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Cystic Fibrosis Mutations in North American Populations of French Ancestry: Analysis of Quebec French-Canadian and Louisiana Acadian Families

Rima Rozen,*,†,‖,# Robert H. Schwartz,** Bettina C. Hilman,†† Pat Stanislovitis,‡‡ Glenn T. Horn,‡‡ Katherine Klinger,‡‡ Jocelyne Daigneault,§§ Marc De Braekeleer,§§ Bat-sheva Kerem,‖‖ Lap-Chee Tsui,‖‖,## T. Mary Fujiwara,*,‖ and Kenneth Morgan‡,§,‖,#

Departments of *Pediatrics, †Biology, ‡Epidemiology and Biostatistics, and §Medicine, ‖Centre for Human Genetics, and #Montreal Children's Hospital Research Institute, McGill University, Montreal; **Department of Pediatrics, University of Rochester Medical Center, Rochester, NY; ††Department of Pediatrics, Louisiana State University Medical Center, Shreveport; ‡‡Integrated Genetics, Framingham, MA; §§S.O.R.E.P., Université du Quebec à Chicoutimi, Chicoutimi, Quebec; and ‖‖Department of Genetics, Research Institute, Hospital for Sick Children; and ##Departments of Medical Genetics and Medical Biophysics, University of Toronto, Toronto

Summary

A 3-bp deletion (ΔF508) in the cystic fibrosis (CF) gene is the mutation on the majority of CF chromosomes. We studied 112 CF families from North American populations of French ancestry: French-Canadian families referred from hospitals in three cities in Quebec and from the Saguenay-Lac St. Jean region of northeastern Quebec and Acadian families living in Louisiana. ΔF508 was present on 71%, 55%, and 70% of the CF chromosomes from the major-urban Quebec, Saguenay-Lac St. Jean, and Louisiana Acadian families, respectively. A weighted estimate of the proportion of ΔF508 in the French-Canadian patient population of Quebec was 70%. We found that 95% of the CF chromosomes with ΔF508 had D7S23 haplotype B, the most frequent haplotype on CF chromosomes. In the Saguenay-Lac St. Jean families, 86% of the CF chromosomes without ΔF508 had the B haplotype, compared with 31% for the major-urban Quebec and Louisiana Acadian families. The incidence of CF in the Saguenay-Lac St. Jean population was 1/895 live-born infants.

Introduction

The cystic fibrosis (CF) gene and the major CF mutation, a 3-bp deletion (ΔF508), have been identified (Kerem et al. 1989; Riordan et al. 1989; Rommens et al. 1989). The overall proportion of ΔF508 in a worldwide survey of 13,179 CF chromosomes was 68%, with a range of 40%–88% in reports of more than 100 CF chromosomes (Cystic Fibrosis Genetic Analysis Consortium 1990).

We determined the proportion of ΔF508 and the distribution of MET–D7S23–D7S8 haplotypes in CF families from North American populations whose French ancestors immigrated to Canada during the period 1608–1759. We studied (1) French-Canadian CF families referred from hospitals in three major cities in the province of Quebec, (2) French-Canadian CF families from a subpopulation in northeastern Quebec—the Saguenay-Lac St. Jean region—in which there is increased incidence of CF, and (3) CF families from the Acadian population of Louisiana.

French-Canadians are descendants of approximately 8,500 immigrants from France, mainly from the northwest region, who settled along the St. Lawrence valley during the period 1608–1759 (Charbonneau and Robert 1987). There are approximately 10 million French descendants in North America, half of whom live in the province of Quebec (Foulds 1988). The Saguenay-Lac St. Jean region is located 250 km north of the city of Quebec. This region was relatively geographically isolated and was settled by approximately 5,000 immigrant families during 1838–1911 (Gauvreau and

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Address for correspondence and reprints: Kenneth Morgan, Ph.D., Department of Epidemiology and Biostatistics, McGill University, 1020 Pine Avenue West, Montreal, Quebec H3A 1A2, Canada.

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Bourque 1988). In 1986 the population size was 285,100, and French was the single ethnic origin for 94% of the individuals (Statistics Canada 1988). The first permanent French colony in Acadia (now Nova Scotia, New Brunswick, and Prince Edward Island) was established in 1610 (Chiasson 1988). French colonists, most of whom were from west-central France, continued to arrive through the 1670s (Brasseaux 1987; Chiasson 1988). During 1758–85 approximately 3,300 Acadians immigrated to Louisiana as a consequence of the dispersal of the Acadian population by the British (Daigle and LeBlanc 1987). The Louisiana Acadian population size is approximately 500,000 (Brasseaux 1987).

Subjects and Methods

CF Families

We studied 112 families, each of which had at least one affected CF child. Ethnic origin was based on either self-reported identification or information obtained from clinic staff. The Louisiana Acadian patients (26 families, also known as "Cajun" families) attended a CF clinic at either Shreveport or New Orleans. The 42 French-Canadian families were referred from the Montreal Children's Hospital and Hôpital Sainte-Justine in Montreal, Centre Hospitalier de l'Université de Laval in Sainte-Foy, and Centre Hospitalier de l'Université de Sherbrooke. The patients of the 44 Saguenay-Lac St. Jean families all attended the CF clinic at l'Hôpital de Chicoutimi. Ten of these families were included in the linkage analysis families reported by Kerem et al. (1989). Two non–Louisiana Acadian spouses and seven non-French-Canadian spouses were excluded. We refer to the three samples of chromosomes from the parents of CF children as being the major-urban Quebec, Saguenay-Lac St. Jean, and Louisiana Acadian families.

DNA Analysis

The following probe/enzyme combinations were used for DNA markers flanking the CF locus: metD/*Ban*I (Spence et al. 1986), metD/*Taq*I (White et al. 1986), metH/*Taq*I (White et al. 1985), XV-2c/*Taq*I and KM.19/*Pst*I (Estivill et al. 1987), and pJ3.11/*Taq*I and pJ3.11/*Msp*I (Bartels et al. 1986). Equivalent D7S23 probes used by Kerem et al. (1989) are H2.3A = XV-2c and JG2E1 = KM.19. Allele 1 corresponds to the larger RFLP band, and allele 2 corresponds to the smaller band. CF and normal haplotypes were assigned by inspection. D7S23 haplotypes are referred to as A, B, C, and D for (XV-2c)-(KM.19) combinations of 1-1, 1-2, 2-1, and 2-2, respectively.

DNA analysis by Southern blotting was performed by conventional procedures. Data for KM.19 and XV-2c were also obtained by polymerase chain reaction (PCR) analysis (Feldman et al. 1988; Rosenbloom et al. 1989) or by PCR analysis using allele-specific oligonucleotides (Horn et al. 1989). The presence or absence of ΔF508 was determined by PCR analysis (Kerem et al. 1989; Klinger et al. 1990; Rommens et al. 1990).

Statistical Analysis

Exact probability tests for two-way contingency tables were computed with IMSL STAT/LIBRARY subroutines, version 1.0 (IMSL 1987). P_{RE} is the probability of a two-way contingency table that is more extreme than that observed. It is obtained by summing the probabilities of the observed and of all other tables which have probability less than or equal to the probability of the observed table. The probability of a table is calculated conditional on fixed row and column marginal totals.

Results and Discussion

The distributions of the MET–D7S23–D7S8 haplotypes for CF and normal chromosomes are given in table 1. The frequency of ΔF508 was 71%, 55%, and 70% of the CF chromosomes from the major-urban Quebec, Saguenay-Lac St. Jean, and Louisiana Acadian families, respectively. The proportion of ΔF508 was significantly lower in the Saguenay-Lac St. Jean families than in the major-urban Quebec families (one-tailed Fisher's exact test; $P = .02$).

A weighted estimate of the proportion of ΔF508 in the Quebec French-Canadian patient population was 70%, the weighting being based on population size and CF gene frequency in the Saguenay-Lac St. Jean region and in the rest of the province of Quebec. This estimate is within the range of 63%–81% ΔF508 in eight reports from France (Cystic Fibrosis Genetic Analysis Consortium 1990). The reports from France were significantly heterogeneous for the proportion of ΔF508 ($\chi^2 = 26.4$, df = 7, $P < .001$).

The three samples were homogeneous for the distribution of D7S23 haplotypes on normal chromosomes (exact probability test; $P_{RE} = .14$). The major-urban Quebec families were similar to the Louisiana Acadian families in the distribution of the D7S23 haplotype–CF mutation combinations ($P_{RE} = .77$) but differed significantly from the Saguenay-Lac St. Jean families ($P_{RE} = .0003$). We found that 95% of CF chromosomes with ΔF508 had the B haplotype, a proportion

Table 1

Distribution of Haplotypes for CF Chromosomes with ΔF508, CF Chromosomes with Other CF Mutations, and Normal Chromosomes

Haplotype[a]			French-Canadians						Louisiana Acadians		
			Major-Urban Quebec			Saguenay-Lac St. Jean Region					
			CF			CF			CF		
MET	D7S23	D7S8	ΔF508	Other	Normal	ΔF508	Other	Normal	ΔF508	Other	Normal
. . .	1 1	. . . . .	0	1	6	0	0	11	0	2	5
1 1 1	1 1	1 1	0	7	3	0	1	2	0	1	0
1 1 1	1 1	1 2	0	0	4	0	0	3	0	0	2
1 1 1	1 1	2 1	0	0	1	0	0	0	0	0	1
1 1 2	1 1	1 1	0	0	0	0	0	2	0	0	0
2 1 2	1 1	1 1	0	0	3	0	0	2	0	0	3
2 1 2	1 1	1 2	0	0	5	0	0	2	0	0	6
2 1 2	1 1	2 1	0	0	1	0	0	0	0	0	0
2 2 1	1 1	1 1	0	0	0	0	0	0	0	0	4
2 2 1	1 1	1 2	0	0	1	0	0	0	0	0	2
Subtotal			0	8	24	0	1	22	0	3	23
. . .	1 2	. . . . .	8	0	1	30	17	5	7	3	2
1 1 1	1 2	1 1	16	1	0	2	3	1	3	0	0
1 1 1	1 2	1 2	15	1	1	1	0	0	6	0	1
1 1 1	1 2	2 1	3	0	0	8	0	0	1	0	0
1 2 1	1 2	2 1	1	0	0	0	0	0	0	0	0
2 1 1	1 2	1 2	0	0	1	0	0	0	0	0	0
2 1 1	1 2	2 1	0	0	1	0	0	0	0	0	0
2 1 2	1 2	1 1	4	1	1	0	1	0	11	1	0
2 1 2	1 2	1 2	1	4	1	0	4	1	0	0	0
2 1 2	1 2	2 2	0	0	1	0	0	0	0	0	0
2 2 1	1 2	1 1	2	0	0	0	0	1	1	0	0
2 2 1	1 2	1 2	1	0	4	0	0	0	3	0	0
2 2 1	1 2	2 1	1	0	0	0	0	0	0	0	0
Subtotal			52	7	11	41	25	8	32	4	3
. . .	2 1	. . . . .	0	1	6	0	2	18	0	0	2
1 1 1	2 1	1 1	0	0	3	0	0	0	0	0	0
1 1 1	2 1	1 2	0	0	7	0	0	1	0	0	3
1 1 1	2 1	2 1	0	0	0	0	0	0	0	0	1
2 1 1	2 1	1 1	0	0	1	0	0	0	0	0	0
2 1 2	2 1	1 1	0	1	6	0	0	0	0	5	1
2 1 2	2 1	1 2	0	1	4	0	1	2	0	0	2
2 2 1	2 1	1 1	0	0	4	0	0	0	0	0	0
2 2 1	2 1	1 2	0	0	3	0	0	0	0	0	0
2 2 1	2 1	2 1	0	0	1	0	0	0	0	0	0
2 2 2	2 1	1 2	0	0	0	0	0	0	0	0	1
Subtotal			0	3	35	0	3	21	0	5	10
. . .	2 2	. . . . .	0	1	0	1	0	5	1	0	1
1 1 1	2 2	1 2	1	1	1	0	0	0	0	0	1
1 1 1	2 2	2 1	0	0	0	1	0	0	0	0	0
2 1 2	2 2	1 1	0	0	2	0	0	0	1	1	0
2 1 2	2 2	1 2	1	0	1	0	0	0	0	0	1
2 1 2	2 2	2 1	1	0	0	0	0	0	0	0	0
2 2 1	2 2	1 1	0	0	1	0	0	0	0	0	1
2 2 1	2 2	1 2	0	1	0	0	0	1	0	1	1
2 2 1	2 2	2 1	0	0	0	0	0	0	0	0	1
2 2 2	2 2	1 2	0	0	1	0	0	0	0	0	0
Subtotal			3	3	6	2	0	6	2	2	6
Total no. unassigned			0	1	1	5	11	31	1	1	8
Total			55	22	77	48	40	88	35	15	50

[a] Order of DNA markers is metD/*Ban*I, metD/*Taq*I, metH/*Taq*I, XV-2c/*Taq*I, KM.19/*Pst*I, pJ3.11/*Taq*I, pJ3.11/*Msp*I.

which is similar to that for North American Caucasian patients of European ancestry (Kerem et al. 1989; Lemna et al. 1990). The B haplotype was present on 86% (25/29) of CF chromosomes without ΔF508 in the Saguenay-Lac St. Jean families, compared with 31% (11/35) in the major-urban Quebec and Louisiana Acadian families. Corresponding proportions were 16% (3/19) for Canadian families excluding the Saguenay-Lac St. Jean families (Kerem et al. 1989) and 54% (57/106) for North American Caucasian families excluding Ashkenazic and Hispanic families (Lemna et al. 1990).

Over the period 1976–85 the incidence of CF in the Saguenay-Lac St. Jean population was 1/895 live-born infants (De Braekeleer, in press). This is higher than the incidence in any of the populations reported by Boat et al. (1989) and is almost three times higher than the frequently quoted incidence of 1/2,500 births in the general Caucasian population. When Hardy-Weinberg equilibrium was assumed, the CF gene frequency was .033, and the frequency of CF carriers was 1/15 individuals. We conclude that CF chromosomes without ΔF508 and having the B haplotype are increased in frequency. On the basis of (*a*) the classification of the 20 Saguenay-Lac St. Jean CF chromosomes in table 3 of Kerem et al. (1989) into groups Ia, Ib, IIa, and IIb, and (*b*) the distribution of 7-marker haplotypes in table 1, there appears to be at least three CF mutations in addition to ΔF508, in the Saguenay-Lac St. Jean population.

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