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ARTICLE

Successes of an innovative population-based carrier screening program for 4 prevalent recessive hereditary diseases in a population with a founder effect in Quebec, Canada

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ABSTRACT

Purpose: The Saguenay-Lac-Saint-Jean, Haute-Côte-Nord, and Charlevoix regions in Canada have a high prevalence of 4 autosomal recessive diseases with high morbidity and/or reduced life expectancy. As a result, a carrier screening program (CSP) was developed in 2010 and has been ongoing since. The program's purpose is to provide information and carrier screening for individuals having a higher probability to have an affected child to allow for informed decision making regarding reproductive choices. This publication provides an overview of the CSP, shares its results, and discusses the growing needs for expanding genetic testing and counseling.
Methods: In 2018, the CSP transitioned from a regional to a provincially available program, supported by an innovative home self-sampling kit that can be requested online and returned by mail for analysis. For the purpose of this study, CSP data from 2010 to 2022 were extracted and analyzed.
Results: The CSP has shown high acceptability. In total, 20,604 participants have been tested, identifying 3578 carriers of at least 1 condition who received genetic counseling. Carrier couples for the same condition ($n = 116$) were offered a subsequent appointment in a genetics clinic to further discuss the result, its potential implications, and available reproductive options. The heterozygote frequencies for the tested conditions ranged from 1 in 18 to 1 in 28.
Conclusion: The relatively inexpensive method could be applied to other populations with a high prevalence of certain autosomal recessive diseases. Given the program's results, we must consider adding the screening of other prevalent recessive conditions to the CSP.

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Introduction

The Saguenay-Lac-Saint-Jean (SLSJ), Haute-Côte-Nord, and Charlevoix regions (collectively referred to in this article as SLSJ/HCN/C) located in the province of Quebec, Canada, share a well-known founder effect which contributed to increasing the prevalence of certain hereditary rare diseases.[1,2] The successive migrations and settlements following the St-Lawrence and the Saguenay River waterways in the province of Quebec between the 17th and 20th centuries are central to this founder effect.[1,3] Consanguinity was excluded as a causal factor in the increased prevalence of certain rare disorders in the SLSJ region.[4,5]

Over the years, over 25 prevalent recessive diseases have been described in the SLSJ/HCN/C population.[2] The 4 most prevalent, excluding cystic fibrosis, have heterozygote frequencies (HF) between 1 in 20 and 1 in 23[2] and show high morbidity. Some are characterized by early childhood mortality and limited treatment options. They represent a public health issue for couples in which both individuals are from regions with a high HF. As a response to this issue and requests from the community, these conditions were included in 2010 in a carrier screening program (CSP) (described below). The HF in individuals with origins other than SLSJ/HCN/C are estimated to be lower but remained unknown until now.

Tyrosinemia type 1 (TYRSN1, OMIM 276700) is caused by pathogenic variants in the fumarylacetoacetate hydrolase (*FAH*, HGNC:3579) gene. The variant NM_000137.4:c.1062+5G>A is estimated to have a HF of 1 in 20 with a prevalence of 1 in 1846 in the SLSJ/HCN/C regions.[6,7] TYRSN1 presents in young children with severe liver and kidney disease, rickets, and neurological crises. Without treatment, individuals typically die in childhood. Treatment with nitisinone and a low-tyrosine diet is associated with a survival rate of 90%, normal growth, improved liver function, secondary rickets prevention, cirrhosis prevention, and correction of renal tubular acidosis.[8]

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS, OMIM 270550) is caused by pathogenic variants in the sacsin molecular chaperone (*SACS*, HGNC:10519) gene. Prevalence is estimated at 1 in 1932 with a HF of 1 in 22 in the SLSJ/HCN/C regions, with 2 variants reported to be more frequent, NM_014363.6:c.7504C>T and NM_014363.6:c.8844del.[9,10] ARSACS usually presents in young children with progressive cerebellar ataxia, peripheral neuropathy, and spasticity. Life expectancy is approximately 60 years of age. The available treatments are not curative, only targeting symptoms.[11]

Leigh syndrome French-Canadian type (LSFC, OMIM 220111) is caused by pathogenic variants in the leucine-rich pentatricopeptide repeat containing (*LRPPRC*, HGNC:15714) gene. The variant NM_133259.4:c.1061C>T is estimated to have a HF of 1 in 23 with a prevalence of 1 in 2063 in the SLSJ/HCN/C regions.[12,13] LSCF is characterized by metabolic and neurological crises with a median age of death estimated at 1.6 years.[14]

Peripheral neuropathy with or without agenesis of the corpus callosum (ACCPN, OMIM 218000) is caused by pathogenic variants in the solute carrier family 12 member 6 (*SLC12A6*, HGNC:10914) gene. The variant NM_001365088.1:c.2436+1del is estimated to have a HF of 1 in 23 with a prevalence of 1 in 2117 in the SLSJ/HCN/C regions.[15,16] Patients with ACCPN present with severe progressive sensorimotor neuropathy with areflexia, developmental delay, and intellectual disability, ranging from mild to severe. Life expectancy is approximately 33 years of age.[17]

Given the increased prevalence of these 4 severe autosomal recessive conditions, a CSP was developed by both the Quebec Ministry of Health and Social Services (QMHSS) and the local SLSJ region health authorities. Providing genetics education and genetic testing via the CSP aims to allow for informed decision making regarding reproductive choices. The CSP educates individuals and couples about their increased probability of being heterozygous for any of the 4 recessive conditions.

The objectives were to analyze data from the CSP (2010-2022) and perform a retrospective evaluation aiming to give an overview of the CSP, its results, and how it has evolved over the years. We also discussed the perspectives of expanding genetic testing and counseling. We show that carrier screening programs can be easily accessible to the population and relatively inexpensive. We hope this experience can be an example to other regions looking to create a similar CSP.

Abbreviations

ACCPN – peripheral neuropathy with or without agenesis of the corpus callosum
ACMG – American College of Medical Genetics
ARSACS – autosomal recessive spastic ataxia of Charlevoix-Saguenay
CORAMH – Corporation d'action et de recherche sur les maladies héréditaires
CSP – carrier screening program
FAH – fumarylacetoacetate hydrolase
HF – heterozygote frequency
LIMS – Laboratory Information Management System
LRPPRC – leucine-rich pentatricopeptide repeat containing
LSFC – Leigh syndrome French-Canadian type
MLII – mucolipidosis type 2
QMHSS – Quebec Ministry of Health and Social Services
SACS – sacsin molecular chaperone
SLC12A6 – solute carrier family 12 member 6
SLSJ – Saguenay-Lac-Saint-Jean
SLSJ/HCN/C – Saguenay-Lac-Saint-Jean/Haute-Côte-Nord/Charlevoix
TYRSN1 – tyrosinemia type 1

Materials and Methods

This methods section is divided in 2 parts. The first part describes the development of our CSP, which was launched as a population-based screening program in the province of Quebec in 2010 and not a research project. The second part describes how the retrospective evaluation of the programs was performed.

Description of our carrier screening program

The CSP has evolved over the years to meet the needs of the population. The CSP was deployed in 2 phases: (1) the regional phase from 2010 to 2018 and (2) the provincial phase from 2018 until now. Both phases are described below. A summary contrasting the 2 phases is presented in Supplemental Table 1.

Ethics evaluation and acceptability assessment

The regional phase was first assessed and recommended in 2007 by the Quebec Public Health Ethics Committee.[18] Since then, research groups have assessed genetics literacy, knowledge, and the social acceptability of the CSP, all of which were high.[19–22] Much of this high understanding is attributed to the Corporation d'action et de recherche sur les maladies héréditaires (CORAMH), a local nonprofit organization whose goals are to inform, raise awareness, and educate the public about hereditary diseases and the genetic determinants of health. The outcomes of the regional phase were also assessed by the Institut national de santé publique in 2014.[23] In their report, they commented on inequities for individuals with origins from SLSJ/HCN/C living outside of SLSJ who could not access the CSP as it was only offered in person living in the SLSJ region. They recommended expanding the CSP to eligible participants province-wide. This led to the development of the program's second phase, the provincial phase, which launched in 2018 (details below).

Regional phase

Target population

The regional phase took place from October 2010 to January 2018. The eligibility criteria were as follows: be at least 18 years old, be planning on having children, have at least 1 grandparent from the SLSJ/HCN/C regions, and reside in the SLSJ region. The CSP was offered prenatally and preconceptionally. However, given the limitations in prenatal diagnosis options for more advanced pregnancies, pregnant individuals over 14 weeks' gestation were ineligible for the program. They were referred to local genetics clinics for genetic counseling.

Analytical method

In preparation for the CSP, a clinically validated panel was developed by ECOGENE-21, a local research group, for the 5 most frequent variants causing the 4 selected diseases described above using the Luminex technology. The test included the following variants: NM_014363.6:c.7504C>T and NM_014363.6:c.8844del in the *SACS* gene, NM_001365088.1:c.2436+1del in the *SLC12A6* gene, NM_133259.4:c.1061C>T in the *LRPPRC* gene, and NM_000137.4:c.1062+5G>A in the *FAH* gene. The test was based on a peripheral blood sample followed by DNA extraction, nucleic acid amplification, and variant detection using a Luminex LiquiChip 200 Workstation. Specific PCR primers and probes coupled with specific xMAP beads targeting each of the 5 pathogenic variants were developed and clinically validated using approximately 1000 samples of known genotypes. An external laboratory provided and confirmed 10 control samples that were blindly analyzed by our laboratory every month. In parallel, we provide them with 10 samples to confirm the genotype every month.

Information and consent process

Many methods were used to promote the CSP in the SLSJ/HCN/C population. Participants were approached by their healthcare professional or through advertising efforts, including television spots, local community advocacy groups' websites, and social media. Interested participants were met in 1 of 6 Local Community Service Centers in the SLSJ region: Chicoutimi, Jonquière, La Baie, Alma, Roberval, and Dolbeau. Pretest counseling was provided by a nurse and included a discussion of the basics of carrier screening, autosomal recessive inheritance, and the 4 conditions tested, as well as the potential personal and familial impacts of testing. All participants provided free and informed consent. Finger-prick peripheral blood sampling was performed by a nurse the same day at the designated centers.

Provincial phase

Target population

The provincial phase began in January 2018 and is ongoing to date. The eligibility criteria are as follows: be at least 18 years old, be planning on having children, and have at least 1 grandparent from the SLSJ/HCN/C regions. Similar to the regional phase, the CSP is offered prenatally and preconceptionally, including the ineligibility of pregnant individuals over 14 weeks' gestation. In March 2020, because of the COVID-19 pandemic and impacts on genetic counseling resources, the threshold for eligibility was increased to 16 weeks of pregnancy and has remained this way since.

Analytical method

The new test was developed for the provincial phase based on buccal cell self-sampling using a buccal swab. DNA is

extracted and amplified, and the variants are detected using specific TaqMan probes. The same 5 pathogenic variants are targeted. Five samples are analyzed blindly annually to serve as quality control in this phase. The genotypes obtained are confirmed by the Laboratoire de santé publique du Québec, which the QMHSS mandated.

The amplification and detection protocol are described in Supplemental Data 1, including the assays and probes used (Supplemental Table 2) and the PCR amplification conditions (Supplemental Table 3). The analytical strategy has been thoroughly validated using thousands of samples for which the carrier status was known (blinded to the technician during analysis) and approved by the Institut national d'excellence en santé et services sociaux du Québec. The test also complies with the Bureau de normalisation du Québec requirements. The analytical approach we have developed is noninvasive, easy to access for the participant, inexpensive, and able to travel by mail in extreme temperatures (able to withstand temperatures ranging from −40 °C in winter to +35 °C in summer).

Information and consent process

An interactive online module was developed to provide education on the CSP's objectives, targeted conditions, autosomal recessive inheritance, potential outcomes, and testing implications. It is available online at sante.gouv.qc.ca/tests4maladies. To request carrier testing, the participant must access the online module and complete the integrated knowledge retention questionnaire. This ensures that the patient has the necessary information to provide informed consent. This online module is similar to one used in another CSP, validated by a randomized control study.[24] Participants are told they can withdraw consent before results are communicated by contacting the laboratory.

Once the request is received, a home self-sampling kit and a consent form are sent to participants by mail. They must return their samples by mail at the cost of approximately 1$ CAN. This is the only cost associated with participating in this CSP; the province's publicly funded health care covers the rest.

Data management

All samples were received and analyzed by trained registered technicians at the Clinical Genetics and Molecular Biology Laboratory at the Chicoutimi Hospital. Results are stored in the Laboratory Information Management System (LIMS) and are validated by a licensed medical biochemist or geneticist.

Results disclosure

All participants receive a letter with their carrier testing results validated by a genetic counselor and a geneticist. Each and every carrier identified by the program is also contacted by phone by a trained nurse (regional phase) or a genetic counselor (current program) who disclose their result and provide counseling including discussion of whether their partner was also tested or whether testing is recommended, family implications, limitations of the testing, etc. They are also counseled that their child may be a carrier and could access carrier screening in adulthood (or when family planning). Discussion regarding the increased probability of their brothers, sisters, cousins, etc being carriers of the same condition is discussed, and they are encouraged to share this information with their families so that other may access the CSP. The contacted individuals have also the opportunity to ask any questions they may have regarding the CSP or their results.

Further genetic counseling is offered to carrier couples to further discuss the result, its potential implications, and the available reproductive options during a subsequent in-person/virtual appointment. Those living outside the SLSJ region are referred to the nearest genetics clinic through an established provincial partnership. For ongoing pregnancies, prenatal diagnosis is offered.

Description of the retrospective evaluation of the CSP

The retrospective evaluation of the CSP's anonymized data was presented to and approved by the director of professional services of the CIUSSS-SLSJ in accordance with the ethical rules in law at this time.

Data extraction

A clinical biochemist extracted data from the LIMS from October 29, 2010, to August 26, 2022. Anonymized data were provided to the researchers. The extracted data included the following: the date of the request, the requesting clinic, the test priority (preconceptional or prenatal), the participant's date of birth, sex, postal code, and genotype result. The analyses were divided into 2 phases: the regional phase ending January 25, 2018, and the provincial phase beginning January 26, 2018.

A total of 136,014 laboratory results were extracted from the LIMS pertaining to 23,304 males and females. Of these results, 2700 individuals were excluded for the following reasons: 2282 were excluded because testing was not requested through the CSP (2211 ordered by the genetics clinic and 71 by a specialized care clinic), 371 had no results available (analysis cancelled), 38 were found in duplicates in the database (concordant results), and because of unmet access criteria (3 male and 3 female were older than 60 years of age—arbitrarily, we postulated that they were unlikely to be planning to have children—and 3 female were younger than 18 years of age).

Table 1 Participants' characteristics

Characteristics	Regional Phase		Provincial Phase		*P* Value[a]
	n	%	*n*	%	
All	11,223	100.0%	9381	100.0%	
Sex					
Male	5127	45.7%	4186	44.6%	0.1311302
Female	6096	54.3%	5195	55.4%	0.1311302
Age					
All (Mean [range])	28.5 (18.0-54.8)		28.8 (18.0-59.0)		0.0012684
Male (Mean [range])	29.9 (18.0-53.4)		30.0 (18.0-56.0)		0.6318536
Female (Mean [range])	27.4 (18.0-54.8)		27.8 (18.0-59.0)		4.85e−06
Indication					
Preconceptional	5036	44.9%	4625	49.3%	2.433119e−10
Prenatal	6187	55.1%	4756	50.7%	2.433119e−10

[a]Wilcoxon test was used for continuous variables and χ^2 test for categorical variables.

Statistical analyses

Normality was assessed by the Anderson-Darling test. The one-sample Wilcoxon test was used to compare quantitative variables between cohorts, and the One-Sample χ^2test was used to compare qualitative variables. The statistical analyses were all done with R version 4.0.5 in R studio version 2022.7.1.554.

Results

Participants' characteristics

A total of 20,604 individuals were included in the analyses, of which 11,223 and 9381 were tested during the regional and provincial phases, respectively (Supplemental Figure 1), for a total of 102,935 genetic analyses.

The self-sampling kit return rate (calculated as the number of kits returned by the number of kits sent out) has increased since 2018. The return rate was 66% in the first year of the CSP's implementation, rising each year to 70%, 71%, 73%, and 77% for the final year in 2022.

On average, 33 samples (165 tests) per week were analyzed. The average turnover between the laboratory's receipt of the samples and the analytical report signature was 5.9 working days, and the analysis cost, including reagent and labor, was 25.00$CA per sample (5 variants for 4 diseases) in the last year, 2023.

Participants' characteristics are summarized in Table 1. In both phases, just over half of the participants were female. The average age of participants was similar between the regional (28.5 [18.0-54.8]) and the provincial phases (28.8 [18.0-59.0]). Figure 1 shows the distribution of age by phase and by sex. The age distribution is similar in both phases, with only a few participants over 45. In both phases, the mean age was higher for males (29.9 for the regional phase and 30.0 for the provincial phase) than for females (27.4 for the regional phase and 27.8 for the provincial phase).

The laboratory results for each variant tested and detected are shown in Supplemental Table 4. More than 99% of participants requested to test all 5 pathogenic variants. Only

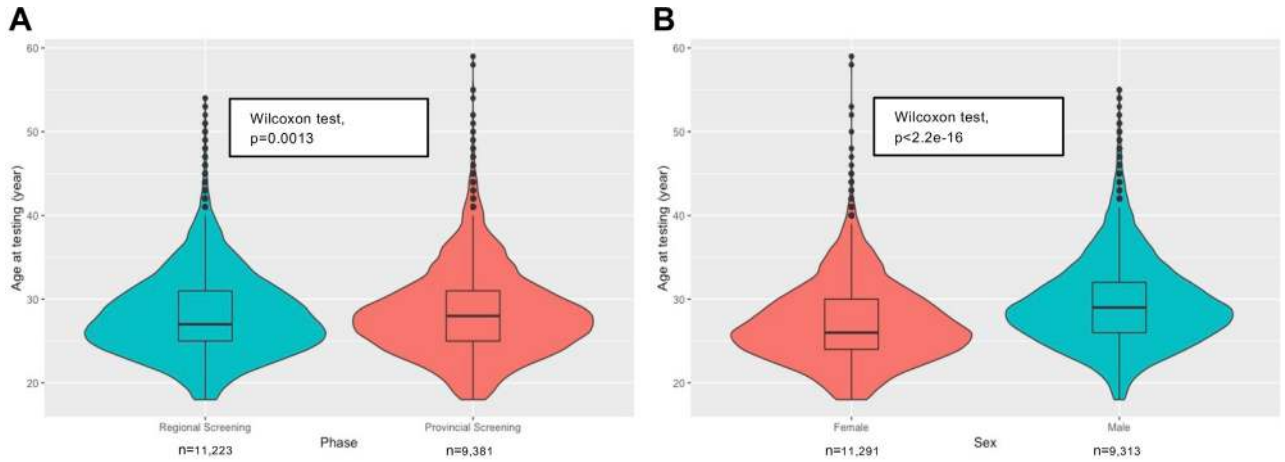

Figure 1 Distribution of the participants' age at testing. A. By phase. The median age is represented by a black line, ie, 27 for the regional screening and 28 for the provincial screening. B. By sex. The median age is 26 for females and 29 for males.

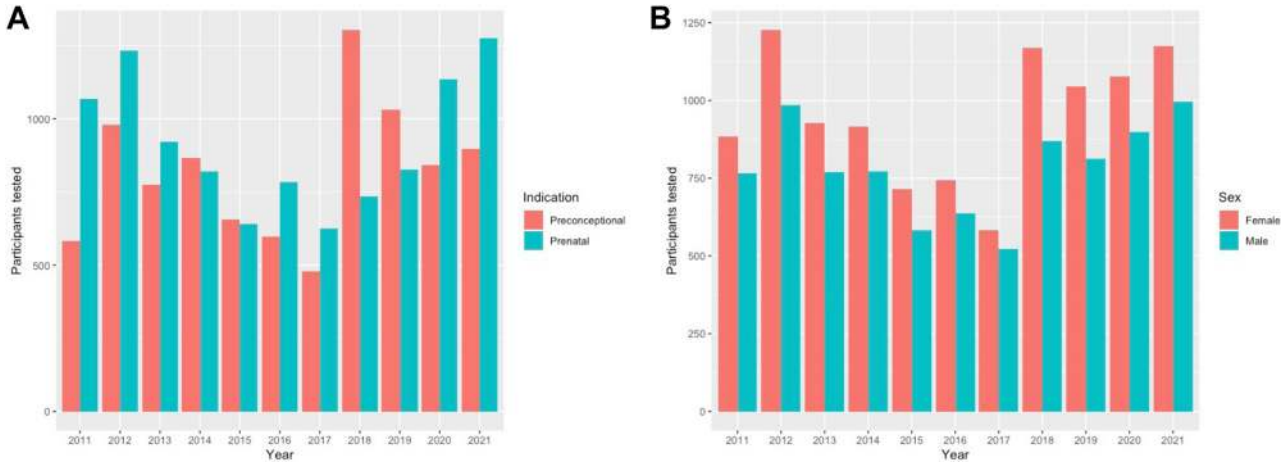

Figure 2 Yearly overview of participants tested. A. By indication. B. By sex. Data for 2010 and 2022 were excluded because recruitment did not occur throughout the entire year (2010) or because data were extracted before the year was complete (2022). A χ^2 test shows a significant difference between the number of tests performed for each indication and sex for each year (<2.2e−16).

39 individuals opted to be tested for only 1 or a few conditions. The CSP identified that 17.97% and 16.96% of individuals were found to be heterozygous of at least 1 condition in the regional and provincial phases, respectively. The percentage of nonheterozygotes was higher in the provincial phase, and the rate of heterozygotes (1 pathogenic variant identified) was higher in the regional phase. These findings were statistically significant ($P = .01$ and $P = .04$). When looking at the total data for both phases, among the heterozygotes, approximately 15% carried one variant, 1% carried 2, 0.05% carried 3, and only 1 individual carried all 4 diseases tested. It should be noted that 2 pathogenic variants are tested for ARSACS. Consequently, no individual was heterozygotes for all 5 pathogenic variants because they would be affected by ARSACS and excluded from the present analyses.

Yearly overview of tested participants

The number of tests carried out each year is shown in Supplemental Figure 2. Figure 2 demonstrates the participation rate by the participants' sex and by indication (preconception vs prenatal). For the regional phase, requests for testing were primarily made in the prenatal context (55.1%). After the Provincial phase was implemented in January 2018, an overall increase in the number of tests requested and the number of participants in preconception was observed, which lasted for 2019 as well. However, the highest number of tests performed in 1 year was observed in 2012, the first year of the regional phase. Every year, more women were tested than men for both phases.

Origin of the participants across the province of Quebec

By design, all samples from the regional phase were collected from participants living in the SLSJ region. For the provincial phase, most participants (68.4%) were from the SLSJ region, followed by the regions of the Capitale-Nationale (which includes Charlevoix and Québec City) (13.0%), Montérégie (4.0%), and Côte-Nord (3.0%) (Supplemental Table 5).

Heterozygotes frequency

The 5 pathogenic variants that were tested and their observed HF are shown in Table 2 for both the regional and provincial phases. The HF ranged between 1 in 18 and 1 in 26 with an associated probability of conceiving an affected child between 1 in 1296 to 1 in 2704 if both partners are from the SLSJ/HCN/C regions (considering the probability of 25% to have an affected child for each pregnancy). The HF were calculated based on the number of heterozygotes over the total number of tests performed for each variant. Overall, the HF were similar to those reported in the literature for all variants. However, observed HF were slightly lower in the provincial than regional phase. These data show that individuals from the SLSJ/HCN/C regions have a combined probability of approximately 1 in 5 of carrying at least 1 of the 5 causal variants. Observed HF for each year since 2010 are provided in Supplemental Table 6.

The HF for the 4 conditions in individuals from other regions of Quebec were also calculated using data from the CARTaGENE database, a public research platform capturing sequencing data from participants recruited in many regions of Quebec (Montreal, Sherbrooke, Quebec, and Saguenay municipalities). In this group, the HF were calculated for the 4 conditions in the 1743 individuals with self-expressed French Canadian (Quebec) origin, excluding those from Saguenay. The HF were lower than those in the SLSJ/HCN/C regions. They ranged from 1 in 92 to 1 in 291.

The zip code was available for 16,771 out of the 20,604 individuals tested, exclusively for people from the SLSJ region. Supplemental Figure 3 illustrates the number of tests conducted by the municipality, typically representing a town

Table 2 Heterozygote frequencies of the 5 pathogenic variants included in the program

Condition (MIM)	Gene (HGNC)	Variant Description (GRCh38)	ClinVar	Screening Program		CARTaGENE
				Regional Phase (n = 11,223) Heterozygote frequency (CI 95%)	Provincial Phase (n = 9381) Heterozygote frequency (CI 95%)	Individuals Living in the Province of Quebec, Excluding Individuals From the SLSJ Region (n = 1743) Heterozygote frequency (CI 95%)
ARSACS (270550)	*SACS* (10519)	NC_000013:g.23335032del NM_014363:c.8844del NP_055178.3:p.(Ile2949PhefsTer4)	VCV000005512.34 (P)	1/18 (1/20-1/17)	1/20 (1/22-1/18)	1/92 (1/59-1/152)
ARSACS (270550)	*SACS* (10519)	NC_000013.11:g.23336372G>A NM_014363.6:c.7504C>T NP_055178.3:p.(Arg2502Ter)	VCV000005513.20 (P)	1/935 (1/2,151-597)	1/1340 (1/5163-1/770)	0
ACCPN (218000)	*SLC12A6* (10914)	NC_000015.10:g.34240661del NM_001365088.1:c.2436+1del	VCV000436730.25 (P)	1/21 (1/23-1/19)	1/28 (1/31-1/25)	1/117 (1/70-1/208)
LSFC (220111)	*LRPPRC* (15714)	NC_000002.12:g.43974244G>A NM_133259.4:c.1061C>T NP_573566.2:p.(Ala354Val)	VCV000003110.23 (P)	1/26 (1/24-1/29)	1/27 (1/30-1/24)	1/291 (1/133-1/769)
TYRSN1 (276700)	*FAH* (3579)	NC_000015.10:g.80180230G>A NM_000137.4:c.1062+5G>A	VCV000011870.82 (P)	1/18 (1/20-1/17)	1/21 (1/23-1/19)	1/175 (1/95-1/357)

CI, Confidence Interval; *FAH*, fumarylacetoacetate hydrolase; *LRPPRC*, leucine-rich pentatricopeptide repeat containing; *P*, pathogenic; *SACS*, sacsin molecular chaperone; *SLC12A6*, solute carrier family 12 member 6.

and its surroundings. The majority of participants lived in the municipality of Saguenay (9157), followed by Alma (1837), Roberval (742), and Saint-Honoré (548). All other municipalities tested had less than 500 participants.

Figure 3 shows the HF by municipality. In brief, the HF are generally higher around the Lac-Saint-Jean than in the municipality of Saguenay for ARSACS, NSM, and LSFC, whereas it is lower for TYRSN1. For ARSACS and TYRSN1, all municipalities with a HF below 1 in 13 had fewer than 30 and 40 people tested, respectively. For ACCPN and LSFC, all municipalities with a HF above 1 in 17 had fewer than 40 and 15 people tested, respectively. Because most municipalities had fewer than 500 participants, results must be interpreted cautiously, considering potential sampling bias.

Couples of carriers for the same condition

Since 2010, the CSP has identified 116 carrier couples of the same condition: 38 couples for ARSACS, 22 for LSFC, 21 for ACCPN, and 34 for TYRSN1 (Table 3). For ARSACS, 2 carrier couples comprised 1 person carrying the rare variant, c.7504, whereas the other carried the frequent variant, c.8844del. The other ARSACS carrier couples both carried the more frequent variant. Because the offer for CSP was extended throughout the province of Quebec in 2018, we still found that most carrier couples lived in the SLSJ region. However, 6 carrier couples were identified in the Capitale-Nationale, the Montreal, the Outaouais, the Nord-du-Québec, and the Lanaudière regions (Table 4).

Discussion

In this study, we have reported results supporting the feasibility of offering carrier screening to populations with a higher prevalence of certain genetic conditions with a reliable, noninvasive, inexpensive test. In brief, 20,604 people have accessed the CSP since 2010. We have identified 116 carriers couples (≈ 1.1% of the tested pairs) having a high probability (25%) of having an affected child. Constant demand over the past 12 years also demonstrates social acceptability, supported by numerous clinical and ethical assessments.[18,20–23,25]

A study conducted in 2017 assessed the experience of carrier couples identified during the regional phase of the CSP between 2010 and 2014. These results showed that all couples recognized the importance of carrier screening and reported promoting accessing carrier screening in their social circles. They also noted that they support the addition of other diseases to the CSP.[26] In recent years, parents of children diagnosed with mucolipidosis type 2 (MLII) at birth have contacted local media requesting to improve the current carrier screening program by adding other common recessive conditions, such as MLII.[27] These families

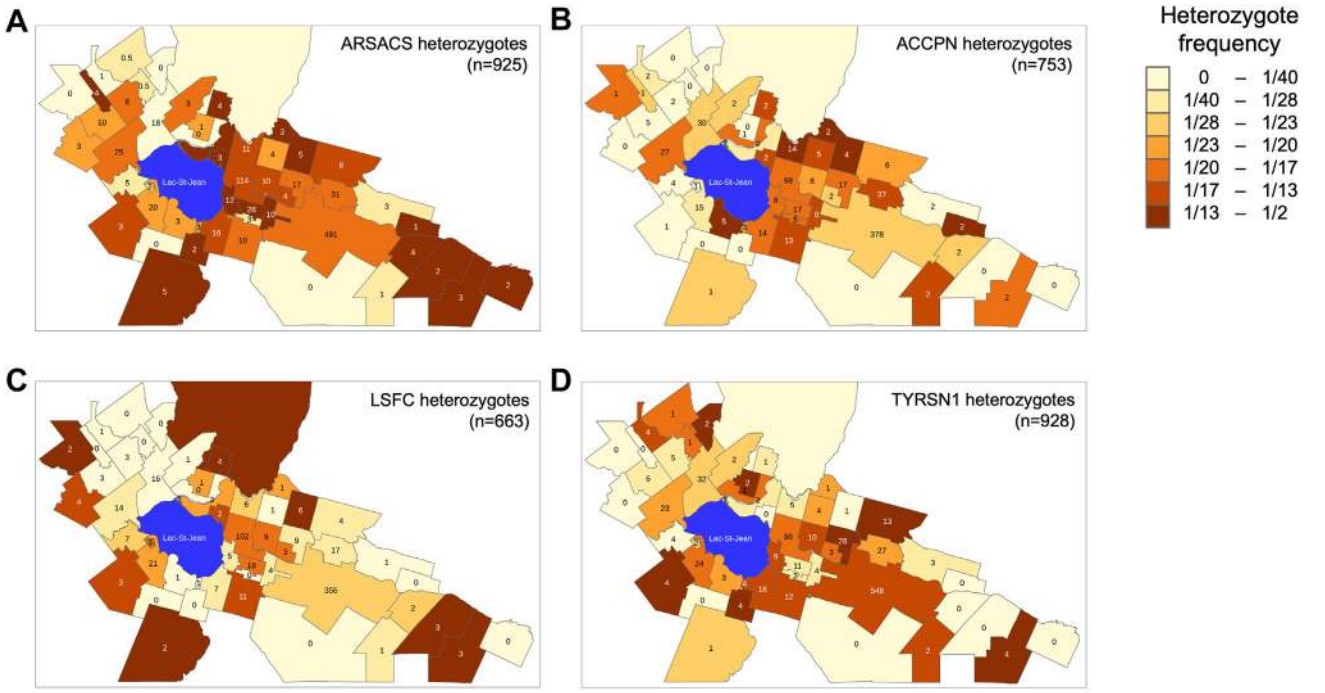

Figure 3 **Heterozygote frequencies by municipality.** The numbers on the maps represent the number of heterozygotes in each municipality. The city of Saguenay includes the following municipalities: Chicoutimi, Jonquière, La Baie, Laterrière, Canton-Tremblay, Lac-Kénogami, and Shipshaw. A. For ARSACS, the HF in Saguenay is between 1 in 20 and 1 in 17, whereas it is higher in the Lac-Saint-Jean region near the municipality of Alma, with a HF between 1 in 17 and 1 in 13. B. For ACCPN, the HF in Saguenay is between 1 in 28 and 1 in 23, whereas it is higher in the Lac-Saint-Jean region, with a HF between 1 in 20 and 1 in 17. C. For LSFC, the HF in Saguenay is between 1 in 28 and 1 in 23, whereas it is higher in the Lac-Saint-Jean region, with a HF between 1 in 20 and 1 in 17. D. For HT1, the HF in Saguenay is between 1 in 17 and 1 in 13, whereas it is lower in the Lac-Saint-Jean region, with a HF between 1 in 20 and 1 in 17.

thought that they were safe from having a child affected by a genetic disease with HF in the region because they had participated to the CSP. This shows the importance of continuous education of families participating in the CSP and the necessity of constant evaluation of the conditions screened.

The American College of Medical Genetics and Genomics (ACMG) criteria for considering populational carrier screening includes the severity of the condition, a high prevalence (>1 in 100) of heterozygotes in the screened population, established analytic validity of screening methods, a predictable genotype-phenotype correlation, an available prenatal diagnosis, and availability of reproductive options.[28] With a HF of 1 in 39 and an estimated prevalence of 1 in 6084 births in the SLSJ region,[2] MLII fits the ACMG criteria, as does the Zellweger syndrome, for which the HF (1 in 55) was established in 2012.[29] Accordingly, a request to add these 2 conditions to the CSP is currently under review by the QMHSS.

In recent years, members of our team have also assessed the HF of 12 additional autosomal recessive conditions for which there was clinical evidence supporting an increased prevalence in the SLSJ/HCN/C regions. Eleven had a HF higher than 1 in 100, with 7 conditions fulfilling the other ACMG criteria.[28] These results and conditions were

Table 3 Number of identified carrier couples

Year	ARSACS	LSFC	ACCPN	TYRSN1
2010-2017	22	11	12	21
2018	2	3	3	2
2019	3	1	1	4
2020	6	1	0	3
2021	4	3	3	4
2022	1	3	2	1
Total	38	22	21	35

ACCPN, agenesis of the corpus callosum with peripheral neuropathy; *ARSACS*, autosomal recessive spastic ataxia of Charlevoix-Saguenay; *LSFC*, Leigh syndrome French Canadian type; *TYRSN1*, tyrosinemia type 1.

Table 4 Region of residence of the carrier couples identified by the provincial phase from 2018 to 2022

Administrative Region	ARSACS	LSFC	ACCPN	TYRSN1
02-Saguenay-Lac-Saint-Jean	15	9	7	14
03-Capitale-Nationale		1		
06-Montréal	1		1	
07-Outaouais			1	
10-Nord-du-Québec		1		
14-Lanaudière		1		
Total	16	11	9	14

ACCPN, agenesis of the corpus callosum with peripheral neuropathy; *ARSACS*, autosomal recessive spastic ataxia of Charlevoix-Saguenay; *LSFC*, Leigh syndrome French Canadian type; *TYRSN1*, tyrosinemia type 1.

described in a previous article published in 2023 by Cruz Marino et al.[2] Members of our team are now developing a novel panel including these 7 additional variants (1 for each condition) and plan to submit a request to the health authorities to evaluate the addition of these conditions to the CSP. This also shows that the CSP will have to evolve as we improve genetic knowledge of severe recessive conditions.

At a population level, the HF have remained high over the last decade, ranging from 1 in 15 to 1 in 30 for all 4 conditions tested (Supplemental Table 6), demonstrating that the CSP remains relevant. Although variable across the different municipalities of the SLSJ region, the HF were higher than in the rest of the world, where the prevalence is unknown, apart from TYRSN1, which has a prevalence of approximately 1 in 100,000 births.[8] Interestingly, the HF for these 4 recessive disorders in the other regions of the Province of Quebec had never been assessed before. As expected, the results showed that the HF are much lower throughout the province of Quebec than in the SLSJ/HCN/C regions.

A similar population-based CSP with an online information tool and consent process has published their experiences in Canada, namely, for the Jewish Ashkenazi population in Montreal. In fact, the online interactive computer module utilized in the provincial phase of our program was modeled in part after their online module and with advice from their team. They evaluated the experience of families of Jewish Ashkenazi descent seeking carrier screening via an online module and an in-person appointment in genetics. They concluded that genetics knowledge, risk perception, or anxiety were not significantly different between the 2 groups.[24] As genetics knowledge continues to grow and the demands for genetic testing are expanding, these positive experiences could be used to develop new service delivery models for different indications for which an in-person appointment might not be mandatory, leading to time savings for patients and genetics professionals alike.

Although the CSP has demonstrated its success over the years, areas remain for improvement. Strategies should be implemented to increase the visibility and awareness of carrier testing for individuals originating from areas with a high HF throughout the province of Quebec but living outside the SLSJ/HCN/C region. In particular, these strategies should promote requests in preconception, which would allow for earlier access to genetic counseling regarding the available reproductive options, allowing individuals more time for decision making. The CSP should also continue to be evaluated over the years, notably by an ethics committee, to assess the relevance of the conditions already included and the potential for others to come. Continually considering the criteria and recommendations of the ACMG and other governing bodies concerning carrier screening offers should remain a priority. As the SLSJ/HCN/C population diversifies and testing costs decrease, the relevance of extending the program should be subject to an economic analysis.

As discussed above, all heterozygotes for at least 1 condition received genetic counseling through a phone appointment by either a trained nurse or a genetic counselor when receiving their results. Additionally, carrier couples of the same condition were offered an in-person/virtual appointment in a genetics clinic to further discuss the result, its potential implications, and available reproductive options. The proportion of people who received this additional genetic counseling at some point (could be postponed to a more opportune time when in preconceptional period) and the outcome of the appointment has not been compiled mostly to respect autonomy and confidentiality of this personal choice. This is in line with the decision we made to not compile the reproductive decision of the carrier couples.

Because the program is based on self-reporting and no independent validation of ancestry is done, there is a possibility that some participants were ineligible for the program when they accessed it. Therefore, the HF reported will likely be underestimated for each condition. Thus, the HF from the regional phase are likely more representative of the SLSJ/HCN/C population. Furthermore, our workflow does not independently validate the participants' identities. It is, therefore, possible that an individual requests the test for another person (for example, a partner) who would not have reviewed the online education module and may not have been able to provide informed consent.

In summary, offering carrier screening for 4 recessive hereditary diseases to the SLSJ/HCN/C region population over the past 12 years has enabled 116 carrier couples to make informed decisions about their reproductive choices and has advised many others of their carrier status. The program is rapid, noninvasive, relatively inexpensive, and socially accepted. Over the years, the HF have remained high in the targeted population. These results show that carrier screening is still relevant and supports adding other prevalent and severe recessive conditions to the program. We hope that this approach may serve as a model for other regions looking to implement a similar CSP.

Data Availability

The data sets generated and/or analyzed during this study are not publicly available to respect the participants' consent but are available from the corresponding author upon request.

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Author Contributions

Conceptualization and Supervision: L.B.; Investigation: M.C.-R., K.T., J.L., A.P., J.T., M.-J.T., J.V., J.M., D.G., M.D., T.C.-M., L.B.; Data Curation: C.-A.F.; Formal Analysis; C.-A.F., C.M., S.G., L.B; Writing-original draft: C.-A.F., L.B.; Writing-review and editing: C.-A.F., K.T., J.L., J.T., M.-J.T., J.V., J.M., D.G., M.D., C.M., S.G., T.C.-M., L.B.

Ethics Declaration

Approval for the secondary use of anonymized data of the carrier screening program was obtained from the CIUSSS-SLSJ's direction of professional services, in accordance with the ethical rules in law at this time. The Research Ethic Board's confirmed that this research met the criteria for waiver of consent.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Additional Information

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