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C9ORF72 Expansion is Not a Significant Cause of Sporadic Spinocerebellar Ataxia

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Hexanucleotide expansions within the first intron of the *C9ORF72* gene are a significant cause of familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), alone or in combination, as well as sporadic ALS worldwide.^{1–3} Several recent reports have described cases which broaden the clinical phenotype to include behavioral variant FTD with or without early psychiatric presentations and parkinsonian features,^{4,5} and primary progressive aphasia.⁶ There is also a report of a patient with a family history of ALS and cerebellar ataxia,⁵ an intriguing finding as neuroimaging of *C9ORF72* patients shows cerebellar atrophy, which is not typically observed with other FTD-related mutations such as *MAPT* or *GRN*.⁷ Cerebellar neuronal cytoplasmic inclusions have also been observed in multiple studies,^{6,7} yet clinical cerebellar ataxia has not been detected in any large cohorts of *C9ORF72* patients with FTD and/or ALS.^{1–3,7} Since a majority of adult-onset ataxia cases are of unknown etiology, these observations raise the possibility that *C9ORF72* may contribute to the development of sporadic spinocerebellar ataxia.

To address this question, we examined 209 adult-onset sporadic ataxia patients for *C9ORF72* hexanucleotide expansion (Table I). All patients were screened for common genetic spinocerebellar ataxias including SCA1, SCA2, SCA3, SCA6, SCA7, and/or Friedreich ataxia. Most patients (40%) had pure cerebellar ataxia but, given the known *C9ORF72* phenotypes, cases associated with upper motor neuron signs, dementia, and parkinsonism were also included. Approximately one-third of these patients met possible or probable

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Author Contributions:

BLF and GC were responsible for the conception and design of the research project. MP and SP were responsible for project execution. SLP and DHG supervised the clinical phenotyping and the molecular aspects of the project, respectively. BLF wrote the manuscript and BLF, GC, SLP, and DHG were responsible for its review and critique.

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criteria for multiple system atrophy. Testing was performed as previously described³ and only one positive case was identified (1/209, 0.5%).

This patient, currently age 53, developed slowly progressive cerebellar dysfunction in her early 20's with falls by age 25. Upper motor neuron features of increased lower extremity tone and hyper-reflexia were present but annual assessments have shown no lower motor neuron involvement or cognitive decline. MRI has shown cerebellar atrophy with no frontal or temporal involvement. Evaluation for other genetic causes involving the *APTX*, *ATN1*, *ATXN1*, *ATXN2*, *ATXN3*, *ATXN7*, *ATXN8*, *ATXN10*, *CACNA1A*, *FMRI*, *FXN*, *KCNC3*, *PRKCG*, *PP2R2B*, *SACS*, *SETX*, *SPTBN2*, and *TBP* genes was unremarkable. She is Caucasian with French-Canadian ancestry. As with the prior reported *C9ORF72* ataxia case,⁵ family history was notable for her father and paternal uncle being diagnosed with ALS and dying within 2 years of symptom onset. There were no other affected family members.

We speculate that the clinical findings seen in our patient represent a rare (<1%) *C9ORF72* phenotype,⁵ however, given the lack of other affected family members or unrelated cases, we cannot confirm this. *C9ORF72* penetrance varies by age, with full penetrance occurring by the 9th decade,¹ and it is possible that our patient will still develop a more classic phenotype. Regardless, this study does not support genetic testing for *C9ORF72* expansion in sporadic spinocerebellar ataxia, although, as our study only examined sporadic-onset cases, it remains possible that *C9ORF72* may contribute more significantly to dominant familial forms. For now, *C9ORF72* testing would only be indicated for ataxia patients with a family history of ALS and/or FTD.

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References

1. Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol*. 2012; 11(4):323–330. [PubMed: 22406228]
2. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011; 72(2):257–268. [PubMed: 21944779]
3. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011; 72(2):245–256. [PubMed: 21944778]
4. Boeve BF, Boylan KB, Graff-Radford NR, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain*. 2012; 135(Pt 3):765–783. [PubMed: 22366793]
5. Lindquist S, Duno M, Batbayli M, et al. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. *Clin Genet*. 2012; 9999(9999)
6. Simon-Sanchez J, Dopper EG, Cohn-Hokke PE, et al. The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. *Brain*. 2012; 135(Pt 3):723–735. [PubMed: 22300876]

7. Whitwell JL, Weigand SD, Boeve BF, et al. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. *Brain*. 2012; 135(Pt 3):794–806. [PubMed: 22366795]

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Table

Patient Demographics (N=209).

Age (years)	57.4 ± 14.7
Sex (Female)	52.6%
Clinical Presentation	N (%)
Pure Cerebellar Ataxia	83 (39.7%)
Ataxia with Autonomic Dysfunction and/or Parkinsonism	61 (29.2%)
Ataxia with Upper Motor Signs	48 (23.0%)
Ataxia with Polyneuropathy	9 (4.3%)
Ataxia with Dementia	8 (3.8%)