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Genome-Wide Association Study Identifies *SLAMF1* Affecting the Rate of Memory Decline

Shi-Dong Chen[a], Hong-Qi Li[a], Xue-Ning Shen[a], Jie-Qiong Li[b], Wei Xu[c], Yu-Yuan Huang[a], Lan Tan[c], Qiang Dong[a,*] and Jin-Tai Yu[a,*], on behalf of Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China*
[b]*Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao, China*
[c]*Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China*

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Abstract.

Background: As cognitive function declines with age, identifying factors affecting the trajectory of cognitive decline is an indispensable step toward developing intervention strategies to improve the quality of the elderly life.

Objective: We performed a genome-wide association study (GWAS) focusing on memory function to explore single nucleotide polymorphisms (SNPs) associated with the rate of memory decline.

Methods: Seven hundred and nine eligible non-Hispanic Caucasians from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were included for analysis after quality control. GWAS was performed with linear regression. We subsequently tested whether the associations remained significant in subgroup analysis and also examined the impact of SNPs on the longitudinal changes in other neuropsychological measures and amyloid pathology.

Results: We identified rs13374761-A in *SLAMF1* gene associated with less memory decline (MAF = 0.071, $\beta = 0.0103$, $p = 4.14 \times 10^{-8}$). Subgroup analysis showed stability of results across groups with different diagnosis at baseline. Rs13374761-A also had protective effects on global cognition ($p = 0.024$), episodic memory ($p = 0.024$), and semantic memory ($p = 0.042$), and exerts protection against a decrease in CSF $A\beta_{42}$ concentration ($p = 0.0463$) and an increase in $A\beta$ loading in cerebral cortex ($p = 0.00666$) among minor allele carriers.

Conclusion: A novel variant in gene *SLAMF1* affects the rate of memory decline in the aged population. Given the protective effect of this variant, *SLAMF1* should be further investigated as a potential preventive and therapeutic target for monitoring cognition trajectories.

Keywords: Alzheimer's disease, amyloid, cognitive decline, genome-wide association study, memory, *SLAMF1*, SNP

[1]Data used in preparation of 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 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.

*Correspondence to: Prof. Jin-Tai Yu, MD, PhD, or Prof. Qiang Dong, MD, PhD Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, 12th Wulumuqi Zhong Road, Shanghai 200040, China. Tel.: +86 21 52888160; Fax: +86 21 62483421; E-mail: jintai_yu@fudan.edu.cn (J.T. Yu); E-mail: dong_qiang@fudan.edu.cn (Q. Dong).

INTRODUCTION

Cognitive function declines in a continuous and gradual pattern with age [1]. Most cognitive domains tend to decline approximately at the age of 55 years, but there is substantial inter-individual variability resulting from both environmental and genetic factors in normal and pathological aging [2, 3]. As cognitive function is an essential determinant of quality of life in old age, identifying factors affecting the trajectory of cognitive decline is an indispensable step toward developing intervention and treatment strategies.

Previous genome-wide association studies (GWAS) using longitudinal data have identified several loci affecting cognitive decline in normal aging or Alzheimer's disease (AD) progression such as *CLU*, *CR1*, *PICALM*, and *SPON1* [4–7]. Some of the them were also validated in subsequent candidate gene association studies enrolling different cohorts [8–11]. However, general cognition is derived from multiple domains, including memory, executive function, attention, language, visuospatial skill, and processing speed. These GWAS results could not manifest the effects of variants on specific domains. Genetic studies only focusing on general cognitive function as a phenotype may not be able to comprehensively illustrate the genetic architecture of cognitive function [12]. Hence, it would be more informative to investigate specific domains as cognitive phenotypes than collapsing all the domains under a unitary construct of global cognition in the study on genetics of cognitive decline [13, 14].

As memory loss is one of the major concerns in clinical settings, memory function is central to research on cognitive decline. Previous GWAS analyses were not able to detect associations between variants and global memory function partly due to lack of a reliable method to integrate memory tests at once, since separately developed neuropsychological tests emphasized on different aspects of memory. As the Alzheimer's Disease Neuroimaging Initiative (ADNI) recently developed a composite score to measure memory status, it becomes feasible to discover single nucleotide polymorphisms (SNPs) mainly affecting memory function [15].

In the present study, we performed a genome-wide association analysis with longitudinal measure of memory function, aiming to find novel variants associated with the rate of memory decline.

METHODS

Description of participants

Participants in the present study were enrolled from the ADNI, which is a longitudinal multicenter study launched in 2003, tracking clinical, imaging, genetic and biospecimen biomarkers in the progression of normal aging or to mild cognitive impairment (MCI) and dementia. The study was approved by institutional review boards of all participating institutions, and written informed consent was obtained from all participants or authorized representatives. We searched for non-Hispanic Caucasians with available genetic data and longitudinal neuropsychological data in the ADNI database (http://adni.loni.usc.edu) and 729 individuals were retained for analysis prior to quality control.

Phenotype measure

ADNI-Mem is a composite score positively correlated with memory function. It was developed and validated for the domain of memory with data from the ADNI neuropsychological battery using item response theory methods, where longitudinal data from the Rey Auditory Verbal Learning Test (RAVLT), memory tasks of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), words repetition of the Mini-Mental State Examination (MMSE), and the Logical Memory Test were integrated to obtain ADNI-Mem for each individual at different follow-up points from baseline to 144 months at most [15]. The rate of memory decline, as a phenotype, was estimated by dividing the difference of the ADNI-Mem by the difference of follow up time between the last follow-up point and the baseline.

Genotyping and quality control

GWAS data were downloaded from the ADNI database. Genotyping was performed using blood samples with illumina Omni 2.5M BeadChip. For our analysis, genotype data underwent stringent quality control, including SNP exclusion for missingness >0.02, individual exclusion for missingness >0.02, Minor Allele Frequency (MAF)<0.05, Hardy-Weinberg Equilibrium (HWE) p value $< 1 \times 10^{-6}$, heterozygosity rate within ± 3 standard deviation from mean, and cryptic relatedness (pi-hat >0.2). Outliers detected with z-score larger than 3 standard deviation units in terms of identity-by-descent (IBD)

were excluded. A total of 1,197,412 SNPs and 709 individuals remained for GWAS. Independent SNPs with linkage disequilibrium (LD) pruning at $r^2 = 0.2$ were then used to calculate the first 5 principle components for population structure. Quality control was performed with PLINK software (version 1.9)

Statistical analysis

GWAS

We performed a GWAS using multiple linear regression with PLINK. Age, gender, years of education, *APOE* ε4 allele count, ADNI-Mem at baseline, and first five principal components for population structure were included as covariates and the rate of memory decline as phenotype. A *p*-value less than 5×10^{-8} was considered significant. This threshold adequately controls for the number of independent SNPs in the entire genome [16]. Suggestive association threshold was $p < 1 \times 10^{-5}$. We also used a linear mixed model to validate our findings in SNP-association analyses. The Manhattan and QQ plots were generated using qqman package installed in R software (version 3.5.3). Regional association results were plotted with LocusZoom web tool (http://locuszoom.org/). To examine the stability of significant association, the variants passing the significance threshold were subsequently tested in subpopulations with different diagnosis at baseline.

Analysis of longitudinal neuropsychological test scores and amyloid level in vivo

The effects of significant SNPs on cognition and biomarker change over time were tested among the participants whose data on longitudinal neuropsychological test scores or biospecimen biomarkers were available from the ADNI database. Generalized estimating equations were utilized in analysis and β coefficient and p-value of the interaction terms between minor allele count and visit time since baseline were the parameters of interest to show the effects of SNPs. ADAS-cog (11 items), RAVLT, Category Fluency Test, Logical Memory Test, ADNI-EF, and Trail Making Test were used to evaluate the associations of SNPs with global cognitive function, episode memory, semantic memory, logical memory, executive function, and visuospatial skill and processing speed, respectively. Like ADNI-Mem, ADNI-EF was also a composite score combining different executive ability tests at once to assess overall executive function [17].

Since amyloid deposition is a defining element of AD and it associates with cognitive decline in aging and AD, SNP effects on amyloid-β (Aβ) level in cerebrospinal fluid (CSF) and cerebral cortex of interest were tested [18]. CSF $A\beta_{42}$ concentration was measured by Roche Elecsys electrochemiluminescence immunoassays [19]. Standard uptake value ratio (SUVr) of florbetapir, a PET scanning radiopharmaceutical compound specifically binding to Aβ, was calculated by dividing weighted florbetapir mean in frontal, cingulate, parietal, and temporal regions by composite reference region to measure amyloid loading in cerebral cortex. We were suggested to use a composite reference region made up of whole cerebellum, brainstem/pons, and eroded subcortical white matter for normalization in longitudinal florbetapir analysis [20].

Every intra-individual cognitive score or biomarker value available throughout follow-up period was included and adjusted for age, gender, years of education, baseline cognition score, baseline diagnosis, *APOE* ε4 allele count, and first five principle components for population structure. The analysis and plotting of change over time in cognition and biomarkers were performed with R software (version 3.5.3).

RESULTS

A total of 709 individuals were included in GWAS for ADNI-Mem change, consisting of 249 participants with normal cognition, 421 with MCI, and 39 with AD at baseline. Table 1 shows the characteristics of included population at baseline. Population substructure was plotted with genomic IBD and multidimensional scaling (MDS) components (Fig. 1A). ADNI samples showed tight clustering with individuals of European ancestry in MDS plot overlaid on 1KG samples (Fig. 1B)

GWAS for the rate of memory decline

One hundred and twelve SNPs passed the suggestive threshold, while only 1 SNP was significantly associated with the rate of ADNI-Mem change. This was rs13374761, an intronic variant located in *SLAMF1* gene on chromosome 1 (160,612,951 base pair, MAF = 0.071, $\beta = 0.0103$, $p = 4.14 \times 10^{-8}$; Fig. 2A and Table 2). Other top two SNPs with strong associations (rs16926287, $p = 9.96 \times 10^{-8}$; rs67435264, $p = 1.94 \times 10^{-7}$) are described in Table 2. A QQ plot was generated to

Table 1
Demographic and clinical characteristics of included population at baseline

	All ($n=709$)	CN ($n=249$)	MCI ($n=421$)	AD ($n=39$)
Percentage (%)	100	34.7	59.4	5.9
#Female (%)	42.2	48.9	39.1	39.5
#Age (SD)	73.5 (6.9)	74.8 (5.5)	72.7 (7.4)	75.0 (8.7)
#Year of education (SD)	16.1 (2.8)	16.4 (2.7)	16.0 (2.8)	15.6 (2.7)
#*APOE* ε4 carrier (%)	41.0	26.7	46.1	72.1
#MMSE score (SD)	28.0 (2.1)	29.0 (1.2)	27.9 (1.7)	22.7 (1.9)
#ADNI-MEM (SD)	0.47 (0.79)	1.02 (0.54)	0.27 (0.67)	–0.92 (0.57)
#ADAS-cog (11 items) score (SD)	8.86 (0.19)	5.87 (2.86)	9.58 (4.21)	20.0 (7.2)
#Recognition score of RAVLT (SD)	11.3 (3.4)	11.6 (3.2)	11.1 (3.4)	9.14 (4.56)
#Category Influency Test score (SD)	18.6 (5.7)	21.0 (5.4)	17.9 (5.1)	11.7 (5.1)

CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; SD, standard deviation; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; *APOE* ε4, apolipoprotein E ε4 allele. *P*-values across three groups are from Kruskal-Wallis test and Chi-square test and #$p<0.05$.

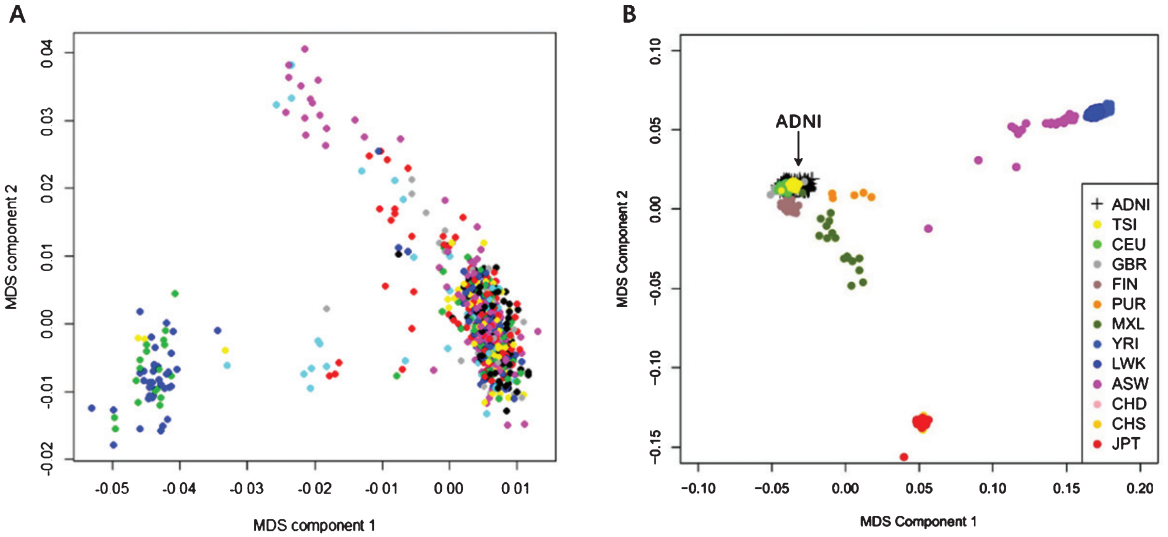

Fig. 1. Population stratification checked with genomic identity-by-descent (IBD) and multidimensional scaling (MDS) components. A) MDS plot of ADNI non-Hispanic white samples. B) MDS plot of ADNI samples overlaid on 1KG samples. The ancestry of the 1KG participants is displayed by the point color. ADNI, Alzheimer's Disease Neuroimaging Initiative; ASW, African ancestry in Southwest USA; CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; CHB, Han Chinese individuals from Beijing, China; CHS, Southern Han Chinese; FIN, Finnish in Finland; GBR, British in England and Scotland; JPT, Tokyo, Japan; LWK, Luhya in Webuye, Kenya; MXL, Mexican ancestry in Los Angeles, California; PUR, Puerto Ricans from Puerto Rico; TSI, Tuscans in Italy; YRI, Yoruba in Ibadan, Nigeria.

examine the difference between the observed and the expected p values for GWAS. As shown in Fig. 2B, there was an obvious distribution deviated from expected p-values among small observed p-values, which indicated the genome-wide significant association. The genomic inflation factor λ was 1.00041, suggesting absence of significant confounding from population stratification. The findings were also validated in the linear mixed model for rs13374761 ($p=0.013$). Figure 2C displays the regional association results in the neighbor region of rs13374761 from 160.4 Mb to 160.8 Mb part of chromosome 1, which showed no linkage disequilibrium between rs13374761 and nearby SNPs. There was no significant change in regional association results after controlling for this variant (Fig. 2D). All the subgroups with different diagnosis at baseline showed the same direction of the significant association between rs13374761 and rate of memory decline, which indicated relatively stable results of GWAS (Fig. 3).

Among the individuals for GWAS, 609 carried no minor alleles, 96 carried one minor allele, and 3 carried a pair of minor alleles at rs13374761. No significant difference was found in age, gender, years of education, *APOE* ε4 status or baseline diagnosis,

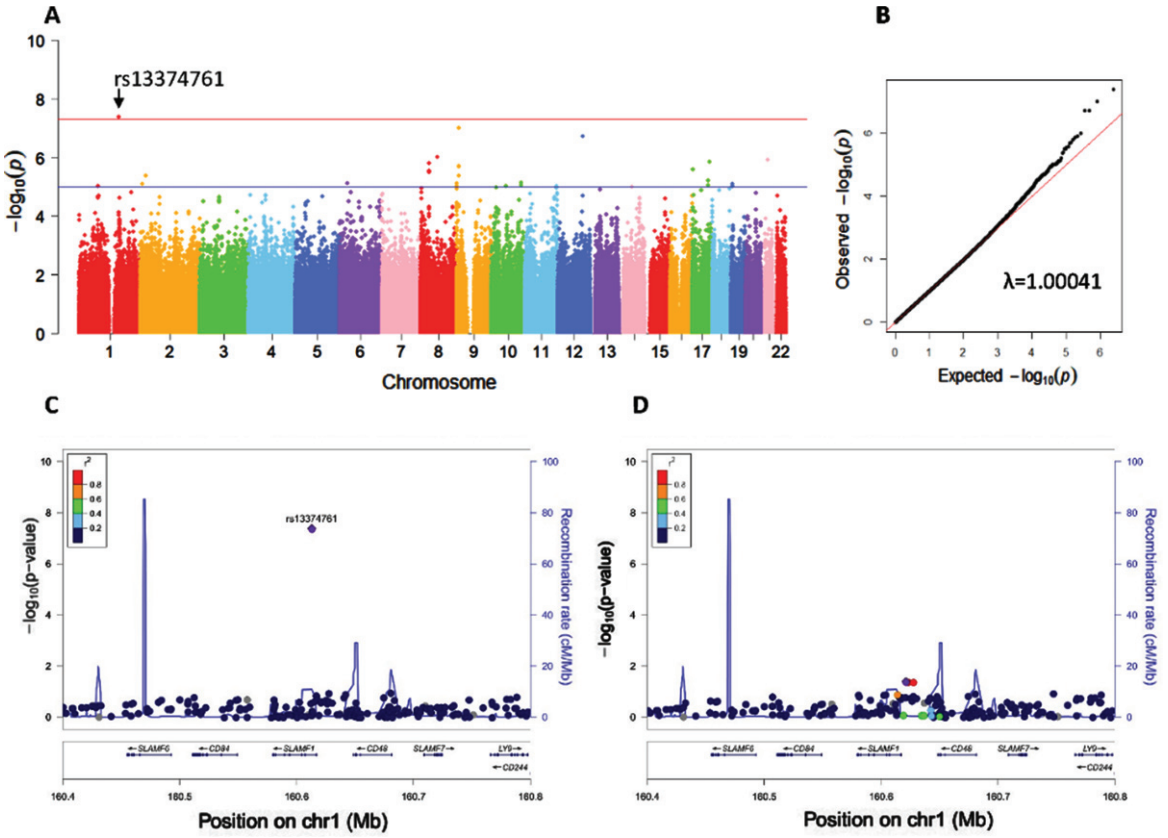

Fig. 2. Manhattan plot (A), quantile-quantile plot (B) and regional plots (C, D) of the Genome-wide association study for memory decline. A) Manhattan plot demonstrating the result of GWAS for the rate of memory decline measured by ADNI-Mem. The blue line represents a suggestive association threshold (1×10^{-5}) and the red line represents the genome-wide association threshold (5×10^{-8}). The arrow indicates the variant passing genome-wide significance threshold located on chromosome 1 in an intronic region of the *SLAMF1* gene. B) Quantile-quantile plot. The genomic inflation factor (λ) was 1.00041. C) Regional association results for the 160.4 Mb to 160.8 Mb region of chromosome 1. D) Regional association results for 160.4 Mb to 160.8 Mb region of chromosome 1 controlling for rs13374761.

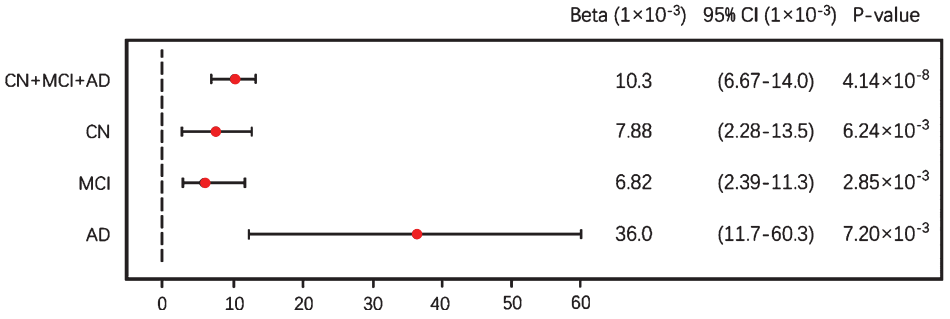

Fig. 3. Association between rs13374761 and memory decline across groups with different diagnosis at baseline. Beta represents mean difference of memory change per month measured by ADNI-Mem across different minor allele counts of rs13374761. CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; CI, confidence interval.

while baseline ADNI-Mem differed across genotype groups. The minor allele of rs13374761 was found to be associated with less ADNI-Mem decline per month, which indicated the modification of global memory function by rs13374761 (Fig. 4A).

Effects of rs13374761 on change in other cognitive measures

We subsequently tested associations between this SNP and the change rates of other cognitive mea-

Table 2
Top three SNPs associated with the rate of memory decline

SNP	CHR	Gene	Observed MAF	SNP Type	BETA	p
rs13374761	1	*SLAMF1*	0.071	Intron variant	0.010	4.14×10^{-8}
rs16926287	9	NA	0.13	Intergenic variant	0.0075	9.96×10^{-8}
rs67435264	12	*MYBPC1*	0.056	Downstream gene variant	0.011	1.94×10^{-7}

CHR, chromosome; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

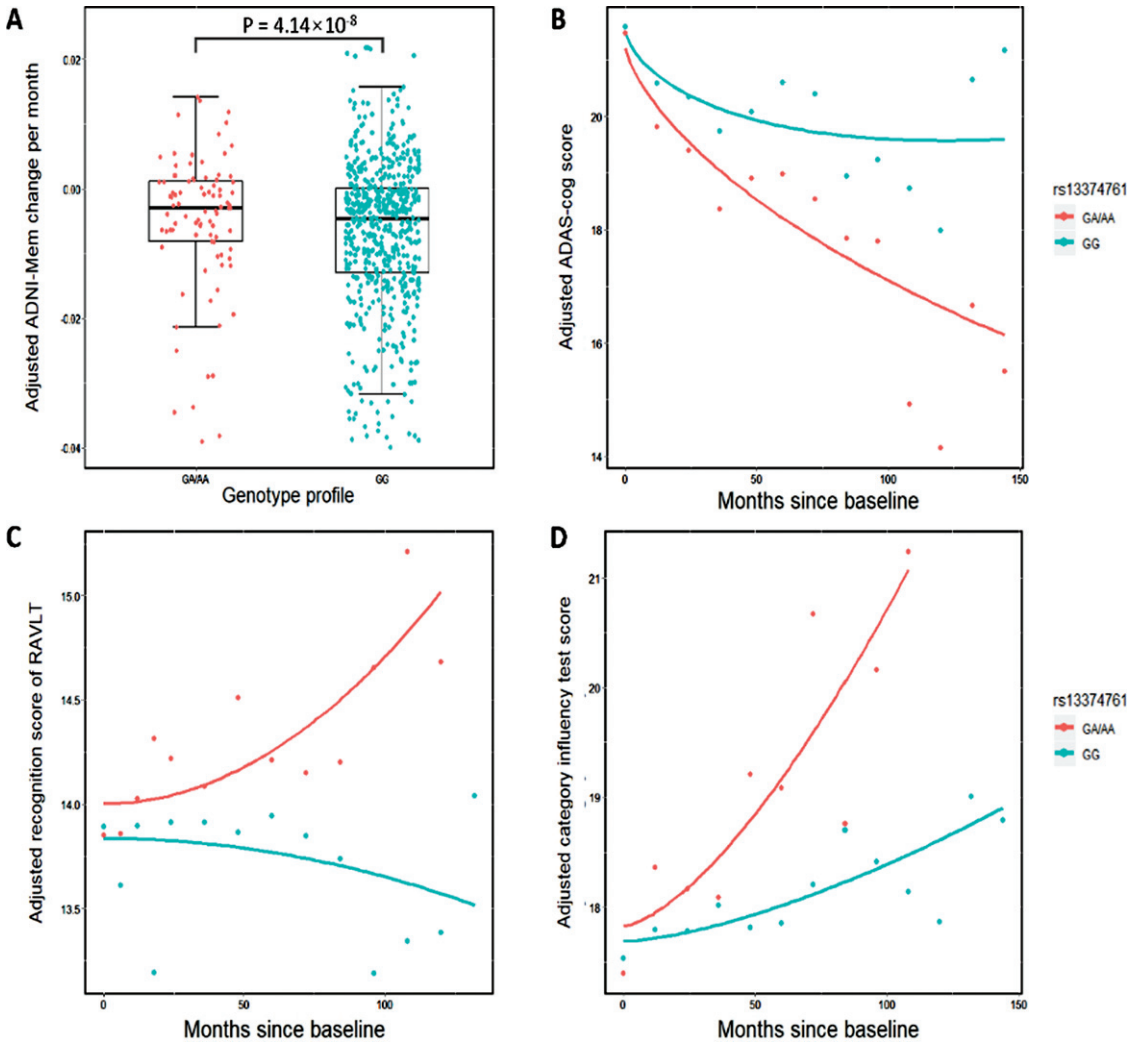

Fig. 4. Rs13374761-A significantly associates with less memory decline and differentially influences neuropsychological measures (B, C, D). A) The A allele associated with a significant slower rate of memory decline measure by ADNI-Mem ($p = 4.14 \times 10^{-8}$), adjusted for age, gender, years of education, *APOE* ε4 status, diagnosis and ADNI-Mem at baseline. Mean ADAS-cog (11-item) score (B), mean recognition score of RAVLT (C), and mean Category Fluency Test score (D) over time in rs13374761 minor allele carriers versus non-carriers, adjusted for age, gender, years of education, *APOE* ε4 status, diagnosis and ADNI-Mem at baseline. ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; RAVLT, Rey auditory verbal learning test.

sures. The result was significant for ADAS-cog (11 items) and the lowering of the score was amplified among minor allele carriers (β = –0.004088, $p = 0.024$; Fig. 4B). Significant association and protective effect of rs13374761-A were also found for recognition part of RAVLT (β = 0.00978, $p = 0.024$; Fig. 4C), and Category Fluency Test (β = 0.01910, $p = 0.042$; Fig. 4D). All the results were significant after adjusting for age, gender, years of education, cognition score, baseline, *APOE* ε4 allele count,

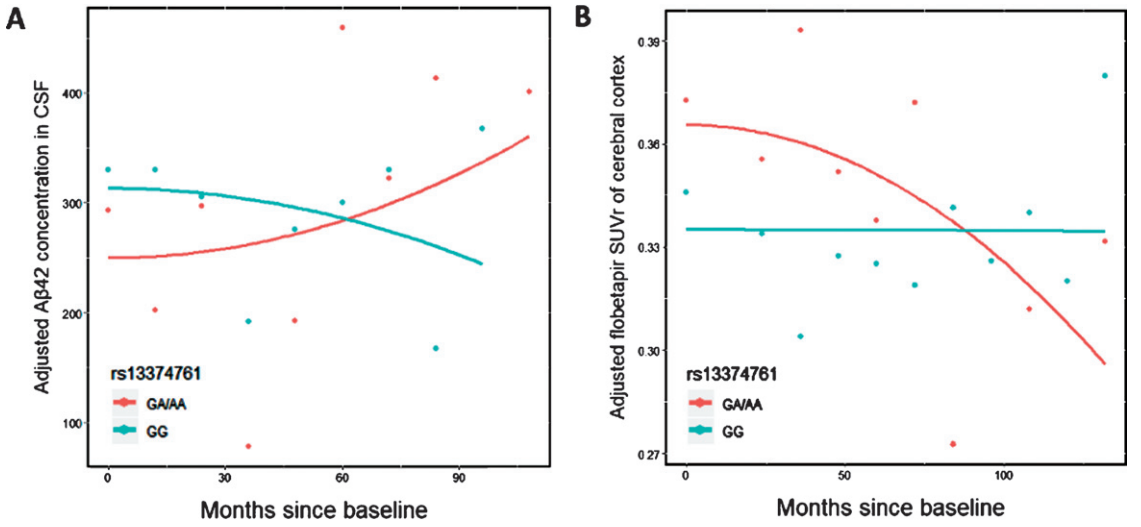

Fig. 5. Effects of rs13374761-A on longitudinal changes of amyloid pathology. CSF $A\beta_{42}$ concentration (A) and florbetapir SUVr of cerebral cortex (B) over time, adjusted for age, gender, years of education, *APOE* ε4 status, diagnosis, and Mini-Mental State Examination; score at baseline. SUVr, standard uptake value ratio.

and first five principle components for population structure at baseline. No significant result was found for ADNI-EF ($\beta = 0.00126$, $p = 0.446$), Trail Making Test ($\beta = -2.1 \times 10^{-5}$, $p = 0.808$), or Logical Memory Test ($\beta = 0.01039$, $p = 0.166$),

Effect of rs13374761 on change in PET imaging and CSF biomarkers

We lastly evaluated the association between rs13374761 and change in Aβ level *in vivo*. There were 268 (MCI = 164, CN = 124) and 628 (AD = 39, MCI = 374, CN = 215) individuals with available longitudinal data respectively collected in association analyses for $A\beta_{42}$ concentration in CSF and for florbetapir SUVr in cerebral cortex. As for CSF $A\beta_{42}$ concentration, rs13374761 showed a significant association. To be precise, individuals with the minor allele had an increase in CSF $A\beta_{42}$ concentration, while CSF $A\beta_{42}$ concentration in non-carriers decreased over time ($\beta = 0.0138$, $p = 0.0463$; Fig. 5A). Florbetapir SUVr in cerebral cortex decreased overtime in minor allele carriers, reaching significance level ($\beta = -6.21 \times 10^{-6}$, $p = 0.00666$; Fig. 5B). The effects of age, gender, years of education, baseline MMSE score, baseline diagnosis, *APOE* ε4 status, and first five principle components for population structure were controlled to display the significant results.

DISCUSSION

In the present study, we have identified a novel genome-wide significant association of *SLAMF1* rs13374761-A with the rate of memory decline in an aged population. This association was examined in subgroup analysis and further validated by other neuropsychological phenotypes, including scores of ADAS-cog, recognition part of AVLT, and the category fluency test, which were widely used measures of global cognitive ability, episodic memory, and semantic memory [21–23]. In comparison, longitudinal analyses of ADNI-EF and Trail Making Test failed to show significant results, which indicated that the effect of rs13374761 SNP on cognitive decline was limited to memory domain rather than executive function. Furthermore, negative results from logical memory test suggested that not all types of memory function were protected by rs13374761-A. The protective advantage conferred by minor allele was also supported by the evidence from endophenotypes at biomolecular level, including CSF $A\beta_{42}$ concentration and florbetapir SUVr in cerebral cortex which represent the earliest evidence of AD neuropathological change [24–26]. Therefore, rs13374761-A plays a protective role in cognitive decline and AD progression.

SLAMF1 gene encodes a protein called signaling lymphocytic activation molecule 1 (Slamf1) or CD150, which was originally found to adhere to the

surface of hematopoietic cells [27]. Previous studies reported its relation with diseases like measles and lymphoproliferative syndrome [27, 28]. Our study is the first to discover its association with cognition decline. As a co-stimulatory molecule, Slamf1 can initiate signal transduction networks among T cells, natural killer cells and antigen-presenting cells, and thus is widely involved in both innate and adaptive immune responses [29]. In the nervous system, it is expressed in activated M2c microglia, which is induced by IL-10 or TGF-β [30, 31]. Recent studies have discovered that Slamf1 promoted phagocytosis of extracellular substance by facilitating membrane fusion and phagolysosomal maturation [29]. Besides, it is potentially related to reduced microglial Aβ clearance in AD [32]. It is likely that *SLAMF1* rs13374761 regulates Slamf1 expression, alters Aβ clearance ability, and hence affects amyloid loading in cerebral cortex or its concentration in CSF. Since Aβ level has been reported to be associated with change rates of global cognition, episodic memory, and semantic memory in cognitively normal older adults or MCI patients, it makes sense that Aβ might mediate the protective effects of the SNP against cognitive decline [33–35]. However, further investigation including *in vivo* and *in vitro* research is needed to describe the detailed mechanism underlying the effects of the SNP on Aβ accumulation and cognitive decline.

As mentioned above, previous studies have established that *CLU*, *CR1*, and *PICALM* associated with cognitive decline using GWAS or candidate approaches [6, 7]. Clusterin, encoded by *CLU*, was able to influence both the aggregation and disaggregation of Aβ by sequestration of the Aβ oligomers [36]. Meanwhile, *CR1* was proved to participate in the clearance of Aβ peripherally by erythrocyte or directly in the brain [37]. As *PICALM* abundantly expressed in capillary endothelium, a recent study discovered that *PICALM* played a central role in transcytosis across the blood–brain barrier, contributing to Aβ elimination [38]. As for *SPON1*, it was also reported to correlate with suppressed Aβ level [39]. Together with our findings, all these studies indicated a strong association between Aβ clearance and cognitive decline, thus reducing the amyloid pathology was likely an effective approach to block the detrimental variants' effects on cognitive trajectories.

The strength of our study is that we used a composite score to perform GWAS at the domain level and then tested the significant association and protective effect at global cognition level and biomolecular level. This provided a comprehensive view of the effects of the SNP on cognition-related phenotypes. Recently, cognitive "stress tests" with higher sensitivity like the LASSI-L were developed to detect cognitive change in very early stage of MCI and AD [40]. These tests are analogous with an exercise electrocardiogram in cardiology that can reveal cardiac deficits which may be undetectable in resting state. Future genetic association studies, particularly those with relatively small sample sizes, may incorporate these tests to explore variants with small effect sizes.

There are some limitations when interpreting our findings. The sample sizes in analyses were relatively small, especially for CSF $A\beta_{42}$, resulting in limited power to detect variants which had small effects on traits of interest. Considering that the accumulation of Aβ in brain tissue is considered to take decades, the follow-up period time of individuals included in our study was actually not long enough to monitor longitudinal changes. Accordingly, replication in larger samples with longer duration of follow-up is demanded to confirm our findings. Subjects in our study were restricted to non-Hispanic whites to minimize confounding from population stratification across ethnicities. Nevertheless, the minor allele frequency of rs13374761 differs among various races. The contradiction determines the racial limitation of our research conclusion and the necessity of replication analysis in other races. In addition, the specific mechanisms for *SLAMF1* affecting phenotypes remained unsolved, as mentioned above. Functional genomics experiments including immunohistochemistry and analyses of *SLAMF1* knockout models are expected in future research.

Conclusions

In summary, we identified a novel protective variant in gene *SLAMF1* which was associated with a slower rate of memory decline in an aged population. Its protective effects were also discovered on other neuropsychological phenotypes of global cognition, episodic memory, and semantic memory. Furthermore, the SNP affected Aβ level in CSF and cerebral cortex, suggesting that its influence on cognition was mediated by amyloid *in vivo*. Further investigation is warranted to explore mechanisms underlying the protective effects conferred by *SLAMF1* on cognitive decline. More importantly, validating this novel genetic association in other cohorts with large samples may provide new insights into

the pathophysiology of cognitive decline and further suggest *SLAMF1* as a potential preventive and therapeutic target.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-1214r1).

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