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Genetic Association of *HLA* Gene Variants with MRI Brain Structure in Alzheimer's Disease

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Abstract There is accumulating evidence that the human leukocyte antigen (HLA) gene variants are associated with Alzheimer's disease (AD). However, how they affect AD occurrence is still unknown. In this study, we firstly investigated the association of gene variants in *HLA* gene variants and brain structures on MRI in a large sample from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to explore the effects of *HLA* on AD pathogenesis. We selected hippocampus, hippocampus CA1 subregion, parahippocampus, posterior cingulate, precuneus, middle temporal, entorhinal cortex, and amygdala as regions of interest (ROIs). According to the previous association studies of *HLA* variants and AD, 12 SNPs in *HLA* were identified in the dataset following quality control measures. In total group analysis, our results showed that *TNF-α* SNPs at rs2534672 and rs2395488 were significantly positively associated with the volume of the left middle temporal lobe (rs2534672: $P = 0.00035$, $Pc = 0.004$; rs2395488: $P = 0.0038$, $Pc = 0.023$) at baseline. In the longitudinal study, *HFE* rs1800562 was remarkably correlated with the lower atrophy rate of right middle temporal lobe ($P = 0.0003$, $Pc = 0.003$) and *RAGE* rs2070600 was associated with the atrophy rate of right hippocampus substructure-CA1 over 2 years ($P = 0.003$, $Pc = 0.035$). Furthermore, we detected the above four associations in mild cognitive impairment (MCI) subgroup analysis, as well as the association of rs2534672 with the baseline

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volume of the left middle temporal lobe in normal cognition (NC) subgroup analysis. Our study provided preliminary evidences that *HLA* gene variants might participate in the structural alteration of AD associated brain regions, hence modulating the susceptibility of AD.

Keywords HLA · Genetics · Alzheimer's disease · Brain structure · Neuroimaging

Introduction

Alzheimer's disease (AD) is the most common form of dementia characterized by loss of memory and other cognitive abilities, severe enough to disrupt daily life activities. It is now widely accepted that AD is a complex disease entity, with occurrence underpinned by both genetic and environmental components [1–4]. Hundreds of candidate gene variants for AD risk have been identified [2], and human leukocyte antigen (HLA) genes are one of them. The *HLA* gene complex, situated on chromosome 6, is the most polymorphic region in the human genome and contains major histocompatibility complex (MHC) class I, II, and III genes. MHC I and II molecules are implicated in antigen presentation to T lymphocytes, by regulating T cell responses against specific antigens. These are the bases for the antigen-specific control of the immune response. Abnormal proteins such as β-amyloid peptide (Aβ) (one of the hallmarks of the pathogenesis of AD) in the AD brains are first endocytosed by antigen-presenting cells and then processed to fragments that are bound to MHC molecules and presented to T lymphocytes. Antigen presentation can lead to B cell stimulation and subsequently to the production of specific autoantibodies. The reactive T cells can be activated at the same time and may eliminate abnormal cells. The processes and responses seem to protect the bodies [5]. However, excessive reactivity could have harmful side effects, and the immune-mediated neuroinflammation had been demonstrated to be involved in the pathogenesis of AD [6]. Otherwise, the infectious AD etiology hypothesis was proposed, and there are the growing evidence associating infectious agents with AD [7]. Moreover, the vigor and degree of an immune response can be different according to the different HLA antigens present. Thus, *HLA* gene might be important in the development/progression of AD.

We reviewed the previous association studies of *HLA* gene variants and AD, many of which indicated that a number of *HLA* gene variants have shown an association with AD. Within the MHC class I gene region, a surrogate marker (rs2743951) for *HLA-B*4402* modified the effects of the putative AD risk phosphoenolpyruvate carboxykinase 1 (*PCK1*) variant on baseline brain volume in multiple sclerosis subjects [8] and the two most common mutations of non-classic *HLA-I* hemochromatosis (*HFE*) gene (H63D: rs1799945, C282Y: rs1800562) were demonstrated to anticipate sporadic AD clinical presentation [9–11]. Within the MHC class II genes region, a large meta-analysis of genome-wide association studies (GWAS) identified a new susceptibility locus (rs9271192) in the *HLA-DRB5–DRB1* region for AD [12] and two independent case–control studies showed that the SNP (rs241448) in transporters associated with antigen processing (*TAP*) gene was associated with AD [13]. For the class III genes, several functional polymorphisms in *TNF-α* (rs1800629, rs361525, rs1799724, rs2395488, and rs2534672) appear to be associated each to a different risk of developing AD in different populations [14–16] and the variants G82S (rs2070600) and −374 T/A (rs1800624) in the receptor for advanced glycation end products (*RAGE*) were involved in genetic susceptibility to AD [16, 17].

With the proposal for "brain reserve" hypothesis by Stern et al. [18, 19], it seemed that the researchers' attention focused more on some brain regions specifically associated with AD, such as hippocampus, hippocampus CA1 subregion, middle temporal area, entorhinal area, posterior cingulate, precuneus, and parahippocampal area than the global situation of the whole brain. These regions were known to be affected by AD [20]. To further characterize complex genes associated with AD, recently, a growing number of studies are using an intermediate phenotype approach, which utilizes specific biomarkers, such as structural brain imaging on MRI, as endpoints in genetic analyses of risk [21, 22]. These measures appear to be shaped by genetic influences with heritability estimates as high as 80 % [23, 24]. The increasing evidence that genetic risk factors for AD impact these neuroimaging markers helps us in understanding the complex disorders of AD, from genetic determinate to cellular process to the complex interplay of brain structure, function, behavior, and cognition.

Thus, our goal was to explore the association of candidate genetic variations in *HLA* with AD-related brain structures on MRI in a large sample from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to give a preliminary analysis on their role in predicting AD risk and progression.

Methods

ADNI Dataset and Subjects

The data used in the preparation of this paper were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://ida.loni.usc.edu/). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit

organizations [10]. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as to lessen the time and cost of clinical trials. The initial goal of ADNI was to recruit 800 subjects, and ADNI has been followed by ADNI-GO and ADNI-2. To date, the three protocols have covered more than 1500 adults, ages 55 to 90 years, to participate in the research. The 1500 adult consists of cognitively normal (CN) older individuals, people with early or late mild cognitive impairment (MCI), and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO (see www.adni-info.org for up-to-date information). The details concerning the ADNI cohort were reported elsewhere [25, 26]. The final dataset for the present analysis comprised 812 individuals, including 281 health controls (normal cognition, NC), 483 MCI, and 48 AD at baseline. The ADNI study was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives.

MRI Brain Structure

ADNI MRIs were acquired at multiple sites with a GE Healthcare (Buckinghamshire, England), Siemens Medical Solutions USA (Atlanta, Georgia), or Philips Electronics 3.0 T system (Philips Electronics North America; Sunnyvale, California). The cerebral image segmentation and analysis were performed with FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu/) based on the 2010 Desikan-Killany atlas [27]. The main work contained that motion correction and averaging of multiple volumetric T1-weighted images (when more than one is available) [28], removal of non-brain tissue using a hybrid watershed/deformable surface algorithm [29], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) [30, 31], intensity normalization [32], tessellation of the gray matter white matter boundary, automated topology correction [33], and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class [34]. All MRIs were processed according to previously published methods [34, 35]. Eight neuroimaging measures were chosen for analysis on the basis of their established roles in predicting AD risk and progression: hippocampal volume, hippocampus-CA1 volume, parahippocampal volume, amygdala volume, posterior cingulate gyrus volume, precuneus volume, middle temporal volume, and entorhinal cortex thickness. These regions are adjacent anatomically and the structural changes of these regions are associated with memory deficits [36]. The atrophy of these regions in AD has been previously validated via MRI studies compared with age-matched controls [20, 37–40], which is consistent with the sequential neuropathological changes described by Braak [41]. The atrophy of these regions is one of the key biomarkers to detect early neurodegenerative changes in the course of Alzheimer's disease and help clinicians to assess MCI to AD conversion. In particular, the multiple uses of the MRI measures associated with these regions have a relatively high sensitivity and specificity for MCI conversion to AD [37, 38, 42]. Moreover, it has been widely accepted that at rest state, important brain areas-posterior cingulate cortex combines precuneus, lateral temporal cortex, medial prefrontal cortex, and inferior parietal lobule organized into a functionally relevant networks, the "default mode network" (DMN), which is demonstrated to be abnormal and correlated with memory defect in AD [43]. Based on the above observation, we chose these eight regions, which were widely researched and known to be affected by AD. In the present analysis, there were 718 (NC = 257, MCI = 422, AD = 39) individuals included in the regional volume/thickness analysis (Table 2).

Genetic Data

According to the associations of *HLA* gene variants with AD, we intended to select 12 candidate SNPs (*HLA-B*: rs2743951, *HFE*: rs1799945 and rs1800562, *HLA-DRB5-DRB1*: rs9271192, *TAP2*: rs241448, *TNF-α*: rs1800629, rs361525, rs1799724, rs2395488 and rs2534672, *RAGE*: rs2070600 and rs1800624) located at the genomic regions of HLA genes. The genotype data for participants included was uploaded to the ADNI website (http://www.loni.ucla.edu/ADNI). 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 $P > 0.0001$. Because the SNPs (rs9271192, rs361525, and rs241448) were not genotyped in ADNI database, we determined proxy-based linkage disequilibrium using the 1000 Genomes Project (http://www.1000genomes.org) on Haploview 4.2 platform. Finally, the three surrogate SNPs (rs9271246, rs3093661, and rs241449) were respectively selected based on their strong linkage disequilibrium with rs92711929 ($D' = 1$, $r^2 = 1$), rs361525 ($D' = 0.88$, $r^2 = 0.97$), and rs241448 ($D' = 1$, $r^2 = 1$) in the 1000 Genomes Project samples. The selected 12 SNPs passed QC (Table 1). AD is a polygenetic disorder with complex traits, and its genetic factor is the accumulation of multiple genetic effects. Every

Table 1 The targeted *HLA* loci in the study

SNP	Chromosome	Physical position	Gene	Call rate (%)	Alleles	MAF	H-W (*P* value)
rs1799945	6	26091179	*HFE*	99.9	C:G	0.141	1.0000
rs1800562	6	26093141	*HFE*	99.9	G:A	0.058	0.9692
rs2743951	6	29709234	*HLA-B*	100.0	G:A	0.447	0.1844
rs2395488	6	31445909	*TNF-α*	100.0	A:G	0.329	0.2345
rs2534672	6	31465558	*TNF-α*	99.9	C:G	0.305	0.7428
rs1799724	6	31542482	*TNF-α*	94.8	C:T	0.103	0.8630
rs1800629	6	31543031	*TNF-α*	99.9	G:A	0.155	0.8022
rs3093661	6	31543758	*TNF-α*	99.9	G:A	0.038	0.6546
rs2070600	6	32151443	*RAGE*	100.0	G:A	0.036	0.1673
rs1800624	6	32152387	*RAGE*	99.9	T:A	0.219	0.4398
rs9271246	6	32580084	*HLA-DRB5-DRB1*	99.8	G:A	0.257	0.1349
rs241449	6	32796653	*TAP2*	93.5	G:T	0.258	0.0089

MAF minor allele frequency, *H-W* Hardy-Weinberg equivalent

susceptibility gene has a small amount of limited effect rather than plays a decisive role, and there is a dose-effect relationship. So, we chose additive genetic model which considers the number of mutant alleles and the possibilities of developing disease. However, from the perspective of statistics, for the SNPs with the MAF < 0.1, it is unreasonable to build additive or recessive genetic model because the statistical power is too low. We had to assess using dominant genetic model to get stronger power. For the SNPs with the MAF < 0.1, we assessed using dominant genetic model (rs1800562: GA + AA versus GG; rs2070600: GA + AA versus GG).

Statistical Analysis

Differences in continuous variables (age, education years, cognitive scores, volume, etc.) were examined using one-way analysis of variance (ANOVA), and categorical data (gender, *ApoE* ε4 status) were tested using the chi-square test. All statistical analyses were performed by R 3.12 and PLINK 8 (http://pngu.mgh.harvard.edu/wpurcell/plink/). Haploview (version 4.2) was used to estimate the linkage disequilibrium (LD) among genotyped variants. Furthermore, we used a multiple linear regression model which considered age, gender, education years, and *ApoE* ε4 status as covariates to estimate coefficients for testing possible correlation between *HLA* loci genotypes and MRI brain structures at baseline and in the follow-up year. Given that Bonferroni correction was inappropriate due to the nonindependence of these tests [44], the false discovery rate (FDR) based on the method developed by Hochberg and Benjamini [45] was used to control for multiple tests. Statistical significance was considered for FDR-corrected $Pc < 0.05$. Analysis of the overall sample indicated significant correlation between positive *HLA-A* loci and the development of AD. Thus, the next step we took was to further investigate the correlation between the MRI brain structures of each subgroup (CN, MCI, and AD) with the positive *HLA-A* loci. We wanted to analyze and identify at which stage these variations impacted the pathological markers in the pathogenesis of AD.

Results

Characteristics of Included Subjects

The information about the included subjects is listed in Table 2. In total, 281 CN (145 women, 74.51 ± 5.56 years), 483 MCI (201 women, 72.28 ± 7.45 years), and 48 AD patients (18 women, 75.51 ± 9.23 years) were recruited in this study. As expected, the AD group had the highest frequency for the ε4 allele within the *ApoE* gene (44.8 %), and the CN group had the lowest frequency (14.9%). Compared to CN and MCI subjects, AD dementia patients displayed the worst cognitive function based on these various neuropsychological scales (CDRSB, MMSE, ADAS-cog, etc.). Likewise, the AD group showed the most severe atrophy in the hippocampus, middle temporal, and entorhinal cortex using MRI method.

Brain Structures and HLA Loci Genotypes in the Total Group

We firstly analyzed the association of these *HLA* loci with AD-related brain structures (hippocampus, hippocampus-CA1, parahippocampus, middle temporal, amygdala, posterior cingulate, precuneus, and entorhinal cortex) in a linear model that treated age, gender, education years, APOE ε4 status, and intracranial volume (ICV) or thickness as covariants at baseline. An allele of rs2534672 and allele of rs2395488 showed a significant association with the larger volume of the left middle temporal lobe, and the two

Table 2 The characteristics of the ADNI subjects at baseline

Characteristics	CN		MCI		AD		*P* value*
Age (years)	281	74.51 ± 5.56	483	72.28 ± 7.45	48	75.51 ± 9.23	–
Gender (male/female)	281	136/145	483	282/201	48	30/18	–
Education (years)	281	16.41 ± 2.66	483	15.98 ± 2.82	48	15.73 ± 2.62	0.08
APOE ε4 (0/1/2)	281	204/70/7	483	262/180/41	48	14/25/9	<0.01
CDR-SB	207	0.03 ± 0.13	406	1.44 ± 0.87	47	4.44 ± 1.69	<0.01
MMSE	281	29.07 ± 1.15	483	27.89 ± 1.69	48	22.96 ± 2.03	<0.01
ADAS-cog	281	9.06 ± 4.23	480	15.30 ± 6.65	48	29.80 ± 8.44	<0.01
RAVLT	280	44.83 ± 9.60	483	36.16 ± 10.86	47	22.32 ± 7.84	<0.01
FAQ	281	0.17 ± 0.66	481	2.85 ± 3.99	48	12.6 ± 7.14	<0.01
Hippocampus (mm^3)	257	7344 ± 895	422	6996 ± 1126	39	5757 ± 948	<0.01
Middle Temporal (mm^3)	257	20298 ± 2600	422	20186 ± 2735	39	17776 ± 3230	<0.01
Entorhinal (mm^3)	257	3803 ± 650	422	3610 ± 723	39	2919 ± 705	<0.01

Data are given as mean ± standard deviation unless otherwise indicated

CN cognitively normal, *MCI* mild cognition impairment, *AD* Alzheimer's disease, *CDR-SB* Clinical Dementia Rating sum of boxes, *ADAS-cog* Alzheimer's disease Assessment Scale Cognition, *MMSE* Mini-Mental State Exam, *RAVLT* Rey Auditory Verbal Learning Test, *FAQ* Functional Activities Questionnaire

**P* values for continuous variables are from one-way analysis of variance (ANOVA). *P* values for categorical data are from chi-square test

associations with the left middle temporal lobe still survived the FDR correction (rs2534672: $P = 0.00035$, $Pc = 0.004$; rs2395488: $P = 0.0038$, $Pc = 0.023$) in cross-section analysis (Fig. 1a, b; Supplementary Table 1). The variations at rs1800629 were related to the volume of the right posterior cingulate ($P = 0.034$), left middle temporal ($P = 0.046$), and right precuneus ($P = 0.046$) at baseline in the overall group; however, the associations did not reach statistically significant levels after the FDR test. Similarly, neither the association of rs3093661 and left posterior cingulate volume ($P = 0.031$) nor the association of rs1800624 and left precuneus volume ($P = 0.034$) survived after FDR correction. In addition, the difference of rs3093661 genotypes in right hippocampus substructure-CA1 ($P = 0.023$) did not reach significant levels in the FDR test (Supplementary Table 1). In the 2-year follow-up study, the variations at rs1800562 were remarkably correlated with the atrophy rate of right middle temporal ($P = 0.0003$, $Pc = 0.002$) (Fig. 1c; Supplementary Table 1). Moreover, the variations at rs2070600 had different atrophy rates of right hippocampus substructure-CA1 over 2 years ($P = 0.003$, $Pc = 0.033$) (Fig. 1d; Supplementary Table 1).

Brain Structures and HLA Loci Genotypes in the Three Subgroups

Sequentially, we conducted subgroup analysis to ascertain whether *HLA* loci (rs2534672 and rs2395488) altered the volume of left middle temporal lobe in AD, MCI, or CN group at baseline and observed that both of the loci altered left middle temporal volume in MCI subgroup at baseline (rs2534672: $P = 0.001$; rs2395488: $P = 0.009$); moreover, rs2534672 was also found to impact left middle temporal volume in NC subgroup at baseline ($P = 0.042$) (Fig. 2a, c, Supplementary Table 2). In the longitudinal study, subgroup analysis discovered that rs1800562 affected the atrophy rate of the right middle temporal only in MCI group ($P = 3.18 \times 10^{-4}$) (Fig. 2d, Supplementary Table 2). And, rs2070600 also showed association with atrophy rates of the right hippocampus substructure-CA1 only in MCI subgroups ($P = 0.001$) (Fig. 2e, Supplementary Table 2).

Discussion

Our imaging-genetics analysis suggested that *TNF-α*, *HFE*, and *RAGE* genetic variations were respectively correlated with particular brain structures on MRI in ADNI subjects. These findings further disclosed that the *HLA* loci, especially the MHC class III genes loci, might participate in the brain structural alteration in AD-associated brain regions. We found that *TNF-α* variations (rs2534672 and rs2395488) and *HFE* C282Y were respectively associated with larger baseline volume of left middle temporal and slower atrophy rate of right middle temporal, every loci of which would be favorable in fighting against AD insults. We also showed that *RAGE* G82S altered the volume of the right hippocampus substructure-CA1 to increase the risk of AD. Unfortunately, we did not found the association of rs9271246 with brain structures on MRI, which were consistent with the result of Chauhan et al.'s study that there was no association of rs9271246 with the total brain volume and hippocampal volume. Our study further revealed the potential pathways by which these genetic

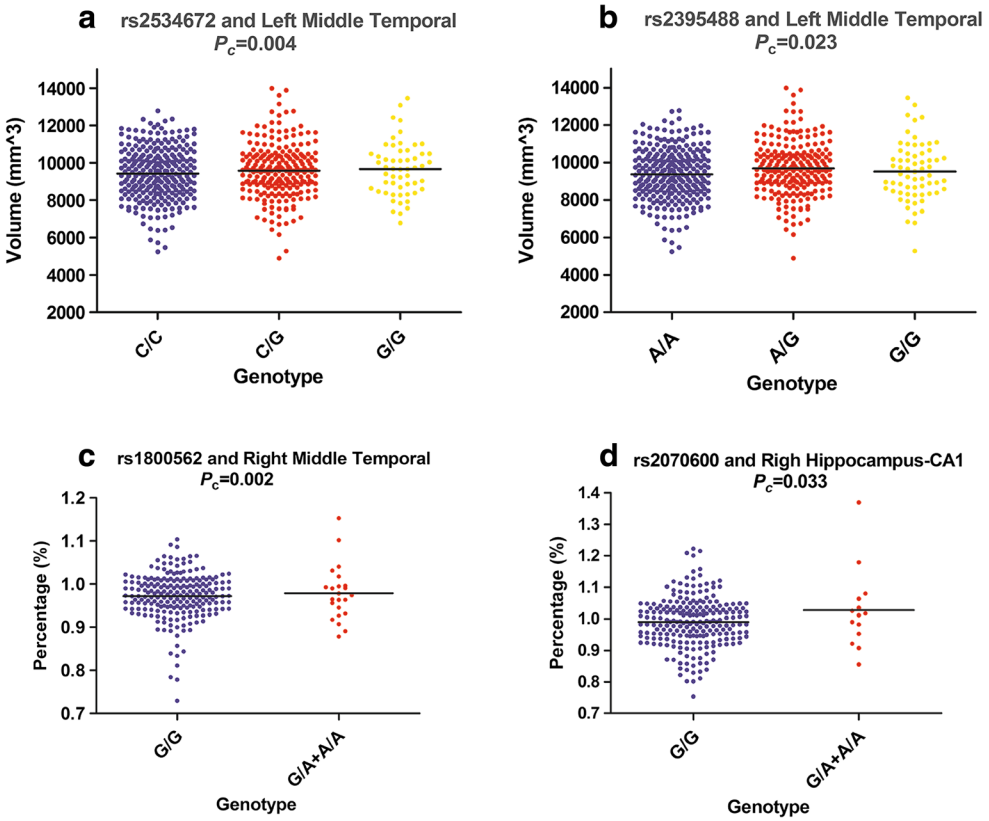

Fig 1 The significant associations of *HLA* loci with AD specific brain structure on MRI in the total group. We identified three loci which associations were still significant after FDR correction in the total group. **a**, **b** depicted that *TNF-α* rs2534672 and rs2395488 (G allele) were associated with the larger baseline volume of the left middle temporal lobe. **c** depicted that *HFE* rs1800562 (G allele) was correlated with the slower 2-year atrophy rate of right middle temporal. **d** depicted that *RAGE* rs2070600 (A allele) was associated with the faster 2-year atrophy rate of right hippocampus substructure-CA1

variations act in modulation of the susceptibility of AD. However, the mechanism was still a mystery.

TNF-α, as the encoding product of *TNF-α* gene, is one of the main pro-inflammatory cytokines. Inflammation is a well-documented feature and purported risk factor for AD [6, 46]; naturally, a number of studies provide evidence for the multiple involvement of in the pathogenesis of AD. For the aspects from the brain structure-related role of TNF-α, TNF-α can induce neuronal apoptosis via binding to and activating its death receptors (DRs) in AD [14] and neuron-produced TNF-α has a positive effect in the regeneration of posttraumatic brain [47, 48]. Moreover, TNF-α was demonstrated to be associated with greater atrophy of total brain and hippocampal volume than expected for age. Our results further showed that rs2534672 and rs2395488 were positively significantly linked to the baseline volume of the left middle temporal and produced protective effect in AD, which concurred with the results that two SNPs showed a trend of protection from Moreno-Grau's study that conducted a meta-analysis with five previous genome-wide association studies and aggregated data [14]. Thus, it can be seen that the two SNPs might modulate the alteration of brain structure to operate their potential to prevent the AD progression. Moreover, middle temporal lobe might be the pivotal region on which the two SNPs target. On the other hand, the abnormalities in the middle temporal lobe occurred in the early stage of AD, and rates and amount of middle temporal lobe atrophy have also been shown to correlate with MCI to AD conversion [49]. The further subgroup analysis confirmed that possession of rs2534672 GG genotype played a protective role for the volume of left middle temporal respectively in the MCI and NC stage and possession of rs2395488 GG genotype also displayed protective function on the volume of left middle temporal in the MCI stage. This suggests that the two SNPs play a role in preventing the middle temporal atrophy in the stage of MCI or NC. Generally, normal aging might play a more important role in causing brain atrophy in the stage of NC than MCI/AD, and the role of abnormal pathologies is increasingly rising and would finally surpass that of normal aging as the stage further progresses (for example, from NC to MCI/AD). It can be thus inferred that the potential pathways by which *TNF-α* variations act may be possibly associated with fighting against negative impacts derived from normal aging or pathological insults of the middle temporal lobe. This may also explain the difference of association which *TNF-α* rs2534672 showed in NC and MCI population.

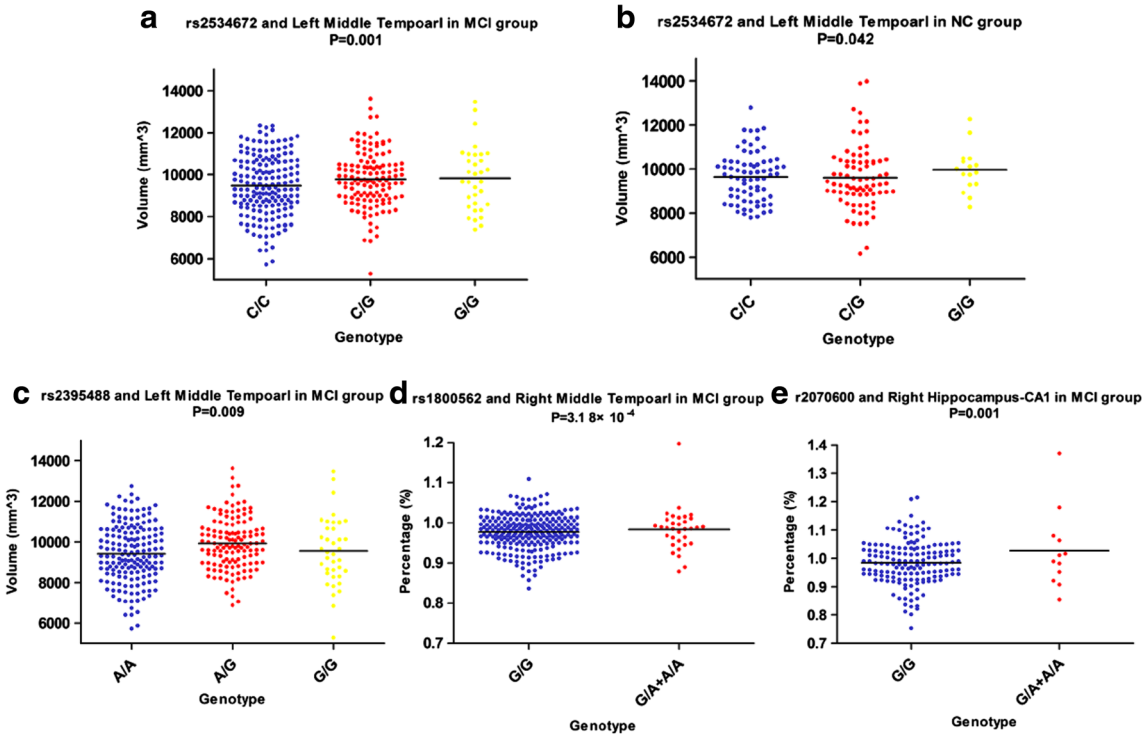

Fig 2 The significant associations of *HLA* loci with AD-specific brain structure on MRI in the subgroups. **a**, **c** depicted that *TNF-α* rs2534672 (G allele) and rs2395488 (G allele) were associated with the larger baseline volume of left middle temporal in MCI group. **b** depicted that *TNF-α* rs2534672 (G allele) was associated with the larger baseline volume of left middle temporal in NC group. **d** depicted that *HFE* rs1800562 (G allele) was associated with the slower 2-year atrophy rate of the right middle temporal in MCI group. **e** depicted that *RAGE* rs2070600 (A allele) also showed association with the faster 2-year atrophy rate of the right hippocampus substructure-CA1 in MCI group. *NC* normal cognition, *MCI* mild cognition impairment, *AD* Alzheimer's disease

HFE (high iron), originally called *HLA-H*, is a major histocompatibility complex (MHC) class I-like gene. It was first identified by Simon et al. [50] in association with an iron overload disorder called hereditary hemochromatosis (HH). *HFE* gene product primarily regulates iron uptake into cells by interacting with the transferrin receptor (TfR: iron uptake) to restrict transferrin (Tf: iron transport) binding. Control of iron homeostasis is essential for healthy central nervous system function, and its imbalance is associated with cognitive impairment. C282Y rs1800562 is a common mutation of *HFE* (in exon 4; 12 % of Caucasian populations). A G-to-A transition at nucleotide 845 results in cysteine to tyrosine substitution at amino acid 282, i.e., C282Y. The wild-type HFE (WT-HFE) bound to TfR allows only one iron-bound Tf (Fe-Tf) to bind per TfR and be taken up by cells. Because C282Y-HFE is retained in the trans-golgi complex due to its inability to be transferred to the cell surface, C282Y-HFE does not interact with TfR and thus results in more iron uptake than WT-HFE. Although the function of one variant is very limited, this iron imbalance can probably impact amyloid processing, plaque formation, response to inflammatory agents, and particularly cause oxidative damage, all of which are closely related with brain structural alteration in AD [9, 51, 52]. Previous studies showed that transferrin levels were related to detectable differences in the macrostructure and microstructure of the living brain and transferrin levels were influenced by the polymorphisms in *HFE* [53]. Moreover, H63D (rs1799945) was associated with white matter fiber integrity in healthy adults. For these observation and understanding about *HFE* gene, it can be thus inferred that *HFE* gene variants might be correlated with brain structure. Our results showed that G allele of C282Y was associated with the lower rate of atrophy in the right middle temporal lobe over time and the MCI subgroup analysis corroborated the total group analysis results, which were consistent with Correia's study supporting a putative protective role of this variant in AD. Furthermore, similarly low frequencies were previously reported in AD patients from Northern Italian, Canadian, and Portuguese populations [54–57]. However, there was synergy between the C2 allele of transferrin and the C282Y allele as risk factors for developing AD [11, 58]. Our study further revealed previously unknown influence of *HFE* C282Y on the atrophy rate of the right middle temporal lobe. Since the rate of brain atrophy had been used to predict MCI to probable AD conversion and this variation association remained significant in the MCI subgroup after stratification, the results may suggest that C282Y-G alleles have the potential to prevent the conversion of MCI to AD.

The receptor for advanced glycation end products (RAGE) is a multi-ligand cell surface receptor, and one of its ligands is the Aβ peptide. RAGE acts as both an inflammatory intermediary and a critical inducer of oxidative stress, inducing Alzheimer-like pathophysiological changes. The critical role of RAGE in AD includes beta-amyloid (Aβ) production and accumulation, the formation of neurofibrillary tangles, failure of synaptic transmission, and neuronal degeneration. RAGE can also be a promoting factor for the synaptic dysfunction and neuronal circuit dysfunction which are both the material structure of cognition, and the physiological and pathological basis of cognition [59]. In addition, RAGE has been involved in the brain endothelial apoptosis [60], neuronal differentiation [61], and cell cycle reentry of neurons [62]. Li et al.'s study firstly reported that *RAGE* G82S (located in exon 3, causes a glycine to serine substitution at codon 82 within the ligand-binding domain of the receptor) was related with AD risk [17]. Daborg et al.'s study further validated the effect of *RAGE* on the risk of AD [63]. These findings were consistent with our study results that rs2070600 was related with atrophy rate of right hippocampus substructure-CA1 over 2 years. In subgroup analysis, rs2070600 was demonstrated to be associated with CA1 in the MCI group. The hippocampus plays a pivotal role in processing episodic memory and is one of the earliest regions affected by AD neuropathology [64, 65]. Previous studies have indicated that hippocampal atrophy is the most prominent structural hallmark of progression from MCI to AD [66, 67]. CA1 is the most important subregion of hippocampus. Although the functional relevance of G82S remains to be investigated, all the above evidence, along with our finding, supported that *RAGE* G82S altered the right hippocampus substructure-CA1 to result in an earlier conversion from MCI to AD.

The strengths of the ADNI database lie in its large sample size, detailed cognitive assessment protocol, and careful diagnostic ascertainments, as well as in the detailed MRI information and processing strategies across multiple sites and meticulous data quality control. Moreover, as a quantitative traits (QTs) association study, our study has advantages over traditional case–control designs. However, some limitations of this study should be highlighted. Firstly, complete data was only available in half of the participants with MRI information. Therefore, our study had a reduced sample size in some cases and had the restricted power. Secondly, our sample was restricted to Caucasians to avoid genetic stratification across ethnicities, but the *HLA* loci show different frequencies and polymorphisms in different populations. Thirdly, not all the subjects have information for all of the measurements; the subdivisions to NC/MCI/AD subgroups and different genotypes make effective sample sizes even smaller for some tests. Fourthly, a follow-up of 2 years may be too short to detect significant influences of *HLA* on AD. Fifthly, association analysis with some other candidate gene variants could not be made (i.e., *C2*: rs9332739, *HFE*: rs1800730) due to the lack of candidate gene variants in the ADNI database.

In summary, *HLA* gene variants (*TNF-α* rs2534672 and rs2395488, *HFE* rs1800562 and *RAGE* rs2070600) might participate in the structural alteration of AD-associated brain regions, hence modulating the susceptibility of AD. Our analysis revealed previously unknown influences of the same gene on brain structure. This discovery might shed light on the neural mechanisms by which *HLA* gene variants affect cognition, neurodevelopment, and neurodegeneration. However, further research using a greater number of large independent samples with diverse ethnicity to correlate genetic variants with AD-related brain structure is required to help us to unveil the mystery of *HLA*'s role in this highly complex neurodegenerative disorder.

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Compliance with Ethical Standards

Conflict of Interest All of the authors declare no conflict of interests.

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