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Variants in *PPP3R1* and *MAPT* are associated with more rapid functional decline in Alzheimer's disease: The Cache County Dementia Progression Study

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Abstract

Background: Single-nucleotide polymorphisms (SNPs) located in the gene encoding the regulatory subunit of the protein phosphatase 2B (*PPP3R1*, rs1868402) and the microtubule-associated protein tau (*MAPT*, rs3785883) gene were recently associated with higher cerebrospinal fluid (CSF) tau levels in samples from the Knight Alzheimer's Disease Research Center at Washington University (WU) and Alzheimer's Disease Neuroimaging Initiative (ADNI). In these same samples, these SNPs were also associated with faster functional decline, or progression of Alzheimer's disease (AD) as measured by the Clinical Dementia Rating sum of boxes scores (CDR-sb). We attempted to validate the latter association in an independent, population-based sample of incident AD cases from the Cache County Dementia Progression Study (DPS).

Methods: All 92 AD cases from the DPS with a global CDR-sb ≤ 1 (mild) at initial clinical assessment who were later assessed on CDR-sb data on at least two other time points were genotyped at the two SNPs of interest (rs1868402 and rs3785883). We used linear mixed models to estimate associations between these SNPs and CDR-sb trajectory. All analyses were performed using Proc Mixed in SAS.

Results: Although we observed no association between rs3785883 or rs1868402 alone and change in CDR-sb ($P > .10$), there was a significant association between a combined genotype model and change in CDR-sb: carriers of the high-risk genotypes at both loci progressed >2.9 times faster than noncarriers ($P = .015$). When data from DPS were combined with previously published data from WU and ADNI, change in CDR-sb was 30% faster for each copy of the high-risk allele at rs3785883 ($P = .0082$) and carriers of both high-risk genotypes at both loci progressed 6 times faster ($P < .0001$) than all others combined.

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Conclusions: We replicate a previous report by Cruchaga et al that specific variations in rs3785883 and rs1868402 are associated with accelerated progression of AD. Further characterization of this association will provide a better understanding of how genetic factors influence the rate of progression of AD and could provide novel insights into preventative and therapeutic strategies.
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Keywords: Alzheimer's disease; Genetics; Association; Rate of progression; *PPP3R1*; *MAPT*

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting over 5 million individuals in the United States alone [1]. Although the ε4 allele of apolipoprotein E (*APOE*) has been identified as the most robust susceptibility variant in the late-onset form of AD, data from recent genome-wide association studies (GWAS) have been successful in identifying additional genetic factors that influence AD risk [2–13]. However, little is known about genetic factors that influence the rate of progression after the onset of dementia due to AD. Recently, several single-nucleotide polymorphisms (SNPs) located in the genes encoding the regulatory subunit of the protein phosphatase 2B (*PPP3R1*, rs1868402) and the microtubule-associated protein tau (*MAPT*, rs3785883) genes were associated with increased cerebrospinal fluid (CSF) tau levels and increased rate of functional decline, or progression of AD as measured by the Clinical Dementia Rating sum of boxes (CDR-sb) [14,15]. In this study, we attempted to replicate these associations by genotyping these two SNPs in an independent sample of 92 AD cases from the Cache County Dementia Progression Study (DPS) and examining their association with the rate of functional decline or "progression" as measured by the CDR-sb. We then pooled our data with data from the original report on these markers and performed a combined analysis to evaluate the association in the combined sample.

2. Materials and methods

2.1. Participants

The Cache County Study on Memory, Health, and Aging (CCSMHA) is a population-based epidemiological study of dementia examining genetic and environmental risk factors and their interactions. All individuals aged >65 years and living in Cache County, Utah, were targeted for enrollment. Beginning in 1995, four triennial waves of dementia ascertainment were completed, with 5092 (90% of eligible) individuals aged >65 years participating in a baseline interview. The study used a multistage dementia ascertainment protocol described elsewhere [16]. In brief, screening began with the Modified Mini-Mental State examination [17] or Informant Questionnaire for Cognitive Decline in the Elderly [18]. "Screened positive" individuals completed an in-depth clinical assessment, including a brief physical evaluation, a detailed history of medical and cognitive symptoms, a structured neurological examination, and a 1-hour battery of neuropsychological tests. After psychiatrist examination and neuroimaging in persons with working diagnoses of dementia, an expert panel reviewed all available data and assigned final consensus diagnoses, with AD diagnoses following the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria [19]. A total of 359 prevalent and 583 incident cases of dementia were identified (including 209 prevalent and 335 incident cases of AD). Informed consent was obtained for each interview. Institutional review boards at Utah State University, Duke University, and Johns Hopkins University approved all study procedures.

All incident AD cases that survived to the commencement of the Cache County DPS in 2002 were invited to participate with ongoing enrollment and annual follow-up after dementia onset [20]. Rate of AD progression was based on functional ability as measured by the CDR-sb. Significant variability in the rate of progression has been previously reported in these individuals, with approximately one third to one half progressing slowly in their disease course, as defined by a one point (or less) per year change in function (CDR-sb) [20]. As in Cruchaga et al [15], participants were selected to have a global Clinical Dementia Rating (CDR) <1 at their initial clinical assessment to maximize the amount of progression information and to minimize possible floor/ceiling effects from individuals who began the study with advanced levels of dementia. They were also selected to have stored DNA samples and CDR-sb data for at least two later time points. Ninety-two participants with incident AD from the DPS met these criteria. Individuals in this cohort were assessed annually at regularly scheduled intervals [20]. Demographic information on this cohort can be found in Table 1.

Data from the Washington University (WU) and Alzheimer's Disease Neuroimaging Initiative (ADNI) samples used in our initial study suggesting that variants in *PPP3R1* and *MAPT* are associated with the rate of progression were used for a larger combined analysis. Samples from WU were enrolled in longitudinal studies at the Knight Alzheimer's Disease Research Center. Demographics of this sample are in Table 1, and sample collection and ascertainment has been described previously [21]. The ADNI samples are part of a longitudinal study designed to measure the progression of mild cognitive impairment (MCI) and early AD. Similar to the DPS samples, the WU and ADNI samples have been assessed using CDR and CDR-sb data for each

Table 1
Sample characteristics

Characteristics	DPS	ADNI	WU
n	92	459	109
Initial age	84.5 (5.3)	75 (6)	68 (11)
Percent male	45	39	56
Percent ε4 positive	47	47	40
Number of assessments	4.0 (2.4)	4.1 (1.6)	3.8 (2.0)
Follow-up time	3.2 (2.1)	1.9 (1.1)	3.2 (2.1)
rs1868402 (CC/CT/TT)	5/46/49	7/40/53	10/44/46
rs3785883 (AA/AG/GG)	5/27/58	3/30/67	2/25/73

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; DPS, Cache County Dementia Progression Study; WU, Washington University.

NOTE. Data presented as mean (SD) unless otherwise indicated.

sample used in this manuscript. Demographics can be found in Table 1, and sample collection and ascertainment has been described previously [22,23]. For up-to-date information, see www.adni-info.org.

2.2. Genotyping

For the WU series, genotyping of rs1868402 and rs3785883 was conducted on DNA from blood samples using an Illumina Golden Gate custom genotyping chip [15]. Genotypes were called using BeadStudio. The DNA from the ADNI samples was obtained from cell lines at the National Cell Repository for Alzheimer's Disease and was also genotyped previously using Taqman® assays [15]. For the DPS samples, DNA from buccal cells was genotyped rs1868402 and rs3785883 and used the same Taqman assays as were used for the ADNI samples, which are available to be ordered from Life Technologies (rs1868402 assay id C__12044272_10, rs3785883 assay id C__27500834_10). Genotype calls from Taqman assays were made using Genotyper using all of the genetic data from the DPS study. DNA from the DPS samples was genotyped in duplicate and concordance rates were 100%. Genotyping rates in all samples attempted were 98.6%. Genotype frequencies for these SNPs did not deviate significantly from the expectations of Hardy-Weinberg equilibrium (evaluated using a χ^2 test to compare the observed vs the expected genotype frequencies).

2.3. Analysis

We first conducted analyses in the DPS samples alone and then in the combined DPS, WU, and ADNI samples. Our analyses were limited a priori to three tests: the two single SNPs and the specific combined genetic model that we identified in our previous report [15]. In specific, we used linear mixed models to estimate associations between specific SNPs and CDR-sb trajectory to test the dominant model for rs1868402, the additive model for rs3785883, and the exact combined genotype model specified in Cruchaga et al (2010) [15]. In all analyses, initial age and initial CDR were included as covariates. *APOE* ε4 genotype and gender were not included as covariates because they were not associated with rate of progression. All samples reported European-American ancestry. Analyses of these samples using array data from WU, ADNI, and DPS indicate no evidence of population substructure. The DPS is population-based sample, and there is a limited amount of relatedness among individuals. We corrected for possible family-based effects in the DPS sample by adding random effect for family to the model. The *P* values with and without inclusion of this variable, *APOE* genotype, or gender were affected minimally. The combined DPS, WU, and ADNI analysis included site in addition to initial CDR and initial age as a variable in the model. For further characterization of significant association, we performed analyses of the highest risk genotype combination against the reference group of all other individuals and tested an rs1868402*rs3785883 interaction term. All analyses were performed using Proc Mixed in the SAS software package (SAS Institute, Inc., Cary, NC).

3. Results

DPS participants had a mean initial age of 84.5 years: 45% were male and 47% were *APOE* ε4 carriers. The mean number of assessments was 4, and the mean time from first to final assessment was 3.2 years. The ADNI sample has significantly shorter follow-up time than the other samples ($P < .05$), and the DPS sample is significantly older ($P < .0001$). The minor allele frequency of rs1868402 in the DPS participants (0.28) was similar to that observed in the pooled WU and ADNI cohorts (0.27) and in the 1000 Genomes Project (0.25). The same was true for the minor allele frequency of rs3785883: 0.19 in DPS, 0.17 in the WU and ADNI data (0.17), and 0.17 in the 1000 Genomes Project. Genotype frequencies for rs1868402 and rs3785883 (Table 1) were not significantly different from each other ($P = .28, .21$, respectively) and did not deviate from the expectations of Hardy-Weinberg equilibrium ($P > .05$). The average rate of functional decline in the DPS cohort was 1.35 CDR-sb per year (sbpy). A summary of the associations observed in the DPS alone, combined WU and ADNI samples (reported previously) and the DPS, WU, and ADNI combined series are in Table 2. In the DPS samples there was not a significant association between rs1868402 (dominant model; $P = .55$) or rs3785883 (additive model; $P = .075$) and increased rate of change in CDR-sb. For rs3785883, the increased rate of progression with each copy of the "A" allele observed was consistent with findings of Cruchaga et al [15]. In the DPS samples alone, the combined genotype model was significantly associated with change in CDR-sb: carriers of the risk genotype at both loci progressed more than 2.9 times faster than all other individuals ($P = .029$, 3.61 sbpy). Analyses using *APOE* genotype, gender, and "family" as covariates did not significantly change our results.

Table 2
P value, risk genotype, and change in CDR-sb per year for the dominant model of rs1868402, the additive model of rs3785883, and the combined genotype model for rs1868402/rs3785883

	rs1868402		rs3785883		Combined model	
Samples	Risk geno/sbpy	*P*	Risk geno/sbpy	*P*	Risk geno/sbpy	*P*
DPS	CC + CT/1.38	.55	AA/1.91	.075	CC + CT, AA/3.61	.029
WU/ADNI*	CC + CT/0.29	.0026	AA/0.34	.057	CC + CT, AA/1.02	<.0001
DPS/WU/ADNI	CC + CT/0.43	.24	AA/0.61	.008	CC + CT, AA/2.39	<.0001

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-sb, Clinical Dementia Rating sum of boxes scores; DPS, Cache County Dementia Progression Study; geno, genotype; sbpy, CDR-sb per year; WU, Washington University.

NOTE. Values are listed for the DPS alone; the WU and ADNI samples combined; and the combined DPS, WU, and ADNI samples.

*WU/ADNI results were previously reported by Cruchaga et al [15].

When the DPS cohort was combined with those from the WU and ADNI series [15], the average rate of change was 0.42 sbpy. In this combined sample, there was no association between rs1868402 and rate of progression ($P = .24$). However, there was a significant association between rs3785883 and progression: participants progressed 30% faster on average for each copy of the risk allele compared with those lacking the risk allele ($P = .008$; no risk alleles 0.37 sbpy, one risk allele 0.49 sbpy, two risk alleles 0.61 sbpy; Table 3). Carriers of risk genotypes at both loci progressed 6 times faster on CDR-sb than carriers of all other genotypes combined (2.37 sbpy for risk genotypes, 0.39 sbpy for all others; $P < .0001$; Table 3). In addition, noncarriers of either risk genotype showed a 20% slower rate of progression compared with all other individuals that neared statistical significance ($P = .084$; 0.37 sbpy for noncarriers, 0.46 sbpy for all others; Table 3). Analysis using an rs1868402*rs3785883 interaction term also yielded a significant interaction ($P = .049$). Analyses using *APOE* genotype and/or gender as a covariate did not significantly change our results.

4. Discussion

Specific genetic variants in *PPP3R1* and *MAPT* may modulate levels of tau and phosphorylated tau (ptau) in the presence of amyloid deposition, thus altering the rate of functional decline in individuals with AD [14,15]. The results reported here provide additional evidence from an independent sample that AD patients who carry the "C" allele of rs1868402 (*PPP3R1*) and are homozygous for the "A" allele at rs3785883 (*MAPT*) have a significantly faster functional decline.

Table 3
Change in CDR-sb per year for select genotypes compared with all other genotypes in the combined WU, ADNI, and DPS samples

Genetic model	Risk genotype	All others	*P*
rs1868402	0.43	0.37	.243
rs3785883	0.61	0.37[†]	.008[‡]
Combined model	2.37	0.39	<.0001
Combined model	0.37*	0.46	.084

*Value is for the nonrisk genotype carriers.
[†]Value is for the nonrisk genotype from the additive model.
[‡]*P* value from the additive model.

The DPS sample was older at initial assessment than the WU and ADNI samples ($P < .0001$). Small sample size and greater initial age may have limited the statistical power of the analyses in the DPS sample alone and may explain the failure to detect significant associations in single SNP tests (power = 0.29). Despite this, the findings for the additive model of rs3785883 were suggestive of association. The direction of the effect observed in DPS alone for both single SNP tests was consistent with the results reported by Cruchaga et al [15]. In addition, results from DPS alone suggested that individuals carrying high-risk genotypes at both markers progressed 2.9 times faster than individuals with other genotypes.

Combined analyses of the three datasets provided greater power (0.96) and evidence of greater acceleration of decline for carriers of high-risk alleles at rs1868402 and rs3785883, resulting in a 6 times faster rate of progression of AD as measured by the CDR-sb. This appears to be more than a simple additive effect, such that these genes interact to produce the observed phenotypic effect ($P = .0498$). We also note that in combined analysis, carriers of the nonrisk genotypes at both loci (GG for rs1868402 and TT for rs3785883) progressed 20% slower than all other individuals (Fig. 1).

Our data are consistent with other recent work indicating that these markers play an important role in the rate of dementia progression in individuals diagnosed with AD. The original report provides evidence that the mechanism of this effect is altered levels of tau in the brain. Other work also supports a role for ptau levels in AD progression. For example, CSF ptau levels have been shown to increase over time in impaired patients [24]. More recently, Liu et al (2012) showed trans-synaptic spread of tau pathology in mouse models, providing direct evidence that tau is an important aspect of early AD pathology and progression. In addition to tau and AD pathology, significant efforts to identify factors that modulate AD progression are also ongoing. Recently, associations between the CSF Visinin-like 1 protein levels [25] and CSF chemokine (C-C motif) ligand 2 protein levels and AD progression have been reported [26]. Although this study was limited to European Americans, further study of AD progression in larger datasets from multiple ethnic groups will provide better understanding of the pathological and genetic basis for faster and

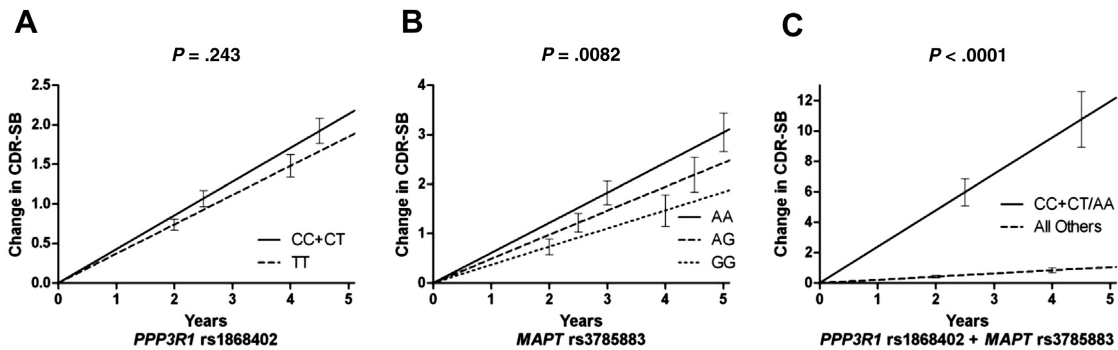

Fig. 1. Rate of progression over 5-year time period genotype groups in the combined Washington University, Alzheimer's Disease Neuroimaging Initiative, and Cache County Dementia Progression Study sample. (A) rs1868402 (dominant model) (B) rs3785883 (additive model), and (C) combined genotypes (carriers of both risk genotypes are compared with all other genotype combinations). Error bars represent the standard error in change in the Clinical Dementia Rating sum of boxes scores over time.

slower progression, thus elucidating novel therapeutic targets for AD.

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D.P. and C.M. contributed equally to this work.

The data used in the preparation of this article were obtained from the ADNI database (http://www.adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

RESEARCH IN CONTEXT

1. Systematic review: We have evaluated the literature on genetic factors that influence the rate of functional decline in AD and identified the 2010 report in PLoS Genetics by Cruchaga et al implicating variation in the *PPP3R1* and *MAPT* genes to be a strongly supported report.
2. Interpretation: We genotyped these markers in an independent dataset from the Cache County Study and performed association analyses. We also combined our data with data from the samples used in Cruchaga et al (2010) and performed a meta-analysis. Our findings clearly support the association of variation in these genes with rate of functional decline in AD patients suggesting that there is a genetic contribution to heterogeneity in functional decline in AD patients.
3. Future directions: Additional work is required to characterize the specific variants and the molecular mechanisms that are responsible for this association.

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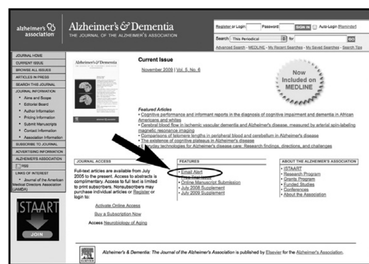

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