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Variability of the Genetic Contribution of Quebec Population Founders Associated to Some Deleterious Genes

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Summary

Relatively high frequencies of some rare inherited disorders can be found in the Saguenay Region (Quebec). To understand this phenomenon, a research project on the 17th-century founder effect that led to the formation of French Canadians' gene pool is being carried out. The focus of this study is on founders who contributed to the Saguenay gene pool and who are related to contemporary probands suffering from any one of five hereditary diseases: cystic fibrosis, tyrosinemia, hemochromatosis, Charlevoix-Saguenay spastic ataxia, and sensorimotor polyneuropathia with or without agenesis of the corpus callosum. A control group has been added for comparison purposes. Altogether, 545 ascending genealogies have been reconstructed, using the Interuniversity Institute for Population Research's RETRO database, leading to >2,500 founders. The genetic contribution of each founder to each group has been measured. Results show that (1) nearly 80% of the individuals' gene pool come from founders who settled in Nouvelle-France in the 17th century, whatever the group; (2) 15% of the founders explain 90% of the total genetic contribution of the founders, but this pattern varies from one group to another; (3) there is no subgroup of founders more related to any given group of individuals.

Introduction

This study is in keeping with a joint research project on migratory and reproductive behaviors of the first French Canadian population founders, involving the Historical Demography Research Program (PRDH, University of Montreal) and the Interuniversity Institute for Population Research (IREP). At a symposium on migrations in Belgium and Quebec held in Montreal in September 1993, a paper was read on this project and on the first results of the research being carried on (Bouchard et al. 1993).

The main object of our research consists in analyzing the peculiar demographic conditions (migratory journeys, differential nuptiality, and fertility) which have characterized the reproduction and distribution of the descendants of the first French Canadian population founders, a certain number of which originated the emergence and the transmission of rare hereditary diseases or diseases relatively peculiar to the Saguenay Region. From previous studies, we know that no common ancestors (i.e., ancestors common to $\geqslant 95\%$ of probands suffering from a given disease) could be found at the Saguenay level (Bouchard and DeBraekeleer 1991*b*). All ascending genealogies have to go back to the 17th century in order to find common ancestors for a particular disease. In addition to this, each of these common ancestors came from France. That explains why this study will focus on French founders born in the 17th century.

In the first stage of this project, we identified, from ascending genealogies of some 700 Saguenay probands, >2,600 founding ancestors (i.e., arrived in Nouvelle-France in the 17th century), whom we regrouped according to the extent of their genetic contribution to the probands' pool. Results have shown that this genetic contribution varied appreciably, depending on the founders, and that the important contribution observed for some of them is in part due to a high reproduction, but differential migration had an equally determinant effect.

Pursuant to some questions raised in the course of this preliminary stage of our research, we looked for some information on the variability of the founders' genetic contribution, based on different hereditary diseases. In the first study, no distinction was made between the different Saguenay groups of probands from whom the genealogies were reconstructed to identify the founders. Now, the question is, do the findings made from the founders as a whole (all groups of probands intermingled) remain the same when the groups of probands are separated according to their specific diseases? Can we assume that these results are peculiar to the diseases, or would we find the same results for a given control group (individuals who are not suffering from an inherited disorder)? In other words, are the high contribution

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of first founders and the high variability in this contribution so only for inherited disorders, or is this a pattern of the whole population? Are these results the same for all diseases, or do they differ? If so, how could that be interpreted with regard to the molecular knowledge we have about each disease?

Furthermore, it would be interesting to look into the possibility that subgroups of founders may have substantially contributed to the gene pool of a certain group of probands and, at the same time, contributed less to another group of probands. Five distinct groups of probands and a control group were therefore investigated. For each of these groups, founders were identified and their genetic contribution to the probands was calculated. The distributions obtained were then compared, and, from regroupings of founders according to their genetic importance or weight, we tried to find out if there were significant disparities between the regroupings obtained for each of the five groups of probands and for the control group.

Material and Methods

Geographical Situation

The Saguenay Region (Province of Quebec, Canada) is located on the north shore of the St. Lawrence River, at about 200 km to the northeast of Quebec City. Its territory covers some 11,000 km^2. White settlement in this region began in the mid-1800s, originating mostly from the relatively small border region called Charlevoix; from 1840 to 1870, 80% of the Saguenay settlers were born in Charlevoix (Pouyez and Lavoie 1983). Historically and genetically speaking, these two regions have maintained a close relationship. Even today, nearly 90% of individuals of the Saguenay population (which approaches 300,000 inhabitants) born between 1950 and 1970 have these first settlers as ancestors (E. Heyer, unpublished data). Both populations are characterized by a relatively high frequency of some rare hereditary diseases, mainly recessive ones (Bouchard et al. 1991). In this study, we investigate the origins of five of these diseases, by analyzing the genetic contribution of the ancestors related to some Saguenay residents who have inherited the deleterious genes.

Database

The basic data that were used to carry out this study come from IREP's RETRO database. The information contained in this database can be used to reconstruct the ascending genealogies of some 3,000 individuals, about three-quarters of whom are Saguenay residents suffering from hereditary diseases (Jomphe and Casgrain 1994). For the purpose of this study, probands suffering from any of the five following diseases were chosen: tyrosinemia (89 probands), Charlevoix-Saguenay spastic ataxia (139 probands), sensorimotor polyneuropathy with or without agenesis of the corpus callosum (84 probands), cystic fibrosis (CF) (102 probands), and hemochromatosis (31 probands). Except for hemochromatosis, each of these diseases are single locus, recessive, and autosomal, with, as far as we know, a complete penetrance and an estimated frequency of carriers of ~5% in the Saguenay population; hemochromatosis reaches a frequency of 21% with a probably incomplete penetrance (Vigneault 1991). The first three diseases may be considered to be more characteristic of the Saguenay Region, since they can be found with a higher frequency than elsewhere in Quebec, while the other two diseases are not particular to the region (for additional information regarding these diseases, see Bouchard and De Braekeleer 1992). At the time the diagnoses were carried out, most of the probands concerned were children (except for those probands suffering from hemochromatosis).

The control group is made of 100 individuals born in the Saguenay between 1950 and 1971. They have been chosen in order to represent the whole population by using a frame based on genetic contribution of immigrants to the Saguenay (E. Heyer, unpublished data). It cannot be excluded that any of these 100 individuals are carriers of any inherited disorders, since no molecular analysis has been done on these individuals.

In total, 445 ascending genealogies were reconstructed for the five diseases, most of which go back some 12 generations (as far back as the beginning of the 17th century). From these genealogies, we identified 2,462 ancestors who arrived in Nouvelle-France before the year 1700. The 100 ascending genealogies for the control group trace back to 2,263 ancestors who arrived in Nouvelle-France before the year 1700, 97% of them being included in the group of 2,462 founders for the probands. These ancestors form the founders corpus from which genetic contribution measures were done. It is to be noted that in the first stage of the project, these data were paired with those of the PRDH population database, in order to verify the concordance of the information used (names, first names, marriage dates) and to specify the founders' immigrant status.

Data Description

Table 1 gives some information on the probands, as well as on the founders who were associated to them, for each of the diseases and the control group. Founders' distribution shows that several of these founders are to be found in more than one group of probands. In fact, 1,095 founders (44.5% of the whole) appeared at least once in each of the five groups of probands. This concentration of common ancestors is, for that matter, characteristic of the Quebec population (Charbonneau et al. 1987; Bouchard and De Braekeleer 1991*a*), which re-

Table 1

Distribution and Characteristics of Probands, Control Group, and Founders

	PROBANDS		FOUNDERS		
DISEASE	Number	Mean Birth Year	Number	Sex Ratio[a]	Mean Birth Year
Tyrosinemia	89	1964	1739	1.71	1639
Ataxia	139	1959	1721	1.67	1639
Polyneuropathy	84	1970	1683	1.68	1638
Fibrosis	102	1978	2309	1.78	1640
Hemochromatosis	31	1940	1229	1.58	1637
All diseases	445	1966	2462	1.83	1641
Control group	100	1959	2263	1.76	1640

SOURCE.—IREP, RETRO database.
[a] Number of males/number of females.

sults, in part, from the "founder effect" phenomenon. The founder effect consists in the implantation, in a new territory, of a relatively limited number of individuals originating from the same population (Mayr 1963). It is the case, for example, of the 17th-century French emigration to Nouvelle-France.

The distribution of founders according to sex is rather peculiar, as we can see in examining the sex ratios. The number of males greatly exceeds that of females, whichever group is considered. As a whole, there are almost twice as many male founders as female founders. This disproportion between sexes mainly results from the consequences of the first immigration waves in Nouvelle-France. As a matter of fact, there were twice as many male immigrants as female immigrants in the 17th century (these immigrants are those who founded a family in the colony), which resulted in a important disproportion within the matrimonial market (Charbonneau et al. 1987). For instance, several founders married Canadian-born women, while the reverse phenomenon (female founders married to Canadian men) was much less frequent. It is to be noted, however, that the sex ratio is somewhat lower when calculated for each of the diseases; this is explained by the fact that the proportion of female founders common to each group is higher than the corresponding proportion of male founders. For the probands, sex ratios are not shown, since the measures we use in this study are not dependent on sex: a sister and her brother are strictly equivalent.

Finally, the comparison of the average birth years shows the extent of the "distances" (in terms of years) that separate individuals from founders. On average, this distance is equivalent to 325 years, the gap being lower for hemochromatosis probands than for the other probands. Here again, the weight of those founders common to several groups is quite perceptible: these founders having been born a little earlier, on average, than the founders appearing in a sole group of genealogies, the average birth years of the founders of each group are slightly earlier than the average birth year of the founders as a whole.

Measure of the Founders' Genetic Contribution

All founders do not appear at the same frequency in the reconstructed genealogies. Some of them can be found at least once (and often several times) in each of the 545 genealogies, while others are found in only one genealogy. Therefore, the proportion of individuals related to such and such founder, as well as the global genetic contribution of a founder to a group of individuals, strongly differs from one founder to another. To illustrate this variability, the sum of transmission probabilities of one gene to each individual of a given group was calculated for each founder. This sum is called the genetic contribution of a founder to a given group:

$$\textit{genetic contribution} = \sum_{i=1}^{p} \sum_{j=1}^{c} \left(\frac{1}{2}\right)^{g_c}, \qquad (1)$$

where p = number of individuals in a given group genealogically related to the founder; c = number of genealogical paths between the founder and the individual; and g_c = number of generations separating the founder from the individual, for each path.

For example, the genetic contribution of a grandfather to his 10 grandchildren is:

$$\textit{genetic contribution} = \sum_{i=1}^{10} \sum_{j=1}^{1} \left(\frac{1}{2}\right)^{2} = 2.5\,. \qquad (2)$$

For more details about this formula, see Roberts (1968) and O'Brien et al. (1988).

Table 2

Genetic Contribution of Founders to Probands of Each Disease and Control Group

Disease	Genetic Contribution	Proportion (%) of the Gene Pool Attributable to Founders
Tyrosinemia	70.4	79.1
Ataxia	109.7	78.9
Polyneuropathy	66.1	78.7
CF	79.2	79.9
Hemochromatosis	24.8	79.7
All diseases	350.2	78.7
Control group	79.4	79.4

SOURCE.—IREP, RETRO database.

The genetic contribution is a summary of all demographic events (nuptiality, fertility, mortality, and migration) that occurred among the descendants of a founder. It enables us to verify whether specific demographic dynamics exist, which could explain the high frequency of disorders in the Saguenay.

Results

Adding the genetic contributions of all founders of a given group of individuals and then dividing the result by the number of individuals in the group, we obtain the proportion of the individuals' gene pool that is attributable to these founders. Table 2 shows that this proportion is considerable: nearly 80% of the probands' gene pool comes from ancestors who settled in Nouvelle-France in the 17th century. This proportion differs very little from one group to another (from 78.7% for probands of the polyneuropathy group to 79.9% for those of the CF). The pattern remains the same for the control group.

Table 3 emphasizes the variability of the founders' genetic contribution. The data obtained clearly show that a small proportion of the founders is accountable for a large proportion of the total genetic contribution. The values are very similar from one group to the other, except for hemochromatosis probands. So, ~80% of the founders' total genetic contribution is attributable to <13% of the founders (20% where hemochromatosis is concerned) and <25% of the founders (35% for hemochromatosis) accounts for >90% of the genetic contribution. When the probands as a whole are considered, the concentration observed is even higher: 8.4% of the founders are responsible for 80% of the total genetic contribution, and 90% of this contribution is imputable to only 15.1% of the founders.

If there were no overlap between diseases for founders who account for 80% (90%) of the genetic contribution, this value would be 43.1% (77.3%).

It is very difficult to compare these results disease by disease because this measure is influenced by the differences between the numbers of founders of each group. The number of founders for each group depends on the number of individuals; in particular, the number of founders who are linked to <5% of individuals in each group increases rapidly with the number of individuals (data not shown). In order to compare the concentration of founders from one disease to the other, we decided to focus on the 1,095 founders who cover at least one individual in each disease. These 1,095 founders, who represent <45% of all founders, supply 98% of the founders' total genetic contribution to probands (343.5/350.2).

Figure 1 shows the cumulative genetic contribution of the 1,095 founders sorted in each group by their genetic contribution. The first 5% of founders with the higher genetic contribution account for 38.5% of the control groups' gene pool; this concentration is comparable for hemochromatosis (39.1%) and CF (39.3%) but differs for tyrosinemia (44.1%), polyneuropathy (43.7%), and ataxia (45.9%). So, the concentration is the lowest for the control group, but CF and hemochromatosis are much closer to that group than are the three other diseases. We will get back to this point in the Discussion.

Now, one question remains: do founders who strongly contribute to the gene pool of probands suffering from a given disease contribute in the same way to the other groups of probands' gene pool? To answer this question, we must first distinguish founders according to their importance in terms of genetic contribution. For the purpose of this study, we chose a distribution com-

Table 3

Proportion (%) of Founders That Is Responsible for 80% and 90% of the Founders' Total Genetic Contribution to the Probands of Each Disease and Control Group

Disease	Proportion of the Founders' Total Genetic Contribution	
	80%	90%
Tyrosinemia	11.2	19.8
Ataxia	9.8	17.8
Polyneuropathy	11.3	20.4
CF	11.2	20.8
Hemochromatosis	20.3	35.0
All diseases	8.4	15.1
Control group	13.0	25.0

SOURCE.—IREP, RETRO database.

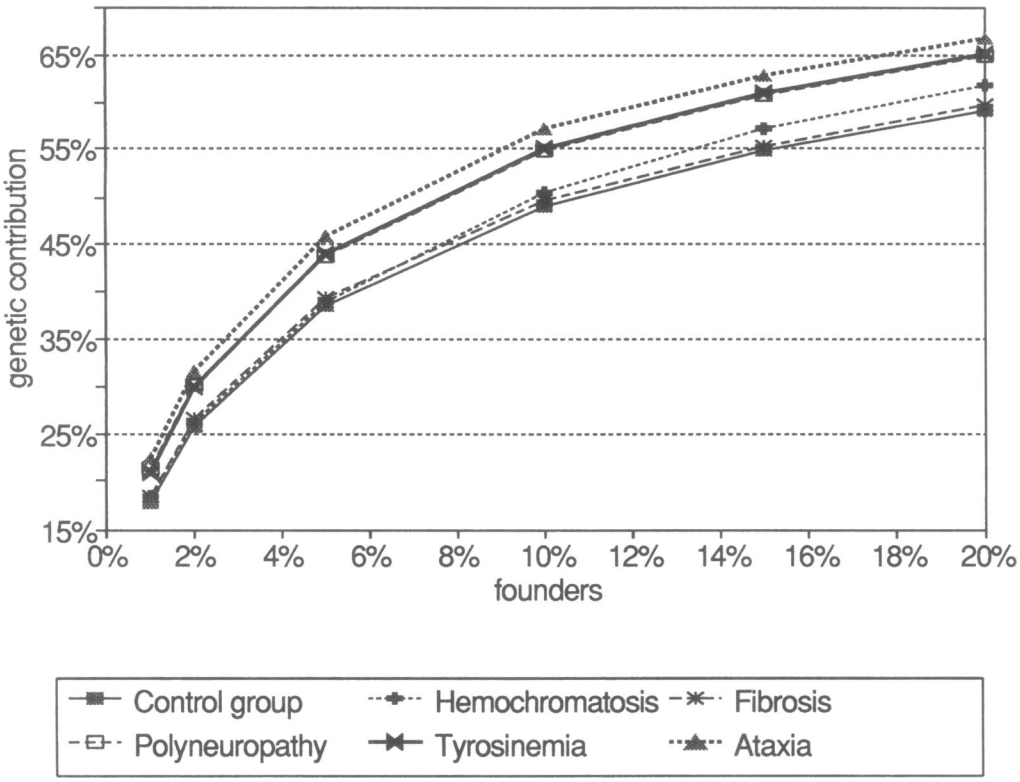

Figure 1 Cumulative percentage of total genetic contribution, by cumulative percentage of the founders

prising three regroupings: founders with a high genetic contribution (group 1), those who have an intermediate genetic contribution (group 2), and those with a low genetic contribution (group 3). For each disease, this distribution was made by selecting, in a genetic contribution decreasing order, the first fifth of the founders (group 1), the second fifth (group 2), and the last three-fifths (group 3). The proportions of the genetic contribution attributable to each of these three groups appear in table 4. Group 1 supplies between 78.5% and 95.7% of the founders' genetic contribution; group 2 supplies from 9.7% to 13.0%; while the last group's contribution is between 4.6% and 8.9%.

To verify whether the genetic importance of a founder greatly differs according to the probands' group, the distribution of the founders, according to the importance of their genetic contribution (1, high; 2, intermediate; or 3, low) for each of the diseases, was analyzed (table 5). In total, this represents a possibility of 243 (3^5) different combinations. Most founders are found in either of the following situations: low genetic contribution for all diseases (combinations that comprise only 3's: 547 founders), intermediate, or high genetic contribution for all diseases (combinations that comprise only 2's or 1's: 363 founders). Among the latter, 172 founders have a high genetic contribution to the five probands' groups. Nearly 75% of the founders are in one of the three perfectly uniform situations (low contribution, intermediate contribution, or high contribution for all probands' groups). Most of the other founders are in one of the mixed situations: low/intermediate (3's and 2's) or intermediate/high (2's and 1's). There remain only five founders whose importance varies from low to high according to the group of probands.

These results show, all things considered, that there is not much discordance in the genetic contribution of a founder according to the group of probands: as a general rule, a founder having a genetic contribution of a given extent for a particular group of probands will have a genetic contribution of a comparable extent for the other groups of probands.

If we now add the control group, this pattern remains the same: founders with a high genetic contribution for all probands' group have also a high genetic contribution to the control group. There is no founder with a high genetic contribution to the control group and a low contribution to any disease. Conversely, no founder was found with a high contribution to one disease and a low contribution to the control group, except for two founders for hemochromatosis. These two founders were classified 33331 for the five diseases, but they are at the bottom line of the first group for hemochromato-

Table 4

Genetic Contribution and Proportion (%) of the Genetic Contribution Attributable to Each Group of Founders, for Each Disease and Control group (1,095 Founders Who Appear at Least Once in the Genealogies of Each Group of Probands)

Disease	Genetic Contribution		Proportion (%) of the Contribution according to the Group of Founders		
	Absolute Value	%[a]	Group 1[b]	Group 2[c]	Group 3[d]
Tyrosinemia	69.2	77.8	83.7	10.9	5.4
Ataxia	108.3	77.9	85.7	9.7	4.6
Polyneuropathy	65.0	77.3	83.9	10.7	5.4
Fibrosis	76.5	75.0	79.5	12.4	8.1
Hemochromatosis	24.5	78.9	78.5	13.0	8.5
All diseases	343.5	77.2	82.7	10.9	6.4
Control group	75.5	75.5	78.2	12.9	8.9

SOURCE.—IREP, RETRO database.
[a] Percent of the gene pool attributable to the 1,095 founders.
[b] First 20% of the founders.
[c] Second 20% of the founders.
[d] Last 60% of the founders.

sis and are linked to only four hemochromatosis probands.

Discussion

Results of this study on the genetic contribution of the distant ancestors of certain Saguenay probands suffering from a hereditary disease have shown that this contribution is (1) *high:* nearly 80% of these probands' gene pool comes from founders who settled in Nouvelle-France in the 17th century; (2) *concentrated:* 15% of the founders are responsible for 90% of the founders' total genetic contribution, but this pattern varies from one group to another; and (3) *homogeneous:* there is no subgroup of founders more related to any given group of individuals.

Other similar studies (with the same time depth) have shown a much lesser contribution for the first founders of certain Caucasian populations. O'Brien et al. (1988) found a genetic contribution of 13% in Sottunga (Finland), while Heyer (1991, 1993) obtained a value of 17% for the founders of the Vallée de la Valserine (French Jura). Since the founders who immigrated before 1700 contribute ~80% of the Saguenay probands' gene pool, it is therefore likely that the deleterious genes were introduced in Nouvelle-France right from the first years of settlement. The high contribution observed for the founders of Nouvelle-France can be explained by the relative isolation of the Quebec Francophone population (due to little immigration) and possibly also by a growing isolation of the founders' descendants who settled in the Saguenay Region. This situation has already been mentioned elsewhere: using a method based on the evolution, from the origins to nowadays, of the relative impact of the various waves of immigration, Charbonneau et al. (1987) estimated that the founders who have settled in Nouvelle-France before 1680 would explain about two-thirds of the present Quebec Francophones' gene pool.

Still, all founders do not evenly participate to the individuals' gene pool, far from that. Whichever group is considered, a small portion of the founders supplies a large portion of the total genetic contribution of these founders. This phenomenon is not exclusive to the population in study (see, for example, Chapman and Jacquard 1971; Jacquard 1974). However, results obtained here are particularly remarkable, considering that the Saguenay population is numerically important (it is not a small isolate).

This variability follows different patterns, according to the group of individuals considered. Clearly, the concentration of genetic contribution shows two subsets: one with a higher concentration for tyrosinemia, polyneuropathy, and ataxia and another for hemochromatosis, CF, and the control group. From molecular data, we know that 90% of tyrosinemia probands' genes are the same splice mutation (Grompe et al. 1994) and that this mutation has a frequency of 16% in probands from other populations. It is therefore expected that only a small number of founders could have introduced the mutation in the population. These results are confirmed by fumarylacetoacetate hydrolase RFLPs with 96% of Saguenay probands sharing the same haplotype (Demers

Table 5

Distribution of the Founders according to Their Genetic Contribution to Each of the Five Groups of Probands (Founders Who Appear at Least Once in the Genealogies of Each Group of Probands)

Disease[a]					Founders		Disease[a]					Founders	
T	A	P	F	H	Number	%	T	A	P	F	H	Number	%
1	1	1	1	1	172	15.71	2	2	2	3	3	9	.82
1	1	1	1	2	10	.91	2	2	3	2	2	1	.09
1	1	1	2	1	1	.09	2	2	3	2	3	1	.09
1	1	1	2	2	3	.27	2	2	3	3	2	2	.18
1	1	2	1	1	2	.18	2	2	3	3	3	8	.73
1	1	2	1	2	4	.37	2	3	2	2	2	3	.27
1	1	2	2	1	1	.09	2	3	2	2	3	2	.18
1	1	2	2	2	3	.27	2	3	2	3	2	4	.37
1	2	1	1	1	7	.64	2	3	2	3	3	10	.91
1	2	1	1	2	10	.91	2	3	3	2	2	2	.18
1	2	1	2	1	1	.09	2	3	3	2	3	4	.37
1	2	2	1	1	1	.09	2	3	3	3	2	1	.09
1	2	2	2	1	4	.37	2	3	3	3	3	5	.46
2	1	1	1	2	4	.37	3	3	2	2	3	3	.27
2	1	1	2	1	3	.27	3	2	2	3	2	1	.09
2	1	1	2	2	3	.27	3	2	2	3	3	2	.18
2	1	2	1	2	4	.37	3	2	3	2	2	3	.27
2	1	2	2	1	4	.37	3	2	3	2	3	8	.73
2	1	2	2	2	4	.37	3	2	3	3	2	3	.27
2	1	2	2	3	1	.09	3	2	3	3	3	11	1.00
2	2	1	1	1	2	.18	3	3	2	2	2	2	.18
2	2	1	2	2	3	.27	3	3	2	2	3	2	.18
2	2	2	1	1	1	.09	3	3	2	3	2	5	.46
2	2	2	1	2	2	.18	3	3	2	3	3	9	.82
2	2	2	2	1	14	1.28	3	3	3	2	2	6	.55
2	2	2	2	2	100	9.13	3	3	3	2	3	18	1.64
2	2	2	2	3	19	1.74	3	3	3	3	1	2	.18
2	2	2	3	1	2	.18	3	3	3	3	2	35	3.20
2	2	2	3	2	1	.09	3	3	3	3	3	547	49.95
							Total					1,095	100.00

SOURCE.—IREP, RETRO database.

[a] T = tyrosinemia; A = ataxia; P = polyneuropathy; F = fibrosis; and H = hemochromatosis. 1 = high contribution; 2 = intermediate contribution; and 3 = low contribution.

et al. 1994). On the other hand, molecular data show that the most frequent CF mutation in the Saguenay is the ΔF508, also the most frequent in Caucasian populations, and that there appear to be at least three CF mutations in addition to ΔF508 in the Saguenay (Rozen et al. 1990); it is therefore expected that not only one but several founders have introduced the gene in the population. Even if we do not have molecular data about hemochromatosis, we know that this disease is one of the most common in Caucasian populations, with a carrier frequency estimated at 10% (Bothwell et al. 1989). One should recall that these two diseases show a pattern of concentration of the founders' genetic contribution that is very similar to that of the control group. It is therefore strongly suspected that a predominant mutation would be found for polyneuropathy and for ataxia. This seems to be concordant with the fact that these two diseases are specific to Saguenay-Charlevoix.

From these results we can also conclude that the high frequencies of CF and hemochromatosis are due to the general demographic dynamic of the population: since the family size was very high, more than seven children per family in the 18th century and the first half of the 19th century (Henripin and Péron 1973), some founders would get a high genetic contribution to the contemporary Saguenay gene pool only by random fluctuation of family size. On the other hand, it seems that to reach the actual frequency for a rare disease, a more specific demographic dynamic is needed in order to increase the gene frequency more than does the overall demographic dynamic in the population. The demographic dynamic of the population can lead to an increase of the frequency of common genes, but to increase the frequency of a rare disorder more specific conditions are needed. The carriers of this rare disease are a subset of the population where the concentration of founders' genetic contribution is

higher than in the population. Concerning the demographic dynamic, one could hypothesize a closer endogamy between ancestors of these carriers—which would have led to a higher kinship between these ancestors, perhaps associated with a higher reproduction to compensate for the selection against the homozygotes (except for ataxia where the selection is lower). This higher reproduction can be achieved either by chance (family-size fluctuation) or by heterozygote advantage.

Finally, it appears that the genetic importance of a founder does not vary appreciably according to the group (probands or control) chosen: a founder who is important for a disease group or the control group is also important for the other groups. Only a few founders show an appreciable variability of their genetic contribution from one group to another. These exceptions, however, are only a manifestation of the fact that a founder cannot contribute in a totally invariable way to the gene pool of each group of probands. Said exceptions cannot enable us to identify a subgroup of founders who would have a high risk of having introduced the corresponding deleterious gene in the population, as suggested by Bouchard et al. (1991). Furthermore, we have established that these founders are only related to a very small number of probands, even for the disease where their genetic contribution was qualified as high (they cannot explain the actual frequency of the gene in Quebec). From our study, we know that no subset of founders is specific to one disease, so there is no subpopulation among founders that could be related to any inherited disorder in the Saguenay. Since some diseases are specific to the Saguenay population, we would have expected different subsets of founders for these diseases than for control or common diseases. However, we already know from previous studies that the kinship coefficients between probands sharing a same disease are higher than those between nondiseased individuals (De Braekeleer 1991), suggesting that we could indeed find a small number of specific founders for each disease.

So, to identify founders specific to any disease, we will have to use Thompson's method (Thompson 1986), lately modified to take into account that no ancestor can be homozygous for a lethal allele (Thompson and Morgan 1989). Fujiwara et al. (1989) have shown on Hutterites that for ancestral inference, it will be necessary to compute, for a given haplotype, the relative likelihoods of joint descent from specific common ancestors to subsets of current carriers of the same haplotype, using this method. This will enable us to measure the probabilities, for each founder, of being bearer of such and such deleterious gene.

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