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ORIGINAL ARTICLE

The incidence and carrier frequency of Tay-Sachs disease in the French-Canadian population of Quebec based on retrospective data from 24 years, 1992–2015

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Abstract

Tay-Sachs disease (TSD) is a hereditary neurodegenerative condition inherited through an autosomal recessive pattern. The incidence and carrier frequency of infantile TSD were found to be increased among French Canadians in specific areas of the province of Quebec or calculated from New England populations with French-Canadian heritage. No accurate infantile TSD carrier frequency for the whole French-Canadian population in Quebec has been published. In this study, we estimate the incidence and carrier frequency of infantile TSD in the Quebec French-Canadian population. The number of TSD cases was ascertained during the 1992–2015 period, as well as the number of births to mothers whose language of use is French. Seven cases of TSD have been diagnosed in Quebec during the period of ascertainment. This corresponds to an incidence of 1/218,144, which in turn corresponds to a carrier frequency of 1/234. In the same 24-year period, there are two French-Canadian couples who had a fetus prenatally diagnosed with TSD. If these cases are included, the incidence of TSD in the French-Canadian population of Quebec is 1/169,668 and the carrier frequency 1/206. These findings can be used for genetic counseling and policy decisions regarding carrier screening for TSD in populations of French-Canadian descent.

KEYWORDS

carrier, carrier testing, French-Canadian population, genetic counseling, genetics services, incidence, Infantile Tay-Sachs disease, population screening, preconception, Quebec, risk assessment

1 | INTRODUCTION

Tay-Sachs disease (TSD) is an autosomal recessive neurodegenerative disorder. It results from pathogenic variants in the *HEXA* gene that lead to deficient activity of the lysosomal β-hexosaminidase A enzyme (HEXA). HEXA consists of an α and a β subunit, encoded by the *HEXA* and the *HEXB* gene, respectively. When a patient is homozygous for a *HEXA* pathogenic variant, GM2 gangliosides are not hydrolyzed, accumulate in neuronal lysosomes and trigger progressive neuronal dysfunction, which begins around 2–6 months of age for infantile TSD and leads to complete disability and death, usually by 3–5 years of age (Gravel et al., 2001; Kaback & Desnick, 2001; Sutton, 2002). A diagnosis of infantile TSD is usually made before a child's third birthday on the basis of absent or significantly reduced level of HEXA activity measured through biochemical testing (Kaback & Desnick, 2001). Molecular analysis can confirm

biochemical test results, which is important to rule out false-positive results due to *HEXA* pseudodeficiency alleles (Kaback & Desnick, 2001).

Infantile TSD is known to have an increased incidence in some populations: A carrier frequency of 1 in 30 has been well established in the Ashkenazi Jewish population (Sutton, 2002) and was found to be increased among French Canadians from Eastern Quebec (Andermann et al., 1973; Andermann, Scriver, Wolfe, Dansky, & Andermann, 1977). There have also been different studies to estimate the carrier frequency of TSD among the French-Canadian population living in different areas, in particular among New England populations with French-Canadian heritage (Table 1). These calculations may, however, not be representative of the carrier frequency in the whole French-Canadian population in Quebec.

Several professional guidelines recommend which populations should be offered carrier screening for TSD. The Canadian Guidelines for Prenatal Diagnosis recommend carrier screening 'for individuals belonging to population groups known to have an increased risk' for TSD (Chodirker et al., 2001). The Canadian Guidelines for Reproductive Genetic Carrier Screening advise that carrier screening for TSD be offered to individuals who 'present a geographic connection to [the Bas-St-Laurent and Gaspésie regions as well as adjacent New-Brunswick territories] or have a family history of this condition' (Wilson et al., 2016). In the United

TABLE 1 List of publications that quote carrier frequencies for infantile TSD in various non-Jewish populations

Reference	Carrier frequency of infantile TSD	Population considered	Method or reference used to calculate or quote carrier frequency
Myrianthopoulos (1962); Myrianthopoulos and Aronson (1967)	1/380–1/300	Population in the United States or in certain areas of the United States.	Incidence of affected children in the 1940s and 1950s.
Andermann et al. (1973)	1/172	Whole French-Canadian population.	No details available about the calculations.
	1/69	Population in areas of Quebec where the incidence of TSD is more important.	No details available about the calculations.
Andermann et al. (1977)	1/13	Population in areas of Quebec where the incidence of TSD is more important.	Biochemical carrier screening done on volunteer distant relatives of confirmed infantile TSD cases and their supposedly unrelated spouses.
	1/34	Population in areas of Quebec where the incidence of TSD is more important.	Incidence of TSD. No precise details are available about the calculations.
Kaback et al. (1993)	1/277	Volunteer individuals in California.	Biochemical carrier screening. Corrections were made to account for the presence of pseudodeficiency alleles.
Triggs-Raine et al. (1995)	1/53	New England residents with French-Canadian background.	Biochemical carrier screening.
Van Bael, Natowicz, Tomczak, Grebner, and Prence (1996)	1/192–1/52	Non-Jewish Americans with Irish background.	Biochemical carrier screening.
	1/53	New England residents with French-Canadian background.	Carrier frequency derived from Triggs-Raine, 1995.
Prence et al., 1997	1/120–1/46	Massachusetts residents with French-Canadian background.	Biochemical carrier screening.
Chodirker et al. (2001) (Canadian Guidelines for Prenatal Diagnosis)	1/14	French Canadians in Eastern Quebec.	Carrier frequency derived from Andermann, 1977.
	1/98–1/41	French Canadians outside of Eastern Quebec.	Carrier frequency derived from Prence, 1997.
Martin et al. (2007)	1/90–1/49	New England residents with French-Canadian background.	Biochemical carrier screening.
Wilson et al. (2016) (Canadian Guidelines for Reproductive Genetic Carrier Screening)	1/14	French Canadians from the Bas-St-Laurent and Gaspésie regions as well as individuals originating from adjacent New Brunswick territories.	Carrier frequency derived from Andermann, 1977.
American College of Obstetricians and Gynecologists (ACOG) Committee on Genetics (2017a)	1/50	Individuals of French-Canadian descent.	Carrier frequency derived from Van Bael, 1996.

States, the American College of Obstetricians and Gynecologists recommends that carrier screening for TSD should be offered when considering or during pregnancy if either member of a couple is of French-Canadian descent (American College of Obstetricians & Gynecologists, 2017a).

In the province of Quebec, TSD carrier screening is generally not offered routinely to French Canadians in any region. As a public health initiative, carrier screening for TSD has been offered through a few field trips to people living in three villages where the incidence of TSD is elevated. TSD carrier screening through biochemical testing is also offered by the Medical Genetics service in Quebec city to individuals from the Portneuf region. Based on Canadian Guidelines (Wilson et al., 2016), carrier screening should be offered to any individual who originates from the Bas-St-Laurent and the Gaspésie regions when they present in one of the Medical Genetics services in the province. When offered, carrier screening is usually done first through biochemical testing. If a carrier couple is identified through biochemical testing, molecular testing would have to be done to exclude the common pseudodeficiency allele and to identify the pathogenic variants, which is necessary for preimplantation genetic diagnosis or prenatal diagnosis.

Outside of Quebec, whether it is in another Canadian province or in the United States, carrier screening is often offered to any French-Canadian individual, regardless of their specific region of origin. This may be because populations are becoming increasingly mobile and geographic origins are not always known. An accurate carrier frequency of infantile TSD among the whole French-Canadian population in Quebec is needed to develop a rational approach to genetic counseling and carrier screening of individuals of French-Canadian descent, especially in healthcare settings where resources are limited and where expanded carrier screening is not necessarily the norm. In this study, we estimate this carrier frequency by using disease incidence during the 1992–2015 period.

2 | METHODS

This study was approved by the McGill University Health Center (MUHC) Research Ethics Board and by the Ste-Justine Hospital (SJH) Research Ethics Committee. The aim of this study is to identify all the new cases of infantile TSD among French-Canadian children and prenatal TSD cases in the Quebec province during the 1992–2015 period. Children born in this period, covered by the Quebec public healthcare system and with a potential diagnosis of TSD would have been tested only at the MUHC and/or at SJH. Prenatal diagnosis samples for TSD would have also been analyzed in one of these two centers. Although very unlikely, it is theoretically possible that cases from different parts of the province and ascertained in different Medical Genetics services could have been tested in another center. However, it was confirmed upon communication with the Medical Genetics service of Quebec city, Chicoutimi, Sherbrooke and of the Children's Hospital of Eastern Ontario (which is located in the province of Ontario but where Quebec patients can go for healthcare services) that if such a case presented to them, samples for biochemical and/or molecular testing would have been sent to the MUHC or SJH.

To ascertain the number of confirmed TSD cases, records at the MUHC molecular genetics laboratory and at the MUHC and SJH biochemical genetics laboratories were searched. Using the laboratory chart for each case and, if necessary, the corresponding hospital chart, the following information was collected, if available: birth date, ethnicity, paternal and maternal region of origin, date of molecular testing, *HEXA* pathogenic variants, paternal and maternal origin of the pathogenic variant, test results of biochemical analysis in plasma, leukocytes or fibroblasts, and family names of all the proband's relatives mentioned in the chart. The proband's MUHC molecular genetics laboratory chart contains test requests for the proband and his/her relatives seeking cascade testing. These test requests ask for the ethnicity and the region of origin of the tested individual. If the proband's ethnicity or region of origin was not available, this information could be deduced from his/her relatives' test requests. Family names of the proband's relatives were recorded in the laboratory chart either when the initial pedigree was drawn, or when relatives came to the attention of the laboratory.

The results of biochemical and molecular testing performed for prenatal diagnosis of TSD, either by chorionic villus sampling (CVS) or by amniocentesis, were also ascertained and the following information was collected from either the laboratory or the hospital chart for each affected pregnancy, if available: date of amniocentesis or CVS, ethnicity, paternal and maternal region of origin, *HEXA* pathogenic variants, paternal and maternal origin of the pathogenic variant, biochemical test results, and family names of all of the proband's relatives mentioned in the chart.

Cases identified from the laboratory charts were only included in the study if they met the following criteria: First, the affected individual or pregnancy had to be referred from within the province of Quebec. Second, at least one parent of the affected individual or pregnancy had to be of French-Canadian descent. Finally, affected individuals or pregnancies had to be diagnosed at the molecular level between 1992 and 2015 inclusively. Molecular testing at the MUHC molecular genetics laboratory was not done routinely before 1992 so cases before this date were not included. Cases diagnosed after 2015 were excluded, as all affected individuals born after 2015 would not necessarily have been diagnosed yet.

In order to calculate the incidence of TSD among French-Canadian couples in Quebec, we considered the number of all TSD cases in the 1992–2015 period. Verifications were made in order to know whether families were independent of each other. First, it was checked whether any mention of a family history of TSD appeared in any of the proband's charts. Second, all the different family names that were recorded in each of the proband's charts were compared to each other to check whether they were different (women in Quebec keep their family name when married). As a denominator for the calculation of incidence, the number of births to mothers whose language of use is French (Institut de la statistique du Québec, 2017a) was chosen as a proxy to estimate

the number of births of French-Canadian descent in Quebec. The confidence intervals for the incidence were calculated considering that this incidence was the mean of a Poisson distribution and using a 95% confidence interval (CI). The Hardy–Weinberg equation allowed to deduce carrier frequency from the incidence value. The CI of the carrier frequencies was calculated by applying the Hardy–Weinberg equation to each limit of the CI of the incidence. This equation allows to perform such a calculation in a large population if two partners in this population meet randomly and if there is no selection of a specific allele, no migration, no new pathogenic variants, and no genetic drift (Nussbaum, McInnes, Willard, Hamosh, & Thompson, 2007).

In order to check whether TSD carrier couples other than the parents of the affected children were identified during the period of ascertainment, and if they could have opted for prenatal diagnosis, preimplantation genetic diagnosis, or possibly another method to have children, the records of the MUHC molecular genetics laboratory and of the SJH biochemical genetics laboratory were searched. All TSD carriers were recorded in the 1992–2015 period and the following information was collected, if available: birth date, ethnicity, date of biochemical and molecular testing, results of biochemical testing, *HEXA* pathogenic variants and possible link to an affected TSD case. It was not possible to search the MUHC biochemical genetics laboratory, as records in the period of ascertainment were not computerized and it was not possible to search manually for biochemical carrier test results and for possible familial links between carriers.

The frequency of the different *HEXA* pathogenic variants in the general population was compiled from the Genome Aggregation Database (gnomAD) (Lek et al., 2016) The Database of Genomic Variants was also consulted (MacDonald, Ziman, Yuen, Feuk, & Scherer, 2014).

3 | RESULTS

Between 1992 and 2015, seven cases of infantile TSD were diagnosed through molecular testing in Quebec (Table 2). Biochemical test results are available for six of these cases. For the other case, results were not available in the paper records of the MUHC or of SJH.

In the same 24-year period, two TSD cases were diagnosed prenatally to a Quebec French-Canadian couple. One prenatal diagnosis (case 3) was done for a French-Canadian couple who had a child diagnosed with TSD in 1981. The second prenatal case was a sibling of case 2. Prenatal diagnosis for this case was made only through biochemical testing. Even though the name of the father of this prenatal case could not be found in medical records, we presume that the father of this pregnancy was the same as the father of case 2 and that the fetus had the same genotype as case 2. The two affected pregnancies were terminated. The parents of case 1 also had prenatal diagnosis for a few pregnancies after their child was diagnosed with TSD, but none of these pregnancies were affected.

All of the nine cases from 8 distinct families diagnosed prenatally or postnatally and taken into consideration for the calculations were referred from within the Quebec province. All couples were fully of French-Canadian descent. Regional descent was available for both parents for six of these nine cases. Regional descent was available for at least one parent for all nine cases.

Verification to ensure that the seven postnatal cases were unrelated was done within the limitations of what was reported in their charts. There was no mention of a family history of TSD in any of these cases' chart. When considering family names recorded in each case's chart, one identical family name was recorded for a carrier individual in the pedigree of both case 3 and case 5. However, the relative of case 5 received the 7.6 kb deletion from her mother's side, who had a different family name. It is therefore unlikely that case 3 and case 5's families are related to each other. For cases 5 and 6, an identical family name was also found in a relative in each pedigree. The *HEXA* pathogenic variants are different for these two cases, so these two cases are not related to each other. Finally, for cases 2 and 8, the family name of the probands was similar (without being identical) so there was a suspicion that these two cases could be related. Again, the *HEXA* pathogenic variants are different for these two cases, so they are not related to each other.

The total number of births to French-speaking mothers was 1,527,012 between 1992 and 2015 inclusively (Institut de la statistique du Québec, 2017a). If we take into consideration seven postnatal cases of TSD, this corresponds to an incidence of 1/218,144 (CI: 1/542,455–1/105,858), which in turn corresponds to a carrier frequency of 1/234 (CI: 1/369–1/163). If we take into consideration the TSD cases diagnosed prenatally, the incidence of TSD for nine cases in the Quebec French-Canadian population is 1/169,668 (CI: 1/371,084–1/89,377) and the carrier frequency 1/206 (CI: 1/305-1/150). It was not possible to calculate disease incidences and carrier frequencies for the different regions of Quebec, since the number of births to French-speaking mothers by regions of Quebec is not available for the 1992–2015 period. It would also have been difficult to have meaningful results as many of the probands' parents came from different regions.

Between 1992 and 2015, 135 carriers were identified in the MUHC molecular laboratory. Out of this group, 57 carriers (42%) were identified in the families of one of the nine cases mentioned above, following the diagnosis of TSD in the proband. The remaining identified carriers (78 individuals or 58%) would have been identified through field trip screening sessions in three villages where the incidence of TSD was known to be elevated, or through screening because of the individual's region of origin, as recommended by Canadian screening guidelines. No carrier couple was identified in this group of 135 individuals, other than the parents of our probands. In the SJH biochemical genetics laboratory, 57 TSD carriers were identified between 1992 and 2015. It was not possible to know how many of them also had molecular testing and could be part of the group of 135 carriers identified in the molecular laboratory. It was not possible either to know what proportion of this group of 57 individuals was tested following the identification of TSD in a proband and what proportion was identified through population screening.

TABLE 2 List of patients or pregnancies diagnosed with infantile Tay-Sachs disease between 1992 and 2015 in a French-Canadian family

Patient identifier	Year of diagnosis	Age at time of molecular diagnosis	Paternal pathogenic variant	Maternal pathogenic variant	Biochemical test results (% of HEXA activity; plasma [P], leukocytes [L], fibroblasts [F] or amniocytes [A][a])	Paternal geographical origin	Maternal geographical origin
1	1992	2 years	c.805+1G>A	7.6 kb deletion	Not available	SLSJ	SLSJ
2	2003[b]	1 year 1 month	7.6 kb deletion	7.6 kb deletion	1 [L]; 7 [F]	Bas-St-Laurent	Bas-St-Laurent
3	1995	Affected fetus diagnosed through CVS	7.6 kb deletion	7.6 kb deletion	Not available	Father of the fetus born in Grand Falls, N.B.	Mother of the fetus born in Grand Falls, N.B.
4	1996	Affected fetus diagnosed through amniocentesis	Presumed 7.6 kb deletion[c]	Presumed 7.6 kb deletion[c]	2 [A]	Bas-St-Laurent (likely same father as case 2's)	Bas-St-Laurent (same mother as case 2's)
5	1996	1 year 7 months	7.6 kb deletion	7.6 kb deletion	4 [F]	Côte-Nord	Côte-Nord
6	2001	1 year 1 month	c.237_253+7del	c.805+1G>A	1.5 [P]	Outaouais	SLSJ
7	2002	1 year 5 months	7.6 kb deletion	7.6 kb deletion	1 [L]	Not available	Bas-St-Laurent/ N.B.
8	2002	1 year 5 months	c.237_253+7del	c.508C>T	12 [P]; 3 [L]	Portneuf	Not available because mother was adopted
9	2013	2 year 5 months	7.6kb deletion	c.237_253+7del	3 [L]	Not available	Quebec city/ Bas-St-Laurent/ Gaspésie

Abbreviations: CVS, chorionic villus sampling; N.B.: New Brunswick, SLSJ: Saguenay-Lac-St-Jean.

[a]The percentage of HEXA activity is expressed in reference to a control sample. HEXA activity in leukocytes and amniocytes was measured with a sulfated substrate.

[b]This proband was born in 1994 and was diagnosed through biochemical testing in 1995. Molecular confirmation was done in 2003 when the baby's parents came to the attention of a Medical Genetics service again.

[c]This proband has the same mother as case 2's. Even though the name of the father could not be found in medical records and even though the diagnosis for this proband was done only through biochemical analysis, we presume that the fetus has the same parents and the same genotype as case 2's (see the 'Results' section in the main text).

TABLE 3 List of *HEXA* pathogenic variants more frequent in the French-Canadian population

Pathogenic variant	Other name used	Amino-acid change	Number of alleles reported among Europeans (non-Ashkenazi Jewish, non-Finnish)	Total number of European alleles tested (non-Ashkenazi Jewish, non-Finnish)	Source of information
c.805+1G>A	IVS7+1G>A	-	1	111,690	gnomAD (old version)
c.508C>T	-	p.Arg170Trp	2	126,500	gnomAD (old version)
c.237_253+7del	-	-	1	111,416	gnomAD (old version)
c.1274_1277dup	1278insTATC	p.Tyr427Ilefs	48	126,682	gnomAD (old version)
c.–2564_253+5128delinsG	7.6 kb deletion	-	Absent in ExAC and the Database of Genomic Variants		

In this group of 57 carriers, it was confirmed that both partners of 3 couples had biochemical results that could be compatible with TSD carrier status (other than the parents of the probands). However, molecular testing was not done to confirm or rule out carrier status. It is possible that some other carrier couples were identified among this group of 57 individuals, but test requisitions and results do not systematically identify partners and it was not possible to review paper records to confirm this or rule it out.

The allele frequency in Europeans of the pathogenic variants that are more commonly found in the general French-Canadian population is available in Table 3.

4 | DISCUSSION

This study aimed to determine the incidence and the carrier frequency of TSD among French Canadians in the province of Quebec by ascertaining the total number of TSD cases in the 1992–2015 period. This was done by reviewing the charts of the only three laboratories that diagnose TSD in the province. Access to healthcare services in Quebec is universal and has been publicly funded since the 1970s so it is highly unlikely that any child with TSD would have remained undiagnosed during the period of ascertainment. Although allele frequencies are available in public databases for certain populations, such public data do not exist specifically for the French-Canadian population. Disease incidence and the Hardy–Weinberg equation were therefore used to calculate *HEXA* allele frequency in this population.

If we consider the nine prenatal and postnatal cases of TSD ascertained in the 1992–2015 period, this corresponds to an overall incidence of TSD of 1/169,668 and an overall carrier frequency of 1/206 among Quebec French Canadians. In clinical practice, few TSD carriers are identified through screening in the different Medical Genetics centers in Quebec, if we exclude cascade testing in families where a child was diagnosed with TSD. Identifying few carriers is consistent with our low calculated carrier frequency. This carrier frequency is also slightly lower than the frequency of 1/172 estimated by Andermann et al. for the whole French-Canadian population (Andermann et al., 1973; Table 1). It is, however, much lower than the carrier frequencies that have been generally quoted in the scientific literature.

4.1 | Geographic origin of alleles and founder effect

Given that we recorded the paternal and maternal regional descent of the different cases, and the paternal or maternal origin of the different pathogenic variants, we are able to comment on the regional origin of the pathogenic variants of our nine probands (Figure 1). The 7.6 kb deletion was recorded in 12 alleles out of 18 in the nine probands, which represents 67% of the recorded alleles. This is in accordance with the literature that describes that this deletion represents the majority (about 80%) of pathogenic alleles responsible for TSD among French Canadians (Triggs-Raine, Richard, Wasel, Prence, & Natowicz, 1995). Existing data also determined the Bas-St-Laurent and Gaspésie regions within the province of Quebec as the origin of this pathogenic allele (De Braekeleer, Hechtman, Andermann, & Kaplan, 1992). Even though some of our cases who harbored this deletion were reported being partly from this region, some others were also reported being from other regions such as Saguenay-Lac-St-Jean (SLSJ), Côte-Nord, and New Brunswick (Figure 1). This may reflect the migration of some of the families from the Bas-St-Laurent/Gaspésie region to other regions in the last decades. The c.805+1G>A allele is reported in the two probands who were reported to be from SLSJ. This is in concordance with the literature describing this variant originating in SLSJ (Hechtman et al., 1992). The c.508C>T variant was traced to French Canadians originating from the Estrie region (Fernandes et al., 1992). This variant was identified in one of our probands, who inherited it from his mother. Since she was adopted, no information is available on her region of origin. No information could be found in the literature about the putative region of origin of the c.237_253+7del variant, identified in three of our probands. Another pathogenic variant, c.1274_1277dup, was shown to be more frequent in the French-Canadian population (Hechtman et al., 1990), but was not identified in any of our probands.

Our carrier frequency of 1/206 for infantile TSD among Quebec French Canadians is slightly higher when compared to the carrier frequency range of 1/380–1/277 postulated for the Non-Jewish population of the United States. This could be explained by the presence of pathogenic variants that are specific to the French-Canadian population. In fact, the most common pathogenic variant (7.6 kb deletion) was actually never identified in French individuals from

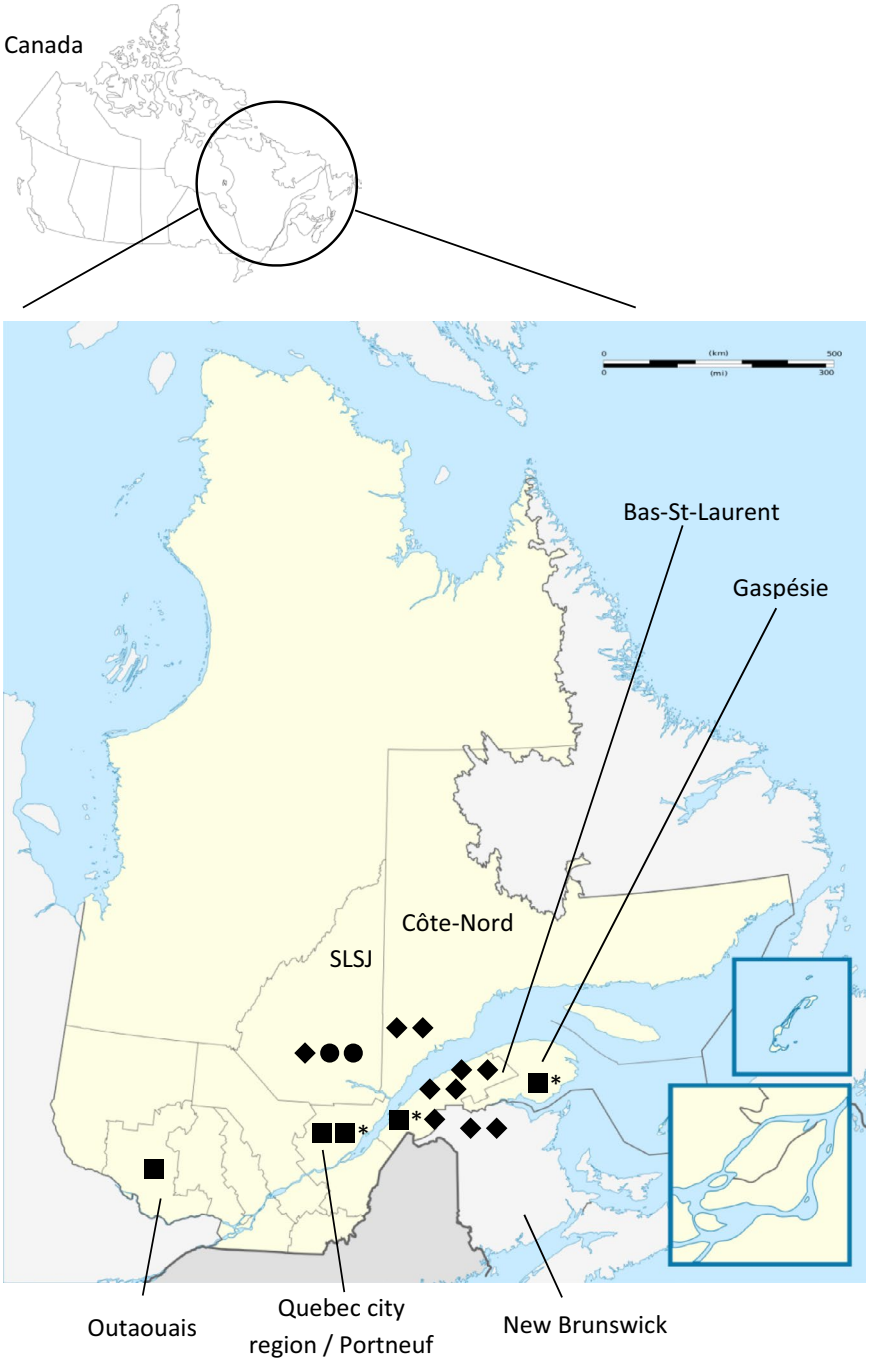

FIGURE 1 Geographic origin of the pathogenic variants identified in the 9 cases of infantile Tay-Sachs disease. This map shows the province of Quebec subdivided in different regions. SLSJ: Saguenay-Lac-St-Jean; ◆: 7.6kb deletion; ■: c.237_253+7del pathogenic variant; ● : c.805+1G>A pathogenic variant. The region of origin is available only for 15 alleles (among the 18 alleles recorded in table 2). The mother of patient 7 stated that her family is from Bas-St-Laurent and New-Brunswick, hence one diamond symbol (◆) being in between these two regions. The mother of patient 9 stated that her family is from the Quebec city, Bas-St-Laurent and Gaspésie regions. The ■* symbol represents her allele and is present in these 3 regions on the map, but actually represents only one allele.

France and is postulated to have appeared in the French-Canadian population after the colonization of the province by the French (De Braekeleer et al., 1992). This hypothesis would be in accordance with the fact that this variant was not found among Europeans in the ExAC database and the Database of Genomic Variants. A founder effect may have also occurred for some or all of the other three pathogenic variants identified in our probands. If we consider our incidence of 1/169,668, this corresponds to an allele frequency of any pathogenic variant in the *HEXA* gene of 1/411. Since the 7.6 kb deletion could represent 80% of pathogenic alleles in the French-Canadian population, the allele frequency of all other pathogenic alleles would be 20% of 1/411, or 1/2,057. If the number of alleles reported in the gnomAD database for the three other variants identified in our probands is compiled among Europeans, an allele frequency of 4/349,606 is found, or 1/87,401 (Table 3). The allele frequency of these three variants is higher in Quebec than in the European population reported by the gnomAD database, suggesting a founder effect for some or all of them.

Since the number of births to French-speaking mothers is not available per region within Quebec, it is not possible to determine the exact TSD carrier frequency per region. It is, however, expected to be higher in some regions due to the founder effect(s) described above, in particular in the Bas-St-Laurent and Gaspésie regions. We can also postulate that the regional TSD

carrier frequency in these two regions decreased over time due to migration out of these regions, in particular for the 7.6 kb deletion that was historically described as originating from there. If we consider interregional migrations within the province of Quebec, official statistics show that the net migration from Bas-St-Laurent and Gaspésie to another region has been almost constantly negative between 2001 and 2015 (official data before 2001 are not available; Institut de la statistique du Québec, 2019a). Although the loss of population in these two regions can seem marginal over this period (2.2% and 3.5% for Bas-St-Laurent and Gaspésie, respectively), it is possible that migration out of these regions played a role in the dissemination of TSD carriers in other regions of Quebec, especially if this migration trend started and was more important before 2001. In fact, a recent thesis by St-Laurent tends to confirm this hypothesis and reports that individuals have emigrated from the Bas-St-Laurent and Gaspésie regions at least since 1991 (St-Laurent, 2010). Our study actually also showed that the 7.6 kb deletion allele was found in parents of probands that came from other regions than Bas-St-Laurent and Gaspésie. Since official interregional migration data are not available before 2001, since the number of births to French-speaking mothers is not available per region, and since the number of TSD probands is very small on a regional scale, it is not possible to estimate the variation of the regional carrier frequency that interregional migration could have caused.

The presence of a clear founder effect for some pathogenic variants in some areas of Quebec is consistent with a higher carrier frequency in the whole Quebec province compared to the carrier frequencies available in the literature for the non-Jewish, non-French-Canadian population of the United States and that range from 1/380 to 1/277 (Kaback et al., 1993; Myrianthopoulos, 1962; Myrianthopoulos & Aronson, 1967; Table 1). However, our calculated carrier frequency is much lower than other carrier frequencies available in the literature. This could have been due to a selection bias by studying populations that are not representative of the Quebec French-Canadian population, and therefore leading to an overestimation of the carrier frequency.

4.2 | Limitations of previous studies

Carrier frequencies for infantile TSD in populations of French-Canadian descent living in New England were calculated to be between 1/120 and 1/46 (Table 1) but these numbers could have been overestimated. Two pseudodeficiency alleles have been shown to account for approximately 38% of biochemically defined non-Jewish carriers (Cao et al., 1993). Triggs-Raine et al. estimated the carrier frequency to be 1/53 among French Canadians living in New England based on biochemical carrier screening (Triggs-Raine et al., 1995). This number could have been an overestimation as there are for example no details about which individuals were selected to be tested, and whether any correction was made for the presence of pseudodeficiency or non-infantile TSD alleles. Prence et al. estimated the carrier frequency to be between 1/120 and 1/46 among individuals with French-Canadian background living in Massachusetts based on biochemical carrier screening (Prence, Jerome, Triggs-Raine, & Natowicz, 1997). A recruitment bias may have been present as the individuals tested were volunteers. Also, even though the authors did not take into consideration for their calculation the probands with benign *HEXA* variants, they included probands for whom no molecular analysis was done, and who could have had pseudodeficiency or non-infantile TSD alleles. Martin et al. estimated the carrier frequency to be between 1/90 and 1/49 among individuals with French-Canadian background living in New England based on biochemical carrier screening (Martin, Mark, Triggs-Raine, & Natowicz, 2007). A recruitment bias may have also been present as the individuals tested were volunteers. The authors discussed the exclusion of benign *HEXA* variants from their calculation and therefore reduced their calculated carrier frequency from an average of 1/65 to 1/73. However, they still included in their calculation individuals who had a positive biochemical screening test and for whom either no molecular analysis was done, no *HEXA* pathogenic variant was found, or a variant of uncertain significance was identified. In all of these studies, it is not mentioned either whether relatives of carriers were removed, as if multiple individuals from the family of a proband or carrier were tested, this would have artificially increased the authors' calculated carrier frequency. Finally, available information on the geographic origins of individuals who emigrated from Quebec to New England in the 19th century suggests that the Bas-St-Laurent region contributed significantly to this wave of immigration (De Braekeleer et al., 1992), which introduces another bias. Carrier frequencies derived from a subset of the French-Canadian population cannot be generalized for the whole Quebec French-Canadian population.

Various carrier frequencies in the French-Canadian population in Quebec have been given in the literature. Andermann et al. quoted in 1973 a carrier frequency of 1/172 among the whole French-Canadian population and of 1/69 in areas where the incidence of TSD was the most important (Andermann et al., 1973). There is, however, no mention in this article of how the authors calculated these carrier frequencies. Another article by Andermann et al., published in 1977, is often cited to discuss the TSD carrier frequency in the French-Canadian population (Andermann et al., 1973). These authors identified eight TSD cases over 10 years in Eastern Quebec. The first carrier frequency that they quote, 1/13, was determined following biochemical carrier screening done in three small towns on volunteer distant relatives of the probands and these relatives' 'supposedly unrelated' spouses. Different factors may have skewed this calculation. First, the authors note that many individuals in this area can be related to a proband in multiple ways, and that these 'supposedly unrelated' spouses may actually have a mean degree of relationship with a proband between the 4th and the 5th degree. Second, the presence of pseudodeficiency alleles could have altered the results. Third, there may have been a selection bias due to the inherent non-randomness of the screening sessions, which offered screening only to volunteers. The authors also quote a carrier frequency of 1/34 in the communities where their probands were identified, based on disease incidence. We could not find, however, any precise calculation of this frequency.

In conclusion, based on available data, we consider that a carrier frequency of 1/13 may be an overestimate of the carrier frequency for infantile TSD in Eastern Quebec and that other available frequencies are likely not representative of the actual carrier frequency in the whole Quebec French-Canadian population.

4.3 | Limitations of this study

Even though we consider that our calculated carrier frequency of 1/206 for the whole Quebec French-Canadian population is realistic, there are a few potential biases and limitations that could have influenced our calculations.

First, it is theoretically possible that over the past few decades, the awareness of genetic disease and the knowledge of the risk of having a child with TSD increased in the communities that were historically more affected. This could have led carrier couples to seek genetic counseling before starting a family and possibly pursue preimplantation genetic diagnosis, gamete donation, prenatal diagnosis, adoption, or choose not to have children. The incidence of TSD may have decreased as a result. In fact, we know that at least three families sought prenatal diagnosis after having a child with TSD (families of cases 1, 2/4 and 3). However, on a population scale, it is unlikely that carrier screening as it is currently put in practice had any major impact on the incidence of TSD. As discussed above, only 78 carriers were identified through carrier screening in the MUHC molecular genetics laboratory outside of the families of the 9 probands of this study. No carrier couple was identified in this group of individuals, so carrier screening did not lead to preimplantation genetic diagnosis or prenatal diagnosis during the 1992–2015 period. During the same period, both partners of three couples had biochemical results at HSJ that could be compatible with TSD carrier status, but did not have confirmatory molecular testing. They could therefore be carriers of a pseudodeficiency allele. Other carrier couples may have been identified through biochemical testing, but this could not be confirmed with absolute certainty. It is theoretically possible that these couples did not opt for preimplantation genetic diagnosis or prenatal diagnosis, and decided to opt for gamete donation, adoption or chose not to have children. This could have led to a reduction of the incidence of TSD. However, since the number and the identity of couples potentially carriers of a pathogenic *HEXA* variant could not be retrieved at the HSJ biochemical laboratory (other than for the parents of our probands), we cannot imply that this really occurred.

Second, our incidence and carrier frequency calculation could have been skewed if we did not consider the right denominator for the calculation of incidence, that is, the number of births to French-speaking mothers in Quebec. Before discussing this, a brief summary of the history of the French-Canadian population and of historical migrations in Quebec needs to be made. Between 1608 and 1759, the colonization of Canada by the French brought about 8,500 pioneers to the Saint-Lawrence Valley, once known as 'Nouvelle-France', and was stopped by the British conquest of 1759 (De Bie, Agatep, Scott, & Ruchon, 2012; De Braekeleer & Dao, 1994; Laberge et al., 2005). In the 18th century, descendants of French pioneers from Acadia (corresponding to the current Canadian provinces of New Brunswick, Nova-Scotia and Prince-Edward Island) and American Loyalists settled in Quebec (De Bie et al., 2012; Laberge et al., 2005). In the 19th century, immigration occurred mostly from Scotland, Ireland, and England; and more recently in the 20th and 21st century, immigration came from diverse countries. In terms of emigration, approximately 900,000 French Canadians emigrated to the United States between 1840 and 1930 (Lavoie, 1981). At that time, French Canadians mostly settled on the east coast. The 2000 US Census showed that 2.3 millions of Americans reported French Canadian as one of their ancestries that French Canadians represented ~ 10% of New Hampshire's population and that French Canadian was a common ancestry in Maine (Brittingham & de la Cruz, 2004). In more recent years, precise data on emigration are scarce and difficult to obtain (Bérard-Chagnon, 2018).

Over the centuries, the Quebec French-Canadian population remained genetically isolated and rarely mixed with the English-speaking population due to linguistic, cultural, religious, and socio-political reasons (De Braekeleer & Dao, 1994; Laberge, 2007). It is estimated that 80% of the modern Quebec population is of French-Canadian descent and derives from the French settlers from the 17th and 18th century (Gagnon & Heyer, 2001; Laberge et al., 2005). In terms of language, the two main languages used in Quebec are French and English (Laberge et al., 2005). Between 2001 and 2016, the proportion of the Quebec population whose mother tongue is French fluctuated between 79.1% and 82% (Institut de la statistique du Québec & the Secrétariat du Québec aux relations canadiennes, 2019). It is expected that French is mostly spoken by French Canadians. However, statistically speaking, it is difficult to estimate the percentage of the current Quebec population that identifies with being 'French-Canadian' and the percentage of French Canadians who actually speaks French. This is because the term 'French-Canadian' has actually not been used by Quebec and Canadian institutions for several decades (Statistics Canada, 2016). Since the 1960s, this term has been progressively replaced colloquially by the term 'Québécois' (Quirion, Chiasson, & Charron, 2017), and institutions have studied the use of French in different settings or offered the terms 'French' or 'Québécois' when asking about ethnicity (Institut de la statistique du Québec & the Secrétariat du Québec aux relations canadiennes, 2019). These two terms would not reflect accurately French-Canadian ethnicity as they could also refer, respectively, to recent immigrant populations from France, or to anyone who considers being part of the population of the Québec province.

To calculate incidence, we used as a denominator the number of births to French-speaking mothers in Quebec. It would have been ideal to use the number of births to French-Canadian mothers but, as described above, such data are not available. Since 80% of the Quebec population is of French-Canadian descent, that this population has not mixed significantly with other populations over time, and that this population is mostly French-speaking, we consider that the number of births to French-speaking mothers is an appropriate proxy to the number of births to French-Canadian mothers.

Third, there could have been an ascertainment bias, as the families of the probands found in the laboratory charts may be of French-Canadian background without being aware of it. We based our ascertainment on the ethnicity reported by families at the time of identification of the probands or of carriers. There was actually one proband referred from within the province of Quebec whose family disclosed that they were of Italian background. This proband was not included in this study, but could theoretically have been of French-Canadian descent several generations back.

Fourth, our incidence and carrier frequency calculations could have been skewed if some assumptions of the Hardy–Weinberg law are not verified, such as the absence of migrations during our period of ascertainment. Recent waves of immigration have brought to the province French speakers from other francophone countries or areas (Ministère de l'Immigration & de la Diversité et de l'Inclusion, 2015). The degree of the underestimation of our incidence calculation could be appreciated by determining what proportion the immigrant population represents in Quebec and what proportion of this immigrant population is French-speaking. The proportion of immigrants in Quebec varied from 8.7% in 1991 and 12.6% in 2011 (Ministère de l'Immigration & de la Diversité et de l'Inclusion, 2015). The proportion of immigrants having knowledge of French varied between about 40% and 60% between 1996 and 2015 (Gouvernement du Québec, 2016). As a rough estimate, if we consider that the proportion of immigrants in Quebec is 15% and that 60% of them are French-speaking, the number of births to exclusively French-Canadian mothers would correspond to a 9% reduction of the total number of births to French-speaking mothers during the 1992–2015 period, which would be 1,389,580 (instead of 1,527,012). The incidence for nine cases and the overall carrier frequency among Quebec French Canadians would be 1/154,397 and 1/196, respectively, which is very close to our original estimate.

Our denominator could have also been different if we take into account the number of births to French-Canadian men partnered with immigrant women. It is estimated that, in 2015, 4% of births in Quebec are to a man born in Canada and an immigrant woman (Institut de la statistique du Québec, 2016). The total number of births in Quebec from 1992 to 2015 was 1,995,993 (Institut de la statistique du Québec, 2017b). Four percent of this number represents 79,840 births. If we add this to our total number of births to French-speaking mothers, this gives us a total of 1,606,852 births. The incidence for nine cases and the overall carrier frequency among Quebec French Canadians would be 1/178,539 and 1/211, respectively, which is again very close to our original estimate.

Lastly, our denominator could have been skewed by not taking into account the possibility that individuals emigrated from Quebec before the birth of a child with TSD. As discussed before, data on emigration are difficult to estimate (Bérard-Chagnon, 2018). There are data about the number of individuals who migrated from Quebec to another province or another country (Institut de la statistique du Québec, 2019a, 2019b) and data about the proportion of women among international emigrants (Bérard-Chagnon, 2018). There are, however, no precise demographic data about the emigrant population such as the fertility rate per woman in this population, the precise percentage of emigrants who speak French, and their precise region of origin within Quebec. Therefore, there are no data to support the fact that the demographic characteristics of emigrants from Quebec could be different from those of the current Quebec population and that individuals who emigrated during our period of ascertainment could have come from a specific pool of population with a high TSD carrier frequency, a phenomenon that could have lowered the global TSD carrier frequency in the whole province of Quebec. In summary, although recent immigration and emigration patterns could have impacted our calculations of incidence and carrier frequency, we do not expect that these had a major influence.

4.4 | Conclusion and practice implications

We calculated a carrier frequency for infantile TSD for the general Quebec French-Canadian population based on incidence data. A maximum of one out of 206 French Canadians in Quebec is a carrier of TSD (CI: 1/305–1/150). Although there are limitations to our retrospective study, their impact seems to be minimal, and we estimate that our calculated TSD carrier frequency is appropriate.

Ethnicity-based screening guidelines in Canada recommend screening for different conditions based on carrier frequencies that range from 1/14 to 1/53 (Wilson et al., 2016). Furthermore, the American College of Obstetricians and Gynecologists recommends screening for conditions that have carrier frequencies of 1/100 or greater (American College of Obstetricians & Gynecologists, 2017b). Even though a carrier frequency of 1/206 as ascertained in this study is elevated over the carrier frequency postulated for the non-Jewish population in the United States, it is much lower than the range of carrier frequencies for which carrier screening is currently recommended in Canada or by the American College of Obstetricians and Gynecologists.

Efforts to facilitate access to TSD carrier screening in some regions of origin have contributed to uniting patients and families affected by a rare condition (Passeport santé, 2008; Regroupement québécois des maladies orphelines). The presence of a founder effect in the Bas-St-Laurent and Gaspésie regions justifies that carrier screening should be offered to French Canadians who know that at least part of their family is from this region, and to individuals who are aware of a family history of TSD, following the current Canadian guidelines (Chodirker et al., 2001; Wilson et al., 2016). In the context of healthcare systems with limited resources, we argue that carrier screening for TSD for all other individuals, including French Canadians who do not have information about the region of origin of their ancestors, should likely not be recommended at this point. Saving healthcare funds would ensue with a likelihood of failing to detect carrier couples that would be very low with a carrier frequency of 1/206.

If, in the future, consideration is given to offering expanded carrier screening for severe TSD alleles to all French-Canadian individuals in a preconception or prenatal setting, consideration should be

given to include in these screening tests all the common pathogenic variants that are known to be responsible for infantile TSD in this population.

4.5 | Future directions

In the current study, data were collected from 1992 onwards. As discussed previously, it is possible that the awareness of an elevated TSD carrier frequency in some communities led to increased population genetic screening over the years and to a decrease in the incidence of TSD. Even though our data do not support this assumption over our period of ascertainment, it would be interesting to know whether the knowledge of TSD in Quebec French-Canadian families at large contributed to a decrease in the incidence of TSD cases over a period longer than 24 years. A retrospective study of prenatal and postnatal TSD cases would be interesting to undertake since the beginning of the 1970s and until 1992, which corresponds to the period when founder effects in French-Canadian families started to be studied. Such a study may be difficult to do, though, as paper records of biochemical testing may not be exhaustive and may be difficult to search through.

Other ways to estimate an accurate carrier frequency include organizing carrier screening in a large and representative portion of the Quebec French-Canadian population. The presence of *HEXA* pseudodeficiency alleles and alleles associated with late-onset disease make it difficult to estimate carrier frequencies derived from biochemical testing. Population screening through molecular testing would avoid these biases and allow having carrier frequencies specific to different regions. Pairing such testing with an analysis of molecular markers that are specific to the French-Canadian population would also allow having carrier frequencies specific to this specific ethnicity. This would give more specific data than basing the incidence calculation on births whose mothers have French as their language of use.

DATA SHARING AND DATA ACCESSIBILITY

Data included in this article have not been shared in a public repository.

AUTHOR CONTRIBUTIONS

Guillaume Sillon contributed to the design of the study, the acquisition, analysis and interpretation of data, and drafted the manuscript. Pierre Allard, Stella Drury, Jean-Baptiste Rivière, and Isabelle De Bie contributed to the design of the study, the acquisition, analysis and interpretation of data, revised the manuscript, and approved the final version to be published.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

All of the authors, Guillaume Sillon, Pierre Allard, Stella Drury, Jean-Baptiste Rivière, and Isabelle de Bie declare that they have no conflict of interest.

Human studies and informed consent

This study was approved by the McGill University Health Center (MUHC) Research Ethics Board and by the Ste-Justine Hospital (SJH) Research Ethics Committee. Informed consent for genetic testing was required of all individuals whose data were included in this study.

Animal studies

No non-human animal studies were carried out by the authors for this article.

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