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Genome-wide association study of the rate of cognitive decline in Alzheimer's disease

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Abstract

Background: Substantial interindividual variability exists in the disease trajectories of Alzheimer's disease (AD) patients. Some decline rapidly whereas others decline slowly, and there are no known explanations for this variability. We describe the first genome-wide association study to examine rate of cognitive decline in a sample of AD patients with longitudinal measures of cognition.

Methods: The discovery sample was 303 AD cases recruited in the Alzheimer's Disease Neuroimaging Initiative and the replication sample was 323 AD cases from the Religious Orders Study and Rush Memory and Aging Project. In the discovery sample, Alzheimer's Disease Assessment Scale–cognitive subscale responses were tested for association with genome-wide single-nucleotide polymorphism (SNP) data using linear regression. We tested the 65 most significant SNPs from the discovery sample for association in the replication sample.

Results: We identified SNPs in the spondin 1 gene (*SPON1*), the minor alleles of which were significantly associated with a slower rate of decline (rs11023139, $P = 7.0 \times 10^{-11}$) in the discovery sample. A *SPON1* SNP 5.5 kb upstream was associated with decline in the replication sample (rs11606345, $P = .002$).

Conclusion: *SPON1* has not been previously associated with AD risk, but is plausibly related because the gene product binds to the amyloid precursor protein and inhibits its cleavage by β-secretase. These data suggest that *SPON1* may be associated with the differential rate of cognitive decline in AD.

Keywords: Alzheimer's disease; GWAS; Cognitive decline

1. Introduction

Alzheimer's disease (AD) is a common form of dementia with an enormous public health impact and for which

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there are no treatments yet available to slow progression. Through the efforts of large consortia that pool data from many genome-wide association studies (GWAS) of late-onset AD, several risk genes have been identified and robustly replicated [1–5]. Only with samples in excess of 10,000 AD cases and similar numbers of controls has consensus been reached on the veracity of these risk variants, and with the exception of the *APOE* ε4 allele, these variants exert very modest effects on overall disease risk, generally with odds ratios less than 1.2. Although these findings have provided valuable insights into AD pathogenesis, the individual predictive value of these small-effect variants is limited.

Although AD is characterized by progressive cognitive deterioration over time, substantial variability exists in the cognitive trajectories of affected individuals. There have been several previous studies of factors reported to be associated with cognitive decline in AD patients that have not examined genetic factors. One suggests that the pathological findings such as neurofibrillary tangles, cerebral infarction, and Lewy bodies that mediate normal and pathological age-related cognitive decline also mediate more rapid cognitive decline in some AD patients [6]. Other reports have postulated superimposed medical factors to be associated with rate of decline in AD, including diabetes [7] and other vascular risk factors [8], kidney function [9], and muscle strength [10]. Two recent candidate gene studies [11,12] tested a limited number of candidate single-nucleotide polymorphisms (SNPs) for association with rate of decline and identified some promising associations.

In this report, we present the first genome-wide association analysis of cognitive decline in a sample of AD cases with longitudinal measures of cognition. By limiting the analysis to AD cases, we hoped to identify novel variants specific to rate of decline. Although identifying variants explaining the heterogeneity in rate of decline is important for understanding AD pathogenesis, it may also produce novel therapeutic targets that are distinct from those associated with the presence or absence of AD.

2. Methods

2.1. Discovery sample

Data used in the discovery sample were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [13]. ADNI was launched in 2003 with the primary goal of testing whether longitudinal magnetic resonance imaging (MRI), positron emission tomography (PET), and other serum or cerebrospinal fluid (CSF) biomarkers could serve as proxy markers for the progression of mild cognitive impairment (MCI) and early AD. After several waves of recruitment, ADNI has enrolled over 1000 individuals with AD, MCI, or with normal cognitive function. Detailed protocols for subject recruitment and biomarker accrual are available at the ADNI website (http://www.adni-info.org/). In brief, subjects were recruited from over 50 sites across the United States and Canada and were measured longitudinally for changes in the brain measured through neuroimaging, biomarkers, and cognitive tests. At the time we accessed the ADNI database, there were 243 cognitively normal, 235 MCI, and 340 AD subjects in total. The subset of ADNI subjects analyzed for the discovery sample included 303 individuals of European descent who either had AD at baseline or converted to AD during follow-up and had cognitive data. Baseline data were defined as data from the examination with the first clinical diagnosis of AD. Seventeen individuals with age at onset younger than 60 years (indicative of familial AD) were excluded.

2.2. Replication sample

We selected the 65 most promising SNPs from the discovery sample on the basis of association with the outcome measure (see *Phenotypic measures*). These SNPs were evaluated for replication in an independent sample of 323 AD cases combined from the Religious Orders Study (ROS; 174 participants) and the Rush Memory and Aging Project (MAP; 149 participants). The ROS and MAP cohorts were developed and are managed by the same group of investigators at the Rush University Medical Center, and information about study design and data collection in these studies has been previously published [14,15]. In brief, subjects free of dementia were enrolled and followed annually for cognitive testing that is the same in both studies. We limited our analyses to subjects of European descent with a clinical diagnosis of AD after the age of 60.

2.3. Phenotypic measures

In ADNI, AD was defined as a participant meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD [16]. Data were collected from participants with MCI at baseline and then at 6-month intervals up to 24 months, followed by a visit at 36 and at 48 months. Data were collected from participants with AD at baseline and then at 6, 12, and 24 months (no visit at 18 months or after 24 months, by design). Cognitive decline was measured based on longitudinally collected Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) items. The ADAS-cog consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities, which are often referred to as the core symptoms of AD. ADAS-cog scores range from 0 to 70, with 0 indicating little or no cognitive impairment and 70 indicating severe cognitive impairment [17].

In the replication sample, we analyzed an independent composite measure of global cognition (GCOG) [18] based on 17 tests of cognition including immediate and delayed recall of the East Boston Story and Logical Memory II; immediate and delayed recall and recognition of a 10-item