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# GWAS-Linked Loci and Neuroimaging Measures in Alzheimer's Disease

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**Abstract** Recently, 19 susceptibility loci for Alzheimer's disease (AD) had been identified through AD genome-wide association studies (GWAS) meta-analysis. However, how they influence the pathogenesis of AD still remains largely unknown. We studied those loci with six MRI measures, abnormal glucose metabolism, and β-amyloid (Aβ) deposition on neuroimaging in a large cohort from Alzheimer's Disease Neuroimaging Initiative (ADNI) database in order to provide clues of the mechanisms through which these genetic variants might be acting. As a result, single nucleotide polymorphisms (SNPs) at rs983392 within *MS4A6A* and rs11218343 within *SOLR1* were both associated with the percentage of increase in the volume of left inferior temporal regions in the follow-up study. Meanwhile, rs11218343 at *SORL1* and rs6733839 at *BIN1* was associated with rate of volume change of left parahippocampal and right inferior parietal, respectively. Moreover, rs6656401 at *CR1* and rs983392 at *MS4A6A* were both associated with smaller volume of right middle temporal at baseline. However, in addition to the APOE locus, we did not detect any influence on glucose metabolism and Aβ deposition. APOE ε4 allele was associated with almost all measures. Altogether, five loci (rs6656401 at CR1, rs983392within MS4A6A, rs11218343 at SORL1, rs6733839 at BIN1, and APOE ε4) have been detected to be associated with one or a few established AD-related neuroimaging measures.

Alzheimer's Disease Neuroimaging Initiative: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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**Keywords** Genome-wide association studies · Alzheimer's disease · Brain structure · Glucose metabolism · Aβ deposition

## Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly and is defined clinically by a gradual decline in memory and other cognitive functions and neuropathologically by gross atrophy of the brain and the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles. To date, no effective treatment is available to reverse the disease as sufficient neuronal injury has occurred prior to the onset of observable cognitive problems. This has therefore raised considerable interest to identify the at-risk individuals who will benefit most from early interventions and prevention [1]. AD is classified into two groups, early-onset AD (EOAD, onset <65 years) and late-onset AD (LOAD, onset ≥65 years), based on its age of onset. Three genes (*APP*, *PSEN1*, and *PSEN2*) cause early-onset AD [2]. However, for more than a decade, only the apolipoprotein E, type ε4 (*APOE*ε4) allele, located on chromosome 19q13, has been established unequivocally as the most important susceptibility gene for LOAD [3]. However, it has been estimated that it influences susceptibility for <50 % of common LOAD [3], suggesting that further risk loci must contribute to risk for the disease.

A recent meta-analysis of GWAS reported 11 new AD susceptibility loci (*CASS4*, *CELF1*, *FERMT2*, *HLA-DRB5/HLA-DRB1*, *INPP5D*, *MEF2C*, *NME8*, *PTK2B*, *SLC24A4/RIN3*, *SORL1*, and *ZCWPW1*) and eight confirmed loci (*ABCA7*, *BIN1*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A6A-MS4A4E*, and *PICALM)* which had been previously reported [4]. However, how these loci play their roles in the occurrence of AD still needs lots of researches. It has been widely accepted that the pattern of Aβ deposits detected in the brains of AD patients using amyloid positron imaging tomography (PET) imaging tracers such as the [F-18]-AV-45 closely matches the histological examination of Aβ in postmortem brain tissue from patients with clinical AD [5, 6]. 18-Fluorodeoxyglucose (FDG)-PET-derived measures of brain glucose metabolism and cerebral blood flow and structural MRI are also imaging techniques that are widely used to assess brain changes in AD subjects. We selected six brain regions for analysis as their established role in predicting AD risk: hippocampal volume, amygdala volume, parahippocampal volume, middle temporal volume, inferior temporal volume, and inferior parietal volume [7–12]. Therefore, we investigated the relation between susceptibility loci and AD-related neuroimaging measures using data collected from Alzheimer's Disease Neuroimaging Initiative (ADNI). We sought to provide clues of the mechanisms through which these genetic variants might be acting.

## Methods

### Alzheimer's Disease Neuroimaging Initiative

Participants we selected were from the ADNI database (http://www.loni.ucla.edu/ADNI). The ADNI is a large, multicenter, longitudinal neuroimaging study, launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The study gathered and analyzed thousands of brain scans, genetic profiles, and biomarkers in blood and cerebrospinal fluid. The major goals of ADNI were to find more sensitive and accurate methods to detect AD at earlier stages and mark its progress through biomarkers. Biomarkers could also be used in clinical trials and to determine the best way to measure the treatment effects of AD therapeutics. The study was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives after extensive description of the ADNI according to the 1975 Declaration of Helsinki.

### Genotype Data

Genotype data of 812 individuals in the ADNI database were downloaded and analyzed by PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/). Population structure was assessed by performing principal component analysis (PCA) to avoid population stratification effects which can lead to spurious genetic associations. We performed the quality control (QC) procedures using PLINK software, and the inclusion criteria were as follows: minimum call rates >90 %, minimum minor allele frequencies (MAF) >0.01, and Hardy-Weinberg equilibrium test $P > 0.001$. A total of 764 individuals passing the QC criteria were reclustered by performing PCA.

### Neuroimaging Measures Data

A positive amyloid imaging on Pittsburgh compound B position emission tomography (PiB-PET), regional volume on MRI, and cerebral metabolic rate for glucose (CMRgl) on FDG-PET were all downloaded from the ADNI dataset during their baseline and two-year follow-up. A detailed description of PET image acquisition and processing can be found at http://adni.loni.usc.edu/data-samples/pet/ [13].

The AV45-PET phenotypic data were obtained from the Jagust Lab, University of Berkeley—AV45 analysis dataset on website (http://adni.loni.usc.edu/data-samples/access-data/). Briefly, we extracted the mean florbetapir uptake of four cortical grey matter regions (temporal,

parietal, frontal, cingulate) as well as cortical standard uptake value ratios (SUVR). SUVR were calculated by averaging across the four cortical regions and dividing this average by the whole cerebellum. Each mean florbetapir uptake of the four main regions and cortical SUVR was used for analysis. Of the 764 participants, we included 491 participants (including 141 NC, 305 mild cognitive impairment (MCI), and 45 AD) with baseline AV45-PET and corresponding genetic data.

FDG analysis data were from UC Berkeley and Lawrence Berkeley National Laboratory on the website (http://adni.loni.usc.edu/data-samples/access-data/) [14]. In this laboratory, five regions (left and right angular gyrus, bilateral posterior cingulate, left and right temporal gyrus) were treated as metaROIs (regions of interest) to analysis. The brief procedures were as follows. Firstly, PET data was downloaded from LONI (http://loni.usc.edu/). PET images were spatially normalized in statistical parametric mapping (SPM) to the MNI PET template. The mean counts from the meta-ROIs for each subject's FDG scans at each time point were extracted, and the intensity values were computed with SPM subroutines. Finally, we intensity-normalized each metaROI mean by dividing it by the pons/vermis reference region mean.

The MR acquisition protocol used in the ADNI subjects has been described in detail in [13]. In brief, MR imaging was acquired at multiple sites using a GE Healthcare, Siemens Medical Solutions USA, or Philips Electronics 1.5T system. High-resolution T1-weighted MRI scans were collected using a sagittal 3-dimensional magnetization-prepared rapid gradient echo (3D MP-RAGE) sequence with an approximate TR = 2400 ms, minimum full TE, approximate TI = 1000 ms, and approximate flip angle of 8° (scan parameters varied between sites, scanner platforms, and software versions). Moreover, correlation matrix analysis indicated that measures are generally independent of each other and thus independent analysis was needed for association with genetic variants [15].

## SNP Selection

We selected 20 susceptibility loci which had been identified by a recent AD GWAS meta-analysis (*APOEε4*, *BIN1*-rs6733839, *CLU*-rs9331896, *PICALM*-rs10792832, *INPP5D*-rs35349669, *MS4A6A*-rs983392, *CR1*-rs6656401, *HLA*-rs9271192, *ZCWPW1*-rs1476679, *EPHA1*-rs11771145, *PTK2B*-rs28834970, *NME8*-rs2718058, *ABCA7*-rs4147929, *MEF2C*-rs190982, *CELF1*-rs10838725, *CD2AP*-rs10948363, *FERMT2*-rs17125944, *SLC24A4/RIN3*-rs10498633, *CASS4*-rs7274581, *SORL1*-rs11218343) (Table 1). Among this, *CLU*-rs9331896, *PICALM*-rs10792832, *INPP5D*-rs35349669, *MS4A6A*-rs983392, *CR1*-rs6656401, *HLA*-rs9271192, *ZCWPW1*-rs1476679, *EPHA1*-rs11771145,

**Table 1** Information of the selected SNP

| Gene | SNP[a] | CHR[b] | GRCh37.p13 CHR POS | PAF(%) | Replacement | D' | $R^2$ |
|---|---|---|---|---|---|---|---|
| APOE | e4 | | | 27.3 | | | |
| BIN1 | rs6733839 | 2 | 127892810 | 8.1 | | | |
| CLU | rs9331896 | 8 | 27467686 | 5.3 | rs867230 | 0.978 | 0.957 |
| PICALM | rs10792832 | 11 | 85867875 | 5.3 | rs3851179 | 1 | 0.98 |
| INPP5D | rs35349669 | 2 | 234068476 | 4.6 | rs28539971 | 1 | 0.979 |
| MS4A6A | rs983392 | 11 | 59923508 | 4.2 | rs920573 | 1 | 0.98 |
| CR1 | rs6656401 | 1 | 207692049 | 3.7 | rs61822967 | 1 | 0.111 |
| HLA | rs9271192 | 6 | 32578530 | 3.2 | rs9271246 | 1 | 1 |
| ZCWPW1 | rs1476679 | 7 | 100004446 | 3.2 | | | |
| EPHA1 | rs11771145 | 7 | 143110762 | 3.1 | | | |
| PTK2B | rs28834970 | 8 | 27195121 | 3.1 | rs1879189 | 1 | 0.106 |
| NME8 | rs2718058 | 7 | 37841534 | 2.9 | rs2722248 | 1 | 0.663 |
| ABCA7 | rs4147929 | 19 | 1063443 | 2.8 | rs7108410 | - | - |
| MEF2C | rs190982 | 5 | 88223420 | 2.7 | rs190982 | | |
| CELF1 | rs10838725 | 11 | 47557871 | 2.4 | rs10742814 | 1 | 0.533 |
| CD2AP | rs10948363 | 6 | 47487762 | 2.3 | rs9296562 | 1 | 0.245 |
| FERMT2 | rs17125944 | 14 | 53400629 | 1.5 | | | |
| SLC24A4/RIN3 | rs10498633 | 14 | 92926952 | 1.5 | | | |
| CASS4 | rs7274581 | 20 | 55018260 | 1.1 | | | |
| SORL1 | rs11218343 | 11 | 121435587 | 1.1 | rs720099 | 1 | 0.742 |

*SNP* single nucleotide polymorphism, *CHR* chromosome

*PTK2B*-rs28834970, *NME8*-rs2718058, *ABCA7*-rs4147929, *MEF2C*-rs190982, *CELF1*-rs10838725, *CD2AP*-rs10948363, *FERMT2*-rs17125944, *SLC24A4/RIN3*-rs10498633, *CASS4*-rs7274581, and *SORL1*-rs11218343 cannot be obtained from ADNI database. We used European population reference (EUR) haplotype data from the 1000 Genomes Project. We selected the closest and the highest level of linkage disequilibrium (estimated by $r^2$ and D') loci as a replacement. Finally, we furthermore investigated the correlations between these loci and AD in a large database from a meta-analysis of GWAS in 74,046 individuals of European descent.

### Genetic Association Analysis

Genotype data were analyzed using an additive model. To explore this association further, we conducted a multiple linear regression analysis which considers age, gender, education, *APOE* ε4 status, and intracranial volume as covariates in the total sample. Neuroimaging analysis was performed independent of diagnostic category. All statistical analyses were performed by R 3.12 and PLINK (http://pngu.mgh.harvard.edu/wpurcell/plink/). We used the false discovery rate (FDR) according to the method developed by Hochberg and Benjamini to control for multiple hypothesis testing. Statistical significance was defined for FDR-corrected $P < 0.05$.

## Results

### Characteristics of Included Subjects

Characteristics of the study sample are presented in Table 1. Totally, 261 cognitively normal (130 women, 74.69 ± 5.48 years), 456 MCI (185 women, 72.48 ± 7.37 years), and 47 AD patients (17 women, 75.48 ± 9.32 years) were recruited in this study. As expected, the AD group had the highest frequency for the ε4 allele within APOE gene (44.7 %) and CN group had the lowest frequency (15 %). There was no significant difference on gender ($P = 0.03$) and education ($P = 0.09$) between the three clinical stages. As expected, the ε4 allele of APOE gene substantially increased the risk of AD with a dose effects, and the cognitive scores on various neuropsychological scales were considerably different across three groups (CN, MCI, and AD). Furthermore, AD patients had marked atrophy in hippocampus, entorhinal, fusiform, and middle temporal with respect to MCI and NC individuals ($P < 0.01$).

### Genetic Risk Factors for MRI Measures

We selected six MRI measures for analysis as their established role in predicting AD risk: hippocampal volume, amygdala volume, parahippocampal volume, middle temporal volume, inferior temporal volume, and inferior parietal volume.

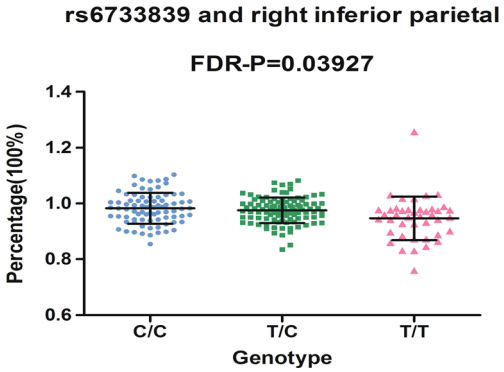


**Fig. 1** rs6733839 at BIN1 was associated with the volume of right inferior parietal in follow-up study

Finally, single nucleotide polymorphisms (SNPs) at rs6733839 within *BIN1* showed marked association with volume of left inferior parietal at baseline ($P = 0.008$). Likewise, rs983392 within *MS4A6A* also significantly associated volume of bilateral inferior parietal at baseline (left $P = 0.049$, right $P = 0.021$). But the associations disappeared after FDR correction. Moreover, in our two-year follow-up study, this locus variation shows significant association with the rate of volume change of right inferior parietal ($P = 0.002$) and right middle temporal ($P = 0.040$), respectively. However, only the former still stands after FDR correction (FDR-corrected $P = 0.039$) (Fig. 1). Similarly, the mutation at rs665640167 within *CR1* produced remarkable influence on the volume of bilateral inferior parietal at baseline (left $P = 0.012$, right $P = 0.011$). Nevertheless, neither of them survived the FDR test.

In addition, rs665640167 within *CR1* showed marked association with bilateral inferior temporal volume at baseline, but the association disappeared after FDR correction. Likewise, locus variation at rs11218343 also generated a marked effect on change percentage of bilateral inferior temporal volume in the follow-up, and the effect exists in the left inferior temporal after FDR test (FDR-corrected $P = 0.024$). Similarly, locus variation at rs983392 within *MS4A6A* also associated with change percentage of the left inferior temporal after FDR test (FDR-corrected $P = 0.024$). As to the middle temporal volume, rs665640167 was significantly related to the bilateral middle temporal volume at baseline. The relationship with the right remained in FDR test (FDR-corrected $P = 0.023$) (Fig. 2). Moreover, rs983392 also strongly related to the middle temporal volume at baseline, and this relation survived the FDR test (FDR-corrected $P = 0.013$).

In contrast to the above loci, rs11218343 within *SOLR1* and rs983392 within *MS4A6A* showed a protective effect. Both at the baseline ($P = 0.005$) and follow-up studies ($P = 0.002$), rs11218343 within *SOLR1* was significantly

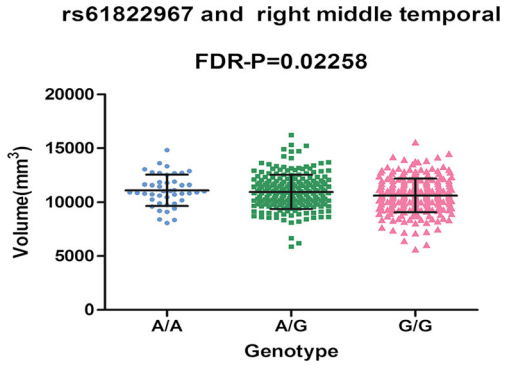


**Fig. 2** rs61822967 at *CR1* was associated with the volume of right middle temporal at baseline

associated with volume of left parahippocampal and its change rate. After FDR correction, only in the longitudinal study, the remarkable relationships still existed (FDR-corrected $P=0.045$). The baseline study remained to be marginal (FDR-corrected $P=0.086$). Moreover, at baseline, three loci showed significant influence on the volume of left parahippocampal (rs17125944 at *FERMT2* $P=0.016$, rs190982 at *MEF2C* $P=0.042$, rs2722248 at *NME8* $P=0.009$). However, the effect did not exist in FDF test. On the other hand, in the longitudinal study, rs10742814 within *CELF1* was detected to be associated with the rate of volume change of bilateral parahippocampal (left $P=0.023$, right $P=0.041$). However, those remarkable influences both disappear after FDR correction. Moreover, rs11218343 within *SOLR1* and rs983392 within *MS4A6A* also both influence the rate of volume change of left inferior temporal (FDR-corrected $P=0.024$) (Fig. 3). Among them, 983392 within *MS4A6A* associated with volume of right middle temporal as well (FDR-corrected $P=0.013$) at baseline (Fig. 4).

In addition, the *APOE* ε4 allele was strongly associated with atrophy of bilateral middle temporal (left FDR-corrected $P=0.002$, right $P=0.028$) and right inferior parietal (FDR-corrected $P=0.028$) at baseline and with change percentage of right parahippocampal, right middle temporal (FDR-corrected $P=0.002$), and left inferior temporal volume (FDR-corrected $P=0.021$) in the 2-year follow-up study (Supplementary Table 1).

Furthermore, subgroup analysis discovered that rs6656401 within *CR1* altered the bilateral middle temporal volume (left $P=0.00333$, right $P=0.02188$), bilateral inferior temporal (left $P=0.01791$, right $P=0.04845$), and left inferior parietal ($P=0.03499$) in MCI subgroup at baseline. This locus also influences left hippocampus volume in AD subgroup at baseline. Moreover, rs6733839 significantly impacted the right inferior parietal atrophy rate and the left inferior parietal volume in MCI subgroup ($P=0.001024$ and 0.02373, respectively) In addition, rs11218343 within *SORL1* effected the atrophy rate of right parahippocampal in the AD group ($P=0.03092$) in follow-up study; it also influences left parahippocampal volume either at the baseline or follow-up study ($P=0.01023$ and 0.0004016, respectively). As to rs983392 at *MS4A6A*, it altered the left inferior temporal and left amygdala atrophy rate either in the MCI or AD subgroup in the follow-up study ($P=0.009022$ and 0.04049, respectively).

## Genetic Risk Factors for Brain Aβ Retention

Using the AV45-PET methods, we observed remarkable relationships between *APOE* ε4 allele and Aβ retention in the frontal cortex (FDR-corrected $P=2.166\times10^{-41}$), cingulate (FDR-corrected $P=2.064\times10^{-36}$), parietal cortex (FDR-corrected $P=3.2\times10^{-33}$), temporal cortex (FDR-corrected $P=1.29\times10^{-36}$), and the SUVRs (FDR-corrected $P=6.97\times10^{-53}$) at baseline (Supplementary Table 2). In

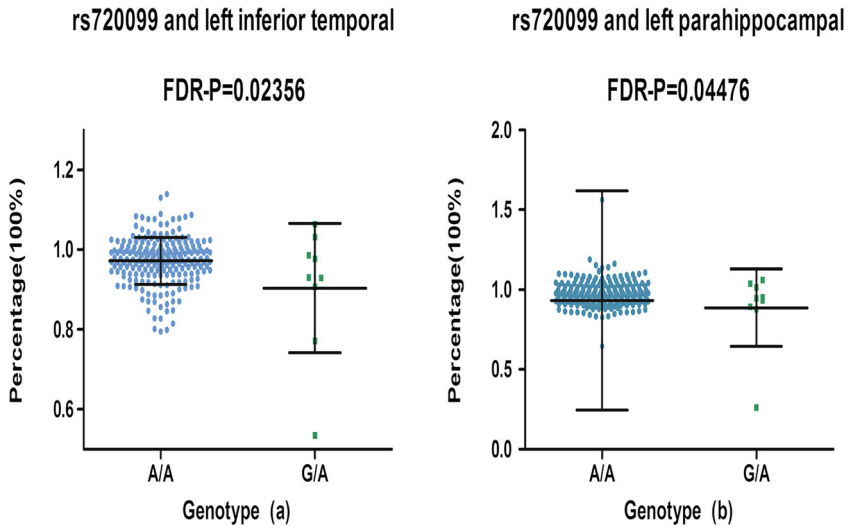


**Fig. 3** The correlation between rs720099 at SOLR1 and AD-related neuroimaging measures. **a** rs720099 at *SORL1* was associated with the volume of left inferior temporal in follow-up study. **b** rs720099 at *SORL1* was associated with the volume of left parahippocampal in follow-up study

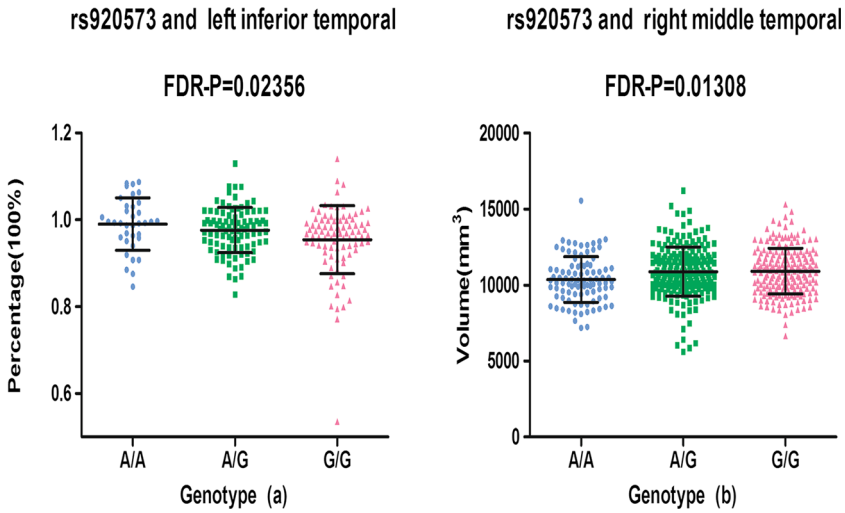


**Fig. 4** The correlation between rs920573 at MS4A6A and AD-related neuroimaging measures. **a** rs920573 at MS4A6A was associated with the volume of left inferior temporal in follow-up study. **b** rs920573 at MS4A6A was associated with the volume of right middle temporal at baseline

the longitudinal study, we did not observe any of these loci showing significant associations with tracer retention.

### Genetic Risk Factors for Brain Glucose Metabolism

We then analyzed the influence of genetic risk factors on cerebral metabolism rate of glucose (CMRgl) in amygdala, posterior cingulate, and temporal cortex on FDG-PET imaging. At baseline, APOEε4 allele showed different CMRgl in the bilateral temporal cortex (left FDR-corrected $P = 5.32 \times 10^{-16}$, right FDR-corrected $P = 5.71 \times 10^{-14}$), bilateral angular gyrus (left FDR-corrected $P = 4.9 \times 10^{-16}$, right FDR-corrected $P = 1.02 \times 10^{-16}$), and bilateral posterior cingulate (FDR-corrected $P = 1.28 \times 10^{-13}$) after the FDR test. In the follow-up study of 2 years, *APOE* ε4 allele showed associations with the decline rate for CMRgl in bilateral temporal cortex (left FDR-corrected $P = 1.6506 \times 10^{-4}$, right FDR-corrected $P = 0.013$) and bilateral posterior cingulate (FDR-corrected $P = 2 \times 10^{-3}$) after FDR correction (Supplementary Table 3).

## Discussion

Our results indicated that among 11 new susceptibility loci, only the *SORL1* variant was associated with rate of volume change of left parahippocampal and inferior temporal in the follow-up study of 2 years. Among nine loci which had been previously identified by GWAS as genetic susceptibility factors, rs6656401 within *CR1* and rs983392 at *MS4A6A* were detected to be associated with smaller right middle temporal volume at baseline. Moreover, the *MS4A6A* variant as well as *BIN1* (rs6733839) also produced remarkable influence in the rate of left and right inferior temporal volume change, respectively. Furthermore, our subgroup analysis confirmed these significant results. Not surprisingly, *APOE* ε4 allele had been verified to be associated with almost all the measures mentioned above. These findings not only provided further evidence to the connection between those susceptibility loci and AD but also suggested that sequence variants may act through their influence on neuroimaging measures.

The observation of reduction expression of *SORL1* in the brain of AD patients suggests a causal role for *SORL1* in the pathogenesis of AD [16]. SNP at rs11218343 within *SORL1* represents newly associated loci in the recent meta-analysis; as a result, few studies have reported on it. Miyashita A and colleagues conducted a three-stage GWAS using three populations which revealed genome-wide significance with rs11218343 ($P = 1.77 \times 10^{-9}$) [17]. As rs11218343 cannot be obtained from ADNI database, instead, we used loci which exist with high linkage disequilibrium with it (rs720099). Rs720099 has been certified to be a preventive locus for late-onset AD [18]. In spite of the significant role of *SORL1* played on Aβ production, we did not detect any associations between rs720099 within *SORL1* and AV45-PET measures. Nevertheless, rs720099 was statistically associated with percent changes of left parahippocampal and inferior temporal volume over 2 years. This finding may supply clues to the mechanisms on how this genetic variant influences AD risk.

The *BIN1* gene is identified as the most important genetic susceptibility locus for LOAD after APOE. Chapuis J analyzed 493 SNPs using the 1000 Genomes data set (http://www.1000genomes.org) in the French EADI12 cohort and observed two SNPs, rs4663105 and rs6733839, associated with AD risk. However, they are likely not functional as indicated by their sequential studies. In line with our study, rs6733839 at *BIN1* did not show associations with tau pathology. On the other hand, a functional variant, rs59335482, could mediate AD risk by increasing *BIN1* cerebral expression in vivo. However, it was in incomplete LD with rs6733839 ($D' = 0.94$, $r^2 = 0.47$). In our study, we detected rs6733839 at *BIN1* to be associated with percentage of decreases in the volume of right inferior parietal in the follow-up study of 2 years. Inferior parietal is considered to

be a predictive measure of the prognosis of AD but also a predictor of the progression from MCI to AD [12, 19, 20]. Combining genetic and neuroimaging strategies may be a potential approach to monitor individuals at risk for diseases. In our previous study, healthy homozygous carrying rs744373 resulted in worse high-load working memory (WM) performance, larger hippocampal volume, and lower functional connectivity between the bilateral hippocampus and the right dorsolateral prefrontal cortex (DLPFC) [21]. However, it was also in incomplete LD with rs6733839 (D' = 0.841, $r^2$ = 0.453).

MS4A6A is not the most studied among *MS4A* gene cluster; however, a recent study indicated that high levels of MS4A6A in blood and brain foreboded increased risk of progressing to an AD diagnosis [22]. Rs983392 at *MS4A6A* had been detected to be a protective locus for AD in line with our study [4, 23]. However, rs920573 which we obtained from the 1000 Genomes Project had no publications reported on it. Its protective effect on AD in our study provided new interest for further study.

It has been detected that *CR1* is involved in the clearance of the brain, which is a crucial component in the pathogenesis of AD [24]. *CR1* rs6656401 was widely accepted to be a risk variant for AD. Carrying rs6656401 has an additional ca. 20 % increased risk [25]. *CR1* rs6656401 polymorphism was first identified to be associated with AD in European ancestry. The same association has been detected in the East Asian population (Chinese, Japanese, and Korean) after using the relatively large-scale samples [26]. Unfortunately, rs6656401 cannot be obtained from ADNI database; instead, we detected rs61822967 which was the closest and had the highest level of linkage disequilibrium with it to be associated with volume of right middle temporal. This finding may provide clues to how *CR1* affected AD pathogenesis.

Several potential limitations of the current study should be interpreted in the context. The crucial limitation of our study is about the small sample size which is not large enough to detect extremely weak interactions. Secondly, except those six brain regions, others, such as middle temporal, precuneus cortex, and posterior cingulate, are also detected to be associated with AD. Replication studies with larger sample sizes and more brain regions are needed to confirm the present findings. Thirdly, 2 years of a follow-up period may be too short to detect the neuroimaging changing on the AD process, and a longer time of follow-up is useful in subsequent study. Fourthly, our participant recourse is restricted to Caucasians to avoid genetic stratification across ethnicities. As a result, our results cannot represent other ethnicities, and replications in other populations are necessary. Moreover, genetic risk was assessed with imaging measures as quantitative traits or continuous phenotypes, and the CSF and neuroimaging data were available only in a subset of participants in some quantitative trait analyses. Therefore, the quantitative trait analysis had a reduced sample size in some cases. Finally, the sample for the G/A subgroup of *SORL1* is too small; it will cause a decline of the statistical power.

In summary, among 20 susceptibility loci reported from a recent meta-analysis of GWAS, we detected three loci (rs11218343 at *SORL1*, rs6733839 at *BIN1*, and *APOE* ε4) to be associated with one or a few established AD-related neuroimaging measures. However, larger sample sizes and more brain regions with longer follow-up period studies are still imperative to confirm the present findings. Moreover, concrete mechanisms of how those genetic variations influence neuroimaging measures and therefore AD remains to be explained in further work.

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**Compliance with ethical standards**

**Conflicts of interest** The authors declare no conflicts of interest.

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