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Analysis of the hexanucleotide repeat in *C9ORF72* in Alzheimer's disease

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Abstract

Frontotemporal lobar degeneration (FTLD) is a highly familial neurodegenerative disease. It has recently been shown that the most common genetic cause of FTLD and amyotrophic lateral sclerosis (ALS) is a hexanucleotide repeat expansion in *C9ORF72*. To investigate whether this expansion was specific to the FTLD/ALS disease spectrum, we genotyped the hexanucleotide repeat region of *C9ORF72* in a large cohort of patients with Alzheimer's disease (AD). A normal range of repeats was found in all cases. We conclude that the hexanucleotide repeat expansion is specific to the FTLD/ALS disease spectrum.

Keywords: *C9ORF72*; Alzheimer's disease; Frontotemporal lobar degeneration

1. Introduction

Frontotemporal lobar degeneration (FTLD) is an umbrella term used to cover the clinical syndromes of frontotemporal dementia, progressive nonfluent aphasia (PNFA), and semantic dementia. In some cases, amyotrophic lateral sclerosis (ALS) is seen in conjunction with FTLD in the same patient. Recently it has been shown that approximately 7% of all cases of FTLD/ALS are caused by a massive expansion of a hexanucleotide (GGGGCC) repeat region in the uncharacterized gene *C9ORF72* on chromosome 9p21 (Dejesus-Hernandez et al., 2011; Renton et al., 2011). Impairment of memory is not a common (early) symptom of FTLD; however, cases of amnesic FTLD do occur, and these can be misdiagnosed as Alzheimer's disease (AD) (Graham et al., 2005). Moreover, patients with linguistic forms of AD (logopenic AD) can be misdiagnosed as PNFA, and vice versa (Hu et al., 2010). Therefore, to investigate whether cryptic cases of FTLD presenting with symptoms of AD can occur, we genotyped the expansion in a large cohort of patients who had been diagnosed by their treating physician with AD, and who fulfilled clinical criteria for AD (McKhann et al., 1984).

2. Methods

All patients were recruited with ethical committee approval from the relevant clinics and provided informed consent. Genomic DNA samples were available for 568 cases of AD, 287 female and 281 male, age range 37–90 years (mean 62.9 years); and 314 control subjects, 158 female and 156 male, age range 26–78 years (mean 50.97

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years). A high proportion of patients (80%) were drawn from a specialist early-onset dementia clinic, hence the youthful mean onset age. Repeat primed polymerase chain reaction (PCR) was performed as previously described (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

3. Results

The number of hexanucleotide repeats in all of the AD patients was within the normal range of those found in control subjects (1–23 repeats) (Dejesus-Hernandez et al., 2011; Renton et al., 2011). The highest number of repeats identified in the AD cohort was 21, in a single patient.

4. Discussion

Given that amnesic FTLD can be misdiagnosed as AD, or that linguistic forms of AD can be interpreted as PNFA, we investigated whether the most common genetic cause of FTLD (i.e., the repeat expansion in *C9ORF72*) was present in a large cohort of patients with clinically diagnosed AD. The repeat region in *C9ORF72* was in the normal range for all cases. Such findings argue that this particular mutation is not associated with amnesic FTLD and confirm that the diagnostic protocols we use to differentiate these disorders operate with high specificity (Snowden et al., 2011). The *C9ORF72* expansion appears, therefore, to be specific to FTLD and ALS and is not a cause of AD.

Disclosure statement

The authors disclose no actual or potential conflicts of interest.

All patients included in this study were recruited with local ethical committee approval and provided informed consent.

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