Relation of genomic variants for Alzheimer disease dementia to common neuropathologies

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ABSTRACT

Objective: To investigate the associations of previously reported Alzheimer disease (AD) dementia genomic variants with common neuropathologies.

Methods: This is a postmortem study including 1,017 autopsied participants from 2 clinicopathologic cohorts. Analyses focused on 22 genomic variants associated with AD dementia in large-scale case-control genome-wide association study (GWAS) meta-analyses. The neuropathologic traits of interest were a pathologic diagnosis of AD according to NIA-Reagan criteria, macroscopic and microscopic infarcts, Lewy bodies (LB), and hippocampal sclerosis. For each variant, multiple logistic regression was used to investigate its association with neuropathologic traits, adjusting for age, sex, and subpopulation structure. We also conducted power analyses to estimate the sample sizes required to detect genome-wide significance ($p < 5 \times 10^{-8}$) for pathologic AD for all variants.

Results: APOE ϵ 4 allele was associated with greater odds of pathologic AD (odds ratio [OR] 3.82, 95% confidence interval [CI] 2.67–5.46, $p = 1.9 \times 10^{-13}$), while ϵ 2 allele was associated with lower odds of pathologic AD (OR 0.42, 95% CI 0.30–0.61, $p = 3.1 \times 10^{-6}$). Four additional genomic variants including rs6656401 (*CR1*), rs1476679 (*ZCWPW1*), rs35349669 (*INPP5D*), and rs17125944 (*FERMT2*) had p values less than 0.05. Remarkably, half of the previously reported AD dementia variants are not likely to be detected for association with pathologic AD with a sample size in excess of the largest GWAS meta-analyses of AD dementia.

Conclusions: Many recently discovered genomic variants for AD dementia are not associated with the pathology of AD. Some genomic variants for AD dementia appear to be associated with other common neuropathologies. *Neurology*® 2016;87:489–496

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **GWAS** = genome-wide association studies; **LB** = Lewy bodies; **MAP** = Rush Memory and Aging Project; **NFT** = neurofibrillary tangles; **NIA** = National Institute on Aging; **NP** = neuritic plaques; **OR** = odds ratio; **QC** = quality control; **ROS** = Religious Orders Study; **SNP** = single nucleotide polymorphisms.

Several cohort studies find that Alzheimer disease (AD) pathology frequently coexists with other pathologies such that mixed disease is a common cause of AD dementia.^{1–6} Further, the sum of common neuropathologies only accounts in part for cognitive aging, suggesting that not all neuropathologic indices associated with AD dementia are known.⁷ Together, these findings suggest that some, perhaps many, risk factors for AD dementia are not related to AD pathology. We provide an overall model illustrating that a risk factor for AD should be more strongly associated with pathologic AD than with AD dementia (figure 1). However, we and others have reported that several risk factors for AD dementia are not related to AD pathology.^{8,9}

Genetics plays an important role in AD susceptibility. Mutations in *PSEN1*, *PSEN2*, and *APP* genes and the *APOE* haplotypes are all strongly related to pathologic AD and AD dementia.^{10–16} Recent genome-wide association studies (GWAS) have discovered a number of additional genomic variants associated with AD dementia.^{17–23} However, the extent to which these

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Figure 1 Model illustrates the association of risk factors with neuropathology and AD dementia

Conceptual model shows that a risk factor previously related to AD dementia may be associated with pathologic AD, with other coexisting neuropathologies, or not with any known neuropathology (association with reserve or resilience markers). AD = Alzheimer disease; MCI = mild cognitive impairment.

variants are risk factors for AD pathology, coexisting pathologies, or other neurobiologic indices is unclear.^{24,25}

We examined the associations of known genomic variants related to AD dementia with pathologic AD and other common neuropathologies. We anticipate that as a result of mixed pathology, some genomic variants would be associated with other coexisting neuropathologies, and others not to any known neuropathology. We next performed power calculations to estimate the sample size needed for GWAS discovery of these variants with pathologic AD.

METHODS Participants. Data were obtained from the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), both community-based clinical-pathologic cohort studies of aging and dementia. Participants were free of known dementia at baseline and agreed to annual clinical evaluations and brain donation. ROS enrolls older Catholic priests, nuns, and brothers from across the United States since 1994. MAP enrolls older residents from northeastern Illinois since 1997. The follow-up participation rate exceeds 95% and the autopsy rate exceeds 85%. Detailed information on ROS and MAP design have been published previously.^{26,27}

At the time of these analyses, 1,412 of 3,063 participants enrolled had died, and 1,221 had undergone autopsy (autopsy

rate = 86.5%). Of these, genome-wide genotype data were available on 1,079 participants. We excluded participants with neuropathologic data that had not yet been completed, resulting in a total of 1,017 participants. The average age at death was 88.6 years with SD of 6.5 years; 649 (63.8%) were female; and the average years of education was 16.4 (SD 3.6).

Standard protocol approvals, registrations, and patient consents. The studies were approved by the Institutional Review Board of Rush University Medical Center. All participants gave written informed consent and signed an Anatomic Gift Act for organ donation.

Postmortem procedures. Removal and processing of the brain followed a standard protocol used in all locations. The mean postmortem interval was 8.3 hours (SD 7.4 hours). Neuropathologic evaluations were performed at the Rush Alzheimer's Disease Center, blinded to clinical data, and reviewed by a board-certified neuropathologist.²⁸

Neuritic plaques (NP) and neurofibrillary tangles (NFT) were identified with modified Bielschowsky stain in 6- μ m sections in 5 different regions (entorhinal cortex, hippocampus at CA1, mid-frontal cortex, middle temporal gyrus, and inferior parietal cortex). Each case received a semiquantitative estimate that assessed the burden of NP as recommended by Consortium to Establish a Registry for Alzheimer's Disease and a Braak score that assessed the distribution and severity of NFT pathology.^{29,30} The final postmortem diagnosis of pathologic AD was based on the recommendations of the National Institute on Aging (NIA)–Reagan criteria.³¹ The diagnosis required an intermediate or high likelihood pathologic AD. Lewy bodies (LB) were identified by α -synuclein immunohistochemistry in one or more neocortical

regions (midfrontal, middle temporal, and inferior parietal) together with either midbrain or limbic LB.³² Macroinfarcts were recorded from gross examination of fixed slabs and were confirmed by histology. Microinfarcts were documented with hematoxylin & eosin.³³ Hippocampal sclerosis was assessed in a hemisection of the mid-hippocampus and defined as neuronal loss and gliosis in CA1/subiculum or other sectors.³⁴

Genotyping. DNA from ROS and MAP participants was extracted from peripheral blood mononuclear cells or frozen post-mortem brain tissue. Genotyping was done in 2 phases. The data from the first phase (n = 889) were generated on the Affymetrix Genechip 6.0 platform at either the Broad Institute's Center for Genotyping or the Translational Genomics Research Institute. The data from the second phase (n = 128) were generated on the Illumina HumanOmniExpress at the Children's Hospital of Philadelphia. These 2 sets of data underwent the same quality control (QC) analysis using PLINK software.³⁵ We applied standard QC measures for participants (genotype success rate >95%, genotype-derived sex concordant with reported sex, excess interheterozygosity/intraheterozygosity) and for single nucleotide polymorphisms (SNPs) (Hardy-Weinberg equilibrium $p > 0.001$; minor allele frequency >0.05, genotype call rate >0.95; mishap test $>1 \times 10^{-9}$). Subsequently, EIGENSTRAT³⁶ was used to identify and remove population outliers using default parameters. Imputation was performed using the BEAGLE software (version 3.3.2). We used reference haplotype panels of Northern European ancestry (CEU) from the 1000 Genomes Project (The 1000 Genomes Project Consortium Interim Phase I Haplotypes, 2010–2011 data freeze).

The susceptibility variants interrogated in this study have been reported to have genome-wide significant associations with AD dementia.^{17–23} The variants in *CRI*, *BIN1*, *CD33*, *CLU*, *ABCA7*, *CD2AP*, *PICALM*, *EPHA1*, *MS4A6A*, and *MS4A4A* were reported in earlier GWAS. The variants in *HLA-DRB5*, *PTK2B*, *SORL1*, *SLC24A4*, *DSG2*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELFI*, *FERMT2*, and *CASS4* were identified in the most recent large-scale meta-analysis with a sample size of nearly 75,000.²¹ Detailed information of variants is included in table e-1 on the *Neurology*® Web site at Neurology.org. We replaced rs3764650 (*ABCA7*) with rs3752246 because the original index SNP had poor imputation quality in our data. *APOE* was directly genotyped by sequencing codon 112 and codon 158 of exon 4 of the gene.³⁷

Statistical analysis. We used multiple logistic regression analyses to examine the association of genomic variants with pathologic AD. In these analyses, the pathologic AD diagnosis of intermediate- or high-likelihood AD by NIA Reagan criteria was used as the binary outcome and we modeled the odds of having pathologic AD regardless of the clinical diagnosis. First, we included *APOE* as a positive control, where we confirmed that the presence of any ε4 allele was associated with greater odds of having pathologic AD and the presence of any ε2 allele was associated with lower odds of pathologic AD, as we have reported previously.³⁸ Next, we repeated the analyses to examine each of the other 22 genomic variants separately. Here, the dosage for each variant was used as the main predictor. The dosage was imputed assuming additive inheritance and was in the form of a continuous variable ranging from 0 to 2. Therefore we chose additive models such that the corresponding regression coefficient, after taken exponential, estimates the odds ratio (OR) of pathologic AD for each additional copy of the coded allele. All the models were adjusted for age at death, sex, and the first 3 principal components from EIGENSTRAT in order to minimize potential

confounding due to subpopulation stratification. Similar regression analyses were performed to examine the associations with the presence of other common neuropathologies. A Bonferroni-corrected α level of 0.002 was used for statistical significance throughout the analysis. This threshold was calculated as 0.05 divided by 24, the total number of susceptibility variants. The association analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

We next evaluated the statistical power by estimating the total sample size required to reach genome-wide significance ($p < 5 \times 10^{-8}$) with 80% power in a 2-tailed test. The sample size calculation depends on the case-to-control ratio, frequency of the variant (with respect to the coded allele), baseline disease risk, as well as the estimated effect size. We obtained these parameters based on our data as well as the results from the association analyses. Specifically, the case-to-control ratio was estimated by the ratio of total numbers of cases with pathologic AD diagnosis and those without. The frequency of the coded allele was used to determine the proportions of copies for each variant. The baseline risk of pathologic AD was the estimated probability of AD for a typical woman with mean age 89 years and absence of the coded allele. The effect size was the estimated OR with respect to the coded allele. These post hoc power analyses were performed using the Quanto program (version 1.2.4). We examined the variance of individual variants explained by the model covariates (R^2), which may also influence the sample size estimation.³⁹ In our data, these R^2 were minimal and ranged from 0 to 0.017 with a median of 0.002. Therefore, the estimated sample size will be slightly larger if correcting for the R^2 s but not at a level sufficient to alter our conclusions.

RESULTS Demographic and neuropathologic characteristics for the study participants are shown in table 1. At the time of death, half of the cases (n = 508) had more than one neuropathology, 34.5% (n = 351) had one pathology, and only 15.5% (n = 158) were free of any of these common neuropathologic diagnoses. A total of 368 (37.1%) of the

Table 1 Characteristics of the study participants (n = 1,017)

Variable	Mean (SD) or n (%)
Age at death, y	88.6 (6.5)
Female sex	649 (63.8)
Education, y	16.4 (3.6)
Clinical AD diagnosis upon death	
No impairment	325 (32.2)
Mild cognitive impairment	252 (25.0)
AD	410 (40.7)
Other dementia	21 (2.1)
Pathologic AD	640 (62.9)
Macroscopic infarcts	360 (35.4)
Microinfarcts	291 (28.6)
Lewy bodies	224 (22.0)
Hippocampal sclerosis	82 (8.1)

Abbreviation: AD = Alzheimer disease.

participants had no or low likelihood AD by NIA-Reagan criteria.

Associations of *APOE* with pathologic AD. We first examined the association of *APOE* with pathologic AD. A total of 25.6% of the autopsied cases had the $\epsilon 4$ haplotype. The presence of $\epsilon 4$ haplotype almost quadrupled the odds of having pathologic AD and easily met genome-wide significance (OR 3.82, 95% confidence interval [CI] 2.67–5.46, $p = 1.9 \times 10^{-13}$). Additionally, 15.5% of cases had the $\epsilon 2$ haplotype. The presence of $\epsilon 2$ allele was associated with more than a 50% lower odds of having pathologic AD, although the association did not meet genome-wide significance (OR 0.42, 95% CI 0.30–0.608, $p = 3.1 \times 10^{-6}$). To illustrate the additional power gained with pathologic AD, we compared the results of the associations with pathologic AD to that of AD dementia. Here, the

presence of $\epsilon 4$ haplotype triples the odds of having AD dementia (OR 3.09, 95% CI 2.26–4.25, $p = 2.5 \times 10^{-12}$), and the presence of $\epsilon 2$ haplotype was associated with about a 40% lower odds of having AD dementia (OR 0.63, 95% CI 0.43–0.92, $p = 0.017$). In both cases, the strength of the association and the p value are markedly attenuated relative to pathologic AD, as previously reported.³⁸ This supports our hypothesis that genomic variants for AD dementia that are also genomic variants for pathologic AD should be found with smaller samples sizes and that the absence of such a finding suggests that the variant may be associated with another pathology or other factors associated with AD dementia.

Associations of other genomic variants with pathologic AD. Next, we examined the association of 22 additional AD dementia genomic variants with the odds

Table 2 Association of genomic variants with pathologic AD

SNP	Gene	Coded allele	Pathologic AD (current study)			AD dementia studies	
			OR	95% CI	p	OR	95% CI
rs6656401	CR1	G	0.618	0.475–0.803	<0.001	0.85 ^{a,b}	0.82–0.88 ^{a,b}
rs744373	BIN1	A	1.051	0.834–1.324	0.68	0.85 ^{b,c}	0.83–0.89 ^{b,c}
rs35349669	INPP5D	T	1.314	1.069–1.616	0.01	1.08 ^a	1.05–1.11 ^a
rs190982	MEF2C	G	0.842	0.688–1.031	0.10	0.93 ^a	0.90–0.95 ^a
rs9271192	HLA-DRB5	A	0.960	0.781–1.180	0.70	0.90 ^{a,b}	0.87–0.93 ^{a,b}
rs9349407	CD2AP	C	1.029	0.835–1.268	0.79	1.11 ^d	1.07–1.15 ^d
rs1476679	ZCWPW1	T	1.367	1.117–1.673	0.002	1.10 ^a	1.06–1.12 ^a
rs11767557	EPHA1	T	1.044	0.824–1.323	0.72	1.11 ^{b,d}	1.08–1.16 ^{b,d}
rs2718058	NME8	A	0.873	0.713–1.068	0.19	1.08 ^{a,b}	1.05–1.11 ^{a,b}
rs28834970	PTK2B	C	0.941	0.776–1.141	0.53	1.10 ^a	1.08–1.13 ^a
rs11136000	CLU	T	1.015	0.836–1.232	0.88	0.86 ^e	0.82–0.90 ^e
rs11218343	SORL1	T	1.416	0.856–2.342	0.18	1.30 ^{a,b}	1.22–1.39 ^{a,b}
rs10838725	CELF1	T	0.970	0.793–1.187	0.77	0.93 ^{a,b}	0.90–0.95 ^{a,b}
rs610932	MS4A6A	T	1.011	0.839–1.219	0.91	0.91 ^c	0.88–0.93 ^c
rs4938933	MS4A4A	T	0.989	0.819–1.193	0.91	1.12 ^{b,d}	1.09–1.15 ^{b,d}
rs3851179	PICALM	T	0.896	0.737–1.089	0.27	0.87 ^e	0.84–0.91 ^e
rs17125944	FERMT2	T	0.709	0.503–1.000	0.05	0.88 ^{a,b}	0.84–0.92 ^{a,b}
rs10498633	SLC24A4	G	1.089	0.875–1.356	0.44	1.10 ^{a,b}	1.06–1.14 ^{a,b}
rs8093731	DSG2	C	2.168	0.874–5.375	0.09	1.37 ^{a,b}	1.16–1.61 ^{a,b}
rs3752246	ABCA7	C	1.025	0.782–1.344	0.86	—	—
rs3865444	CD33	C	1.204	0.986–1.470	0.07	1.06 ^{a,b}	1.09–1.04 ^{a,b}
rs7274581	CASS4	T	0.967	0.684–1.367	0.85	1.14 ^{a,b}	1.09–1.19 ^{a,b}

Abbreviations: AD = Alzheimer disease; CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.

^aEffect sizes (OR and 95% CI) obtained from the largest genome-wide association study meta-analysis of AD dementia.²¹

^bValues of OR and 95% CI were flipped from the original reference to match with the coded alleles in our analysis.

^cEffect sizes obtained from reference 19, table 1.

^dEffect sizes obtained from reference 22, table 2.

^eEffect sizes obtained from reference 17, table 1.

of having pathologic AD (table 2). We found 1 variant in the *CR1* gene where the G allele of rs6656401 was associated with a lower odds of pathologic AD (OR 0.62, $p = 0.0003$), as previously reported.^{24,25} In addition, the associations of 3 other variants with pathologic AD reached $p < 0.05$. Specifically, the T allele of rs1476679 in the *ZCWPW1* gene was associated with greater odds of pathologic AD (OR 1.37, $p = 0.002$), as previously reported.²⁴ The minor allele (T) from rs35349669 of the *INPP5D* gene was associated with a greater odds of pathologic AD (OR 1.31, $p = 0.009$) and the major allele (T) of rs17125944 in the *FERMT2* gene was associated with a lower odds of pathologic AD (OR 0.71, $p = 0.050$). The directions of these associations are consistent with the findings from the recent GWAS analysis on AD dementia. By contrast, the remaining 18 previously reported genomic variants for AD dementia had $ps > 0.05$ with our sample size.

Associations of genomic variants with other neuropathologies. We repeated the analysis to examine potential associations of these genomic variants with presence of cerebrovascular infarcts, LB, and hippocampal sclerosis (table e-1). The results are illustrated in figure 2. While none of these associations survived stringent Bonferroni correction, we found some evidence that a few variants may be associated with non-AD neuropathologies. Briefly, the C allele of rs3865444 in the *CD33* gene was associated with

lower odds of having macroscopic infarcts (OR 0.809, $p = 0.037$) and the T allele of rs10838725 in the *CELFI* gene was associated with greater odds of having microinfarcts (OR 1.371, $p = 0.005$). Interestingly, the same variant in *CELFI* was associated with lower odds of LB (OR 0.764, $p = 0.019$). The presence of *APOE* $\epsilon 4$ was associated with greater odds for having hippocampal sclerosis (OR 2.396, $p = 0.0006$), as was the T allele of rs11767557 in the *EPHA1* gene (OR 1.728, $p = 0.029$).

Sample size estimation to reach genome-wide associations. We next estimated the sample sizes needed for all of the genomic variants to achieve genome-wide significance with pathologic AD (figure 3, truncated to $n = 75,000$). Given the model outlined in figure 1, we expect that variants associated with AD dementia that are also associated with pathologic AD should be identifiable with a sample size less than 75,000, the size of the most recent AD dementia GWAS. We illustrate our calculation by using the *CR1* variant (rs6656401). Based on the percentage of pathologic AD in our sample (62.9%), we assume that for every 100 AD cases there are 60 controls. The coded allele (G) had an estimated allele frequency of 0.81. According to the logistic regression result, the estimated probability of having pathologic AD for a typical woman who died at age 89 and was rs6656401^{AA} homozygote was 0.81. Our power calculation shows that, at α level of

Figure 2 Association of genomic variants with non-AD pathologies

Plot shows the association of genomic variants with non-AD pathologies (horizontal line marks $p < 0.05$). Multiple logistic regression analysis adjusted for age at death, sex, and the first 3 principal components from EIGENSTRAT. The y-axis shows the $-\log_{10}$ of the p values, such that the higher the value, the more significant the association. AD = Alzheimer disease.

Figure 3 Sample size calculation for association of genomic variants with pathologic AD (truncated at $n = 75,000$)

Plot shows sample size estimation for association of genomic variants with pathologic AD (truncated at $n = 75,000$). Sample size required to reach genome-wide significance ($p < 5 \times 10^{-8}$) with 80% power. The sample size calculation depends on the case-to-control ratio, frequency of the variant (with respect to the coded allele), baseline disease risk, as well as the effect size (estimated from logistic regression models adjusted for age at death, sex, and the first 3 principal components from EIGENSTRAT). The case-to-control ratio was estimated by the ratio of total numbers of participants with pathologic AD diagnosis (considered as cases) and those without (considered as controls). The baseline risk of pathologic AD was the estimated probability of AD for a typical woman with mean age 89 years and absence of the coded allele. Colors represent different chromosomes. AD = Alzheimer disease.

5×10^{-8} and 80% power, we need a minimum of 2,614 participants to detect an additive effect as large as 0.62, the OR obtained from our regression model.

We repeated this post hoc power analysis for the remaining variants (table e-2). The results are illustrated in figure 3. As expected, the only variant detectable with our current sample size is the *APOE* $\epsilon 4$. Four variants, including *APOE* $\epsilon 2$, *CR1*, *INPP5D*, and *ZCWPW1*, could be detected with a sample size of 5,000 or less. Overall, besides *APOE*, 11 of the 22 interrogated variants were detectable with sample sizes up to 75,000. The results suggest that half of the previously reported genomic variants associated with AD dementia are not likely to be genomic variants for pathologic AD. Figure e-1 illustrates how many genomic variants are detectable with sample sizes 2 $\times$, 3 $\times$, 4 $\times$ or more the size of the largest GWAS for AD dementia (truncated at $n = 1,000,000$).

DISCUSSION We examined the relation of known genomic variants for AD dementia with pathologic

AD. Besides *APOE*, all other associations were weak and only 1 variant was significant with our sample size of just over 1,000 after correcting for multiple testing. We found evidence that some of these variants might be associated with other common pathologies. We next estimated the sample size required to detect genome-wide significant associations of previously reported AD dementia genomic variants with AD pathology. Our results suggest that, for half of these AD susceptibility variants, it would require a sample size larger than 75,000 to find associations with pathologic AD. We conclude that these variants are very unlikely to be associated with AD pathology.

Clinical-pathologic correlation studies performed by our group and others have consistently demonstrated that AD dementia is often a result of mixed pathology showing not only NPs and NFTs but also non-AD pathologic findings such as macroinfarcts and microinfarcts and LB disease.¹⁻⁶ Thus, it is likely that some genomic risk factors for AD dementia are related to other neuropathologies that coexist with

AD pathology. In this study, we demonstrated novel associations of genomic variants to non-AD pathologic traits. The associations of *CELF1* with both microvascular disease and LB pathology were not previously described. Interestingly, *CELF1* regulates pre-mRNA alternative splicing and experimental studies show that this gene may be associated with myotonic dystrophy type 1 via interactions with the *DMPK* gene.⁴⁰ Similarly, the association of *CD33* with macroscopic infarcts was not previously described by GWAS for stroke or cerebrovascular disease.

While it is expected that some genomic variants for AD dementia will not be associated with pathologic AD, we provide evidence by illustrating that half of the known genomic variants for AD dementia would require a much larger sample size to demonstrate associations with pathologic AD. Our study used *APOE* haplotypes as positive controls and demonstrated that when a gene is directly involved with pathology, the sample size needed to demonstrate an association with AD pathology is smaller compared to the sample needed for AD dementia.

A recent GWAS meta-analysis for neuropathologic AD and related dementias that includes nearly 5,000 participants showed that only 12 of 21 susceptibility variants for clinically defined AD dementia were associated with clinicopathologic phenotypes.²⁴ The results share some similarities with ours. However, in our study, of these 12 variants, only 6 had estimated sample size lower than 75,000 participants to demonstrate association with AD pathology. *BIN1*, *CLU*, *MS4A6A*, *ABCA7*, *PTK2B*, and *CASS4* would require more participants to be associated with pathologic AD. These inconsistencies are likely related to methodologic differences. First, in our study the endpoint is exclusively pathologic AD without regard to clinical status, while the meta-analysis used a combination of clinical and pathologic features to determine AD case and control status, and excluded persons with mild cognitive impairment and participants who show AD pathology but do not fulfill criteria for dementia. Second, our study was of community-based individuals, whereas the meta-analysis consisted primarily of clinic-based cases. Finally, our study participants were older, with an average age at death of 88.6 years. The meta-analysis had an average age at death of 82.1 years. Some evidence suggests that the association of genomic variants with AD dementia diminishes with age.⁴¹

This study has some limitations. We used the NIA-Reagan criteria for pathologic diagnosis of AD and not the most recent NIA-AA criteria. Requiring amyloid deposits or examining specific subsets of AD pathology such as NPs could modify the results as genomic variants may show marked differences in

association with specific AD pathologic features. Second, we did not investigate associations of AD dementia genomic variants to other neuropathologic indices such as the deposits of TDP-43 and the presence of cerebral amyloid angiopathy. Third, the power calculation is dependent on the effect sizes estimated using our current data. The estimates for many variants are so small that they may fluctuate, which consequently may yield imprecise sample size estimation. Replication of these results from other studies is warranted.

The main strengths of this study are the sample size of more than 1,000 participants from 2 community-based cohort studies with extensive and detailed pathologic examination, the high follow-up rate, and the high autopsy rate further reducing bias.

AUTHOR CONTRIBUTIONS

Dr. Farfel, Dr. Yu, and Dr. Bennett were responsible for study design. Dr. Farfel, Dr. Yu, and Dr. Bennett contributed to manuscript writing. Dr. Farfel, Dr. Yu, Dr. Buchman, Dr. Schneider, Dr. De Jager, and Dr. Bennett were responsible for data analysis or interpretation. Dr. Schneider was responsible for neuropathologic readings. All authors reviewed the manuscript.

ACKNOWLEDGMENT

The authors thank the staff of Rush Alzheimer's Disease Center.

STUDY FUNDING

Supported by National Institute of Aging grants P30AG10161, RF1AG15819, R01AG17917, R01AG42210, and U01AG46152.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 31, 2015. Accepted in final form March 25, 2016.

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