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 used in the the data collection stage.
Data analysis	fastp/0.22.0, Salmon/1.10.0, DESeq2/1.38.3, BBduk/39.01, STAR/2.7.10a, regtools/1.0.0, LeafCutter/v0.2.1, APAlyzer/1.12.0, QAPA/1.3.3, LAPA/0.0.4, DEXSeq/1.44.0, Samtools/1.17, Picard/2.27.4, StringTie/2.2.1, Deeptools/3.5.1, Python/3.10.11, R/4.2.0, GraphPad Prism 10, Aparent2, snakemake/7.32.4. The code are available on Zenodo (https://doi.org/10.5281/zenodo.14214058) and on Github (https://github.com/koryant/tdp43_apa).

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 sequencing data generated in this study is available at GEO: GSE252892. The following publicly available GEO data are used in this study: GSE126542,

GSE121569, GSE147544, GSE196144, and ERP126666. The human genome (hg38) and transcriptome reference (v42) are available at GENCODE (https://www.gencodegenes.org/human/release_42.html). Source data are included with this paper and available on Zenodo (https://doi.org/10.5281/zenodo.14214058).

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 of the de-identified patient samples are included as summary in supplementary table 8.
Reporting on race, ethnicity, or other socially relevant groupings	Relevant information on race and ethnicity are included in supplementary table 8.
Population characteristics	We have everything listed in supplementary table 8.
Recruitment	Written informed consent was obtained before study entry from all subjects or their legal kin if they were unable to give written consent and biological samples were obtained with Mayo Clinic Institutional Review Board (IRB) approval.
Ethics oversight	Mayo Clinic Institution Review Board and Ethics committee.

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 sample size calculation was performed; for in vitro experiments, sample sizes were chosen such that statistical significance could be confidently established and are similar to previous studies on similar topics (Ma et al. 2022, PMID:35197626; Rot et al., 2017, PMID: 28467899); or analysis using patient data, sample sizes were chosen based on data availability.
Data exclusions	No data from in vitro experiments were excluded. Minimal patient data were excluded based on criteria described in Methods.
Replication	All attempts at replication were successful. At least three independent replications are performed for each experiment except for Figure s3r, which had 2 replicates. Key findings are also validated by orthogonal experiments.
Randomization	Experimental conditions were not randomized as they were predetermined to access the impact of specific treatments on alterantive polyadenylation, splicing, RNA levels, or protein levels.
Blinding	The researchers were not blinded to the identity of the samples but findings have been replicated by independent researchers within the lab and across multiple laboratories. Key findings are also validated by orthogonal experiments.

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	TMEM106B (clone EZH7Z, 1:500, Cell Signaling Technology 93334), TDP-43 (1:1,500, Proteintech 10782-2-AP), ELP1 (1:500, Cell Signaling Technology 5071S), ELP3 (1:1000, Proteintech 17016-1-AP), NEFL (clone T.400.5, 1:1000, Thermo Fisher MA5-14981), GAPDH (clone 71.1, 1:2,000, Sigma-Aldrich G8795), SFPQ (clone EPR11847, 1:1000; Abcam, ab177149) VAT1L (1:500; Thermo Scientific, PA5-98934) NeuN (clone A60, 1:500; EMD Millipore, MAB377) Tuj1 (1:1000; Covance, MMS-435P) UPF1 (clone EPR4681, 1:1,000; Abcam ab109363) pUPF1 (1:1,000; EMD Millipore, 07-1016)
Validation	All commerical antibodies were validated by their corresponding manufacturers, as follows: - TMEM106B: https://www.cellsignal.com/products/primary-antibodies/tmem106b-e7h7z-rabbit-mab/93334. The specificity of this antibody was also validated independently in house by knocking down TMEM106B in iNeurons, HEk293 cells or using a TMEM106B KO cell line. - TDP-43: https://www.ptglab.com/products/TARDBP-Antibody-10782-2-AP.htm. The specficity of this antibody was validated independently in house by knocking down TDP-43 in various cell lines or using a TDP-43 KO cell line. - ELP1: https://www.cellsignal.com/products/primary-antibodies/elp1-ikbkap-antibody/5071. The specficity of this antibody was tested by the vendor across multiple cell lines. - ELP3: https://www.ptglab.com/products/ELP3-Antibody-17016-1-AP.htm. The band with expected molecular weight for ELP3 was detected by WB in house. - NEFL: https://www.thermofisher.com/antibody/product/NEFL-Antibody-clone-T-400-5-Monoclonal/MA5-14981. The specificity of this antibody was validated by the vendor in a NEFL KO cell line. - GAPDH: https://www.sigmaaldrich.com/US/en/product/sigma/g8795. The specicifty of this antibody was tested by the vendor across multiple cell lines. - SFPQ: https://www.abcam.com/en-us/products/primary-antibodies/sfpq-antibody-epr11847-ab177149. The specicifty of this antibody was tested by the vendor across multiple cell lines. - VAT1L: https://www.thermofisher.com/antibody/product/VAT1L-Antibody-Polyclonal/PA5-98934. N/A - NeuN: https://www.sigmaaldrich.com/US/en/product/mm/mab377. The specificity of this antibody was validated by numerous studies, see here: https://www.citeab.com/antibodies/226230-mab377-anti-neun-antibody-clone-a60. - Tuj1: https://www.biolegend.com/ja-jp/products/purified-anti-tubulin-beta-3-tubb3-antibody-11580. The specificity of this antibody was validated by numerous studies. - UPF1: https://www.abcam.com/en-us/products/primary-antibodies/rent1-hupf1-antibody-epr4681-ab109363#. The specificity of this antibody was tested by the vendor across different cell lines and by immunoprecipitation - pUPF1 https://www.sigmaaldrich.com/US/en/product/mm/071016. The specificity of this antibody was tested via immunoprecipitation and phosphorylated pepetides.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293 cells were purchased from purchased from ATCC (CRL-3216). Parental H1 embryonic stem cell line is from WiCell. H1 with inducible NGN2 expression is made in house.
Authentication	HEK293 cells and H1 embryonic stem cell line were authenticated by the vendors using STR analysis.
Mycoplasma contamination	Cells were tested to be negative for mycoplasma using VENORGEM mycoplasma detection kit (Sigma, MP0025).
Commonly misidentified lines (See ICLAC register)	Cell lines were not listed in ICLAC register.

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	N/A
Study protocol	N/A
Data collection	The clinical data we used in this study were from tissues donated by deceased patients.
Outcomes	N/A

Plants

Seed stocks: N/A

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.*