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Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Experimental design

1. Sample size

   Describe how sample size was determined.

   Sample size was based on literatures in the field and tissue sample availability within the CNDR biobank (University of Pennsylvania) with following selection criteria: age, gender, disease stage and neuronal loss. Study group (Young, Old and AD) comparisons were subject to a Welch's t-test (2-way comparison) or 1-way Anova (3-way comparison).

2. Data exclusions

   Describe any data exclusions.

   No data were excluded from the analyses

3. Replication

   Describe the measures taken to verify the reproducibility of the experimental findings.

   Because tissue samples were collected and ChIP-sequenced in two replication sets, their similarity was assessed by clustering over the three classes of peaks (Age-regulated; Age-dysregulated; Disease-specific) - see Fig. S7. All attempts at replication were successful.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   Tissue samples were allocated (no randomization) into three different study groups based on age and disease: cognitively normal elder individuals ("Old", N=10, mean age=68), AD subjects ("AD", N=12, mean age=68), or younger cognitively normal subjects ("Young", N=9, mean age=52) - see Table S1 for patient information. In order to reduce the number of explanatory variables to a minimum, we controlled for gender (mainly male subjects), comorbidity (excluding cases with other neuropathologies) and neuronal loss (excluding cases with sever loss).

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   Tissue samples were selected based on criteria matching each study group (Young; Old or AD) and therefore not subject to blinding. However, NeuN stained nuclei (Fig. S1) were counted in a blind fashion for each tissue sample.

Note: all in vivo studies must report how sample size was determined and whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☒	☐ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ A statement indicating how many times each experiment was replicated
☐	☒ 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 any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ Test values indicating whether an effect is present *Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes noted.*
☒	☐ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars in all relevant figure captions (with explicit mention of central tendency and variation)

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.

For ChIP-seq analysis, we used: Bowtie v1.1.1 (to align sequencing tags to the human reference genome); MACS2 (to call peaks); MTL method (Chen et al., 2008) (to compare ChIP-seq enrichment across the three study groups). For RNA-seq analysis, we used: STAR (to align sequencing tags to the human reference genome); SAMtools and BEDtools (to remove tags with mapping score < 10 or mitochondria tags); DESeq2 R package for differential gene expression analysis. Pipeline and code for the ChIP-seq analysis are available at http://165.123.66.72/btracks/sulfa/Nativio.11112017. For AD SNP and AD eQTL enrichment analysis, we used INRICH and custom awk-based bash scripts (available by request), respectively.
For neuronal quantification by IF, we used: Slidebook 5.5 software (to visualize slides on the Olympus BX60 Microscope); Microsoft Paint (to mark NeuN positive nuclei) and Cell Profiler (to count DAPI+ objects).

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a third party.

No unique materials were used

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

For ChIP-seq:
- H4K16ac antibody: cat # 07-329; Millipore at http://www.emdmillipore.com/US/en/product/Anti-acetyl-Histone-H4-Lys16-Antibody,MM_NF-07-329

For neuron quantification by IF:
- NeuN antibody: cat # MAB377; EMD Millipore at http://www.emdmillipore.com/US/en/product/Anti-NeuN-Antibody-clone-A60,MM_NF-MAB377
- Oregon Green 488 anti-mouse antibody (Life Technologies)

For neuron quantification by flow cytometry:
- NeuN antibody (Alexa Fluor®488 conjugated): cat # MAB 377X, EMD Millipore at http://www.emdmillipore.com/US/en/product/Anti-NeuN-Antibody-clone-A60-Alexa-Fluor488-conjugated,MM_NF-MAB377X
- anti-mouse IgG antibody (Alexa Fluor®488 conjugated): cat # A21202, ThermoFisher at https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21202

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

No eukaryotic cell lines were used

b. Describe the method of cell line authentication used.

No eukaryotic cell lines were used

c. Report whether the cell lines were tested for mycoplasma contamination.

No eukaryotic cell lines were used

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

No commonly misidentified cell lines were used

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide all relevant details on animals and/or animal-derived materials used in the study.

no animals were used

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Tissue samples were categorized based on age, gender, disease stage and neuronal loss. Detailed patient information is provided in Table S1.

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ChIP-seq Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data deposition

1. For all ChIP-seq data:

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

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

2. Provide all relevant data deposition access links. *The entry may remain private before publication.*	The ChIP-seq and RNA-seq data are available through NCBI Gene Expression Omnibus (GEO) repository under accession number GSE84618.
3. Provide a list of all files available in the database submission.	Files available in the GEO: Fastq; bigWig and BED files.
4. Provide a link to an anonymized genome browser session (e.g. UCSC), if available.	No longer applicable

Methodological details

5. Describe the experimental replicates.	Tissue samples were categorized into three different study groups based on age and disease: Young (N=9, mean age=52); Old (N=10, mean age=68); AD (N=12, mean age=68) - see Table S1 for patient information. Because tissue samples were collected and ChIP-sequenced in two replication sets, their similarity was assessed by clustering over the three classes of peaks (Age-regulated; Age-dysregulated; Disease-specific) - see Fig. S7.
6. Describe the sequencing depth for each experiment.	Sequencing and alignment statistics (number of total tags, uniquely aligned tags and % uniquely aligned tags) is provided for each of the 31 samples in Table S2 (ChIP-seq) and Table S3 (RNA-seq).
7. Describe the antibodies used for the ChIP-seq experiments.	- H4K16ac antibody: cat # 07-329; Millipore at http://www.emdmillipore.com/US/en/product/Anti-acetyl-Histone-H4-Lys16-Antibody,MM_NF-07-329
8. Describe the peak calling parameters.	Peaks were detected using MACS 2 (tag size = 75 bp; FDR < 1x10-3)
9. Describe the methods used to ensure data quality.	ChIP-seq data quality was assessed by comparing the genomic sites of H4K16ac enrichment with previously published H4K16ac data from other cell lines.
10. Describe the software used to collect and analyze the ChIP-seq data.	ChIP-seq libraries were sequenced (75bp) on the NextSeq 500 platform (Illumina) and data collected using BaseSpace (Illumina). For the ChIP-seq analysis we used: Bowtie v1.1.1 (to align sequencing tags to the human reference genome); MACS2 (to call peaks); MTL method (Chen et al., 2008) (to compare ChIP-seq enrichment across the three study groups). Pipeline and codes for the ChIP-seq analysis are available at http://165.123.66.72/btracks/sulfa/Nativio.11112017