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<br>*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<br>*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 | Trim Galore (v0.6.10), BWA-MEM (v0.7.17), GATK (v4.2.4.1), Cell ranger (v6.1.2) |
| Data analysis | Hail (v0.2.68), PLINK (v1.90), KING (v2.0), ensembl-vep (v108.1), REGENIE (v2.2.4), UCSC genome browser (as of Feburary, 2024), LocusZoom (v1.4), R (v4.3.1, v4.2.2), SCANPY (v1.9.8), Scrublet (v0.2.3), tensorQTL (v1.0.2), COLOC (v3.2-1), CWAS-Plus (v1.2), parliament2 (v0.1), ExpansionHunter (v5.0.0), ClusterProfiler (v4.6.2), DBSCAN (v1.1-12), PRScs (v1.0.0) |

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 GWAS summary statistics for the Korean cohort are available in the NHGRI-EBI GWAS Catalog under accession number GCST90566388 and GCST90566389

[https://www.ebi.ac.uk/gwas]. The Japanese GWAS summary statistics used in this study were provided by Prof. Daichi Shigemizu. The single-nuclei RNA-seq data for the Korean participants are accessible for collaborative research under restricted conditions to protect participant privacy. For inquiries regarding data access, please contact the corresponding author (S.W. Seo (sangwonseo@empas.com)). Data access requests will be reviewed and responded to within 2 to 4 weeks of receipt. The summary statistics of cell type-specific eQTLs (https://zenodo.org/records/7276971), MiGA eQTLs (https://doi.org/10.5281/zenodo.4118605), multi-ethnic eQTLs (http://icahn.mssm.edu/brema), and MetaBrain eQTLs (https://www.metabrain.nl/) are available in public repositories. The results of single-cell analyses from ROSMAP-MIT, including DEGs, are available at the AD/Aging Brain Atlas (https://compbio.mit.edu/ad_aging_brain/). The SEA-AD analysis results are available at the Allen Brain Map (https://portal.brain-map.org/explore/seattle-alzheimers-disease). The cell type-specific regulatory elements derived from single-cell data obtained from postmortem AD brain samples are available at [https://personal.broadinstitute.org/bjames/AD_snATAC/] and [https://compbio.mit.edu/microglia_states/]. AD-specific epigenomic histone acetylation data from postmortem human brains, available at [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE130746]. The chromatin interaction data are available at 3DIV (http://3div.kr/hic). The ExpansionHunter input variant catalogs are available from Guo et al. [https://github.com/mhguo1/AD_STR]. Source data are provided as a Source Data file.

## 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 | This study does not apply to specific sexes or genders. Sex was adjusted in GWAS and regression analyses as a covariate. The clinically reported sex was utilized, and a sex check using genomic data was conducted. There are 608 males and 951 females. |
| Reporting on race, ethnicity, or other socially relevant groupings | The self-reported race of all participants (n=1,824) was Korean, East Asian, and this was verified through PCA analysis. |
| Population characteristics | Population characteristics are delineated in Supplementary Data 1A. |
| Recruitment | Participants were recruited from the K-ROAD cohort, a hospital-based dementia registry involving 25 university-affiliated hospitals in South Korea. A total of 1,824 samples were included in this study. All participants underwent standardized clinical assessment and amyloid PET imaging with informed consent under IRB approval. As recruitment was conducted through routine clinical pathways rather than open public solicitation, the risk of self-selection bias is minimal. However, as a hospital-based cohort, generalizability to the broader population may be limited, which we have acknowledged in the manuscript's discussion section. |
| Ethics oversight | This study obtained approval from the institutional review board, and written informed consent was obtained from all participants. |

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 | Raw data was collected by the K-ROAD cohort. The sample size was not pre-determined and was chosen based on all available K-ROAD cohorts with whole-genome sequencing (WGS) data, resulting in a total of 1,824 samples being selected. |
| Data exclusions | Quality control procedures were implemented, resulting in the exclusion of 76 samples due to low-quality WGS data or relatedness. Additionally, 189 individuals with other types of dementia were further excluded. |
| Replication | Independent replication using external cohorts was not feasible due to the lack of comparable WGS and amyloid PET datasets. Nevertheless, we ensured internal reproducibility through stringent QC processes and convergence of results across multiple variant types and phenotypes. |
| Randomization | The use of randomization is not applicable in this observational study. |
| Blinding | Blinding is not applicable because this study involves data-generation efforts and is free from specific hypotheses. |

# 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.*