Negative results

CGG-repeat expansion in \textit{FMR1} is not associated with amyotrophic lateral sclerosis

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Abstract

Recently, repeat expansions in several genes have been shown to cause or be associated with amyotrophic lateral sclerosis (ALS). It has been demonstrated that an intronic hexanucleotide repeat expansion in \textit{C9ORF72} is a major cause of both familial (approximately 40%) and sporadic (approximately 5%) ALS, as well as frontotemporal dementia (FTD). In addition, a CAG-repeat expansion in exon 1 of \textit{ATXN2}, otherwise known to cause spinocerebellar ataxia type 2, has been identified as a major risk factor for sporadic ALS. Intermediate repeat expansions in the fragile X mental retardation 1 (\textit{FMR1}) gene (55–200 repeats) are known to cause fragile X-associated premature ovarian insufficiency [(FX)POI; female carriers] or fragile X-associated tremor/ataxia syndrome (FXTAS; male carriers) by CGG-mediated RNA toxicity. The present investigation involves screening \textit{FMR1} repeat length in 742 sporadic ALS patients and 792 matched controls. Our conclusion is that \textit{FMR1} repeat expansions are not associated with ALS.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of motor neurons. Several genes are known to cause familial ALS, including \textit{SOD1}, \textit{TARDBP}, \textit{FUS}, \textit{VCP}, and \textit{OPTN}. The other 90% of ALS cases are thought to be sporadic in nature. Interestingly, recent research led to the discovery that 2 repeat expansions are a major risk factor and a cause of the disease. First, a polyglutamine (polyQ) repeat expansion in ataxin-2 (\textit{ATXN2}, \textit{SCA2}) was found to be a major risk factor for sporadic ALS (Elden et al., 2010). Secondly, a hexanucleotide (GGGGCC) expansion in the first intron of \textit{C9ORF72} was identified as the most common monogenetic cause of ALS so far; in several populations it is the cause of up to 40% of familial ALS cases and up to 5% of apparently sporadic ALS cases, as well as a major cause of frontotemporal dementia (FTD) (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

A CGG-repeat expansion in the 5' untranslated region (UTR) of the \textit{FMR1} gene from less than 55 (wild type) to more than 200 CGG-repeats has long been known to cause fragile X mental retardation syndrome (FXS), the most common form of inherited mental retardation. In contrast, an intermediate CGG-expansion ranging from more than 55 up to 200 repeats can lead to fragile X-associated premature...
ovarian insufficiency [(FX)POI; female carriers] or fragile X-associated tremor/ataxia syndrome (FXTAS; male carriers). Fragile X-associated tremor/ataxia syndrome is characterized by tremor, ataxia, intellectual decline compatible with dementia syndrome, parkinsonism, and autonomic dysfunction. In addition, neuromotor disturbances are observed in mouse models of this condition.

Due to the fact that recently several different repeat expansions have been implicated in ALS pathogenesis, interest has arisen in the investigation of known disease-causing repeat expansions in ALS. In the present study we, therefore, screened a large cohort of 742 ALS patients and 792 matched controls to determine FMR1 CGG-repeat length.

2. Methods

Seven hundred forty-two patients and 792 matched controls from the Dutch national ALS referral center were included for FMR1 CGG-repeat length analysis (Supplementary Table 1). Patients were negative for a C9ORF72 repeat expansion. Polymerase chain reaction (PCR)-based fragment analysis was used to screen for intermediate FMR1 CGG-repeat expansions.

3. Results

Receiver operating characteristic analysis was unable to determine a CGG-repeat length cutoff to distinguish ALS patients from controls. Repeat length distribution in patients and controls is shown in Supplementary Fig. 1. In addition, neuromotor disturbances are observed in mouse models of this condition.

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3. Results

Receiver operating characteristic analysis was unable to determine a CGG-repeat length cutoff to distinguish ALS patients from controls. Repeat length distribution in patients and controls is shown in Supplementary Fig. 1. In addition, CGG-repeat length of either longer than wild type (>32), gray zone (41–54), or intermediate (>55) length was not associated with ALS (p = 0.264, 0.4726, and 1, respectively) (Supplementary Table 2). Furthermore, CGG-repeat length did not correlate with age at onset in 742 ALS patients (correlation R² = 0.003; p = 0.9271) (Supplementary Fig. 2).

4. Discussion

In this study of adequate sample size and power, we were unable to show an association between FMR1 intermediate repeat length or shorter, gray zone alleles and ALS.

The association of 2 repeat expansions with ALS has sparked much interest in this field. CAG-repeat expansions larger than 34 repeats in ATXN2 have long been known to cause spinocerebellar ataxia type 2. Recently, it was shown that intermediate repeat expansions (>29 repeats) are associated with sporadic as well as familial ALS. Subsequently, ATXN2 repeats were also investigated in other neurological diseases, including Alzheimer’s disease (AD), Parkinson’s disease (PD), FTD, and progressive supranuclear palsy (PSP). Although no association between expanded CAG-repeats and AD, PD, or FTD was found, expanded CAG-repeats showed a significant association with the development of progressive supranuclear palsy. Additionally, overlap between ALS and PD has been described, both clinically and genetically.

Fragile X syndrome is caused by the complete silencing of FMR1 transcription due to hypermethylation of the 5′-untranslated region due to full mutation CGG-repeat expansion. In contrast, FMR1 intermediate repeat expansion leads to RNA-mediated toxicity. Recently, it has been suggested that a hexanucleotide expansion in C9ORF72 causes ALS through a similar mechanism of RNA toxicity.

Overall, the recurring findings that demonstrate overlap between different neurological diseases, both clinically and genetically, combined with the recent association of expanded repeats and ALS, justify the screening of CGG-repeats in FMR1. We conclude that CGG-repeat expansion in FMR1 is not a genetic risk factor for ALS.

Disclosure

The authors report no conflict of interest.

Written informed consent was obtained from all individuals and the study was approved by the local ethical committee.

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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.2012.03.007.

References

