


C9orf72 Repeat Expansions as Genetic Modifiers for Depression in Spinocerebellar Ataxias

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 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.1 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 cohort,2 and we determined the C9orf72 repeat length as previously described.1 The Scale for Assessment and Rating of Ataxia and the 9-item Patient Health Questionnaire 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 8-30.3,5

We identified 7 patients (3 of 51 SCA1, 2 of 58 SCA2, 1 of 109 SCA3, 1 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). When compared with the cognitively normal control population (the original paper cites 1039 Europeans and 620 African Americans),3 the frequencies of expanded C9orf72 repeats in our cohort were significantly higher in SCA1, 2, and 6, but not in SCA3 (Supplemental Table 1). Of SCA patients, 40% carry intermediate C9orf72 repeat expansions, and the demographic and clinical features of SCA patients 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, β = −1.90, P < .005; SCA3, β = 3.48, P < .001; SCA6, β = −1.72, P < .05; Supplemental Table 3).

In the present study, we identified patients of SCA1, 2, 3, and 6 who also carried pathogenic C9orf72 repeat expansions. Intermediate C9orf72 repeat expansions might influence the nonmotor symptom (ie, 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,6 which may destabilize C9orf72 repeat expansions and explain the coexistence of C9orf72 repeat expansions and expanded CAG repeats. Because cerebellar pathology could be found in C9orf72-linked amyotrophic lateral sclerosis, the presence of C9orf72 repeat expansions might affect polyglutamine aggregates preferentially in the cerebellum or brain stem 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.7 Therefore, the interplay of repeat expansions in 2 different loci may lead to diverse clinical phenotypes in degenerative cerebellar ataxia.
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 Gender</th>
<th>Age of onset</th>
<th>SARA Mental status</th>
<th>Motor neuron deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>30/44</td>
<td>5/&gt;-30 Woman</td>
<td>38</td>
<td>10.5 MoCA 25/30</td>
<td>Present None Hyperreflexia in biceps, patellar, and Achilles Extensor Mild in lower and upper limbs</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>30/42</td>
<td>10/&gt;-30 Woman</td>
<td>45</td>
<td>0.5 MoCA 30/30</td>
<td>Present None Hyperreflexia in biceps, patellar, and Achilles Flexor Not evaluated</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>30/42</td>
<td>10/&gt;-30 Woman</td>
<td>52</td>
<td>8.5 MoCA 25/30</td>
<td>Present None Hyperreflexia in biceps, patellar, and Achilles Flexor Mild in lower limbs</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>22/39</td>
<td>6/&gt;-30 Man</td>
<td>35</td>
<td>24 Not evaluated</td>
<td>None None Areflexia in biceps, patellar, and Achilles Extensor Moderate in lower limbs, mild in upper limbs</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>22/39</td>
<td>2/&gt;-30 Woman</td>
<td>40</td>
<td>24.5 Poor in serial 7s Mild in tongue/facial and 4 limbs Mild in 4 limbs Extensor Areflexia in biceps, patellar, and Achilles Flexor None</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>28/70</td>
<td>2/&gt;-30 Woman</td>
<td>48</td>
<td>30.5 Not evaluated Moderate in tongue and face Mild in 4 limbs Extensor Areflexia in biceps, hyperreflexia in patellar and Achilles Flexor Moderate in 4 limbs</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>11/23</td>
<td>8/&gt;-30 Man</td>
<td>59</td>
<td>12.5 Not evaluated None None Areflexia in biceps, hyperreflexia in patellar and Achilles Extensor None None</td>
<td></td>
</tr>
</tbody>
</table>

SCA, spinocerebellar ataxias; SARA, Scale for Ataxia Rating and Assessment; serial 7s, Serial Sevens Subtraction Test.

References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s website.