Association of the top 20 Alzheimer’s disease risk genes with $[^{18}\text{F}]$flortaucipir PET

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Abstract

Introduction: We previously reported genetic associations of the top Alzheimer’s disease (AD) risk alleles with amyloid deposition and neurodegeneration. Here, we report the association of these variants with $[^{18}\text{F}]$flortaucipir standardized uptake value ratio (SUVR).

Methods: We analyzed the $[^{18}\text{F}]$flortaucipir scans of 352 cognitively normal (CN), 160 mild cognitive impairment (MCI), and 54 dementia (DEM) participants from Alzheimer’s Disease Neuroimaging Initiative (ADNI)2 and 3. We ran step-wise regression with log-transformed $[^{18}\text{F}]$flortaucipir meta—region of interest SUVR as the outcome measure and genetic variants, age, sex, and apolipoprotein E ($\text{APOE}$) ε4 as predictors. The results were visualized using parametric mapping at familywise error cluster-level—corrected $P < .05$.

Results: $\text{APOE}$ ε4 showed significant ($P < .05$) associations with tau deposition across all disease stages. Other significantly associated genes include variants in $\text{ABCA7}$ in CN, $\text{CR1}$ in MCI, $\text{BIN1}$ and $\text{CASS4}$ in MCI and dementia participants.

Discussion: We found significant associations to tau deposition for $\text{ABCA7}$, $\text{BIN1}$, $\text{CASS4}$, and $\text{CR1}$, in addition to $\text{APOE}$ ε4. These four variants have been previously associated with tau metabolism through model systems.

Keywords
Alzheimer’s disease, Alzheimer’s Disease Neuroimaging Initiative, flortaucipir, imaging genetics, risk genes

1 | INTRODUCTION

An estimated 5.8 million people in the United States are currently living with Alzheimer’s disease (AD), of which 99% of cases are considered sporadic in origin. In contrast to the Mendelian autosomal dominant inheritance of single gene mutations in amyloid precursor protein ($\text{APP}$), presenilin 1 ($\text{PSEN1}$), and presenilin 2 ($\text{PSEN2}$) in familial early-onset AD, the risk for sporadic AD is conferred by a large number of genetic and environmental risk factors.

Understanding the complex network of genetic risk factors contributing to sporadic AD has been challenging. For many years, the only risk gene associated with sporadic AD was the apolipoprotein E ($\text{APOE}$) ε4.
gene. APOE has a dose-dependent risk, where one copy of the ε4 allele triples AD risk while two copies increase risk by as much as 12-fold. Although this variant confers significant risk, it has been estimated that APOE ε4 accounts for less than half of the total genetic hazard.5,6

To explain the remaining genetic risk, large-scale genome-wide association studies (GWAS) and meta-analysis of GWAS studies have identified risk variants in or near 20 genes involved in pathways such as cholesterol metabolism, immune response, and endocytosis.7–12 Though each of these variants contributes a relatively small amount of the overall risk, inheriting multiple risk variants results in a risk summation. While many of the genes have been attributed to known dysfunctional pathways in AD, the precise mechanisms of action of a significant number of them are still yet to be uncovered.

Through the use of imaging genetics, our group previously associated the top AD GWAS-identified variants with imaging biomarkers of amyloidosis, brain hypometabolism, and atrophy using data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI).13,14 We used a multivariable model to find variant associations with AD-specific disease biomarker endophenotypes, across the three diagnostic categories—cognitively normal (CN), mild cognitive impairment (MCI), and dementia (DEM)—as well as in a pooled sample, to capture disease-specific associations across the AD spectrum. We reported stage-dependent associations of FERMT2 rs17125944 with amyloid deposition;15 EPHA1 rs11771145 and SLC24A4/RIN3 rs10498633 with brain atrophy;14 and CD2AP rs9349407, CLU rs9331949, and NME8 rs2718058 with brain metabolic activity14 indicating that the genetic impact on AD evolves as the disease progresses.

With the addition of tau positron emission tomography (PET) neuroimaging to the ADNI protocol, we were able to expand on the previous work to conduct a multivariable analysis of the associations of GWAS-validated AD risk variants with cortical tau burden, which was measured via [18F]flortaucipir PET standardized uptake value ratio (SUVR). The goal of this study was to establish the relative genetic contribution to tau burden using stepwise multivariable regression as we have done previously for brain amyloidosis and neurodegeneration.13,14

2 METHODS

2.1 Participants

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu/). ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

The clinical description of the ADNI cohort has been previously published.15–17 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.18–20 Individuals with AD dementia 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 individuals with 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. 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 are listed in 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. Only de-identified data were used in these analyses.

All non-Hispanic White ADNI subjects who enrolled or rolled over into ADNI2/3 were included if they had both genetic data and
Gene variant selection and imputation

Participants were genotyped using either the Illumina Human610-Quad BeadChip (ADNI1), Illumina HumanOmnimatrix BeadChip (ADNIGO/2), or Illumina Infinium Global Screening v2 (ADNI3) arrays. Intensity data were processed using either GenomeStudio v2009.1 (ADNI1/GO/2) or GenomeStudio v2.0.4 (ADNI3) according to Illumina Inc. protocols. More information on the genetics core can be found at http://adni.loni.usc.edu/data-samples/data-types/genetic-data/.

Similar to our previous studies, we narrowed our focus to variants in the top 20 well-established AD risk genes identified and validated in the largest AD GWAS to date.7–12 We also included all other variants contained within these genes that have previously been associated with brain amyloidosis, a key pathological hallmark of AD. The full list of the 36 variants considered in our analysis can be seen in Table S1 in supporting information.

Missing genotypes (Table S2 in supporting information) were imputed using MaCH and minicam, relying on the 1000 Genomes project data as a reference panel. We applied a low genotype threshold of 0.05, meaning subjects missing >5% of the genotypes were removed. Posterior probabilities of the imputed genotypes for each individual were determined in minicam. We used an imputation threshold of \( r^2 = 0.30 \) to accept the imputed genotype per MaCH recommendations (https://genome.sph.umich.edu/wiki/MaCH_FAQ).

For the nine genes containing more than one single nucleotide polymorphism (SNP), we performed linkage disequilibrium (LD) analysis, followed by Cohen x statistics to guard against collinearity bias (Table S3 and Figure S1 in supporting information). In situations in which variants had significant overlap (\( D' \geq 0.4 \)), we retained the variant with the least missing data. A total of 27 variants were included in our final regression models including several variants from the ABCA7, BIN1, CLU, CR1, EPHA1, and SORL1 genes that were not in LD.

Genotypes were coded by the number of minor alleles (0/1/2 copies); however, when minor allele homozygote frequency was less than 2% the genotype was collapsed into the presence or absence of minor allele (coded as 1 or 0). This was the case for five of the variants: ABCA7 rs3764650, CASS4 rs7274581,CLU rs9331949, DSG2 rs8093731, and SORL1 rs11218343.

2.2 Gene variant selection and imputation

2.3 [18F]Flortaucipir PET data acquisition protocol and analyses

Standardized [18F]Flortaucipir acquisition and preprocessing protocols can be found at www.adni-info.org. In our main analysis, we downloaded the ADNI University of California (UC) Berkeley [18F]Flortaucipir partial volume corrected (PVC) SUVR FreeSurfer 6.0 data from ADNI’s website (http://adni.loni.usc.edu). This website also houses the detailed description of the processing methods for UC Berkeley. We computed a size-weighted AD-specific meta-region of interest (ROI) using the a priori regions defined by Jack et al., containing entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions.21 The meta-ROI was then intensity-normalized to the inferior cerebellar gray-matter reference region (defined by UC Berkeley).

2.4 Statistical analysis

Clinical, demographic, and biomarker values of interest (age, sex, number of APOE e4 alleles, MMSE, and [18F]Flortaucipir meta-ROI SUVR) for each diagnostic group (CN, MCI, and DEM) were compared using analysis of variance (ANOVA) or \( \chi^2 \) tests with 2-sided \( P \)-values as appropriate. Because the meta-ROI SUVR data were highly skewed, we normalized the data using a natural log-transformed meta-ROI SUVR as the outcome measure. Variant association with the [18F]Flortaucipir meta-ROI SUVR was determined using multivariable stepwise linear regression models in SAS 9.4, with all 27 AD risk variants included as predictors, adjusting for age, sex, and APOE e4 genotype. For the pooled sample we also controlled for diagnosis. Model selection was based on the Akaike information criterion (AIC) critical \( P \)-value threshold of 0.157.22 We used false discovery rate (FDR)-corrected \( P \)-values to protect against type I errors using the Yekutieli and Benjamini23 method. We report gene variant selections in Table 2, though it is worth noting that we also included APOE e4 outputs (despite being a covariant in all models) as it plays a crucial role in AD and in general had a very large effect. In addition, we report mean SUVR by copy number of each risk variant retained in each model.

2.5 Analysis in imaging space

Next, we visualized the selected variant spatial effects in SPM12. Preprocessed [18F]Flortaucipir scans were downloaded from ADNI (http://adni.loni.usc.edu/), where PET frames were coregistered, averaged, and image and voxel sizes were standardized and smoothed to a uniform resolution. Using SPM12, each subject’s preprocessed [18F]Flortaucipir scan was then coregistered to that subject’s closest-visit MRI, spatially normalized into Montreal Neurological Institute space, and intensity normalized to the cerebellar crus to generate SUVR images. To visualize the spatial distribution of the genetic associations, we reproduced the regression models using voxelwise regression in SPM12. For display purposes our figures only include variants that were significant (uncorrected \( P < .05 \)) or trending (uncorrected \( P < .10 \)) in the models for meta-ROI SUVR. As with our regression modeling in SAS, we covaried for age, sex, and APOE e4 genotype, including diagnosis as a covariate in the pooled sample. The variant associations were displayed at a cluster-level familywise error (FWE)-corrected \( P < .05 \), which was used instead of FDR as it is more easily integrated into an SPM analysis.
TABLE 1  Demographic, biomarker data, and minor allele distribution for variants retained in the regression models in each diagnostic group

| Variables                          | CN (N = 352) | MCI (N = 160) | DEM (N = 54) | P-value   |
|------------------------------------|--------------|---------------|--------------|-----------|
| Age, years, mean (SD)              | 73.6 (7.1)   | 75.7 (8.2)    | 77.4 (9.1)   | <.001     |
| Sex, % male                        | 43.5         | 65.0          | 53.7         |           |
| APOE ε4 alleles, % 0/1/2            | 66/31/3      | 61/28/11      | 43/33/24     | <.001     |
| MMSE, mean (SD)                    |               |               |              |           |
| Meta-ROI flortaucipir SUVR, mean (SD) | 1.48 (0.19) | 1.63 (0.35)   | 2.33 (0.77)  | <.001     |
| ABCA7 rs3752246, % 0/1/2            | 63/34/4b     | 73/26/1       | 63/33/4      | .098      |
| ABCA7 rs3764650, % 0/1a             | 80/20        | 85/15         | 85/15        | .334      |
| BIN1 rs6733839, % 0/1/2             | 40/43/17     | 34/52/14      | 35/46/19     | .394      |
| CASS4 rs7274581, % 0/1a             | 85/15        | 81/19         | 83/17        | .627      |
| CLU rs9331949, % 0/1b               | 94/6         | 96/4          | 96/4         | .433      |
| CR1 rs12034383, % 0/1/2             | 15/49/36     | 16/48/36      | 9/52/39      | .807      |
| CR1 rs3818361, % 0/1/2              | 68/29/4b     | 64/32/4       | 63/35/2      | .757      |
| DSG2 rs8093731, % 0/1a              | 97/3         | 98/2          | 98/2         | .869      |
| EPHA1 rs11767557, % 0/1/2           | 66/30/4      | 66/31/3       | 63/35/2      | .913      |
| NME8 rs2718058, % 0/1/2             | 38/48/15b    | 41/48/12b     | 46/43/11     | .734      |
| SORL1 rs11218343, % 0/1a            | 90/11b       | 92/8          | 89/11        | .670      |
| ZCWPW1 rs1476769, % 0/1/2           | 51/41/8      | 46/43/11      | 67/32/2b     | .050      |

Note: This table shows a demographic, neuropsychological, and imaging measure comparison across each of the diagnostic groups. We also display the percentage of subjects who had each copy number for the genes retained in any of the four regression models. P-values were generated using ANOVA and Chi-square where necessary.

aCollapsed because minor allele homozygote frequency was <2%.
bDoes not add up to 100% due to rounding.

Abbreviations: ANOVA, analysis of variance; APOE, apolipoprotein E; CN, cognitively normal; DEM, dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ROI, region of interest; SD, standard deviation; SUVR, standardized uptake value ratio.

3  | RESULTS

Group comparisons of clinical, demographic, biomarker, and carrier distribution of variants retained in the regression models are seen in Table 1. Our sample included 352 CN, 160 MCI, and 54 DEM subjects who had available GWAS and [18F]flortaucipir data. There were significant differences in age, sex, APOE ε4 carrier percentage, MMSE, and meta-ROI SUVR among diagnostic groups (P < .001 for all). All gene variant selection models were corrected for age, sex, and APOE ε4.

There were no significant diagnostic group differences in minor allele distribution for any of the gene variants selected in our regression models.

In addition, we investigated demographic differences between risk variant minor allele carriers and noncarriers among the variants retained in our regression (not shown). We observed no significant differences in age, sex, or APOE ε4 carrier percentage.

3.1  | Pooled sample

In the pooled sample, our stepwise regression model achieved an \( R^2 \) value of 0.397 (Table 2). APOE ε4 was significantly associated with the meta-ROI SUVR (P < .0001). While ABCA7 rs3752246 (P_{FDR} = 0.1395), NME8 rs2718058 (P_{FDR} = 0.1395), and ZCWPW1 rs1476679 (P_{FDR} = 0.1395) were associated with tau meta-ROI SUVR at an uncorrected trend level, they did not survive FDR correction. Visual assessment of voxelwise analysis displayed significant large clusters of association to tau deposition with APOE ε4 and ABCA7 rs3752246 in an AD-like pattern including temporoparietal and frontal regions (Figure 1). ZCWPW1 rs1476679 showed a more restricted right lateralized association pattern primarily in the inferior and temporal polar regions.

3.2  | CN sample

In CN subjects, the regression model achieved an \( R^2 \) of 0.0971 (Table 2). APOE ε4 (P = .0195) and ABCA7 rs3764650 (P_{FDR} = 0.0057) were significantly associated with tau meta-ROI SUVR, while CR1 rs12034383 (P_{FDR} = 0.0799) was associated at a trend level. Voxelwise analysis shows that all three variants have significant associations with tau deposition in the temporal, parietal, and frontal lobes. APOE ε4 and CR1 rs12034383 showed additional associations in the occipital region (Figure 2).
TABLE 2  Regression results in each diagnostic group

| Variants selected | Parameter estimate | Standard error | Parameter P-value/FDR-corrected P-value | Parameter [18F]flortaucipir SUVR by risk allele | SUVR P-value |
|-------------------|--------------------|----------------|----------------------------------------|-----------------------------------------------|--------------|
| APOE ε4           | 0.052              | 0.011          | <.0001                                 | 1.54/1.64/2.01                                | <.001        |
| ABCA7rs3752246    | 0.024              | 0.013          | .0567/1395                             | 1.59/1.62/1.81                                | .097         |
| BIN1rs6733839     | 0.014              | 0.010          | .1395/1395                             | 1.56/1.64/1.62                                | .100         |
| CR1rs3818361      | 0.019              | 0.012          | .1211/1395                             | 1.59/1.64/1.61                                | .325         |
| NME8rs2718058     | -0.018             | 0.010          | .0785/1395                             | 1.66/1.57/1.56                                | .037         |
| ZCWPW1rs1476679   | -0.017             | 0.011          | .0991/1395                             | 1.66/1.54/1.58                                | .007         |

Pooled sample, model $R^2 = 0.3970$/adjusted $R^2 = 0.3861$, $P < .0001$

| Variants selected | Parameter estimate | Standard error | Parameter P-value/FDR-corrected P-value | Parameter [18F]flortaucipir SUVR by risk allele | SUVR P-value |
|-------------------|--------------------|----------------|----------------------------------------|-----------------------------------------------|--------------|
| APOE ε4           | 0.0255             | 0.011          | .0195                                  | 1.47/1.48/1.65                                | .014         |
| ABCA7rs3764650    | 0.044              | 0.014          | .0028/0057                             | 1.46/1.54                                     | .003         |
| CR1rs12034383     | -0.015             | 0.008          | .0799/0799                             | 1.50/1.49/1.46                                | .100         |

CN sample, model $R^2 = 0.0971$/adjusted $R^2 = 0.0840$, $P < .0001$

| Variants selected | Parameter estimate | Standard error | Parameter P-value/FDR-corrected P-value | Parameter [18F]flortaucipir SUVR by risk allele | SUVR P-value |
|-------------------|--------------------|----------------|----------------------------------------|-----------------------------------------------|--------------|
| APOE ε4           | 0.076              | 0.020          | .0002                                  | 1.55/1.76/1.78                                | .001         |
| BIN1rs6733839     | 0.045              | 0.020          | .0272/0464                             | 1.54/1.68/1.68                                | .037         |
| CASS4rs7274581    | 0.074              | 0.035          | .0348/0464                             | 1.61/1.74                                     | .065         |
| CLUrs9331949      | 0.113              | 0.070          | .1091/1091                            | 1.63/1.81                                     | .206         |
| CR1rs3818361      | 0.051              | 0.024          | .0324/0464                            | 1.59/1.70/1.80                                | .099         |

MCI sample, model $R^2 = 0.2108$/adjusted $R^2 = 0.1744$, $P < .0001$

| Variants selected | Parameter estimate | Standard error | Parameter P-value/FDR-corrected P-value | Parameter [18F]flortaucipir SUVR by risk allele | SUVR P-value |
|-------------------|--------------------|----------------|----------------------------------------|-----------------------------------------------|--------------|
| APOE ε4           | 0.095              | 0.046          | .0455                                  | 2.21/2.29/2.60                                | .332         |
| BIN1rs744373      | -0.177             | 0.064          | .0085/0423                            | 2.38/2.37/1.72                                | .271         |
| CASS4rs7274581    | 0.257              | 0.104          | .0176/0441                            | 2.27/2.63                                     | .206         |
| DSG2rs8093731     | -0.426             | 0.276          | .1296/1296                            | 2.35/1.49                                     | .278         |
| EPHA1rs11767557   | 0.110              | 0.071          | .1264/1296                            | 2.23/2.47/2.99                                | .406         |
| SORL1rs11218343   | -0.208             | 0.116          | .0794/1296                            | 2.36/2.05                                     | .350         |

Note: Final results from stepwise linear regression models using 27 AD risk variants, including covariates of age, sex, and APOE ε4 (and diagnosis for pooled model) and log-transformed outcome measure. Model selection for the risk variants was $P = .157$.

Abbreviations: AD, Alzheimer’s disease; ANOVA, analysis of variance; APOE, apolipoprotein E; CN, cognitively normal; DEM, dementia; FDR, false discovery rate; MCI, mild cognitive impairment; SUVR, standardized uptake value ratio.

3.3  MCI sample

In MCI subjects, the regression model achieved an $R^2$ of 0.2108 (Table 2). APOE ε4 ($P = .0002$), BIN1 rs6733839 ($P_{FDR} = 0.0464$), CASS4 rs7274581 ($P_{FDR} = 0.0464$), and CR1 rs3818361 ($P_{FDR} = 0.0464$) were significantly associated with tau deposition. Voxelwise analysis displayed right greater than left significant associations to tau burden for APOE ε4 and CR1 rs3818361 in temporal, parietal, and occipital cortices (Figure 3). CASS4 rs7274581 showed significant association in temporoparietal regions. Interestingly, voxelwise analysis of BIN1 rs6733839 did not show any FWE cluster-level corrected associations to tau deposition.

3.4  DEM sample

In DEM subjects, the regression model achieved an $R^2$ of 0.4240 (Table 2). APOE ε4 ($P = .0455$), BIN1 rs744373 ($P_{FDR} = 0.0423$), and
FIGURE 1  Regression results in the pooled sample. SPM visualization of association patterns for the regression selected significant or trending genes ($P < .10$). Results are displayed at a familywise error (few)-cluster–level correction of $P < .05$

CASS4 rs7274581 ($P_{\text{FDR}} = 0.0464$) were significantly associated with [18F]flortaucipir meta-ROI SUVR. SORL1 rs11218343 ($P_{\text{FDR}} = 0.1296$) was associated to tau at an uncorrected trend level. Voxelwise analysis of BIN1 rs744373 showed significant association with tau in left temporal and parietal and bilateral occipital lobes (Figure 4). CASS4 rs7274581 showed association to tau burden in the bilateral occipital and temporo-occipital, right inferior temporal regions, and sensorimotor cortices. APOE ε4 was significantly associated to tau in left medial temporal and temporoparietal cortices.

4 | DISCUSSION

To our knowledge, this is the first comprehensive analysis of the association of the top 20 AD risk genes with tau burden. This work highlights the importance of modeling genetic associations in AD, as well as other complex diseases, in a polygenic fashion. Associations with tau burden were seen in each diagnostic group, for some variants across multiple diagnostic groups. The reason behind this likely is very complex and involves direct and indirect relationships to tau burden with regional associations that complicate our understanding further. We replicated previously reported associations to tau for ABCA7, BIN1, CASS4, CLU, CR1, EPHA1, NME8, and SORL1, while identifying novel associations for DSG2 and ZCWPW1.24–29 Like with our previous work,13,14 we also visualized the spatial associations using voxelwise regression maps (Figures 1–4).

In total, we found 10 of the top 20 genes implicated in late-onset AD to have an association with tau burden. To better understand the potential role each gene may play in tau pathology, we provide a brief literature review that includes probable functions as well as a previous association to tau (if applicable) and any associations to amyloidosis or neurodegeneration from our earlier publications13,14 using a similar technique and sample.

4.1 | APOE

Apolipoprotein E encodes a 317 amino acid apolipoprotein involved in a variety of pathways from lipoprotein metabolism to neuronal maintenance and repair.30,31 APOE has three major alleles, ε2, ε3 (the most common), and ε4 (the risk allele for sporadic AD). Though the APOE ε4 variant has long been associated with the amyloid pathway,32 recent work has also linked APOE ε4 to tau pathology and neurodegeneration.33 We previously identified a strong effect of APOE ε4 on amyloid deposition across all diagnostic stages and with atrophy and hypometabolism in dementia and MCI, respectively.13,14 APOE
**FIGURE 2**  Regression results in the cognitively normal (CN) sample. SPM visualization of association patterns for the regression selected significant or trending genes \( (P < .10) \). Results are displayed at a familywise error (few)-cluster–level correction of \( P < .05 \)

4.2 | **ABCA7**

ATP-binding cassette subfamily A member 7 (ABCA7) encodes a 2146 amino acid member of the ABC transporter family comprising proteins involved in lipid transport and plays a role in macrophage-mediated phagocytosis.\(^3\) ABCA7 loss of function was associated with increased production of amyloid beta.\(^3\) ABCA7 has also been linked to cerebrospinal fluid (CSF) and \([18F]\)florbetapir measured amyloidosis,\(^3\) while expression of ABCA7 has been associated with tangle density.\(^2\)

In our earlier work, ABCA7 was associated with amyloidosis early in the disease course (i.e., in CN and MCI) and with atrophy in the later disease stages (i.e., DEM).\(^1\) Here, ABCA7 association to the AD meta-ROI was found in our pooled sample for ABCA7 rs3752246 and in the CN sample for ABCA7 rs3764650 variant. This staged effect (early association with amyloid and tau and late association with brain atrophy) is consistent with the notion that tau deposition precedes, and potentially drives, neurodegeneration in AD.

4.3 | **BIN1**

Bridging integrator 1 (BIN1) encodes a 593 amino acid protein that may be involved with endocytosis of synaptic vesicles and trafficking as well as control of amyloid production.\(^7\) Additionally, the gene product of BIN1 has been shown to directly interact with tau and further impact phosphorylation of tau.\(^2\) BIN1 was recently associated with increased binding of \([18F]\)flortaucipir.\(^2\) We failed to find BIN1 associations with amyloidosis or atrophy/hypometabolism in our prior work.\(^1\) Here we found associations with tau of BIN1 rs6733839 variant in the prodromal and BIN1 rs744373 in the dementia stages.

4.4 | **CASS4**

Cas Scaffold Protein Family Member 4 (CASS4) encodes a 786 amino acid scaffolding protein that regulates focal adhesion kinase (FAK) signaling and activation, ultimately impacting cellular adhesion and spreading.\(^3\) A recent study linked the CASS4 Drosophila ortholog, p130CAS, as a modulator of tau toxicity.\(^2\) CASS4 was not associated with either amyloidosis or neurodegeneration in our previous work.\(^1\) Here, we found a significant association of CASS4...
rs7274581 variant with the [18F]flortaucipir meta-ROI SUVR in our MCI and DEM samples.

4.5 | CR1

Complement Receptor Type 1 (CR1) encodes a 2039 amino acid membrane glycoprotein that has been linked to mediation of the binding between immune cells and their targets. Deletion of the murine ortholog of CR1, Crry, was previously shown to significantly reduce tau phosphorylation. Here, we found that CR1 rs3818361 was associated with the AD tau meta-ROI in a pooled and MCI sample, while CR1 rs12034383 showed associations in the CN sample. In our earlier work, CR1 was associated with hypometabolism in preclinical subjects while having no associations with amyloidosis.

4.6 | Trend-level associations

It is worth briefly mentioning the trend-level associations (P < .10) here as some of these genes have been previously associated with tau in AD in the pre-existing literature. Carrying the Clusterin (CLU) rs11136000 minor allele was associated with CSF tau levels in AD patients and intracellular CLU was found to interact with tau in cell culture. The Drosophila ortholog of EPH receptor A1 (EPHA1), Eph, has been identified as a tau toxicity modifier. NME/NM23 Family Member 8 (NME8) rs2718058 genotype was shown to be significantly associated to CSF tau levels. Sortilin related receptor 1 (SORL1) has previously been associated with CSF total and phospho-tau protein levels. Zinc finger CW-type and PPWP domain containing 1 (ZCWPW1) has no previous reported associations with tau. To date, there have been no reported associations of Desmoglein 2 (DSG2) to tau. All five genes were associated with neurodegeneration (atrophy and/or hypometabolism) in our previous work and all but NME8 were also associated with brain amyloidosis.

5 | STRENGTHS AND LIMITATIONS

This study has several strengths and limitations that merit discussion. One of the main strengths lies in the rigorous clinical, biomarker, and genetic characterization of all individuals enrolled in ADNI. ADNI uses standardized subject assessment, data collection, and quality control practices as well as an imaging normalization to bring images from different scanner types and locations to their closest alignment. Another strength of ADNI is that it is a well-characterized cohort. A major
limitation of our study is that we report only cross-sectional analyses, making it difficult to determine with certainty that specific genetic variants exert stage-specific effects. However, leveraging the full dementia continuum, we suggest that there are differential early and late genetic influences on cortical tau burden. We also have not included any analysis for combined risk of carrying a variant within a loci, which possibly may identify additional associations that may otherwise have been too small at a SNP level. However, this assumes that variants within a loci associate with AD in a similar manner (conferring risk or offering protection), which was not the case in our analysis. Another limitation of our work is the sample size limiting our power to detect smaller associations, a product of the relative newness of [18F]flortaucipir scanning in ADNI. This is an emerging field of research and warrants future studies as more subjects with genotyping and imaging are added. Finally, ADNI is a clinic-based research cohort that is not necessarily representative of the general population; thus, the continuation of our study will aim to validate our findings in a large, independent, longitudinal cohort.

6 | CONCLUSIONS

Using a multivariable regression modeling approach across the cognitive continuum, we found associations of 10 of the top 20 AD risk genes to tau deposition in an AD-specific meta-ROI. Some of the genes showed stage-dependent association. These observations may inform future studies on potential gene targets for further in vivo research.

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CONFLICTS OF INTEREST
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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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