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RESEARCH ARTICLE

Immunity gene *IFITM3* variant: Relation to cognition and Alzheimer's disease pathology

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Abstract

Introduction: We investigated single-nucleotide polymorphisms (SNPs) in *IFITM3*, an innate immunity gene and modulator of amyloid beta in Alzheimer's disease (AD), for association with cognition and AD biomarkers.

Methods: We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; $N = 1565$) and AddNeuroMed ($N = 633$) as discovery and replication samples, respectively. We performed gene-based association analysis of SNPs in *IFITM3* with cognitive performance and SNP-based association analysis with cognitive decline and amyloid, tau, and neurodegeneration biomarkers for AD.

Results: Gene-based association analysis showed that *IFITM3* was significantly associated with cognitive performance. Particularly, rs10751647 in *IFITM3* was associated with less cognitive decline, less amyloid and tau burden, and less brain atrophy in ADNI. The association of rs10751647 with cognitive decline and brain atrophy was replicated in AddNeuroMed.

Discussion: This suggests that rs10751647 in *IFITM3* is associated with less vulnerability for cognitive decline and AD biomarkers, providing mechanistic insight regarding involvement of immunity and infection in AD.

KEYWORDS
Alzheimer's disease pathology, amyloid, biomarkers, clinical progression, cognitive decline, *IFITM3*, neurodegeneration, single nucleotide polymorphisms, tau

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Highlights

- *IFITM3* is significantly associated with cognitive performance.
- rs10751647 in *IFITM3* is associated with cognitive decline rates with replication.
- rs10751647 is associated with amyloid beta load, cerebrospinal fluid phosphorylated tau levels, and brain atrophy.
- rs10751647 is associated with *IFITM3* expression levels in blood and brain.
- rs10751647 in *IFITM3* is related to less vulnerability to Alzheimer's disease pathogenesis.

1 | INTRODUCTION

Because herpes simplex virus was observed in *post mortem* brains of patients with Alzheimer's disease (AD) in the 1990s,[1] association between microbial infection and AD has been discussed with controversy. Previous studies have shown that infection from pathogens increased amyloid beta (Aβ) production in the brain, which may suggest that Aβ is a defense reaction with an antimicrobial function;[2–4] however, its regulatory mechanism in innate immunity and its association with AD pathogenesis are largely unknown.

Recent large-scale genome-wide association studies (GWAS) have provided genetic insight of the link between immunity and AD pathology, revealing several AD-related genes with immune functions.[5] Interferon-induced transmembrane protein 3 (*IFITM3*) is an innate immune responder to viral infection and is known to restrict progression of viral infection.[6] A recent study reported that *IFITM3* binds to γ-secretase, upregulates its activity, and increases production of Aβ in AD.[7] Additionally, expression levels of *IFITM3* were significantly higher in the brains of patients with AD compared to cognitively normal older adult controls and positively correlated with Aβ load in the brain.[7] This implicates *IFITM3* as an immune mediator with γ-secretase modulatory function with the ability to affect AD pathogenesis. Another study showed that vulnerability to influenza may be altered, depending on a single nucleoid polymorphism (SNP) in *IFITM3*.[8] Considering *IFITM3* as a regulator of Aβ production, vulnerability to AD may also vary depending on SNPs in *IFITM3*, which has not been studied.[8]

Therefore, in this study, we aimed to identify SNPs in *IFITM3* as associated with clinical outcome and AD biomarkers. First, we performed gene-based association analysis of SNPs in *IFITM3* with cognitive performance. Then, we performed SNP-based association analysis in *IFITM3* with cognitive decline; disease progression from mild cognitive impairment (MCI) to AD; and amyloid (A), tau (T), and neurodegeneration (N) biomarkers measured from multimodal neuroimaging (amyloid positron emission tomography [PET] and magnetic resonance imaging [MRI]), and cerebrospinal fluid (CSF). Finally, we performed expression quantitative trait loci (eQTL) analysis to investigate association between SNPs and *IFITM3* expression levels.

2 | METHODS

2.1 | Participants

Participants in the study were non-Hispanic White participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and AddNeuroMed cohorts as discovery and replication samples, respectively. The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Dr. Michael W. Weiner.[9] The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to accurately measure the progression of MCI and early AD. The AddNeuroMed is a cross European, public/private consortium developed for AD biomarker discovery.[10] AD was diagnosed clinically according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Dementias Association criteria for probable AD in ADNI and AddNeuroMed.[11] MCI was diagnosed when there was objective memory impairment but without meeting the criteria for dementia.[9,10] Written informed consent was obtained at the time of enrollment and included permission for analysis and data sharing. The protocol and informed consent forms were approved by the institutional review board at each participating site.

2.2 | Genotyping and imputation

Genome-wide genotyping was performed using Illumina GWAS array platforms (Illumina Human610-Quad BeadChip, Illumina HumanOmni Express BeadChip, and Illumina HumanOmni 2.5M BeadChip).[12,13] Apolipoprotein E genotyping was separately conducted.[13] Using PLINK 1.9 (www.cog-genomics.org/plink2/),[14] we then performed standard quality control (QC) procedures for samples and SNPs as described previously.[15] SNPs with a SNP call rate <95%, Hardy-Weinberg *P*-value $<1 \times 10^{-6}$, and a minor allele frequency (MAF) <1% were discarded. Samples with sex inconsistencies and sample call rate <95% were eliminated. To prevent spurious associations due to population stratification, we used multidimensional scaling

analysis to select only non-Hispanic participants of European ancestry that clustered with HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) or TSI (Toscani in Italia) populations.[16,17] After QC procedures, because these cohorts used different genotyping platforms, we imputed un-genotyped SNPs separately in each platform using MaCH software with the Haplotype Reference Consortium data as a reference panel.[18,19]

2.3 | Amyloid (A), tau (T), and neurodegeneration (N) biomarkers for AD

Brain amyloid deposition from amyloid PET as an amyloid biomarker, CSF phosphorylated tau (CSF p-tau) levels as a tau biomarker, and entorhinal cortex thickness from MRI as a neurodegeneration biomarker were used. For assessment of cortical amyloid burden in ADNI, we used preprocessed (co-registered, averaged, standardized image and voxel size, uniform resolution) [18F] florbetapir PET scans[20] and calculated a mean standardized uptake value ratio (SUVR) using a whole cerebellum reference region as previously described.[21] CSF p-tau levels were measured by validated and highly automated Roche Elecsys electrochemiluminescence immunoassays (Roche Diagnostics).[22] Details of CSF collection are explained on the ADNI website (http://www.adni.loni.usc/edu/data-samples/biospecimen-data). CSF p-tau values were log-transformed to follow a normal distribution. Amyloid PET and CSF p-tau data were not available in AddNeuroMed. As a neurodegeneration biomarker, entorhinal cortex thickness from T1-weighted brain MRI scans was measured using FreeSurfer version 6.0 (surfer.nmr.mgh.harvard.edu).[23]

2.4 | Cognitive performance

To assess cognitive performance, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)[24] was used in ADNI and AddNeuroMed. ADAS-Cog is a cognitive test battery that evaluates learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using a PubMed and Google Scholar search. There is increasing evidence that *IFITM3* modulates amyloid beta production in Alzheimer's disease (AD). It is therefore possible that single-nucleotide polymorphisms (SNPs) in *IFITM3* could be associated with cognition and AD biomarkers.
2. **Interpretation**: This is the first study to show that rs10751647 in *IFITM3* is associated with less amyloid and tau burden, less brain atrophy, and less cognitive decline, providing mechanistic insight regarding involvement of immune activity and infection in AD.
3. **Future Directions**: Functional studies in larger independent cohorts and animal models should be performed to investigate the mechanistic roles of rs10751647 in cognitive decline and AD pathology.

2.5 | Statistical analysis

Gene-based association analysis of *IFITM3* with ADAS-Cog in ADNI was performed using a gene-based test in PLINK with additive genetic models adjusted for age, sex, and education, where common SNPs (MAF > 5%) located within ±20kb of upstream and downstream regions of *IFITM3* were selected. Permutation (20,000 permutations) was used to adjust for multiple testing. Independently associated SNPs based on $P = .05$ and an r^2 threshold of 0.5 were selected and used in gene-based analysis of *IFITM3*. Association results of SNPs in *IFITM3* were visualized using LocusZoom.[25]

Association analysis between SNPs and longitudinal cognitive decline in ADNI and AddNeuroMed was performed using a linear mixed effects model. The variable of interest was the interaction of SNPs and time. The dependent variable was ADAS-Cog, with the fixed effects being age, sex, and education and the random effect being subject.

The identified significant SNPs were used for further analysis to explore association with disease progression and A/T/N biomarkers for

TABLE 1 Demographics of the study sample

Cohort	Diagnosis at baseline	*N*	Female (%)	Age, mean (SD)
ADNI (*N* = 1565)	CN	458	228 (49.8%)	74.1 (5.70)
	MCI	794	317 (39.9%)	72.7 (7.62)
	AD	313	135 (43.1%)	74.7 (7.80)
AddNeuroMed (*N* = 633)	CN	221	142 (64.2%)	76.5 (6.17)
	MCI	201	108 (53.7%)	74.3 (5.92)
	AD	211	120 (56.8%)	74.9 (5.78)

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CN, cognitively normal older adults; MCI, mild cognitive impairment; SD, standard deviation.

AD. The effect of SNPs on disease progression from MCI to dementia was assessed using a Cox proportional hazard model adjusted for age, sex, and education. Association analysis between SNPs and A/T/N biomarkers including brain amyloid deposition from amyloid PET, CSF p-tau levels, and entorhinal cortex thickness from MRI was performed using linear regression models adjusted for age, sex, and education. For entorhinal cortical thickness, MRI field strength and intracranial volume (ICV) in ADNI and ICV in AddNeuroMed were additionally adjusted for, respectively. Furthermore, the SurfStat software was used to perform whole brain surface-based analysis of cortical thickness to examine the effect of SNPs on brain structural atrophy on vertex-by-vertex bases by applying a general linear model (GLM) approach.[26] GLM approaches were developed using age, sex, education, ICV, and MRI field strength as covariates. In the whole brain surface-based analysis, the adjustment for multiple comparisons was performed using the random field theory (RFT) correction method at a 0.05 level of significance. Statistical parametric mapping (SPM) was used to perform whole brain analysis of brain amyloid deposition to examine the effect of SNPs on amyloid burden across the whole brain using a linear regression analysis with age and sex as covariates.[27] The adjustment for multiple comparisons was performed using the false discovery rate (FDR) correction method at a 0.05 level of significance.

Linear mixed effect analysis, Cox proportional hazard analysis, and linear regression analysis were performed using R version 4.0.5 (www.R-project.org).

In addition, Genotype-Tissue Expression (GTEx; https://gtexportal.org/home/) data from GTEx Analysis Release V8 (dbGaP Accession phs000424.v8.p2) were used to investigate eQTL in tissue-specific gene expression.

3 | RESULTS

A total of 2198 participants were included from two independent cohorts (1565 from ADNI and 633 from AddNeuroMed) in this study (Table 1).

3.1 | Gene-based association analysis of *IFITM3* with cognitive performance

Gene-based analysis of *IFITM3* using 112 common SNPs (MAF > 5%) within ±20kb regions surrounding the *IFITM3* gene showed that *IFITM3* was significantly associated with ADAS-Cog (permutation-corrected *P*-value = 1.25×10^{-3}), and five independently associated SNPs were identified based on $P = .05$ and an r^2 threshold of 0.5 (Table S1 and Figure S1 in supporting information). Two SNPs (rs10751647 and rs2091850) in *IFITM3* were significant (*P*-value $<4.46 \times 10^{-4}$ [= 0.05/112]) after the Bonferroni correction and were used for further analyses. Genotypes of rs10751647 and rs2091850 and its corresponding participant numbers are shown in Table S2 in supporting information. As minor alleles, rs10751647 and rs2091850 have C and T alleles, respectively.

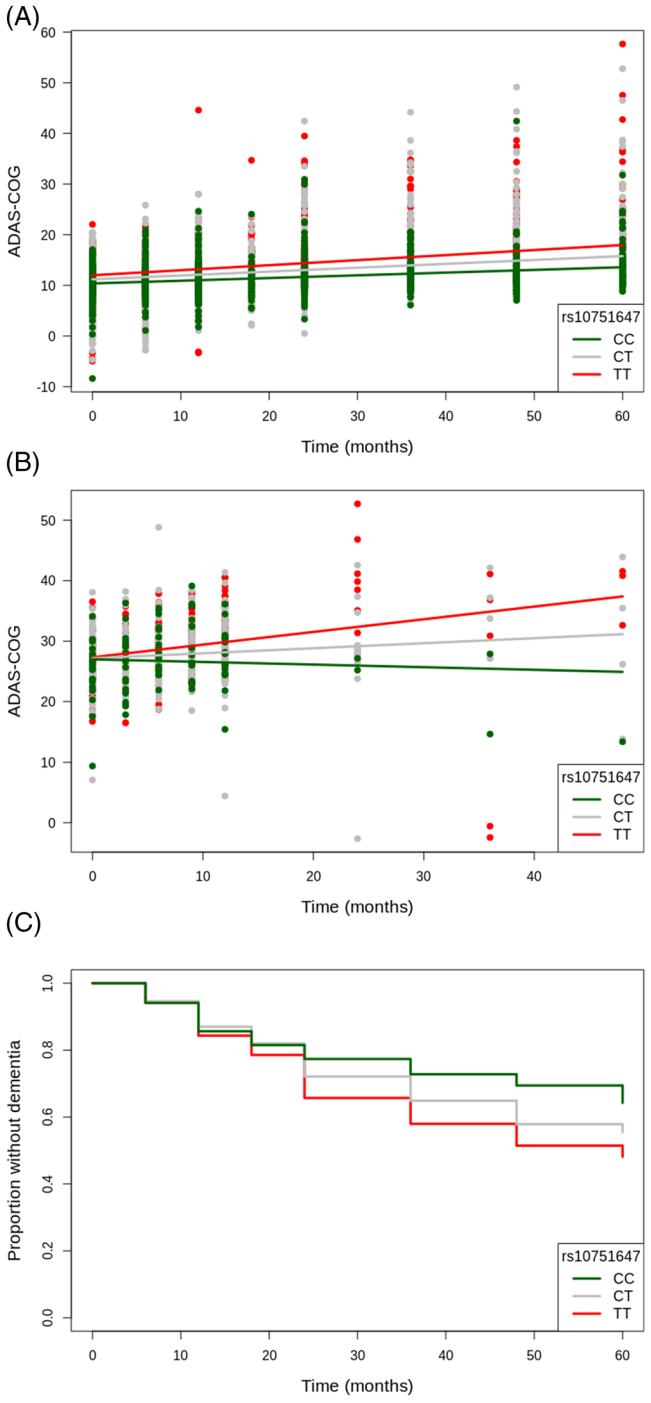

FIGURE 1 Association of rs10751647 with longitudinal cognitive decline and disease progression from MCI to dementia. Association of rs10751647 with longitudinal cognitive decline and disease progression from MCI to dementia was analyzed using a linear mixed effects model and Cox proportional hazard model, respectively, adjusted for age, sex, and education. As the number of minor alleles of rs10751647 increases, rs10751647 was associated with less cognitive decline rates (*P*-value of 6.63×10^{-8} in ADNI [A] and 2.30×10^{-3} in AddNeuroMed [B]) and decreased risk of disease progression from MCI to dementia (HR 0.79 in ADNI [C]). ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; HR, hazard ratio; MCI, mild cognitive impairment

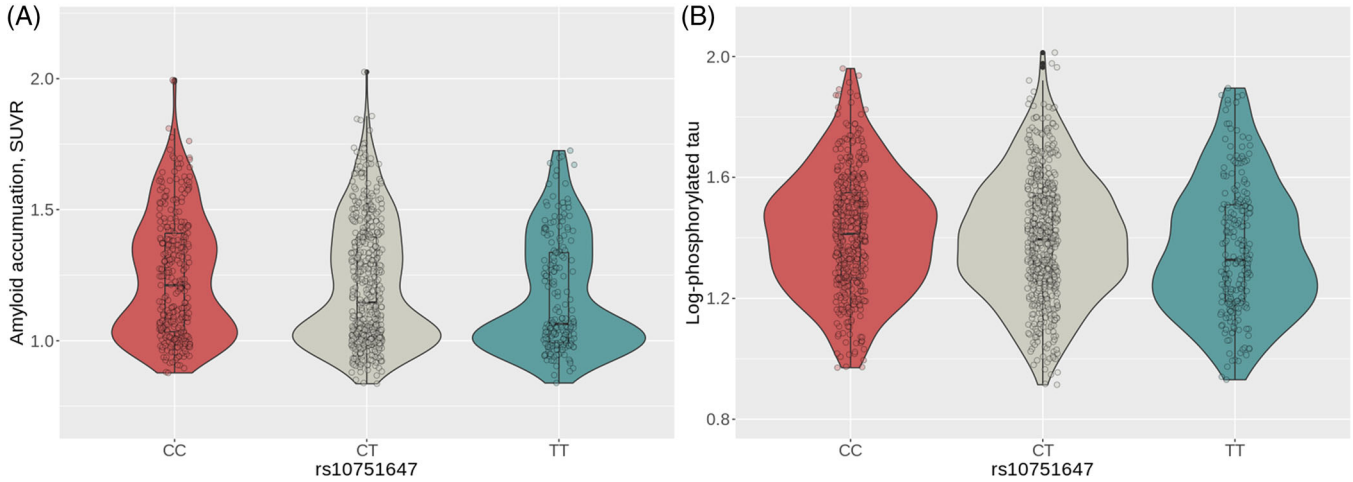

FIGURE 2 Association of rs10751647 with brain amyloid deposition in amyloid PET and p-tau levels in CSF in ADNI. Association of rs10751647 with amyloid and tau burden was analyzed using linear regression models adjusted for age, sex, and education. As the number of minor alleles of rs10751647 increases, rs10751647 was associated with less amyloid burden in amyloid PET (*P*-value = 8.65×10^{-4}) (A) and less p-tau levels in CSF (*P*-value = 6.59×10^{-3}) (B). ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio

3.2 | Longitudinal association analysis of rs10751647 and rs2091850 in *IFITM3* with cognitive decline

More minor alleles for rs10751647 were significantly associated with less longitudinal cognitive decline with beta-value (*P*-value) of -1.07×10^{-2} (4.69×10^{-5}) in ADNI and -1.26×10^{-1} (2.30×10^{-3}) in AddNeuroMed (Figure 1A,B). However, rs2091850 was not associated with longitudinal cognitive decline in ADNI or AddNeuroMed with beta-value (*P*-value) of -3.39×10^{-3} (2.73×10^{-1}) and -1.05×10^{-1} (5.63×10^{-2}), respectively. rs10751647 replicated in association with longitudinal cognitive decline and was used for further analysis.

3.3 | Disease progression: MCI conversion to dementia

The effect of rs10751647 on disease progression from MCI to dementia was evaluated using a Cox proportional hazards model. In ADNI, more minor alleles for rs10751647 were associated with decreased risk of disease progression with HR 0.79 and 95% confidence interval (CI; 0.67, 0.94; Figure 1C). The result was not replicated in AddNeuroMed.

3.4 | Association of rs10751647 in *IFITM3* with A/T/N biomarkers for AD

3.4.1 | Amyloid biomarker (amyloid burden measured by amyloid PET)

Association analysis between brain amyloid deposition and rs10751647 showed that more minor alleles for rs10751647 were significantly associated with less amyloid burden with beta-value (*P*-value) of −0.03 (8.65×10^{-4}). The results were shown in violin plots (Figure 2). In addition, in an unbiased way, we performed a detailed whole-brain analysis to determine the effect of rs10751647 on brain amyloid deposition on a voxel-wise level. We identified significant associations (FDR-corrected $P < .05$; Figure 3). More minor alleles were significantly associated with reduced amyloid deposition in a widespread pattern, especially in the bilateral frontal, parietal, and temporal lobes.

3.4.2 | Tau biomarker (CSF p-tau levels)

Association analysis between CSF p-tau levels and rs10751647 showed that more minor alleles for rs10751647 were significantly associated with smaller CSF p-tau levels with beta-value (*P*-value) of −0.02 (6.59×10^{-3}). The association results were shown in violin plots (Figure 2).

3.4.3 | Neurodegeneration biomarker (entorhinal cortical thickness on MRI)

In ADNI, more minor alleles for rs10751647 were associated with larger entorhinal cortical thickness with an odds ratio (*P*-value) of 1.03 (4.00×10^{-2}), which was replicated in AddNeuroMed with an odds ratio (*P*-value) of 1.08 (2.00×10^{-2}). Further, we performed a detailed whole-brain surface-based analysis using multivariable regression models and assessed the effect of rs10751647 on whole-brain cortical thickness in an unbiased way. We identified significant associations for rs10751647 (RFT-corrected $P < 0.05$; Figure 3). More minor alleles of rs10751647 were significantly associated with larger cortical thickness in bilateral temporal lobes including the entorhinal cortex (Figure 3).

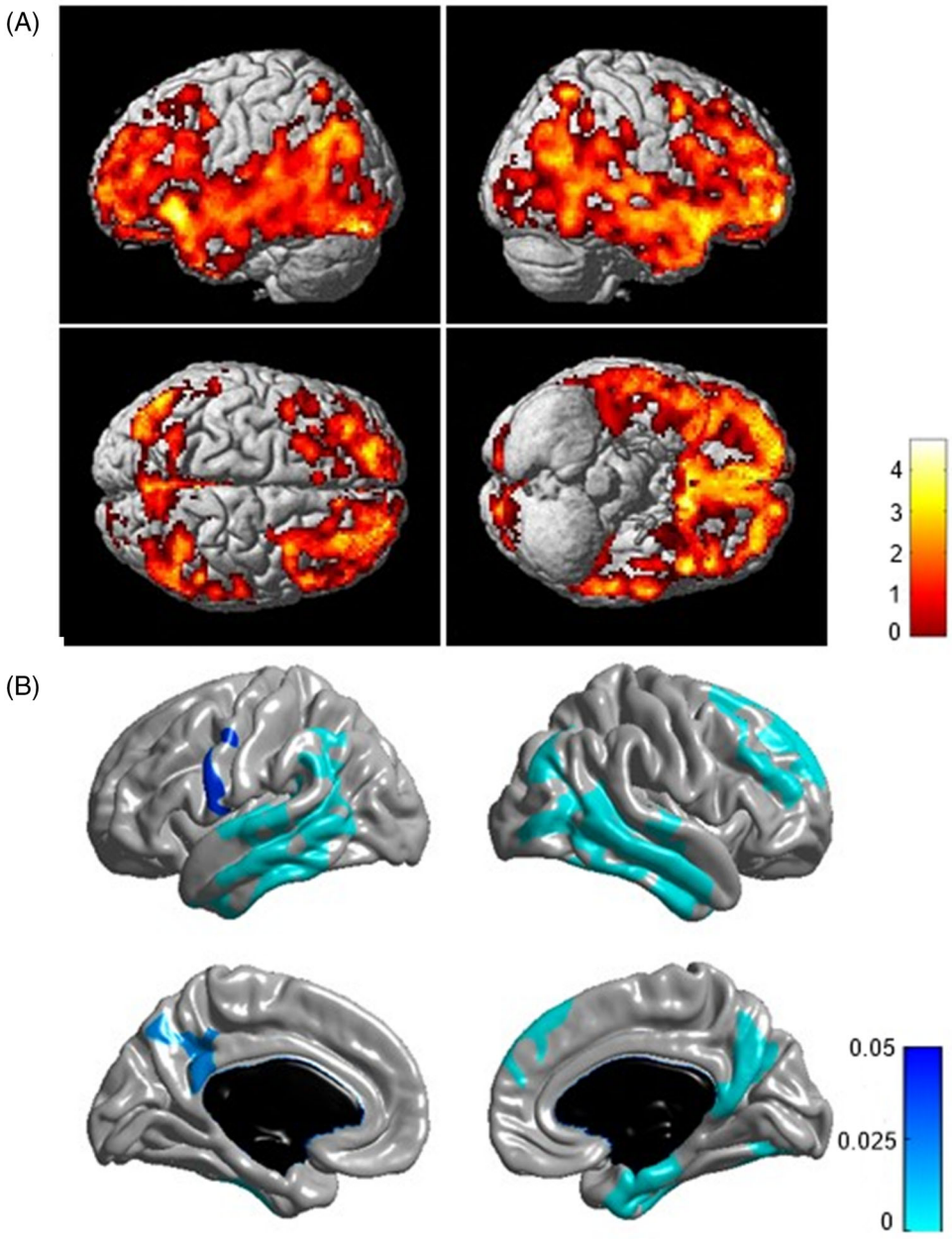

FIGURE 3 Whole brain association analysis of rs10751647 with amyloid deposition (amyloid PET) (A) and cortical thickness (MRI) (B) in ADNI. Whole-brain voxel-based imaging analysis (A) of amyloid deposition showed that more minor alleles of rs10751647 were significantly associated with reduced amyloid deposition in a widespread pattern, especially in the bilateral frontal, parietal, and temporal lobes. Statistical maps were thresholded using a false discovery rate for a multiple testing adjustment to a corrected significance level of 0.05. Whole-brain surface-based analysis (B) of cortical thickness across the brain surface showed that more minor alleles of rs10751647 were significantly associated with larger cortical thickness in the bilateral temporal lobes including the entorhinal cortex. Statistical maps were thresholded using a random field theory for a multiple testing adjustment to a corrected significance level of 0.05. ADNI, Alzheimer's Disease Neuroimaging Initiative; MRI, magnetic resonance imaging; PET, positron emission tomography

3.5 | Expression quantitative trait loci analysis

To explore association between rs10751647 and expression levels of *IFITM3*, we looked at tissue-specific eQTL results in the GTEx database (Figure S2 in supporting information). More minor alleles for rs10751647 were associated with increased *IFITM3* expression levels in blood and brain.

4 | DISCUSSION

In this study, we found that *IFITM3* was significantly associated with cognitive performance by gene-based association analysis (permutation-corrected $P = 1.25\times10^{-3}$), and two SNPs (rs10751647, rs2091850) in *IFITM3* were significantly associated with cognitive performance. Particularly, rs10751647 was associated with cognitive

decline rates in ADNI, which was replicated in an independent cohort, AddNeuroMed. In addition, rs10751647 was significantly associated with Aβ deposition measured by amyloid PET scan, CSF p-tau levels, and entorhinal cortical thickness measured by MRI scan in ADNI. The association of rs10751647 with entorhinal cortical thickness was replicated in AddNeuroMed. Participants with minor alleles (C) of rs10751647 have less cognitive decline, less amyloid and tau burden, and less brain atrophy. Tissue-specific eQTL analysis in healthy individuals showed that rs10751647 is associated with *IFITM3* expression levels in blood and brain.

For amyloidopathy of AD pathogenesis, our study showed that an increasing number of minor alleles of rs10751647 was related to less amyloid burden. In particular, whole-brain imaging genetics analysis showed the association of rs10751647 with reduced amyloid deposition, especially in the bilateral frontal, parietal, and temporal lobes. A recent study suggested direct association between *IFITM3* and Aβ production. Immune activation by infection or inflammatory condition induces proinflammatory cytokines, which upregulate *IFITM3* expression binding presenilin1 in a γ-secretase complex near the active site promoting cleavage of Aβ.[7] In the study, *IFITM3* expression was higher in AD compared to the control group in the temporal cortex. This shared brain region with our results might suggest that the temporal area could be associated with *IFITM3* activity.

For tauopathy and neurodegeneration, our study showed that rs10751647 was related to tau burden and brain atrophy. *IFITM3* was suggested to inhibit virus-triggered induction of type I interferon,[28] which may affect pathological tau phosphorylation and subsequent neurodegeneration.[29]

One of the limitations in our study is that we chose the ±20kb window around *IFITM3* as the gene boundary for gene-based association analysis. Although the 20kb window provides an optimal width for including regulatory SNPs of *IFITM3*, this may exclude the possibility of identifying significant *IFITM3*-related SNPs outside this region. Another factor that should be considered is that our study is contradictory to a recent study showing that increased expression levels of *IFITM3* in AD brains was associated with increased amyloid load,[7] whereas our study showed that the minor allele of rs10751647 was associated with increased expression of *IFITM3* in brain and blood of healthy individuals and less cognitive decline, less amyloid and tau burden, and less brain atrophy in MCI and AD. Functional studies are warranted to investigate the mechanism of the effect of rs10751647 on cognitive decline, amyloid and tau burden, and brain atrophy. Additionally, our study was performed with modest sample sizes from two independent cohorts, and our results need to be validated by replication studies in independent larger data sets.

In conclusion, we found that *IFITM3* SNP, rs10751647, was associated with less vulnerability to amyloid, tau burden, neuronal degeneration, clinical progression, and cognitive decline rates. Association of the SNP with neuronal degeneration and cognitive decline rates was replicated in the independent cohort, AddNeuroMed. This study provides further supporting evidence of the relationship between *IFITM3* and AD pathogenesis.

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CONFLICTS OF INTEREST

The authors declares that there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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