Effect of CRI Genetic Variants on Cerebrospinal Fluid and Neuroimaging Biomarkers in Healthy, Mild Cognitive Impairment and Alzheimer's Disease Cohorts

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Abstract The complement component (3b/4b) receptor 1 gene (CRI) is considered as one of the most important genetic susceptibility loci in Alzheimer’s disease (AD). However, to date, few studies were performed to discover the possible effect of CRI genetic variants on AD pathology in the brain. Here, we evaluated the potential role of CRI common variants in AD-related pathology by assessing neuroimaging biomarkers and cerebrospinal fluid (CSF) proteins. Finally, a total of 812 subjects from the Alzheimer’s disease Neuroimaging Initiative database and eight single nucleotide polymorphisms (SNPs) after quality control procedures are enrolled in our analysis. After applied to multiple linear regression models, significant associations were proved to exist between rs4844609 and amyloid deposition in cingulated, frontal, parietal, and temporal on florbetapir 18F amyloid positron emission tomography. In the analysis of the impacts of CRI genetic variants on brain structures, three SNPs (rs12034383, rs3737002, and rs6691117) were significantly linked to the changes in volume of middle temporal. In addition, rs10779339 showed a negative connection with the cerebral...

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metabolism rate of glucose in the right temporal on 18F-fluorodeoxyglucose PET imaging. However, no significant statistical findings were detected between CR1 genetic variants and CSF proteins (amyloid β, total-tau, and p-tau) at baseline diagnosis or in the follow-up study of 2 years. The results of our study indicated that CR1 plays a vital role in AD pathology mainly by influencing Aβ deposition, brain structure, and glucose metabolism during AD progression.

Keywords CR1 · Alzheimer’s disease · Amyloid deposition · Brain structure · CSF · Glucose metabolism · Neuroimaging

Introduction

Alzheimer’s disease (AD), the most common form of dementia, has affected over 35.6 million people worldwide, and the number will rise to 65.7 million by 2030 [1]. Epidemiologic studies have identified that AD is a multifactorial disease, including age, positive history, and genetic factors [2, 3]. Genetics has been confirmed to play a significant role in late onset AD with heritability estimates of 60 to 80 % [4]. Recently, several genome-wide association studies (GWAS) have disclosed a significant association between AD and single nucleotide polymorphisms (SNPs) in nine novel AD loci of large case-control datasets [5–10]. Among these identified genes, the complement component (3b/4b) receptor 1 gene (CR1) is considered as one of the most important genetic susceptibility loci in AD according to the Alzgene database (http://www.alzgene.org/). After first GWAS conducted by Lambert et al. revealed CR1 SNPs linked closely to AD risk [8], before long, the global experts continually found that CR1 is closely related to the AD susceptibility across different districts and ethnic groups [5, 11–16].

Allowing for the strong association between CR1 and AD susceptibility, it emerges to be necessary to disclose the concrete role of CR1 in AD pathology. To date, the current studies mainly disclosed that CR1 influenced on AD pathology by modulating the metabolism of amyloid protein (Aβ) [17, 18]. As reported, on erythrocytes, one of the major sites of CR1 expression, CR1 modulates the cleavage of C3 to take part in the clearance of Aβ [18–20]. In addition, CR1 is a key ingredient of the complement system. Hence, AD-related risk variants of CR1 might influence brain Aβ clearance and/or deposition may partly come from the vital role of the complement system in modulating AD pathogenesis [21]. Recently, the group of Chibnik proved that common variation at the CR1 locus has a broad effect on cognition and that this impact is largely mediated by amyloid plaque burden [22]. However, to date, the current studies mainly focused on Aβ metabolism, and fewer studies were performed to explore the relationship between CR1 genetic variants and other AD-related neuronal degeneration biomarkers. Hence, in the current study, we use neuroimaging methods and CSF biomarkers to test the effect of CR1 genetic variants on more AD-related pathology (Aβ accumulation including abnormal Aβ deposition on imaging and Aβ42 in cerebrospinal fluid (CSF), atrophy and hypometabolism on imaging, and tau/phosphorylated tau in CSF) in the brain.

Now multiple neuroimaging analysis methods are accepted as an important pathway to clarify the genetics of AD pathology, risk, and variability in human [23–26]. Moreover, neuroimaging phenotypes can directly describe the characters of genetic effects on brain structure and potential function on AD pathology [23]. In addition, it is reported that multiple neuroimaging measures may disclose the role of genetic variants and AD risk [27–30], and multiple neuroimaging measures have been proposed as new crucial markers in biological researches and clinical trials for their strong associations with AD pathophysiological process [29]. The increasing evidence highlights the close connection of these genetic risk factors in CSF and neuroimaging markers. Hence, in this study, we use multiple neuroimaging measures combined with CSF biomarkers to explore the potential mechanisms of CR1 common variants in AD pathology.

Methods

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

The included participants in our study are chosen from the ADNI database (http://www.loni.ucla.edu/ADNI). The ADNI database is launched in 2003 with a large, multisite, collaborative effort by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The ADNI serves as a public-private partnership aimed at testing whether serial magnetic resonance imaging (MRI), positron emission tomography, biological markers, clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and AD. The data in ADNI are got from a broad range of academic institutions and private corporations, and the included patients were recruited from more than 50 sites across the USA and Canada. More details see http://www.adni-info.org.

Participants

The included participants were enrolled according to specific criteria outlined in the ADNI protocol (http://www.adni-info.org/scientists/adnistudyprocedures.aspx). Participants were divided into three groups, normal control (NC), MCI, and AD, based on the demands on the website http://adni.loni.
Supplementary Table 1. According to above criteria, eight other experimental studies, the details were summarized in previous publications [35, 36]. At last, 812 individuals fulfilled quality control for genotype data, and they were included in this study, including 48 AD, 483 MCI, and 281 NC.

**Genotyping Data**

The genotyping of SNPs in CR1 was collected from ADNI participants by utilizing Illumina Infinium Human610-Quad Bead Chip (Illumina, Inc., San Diego, CA) or Illumina Human Omni Express BeadChip. The initial SNP genotypes were generated in Illumina Bead Studio software v3.2 from bead intensity data. Then PLINK software was performed to conduct the quality control procedures. The SNPs with one of these characteristics, minimum minor allele frequencies (MAF) <0.01 and Hardy-Weinberg equilibrium test p<0.05, were excluded. Finally, we only enrolled SNPs which have been verified by GWAS studies, large case-control trials or other experimental studies, the details were summarized in Supplementary Table 1. According to above criteria, eight SNPs (rs10779339 [35], rs12034383 [36–38], rs2025935 [35], rs3737002 [39], rs3838361 [40–43], rs4844609 [15, 44], rs4844610 [14], and 6691117 [39]) were included at last.

**MRI**

UCSF FreeSurfer datasets were utilized to assess the association between CR1 genotypes and brain structure, and the FreeSurfer version 5.1 was performed to analyze the image segmentation according to the 2010 Desikan-Killany atlas (http://surfer.nmr.mgh.harvard.edu/) [46]. The concrete technical details of MR1 are described in previous publications [47, 48]. For the MRI data, we evaluated the relationship of CR1 SNPs in cortical volume (entorhinal, middle temporal, posterior cingulate, precuneus, and parahippocampal) and volume of subcortical (amygdale and hippocampus), and these regions have been reported to link to AD closely [49, 50–56]. Furthermore, since CA1 is the most associated area with the AD-specific amnestic syndrome in hippocampus [57], we also chose CA1 as regions of interest (ROI).

**FDG-PET**

We extract FDG data from the UC Berkeley and Lawrence Berkeley National Laboratory [58]. In our study, five regions (left angular gyrus, right angular gyrus, bilateral posterior cingular, left inferior temporal gyrus, and right inferior temporal gyrus) based on a literature review were chosen as ROIs to analysis [58]. The brief procedures were summarized as follows: (1) downloading PET data from LONI (http://loni.usc.edu/), (2) spatially normalizing the downloaded images in statistical parametric mapping (SPM) to the MNI PET template, (3) extracting the mean counts from the ROIs for each subject’s FDG scans at baseline and 24-month and computing the intensity values with SPM subroutines, and (4) finally each ROIs mean was normalized by dividing it in pons/vermis reference region mean.

**CSF Proteins**

The CSF data were extracted from ADNI dataset. As described before, these CSF samples were collected then transferred into polypropylene transfer tubes, then kept in dry ice within 1 h, and transported to ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center in dry ice. After thawing (1 h) at room temperature and gentle mixing, preparation of aliquots (0.5 ml) from these samples was done. Then, CSF proteins, including Aββ42, total-tau, and...
p-tau, were examined on the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use only reagents) immunoassay kit-based reagents [59].

Statistical Analyses

Demographic characteristics in our study were extracted with proportions for categorical variables and means and standard deviations (SD) for continuous variables. t test or chi-square test was performed to analyze demographics and genotypic frequencies. A multiple linear regression model was performed to estimate coefficients for testing possible correlation between various phenotypes and CR1 genotypes in overall, AD, MCI, and NC cohorts which also considered age, gender, education, and apolipoprotein E (ApoE) ε4 status. Previous studies revealed limited association between multiple neuro-imaging measures, and independent analysis was needed for association with genetic variants [27]; moreover, according to the method developed by Hochberg and Benjamin, it is not appropriate to use Bonferroni correction to examine the non-independence of tests. Hence, we use the false discovery rate (FDR) test to control for multiple hypothesis testing [60]. FDR-corrected P value was considered statistically significant when its value is less than 0.05. IBM SPSS software (version 19.0 for windows; Chicago, IL, USA) and PLINK (http://pngu.mgh.harvard.edu/wpurcell/plink/) were utilized in statistical analyses.

Results

Characteristics of Included Participants

Finally, we enrolled 48 AD patients (18 women, 75.51 ± 9.23 years), 483 MCI samples (201 women, 72.28 ± 7.45 years), and 281 NC (145 women, 74.51 ± 5.56 years) in our study (Table 1). In consistent with previous studies, the frequency of the ε4 allele within ApoE gene is the highest in the AD group (70.8 %) compared to the MCI group (45.8 %) and the NC group (26.3 %). In addition, the included AD patients have worst cognitive function according to the scores of the five neuropsychological scales (CDRSB, ADAS, MMSE, RAVLT, and FAQ).

Characteristics of Included CR1 SNPs

Finally, eight SNPs are enrolled in our study, and they are rs10779339, rs12034383, rs2025935, rs3737002, rs3818361, rs4844609, rs4844610, and rs6691117. The characteristics of included CR1 SNPs were summarized in supplementary Table 1. Most included SNPs (rs12034383, rs2025935, rs3818361, rs4844609, rs4844610, and rs6691117) are located in intron variant in CR1 gene. Rs10779339 is in utr variant 3 prime, and rs3737002 is in missense. All the eight SNPs have MAF >0.01 and the P value of Hardy-Weinberg equilibrium test was more than 0.05. After analyzed by Haploview version 4.2, we discovered that most SNPs in CR1 were located in one haplotype block (Fig. 1). All the final included eight SNPs have been evaluated their effects on AD by GWAS studies, large population based case-control studies or experimental trials, and these reported studies were summarized in supplementary Table 1. Among these SNPs, rs10779339 and rs2025935 were proved to show no association with AD susceptibility of Korean population [35]; rs3737002 was associated with an decreased risk for LOAD in Han Chinese, and the minor allele (T) of rs3737002 was the protective factor for AD incidence [39]; the minor allele (T) of rs3818361 was a risk factor for AD development in Germany, Canada, Belgium, America, Spain, and China [5, 11, 13, 15, 16, 41, 61]; and the minor allele (G) of rs3818361 was a risk factor for AD development in China [39].

Impacts of CR1 Genetic Variants on AV-45 PET

The data of the AV-45 retention on amyloid PET imaging represented the biomarkers of Aβ accumulation. Our results indicated, rs4844609, the previous reported SNPs, showed significant positive association with the level of tracer retention on amyloid PET imaging in cingulated, frontal, parietal, and temporal in the follow-up study of 2 years (Fig. 2a-d). In further analyses of these positive results, rs4844609 mainly effected MCI and NC population (Table 2). Although the raw P values indicated a significantly positive association between Aβ deposition and variants at rs3818361 in cingulated gyrus and rs4844610 in cingulated gyrus and frontal in the follow-up study of 2 years (P = 0.03154, P = 0.01141 and P = 0.04498), the corrected P value showed no significant results after corrected by FDR test (FDR-corrected P = 0.09462, FDR-corrected P = 0.05135, and FDR-corrected P = 0.2024). Apart from these positive results, full information about the impacts of CR1 genetic variants on AV-45 PET was seen in supplementary Table 2.

Impacts of CR1 Genetic Variants on Regional Volume

Regarding to cortical volume, as showed in Fig. 3a and b, rs12034383 is demonstrated negatively associated with the volume of left and right middle temporal at baseline diagnose (P = 0.003563, FDR-corrected P = 0.01615; P = 0.002962, FDR-corrected P = 0.02666). Rs3737002 shows significant positive connection with the left and right middle temporal at baseline diagnose (P = 0.005632, FDR-corrected P = 0.0169; P = 0.006568, FDR-corrected P = 0.02956, Fig. 3c, d). In addition, a negative associate is confirmed between rs6691117 and left middle temporal at baseline diagnose (P = 0.01042, FDR-corrected P = 0.02344, Fig. 3e).
Interestingly, after stratifying into AD, MCI, and NC groups, positive findings were most significant in MCI cohorts in Table 1. However, no SNPs were proved that has a close connection with other cortical volumes, such as entorhinal, parahippocampal, posteriorcingulated, or precuneus.

In the analysis of volume of subcortical regions, the included \textit{CR1} variants show no significant connection with the volume of amygdale or hippocampus at the baseline diagnose or in the follow-up study of 2 years. In addition, no MRI data indicated any included variants in \textit{CR1} were significantly linked to the volume of CA1. The information of all SNPs in volume of brain regions was summarized in supplementary Table 3.

### Impacts of CRI Genetic Variants on Glucose Metabolism and CSF Biomarkers

In the analysis of impacts of \textit{CRI} genetic variants on glucose metabolism, we evaluate the cerebral metabolism rate of glucose on FDG-PET imaging. Our data disclosed that the raw $P$ value of rs10779339 was significantly to decrease the metabolism rate of glucose in the left angular, left/right temporal in the follow-up study of 2 years on FDG-PET imaging ($P = 0.005665$, $P = 0.01621$, and $P = 0.000448$, respectively); however, the corrected $P$ value only showed significant result in the right temporal after corrected by FDR test (FDR-corrected $P = 0.004031$), and the significant results were mainly in AD and MCI cohorts (Fig. 4, Table 2). More comments about \textit{CRI} variants in metabolism rate of glucose on FDG-PET imaging were shown in supplementary Table 4.

At last, we investigated the correlations between \textit{CRI} genetic variants and CSF biomarkers. However, no significant associations were confirmed between \textit{CRI} genetic variants and the levels of $A\beta_{42}$, total-tau, and p-tau in a multiple linear regression model (supplementary Table 5).

### Discussion

\textit{CRI}, also known as CD35, lies in chromosome 1 at the locus 1q32 in a genetic cluster of complement-related genes whose products belong to the complement activation family [20]. Initially, the \textit{CRI} gene locus was considered have a possible relationship between AD in the Genetic and Environmental Risk in AD Consortium 1 study [6], and this association was then confirmed by studies across different districts and ethnic groups [5, 11–16]. However, to date, even an amount of studies reported that \textit{CRI} is an important genetic locus in AD susceptibility, and there are still few studies to report the association between \textit{CRI} genetic variants and AD pathology in...
brain. To our knowledge, this is the first study to evaluate the relationship between \textit{CR1} genetic variants and A\textsubscript{\textbeta} deposition, brain structure, glucose metabolism, and CSF biomarkers by neuroimaging methods and CSF examination to discover the potential mechanisms of \textit{CR1} genetic variants in AD pathology.

The abnormal processing of amyloid precursor protein may finally lead to the cerebral amyloid deposition which is considered as a primary etiologic factor in AD [62, 63]. CR1 was proved to participate in the clearance of A\textsubscript{\textbeta} in two pathways, peripherally by erythrocyte and directly in the brain [17–20]. Hence, it would be reasonable to draw the conclusion that certain genetic variants in \textit{CR1} could alter A\textsubscript{\textbeta} deposition for genetic variants in \textit{CR1} may change the expression of CR1 protein to influence its role in the clearance of A\textsubscript{\textbeta}. This hypothesis may be partly proved by previous studies which reported that genetic variants in \textit{CR1} would increase the risk of cerebral amyloid angiopathy [64, 65]. Moreover, AV45-PET imaging is widely utilized to mark the presence and deposition of A\textsubscript{\textbeta}. In line with previous studies, our study also disclosed the relationship between \textit{CR1} genetic variants and A\textsubscript{\textbeta} in the brain according to the results of AV45-PET imaging. Interestingly, our study discovered rs4844609 positively linked to A\textsubscript{\textbeta} deposition. It is reported that rs4844609 was identified to link to a decline in episodic memory accompanied with AD neuropathological features [44]. Furthermore, our results revealed that this phenomenon may come from the variants at rs4844609 inducing the amyloid deposition in cortical frontal, parietal, cingulated, and temporal. Hence, it may be reasonable to draw the conclusion that rs4844609 influenced episodic memory and associated AD neuropathological features by increasing the amyloid deposition in various brain regions. In addition, in the stratified analyses of AD, MCI, and NC group, we discovered variants at rs4844609 significantly increased A\textsubscript{\textbeta} deposition in both MCI and NC population in cingulated, frontal, and parietal in the follow-up study of 2 years, and
variants at rs4844609 altered Aβ deposition in temporal only in NC cohorts (Table 2). Moreover, our findings were in accordance with previous pathologic and biomarker studies which indicated that Aβ changes in the brain begin possibly

**Table 2** Stratified of positive results in AD, MCI and NC group

| Kind       | SNP                  | Time     | Region             | Group | Value (mean ± SD) | βa  | P value |
|------------|----------------------|----------|--------------------|-------|-------------------|-----|---------|
| AV45-PET   | rs4844609            | 2-year   | cingulate          | ALL   | 1.017 ± 0.09035   | –   | 0.06099 |
|            |                      |          |                    | AD    | 1.014 ± 0.1344    | –   | 0.05571 |
|            |                      |          |                    | MCI   | 1.013 ± 0.08943   | –   | 0.0589  |
|            |                      |          |                    | NC    | 1.023 ± 0.08302   | –   | 0.1062  |
| rs4844609  | 2-year               | frontal  |                    | ALL   | 1.016 ± 0.08745   | –   | 0.06321 |
|            |                      |          |                    | AD    | 1.017 ± 0.1311    | –   | 0.05335 |
|            |                      |          |                    | MCI   | 1.014 ± 0.08764   | –   | 0.054   |
|            |                      |          |                    | NC    | 1.02 ± 0.07809    | –   | 0.1214  |
| rs4844609  | 2-year               | parietal |                    | ALL   | 1.018 ± 0.08441   | –   | 0.06058 |
|            |                      |          |                    | AD    | 1.016 ± 0.1257    | –   | 0.06511 |
|            |                      |          |                    | MCI   | 1.016 ± 0.08576   | –   | 0.04803 |
|            |                      |          |                    | NC    | 1.022 ± 0.07308   | –   | 0.1261  |
| rs4844609  | 2-year               | temporal |                    | ALL   | 1.011 ± 0.08072   | –   | 0.05379 |
|            |                      |          |                    | AD    | 0.9959 ± 0.1272   | –   | 0.07617 |
|            |                      |          |                    | MCI   | 1.009 ± 0.08087   | –   | 0.03762 |
|            |                      |          |                    | NC    | 1.016 ± 0.06998   | –   | 0.1244  |
| MRI        | rs12034383           | baseline | left middle temporal | ALL   | 9711 ± 1267       | 9427 ± 1510 | 9368 ± 1484 | −216.6 | 0.003563 |
|            |                      |          |                    | AD    | 8615 ± 1071       | 8093 ± 1652 | 7877 ± 453.5 | −127.6 | 0.6718  |
|            |                      |          |                    | MCI   | 9822 ± 1325       | 9556 ± 1443 | 9404 ± 1462 | −206.2 | 0.02683 |
|            |                      |          |                    | NC    | 9705 ± 1089       | 9637 ± 1364 | 9639 ± 1508 | −170.3 | 0.1429  |
| rs12034383 | baseline             | right middle temporal | ALL   | 10960 ± 1538   | 10065 ± 1570 | 10560 ± 1514 | −236.8 | 0.002962 |
|            |                      |          |                    | AD    | 10180 ± 1804      | 9450 ± 1966 | 9126 ± 1197 | −113   | 0.7758  |
|            |                      |          |                    | MCI   | 11010 ± 1678      | 10800 ± 1445 | 10520 ± 1575 | −234.9 | 0.02064 |
|            |                      |          |                    | NC    | 11010 ± 1131      | 10770 ± 1505 | 10950 ± 1277 | −171.1 | 0.1468  |
| rs3737002  | baseline             | left middle temporal | ALL   | 9398 ± 1503   | 9609 ± 1332 | 9840 ± 1413 | 230.9 | 0.005632 |
|            |                      |          |                    | AD    | 7751 ± 1167       | 8665 ± 1589 | 8848 ± 0   | 536.8  | 0.1004  |
|            |                      |          |                    | MCI   | 9494 ± 1408       | 9744 ± 1347 | 10000 ± 1719 | 248.5  | 0.0284  |
|            |                      |          |                    | NC    | 9694 ± 1522       | 9634 ± 1140 | 9645 ± 719.5 | 66.36  | 0.6125  |
| rs3737002  | baseline             | right middle temporal | ALL   | 10600 ± 1588   | 10870 ± 1536 | 11010 ± 1375 | 243.3 | 0.006568 |
|            |                      |          |                    | AD    | 9294 ± 1598       | 9774 ± 2123 | 10830 ± 0   | 189.6  | 0.6656  |
|            |                      |          |                    | MCI   | 10690 ± 1565      | 10990 ± 1515 | 11110 ± 1634 | 248.5  | 0.0284  |
|            |                      |          |                    | NC    | 10820 ± 1460      | 10970 ± 1281 | 10850 ± 903.4 | 141.2  | 0.287   |
| rs6691117  | baseline             | left middle temporal | ALL   | 9628 ± 1346   | 9358 ± 1591 | 9256 ± 1344 | −207.1 | 0.01042 |
|            |                      |          |                    | AD    | 8604 ± 1480       | 7788 ± 1322 | 7580 ± 340 | −477.8 | 0.09877 |
|            |                      |          |                    | MCI   | 9721 ± 1400       | 9486 ± 1435 | 9328 ± 1392 | −139.3 | 0.1722  |
|            |                      |          |                    | NC    | 9675 ± 1072       | 9654 ± 1677 | 9599 ± 1103 | −219.8 | 0.08811 |
| FDG        | rs10779339           | 2-year   | right temporal      | ALL   | 0.9947 ± 0.06501 | 0.9844 ± 0.05817 | 0.9631 ± 0.05547 | −0.01712 | 0.000448 |
|            |                      |          |                    | AD    | 0.9619 ± 0.03705 | 0.96 ± 0.0655 | 0.9086 ± 0.05691 | −0.01954 | 0.005791 |
|            |                      |          |                    | MCI   | 0.9931 ± 0.0723  | 0.9809 ± 0.06258 | 0.9679 ± 0.06099 | −0.01433 | 0.02628 |
|            |                      |          |                    | NC    | 1.005 ± 0.04955  | 0.9956 ± 0.04455 | 0.9608 ± 0.03998 | 0.01562  | 0.5829  |

AD Alzheimer’s disease, AV45-PET florbetapir retention on florbetapir 18F amyloid positron emission tomography, CN cognitively normal, FDG 18F-fluorodeoxyglucose PET, MCI mild cognition impairment, MRI magnetic resonance imaging, SNP single nucleotide polymorphism, M major allele, m minor allele
MM, Mm, mm: M stands for the major allele and m stands for the minor allele

*β is a parameter which indicates the positive (β>0) or negative (β<0) relations of original data
decades before cognitive symptoms emerge, and biomarker studies of older asymptomatic and MCI subjects have suggested an increased rate of pathologic Aβ changes [66–68]. Take together, variants at rs4844609 may increase Aβ deposition in wide brain regions among MCI or NC population, and finally increased AD risk. Hence, it would meaningful to screen the crowd to identify variants in rs4844609 to bring new directions for the monitoring and forecasting of AD. Apart from Aβ, certain imaging features of brain atrophy were also an important underlying pathology of AD [69]. Therefore, in the current study, we detected the influence of CR1 genetic variants in the brain volumes. The team of Brouwers disclosed a significant association between rs12034383 and the levels of Aβ [70]. Although our data did not reveal any association between rs12034383 and Aβ, our results indicated that the person who has variants at rs12034383 may have lower volume of the left and right middle temporal which is believed to affect the cognitive function [71]. Our study shows that variants at rs3737002 would increase the volume of the left and right middle temporal, and rs6691117 would decrease the volume of the left middle temporal. Since the middle temporal has been identified to influence the awareness of language deficits during AD progression [72], the variants at rs3737002 may play a protective role in AD pathology, and the variants at rs6691117 may be detrimental in AD pathology, and this results were consistent with the findings of Tan group [39]. Interestingly, the most significant results were discovered between CR1 genetic variants and the volume of medial temporal lobe. Middle temporal is
implicated as a key brain region involved in the pathogenesis of AD and consequent memory loss, and the group of Song has proved brain Aβ burden is associated with disruption of intrinsic functional connectivity within the medial temporal lobe in cognitively normal elderly [49]. Allowing for these previous research results and our results of the significant association between CRI genetic variants and Aβ burden, as well as the volume of medial temporal, we may hypothesize a potential connection between CRI and AD pathology by increasing Aβ deposition and affecting the volume of medial temporal. The group of Kandiah confirmed that medial temporal atrophy showed a strong association in the stage of MCI and mild AD which was inconsistent with our results [73]. Our findings of a significant association between medial temporal atrophy at the stage of MCI has important clinical implications for timely making treatment plans for patients who present with milder cognitive symptoms, and it would may be meaningful to mitigate AD pathogenesis and reduce the prevalence or delay the onset of more severe stages of AD dementia.

The drastic reduction of glucose metabolic activity in specific brain regions could be determined by FDG PET [74]. Furthermore, cerebral glucose metabolic activity is a characteristic feature of synaptic function and density, and it could be accepted as the marker of neurodegeneration. Previous studies reported that the decline of cerebral glucose metabolic rate can be observed in wide regions of the brains in MCI person [75–77], and hypometabolism was also discovered in the brains of AD patients [78, 79], and our results also confirmed variants at rs10779339 would significant influence glucose metabolic activity also in MCI and AD cohorts. In the current study, we discovered variants at rs10779339 would significantly decrease the cerebral glucose metabolic rate, indicating that variants at rs10779339 may increase AD risk. However, Sun and his colleagues detected no association between rs10779339 and AD susceptibility in the GWAS in Korean population. The different findings of the connection between rs10779339 and AD may mainly attribute to the different ethnic origins.

Hyperphosphorylated tau is an identical pathological feature of AD, and the Haroutunian laboratory found that CR1 mRNA levels correlate with neurofibrillary tangle density and phosphorylated tau abundance [80]. Moreover, the group of R. Killick discovered that CR1 impacts tau phosphorylation and brain CFH in vivo [81]. However, the current results discovered variants at these included CRI SNPs did not significant alter the levels of AD-related tau proteins (total-tau and p-tau). The contrast may come from the different designs of experiments and genetic background. Taking together, the inconsistent results imply more studies are needed to perform to confirm these phenomena and discover related mechanisms.

In conclusion, our study first provides the evidence of the possible role of CRI genetic variants in affecting AD-related neuroimaging phenotypes, including Aβ loads, the volume brain structures and glucose metabolism during AD progression. According to the collected data at baseline and 24-month, there is some conversion or diagnosis change during the 24-month follow-up, and these conversions or diagnosis change may effect on the results. Moreover, it would be meaningful to stratify the MCI group in MCI converting to dementia vs MCI non-converting to dementia; hence, more studies are needed to perform to discover this relation. However, more available independent population for replication should be performed to examine the conclusions we draw, and further work needs to be conducted to explain the concrete mechanisms of these CRI genetic variants during AD progression.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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