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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	All code for the data collection is available at https://github.com/sterding/BRAINcode.
Data analysis	PLINK2 (v1.9beta), SHAPEIT2 (v2.5), IMPUTE2 (v2.3.1), fastq-mcf, FastQC, kpal, Tophat(v2.0.8), Cuffquant (v2.2.1), sva, ComBat, UCSC Kent Utilities, eulerAPE, Primer3web (v4.0.0), Marix-eQTL, TagDust (v1.12), BWA (v0.5.9), R (v3.4.4)

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 upon request. 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

BRAINcode RNA-seq and genotyping raw data have been deposited in dbGAP under accession number phs001556.v1.p1. The processed data and eQTL results for

BRAINcode project can be queried at http://www.humanbraincode.org through a user-friendly interface. The BRAINcode data sets submitted to dbGAP include the raw data used for figures: Fig. 1b-e, Fig. 2a,c,d; Fig. 3a,3c-d; Fig. 4a; and Fig. 5a-c,5e-g.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were based on the total number of available high-quality brain samples that met inclusion and exclusion criteria. No statistical methods were used to pre-determine sample sizes but our sample sizes are consistent with those recommended by the Genotype-Tissue Expression Consortium (GTEX consortium, Nature, 2017).
Data exclusions	Inclusion criteria: (1) absence of clinical or neuropathological diagnosis of a neurodegenerative disease e.g. Parkinson's disease according to the UKPDBB criteria45, Alzheimer's disease according to NIA-Reagan criteria, dementia with Lewy bodies by revised consensus criteria. For the purpose of this analysis incidental Lewy body cases (not meeting clinico-pathological diagnostic criteria for PD or other neurodegenerative disease) were accepted for inclusion. (2) PMI ≤ 48 hours; (3) RIN48 ≥ 6.0 by Agilent Bioanalyzer (good RNA integrity); (4) visible ribosomal peaks on the electropherogram. Exclusion criteria were: (1) a primary intracerebral event as the cause of death; (2) brain tumor (except incidental meningiomas); (3) systemic disorders likely to cause chronic brain damage. We also included eight non-brain tissue samples as controls, including five samples of peripheral blood mononuclear cell (PBMC) and three fibroblasts (FB), provided by Harvard Biomarker Study and Coriell Institute. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.
Replication	Attempts at replication were successful. Replication of TNE was performed in four independent cohorts as delineated in Fig. 3. Moreover, select TNE were confirmed by a second method, qPCR, as shown in Fig. 3. The inverse eQTL relation between the lead GWAS-derived SNP rs17649553 and KANSL1-TNE1 and LRRC37A4P, respectively, was confirmed by a second method, cell type-specific qPCR (Supplementary Fig. 12a). Moreover, this association was independently replicated in a second cohort of neurons laser-captured from 31 high-quality control brains (Supplementary Fig. 12b, Supplementary Table 12). Furthermore, the rs17649553-LRRC37A4P eQTL association was further confirmed in 56 substantial nigra and 96 frontal cortex samples from GTEx (Supplementary Fig. 12c,d), which used a polyA+ selecting protocol that does not allow for assaying KANSL1-TNE1 RNA.
Randomization	Allocation was not random and covariates (such as age, sex, PMI) were adjusted in the analysis.
Blinding	All samples were from controls (see eligibility criteria above). Blinding to case/control status is not applicable.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HeLa and SK-N-MC cell lines were obtained from ATCC.
Authentication	HeLa and SK-N-MC cells were used from ATCC and their identity was confirmed by microsatellite testing.
Mycoplasma contamination	All cell lines tested are negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register)	SK-N-MC cells were used from ATCC and their identity was confirmed by microsatellite testing.

Animals and other organisms

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

Laboratory animals	Zebrafish (Danio rerio) were used. Both males and females, adults, and embryos were used.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Characteristics are shown in Supplemental Table 1. Briefly, the mean age at death (standard deviation) was 81 (10.2) for autopsy brains used for lcRNAseq of nigral dopamine neurons. The male:female ratio was 2:1. The median post-mortem interval (stdev) was 3 hours (6.6 hours). The median (stdev) RIN number was 7.8 (0.8).
Recruitment	We started with 107 high-quality, frozen postmortem human control brain samples identified from Banner Sun Health Institute, Brain Tissue Center at Massachusetts General Hospital, Harvard Brain Tissue Resource Center at McLean Hospital, University of Kentucky ADC Tissue Bank, University of Maryland Brain and Tissue Bank, Pacific Northwest Dementia and Aging Neuropathology Group (PANDA) at University of Washington Medicine Center, and Neurological Foundation of New Zealand Human Brain Bank.