LETTER TO THE EDITOR

Higher than expected incident cases of spinal bulbar muscular atrophy in western Canada

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Spinal bulbar muscular atrophy (also known as Kennedy disease) was recently described to have a high prevalence among Indigenous people in the prairie provinces of western Canada due to a genetic founder effect.1 In this work, the prevalence was estimated at 1/6,802 (i.e: 14.7/100,000), the highest known prevalence in the world, but based on the study design was considered to be an underestimate. This compares to estimates of the global prevalence at 1-2/100,000. Recently, © The Author(s) 2024. Published by Oxford University Press on behalf of the Guarantors of Brain. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
an analysis of whole genome sequence data from large genomic datasets suggests a much higher-than-expected carrier frequency of the AR expansion, with a possible disease prevalence as high as 1/6,887 males (or approximately 1/13,774 population). The massive underdiagnosis of spinal bulbar muscular atrophy is likely to be multifactorial and may be related to variable penetrance, expressivity and social determinants of health, among other factors.

To obtain further evidence regarding apparent underdiagnosis of spinal bulbar muscular atrophy, we conducted a survey of diagnostic testing results for the AR trinucleotide repeat at the Molecular Genetics Laboratory at the Alberta Children’s Hospital. Since 2018, this lab has received and reported on all diagnostic testing for spinal bulbar muscular atrophy for the provinces of Alberta and Saskatchewan, and the Northwest Territories, covering a total population of 5.59 million people. Research ethics board approval was obtained from the University of Calgary Conjoint Health Research Ethics Board (REB23-0215). Community consent was obtained after consultation with our patient advisory council, an Indigenous Community Guiding Circle consisting of five people affected by SBMA from Indigenous communities, and a Saulteaux Knowledge Holder from an affected community (the Key First Nation), and specific agreement for the submission and publication of this letter was obtained during a meeting on November 8, 2023.

We performed a retrospective chart review of diagnostic and carrier testing, reporting all cases with AR exon 1 expansions containing 38 or more CAG repeats. Clinical information collected from the records included sex and province of residence. Prevalence of incident cases was calculated relative to the total population of each region (Statistics Canada). During the 5.5-year period (January 2018 until July 2023) we identified 59 new cases of spinal bulbar muscular atrophy. The incident cases over this period are summarised in the table below and is 1.06/100,000 population across the three regions covered by our lab (Table 1).

The incident cases from only 5.5 years’ worth of testing in the regions covered by our diagnostic lab is similar to the estimated total global prevalence. This certainly suggests that the total
prevalence in our regions is likely to be several-fold higher. This only includes cases which have been clinically ascertained, and the true prevalence is likely underestimated due to diagnostic delay, late onset of symptoms, or lack of access to testing and healthcare resources. There is also an important interaction of Indigenous health determinants that affects the ascertainment of cases.

It is noteworthy that a very small number of female carriers were identified by our lab during this period. This indicates that family genetic counselling and carrier testing may be under-utilised in our regions. Better access to these resources would be of benefit to help people obtain education about risks of passing on the mutation and to improve diagnosis in family members.

We have previously reported the high prevalence of spinal bulbar muscular atrophy among Indigenous peoples in these regions. Our experience is that over 80% of patients in our clinics self-report Indigenous ancestry, usually from Cree, Saulteaux or Métis Nations. If it holds true that 80% of these positive results are from Indigenous people, then when compared to the Indigenous population of these regions (approximately 491,000), this would also indicate a very high number of incident cases over the 5.5 year period (11/100,000). For comparison, we had previously estimated the prevalence in this population as 14.7/100,000, and these newer data from incident cases suggest the true total prevalence is likely to be several-fold higher. Given the findings of Zanavello and colleagues, the carrier frequency of the AR expansion is likely also underestimated by at least ten-fold, which explains findings such as the presence of homozygous females with the AR expansion from an Indigenous community in Manitoba, an adjacent province. We emphasize the importance of ongoing engagement with communities to aid in the ascertainment of cases. This will help affected patients gain access to necessary supportive care resources, and importantly, access to future therapies that are currently in development for spinal bulbar muscular atrophy.

**Data availability**

The authors confirm that the data supporting the findings of this study are available within the article.
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Competing interests

The authors have no competing interests to disclose.

References


Table 1 Incident cases of spinal bulbar muscular atrophy over the 5.5 year period

<table>
<thead>
<tr>
<th>Region</th>
<th>Regional population in 100 000</th>
<th>n of positive male cases</th>
<th>n of positive female carrier cases</th>
<th>Total positive cases</th>
<th>Incident cases /100 000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>43.71</td>
<td>39</td>
<td>8</td>
<td>47</td>
<td>0.89</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>11.74</td>
<td>19</td>
<td>1</td>
<td>20</td>
<td>1.62</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>0.448</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2.23</td>
</tr>
<tr>
<td>Total</td>
<td>55.9</td>
<td>59</td>
<td>9</td>
<td>68</td>
<td>1.06</td>
</tr>
</tbody>
</table>

*Male spinal bulbar muscular atrophy cases per total population (males + females).