article

Distribution of *CFTR* mutations in Saguenay–Lac-Saint-Jean: proposal of a panel of mutations for population screening

Anne-Marie Madore, MSc[1,2,3], Claude Prévost, MSc[4], Ruslan Dorfman, PhD[5], Chelsea Taylor, MSc[5], Peter Durie, MD, FRCP[5], Julian Zielenski, PhD[5], and Catherine Laprise, PhD[2,3]

Purpose: Saguenay–Lac-Saint-Jean is a region located in the northeastern part of the Province of Quebec, Canada, and is characterized by a founder effect. In this region, it has been documented that the incidence of cystic fibrosis reached 1/902 live births between 1975 and 1988, three times higher than the average incidence of 1/2500 live births reported in other Caucasian populations. This corresponds to a carrier rate of 1/15. **Methods:** Using genotyping data from the Canadian Consortium for Cystic Fibrosis Genetic Studies, this article describes the cystic fibrosis transmembrane conductance regulator profile of the cystic fibrosis population living in the Saguenay–Lac-Saint-Jean region and compares it with cystic fibrosis populations living in three other regions of the Province of Quebec. **Results:** Significant differences in allelic frequencies of common mutations (as △F508, 621 + 1G>T and A455E), and in percentage of covered allele with three or six mutations, were found in Saguenay–Lac-Saint-Jean compared to other regions. Based on this result, two mutation panels exceeding 90% sensitivity threshold are now proposed for cystic fibrosis carrier screening in this region. **Conclusion:** The implementation of the proposed carrier screening program could diminish the incidence of this disease in this region and allow future parents to make informed decisions about family planning. ***Genet Med* 2008:10(3):201–206.**

Key Words: *Cystic fibrosis, Saguenay–Lac-Saint-Jean, carrier screening, mutations, CFTR*

The Quebec population numbers more than seven million, of which roughly six million have descended from French settlers. Among the 25,000 settlers who came from various provinces of France between the beginning of the 17th century and the British conquest of 1763, only about 8,500, including 1,600 women, settled permanently.[1–3] It was demonstrated that the 2,600 settlers established in "Nouvelle-France" before 1680 contributed about two thirds of the gene pool of the current Francophone population.[1,4] A mosaic of founder effects was observed in rural regions recently opened to colonization and, while inter-regional migrations have increased with time, regional genetic variation persists throughout the Province of Quebec (PQ). The Saguenay–Lac-Saint-Jean (SLSJ) region is a well-documented example of this phenomenon.[5] It is a geographically isolated region located in the northeastern part of Quebec. Several studies have demonstrated an increased incidence of autosomal dominant and recessive disorders in this region.[6,7] In SLSJ, it was documented that the incidence of cystic fibrosis (CF) reached 1 live birth per 902 between 1975 and 1988, which corresponds to a carrier rate of 1/15.[8,9] This is three times higher than the average incidence of 1/2500 live births in other Caucasian populations (or a carrier rate of 1/25).

CF is a multisystemic disorder caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene.[10] It affects both the respiratory and the digestive systems, and can also induce infertility in men.[11] A variable genetic correlation was observed between *CFTR* mutations and pulmonary function,[12] pancreatic insufficiency,[13] and congenital bilateral absence of the vas deferens.[14] This subject is reviewed at length in a recent review by Dorfman and Zielenski.[15] Since it was cloned in 1989, over 1,500 *CFTR* mutations have been documented.[16,17] Some of them, such as *△F508*, are commonly distributed, whereas others are found in specific populations or ethnic groups, such as the *M1101K* in Hutterites.[18,19] The protein encoded by the *CFTR* gene is expressed in the apical membrane of exocrine epithelial cells, and is a cyclic adenosine monophosphate (cAMP)-induced chloride channel that can also regulate other ion channels.[10,20]

For CF neonatal screening, many programs throughout the world have adopted a two-tier combination of trypsinogen and DNA analysis with either *△F508* allele alone or a panel of CF-causing mutations.[21] In the same way, multimutation plat-

From the [1]Université Laval, Québec, Canada; [2]Université de Montréal Community Genomic Medicine Center, Saguenay, Canada; [3]Université du Québec à Chicoutimi, Saguenay, Canada; [4]Service de conseil génétique, Centre de santé et de services sociaux de Chicoutimi, Saguenay, Canada; and [5]Hospital for Sick Children, Toronto, Canada.

Catherine Laprise, PhD, Université du Québec à Chicoutimi, 555 blvd de l'Université, Chicoutimi (Québec), Canada G7H 2B1. E-mail: catherine_laprise@uqac.ca.

Disclosure: The authors declare no conflict of interest.

Submitted for publication October 10, 2007.

Accepted for publication December 1, 2007.

DOI: 10.1097/GIM.0b013e318164cb1c

forms can be built to offer carrier screening in different populations. To do so, there is a need to determine which mutations should be part of a *CFTR* mutation screening panel to reach a high sensitivity (>90%) in a particular population.[22] In this report, after having assessed and compared the distribution of *CFTR* mutations in the SLSJ region with that of three other regions of PQ, we propose a mutation panel for carrier screening purposes in the SLSJ population.

MATERIALS AND METHODS

Subjects

The Canadian Consortium for Cystic Fibrosis Genetic Studies has genotyped samples from 6 of the 10 different CF clinics of the PQ, totaling 482 patients with CF (Canadian Consortium for Cystic Fibrosis Genetic Studies, unpublished data). It represents 45% of the patients with CF living in the PQ. All patients have an established diagnosis of CF. The phenotypic description of these patients, including sex ratio, mean age, percent predicted value of forced expiratory volume in one second (FEV_1), and body mass index (BMI), is shown in Table 1. The project was approved by the ethics committee of the Hospital for Sick Children and informed consent was obtained from all subjects. In this study, we grouped the samples of the six clinics into four populations (see Fig. 1). The first population is from the SLSJ region, and is mainly composed of Francophones (Centre de santé et de services sociaux de Chicoutimi; $n = 85$). The second population, also mainly composed of Francophones, is from Sherbrooke (Centre hospitalier universitaire de Sherbrooke; $n = 42$), a city located southeast of Montreal and close to the United States border. Montreal is the largest city of the PQ and the most ethnically diversified. It is composed of individuals (Francophones and Anglophones) who have been living there for many generations, individuals (mostly Francophone) coming from all other regions of the PQ, and immigrants (multiethnics). Samples from the four CF clinics in Montreal were grouped into

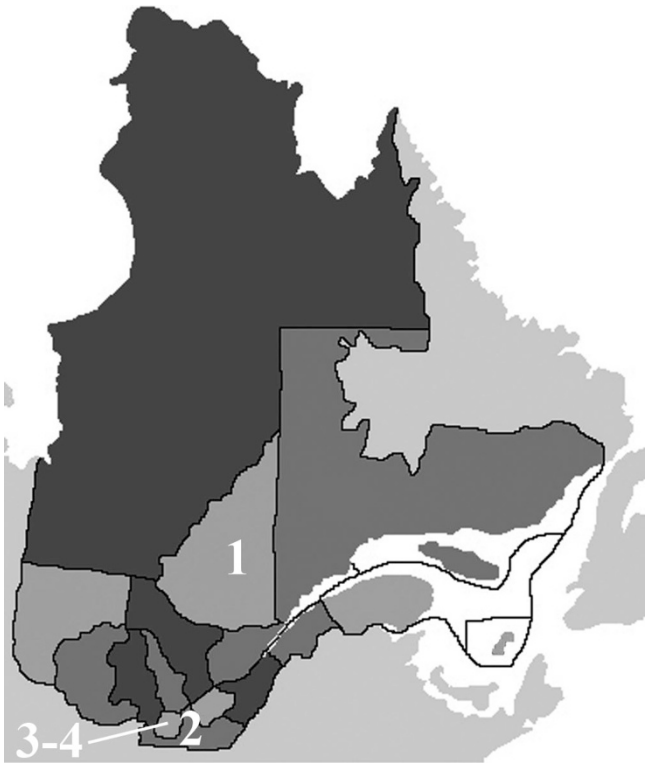

Fig. 1. Map of the Province of Quebec. The different regions of the Province of Quebec. The numbers one, two, three, and four represent the Saguenay–Lac-Saint-Jean region (Chicoutimi CF clinic), the Sherbrooke CF clinic, the Montreal Francophone CF clinics, and the Montreal Anglophone and multiethnic CF clinics, respectively.

Table 1
Phenotypic description of the subjects

	Population[a]					
	1	2	3		4	
Institution[b]	CSSSC ($n = 85$)	CHUS ($n = 42$)	CHUM ($n = 196$)	CHUSJ ($n = 96$)	MCH ($n = 53$)	MCI ($n = 10$)
Children						
Mean age (yr)	12	10	NA	10	9	NA
Mean FEV_1 (% pred)	85.56	83.30	NA	89.25	70.5	NA
Mean BMI (kg/m^2)	17.17	17.28	NA	17.65	16.75	NA
Adults						
Mean age (yr)	29	27	27	NA	NA	32
Mean FEV_1 (% pred)	52.74	54.79	61.27	NA	NA	43.21
Mean BMI (kg/m^2)	21.93	21.19	21.77	NA	NA	21.27

[a]1, Saguenay–Lac-Saint-Jean (Chicoutimi CF clinic); 2, Sherbrooke CF clinic; 3, Montreal mostly Francophone CF clinics; and 4, Montreal mostly Anglophone and multi-ethnic CF clinics.
[b]CSSSC, Centre de santé et de services sociaux de Chicoutimi; CHUS, Centre hospitalier universitaire de Sherbrooke; CHUM, Centre hospitalier de l'Université de Montréal; CHUSJ, Centre hospitalier universitaire Sainte-Justine; MCH, Montreal Children's Hospital; MCI, Montreal Chest Institute.
NA, not available; FEV_1, (% pred), forced expiratory volume in one second (% predicted value); BMI, body mass index.

two populations: the third and the fourth populations of this study; one is mostly composed of Francophones (Centre hospitalier de l'Université de Montréal and Centre hospitalier universitaire Sainte-Justine; $n = 292$) and the other is mostly composed of Anglophones and immigrants (Montreal Children's Hospital and Montreal Chest Institute; $n = 63$).

CFTR mutation screening

The *CFTR* genotyping was performed using two methods: multiplexed heteroduplex analysis[23] and high-resolution melt analysis with SYTO9 (Invitrogen, Burlington, Canada) and Corbett Rotor-Gene 6000HRM (Corbett Life Science, Sydney, Australia) instrument[24] followed by resequencing of the identified fragments. Large deletion detection was performed using established conditions.[25,26] Some samples with incomplete *CFTR* genotype ($n = 128$) were screened for large deletions by Quest Diagnostics (Madison, NJ).[27,28]

Statistical analysis

A χ^2 test was used to make comparisons between the allele distributions of the different populations, a P-value <0.05 was considered significant.

RESULTS

Data from the Canadian Consortium for Cystic Fibrosis Genetic Studies make it possible to describe the distribution of *CFTR* mutations in the SLSJ region and to compare it with that of three other regions in the PQ (see Table 2 for allelic frequencies). Three mutations are prevalent in the SLSJ population (△F508, 621 + 1G>T, and A455E); according to data provided by the genetic counseling services and the Chicoutimi CF clinic, three other mutations are present in at least three different families (711 + 1G>T, 3199del6, and Y1092X). Figure 2 illustrates the differences in the distribution of these six mutations in the SLSJ region compared with the three other regions. Although the △F508 and 621 + 1G>T mutations are more frequent in all populations studied, their distribution in the SLSJ region is different. The mutation △F508 is less represented in the SLSJ (Fig. 2, A) population than in the other French populations studied ($P = 0.011$) (Fig. 2, B and C). Moreover, the 621 + 1G>T is three to four times more frequent in the SLSJ population than in the two other Francophone population described here ($P < 10^{-12}$) and more than 25 times more frequent than in the Anglophone and multiethnic population of Montreal ($P < 10^{-7}$) (Fig. 2, D). Similarly, the A455E mutation frequency is two to three times higher in the SLSJ population compared with the other Francophone population studied ($P = 0.004$) and eight times higher than in the Anglophone and multiethnic population of Montreal ($P = 0.013$). Moreover, there is only one unknown CF allele in the SLSJ population compared with 25 only in the Francophone populations ($P = 0.027$) and also 25 in the Anglophone and multiethnic population ($P < 10^{-8}$). Altogether, the six mutations represent 95.89% of the *CFTR* allele of CF patients in the SLSJ population, whereas the proportions are 86.85, 85.27, and

Table 2
Cystic fibrosis mutations present in the four populations studied

	Allelic frequency (number of alleles [%]) Population[b]			
Mutation[a]	1	2	3	4
△F508	**106 (62.35)**	**55 (72.37)**	**398 (72.36)**	**67 (57.78)**
621 + 1G>T	**42 (24.71)**	**6 (7.89)**	**30 (5.45)**	**1 (0.85)**
A455E	**12 (7.06)**	**2 (2.63)**	**14 (2.55)**	**1 (0.85)**
3199del6	**1 (0.59)**	**1 (1.32)**	**7 (1.27)**	**1 (0.85)**
711 + 1G>T	**1 (0.59)**	**1 (1.32)**	**15 (2.73)**	**1 (0.85)**
Y1092X	**1 (0.59)**	**1 (1.32)**	**5 (0.91)**	**0**
R117C	2 (1.18)	0	0	0
△I507	1 (0.59)	2 (2.63)	10 (1.82)	0
L206W	1 (0.59)	1 (1.32)	9 (1.64)	0
R1158X	1 (0.59)	0	0	0
S489X	1 (0.59)	0	1 (0.18)	0
R553X	0	2 (2.63)	2 (0.36)	0
R334W	0	1 (1.32)	2 (0.36)	0
G542X	0	0	10 (1.82)	0
G85E	0	0	6 (1.09)	5 (4.24)
N1303K	0	0	5 (0.91)	1 (0.85)
IVS8-5T	0	0	4 (0.73)	0
W1282X	0	0	3 (0.55)	7 (5.93)
R347P	0	0	1 (0.18)	2 (1.69)
V520F	0	0	1 (0.18)	0
I1027T	0	0	1 (0.18)	0
R1066C/IVS	0	0	1 (0.18)	0
Q1313X	0	0	1 (0.18)	0
1898+3G>A	0	0	1 (0.18)	0
2183AA>G	0	0	1 (0.18)	0
2951insA	0	0	1 (0.18)	0
G551D	0	0	0	2 (1.69)
1525-iG-A	0	0	0	2 (1.69)
Y109C	0	0	0	1 (0.85)
S549N	0	0	0	1 (0.85)
3154del1G	0	0	0	1 (0.85)
UNKNOWN	1 (0.59)	4 (5.26)	20 (3.82)	25 (21.19)
Number of alleles genotyped[c]	170 (100)	76 (100)	550 (100)	118 (100)

[a]The six mutations included in the panels proposed are in bold.
[b]1, Saguenay–Lac-Saint-Jean (Chicoutimi CF clinic); 2, Sherbrooke CF clinic; 3, Montreal mostly Francophone CF clinics; 4, Montreal mostly Anglophone and multi-ethnic CF clinics.
[c]For each population, some alleles could not be genotyped (mean call rate for population 1: 100%; population 2: 90.48%; population 3: 94.18%; population 4: 93.65%).

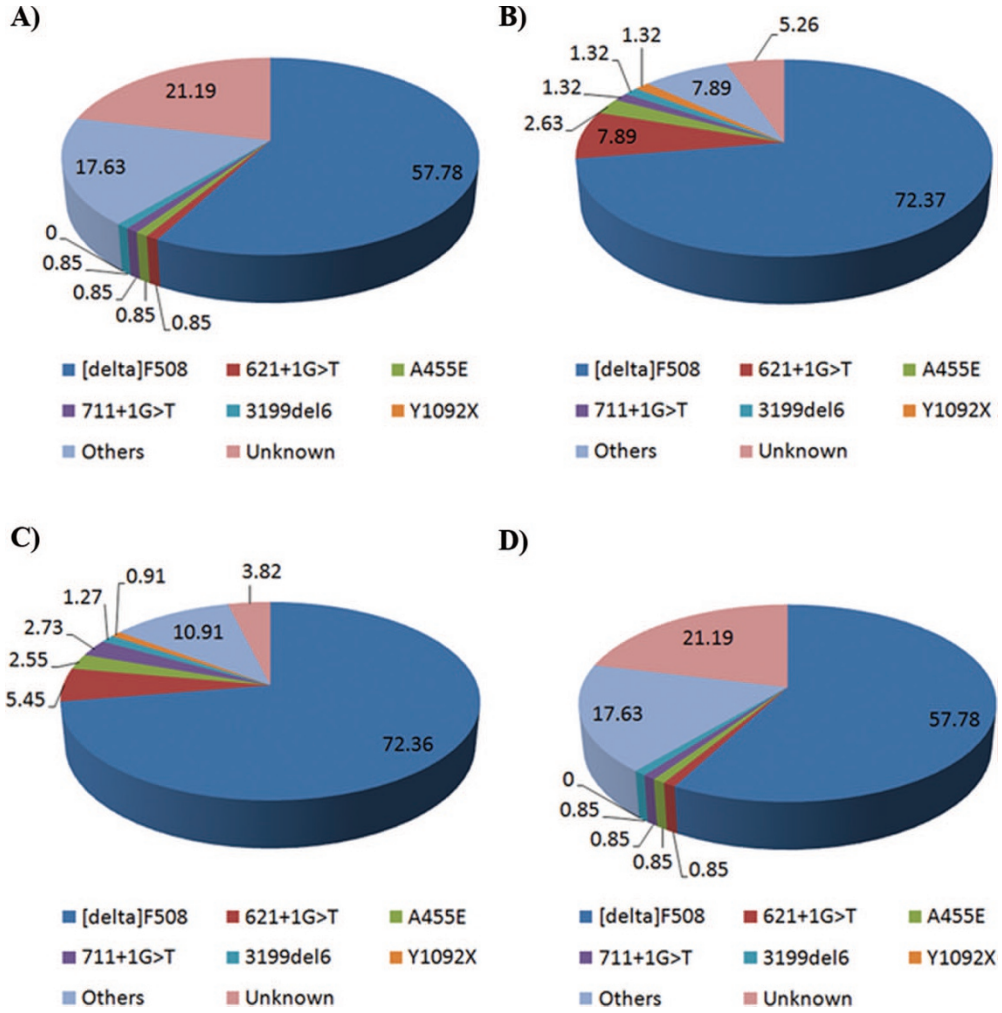

Fig. 2. Distribution of the *CFTR* alleles in the Saguenay–Lac-Saint-Jean population in comparison with three other populations of the Province of Quebec. The percentage of six cystic fibrosis transmembrane conductance regulator (*CFTR*) alleles in four populations; subjects from (A) the Chicoutimi CF clinic in the Saguenay–Lac-Saint-Jean (SLSJ) region, (B) the Sherbrooke CF clinic, (C) the two CF clinics representing the Francophone population of Montreal, and (D) the two CF clinics representing the Anglophone and multiethnic population of Montreal. The three most common alleles in the SLSJ population are the △F508, 621 + 1G>T and A455E mutations. The frequency of the △F508 mutation is lower in the SLSJ population than in the other Francophones population ($P = 0.011$) but the frequency of the 621 + 1G>T and A455E mutation is greater in this region than in any other region described here ($P < 10^{-12}$ and $P = 0.004$ for the Francophone populations, and $P < 10^{-7}$ and $P = 0.013$ for the Anglophone and multiethnic population, respectively). Moreover, the percentage of unknown alleles is only 0.59% in the SLSJ region. It is lower than any other regions described in this study ($P = 0.027$ in Francophone and $P < 10^{-8}$ in Anglophone and multiethnic populations).

61.18% for the Sherbrooke CF clinic, the Montreal Francophone CF clinics, and the Montreal Anglophone and multiethnic CF clinics, respectively ($P = 0.010$, $P < 10^{-3}$, and $P < 10^{-13}$, respectively) (Figs. 2 and 3).

DISCUSSION

Bobadilla et al.[21] proposed a 50-mutation platform for CF neonatal diagnosis, considering the most prevalent mutations and those that are present in different ethnic subgroups in the US population. Previously, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG), in conjunction with the National Human Genome Research Institute, have also proposed a panel for CF screening in the US population comprising 23 mutations.[29,30] Those examples illustrate the great challenge encountered when building a multimutation screening program for CF disease in multiple populations, i.e., reaching a high sensitivity (>90%) while avoiding exclusion of any minority populations.[22] In the SLSJ population, a founder effect occurred during the settlement of the region, thus diminishing the genetic diversity of its population; this effect is well illustrated for the CF population.[31] Moreover, the SLSJ region is characterized by a low immigration rate; according to the 2001 census of the Quebec population made by the "Instituts de la statistique du Québec," immigrants represent only 0.73% of the population (2,040/278,279 individuals).[32] Finally, because there are few rare CF mutations in the SLSJ region, researchers have identified almost all the patients with *CFTR* mutations.

Table 1 gives phenotypic data about the subjects of the four regions studied. The mean age and body mass index (kg/m^2) are similar for the four groups of children and adults who live in those regions. The only difference observed is for the FEV_1 (% pred), which is lower for the children and adults

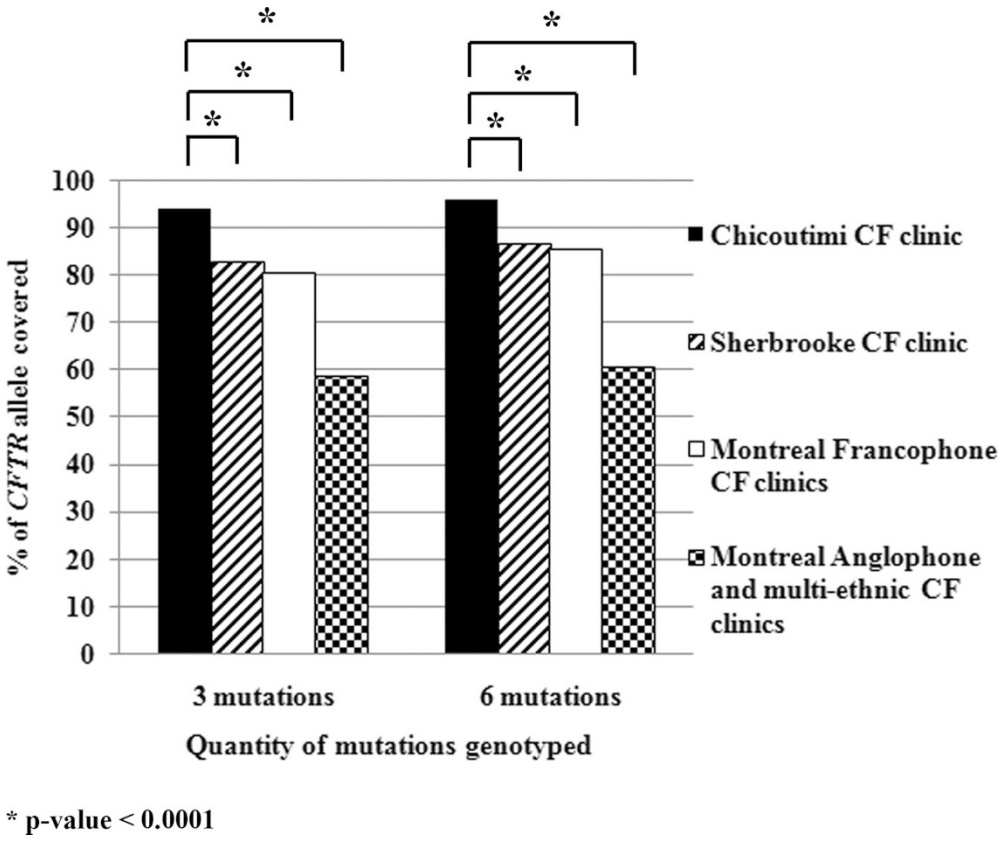

Fig. 3. Percentage of *CFTR* allele covered with three or six mutations in the Saguenay–Lac-Saint-Jean population in comparison with three others populations of the Province of Quebec. With only three mutations, the rate of covered cystic fibrosis transmembrane conductance regulator (*CFTR*) allele obtained in the Saguenay–Lac-Saint-Jean (SLSJ) population (Chicoutimi CF clinic) is significantly higher than in the other regions, reaching 94.12% compared with 82.89, 80.36, and 59.48% for the Sherbrooke population, the Francophone population of Montreal, and the Anglophone and multiethnic population of Montreal, respectively ($P = 0.005$, $P < 10^{-4}$, and $P < 10^{-12}$). Moreover, with six mutations the rate is 95.89% for the SLSJ region, also significantly higher than 86.85, 85.27, and 61.18% for the other ones ($P = 0.010$, $P < 10^{-3}$, and $P < 10^{-13}$, respectively).

from the Anglophone and multiethnic population of Montreal than for subjects of Francophone populations studied. As observed in the data from the Canadian Consortium for Cystic Fibrosis Genetic Studies (Figs. 2 and 3), the distribution of *CFTR* mutations in SLSJ region is different from that in other regions in the PQ. In the study of Rozen et al.,[33] the authors also observed that the frequency for △F508 mutation was lower in SLSJ region (58.0%) than in the other regions of the PQ (71%) ($P = 0.047$), and that subjects from the SLSJ region also have a higher 621 + 1G>T (23.2%) frequency than those of the remaining regions of the PQ (12.84%) ($P = 10^{-5}$).[21,33]

Four of our six most frequent mutations (△F508, 621 + 1G>T, A455E, and 711 + 1G>T) are present in the ACMG-ACOG panel of 23 mutations, representing a detection rate of 94.71% in the SLSJ population. However, according to our results, a multimutation panel for carrier screening in the SLSJ region could include only the three principal mutations (△F508, 621 + 1G>T, and A455E), covering a total of 94.12% of the *CFTR* alleles present in the SLSJ region (Fig. 3). Another possibility is to include the three additional mutations that are at least present in three different families (711 + 1G>T, 3199del6, and Y1092X), reaching a detection rate of the *CFTR* alleles of 95.89% (Fig. 3). These two possibilities are greater than the 90% sensitivity threshold accepted for screening tests and would be at a low cost.[22] The implementation of a CF carrier screening program could diminish the incidence of CF in the SLSJ region and, more importantly, allow future parents to make informed decisions about family planning.

ACKNOWLEDGMENTS

A.-M. Madore is supported by the Canadian Institutes of Health Research (CIHR). R. Dorfman is supported by the joint Fellowship of CIHR and Ontario Women's Health Council. C. Taylor is supported by the CIHR-University of Toronto Collaborative Graduate Training Program in Molecular Medicine Studentship. C. Laprise is the chairholder of the Canada Research Chair for genetic determinants in asthma (www.chairs.gc.ca). This project was supported by Genome Canada through the Ontario Genomics Institute (no. 2004-OGI-3-05) and the Canadian Cystic Fibrosis Foundation, and donations from the Lloyd Carr-Harris Foundation. The authors express their gratitude to all patients with CF and their families for participating in the study. The authors acknowledge the individual members of The Canadian Consortium for CF Genetic Studies for submission of patient data and sending blood samples from patients with CF and their families.

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