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# Genetic Susceptibility for Alzheimer's Disease Neuritic Plaque Pathology

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ONLINE-ONLY MATERIAL

Online-only material, consisting of 9 eTables, 3 eFigures, eMethods, additional Acknowledgements and References, is available for download:

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## Abstract

**Objective—**To investigate whether Alzheimer's disease (AD) susceptibility loci from genome-wide association studies (GWAS) impact neuritic plaque pathology and to additionally identify novel risk loci for this trait.

**Design—**Candidate analysis of single nucleotide polymorphisms (SNPs) and GWAS in a joint clinicopathologic cohort study, followed by targeted validation in independent neuroimaging cohorts.

**Participants and Setting—**725 deceased subjects from the Religious Orders and Rush Memory and Aging Project, two prospective, community-based studies of aging; the validation neuroimaging cohort consisted of 114 subjects from multiple clinical and research centers.

**Main Outcome Measures—**A quantitative measure of neuritic plaque pathologic burden, based on assessments of silver-stained tissue averaged from multiple brain regions. Validation based on β-amyloid load by immunocytochemistry, and replication with fibrillar β-amyloid Positron Emission Tomography (PET) imaging with Pittsburgh Compound B or florbetapir.

**Results—**Besides the previously reported *APOE* and *CR1* loci, we find that *ABCA7* (rs3764650, P=0.02) and *CD2AP* (rs9349407, P=0.03) AD susceptibility loci are associated with neuritic plaque burden. In addition, among the top results of our GWAS, we discovered a novel variant near the *amyloid precursor protein* gene (*APP*, rs2829887) that is associated with neuritic plaques ($P=3.3\times10^{-6}$). This polymorphism was associated with postmortem β-amyloid load, as well as fibrillar β-amyloid in two independent cohorts of adults with normal cognition.

**Conclusion—**These findings enhance understanding of AD risk factors by relating validated susceptibility alleles to increased neuritic plaque pathology and implicate common genetic variation at the *APP* locus in the earliest, pre-symptomatic stages of AD.


Alzheimer's disease (AD) is the most common cause of age-related cognitive impairment and dementia. At autopsy, AD neuritic plaque pathology consists of extracellular aggregates of the amyloid-β (Aβ) peptide, which is derived from proteolysis of the Amyloid Precursor Protein (APP). Rare gene mutations in *APP* along with *presenilin-1* (*PSEN1*) and *presenilin-2* (*PSEN2*), encoding components of the gamma secretase enzyme involved in APP processing, cause early-onset familial AD[1]. Further, an uncommon *APP* coding variant (frequency < 1%) was recently discovered to be protective against AD in the Icelandic population[2]. However, common genetic variation at these loci has not been definitively linked to the later onset form of disease that accounts for the majority of AD in the population[3–6]. Common polymorphisms in the *apolipoprotein E* (*APOE*) gene are well established risk factors for late-onset AD, and recent investigations suggest that *APOE* participates in the aggregation and/or clearance of Aβ within the central nervous system[7]. Genome-wide association studies (GWAS) have identified several additional AD susceptibility loci[8–12], and emerging evidence suggests that alterations in Aβ dynamics may explain some of these associations. One susceptibility locus, *clusterin* (*CLU*), encodes an apolipoprotein that binds Aβ, similar to APOE, and these proteins may jointly regulate Aβ accumulation[13]. In addition, we previously reported that the effects of both *APOE* and *complement receptor 1* (*CR1*) on memory decline are mediated in part by an association with neuritic plaque burden[14,15], and the complement pathway has also been implicated in brain Aβ deposition in murine models[16]. Lastly, the *phosphatidylinositol binding clathrin assembly protein* (*PICALM*) has been shown to modulate Aβ toxicity in a yeast model system and in rat cortical neuron culture[17]. These studies reinforce the broader hypothesis that genetic networks impacting Aβ accumulation and/or aggregation in the brain may be important determinants of AD susceptibility. However, it is possible that not all AD risk variants will similarly affect the development of neuritic plaque pathology, as many other

cellular processes likely impinge on the clinical manifestation of disease. Notably, genome-wide meta-analyses have identified a number of additional susceptibility loci with still undefined roles in AD pathogenesis[9,10].

Although gene discovery in AD has largely focused on clinically diagnosed disease in case-control studies, it is now recognized that the AD pathophysiological process, including Aβ deposition in the brain, begins years before the development of dementia. In prospective, community-based autopsy studies, about 90% of persons with clinically diagnosed AD have the disease proven at autopsy[18,19]. However, AD is also the predominant brain lesion accounting for mild cognitive impairment (MCI), now recognized as a prodromal form of AD. Further, in older autopsy cohorts of subjects with normal cognition, a substantial minority of brains meet pathologic diagnostic criteria for AD[18,19]. More recently, PET imaging ligands, including Pittsburgh Compound B (PiB), have been developed to detect fibrillar β-amyloid pathology in living subjects[20–22]. Similar to postmortem studies, positive PiB imaging is detected in a substantial minority of subjects with normal cognition, and this proportion increases with age. The realization that β-amyloid pathology may represent the earliest changes of AD informed the recent revision of diagnostic criteria, including the development of research guidelines for preclinical AD for individuals with biomarker changes, such as increased PiB amyloid, but with preserved cognition[23]. Many genetic and environmental risk factors might be expected to accelerate preclinical AD brain changes, and ultimately promote susceptibility for clinical disease. Indeed, the *APOE ε4* risk allele is associated with increased fibrillar β-amyloid deposition, based on PiB-PET, as well concomitant changes in cerebrospinal fluid Aβ, even in individuals with normal cognition[22,24].

The presence of substantial amounts of AD pathology in older subjects with little or no cognitive impairment might be expected to degrade the power of AD case-control GWAS to discover variants impacting the earliest brain pathologic correlates of AD. We and others have promoted using disease endophenotypes, including AD pathology, as a complementary approach[25,26]. Here, extending our prior work on *APOE, CR1, CLU*, and *PICALM*, we investigate whether newly reported AD risk alleles[9,10,12] are also associated with a quantitative measure of neuritic plaque burden in a large autopsy cohort. We identify associations at two other loci, *CD2-associated protein* (*CD2AP*) and the *ATP-binding cassette, sub-family A, member 7* (*ABCA7*). We then perform a GWAS to discover additional susceptibility loci for neuritic plaque pathology. Among our top results, we discover a variant near the *APP* locus that is also associated with fibrillar β-amyloid in two independent cohorts of cognitively normal subjects with PET imaging. Our findings relate validated AD susceptibility alleles to the development of AD neuritic plaques, and begin to reveal the genetic architecture underlying the earliest known brain pathologic changes of AD.

## METHODS

Additional detailed methods and references are provided in the online-only material.

### Subjects

Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP) participants were free of known dementia at enrollment, agreed to annual clinical evaluations, and signed an informed consent and Anatomic Gift Act donating their brains at death[27,28]. The studies were approved by the Institutional Review Board of Rush University Medical Center. For analyses of candidate SNPs, the joint ROS/MAP cohort included 725 subjects (408 ROS and 317 MAP) with genotyping and completed autopsies. The GWAS was based on a previously published subset of 651 subjects[29]. For replication, we relied on two additional study

cohorts with brain PET imaging of fibrillar β-amyloid (eTable 5): the Arizona *APOE* cohort (n=56) and Alzheimer's Disease Neuroimaging Initiative (ADNI) (n=58). The Arizona *APOE* cohort is a longitudinal study of cognitively normal subjects including *APOE ε4* homozygotes, heterozygotes, and non-carriers, including PiB-PET imaging[22]. The cognitively normal sub-sample of ADNI (www.adni-info.org), included subjects with genotyping and PET imaging using the fluorbetapir ligand, Avid-45 (AV-45).

### Clinical and Postmortem Evaluation

The clinical diagnoses of dementia and AD were made following NINCDS-ADRDA recommendations[30]. Level of cognition was based on 17 cognitive tests performed at annual evaluations proximate to death[14]. Modified Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in tissue sections from the midfrontal, middle temporal, inferior parietal, entorhinal cortices, and the hippocampal CA1 sector. As in prior work[14,25], a quantitative composite score for neuritic plaque pathologic burden was created by dividing the raw counts in each region by the population standard deviation of the region specific counts, and then averaging the scaled counts over the 5 brain regions to create a single standardized summary measure. β-amyloid load was additionally measured based on anti-Aβ immunohistochemistry. Neuropathologic diagnosis of AD was made based on intermediate or high likelihood of AD by NIA-Reagan criteria[31].

### Statistical Analyses

Genome-wide genotyping, quality-control procedures, and imputation have been previously reported[29]. Dosage values for each of 2,465,581 imputed SNPs were coded additively in terms of the minor allele. Linear regression was used to relate each SNP to the square-root transformed summary measure of neuritic plaques, adjusting for age at death, study membership (ROS vs. MAP) and the first 3 principal components from our population structure analysis. In the candidate analyses of AD SNPs, $p < 0.05$ was considered significant. For the genome-wide association analyses, significance was set at a $p < 5\times10^{-8}$, and a $p < 1\times10^{-4}$ was considered suggestive evidence of association. Secondary analyses included adjustment for cognitive status proximate to death (eTable 7) and *APOE ε4* genotype (0, 1, or 2 copies) (eTable 3, eTable 8), and we also tested for associations with AD susceptibility (eTable 9). Analyses of SNP effects on global cognitive and episodic memory decline and incident AD were performed as in prior work[14].

For the analysis of SNP associations with β-amyloid PET measurements, cerebral-to-cerebellar florbetapir standard uptake value ratio (SUVR) images were generated in cognitively normal ADNI subjects and PiB SUVR images were generated in Arizona *APOE* cohort subjects. Statistical brain maps reflect the additive association of the minor allele of interest and SUVR measurements in the aggregate subject group, adjusting for age, *APOE ε4* allele dose, and cohort membership. A Monte-Carlo simulation (MCS) procedure, involving 1,000 iterations, was used to demonstrate that the number of voxels with increased SUVRs ($p < 0.05$) was significantly increased in the implicated direction. We also performed region of interest analysis on individual PET images, based on previously defined mean cortical and whole-cerebellar templates.

## RESULTS

We studied 725 deceased subjects for which complete neuropathological evaluation and genotype data were available (eTable 1). Proximate to death, 42.2% had clinically diagnosed AD, 24.6% had MCI, and 31.7% retained normal cognition. The remaining subjects (n=21) had dementia due to other causes, as they did not meet clinical criteria for AD[30]. On post-mortem examination, 62.5% met NIA-Reagan pathologic criteria for AD, consistent with the

advanced age of this cohort (mean=88.1 years). We used a quantitative measure of neuritic plaque burden to assess genetic susceptibility for AD neuritic plaque pathology.

We first evaluated published AD susceptibility loci from recent clinical case-control genome-wide association studies[9,10]. As previously reported[14], the *CR1* locus was associated with neuritic plaque burden (rs6701713, p=0.029), and we additionally found evidence that variants in *ABCA7* (rs3764650, p=0.030) and *CD2AP* (rs9349407, p=0.029) were associated with neuritic plaque pathology (Table 1). For all three SNPs, AD risk alleles showed consistent direction of effects for increased neuropathology. By contrast, other recently validated susceptibility loci, including *CLU, PICALM, BIN1, MS4A, CD33*, and *EPHA1*, were not associated with neuritic plaques in this cohort. These results suggest that, at least for 3 out of the 9 loci discovered in GWAS, effects on neuritic plaque pathology may mediate the association of these polymorphisms with clinical AD risk.

To identify novel variants associated with neuritic plaque burden, we performed a genome-wide scan in ROS and MAP using the quantitative pathologic trait. The genomic inflation factor did not reveal any evidence of systematic inflation in our test statistic ($\lambda_{GC}$=1.009, eFigure 1). The only genome-wide significant SNP associations ($p < 5\times10^{-8}$) were detected on chromosome 19 near *APOE* (rs4420638, $p=1.5\times10^{-17}$). The top, independent loci ($p < 10^{-5}$) associated with neuritic plaque burden are shown in Table 2 (See eTable 2 for detailed results). Among our strongest associations, we identified variants near candidate genes with roles in inflammation and immunity, including *prostaglandin-endoperoxide synthase 1* (*PTGS1*, rs12551233, $p=4.8\times10^{-7}$) and the human leukocyte antigen (HLA) class II region of the Major Histocompatibility Complex (MHC) (*HLA-DQA2*, rs3892710, $p=2.3\times10^{-6}$). Notably, we also identify a common chromosome 21 SNP (rs2829887, Freq=0.43, $p=3.3\times10^{-6}$) which is located 149.2 kb from the 3'-end of the *APP* gene (Figure 1) and is found in an intron of the *ATP5J* gene. In addition, our GWAS detected evidence of associations at *KCNIP4* (rs6817475, $p=3.8\times10^{-7}$) and *NMNAT3* (rs4564921, $p=6.1\times10^{-6}$), two additional genes previously implicated in AD[32,33].

Given the proximity of rs2829887 to *APP*, a gene known to be associated with familial AD, we investigated this locus in more detail (Table 3). Based on the absence of a statistical interaction (p=0.77), the effect of rs2829887 did not vary by cohort, demonstrating consistent associations with neuritic plaque burden in both the ROS ($\beta=-0.124$, $p=4.0\times10^{-4}$) and the smaller MAP sample ($\beta=-0.106$, p=0.014). Further, the *APP* locus variant was also strongly associated with postmortem Aβ load ($p=9.5\times10^{-5}$), which is measured in the same subjects using anti-Aβ immunohistochemistry. The associations between rs2829887 and these neuropathologic traits were robust to adjustment for *APOE* genotype (eTable 3). While rare mutations in *presenilin-1* and *presenilin-2* are also associated with early-onset familial AD[1]; however, common genetic variation at either locus (+/− 500kb) was not found in association with amyloid neuritic plaques in our GWAS data ($p > 0.01$).

There are few existing prospective, community-based cohorts such as ROS/MAP with large numbers of brain autopsies and assessments of quantitative neuropathology and genome-wide data with which to replicate our findings. To further validate our results, we leveraged data from subjects with PET imaging of fibrillar β-amyloid (eTable 5). The Arizona *APOE* cohort consists of 56 subjects with normal cognition and assessment with PiB-PET. Subjects carrying the *APOE ε4* risk allele were previously shown to have increased levels of PiB amyloid, consistent with early AD pathologic changes in this genetically susceptible subgroup[22]. Compared to ROS/MAP, the Arizona *APOE* cohort is significantly younger (mean age=64.6), and subjects uniformly have preserved cognition (mean MMSE=29.7). We additionally used data from 58 cognitively normal older adults (mean age=80.4; mean MMSE=29.4) from the ADNI cohort with florbetapir-PET. In a voxel-based, joint analysis

of the Arizona *APOE* and ADNI cohorts, rs2829887 was associated with extensive fibrillar β-amyloid deposition across numerous brain regions, including the cingulate, frontal, temporal, and parietal cortices ($p < 0.005$, Figure 2). These results were robust to adjustment for age and *APOE ε4* genotype. Using a Monte-Carlo simulation to address multiple regional comparisons, we found 64,743 voxels in which rs2829887 dosage was associated with increased fibrillar β-amyloid compared to 1,313 voxels--in smaller clusters--in which this allele was associated with decreased signal ($p < 0.001$). In a complementary analysis based on pre-defined brain regions of interest, rs2829887 was associated with level of mean cortical fibrillar β-amyloid (p=0.028; see eTable 6 for full results). However, the direction of the association between rs2829887 and fibrillar β-amyloid in the PET cohorts was opposite to the association with neuritic plaque pathology in ROS/MAP. Specifically, the minor allele, $rs2829887^{T}$ ($Freq_{ROS/MAP}$=0.43, $Freq_{AZ+ADNI}$=0.45) was associated with reduced postmortem neuritic plaques in ROS/MAP but increased PiB/florbetapir standard uptake value ratios (SUVRs) in the Arizona *APOE* and ADNI cohorts. Separate analyses of the independent ADNI and Arizona *APOE* cohorts revealed associations between $rs2829887^{T}$ and increased β-amyloid across numerous brain regions ($p < 0.005$, eFigure 2), consistent with the joint analysis.

Subjects enrolled in ROS and MAP also receive annual assessment with a comprehensive neuropsychiatric battery, allowing genetic analyses of cognitive decline, as in prior studies[14]. We found that many, but not all, of the SNPs discovered for associations with neuritic plaque pathology also showed associations with longitudinal decline in global cognition and episodic memory (eTable 4); pathology-increasing alleles showed consistent direction-of-effects on the cognitive outcomes, accelerating rate of decline. We further developed an aggregate genetic risk score model incorporating the top 53 independently associated SNPs ($p<10^{-4}$), from the neuritic plaque GWAS. This model was strongly associated with global cognitive ($p=1.1\times10^{-16}$) and episodic memory decline ($p=7.9\times10^{-21}$), and remained highly significant after excluding *APOE* SNPs from the model ($p_{global}=4.8\times10^{-14}$, $p_{memory}=1.2\times10^{-17}$). Thus, the top of the results distribution from our AD neuritic plaque pathology GWAS is significantly enriched for loci that are also pertinent for decline in cognitive function.

Notably, the *APP* locus SNP, rs2829887, was not related to clinical AD diagnosis (p=0.63) (Table 3), change in global cognition (p=0.58), change in episodic memory (p=0.41), or incident AD (p=0.38). These results may be explained by the presence of substantial AD pathology in individuals with mild or sub-clinical disease (classified as controls in a standard AD case/control analysis). Despite smaller sample sizes, the association was significant (OR=0.64, p=0.002) in an analysis limited to clinically diagnosed and pathologically confirmed cases (n=244) and controls without substantial AD pathology (n=212). We further found that the association of rs2829887 with neuritic plaque pathology does not vary by clinical diagnosis proximate to death, demonstrating consistent effects (β values) in subjects with (β=−0.109, p=0.008) or without dementia (β=−0.108, $p=6.1\times10^{-4}$). In an analysis restricted to the relatively few subjects with no cognitive impairment similar to our PET samples (n=229), rs2829887 remained associated with Aβ load (β=−0.173, p=0.046) and showed a trend toward an association with neuritic plaque burden (β=−0.068, p=0.088). These results suggest that rs2829887 impacts susceptibility for the earliest brain amyloid changes preceding overt cognitive impairment.

## COMMENT

Besides *APOE* and *CR1*, we found that AD susceptibility alleles at the *ABCA7* and *CD2AP* loci were associated with increased neuritic plaque pathology. The results suggest a potential mechanism for the impact of these loci on the clinical manifestations of AD. While our

study was not sufficiently powered to definitively exclude associations for the other AD susceptibility variants (see below), it is possible that some of these loci predominantly impact pathogenic steps downstream of neuritic plaque deposition, such as synaptic loss, neuronal death, or the manifestation of cognitive changes. It is also plausible that some AD susceptibility loci impact other, non-AD related mechanisms that contribute to cognitive changes and the development of the clinical AD phenotype, which is known to be pathologically heterogeneous[19].

The strongest support for a genetic link between β-amyloid pathology and AD risk comes from the established connection between rare mutations in the *APP* gene and autosomal dominant, early-onset familial AD[1]. Further, an uncommon *APP* variant, A673T (freq. < 1%), was recently discovered to confer protection against AD[2]. Although common *APP* polymorphisms have been evaluated in numerous association studies of late-onset AD, a definitive link has yet to be established[3–6], nor has *APP* emerged from AD GWAS[9,10]. It is intriguing that our study discovered common variants near *APP* among the top loci associated with neuritic plaque burden. The strongest variant, rs2829887, fell within 150kb of the 3'-end of the *APP* transcription unit, within an intron of the *ATP5J* gene. None of the other adjacent genes (*JAM2, GABPA, MRPL39*) are known to be involved in amyloidogenesis. While *APP* is a compelling candidate, the causal variant(s) and responsible gene(s) require confirmation. rs2829887 may tag a haplotype associated with altered APP protein processing or gene expression, similar to other rare disease causing mutations or duplications[34]. We found additional support for the *APP* locus based on evaluation of two independent cohorts of cognitively-normal, older adults with PET imaging. While intriguing, this association was in the opposite direction for PET β-amyloid compared to directly measured neuritic plaques or β-amyloid load, which may be due to differences in the cohorts (e.g. participant age) or the outcome phenotypes (postmortem Aβ load vs. PET Aβ).

Our GWAS identified other candidate susceptibility genes that will require replication. rs6817475 falls within the intron of *KCNIP4*, encoding a potassium channel interacting protein. Notably, KCNIP4 physically interacts with PSEN2[35], and alters Aβ dynamics in cultured cells[32]; further, insertion/deletion polymorphisms in the *KCNIP4* promoter were associated with AD in a small case-control autopsy cohort. Also, rs12551233 is within an intron *PTGS1*, also known as *cyclooxygenase 1* (*COX1*), which encodes a key regulator of inflammation. Increased COX1 along with other inflammatory markers have been previously described in association with neuritic plaque pathology[36]. We also detected a SNP, rs3892710 within the *HLA* locus (*HLA-DQA2*), which encodes the class II MHC on antigen presenting cells and regulates adaptive immune responses. Our finding of associations at *COX1* and the *MHC* locus, along with the established roles of *CR1, CD33*, and *MS4A*, supports immune responses and neuroinflammation as important determinants of AD pathogenesis. Finally, we note an association between a SNP in the *nicotinamide nucleotide adenylyltransferase 3* gene (*NMNAT3*, rs4564921) and neuritic plaque burden. This enzyme family has demonstrated neuroprotective activities in experimental models[37], and the *NMNAT3* locus was previously implicated in an AD genome-wide scan[33].

The main strength of our study comes from its use of two prospective, community based, autopsy cohorts with uniform, quantitative assessment of neuritic plaque pathology along with thorough clinical assessment proximate to death. However, we ultimately had insufficient power to discover novel genome-wide significant susceptibility loci for neuritic plaque pathology. Importantly, both cohorts are ongoing which will allow better powered studies in the future, including genetic analyses of other informative pathologic traits (e.g. neurofibrillary tangles, neurons, dendritic spines, and synaptic protein markers)[38]. Given our current sample size, a polymorphism would need to explain at least 6.7% of the variance in

pathologic burden in order for us to have 90% power for discovery at genome-wide significance. Based on the effect size of rs2829887 in the *APP* locus, which explains 3.5% of the variance in neuritic plaque burden, we estimate that a sample size of 1,300 will be needed to have 90% power to establish a significant association.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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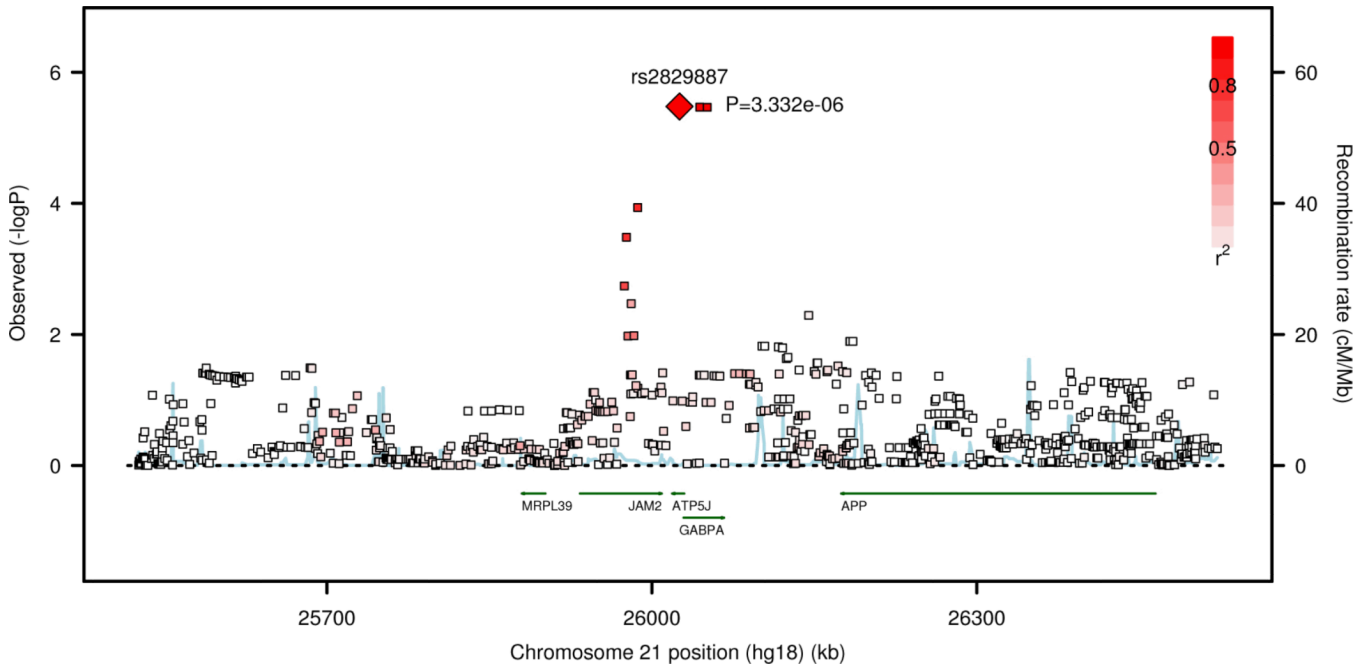


**FIGURE 1. Plot showing rs2829887 at the *APP* locus in association with neuritic plaque pathology**

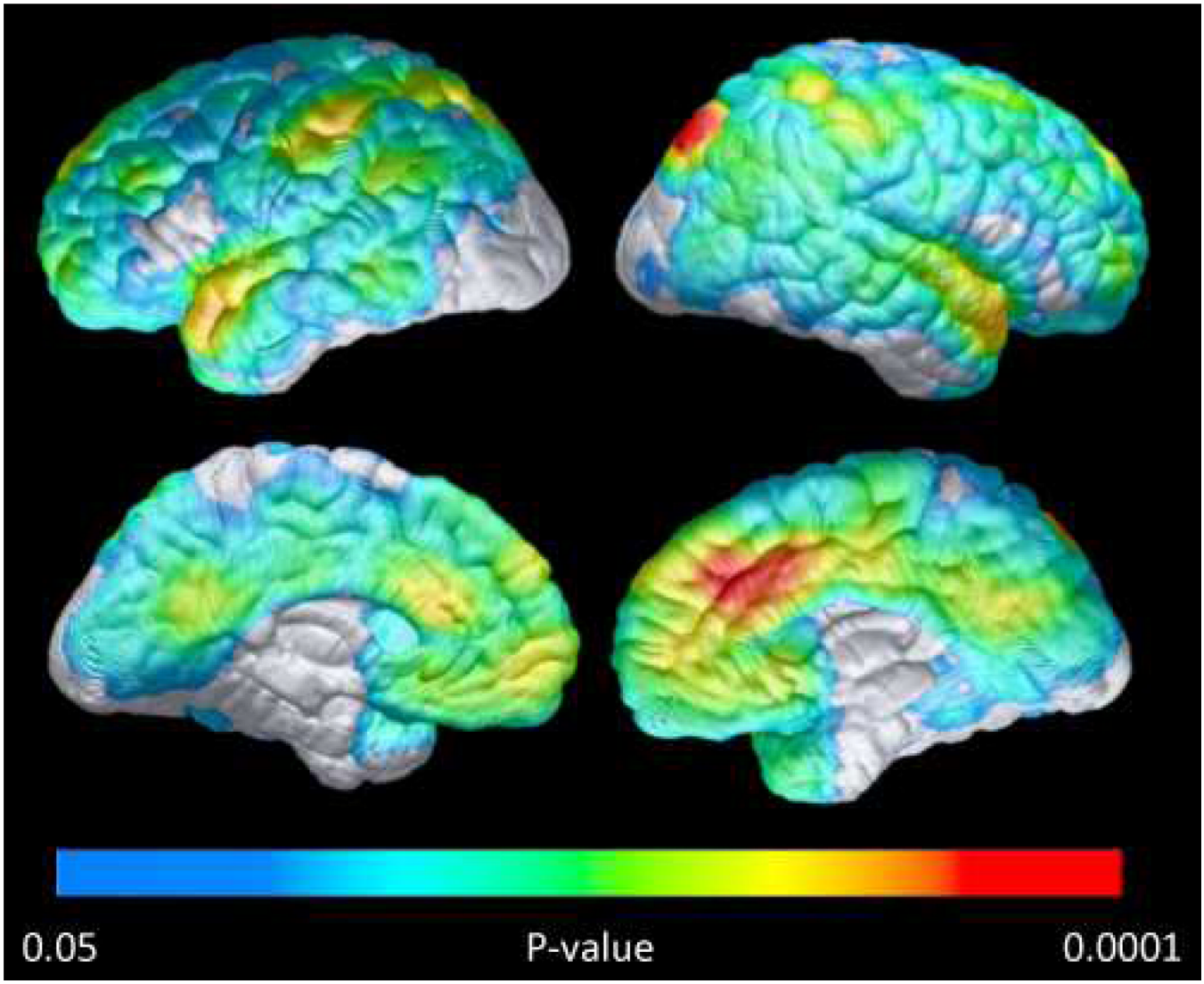


**FIGURE 2. Association of rs2829887 with fibrillar amyloid in cognitively normal subjects from ADNI and the Arizona *APOE* cohorts**

Statistical map of rs2829887$^{T}$ association with fibrillar amyloid projected onto the medial and lateral surfaces of a standardized brain, based on joint analysis of PiB or AV-45 SUVR images from 114 cognitively-normal subjects in the Arizona *APOE* and ADNI cohorts. Analyses were adjusted for subject age, *APOE ε4* genotype, and cohort membership.

**Table 1**

Association of AD susceptibility loci with neuritic plaque pathologic burden.

| GENE | SNP | A1 | A2 | MAF | BETA | SE | 95% CI | P |
|---|---|---|---|---|---|---|---|---|
| CR1 | rs6701713 | A | G | 0.20 | 0.077 | 0.03508 | (0.0082,0.1457) | **0.029** |
| CLU | rs1532278 | T | C | 0.39 | 0.000 | 0.03058 | (−0.0595,0.0603) | 0.992 |
| PICALM | rs561655 | G | A | 0.35 | −0.045 | 0.02883 | (−0.1017,0.0113) | 0.117 |
| BIN1 | rs7561528 | A | G | 0.34 | −0.009 | 0.02801 | (−0.0635,0.0463) | 0.757 |
| ABCA7 | rs3764650 | G | T | 0.09 | 0.180 | 0.08262 | (0.0183,0.3422) | **0.030** |
| MS4A | rs4938933 | C | T | 0.43 | −0.004 | 0.02772 | (−0.0583,0.0503) | 0.889 |
| CD33 | rs3865444 | A | C | 0.30 | −0.040 | 0.02954 | (−0.0981,0.0177) | 0.174 |
| CD2AP | rs9349407 | C | G | 0.25 | 0.071 | 0.03223 | (0.0075,0.1338) | **0.029** |
| EPHA1 | rs11767557 | C | T | 0.18 | 0.024 | 0.04087 | (−0.0558,0.1044) | 0.555 |

SNP, single nucleotide polymorphism based on published AD susceptibility loci[9,10]; A1/A2, minor/major allele; MAF, minor allele frequency; BETA, Estimate based on effect of increasing dosage of SNP minor allele, adjusted for age of death, study membership, and 3 principal components; SE, standard error; P, p-value

**Table 2**

Top Results of the neuritic plaque GWAS

| CHR | SNP | POSITION | A1 | A2 | MAF | BETA | SE | P | GENES |
|---|---|---|---|---|---|---|---|---|---|
| 19 | rs4420638 | 50114786 | G | A | 0.18 | 0.3463 | 0.0395 | $1.49\times10^{-17}$ | *APOE* |
| 4 | rs6817475 | 20370609 | G | T | 0.33 | 0.1672 | 0.0326 | $3.80\times10^{-7}$ | *KCNIP4* |
| 9 | rs12551233 | 124190709 | G | A | 0.06 | −0.3216 | 0.0632 | $4.79\times10^{-7}$ | *PTGS1* |
| 6 | rs3892710 | 32790840 | T | C | 0.15 | −0.2007 | 0.0421 | $2.32\times10^{-6}$ | *HLA-DQA2* |
| 21 | rs2829887 | 26025485 | T | C | 0.43 | −0.1384 | 0.0295 | $3.33\times10^{-6}$ | *ATP5J-APP* |
| 9 | rs9407730 | 16221985 | G | A | 0.13 | −0.2118 | 0.0453 | $3.61\times10^{-6}$ | |
| 6 | rs4642480 | 96321020 | G | A | 0.48 | 0.1432 | 0.0307 | $3.65\times10^{-6}$ | |
| 3 | rs4564921 | 140761248 | C | G | 0.37 | 0.1388 | 0.0304 | $6.12\times10^{-6}$ | *NMNAT3* |
| 14 | rs187911 | 57084834 | G | A | 0.41 | −0.1434 | 0.0315 | $6.23\times10^{-6}$ | *SLC35F4* |
| 14 | rs10149826 | 33380164 | T | C | 0.12 | 0.221 | 0.0494 | $9.15\times10^{-6}$ | *NPAS3* |
| 2 | rs12613305 | 205054912 | A | G | 0.47 | 0.1311 | 0.0293 | $9.36\times10^{-6}$ | *PARD3B* |

Based on analysis of sub-sample consisting of n=651 ROS/MAP autopsy cases. CHR, chromosome; SNP, single nucleotide polymorphism; POSITION, based on hg18 coordinates; A1/A2, minor/major allele; MAF, minor allele frequency; BETA, Estimate based on effect of increasing dosage of SNP minor allele, adjusted for age of death, study membership, and 3 principal components; SE, standard error; P, p-value

**Table 3**

Association of rs2829887 with AD traits in ROS/MAP

| | n | Estimate | 95% CI | p |
|---|---|---|---|---|
| **Neuritic Plaques** | 725 | −0.115 | (−0.170, −0.063) | $1.54\times10^{-5}$ |
| **Amyloid load** | 716 | −0.216 | (−0.324,−0.108) | $9.52\times10^{-5}$ |
| **Clinical AD** | 328/470 | 1.050 | (0.86,1.29) | 0.632 |
| **Clinico-pathologic AD** | 244/212 | 0.643 | (0.48,0.85) | 0.002 |

Sample size (n) expressed as total subjects or cases/controls. Estimate represents Beta values for quantitative pathologic traits or odds ratios for AD diagnosis, reflecting increasing dosage of the rs2829887 minor allele (T), adjusted for age at death, study membership, and 3 principal components. Neuritic plaque burden was based on silver-stained tissue, and amyloid load was determined from Aβ immunohistochemistry. Clinico-pathologic AD based on NINCDS clinical diagnosis and NIA-Reagan pathologic confirmation of cases versus non-demented controls with NIA-Reagan no or low likelihood AD.