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Investigation of an APP protective mutation (A673T) in a North American case-control sample of late-onset Alzheimer's disease

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Abstract

A rare amyloid precursor protein (APP) gene variant, A673T (rs63750847) was recently reported to protect against Alzheimer's disease (AD) and age-related cognitive decline among Icelanders and the same rare variant was observed also in Finnish, Norwegian, and Swedish populations. We investigated this variant in 1,674 late-onset AD cases and 2,644 elderly controls, all North American Whites (U.S. Whites). We did not observe any example of the A673T variant in our large sample. Our findings suggest that this rare variant could be specific to the individuals of the origin from the Nordic countries.

Keywords

Alzheimer's disease; cognitive decline; cognitive impairment; Amyloid precursor protein; APP; rs63750847; A673T

1. Introduction

Recently, Jonsson et al. (2012) have reported that an *APP* rare missense variant, A673T (rs63750847), is protective against late-onset Alzheimer's disease (AD) and cognitive impairment in non-AD elderly among Icelanders and they observed the same variant also in Finnish, Norwegian, and Swedish populations. The A673T variant is adjacent to the β–site APP cleaving enzyme 1 (BACE1) cleavage site and thus may affect the production of amyloid-β (Aβ), as supported by *in vitro* findings (Jonsson et al. 2012). In fact, this variant was recently detected also in a 104.8 year-old Finnish demented subject who showed little β-amyloid pathology (Kero et al., 2013), further supporting the possibility that this mutation might protect against Aβ accumulation. Recent studies conducted in Asians, however, have found no example of this rare variant among Chinese individuals (Liu et al., 2013; Ting et al., 2013).

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Disclosure
The authors declare that they have no conflict of interest in regard to this work.

In this study, we genotyped 4,318 late-onset AD cases and older controls to determine the frequency of this variant among U.S. Whites and its effect on modulating AD risk in this population.

2. Methods

The 4,318 subjects included in this study were derived from two cohorts. The first cohort from the University of Pittsburgh Alzheimer Disease Research Center (Kamboh et al., 2012) consisted of 1,390 late-onset AD cases (mean age = 73.8 ± 6.9 [s.d] years; age-at-onset = 72.9 ± 6.4 years) and 1,031 controls (mean age= 80.7±6.4 years). Diagnosis of AD was based on established criteria (DSM-IV) via multidisciplinary consensus conference as described in Lopez et al. (2000). The second cohort derived from the Ginkgo Evaluation of Memory (GEM) study (DeKosky et al., 2008) was comprised of 284 AD cases (mean age = 84.0 ± 3.9 years; age-at-onset = 72.8 ± 3.7 years) and 1,613 non-AD elderly subjects (mean age 84.1± 3.3 years). AD diagnosis was also based on consensus conference as reported in detail in DeKoskty et al. (2008). All subjects were North American Whites and were recruited based on the University of Pittsburgh Institutional Review Board - approved guidelines and selection criteria.

The APP variant A673T (rs63750847) was genotyped using a TaqMan SNP genotyping assay (C_89522366_10; Life technologies, Grand Island, NY). A sample heterozygous for the A673T variant (kindly provided by Dr. Carlos Cruchaga, Washington University) was included on each assay plate as a positive control.

3. Results & Discussion

We genotyped a total of 4,318 subjects consisting of 1,674 late-onset AD cases and 2,644 elderly controls to determine the frequency of the A673T variant in U.S. Whites. All of our genotyped samples demonstrated the absence of the A673T variant, except for the positive control included for assay verification. It should be noted that the previous positive reports about the identification of this variant were primarily in subjects from the Nordic countries but it seems to be extremely rare in North Americans (Jonsson et al., 2012; Kero et al., 2013) and no example of this variant was found in two Chinese studies comprising 11,362 subjects (Liu et al., 2013; Ting et al., 2013). Our results along with the previous studies suggest that A673T is a rare variant that is mainly confined to the populations from the Nordic countries. If this variant had existed in our sample then we would have 80% power at α=0.05 to detect the reported variant allele frequency difference between cases (0.62%) and controls (0.13%) in Icelanders. Although this variant seems to have a biological basis to provide protection against AD, its absence in our large sample suggests that its contribution to the modulation of AD risk would be extremely small even if larger case-control studies would find some examples of this variant among U.S. Whites.

Acknowledgments

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