (1:5000 LICOR 680)
Goat anti Rabbit 925-32211 (1:5000 LICOR 800)
Odyssey IRdye donkey anti-gota 680 (1:10,000, LICOR)

Mouse anti NeuN Clone: A60 MAB377 (1:500)
Chicken anti-GFAP Lot: GR3257843-1 ab4674 (1:500)
Rabbit anti-Tuj1 Lot: GR3180223-2 ab18207 (1:500)

Validation

NG2 ab5320 1:1000 Millipore Rabbit
http://www.emdmillipore.com/US/en/product/Anti-NG2-Chondroitin-Sulfate-Proteoglycan-Antibody,MM_NFAB5320#anchor_Product Usage Statements
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2614367/
https://www.sciencedirect.com/science/article/pii/S1873506113001165
CC-1 OP80-100UG 1:500 Calbiochem Mouse
Bhat, R.V., et al. 1996. Glia 17, 169.
Bhat, R.V., et al. 1994. Neuroscience Proceedings.
Smith, K.J., et al. 1994. Cancer Res. 54, 3672.
Smith, K.J., et al. 1993. Proc. Natl. Acad. Sci. USA 90, 2846.
Su, L.-K., et al. 1993. Cancer Res. 53, 2728.
Su, L.-K., et al. 1993. Science 262, 1734.
Groden, J., et al. 1991. Cell 66, 589.
PDGFa 558774 1:500 BD Pharmagen Rat
Takakura N, Yoshida H, Kunisada T, Nishikawa S, Nishikawa SI. Involvement of platelet-derived growth factor receptor-alpha in hair canal
formation. J Invest Dermatol. 1996; 107(5):770-777
Heldin CH. Structural and functional studies on platelet-derived growth factor. EMBO J. 1992; 11(12):4251-4259
Fruttiger M, Calver AR, Krüger WH. PDGF mediates a neuron-astrocyte interaction in the developing retina. Neuron. 1996; 17(6):1117-1131
CNPase MAB326 1:500 Millipore Mouse
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4244045/
MBP Sc-271524 1:500 Santa Cruz Mouse
Jiménez-Maldonado, A. et al. 2018. Short-term fructose ingestion affects the brain independently from establishment of metabolic syndrome.
Biochim. Biophys. Acta. 1864: 24-33.
Linden, JR. et al. 2015. Clostridium perfringens Epsilon Toxin Causes Selective Death of Mature Oligodendrocytes and Central Nervous System
Demyelination. mBio. 6: e02513.
Olig2 AB9610 1:500 Millipore Rabbit
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3400969/
MBP MCA4095 1:100 Bio Rad Rat
Müller, C. et al. (2015) SncRNA715 Inhibits Schwann Cell Myelin Basic Protein Synthesis.
Brügger V et al. (2015) HDAC1/2-Dependent P0 Expression Maintains Paranodal and Nodal Integrity Independently of Myelin Stability through
Interactions with Neurofascins.
Natrajan, M.S. et al. (2015) Retinoid X receptor activation reverses age-related deficiencies in myelin debris phagocytosis and remyelination.
Fernandes, A.R. & Chari, D.M. (2016) Part I: Minicircle vector technology limits DNA size restrictions on ex vivo gene delivery using nanoparticle
vectors: Overcoming a translational barrier in neural stem cell therapy.
MOG MA5680 1:500 Millipore Mouse
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4576870/
anti-ITF-2 (N-16) (1:500, Santa Cruz)
Rannals et al., 2016
Mouse anti-MOG, (abcam, 1:500)
Wang CY et al. Function of B-Cell CLL/Lymphoma 11B in Glial Progenitor Proliferation and Oligodendrocyte Maturation. Front Mol Neurosci
11:4
Beckmann N et al. Brain region-specific enhancement of remyelination and prevention of demyelination by the CSF1R kinase inhibitor
BLZ945.Acta Neuropathol Commun 6:9 (2018)
Bruce KD et al. Lipoprotein Lipase Is a Feature of Alternatively-Activated Microglia and May Facilitate Lipid Uptake in the CNS During
Demyelination. Front Mol Neurosci 11:57 (2018)
anti-GAPDH (1:1000, Abcam)
Fan D et al. MicroRNA 26b promotes colorectal cancer metastasis by downregulating phosphatase and tensin homolog and wingless-type
MMTV integration site family member 5A. Cancer Sci 109:354-362 (2018)
Munkonda MN et al. Podocyte-derived microparticles promote proximal tubule fibrotic signaling via p38 MAPK and CD36. J Extracell Vesicles
7:1432206 (2018
Chen H et al. Plumbagin induces RPE cell cycle arrest and apoptosis via p38 MARK and PI3K/AKT/mTOR signaling pathways in PVR. BMC
Complement Altern Med 18:89 (2018)
Mouse anti NeuN MAB377 (1:500, EMD Millipore)
Pre-existing astrocytes form functional perisynaptic processes on neurons generated in the adult hippocampus.Krzisch, M; Temprana, SG;
Mongiat, LA; Armida, J; Schmutz, V; Virtanen, MA; Kocher-Braissant, J; Kraftsik, R; Vutskits, L; Conzelmann, KK; Bergami, M; Gage,

FH;
Schinder, AF; Toni, N Brain structure & function 220 2027-42 2015
Enrichment rescues contextual discrimination deficit associated with immediate shock.Clemenson, GD; Lee, SW; Deng, W; Barrera, VR;
Iwamoto, KS; Fanselow, MS; Gage, FH Hippocampus 25 385-92 2015
Chicken anti-GFAP ab4674 (1:500, abcam)
Gunther EC et al. Rescue of Transgenic Alzheimer's Pathophysiology by Polymeric Cellular Prion Protein Antagonists. Cell Rep 26:145-158.e8
(2019).
Rosenzweig N et al. PD-1/PD-L1 checkpoint blockade harnesses monocyte-derived macrophages to combat cognitive impairment in a
tauopathy mouse model. Nat Commun 10:465 (2019).
Rabbit anti-Tuj1 ab18207 (1:500, Abcam)
Dolan CP et al. Axonal regrowth is impaired during digit tip regeneration in mice. Dev Biol 445:237-244 (2019).
Farahani RM et al. Neural microvascular pericytes contribute to human adult neurogenesis. J Comp Neurol 527:780-796 (2019).

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Tcf4+/tr mouse model - B6;129-TCF4tm1Zhu/J; stock number 013598, Jackson Laboratory, Bar Harbor, ME, backcrossed 6 generations into C57/BL6 - P1 to adult. Tcf4+/R579W, Tcf4+/△574-579, Actin-Cre::Tcf4+/floxed, and Nestin-Cre::Tcf4+/floxed mice C57/BL6 background - adult age Actin-Cre (JAX stock # 019099), Nestin-Cre (JAX stock #003771), and Olig2-cre (JAX stock #025567) mice were purchased from Jackson Laboratories - adult age. For all mouse lines and all experiments, both male and female mice were used.
Wild animals	study did not involve wild animals
Field-collected samples	study did not involve field collected samples
Ethics oversight	All the procedures were in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the institutional animal care and use committee

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