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Evidence against a role for rare *ADAM10* mutations in sporadic Alzheimer Disease

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Abstract

The Alzheimer amyloid protein precursor (APP) is subject to proteolysis by ADAM10 and ADAM17, precluding the formation of A β . Recently, coding variations in ADAM10 resulting in altered function have been reported in familial Alzheimer disease (AD). We carried out a large-scale (n=576: Controls, 271; AD, 305) resequencing study of *ADAM10* in sporadic AD. Our results do not support a significant role for *ADAM10* mutations in AD. Our results also make it clear that the careful examination of ancestry required in any case-control comparison is especially true with rare variations, where even a very small number of variations might form the basis of scientific conclusions.

Keywords

Mutation; rare variation; genetics; association

Introduction

The Alzheimer amyloid protein precursor (APP) is subject to distinct proteolytic cleavage events which can lead to or preclude the formation of the A β peptide (Thinakaran and Koo,

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2008). The α -secretase pathway, which precludes the formation of A β , involves the ADAM10 and ADAM17 proteases, responsible for constitutive and regulated proteolysis, respectively. Recently, non-synonymous coding variations (Q170H and R181G) in ADAM10 resulting in altered function have been reported in familial Alzheimer disease (Kim et al., 2009). These coding variations showed reduced proteolytic activity and it was concluded that this could contribute to AD. In the current study, we sequenced ADAM10 exons in a large series of well-characterized sporadic AD cases and age-matched controls to further examine the role of ADAM10 coding variation in AD.

Methods

Neuropathologically-confirmed AD cases were derived from the Mount Sinai Brain Bank (Haroutunian et al., 1998). Controls were derived from the Mount Sinai Brain Bank, the NIMH, and the longevity study of the Albert Einstein College of Medicine (Barzilai et al., 2006). Sanger sequencing of all coding exons was carried out. Genotyping was carried out with Pyrosequencing. Further details regarding subjects, sequencing and genotyping, as well as references and Table 1, are found in Supplementary Materials.

Results and Discussion

We sequenced the coding sequences of the *ADAM10* gene in 305 unrelated AD patients and 271 age-matched controls, all of self-described European ancestry. We identified three rare and novel missense variations, L9V (c.25C>G), T255A (c.763A>G) and T279I (c.836C>T). The L9V variation was found in 5 AD patients and no control, while the T255A and T279I variations were found in 1 and 2 control samples, respectively. Additional exonic variations are shown in Supplementary Table 1.

Global missense variation did not differ between cases (5/305 in AD, or 1.6%) and controls (3/271 in controls, or 1.1%) ($P=0.73$). There was, however, an increase in the L9V variant in cases, as compared to the controls. In case-control studies there is a high risk of false-positive (but not false-negative) findings due to population stratification and this is an important concern with rare variation [discussed in (Keen-Kim et al., 2006)]. To determine whether the increased rate of L9V was due to case status or to cryptic differences in ancestry, we took advantage of genome-wide single nucleotide polymorphism (SNP) data in all Mount Sinai samples to analyze ancestry and population substructure. All 5 AD patients with the L9V variant were clearly grouped by STRUCTURE (Pritchard et al., 2000a, 2000b) within an Ashkenazi subgroup. This raised the likelihood that the L9V variation related to Ashkenazi ancestry, rather than AD.

To confirm that ancestry explained the presence of the L9V variant in Ashkenazi cases, we next genotyped 333 aged (mean $\pm$ SEM of 71 $\pm$ 0.5 years old) and 361 centenarian (97.7 $\pm$ 0.1 years old) Ashkenazi controls and identified 11 with this variant. Comparing the frequency of the L9V variant in Ashkenazi AD cases (5/175, or 2.9%) and controls (11/732 or 1.5%) demonstrated a lack of association of this variant with AD ($P=0.21$). In contrast, comparing the rate of the L9V variant in Ashkenazi versus other individuals of European ancestry,

regardless of case status, demonstrated an association with ancestry (16/910 Ashkenazi versus 0/363 for other European ancestries; $P=0.009$).

We did not observe the Q170H and R181G variations in our study. Although rare (frequency $< 0.5\%$; Kim et al., 2009), we have reasonable (88%) power to detect one or the other in the current sample. The prior report includes familial cases and there may be differing frequencies of these variations in familial cases. These variations may also have altered frequencies in different ancestries.

It is now universally accepted that carefully controlling for ancestry is a requirement in any well-designed case-control comparison. Our results show how this is especially true with rare variation, where even a very small number of variations might form the basis for scientific conclusions. We have very good (95%) power to detect rare variants that occur with a frequency of $\geq 1\%$. From our studies, we can conclude that the Q170H and R181G variations, as well as other rare coding variation in *ADAM10*, do not play a significant role in sporadic AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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