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Negative results

Androgen receptor gene and sex-specific Alzheimer's disease

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ABSTRACT

Women are at a 2-fold risk of developing late-onset Alzheimer's disease (AD) (onset at 65 years of age or older) compared with men. During perimenopausal years, women undergo hormonal changes that are accompanied by metabolic, cardiovascular, and inflammatory changes. These all together have been suggested as risk factors for late-onset AD. However, not all perimenopausal women develop AD; we hypothesize that certain genetic factors might underlie the increased susceptibility for developing AD in postmenopausal women. We investigated the Androgen Receptor gene (*AR*) in a clinical cohort of male and female AD patients and normal control subjects by sequencing all coding exons and evaluating the length and distribution of the CAG repeat in exon 1. We could not establish a correlation between the repeat length, sex, and the disease status, nor did we identify possible pathogenic variants. *AR* is located on the X chromosome; to assess its role in AD, X-inactivation patterns will need to be studied to directly correlate the actual expressed repeat length to a possible sex-specific phenotypic effect.

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1. Introduction

Age is a major risk factor for Alzheimer's disease (AD) (Rocca et al., 1986). Sex differences and hormonal changes have also been reported as possible risk factors leading to the development of AD. Women are at a 2-fold risk of developing late-onset AD (LOAD) (onset at 65 years of age or older) compared with men (Alzheimer, 2012), regardless of life expectancy. Menopause in women is characterized by dramatic hormonal changes, primarily, an increase in the androgen/estrogen ratio because of the sudden drop in ovarian hormones, accompanied by metabolic, cardiovascular, and inflammatory changes. Aging men also experience a decrease in their primary sex hormones, although in a much more gradual manner than women (Morley et al., 1997). Our driving questions are: what is the cause of sex divergence and/or bias in the pathogenesis of AD? Why are not all perimenopausal women, who undergo hormonal changes, cognitively affected in a similar way?

We hypothesized that there must be other factors, specifically genetic differences, that confer susceptibility and increase the risk of developing AD in women. In our ongoing longitudinal study, using a targeted multiplex genotyping assay, we identified the Androgen Receptor gene (*AR*) as associated with the AD status in women in our cohort (unpublished data). Exon 1 of *AR* encodes for a highly polymorphic polyglutamine repeat stretch (CAG) located in the N-terminal domain of the Androgen Receptor protein. The *AR* CAG repeat length has been shown to be involved in spinal bulbar muscular atrophy, Kennedy disease, androgen insensitivity, and predisposition to Alzheimer's disease in men (Lehmann et al., 2003). In this study we sought to examine the role of the *AR* gene in the pathogenesis of AD in women by screening the CAG repeat in exon 1 and sequencing exons 2–8 in a cohort of AD patients and neurologically normal control subjects from the Texas Alzheimer's Research and Care Consortium.

2. Methods

The cohort included 696 individuals subdivided into 241 female AD patients, 164 male AD patients, 198 female neurologically normal control subjects and 93 male neurologically normal control subjects

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enrolled by the Texas Alzheimer's Research and Care Consortium; in addition, 131 DNA samples of neurologically normal control subjects ($n = 68$ female and $n = 63$ male), obtained from Coriell Institute. We screened the DNA samples for the CAG repeat in exon 1 and sequenced the exons 2–8 of the *AR* gene. Subsequently we analyzed 5 modes of CAG repeat allelic presentations comparing: (1) male alleles: AD versus normal control; (2) average allelic length for women: AD versus normal control; (3) long allelic length for women: AD versus normal control; (4) short allelic length for women: AD versus normal control; and (5) long and short allelic length for female AD and NC subjects. A 2-factor analysis of variance and IBM SPSS Statistics V20 were used for statistical analysis. Full details of the cohort and the genetic screening and statistical methods are presented in the Supplementary data.

3. Results

AR CAG repeats in our cohort ranged from 7 to 40. The range of CAG allelic distribution, mean, the median, standard deviation, percentile, and number of alleles in each group of our cohort are summarized in Supplementary Tables 1a–c. The details of 5 modes of statistical analysis of CAG repeat in the 4 groups of our cohort, as suggested in section 2. Methods, can be found in Supplementary Figs. 1–3 and Supplementary Tables 2, 3, and 4a–c. The sequencing of exons 2–8 resulted in identification of 3 variants in 6 subjects (Supplementary Table 5). All variants were isolated in female subjects (5 AD and 1 control) but none of the variants could be linked to the pathogenesis of AD.

4. Discussion

In our study, we could not establish significant correlation between the CAG repeat length and the disease status or sex nor did we identify pathogenic variants. At this point, we could not establish a direct link between genetic variability in *AR* and sex-specific phenotypic effects in our cohort. In the study of LOAD, with specific focus on the subpopulation of female patients, it is difficult to define a simple genotype–phenotype effect. Genetic characteristics of LOAD have proven to be complex and are thought to be the result of a multitude of genetic factors with small effects. Our study and focus on *AR* however, was based on the results of a preliminary association study in our cohort (unpublished data). The association of *AR* implies the involvement of *AR* in the pathogenesis of AD. Considering our results and that *AR* is located on the X chromosome, the most plausible hypothetical mechanism which could explain higher prevalence of AD in women compared with men could be X-inactivation and mosaicism in women. Because our cohort was clinical, we could not verify the X-inactivation pattern in the brains of the female subjects. This is the crucial point in determining what allele is associated with the disease status. In the future, the correlation between the *AR* repeat length and its expression needs to be verified in the brain samples of male and female AD patients and control subjects, to identify the role of the *AR* and the X chromosome in the pathogenesis of AD in women.

Disclosure statement

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2013.02.017.