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ATXN2 intermediate repeat expansions influence the clinical phenotype in frontotemporal dementia

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ABSTRACT

Common genetic risk factors are associated with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Intermediate repeat expansions at the Ataxin-2 locus (*ATXN2*) are a risk factor for ALS and influence the phenotype. We assessed whether *ATXN2* is a risk factor for FTD or modify clinical features in a data set of Italian patients. Three hundred sixty-eight unrelated FTD cases and 342 controls were enrolled. The frequency of intermediate CAG repeats in *ATXN2* gene was not different comparing patients and controls. CAG repeats were interrupted by CAA in all patients carrying intermediate repeats. Interestingly, patients with an increased number of CAG repeats had an earlier onset of the disease than those without expansions ($p = 0.011$), and presented more frequently with parkinsonism ($p = 0.010$), and psychotic symptoms ($p = 0.013$) at disease onset. Our study does not support a major role of *ATXN2* intermediate CAG expansions in predisposing to FTD but suggests that *ATXN2* may act as a phenotype modifier.

1. Introduction

Several studies showed that frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are part of the same clinical, genetic, and pathologic continuum (Van Langenhove et al., 2012). Indeed, these two disorders have a shared genetic background with genes causing either one or the other condition. In both diseases, beyond Mendelian inherited forms, the great majority of cases underlay complex pattern of inheritance; the combination of multiple gene variants acts as predisposing factors, also behaving as genetic modifiers, able to modulate the clinical phenotype.

The boundary between causative and modifiers genes is often blurry, as exemplified by the *ATXN2* gene. A number of polyglutamine-encoding CAG triplets above 34 cause spinocerebellar ataxia type 2 (Pulst et al., 1996). However, intermediate repeat expansions (27-33 CAG repeats) in *ATXN2* gene have been reported as a genetic risk factor or phenotype modifier in ALS (Elden et al., 2010; Lu et al., 2015). Conversely, the potential role of *ATXN2* gene repeats in FTD has been scarcely investigated (Ross et al., 2011; Lattante et al., 2015).

Interestingly, the CAG tract can be pure or interrupted by the presence of CAA repeats. Both CAG and CAA encode for glutamine, but CAAs are known to stabilize the repeat and avoid expansions at somatic and germinal level. CAA interruptions have been identified in intermediate alleles both in healthy and ALS patients but are lost in spinocerebellar ataxia type 2–associated alleles (Tsai et al., 2004; Yu et al., 2011).

Thus, the aim of this study was to evaluate the role of *ATXN2* CAG repeats in Italian patients with frontotemporal dementia.

2. Methods

We measured the number of CAG repeats in exon 1 of the *ATXN2* gene (NM_002973.3) by polymerase chain reaction amplification

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and fluorescent fragment analysis by capillary electrophoresis (ABI Prism 3730xl, Applied Biosystems) in 368 FTD patients (188 males, 180 females; mean age ± SD: 65.8 ± 9.3 years), attending the Department of Neuroscience, University of Torino. Three hundred forty-two healthy subjects were included as controls. Written informed consent was obtained from all participants, and the internal ethics review board approved the study. CAG expansions and the interrupted sequences in intermediate alleles were verified by cloning the polymerase chain reaction product and Sanger sequencing (additional data in Supplemental 1).

3. Results

The distribution of the *ATXN2* CAG repeats in FTD patients and controls is shown in Fig. 1. The repeat length ranged from 14 to 32 repeats in FTD, and from 14 to 30 repeat units in controls, with 22 repeats being the most common allele. We did not find any fully expanded *ATXN2* allele. An intermediate repeat expansion was found in 18 of 368 (4.9%) FTD patients and in 8 of 342 (2.3%) controls. No significant difference in the frequency of intermediate CAG expansions in *ATXN2* was found between cases and controls ($p = 0.07$). Two patients with behavioral variant FTD were identified with a 32 allele, which was absent in our control population. When analyzing the CAA interruptions, CAG repeats in the *ATXN2* locus were interrupted by CAA in all of patients carrying intermediate repeats (additional data in Supplemental 1).

All patients carrying an intermediate expansion in *ATXN2* gene showed a behavioral variant FTD phenotype, except one presenting with progressive nonfluent aphasia (additional data in Supplemental 1). Age at onset was lower in patients with intermediate number of CAG repeats (≥27) ($p = 0.011$; mean age at onset 60.4 ± 3.3 years) than in those with repeats in a normal range (mean age at onset 65.7 ± 8.3 years). Intriguingly, patients with intermediate repeats showed more frequently parkinsonism as the first symptom at onset when compared to patients with CAG repeats in normal range ($p = 0.01$). Finally, FTD patients with intermediate expansions also showed more frequently psychosis at disease onset ($p = 0.013$).

4. Discussion

Our study confirms previous reports suggesting that CAG intermediate repeats in the *ATXN2* gene are not likely to be associated with frontotemporal dementia. However, a detailed clinical evaluation allowed us uncovering that intermediate-length repeats may influence the clinical features of the disease. In our data set, carriers of intermediate repeats had a younger age at onset and increased frequency of parkinsonism and psychotic symptoms at the onset of the disease. This suggests that even if *ATXN2* expansions are not causative, they may act as a phenotype modifier in FTD.

ATXN2 intermediate CAG repeats were previously reported in families with atypical parkinsonism with CAG repeats in the low expansion range and interrupted by CAA (Kim et al., 2007). A recent article reported an FTD patient with TDP-43–proven pathology without pathogenic variants in known FTD genes; interestingly, this subject carried an interrupted CAG expansion in *ATXN2* gene (Fournier et al., 2018). All these observations suggest that the configuration of the *ATXN2* repeat expansions might play a role in the phenotype variability: the presence of CAA interruptions might influence patients' clinical features, as pathological uninterrupted

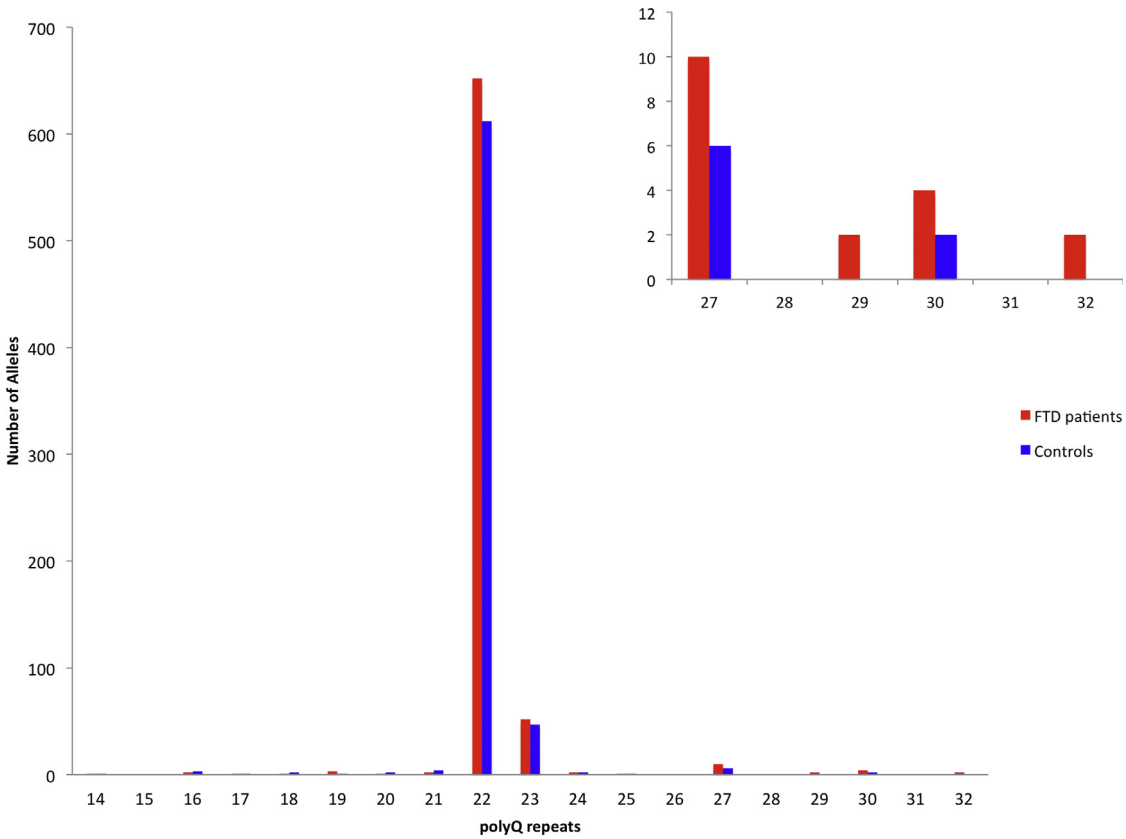

Fig. 1. Distribution of *ATXN2* intermediate repeat lengths in FTD patients and controls. In the upper right panel, histograms with ≥27 CAG repeats are magnified. Abbreviation: FTD, frontotemporal dementia.

ATXN2 repeat may not have the same modifying effect as intermediate interrupted alleles.

In conclusion, we reported that *ATXN2* intermediate repeat expansions are not associated with FTD, but might influence the phenotype, being associated with an earlier age at onset, parkinsonism, and psychotic symptoms in the initial phase of the disease. Although a possible limit of the study is its retrospective nature, patients' clinical data were recorded from neurologists without prior knowledge of patients' genetic background. Further clinical and experimental investigations are needed to analyze the role of *ATXN2* intermediate repeats in FTD.

Disclosure statement

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.09.009.

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