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Fragile X gene expansions are not associated with dementia

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Abstract

The purpose of this study was to determine the frequency of *fragile X mental retardation 1 (FMR1)* premutation size expansions in individuals with Alzheimer disease (AD) and other cognitive disorders compared to controls. *FMR1* genetic screening was completed in patients being seen in a neurobehavioral or AD clinics. Appropriate controls were also collected. A second cohort was a community based, autopsy confirmed, sample of individuals with normal cognitive function, mild cognitive impairment, or AD. There was not an increased frequency of *FMR1* expansions in individuals with cognitive disorders, including AD, compared to controls.

Keywords

FMR1; fragile X; Alzheimer disease

Introduction

Trinucleotide repeat expansions (CGG) in the *fragile X mental retardation gene 1 (FMR1)* gene are associated with neurological signs in both children and adults. Carriers of 'premutation' size (55–200 CGG) repeats are at risk for fragile X-associated tremor/ataxia syndrome (FXTAS); which is characterized by kinetic tremor, gait ataxia, and executive dysfunction. As FXTAS progresses, more significant cognitive deficits develop; with

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impairments in verbal comprehension, perceptual organization, working memory, processing speed, and behavioral self-regulation. In comparison to Alzheimer disease (AD), patients with FXTAS have more severe deficits in executive function, but better language performance and attentional control (Seritan et al. 2008). Patients with FXTAS are frequently misdiagnosed with AD (Hall et al. 2005), but, there have been no *FMRI* screening studies in primary dementia populations. Individuals who carry a gray zone expansion of 41–54 CGG repeats are frequently ascertained in screening studies and the role of this smaller expansion in association with neurological phenotypes is still to be determined. The purpose of this study was to determine the frequency of *FMRI* expansions in individuals with AD and other cognitive disorders.

Methods

Three separate sources of subjects were tested for this study. Two tertiary care clinics: the Neurobehavior Clinic at the University of Colorado and the Rush Alzheimer Disease Center Memory Clinic supplied patients and controls, and a third group, the Religious Orders Study, supplied older persons with and without dementia. Primarily spousal controls with a mental status examination score $>28/30$ were recruited from the same clinics and from movement disorders clinics at each university. Genotyping of CGG repeat length in *FMRI* was performed using a PCR assay previously described or with a recently developed highly sensitive *FMRI* PCR method (Asuragen, Inc., Austin TX).

Results

Clinic-Based Cases and Controls: There was no difference between cases and controls in the frequency of *FMRI* premutation expansions (1/151 cases vs. 2/177 controls, $p=1$) or *FMRI* gray zone expansions (10/151 cases vs. 7/177 controls, $p=0.28$). Religious Orders Study: There were no *FMRI* premutation carriers in any of the groups: controls, MCI, or AD. There was no difference in the frequency of *FMRI* gray zone expansions between normal controls (3/136, 2.2%), MCI (4/64, 6.2%), and AD (3/68, 4.4%; $p=0.29$).

Discussion

These results suggest that the frequency of *FMRI* expansions is not more common in individuals presenting with memory complaints or AD compared to controls. Only a few studies have evaluated the prevalence of cognitive disorders in association with a *FMRI* expansion. A case series reported three of five female *FMRI* premutation carriers with dementia or cognitive decline showing pathological changes consistent with AD, in addition to intraneuronal inclusions typically seen in FXTAS (Tassone et al., 2012). A second study reported genotyping 95 individuals with a Huntington disease phenotype who had normal huntingtin gene testing and found only one *FMRI* premutation carrier (Rodriguez-Revenga et al., 2008).

There is an activity-dependent regulatory relationship between the fragile X mental retardation protein (FMRP) and amyloid precursor protein (APP), which when cleaved, is a major component of cerebral amyloid plaques found in AD (Sokol et al., 2011). This

relationship is mediated by metabotropic glutamate receptor 5 (mGluR5) signaling. In the *FMRI* knockout mouse model (>200 CGG repeats); there is loss of FMRP, high basal levels of APP and absence of activity-dependent regulation of APP levels.¹¹ In *FMRI* expansion carriers with less than 200 CGG repeats, FMRP levels remain normal to low normal and any effect on APP would be more subtle. This may explain why we did not see an association between *FMRI* premutation expansions and clinically diagnosed or autopsy confirmed AD cases. Based on our results, we conclude that *FMRI* premutation size repeat expansions are not a genetic risk factor for AD, but that a larger sample size may be warranted to definitively exclude an association with *FMRI* gray zone expansions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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