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Associations of the Top 20 Alzheimer Disease Risk Variants With Brain Amyloidosis

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IMPORTANCE Late-onset Alzheimer disease (AD) is highly heritable. Genome-wide association studies have identified more than 20 AD risk genes. The precise mechanism through which many of these genes are associated with AD remains unknown.

OBJECTIVE To investigate the association of the top 20 AD risk variants with brain amyloidosis.

DESIGN, SETTING, AND PARTICIPANTS This study analyzed the genetic and florbetapir F 18 data from 322 cognitively normal control individuals, 496 individuals with mild cognitive impairment, and 159 individuals with AD dementia who had genome-wide association studies and ^{18}F-florbetapir positron emission tomographic data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a prospective, observational, multisite tertiary center clinical and biomarker study. This ongoing study began in 2005.

MAIN OUTCOMES AND MEASURES The study tested the association of AD risk allele carrier status (exposure) with florbetapir mean standard uptake value ratio (outcome) using stepwise multivariable linear regression while controlling for age, sex, and apolipoprotein E ε4 genotype. The study also reports on an exploratory 3-dimensional stepwise regression model using an unbiased voxelwise approach in Statistical Parametric Mapping 8 with cluster and significance thresholds at 50 voxels and uncorrected $P < .01$.

RESULTS This study included 977 participants (mean [SD] age, 74 [7.5] years; 535 [54.8%] male and 442 [45.2%] female) from the ADNI-1, ADNI-2, and ADNI–Grand Opportunity. The adenosine triphosphate–binding cassette subfamily A member 7 (*ABCA7*) gene had the strongest association with amyloid deposition ($\chi^2 = 8.38$, false discovery rate–corrected $P < .001$), after apolioprotein E ε4. Significant associations were found between *ABCA7* in the asymptomatic and early symptomatic disease stages, suggesting an association with rapid amyloid accumulation. The fermitin family homolog 2 (*FERMT2*) gene had a stage-dependent association with brain amyloidosis (*FERMT2* × diagnosis $\chi^2 = 3.53$, false discovery rate–corrected $P = .05$), which was most pronounced in the mild cognitive impairment stage.

CONCLUSIONS AND RELEVANCE This study found an association of several AD risk variants with brain amyloidosis. The data also suggest that AD genes might differentially regulate AD pathologic findings across the disease stages.

Supplemental content

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Sporadic Alzheimer disease (AD) is 70% to 80% heritable.[1,2] The strongest genetic risk factor for AD is the apolipoprotein E (*APOE*) gene (OMIM 107741). The *APOE* ε4 allele carries the greatest risk through the reduction of β-amyloid (Aβ) clearance.[3-5] *APOE* ε4 carriers have a significantly higher prevalence of Pittsburgh compound B uptake than noncarriers across all disease stages,[6] including presymptomatic amyloidosis in cognitively normal control individuals.[7] Peripheral blood apoE protein levels correlate with amyloid positron emission tomography (PET) binding.[8,9] These data indicate that imaging phenotypes can provide meaningful information related to gene function and pathophysiologic findings.

Previous large-scale genome-wide association studies (GWASs)[10-15] have identified and validated 20 novel AD genetic risk loci. Few of these loci are in or near genes associated with Aβ aggregation and clearance and are thought to influence amyloid deposition.[15,16] For the remainder, the precise disease-associated mechanism remains unknown.

Several imaging genetics studies[16-20] have reported associations of some of the AD risk genes with brain amyloidosis or neurodegeneration. Phosphatidylinositol-binding clathrin assembly protein (*PICALM*) (OMIM 603025) rs3851179, bridging integrator 1 (*BIN1*) (OMIM 601248) rs7561528, complement component receptor 1 (*CR1*) rs1408077 (OMIM 120620), adenosine triphosphate–binding cassette subfamily A member 7 (*ABCA7*) (OMIM 605414) rs3764650, and membrane-spanning 4-domains, subfamily A, member 6a (*MS4A6A*) (OMIM 606548) rs610932 are associated with cortical and hippocampal atrophy.[21,22] *ABCA7* rs3764650 and rs3752246; *BIN1* rs744373; *CR1* rs6701713, rs3818361, and rs6656401; and clusterin (*CLU*) rs3818361 (OMIM 185430) are associated with amyloid deposition. Although these studies enrich the imaging genetics field, they also have significant shortcomings. Many of these research studies have focused on a single variant[19] or a few variants[16-18,22-25] while ignoring the complex polygenic disease background. In addition, all analyses of gene-endophenotype associations to date have largely used averaged phenotypic records across all disease stages. Such an approach is justified if the risk variant has a static or conserved effect during the disease course. However, considering the complicated and constantly evolving disease pathophysiologic process with early amyloid deposition, later onset of neuronal degeneration, and variable degree of inflammation, we considered stage-dependent genetic associations. Furthermore, improved understanding of the polygenetic risk factors for AD could enable personalized risk assessment, whereas an in-depth characterization of disease-associated mechanism could lead to new therapeutic avenues.

We report a comprehensive analysis of the associations of all well-validated AD risk variants with brain amyloidosis. Our goal was to establish their relative contribution to the amyloid burden. We hypothesized that our multivariable analytic approach would help us more accurately model the probability distribution of our imaging outcome measure and that we would detect several genetic variants in addition to *APOE* ε4 that are associated with brain amyloidosis. In addition, we hypothesized that we might also find stage-dependent associations with amyloid accumulation.

Key Points

Question Which of the recently validated Alzheimer disease genetic risk variants are associated with brain amyloidosis?

Findings In this study of 977 individuals from the Alzheimer's Disease Neuroimaging Initiative, the adenosine triphosphate–binding cassette subfamily A member 7 gene had the strongest association with brain amyloidosis after apolipoprotein E ε4. The fermitin family homologue 2 gene had a stage-dependent association with brain amyloidosis, which was most pronounced in the mild cognitive impairment stage.

Conclusions This study found an association of AD risk variants with brain amyloidosis.

Methods

Participants

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI is a longitudinal study with approximately 50 sites across the United States and Canada that was launched in 2003 (http://adni.loni.usc.edu). The goal of the ADNI is to track the progression of AD by using clinical and cognitive tests, magnetic resonance imaging (MRI), fludeoxyglucose PET, amyloid PET, cerebrospinal fluid, and blood biomarkers. The institutional review boards of all sites participating in the ADNI provided review and approval of the ADNI data collection protocol.

The clinical description of the ADNI cohort has been previously published.[26-28] Diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[29-31] Individuals with AD dementia were required to have Mini-Mental State Examination (MMSE)[32] scores between 20 and 26 and a Clinical Dementia Rating (CDR) score of 0.5 to 1 at baseline.[33] Qualifying individuals with mild cognitive impairment (MCI) had memory concerns but no significant functional impairment, scored between 24 and 30 on the MMSE, had a global CDR score of 0.5, had a CDR memory score of 0.5 or greater, and had objective memory impairment on the Wechsler Memory Scale–Logical Memory II test.[34] The controls had MMSE scores between 24 and 30, had a global CDR score of 0, and did not meet criteria for MCI and AD. Individuals were excluded if they refused or were unable to undergo MRI; had other neurologic disorders, active depression, a history of psychiatric diagnosis, a history of alcohol or other substance dependence within the past 2 years; had less than 6 years of education; or were not fluent in English or Spanish. The full list of inclusion and exclusion criteria can be accessed on pages 23 to 29 of the online ADNI protocol (http://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf). Written informed consent was obtained from all participants, and all data were deidentified.

Gene Variant Selection and Imputation

The ADNI-1 participants were genotyped using the Illumina Human610-Quad BeadChip array (Illumina Inc), whereas the

ADNI-2 and the ADNI-Grand Opportunity (GO) participants were genotyped using the Illumina HumanOmniExpress BeadChip (Illumina Inc) according to the manufacturer's protocol. We focused on the 20 well-established AD risk genes identified and validated in the largest AD GWASs to date.[10-15] In addition to the variants reported in these articles, we included all other variants that were previously associated with brain amyloidosis[16-19] (eTable 1 in the Supplement), which yielded a total of 36 variants.

Missing genotypes (eTable 2 in the Supplement) were imputed using MACH and minimac in a 2-stage procedure using the 1000 Genomes project pilot data as a reference panel. Minimac yielded the posterior probabilities of the imputed genotypes at ungenotyped marker loci for each individual. The threshold to accept each imputed genotype was set at $r^2 = 0.30$.[35]

Nine genes were represented by more than 1 single-nucleotide polymorphism (SNP). Because linkage disequilibrium (LD) introduces colinearity bias, we performed LD analyses followed by Cohen κ statistics (eFigure 1 and eTable 3 in the Supplement). When choosing between 2 variants with significant overlap (high LD and high κ), we retained the variant with least data missingness. Our final number of variants was thus reduced to 27. *ABCA7, BIN1*, *CLU*, *CR1,* ephrin receptor EphA1 (*EPHA1*) (OMIM 179610), and sortilin-related receptor (*SORL1*) (OMIM 602005) were represented with more than 1 variant in the analyses (eTable 3 in the Supplement).

Allele frequencies for each gene variant were assessed. Genotypes were collapsed when the minor allele homozygote frequency was less than 2% as follows: *ABCA7* rs3764650 GG/GT vs TT, Cass scaffolding protein family member 4 (*CASS4*) (HGNC 15878) rs7274581 CC/TC vs TT, *CLU* rs9331949 AG/GG vs AA, desmoglein 2 (*DSG2*) (OMIM 125671) rs8093731 TT/TC vs CC, fermitin family homologue 2 *FERMT2* (OMIM 607746) rs17125944 CC/TC vs TT, and *SORL1* rs112183431 CC/TC vs TT. The remaining variants were coded by minor allele dosage.

Florbetapir F 18 PET Data Acquisition Protocol and Analyses

The florbetapir F 18 PET acquisition and preprocessing protocols are available at http://www.adni-info.org. In our main analyses, we used the mean whole-`brain standard uptake volume ratios (SUVRs) from University of California, Berkeley downloaded from the ADNI database (http://adni.loni.usc.edu). This variable was obtained by averaging the SUVRs obtained using whole cerebellum as the reference region across the frontal, anterior-posterior cingulate, lateral-parietal, and lateral-temporal gray matter regions.[36] The University of California, Berkeley, protocols for ^{18}F-florbetapir preprocessing, coregistration, and normalization have been previously described.[36]

To visualize the regional pattern of associations in 3 dimensions, we downloaded all preprocessed ^{18}F-florbetapir data from the Laboratory of Neuroimaging Image Data Archive (https://ida.loni.usc.edu). We aligned the images to the corresponding MRI from the same visit, normalized to MNI space using measures obtained from the MRI spatial transformation and intensity normalized to the intensity of the whole cerebellum reference region to create SUVR images, as previously described.[37]

Statistical Analysis

R Statistical Analyses

Clinical and demographic characteristics (age, sex, educational level, MMSE, *APOE* ε4 genotype, and diagnosis) for each variant were compared using *t* tests or χ^2 tests with 2-sided *P* values as appropriate. Stepwise multivariable linear regression models with all 27 AD risk variants were performed first in the pooled sample and second in each diagnostic category using amyloid PET mean SUVR as the outcome measure. An additional model in the pooled sample using only amyloid-positive individuals (SUVR>1.17) is available in the eResults in the Supplement. All regression models included age, sex, and *APOE* ε4 genotype as covariates. The regression model for the pooled sample was also corrected for diagnosis. The decision to exclude variables was based on the Akaike information criterion critical *P* value threshold of .16.[38] Because we included only previously validated candidate genes, our significance threshold was set at $P < .05$. Correction for false discovery rate (FDR) was applied.

Analyses in Imaging Space

All imaging analyses were performed in an exploratory fashion. To explore the spatial distribution of the associations, we reproduced the final stepwise regression models using voxelwise regression in Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neuroscience). The SPM8 models included all variants retained in the R statistical models (including those that were retained based on the Akaike information criterion) covaried for age, sex, and *APOE* ε4 genotype. The pooled model also included diagnosis as a covariate. Because of the exploratory nature of our secondary results, we allowed a less stringent visualization threshold: voxelwise threshold of $P < .01$ (uncorrected) with a minimum cluster size (k) of 50 voxels. We also computed familywise error (FWE) and FDR-corrected cluster and peak statistics as appropriate.

Results

The study population was composed of participants from the ADNI-1, ADNI-2, and ADNI-GO stages[39] and consisted of 322 controls, 496 individuals with MCI, and 159 individuals with AD who had available GWAS and ^{18}F-florbetapir PET data (mean [SD] age, 74 [7.5] years; 535 [54.8%] male and 442 [45.2%] female). Group comparisons of demographic characteristics and distribution of the genotypes that were retained in the regression models are given in **Table 1**. *APOE* ε4 had significant associations with brain amyloidosis (eFigure 2 in the Supplement). There were no significant differences in age, sex, educational level, MMSE score, and *APOE* ε4 distribution between carriers and noncarriers or by allele dosage for any of the genotypes except for zinc finger CW-type and PWWP domain containing 1 (*ZCWPW1*) (HGNC 23486) for which risk allele homozygotes were less educated ($P = .02$).

Pooled Sample

In the pooled sample, the stepwise linear regression model achieved an R^2 of 0.35 (95% CI, 0.33-0.37; $P < .001$). *ABCA7*

Table 1. Demographic Characteristics and Distribution of Genotypes

Variable	Control Group (n = 322)	MCI Group (n = 496)	AD Dementia Group (n = 159)	*P* Value
Age, mean (SD), y	75 (6.5)	73 (7.8)	75 (7.8)	<.001
Male sex, No. (%)	156 (48.4)	284 (57.3)	95 (59.7)	.02
Educational level, mean (SD), y	16.6 (2.6)	16.2 (2.7)	15.9 (2.7)	.03
MMSE score, mean (SD)	28.9 (2.1)	27.8 (2.6)	22.8 (2.9)	<.001
APOE ε4, 0/1/2, %	72.4/25.8/1.9	53.4/37.3/9.3	32.7/48.4/18.9	<.001
Amyloid positive, No. (%)	85 (26.4)	252 (50.8)	133 (83.6)	<.001
ABCA7 rs3752246, % 0/1/2 alleles	69.3/28.3/2.5	67.7/28.4/3.8	64.8/30.8/4.4	.47
ABCA7 rs3764650, % 0/1 or 2 alleles	82.9/17.1	81.3/18.8	83.6/16.4	.72
CLU rs11136000, % 0/1/2 alleles	35.4/50.6/14.0	35.9/49.6/14.5	39.6/44.7/15.7	.91
CLU rs9331949, % 0/1 or 2 alleles	94.7/5.3	96.6/3.4	94.3/5.7	.32
DSG2 rs8093731, % 0/1 or 2 alleles	97.8/2.2	98.0/2.0	98.1/1.9	.98
EPHA1 rs11771145, % 0/1/2 alleles	44.7/43.8/11.5	44.8/42.3/12.9	33.3/49.7/17.0	.02
FERMT2 rs17125944, % 0/1 or 2 alleles	82.9/17.1	85.1/14.9	81.8/18.2	.53
PICALM rs3851179, % 0/1/2 alleles	40.4/46.6/13.0	42.3/45.2/12.5	42.8/48.4/8.8	.59
PTK2B rs28834970, % 0/1/2 alleles	42.2/41.9/15.8	43.1/42.7/14.1	39.0/46.5/14.5	.74
SORL1 rs1131497, % 0/1/2 alleles	33.5/47.8/18.6	31.9/52.0/16.1	38.4/48.4/13.2	.26
ZCWPW1 rs1476679, % 0/1/2 alleles	50.6/40.1/9.3	52.4/39.5/8.1	54.7/37.7/7.5	.62

Abbreviation: MMSE, Mini-Mental State Examination.

rs3752246 (χ^2 = 8.38, FDR-corrected P < .001), *EPHA1* rs11771145 (χ^2 = 4.08, FDR-corrected P = .03), and *PICALM* rs3851179 (χ^2 = 3.67, FDR-corrected P = .04) were significantly associated with mean SUVR in the pooled sample. Other associations were as follows: *ZCPWPW1* rs1476679 (χ^2 = 2.74, FDR-corrected P = .08), *FERMT2* rs17125944 (χ^2 = 3.63, FDR-corrected P = .08), and protein tyrosine-kinase 2β (*PTK2B*) rs28834970 (OMIM 601212) (χ^2 = 2.52, FDR-corrected P = .01). *ABCA7* rs3764650 and *CLU* rs11136000 were included in the model based on the Akaike selection criterion. A reduced model that included only age, sex, educational level, and *APOE ε4* achieved a reduced R^2 of 0.31 (95% CI, 0.29-0.33). The between-model difference in R^2 and reduced R^2 was 0.038 (95% CI, 0.029-0.047). **Figure 1** and **Figure 2** show these associations and **Table 2** gives FWE- and FDR-corrected cluster-level results and within-cluster peak associations for genetic variants identified in our models.

Interaction Analyses

To further test for the presence of a stage-specific association, we conducted a linear regression analysis in the pooled sample including interaction terms. *FERMT2* was the only variant that had a significant interaction (*FERMT2* × diagnosis χ^2 = 3.53, FDR-corrected P = .05). The effect sizes for the remaining genes remained unchanged. **Figure 3** shows the β-coefficient maps of the main effect size of *FERMT2* and its interaction with diagnosis as well as the *FERMT2* effect size within each diagnostic group.

Exploratory Analyses Within Diagnostic Groups

In the control group, the model achieved an R^2 of 0.17 (95% CI, 0.14-0.21; P < .001; reduced R^2 = 0.14; 95% CI, 0.11-0.17; R^2-reduced R^2 difference = 0.032; 95% CI, 0.015-0.05). Significant associations were seen for *PICALM* rs3851179 (χ^2 = 3.56, FDR-corrected P = .04). The association for *ABCA7* rs3764650 was χ^2 = 3.16 (FDR-corrected P = .09). *ABCA7* rs3752246 was included in the model based on the Akaike selection criterion.

In the MCI group, the model achieved an R^2 of 0.3 (95% CI, 0.27-0.32; P < .001; reduced R^2 = 0.24; 95% CI, 0.21-0.27; R^2-reduced R^2 difference = 0.058; 95% CI, 0.042-0.074). *ABCA7* rs3752246 (χ^2 = 7.22, FDR-corrected P = .002), *EPHA1* rs11771145 (χ^2 = 3.74, FDR-corrected P = .03), *FERMT2* rs17125944 (χ^2 = 10.38, FDR-corrected P = .002), and *SORL1* rs1131497 (χ^2 = 3.66, FDR-corrected P = .03) were significantly associated with mean SUVR. The association for *ABCA7* rs3764650 was χ^2 = 2.9 (FDR-corrected P = .09).

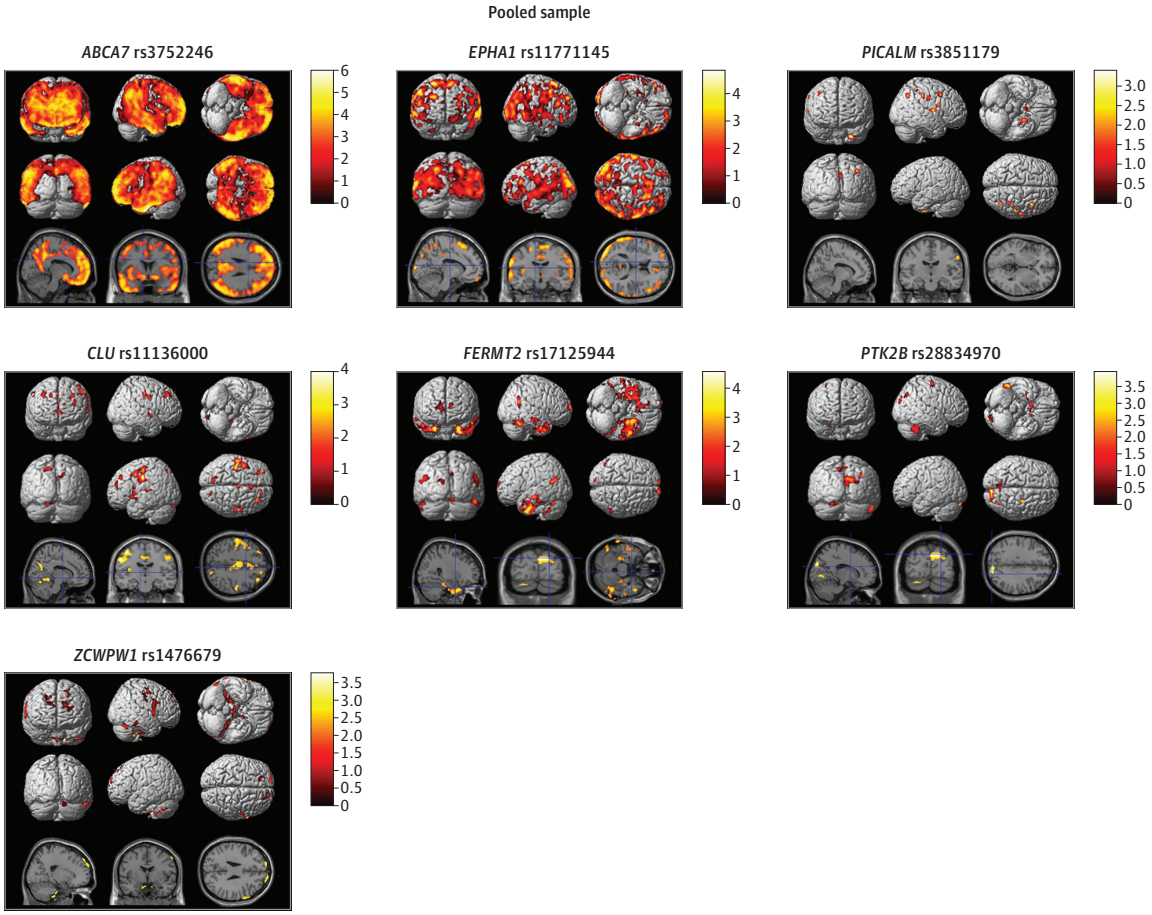
In the dementia group, the model achieved an R^2 of 0.35 (95% CI, 0.29-0.41; P < .0001; reduced R^2 = 0.22; 95% CI, 0.16-0.28; R^2-reduced R^2 difference = 0.13; 95% CI, 0.09-0.17). Other associations were as follows: *EPHA1* rs11771145 (χ^2 = 5.05, FDR-corrected P = .01), *ZCWPW1* rs1476679 (χ^2 = 3.79, FDR-corrected P = .04), *DSG2* rs8093731 (χ^2 = 3.27, FDR-corrected P = .08), *CLU* rs9331949 (χ^2 = 4.09, FDR-corrected P = .058), and *SORL1* rs1131497 (χ^2 = 2.51, FDR-corrected P = .08).

Figure 1 and Figure 2 present exploratory visualization of these associations, and Table 2 presents the FWE- and FDR-corrected cluster-level results and within-cluster peak associations for genetic variants identified in our models.

Discussion

Improved understanding of the polygenetic risk factors that are associated with AD could enable personalized risk assessment. To our knowledge, this is the first comprehensive analysis of the association of the top 20 AD risk variants with brain amyloidosis. We were able to confirm the previously reported association between *ABCA7* and brain amyloidosis as described by Shulman et al[16] and Hughes et al.[18] Our study found that after *APOE* ε4, *ABCA7* has the strongest associa-

Figure 1. Association of Alzheimer Disease Risk Genes With Brain Amyloidosis in the Pooled Sample



Images were visualized using $P < .01$ (uncorrected) and cluster size (k) of 50 voxels. Scale indicates T values.

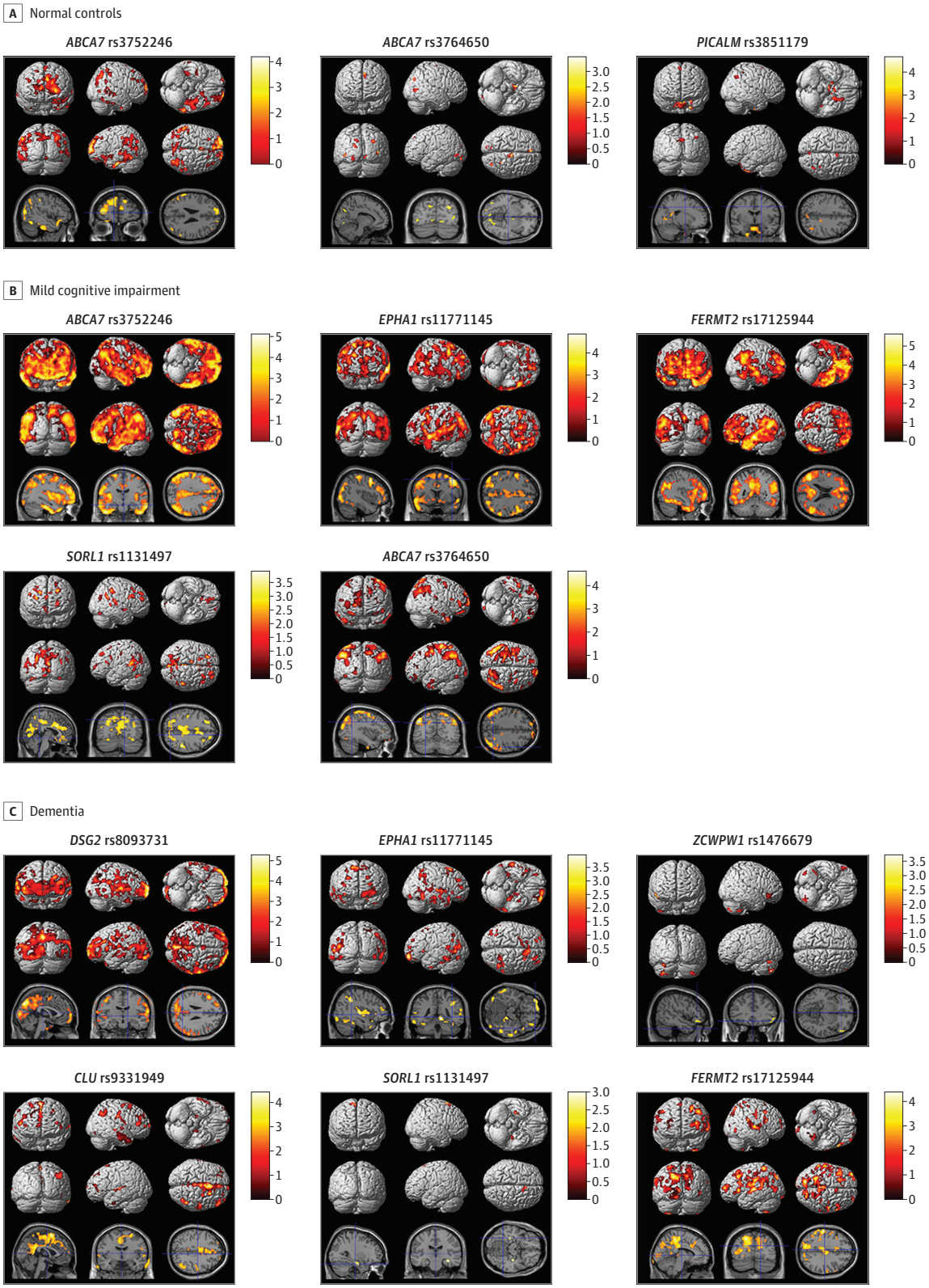
tion with amyloid deposition. We were unable to confirm the reported associations of *CR1*[20] likely because the associations previously reported were determined using a univariable approach. It is plausible that the previously reported *CR1* association is better accounted for by other AD-related genes, which were not part of the original analysis. We also found evidence of a stage-dependent gene association of *FERMT2* with brain amyloidosis. This is, to our knowledge, the first report of such an association.

Several genes had associations with brain amyloidosis. *ABCA7* encodes a 2146-amino acid ABC family transporter protein.[40] The ABC protein family is responsible for the transport of a variety of molecules across cellular membranes, primarily lipids. *ABCA7* is expressed in nervous tissue, with the highest expression in microglia.[41] Loss of function of *ABCA7* was associated with increased β-secretase cleavage of amyloid precursor protein (APP), leading to higher levels of Aβ in vitro and in vivo.[42] A previous ADNI study[43] analyzed the associations of 15 *ABCA7* loci with cerebrospinal fluid Aβ and florbetapir SUVR. Three variants (rs3752242, rs3752240, and rs4147912) were significantly associated with brain amyloidosis but not with brain atrophy. One of these 3 SNPs (rs3752242) is in LD with *ABCA7* rs3752246, lending support to our findings. Further evidence of the role of *ABCA7* in AD comes from a study[44] that reported one rare missense variant (rs72973581; minor allele frequency of 4.3%) to confer a significant protection against AD. In a previous publication,[45] a late but profound effect of *ABCA7* was found on neurodegeneration. Individuals with AD dementia had significant associations of *ABCA7* rs3752246 with gray matter density throughout the brain. Individuals with MCI and controls did not have such an association.

CLU encodes for clusterin, an extracellular chaperone protein that consists of 427 amino acids. *CLU* is highly expressed in neurons and ependymal cells.[46] It seems to be involved in a variety of processes throughout the body, including synaptic maintenance and programmed cell death.[47,48] Under physiologic conditions, clusterin reduces aggregation and promotes clearance of Aβ.[49] *CLU* is highly expressed in the hippocampi in patients with AD and Pick disease.[50] Clusterin protein levels are also elevated in AD, and its pattern of distribution correlates positively with that of Aβ42 and Aβ40 in postmortem tissue.[51]

DSG2 encodes a cell adhesion desmosome cadherin protein. *DSG2* binds plaque proteins and intermediate filaments and seems to play a role in inflammation.[52] Although this gene

Figure 2. Association of Alzheimer Disease Risk Genes With Brain Amyloidosis in the Normal Control, Mild Cognitive Impairment, and Dementia Groups



Images were visualized using $P < .01$ (uncorrected) and cluster size (k) of 50 voxels. Scale indicates T values.

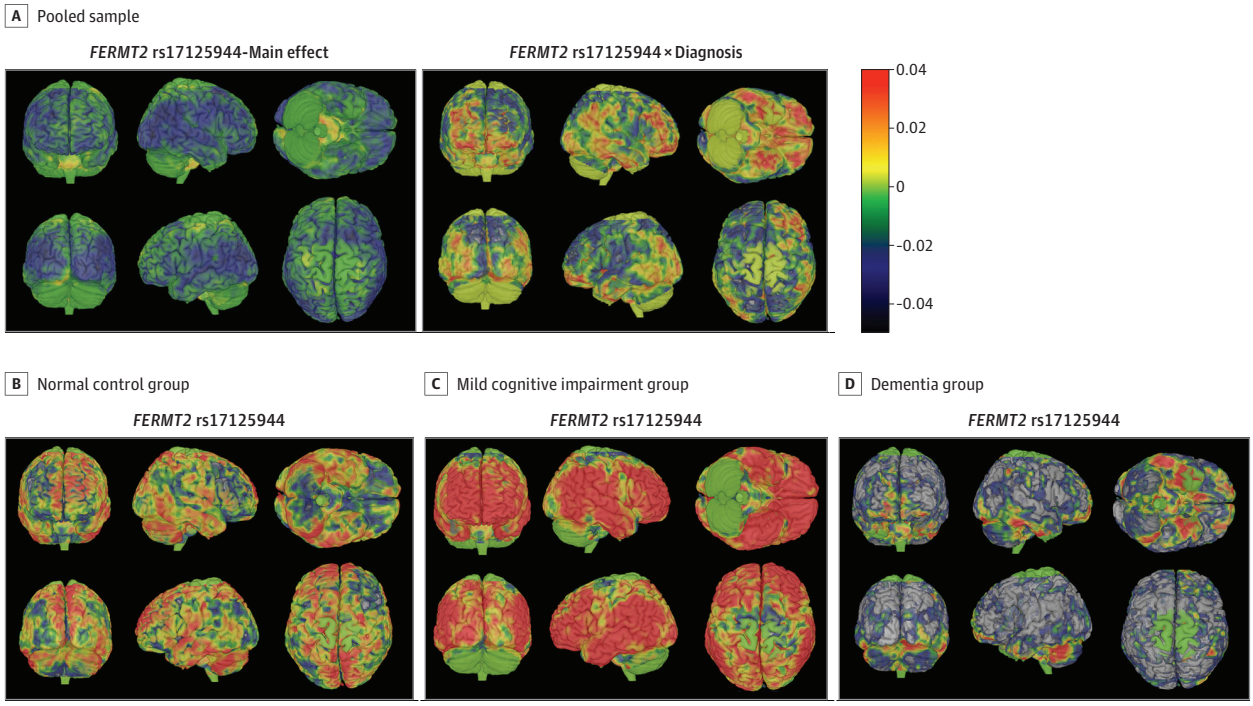
Table 2. FWE- and FDR-Corrected Cluster Analyses and Within-Cluster Peak Effects[a]

Gene Variant	Cluster Level				Peak Level			
	FWE-Corrected *P* Value	FDR-Corrected q Value	Cluster Size, Voxels	Uncorrected *P* Value	*T*	Uncorrected *P* Value	Talairach Coordinates, x/y/z	Brain Region
Pooled Sample								
ABCA7 rs3752246	<.001	<0.0001	96 687	<.001	6.01	<.001	−32/−8/−44	Left inferior temporal gyrus (BA20)
CLU rs11136000	.07	0.101	1246	.002	3.64	<.001	4/−48/0	Right cerebellum
EPHA1 rs11771145	.03	0.033	1484	.001	4.18	<.001	−22/−72/48	Left precuneus (BA7)
	.03	0.033	1520	.001	3.57	<.001	44/−82/0	Right middle occipital gyrus (BA18)
FERMT2 rs17125944	.01	0.020	1871	<.001	4.48	<.001	−28/6/−44	Left superior temporal gyrus (BA38)
ZCWPW1 rs1476679	.047	0.082	1380	.001	3.57	<.001	10/18/−26	Right rectal gyrus (BA11)
Normal Control Group								
ABCA7 rs3752246	.006	0.008	1914	<.001	4.14	<.001	−22/66/8	Left middle frontal gyrus (BA10)
	.01	0.008	1728	<.001	3.79	<.001	−34/−6/−42	Left inferior frontal gyrus (BA20)
	.054	0.027	1236	.001	3.61	<.001	−56/−44/40	Left inferior parietal lobule (BA40)
Mild Cognitive Impairment Group								
ABCA7 rs3752246	<.001	<0.0001	74 749	<.001	5.09	<.001	46/−66/40	Right inferior parietal lobule (BA39)
ABCA7 rs3764650	.02	0.038	1628	.001	4.61	<.001	−46/−64/42	Left inferior parietal gyrus (BA39)
	.006	0.021	2067	<.001	4.03	<.001	−36/−40/66	Left postcentral gyrus (BA5)
	.07	0.091	1228	.002	3.92	<.001	46/−66/42	Right inferior parietal lobule (BA39)
EPHA1 rs11771145	<.001	<0.0001	16 281	<.001	4.72	<.001	−64/−34/10	Left superior temporal gyrus (BA13)
	.07	0.041	1244	.002	3.73	<.001	24/50/32	Right superior frontal gyrus (BA9)
	.002	0.001	2540	<.001	3.52	<.001	46/34/−16	Right inferior frontal gyrus (BA47)
FERMT2 rs17125944	<.001	<0.0001	57 283	<.001	5.6	<.001	−56/−18/−12	Left middle temporal gyrus (BA21)
SORL1 rs1131497	.009	0.009	1911	<.001	3.77	<.001	10/20/36	Right cingulate gyrus (BA32)
	<.001	<0.0001	5880	<.001	3.59	<.001	−26/−76/30	Left cuneus (BA19)
Dementia Group								
CLU rs9331949	.01	0.017	1966	<.001	3.99	<.001	2/10/62	Right superior frontal gyrus (BA6)
DSG2 rs8093731	<.001	<0.0001	5428	<.001	4.96	<.001	0/−78/38	Left cuneus (BA19)
	<.001	<0.0001	4200	<.001	4.39	<.001	10/66/−10	Right superior frontal gyrus (BA10)
	.047	0.049	1480	.001	4.09	<.001	66/−12/14	Right postcentral gyrus (BA43)
ZCWPW1 rs1476679	<.001	<0.0001	17 559	<.001	5.14	<.001	68/14/34	Right inferior frontal gyrus (BA9)

Abbreviations: BA, Brodmann area; FDR, false discovery rate; FWE, familywise error.

[a] In the pooled sample, *ABCA7* rs3764650, *PICALM* rs3851179, and *PTK2B* rs28834970 had no significant clusters; in the control group, *ABCA7* rs3764650 and *PICALM* rs3851179 had no significant clusters; and in the dementia group, *EPHA1* rs11771145 and *SORL1* rs1131497 had no significant clusters.

Figure 3. β-Coefficient Maps of the Main Association of *FERMT2* and Its Interaction With Diagnosis and the Association of *FERMT2* Within Each Diagnostic Group



Main association of *FERMT2* with brain amyloidosis (A), its interaction with diagnosis (B), and the association of *FERMT2* with brain amyloidosis in each diagnostic group (C) displayed using Statistical Parametric Mapping 8.

was reported to be associated with AD risk, a mechanistic explanation of this association has not yet been elucidated. *DSG2* is expressed in epithelial-derived tissues, such as epithelial cell lines,[53] epithelial malignant tumors,[54] and the brain, especially the corpus callosum region.[55-57] We found an association with amyloid deposition later in the disease course, indicating a late modulatory effect on amyloid deposition.

EPHA1 encodes a 976-amino acid protein that belongs to the EPH family of receptor tyrosine kinases.[58] *EPHA1* plays a role in contact-dependent signaling and nervous system development.[59-62] *EPHA1* is highly expressed in the cerebral cortex and hippocampus.[63] A previous analysis[64] of ADNI-1 data reported that *EPHA1* rs11771145 is associated with less brain atrophy and higher cerebral metabolic rate in MCI. Analyses of the cognitively normal imaging subcohort of the Ginkgo Evaluation of Memory study implicated another *EPHA1* allele (rs11767557), which is in LD with ours, to have a negative effect on brain amyloidosis.[18]

FERMT2 encodes for a 680-amino acid scaffolding extracellular matrix protein that plays a role in cell adhesions.[65,66] *FERMT2* is expressed in the brain (http://www.proteinatlas.org/ENSG00000073712-FERMT2/tissue). *FERMT2* is upregulated in atherosclerotic plaques, suggesting a possible role in inflammation and leukocyte extravasation.[67] *FERMT2* is a coactivator of β3-integrin[68]—a microglial and reactive astrocyte marker that plays a role in poststroke brain tissue recovery.[69,70] *FERMT2* has also been associated with a cognitive decline in AD[71] and modifies tau neurotoxicity in a *Drosophila* model.[72]

PICALM encodes a 652-amino acid protein that binds to clathrin's heavy chain and assists in vesicle assembly and endocytosis.[73] *PICALM* was recently identified as a risk gene for late-onset AD.[74] PICALM colocalizes with APP. *PICALM* knockdown resulted in a reduction in the amount of APP internalized and a reduction in Aβ generation.[75] In a previous study,[76] *PICALM* was found to modulate the clearance of tau and thus autophagy. *PICALM* has been associated with brain changes in AD. Morgen et al[77] reported a negative association with prefrontal brain volume and working memory, whereas Biffi et al[78] found associations with hippocampal amygdalar and white matter lesion volume, as well as with entorhinal, parahippocampal, and temporal pole cortical thickness.

SORL1 encodes a 2186-amino acid protein from the low-density lipoprotein receptor family.[79] SORL1 readily binds APOE and lipoprotein lipase and localizes to both the Golgi apparatus and the plasma membrane, where it likely mediates endocytosis.[80] *SORL1* plays a role in APP trafficking and recycling.[81] *SORL1* is downregulated in lymphoblasts and cortical pyramidal neurons of patients with AD.[82] The neuronal SORL1 protein level determines cognitive decline and conversion from MCI to AD.[83] The protein level also correlates with the levels of the APP soluble products that result from β-secretase cleavage.[84] An SNP in LD with our variant (rs1133174) has also been linked to brain atrophy in AD.[85]

The *ZCWPW1* gene codes for a 648-amino acid protein. *ZCWPW1* is considered to be a risk gene for late-onset AD.[86]

Its proposed mechanism of action is through epigenetic regulation of gene expression.[87-89]

Strengths and Limitations

Several strengths and limitations of our study warrant discussion. One of the major strengths lies in the careful clinical, biomarker, and genetic characterization of all individuals enrolled in the ADNI. The ADNI protocol uses unified subject assessment, standardization of all imaging, biofluid and DNA and RNA data collection and processing, and meticulous data quality control across all study sites. Another strength of the study is the fairly large sample size that allowed us to achieve enough statistical power to test the associations of 27 AD-associated risk variants using a polygenic model.

A major limitation of our study is that we only report cross-sectional analyses; thus, we cannot make definitive conclusions regarding genetic effects on amyloid deposition over time. From our cross-sectional observations across the disease continuum, we drew conclusions about early vs late genetic influences on brain amyloidosis that will need to be further tested using a longitudinal design, which is what we plan to do next. Another limitation of our work is that the sample size was not big enough to allow us to test for gene-gene and gene-environment interactions. Last but not least, the ADNI uses rigorous exclusion criteria typical of clinical trials, rendering the ADNI cohort not representative of the general population, which may negatively affect the generalizability of our results. Thus, our next steps will be to validate our findings in a large, independent, longitudinal cohort.

Conclusions

We found an association of genetic variants with brain amyloidosis, the salient pathognomonic feature of AD. Four of the genetic variants reported here, *ABCA7*, *CLU*, *EPHA1*, and *SORL1*, have been previously linked to the amyloidogenic AD pathways. To our knowledge, we are the first to report a stage-specific association for a genetic variant (ie, *FERMT2*).

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