

Alzheimer risk genes modulate the relationship between plasma apoE and cortical PiB binding

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ABSTRACT

Objective: We investigated the association between apoE protein plasma levels and brain amyloidosis and the effect of the top 10 Alzheimer disease (AD) risk genes on this association.

Methods: Our dataset consisted of 18 AD, 52 mild cognitive impairment, and 3 cognitively normal Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) participants with available [¹¹C]-Pittsburgh compound B (PiB) and peripheral blood protein data. We used cortical pattern matching to study associations between plasma apoE and cortical PiB binding and the effect of carrier status for the top 10 AD risk genes.

Results: Low plasma apoE was significantly associated with high PiB SUVR, except in the sensorimotor and entorhinal cortex. For *BIN1* rs744373, the association was observed only in minor allele carriers. For *CD2AP* rs9349407 and *CR1* rs3818361, the association was preserved only in minor allele noncarriers. We did not find evidence for modulation by *CLU*, *PICALM*, *ABCA7*, *BIN1*, and *MS4A6A*.

Conclusions: Our data show that *BIN1* rs744373, *CD2AP* rs9349407, and *CR1* rs3818361 genotypes modulate the association between apoE protein plasma levels and brain amyloidosis, implying a potential epigenetic/downstream interaction. *Neurol Genet* 2015;1:e22; doi: 10.1212/NXG.000000000000022

GLOSSARY

AD = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **Aβ** = β-amyloid; **CDR** = Clinical Dementia Rating; **GWAS** = genome-wide association studies; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MVB** = multivesicular body; **NIA** = National Institute on Aging; **PiB** = Pittsburgh compound B; **SNP** = single nucleotide polymorphism; **SUVR** = standardized uptake value ratio.

The strongest genetic risk factor for late-onset Alzheimer disease (AD) is the apolipoprotein E gene (*APOE*), with the *APOE* ε4 allele carrying the greatest risk via effects on β-amyloid (Aβ) metabolism.¹ *APOE* codes for the apolipoprotein E protein (apoE), which plays an essential role in cholesterol metabolism, neuronal trafficking, synaptogenesis, and blood–brain barrier integrity.^{1,2} ApoE-containing lipoproteins bind Aβ and promote its clearance and degradation.^{1,2} The apoE4 isoform is preferentially degraded by astrocytes, leading to reduced overall brain apoE levels, reduction of Aβ clearance,³ and higher Aβ levels in the brain and plasma.^{1,4–6} Hence apoE protein plasma levels are significantly lower in patients with AD and in *APOE* ε4 carriers.⁷

Amyloid PET tracers provide reliable in vivo visualization of cortical fibrillar Aβ plaque deposition. The *APOE* ε4 genotype has been shown to positively associate with brain amyloid levels.

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APOE $\epsilon 4$ carriers show significantly higher prevalence of Pittsburgh compound B (PiB) uptake than noncarriers across all disease stages.^{8,9}

ApoE protein plasma levels were reported to be lower in research subjects with high PiB–PET binding in one study⁷ but not in another.¹⁰ Such discrepant results are difficult to reconcile and raise the question whether other genetic and perhaps even environmental factors influence this association.

Genome-wide association studies (GWAS) have identified novel AD risk variants. Of those, *PICALM* rs3851179, *BINI* rs7561528, and *CR1* rs1408077 have been associated with cortical and hippocampal atrophy,¹¹ and *ABCA7* rs3764650,¹² *ABCA7* rs3752246,¹³ *BINI* rs744373,¹⁴ *CR1* rs6701713,¹¹ *CR1* rs3818361,¹⁰ *CR1* rs6656401, and *CLU* rs3818361¹⁴ have been associated with PET amyloid deposition. An association between postmortem amyloid burden and *CD2AP* rs9349407 was reported by one group,¹² but no significant relationship with PiB binding in nondemented elderly was observed by others.¹³

The exact mechanism through which these genes exert an association with amyloid burden is not clear. In this study, we assess the associations between the plasma levels of the *APOE* gene product—the apoE protein—and cortical PiB binding, and examine whether the presence of other AD risk variants modulates this association.

METHODS Standard protocol approvals, registrations, and patient consents.

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a \$60-million, 5-year, public–private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure clinical progression in mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and participants have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, aged 55 to 90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3

years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

The clinical description of the ADNI cohort has been previously published.¹⁵ The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) criteria. Participants with AD were required to have Mini-Mental State Examination (MMSE) scores between 20 and 26 and a Clinical Dementia Rating (CDR) score of 0.5 to 1 at baseline. Qualifying MCI participants had memory complaints but no significant functional impairment, scored between 24 and 30 on the MMSE, had a global CDR score of 0.5, a CDR memory score of 0.5 or greater, and objective memory impairment on Wechsler Memory Scale–Logical Memory II test. Healthy control participants had MMSE scores between 24 and 30, a global CDR score of 0, and did not meet criteria for MCI and AD. Participants were excluded if they refused or were unable to undergo MRI; had other neurologic disorders, active depression, or a history of psychiatric diagnosis, alcohol, or 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/exclusion criteria may be accessed on pages 23–29 of the online ADNI protocol (see <http://www.adni-info.org/Scientists/ADNIScientistsHome.aspx>). Written informed consent was obtained from all participants. The subset of 18 AD, 52 MCI, and 3 cognitively normal ADNI participants who received [¹¹C]-PiB have been included in this study.

PiB analyses. We downloaded all available PiB ADNI1 scans from the ADNI Web site (<http://adni.loni.usc.edu>) in October 2008. A detailed description of PiB–PET acquisition may be found at www.adni-info.org. Briefly, ADNI PiB images were collected at 12 ADNI sites. [¹¹C]-PiB with minimum 90% radiochemical purity and minimum specific activity of 300 Ci/mmol was synthesized. Participants were injected with 15 ± 1.5 mCi PiB. Dynamic acquisition frames were obtained on a PET scanner 50–70 minutes after injection. A PiB standardized uptake value ratio (SUVR) image was obtained by averaging the individual 50–70 minutes after injection frames.

PiB scans were normalized to the mean PiB retention value of the cerebellar cortex (SUVR_{CbGM}). After normalization, the PiB SUVR_{CbGM} data were spatially coregistered to the participants' baseline MRI scan using the Minctrac algorithm and 9-parameter (9P) transformation (3 translations, 3 rotations, 3 scales). The PiB data were smoothed with a 15-mm kernel and convected onto the 3D hemispheric models derived with the cortical pattern matching technique as previously described.^{16,17}

Genetic analyses. Genotypic data were extracted from the publicly accessible GWAS data from the ADNI Web site (<http://adni.loni.usc.edu>). The detailed GWAS genotyping protocol has been previously described.¹⁸ Briefly, single nucleotide polymorphism (SNP) genotyping was completed on all ADNI participants for more than 620,000 target SNPs using a total of 7 mL of blood from all participants. Genomic DNA was extracted using the QIAamp DNA Blood Maxi Kit (Qiagen, Inc, Valencia, CA) and analyzed using Human 610-Quad BeadChip (Illumina, Inc, San Diego, CA) according to the manufacturer's protocols (Infinium HD Assay; Super Protocol Guide; rev. A, May 2008).

APOE genotyping was carried out by PCR amplification, HhaI restriction enzyme digestion, and subsequent standard gel resolution and visualization processes.^{19,20} We classified participants as carriers and noncarriers for the following AD risk SNPs: *BINI* rs744373 and rs7561528; *CLU* rs11136000, rs2279590, and rs9331888; *PICALM* rs3851179 and rs541458; *CR1* rs3818361; *ABCA7* rs3764650; *MS4A6A* rs610932; *CD33* rs3826656 and rs3865444; *MS4A4E* rs670139; *CD2AP* rs9349407 and rs3865444. The following SNPs had balanced carrier/noncarrier status and were further analyzed:

CD2AP rs9349407 (40 carriers, 33 noncarriers), *CRI* rs3818361 (30 carriers, 43 noncarriers), *BINI* rs744373 (42 carriers, 31 noncarriers), *CD33* rs3826656 (31 carriers, 42 noncarriers), *CLU* rs9331888 (44 carriers, 29 noncarriers), and *CLU* rs2279590 (47 carriers, 26 noncarriers).

Plasma biomarkers. Plasma collection was conducted according to ADNI standard operating protocols.²¹ Briefly, morning fasting plasma samples were obtained at each visit. The plasma samples were then sent to Rules-Based Medicine (RBM, Austin, TX) for measurement of 190 protein analytes with an immunoassay panel developed on the Luminex xMAP (Austin) platform. Each plate was run with 3 levels of quality control, and each analyte had a validation report; samples from the total ADNI plasma cohort were run on 15 plates. ApoE protein plasma levels were freely downloaded from <http://adni.loni.usc.edu>.

Statistical analyses. The 3D association between apoE protein plasma levels and cortical PiB SUVR_{CbGM} was studied using linear regression in the pooled sample using age and sex as covariates. Next, we split the pooled sample based on the presence or absence of disease-

associated alleles for *CD2AP* rs9349407, *CRI* rs3818361, *BINI* rs744373, *CD33* rs3826656 and *CLU* rs9331888 and studied the associations of the plasma apoE levels and PiB SUVR_{CbGM} separately in minor SNP carriers and noncarriers while adjusting for age and sex. The 3D associations between cortical PiB SUVR_{CbGM} and risk genotypes were studied using linear regression with age and sex as covariates. We additionally ran maps correcting for *APOE* genotype and diagnosis.

Our linear regression 3D statistical maps were subjected to multiple comparison correction by permutation analyses (permuting the predictor variables). Using a set-level inference approach, we defined a single corrected *p* value for each map based on the number of points surviving a particular a priori threshold (set to 0.01 in our analyses). This approach tends to be more sensitive for detecting a distributed pattern of weak effects as opposed to the peak height of the maximum statistic, which is best for detecting a spatially highly concentrated effect.

RESULTS Demographic comparisons. All demographic variables and comparisons are shown in table 1.

Table 1 Demographic statistics of participant pool, indicated by the pooled sample and genotype

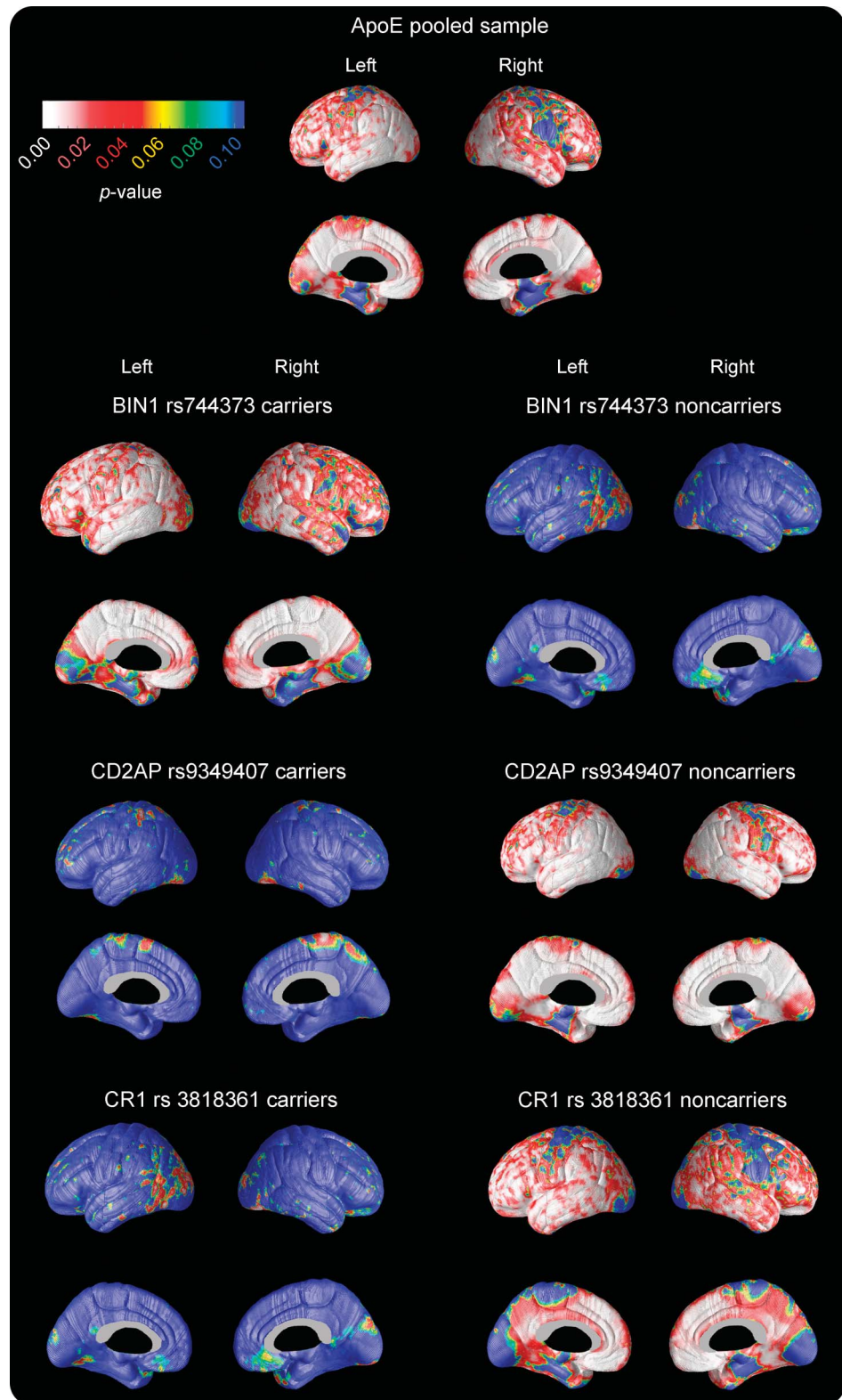
	Age, y	Sex		Education, y	MMSE	Diagnosis			APOE ε4	
		M	F			HC	MCI	AD	Carriers	Noncarriers
Pooled sample	75.3 ± 8	47	26	15.9 ± 3	26.1 ± 3	3	53	17	42	31
<i>BINI</i> rs744373										
Carriers	74.7 ± 7	29	13	15.5 ± 3	25.7 ± 3	2	28	12	23	19
Noncarriers	76.2 ± 9	18	13	16.5 ± 3	26.5 ± 3	1	25	5	19	12
χ ² (p value)	0.479	0.333		0.457	0.005 ^a	0.413			0.577	
<i>CD2AP</i> rs9349407										
Carriers	75.7 ± 8	22	18	15.8 ± 3	25.3 ± 3	1	25	14	25	15
Noncarriers	74.9 ± 8	25	8	15.9 ± 3	27.0 ± 2	2	28	3	17	16
χ ² (p value)	0.478	0.065		0.858	0.047 ^a	0.03 ^a			0.345	
<i>CD33</i> rs3826656										
Carriers	75.5 ± 7	17	14	15.9 ± 3	25.8 ± 2	2	22	7	20	11
Noncarriers	75.2 ± 9	30	12	15.9 ± 3	26.3 ± 3	17	31	10	22	20
χ ² (p value)	0.412	0.143		0.904	0.159	0.687			0.3	
<i>CLU</i> rs2279590										
Carriers	26.1 ± 3	29	18	15.8 ± 3	26.1 ± 3	2	34	11	30	17
Noncarriers	76.0 ± 7	18	8	16.0 ± 3	26.0 ± 3	1	19	6	12	14
χ ² (p value)	0.484	0.52		0.209	0.967	0.996			0.143	
<i>CLU</i> rs9331888										
Carriers	77.2 ± 8	29	15	15.9 ± 3	26.2 ± 3	0	25	5	23	21
Noncarriers	72.4 ± 7	18	11	15.8 ± 3	25.9 ± 4	3	28	12	19	10
χ ² (p value)	0.412	0.737		0.315	0.531	0.145			0.263	
<i>CRI</i> rs3818361										
Carriers	76.4 ± 8	19	11	16.4 ± 3	25.9 ± 3	1	34	9	16	14
Noncarriers	74.6 ± 8	28	15	15.5 ± 3	26.1 ± 3	2	19	8	26	17
χ ² (p value)	0.48	0.876		0.507	0.92	0.444			0.544	

Abbreviations: AD = Alzheimer disease; HC = healthy control; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.

Age, sex, and MMSE displayed in mean ± SD.

^aTwo-tailed χ² test p value with significant differences. Only genes that had balanced distribution between carriers and noncarriers were considered.

Figure 1 Significance maps displaying the associations between cortical Pittsburgh compound B (PiB) binding and plasma apoE protein in the pooled sample (top panel) and stratified by the *BIN1*, *CD2AP*, and *CR1* risk genotypes (bottom 3 panels)



We found no significant differences in age, sex distribution, or level of education between carriers and non-carriers for each gene. There were significantly more MCI than AD and healthy control subjects among

CD2AP noncarriers ($p = 0.03$). *BIN1* and *CD2AP* carriers had lower MMSE scores than noncarriers (*BIN1* mean MMSE 25.7 vs 26.5, $p = 0.005$; *CD2AP* mean MMSE 25.3 vs 27.0 $p = 0.047$). Of note, there

were no significant differences in *APOE* $\epsilon 4$ status between carriers and noncarriers for any risk gene.

None of the AD risk genotypes showed significant association with PiB SUVR_{CbGM} in the pooled sample. Plasma apoE levels showed an association with PiB SUVR throughout the brain with the exception of the sensorimotor and entorhinal cortex (figure 1) across the pooled sample (left $p_{\text{corr}} = 0.004$, right $p_{\text{corr}} = 0.008$).

Our analyses showed no evidence of modulation of the apoE protein–PiB association by *CLU* rs9331888 and *CLU* rs2279590. Plasma apoE levels showed an association with PiB SUVR_{CbGM} only in *CD2AP* rs9349407 and *CR1* rs3818361 minor allele noncarriers (*CD2AP* rs9349407 noncarriers left $p_{\text{corr}} = 0.003$, right $p_{\text{corr}} = 0.004$; *CR1* rs3818361 noncarriers left $p_{\text{corr}} = 0.008$, right $p_{\text{corr}} = 0.01$, figure 1 and table 2). These results remained unchanged after correcting for diagnosis (*CD2AP* rs9349407 noncarriers left $p_{\text{corr}} = 0.009$, right $p_{\text{corr}} = 0.008$; *CR1* rs3818361 noncarriers left $p_{\text{corr}} = 0.014$, right $p_{\text{corr}} = 0.025$, table 2 and figure e-1 at Neurology.org/ng). After correcting for *APOE* $\epsilon 4$, the association between apoE protein plasma levels and PiB binding remained for *CD2AP* (left $p_{\text{corr}} = 0.03$, right $p_{\text{corr}} = 0.03$) but not *CR1* (table 2 and figure e-1). Plasma apoE showed an association with PiB SUVR_{CbGM} in *BIN1* rs744373 minor allele carriers (left $p_{\text{corr}} = 0.006$, right $p_{\text{corr}} = 0.01$, figure 1 and table 2). This *BIN1* association remained after correcting for diagnosis (left $p_{\text{corr}} = 0.007$, right $p_{\text{corr}} = 0.017$, figure e-1) and *APOE* $\epsilon 4$ genotype (left $p_{\text{corr}} = 0.028$, right $p_{\text{corr}} = 0.038$, table 2 and figure e-1).

DISCUSSION Our data show that *BIN1* rs744373, *CD2AP* rs9349407, and *CR1* rs3818361 genotypes modulate the association between apoE protein

plasma levels and brain amyloidosis. In the pooled sample, we saw the expected association between plasma apoE levels and PiB SUVR throughout the brain. Yet, when stratified by AD risk genotypes, plasma apoE showed a significant association with PiB SUVR_{CbGM} only in noncarriers of the minor allele of *CD2AP* rs9349407 and *CR1* rs3818361 and only in carriers of the *BIN1* rs744373 minor allele. These findings imply a downstream interaction between these genes and the apoE disease-associated pathways and suggest a direct or modulatory role on A β accumulation and clearance. Brain and plasma apoE4 levels are believed to be lower than apoE3 levels because of a difference in their fate after they are endocytosed and routed to multivesicular bodies that function as sorting endosomes. ApoE3 is packaged into recycling endosomes and retroendocytosed back to the surface and secreted, whereas apoE4 is typically trafficked on through to the lysosome and degraded. Plasma apoE levels reflect this difference in processing between apoE3 and apoE4.^{22,23}

Bridging integrator 1, or *BIN1*, encodes a nucleocytoplasmic adaptor protein abundantly expressed in the CNS that is involved in synaptic vesicle endocytosis, immune response, calcium homeostasis, and apoptosis.²⁴ The protein encoded by *BIN1* has been shown to link the microtubule cytoskeleton and cellular membrane²⁵ and has been implicated in amyloid precursor protein turnover and hence A β production through clathrin-mediated amyloid precursor protein endocytosis.^{24,26} *BIN1* rs744373 minor allele carriers have been reported to have an increased risk of AD.²⁷ Increased *BIN1* rs744373 expression is associated with later disease onset and shorter disease duration.²⁴ Post-mortem, no association with amyloid plaque burden

Table 2 Significant p values of the association between plasma apoE levels and cortical PiB binding stratified by *BIN1*, *CD2AP*, and *CR1* carrier status

	Covariates					
	Age/sex		Age/sex/diagnosis		Age/sex/ <i>APOE</i> $\epsilon 4$	
	L hemisphere	R hemisphere	L hemisphere	R hemisphere	L hemisphere	R hemisphere
<i>BIN1</i>						
Carriers	0.006 ^a	0.01 ^a	0.007 ^a	0.017 ^a	0.028 ^a	0.038 ^a
Noncarriers	NS	NS	NS	NS	NS	NS
<i>CD2AP</i>						
Carriers	NS	NS	NS	NS	NS	NS
Noncarriers	0.003 ^a	0.004 ^a	0.009 ^a	0.008 ^a	0.03 ^a	0.03 ^a
<i>CR1</i>						
Carriers	NS	NS	NS	NS	NS	NS
Noncarriers	0.008 ^a	0.01 ^a	0.014 ^a	0.025 ^a	NS	NS

Abbreviations: NS = not significant; PiB = Pittsburgh compound B.

^aSignificant.

has been observed for *BINI* rs7561528,¹² and *BINI* rs744373,²⁴ consistent with our results in the pooled sample. An association of *BINI* rs744373 minor allele with in vivo amyloid deposition measured with ¹⁸F-florbetapir has been reported,¹⁴ but this effect disappeared in the presence of the protective *PICALM* minor allele at rs3851179. *BINI* rs744373 also failed to show an association with CSF A β levels.²⁸ In our study, the presence of the *BINI* rs744373 risk variant was associated with preserved and potentially enhanced association between apoE protein plasma levels and PiB binding, lending evidence for a potential downstream functional interaction between the *BINI* and *APOE* genes. *BINI* rs744373 increases mRNA expression and protein expression.²⁹ As mentioned above, apoE levels are strongly related to the classic clathrin-dependent receptor-mediated endocytosis with impaired recycling of apoE4 isoforms.²² *BINI* is an integral part of the sorting nexin-4/BAR complexes. These complexes have been shown to regulate the Rab5/7 switch that influences the transition from early to late endosomes and controls traffic to the lysosomes. They also seem to regulate Rab4/Rab11 transition to recycling endosomes.³⁰ A β and apoE are known for trafficking through Rab5/Rab7 to lysosomes and to Rab11 recycling endosomes for degradation. This occurs in an apoE isoform-dependent manner in which apoE3 promotes greater A β and apoE traffic to the lysosome for clearance.³¹ Therefore, *BINI* is ideally positioned to regulate both A β and apoE influx into lysosomes and trafficking toward degradation or recycling through retroendocytosis. Thus higher *BINI* expression can be hypothesized to increase apoE recycling and elevate protein levels notably, and this would be linked to faster amyloid clearance and less deposition associated with higher apoE levels.

CD2AP, the CD2-associated protein gene, codes for a scaffolding protein that plays a role in the formation of tight junctions, endocytosis, cellular waste management, and immune response.²⁴ *CD2AP* has an established role in endocytosis, vesicle trafficking within the cell, and formation of the cytoskeleton.³² *CD2AP* is involved in endosome trafficking,³³ binds directly to Rab4, and regulates recycling endosomes,³⁴ which play an essential role in the retroendocytosis of apoE that controls apoE levels.²² Consistent with this, *CD2AP*-knockout mice have deficits in multivesicular body (MVB) formation and endosomal-lysosomal trafficking.²⁹ Intraneuronal A β accumulation occurs in MVBs, thereby impairing their function.³⁵ This supports a possible interaction between *CD2AP* and A β metabolism. *CD2AP* rs9349407 has been associated with postmortem plaque burden and AD status.^{36,37} However, studies have failed to find a direct association between this SNP and PiB binding in ADNI.¹³ Our results further elaborate on this complex relationship.

We found that the association between apoE protein plasma levels and PiB binding is no longer present in minor allele carriers, indicating that *CD2AP* influences amyloid pathology. Since *CD2AP* rs9349407 trends toward reducing *CD2AP* expression in human brain,²⁹ one might hypothesize that decreased *CD2AP* (or altered interaction with binding partners) could reduce apoE's isoform-dependent recycling and endosomal-lysosomal traffic that regulates both apoE levels and A β clearance in lysosomes.³¹ The latter has been implicated as a cause for both low plasma apoE4 and defects in A β clearance.³¹ Furthermore, endocytosed apoE isoforms differentially recycle and degrade in lysosomes.²² They also regulate endosomal-lysosomal A β clearance.³¹ Since *CD2AP* rs9349407 trends toward reducing *CD2AP* expression in human brain,²⁹ one might hypothesize that decreased *CD2AP* (or altered interaction with binding partners) could reduce apoE's isoform-dependent recycling and endosomal-lysosomal traffic that regulates both apoE levels and A β clearance in lysosomes.³¹ Thus, lowering *CD2AP* could diminish the correlations between PiB and plasma apoE.

The *CRI* gene encodes complement component 3b/4b receptor 1—a membrane glycoprotein found on erythrocytes, leukocytes, glomerular podocytes, and splenic follicular dendritic cells. This protein mediates cell binding and removal of complement-activated immune complexes.²⁴ *CRI* serves to mediate clearance of immune complexes and phagocytosis by neutrophils and monocytes³⁸ and plays a role in antigen presentation to B lymphocytes.³⁹ Increased *CRI* expression has been associated with AD diagnosis and worse cognition.²⁴ The presence of the *CRI* rs3818361 risk variant is associated with lower PiB binding in 2 separate cognitively normal cohorts including an ADNI subsample¹⁰ but not in the full ADNI1 sample.¹⁴ At the same time, 2 other SNPs, *CRI* rs6656401 and rs6701713, showed an association with increased amyloid plaque burden postmortem.^{12,40} In this study we observed that *CRI* rs3818361 minor allele carrier status leads to a loss of the association between apoE protein plasma levels and PiB binding, which disappeared in the presence of *APOE* ϵ 4 as covariate. An epistatic interaction between the *APOE* genotype and *CRI* rs3818361 has been previously reported.^{41,42}

Several strengths and limitations of this study should be acknowledged. ADNI is the premier longitudinal biomarker study in AD. ADNI uses unified subject assessment, MRI, PiB-PET, CSF, and peripheral blood collection protocols and meticulous data quality control across all study sites. One of the major limitations of our study is its small sample size limited by PiB availability in ADNI1. Significant disproportion between carriers and noncarriers for the remaining ADNI risk SNPs led to the exclusion of these variants,

allowing us to test our hypothesis for only 6 SNPs across 5 AD risk genes. Furthermore, other unknown genetic interactions may also affect the plasma apoE–cortical PiB associations. Last but not least, ADNI uses rigorous exclusion criteria typical of clinical trials and the study population is not representative of the general population, which may negatively affect the generalizability of our results.

The ADNI PET core chose cerebellar gray matter as the reference region for intensity normalization of ADNI1 PiB data. This is one of the commonly used approaches. Other regions that have been used in the amyloid PET literature include whole cerebellum, periventricular white matter, whole brainstem, and composite regions derived from more than one of these measures. Recently, a group of PET experts compared the performance of 4 of these normalization regions: whole cerebellum, cerebellar gray matter, pons, and whole cerebellum plus brainstem. The authors concluded that normalization to the pons performed worse than normalization strategies including the cerebellum. The 2 regions that performed best (i.e., had lowest SUVR variance) were whole cerebellum and whole cerebellum plus brainstem.⁴³ Our study uses the cerebellar gray matter, which performed better than pons but resulted in more noise (higher SUVR variance) in the normalized data. Yet despite this potentially suboptimal signal-to-noise ratio, we were able to find significant associations.

Overall, our findings imply an interaction between several AD risk gene minor alleles and *APOE* genotype–driven brain amyloidosis. In the absence of a direct association with brain amyloidosis, we found that several AD risk genes nonetheless exert a modulatory effect on one of the most fundamental disease-associated pathophysiologic events—*APOE* $\epsilon 4$ -facilitated brain amyloid deposition. These findings lend the basis for further exploration of the exact AD-related pathophysiologic mechanisms of these genes and their products, which might ultimately lead to new therapeutic strategies.

AUTHOR CONTRIBUTIONS

Andreas Lazaris is a co-first author of the manuscript, responsible for study design, data processing, statistical analyses, and drafting of the manuscript. Kristy S. Hwang is a co-first author of the manuscript, assisting with study design, data processing, and the completion of integral statistical analyses. Ms. Hwang also authored several segments of the manuscript and took part in all revisions. Naira Goukasian completed some of the final analysis of our data and took part in revising of the manuscript. Leslie M. Ramirez completed some of the initial analyses of our data and took part in revising of the manuscript. Jennifer Eastman completed some of the initial analyses of our data and took part in revising of the manuscript. Anna E. Blanken completed some of the final analyses of our data and took part in revising of the manuscript. Edmond Teng took part in some analysis and interpretations of the data and participated in revising of the manuscript. Karen Gylys provided critical insights for interpretation of our results and participated in revising of the manuscript. Greg Cole provided critical insights for interpretation of our results

and participated in revising of the manuscript. Andrew Saykin contributed to the overall ADNI study design, data collection, and genetic analyses. He also provided critical insights for interpretation of our results and participated in revising of the manuscript. Leslie Shaw contributed to the overall ADNI study design, data collection, and proteomic analyses. He also provided critical insights for interpretation of our results and participated in revising of the manuscript. John Q. Trojanowski contributed to the overall ADNI study design, data collection, and proteomic analyses. He also provided critical insights for interpretation of our results and participated in revising of the manuscript. William J. Jagust contributed to the overall ADNI study design, data collection, and amyloid PET data analyses. He also provided critical insights for interpretation of our results and participated in revising of the manuscript. Michael W. Weiner is the principal investigator of ADNI. He has contributed to the overall ADNI study design, data collection, and data analyses. He provided critical insights for interpretation of our results and participated in revising of the manuscript. Liana G. Apostolova is the senior author of this manuscript and is responsible for the study concept and design. She provided major oversight over all analyses, interpretation of results, and participated in writing of the manuscript.

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DISCLOSURE

Andreas Lazaris, Kristy S. Hwang, Naria Goukasian, Leslie M. Ramirez, Jennifer Eastman, and Anna E. Blanken report no disclosures. Edmond Teng owns stock in General Electric and Cerner Corporations; has served on the editorial board for Dementia and Geriatric Cognitive Disorders; and has received research support from Eli Lilly, Biogen, Genentech, Merck, and K08 AG 34628 (jointly sponsored by NIA, AFAR, the John A. Hartford Foundation, the Atlantic Philanthropies, the Starr Foundation, and an anonymous donor). Karen Gylys has served on the editorial

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Alzheimer risk genes modulate the relationship between plasma apoE and cortical PiB binding

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