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Screening for *C9orf72* repeat expansions in parkinsonian syndromes

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Abstract

Parkinsonism might precede, coincide, or follow the behavioral or language-predominant cognitive impairments characteristic of frontotemporal dementia (FTD). In this study, we analyze the hexanucleotide repeat expansions within *C9orf72* gene in various parkinsonian syndromes because it is a recently identified important genetic cause of FTD. The expanded hexanucleotide repeat is only identified in our familial FTD patients but not in patients with predominant parkinsonism. The lack of association between abnormal *C9orf72* repeat expansion and parkinsonian syndromes might imply pathogenic mechanisms other than tau or Lewy body pathology.

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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. 09.002.

Keywords

C9orf72; GGGGCC hexanucleotide repeat expansion; Frontotemporal dementia (FTD); Parkinson's disease with dementia (PDD); Progressive supranuclear palsy (PSP); Corticobasal syndrome (CBS); Dementia with Lewy bodies (DLB)

1. Introduction

The syndromes overlapping with frontotemporal dementia (FTD) had been noticed in various parkinsonian syndromes such as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), dementia with Lewy bodies (DLB), and a number of additional clinical variants such as FTD-Parkinsonism (Espay and Litvan, 2011). The motor symptoms might precede, coincide, or follow the behavioral or language-predominant cognitive impairments characteristic of FTD. These disorders might also share the same genetic or pathologic findings. Recent studies have identified that a large hexanucleotide (GGGGCC) repeat expansions in the first intron of *C9orf72* gene is the genetic cause for a significant proportion of sporadic or familial FTD cases (DeJesus-Hernandez et al., 2011; Majounie et al., 2012b; Renton et al., 2011). In the present study, we aimed to determine the prevalence of abnormal *C9orf72* hexanucleotide repeat expansions in a Taiwanese cohort of patients with Parkinson's disease with dementia and various parkinsonian syndromes.

2. Methods

We enrolled 153 parkinsonian patients, including 71 patients with Parkinson's disease with dementia, 34 with DLB, 35 with PSP, and 13 with CBS. The fluorescent repeat-primed polymerase chain reaction assay was performed to detect abnormal hexanucleotide (GGGGCC) repeat expansion within the *C9orf72* gene following the protocol reported previously (Renton et al., 2011). The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and written informed consent was given by all participants.

3. Results

The demographic data and estimated repeat numbers for all tested subjects are summarized in Supplementary Table 1. The sequence traces obtained from repeat-primed polymerase chain reaction are illustrated in Supplementary Fig. 1. The abnormal repeat expansions produce a characteristic saw tooth pattern with a 6 base pair periodicity. We only identified large *C9orf72* repeat expansions in 3 patients of a FTD family but not in 153 patients with various parkinsonian syndromes. The pedigree of this family and the brief clinical information of the index patient are shown in Supplementary Fig. 2. The distribution of the estimated repeat numbers for each group are shown in Supplementary Fig. 3.

4. Discussion

Substantial evidence supports the concept that various neuro-degenerative disorders share overlapping clinical, genetic, and pathologic features. The clinical manifestations are varied and some FTD patients can develop associated features of motor neuron disease or

parkinsonian syndromes characterized with PSP, CBS, DLB, or FTD-Parkinsonism. Some of them can have very similar pathologic findings. The phenotypic heterogeneity was also demonstrated by the recent identification of large *C9orf72* hexanucleotide repeat expansions in 2 clinically distinct disorders, amyotrophic lateral sclerosis and FTD. In addition to the motor neuron syndrome, the following reports revealed that Parkinsonism was not an infrequent clinical presentation in patients with expanded *C9orf72* repeats, accounting for 14%–35% of cases: Boeve et al., 2012; Simon-Sanchez et al., 2012; and Snowden et al., 2012. We hypothesized that *C9orf72* repeat expansion might be associated with those parkinsonian syndromes but, similar to the latest report of a cohort of 781 patients with Parkinson's disease (Majounie et al., 2012a), we could not detect abnormal *C9orf72* repeat expansions in our cohort of various parkinsonian syndromes. The large hexanucleotide repeat expansions are only found in our 3 FTD patients from a single family. We conclude that *C9orf72* repeat expansions are not a common genetic cause for Taiwanese patients with predominant parkinsonian syndromes such as Parkinson's disease with dementia, DLB, PSP, or CBS. The lack of association of expanded *C9orf72* repeats might suggest a pathogenic mechanism other than tau or Lewy body pathology being involved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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