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Journal Title: Movement Disorders
Volume: Volume 33, Number 3
Publisher: Wiley | 2018-03-01, Pages 497-498
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1002/mds.27258
Permanent URL: https://pid.emory.edu/ark:/25593/tnvhs

Final published version: http://dx.doi.org/10.1002/mds.27258

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Accessed February 13, 2020 5:03 PM EST
C9orf72 Repeat Expansions as Genetic Modifiers for Depression in Spinocerebellar Ataxias

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Ms. Figueroa: study concept and design, statistical analysis and interpretation, writing the manuscript, critical revision of the manuscript for important intellectual content.
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Dr. Perlman: acquisition of data.
Dr. Wilmot: acquisition of data.
Dr. Gomez: acquisition of data.
Dr. Schmahmann: acquisition of data.
Dr. Paulson: acquisition of data.
Dr. Shakkottai: acquisition of data.
Dr. Ying: acquisition of data.
Dr. Zesiewicz: acquisition of data.
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Dr. Geschwind: acquisition of data.
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Dr. Subramony: study concept and design, acquisition of data, study supervision.
Dr. Ashizawa: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision.
Dr. Pulst: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision.
Dr. Kuo: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content.

Disclosure: Dr. Zesiewicz has served as a clinical advisor for Steminent Biotherapeutics, and she has received travel reimbursement from the department of neurology at University of Southern Florida; has received travel reimbursement for a Biohaven Pharmaceuticals meeting. Dr. Zesiewicz has served on the editorial board for Neuromodulatory Disease Management and Tremor and other Hyperkinetic Movements, and has received research support for her division for approximately 20 clinical trials for Parkinson’s disease, Friedreich’s ataxia, and spinocerebellar ataxias. Dr. Zesiewicz’s division is a site in a multi-site trial of Parkinson’s disease patients with the LRRK2 mutation and is sponsored by the National Institutes of Health but funded by Emory University.

The rest of authors report no conflicts of interest.
The genetic interactions between pathological repeat expansions have been of major interests in neurodegenerative disorders. Recently, pathogenic C9orf72 repeat expansions, a main genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia and pathogenic ATXN2 repeat expansions, the causative gene for spinocerebellar ataxia (SCA) type 2, are reported to coexist in a single family with ataxia. Therefore, this observation raises an interesting possibility that C9orf72 repeat expansions could be genetic modifiers in CAG-repeat SCAs and might influence the disease progression.

Therefore, we studied 277 patients with SCA1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) cohort, and we determined the C9orf72 repeat length as previously described. The Scale for Assessment and Rating of Ataxia (SARA) and the 9-item Patient Health Questionnaire (PHQ-9) were used to measure the severity of ataxia and depression, respectively. We studied the rate of ataxia and depression progression using generalized estimating equation to test whether the intermediate repeats of C9orf72 were associated with ataxia or depression progression in SCAs. As described previously, full repeat expansions of C9orf72 were defined as ≥31 hexanucleotide repeats whereas intermediate repeat expansions were 8–30.

We identified seven patients (3 out of 51 SCA1; 2 out of 58 SCA2; 1 out 109 SCA3; 1 out of 59 SCA6) with pathogenic C9orf72 repeat expansions. None of the 7 cases had motor neuron disease, but they had various degrees of motor neuron signs (Table 1). Compared to cognitively normal control (The original paper cites 1039 Europeans and 620 African American) population, the frequencies of expanded C9orf72 repeats in our cohort were significantly higher in SCA1, 2, and 6 but not in SCA3 (Supplemental table 1). Forty percent of SCA patients carry intermediate C9orf72 repeat expansions, and the demographic and clinical features of SCA subjects with normal and intermediate alleles of C9orf72 are shown in Supplemental table 2. Intermediate C9orf72 repeat expansions did not influence the rate of ataxia progression but were associated with different rates of depressive symptom progression in SCA1, 3, and 6 (SCA1: \( \beta = -1.90, p < 0.005 \); SCA3: \( \beta = 3.48, p < 0.001 \); SCA6: \( \beta = -1.72, p < 0.05 \); Supplemental table 3).
In the present study, we identified patients of SCA1, 2, 3, and 6 who also carry pathogenic C9orf72 repeat expansions. Intermediate C9orf72 repeat expansions might influence the non-motor symptom (i.e. depression) progression in SCAs. Our study highlights the genetic interactions between repeat expansions.

The presence of CAG repeat expansions could interfere with the DNA repair process, which may destabilize C9orf72 repeat expansions and explain the co-existence of C9orf72 repeat expansions and expanded CAG repeats. Since cerebellar pathology could be found in C9orf72-linked ALS, the presence of C9orf72 repeat expansions might affect polyglutamine aggregates preferentially in the cerebellum or brainstem structures implicated in depression.

In conclusion, our study provides supporting evidence that repeat expansions of C9orf72 may be genetic modifiers in SCAs, and perhaps ataxia patients in general. Therefore, the interplay of repeat expansions in two different loci may lead to diverse clinical phenotypes in degenerative cerebellar ataxia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: The CRC-SCA natural history study is supported by the Rare Disease Clinical Research Network (RDCRN) (RC1NS068897), and the National Ataxia Foundation. Dr. Stefan Pulst is supported by NIH/NINDS RC4NS073009, R01NS033123, R37NS033123. Dr. Kuo is supported by the NINDS K08 NS083738, Louis V. Gerstner Jr. Scholarship, American Brain Research Training Fellowship, Parkinson Disease Foundation, American Parkinson’s Disease Association, Rare Disease Clinical Research Network (RDCRN) (RC1NS068897), International Essential Tremor Foundation, and NIEHS pilot grant ES009089, the Smart Foundation. Dr. Gan is supported by the National Natural Science Foundation of China (U1505222).

References

Table 1.

Demographic and clinical features of 7 SCA patients with full C9orf72 repeat expansions

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>SCA Type</th>
<th>CAG Repeats Number (Small/Large)</th>
<th>C9orf72 Repeats</th>
<th>Gender</th>
<th>Age of Onset</th>
<th>SARA Mental Status</th>
<th>Fasculation</th>
<th>Weakness</th>
<th>Reflexes of Extremities</th>
<th>Plantar Reflex</th>
<th>Spasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>30/44</td>
<td>5/&gt;30</td>
<td>Woman</td>
<td>38</td>
<td>10.5</td>
<td>MoCA 25/30</td>
<td>Present</td>
<td>None</td>
<td>Hyperreflexia in biceps, patellar and Achilles</td>
<td>Extensor</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>30/42</td>
<td>10/&gt;30</td>
<td>Woman</td>
<td>45</td>
<td>0.5</td>
<td>MoCA 30/30</td>
<td>Present</td>
<td>None</td>
<td>Hyperreflexia in biceps, patellar and Achilles</td>
<td>Flexor</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>30/42</td>
<td>10/&gt;30</td>
<td>Woman</td>
<td>52</td>
<td>8.5</td>
<td>MoCA 25/30</td>
<td>Present</td>
<td>None</td>
<td>Hyperreflexia in biceps, patellar and Achilles</td>
<td>Flexor</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>22/39</td>
<td>6/&gt;30</td>
<td>Man</td>
<td>35</td>
<td>24</td>
<td>Not evaluated</td>
<td>None</td>
<td>None</td>
<td>Areflexia in biceps, patellar and Achilles</td>
<td>Extensor</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>22/39</td>
<td>2/&gt;30</td>
<td>Woman</td>
<td>40</td>
<td>24.5</td>
<td>Poor in serial 7s</td>
<td>Mild in tongue and face and four limbs</td>
<td>Mild in four limbs</td>
<td>Areflexia in biceps, patellar and Achilles</td>
<td>Flexor</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>28/70</td>
<td>2/&gt;30</td>
<td>Woman</td>
<td>48</td>
<td>30.5</td>
<td>Not evaluated</td>
<td>Moderate in tongue and face</td>
<td>Mild in four limbs</td>
<td>Areflexia in biceps, hyperreflexia in patellar and Achilles</td>
<td>Extensor</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>11/23</td>
<td>8/&gt;30</td>
<td>Man</td>
<td>59</td>
<td>12.5</td>
<td>Not evaluated</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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