Received: 24 May 2021 | Revised: 3 October 2021 | Accepted: 12 October 2021

DOI: 10.1002/alz.12524

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

ALTERNATE FORMAT RESEARCH ARTICLE

# Integration of GWAS and brain transcriptomic analyses in a multiethnic sample of 35,245 older adults identifies *DCDC2* gene as predictor of episodic memory maintenance

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## Abstract

Identifying genes underlying memory function will help characterize cognitively resilient and high-risk declining subpopulations contributing to precision medicine strategies. We estimated episodic memory trajectories in 35,245 ethnically diverse older adults representing eight independent cohorts. We conducted apolipoprotein E (*APOE*)-stratified genome-wide association study (GWAS) analyses and combined individual cohorts' results via meta-analysis. Three independent transcriptomics datasets were used to further interpret GWAS signals. We identified *DCDC2* gene significantly associated with episodic memory (Pmeta = 3.3 x $10^{-8}$) among non-carriers of *APOE* ε4 (N = 24,941). Brain transcriptomics revealed an association between episodic memory maintenance and (1) increased dorsolateral prefrontal cortex *DCDC2* expression ($P$ = 3.8 x $10^{-4}$) and (2) lower burden of pathological Alzheimer's disease (AD) hallmarks (paired helical fragment tau $P$ = .003, and amyloid beta load $P$ = .008). Additional transcriptomics results comparing AD and cognitively healthy brain samples showed a downregulation of *DCDC2* levels in superior temporal gyrus ($P$ = .007) and inferior

  

frontal gyrus ($P = .013$). Our work identified *DCDC2* gene as a novel predictor of memory maintenance.

**KEYWORDS**
apolipoprotein E stratified analyses, brain transcriptomics, episodic memory trajectories (EMTs), genome-wide association studies, meta-analysis, rare/common genetic variation

# 1 | NARRATIVE

## 1.1 | Contextual background

As we age, our cognitive abilities deteriorate,[1] without necessarily progressing to dementia. One of the earliest and most striking cognitive changes in the aging process is the alteration of memory. Episodic memory, our ability to remember recently acquired experiences, gradually deteriorates from middle age to older age. Our ability to create and store memories (encoding and storage) along with retrieval[2] becomes less efficient, interfering with our daily activities.

Major research efforts have focused on trying to distinguish the memory decline attributable to normal aging from that indicating pathological aging. Such studies show that the effects of aging on our memory performance are very heterogeneous, with clear interindividual vulnerabilities. Some people exhibit little change in their memory ability to extreme old age, while others experience a rapid and severe memory decline that might culminate in a clinical diagnosis of Alzheimer's disease (AD). Understanding the causal factors underlying over-time memory performance is increasingly important given the health-care crisis of an aging world's population. Psychological, health-related, environmental, education, and genetics[3] factors have been reported as significant contributors to the variability observed in the trajectories of episodic performance across individuals.

Twin and family studies support the notion that episodic memory is under strong genetic influence in older persons in healthy and demented populations.[4] In recent years, different study designs and approaches have been used to genetically characterize episodic memory trajectories. The majority of the genetic studies on episodic memory have been cross-sectional either using genome-wide arrays[5–7] or candidate gene approaches.[8–18] Genetic studies based on longitudinal measures of episodic memory are few, and predominantly focused on candidate genes.[19,20] Genome-wide association studies (GWAS) of cognitive abilities assessing the contribution of common variants[11,17,18,21–29] have consistently reported modest genetic effects, partially due to limited sample sizes that compromise the statistical power to identify loci at a genome-wide significance level. As reported for other complex phenotypes,[30,31] such as autoimmune and cardiovascular diseases, genomic analysis including rare variants might reveal its unique roles in cognitive genetics.

In the present study, we integrated common and rare genetic variants and transcriptomics data for the identification of novel episodic memory loci.

## 1.2 | Study design and main results

To guarantee a better understanding of the impacts of aging, cohort differences, and period effects in the trajectories of memory performance, we considered a longitudinal study design.

The identification of genetic risk/protective factors underlying memory function is commonly based on cross-sectional data and genetic studies based on longitudinal data are less frequently implemented. Contrary to cross-sectional designs in which a temporal sequence cannot be established, longitudinal methods are uniquely able to capture genetic variation associated with the rate of cognitive decline,[32] allowing the separation of population trends (fixed effects) and individual differences about the trends (random effects). The availability of longitudinal measures of memory performance allows us to expand genetic analyses beyond the dichotomous case-control phenotype, typically resulting in loss of measurement information as well as effect size and statistical power.

To study trajectories of memory performance in elderly cohorts, we have used a previously described latent curve models (LCM) approach.[33] The resulting slopes of repeated measures of memory are used as quantitative phenotype for genetic analyses.[32]

Because GWAS of common variants explain a modest fraction of the genetic variance of cognitive abilities,[25] low-frequency and rare genetic variants have been proposed as responsible for the uncharacterized genetic risk underlying cognitive traits.[30] A cost-efficient approach to characterize the contribution of rare variants to memory function is their genotype imputation, that is, statistical inference of untyped rare variants' genotypes based on a reference panel of whole genome sequenced individuals.[34] The publicly available Haplotype Reference Consortium (HRC) reference panel contains more than 39 million single nucleotide polymorphisms (SNPs) from 27,165 individuals, and reported high performance and accuracy for imputation for admixed populations such as Blacks[35] and Caribbean Hispanics.[36]

In addition to the traditional SNP-based approaches,[37] we have also considered gene-based GWAS tests. Gene-based analyses increases the statistical power of discovery by (1) aggregating the disparate signals from multiple independent causal variants within the gene and (2) reducing the multiple testing burden (≈1,000,000 million SNPs vs. ≈20,000 genes). Moreover, because the impact of genetic heterogeneity due to underlying linkage disequilibrium patterns (different SNPs being linked to the causal variants) is reduced when considering the gene as the unit of analysis, it can alleviate limitations in replication leading to more consistent results.[38]

In an attempt to improve our understanding of the genetic architecture of memory function, our study has included participants from ethnically diverse populations: Caribbean Hispanics and Blacks. A disproportionate majority of participants in cognitive genetics research are of European descent. However, it is well established that the effect of genetic variants vary between populations based on the reported differences in the genetic architecture of populations.[39] Moreover, low-frequency and rare variants tend to be ethnic specific (i.e., exhibit little sharing among diverged populations) and enriched in admixed populations.[40] The inclusion of multi-ancestry cohorts in genetics studies is needed to fully characterize human genomic variation, bolster our understanding of disease etiology, and ensure that genetic testing is broadly accessible.

Results from apolipoprotein E (*APOE*)-stratified GWAS analyses and brain transcriptomics identified doublecortin domain-containing 2 (*DCDC2*) gene as a novel predictor of memory maintenance among non-carriers of *APOE* ε4. *DCDC2* brain expression appeared associated with episodic memory maintenance and lower burden of pathological AD hallmarks. Moreover, when AD cases were compared to cognitively healthy participants, *DCDC2* expression was decreased across all brain areas.

### 1.3 | Study conclusions, disease implications, and therapeutic opportunities

Our multiomics data integrative approach using meta-analysis results from eight independent GWAS of episodic memory trajectories and brain transcriptomics for three independent cohorts identified *DCDC2* as a putative gene for protection against episodic memory decline and a potential to reduce risk of dementia.

To our knowledge, this is the first study reporting *DCDC2* association with longitudinal changes in episodic memory performance. Interestingly, the *DCDC2* gene was previously reported as genome-wide significantly associated with general cognitive function ($P < 5 \times 10^{-8}$) in a sample of more than 300,000 subjects from three different European cohorts including United Kingdom Biobank (UKBB).[25]

The *DCDC2* gene is one of the most conserved genes of the doublecortin (DCX) superfamily, a group of proteins that regulate filamentous actin structure in developing neurons. *DCDC2* binds to tubulin and enhances microtubule polymerization[41,42] influencing synaptic plasticity.[43] It is well documented that cytoskeleton dynamics in the adult brain affect fundamental processes, such as memory and learning, which are often compromised in neurodegenerative diseases.[44,45] In fact, genetically modified mice studies showed that *DCDC2* mutations resulted in persistent memory impairments.[46,47] Multiple epidemiological genetic studies linked variants within the *DCDC2* gene to reading abilities including dyslexia.[48–55] A recent re-evaluation suggested that evidence in support of the *DCDC2* deletion as a risk factor for dyslexia was statistically weak.[56] Our results in the non-Hispanic White sample of the Washington Heights-Inwood Columbia Aging Project (WHICAP) cohort did not find significant association between *DCDC2* and language trajectories.

**RESEARCH IN CONTEXT**

1. **Systematic review**: Genetic variation contributes to age-related changes in episodic memory. Genome-wide and candidate gene approaches to genetically characterize episodic memory trajectories have predominantly investigated common variants. Multiomics approaches integrating common and rare variation may enhance the identification of novel loci associated with episodic memory maintenance.
2. **Interpretation**: Episodic memory trajectories were estimated in an ethnically diverse sample of 35,349 elderly with available genome-wide association study (GWAS) and transcriptome data. Data integration of GWAS meta-analysis and brain expression results provided evidence for *DCDC2* gene as a novel candidate gene providing protection against episodic memory decline. The discovery of new genes associated with maintenance of episodic memory performance might allow the development of treatments specifically targeted for different risk-level subpopulations.
3. **Future directions**: *DCDC2* enhances microtubule polymerization and promotes neuronal migration. Future functional studies will investigate cytoskeleton dynamics as potential molecular mechanisms underlying the association between *DCDC2* and episodic memory maintenance.

Reinforcing its role in brain development, *DCDC2* has also been found to interact with ciliary proteins. Ciliary proteins play an important role in neurogenesis and neuronal migration, and underlie a growing list of human disorders, including developmental delays and cognitive deficits. Protein–protein interaction network analysis[57] revealed a link between cilia function, neuronal function, and neurological disorders such as AD. These results provide a novel therapeutic avenue in which drugs targeting proteins in the cilia interactome might be repurposed for treating neurological disorders.

The inverse association between brain expression levels and lower amyloid and tau pathology may selectively upregulate *DCDC2* expression in the dorsolateral prefrontal cortex, conferring protection against AD pathology. Follow-up studies are needed to determine whether reserve mechanisms (brain reserve,[58,59] cognitive reserve,[58,59] and brain maintenance[59,60]) might act as moderators.

Our results found differential brain expression of *DCDC2* when AD cases and cognitively healthy participants were compared. Specifically, gene expression in AD cases appeared nominally downregulated for two brain areas, superior temporal gyrus (temporal lobe), and inferior frontal gyrus (prefrontal cortex). Future studies incorporating neuroimaging data will be needed to validate these results and gain a better understanding of its neuroanatomical correlates.

The identification of *DCDC2* gene as a predictor of memory maintenance in older adulthood provides the possibility of identifying population subgroups at risk of memory decline and dementia, paving the way for precision medicine intervention.[32,61–63] Compared to the universal "one-size-fits-all" approach (generalized prevention strategies for all individuals), a precision medicine approach offers the opportunity to personalize interventions that hold the promise of advancing memory decline prevention strategies.[64] To be used as a diagnostic system and more efficient treatment of age-related memory impairment, it will require (1) defining groups of individuals for whom a cognitive intervention is warranted and (2) developing and testing novel treatments and interventions that can be applied with a degree of specificity to distinct subpopulations of individuals.[65] Finally, it is important to consider that relying solely on genetics may miss unknown underlying memory decline mechanisms. In addition to genetics, a precision medicine approach should also encompass recommendations to target lifestyle factors and medical comorbidities on an individual basis.

### 1.4 | Limitations, unanswered questions, and future directions

Our study has some limitations. First, trajectories of episodic memory were modelled as a linear function of time, hence we did not consider potential nonlinear age effects. Second, we did not consider the contribution of additional protective or/and risk factors, socioeconomic status, mental or behavioral health, and clinical comorbid conditions that may be associated with maintenance/decline of memory. Third, potential interactions between genetic variants and these risk/resilience additional factors may also contribute to set courses toward memory progression over time. Fourth, we cannot rule out the possibility that additional regulatory mechanisms might regulate *DCDC2* expression variation.

Future translational studies will investigate the role of *DCDC2* variants in cytoskeleton dynamics via generation of CRISPR-pluripotent cellular models expressing different variants of *DCDC2* gene and differentiated into neurons (cortical or hippocampal). Cytoskeleton structure and organelle distribution can be assessed by confocal imaging using these cell models. Furthermore, expression of proteins involved in posttranslational modifications of microtubules, such as acetylation, can be also investigated by western blot and quantitative polymerase chain reaction analysis.

## 2 | CONSOLIDATED RESULTS AND STUDY DESIGN

Using latent class models, we estimated episodic memory trajectories in 35,245 ethnically diverse older adults representing eight independent cohorts. We conducted *APOE*-stratified GWAS analyses and combined individual cohorts' results via meta-analysis. Three independent transcriptomics datasets were used to further interpret GWAS signals.

We identified *DCDC2* gene significantly associated with episodic memory ($P_{meta} = 3.3 \times 10^{-8}$) among non-carriers of *APOE* $\varepsilon 4$. Brain transcriptomics revealed an association between episodic memory maintenance and (1) increased dorsolateral prefrontal cortex *DCDC2* expression ($P = 3.8 \times 10^{-4}$) and (2) lower burden of pathological AD hallmarks (paired helical fragment tau $P = .003$, and amyloid beta [A$\beta$] load $P = .008$). Additional transcriptomics results comparing AD and cognitively healthy brain samples showed a downregulation of *DCDC2* levels in superior temporal gyrus ($P = .007$) and inferior frontal gyrus ($P = .013$).

## 3 | DETAILED METHODS AND RESULTS

### 3.1 | Methods

#### 3.1.1 | Study cohorts

All study participants provided written informed consent and the study procedures were approved by the institutional review boards within each of the corresponding institutions. All study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research.

The present study includes eight independent study cohorts: (1) the Alzheimer's Disease Genetics Consortium and National Alzheimer's Coordinating Center (ADGC_NACC), (2) the National Institute on Aging Late-Onset Alzheimer Disease Family Based Study (NIA-LOAD), (3) the Chicago Health and Aging Project (CHAP), (4) the Religious Orders Study and Rush Memory and Aging Project (ROSMAP), (5) WHICAP, (6) the Long Life Family Study (LLFS), (7) the Alzheimer's Disease Neuroimaging Initiative (ADNI), and (8) the UKBB. Detailed characteristics and methodologies for study cohorts can be found elsewhere.[33,66–68]

Within each of the study cohorts, inclusion criteria for participants were based on the availability of longitudinal episodic memory scores (minimum of 2 visits to a maximum of 15), sociodemographic variables (sex, age, education, and ethnic background), and imputed GWAS genotyped data using the HRC v1.1.

An overview of the study design is summarized in Figure S1 in supporting information.

#### 3.1.2 | Episodic memory

In the WHICAP cohort, episodic memory was derived as the average of standardized measures for total immediate recall, delayed recall, and delayed recognition of the Selective Reminding Tests.[69] In the ADNI cohort, the Rey Auditory Verbal Learning Test (RAVLT)[27,70] served as a measure of episodic memory. In the UKBB, as previously described,[23] participants' scores on the pairs matching test can be used as a measure of episodic visual memory. As previously described,[33] in the rest of the cohorts, episodic memory was quantified as the average of the standardized Wechsler Memory Scale tests.

#### 3.1.3 | Alzheimer's disease

In all study cohorts, except for LLFS and UKBB, participants were classified as dementia patients or non-cognitively impaired (NCI) participants using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[71] In the LLFS cohort, dementia status was categorized based on a previously described diagnostic algorithm.[72] In the UKBB cohort, cognitive impairment was defined using a 1.5-standard deviation (SD) cut-off below demographically adjusted episodic memory scores (age, education, and sex). UKBB study participants were classified as NCI if their standardized adjusted memory scores were greater than 1.5 SD below the mean.

### 3.2 | Statistical analysis

Statistical analyses were performed using a dataset freeze from 2019, for which complete and accurate phenotypic and genomic information was available.

#### 3.2.1 | Episodic memory trajectories

As previously described,[33] episodic memory trajectories (EMTs) were derived using latent class mixed models (LCMM). The LCMM estimated episodic memory slope was used as quantitative outcome.

#### 3.2.2 | GWAS imputation

Genome-wide genotyped data was imputed using the HRC panel (v1.1) through the Michigan Imputation Server.[73]

#### 3.2.3 | Quality control metrics

Samples were excluded for analyses purposes based on cryptic relatedness (duplicates or first-degree relatives) calculated as identity by descent estimates using PLINK[74] software, and genotype call missing rate greater than 10%. Only variants with high imputation quality ($r^2 \geq 0.8$) were retained for analyses purposes.

#### 3.2.4 | Population substructure

To account for population stratification, principal component analysis was conducted using PLINK software[74] and the top three principal components were retained as covariates in regression models.

#### 3.2.5 | Gene-based association analyses

Gene-based annotations were generated using ANNOVAR software[75] and were limited to intronic, exonic, 3′ and 5′ untranslated regions variants. Analyses were conducted only for genes with at least 10 annotated variants. Gene-based tests were run using the SNP–set optimal sequence kernel association test (SKAT-O) as implemented in EPACTS software.[76] Covariates in the linear regression models included sex, age at last evaluation, education, and the top three principal components. For the LLFS cohort, further covariate adjustment included kinship correlation matrix. All analyses were conducted independently in three different *APOE* strata: no *APOE* stratification and *APOE* ε4 carriers versus non-carriers. Gene-level significance was established as $P \leq 2.7 \times 10^{-6}$ after Bonferroni correction for multiple testing (an average of 20,000 genes annotated across all cohorts).

#### 3.2.6 | SNP-based and gene-based meta-analysis

Meta-analysis of the gene-based and SNP-based association results was carried out using inverse variance–weighted model based on *P*-values/sample size and metrics to measure between-study heterogeneity (Cochran Q-test)[77] as implemented in METAL software.[78] Using Bonferroni for multiple testing correction, a conservative threshold for significance was set as $P \leq 2.5 \times 10^{-6}$ and $P \leq 1.6 \times 10^{-4}$ for gene-based and SNP-based respectively.

#### 3.2.7 | *DCDC2* SNP-based analyses in *APOE* ε4 non-carriers

Variants in *DCDC2* gene were individually tested for association with episodic memory using EPACTS software. Sex, age at last evaluation, education, principal components, and kinship matrix (only for the LLFS cohort) were included as covariates in the model. SNP-level significance was established as $P \leq 1.5 \times 10^{-5}$ after Bonferroni correction for multiple testing based on the total number of SNPs tested in the meta-analysis.

#### 3.2.8 | SNP-based *APOE* interaction analyses

The regression-based approach implemented in the epistasis module of PLINK[74] was used to run test pair-wise interactions between the strongest *DCDC2*-associated variant in the SNP-based meta-analysis (rs1340698) and *APOE* genotype, carriers, and non-carries of *APOE* ε4.

#### 3.2.9 | Brain transcriptomic analyses

RNA sequencing data processed in the present study can be accessed on the Accelerating Medicines Partnership–Alzheimer's Disease (AMP-AD) Synapse knowledge portal (https://www.synapse.org). The AMP-AD is a public–private partnership focused on the development of new drug targets to prevent or treat AD. The threshold for nominal significance was defined as *P*-values ≤.05.

#### 3.2.10 | Brain transcriptomic analysis ROSMAP study

RNA sequencing (RNA-seq) data generated by ROSMAP[79–82] consisted of *post mortem* dorsolateral prefrontal cortex (DLPFC) brain

tissue from 624 participants (254 syndromic AD, 169 mild cognitive impairment, and 201 NCI).

### 3.2.11 | Brain transcriptomic analysis in the Mount Sinai Brain Bank study

The Mount Sinai Brain Bank (MSBB) analyses included a total of 476 samples collected from four different brain areas: parahippocampal gyrus (PHG), inferior frontal gyrus (IFG), superior temporal gyrus (STG), and the frontal pole (FP; n = 476). Detailed specific sample characteristics and methodological pipeline can be found elsewhere.[83]

### 3.2.12 | Brain transcriptomic analysis in the Mayo clinic dataset

The analyses of the Mayo RNA-seq dataset included samples harvested from temporal cortex and cerebellum. Detailed specific sample characteristics and methodological pipeline can be found elsewhere.[84]

### 3.2.13 | Summary data-based Mendelian randomization

We used a Mendelian randomization (MR) approach to investigate whether *DCDC2* variants associated with episodic memory performance could act through *DCDC2* gene expression levels in the brain. Expression quantitative trait loci (eQTL) analyses were performed using SMR software.[85] Because of the lack of publicly available episodic memory GWAS summary statistics, we relied on SNP-based association results from the largest cohort in our study, UKBB cohort (*DCDC2*_noE4 strata, n = 14,874). Reference eQTL data were obtained from the Brain-eMeta dataset, which includes brain tissue eQTL data from the Genotype Tissue Expression (GTEx) project v6, the CommonMind Consortium (CMC), ROSMAP, and the Brain eQTL Almanac (Braineac) project. The linkage disequilibrium (LD) estimation was based on the entire UKBB sample (n = 20,184). Software and reference database details can be accessed at https://cnsgenomics.com/software/smr/#SMR&HEIDIanalysis.

### 3.2.14 | *DCDC2* patterns of linkage disequilibrium

We investigated the LD pattern between most significant associated SNPs in the MR analyses (topSMR) and *DCDC2* topSNPs in the GWAS meta-analysis (noE4 SNP-based association strata). All LD analyses were performed using National Institutes of Health (NIH) web-based application LDlink (LD matrix module; https://ldlink.nci.nih.gov/?tab = home) (Myers, 2020).

### 3.2.15 | *DCDC2* and *APOE* interaction

Gene–gene interaction was tested using epistasis module of PLINK.[74]

**TABLE 1** Characteristics of the study participants by cohort

| | N | Women | | $age_{BA}$ | $age_{LE}$ | educ | $EMT_{Stables}$ | | $EMT_{Decliners}$ | | $dem_{BA}$ | | $non\text{-}dem_{BA}$ | | $APOE\_\varepsilon4$ | | $APOE\_non\varepsilon4$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| ADNI | 1090 | 634 | 58 | 74 ± 7 | 79 ± 8 | 16 ± 3 | 380 | 35 | 710 | 65 | 322 | 30 | 768 | 70 | 501 | 46 | 589 | 54 |
| CHAP | 696 | 431 | 62 | 72 ± 5 | 82 ± 6 | 15 ± 3 | 362 | 52 | 334 | 48 | 10 | 1 | 686 | 99 | 165 | 24 | 531 | 76 |
| LLFS | 1874 | 1040 | 55 | 64 ± 11 | 71 ± 11 | 12 ± 3 | 1047 | 56 | 827 | 44 | 131 | 7 | 1743 | 93 | 400 | 21 | 1474 | 79 |
| NACC_ADGC | 6774 | 3845 | 57 | 74 ± 9 | 78 ± 9 | 16 ± 3 | 4014 | 59 | 2760 | 41 | 3016 | 44 | 3758 | 55 | 2731 | 40 | 4043 | 60 |
| NIA-LOAD | 460 | 298 | 65 | 73 ± 9 | 77 ± 8 | 16 ± 3 | 253 | 55 | 207 | 45 | 31 | 7 | 429 | 93 | 152 | 34 | 308 | 64 |
| ROSMAP | 1265 | 883 | 70 | 79 ± 8 | 87 ± 7 | 16 ± 4 | 651 | 51 | 614 | 49 | 952 | 75 | 313 | 25 | 317 | 25 | 948 | 75 |
| UKBB | 20,184 | 10,322 | 51 | 55 ± 8 | 63 ± 7 | 91% | 17,451 | 86 | 2,733 | 14 | 1390 | 7 | 18,794 | 93 | 5310 | 26 | 14,874 | 74 |
| WNHW | 619 | 370 | 60 | 76 ± 7 | 80 ± 8 | 13 ± 4 | 597 | 93 | 22 | 7 | 45 | 7 | 574 | 93 | 121 | 19 | 498 | 81 |
| WAA | 736 | 532 | 72 | 75 ± 6 | 79 ± 7 | 12 ± 4 | 712 | 97 | 24 | 3 | 37 | 5 | 699 | 95 | 244 | 33 | 492 | 67 |
| WCH | 1547 | 1093 | 71 | 76 ± 6 | 81 ± 7 | 7 ± 4 | 972 | 61 | 614 | 39 | 561 | 35 | 1025 | 65 | 402 | 25 | 1184 | 75 |

Abbreviations: *APOE*, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; $age_{BA}$, age at baseline evaluation; $age_{LE}$, age at last evaluation; CHAP, Chicago Health and Aging Project; $dem_{BA}$, dementia status at baseline evaluation; EMTs, episodic memory trajectories; LLFS, Long Life Family Study; NACC_ADGC, National Alzheimer's Coordinating Center and Alzheimer's Disease Genetics Consortium; NIA-LOAD, National Institute on Aging–Late Onset Alzheimer's Disease Family Based Study; non-demBA, non-dementia status at baseline evaluation; ROSMAP, Religious Orders Study Rush Memory and Aging Project; UKBB, UK Biobank; WAA, WHICAP African-Americans; WCH, WHICAP Caribbean-Hispanics; WHICAP, Washington Heights-Inwood Columbia Aging Project; WNHW, WHICAP Non-Hispanic Whites.

**TABLE 2** Top significant genes ($P \leq 10^{-6}$) in the genome-wide gene-based meta-analysis stratify by *APOE* status

| | | Meta-analysis | | | ADNI | | CHAP | | LLFS | | NACC | | NIA-LOAD | | ROSMAP | | UKBB | | WNHW | | WAA | | WCH | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chr_Gene | N | $P_{meta}$ | $P_{Het}$ | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* | N | *P* |
| no*APOE* | 6_*DCDC2* | 35,250 | 3.3E-07 | .204 | 1090 | .377 | 696 | .741 | 1874 | 0.030 | 6774 | .473 | 460 | .536 | 1265 | .006 | 20,184 | 6.7E-04 | 619 | .953 | 736 | .732 | 1547 | .002 |
| | 16_*FBXL19* | 35,245 | 4.5E-06 | .208 | 1090 | .384 | 696 | .278 | 1874 | .667 | 6774 | .048 | 460 | .029 | 1265 | .093 | 20,184 | .018 | 619 | .280 | 736 | .506 | 1547 | 3.5E-04 |
| | 15_*ICE2* | 35,245 | 2.8E-06 | .262 | 1090 | .780 | 696 | .294 | 1874 | .854 | 6774 | .006 | 460 | .703 | 1265 | .016 | 20,184 | .006 | 619 | .318 | 736 | .001 | 1547 | .434 |
| | 17_*KRT37* | 35,245 | 9.0E-06 | .445 | 1090 | .034 | 696 | .066 | 1874 | .550 | 6774 | .605 | 460 | .298 | 1265 | .352 | 20,184 | 8.5E-04 | 619 | 1.000 | 736 | .567 | 1547 | .275 |
| | 16_*MTHFSD* | 35,245 | 8.3E-06 | .769 | 1090 | .504 | 696 | .188 | 1874 | .299 | 6774 | .850 | 460 | .308 | 1265 | .430 | 20,184 | 1.7E-04 | 619 | .417 | 736 | .115 | 1547 | .085 |
| | 16_*NPRL3* | 35,245 | 9.5E-06 | .642 | 1090 | .323 | 696 | .787 | 1874 | .334 | 6774 | .000 | 460 | .140 | 1265 | .207 | 20,184 | .041 | 619 | .805 | 736 | .219 | 1547 | .659 |
| | 11_*OR4C45* | 35,245 | 6.6E-06 | .834 | 1090 | .735 | 696 | .066 | 1874 | .638 | 6774 | .005 | 460 | .495 | 1265 | .069 | 20,184 | .008 | 619 | .933 | 736 | .588 | 1547 | .476 |
| *APOE*_ε4 | 6_*AKAP12* | 10,333 | 2.8E-06 | .815 | 502 | .003 | 165 | .445 | 400 | .110 | 2731 | .059 | 152 | 1.000 | 316 | .753 | 5310 | .001 | 121 | 1.000 | 241 | .486 | 395 | .436 |
| | 16_*ANXA11* | 10,332 | 6.1E-06 | .421 | 501 | .043 | 165 | .548 | 400 | .589 | 2731 | .140 | 152 | .076 | 316 | .106 | 5310 | .007 | 121 | .091 | 241 | .894 | 395 | .009 |
| | 15_*FIBP* | 10,332 | 8.6E-06 | .962 | 501 | .844 | 165 | .273 | 400 | .336 | 2731 | .122 | 152 | .326 | 316 | .077 | 5310 | .000 | 121 | .994 | 241 | .336 | 395 | .374 |
| | 17_*KBTBD12* | 10,332 | 5.6E-06 | .809 | 501 | .009 | 165 | .751 | 400 | .379 | 2731 | .003 | 152 | .561 | 316 | .793 | 5310 | .019 | 121 | .740 | 241 | .859 | 395 | .077 |
| | 16_*KIT* | 10,332 | 2.3E-06 | .952 | 501 | .454 | 165 | .037 | 400 | .160 | 2731 | .046 | 152 | .459 | 316 | .481 | 5310 | .001 | 121 | .355 | 241 | .194 | 395 | .378 |
| | 16_*L3MBTL3* | 10,333 | 2.9E-06 | .946 | 502 | .193 | 165 | .432 | 400 | .179 | 2731 | .001 | 152 | .697 | 316 | .051 | 5310 | .018 | 121 | .671 | 241 | .737 | 395 | .334 |
| | 11_*MERTK* | 10,332 | 3.9E-06 | .304 | 501 | .002 | 165 | .062 | 400 | .024 | 2731 | .246 | 152 | .138 | 316 | .293 | 5310 | .006 | 121 | .347 | 241 | .584 | 395 | .392 |
| | 6_*PADI4* | 10,332 | 9.6E-06 | .407 | 501 | .291 | 165 | .412 | 400 | .509 | 2731 | .026 | 152 | .158 | 316 | .042 | 5310 | .050 | 121 | .591 | 241 | .011 | 395 | .024 |
| | 10_*SUCLG1* | 10,332 | 6.5E-06 | .103 | 501 | .253 | 165 | .131 | 400 | .492 | 2731 | 1.000 | 152 | .249 | 316 | .370 | 5,310 | 3.0E-05 | 121 | 1.000 | 241 | .001 | 395 | .472 |
| *APOE*_noε4 | 6_*DCDC2* | 24,913 | 3.4E-08 | .284 | 593 | .087 | 531 | .351 | 1474 | .038 | 4043 | .307 | 308 | .400 | 948 | .010 | 14,874 | 5.3E-04 | 498 | .003 | 492 | .181 | 1152 | .132 |
| | 16_*MTHFSD* | 24,909 | 7.8E-07 | .560 | 589 | .100 | 531 | .212 | 1474 | .046 | 4043 | 1.000 | 308 | .112 | 948 | .778 | 14,874 | 4.1E-05 | 498 | .248 | 492 | .330 | 1152 | .140 |
| | 15_*ARSK* | 24,909 | 2.5E-06 | .937 | 589 | .849 | 531 | 1.000 | 1474 | .270 | 4043 | .002 | 308 | .881 | 948 | .824 | 14,874 | 2.0E-04 | 498 | .897 | 492 | .261 | 1152 | .705 |
| | 17_*RALGDS* | 24,909 | 3.9E-06 | .986 | 589 | .415 | 531 | .286 | 1474 | .578 | 4043 | .061 | 308 | .816 | 948 | .629 | 14,874 | 3.1E-04 | 498 | .062 | 492 | .443 | 1152 | .444 |
| | 16_*CYP2W1* | 24,909 | 6.9E-06 | .955 | 589 | .437 | 531 | 1.000 | 1474 | .087 | 4043 | 0.273 | 308 | .566 | 948 | .607 | 14,874 | 9.5E-05 | 498 | .245 | 492 | .216 | 1152 | 1.000 |
| | 16_*TTC37* | 24,909 | 5.7E-07 | .956 | 589 | .676 | 531 | .727 | 1474 | .333 | 4043 | 1.000 | 308 | .169 | 948 | .780 | 14,874 | 1.6E-04 | 498 | .289 | 492 | .002 | 1152 | .669 |
| | 11_*DHX36* | 24,909 | 8.4E-06 | .138 | 589 | .025 | 531 | .002 | 1474 | .141 | 4043 | .004 | 308 | .916 | 948 | .064 | 14,874 | .031 | 498 | .921 | 492 | 0.884 | 1152 | .800 |
| | 6_*CASP3* | 24,909 | 9.2E-06 | .041 | 589 | .191 | 531 | .032 | 1474 | .009 | 4043 | .022 | 308 | .027 | 948 | .204 | 14,874 | .153 | 498 | .007 | 492 | .931 | 1152 | .085 |

Abbreviations: *APOE*, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; CHAP, Chicago Health and Aging Project; LLFS, Long Life Family Study; NACC_ADGC, National Alzheimer's Coordinating Center and Alzheimer's Disease Genetics Consortium; NIA-LOAD, National Institute on Aging–Late Onset Alzheimer's Disease Family Based Study; ROSMAP, Religious Orders Study Rush Memory and Aging Project; UKBB, UK Biobank; WAA, WHICAP African-Americans; WCH, WHICAP Caribbean-Hispanics; WHICAP, Washington Heights-Inwood Columbia Aging Project; WNHW, WHICAP Non-Hispanic Whites.

**TABLE 3** Top significant SNPs ($P \leq 10^{-7}$) in the meta-analysis of *DCDC2* no-*APOE*_ε4 strata

| | | Common variants | | | | | | | | Rare+ultra-rare variants | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | rs | rs1340698 | rs114941574 | rs112854846 | rs6933291 | rs73394040 | rs73394022 | rs114540201 | rs75359737 | rs147661578 | rs116394689 | rs807711 | rs73727536 | rs150137064 | rs73727537 |
| | bp | 24256726 | 24310169 | 24236194 | 24346573 | 24245058 | 24225761 | 24315294 | 24350002 | 24318524 | 24335865 | 24294560 | 24357033 | 24191780 | 24366667 |
| | A1/A2 | A/G | T/C | A/G | C/G | A/G | A/C | A/G | A/G | A/C | A/G | T/C | C/G | A/G | T/C |
| Metal | N | 24890 | 24897 | 24902 | 24856 | 24898 | 24903 | 24873 | 24829 | 24873 | 24877 | 24900 | 24883 | 24834 | 24883 |
| | $P_{meta}$ | 1.3E-07 | 1.8E-07 | 1.9E-07 | 1.9E-07 | 2.2E-07 | 2.3E-07 | 2.4E-07 | 2.6E-07 | .002 | .004 | .012 | .017 | .032 | .041 |
| | $P_{het}$ | .348 | .631 | .618 | .255 | .610 | .636 | .607 | .287 | .512 | .082 | .183 | .221 | .093 | .157 |
| ADNI | MAF | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.0084 | 0.0059 | 0.0051 | 0.0076 | 0.0067 | 0.0067 |
| n = 589 | B | −0.04 | 0.03 | 0.03 | 0.06 | 0.03 | 0.03 | 0.03 | 0.06 | 0.02 | 0.09 | 0.06 | 0.08 | −0.07 | 0.08 |
| | SE | 0.02 | 0.03 | 0.02 | 0.03 | 0.02 | 0.02 | 0.03 | 0.03 | 0.04 | 0.05 | 0.05 | 0.04 | 0.05 | 0.05 |
| | *P* | .111 | .358 | .253 | .029 | .253 | .253 | .358 | .029 | .675 | .073 | .222 | .074 | .140 | .070 |
| CHAP | MAF | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.0066 | 0.0028 | 0.0028 | 0.0047 | 0.0066 | 0.0047 |
| n = 531 | B | 0.02 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | −0.02 | 0.03 | −0.02 | 0.00 | −0.02 |
| | SE | 0.01 | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | 0.02 | 0.04 | 0.04 | 0.03 | 0.02 | 0.03 |
| | *P* | .157 | .155 | .157 | .062 | .157 | .157 | .155 | .073 | .347 | .585 | .415 | .515 | .975 | .515 |
| LLFS | MAF | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.0054 | 0.0017 | 0.0041 | 0.0024 | 0.0126 | 0.0024 |
| n = 1474 | B | 0.00 | −0.01 | −0.01 | −0.01 | −0.01 | −0.01 | −0.01 | −0.01 | −0.01 | 0.09 | 0.03 | 0.05 | −0.03 | 0.05 |
| | SE | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.03 | 0.05 | 0.03 | 0.04 | 0.02 | 0.04 |
| | *P* | .788 | .498 | .676 | .628 | .676 | .676 | .498 | .691 | .679 | .094 | .458 | .286 | .179 | .286 |
| NACC | MAF | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.0075 | 0.0043 | 0.0019 | 0.0047 | 0.0119 | 0.0046 |
| n = 4043 | B | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | −0.02 | 0.00 | −0.02 | 0.02 | −0.01 | 0.01 |
| | SE | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.02 | 0.03 | 0.02 | 0.01 | 0.02 |
| | *P* | .364 | .224 | .278 | .241 | .278 | .278 | .244 | .183 | .178 | .845 | .474 | .458 | .512 | .526 |
| NIA-LOAD | MAF | 0.02 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.03 | 0.0065 | 0.0065 | NA | 0.0065 | 0.0097 | 0.0065 |
| n = 308 | B | 0.01 | 0.01 | 0.02 | −0.01 | 0.01 | 0.02 | 0.01 | −0.01 | −0.12 | 0.05 | NA | 0.05 | 0.04 | 0.05 |
| | SE | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.06 | 0.06 | NA | 0.06 | 0.05 | 0.06 |
| | *P* | .775 | .673 | .540 | .782 | .673 | .540 | .673 | .774 | .038 | .370 | NA | .370 | .386 | .370 |

(Continues)

**TABLE 3** (Continued)

| | | Common variants | | | | | | | | Rare+ultra-rare variants | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | rs | rs1340698 | rs114941574 | rs112854846 | rs6933291 | rs73394040 | rs73394022 | rs114540201 | rs75359737 | rs147661578 | rs116394689 | rs807711 | rs73727536 | rs150137064 | rs73727537 |
| ROSMAP | MAF | 0.02 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.03 | 0.0053 | 0.0042 | 0.0016 | 0.0042 | 0.0127 | 0.0042 |
| n = 948 | B | −0.03 | −0.02 | −0.02 | −0.02 | −0.02 | −0.02 | −0.02 | −0.02 | 0.01 | 0.06 | −0.09 | 0.07 | −0.04 | 0.07 |
| | SE | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.03 | 0.03 | 0.05 | 0.03 | 0.02 | 0.03 |
| | *P* | .018 | .129 | .066 | .048 | .066 | .066 | .129 | .055 | .626 | .059 | .087 | .031 | .045 | .031 |
| UKBB | MAF | 0.03 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.03 | 0.0049 | 0.0039 | 0.0025 | 0.0041 | 0.0100 | 0.0042 |
| n = 14,857 | B | 0.01 | 0.02 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | −0.02 | −0.01 | 0.01 | −0.01 | 0.00 | 0.00 |
| | SE | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| | *P* | 1.4E-04 | 9.6E-05 | 1.6E-04 | 1.7E-04 | 1.7E-04 | 1.7E-04 | 8.3E-05 | 2.8E-04 | .057 | .291 | .479 | .560 | .603 | .850 |
| WNHW | MAF | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.0191 | 0.0050 | 0.0070 | NA | NA | NA |
| n = 498 | B | −0.03 | −0.03 | −0.03 | −0.03 | −0.03 | −0.03 | −0.03 | −0.03 | 0.00 | 0.00 | −0.02 | NA | NA | NA |
| | SE | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | NA | NA | NA |
| | *P* | .002 | .010 | .002 | .014 | .002 | .000 | .010 | .014 | .653 | .787 | .233 | NA | NA | NA |
| WAA | MAF | 0.16 | 0.05 | 0.15 | 0.06 | 0.15 | 0.15 | 0.05 | 0.06 | 0.0007 | 0.0641 | 0.1606 | 0.0385 | 0.0020 | 0.0385 |
| n = 492 | B | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | −0.01 | 0.00 | 0.00 | 0.00 | 0.01 | NA |
| | SE | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | NA |
| | *P* | .153 | .052 | .151 | .058 | .152 | .155 | .052 | .038 | .032 | .057 | .166 | .038 | .003 | NA |
| WCH | MAF | 0.09 | 0.03 | 0.08 | 0.04 | 0.08 | 0.09 | 0.03 | 0.04 | 0.0030 | 0.0196 | 0.0745 | 0.0192 | 0.0040 | 0.0192 |
| N = 1151 | B | −0.01 | −0.01 | −0.01 | 0.00 | −0.01 | −0.01 | −0.01 | 0.00 | 0.02 | −0.01 | −0.01 | 0.01 | 0.00 | 0.01 |
| | SE | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.00 | 0.01 | 0.01 | 0.02 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 |
| | *P* | .040 | .314 | .066 | .686 | .061 | .074 | .471 | .627 | .490 | .580 | .172 | .323 | .911 | .323 |

Abbreviations: *APOE*, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; CHAP, Chicago Health and Aging Project; LLFS, Long Life Family Study; NACC_ADGC, National Alzheimer's Coordinating Center and Alzheimer's Disease Genetics Consortium; NIA-LOAD, National Institute on Aging–Late Onset Alzheimer's Disease Family Based Study; ROSMAP, Religious Orders Study Rush Memory and Aging Project; SNP, single-nucleotide polymorphism; UKBB, UK Biobank; WAA, WHICAP African-Americans; WCH, WHICAP Caribbean-Hispanics; WHICAP, Washington Heights-Inwood Columbia Aging Project; WNHW, WHICAP Non-Hispanic Whites.

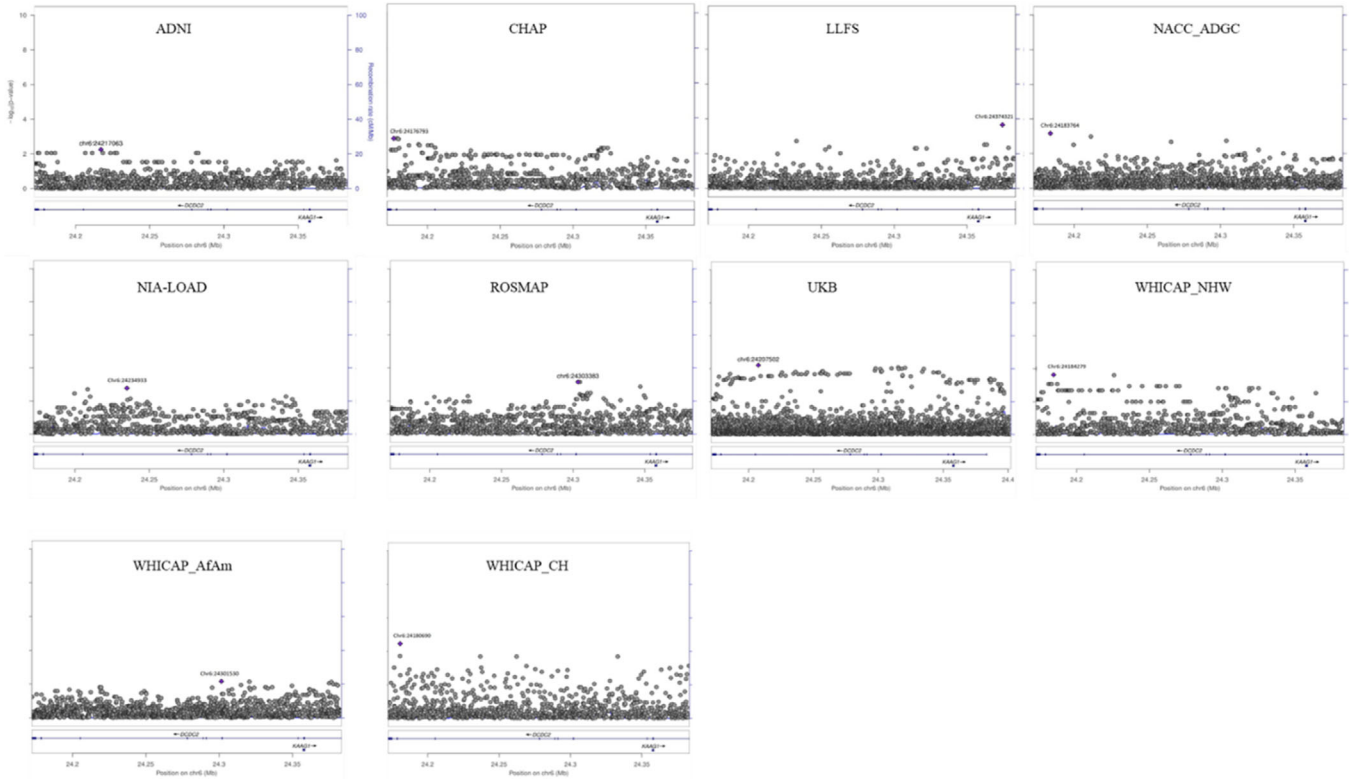


**FIGURE 1** Regional association plots for SNP-based *DCDC2* analysis in the apolipoprotein E no$\varepsilon$4 strata. The *x*-axis represent the GRCh37/hg19 chromosomal position (Mb) of the tested SNP variant(s); the left *y*-axis correspond to the statistical strength of the SNP association (log10 [*P* value]). The right *y*-axis displays the estimated recombination rates (cM/Mb) to reflect the local LD structure. ADNI, Alzheimer's Disease Neuroimaging Initiative; AfAm, African-Americans; CH, Caribbean-Hispanics; CHAP, Chicago Health and Aging Project; LD, linkage disequilibrium; LLFS, Long Life Family Study; NACC_ADGC, National Alzheimer's Coordinating Center and Alzheimer's Disease Genetics Consortium; NHW, non-Hispanic Whites; NIA-LOAD, National Institute on Aging–Late Onset Alzheimer's Disease Family Based Study; ROSMAP, Religious Orders Study Rush Memory and Aging Project; SNP, single-nucleotide polymorphism; UKB, UK Biobank; WHICAP, Washington Heights-Inwood Columbia Aging Project

## 3.3 | Results

The characteristics of the participants are summarized in Table 1. A higher percentage of women was observed across all cohorts. The average age (at baseline and at last evaluation) and education of the participants were 72 ± 8, 78 ± 8, and 14 ± 3, respectively. Most participants across cohorts were non-carriers of the *APOE* $\varepsilon$4 allele, and as expected, had lower frequency of dementia compared to *APOE* $\varepsilon$4 carriers.

### 3.3.1 | Episodic memory trajectories

Within-study cohorts' trajectories of episodic memory are shown in Figure S2 in supporting information. Consistent with previous literature, most participants were aggregated into the $EMT_{Stables}$ cluster (individuals exhibiting sustained or improved memory function over time). LCMM plots could not be generated for the LLFS cohort because, as described in the Methods section, a different regression framework was used.

### 3.3.2 | Meta-analysis of genome-wide gene-based test of association

The quantile–quantile plots for the gene-based association results within each of the cohorts stratify by *APOE* status are shown in Figures S3-S5 in supporting information. The average statistics for SNP allele frequencies (minimum, maximum, average, and SD) stratify by study cohort are shown in Table S1 in supporting information. In the non-*APOE* stratified sample, the meta-analysis results (Table 2) revealed the *DCDC2* gene as the strongest association signal ($P_{meta} = 3.7 \times 10^{-7}$). More interestingly, the *DCDC2*–EM association was significant stronger among non-*APOE* $\varepsilon$4 study participants ($P_{meta} = 3.3 \times 10^{-8}$). Additional potential novel loci were observed in both *APOE* strata; however, none of the associations reached the same significance level as *DCDC2*. Secondary analyses excluding the UKBB cohort (Table S2 in supporting information) corroborated that associations reported (Table 2) were not solely driven by the largest cohort in the study.

**TABLE 4** Common SNP-based *DCDC2-APOE* epistasis models by study cohort

| | | rs1340698 | | | |
|---|---|---|---|---|---|
| **Cohort** | **TEST** | **A1** | **N** | **B** | ***P*** |
| ADNI | SNP | G | 1090 | 0.04 | .134 |
| | E4 | G | 1090 | −0.07 | 1.7E-15 |
| | SNP*ε4 | G | 1,090 | −0.07 | .078 |
| CHAP | SNP | G | 696 | 0.00 | .919 |
| | E4 | G | 696 | −0.02 | .002 |
| | SNP*ε4 | G | 696 | 0.00 | .908 |
| LLFS | SNP | G | 1874 | 0.01 | .731 |
| | E4 | G | 1874 | 0.00 | .671 |
| | SNP*ε4 | G | 1874 | 0.03 | .514 |
| NACC | SNP | G | 6774 | 0.01 | .376 |
| | E4 | G | 6774 | −0.04 | 1.4E-25 |
| | SNP*ε4 | G | 6774 | −0.01 | .382 |
| NIA-LOAD | SNP | G | 482 | 0.01 | .877 |
| | E4 | G | 482 | −0.03 | .007 |
| | SNP*ε4 | G | 482 | 0.04 | .393 |
| ROSMAP | SNP | G | 1265 | −0.03 | .022 |
| | E4 | G | 1265 | −0.03 | 8.6E-08 |
| | SNP*ε4 | G | 1265 | −0.01 | .837 |
| UKB | SNP | G | 20,174 | 0.01 | 9.8E-05 |
| | E4 | G | 20,174 | 0.00 | .529 |
| | SNP*ε4 | G | 20,174 | −0.01 | .097 |
| WHICAP_NHW | SNP | G | 619 | −0.03 | 3.6E-04 |
| | E4 | G | 619 | 0.00 | .383 |
| | SNP*ε4 | G | 619 | 0.04 | .008 |
| WHICAP_AfAm | SNP | G | 741 | 0.00 | .519 |
| | E4 | G | 741 | 0.00 | .461 |
| | SNP*ε4 | G | 741 | 0.00 | .871 |
| WHICAP_CH | SNP | G | 1529 | 0.00 | .220 |
| | E4 | G | 1529 | −0.01 | 1.7E-05 |
| | SNP*ε4 | G | 1529 | −0.01 | .452 |

Abbreviations: *APOE*, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; CHAP, Chicago Health and Aging Project; LLFS, Long Life Family Study; NACC_ADGC, National Alzheimer's Coordinating Center and Alzheimer's Disease Genetics Consortium; NIA-LOAD, National Institute on Aging–Late Onset Alzheimer's Disease Family Based Study; ROSMAP, Religious Orders Study Rush Memory and Aging Project; SNP, single-nucleotide polymorphism; UKBB, UK Biobank; WAA, WHICAP African-Americans; WCH, WHICAP Caribbean-Hispanics; WHICAP, Washington Heights-Inwood Columbia Aging Project; WNHW, WHICAP Non-Hispanic Whites.

### 3.3.3 | Meta-analysis of *DCDC2* single-SNP association in the non-carriers of *APOE* ε4

A total of 1144 variants in *DCDC2* appeared to be present in all study cohorts. The results from the SNP-based meta-analysis are summarized in Table 3, and study regional association plots are shown in Figure 1. The strongest SNP-based association corresponded to intronic common SNP rs1340698 ($P_{meta} = 1.3 \times 10^{-7}$). As seen in Figure S6 in supporting information, the strong regional LD block ($r^2 \geq 0.6$) included the top-associated SNP rs1340698. The top SNP is located in the vicinity of a weak neuronal enhancer that connects to one of the two *DCDC2* promoters. However, neither the SNP nor the LD block yielded significant eQTL effects in standard datasets (GTEx, GRASP).

### 3.3.4 | *DCDC2* and *APOE* interaction

The results from epistatic models (Table 4) revealed that there is no significant interaction between the strongest *DCDC2*-associated variant in the SNP-based meta-analysis (rs1340698) and *APOE* genotype.

**TABLE 5** Association of *DCDC2* mRNA levels with cognitive and pathological phenotypes in the ROSMAP cohort

| Trait | n | logFC | t | *P* | $P_{adj}$ | $FDR_{Padj}$ |
|---|---|---|---|---|---|---|
| Slope of global cognition | 661 | 1.10 | 4.73 | 2.8E-06 | 7.4E-05 | 0.002 |
| Slope of episodic memory | 660 | 0.97 | 4.31 | 1.9E-05 | 3.8E-04 | 0.004 |
| Neuronal neurofibrillary tangles | 691 | −0.06 | −3.70 | 2.3E-04 | .003 | 0.021 |
| Amyloid beta protein | 692 | −0.06 | −3.26 | 0.001 | .008 | 0.042 |
| Neurofibrillary tangle burden | 698 | −0.17 | −3.32 | 0.001 | .009 | 0.038 |
| Neuritic plaque burden | 698 | −0.13 | −3.17 | 0.002 | .011 | 0.039 |
| Pathological AD diagnosis | 698 | −0.11 | −3.46 | 0.001 | .012 | 0.036 |
| Global measure of pathology | 698 | −0.10 | −2.88 | 0.004 | .024 | 0.063 |
| Neuronal loss substantia nigra | 696 | −0.08 | −2.97 | 0.003 | .026 | 0.061 |
| Transactive response DNA binding protein | 640 | −0.05 | −2.50 | 0.013 | .138 | 0.290 |
| Pathologic diagnosis of Lewy body diseases | 674 | −0.04 | −2.07 | 0.039 | .332 | 0.634 |
| Diffuse plaque burden | 698 | −0.06 | −1.47 | 0.142 | .455 | 0.796 |
| Global Parkinsonian Summary Score | 696 | −0.03 | −1.81 | 0.071 | .482 | 0.779 |
| Arteriolosclerosis | 692 | −0.03 | −1.37 | 0.173 | .665 | 0.998 |
| Any distribution of α-synuclein | 674 | −0.06 | −1.78 | 0.075 | .668 | 0.935 |
| Gross cerebral infarctions | 698 | 0.03 | 0.93 | 0.354 | .798 | 1.047 |
| Micro cerebral infarctions | 698 | −0.03 | −1.03 | 0.303 | .821 | 1.014 |
| Cerebral amyloid angiopathy | 683 | −0.02 | −0.71 | 0.481 | .875 | 1.021 |
| Diagnosis of Parkinson's | 695 | 0.03 | 0.48 | 0.630 | .891 | 0.985 |
| Hippocampal sclerosis | 694 | −0.04 | −0.80 | 0.423 | .898 | 0.943 |
| Cerebral atherosclerosis | 695 | 0.00 | 0.17 | 0.863 | .964 | 0.964 |

Abbreviations: AD, Alzheimer's disease; FDR, false discovery rate; ROSMAP, Religious Orders Study Rush Memory and Aging Project.

### 3.3.5 | Brain transcriptome results

ROSMAP results (Table 5) revealed false discovery rate (FDR)-adjusted association between episodic memory maintenance and increased *DCDC2* expression in DLPFC ($P = 3.8 \times 10^{-4}$). When evaluating additional ROSMAP neuropathological traits, the increased *DCDC2* expression levels were associated with: tau protein (measured as the average cortical density of antibodies to abnormally phosphorylated tau in eight brain regions, $P = .003$), overall Aβ level (measured as the average of the percent area that is occupied by Aβ in eight different brain regions, $P = .008$), neurofibrillary tangle burden (measured as the average of tangle count in silver-stained slides from five regions, $P = .009$), neuritic plaque burden (measured as the average of neuritic plaque count in silver-stained slides from five regions, $P = .011$), and global burden of AD pathology (measured as the average of counts in three pathologies: neurofibrillary tangles, and neuritic and diffuse plaques in silver-stained slides from five regions, $P = .012$).

Differential brain expression results from MSBB and Mayo datasets (Figure 2) revealed an overall decreased *DCDC2* expression (across all brain areas when AD cases were compared to controls). *DCDC2* downregulated expression achieved nominally statistical significance (≈2-fold change, $P < .05$) in two specific brain areas: STG ($P = .007$) and IFG ($P = .013$).

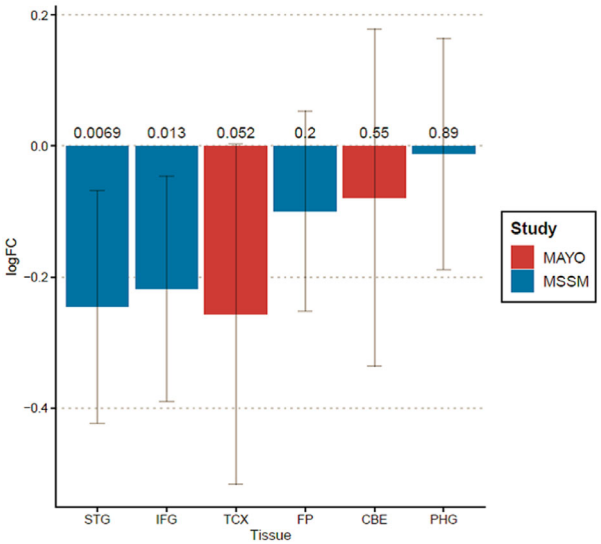


**FIGURE 2** *DCDC2* brain transcriptome results from Mount Sinai Brain Bank (MSBB) and Mayo Clinic datasets. The *x*-axis represents the brain regions analyzed from each cohort: MSBB: superior temporal gyrus (STG), inferior frontal gyrus (IFG), frontal pole (FP), and parahippocampal gyrus (PHG); Mayo Clinic: temporal cortex (TCX) and cerebellum (CBE). The *y*-axis corresponds to the estimated tissue-specific fold change in *DCDC2* expression (in red upregulation, in blue downregulation) and the 95% confidence intervals

MR results identified common variant rs12216513 as significant eQTL for *DCDC2* expression (B = 0.29, standard error [SE] = 0.04, $P = 1.1 \times 10^{-11}$). This *DCDC2* variant is in tight LD with meta-analysis topSNPs, common (rs1340698, D' = 0.88) and rare (rs147661578, D' = 0.84). However, the effect of *DCDC2* variants on episodic memory performance over time is not mediated by its brain expression (SMR *P*-value = .950; Figure S7 in supporting information).

Because of the widely reported association of *DCDC2* with phonological awareness and phonemic decoding,[86] secondary analyses in WHICAP tested the *DCDC2* association with LCMM estimated trajectories of language.[87] The gene-based association results indicated no significant association between *DCDC2* and decay of language in any of the *APOE* strata considered (Figure S8 in supporting information).

## ACKNOWLEDGEMENTS

This research has been conducted using data from UK Biobank project 50442 (www.ukbiobank.ac.uk)

## CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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## SUPPORTING INFORMATION

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**How to cite this article:** Gao Y, Felsky D, Reyes-Dumeyer D, et al. Integration of GWAS and brain transcriptomic analyses in a multiethnic sample of 35,245 older adults identifies *DCDC2* gene as predictor of episodic memory maintenance. *Alzheimer's Dement*. 2021;1–15. https://doi.org/10.1002/alz.12524