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Large *C9orf72* repeat expansions are not a common cause of Parkinson's disease

Elisa Majounie[a], **Yevgeniya Abramzon**[b], **Alan E. Renton**[b], **Margaux F. Keller**[a,c], **Bryan J. Traynor**[b,d], and **Andrew B. Singleton**[a]

[a]Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

[b]Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

[c]Department of Biological Anthropology, Temple University, Philadelphia, PA, USA

[d]Department of Neurology, Brain Sciences Institute, Johns Hopkins Hospital, Baltimore, MD, USA

Abstract

The concept of a pathological overlap between neurodegenerative disorders is gaining momentum. We sought to determine the contribution of *C9orf72* repeat expansions, recently discovered as a cause of frontotemporal dementia and amyotrophic lateral sclerosis, in a large number of Parkinson's disease patients. No large expansions were identified in our cohort.

Keywords

Parkinson's disease; *C9orf72*

1. Introduction

Parkinson's disease (PD; OMIM 168600) is 1 of the most common neurodegenerative disorders, affecting 1%–2% of the population older than 65 years old. The rare monogenic forms of PD have offered insight into the genetic etiology of this disease (Lesage and Brice, 2012), and the use of genome-wide association has revealed a large number of risk loci for PD (IPDGC-WTCCC2, 2011; Nalls et al., 2011).

We recently identified a hexanucleotide repeat expansion within *C9orf72* that accounts for a significant proportion of familial amyotrophic lateral sclerosis (ALS; OMIM #105400105400) and frontotemporal dementia (FTD; OMIM #600274600274; Renton et al., 2011; Majounie et al., 2012b). Several lines of evidence support the concept of a pathological overlap between neurodegenerative disorders. First, predominantly FTD/ALS families harboring concomitant symptoms of parkinsonism have been described (Chio et al.,

Disclosure statement

Bryan J. Traynor has a patent pending on the clinical testing and therapeutic intervention for the hexanucleotide repeat expansion of *C9orf72*. All other authors declare that they have no conflicts of interest.

2011; Gilbert et al., 2010). Second, recent evidence suggests that classic FTD/ALS genes may give rise to rare cases of clinical PD (Kacem et al., 2012; Quadri et al., 2011). Finally, studies of *C9orf72*expansion carriers reported both clinical features of parkinsonism in the probands and increased incidence of PD in their relatives (Cooper-Knock et al., 2012; Hsiung et al., 2012). Consequently, we investigated a large cohort of PD cases under the hypothesis that the *C9orf72* expansion may also contribute to idiopathic PD.

2. Methods

The PD cohort consisted of sporadic and familial cases from the United States obtained from the Coriell Institute for Biomedical Research. All subjects were Caucasian, non-Hispanic individuals. The average age of symptom onset was 60 years old (range, 12–91 years). The number of (GGGGCC) n repeat within *C9orf72*was assayed using a fluorescent repeat-primed (RP)-polymerase chain reaction approach, as previously described (Renton et al., 2011). Additional statistical analysis of repeat length correlation to age of symptom onset, family history, and Mini Mental State Examination scores was conducted using a generalized linear model.

3. Results

We screened a total of 781 PD cases, including 245 individuals with a familial history of the disease, for the hexanucleotide expansion in the *C9orf72* gene. The repeat-primed polymerase chain reaction assays can resolve up to approximately 60 repeats, allowing for rapid discrimination of wild type (< 20 repeats) and expanded (> 30 repeats) alleles (Renton et al., 2011). We did not observe any large (GGGGCC) n expansions in our PD cohort. Four samples harbored marginally larger-than-normal alleles (at 21, 23, 24, and 38 repeats) but did not show a classic large expansion pattern (Supplementary Figs. 1 and 2). The contribution of such alleles to disease is unclear (Traynor BJ, Renton AE and Majounie E, unreported observations). These 4 cases showed classic signs of PD (activation tremor, asymmetric onset, bradykinesis, gait difficulties, and postural instability). The 38-repeat allele did not segregate with disease in the proband's sibling, also affected with PD. On average, the number of repeats detected were 3 (range, 0–38) and the allelic distribution is represented in Supplementary Fig. 3. These results are similar to that observed in a previously reported outbred control Caucasian population (Supplementary Fig. 4; Renton et al., 2011; Majounie et al., 2012b). There was no correlation between repeat length and family history or age of onset.

4. Discussion

To our knowledge, we report here the first investigation of the *C9orf72* hexanucleotide repeat in a large cohort of PD patients. Although it is possible that our cohort was underpowered to detect the *C9orf72* expansion, our study demonstrates that such expansions are likely to be a rare occurrence in PD; certainly rarer than that seen in Alzheimer's disease, where approximately 1% of clinically diagnosed patients harbor the mutation (Majounie et al., 2012a). The pathogenic mechanism underlying *C9orf72* expansion is largely unknown, and changes in *C9orf72* isoform expression or formation of toxic RNA inclusions may

contribute to disease (Renton et al., 2011). We did not screen the length of the *C9orf72* gene for single nucleotide variants that may influence expression and contribute to disease risk.

Cases with concomitant dementia represent approximately a quarter of PD (Aarsland et al., 2005) and may be of particular interest in future studies. Limited phenotypic data were available in our cohort. However, Mini Mental State Examination scores for 217 PD patients did not correlate with allelic length. In conclusion, our data show that the *C9orf72* expansion is not commonly associated with PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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