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Assessment of TREM2 R47H association with Alzheimer's disease in a population-based sample: The Cache County Study

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Abstract

Recent studies have identified the R47H variant in *TREM2* as an Alzheimer's disease (AD) risk factor with estimated odds ratio ranging from 2.9–5.1. The Cache County Memory Study is a large, population-based sample designed for the study of memory and aging. We genotyped rs75932628 (R47H) in 2974 samples (427 cases and 2540 controls) from the Cache County study using a custom Taqman Assay. We observed 7 heterozygous cases and 12 heterozygous controls with an odds ratio of 3.5 (95% confidence interval, 1.3–8.8; $p = 0.0076$). The minor allele frequency and population attributable fraction for R47H were 0.0029 and 0.004, respectively. This study replicates the association between R47H and AD risk in a large, population-based sample and estimates the population frequency and attributable risk of this rare variant.

Keywords

Alzheimer's disease; human; TREM2; rare variant; R47H

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Disclosure Statement

No authors report conflicts of interest, financial or otherwise.

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1. Introduction

Alzheimer's disease (AD) is a fatal neurodegenerative disorder and is the leading cause of dementia in the elderly (Jonsson, et al., 2013). It is the sixth leading cause of death in the United States, and of the six, the only one lacking adequate treatment or prevention. AD is characterized by a progressive loss in cognitive function, and strikes memory early in the course. Neuropathological changes include loss of neurons and synapses, extensive accumulation of amyloid plaques, and neurofibrillary tangles. AD has been identified as a proteopathic disease due to its extensive accumulation of amyloid plaques and neurofibrillary tangles (Guerreiro, et al., 2013, Jonsson, et al., 2013).

Recent research has focused on finding rare genetic variants that increase risk for AD. Specifically, a rare variant known as R47H in exon 2 of the *TREM2* gene has been identified as a risk factor with odds ratio estimates between 2.9 and 5.1 (Guerreiro, et al., 2013, Jonsson, et al., 2013). Here we have assessed the R47H variant in a true population-based sample to estimate the relative risk and population attributable fraction of this variant.

2. Methods

2.1 Subjects

The Cache County Study on Memory Health and Aging is a large population-based study initiated in 1994. The 5092 subjects represented approximately 90% of all residents in Cache County, Utah aged 65 years or older. For the present study, DNA samples were available for 2974 subjects. A more detailed summation of the Cache County Study has been reported previously (Breitner, et al., 1999). Briefly, case-control status was determined through a series of cognitive tests and dementia evaluations that were administered triennially for four examination waves. In the first stage of screening, cognitive function was measured by the Modified Mini-Mental State Exam-Revised (3MS-R). Individuals who were screened as positive cases and also a randomly selected subset (19%) of individuals were invited to participate in subsequent stages of evaluation. These consisted of an informant interview and a clinical assessment, reviewed by a geropsychiatrist and neuropsychologist. At this time a preliminary diagnosis was assigned as dementia or another cognitive disorder. Those who were diagnosed with dementia were invited to participate in standard laboratory tests for dementia, an MRI scan, and a geropsychiatrist examination. At the conclusion of these tests, the final cognitive status of participants was determined by an expert panel consisting of neuropsychologists, geropsychiatrists, a neurologist and a cognitive neuroscientist. By consensus, diagnoses of AD were assigned by NINCDS-ADRDA criteria (McKhann, et al., 1984) and included probable AD cases. Cases for this study were those diagnosed with AD only and no comorbid types of dementia. The controls were identified as those individuals who had negative test results in all examinations and who showed no signs of dementia.

2.2 Genotyping

We performed SNP Genotyping for 2974 DNA samples from participants in the Cache County Study for rs75932628 (R47H) using a custom Taqman Assay. Included in the 2974 samples were 427 clinically ascertained prevalent and incident Alzheimer's disease cases and 2540 cognitively normal participants.

2.3 Analysis

Association between R47H and case control status was tested using logistic regression models with adjustment for age, gender and *APOE* 4 genotype. We calculated population attributable fractions using equation 1 (Ebbert, et al., 2013, International Parkinson Disease

Genomics, et al., 2011, Naj, et al., 2011), where p equals the allele frequency and OR represents the odds ratio.

$$PAF = \frac{p(OR-1)}{p(OR-1)+1} \quad \text{EQUATION 1}$$

3. Results

Our results replicated the significant association between R47H and AD. Of our 2974 samples we observed 7 heterozygous cases and 12 heterozygous controls with a Odds Ratio of 3.5 (95% confidence interval, 1.3–8.8; $p = 7.6E-03$). The minor allele frequency and population attributable fraction for R47H were 0.0029 and 0.004, respectively.

4. Discussion

Recent studies (Guerreiro, et al., 2013, Jonsson, et al., 2013) identified an R47H variant in *TREM2* as a risk factor for late-onset Alzheimer's disease. Several studies have replicated this work using different ethnic cohorts, study designs and sample sizes. One study (Pottier, et al., 2013) examined the association between the R47H variant and early-onset AD in Caucasian subjects of French origin, consisting of 726 AD cases and 783 controls. The study concluded that the variant increases risk for AD with onset earlier than 65 years (OR, 4.07 and $p=0.009$). Another study (Benitez, et al., 2013) researched a Spanish population and directly genotyped the R47H variant in 504 AD cases and 550 controls. R47H was found in 1.4% (7/504) of AD cases and in 0% (0/550) of controls ($p < 0.009$). A familial study (Giraldo, et al., 2013) tested a consanguineous Colombian family, that included 3 cases and 5 controls, reporting a missense mutation in exon 4 of *TREM 2* causing frontotemporal dementia. They also found the R47H variant to increase risk for late and early onset AD in 185 AD cases and 183 controls (OR, 3.3). Despite the differences in demographics and size, each study concludes that the rs75932638 variant increases AD risk.

Our work further supports the R47H variant increases risk for late-onset AD. Unlike previous studies, however, the Odds Ratio and Population Attributable fractions estimated here are from a large population-based sample. As such, they better estimate the effects of this allele in the general population. The estimated Odds Ratio of 3.5 in our study suggests that the increased AD risk for R47H is comparable to the *APOE 4* allele. However, due to the low frequency of this variant in the general population, the population attributable fraction of the R47H variant is very low (0.004 vs. 0.20 for the *APOE 4* allele in this sample). Therefore, the population effects are much lower than those of the *APOE 4* allele, lessening the potential clinical and diagnostic impact of this discovery. In conclusion, while the population-level effects of the R47H variant do not approach those of the *APOE 4* allele, *TREM2* has a clear and replicable effect on AD risk. The loss-of-function caused by the R47H variant contributes to the disruption of an immune response that triggers an inflammatory response leading to neuronal cell death and may contribute to the degeneration of phagocytic pathways that aid in the clearance of neuronal cell debris (Neumann and Daly, 2013). These functions clearly play a role in AD and future preventative and therapeutic efforts can leverage this important new information.

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