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Genetics

Single-nucleotide polymorphisms are associated with cognitive decline at Alzheimer's disease conversion within mild cognitive impairment patients

Eunjee Lee[a], Kelly S. Giovanello[b], Andrew J. Saykin[c], Fengchang Xie[d], Dehan Kong[e], Yue Wang[f], Liuqing Yang[g], Joseph G. Ibrahim[f], P. Murali Doraiswamy[h], Hongtu Zhu[i,*], for the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA*
[b]*Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
[c]*Department of Radiology and the Indiana Alzheimer Disease Center, IUPU, Indianapolis, IN, USA*
[d]*School of Mathematical Sciences, Nanjing Normal University, Nanjing, China*
[e]*Department of Statistical Science, University of Toronto, Toronto, Ontario, Canada*
[f]*Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
[g]*Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
[h]*Department of Psychiatry and Duke Institute for Brain Sciences, Duke University, Durham, NC, USA*
[i]*Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Abstract

Introduction: The growing public threat of Alzheimer's disease (AD) has raised the urgency to quantify the degree of cognitive decline during the conversion process of mild cognitive impairment (MCI) to AD and its underlying genetic pathway. The aim of this article was to test genetic common variants associated with accelerated cognitive decline after the conversion of MCI to AD.

Methods: In 583 subjects with MCI enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI; ADNI-1, ADNI-Go, and ADNI-2), 245 MCI participants converted to AD at follow-up. We tested the interaction effects between individual single-nucleotide polymorphisms and AD diagnosis trajectory on the longitudinal Alzheimer's Disease Assessment Scale-Cognition scores.

Results: Our findings reveal six genes, including *BDH1*, *ST6GAL1*, *RAB20*, *PDS5B*, *ADARB2*, and *SPSB1*, which are directly or indirectly related to MCI conversion to AD.

Discussion: This genome-wide association study sheds light on a genetic mechanism of longitudinal cognitive changes during the transition period from MCI to AD.

Keywords: Alzheimer's disease; GWAS; Mild cognitive impairment; Cognitive decline; Longitudinal study

1. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that imposes social, psychological, and financial burden on both patients and their caregivers. Hebert et al. predict that the total number of individuals with AD dementia will be 13.8 million by 2050 [1]. This prediction, coupled with a lack of disease-modifying treatments, is estimated to have cumulative costs of more than $20 trillion by 2050 for the care of AD patients [2]. To date, extensive efforts have been made to delineate a set of risk factors that affect the development of AD. In particular, genome-wide association studies (GWASs) have been used to identify genetic variants that may contribute to AD. Most GWASs of AD have focused on the detection of single-nucleotide polymorphisms (SNPs) that are associated with the susceptibility

*Corresponding author. Tel.: +1-346-814-0191; Fax: ■■■.
E-mail address: hzhu5@mdanderson.org

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of developing AD [3–8]. The early onset of AD is known to result from mutations in one of three genes: the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) [9,10]. The inheritance of the e4 allele of the apolipoprotein E (APOE) has a substantial impact on the late onset of sporadic AD [11,12]. Recent GWASs have identified additional AD-related genes, including clusterin (CLU), complement receptor 1 (CR1), and phosphatidylinositol-binding clathrin assembly protein gene (PICALM) [13,14], whereby those genes alter production of the amyloid-β peptide (Aβ) [15–17].

In the present study, we aimed to detect genetic common variants associated with accelerated cognitive decline after the conversion of mild cognitive impairment (MCI) to AD. MCI is a clinical syndrome characterized by insidious onset and progression of cognitive impairments. It is often considered as a transitional stage between normal aging and AD, because approximately 50% of MCI patients develop AD in 5 years from diagnosis [18]. Critically, therapeutic interventions and disease-modifying drugs appear to be more effective during the MCI or early stage of AD than at the more severe stages of AD [19–21]. As such, it is an ongoing quest to delineate a set of risk factors that affect conversion from MCI to AD. Recent GWASs have focused on the following phenotypes related to MCI-AD progression: binary outcome indicating MCI-AD conversion, time to conversion from MCI to AD, and cognitive decline. For example, Hu et al. (2011) found novel loci to be associated with longitudinal cognitive changes of MCI patients [22] and those loci were also associated with time to conversion from MCI to AD. Here, we only focus on an MCI-AD conversion group to identify genetic common variants contributing to rapid cognitive decline after an MCI patient develops AD.

We analyzed the Alzheimer's Disease Neuroimaging Initiative (ADNI; ADNI-1, ADNI-2, and ADNI-GO) cohort data. Among them, there remained 245 participants who converted to AD at follow-up. Longitudinal Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) scores were used to measure cognitive function including memory, language, praxis, and orientation domain scores indicated greater cognitive impairment. To identify SNPs associated with longitudinal cognitive changes, we tested interaction effects between individual SNPs and AD diagnosis trajectory (MCI = 0, AD = 1) on the longitudinal ADAS-Cog scores. To account for individual variability of (1) baseline ADAS-Cog score and (2) the effect size of AD diagnosis trajectory, random effects for intercept and slope of AD diagnosis trajectory were incorporated in our model.

2. Materials and methods

2.1. Alzheimer's Disease Neuroimaging Initiative

The study population was obtained from the ADNI database (www.loni.usc.edu/ADNI). The ADNI study has aimed to detect and monitor the early stage of AD by investigating serial magnetic resonance imaging, positron emission tomography, genetic, biochemical biomarkers, and neuropsychological and clinical assessment. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. The ADNI began in 2004 and recruited 400 subjects with MCI, 200 subjects with early AD, and 200 cognitively normal elderly from more than 50 sites across the United States and Canada. This multisite, longitudinal study was financially supported as $67 million by National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, and 13 private pharmaceutical companies. This initial phase, called ADNI-1, was extended with ADNI-GO in 2009. ADNI-GO investigated the existing ADNI-1 cohort and included 200 participants diagnosed as having early MCI. In 2011, ADNI-2 began to study participants from the ADNI-1/ADNI-GO and added 150 elderly control subjects, 100 early MCI participants, 150 late MCI participants, and 150 MCI patients. For up-to-date information, see www.adni-info.org.

2.2. Data description

In the sample of this study, we considered White participants who had developed AD from MCI at the baseline. During 120 months of follow-up, 245 MCI patients progressed to AD before study completion and the remaining 338 MCI patients did not convert to AD before study end. We considered only 245 patients who developed AD by their follow-up. The data included basic demographic and clinical information at the baseline: age, education length, and gender. Their ADAS-Cog scores were recorded about every 9 months in average with the mean follow-up duration of 48 months. Genotyping for the ADNI-1, ADNI-GO, and ADNI-2 data was performed using the Human 610-Quad BeadChip, Illumina Human Omni Express BeadChip, Illumina Omni 2.5 M (WGS Platform), respectively. It was completed on all ADNI participants using the genotyping protocol whose details are described in [23] and http://adni.loni.usc.edu/methods/genetic-data-methods.

2.3. Quality control and genotype imputation

We performed quality control (QC) steps on the raw genotype data to ensure that only high-quality data were included in the final analysis. QC procedures included (1) call rate check per subject and per SNP marker, (2) gender check, (3) sibling pair identification, (4) the Hardy-Weinberg equilibrium test, (5) marker removal by the minor allele frequency, and (6) population stratification. We also calculated an inbreeding coefficient (F) that represents the expected percentage of homozygosity. There were no subjects with excessive heterozygosity ($|F| > 0.15$) [53]. The second line preprocessing steps included removal of SNPs