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Featured Article

Genome-wide association study of Alzheimer's disease endophenotypes at prediagnosis stages

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Abstract

Introduction: Genetic associations for endophenotypes of Alzheimer's disease (AD) in cognitive stages preceding AD have not been thoroughly evaluated.

Methods: We conducted genome-wide association studies for AD-related endophenotypes including hippocampal volume, logical memory scores, and cerebrospinal fluid $A\beta_{42}$ and total/phosphorylated tau in cognitively normal (CN), mild cognitive impairment, and AD dementia subjects from the Alzheimer's Disease Neuroimaging Initiative study.

Results: In CN subjects, study-wide significant ($P < 8.3 \times 10^{-9}$) loci were identified for total tau near *SRRM4* and *C14orf79* and for hippocampal volume near *MTUS1*. In mild cognitive impairment subjects, study-wide significant association was found with SNPs near *ZNF804B* for logical memory test of delayed recall scores. We found consistent expression patterns of *C14orf40* and *MTUS1* in carriers with risk alleles of expression SNPs and in brains of AD patients, compared with in the noncarriers and in brains of controls.

Discussion: Our findings for AD-related brain changes before AD provide insight about early AD-related biological processes.

Keywords: Alzheimer's disease; Genome-wide association; Endophenotypes; Cerebrospinal fluid; MRI; Logical memory; Biomarker; ADNI; Tau; Coexpression network

The authors have declared that no conflict of interest exists.

[1]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/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and typically occurs after the age of 65 years. It is highly heritable, but the known genetic risk factors (currently numbering more than 25 loci including apolipoprotein E [*APOE*]) account for no more than 50% of the heritability of the disorder [1]. However, genetic association findings based on AD risk do not explain the whole genetic architecture of AD because the mechanistic complexity underlying AD is not captured entirely by disease status, especially in preclinical stages [2,3]. To overcome this limitation and understand preclinical stages of AD, researchers have examined the genetic underpinnings of AD-related endophenotypes including cerebrospinal fluid (CSF) levels of amyloid β peptide (amyloid β 42 [$A\beta_{42}$]) and tau proteins, structural brain changes quantified by magnetic resonance imaging (MRI), and neuropsychological test measures of cognitive functioning, including memory loss [4,5]. Genome-wide association (GWA) studies for AD-related endophenotypes have identified novel loci in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that enrolled appreciable numbers of subjects across three stages: AD dementia, mild cognitive impairment (MCI), and normal cognitive functioning [6]. Previous ADNI studies indicated the importance of delineating different stages of subjects [7,8]. We hypothesized that some genes may contribute to AD-related processes specifically during stages before AD dementia onset. Genes and pathways that are strongly associated with AD-related endophenotypes in early disease stages may be promising targets for developing AD biomarkers and preventive medicines. To test this hypothesis, we conducted GWA analyses for AD-related endophenotypes in the ADNI sample stratified by stage. Here, we focused on the association tests in the cognitively normal (CN) and MCI subgroups because we were interested in identifying genes that may contribute to AD-related processes before AD dementia onset.

2. Subjects and methods

2.1. Subjects

GWA and phenotype data for ADNI participants were downloaded from a public-access database (http://www.loni.usc.edu). A total of 1189 subjects before QC were available with GWA data from two different chips (ADNI-1, n = 757 and ADNI-GO/2, n = 432). We stratified subjects by stage (CN, MCI, and AD dementia) based on diagnosis at the baseline assessment as defined by the standard ADNI protocol. Demographic information and mean endophenotype values stratified by stage as well as for the entire sample are presented in Supplementary Table 1. Age is similarly distributed in each subgroup. Sample sizes for analyses of CSF biomarkers were considerably smaller than for those of other traits.

2.2. Phenotypic evaluation

Previously suggested AD-related endophenotypes including CSF biomarkers [9], MRI brain imaging measures [10], and episodic memory tests [11] were selected for GWA analyses in this study. CSF biomarkers of $A\beta_{42}$, total tau (t-Tau), and phosphorylated tau (p-Tau), brain MRI measure for hippocampal volume (HPV), and scores for logical memory tests of immediate and delayed recall (LMiT and LMdT) which were all measured at baseline were analyzed in this study. Details about collection of CSF biomarkers, brain MRI scan data, and neuropsychological tests are reported elsewhere [12–15].

2.3. Genotyping, quality control, imputation, and population substructure analysis

Details of quality control, genotype imputation, and population substructure analyses are described in Supplementary Information. After QC, the ADNI-1 sample with genotype data consisted of 187 CN, 329 MCI, and 163 AD dementia subjects, and the ADNI-GO/2 sample contained 118 CN, 252 MCI, and 27 AD dementia subjects with genotype data.

2.4. Statistical methods

2.4.1. GWA tests

Before the association tests, each of the six endophenotypes was adjusted for covariates using linear regression. Age and sex were used as covariates for the six endophenotypes. A term for education level was also included in the regression models for LMiT and LMdT, and the model for HPV was further adjusted for total intracranial volume. The residuals derived from the regression models were rank-transformed for normalization as previously described [16]. Analyses were conducted for all autosomal SNPs using the expected genotype dose, a quantitative measure between 0 and 2 of the number of effect alleles computed from the imputed genotype probabilities as the predictor. Association of the rank-normalized endophenotypes with each SNP was evaluated using a linear regression model including covariate terms for the first three principal components of population substructure using the R software package. The two ADNI data sets were analyzed independently for the CN and MCI subjects, and the results from the two ADNI data sets were combined by meta-analysis using inverse variance weights as implemented in the METAL program [17]. AD cases from the two ADNI data sets were analyzed as one group because the ADNI-GO/2 sample included only 27 AD subjects and regression models for this group included an extra covariate for ADNI data set. The genome-wide significant (GWS) threshold was set at 5.0×10^{-8}. We determined a conservative study-wide significant (SWS) level of 8.3×10^{-9}, which was calculated as the GWS level divided by the effective number of two independent endophenotypes and three clinical subgroups. The effective number of independent