Association Between Common Variants in\textit{RBFOX1}, an RNA-Binding Protein, and Brain Amyloidosis in Early and Preclinical Alzheimer Disease

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**Importance**
Genetic studies of Alzheimer disease have focused on the clinical or pathologic diagnosis as the primary outcome, but little is known about the genetic basis of the preclinical phase of the disease.

**Objective**
To examine the underlying genetic basis for brain amyloidosis in the preclinical phase of Alzheimer disease.

**Design, Setting, and Participants**
In the first stage of this genetic association study, a meta-analysis was conducted using genetic and imaging data acquired from 6 multicenter cohort studies of healthy older individuals between 1994 and 2019: the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Study, the Berkeley Aging Cohort Study, the Wisconsin Registry for Alzheimer’s Prevention, the Biomarkers of Cognitive Decline Among Normal Individuals cohort, the Baltimore Longitudinal Study of Aging, and the Alzheimer Disease Neuroimaging Initiative, which included Alzheimer disease and mild cognitive impairment. The second stage was designed to validate genetic observations using pathologic and clinical data from the Religious Orders Study and Rush Memory and Aging Project. Participants older than 50 years with amyloid positron emission tomographic (PET) imaging data and DNA from the 6 cohorts were included. The largest cohort, the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Study (n = 3154), was the PET screening cohort used for a secondary prevention trial designed to slow cognitive decline associated with brain amyloidosis. Six smaller, longitudinal cohort studies (n = 1160) provided additional amyloid PET imaging data with existing genetic data. The present study was conducted from March 29, 2019, to February 19, 2020.

**Main Outcomes and Measures**
A genome-wide association study of PET imaging amyloid levels.

**Results**
From the 4314 analyzed participants (age, 52-96 years; 2478 participants [57%] were women), a novel locus for amyloidosis was noted within\textit{RBFOX1} (β = 0.61, $P = 3 \times 10^{-9}$) in addition to\textit{APOE}. The RBFOX1 protein localized around plaques, and reduced expression of\textit{RBFOX1} was correlated with higher amyloid-β burden (β = −0.008, $P = .002$) and worse cognition (β = 0.007, $P = .006$) during life in the Religious Orders Study and Rush Memory and Aging Project cohort.

**Conclusions and Relevance**
\textit{RBFOX1} encodes a neuronal RNA-binding protein known to be expressed in neuronal tissues and may play a role in neuronal development. The findings of this study suggest that\textit{RBFOX1} is a novel locus that may be involved in the pathogenesis of Alzheimer disease.

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Alzheimer disease (AD) is a complex polygenic disease with high heritability. Genome-wide association studies (GWAS) have identified more than 25 risk loci that highlight amyloid processing, lipid metabolism, endocytosis, and innate immunity as important biological factors in the development of AD. While much of the genetic work on AD has focused on clinical diagnosis as the primary outcome, AD is heterogeneous and has a long preclinical phase when brain amyloid deposition accumulates before the onset of cognitive impairment. The development of amyloid positron emission tomographic (PET) imaging tracers has provided a biomarker for diagnosing and risk assessment enabling in vivo detection of fibrillar amyloid-β before the onset of symptoms. The approval by the US Food and Drug Administration of additional ligands facilitated the application of amyloid PET imaging in clinical practice and in research. Advancing this biomarker, Jack et al proposed a model in which brain amyloid-β deposition precedes the onset of neurodegeneration and cognitive dysfunction. This model also implied that an amyloid-β biomarker, such as PET imaging, could identify individuals at the highest risk for AD long before the diagnosis. Several previous genetic investigations of brain amyloidosis using amyloid PET imaging have found an association with the APOE locus. However, to our knowledge, there has been no consistent confirmation of other loci.

Therapeutic efforts have begun to shift focus toward identifying and treating individuals in the preclinical phase of disease before onset of neurodegeneration and cognitive decline. Using a PET biomarker of brain amyloidosis to screen participants, the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4 Study) clinical trial screened more than 4000 asymptomatic older individuals with amyloid PET imaging, of whom 1169 had elevated amyloid levels and were eligible for a prevention trial. Clinical information and DNA from these at-risk, asymptomatic study participants provided an opportunity to identify novel genetic associations with brain amyloidosis during the preclinical phase of disease. In addition, the analyses of such data could provide insight into the mechanisms underlying cerebral amyloid accumulation.

Methods

In this genetic association study, participant data were acquired during the screening process in the A4 Study. We also included other cohort studies: the Alzheimer Disease Neuroimaging Initiative (ADNI), the Berkeley Aging Cohort Study, the Wisconsin Registry for Alzheimer’s Prevention (WRAP), the Biomarkers of Cognitive Decline Among Normal Individuals: the BIOCARD cohort, and the Baltimore Longitudinal Study of Aging (BLSA). Vanderbilt University and Columbia University institutional review boards approved the data analyses. The present study was conducted from March 29, 2019, to February 19, 2020. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline for genotyping, population stratification, haplotype modeling, Hardy-Weinberg equilibrium, and replication. We also describe how the participant data were selected, how quantitative traits were harmonized before analyses, the statistical methods used, and the sources of data.

The A4 Study clinical trial began screening in 2014, recruiting healthy adults aged 65 to 85 years with amyloid PET imaging. The ADNI study was launched in 2003 and has included more than 1500 participants aged 55 to 90 years with normal cognition, mild cognitive impairment, or AD. In 2001, WRAP began recruiting participants aged 40 to 65 years who had a parent with autopsy-confirmed or clinically verified AD. The BIOCARD study enrolled middle-aged participants who were cognitively intact; 75% of the participants had a first-degree relative with AD. The study began in 1995, stopped in 2005, and was reestablished in 2009, with annual clinical and cognitive assessments. The neuroimaging substudy of the BLSA began in 1994 and included participants without dementia aged 59 to 85 years who had up to 10 years of prospective data collection at baseline. Amyloid imaging with PET and carbon 11 Pittsburgh Compound B (C11PiB) was introduced into the study in 2005. The Berkeley Aging Cohort Study began enrolling cognitively normal individuals recruited from the local community in 2005. For the amyloid PET imaging GWAS, we filtered each data set to individuals older than 50 years who had amyloid PET imaging (either C11PiB or florbetapir) and genetic data available for analysis. Informed consent was obtained from participants in each study.

To validate genetic findings, we used autopsy data from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP), which were 2 harmonized longitudinal studies enrolling older adults without dementia who underwent annual clinical evaluations and organ donation at death. Both studies were approved by an institutional review board of Rush University Medical Center. All participants in ROS/MAP signed an informed consent, an Anatomical Gift Act form, and a repository consent that allows their data to be repurposed. The Rush Alzheimer Disease Center resource sharing hub (https://www.radc.rush.edu/) and the Accelerating Medicines Partnership—AD Knowledge Portal (syn3219045) provided access to the data and are available on request with a data use agreement.

Key Points

**Question** Is RBFOX1 associated with brain amyloidosis, as measured by positron emission tomographic imaging, in early and preclinical Alzheimer disease?

**Findings** In this genetic association study, a meta-analysis of amyloid positron emission tomographic imaging data collected on 4314 participants in 6 studies noted genome-wide significant associations with single-nucleotide variants in a novel locus, RBFOX1, as well as in APOE. In addition, reduced expression of RBFOX1 appeared to be associated with increased amyloid burden and global cognitive decline during life.

**Meaning** In this study, RBFOX1 appeared to be a novel locus associated with positron emission tomographic imaging-derived brain amyloidosis and may be involved in the pathogenesis of Alzheimer disease.
Genotyping was performed in each study on different platforms. Data from all cohorts underwent a quality control process to filter variants not successfully genotyped (missing >5%), out of Hardy-Weinberg equilibrium (P > 1 × 10⁻⁶), or with low minor allele frequency (<1%). Participants were excluded for poor genotypic efficiency (missing >1% of variants) if reported and genotyped sex differed if cryptic relatedness was identified (removed second-degree or closer relatives) or if large-scale differences in ethnicity/race were identified by principal component detection. After these filters, imputation was performed using the European samples from the HRC r1.1.2016 reference panel (Build 37 Assembly 19) and SHAPEIT phasing on the Michigan imputation server. Gaussian mixture models were estimated among a modification of a recently developed harmonization approach to harmonization is to use the characteristics of both gaussian distributions to transform all C11PiB values to 18F-florbetapir values. As a sensitivity analysis, we performed harmonization using this full transformation and compared results. Data on RNA sequencing from the dorsolateral prefrontal cortex of individuals participating in ROS/MAP were used for validation of candidate genes from the GWAS analysis. Details of the RNA sequencing methods have been published previously.

Harmonization of Amyloid Data
Harmonization was performed from composite cortical values within each site. To ensure that all amyloid values were on the same scale, we applied a gaussian mixture model using a modification of a recently developed harmonization algorithm. Gaussian mixture models were estimated among individuals who were cognitively normal within each cohort, and the mean (SD) was applied to the entire sample. In all cases, a 2-component model fit the data, confirming that global amyloid PET imaging followed a bimodal distribution reflecting amyloid-negative and amyloid-positive groups. Mean standard uptake value ratios and distribution volume ratio calculations varied by site; all sites used whole or gray matter cerebellum as the reference region.

Statistical Analysis
Genome-wide association studies were completed using PLINK, version 1.931 and R, version 3.6.2 (R Project for Statistical Computing), with additive coding and the harmonized continuous amyloid PET metric set as a quantitative outcome. Genome-wide association studies were completed in each cohort separately. Covariates included age, sex, and the first 3 principal components to account for unmeasured population stratification. Meta-analyses of all results were performed using the inverse-weighted method in METAL.
Table 1. Amyloid PET GWAS Participant Characteristics by Data Set

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>A4 NHW</th>
<th>A4 AA</th>
<th>A4 Hispanic</th>
<th>ADNI</th>
<th>ADNI</th>
<th>Berkeley</th>
<th>BIOCARD</th>
<th>BLSA</th>
<th>WRAP</th>
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</thead>
<tbody>
<tr>
<td>Amyloid acquisition</td>
<td>18F-florbetapir</td>
<td>18F-florbetapir</td>
<td>18F-florbetapir</td>
<td>18F-florbetapir</td>
<td>C 11PiB</td>
<td>C 11PiB</td>
<td>C 11PiB</td>
<td>C 11PiB</td>
<td>C 11PiB</td>
<td>C 11PiB</td>
</tr>
<tr>
<td>No. of participants</td>
<td>2960</td>
<td>89</td>
<td>105</td>
<td>623</td>
<td>88</td>
<td>172</td>
<td>44</td>
<td>144</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>1768 (60)</td>
<td>63 (71)</td>
<td>63 (60)</td>
<td>279 (45)</td>
<td>27 (31)</td>
<td>101 (59)</td>
<td>28 (64)</td>
<td>91 (63)</td>
<td>58 (65)</td>
<td></td>
</tr>
<tr>
<td>Normal cognition, No. (%)</td>
<td>2960 (100)</td>
<td>89 (100)</td>
<td>105 (100)</td>
<td>217 (33)</td>
<td>63 (72)</td>
<td>172 (100)</td>
<td>44 (100)</td>
<td>138 (96)</td>
<td>87 (98)</td>
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<tr>
<td>Age, y</td>
<td>71.4 (4.8)</td>
<td>70.3 (4.6)</td>
<td>71.9 (4.9)</td>
<td>74.6 (7.6)</td>
<td>76.5 (7.3)</td>
<td>74.4 (6.4)</td>
<td>76.8 (6.1)</td>
<td>77.2 (7.9)</td>
<td>67.3 (6.2)</td>
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<tr>
<td>APOE4 carriers, No. (%)</td>
<td>1057 (36)</td>
<td>33 (37)</td>
<td>33 (31)</td>
<td>255 (41)</td>
<td>45 (51)</td>
<td>48 (28)</td>
<td>14 (32)</td>
<td>39 (27)</td>
<td>35 (39)</td>
<td></td>
</tr>
<tr>
<td>Amyloid (Standardized)</td>
<td>1.4 (2.5)</td>
<td>0.49 (1.5)</td>
<td>2.2 (4.5)</td>
<td>2.7 (3.4)</td>
<td>3.9 (3.0)</td>
<td>1.8 (4.1)</td>
<td>2.0 (4.5)</td>
<td>3.9 (6.4)</td>
<td>2.7 (5.1)</td>
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</tr>
<tr>
<td>NC participants only</td>
<td>1.4 (2.5)</td>
<td>0.49 (1.5)</td>
<td>2.2 (4.5)</td>
<td>1.4 (2.8)</td>
<td>2.2 (2.6)</td>
<td>1.8 (4.1)</td>
<td>2.0 (4.5)</td>
<td>3.5 (6.1)</td>
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<td>NA</td>
<td>NA</td>
<td>5.2 (3.1)</td>
<td>5.1 (2.7)</td>
<td>NA</td>
<td>NA</td>
<td>15.3 (11.3)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease screening cohort; AA, African American; AD, Alzheimer disease; ADNI, Alzheimer Disease Neuroimaging Initiative; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals cohort; BLSA, Baltimore Longitudinal Study of Aging; GWAS, genome-wide association studies; NA, not applicable; NC, normal cognition; NHW, non-Hispanic white; PET, positron emission tomographic; C 11PiB, Pittsburgh Compound B; WRAP, Wisconsin Registry for Alzheimer’s Prevention.

Results

Clinical data for the 3154 individuals in the A4 Study included those whose race/ethnicity was determined genetically to be non-Hispanic white (n = 2960), African American (n = 89), and Hispanic (n = 105). In addition, 6 amyloid PET data sets with participants of non-Hispanic white ethnicity (n = 1160) were analyzed (Table 1). Together, the participants ranged from age 52 to 96 years; 2478 of the participants (57%) were women. With the exception of the 2 ADNI cohorts, 99% of the participants had normal cognition; with those cohorts added, cognition was normal in 90% of the participants. Analysis of variance of each demographic variable indicated significant differences across the cohorts (Table 1). For example, percent women (F 8,4305 = 10.8, P < .001), age (F 8,4305 = 58.5, P < .001), and percent APOE-positive (F 8,4305 = 3.2, P < .001) were significantly different between groups.

Combining GWAS statistics and harmonized PET imaging amyloid data from each cohort, we completed a meta-analysis of all 6 studies to identify novel genetic associations with brain amyloid levels (n = 4314). We observed a robust association with brain amyloidosis at the APOE locus (top single-nucleotide variant [SNV; formerly SNP]: rs6857, β = 1.67, P = 5.79 × 10^{-122}), similar in magnitude to previous reports.2-11 To determine whether other genes in the APOE region contributed to the association, we performed conditional analyses covarying for APOE e4 and APOE e2 status. All associations in the region were no longer significant (eFigure 2 in the Supplement).

We observed a novel risk locus on chromosome 16p.13.3 (top SNV: rs56081887, β = 0.63, P = 3 × 10^{-18}) that included RBFOX1 (Figure 1A and B). Ten SNVs within RBFOX1 reached genome-wide significance in meta-analysis; the top 2 are displayed in Table 2. RBFOX1 variants were associated with increased amyloid levels in all data sets except for Hispanic individuals in the A4 Study (Figure 1C); however, the small sample size of the Hispanic cohort and the observation that a higher proportion of amyloid-positive individuals were Hispanic (40%) compared with the African American cohort (16%) precluded firm conclusions. All genome-wide significant SNVs in RBFOX1 were in moderate to high linkage disequilibrium (non-Hispanic white r2 all >0.84; African American r2 all >0.53). Results for all variants with P < 19 × 10^{-8} are presented in eTable 3 in the Supplement. The corresponding QQ-plot is presented in eFigure 3 in the Supplement. There was no compelling evidence for an interaction with APOE e4. Results were consistent when applying the alternative harmonization algorithm.

To validate and augment genetic findings, we analyzed RNA sequencing data from the prefrontal cortex in 600 individuals from the ROS/MAP study (Table 3). Lower levels of RBFOX1 messenger RNA (mRNA) in prefrontal cortex were assoc...
associated with a higher amyloid β burden ($\beta = -0.008, P = .002$) (eFigure 4 in the Supplement). Associations remained significant when covarying for differences in cell type composition across samples (eTable 4 in the Supplement). Lower RBFOX1 mRNA levels were also associated with poorer global cognitive performance at the final visit before death ($\beta = 0.007,$
**Discussion**

The goal of this investigation was to examine the genetic basis of brain amyloidosis in preclinical AD. Using a collection of 6 publicly available data sets in a meta-analysis, we replicated the previously reported association between APOE and brain amyloidosis. In addition, we identified a novel locus on chromosome 16p13.3, **RBFOX1**, which encodes ataxin-2 binding protein, an RNA-binding protein. In support of the genetic findings reported herein, evidence for an association between variants in the **RBFOX1** locus and AD were observed in an African American GWAS of AD (rs79337509, \(P = 5.3 \times 10^{-5}\)) (B. Kunkle, PhD, written communication, September 19, 2019), in a family-based study,\(^37 in a study of cerebral glucose metabolism in ADNI.\(^38 in a family-based study,\(^37 in a study of cerebral glucose metabolism in ADNI.\(^38

Previous studies have used amyloid PET imaging to investigate the genetic basis of brain amyloidosis. A meta-analysis of 3 PET-PiB GWAS (n = 983) showed an association with APOE but no other genome-wide significant loci.\(^8 In contrast, using 18F-florbetapir PET imaging within the ADNI cohort, 2 GWAS studies by Ramanan et al.\(^10,11 reported associations between brain amyloidosis and APOE and 2 other loci in a cross-sectional and longitudinal analysis, respectively: **BCHE** (butyrylcholinesterase) and **IL1RAP** (interleukin-1 receptor accessory protein). Although we observed an association for the **BCHE** SNV (rs509208, \(P = .007\)), the association was solely driven by the ADNI cohort. Therefore, neither previous locus was detected in the present study. The small sample size of previous studies likely limited the ability to detect the association with **RBFOX1**.

**RBFOX1** encodes an RNA-binding protein expressed in muscle, heart, and neurons and is a member of the evolutionarily conserved Fox-1 family of RNA-binding proteins that bind to ataxin-2 and regulate alternative splicing.\(^39 In addition, mammalian RBFOX1 is present in the cytoplasm where it binds to 3 prime untranslated regions of multiple mRNAs, regulating their stability.\(^39 RBFOX1 is a highly conserved protein that can regulate splicing and transcriptional networks in human neuronal development, particularly in neuronal migration and synapse network formation within the cerebral cortex.\(^40,41 In addition to a potential role as the binding protein for ataxin-2 in spinocerebellar ataxia type 2, deletions and other structural variants in the **RBFOX1** gene increase the risk of generalized epilepsy, intellectual disability, autism spectrum disorder, and developmental disorders associated with aggression.\(^42,44

While the exact mechanisms relating dysfunctional human **RBFOX1** proteins with various neuropsychiatric disorders are not fully understood, there is evidence for multiple possible molecular causal pathways. Downregulation of **RBFOX1** leads to destabilization of both nuclear and cytoplasmic mRNAs encoding for synaptic transmission proteins and loss of synaptic function in AD.\(^45,46 RBFOX1 may regulate al-
alternative splicing of APP, which may be particularly relevant to the amyloid associations observed in the present analysis. Alternatively, downregulation of RBFOX1 in AD may directly affect the stability and abundance of mRNAs that encode synaptic transmission proteins. Furthermore, because FOX1 and ataxin-2 are also present in the trans-Golgi network, a trafficking or recycling mechanism might be implicated. Clearly, additional experimental work will be needed to clarify the potential role of RBFOX1 in brain amyloidosis and AD dementia.

We also observed associations between variants in the APOE region and brain amyloidosis, consistent with previous reports leveraging autopsy measures of neuropathologic characteristics, cerebrospinal fluid biomarkers of amyloidosis, and PET biomarkers of amyloidosis. The locus surrounding APOE, chromosome 19q13.32, includes a number of potential genes, such as TOMM40, APOC1, and PVRL2 (eFigure 2 in the Supplement), but conditional analyses indicated that the genetic association was driven by APOE. APOE is thought to relate to AD through an amyloid clearance pathway, with APOE ε4 associated with earlier deposition of amyloid even during preclinical stages of disease.

**Strengths and Limitations**

The strengths of this study include the large sample size, the number of asymptomatic individuals allowing a focus on preclinical disease, and comprehensive validation analyses at the RNA and protein level. Study limitations include clinical heterogeneity across studies, overrepresentation of non-Hispanic white women with high levels of education, and our reliance on harmonized data acquired on different scanners and processed in different ways. Although we limited these factors statistically when possible, residual confounding cannot be ruled out.

**Conclusions**

To our knowledge, this is the largest GWAS of PET amyloid imaging; we report a novel genetic risk locus for brain amyloidosis within RBFOX1. Additional evidence at the transcript and protein level may further implicate RBFOX1 as a novel genetic risk locus for brain amyloidosis and a candidate for early progression in AD.
Association Between Common Variants in APOE and Brain Amyloidosis in Alzheimer Disease

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**Accession, analysis, or interpretation of data:** Raghavan, Dumitrescu, Mormino, Mahoney, Lee, Gao, Bilgel, Engelman, Saykin, Whelan, Jagust, Albert, S. C. Johnson, Yang, K. Johnson, Aisen, Resnick, Sperling, De Jager, Schneider, Bennett, Schrag, Vardarajan, Homan, Mayeux.

**Original Investigation Research**

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Association Between Common Variants in APOE4 and Brain Amyloidosis in Alzheimer Disease

Original Investigation Research

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