FACULTÉ DE MÉDECINE

EPIDÉMIOLOGIE GÉNÉTIQUE DE LA FIBROSE KYSTIQUE AU SAGUENAY-LAC-ST-JEAN

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RÉSUMÉ

Le Saguenay-Lac-St-Jean est une région isolée géographiquement située à 200 kilomètres au nord-est de la ville de Québec. La fibrose kystique, maladie héréditaire autosomale récessive, atteint une prévalence à la naissance de 1/902 naissances vivantes et un taux de porteurs de 1/15 habitants dans cette région. Les caractéristiques cliniques des 127 patients atteints de fibrose kystique semblent montrer un état général très satisfaisant ce qui pourrait être le résultat d'une fréquence moindre de la mutation ΔF508 au profit de la présence d'autres mutations moins sévères.

Une étude de la distribution par mois de naissance ne montre pas de distribution aberrante saisonnière ou mensuelle parmi ces patients. Par contre la distribution spatiale montre des foyers où la prévalence à la naissance est plus élevée. Alors que le coefficient moyen de consanguinité des patients atteints de fibrose kystique est marginalement plus élevé que celui des témoins appariés, le coefficient moyen de parenté est nettement plus élevé. Ces résultats combinés à des facteurs historiques, démographiques et sociaux expliquent cette prévalence à la naissance élevée pour la fibrose kystique dans cette région. De plus, elle est probablement le résultat d'un effet fondateur et d'une dérive génétique pour plusieurs mutations de fibrose kystique.

Jocelyne Daigneault.
Jocelyne Daigneault

Marc De Braekeleer

SUMMARY

Saguenay-Lac-St-Jean is an geographically isolated region situated at 200 kilometers northeast of Quebec city. Cystic fibrosis (CF) is an hereditary autosomal recessive disease that has a prevalence at birth of 1/902 liveborns and carrier rate of 1/15 inhabitants in that region. The clinical features of 127 patients with cystic fibrosis appeared to show a very satisfactory general health status which might be the result of a lower frequency of the ΔF508 mutation than in other population and the presence of other less severe mutations.

The monthly distribution of the CF births did not show any particular seasonal or monthly distribution among these patients. However spatial distribution showed clusters in which the prevalence at birth was higher. Although the mean coefficient of inbreeding in the CF group was somewhat higher than in the control groups, the mean coefficient of kinship was much higher. Those results combined with historical, demographical and social factors explains why the prevalence at birth of CF is high in this region. Furthermore, this high prevalence at birth is probably due to a founder effect and genetic drift for several CF mutations.

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INTRODUCTION GÉNÉRALE

La fibrose kystique ou mucoviscidose est une maladie héréditaire autosomale récessive léthale, la plus commune chez les Caucasiens. Son incidence est de 1 pour 2000-2500 naissances vivantes dans les populations blanches. Le gène de la fibrose kystique a été localisé sur le bras long du chromosome 7 dans la bande q 31. La découverte du gène de la fibrose kystique a créé de grands espoirs chez les malades et leurs familles. La découverte était immédiatement associée à guérison dans l'esprit des gens. Malheureusement la découverte du gène n'est que la lumière au bout du tunnel et il reste encore beaucoup de recherches à effectuer pour mieux connaître ce gène, c'est-à-dire le défaut biochimique de base, les différentes mutations, les relations qui existent entre le génotype et le phénotype.

La région du Saguenay-Lac-St-Jean (SLSJ), entité isolée géographiquement, est située à 200 kilomètres au nord-est de Québec. Elle a été ouverte au peuplement blanc en 1838. La population est en grande majorité canadienne-française, de religion catholique et compte 285,000 habitants.

Le type de formation de la population, l'immigration familiale, la fécondité très élevée et les mariages préférentiels expliquent la présence de maladies génétiques "propres" à Charlevoix et au SLSJ telles que l'ataxie Charlevoix-Saguenay et la polyneuropathie sensori-motrice avec ou sans agénésie du corps calleux.

La clinique de fibrose kystique de l'hôpital de Chicoutimi a été fondée au printemps de 1973, sous l'égide du Dr Gervais Aubin qui a répertorié les cas examinés et traités depuis son ouverture jusqu'à aujourd'hui. Depuis les dernières années, il était devenu évident que la fibrose kystique devait avoir une incidence élevée dans cette région. Cependant aucune étude épidémiologique ou génétique n'avait encore été réalisée.

C'est à partir de toutes les données disponibles à la clinique de fibrose kystique que nous avons tenté de mieux connaître cette maladie dans la région du SLSJ (incidence, distribution géographique, caractéristiques cliniques) et de voir quelle place elle occupait parmi les autres populations. La découverte du gène durant cette étude a aussi permis d'envisager une meilleure connaissance des différentes mutations présentes dans la population du SLSJ. Finalement, la découverte de la mutation ΔF508 nous a incité à étudier sa distribution dans la race blanche.

CHAPITRE I

LA FIBROSE KYSTIQUE AU SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA): DISTRIBUTION SELON LE MOIS DE NAISSANCE.

[BIRTH DISTRIBUTION IN CYSTIC FIBROSIS IN SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA)].

* "Birth distribution in cystic fibrosis in Saguenay-Lac-St-Jean, Quebec, Canada" Jocelyne Daigneault, Gervais Aubin, Fernand Simard, Marc De Braekeleer accepté pour publication dans: *Journal of Medical Genetics*

I.1 RÉSUMÉ

La distribution par mois de naissance de la fibrose kystique rapportée dans la littérature démontre une tendance à la saisonnalité, cependant ces résultats sont controversés.

La distribution par mois de naissance de 111 patients atteints de fibrose kystique nés au Saguenay-Lac-St-Jean a été analysée selon deux méthodes statistiques différentes. Nos résultats ne démontrent aucune variation mensuelle ou saisonnière. Il est probable qu'un biais causé par un échantillonnage incomplet explique en partie les résultats obtenus dans d'autres études qui démontraient une tendance saisonnière pour les mois de naissance des enfants atteints de fibrose kystique.

I.2 ABSTRACT

Although a seasonal trend in the birth distribution was reported in cystic fibrosis (CF), this finding is still very controversial. The birth distribution of 111 patients with cystic fibrosis born in Saguenay-Lac-St-Jean (complete ascertainment) was analyzed using two different statistical methods. Our results showed no monthly or seasonal birth variation. It is likely that a bias due to incomplete ascertainment might explain why some previous studies found a seasonal trend in the CF birth distribution.

I.3 INTRODUCTION

Saguenay-Lac-St-Jean (SLSJ) is a geographically isolated region located 125 miles northeast of Quebec City that was opened to white settlement around 1840. Its population, 98% French speaking and of Catholic faith, rose from 5,000 inhabitants in 1852 to 50,000 in 1911 and 285,000 today. Several dominant and recessive autosomal disorders have a higher prevalence (myotonic dystrophy, cystic fibrosis, etc.) while others, frequently found in the SLSJ region and Charlevoix, are almost nonexistent elsewhere (spastic ataxia Charlevoix-Saguenay type, polyneuropathy with or without agenesis of the corpus callosum, etc.) [1].

Over the past 20 years, monthly or seasonal birth variation have been reported in various chromosomal and congenital anomalies such as Down's syndrome, Klinefelter's syndrome and anencephaly. A seasonal trend was also suggested in cystic fibrosis (CF) by several workers [2-5]. However, the issue remained controversial since two studies failed to show any uneven monthly birth distribution [6,7].

This study was aimed at analyzing the monthly birth distribution of patients with cystic fibrosis born in Saguenay-Lac-St-Jean (SLSJ).

I.4 MATERIAL AND METHODS

The great majority of the individuals affected with CF living in SLSJ have been followed at the CF clinic in Chicoutimi since spring 1973, date of its opening. Of a total of 127 CF individuals known in the SLSJ region on December 31th, 1989, 125 patients had been or were

still followed at the CF clinic in Chicoutimi. The diagnosis of cystic fibrosis was based on the patient and family histories, clinical, radiological, and biochemical results. All CF cases were confirmed by at least a positive sweat test. For the present study, only the 111 CF individuals born in SLSJ were considered.

The statistical significance was sought using two methods. The observed number of patients, altogether, for each month was compared to the expected number and a chi-square test performed. The expected rates were calculated using all live births in the area during the range of years of birth of the 111 patients (1954 - 1988). For each month, the expected number of patients was calculated using the formula of Nielsen et al. [8]

$$E_m = \frac{n_m}{N} \times A$$

where E_m = expected number of patients for a given month
n_m = total number of livebirths of a given month in the period studied
N = total number of livebirths in the period studied
A = total number of affected individuals in the period studied.

The second method consisted in a Monte Carlo simulations procedure. The total number of patients was simulated 5000 times under the null hypothesis that the cumulative number of CF births by month should be proportional to the cumulative number of live births by month over the period of study; the probabilities were then determined.

I.5 RESULTS

The distribution by month of birth of the CF patients was compared to the expected distribution calculated according to the method of Nielsen et al. Table 1.1 shows the number of patients born in each month, the mean number of live births by month in the SJSL region during the period studied (1954-1988) and the number of CF births expected by month. As shown in figure 1.1, the frequency of the CF births was markedly increased in January and decreased in May. However, no statistically significant difference was found between the observed and the expected distributions ($X^2_{11} = 9.33$; $p > 0.05$). The Monte Carlo simulations also failed to show any month to have a significantly higher or lower number of CF births than expected ($p > 0.05$).

Although there was a slight excess of winter births (December - February) over summer births (June - August) (33 compared to 28), the difference was not statistically significant ($X^2 = 2.12$; $p > 0.05$).

I.6 DISCUSSION

No monthly or seasonal trend in the births of the CF individuals was found in this series from Saguenay-Lac-St-Jean. Although there were only 111 cases analyzed, this series relies on the fact that all CF patients were born in a well-defined region and on a complete ascertainment. Our results are in agreement with those obtained by David et al. [6] and Machill et al. [7].

As already suggested by both groups [6,7], it is most likely that the seasonal variation in CF births observed in previously reported

series [2-5] was the result of sampling bias mostly due to incomplete ascertainment or chance.

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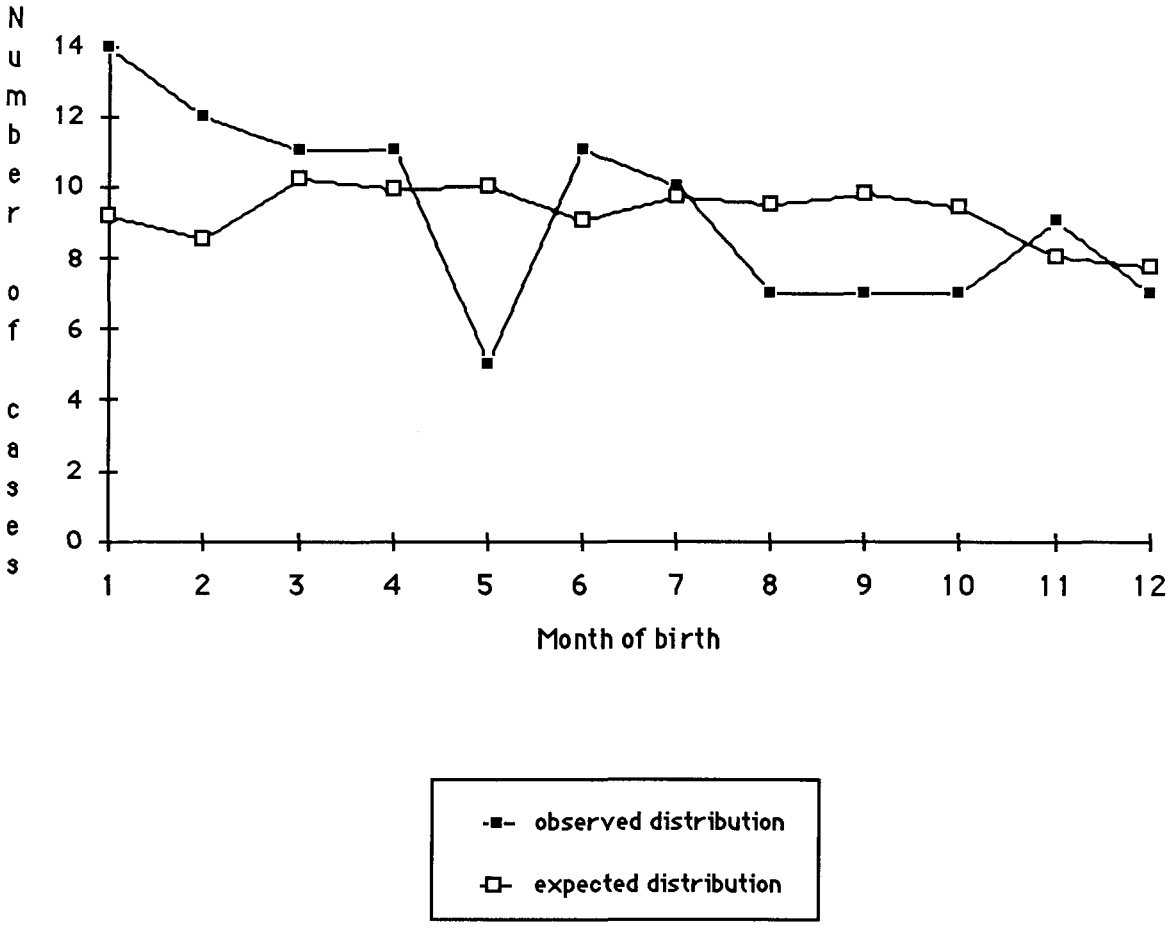
I.8 FIGURE

Figure 1.1 Cumulative monthly distribution in cystic fibrosis in Saguenay-Lac-St-Jean


Number of cases
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
Month of birth
observed distribution
expected distribution

I.9 TABLE

Table 1.1 Number of CF patients born and expected in each month during the period studied (1954-1988) in the SLSJ region.

Month	Number of CF patients	Mean number of live births	Expected number of CF births
1	14	468	9.2
2	12	433	8.5
3	11	517	10.2
4	11	502	9.9
5	5	500	10.0
6	11	458	9.0
7	10	494	9.7
8	7	484	9.5
9	7	499	9.8
10	7	480	9.4
11	9	455	8.0
12	7	447	7.7

CHAPITRE II

EPIDÉMIOLOGIE GÉNÉTIQUE DE LA FIBROSE KYSTIQUE AU SAGUEAY-LAC-ST-JEAN (QUÉBEC, CANADA)

[GENETIC EPIDEMIOLOGY OF CYSTIC FIBROSIS IN SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA)].

* "Genetic epidemiology of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada) Jocelyne Daigneault, Gervais Aubin, Fernand Simard, Marc De Braekeleer accepté pour publication dans: *Clinical Genetics*

II.1 RÉSUMÉ

La fibrose kystique est une maladie transmise selon un mode autosomal récessif dont la prévalence à la naissance varie entre 1/2000 à 1/2500 naissances vivantes dans les populations caucasiennes. Quelque 127 individus atteints de fibrose kystique sont connus dans la région du Saguenay-Lac-St-Jean, une région isolée géographiquement du Québec.

La prévalence à la naissance de la fibrose kystique pour cette région (SLSJ) est estimée à 1/902 naissances vivantes et le taux de porteurs est estimé à 1/15 habitants. Le coefficient moyen de consanguinité est légèrement plus élevé dans le groupe atteint de fibrose kystique comparativement à trois groupes témoins. Cette augmentation est due à une consanguinité éloignée. Le coefficient moyen d'apparentement est 2,4 fois plus élevé dans le groupe atteint de fibrose kystique que dans les groupes contrôles. Dans la région du SLSJ, la distribution des lieux de naissance des individus atteints ainsi que de leurs parents, n'a montré aucune distribution particulière. L'endogamie n'est d'ailleurs pas plus élevée dans le groupe atteint que parmi les groupes témoins.

II.2 ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive disorder with a prevalence at birth estimated at 1/2000-1/2500 livebirths in Caucasian populations. Some 127 CF individuals are known in Saguenay-Lac-St-Jean (SLSJ), a geographically isolated region of Quebec. The prevalence at birth was estimated at 1/902 live borns, and the carrier rate was estimated at 1/15 inhabitants in the SLSJ region. The mean inbreeding coefficient was only slightly elevated in the CF group compared with three control groups and was due to remote consanguinity. The mean kinship coefficient was 2.4 times higher in the CF group than in the control groups. In SLSJ region, the places of origin of the CF individuals and their parents did not show a clustered nonuniform distribution. Endogamy was not higher in the CF group than in control groups.

II.3 INTRODUCTION

Saguenay-Lac-St-Jean (SLSJ) is a geographically isolated region located 200 kilometers northeast of Quebec City (Figure 2.1). The region under study has been described in full details elsewhere (De Braekeleer & Larochelle 1990; De Braekeleer 1991).

Cystic fibrosis (CF) is an autosomal recessive disorder that affects one child in every 2000-2500 liveborns in Caucasian populations (Boat et al. 1989). In the past few years, it became evident that cystic fibrosis had a higher prevalence at birth in the SLSJ region than reported in most Caucasian populations.

The present study was aimed at analyzing the prevalence at birth and the carrier rate of cystic fibrosis in Saguenay-Lac-St-Jean. Inbreeding, kinship, endogamy, and geographical distribution of CF homozygotes and obligate heterozygotes were also studied.

II.4 MATERIAL AND METHODS

Since spring 1973, date of its opening, the great majority of the individuals affected with CF and living in SLSJ have been followed at the CF clinic in Chicoutimi. A database containing all CF cases known in SLSJ, therefore including all patients followed at the CF clinic in Chicoutimi, was established at SOREP. Birthdates of the affected individuals were extracted from the patient files whereas their birthplaces were obtained from the families.

The prevalence at birth was calculated by dividing the total

number of newborns later diagnosed as having CF by the total number of liveborns during the same period. The carrier rate was estimated using the Hardy-Weinberg equilibrium law. The diagnosis of CF was based on the patient and family histories, clinical, radiological, and biochemical results; it was confirmed by at least one positive sweat test.

The places of residence of the parents (obligate carriers) at the time of birth of the CF individuals in SLSJ were obtained from the families, as were the places of residence of the parents (grandparents of the CF individuals) at the time of birth of the obligate carriers.

Three control groups were created using the SLSJ population register developed and maintained at SOREP (Interuniversity Centre for Research on Populations), as previously described in details elsewhere (De Braekeleer & Larochelle 1990). They were used in the study of consanguinity, kinship and the geographical distribution of the places of residence, as previously described (De Braekeleer and Larochelle 1990).

II.5 RESULTS

A total of 127 individuals affected wih CF were known in SLSJ on December 31st 1989. This number included the 125 patients who had been or were still followed at the CF clinic in Chicoutimi. The remaining two CF patients were followed in Quebec City. These 127 patients were distributed in 91 families with one affected individual, 15 with two and two families with three affected individuals.

The prevalence at birth of cystic fibrosis remained quite stable between 1975 and 1988, as shown in table 2.1. The carrier rate as

estimated using the Hardy-Weinberg law was found to be 1 in 15 inhabitants.

The places of residence of the parents at the time of birth of the 127 CF individuals is shown in figure 2.1. Sixteen places of residence were located outside the SLSJ region. Among them, two were situated in the neighboring province of Ontario. The 111 places of residence within SLSJ were distributed in 31 of the 66 municipalities. The Monte Carlo simulations performed on the places of residence of the parents at the time of birth of the 93 CF probands from the SLSJ region showed four municipalities to have a higher number of places of residence than expected ($p < 0.05$).

The analysis of the places of residence of the parents of the 216 obligate carriers (that is the grandparents of all CF probands) showed that 33 places were located outside the SLSJ region, including 2 in England, 3 in Ontario, and 11 on the Haute Cote Nord, a region located east of the SLSJ region and partially settled by immigrants from SLSJ and Charlevoix county (figure 2.2). Three obligate carriers were adopted; therefore, the places of residence of their biological parents remained unknown. The geographical distribution of the 180 places of residence of the parents within the SLSJ region is also shown in figure 2.2. The places of residence were distributed in 41 municipalities. The Monte Carlo simulations showed 4 municipalities (identified by an asterisk in figure 2.2) to have a higher number of places of residence than expected ($p < 0.05$). No municipality was found to have a lower number of places of residence than expected.

A total of 93 couples ascertained through the birth of an individual affected with cystic fibrosis got married in the SLSJ region. These parents and those of control children were equally likely to have been born in the SLSJ region or outside (chi-square=2.37, p=0.31). Among parents born in SLSJ, parents of affected children and parents of control children were equally likely to have been born in the same municipality, in contiguous municipalities or in non-contiguous municipalities (chi-square=2.01; p=0.37). Although minor variations were found between the three control groups, none reached statistical significance at the level 0.05; therefore, they were pooled.

The mean coefficients of inbreeding and kinship of the CF and control groups are given in table 2.2. The mean coefficient of inbreeding in cystic fibrosis was found to be 1.6 times higher than the average value of the mean coefficients of inbreeding of the three control groups. No marriages between first-degree obligate carrier cousins were found. There were only one marriage between first-degree cousins once removed and one marriage between second-degree cousins once removed. More remote consanguinity was found in 9 other families.

The mean kinship coefficient was found to be 2.4 times higher in the CF group than the average value of the mean kinship coefficients of the three control groups pooled together. Seven CF patients were related as first-degree cousins, 8 as first-degree cousins once removed, and 30 as second-degree cousins; finally, two patients were related as uncle-nephew.

II.6 DISCUSSION

Cystic fibrosis is a frequent hereditary disorder in Caucasian populations, with a prevalence at birth estimated at 1/2000-1/2500 liveborns (Boat et al. 1989). Four populations were found to have a higher birth prevalence than the SLSJ population. These are the population of Windhoek in Southwest Africa (1/622) (Super 1975), the population of Celtic origin of the district of Plouzevede in Brittany (1/377) (Bois et al 1978), the Old Order Amish population of Holmes County, Ohio (1/569) (Klinger 1983), and the Hutterite population of Alberta, Canada (1/313) (Fujiwara et al 1989). All four populations are of small size and have been isolated for long periods of time. On the contrary, the SLSJ population has not been isolated since the beginning of the white settlement in 1838 and has 285,000 inhabitants. Such a high prevalence at birth is presumably the result of founder effect and genetic drift which may have occurred in Charlevoix for several CF mutations.

A genetic epidemiological study was recently conducted on hereditary tyrosinemia in Saguenay-Lac-St-Jean (De Braekeleer & Larochelle 1990). Comparison of both studies shows similarities. In both diseases, it was found that the mean inbreeding and kinship coefficients had low values, therefore indicating that both genes were very frequent in SLSJ and were introduced into the region by quite a large number of founders. Also, the places of origin in the SLSJ region of the patients and their parents did not show a clustered nonuniform distribution. However, it should be noted that the number of places of residence of the parents at the time of birth of the obligate carriers were higher than expected in seven municipalities in tyrosinemia and in four in

cystic fibrosis; none of these municipalities were common to both diseases. Finally, endogamy was not found to be higher in either disease than in the control groups.

The recent identification of the cystic fibrosis gene and the most common mutation in Caucasian populations (ΔF508) may give new insights into the genetic epidemiology of CF in SLSJ (Riordan et al. 1989; Kerem et al. 1989). Blood samples have now been obtained from all the 88 families having at least one living CF individual. Preliminary results on 44 families showed the frequency of the ΔF508 mutation to be 55% in the SLSJ region (Rozen et al. 1990) whereas the overall proportion of ΔF508 in a worldwide survey of 13,179 CF chromosomes was 68% (Cystic Fibrosis Genetic Analysis Consortium 1990). We are in the process of identifying the CF mutations present in SLSJ, notably to better understand why cystic fibrosis is so frequent in Saguenay-Lac-St-Jean.

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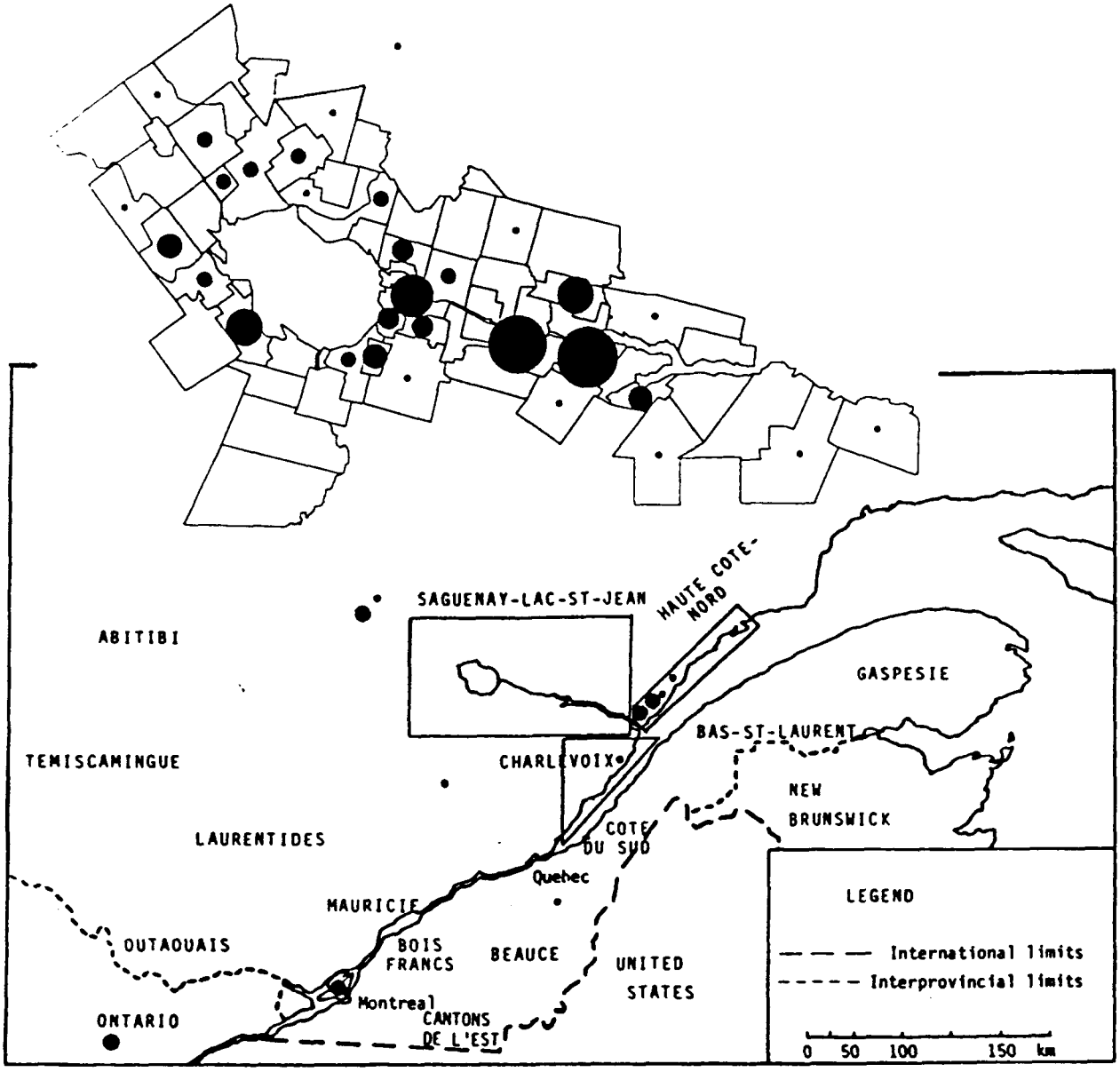
II.8 FIGURES

Figure 2.1 Geographical distribution of the birthplaces of the individuals affected with cystic fibrosis known in Saguenay-Lac-St-Jean.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ABITIBI
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BAS-ST-LAURENT
TEMISCAMINGUE
CHARLEVOIX
NEW BRUNSWICK
LAURENTIDES
COTE DU SUD
Quebec
MAURICIE
OUTAOUAIS
BOIS FRANCS
BEAUCE
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ONTARIO
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International limits
Interprovincial limits
0 50 100 150 km

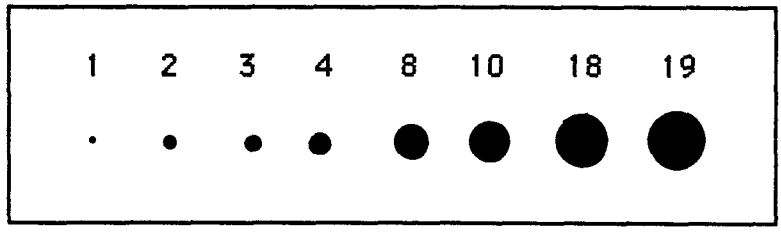
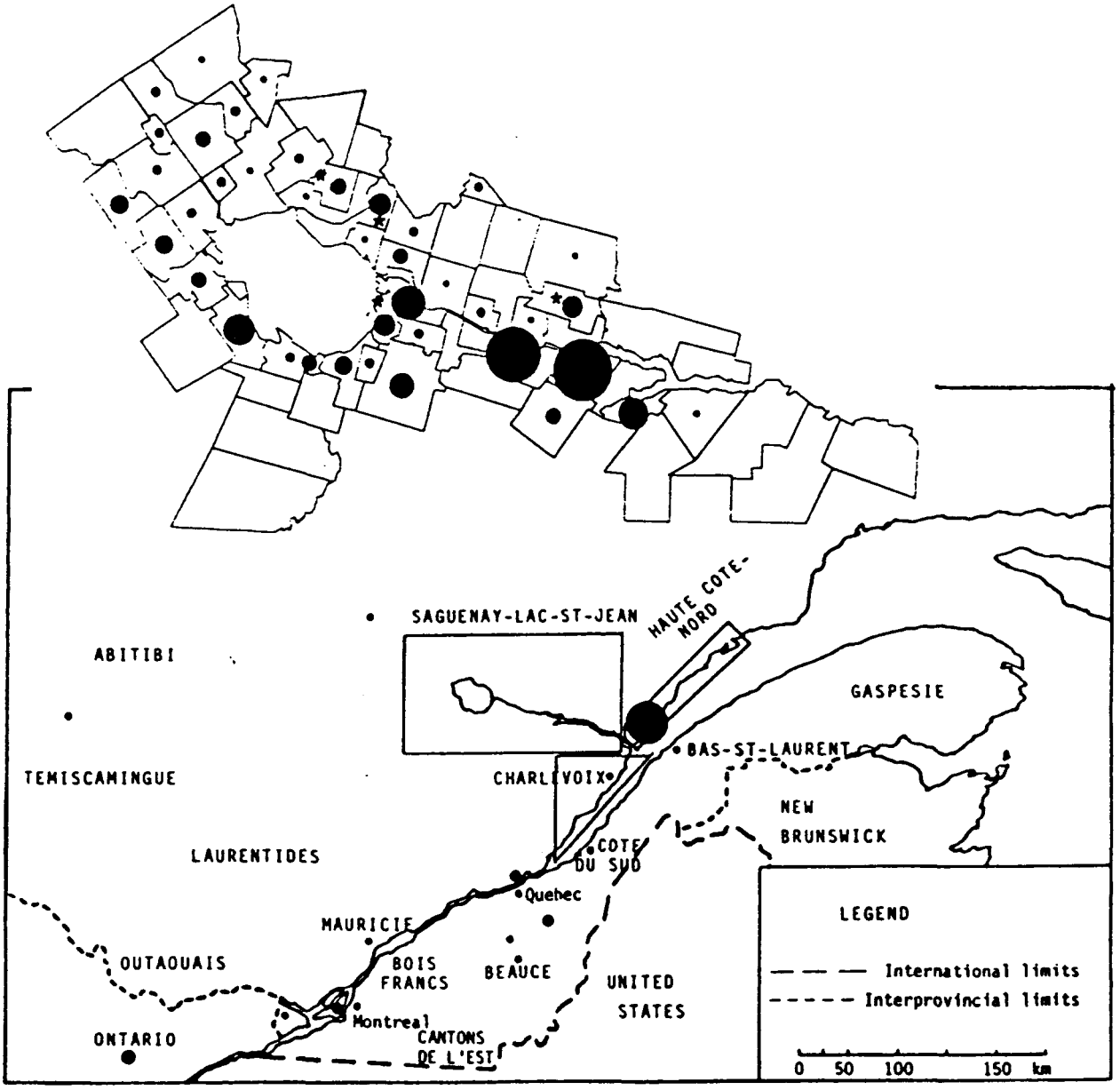

1 2 3 4 8 10 18 19

Figure 2.2 Geographical distribution of the places of origin of the parents who are obligate carriers of the cystic fibrosis gene.

(An asterik means that the number of places of origin in that municipality of the SLSJ region is statistically significantly higher than expected ($p < 0.05$).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LAURENTIDES
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Quebec
MAURICIE
OUTAOUAIS
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UNITED STATES
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ONTARIO
CANTONS DE L'EST
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International limits
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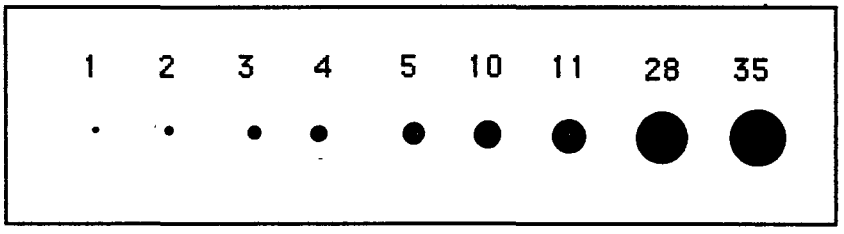
1 2 3 4 5 10 11 28 35

II.9 TABLES

Table 2.1 Incidence and carrier rate of cystic fibrosis in Saguenay-Lac-St-Jean (1975-1988).

Periods	Number of CF births	Number of live births	Incidence	Carrier rate
1975-1978	23	20881	1/908	
1979-1983	31	27746	1/895	
1984-1988	24	21724	1/905	
1975-1988	78	70351	1/902	1/15

Table 2.2 Mean coefficients of inbreeding and kinship in cystic fibrosis and control groups in SLSJ.

Group	Mean coefficient of inbreeding x 10^{-4}	Mean coefficient of kinship x 10^{-4}
Cystic fibrosis	7.58	4.16
Controls 1	10.20	1.76
Controls 2	2.57	1.75
Controls 3	1.35	1.76

CHAPITRE III

LA FIBROSE KYSTIQUE AU SAGUENAY-LAC-ST-JEAN (QUÉBEC, CANADA): ETUDE CLINIQUE.

[A CLINICAL STUDY OF CYSTIC FIBROSIS IN SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA)].

III.1 RÉSUMÉ

Les caractéristiques cliniques de 127 individus atteints de fibrose kystique, d'une région du Québec isolée géographiquement, sont décrites. Bien que la présente série soit plus petite que des séries publiées, son avantage repose sur un recensement complet des malades et sur la présence de la même équipe médicale depuis 1973. Les résultats démontrent une tendance en faveur du sexe féminin chez les individus vivants par catégorie d'âge, mais il n'y a pas de différence entre les sexes pour l'âge au décès. On ne retrouve que 7% d'iléus méconial dans notre population. Les résultats du score de Shwachman démontrent que 72,5% de nos individus atteints de fibrose kystique sans considération d'âge ou du sexe, ont des résultats d'état de santé général de bon à excellent. Ces résultats sont peut-être associés à la fréquence relativement basse, soit 55% , que représente la mutation ΔF508 dans notre population, ainsi que la présence d'autres mutations moins sévères.

III.2 ABSTRACT

The clinical features of 127 individuals with cystic fibrosis (CF) from a geographically isolated region of Quebec were reviewed. Although this series was smaller than most others, it relied on a complete ascertainment and on the presence of the same medical team since 1973. The results showed a distorted sex ratio in favor of females but no difference in the age at death between sexes. Only 7% of the patients presented with meconium ileus. The results of the Shwachman score showed that 72.5% of the CF patients, regardless of their sex and age, had a good or excellent health status. These results could be the result of a low frequency (55%) of the ΔF508 mutation in this population and the presence of other milder mutations.

III.3 INTRODUCTION

Saguenay-Lac-St-Jean (SLSJ) is a geographically isolated region located 200 kilometers northeast of Quebec City (Figure 3.1). It was opened to white settlement around 1840. From 1838 to 1911, some 50 % of the 28,656 immigrants came from Charlevoix, a region situated east of Quebec City, on the north shore of the St Lawrence river, whereas the remaining 50% came mostly from other eastern regions of the province (Figure 3.1). [12]. The immigration has considerably diversified since 1911. Although the migration balance has been negative since 1870, the population 98% French speaking and of catholic faith, rose from 5,000 inhabitants in 1852 to 50,000 in 1911 and 285,000 today. Several dominant and recessive autosomal disorders have a higher prevalence (myotonic dystrophy, tyrosinemia, etc.) while others, frequently found in the SLSJ region and Charlevoix, are almost nonexistent elsewhere (spastic ataxia Charlevoix-Saguenay type, polyneuropathy with or without agenesis of the corpus callosum, etc.) [10]. Cystic fibrosis (CF) is an autosomal recessive disorder that affects one child in every 2000-2500 liveborns in Caucasian populations [2]. In the past few years, it became evident that cystic fibrosis had a higher prevalence at birth in the SLSJ region than reported in most Caucasian populations. Indeed, the prevalence at birth for the period 1975-1988 was found to be 1/902 livebirths and the carrier rate was estimated at 1/15 inhabitants (Daigneault et al. submitted).

The purpose of this report is to describe several clinical aspects of cystic fibrosis in Saguenay-Lac-St-Jean based on a database established at SOREP.

III.4 MATERIAL AND METHODS

Since spring 1973, date of its opening, the great majority of the individuals affected with CF have been followed at the CF clinic in Chicoutimi. A database containing all CF cases known in SLSJ, therefore including all patients followed at the CF clinic in Chicoutimi, was established at SOREP. Birthdates of the affected individuals, sex, age at diagnosis and, if applicable, at death, Shwachman score, presence or absence of meconium ileus and sweat test results were extracted from the patient files. The diagnosis of CF was based on the patient and family histories, clinical, radiological and biochemical results; it was confirmed by at least one positive sweat test. The age at diagnosis was the age at the time of the hospitalization during which, based on clinical and biochemical results and the evolution of the disease, the diagnosis became evident. The Shwachman-Kulczycki [22] score was used to evaluate the health status of the affected individuals. It was modified by Doershuk [11] and also includes the Brasfield score [4] for pulmonaray X-rays results. It is divided in four categories: day life activity, clinical examination (mostly related to the cardio-pulmonary exam), gastrointestinal status (including failure to thrive) , and X-rays score. For each of the four categories, 5, 10, 15, 20, or 25 points are attributed according to the scale described by Shwachman and Kulczycki [22]. Once a year, each CF patient is assessed independently by both physicians at the CF clinic. In case of disagrement, the mean score is retained. The scores used in this study were determined at the end of 1989.

III.5 RESULTS

A total of 127 individuals affected with CF were known in SLSJ on December 31st, 1989. This number included 125 patients who had been or were still followed at the CF clinic in Chicoutimi. The remaining 2 CF patients were followed in Quebec city. These 127 patients were distributed in 91 families with one affected individual, 15 families with two, and 2 families with three affected individuals.

The total CF population consisted of 70 females (55%) and 57 males (45%). Figure 3.2 shows the distribution of the 109 individuals who were alive on December 31st, 1989 by sex and by 5-year age groups. The alive CF population consisted of 60 females (55.0%) and 49 males (45.0%). The mean age was 11.8 years (SD:7.7); no difference was found between sexes ($p > 0.05$). Figure 3.2 also shows the distribution of the 18 deceased CF individuals by sex and by 5-year age groups. The mean age of the deceased CF individuals was 9.9 years (SD:7.4), the mean ages for females and males being 10.8 years (SD:6.1) and 8.9 years (SD:9.l) respectively (Student t test=0.537, p=.5988). The sex ratio in the deceased group was similar to the ratio observed in the alive group.

Figure 3.3 shows the distribution of the age at diagnosis for the 107 CF patients for whom the information was available. Seventy three CF patients (68.2%) were diagnosed during the first year of life, a large proportion of them having been diagnosed before six months of age. Also included in this group were 9 patients with meconium ileus and 2 with intestinal obstruction. The remaining 34 patients were diagnosed after one year of age; from this group, only 4 were diagnosed after age 10. This included a female with a positive sweat test and a very mild

clinical evolution who was diagnosed at 29 years old. The overall mean age at diagnosis was 23 months (S.D.:50 months). No significant difference in the mean age at diagnosis was observed when comparing females (29 months, S.D.: 62 months) and males (16 months, S.D.: 28 months) (Student t test=1.326, p=0.1876).

The Shwachman score compiled at the end of 1989 for the 102 CF individuals still alive and followed at the CF clinic in Chicoutimi is shown in figure 3.4. Most of the patients had a satisfactory condition. A great variability in the score was observed for each age group. Furthermore, the distribution of the Shwachman score was similar in older patients than in younger patients and no difference was found between sexes ($p > 0.05$).

Two patients were also diagnosed with diabetes mellitus when they were 22 and 36 years old.

III.6 DISCUSSION

Although the CF series reported here is small (127 patients), it presents several advantages over other larger published series [1,7,13,15,16,18,23,24]. The CF clinic in Chicoutimi is the only CF specialized care facility for the whole Saguenay-Lac-St-Jean region; therefore, the large majority of the patients (125/127) are or have been followed in this clinic. Furthermore, this study relies on a complete ascertainment of the patients [10, Daigneault et al. submitted]. Finally, since the opening of the clinic in 1973, the same two physicians have cared for all the patients.

The analysis of the sex ratio showed a larger proportion of females than males (55% compared to 45%). A review of the literature published during the past 10 years showed that, in all series, the sex ratio was in favor of males (53.5-58.3% for males compared to 41.7-46,5% for females) [7,13,16,23,24]. A similar sex ratio was noted among the 18 deceased CF patients. Sturgess reported that males were more likely to decease during the first three years of life and females after two years old [23] . Lenoir noted that there was usually an increased mortality of females during the pubertal period [16]. Although the number of deceased CF patients in our series is small, the mean age at death in females is not significantly different than in males.

The distribution of the age at diagnosis showed that 68.2% of the patients were diagnosed during the first year of life, which is comparable to the 60% to 75% reported by several workers [7,13,23]. The proportion of patients diagnosed before age 1 was similar whether the patient lived in the Lac-St-Jean or in the Saguenay area (Figure 3.1) (70.2% and 68.8% respectively). However, among the 15 patients diagnosed outside the region for whom the age at diagnosis was available, only 60% (9/15) were diagnosed before age 1. Four patients were diagnosed after 10 years of age; these are milder cases who have had repeatedly a positive sweat test and clinical features, mainly respiratory, compatible with cystic fibrosis.

Also, in all families but one in which more than one child was affected, the age at diagnosis was lower for the second CF born than for the first CF born. Sometimes, it also helped clarify the diagnosis for the first CF born.

Seven percents of the patients presented with meconium ileus. An extensive review of the literature on this subject was published by Sturgess in 1988 [23]. It showed that the frequency of meconium ileus was included between 7 and 25%. The low frequency of meconium ileus, which is a sign of pancreatic insufficiency, in SLSJ could be the result of a low proportion of ΔF508 mutation in this population (55% compared to 70-80% elsewhere in North America) [9,20]. Indeed, recent results showed that pancreatic insufficiency and meconium ileus were more likely to be associated with ΔF508 than with other mutations [8,14,17,21].

Diabetes mellitus was found in two CF adults. This result is in agreement with those of Reisman et al. who recently showed that diabetes mellitus was, in a few cases, a late complication of cystic fibrosis [19].

The results of the Shwachman score showed that 72.5% of the CF patients had a good to excellent score (score ≥ 71/100) whereas only 10.7% had a bad to severe score (score ≤55). Unfortunately, few workers have studied the distribution of their CF population according to the Shwachman score. Only one extensive study from France based on 275 patients was published by Lenoir [16]. It showed that 48.7% of the patients had a score higher than 80, compared to 62.7% in the SLSJ study. Such a difference could be the result of different treatments applied in different centers in France or the presence of milder mutations which account for 45% of the CF population in SLSJ [20].

Although it still remains to be determined whether ΔF508 is a severe mutation [3, 5, 6, 14], most of our results might be the

consequence of a low proportion of ΔF508 mutation in this population combined with the presence of more benign mutations. Blood samples have been collected from all 90 SLSJ families having at least one living CF individual. We are now determining the frequencies of the other CF mutations in this population in order to try to correlate these clinical findings and the evolution of the disease with the several genotypes.

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American populations of French ancestry: analysis of Quebec French-Canadian and Louisiana Acadian families. Am J Hum Genet 47:606-610

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III.8 FIGURES

Figure 3.1 Geographical location of Saguenay-Lac-St-Jean in the province of Quebec.

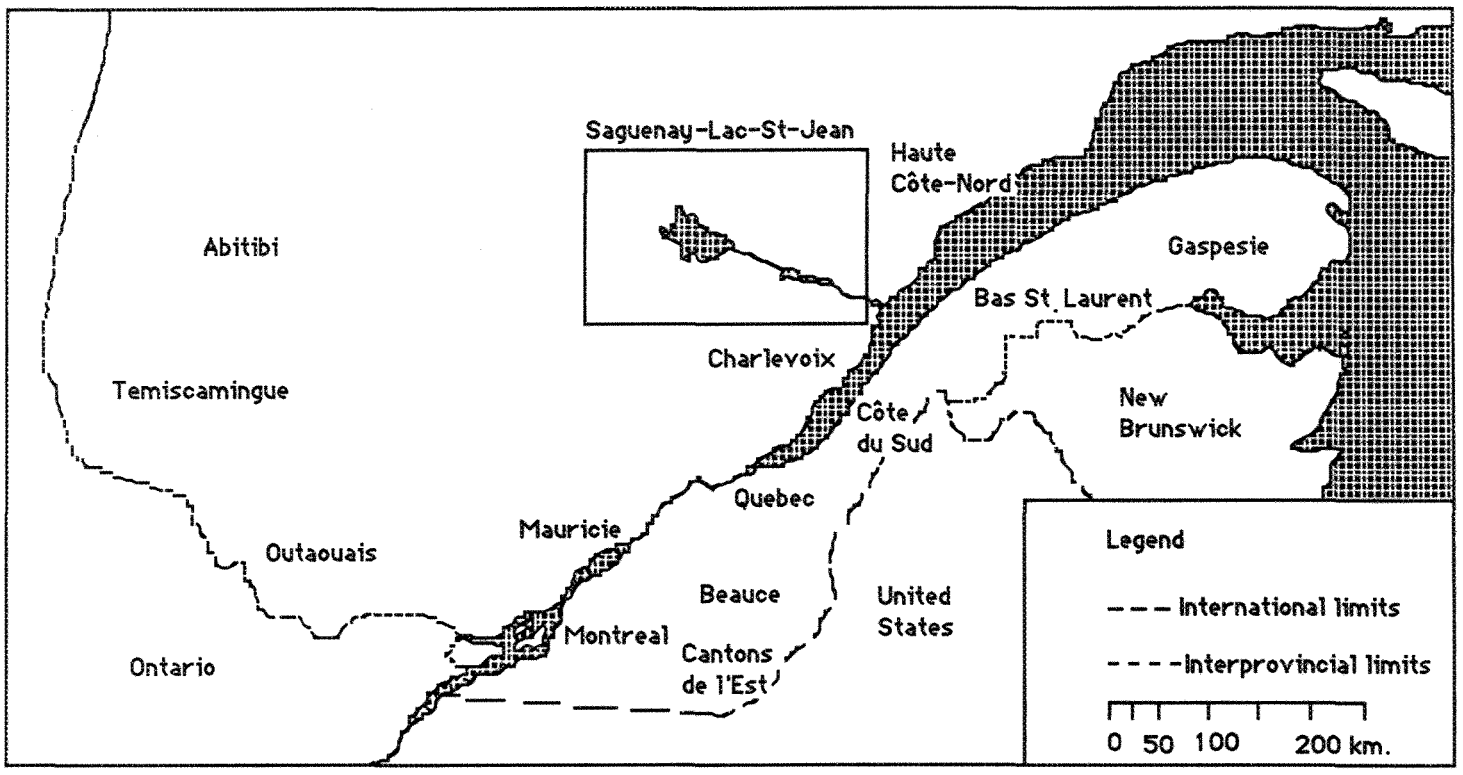

Saguenay-Lac-St-Jean
Haute
Côte-Nord
Abitibi
Gaspesie
Bas St. Laurent
Charlevoix
Temiscamingue
Côte
du Sud
New
Brunswick
Quebec
Mauricie
Outaouais
Beauce
United
States
Montreal
Ontario
Cantons
de l'Est
Legend
International limits
Interprovincial limits
0 50 100 200 km.

Figure 3.2 Distribution of the 127 CF individuals by sex and by 5-year age groups.

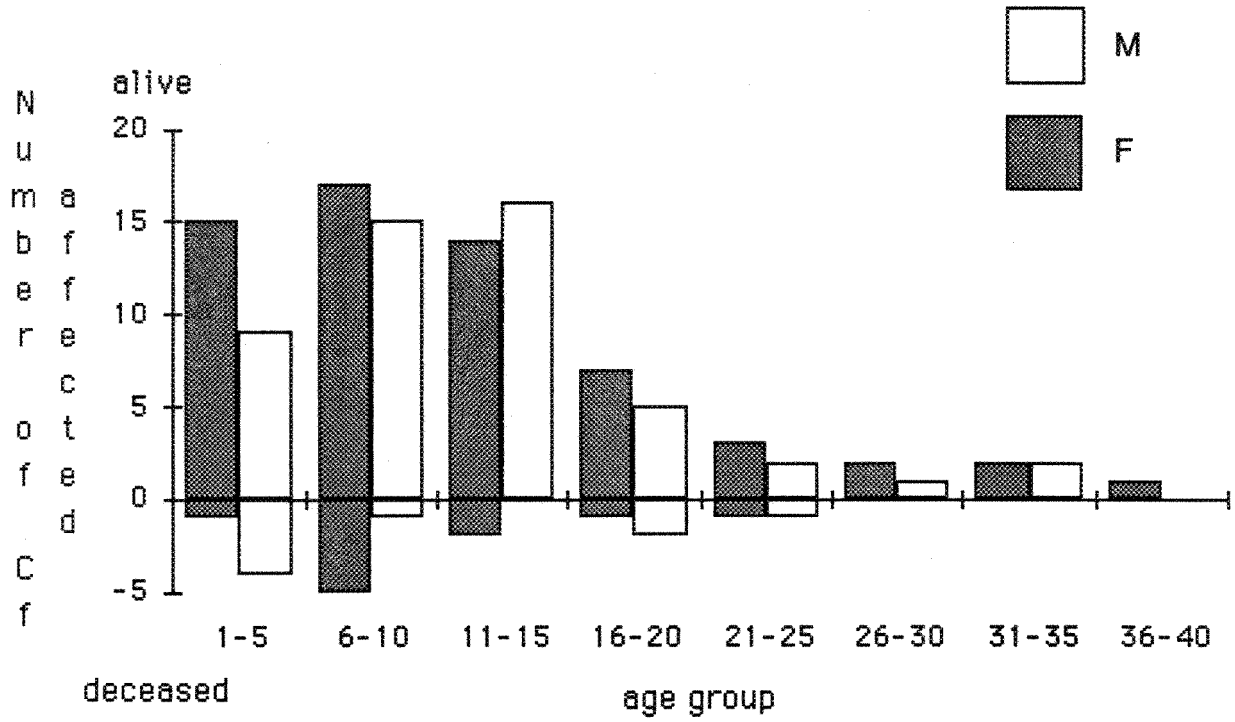

M
F
alive
20
15
10
5
0
-5
Number of affected deceased
1-5
6-10
11-15
16-20
21-25
26-30
31-35
36-40
age group

Figure 3.3 Histogram of the age at diagnosis of 107 CF individuals. The distribution is shown by month for those individuals diagnosed before one year of age.

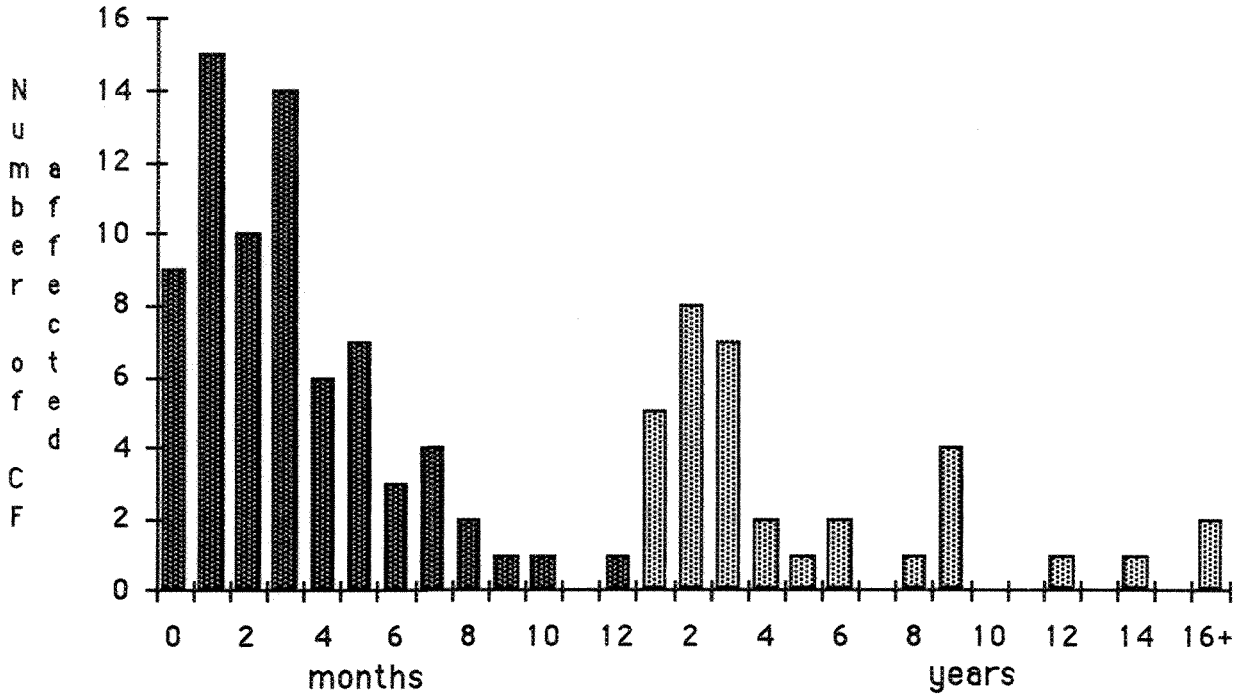
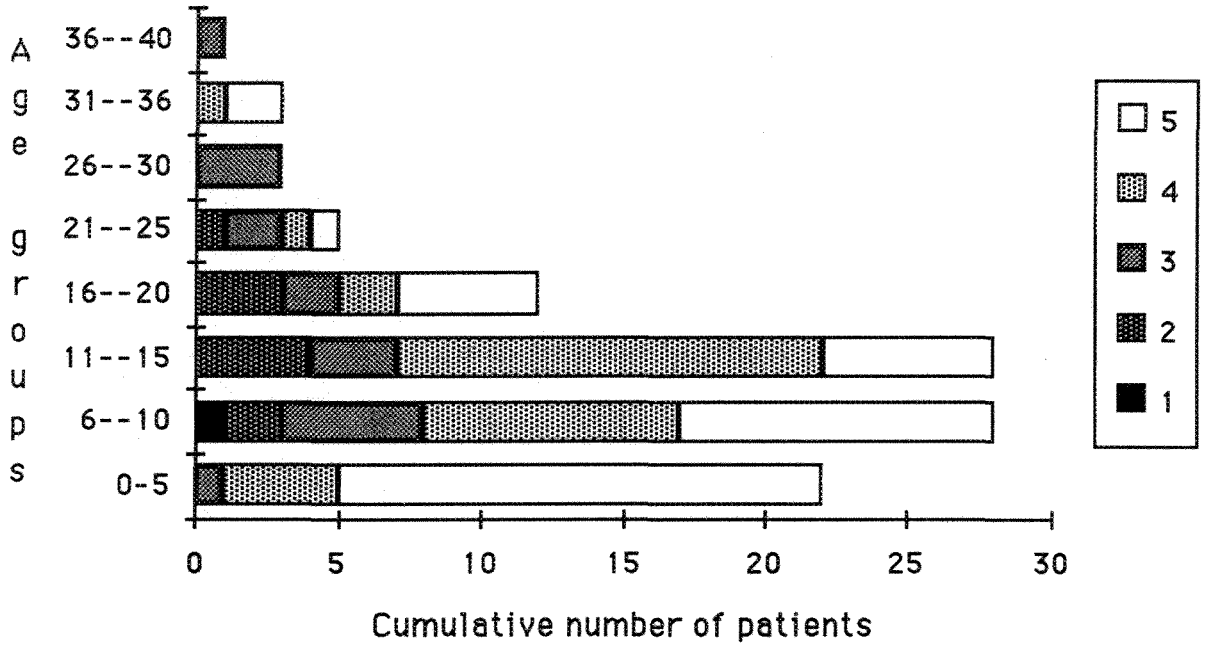

Number of CF affected
16
14
12
10
8
6
4
2
0
0 2 4 6 8 10 12 2 4 6 8 10 12 14 16+
months
years

Figure 3.4 Histogram of the Shwachman-Kulczycki score by 5-year age groups.

1	score $\leq$ 40/100
2	41 < score $\leq$ 55
3	56 < score $\leq$ 70
4	71 < score $\leq$ 85
5	86 < score $\leq$ 100


Age groups
36--40
31--36
26--30
21--25
16--20
11--15
6--10
0-5
0
5
10
15
20
25
30
Cumulative number of patients
5
4
3
2
1

CHAPITRE IV

INCIDENCE DE LA FIBROSE KYSTIQUE AU SAGUENAY-LAC-ST-JEAN (QUÉBEC, CANADA).

[INCIDENCE OF CYSTIC FIBROSIS IN SAGUENAY-LAC-ST-JEAN, (QUEBEC, CANADA)].

* " Incidence of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada)" Jocelyne Daigneault, Gervais Aubin, Fernand Simard, Marc de Braekeleer accepté pour publication dans: *Human Biology*

IV.1 RÉSUMÉ

L'incidence de la fibrose kystique au Saguenay-Lac-St-Jean, une région isolée géographiquement du Québec, a été estimée à 1/902 naissances vivantes pour la période 1975-1988. Le taux de porteurs est de 1/15 habitants. L'incidence élevée de la fibrose kystique au SLSJ semble être le résultat d'un effet fondateur et d'une dérive génétique pour une ou plusieurs mutations. Des facteurs historiques, démographiques et sociaux semblent aussi avoir contribué à cette forte incidence.

IV.2 ABSTRACT

The incidence of cystic fibrosis (CF) in Saguenay-Lac-St-Jean, a geographically isolated region of Quebec, was estimated to be 1/902 during the period 1975-1988. The carrier rate was calculated to be 1 in 15 inhabitants. The high incidence of CF in Saguenay-Lac-St-Jean is likely to be the result of founder effect and genetic drift for one or more mutations. Historical, demographical, and social factors may also have contributed to the high incidence.

IV.3 INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder that affects approximately one child in every 2000-2500 liveborns in Caucasian populations (Boat et al. 1989). In the past few years, it became evident that cystic fibrosis had a higher incidence in SLSJ than reported in most Caucasian populations.

The purpose of this report is to describe the incidence of CF in Saguenay-Lac-St-Jean for the period 1975-1988 and to compare it to the incidence of other populations.

IV.4 MATERIAL AND METHODS

Saguenay-Lac-St-Jean (SLSJ) is a geographically isolated region located 125 miles northeast of Quebec City (Figure 4.1). It was opened to white settlement around 1840. From 1838 to 1911, some 50% of the 28,656 immigrants came from Charlevoix, a region situated east of Quebec City, on the north shore of the St Lawrence River, whereas the remaining 50% came mostly from other eastern regions of the province (Figure 4.1) (Gauvreau et al. 1991). The immigration has considerably diversified since 1911. Although the migration balance has been negative since 1870, the population, 98% French speaking and of Catholic faith, rose from 5,000 inhabitants in 1852 to 50,000 in 1911 and 285,000 today.

Several dominant and recessive autosomal disorders have a higher prevalence (myotonic dystrophy, cystic fibrosis, etc.) while others, frequently found in the SJSL region and Charlevoix, are almost

nonexistent elsewhere (spastic ataxia Charlevoix-Saguenay type, polyneuropathy with or without agenesis of the corpus callosum, etc.) (De Braekeleer, 1991).

Since spring 1973, date of its opening, all the CF individuals born in Saguenay-Lac-St-Jean have been followed at the CF clinic in Chicoutimi. Birthplaces of the CF patients were obtained from the families.

The diagnosis of cystic fibrosis was based on the patient and family histories, clinical, chest X-ray, and biochemical results; it was confirmed by at least one positive sweat test.

The incidence was calculated by dividing the total number of newborns who were later diagnosed as having CF by the total number of liveborns during the same period (1975-1988). The carrier rate was estimated by using the Hardy-Weinberg equilibrium law.

IV.5 RESULTS AND DISCUSSION

Table 4.1 shows the incidence of cystic fibrosis in Saguenay- Lac-St-Jean for the periods 1975-1978, 1979-1983, 1984-1988, and 1975-1988. As shown in table 4.1, the incidence remained quite stable between 1975 and 1988. The carrier rate was estimated to be 1 in 15 inhabitants.

Four populations were found to have a higher incidence than the SLSJ population. These are the population of Windhoek in Southwest Africa (1/622) (Super, 1975), the population of Celtic origin of the

district of Plouzevede in Brittany (1/377) (Bois et al. 1978), the Old Order Amish population of Holmes County, Ohio (1/569) (Klinger, 1983), and the Hutterite population of Alberta, Canada (1/313) (Fujiwara et al. 1989). All four populations are of small size and have been isolated for long periods of time. On the contrary, the SLSJ population has not been isolated since the beginning of the white settlement in 1838 and has 285,000 inhabitants.

Since the incidence of CF does not appear to be higher in Quebec than in other western european populations including France, one can hypothesize that the carriers of the CF gene were not overrepresented in the founding nucleus of the French-Canadian population. During the first 30 years of the SLSJ settlement, some 70% of the 28,656 immigrants came from Charlevoix (Gauvreau et al. 1991). The majority of the ancestors of the present-day CF families from Saguenay-Lac-St-Jean can still be traced back to Charlevoix. The Charlevoix population is mainly issued from 599 founders who settled in the region between 1650 and 1725 (Jetté et al. 1991). It remained isolated for over two centuries and the inbreeding was high (Morissette 1991). A possible scenario is that the founders who introduced the CF mutations into Charlevoix were disproportionately randomly drawn from a pool of French-Canadian and western european CF heterozygotes (founder effect). The frequencies of some of these mutations may have increased by random genetic drift in Charlevoix. Unfortunately, at the present time, no data on the incidence of the CF is available for the Charlevoix region. Contacts were made with both West and East Charlevoix sections of the Canadian CF Foundation in order to know how many CF individuals were registered. A total of 18 patients were known in this 30,000 inhabitants population, which indicates that the incidence in Charlevoix

might be as high, if not higher, than in Saguenay-Lac-St-Jean. Since the SLSJ population took its roots in the Charlevoix population, it is likely that a large number of CF carriers may have settled in Saguenay-Lac-St-Jean. Furthermore, at least at the beginning of the SLSJ settlement, the individuals for whom their origins were in Charlevoix had more children than those who had their origins in other regions of Quebec; they also had more children who married in Saguenay-Lac-St-Jean and were less likely to emigrate (Roy et al. 1988). Therefore, all these factors may have contributed to increase the carrier rate and the incidence of cystic fibrosis in Saguenay-Lac-St-Jean.

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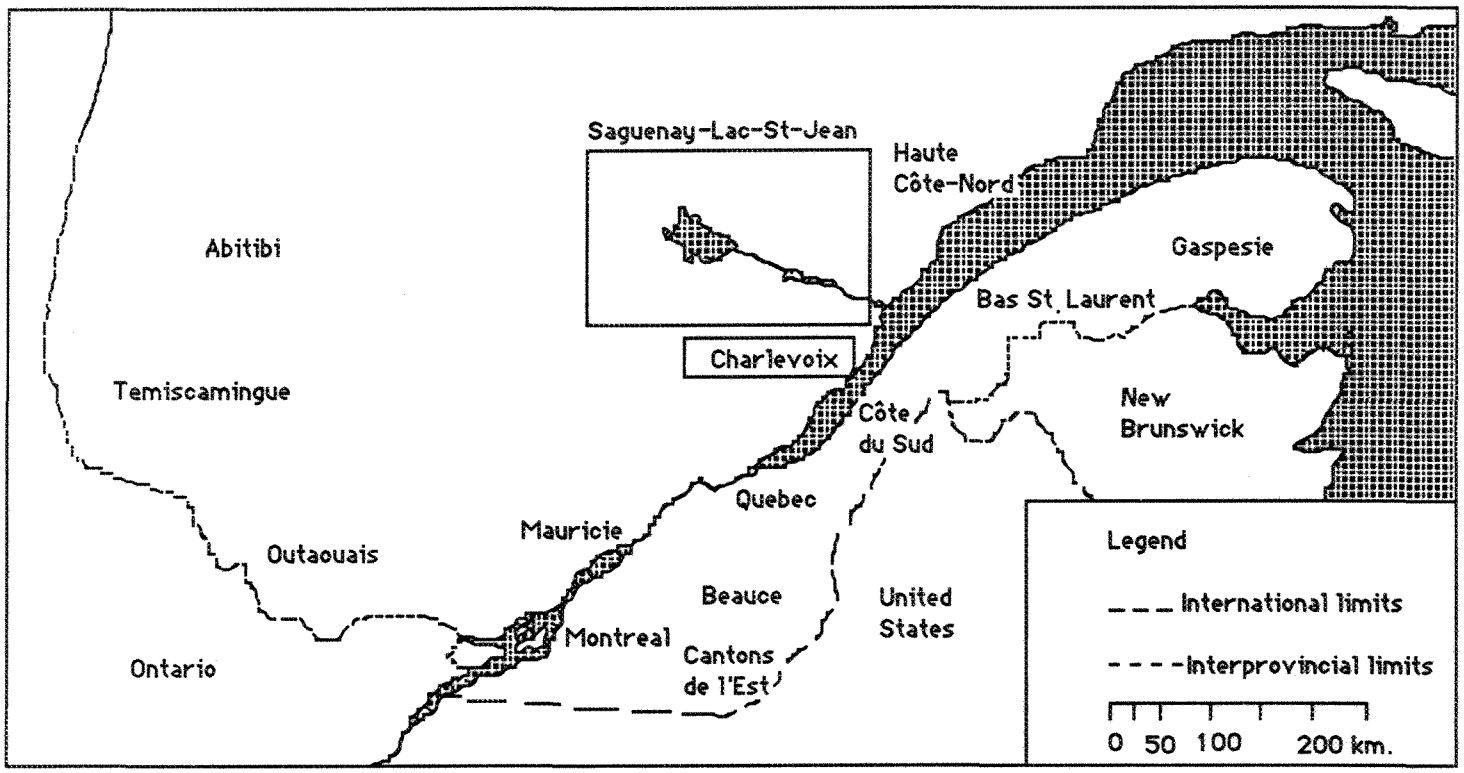
IV.7 FIGURE

Figure 4.1 Localization of the Saguenay-Lac-St-Jean region and Charlevoix County in the province of Quebec.


Saguenay-Lac-St-Jean
Haute
Côte-Nord
Abitibi
Gaspesie
Bas St. Laurent
Charlevoix
Temiscamingue
New
Brunswick
Côte
du Sud
Quebec
Mauricie
Outaouais
Beauce
United
States
Montreal
Ontario
Cantons
de l'Est
Legend
International limits
Interprovincial limits
0 50 100 200 km.

IV. 8 TABLE

Table 4.1 Incidence and carrier rate of cystic fibrosis in Saguenay-Lac-St-Jean (1975-1988).

Periods	Number of CF births	Number of live births	Incidence	Carrier rate
1975-1978	23	20881	1/908	
1979-1983	31	27746	1/895	
1984-1988	24	21724	1/905	
1975-1988	78	70351	1/902	1/15

CHAPITRE V

DISTRIBUTION SPATIALE DE LA MUTATION ΔF508 DANS LA FIBROSE KYSTIQUE: ÉTUDE DES DONNÉES DISPONIBLES.

(SPATIAL DISTRIBUTION OF THE ΔF508 MUTATION IN CYSTIC FIBROSIS. A REVIEW OF AVAILABLE DATA).

* "Spatial distribution of the ΔF508 mutation in cystic fibrosis. A review of the available data"

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V.1_ RÉSUMÉ

La découverte récente de la mutation ΔF508, la plus commune pour la fibrose kystique dans les populations caucasiennes a mené à la publication d'un grand nombre de résultats concernant sa distribution et sa fréquence. Une revue de la littérature et des résultats disponibles démontre une relation possible entre l'incidence de la fibrose kystique et la fréquence de la mutation ΔF508 en Europe; les valeurs les plus élevées ont été observées en Europe de l'ouest. Une hypothèse probable pourrait être que la mutation ΔF508 était présente dans la population de l'ouest de l'Europe avant l'arrivée des Indo-Européens du Moyen-Orient; la mutation s'est ensuite disséminée à travers ces populations migrantes.

V.2 ABSTRACT

The recent finding of the most common mutation (ΔF508) in cystic fibrosis in Caucasian populations has led to the publication of a large number of data regarding its distribution and its frequency. A review of the available data showed that there was a gradient in both the incidence of cystic fibrosis and the frequency of ΔF508 in Europe, the highest values having been found in western Europe. It is postulated that ΔF508 is a mutation that was present in a western European population before the arrivals of the Indo-Europeans from the Middle East; the mutation then spread into these migrating populations.

V.3 INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder that affects approximately one child in every 2000-2500 liveborns in Caucasian populations (Boat et al. 1989). It is a complex disorder characterized mainly by chronic obstruction and infection of the respiratory tract, exocrine pancreatic insufficiency, and elevated levels of sweat electrolytes (Boat et al. 1989). Thick mucous secretions are associated with chronic obstructive lung disease and recurrent and persistent infections leading to bronchiectasis and respiratory and heart failure, responsible for the death of most (99%) CF patients.

The CF gene has now been identified, as was the most common mutation in Caucasian populations (ΔF508) (Rommens et al. 1989; Kerem et al. 1989; Riordan et al. 1989). These findings led to a worldwide survey of the ΔF508 mutation (Cystic Fibrosis Genetic Analysis Consortium 1990); 35 reports from European workers have appeared in the September issue of Human Genetics (Romeo and Devoto, 1990)

The purpose of this review is to analyze the worldwide distribution of the ΔF508 mutation in Caucasian populations and to correlate it with the incidences published for various populations.

V.4 Incidence of CF in Caucasian populations

The distribution of the incidences in Europe is highly uneven. The analysis of figure 5.1 shows that the higher incidences were found in the British Islands (~1/2000-1/2500) and in France (~1/2500). From that "epicenter", the incidence decreased when going North (~1/3700 in

Belgium and the Netherlands, ~1/4700 in Denmark, ~1/6300 in Norway and Sweden), East (~1/3200 in Germany, ~1/3300 in Czechoslovakia, ~1/4900 in the USSR, and ~1/6000 in Poland), and South (~1/3500 in Spain, Italy and Greece).

The incidence of CF in Caucasian descendants in Canada, the USA, Australia, and New Zealand can be estimated to be 1/2500-1/3000. Such result is due to the immigration of individuals from western European countries during the past centuries. In 1985, Allan and Phelan reported that the incidences of CF among the Australian children of parents born in Italy and Greece (1/3625 and 1/3726 respectively) were significantly lower than the CF incidence of children born to Australian parents whose ancestors came from the British Islands (1/2021). Therefore, this study confirmed that there were variations in the incidence of CF in different European populations. It also showed that these variations were unlikely to be the result of the great variety of methods used to determine the CF incidence (Allan and Phelan 1985).

Variations were also found in the CF Jewish population of Israel (Katznelson and Ben-Yishay 1978). Of the 87 ascertained families for whom the origins were known, 54 (62.1%) were of Ashkenazic origin (ancestors from eastern and central Europe), 27 (31.0%) of Sephardic origin (ancestors from Spain, Portugal and North African countries bordering the Mediterranean Sea), 1 (1.1%) was of Yemenite origin, and 5 (5.8%) were of mixed origin (Ashkenazic/Sephardic). No Jewish CF family from Iran and only one parent from Iraq was found. Since the population of non-Ashkenazic origin constituted more than 50% of the young Jewish population of Israel in 1975, it is likely that the variations observed between the several groups corresponded to true

differences in their CF incidences (Katznelson and Ben-Yishay 1978). These results are in accordance with the several autosomal recessive disorders found in Jews of specific origin (Adam 1973); they are presumably due to different founder effects followed by genetic drift.

V.5 Incidence of the ΔF508 mutation in Caucasian populations

The recent identification of the cystic fibrosis gene and the most common mutation in Caucasian populations (ΔF508) may give some new insights into the variations in the CF incidences in different populations (Rommens et al. 1989; Riordan et al. 1989; Kerem et al. 1989). A worldwide survey of the ΔF508 mutation was published by the Cystic Fibrosis Genetic Analysis Consortium in 1990; 35 reports from European workers appeared in the September issue of Human Genetics 1990 (Romeo and Devoto 1990). Unfortunately, for quite a few populations surveyed for the ΔF508 mutation, no data on the overall incidence of CF in these populations is available. The data on the proportions of ΔF508 in Europe is shown in figure 5.2.

Although the populations of the Republic of Ireland (mostly of Protestant faith) and of North Ireland (mostly of Catholic faith) had the same CF incidence (~1/1800), they differed in the proportion of the ΔF508 mutation (76% and 54% respectively).

The mutation reached its highest proportions (70-80%) in the populations of western Europe (British Isles, France, Belgium, West Germany, Netherlands), a maximum of 87% having been found in the Danish population. The CF incidences in these populations of western Europe varied from 1/1800 to 1/4700. As a consequence, the

frequencies of the ΔF508 mutation were included between 70 and 84% in the North American populations of western European extraction (Lemna et al. 1990).

However, two North American populations, which have a high CF incidence, show a low proportion of ΔF508. These are the Hutterites and the population of Saguenay-Lac-St-Jean (SLSJ) in northeastern Quebec. In the Hutterite population of Alberta, a religious isolate, in which the CF incidence was 1/313, the ΔF508 mutation only accounted for 35% of the mutations (Fujiwara et al. 1989; Klinger et al. 1990; Cystic Fibrosis Genetic Analysis Consortium 1990). In Saguenay-Lac-St-Jean, a region in which the incidence of CF was calculated to be 1/902 (Daigneault et al, submitted), the ΔF508 mutation only represented 55% of the CF mutations compared to 71% in the non-SLSJ French-Canadian population of Quebec (Rozen et al. 1990; Cystic Fibrosis Genetic Analysis Consortium 1990).

The ΔF508 mutation only represented 40 to 60% of all CF mutations in the European countries bordering the Mediterranean Sea (Portugal, Spain, Italy, Yugoslavia, and Greece) whereas the CF incidence in these populations was close to 1/3500. A similar frequency for the ΔF508 mutation was found in the Italian and Hispanic populations of France and the USA (45-55%).

The frequency of the ΔF508 mutation was also found to be lower (42-66%) in eastern European populations (Bulgaria, Czechoslovakia, Poland, and USSR); the incidences of CF in these populations varied from 1/3300 to 1/6000.

It should be noted that the Ashkenazic Jewish CF population, which had its roots in central and eastern Europe, has a proportion of ΔF508 included between 32 and 50%, which is close to the values observed in the non-Jewish population of these regions (Cystic Fibrosis Genetic Analysis Consortium 1990; Lerer et al. 1990). The same conclusion applies for the Sephardic Jewish CF population which shows a proportion of ΔF508 close to that observed in the populations around the Mediterranean Sea (Lerer et al. 1990).

Studies of RFLP closely linked to the cystic fibrosis locus throughout Europe led to the conclusion that the ΔF508 mutation was a unique ancestral mutation that has arisen on a B haplotype chromosome in an ancestral proto-Indo-European population more than 5,000 years ago (Serre et al. 1990; Serre 1990). Furthermore, the frequency of recombinations between close RFLP and the CF locus suggested that the ΔF508 mutation may have originated in the Middle East. Then, it spread through Europe, from the South-East to the North-West (Serre et al. 1990; Serre 1990; European Working Group on CF Genetics 1990). It remains to be explained why both CF incidence and ΔF508 proportion have higher values in western European populations and lower values in eastern and southern Europe (Figures 5.1 and 5.2). It is likely that the presence of cystic fibrosis and ΔF508 is the result of a founder effect, but it is unlikely that the high CF incidence in so many populations is the result of genetic drift. Therefore, the hypothesis of a selective advantage of CF heterozygotes remains the most likely explanation for the high frequency of the CF gene (Romeo et al. 1989).

More recently, Casals et al. (1990) reported that 81% of the CF chromosomes of Basque origin carried the ΔF508 mutation. Since the

Basque language appears to have no clear ties with the Indo-European languages (Catford 1977; Renfrew 1989; Gamkrelidze and Ivanov 1990), and might even be more ancient and issued from a different root (dene-caucasian) (Ross 1991), Casals'findings seem to contradict the hypothesis that the CF gene and the ΔF508 mutation were brought by migrants from the Middle-East. However, it is not excluded that the CF gene may have been passed to the Basque population by the Indo-European migrants. The gene may have then acquired a high frequency by genetic drift and selective heterozygote advantage. It rather appears that cystic fibrosis was already present in western Europe at the time of arrival of these immigrants (Casals et al. 1990). If one agrees that the ΔF508 mutation only occurred once on a B haplotype chromosome, one can hypothesize that this event occurred long ago in a population based in Europe before Indo-Europeans disseminated through western Europe. Contacts between such an early European population and the migrants from the Middle-East could have allowed the gene to spread into one of these migrating populations, the Celts for example. However, controversies have emerged as to the origins of the Celts (Renfrew 1987). It is not excluded that the Celts might represent such a European population present in western Europe before the arrival of the Indo-Europeans. Because of "environmental" pressures from these migrating populations, they could have then started using their language and habits. Although the Celtic speakers are now confined to the British Islands and Brittany, their ancestors once dominated western and central Europe, invaded Italy and Greece, and occupied part of eastern Europe and Turkey (Mallory 1989). An intriguing feature is that both the distribution of the Celtic languages during the Iron Age and the Celtic expansion during La Tene (Mallory 1989) correspond to most of the regions which now show the highest CF incidence and the highest

proportion of ΔF508 in Europe; these are the British Isles, France (and more particularly Northern France), Belgium, the Netherlands, part of Germany, Switzerland, and Czechoslovakia.

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V.7 FIGURES

Figure 5.1 Distribution of the incidence of cystic fibrosis in several European countries. (The legend should be read as 1 over the indicated range).

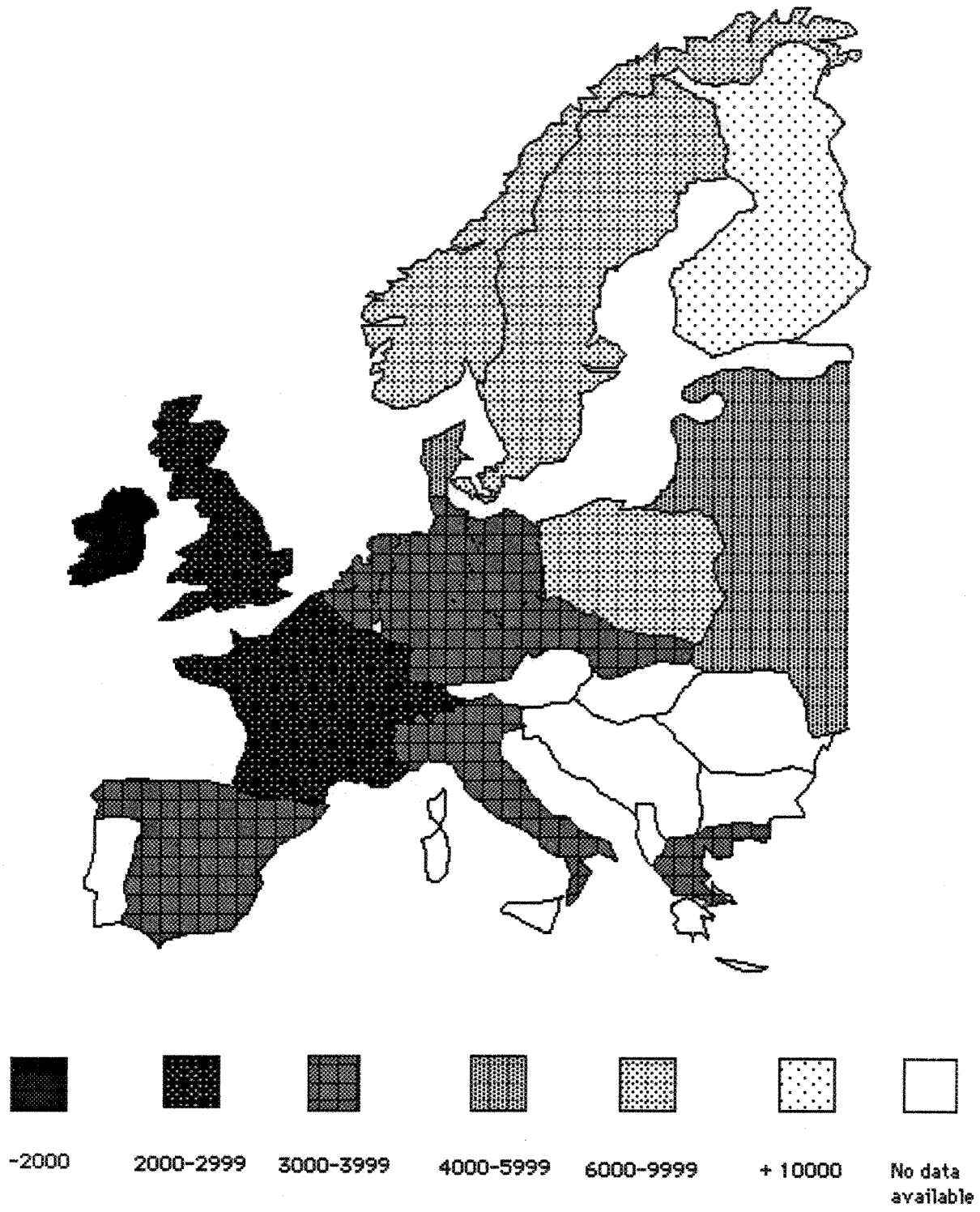
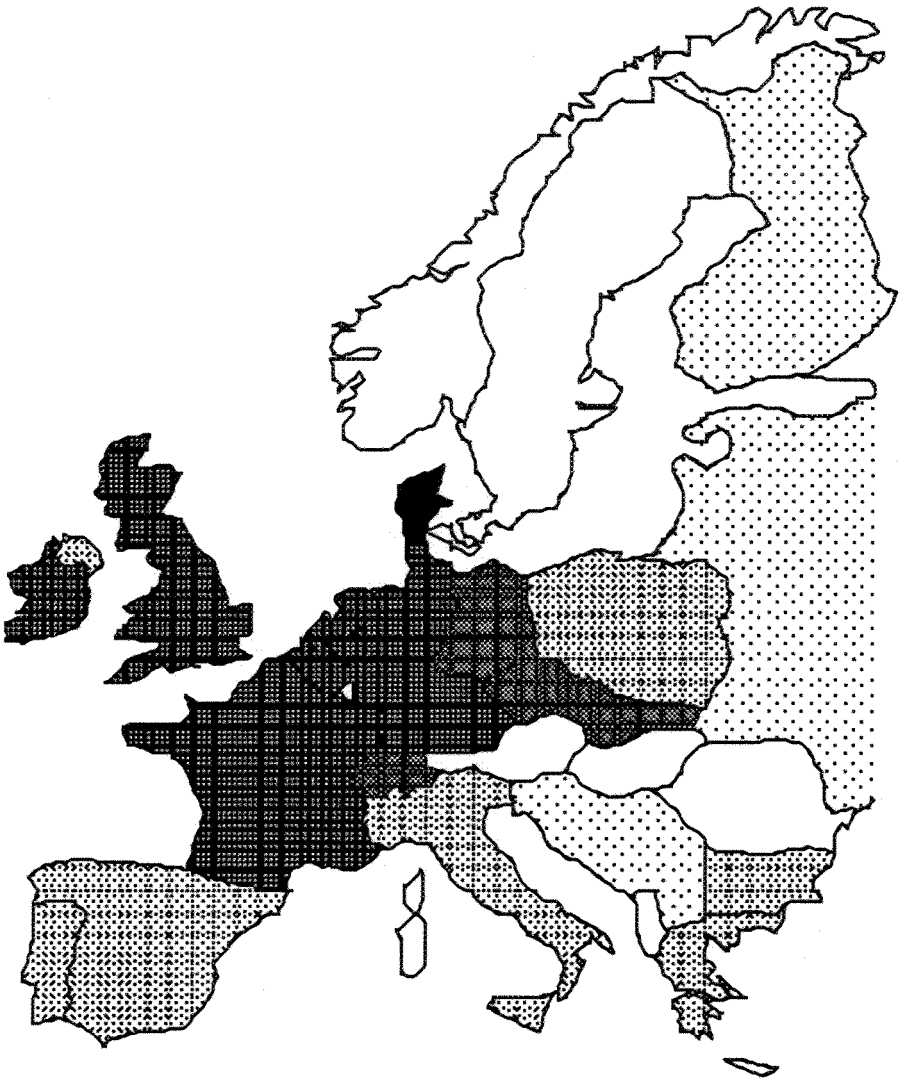

-2000
2000-2999
3000-3999
4000-5999
6000-9999
+ 10000
No data available

Figure 5.2 Distribution of the proportion of the ΔF508 mutation in several European countries. (The indicated values are expressed in percentage).



No data available

40-49

50-59

60-69

70-79

80-89

CONCLUSION GÉNÉRALE

Au terme de cette étude, il est maintenant évident que la fibrose kystique est une maladie héréditaire à incidence élevée dans la région du SLSJ.

L'étude sur les mois de naissance suggère, en utilisant deux méthodes statistiques différentes, qu'il n'y a pas de variation mensuelle ou saisonnière du nombre de cas observés à l'intérieur de notre population. Nous savons de plus que malgré la petitesse de notre population de fibrose kystique, nous avons un recensement complet, ce qui nous permet d'émettre l'hypothèse d'un biais d'échantillonnage ou de constater la présence d'un phénomène aléatoire dans d'autres études qui tendaient à trouver un cycle temporel.

L'étude de la prévalence à la naissance, le calcul du taux de porteurs, les coefficients moyens de consanguinité, d'apparentement et d'endogamie ainsi que la distribution géographique des malades et de leurs parents (porteurs obligatoires) nous ont amené à envisager l'hypothèse d'un effet fondateur et d'une dérive génétique. En effet, à la lumière des résultats obtenus, soit une incidence de 1/902 naissances vivantes, un taux de porteurs de 1/15 habitants, un coefficient moyen de consanguinité dont la valeur est de 1,6 fois plus élevé que dans trois groupes témoins et le coefficient moyen d'apparentement qui est de 2,4 fois plus élevé que les groupes contrôles, nous constatons donc un ensemble de facteurs qui ont contribué à la forte présence de cette

maladie dans notre population. L'identification du gène, sa localisation chromosomique et une meilleure connaissance des différentes mutations qui lui sont associées pourront offrir de nouvelles pistes de recherches face à ces différentes hypothèses.

La fibrose kystique est une maladie héréditaire autosomale récessive dont les manifestations cliniques sont très variables. L'étude des 127 individus atteints, soit un recensement complet des malades qui sont suivis par la même équipe médicale depuis 1973, permet de mettre en lumière certaines caractéristiques particulières à notre population atteinte de fibrose kystique: une tendance en faveur du sexe féminin chez les malades vivants par catégorie d'âge, 7% de malades avec un iléus méconial à la naissance, et un score de Shwachman qualifié de bon à excellent dans 72,5% des cas. Ces quelques paramètres cliniques permettent de penser qu'il pourrait y avoir une relation entre les différentes mutations et les manifestations cliniques.

L'hypothèse d'un effet fondateur et d'une dérive génétique pour expliquer l'incidence élevée dans la population atteinte de fibrose kystique peut trouver ses origines dans la population mère de Charlevoix. En effet, la majorité des ancêtres de la population du SLSJ vient de cette région qui, à l'origine, a eu peu de fondateurs, fut longtemps isolée et dont certaines caractéristiques démographiques (grandes familles, consanguinité élevée) ont été le moteur de transmission de cette maladie.

Depuis la découverte du gène, les mutations qui lui sont associées sont de plus en plus nombreuses. Puisque la mutation ΔF508 est la plus ancienne et la mieux connue à travers le monde, une étude de sa

distribution et de sa fréquence mise en relation avec l'incidence mondiale de la fibrose kystique semblait opportune. C'est ainsi qu'une analyse mondiale de la distribution de la mutation ΔF508 en association avec l'incidence de la fibrose kystique dans diverses populations amènent à constater une variation de l'incidence à l'intérieur des différentes populations dont les résultats ne peuvent probablement pas être associés à l'utilisation de différentes méthodes d'analyse. S'il est vraisemblable qu'une augmentation de l'incidence et une augmentation de la fréquence de la mutation ΔF508 soient associées aux populations de l'Europe de l'ouest, il peut aussi être possible qu'une fréquence moindre de la mutation ΔF508 et une incidence plus faible soient associées aux populations de l'est et du sud de l'Europe. Par ailleurs l'étude récente sur les différentes mutations de fibrose kystique dans la population canadienne-française (plus particulièrement au SLSJ) (Rozen et al. 1991) tend à démontrer que la plus commune des mutations de fibrose kystique, soit ΔF508, est moins fréquente dans cette population (SLSJ)(58%) que dans d'autres. Elle atteint d'ailleurs 71% dans d'autres centres urbains québécois. Il est donc de plus en plus évident qu'il doit y avoir une relation probable entre les aspects génétiques et phénotypiques dans la fibrose kystique. Dès lors, les résultats des différents paramètres génétiques, épidémiologiques et cliniques, qui ont fait l'objet de cette étude, permettent de se faire une meilleure idée de la situation. Par ailleurs, les résultats en épidémiologie génétique pour la fibrose kystique pourraient servir de base de comparaison avec d'autres maladies autosomales récessives au Saguenay-Lac-St-Jean, qui font présentement l'objet d'études.

Au cours des derniers mois de la rédaction de ce mémoire, grâce à une subvention de recherche obtenue de la *Fondation Canadienne de la*

Fibrose Kystique (responsables du projet: Kenneth Morgan, Mary Fujiwara, Rima Rozen, Gervais Aubin, Fernand Simard, Jocelyne Daigneault, Marc De Braekeleer), les différentes mutations présentes dans le gène de la fibrose kystique ont maintenant été identifiées pour la région du Saguenay-Lac-St-Jean (Rozen et al. accepté dans *American Journal of Medical Genetics*). Cette étude a mis en évidence la présence de deux autres mutations majeures au SLSJ, à savoir la 621G->T présente sur 23% des chromosomes de fibrose kystique et la A455E présente sur 8% des chromosomes de fibrose kystique. Ces deux fréquences sont nettement plus élevées que celles rapportées dans d'autres études, ce qui semble confirmer que la prévalence à la naissance élevée de la fibrose kystique au Saguenay-Lac-St-Jean est due à un effet fondateur et une dérive génétique de plusieurs mutations. Devant l'intérêt de ces résultats, la *Fondation Canadienne de la Fibrose Kystique* vient d'octroyer à ces mêmes chercheurs une subvention d'un an(1991-1992), renouvelable, afin d'étudier les corrélations entre le génotype et le phénotype pour cette maladie.

Les connaissances acquises grâce à cette dernière étude auront des impacts majeurs au niveau du suivi et du traitement offert par la clinique de fibrose kystique de l'hôpital de Chicoutimi. L'espoir créé par la découverte du gène et les recherches subséquentes, permet d'envisager une meilleur qualité de vie pour les malades atteints de fibrose kystique dans cette région. Il ne faut cependant pas oublier que l'identification des mutations ouvre la porte au dépistage des porteurs au Saguenay-Lac-St-Jean avec toutes les interrogrations et les problèmes éthiques, familiaux, légaux et sociaux qu'un tel dépistage peut entraîner.