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	We aligned raw sequencing reads from the RNA-seq datasets to the GRCh38 human reference genome using STAR v.2.7.8a31 in chimeric alignment mode for DCC. Alignment of reads for CIRI2 was performed using BWA-MEM. DCC software was used to quantify circRNA reads from the chimeric junctions identified during STAR alignment. Transcript integrity number (TIN) was calculated per sample using the RSeQC software.
Data analysis	Differential expression and correlation analyses of the blood circRNA counts with clinical AD status was performed using negative binomial family logistic regression in the R package DESeq2. Diagnostic utility of the models were analyzed by ROC curve and AUC analysis using the R packages pROC and ROCR. CircRNA read counts were normalized based on library size and sequencing depth using VST from the DESeq2 R package. Cox proportional hazard was performed using the R package survival and Kaplan Meier (KM) curves were plotted via the R package survminer. Principal components analysis was performed to generate genetic ancestry covariates using PLINK and genetic variant array data. The linear mRNA RNA-Seq pipeline included raw sequence data quality control (QC) checks using FastQC, STAR alignment, Picard (Broad Institute) summary statistics, and transcript quantification using Salmon.

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

Knight ADRC sequencing data is available to approved investigators through https://knightadrc.wustl.edu/data-request-form/. A4 sequencing data is available to approved investigators through https://vmacdata.org/vmap/data-requests.

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	Self-reported sex was included as a covariate in the differential expression and prediction model analyses. Both sexes were included in analyses.
Reporting on race, ethnicity, or other socially relevant groupings	Genetic ancestry was determined using principle component analyses of genotype with 1000 genomes as reference.
Population characteristics	Covariate-relevant population characteristics are summarized in Table 1, Supplementary Table 1, and Supplementary Tables 15-17.
Recruitment	The Knight ADRC recruits participants with asymptomatic or mild dementia at enrollment and the age of 45 or older. The A4 study recruited cognitively unimpaired individuals at enrollment with evidence of amyloid accumulation based on amyloid-PET.
Ethics oversight	The ethics committee of Washington University School of Medicine in St. Louis approved this study (IRB ID#: 201109148).

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. The sample sizes of the two cohorts are summarized in Table 1, Supplementary Table 1, and Supplementary Tables 15-17.
Data exclusions	Related and duplicate samples were removed using cryptic relatedness through identity by descent (IBD; PIHAT ≥ 0.25) in PLINK. The Knight ADRC blood cohort included 3,656 blood samples. Samples with the covariates age at blood draw, sex, median TIN, batch, number of APOE4 alleles, and AD clinical status were kept, with 1,221 individuals passing QC in the Knight ADRC. The A4 dataset included 1,767 individuals with amyloid-PET data and the covariates age at blood draw, sex, and number of APOE4 alleles.
Replication	Differential expression and prediction models were performed using circRNA counts quantified by DCC and replicated well using circRNA counts quantified by CIRI2. The AD progression, amyloid-PET, and pTau217 prediction models were replicated in the independent A4 dataset.
Randomization	Samples were distributed into experiment groups based on neuropathological diagnosis and all samples were randomly assigned to a sequencing pool prior to RNA sequencing. Analyses were controlled for individual-level covariates including RNA quality based on median TIN, age at blood draw, sequence batch, and sex.
Blinding	Data collection including sequencing and quality control was blind to neuropathological case-control status.

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

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.