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Supplementary information

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GWAS of multiple neuropathology endophenotypes identifies new risk loci and provides insights into the genetic risk of dementia

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Table of Contents

Table of Contents

Supplementary Methods

Quality control

Quality control on genotype data was performed separately for each data source. Quality control and inclusion/exclusion criteria closely followed that used in our previous brain arteriolosclerosis genome-wide association study (GWAS)[1]. After imputation, we first identified and subsequently removed duplicate samples using the KING software "--duplicate" option[2]. We then removed participants without autopsy data available by merging genotype sample identification data with neuropathology data sets and retaining only samples present in both data sets. We then iteratively removed genetic variants and participants until no variants were missing in more than 5% of participants and no participants were missing more than 5% of variants (however, average genotype coverage was 99.7%, and no variants or participants were actually removed during this process). We then excluded participants with unusually high or low ($\pm$ 3 standard deviations from mean) genetic heterogeneity, as measured by the PLINK 1.9 "--het" flag (https://www.cog-genomics.org/plink/1.9/). Finally, we merged participants with the 1000 Genomes Phase 3 (1000 Genomes) cohorts[3] and performed principal components analysis (PCA) on a subset of independent variants (measured by pairwise $r^2 < 0.2$). We excluded participants with substantial non-European ancestry, as determined by distance from the 1000 Genomes EUR superpopulation centroid using the first two principal components (PCs).

NACC Exclusion Criteria

National Alzheimer's Coordinating Center (NACC) participants were excluded if they had any of the conditions in the NACC Neuropathology Data Set shown in **Supplementary Table 6**. Variable names and descriptions are taken from https://files.alz.washington.edu/documentation/rdd-np.pdf. Variable descriptions may be lightly edited. Participants were not excluding for missing data in any fields.

Harmonization of NPE

We harmonized 11 neuropathology endophenotypes (NPE) across the three data sources used: NACC, Religious Orders Study (ROS) and the Memory and Aging Project (MAP; together, ROSMAP), and Adult Changes in Thought (ACT). Arteriolosclerosis, Braak neurofibrillary tangle (NFT) stage, cerebral amylois angiopathy (CAA), atherosclerosis, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score for neuritic plaques, microinfarcts, and gross infarcts had variables in each cohort with directly comparable coding definitions and were straightforwardly harmonized with minimal recoding. Arteriolosclerosis, CAA, atherosclerosis, and CERAD score variables each had four stages with the following labels: 0 ("none"), 1 ("mild"), 2 ("moderate"), and 3 ("severe"). Microinfarcts and gross infarcts were labeled either 0 ("absent") or 1 ("present"). Braak NFT Stage followed the staging criteria previously described in the literature and had seven levels, ranging from 0 (absent NFT) to six (diffuse NFT throughout cortex and large loss of neurons)[4].

Limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) neuropathologic change (LATE-NC) was recorded differently in several of the data sets and was harmonized to a four-level outcome variable following the simplified staging of TDP-43 pathology outlined in Figure 3B of the 2019 LATE working group report[5]. The following levels were used in the analyzed LATE-NC variable: 0, indicating lack of recorded TDP-43 proteinopathy; 1, indicating TDP-43 deposits in the amygdala only; 2, indicating deposits in the hippocampus or entorhinal cortex; and 3, indicating deposits in the neocortex. In ROSMAP, TDP-43 pathology is recorded as a single variable following the same staging detailed above. In NACC, the presence of TDP-43 pathology in each region of the brain is recorded as a separate binary indicator variable. To collapse TDP-43 pathology to a single ordinal variable, we assigned a value based on the presence of the "highest" region where TDP-43 was present (*e.g.* a participant with TDP-43 pathology in both the hippocampus and the neocortex would be assigned a value of 3). Participants were labeled as 0 if they met two conditions: (1) they had recorded TDP-43 data available for at least one of the brain regions used for staging and (2) TDP-43 pathology was noted as absent in all the regions for which they had data available.

Diffuse amyloid plaque pathology was recorded as a four-stage Thal phase of amyloid deposition in NACC, ACT, and ADNI with the following levels: 0 ("none"), 1 ("mild"), 2 ("moderate"), and 3 ("severe"). In ROSMAP, diffuse plaques were examined and quantified in five regions (midfrontal cortex, entorhinal cortex, inferior parietal cortex, and hippocampus), then scaled by each region's standard deviation and averaged. To discretize this continuous variable in ROSMAP participants to a four-level variable, as recorded in the other data sets, we assigned participants a value of 0 ("none") if their averaged score was equal to 0 (18.8%), 1 ("mild") if their score was higher than 0 but ≤ 0.5 (29.7%), 2 ("moderate") if their score was between 0.5 and one (23.5%), and 3 ("severe") if their score was above 1 (26.8%). These labels roughly corresponded to score quartiles in ROSMAP (**Table 1** in main text).

Hippocampal sclerosis is recorded as a binary indicator of the presence or absence of pathology in the NACC Neuropathology data set form version 1-9, ROSMAP, and ACT. In versions 10 and 11 of the NACC Neuropathology form, hippocampal sclerosis pathology is recorded as being absent, unilateral, or bilateral. To harmonize, we dichotomized hippocampal sclerosis pathology as being present if either unilateral or bilateral pathology was indicated.

The Lewy body pathology variable we analyzed had four levels: 0, indicating absent Lewy body pathology in all regions examined or limited to the olfactory bulb; 1, indicating Lewy body pathology limited to the brainstem, including the substantia nigra; 2, indicating Lewy body pathology involving the limbic system or amygdala; and 3, indicating Lewy body involvement in the neocortex. In NACC and ROSMAP, Lewy body pathology was graded in ordinal variables with levels corresponding to the levels in the final harmonized outcome variable analyzed. In ACT, separate binary indicator variables were used to indicate presence of Lewy body pathology in each brain region checked. To harmonize, we created a new variable that coded Lewy body pathology stage according to the "highest" stage present in an individual (*e.g.* if pathology was present in both the amygdala and the neocortex, we assigned a value of 3).

Sensitivity analyses for *APOC2* locus association with CAA

We performed several sensitivity analyses to further investigate the novel CAA-associated locus on Chromosome 19 near *APOC2* identified when adjusting for *APOE* ϵ diplotype with individual cohorts (NACC n = 5,927, ROSMAP n = 1,172, ACT n = 677) and meta-analysis (n = 7,776) using METAL. First, for each of the NACC, ROSMAP, and ACT data sources, we re-analyzed the association between CAA and lead variant rs7247551 from the meta-analysis while stratifying by *APOE* ϵ diplotype and visually compared effect sizes across groups. Due to low sample sizes preventing model convergence, APOE ϵ4 carriers (diplotypes ϵ3/ϵ4, ϵ4/ϵ4, ϵ3/ϵ4) were merged in analyses for ROSMAP and ACT. Then, for each data source, we performed an association analysis between CAA and rs7247551 that included interaction effects between rs7247551 and *APOE* ϵ diplotype. We then performed ANOVA between these models and nested models which did not include interaction effects and performed Chi-Square tests to test whether any interaction terms were significant. We used P <0.05 for the significance threshold.

Software

The following software was used in the current study. Links to websites containing downloads for software are provided.

bcftools 1.10.2 https://samtools.github.io/bcftools/
KING 2.2.7 https://www.kingrelatedness.com/Download.shtml
MAGMA 1.10 https://cncr.nl/research/magma/
METAL 2011-03-25 https://csg.sph.umich.edu/abecasis/Metal/download/
Minimac 4 https://github.com/statgen/Minimac4
PLINK 1.9 and 2.0 https://www.cog-genomics.org/plink/
Python 3.8.16 and 3.10.8 https://www.python.org/downloads/
R 4.2.1 and 4.2.2 https://cran.r-project.org/
R package coloc 5.2.2 https://github.com/chr1swallace/coloc
R package data.table 1.14.10 https://cran.r-project.org/
R package GENESIS 2.26.0 https://bioconductor.org/packages/3.18/bioc/
R package ggplot2 3.4.2 https://cran.r-project.org/
R package GRAB 0.1.1 https://wenjianbi.github.io/grab.github.io/
R package GWASTools 1.42.1 https://bioconductor.org/packages/3.18/bioc/
R package LDlinkR 1.2.3 https://bioconductor.org/packages/3.18/bioc/
R package ordinal 2023.12-04 https://cran.r-project.org/
R package pheatmap 1.012 https://cran.r-project.org/
R package POLMM 0.2.3 https://github.com/WenjianBI/POLMM
R package SAIGE 1.1.3 https://saigegit.github.io/SAIGE-doc/
R package SNPRelate 1.30.1 https://bioconductor.org/packages/3.18/bioc/
R package stringi 1.8.3 https://cran.r-project.org/
R package polycor 0.8-1 https://cran.r-project.org/package=polycor
R package psych 2.3.3 https://cran.r-project.org/package=psych
samtools 1.10 https://github.com/samtools/samtools
TOPMed Imputation Server 1.7.3 https://imputation.biodatacatalyst.nhlbi.nih.gov/#!

Supplementary Results

Polychoric Correlations of Neuropathology Endophenotypes

We identified three positively correlated clusters of endophenotypes: a "vascular" cluster consisting of gross infarcts, microinfarcts, arteriolosclerosis, and atherosclerosis; an "Alzheimer's disease" cluster consisting of Braak NFT stage, neuritic plaques, amyloid-beta plaques, and CAA; and a "LATE" cluster consisting of LATE-NC and hippocampal sclerosis (**Extended data Figure 1**). These results demonstrate that, as expected, many NPEs are not independent, though our GWAS results also suggest the genetic underpinnings are not identical.

Suggestive Loci Identified in NPE GWAS

Here, we report suggestive hits from the NPE GWAS meta-analysis that met at least one of two criteria (**Figure 2**): (1) a suggestive threshold of $P < 5 \times 10^{-7}$, or (2) were previously reported by other studies (e.g., Bellenguez et al.[6]) as a disease-associated locus and met a threshold of $P < 1 \times 10^{-5}$. See **Supplementary Table 7** for gene list reported by other studies, beyond Bellenguez et al.

For previously reported loci meeting the threshold of $P < 1 \times 10^{-5}$, we observed twelve potential associations (**Figure 2** in main text purple; **Supplementary Table 8**). Nine of the twelve were reported in Bellenguez et al., including: (1) *CASS4* and amyloid-β plaques (single-nucleotide polymorphism (SNP) located at chr20:56451506; odds ratio (OR) = 0.82; $P = 1.8 \times 10^{-6}$; **Figure 2a**); (2) *EED* (from the broader *PICALM* locus) and CERAD (rs3851179; OR = 0.84; $P = 1.1 \times 10^{-6}$; **Figure 2c**); (3) *RIN3* and CERAD (rs8015844; OR = 0.85; $P = 5.3 \times 10^{-6}$; **Figure 2c**); (4) *PTK2B* and CAA (rs4733054; OR = 1.15; $P = 9.9 \times 10^{-6}$; **Figure 2f**); (5) *TMEM106B* and gross infarcts (rs12534231; OR = 0.75, $P = 2.4 \times 10^{-6}$; **Figure 2g**); (6) *GRN* and LATE-NC (rs5848; OR = 1.32; $P = 1.3 \times 10^{-6}$; **Figure 2i**); (7) *APOE* and Lewy bodies (rs429358; OR = 1.23; $P = 1.1 \times 10^{-6}$; **Figure 2j**); (8) *FOXF1* and hippocampal sclerosis (rs1728394; OR = 0.74 $P = 6.4 \times 10^{-6}$; **Figure 2k**); and (9) *MAPT* and hippocampal sclerosis (rs7210219; OR = 0.71; $P = 4.9 \times 10^{-6}$; **Figure 2k**).

The other three loci, where we observed a single suggestive association each, were reported in previous phenotype association studies, including: (1) *LINC-PINT* and CERAD score (rs62471587; OR = 1.19; $P = 4.0 \times 10^{-6}$; **Supplementary Table 8**; **Figure 2c**); (2) *HLA-C* and atherosclerosis (position chr6:31265340; OR = 0.53; $P = 6.9 \times 10^{-6}$; **Figure 2e**); and (3) *ABCC9* and hippocampal sclerosis (rs4148674; OR = 1.30; $P = 5.8 \times 10^{-6}$; **Figure 2k**). *HLA-C* (and *HLA-B*) was previously associated with atherosclerosis in the carotid arteries of patients with psoriasis[7]—a different cohort and tissue, but the same underlying pathology. Similarly, *LINC-PINT* was previously associated with CAA in non-*APOE ϵ4* carriers by Reddy et al.[8] while *ABCC9* was previously associated with hippocampal sclerosis in several studies[9-11].

For genes meeting the suggestive threshold of $P < 5 \times 10^{-7}$ (**Figure 2** in gold), we observed 27 suggestive associations, where three were from previously reported loci: (1) *BIN1* and CERAD score (rs6733839; OR = 1.19; $P = 3.2 \times 10^{-7}$; **Supplementary Table 8;**

Figure 2c); (2) *PICALM* and CAA (rs57929351; OR = 1.23; $P = 1.7 \times 10^{-7}$; **Figure 2f**); and (3) *CTNNA3* and hippocampal sclerosis (rs10997204; OR = 1.53; $P = 4.7 \times 10^{-6}$; **Figure 2k**). *PICALM*[12] and *BIN1*[13] have long been associated with clinical AD diagnosis, while the *CTNNA3* locus was only recently associated with Lewy body dementia[14]. Of the other 24 (novel) suggestive loci reaching $P < 5 \times 10^{-7}$, twelve were associated with hippocampal sclerosis (**Figure 2k**), whereas the next highest number of suggestive associations was gross infarcts, with four. One intronic locus of *SPATA48* (formerly *C7orf72*) was close to genome-wide significance with circle of Willis atherosclerosis (rs62447817; OR = 1.35; $P = 5.5 \times 10^{-8}$; **Figure 2e**), but future studies will need to assess these suggestive associations more carefully. Notably, there were zero genome-wide significant associations with gross infarcts, microinfarcts, or Lewy body pathologies. Of the four suggestive loci for gross infarct pathology, one was from a known gene in *TMEM106B* (rs12534231; OR = 0.75; $P = 2.4 \times 10^{-6}$). Microinfarct pathology had a single suggestive association in *HSD17B12* (SNP located at chr11:43817807; OR = 1.74; $P = 4.0 \times 10^{-7}$; **Figure 2h**). There were two suggestive associations for Lewy bodies in *HMOX1* (rs75125910; OR = 14.52, $P = 3.5 \times 10^{-7}$; **Figure 2j**) and *APOE* (rs429358; OR = 1.23 $P = 1.1 \times 10^{-6}$).

rs7247551 shows consistent association with CAA across *APOE* ε diplotypes

Forest plots for study- and *APOE* ε diplotype-stratified analysis for association between rs7247551 and CAA are shown in **Extended data Figure 3**. Visual inspection of forest plots did not reveal substantial variation in effect size across diplotypes within data sources. Point estimates of OR for all diplotypes studied in NACC and ROSMAP were <1, consistent with meta-analysis, and only 95% CI for *ε4/ε4* in NACC and *ε2/ε3* in ROSMAP crossed 1. In ACT, *ε3/ε3* and *ε4* carriers had point estimates of OR <1, but the OR of the smallest group, ε2/ε3, was ~1.4, although it still overlapped with the estimates of *ε3/ε3* and *ε4* carriers. No interaction terms between rs7247551 and diplotype were significant in the models testing interaction effects in any of the data sources (NACC Chi-Square $P = 0.84$; ROSMAP Chi-Square $P = 0.13$; ACT Chi-Square $P = 0.91$). These results indicate that rs7247551 shows a consistent pattern of association with CAA in each of the data sources used in our study.

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Supplement References

1. Shade, L. M. et al. Genome-wide association study of brain arteriolosclerosis. *J. Cereb. Blood Flow Metab.* **42**, 1437-1450 (2022).
2. Manichaikul, A. et al. Robust relationship inference in genome-wide association studies. *Bioinformatics* **26**, 2867-2873 (2010).
3. Abecasis, G. R. et al. An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65 (2012).
4. Braak, H. & Braak, E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* **82**, 239-259 (1991).
5. Nelson, P. T. et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain* **142**, 1503-1527 (2019).

6. Bellenguez, C. et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat. Genet.* **54**, 412-436 (2022).
7. Eder, L. et al. The Association of HLA-class I Genes and the Extent of Atherosclerotic Plaques in Patients with Psoriatic Disease. *J. Rheumatol.* **43**, 1844-1851 (2016).
8. Reddy, J. S. et al. Genome-wide analysis identifies a novel LINC-PINT splice variant associated with vascular amyloid pathology in Alzheimer's disease. *Acta Neuropathol. Commun.* **9**, 93 (2021).
9. Katsumata, Y. et al. LATE-NC risk alleles (in TMEM106B, GRN, and ABCC9 genes) among persons with African ancestry. *J. Neuropathol. Exp. Neurol.* **82**, 760-768 (2023).
10. Dugan, A. J. et al. Analysis of genes (TMEM106B, GRN, ABCC9, KCNMB2, and APOE) implicated in risk for LATE-NC and hippocampal sclerosis provides pathogenetic insights: a retrospective genetic association study. *Acta Neuropathol. Commun.* **9**, 152 (2021).
11. Nelson, P. T. et al. ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology. *Acta Neuropathol.* **127**, 825-843 (2014).
12. Harold, D. et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet.* **41**, 1088-1093 (2009).
13. Seshadri, S. et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* **303**, 1832-1840 (2010).
14. Gibbons, E. et al. Identification of a sex-specific genetic signature in dementia with Lewy bodies: a meta-analysis of genome-wide association studies. *medRxiv*, 2022.2011.2022.22282597 (2022).
15. Pruim, R. J. et al. LocusZoom: regional visualization of genome-wide association scan results. *Bioinformatics* **26**, 2336-2337 (2010).