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Short Communication

Common Variants in *ABI3* Influence Cerebrospinal Fluid Total Tau Levels and Cognitive Decline in Progressive Mild Cognitive Impairment Patients

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Abstract. A potential role for *ABI3* gene has been suggested in the risk of Alzheimer's disease (AD), but the detailed mechanism before typical AD onset was unclear. In this study, we investigated the associations of *ABI3* common variants with cerebrospinal fluid biomarkers and cognitive function scores among non-demented elderly from the ADNI database. We found that, in the progressive mild cognitive impairment group, rs5978930 was associated with total tau levels and rs16947151 was associated with cognitive function scores at baseline and over time, suggesting that *ABI3* variants may be associated with cognitive decline and may influence AD onset through tau pathology.

Keywords: *ABI3*, biomarkers, mild cognitive impairment, total tau, variant

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in the elderly. Genetic factors have been reported to play important roles in AD pathogenesis. Recently, a rare variant in *ABI3* (rs616338-T) was found to increase the risk of AD in cohort of European

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[2]Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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descent [1]. Located at chromosome 17q21.32, *ABI3* encodes the Abelson interactor (Abi) family protein 3, which is highly expressed on microglia [1–3]. The association of rs616338 with AD risk was successfully replicated in an independent Caucasian cohort [2]. Additionally, the expression level of *ABI3* was significantly increased in a mouse model of AD [4]. These evidences strongly suggested that *ABI3* was a risk gene for AD. Therefore, common variants in *ABI3* may also play important roles in AD. However, little is known about the influence of *ABI3* common variations on cerebrospinal fluid (CSF) biomarkers and cognitive function scores.

AD has a long pre-clinical phase with mild symptoms and abnormal CSF biomarkers[5]. The pathophysiological processes of AD and the impairment of cognitive function could begin many years before the diagnosis of AD can be made. Considering this, research focusing on how genes are involved in the occurrence of AD before the typical onset are warranted. The goal of this study was to explore the potential effect of *ABI3* alleles on pathological features of AD and on aging-related cognitive decline in elderly without clinical evidence of dementia. We explored the influence of *ABI3* common variants on cognitive function scores and CSF biomarkers in subjects who were cognitively normal or diagnosed with mild cognitive impairment (MCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

METHODS

Alzheimer's disease neuroimaging initiative dataset

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

Participants

Individuals who were judged clinically to have no cognitive impairment or MCI at baseline from ADNI cohort were included. To avoid spurious genetic effects due to population stratification, only Caucasian participants were included. The participants were classified into cognitively normal (CN), stable MCI (sMCI), and progressive MCI (pMCI) groups. Individuals with pMCI or sMCI were defined as patients who had MCI at baseline and converted to AD or those who had MCI at baseline and stayed stable within two years' follow up, respectively. Written informed consent was required from all participants, and study protocols were approved by participating studies and sites' institutional review boards.

Genotyping and SNP selection

The genotype data from the ADNI database and the Haploview v4.2 program were used to select tag single nucleotide polymorphisms (SNPs), basing on an r^2 threshold of 0.8 and a minor allele frequency (MAF) threshold of 0.05. After quality control, common variants were selected as the targeted *ABI3* loci in further analyses. The ADNI samples were genotyped with the Omni 2.5 M BeadChip (Illumina, Inc., San Diego, CA) or the Human610-Quad BeadChip (Illumina, Inc., San Diego, CA) [6].

CSF measurements and cognitive assessments

Data on CSF Aβ, total tau (*t*-tau), and phosphorylated tau (*p*-tau) as well as neuropsychological tests were downloaded from the ADNI database. Cognition was assessed by Mini-Mental State Examination (MMSE), Clinical Dementia Rating scale-sum of boxes (CSR-SB), Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog), and Rey Auditory Verbal Learning Test (RAVLT). Details about the measurements of CSF biomarkers can be found elsewhere [7]. In brief, CSF was analyzed using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use–only reagents) immunoassay kit-based reagents.

Statistical analysis

Demographics, neuropsychological tests, and levels of CSF biomarkers were compared using one-way analysis of variance (ANOVA) or chi-square tests. Each of the SNPs was calculated for its associations with neuropsychological tests and CSF analytes levels. Dominant genetic model was used because of the small number of homozygotes for the minor allele. Multiple linear regression model was used to test

possible associations of *ABI3* loci with neuropsychological tests and CSF biomarkers at baseline. The longitudinal associations were tested with linear mixed-effects model. Haplotype-based association analysis was also performed to detected the possible correlation. Age, gender, education, and *APOE* ε4 status were used as covariates. The *APOE* genotypes were coded as 0, 1, and 2 for the presence of 0, 1, and 2 ε4 alleles, respectively. To facilitate comparisons among modalities, all outcome variables were standardized to z scores. All statistical analyses were performed using R (Version 3.4.4). The corrected p-values were calculated by the Bonferroni method. The Genome-wide Complex Trait Analysis (GCTA) was used to estimate the variance in phenotypes explained by *ABI3* common variants [8].

RESULTS

The demographic characteristics and clinical data at baseline were summarized in Table 1. A total of 1001 Caucasian individuals from ADNI cohort were enrolled, including 346 CN, 524 sMCI and 131 pMCI subjects. Compared to CN subjects, sMCI ($p < 0.001$) and pMCI ($p < 0.001$) patients had higher frequencies of *APOE* ε4 allele. As expected, CN participants had better performance on neuropsychological tests than sMCI and pMCI patients ($p < 0.001$ for all). Among the 1,001 individuals, 696 (69.5%) participants have the data of CSF biomarkers, which consisted of 233 CN, 378 sMCI, and 85 pMCI subjects. The patients with pMCI showed the highest levels of CSF t-tau and p-tau and lowest level of CSF Aβ among the three groups ($p < 0.001$ for all).

Five tag SNPs (rs55978930, rs16947151, rs2158512, rs66534734, and rs658979) can explain 71% of the total variability. Among them, rs16947151 and rs2158512 were available in genotype data from both ADNI1/GO/2 cohort and ADNI1 cohort. rs55978930, rs66534734, and rs658979 were available only in genotype data from ADNI1/GO/2 cohort. The linkage disequilibrium (LD) between genotyped variants can be found in Supplementary Figure 1, and one LD block were identified. Furthermore, we evaluated the associations between *ABI3* variants and CSF biomarkers and cognitive function scores which were measured at baseline (Table 2). Bonferroni correction for multiple testing involving five SNPs was applied to the significance threshold of $p < 0.05$. *P* value for a truly significant result was calculated as 0.05/(5 SNPs) = 0.01. In the total non-demented group, rs16947151 was associated with CDR-SB score ($\beta = 0.1\,179$, $p = 0.0302$) and rs2158512 was associated with ADAS-cog score ($\beta = 0.2029$, $p = 0.0318$). However, neither of them was survived after Bonferroni correction. After stratifying the participants based on diagnosis, rs55978930 was found to be significantly associated with CSF t-tau levels at baseline in pMCI group ($\beta = -0.819$, $p = 0.006$) (Fig. 1a). Besides, rs16947151 was associated with baseline CDR-SB scores in pMCI group ($\beta = 0.564$, $p = 0.006$) (Fig. 1b). Both of the above associations still survived after Bonferroni correction. However, the analysis did not detect any significant relations between *ABI3* common variants and CSF Aβ levels, despite the fact that *ABI3* has been considered to be associated with cortical Aβ amyloidosis. As for other *ABI3* variants, there was

Table 1
Demographics and clinical characteristics of study participants

Characteristics	CN	sMCI	pMCI	*p*
n	346	524	131	—
Age (y)	75.13 ± 5.35	73.23 ± 7.62	73.86 ± 7.09	—
Gender (male/female)	177/169	318/206	78/53	—
Education (y)	16.28 ± 2.67	15.97 ± 2.83	15.56 ± 2.92	0.0327
***APOE* ε4 (0/1/2)**	250/87/9	293/189/42	42/65/24	<0.001
CDR-SB (scores)	0.03 ± 0.13	1.37 ± 0.78	2.04 ± 1.02	<0.001
MMSE (scores)	29.08 ± 1.11	27.81 ± 1.73	26.72 ± 1.69	<0.001
ADAS-cog (scores)	6.09 ± 2.87	9.50 ± 4.07	13.74 ± 4.28	<0.001
RAVLT (scores)	43.90 ± 9.38	35.66 ± 10.74	27.47 ± 6.19	<0.001
CSF Aβ (pg/mL)	199.32 ± 53.11	177.37 ± 52.05	139.41 ± 36.40	<0.001
CSF *t*-tau (pg/mL)	70.57 ± 31.87	85.46 ± 52.47	111.63 ± 47.30	<0.001
CSF *p*-tau (pg/mL)	31.06 ± 16.17	37.16 ± 21.15	47.79 ± 27.14	<0.001

Data are given as mean ± standard deviation unless otherwise indicated. Aβ, amyloid-β; ADAS-cog, Alzheimer's disease Assessment Scale-Cognitive subscale; CDR-SB, Clinical Dementia Rating scale-sum of boxes; CN, cognitively normal; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; pMCI, progressive mild cognitive impairment; *p*-tau, phosphorylated tau; RAVLT, Rey Auditory Verbal Learning Test; sMCI, stable mild cognition impairment; *t*-tau, total tau.

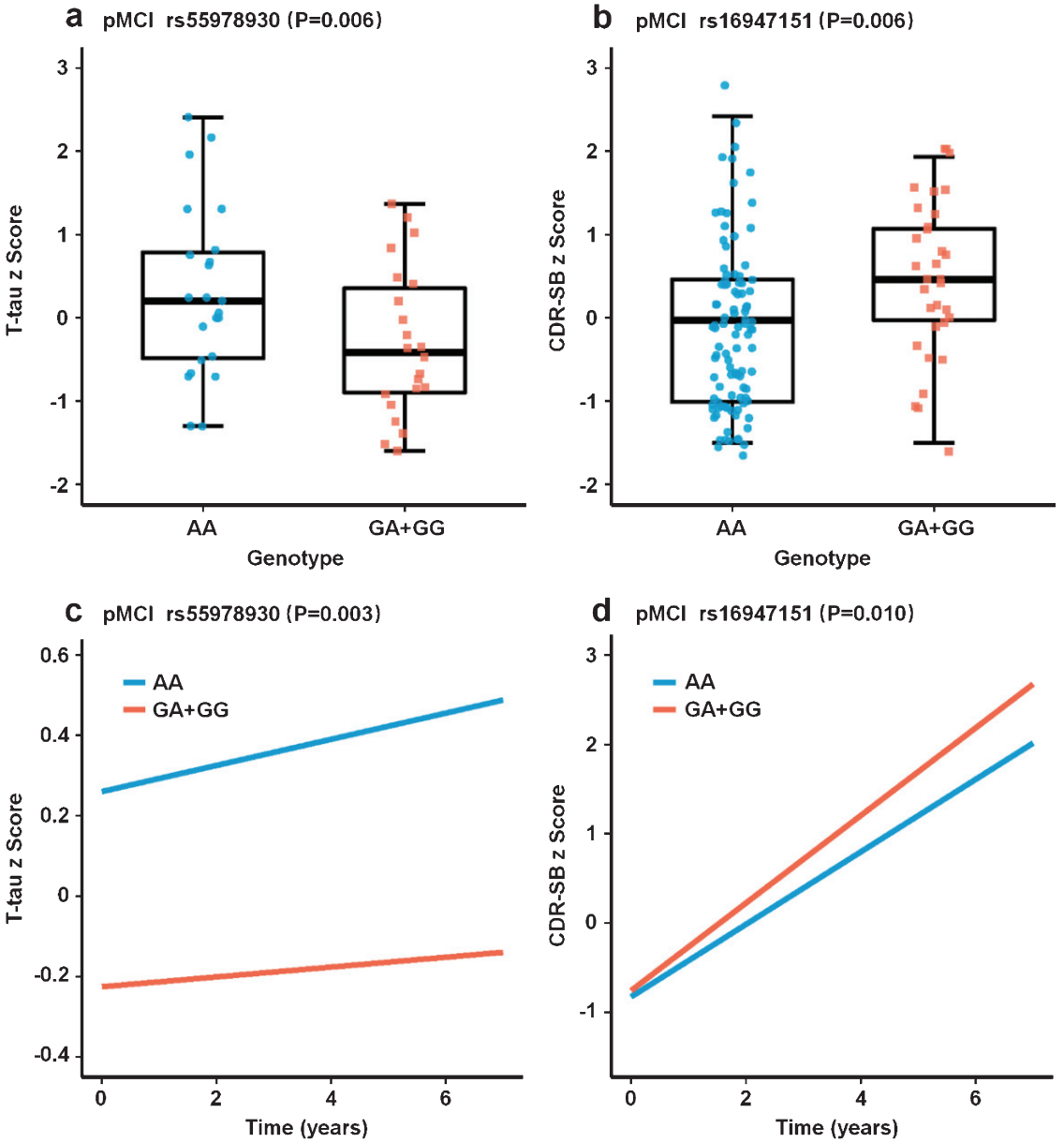

Fig. 1. The correlations between ABI3 variants and CSF biomarkers and cognitive function scores in pMCI group at baseline and over time. All the analyses included age, gender, education, and *APOE* ε4 status as covariates. a) rs55978930 was associated with higher CSF *t*-tau levels at baseline (β=–0.819, $p = 0.006$). b) rs16947151 was associated with CDR-SB scores at baseline (β=0.564, $p = 0.006$). c) The minor allele of rs55978930 (G) was associated with a decreased level of CSF *t*-tau within seven years' follow-up (β = –0.772, $p = 0.003$). d) The minor G allele of rs16947151 was associated with an elevated CDR-SB score within seven years' follow-up (β = 0.174, $p = 0.010$). CDR-SB, Clinical Dementia Rating scale-sum of boxes; CSF, cerebrospinal fluid; pMCI, progressive mild cognitive impairment; t-tau, total tau.

no association detected with CSF biomarkers or cognitive function scores at baseline. Then, we further tested whether the identified influence of *ABI3* variants at baseline could survive in the longitudinal analysis (Table 2). Consistent with the results in baseline analysis, for patients with pMCI, the minor allele of rs55978930 (G) was associated with a decreased level of CSF t-tau (Fig. 1c, β = –0.772, $p = 0.003$) and the minor G allele of rs16947151 was associated with an elevated CDR-SB score (Fig. 1d, β = 0.174, $p = 0.010$) within the seven years' follow-up. Moreover, in the haplotype-based analysis (rs16947151–rs55978930–rs658979–rs66534734) of pMCI patients, the haplotype AGGA was

Table 2
Associations of *ABI3* variants with CSF biomarkers and cognitive function scores[a]

Characteristics	SNP	CN		sMCI		pMCI		Non-demented elderly	
		β	*p*	β	*p*	β	*p*	β	*p*
CSF Aβ	rs55978930	–0.213	0.113	–0.093	0.347	0.138	0.604	–0.113	0.118
	rs16947151	0.241	0.102	0.207	0.071	–0.301	0.199	0.150	0.058
	rs2158512	–0.219	0.295	0.005	0.979	0.959	0.022	–0.033	0.789
	rs66534734	0.043	0.785	0.088	0.449	0.040	0.896	0.070	0.404
	rs658979	0.067	0.651	0.159	0.150	0.323	0.235	0.126	0.111
CSF *t*-tau	rs55978930	0.064	0.655	0.173	0.098	**–0.819**	**0.006***	0.059	0.456
	rs16947151	–0.179	0.252	–0.061	0.610	–0.032	0.902	–0.087	0.313
	rs2158512	0.287	0.193	–0.159	0.409	–0.525	0.266	–0.082	0.538
	rs66534734	0.092	0.578	–0.175	0.161	0.372	0.297	–0.072	0.428
	rs658979	0.087	0.583	–0.274	0.018	0.156	0.626	–0.142	0.098
CSF *p*-tau	rs55978930	–0.012	0.934	0.098	0.367	–0.028	0.930	0.063	0.439
	rs16947151	–0.219	0.165	–0.167	0.182	–0.030	0.908	–0.146	0.102
	rs2158512	0.355	0.111	–0.224	0.256	–0.563	0.230	–0.080	0.559
	rs66534734	0.220	0.187	–0.238	0.065	0.205	0.574	–0.070	0.453
	rs658979	0.216	0.175	–0.293	0.016	0.009	0.978	–0.112	0.207
CDR-SB	rs55978930	0.098	0.431	–0.059	0.570	0.147	0.568	0.012	0.822
	rs16947151	0.130	0.327	0.108	0.326	**0.564**	**0.006***	0.118	0.030
	rs2158512	–0.134	0.467	–0.005	0.978	–0.460	0.247	–0.050	0.536
	rs66534734	0.280	0.050	0.077	0.522	0.272	0.338	0.044	0.448
	rs658979	0.125	0.355	0.063	0.581	0.260	0.319	0.036	0.513
ADAS-cog	rs55978930	–0.020	0.871	–0.058	0.559	0.058	0.813	–0.038	0.534
	rs16947151	–0.042	0.745	–0.033	0.755	0.038	0.845	–0.023	0.715
	rs2158512	0.210	0.244	0.167	0.281	0.974	0.013	0.203	0.032
	rs66534734	0.036	0.798	–0.014	0.908	0.158	0.562	0.008	0.913
	rs658979	–0.016	0.906	–0.011	0.920	0.254	0.306	0.020	0.770
MMSE	rs55978930	0.009	0.940	0.009	0.929	0.095	0.663	0.028	0.679
	rs16947151	0.005	0.970	–0.050	0.642	–0.362	0.061	0.360	0.360
	rs2158512	–0.229	0.199	–0.235	0.136	–0.151	0.686	–0.185	0.064
	rs66534734	–0.111	0.430	–0.121	0.302	–0.385	0.109	–0.115	0.132
	rs658979	–0.072	0.586	–0.064	0.560	–0.530	0.014	–0.106	0.142
RAVLT	rs55978930	0.015	0.897	–0.114	0.209	–0.059	0.806	–0.055	0.364
	rs16947151	–0.039	0.750	0.049	0.611	–0.224	0.263	–0.003	0.962
	rs2158512	–0.269	0.116	–0.029	0.839	–0.114	0.768	–0.110	0.236
	rs66534734	–0.040	0.764	0.058	0.585	–0.121	0.652	0.025	0.724
	rs658979	–0.172	0.169	0.043	0.668	–0.221	0.362	–0.044	0.503

Significant correlations ($p < 0.01$) are highlighted in bold with asterisk*. Aβ, amyloid-β; ADAS-cog, Alzheimer's disease Assessment Scale-Cognitive subscale; CDR-SB, Clinical Dementia Rating - Sum of Boxes; CN, cognitively normal; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Exam; pMCI, progressive mild cognitive impairment; p-tau, phosphorylated tau; RAVLT, Rey Auditory Verbal Learning Test; sMCI, stable mild cognition impairment; SNPs, single nucleotide polymorphisms; t-tau, total tau. [a]All phenotypes were standardized to *z* scores.

associated with the decreased *t*-tau levels ($p = 0.0032$) and the haplotype AAGA was related to the increased CSF *t*-tau levels ($p = 0.0080$). The haplotype GAAG was associated with the elevation of CDR-SB in pMCI ($p = 0.0457$). The proportion of the variance in CSF *t*-tau and CDR-SB explained by *ABI3* common variants were rather small. But when limited the analysis in pMCI group, 16.0% of the variability of CSF *t*-tau levels can be explained by *ABI3* common variants, and the proportion of phenotypic variance for CDR-SB explained by the SNPs was 9.8%.

To further investigate the associations of ABI3 common variants with CSF biomarkers and cognitive function scores, we additionally performed the analyses in AD group. We only found that rs2158512 was associated with p-tau levels ($p = 0.0004$) at baseline. However, this association was not detected in the longitudinal analysis.

DISCUSSION

Recently, a rare variant of *ABI3* (rs616338-T) has been identified as a genetic locus associated with the risk of AD [1, 2]. However, the potential mechanism of *ABI3* in AD onset was unclear. In our study, we demonstrated that in pMCI group one common variant of *ABI3* (rs55978930) was associated with CSF *t*-tau levels and another (rs16947151) was associated with the CDR-SB. To our knowledge, our study is

the first to identify the associations of ABI3 common variants with CSF *t*-tau levels and CDR-SB scores.

Previous study has suggested that *ABI3* may influence AD risk through its potential effects on microglial function [2]. Besides, the expression of *ABI3* was significantly upregulated in the cortex of $App^{NL-G-F/NL-G-F}$ mouse model, indicating there is an association between cortical Aβ amyloidosis and *ABI3* [4]. The associations between common variants in *ABI3* and CSF Aβ was also examined in our study. Rs2158512 was associated with CSF Aβ ($p = 0.022$), but this association did not survive after Bonferroni correction. Although no significant effects were found between CSF levels of Aβ and *ABI3* common variants in the present study, we detected that rs55978930 was associated with CSF *t*-tau at baseline and over time in pMCI group. These associations remained significant in haplotype association analysis. CSF *t*-tau is considered to be an indicator of neurodegeneration and neuronal injury according to National Institute on Aging-Alzheimer's Association (NIA-AA) research framework [9]. And the levels of t-tau can be used in predicting conversion from MCI to AD dementia [10, 11]. Our findings suggested that the effect of *ABI3* common variants on CSF tau might be mainly exert on MCI patients. We also found that rs16947151 was associated with CDR-SB scores, which could reflect the severity of cognitive symptoms. This indicated that rs16947151 might be associated with cognitive decline in pMCI patients. These significant associations were both identified in pMCI group, indicating that the genetic factors of *ABI3* may play roles in the onset of AD.

Several recent studies on *ABI3* have been published [1, 2]. Our study is similar to previous exploring the effect of *ABI3* on AD. Compared to these, our study is novel by exploring the correlations of *ABI3* common variants to CSF biomarkers and cognitive function scores mainly in a non-demented elderly population from ADNI dataset. This research may provide better insight into the changes of cognition and CSF biomarkers' concentrations before the disease onset among individuals with different genotypes. However, our study also has limitations. The correlation between CSF *t*-tau levels and cognitive performance have been proved by previous studies [12, 13]. This correlation also has been validated in ADNI database. However, in our study, rs55978930 and rs16947151 were associated with CSF *t*-tau levels and CDR-SB scores separately. Moreover, some of the associations we observed are statistically relatively weak. These might be due to the relatively small sample sizes of subgroups. This factor may have made it difficult to detect small effects of variants. The restriction of participants to avoid genetics stratification make our findings cannot represent other ethnicities. Due to the restriction of ADNI, we cannot get access to enough genetic information and five tag SNPs may be less representative. Future exploration with a larger population-based cohort is needed to confirm our findings and increase power to elevate the significance of true associations. Also, more research is needed to understand the underlying mechanism of the observed associations.

In summary, we found common variants in *ABI3* were associated with CSF *t*-tau and CDR-SB, suggesting the potential role of *ABI3* in AD. It could provide new insights into the association between *ABI3* and AD at the pMCI stage. More studies are warranted to further explore the molecular mechanisms of *ABI3* involved in AD.

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Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.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 analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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SUPPLEMENTARY MATERIAL

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