

# Highly Elevated Prevalence of Spinobulbar Muscular Atrophy in Indigenous Communities in Canada Due to a Founder Effect

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## Abstract

### Objective

Spinobulbar muscular atrophy (SBMA) is an X-linked adult-onset neuromuscular disorder that causes progressive weakness and androgen insensitivity in hemizygous males. This condition is reported to be extremely rare, but has higher prevalence in certain populations due to multiple founder effects. Anecdotal observations of a higher prevalence of SBMA in patients of Indigenous descent in Saskatchewan led us to perform this study, to estimate the disease prevalence, and to attempt to identify a founder effect.

### Methods

For our prevalence estimation, we identified patients with confirmed SBMA diagnosis from the Saskatoon neuromuscular clinic database for comparison with population data available from Statistics Canada. For our haplotype analysis, participants with SBMA were recruited from 2 neuromuscular clinics, as well as 5 control participants. Clinical data were collected, as well as a DNA sample using saliva kits. We performed targeted quantification of DXS1194, DXS1111, DXS135, and DXS1125 microsatellite repeats and the *AR* GGC repeat to attempt to identify a disease haplotype and compare it with prior studies.

### Results

We estimate the prevalence of SBMA among persons of Indigenous descent in Saskatchewan as 14.7 per 100,000 population. Although we believe that this is an underestimate, this still appears to be the highest population prevalence for SBMA in the world. A total of 21 participants were recruited for the haplotype study, and we identified a unique haplotype that was shared among 13 participants with Indigenous ancestry. A second shared haplotype was identified in 2 participants, which may represent a second founder haplotype, but this would need to be confirmed with future studies.

### Conclusions

We describe a very high prevalence of SBMA in western Canadians of Indigenous descent, which appears to predominantly be due to a founder effect. This necessitates further studies of SBMA in these populations to comprehensively ascertain the disease prevalence and allow appropriate allocation of resources to support individuals living with this chronic disease.

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## Glossary

AR = androgen receptor; CI = confidence interval; FRS = Functional Rating Scale; SMBA = spinobulbar muscular atrophy.

Spinobulbar muscular atrophy (SBMA), also known as Kennedy disease, is an X-linked, progressive neuromuscular disorder in men, caused by a CAG repeat expansion (>38 CAGs) in the first exon of the androgen receptor (AR) gene. SBMA is characterized by the development of spinal and bulbar lower motor neuron disease presenting in adulthood, resulting in debilitating symptoms of muscle weakness, fasciculations, dysarthria, and difficulty swallowing.<sup>1</sup> Androgen insensitivity can also be observed, including symptoms of gynecomastia, testicular atrophy, and reduced fertility.<sup>2</sup> SBMA causes chronic disability and elevated risk of early mortality due to bulbar dysfunction and aspiration pneumonia.<sup>3,4</sup>

SBMA is a rare neuromuscular disorder and has an estimated population prevalence ranging from 1 to 2 per 100,000.<sup>2</sup> Determining the precise prevalence is challenging because of the extensive clinical variability of this condition,<sup>5</sup> and 1 prior study suggested a higher carrier frequency than expected for a disease of this rarity.<sup>6</sup> This disease has been observed at a higher prevalence in specific populations, presumably due to founder effects.<sup>7,8</sup> Genetic studies have identified unique haplotypes suggesting founder effects for the origins of disease for differing populations.<sup>8–11</sup>

We are aware of multiple anecdotal observations (both from colleagues and from reports in the literature) that suggest that a higher prevalence of SBMA may exist in individuals of Indigenous descent in Canada. One of the families in the original description of SBMA by Dr. Kennedy is alternately described as French Canadian or French Indian who immigrated to Minnesota in the early 19th century.<sup>12,13</sup> Another reported family was of Ojibwe descent<sup>14</sup> (personal email communication, Dr. Rockman-Greenberg, December 2020). In addition, a worldwide genomic study in 2001 described Indigenous representation from 3 of the 9 participants from the contributing author in Vancouver.<sup>11</sup> The possibility of a high SBMA prevalence is also suggested by a prior report of homozygous females with SBMA,<sup>15</sup> who are also of Indigenous descent (personal email communication, Dr. Rockman-Greenberg, December 2020).

This led us to perform the following study to attempt to estimate the prevalence of SBMA in the western Canadian province of Saskatchewan, as well as to perform a genetic analysis to identify a potential founder haplotype for comparison to previously published literature.<sup>10,11</sup>

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was obtained from the University of Saskatchewan Biomedical Research Ethics Board (Bio-REB 536)

and the University of Calgary Conjoint Health Research Ethics Board (REB15-2763). All participants provided written informed consent for clinical data collection, DNA sample collection, and genetic analyses.

### Prevalence Estimation

Saskatchewan is a province of approximately 1.1 million persons.<sup>16</sup> The only multidisciplinary motor neuron disease clinic is in the city of Saskatoon and is directed by one of the authors (K.L.S.). In general, all patients with motor neuron disease (including SBMA) in Saskatchewan are referred to this clinic for assessment. To attempt to account for all patients with SBMA in Saskatchewan, we reviewed data from the Saskatoon clinic and contacted other neurologists and physiatrists in Saskatchewan who care for patients with neuromuscular disease (listed in acknowledgements). Based on Saskatoon clinic database information, the clinic follows 29 patients with SBMA, 26 of which have self-declared Indigenous ancestry (personal communication, K.L.S.). None of the additional physicians contacted were actively following patients with SBMA, and if physicians had done so in the past, they had either already referred these patients to the clinic in Saskatoon or the patients had been lost to follow-up. To avoid potential duplication of patients, these former patients of colleagues were not included in the total numbers identified. We relied on participants recruited to our study to disclose how many additional family members they had who also had a confirmed diagnosis of SBMA. We used the most recent Statistics Canada population data from the 2016 census<sup>16</sup> as the denominators for our prevalence estimates.

### Recruitment of Participants

Our inclusion criteria included (1) confirmed diagnosis of SBMA based on clinical genetic testing, (2) age 18 years or older, and (3) ability to provide written informed consent. We identified participants from the clinics of 2 of the authors (K.L.S. and L.W.K.) as they presented for clinical follow-up over a 6-month period and invited them to participate. As part of this study, we also collected data including their age at onset (according to patient recollection and self-report), forced vital capacity, and SBMA Functional Rating Scale (SBMA-FRS) score.<sup>17</sup> We also recruited 5 male participants who did not have a diagnosis of SBMA, for purposes of providing control comparison data for our allele sizing assays.

### DNA Collection and Quality Control

Saliva samples were collected from all participants into Oragene OG-500 kits (DNA Genotek, Ottawa, Canada) according to the manufacturer's protocol. DNA was extracted according to the manufacturer's suggested protocols and DNA concentration/purity assessed with NanoDrop One Spectrophotometer (Thermo Fisher Scientific, Waltham, MA).

## Microsatellite Analysis

Using PCR and fluorescently labeled primers, we performed microsatellite sizing to determine the haplotypes. We used previously published primer sequences for the AR CAG disease expansion, the AR GGC repeat, and the DXS1194, DXS1111, DXS135, and DXS1125 microsatellites.<sup>9,18-23</sup> Primers for the microsatellite located in the DXS123 locus were created using Primer3web (primer3.ut.ee). All primer sequences and optimized protocols are available on request. Forward primers for each primer pair were labeled with either 5-FAM or CAL Fluor Gold 540 (Biosearch Technologies, Hoddesdon, United Kingdom).

PCR was performed using 20  $\mu$ L reaction volume and Phusion High-Fidelity DNA Polymerase (Thermo Fisher Scientific), according to the manufacturer's protocols, for 40–42 cycles. The amplification of unique products was confirmed with agarose gel electrophoresis. The amplified products were analyzed in duplex (5-FAM/CAL Fluor Gold 540) for cost-efficiency, using capillary electrophoresis (3730xl 96 capillary DNA Analyzer; Applied Biosystems, Waltham, MA). Fragment analysis was performed using Microsatellite Analysis Software (Applied Biosystems).

## Identification of Haplotypes

Fragment sizes were recorded, and haplotypes were manually reconstructed in tabular format for comparison between participants and for comparison with previously published data.<sup>10,11</sup>

## Allele Age Estimation

The time to the most recent common ancestor at the disease locus was estimated using a maximum likelihood method based on the length of the shared haplotypes across a group of patients.<sup>24</sup> Briefly, the likelihood that the pathogenic variation occurred  $n$  generations ago is estimated based on the probability that recombination events occurred on either side of the variant assuming a star genealogy.<sup>24</sup> The physical position of each locus on the X chromosome was identified from Ensembl. Genetic distance was estimated to be 1.272 cM/Mbp for the region based on the genetic distances of DXS1213 and DXS1194, from the archived Genethon human genetic linkage map in National Center for Biotechnology Information's retired ProbeDB.<sup>25</sup> Recombination fractions were calculated from genetic distance with Kosambi mapping function. Likelihoods were normalized across all tested generations (0–1,000) for graphical representation. When the longest haplotype where individuals share all but the furthest markers could not be identified from the sampled markers, recombination was assumed to occur at a recombination fraction of 0.5.

## Participant Engagement

On completion of the study, we offered all participants the opportunity to attend an online presentation. Our objective was to present study results to the research participants and receive direction from them regarding future directions for this work.

## Data Availability

Original data will be made available to any qualified investigator on request to the corresponding author. To protect the confidentiality of participants, data will be provided in aggregate and anonymized.

## Results

### Prevalence Estimation

Based on the review of the Saskatoon neuromuscular clinic database, we identified a total of 29 individuals with SBMA who were being followed by the Motor Neuron Disease Clinic in Saskatoon, 26 of whom reported Indigenous ancestry.

Using publicly available data from the most recent Canadian census in 2016 from Statistics Canada,<sup>16</sup> the total number of residents of Saskatchewan reporting single or mixed Aboriginal ancestry is 177,350. Therefore, we estimated the prevalence of SBMA among those of Indigenous descent in Saskatchewan as 14.7 per 100,000 population. The total number of Saulteaux in Saskatchewan (single or mixed ancestry) is 9,770, and in this study, 4 unrelated participants reported Saulteaux ancestry and 14 additional relatives with SBMA (Table). If this is correct, 18 patients with SBMA in a population of only 9,770 persons would equate to a prevalence of 184.24 per 100,000 population.

### Participant Recruitment and Clinical Data

As described in Methods, we recruited consecutive participants meeting our inclusion criteria over a 6-month period. A total of 23 participants with SBMA were recruited and provided DNA samples. None of the patients with SBMA attending our clinics in the study period declined participation. Of these, DNA from 21 participants met our DNA quality control criteria. Seventeen of these participants were from Saskatchewan, and 4 participants were from Calgary. All participants had a confirmed genetic diagnosis of SBMA and self-declaration of their ethnicity. None of the participants were known to be related to each other, except for participants 4 and 5 who identified as cousins.

Clinical data were available from 19 of the participants recruited to this study (including 2 participants who consented to participate but whose DNA samples failed quality control). Their data are summarized in the table. Their average age at onset was 39.2 years (range 25–65 years), and this was correlated with the size of their CAG repeat expansions (Figure 1A). Their average SBMA-FRS score was 31.5 (range 19–48) after an average disease duration of 16.3 years (range 3–34 years), and the SBMA-FRS score was correlated with disease duration (Figure 1B). When separating the bulbar and limb subscores of the SBMA-FRS (respectively, components 1–5 and 6–13), limb scores, but not bulbar scores, appeared to be correlated with disease duration (Figure 1, C and D). Participants of Indigenous descent who reside in the province of Saskatchewan totaled 14, and they reported an additional 23 relatives with confirmed diagnoses of SBMA.

**Table** Clinical Data Summary of Recruited Participants

ID	CAG expansion size	Onset age, y	Disease duration, y	SBMA-FRS (maximum score 56)	FVC (% predicted)	Other family with SBMA <sup>a</sup>	Ethnicity
1	55	26	25	33	65	0	Saulteaux
2	52	31	11	43	69	2	Cree
3	44	36	22	26	43	4	Cree/Saulteaux
4	52	32	25	27	73	3	Cree
5	52	37	15	39	51	1	Cree
6	54	25	26	22	55	7	Saulteaux
7	44	50	7	48	86	1	Cree
8	40						Indigenous
9	49					2	Cree/French
10	43	59	3	19	61	0	Cree
11	42	25	34	28	81	0	Cree
12	41	65	5	38	55	0	Cree
13	52	45	6	23	43	0	Cree
14	41	58	6	44	85	0	Czech
15	40	52	17	32	58	2	Swedish
16	40	31	4	46	90	1	Unknown
17	42						Northern European
18	41	40	10	28	76	1	Métis/European
19	44	45	17	30	61	2	Métis/English
20	41	40	23	37	77	2	Métis/Scottish
21	45						Indigenous
22 <sup>b</sup>	63	33	21	21	69	3	Saulteaux
23 <sup>b</sup>	51	41	15	40	72	5	Cree

Abbreviations: FVC = forced vital capacity; ID = participant number; SBMA-FRS = Spinobulbar Muscular Atrophy Functional Rating Scale. Blanks indicate that data were not collected/available for that metric/participant.

<sup>a</sup> As provided from individual participants, we asked them to state number of other family members with confirmed diagnosis of SBMA.

<sup>b</sup> Participant recruited to study, but DNA sample failed quality control.

## Haplotype Analysis

A summary of the results is presented in Figure 2. Thirteen of the participants (numbered 1–13) clearly shared a single haplotype, and all these participants declared themselves to be of Indigenous ancestry. As anticipated, participants 4 and 5 who are cousins shared an identical haplotype. Four additional participants (who did not report Indigenous ancestry) shared a small portion of this same haplotype, but it is possible that this could have occurred by chance. A second haplotype was identified in participants 18 and 19 who were not known to be related to each other and who also reported Indigenous ancestry. Two additional participants with SBMA did not share these haplotypes. The control participants all had unique findings and normal AR repeat lengths, which was expected.

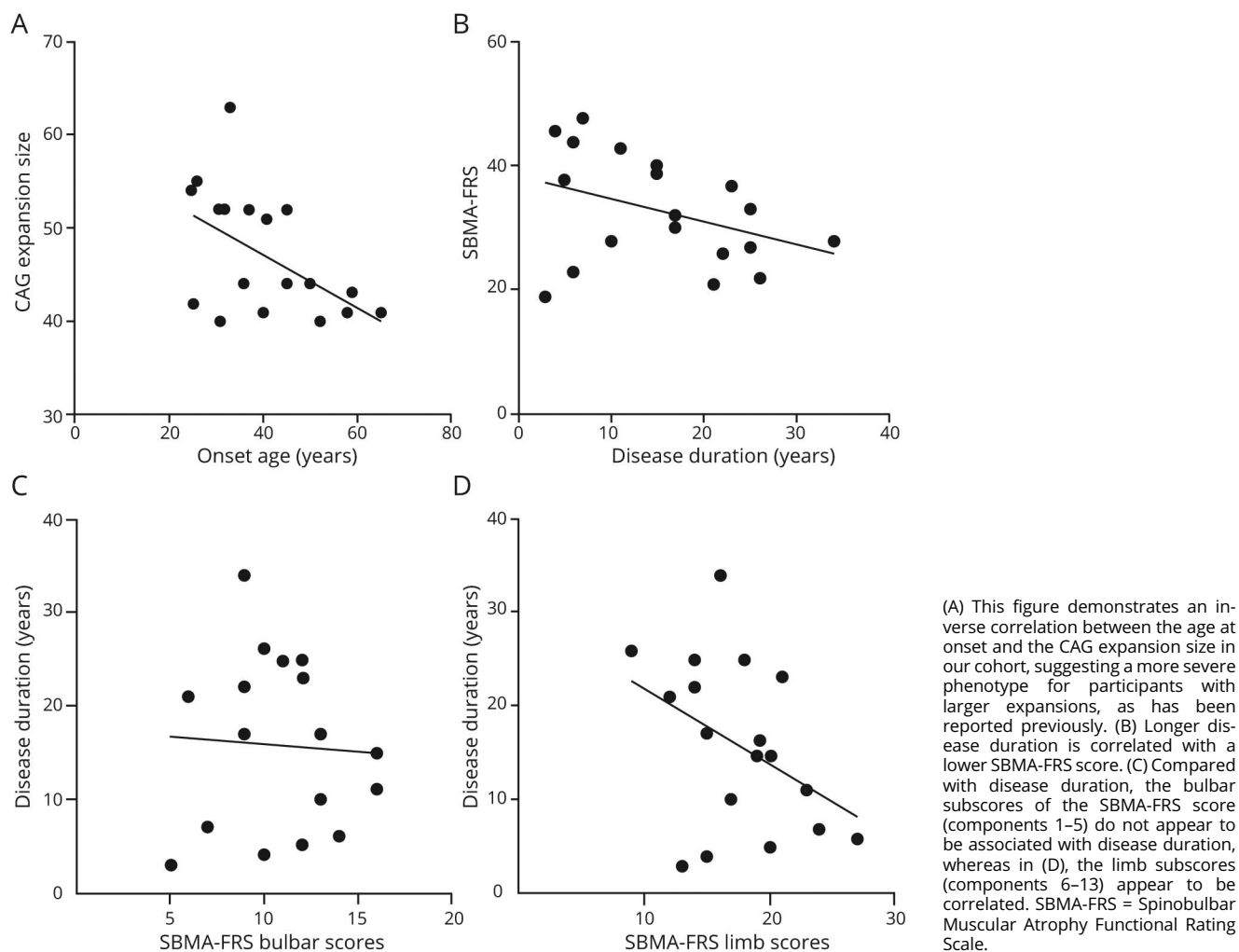
## Estimated Age of the Haplotype

The maximum likelihood age of the haplotype in participants 1–13 is 10 generations (95% confidence interval [CI]: 5–24 generations; Figure 3). Assuming a generation time of approximately 25 years, this would age the variant at 250 years (95% CI: 125–600 years). This is likely a liberally young estimate, given recombination of the X chromosome occurs predominantly in females.

## Participant Engagement

We invited all participants to an online meeting using a secure platform. This meeting was held in December 2020 and provided background regarding the project and a description of the research findings. Presentations from the researchers were 45 minutes in duration, and we had a further 30 minutes of discussion and questions. Feedback from participants

**Figure 1** Clinical Data in This SBMA Cohort



emphasized several themes, namely the need for future research to better understand the high SBMA prevalence in their communities, motivation to increase awareness of SBMA in their communities, and a need for additional resources to support individuals affected by SBMA. There was interest in connecting researchers with Indigenous Knowledge Holders, Elders and local community leadership to discuss the findings. There was also discussion of a patient- and community-led conference to raise awareness about SBMA and connect affected individuals with each other and necessary resources, including Indigenous Elders, Healers and Knowledge Holders. For all participants who could not attend the meeting, we mailed out a letter summarizing the findings and encouraging contact with any questions. Future engagement activities include an educational conference about SBMA, which is planned for spring of 2021.

## Discussion

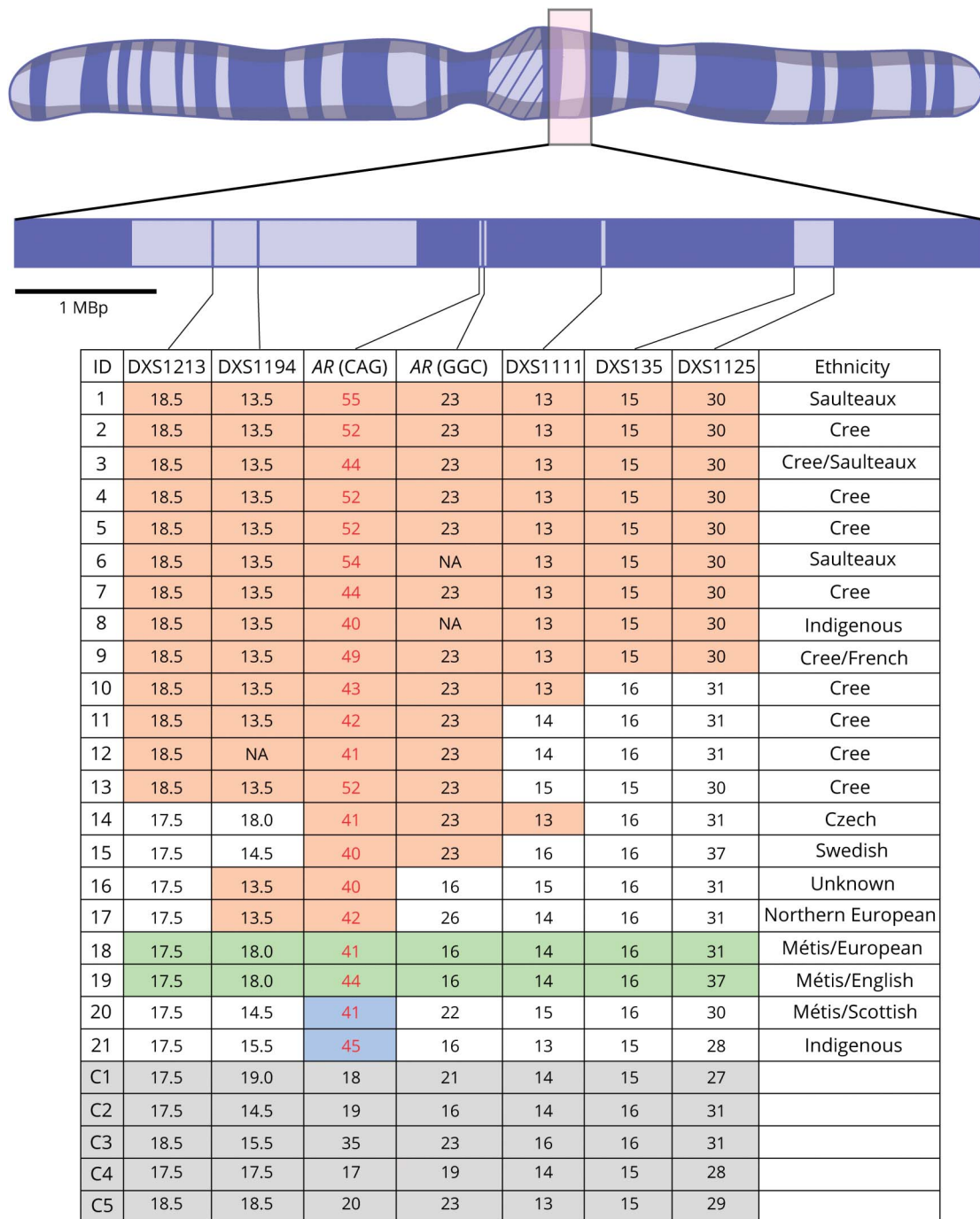
We report a very high prevalence of SBMA in Indigenous persons residing in Canada, which, our genetic analysis

indicates, is due to a founder effect, which may have originated or been introduced in this population approximately 250 years ago. Specifically, the majority of participants in our study report their descent as being from the Cree or Saulteaux nations. Because these nations are geographically distributed across several Canadian provinces and territories, this high prevalence and founder effect may exist in other parts of Canada. Indeed, 2 of the participants in this study (8 and 9) were recruited from the neighboring province of Alberta.

In this study, we estimated the prevalence of SBMA in Indigenous persons residing in Saskatchewan as being 14.7 per 100,000 population. This prevalence is several fold higher than the estimated global prevalence for this disease of 1–2 per 100,000 population. One of the expert reviews on SBMA states that it has not been described in Indigenous populations,<sup>26</sup> although in retrospect, SBMA has been identified in Indigenous people in scattered reports starting with the original description of this disease.<sup>11–15</sup> In Veneto, Italy, an elevated prevalence of 2.58 per 100,000 males (i.e., 1.29 per 100,000 population) was reported and attributed to multiple founder



**Figure 2** Manually Reconstructed Haplotypes From the Participants in This Study

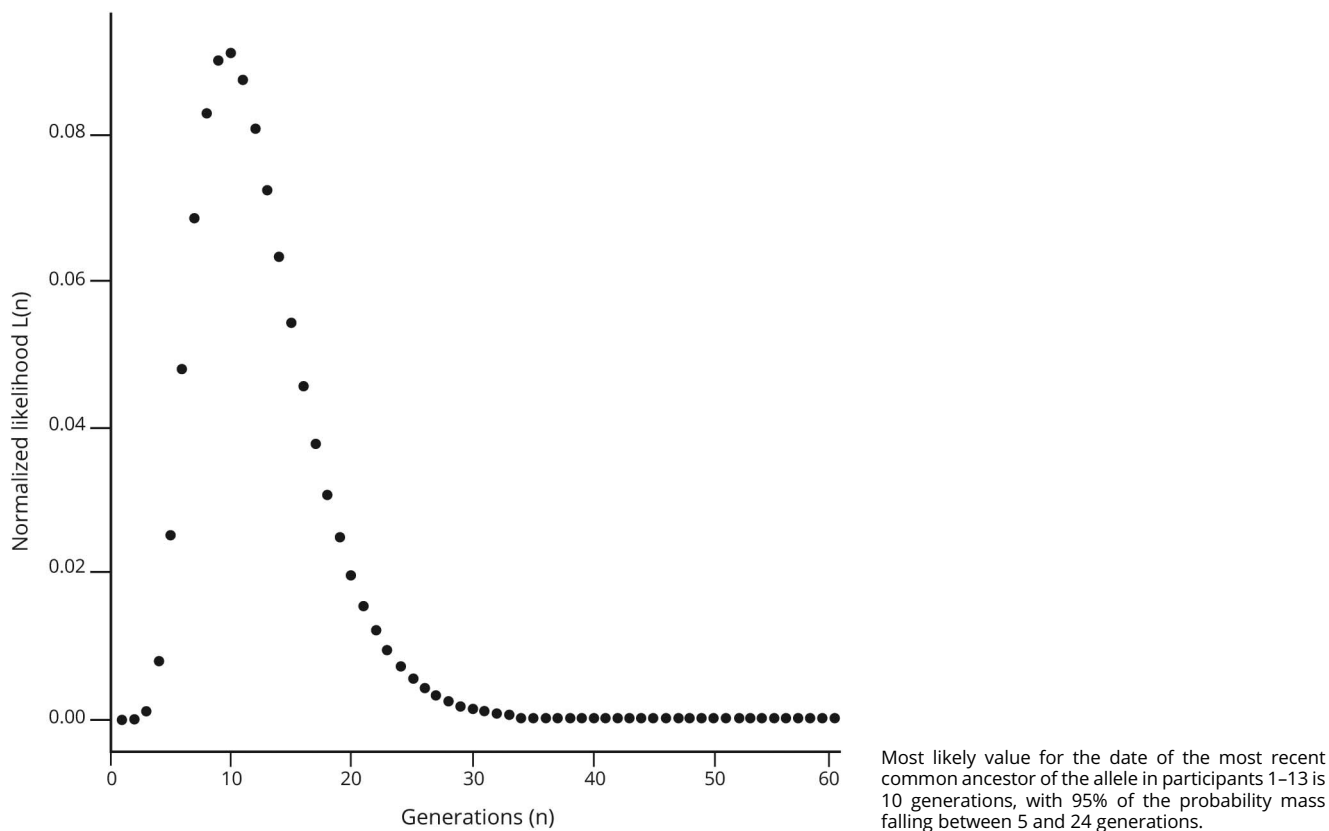


This figure demonstrates the location of the haplotype on the X chromosome and the loci of the different markers drawn to scale. The table represents allele sizes at different microsatellite loci, and AR repeat locations, for participants in this study. The mutant expansion in AR associated with SBMA is in the column designated "AR (CAG)." The shared haplotypes are shaded for ease of reference. In the "ID" column, participants numbered 1–21 have a diagnosis of SBMA, and their declared ethnicity is provided. Participants C1–C5 are control participants with other neuromuscular disorders (for comparison). Assuming the minimum number of recombinations, there may be up to 17 participants in this study who share a single haplotype, although for participants labeled 14–17, the small amount of similarity may have arisen by chance. Participants 18–19 appear to share a distinct haplotype. Two other participants (20 and 21) did not share either haplotype. For 2 of the participants, quantification of the AR GGC repeat failed and is represented as "NA" (not available). SBMA = spinobulbar muscular atrophy.

effects.<sup>8</sup> A founder effect has also been reported in Japan, although population prevalence estimates were not provided.<sup>9</sup> The highest previously reported prevalence for SBMA is in the Vasa region of Western Finland, of 13 patients for 85,000

males<sup>7</sup> (i.e., 7.65 per 100,000 population). If correct, the prevalence of SBMA in Indigenous people in Saskatchewan is nearly double this and could represent the highest described carrier rate for this disease in the world.

**Figure 3** Calculated Probability That the Pathogenic Allele Occurred at Each Generation



It should be emphasized that based on the approach we applied to ascertain SBMA cases in persons of Indigenous descent in Saskatchewan, our prevalence estimate is likely to be a substantial underestimate. This is also based on anecdotal observations that many affected family members of clinic attendees do not access the clinic and reports from colleagues that patients are frequently lost to follow-up. This question deserves further study to correctly identify the prevalence of this condition in these populations, ideally with the development of a Canadian disease registry for SBMA. This would identify populations and regions that would benefit from additional resources to support patients living with this chronic and disabling condition.

An important question to answer is whether the phenotype of Indigenous people who have SBMA differs from that which has been described in studies of other populations (recently reviewed<sup>27</sup>). The age at onset in our cohort was inversely correlated with the size of the expanded AR repeat, consistent with prior studies.<sup>28</sup> Based on the clinical data in our study (presented in the Table and Figure 1), our patient cohort appears to share similar clinical characteristics with previous studies, including the inverse correlation of CAG repeat size with onset age and the gradual accumulation of disability with longer disease duration. However, the small sample size, lack of longitudinal measurements, and determination of disease

onset based on participant recollection are limitations of the clinical aspects of this project. Future study will be required to confirm whether the phenotype of SBMA differs in these Indigenous populations.

This study defines the founder haplotype for SBMA in the majority of participants of Indigenous descent who were recruited. This haplotype was identified in participants recruited from both Saskatchewan and Alberta and as mentioned above may be more geographically widespread. A separate distinct haplotype is shared by 2 other participants reporting Métis descent, and future study may determine whether this haplotype is also responsible for a large proportion of SBMA cases in Métis and other Indigenous populations.

Previous studies have identified possible founder effects in different countries by studying the same 5 microsatellites.<sup>10,11</sup> However, the results yielded by these studies differ substantially from the typically reported microsatellite repeats reported for these markers. It is possible that methodologic differences contributed to these discrepancies. As a result, it was unfortunately not possible to compare results from our study to the previously described studies.

Some limitations of our study include the small sample size and the small number of participants with SBMA from other

populations. The finding of a major shared haplotype in most of the participants could have occurred if the participants are all in fact directly related to each other, but we believe this to be unlikely, especially given that 2 of the participants with the same haplotype resided in Alberta and were not aware of any relatives in Saskatchewan. For future studies, relatedness analyses and more thorough genetic investigations would be of value to give even greater confidence to the findings. Further investigation would also benefit from the inclusion of a larger number of ethnically matched controls. This may demonstrate whether the founder event occurred *de novo* on a common haplotype in Indigenous populations, or whether the haplotype is unique, which could provide information regarding the origins of the mutation.

The estimation of the age of the haplotype in this population preliminarily suggests that this is a fairly recent mutation in this population, occurring in the last 250 years. Despite the plausibility of this finding, it should be interpreted in light of the simplicity of the underlying method, which did not consider the potential effects of mutation, selection, population demography, or differential relatedness. Among 4 participants who share a small portion of the main common haplotype, 3 declared European descent. Further study would be required to confirm whether there is any possible relationship between this founder haplotype and European populations. Ideally, such future study would include large numbers of participants from diverse Canadian and international populations and apply more comprehensive genetic analyses. As we develop engagement with affected communities, we aim to incorporate Indigenous concepts of health in educational initiatives and future research.

There are significant health inequalities between Indigenous and non-Indigenous people in Canada, influenced by a variety of historical and sociopolitical factors.<sup>29</sup> Many Indigenous populations have reduced access to specialist assessment and testing<sup>30</sup> and have historically been underrepresented or even exploited in genetic research.<sup>31</sup> Recent efforts have attempted to engage and include Indigenous populations.<sup>32</sup> This may yet reveal other important genetic discoveries that could have an impact on the diagnosis and care for genetic conditions in Indigenous communities or other underserved populations.

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## Disclosure

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<b>Jamie N. Leckie, BSc</b>	University of Calgary, Alberta, Canada	Assay design, collection/analysis of laboratory data, and manuscript authorship
<b>Matthew M. Joel, BSc</b>	University of Calgary, Alberta, Canada	Data analysis and manuscript authorship
<b>Kristina Martens, BSc</b>	University of Calgary, Alberta, Canada	Assay design and collection/analysis of laboratory data
<b>Alexandra King, MD</b>	University of Saskatchewan, Saskatoon, Canada	Participant engagement activities and revision of the manuscript for intellectual content
<b>Malcolm King, PhD</b>	University of Saskatchewan, Saskatoon, Canada	Participant engagement activities and revision of the manuscript for intellectual content
<b>Lawrence W. Korngut, MD, MSc</b>	University of Calgary, Alberta, Canada	Clinical data analysis and identification of participants
<b>A.P. Jason de Koning, PhD</b>	University of Calgary, Alberta, Canada	Data analysis and revision of the manuscript for intellectual content
<b>Gerald Pfeffer, MD, PhD</b>	University of Calgary, Alberta, Canada	Conceptualization of the study, identification of participants, supervision of laboratory studies, and manuscript authorship



## Appendix (continued)

Name	Location	Contribution
<b>Kerri L. Schellenberg, MD, MMedEd</b>	University of Saskatchewan, Saskatoon, Canada	Conceptualization of the study, identification of participants, collection of clinical data, collection of prevalence data, and revision of the manuscript for intellectual content

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