Novel Genetic Variants in \textit{TP37}, \textit{PIK3R1}, \textit{CALM1}, and \textit{PLCG2} of the Neurotrophin Signaling Pathway Are Associated with the Progression from Mild Cognitive Impairment to Alzheimer’s Disease

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Abstract.
Background: Alzheimer’s disease (AD) is a common neurodegenerative disease and mild cognitive impairment (MCI) is considered as the prodromal stage of AD. Previous studies showed that changes in the neurotrophin signaling pathway could lead to cognitive decline in AD. However, the association of single nucleotide polymorphisms (SNPs) in genes that are involved in this pathway with AD progression from MCI remains unclear.
Objective: We investigated the associations between SNPs involved in the neurotrophin signaling pathway with AD progression.
Methods: We performed single-locus analysis to identify neurotrophin-signaling-related SNPs associated with the AD progression using 767 patients from the Alzheimer’s Disease Neuroimaging Initiative study and 1,373 patients from the National Alzheimer’s Coordinating Center study. We constructed polygenic risk scores (PRSs) using the identified independent non-\textit{APOE} SNPs and evaluated its prediction performance on AD progression.

\textsuperscript{1}Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (https://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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Results: We identified 25 SNPs significantly associated with AD progression with Bayesian false-discovery probability \( \leq 0.8 \). Based on the linkage disequilibrium clumping and expression quantitative trait loci analysis, we found 6 potentially functional SNPs that were associated with AD progression independently. The PRS analysis quantified the combined effects of these SNPs on longitudinal cognitive assessments and biomarkers from cerebrospinal fluid and neuroimaging. The addition of PRSs to the prediction model for 3-year progression to AD from MCI significantly increased the predictive accuracy.

Conclusion: Genetic variants in the specific genes of the neurotrophin signaling pathway are predictors of AD progression. eQTL analysis supports that these SNPs regulate expression of key genes involved in the neurotrophin signaling pathway.

Keywords: Mild cognitive impairment, neurotrophins, single nucleotide polymorphism, survival analysis

INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by memory loss and progressive cognitive impairment, currently without any efficient ways to cure, prevent, or significantly slow down its progression [1, 2]. AD, as the top tenth leading causes of death in the United States in 2020, accounted for approximately 60–80% cases of dementia [3, 4]. Current studies have shown that genetic risk factors play a main role in AD, which accounts approximately 56–79% AD risk among the late-onset AD patients (onset \( \geq \) 65 years old), and 90% risk among the early-onset AD patients (onset <65 years old) [5, 6]. Also, the single nucleotide polymorphism (SNP)-based heritability can account for 24–53% among the genetic risk factors [7]. Therefore, it is important to further identify the specific genetic factors in pivotal genes and pathways that impact the AD, especially the progression from mild cognitive impairment (MCI) to AD.

MCI is the transitional stage between normal aging and AD, and each year 10–15% of patients with MCI will progress to AD [8]. Currently, different models have been developed to predict the conversion from MCI to AD by applying various factors, such as cerebrospinal fluid (CSF) biomarkers, genetic markers, neuroimaging, and clinical markers [9–11]. However, the studies on genetic markers are not sufficient. To better predict the conversion from MCI to AD and study the mechanisms of AD progression, it is necessary to further identify genetic factors that may affect the progression of AD.

The recent genome-wide association studies (GWAS) have identified more than 40 susceptibility loci associated with AD [12–14]. However, they only explain a small fraction of genetic variance (\( \sim 30\% \)) [15], suggesting that the remaining heritability may be attributed to common genetic variants with minor effects that cannot reach genome-wide significance or rare variants with large effects in other loci. Additionally, most of the GWAS-identified loci reside in the non-coding regions of the genome, or do not have a clear biological function [16, 17]. Hence, identification of certain genetic variants which has minor but detectable effects in revealing the biological functions could provide powerful insights into the molecular mechanism of AD progression.

Neurotrophins are a family of small proteins vital for neuronal development, survival and plasticity, and the common members include the nerve growth factor (NGF), brain-derived growth factors (BDNF), and neurotrophin-3 and -4 (NT-3 and NT-4) [18, 19]. It has been shown that higher BDNF serum levels are associated with a slower rate of cognitive decline in AD patients [20]. Certain neurotrophins exert their effect on cellular signaling by interacting with Trk tyrosine kinase receptors, and a previous study has indicated that the Trk defects might be a marker for the conversion from MCI to AD [21, 22]. Furthermore, changes in the neurotrophic signaling pathway are correlated with the cholinergic dysfunction and cognitive decline in AD [23]. However, the genetic variants in specific loci of the candidate neurotrophin signaling pathway and their biological functions in the progression of MCI to AD are still unclear.

In this study, we hypothesize that the genetic variants in genes related to the neurotrophin signaling pathway are associated with the progression from MCI to AD. We used the available GWAS and clinical data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and National Alzheimer’s Coordinating Center (NACC) studies to test this hypothesis.

MATERIALS AND METHODS

Study populations

In this study, as shown in the study flowchart (Fig. 1), the discovery stage used the dataset from
the ADNI study (https://adni.loni.ucla.edu) and only included the patients diagnosed as MCI at baseline or during follow-up (from September 2005 to January 2020) [24, 25]. For ADNI, there were 916 participants who were diagnosed with MCI at baseline or during follow-up, and only 767 participants remained for further analysis after merging the clinical and genotyping data. Among the 767 participants, 294 of them were diagnosed as dementia with AD as the etiologic diagnosis during follow-up time.

For the replication stage, we used the dataset from the NACC study (https://naccdata.org) [24, 25]. In this phase, the clinical and genotyping data was only available for 1,373 participants who were diagnosed with MCI at baseline or during follow-up period (from June 2005 to August 2019), and 864 of them were diagnosed as AD-type dementia during follow-up period.

The two studies were both approved by local institutional review board (IRB), and the written informed consent were both obtained from all the participants. Further information about the two studies is available at the websites, http://www.adni-info.org and https://naccdata.org.

Gene and SNP selection

The 126 genes involved in the neurotrophin signaling pathway were selected using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database with the keyword “neurotrophin” (https://www.genome.jp/kegg/).

For the GWAS data from the ADNI study, genotyping was performed by using the Illumina Human610-Quad in ADNI 1 phase, Illumina Human OmniExpress in GO phase, and Illumina Omni 2.5M in ADNI 2 phase. We performed haplotype phasing with the SHAPEIT and imputation with the minic4 on the Michigan imputation server (https://imputationserver.sph.umich.edu) with the HRC reference panel (Version r1.1 2016) consisting of 64,940 haplotypes which were predominantly European ancestry [26]. During imputation, we used a set of high-quality SNPs with the following conditions: minor allele effect (MAF) > 0.01, call rate > 95%, p-value of the Hardy-Weinberg equilibrium test > 10^{-6}, and allele frequency difference between the sample data and the reference panel ≤ 0.20. The GWAS data from NACC study was genotyped on the 10,256 sub-
jects from NACC AD Centers 1–7 by the platforms of Human660W-Quad_v1A, HumanOmniExpress-12v1_A/H, and humanomniexpressexome-8v1-2 (https://www.alz.washington.edu/ADGC/GENOtype.html) [25]. For the replication sample, the same parameters and criteria for genotyping quality control (QC) and imputation as used for the discovery sample were applied.

For discovery dataset, after removing SNPs located on X chromosome and duplicated SNPs, we extracted the imputation data of 17,545 SNPs involved in neurotrophin signaling pathway with MAF ≥0.05 (considering the relative small sample size of the discovery study) and imputation $r^2 \geq 0.3$ [27, 28]. Before performing the single-locus analysis for the association between these SNPs and AD progression, we performed QC to further remove the SNPs with missing rate in ADNI dataset ≥0.2 and located within the 500 kb region surrounding the $APOE$ gene (chr19:45,409,011-45,412,650; GRCh37/hg19 assembly) [29–31]. Bayesian false discovery probability (BFDP) was applied for multiple testing correction to decrease the potentially false-positive results [32]. Based on the original publication, the BFDP ≤0.8 was an appropriate and well-precedented threshold when applying BFDP as the multiple correction method. The SNPs with BFDP ≤0.8 were further selected to be replicated in the NACC dataset. During the replication stage, it was essential to perform the same QC process as completed for the discovery stage before the single-locus analysis.

**Statistical analysis and in-silico functional annotation**

In the single-locus analysis to explore the association between single SNPs and the AD progression, we used the Cox proportional hazards regression with the adjustment for various variables, including age at baseline, gender, race, years of education, top three principal components (PCs) from the genetic data, the number of allele copies of $APOE$ E2 and $APOE$ E4 by using the **nle** package in R. The c-statistic of the single-locus analysis, we assigned a prior probability of 0.10 to detect an HR upper bound which was the 97.5% point of median HR given all the post-QC SNPs. After selecting SNPs with independent effects by the consistent directions for HR (null value is 1.0) in both datasets and the linkage disequilibrium (LD) clumping (pairwise $r^2 < 0.1$), we used those SNPs to construct the polygenic risk scores (PRSs) of the candidate pathway with the PLINK2 and PRSICE-2 [33, 34]. LD could describe the nonrandom association of alleles at different loci, and using the LD-clumping could keep the most significant SNP as an index SNP and remove the SNPs having $r^2 \geq 0.1$ with the index SNP, then repeat the process on the next significant SNP which had not been removed until all the remaining SNPs were independent with each other (i.e., $r^2 < 0.1$). We used the default parameter settings of PRSice-2 to build PRS. The standardized Z-scores of PRSs would be applied in the further analysis.

We then constructed the time-dependent receiver operation characteristic (ROC) curves and compared the area under ROC curves (AUCs) to evaluate the predictive accuracy of the model with PRS and covariates including age, gender, race, years of education, top three PCs from the genetic data, the number of allele copies of $APOE$ E2 and $APOE$ E4 by using the **timeROC** package in R, where the test of comparing AUC was the extension of the DeLong test [35].

To investigate the correlation between PRSs and the longitudinal changes of cognitive assessments, CSF biomarkers and imaging biomarkers, we used a linear mixed model with a random intercept, a random slope of follow-up time, and the adjustment for age at baseline, gender, years of education, race, top three PCs, the number of allele copies of $APOE$ E2 and $APOE$ E4 by using the **nlme** package in R. The cognitive assessments included clinical dementia rating scale sum of boxes (CDR-SB), Alzheimer’s Disease Assessment Scale test (ADAS) 11/13, ADAS score of the task 4 (ADASQ4), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), and Functional Activities Questionnaire (FAQ). The CSF biomarkers Aβ12 TF, Tau, and P Tau181 were log-transformed, and the imaging biomarkers were the percentages of the volumes of the five regions, i.e., ventricles, hippocampus, entorhinal, fusiform gyrus, and middle temporal gyrus, in the intracerebral volume (ICV). For the NACC study, because most of the above phenotypes were not available, the analysis was only conducted on the available phenotypes, MMSE and CDR-SB.
six independent-effect single nucleotide polymorphisms (SNPs) associated with Alzheimer’s disease (AD) progression in both Alzheimer’s Disease Neuroimaging Initiative (ADNI) and National Alzheimer’s Coordinating Center (NACC) studies

<table>
<thead>
<tr>
<th>SNP/PRS</th>
<th>Gene</th>
<th>Chr Position (hg19)</th>
<th>A1</th>
<th>A2</th>
<th>ADNI Beta±3</th>
<th>p</th>
<th>BFDP</th>
<th>NACC Beta±3</th>
<th>p</th>
<th>BFDP</th>
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<tbody>
<tr>
<td>rs2096224</td>
<td>TP73</td>
<td>1 3645844 G A</td>
<td>0.300</td>
<td>0.001</td>
<td>0.32</td>
<td>0.142</td>
<td>0.012</td>
<td>0.64</td>
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<tr>
<td>rs173703</td>
<td>PIK3R1</td>
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<td>0.142</td>
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<tr>
<td>rs13167294</td>
<td>PIK3R1</td>
<td>5 67555580 A C</td>
<td>-0.202</td>
<td>0.031</td>
<td>0.77</td>
<td>-0.117</td>
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<td>rs8006462</td>
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<td>0.76</td>
<td>0.138</td>
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<tr>
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<td>PLCG2</td>
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<td>0.183</td>
<td>0.036</td>
<td>0.78</td>
<td>0.112</td>
<td>0.026</td>
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<tr>
<td>rs4073828</td>
<td>PLCG2</td>
<td>16 81970495 A G</td>
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<td>0.029</td>
<td>0.75</td>
<td>-0.177</td>
<td>&lt;0.01</td>
<td>0.13</td>
<td></td>
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</tr>
</tbody>
</table>

1A1 = effect allele, A2 = reference allele. 2Beta is log (HR). 3Adjusted for age, sex, years of education, race, the top 3 PCs, the copy numbers of APOE E2, and E4.

All the above analyses were performed using the R (version 4.2.0) if not specified otherwise. The details of the ADNI MR and PET imaging protocols are listed on the ADNI website (https://adni.loni.usc.edu/methods/mri-tool/mri-analysis; https://adni.loni.usc.edu/methods/pet-analysis-method). Briefly, the MRI data were acquired on 1.5T or 3T MRI scanners, and volumes of the region of interests (ROIs) were reconstructed through automatic image processing pipeline of the Freesurfer software. PET data were acquired on multiple instruments of varying resolution. The uptakes of PIB, AV-45, and FDG were measured using the standardized uptake value ratios and averaged across core ROIs. Finally, to identify the possibly biological functions of the independent-effect SNPs, we performed the in silico functional annotation by expression quantitative trait loci (eQTL) given the data from the Genotype-Tissue Expression (GTEx) projects [36].

RESULTS

Characteristics of the study populations

The overall flowchart of this study is shown in Fig. 1. The distributions of the demographic and clinical variables in the ADNI dataset and the NACC dataset are in Supplementary Tables 1 and 2, respectively. When performing the Cox proportional hazards regression on these variables respectively, we found that, in the ADNI dataset, only baseline age and the number of APOE E2 and E4 alleles were significantly associated with AD progression for the patients with MCI. Whereas, in the NACC dataset, we found that race and the number of APOE E2 and E4 alleles were significantly associated with AD progression for the patients with MCI.

Association between the SNPs involved in the neurotrophin signaling pathway and AD progression

Before using the Cox proportional hazards model to investigate the association between the SNPs of the candidate pathway and AD progression, we needed to complete the QC process where we removed 2 SNPs with missing rate ≥0.2. For the discovery stage with the ADNI dataset, we found 911 SNPs with p ≤0.05 and 646 of them with BFDP ≤0.8 and the overall association results were show in Supplementary Figure 1. For replication stage with the NACC dataset, we independently performed the single-locus analysis by using the Cox proportional hazards regression given the 646 SNPs identified in the discovery stage, and found 26 SNPs with BFDP ≤0.8. After further comparing the directions of HR with null value equaling to 1 in the results of the two stages, we found there were 25 SNPs were successfully replicated (Supplementary Table 3).

Based on the LD clumping, we selected 6 SNPs with independent effects on AD progression. The association results of the 6 SNPs for the two stages can be found in Table 1. The variant alleles of the two SNPs (i.e., rs13167294 in PIK3R1 and rs4073828 in PLCG2) were associated with slower AD progression from MCI in both the ADNI and NACC studies; while the variant allele carriers of the four other SNPs (i.e., rs2096224 in TP73, rs173703 in PIK3R1, rs8006462 in CALM1, and rs4369658 in PLCG2) showed faster AD progression in the two studies. It should be noted that there were two SNPs located in PLCG2, where five variants had been reported to be significantly associated with AD by the GWAS (https://www.ebi.ac.uk/gwas/efotraits/MONDO_0004975) [37–39]. Given Supplementary Table 4, however, we could find that the two variants we
<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>p</th>
</tr>
</thead>
<tbody>
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<td>ADNI dataset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PRS model</td>
<td>0.682</td>
<td></td>
</tr>
<tr>
<td>PRS model</td>
<td>0.720</td>
<td>0.003</td>
</tr>
<tr>
<td>NACC dataset</td>
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<td></td>
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<tr>
<td>Non-PRS model</td>
<td>0.586</td>
<td></td>
</tr>
<tr>
<td>PRS model</td>
<td>0.609</td>
<td>0.012</td>
</tr>
</tbody>
</table>

1 The model including age, sex, education, race, the top 3 PCs, the copy numbers of APOE E2, and E4.
2 The model including age, sex, education, race, the top 3 PCs, the copy numbers of APOE E2, APOE E4, and PRS.
3 Results of PRS model versus non-PRS model by using the function of timeROC package, as the extension of DeLong test.

Association between PRS and AD progression

To investigate the combined effect of the identified SNPs on AD progression, we constructed PRS using the 6 SNPs and tested their association with the progression from MCI to AD. The effect sizes of the SNPs during the PRS construction, shown in Supplementary Table 3, were from the meta-analysis results of the ADNI and the NACC dataset [40]. As shown in Table 1, we found the PRSs had statistically-significant and consistent (same direction) effects supporting the acceleration of the AD progression in both the ADNI and NACC dataset (both \( p < 10^{-7} \)).

To evaluate the predictive accuracy of different models, we applied the time-dependent ROC analysis and obtained the corresponding AUCs for the 3-year survival to lack of progression from MCI to AD. As shown in Table 2 and Fig. 2, after adding the PRS into an initial model that included demographic variables and APOE statuses, the time-dependent AUC increased to 0.720 from 0.682 in the ADNI dataset, and it significantly improved the prediction performance of the model at the 3-year survival of AD-progression (\( p = 0.003 \)). Also in the NACC dataset, the addition of PRS to the prediction model of 3-year survival of AD-progression significantly increased from 0.586 to 0.609 (\( p = 0.012 \)).

Moreover, we also investigated the association between the PRSs and longitudinal changes of cognitive abilities, CSF biomarkers and imaging biomarkers adjusted for age at baseline, sex, years of education, race, top three PCs, and the allele copies of APOE E4 and APOE E2. As shown in Tables 3 and 4, there were significant associations between the ADNI PRS and worse cognitive performance (with higher values of the ADAS11, ADAS13, ADASQ4,

Fig. 2. Time-dependent ROC curves for different models in ADNI and NACC dataset. A) Patients in the ADNI dataset; B) Patients in the NACC dataset. 1. The non-PRS model including age, sex, education, race, the top 3 PCs, the copy numbers of APOE E2, and E4. 2. The PRS model including age, sex, education, race, the top 3 PCs, the copy numbers of APOE E2, APOE E4, and PRS.
and lower value of MMSE), increased CSF levels of the Tau and PTau181 level, decreased CSF Aβ level, and reduced volumes of the hippocampus and entorhinal regions. However, the association between the PRS and MMSE decline was not significant in the NACC dataset ($p = 0.671$).

**Functional annotation of the identified SNPs**

The results of eQTL analysis by GTEx (https://gtexportal.org/home/) for the identified SNPs with independent effects are reported in Supplementary Figure 2. We found that the TP73 rs2096224 G allele was significantly associated with a lower mRNA expression level of TP73 in both the brain-cortex ($n = 205$) and brain-amygdala ($n = 129$) tissues. And the PLCG2 rs4369658 C allele was significantly associated with a decreased mRNA expression level of PLCG2 in the brain-amygdala ($n = 129$), brain-hippocampus ($n = 165$), brain-anterior cingulate cortex ($n = 147$), brain-substantia nigra ($n = 114$), and brain-cerebellum ($n = 209$) tissues. The other 4 SNPs did not show significant association with mRNA expression levels in the 10 normal brain tissues.

**DISCUSSION**

In this study, we identified six SNPs with independent effects in genes that regulate the neurotrophin signaling pathway that are associated with the progression from MCI to AD using the ADNI and NACC datasets. Based on the analysis of PRSs, we quantified the combined effects of the 6 identified SNPs on AD progression, and longitudinal changes of cognitive performance and AD-related
biomarkers from CSF and imaging. Moreover, the addition of the neurotrophin-based PRS to the basic prediction model derived from demographic and clinical data significantly increased the model predictive accuracy.

TP73, located on chromosome 1, encodes the p73 transcription factor. Previous studies indicated that p73 protein was essential for normal development and survival of neurons, as well as preventing neurodegeneration [41–43]. Also, several studies revealed that p73 haploinsufficiency could increase the deposition of tau aggregates which is a hallmark of AD pathology [42–44]. In our study, the variant allele G of SNP rs2096224 was associated with increased risk of AD progression and decreased mRNA expression level in the brain tissues. Such results were consistent with previous findings on TP73 functions, which indicated that the rs2096224 was possibly associated with faster progression from MCI to AD by decreasing the mRNA expression level of TP73.

We also found the C allele of the SNP rs4369658 has significant association with faster AD progression and decreased mRNA expression level of PLCG2 in the brain tissue. PLCG2 encodes phospholipase C-γ2 (PLC γ2), which could regulate the inflammatory response and be selectively expressed by microglia in the brain [45]. A recent study indicated the activation of PLC γ2 was a potentially therapeutic method for AD [46]. Even though previously GWAS has reported five AD-associated variants resided in the PLCG2 region, we found the two SNPs rs4369658 C>T and rs4073828 A>G in this study did not have linkage disequilibrium with the reported five GWAS SNPs, which indicated their effect on AD progression were possibly due to an independent biological regulatory function rather than the genetic linkage to the GWAS tagging SNPs. The two SNPs rs173703 G>A and rs13167294 A>C located in the PIK3R1, which encodes PI3K catalytic subunit p85α, and was potentially involved in AD progression and the treatment target of patients with AD [47]. But none of the two SNPs were associated with mRNA expression levels in the brain tissue in the GTeX projects. Also, there was no eQTL evidence for the two other SNPs CALM1 rs8006462 C>T and PLCG2 rs4073828 A>G. CALM1 is related to the tau phosphorylation and the accumulation of phosphorylated tau is also a hallmark of AD pathology [48, 49]. Therefore, it was possible that these SNPs affected the AD progression by a biological mechanism independent of gene expression, which needed to be further investigated.

Additionally, all the six identified genetic variants had not been previously reported in any AD study. Except the PIK3R1 rs13167294 A>C which had been reported to be associated with poor survival in a pancreatic cancer study [50], none of the other five SNPs had been found in any non-AD study. The limitations in the present study included that the NACC dataset lacked most of the variables used in longitudinal analysis for ADNI dataset, and some of our findings from the longitudinal analysis of cognitive assessment, CSF biomarkers, and imaging markers in the ADNI dataset need to be replicated in future studies. And even though we conducted the eQTL analysis, the underlying causal molecular mechanisms associated with the progression from MCI to AD are still unclear and need to be further investigated.

In conclusion, we identified 6 novel SNPs (i.e., TP73 rs2096224 G>A, PIK3R1 rs173703 G>A and rs13167294 A>C, CALM1 rs8006462 C>T, PLCG2 rs4369658 C>T, and rs4073828 A>G) with independent effects and potential biological function that were significantly associated with AD progression and had not been previously reported in any AD study. Based on the eQTL results, we also provide functional gene expression regulatory evidence for two identified SNPs. It is necessary to further replicate these findings and perform more functional analysis for these identified SNPs to uncover the biological mechanisms underlying the observed associations with AD progression.

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SUPPLEMENTARY MATERIAL

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