

The Founder Effect in Québec

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French-Canadians suffer from several disorders which are rare elsewhere and even a few which are seen nowhere else. Why is this so and how significant is it to French-Canadian families today?¹

The Founder Effect

Genetic mutations happen in all populations. Some have good effects and some bad while others are neutral. As long as the gene pool (the population of marriageable couples) is large enough, bad mutations will seldom meet. But when a small group migrates to an isolated area, rare mutations are bound to find expression over time, and disorders will surface that are rarely seen (or are totally absent) in the larger gene pool of the country of origin. Even if the settlers are careful not to marry too close, chance and the fact that nearly everyone descends from the same small group of early founders means that rare genetic disorders will pop up from time to time.² This phenomenon is called "The Founder Effect," and the chance occurrence of some mutations arriving with the founders (rather than others) is called "genetic drift."

In Quebec, the founders in question were mainly from Perche, those early colonists, beginning with Robert Giffard's first settlers in 1634, from whom nearly all of us are descended.³ These are the Cloutiers, Guyons, Goulets, Drouins, Bouchers, Tremblays and about 120 others at the base of your tree. As Gagné put it:

Though it was not the biggest contributor of immigrants to New France, providing a little over 7% of pioneers, Perche makes up only about 0.3% of the area of France, and when considered proportionally, sent 10 to 15 times as many immigrants per area. Perche also has the distinction of sending some of the first settlers to the colony. Most of them arrived before 1662.⁴

These Perche settlers did, therefore, provide the baseline population of Québec, and they no doubt brought a lot of excellent genes with them. But, as any founding population would have done, they also brought, by chance, some rare deleterious mutations, and when these mutations (many of which cause no problems when contributed by just one parent) met up with a like mutation, rare conditions surfaced. Not all of these diseases and disorders can be traced to the settlers from Perche, but, as early founders, their genes were most pervasive and most likely to meet up again and again in succeeding generations of marriages for better or for worse. To date, 19 of the 21 hereditary diseases with known origins have been traced to Perche founders with some founders (34 of 48) contributing to more than one disease.⁵

Geography

In most of Quebec, the gene pool grew large enough to diminish the significance of the founder effect, but the unique history of the Saguenay region of northeastern Quebec, including Chicoutimi and Lac-St-Jean, amplified its effect there. This traces back to Chicoutimi's small size and the fact that it was settled by just a few dozen families from Charlevoix County (and ultimately from the Beaupré *seigneurie* with its strong Perche heritage).⁶

¹ This is a brief summary of a complex topic about which hundreds of articles have been written over the past four decades. For a more-detailed discussion see A-M. Laberge, J. Michaud, A. Richter, E. Lemyre, M. Lambert, B. Brais and G. A. Mitchell, "Population History and its impact on medical genetics in Quebec," *Clinical Genetics*, Vol. 68, 2005: 287-301.

² Marriages closer than third cousins were discouraged by the Church in New France.

³ Now the department of Orne and some of Eure-et-Loire in Lower Normandy.

⁴ Peter J. Gagné, *French-Canadian Pioneers from Perche* (Pawtucket, RI: Quintin Publications, 2005), 27.

⁵ M. DeBraekeleer and T. N. Dao, "Hereditary disorders in the French Canadian population of Quebec. I. In search of founders," *Human Biology*, Vol. 66, #2, 1994: 205-223. M. DeBraekeleer and T. N. Dao, "Hereditary disorders in the French-Canadian population of Quebec. II. Contribution of Perche," *Human Biology*, Vol. 66, #2, 1994: 225-249.

⁶ A-M. LaBerge *et al.*, 289. <http://ublib.buffalo.edu/libraries/projects/cases/pier6.htm>

The Hereditary Conditions

There are at least 30 diseases or disorders found in French Canadians that have been attributed to the founder effect, and the list keeps growing as research intensifies. I will not discuss their etiologies in detail here. (For more information on the nature of these conditions and the mutations involved, enter their names into your search engine). Instead, I will list them, describe them briefly, and explain how they are passed on. When possible, I will give information on the colonist thought to have brought the deleterious gene to New France. For privacy reasons, however, names are seldom provided by researchers. This information is summarized in the chart below.

DISEASE OR DISORDER	TYPE	HOW	FOUNDER
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	Characteristic of FC	Autosomal Recessive	Jean Guyon Mathurine Robin?
Agenesis of corpus callosum and peripheral neuropathy	Characteristic of FC	Autosomal Recessive	A 1657 QC marriage
Leigh syndrome (French-Canadian type)	Characteristic of FC	Autosomal Recessive	
Hereditary multiple intestinal atresias	Characteristic of FC	Autosomal Recessive	
Jumping Frenchmen of Maine	Characteristic of FC	Autosomal Dominant	
Tyrosinaemia type I	Rare, but more frequent in FC	Autosomal Recessive	Louis or Marie Gagné
Tay Sachs	Rare, but more frequent in FC	Autosomal Recessive	
Pseudo-vitamin D deficiency rickets	Rare, but more frequent in FC	Autosomal Recessive	
Oculopharyngeal muscular dystrophy	Rare, but more frequent in FC	Autosomal Dominant	Z.Cloutier Jr./ Emard sisters?
HHH (hyperornithinaemia-hyperammonaemia-homocitrullinuria)	Rare, but more frequent in FC	Autosomal Recessive	
Cystinosis	Rare, but more frequent in FC	Autosomal Recessive	
Clouston hidrotic ectodermal dysplasia (HED)	Rare, but-more frequent in FC	Autosomal Dominant	
Congenital disorder of glycosylation type Ib	Rare, but more frequent in FC	Autosomal Recessive	
HSAN type II	Rare, but more frequent in FC	Autosomal Recessive	
Leber's hereditary optic neuropathy	FC type	mtDNA	Catherine Suret
Myotonic dystrophy	FC type	Autosomal Dominant	Couple from Beaupré, m. 1657

⁷ Primarily after A-M Laberge *et al*, Table 1, 291. It is not known which of the spouses is responsible for the mutation. The question mark indicates there is controversy or uncertainty as to whether or not this couple is the one who introduced the mutation.

Phenylketonuria	FC type	Autosomal Recessive	
Friedreich's ataxia	FC type	Autosomal Recessive	Jean Guyon Mathurine Robin
Fragile X syndrome	FC type	X-linked	
Familial hypercholesterolaemia	FC type	Autosomal Dominant	
Familial hyperchylomicronaemia	FC type	Autosomal Recessive	
Hereditary haemochromatosis	FC type	Autosomal Recessive	
Cystic fibrosis	FC type	Autosomal Recessive	
Familial breast cancer BRCA1	FC type	Autosomal Dominant	
Familial breast cancer BRCA2	FC type	Autosomal Dominant	
Beta-Thalassaemia (minor)	FC type	Autosomal Recessive	
X-linked hereditary neuropathy	FC type	X-linked	
Mednik syndrome	Characteristic of FC	2 copies of Autosomal Recessive	

But first, a brief primer on how genetic disorders are transmitted. The table shows four pathways for inheritance: Autosomal Dominant; Autosomal Recessive; X-linked; and mtDNA. Recall that at conception, one receives 23 chromosomes from the father and 23 from the mother. "Autosomal" refers to the 22 matched (non-sex determining) pairs. The remaining pair, XX or XY, determines sex. Picture mother as XX and father as XY. If father contributes his X, then it will match up with mother's X and form XX, a daughter. If father's Y lines up with mother's X, then the resulting XY will be a son.

Each chromosome contains many genes. These genes determine our physical traits (*e. g.*, eye color, skin color, height, etc). In the case of genetic disorders, a misprint (a mutation) can program a child for a particular disorder. "Dominant" means that only one copy of the deleterious gene is needed to program the disorder in the child. "Recessive" means that two copies are needed – one from each parent – before the disorder will show up. "X-linked" disorders are passed along on the X chromosome. The deleterious gene is recessive, meaning that if a daughter has a copy on one of her X chromosomes, she will not develop the disorder as long as her other X is normal. But a male has only one X, so if the deleterious gene is on that one X (he gets from his mother), he will always show it.⁸

The final pathway for inheritance is through mtDNA.⁹ These disorders are rare. So far only one has been identified among the French-Canadian hereditary disorders. The deleterious gene in this case is not among the 23 pairs in the

⁸ This is the case with the bleeding disease hemophilia. A famous example of its transmission is seen in the tragic history of Queen Victoria's grandsons through her daughters. None of her granddaughters had the disease since each had a normal X chromosome from her father to mask the X with the disease. But several grandsons had only the abnormal X from the mother, and they suffered from painful internal bleeding.

⁹ In my October 2009 article, I discounted the role of mtDNA in inheritance, implying that its mutations can be used as markers to trace maternal heritage but have no effect on one's traits. Actually, there are some disorders associated with some mtDNA mutations. For this discussion of mtDNA see Susan Colby "French-Canadian DNA Part 2: Maternal Heritage and Mitochondrial DNA (mtDNA)," *MHH*, Vol. 30, #4, October 2009: 175-184.

nucleus of the cell (as discussed above). It is from the mother's egg cell and is found within the non-nuclear area of all the children's cells (but is passed on only through the daughters).

With these basic mechanisms for inheritance in mind, here is a summary of the 27 conditions mentioned in the review article by LaBerge *et al* (2005) plus a few others:

Disorders with markedly increased incidence in French Canadians

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

ARSACS was first described in 1978.¹⁰ It is a progressive, crippling, spastic, neurodegenerative disease characterized by early-onset ataxia (uncoordinated muscle movement) of gait and lower limb spasticity. Intelligence is normal. It is related to Friedreich's ataxia, and both are generally believed to have originated with the same founder, Jean Guyon or his wife, Mathurine Robin.¹¹ Richter *et al*¹² noted that most ARSACS sufferers were from the Charlevoix-Saguenay region of northeastern Quebec or from southern Italy or Japan. Incidence at birth in French Canadians of the Saguenay-Lac St. Jean region is one in 1,932.¹³

Friedreich's ataxia

This condition is related to ARSACS but has its own characteristics, including higher IQs than seen in ARSACS cases. Gait ataxia, among other symptoms, is present from childhood. As was mentioned for ARSACS, it is believed to have originated with Jean Guyon or Mathurine Robin.¹⁴ The regional clustering of Friedreich's ataxia is seen in the Rimouski area on the south shore of the Saint Lawrence River,¹⁵ but it is found in all regions of Quebec and also among the Acadians of Nova Scotia and New Brunswick.¹⁶ Acadian cases, however, have milder ataxia and progress more slowly.¹⁷

Other recessive ataxias

In addition to ARSACS and Friedreich's ataxia, at least one other ataxia (ARSAL) has been identified in the French-Canadian population.¹⁸ This one clusters within Portneuf County, the same county in Quebec with a genetic founder effect for Tay-Sachs.¹⁹

¹⁰ J. P. Bouchard, A. Barbeau, R. Bouchard and R. W. Bouchard, "Autosomal recessive spastic ataxia of Charlevoix-Saguenay," *Canadian Journal of Neurological Science*, Vol. 5, 1978: 61-69.

¹¹ J. P. Bouchard, A. Barbeau, R. Bouchard and R. W. Bouchard, "Electromyography and nerve conduction studies in Friedreich's ataxia and autosomal recessive spastic ataxia of Charlevoix-Sanguenay (ARSACS)," *Canadian Journal of Neurological Science*, Vol. 6, 1979: 185-189. A. Barbeau, M. Sadibelouiz, M. Roy, B. Lemieux, J. P. Bouchard and G. Geoffroy, "Origin of Friedreich's disease in Quebec," *Canadian Journal of Neurological Science*, Vol. 11 (4 Suppl.), 1984: 506-509.

¹² A. Richter, J. Poirier, J. Mercier, D. Julien, K. Morgan, M. Roy *et al*, "Friedreich ataxia in Acadian families from eastern Canada: clinical diversity with conserved haplotypes," *American Journal of Medical Genetics*, Vol. 64, 1996: 594-601.

¹³ M. DeBraekeleer, F. Giasson, J. Mathieu, M. Roy, J. P. Bouchard and K. Morgan, "Genetic epidemiology of autosomal recessive spastic ataxia of Charlevoix-Saguenay in northeastern Quebec," *Genetic Epidemiology*, Vol. 10, 1993: 17-25.

¹⁴ A. M. Barbeau *et al*, 1984: 506-509.

¹⁵ Bouchard *et al*, 1979.

¹⁶ B. J. Keats, L. J. Ward, M. Lu, S. Krieger, M. A. Wilensky *et al*, "Linkage Studies of Friedreich's Ataxia by means of blood group and protein markers," *American Journal of Human Genetics*, Vol. 41, #4, 1987: 627-634. A. Richter, J. Poirier, J. Mercier, D. Julien, K. Morgan, M. Roy *et al*, "Friedreich ataxia in Acadian families from eastern Canada: clinical diversity with conserved haplotypes," *American Journal of Medical Genetics*, Vol. 64, 1996: 594-601.

¹⁷ LaBerge *et al*, 2005: 294

¹⁸ I. Thiffault, M. F. Rioux, M. Tetreault, J. Jarry, L. Loiselle *et al*, "A new autosomal recessive spastic ataxia associated with frequent white matter changes maps to 2q33-34," *Brain*, Vol. 129, #9, 2006: 2332-2340.

¹⁹ LaBerge *et al*, 2005.

Agenesis of corpus callosum and peripheral neuropathy (ACCPN, Andermann syndrome)

This autosomal recessive disorder causes progressive developmental delay and mental retardation leading to an inability to walk due to agenesis (failure to develop) of the corpus callosum area of the brain. Most sufferers develop seizures and psychoses. Incidence at birth was calculated as one in 2,117 in the Saguenay/Lac St. Jean region, but the gene is carried by one in 23.²⁰ Andermann *et al*²¹ traced it to a couple who married in Quebec City, Charlevoix County, in 1657.

Leigh syndrome, French-Canadian type

Leigh syndrome is an autosomal recessive form of cytochrome oxidase deficiency (a deficiency of an enzyme important in cell respiration). It is characterized by developmental delay and high infant mortality among other deleterious effects including stroke-like episodes. It affects one in 2,178 live births in the Saguenay/Lac St. Jean region.²²

Hereditary multiple intestinal atresias

This is a rare disease characterized by neonatal intestinal obstruction resulting in death in infancy.²³ Guttman *et al* described three aspects: 1) multiple intestinal atresias (closures) from stomach to rectum; 2) calcification; 3) autosomal recessive inheritance and usually also present in siblings.²⁴ It was first described in three families from the Lac St. Jean region.²⁵

Jumping Frenchmen of Maine

On a lighter note, I give you the "Jumping Frenchmen of Maine." First described in late 19th century logging communities, this disorder was characterized by "complex startle reactions like jumping, raising the arms, shouting, hitting or repeating sentences."²⁶ All these loggers were French Canadians, mostly from Beauce (south of Quebec City), working in the Moosehead Lake area of Maine. Based on family histories, it was classified as an autosomal dominant disorder, but a detailed study concluded the mechanism was actually a conditioned response to life in the lumber camps.²⁷ No recent cases have come to light, and this probably has nothing to do with the founder effect, but it makes good comic relief before plunging into more of these tragic founder-effect disorders below.

²⁰ LaBerge *et al*, 2005. A. Larbrisseau, M. Vanesse, P. Brochu and G. Jasmin, "The Andermann syndrome agenesis of the corpus callosum associated with mental retardation and progressive sensorimotor neuropathy," *Canadian Journal of Neurological Science*, Vol. 11, #2, 1984: 257-261. M. DeBraekeleer, A. Dallaire and J. Mathieu, "Genetic demiology of sensorimotor polyneuropathy with or without agenesis of the corpus callosum in northeastern Quebec," *Canadian Journal of Neurological Science*, Vol. 91, #3, 1993: 223-227.

²¹ A. Andermann, F. Andermann, S. Carpenter, G. Carpati, A. Eisen, D. Melanson and J. Bergeron, "Agenesis of the corpus callosum with sensorimotor neuropathy: a new autosomal recessive malformation syndrome with high frequency in Charlevoix County, Quebec," *Vth International Conference on Birth Defects, Montreal*, 1977.

²² LaBerge *et al*, 2005. M. DeBraekeleer, F. Giasson, J. Mathieu, M. Roy, J. P. Bouchard and K. Morgan, "Genetic epidemiology of autosomal recessive spastic ataxia of Charlevoix-Saguenay in northeastern Quebec," *Genetic Epidemiology*, Vol. 10, #1, 1993: 17-25. C. Morin, G. Mitchell, J. Laroche *et al*, "Clinical, metabolic and genetic aspects of cytochrome C oxidase deficiency in Saguenay-Lac-Saint-Jean," *American Journal of Human Genetics*, Vol. 53, #2, 1993: 488-496. C. Morin, J. Dubé, B. H. Robinson *et al*, "Stroke-like episodes in autosomal recessive cytochrome deficiency," *Annual Neurology*, Vol. 45, #3, 1999: 389-392.

²³ LaBerge *et al*, 2005.

²⁴ L. Dallaire and G. Perreault, "Hereditary multiple intestinal atresia, Birth Defects," *Original Articles Series*, Vol. 10, #4, 1974: 259-264.

²⁵ F. Pombo, F. Arnal-Monreal, R. Soler-Fernandez, J. C. Alvarez-Fernandez and J. Carames, "Multiple gastrointestinal atresias with intraluminal calcification," *British Journal of Radiology*, Vol. 55, 1982: 307-309.

²⁶ LaBerge *et al*, 2005.

²⁷ M. H. Saint-Hilaire, J. M. Saint-Hilaire and L. Granger, "Jumping Frenchmen of Maine," *Neurology*, Vol. 36, #9, 1986: 1269-1276. M. H. Saint-Hilaire and J. M. Saint-Hilaire, "Jumping Frenchmen of Maine," *Movement Disorders*, Vol. 16, #3, 2001: 530.

Mednik syndrome

This is a recently-described, severe and rare, founder-effect disorder that requires two copies of the recessive mutation and usually kills before age two. This disorder is caused by the impaired development of various neural networks, including the spinal cord, inner ear, and possibly the brain. Symptoms include severe mental retardation, red scaly skin patches, complete deafness, poor absorption of food in the gut and other problems. It has been traced to families from Kamouraska in eastern Quebec who share a common ancestor.²⁸

Disorders with higher frequency in French Canadians

Tyrosinaemia type I (hepatorenal tyrosinaemia)

This autosomal recessive disorder can cause cirrhosis, hepatocellular carcinoma (cancer of the liver), and other debilitating and painful effects. It occurs worldwide and in as many as one in 6,806 births in some regions of Scandinavia. In the Saguenay/Lac St Jean area, one in 1,846 newborns is affected. One in 22 is a carrier.²⁹ There is an effective treatment for those identified in screening programs.³⁰ If not diagnosed early, however, the liver disease that develops frequently requires liver transplantation. French-Canadian tyrosinaemia victims can be traced to one couple, Louis Gagné and Marie Michel, who passed it on to some of their nine children and many grandchildren, at least two of whom moved to Charlevoix and on to Chicoutimi.³¹

Tay Sachs disease

This is an autosomal recessive neurodegenerative storage disorder. The first sign is an exaggerated startle response, which is followed at four to six months by psychomotor deterioration. Progressive neurologic deterioration leads to death by age four. This disorder is also found in Ashkenazi Jews (Eastern Europe), and this same mutation is also found in some Cajuns; but the mutation in the French-Canadian cases is different and is only found in French Canadians. The Cajun founder was a South Louisiana couple, not known to have been Jewish, who lived in France in the 18th century. The French-Canadian founder lived in South Québec in the late 17th century.³² The center of diffusion for the French-Canadian variant is in Gaspésie-Bas-St-Laurent.³³ Since a screening program was introduced in Montreal High Schools in 1973, incidence of this disorder has fallen by 90%.³⁴ There is no treatment for those afflicted.

²⁸ Charlie Fidelman, "New Illness unique to French Canadians: Scientists," *Canwest News Service*, December 4, 2008. A. Montpetit, S. Côté, E. Brustein, C. A. Drouin, L. Lapointe *et al*, "Disruption of *APISI*, Causing a Novel Neurocutaneous Syndrome, Perturbs Development of the Skin and Spinal Cord," *PloS Genetics*, Vol. 4 (12), 2008: e1000296.doi:10.1371/journal.pgen.1000296.

²⁹ M. DeBraekeleer and J. Larochelle, "Genetic epidemiology of hereditary tyrosinemia in Quebec and in Saguenay-Lac-St-Jean," *American Journal of Human Genetics*, Vol. 47, #2, 1990: 302-307.

³⁰ A. Grenier, J. H. Dussault, C. Laberge and J. Morissette, "Maladies congénetales et héréditaires; l'importance d'un dépistage précoce," *Le Clinicien*, Vol. 3, 1988: 57-69.

³¹ "The Death of Baby Pierre: A Genetic Mystery" – Case Study Collection – National Center for Case Study <http://ublib.buffalo.edu/libraries/projects/cases/pier6.htm> M. Grompe, M. St-Louis, S. Demers, M. Al-Dhalimy, B. Leclerc and R. M. Tanguay, "A Single Mutation of the Fumarylacetoacetate Hydrolase Gene in French Canadians with Hereditary Tyrosinemia Type I," *The New England Journal of Medicine*, Vol. 331, #6, August 11, 1994, 353-357.

³² "Tay Sachs Disease Pathophysiology," *The Medical News medicanews.com* <http://www.news-medical.net/health/Tay-Sachs-Disease-Pathophysiology.aspx>.

³³ M. DeBraekeleer, P. Hechtman, E. Andermann and F. Kaplan, "The French-Canadian Tay Sachs Disease deletion mutation; identification of probable founders," *Human Genetics*, Vol. 89, #1, 1992: 83-87.

³⁴ J. J. Mitchell, A. Capua, C. Clow and C. R. Scriver, "Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools," *American Journal of Human Genetics*, Vol. 59, #4, 1996: 793-798.

Pseudo-vitamin D-deficiency rickets

This treatable autosomal recessive disorder, which resembles rickets, originates from separate Acadian and French-Canadian founders. It occurs in one of 2,916 live births in the Charlevoix-Saguenay/Lac St Jean region, where the carrier ration is one in 27.³⁵ The French-Canadian founder is thought to go back twelve generations.³⁶

Oculopharyngeal muscular dystrophy

This autosomal dominant neuromuscular disorder of the eye muscles, found in both French Canadians and Cajuns, can lead to paralysis of the eye muscles, weak facial muscles, difficulty swallowing, and proximal limb weakness. It usually does not appear until the fifth decade of life. It affects about one in 1,000 *Québécois* (compared with one in 200,000 in France). There is no specific therapy, but surgery can give some relief.³⁷ In French Canadians it has been traced to a single founder couple, but the Cajun cases show a unique mutation insertion proving a separate founder for this population.³⁸

Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome

This autosomal recessive disorder results in developmental delay, growth retardation and intermittent vomiting, and sometimes also involves seizures and spasticity. Birthplaces of patients' grandparents vary throughout southern Quebec. Occurrence in a First Nations community in Northern Saskatchewan suggests "a possible founder effect related to early French-Canadian explorers."³⁹ There is a treatment regimen.

Cystinosis

This is a severe multivisceral autosomal recessive disorder characterized by failure to thrive, ocular photosensitivity, rickets, proximal renal tubular acidosis, and progressive renal insufficiency. It affects one in 6,237 newborns in Saguenay/Lac-St Jean with a carrier frequency of one in 39. Drugs are used for treatment.⁴⁰ The French-Canadian mutation may have an Irish origin.⁴¹

Clouston's hidrotic ectodermal dyslasia (HED)

This is an autosomal dominant skin disorder particularly common among French Canadians of southwest Quebec. It is characterized by scalp hair that is wiry, brittle, and pale, and it is often associated with patchy alopecia (hair loss). It is the first example of the founder effect in that region.⁴²

Congenital disorder of glycosylation type Ib

This autosomal recessive disease causes abdominal pain and protein-losing (sometimes cystic) pathologies of the intestine. If diagnosed in time, it can be controlled orally with a drug called mannose. A patient in Nantes, France, was found to be homozygous (have two copies) for the same mutation and to share the same haplotype as French Canadians with the mutation. Therefore, this mutation is thought to be a rare example of French and French-Canadian disease alleles identical by descent.⁴³

³⁵ LaBerge *et al*, 2005.

³⁶ M. Labuda, D. Labuda, M. Korab-Laskowska, D. E. Cole, E. Zietkiewicz, J. Weissenbach, E. Popowska, E. Pronicka, A. W. Root and F. H. Glorieux, "Linkage disequilibrium analysis in young populations: pseudo-vitamin D-deficiency rickets and the founder effect in French Canadians," *American Journal of Human Genetics*, Vol. 59, #3, 1996: 633-643.

³⁷ LaBerge *et al*, 2005.

³⁸ P. C Seachen, C. Garcia, R. Hébert and E. P. Hoffman, "Unique PABP2 mutations in 'Cajuns' suggests multiple founders of oculopharyngeal muscular dystrophy in populations with French ancestry," *American Journal of Medical Genetics*, Vol. 86, #5, published online October 1, 1999: 477-481.

³⁹ LaBerge *et al*, 2005.

⁴⁰ LaBerge *et al*, 2005.

⁴¹ J. McGowan-Jordan, K. Stoddard, L. Podolsky, E. Orrbine, P. McLaine, M. Town, P. Goodyer, A. MacKenzie and H. Heick, "Molecular Analysis of Cystinosis: Probable Irish Origin of the Most Common French-Canadian Mutation," *European Journal of Human Genetics*, Vol. 7, #6, 1999: 671-678.

⁴² Z. Kibar, M-P. Dubé, J. Powell, C. McCuaig, S. J. Hayflick *et al*, "Clouston hidrotic ectodermal dysplasia (HED): genetic homogeneity, presence of a founder effect in the French-Canadian population and fine genetic mapping," *European Journal of Human Genetics*, Vol. 8, #5, May 2000: 372-380.

Hereditary sensory and autonomic neuropathy type II (HSAN II)

This is an autosomal recessive disorder, usually diagnosed in childhood, which causes impairment of pain, temperature, and touch sensations due to the absence of peripheral sensory neurons. It has been found in southern Quebec and Nova Scotia.⁴⁴

Disorders with distinctive features in French Canadians

Leber's hereditary optic neuropathy

This optic disease causes acute or subacute central vision loss, followed by optic atrophy. It is associated with three major mutations in the mitochondrial DNA (mtDNA). Haplotype analysis suggests that most French Canadians with this disease descend from one founder, *fille du roi* Catherine Suret, with the mutation T14484C. This mutation accounts for 86% of all French-Canadian cases of Leber's.⁴⁵ Dutch victims with the same mutation share the same haplotype with the French-Canadian victims, suggesting a possible common origin of this mutation prior to 1600.⁴⁶ Leber's primarily strikes young adult males (only one in four victims is female). In some cases vision eventually improves, but most remain legally blind.⁴⁷

Phenylketonuria (PKU)

This autosomal recessive disorder results in microcephaly (small brain) and severe mental retardation if a diet enriched with phenylalanine (an essential amino acid) is not implemented. Fortunately, it is screened for at birth where one in 25,598 live births in Quebec is diagnosed with the condition.⁴⁸ One mutation that causes PKU has been traced to northwestern France, but this accounts for only 1.1% of cases.⁴⁹ Another mutation accounting for 4.3% of cases is Celtic. Five other mutations are unique to Quebec.⁵⁰

Myotonic dystrophy

This autosomal dominant disorder is characterized by weakness of facial and distal limb muscles, cataracts, cardiac conduction defects, and diabetes mellitus. It is found worldwide but of higher incidence in Charlevoix and Saguenay-Lac-Saint-Jean in northeastern Quebec where it affects one in 530 births. It was traced through genealogical records to a couple who married in 1657 in the Beupré *seigneurie*.⁵¹

⁴³ LaBerge *et al*, 2005.

⁴⁴ LaBerge *et al*, 2005. R. G. Lafrenière, M. L. E. MacDonald, M-P. Dubé, J. MacFarlane *et al*, "Identification of a Novel Gene (HSN2) Causing Hereditary Sensory and Autonomic Neuropathy Type II through the Study of Canadian Genetic Isolates," *American Journal of Human Genetics*, Vol. 74, #5, May 2004: 1064-1073.

⁴⁵ Mutations G11778A and G3640A account for 12% and 2%, respectively. C Macmillan, T. Kirkham, K. Fu, V. Allison, E. Andermann, D. Chitayat, D. Fortier, M. Gans, H. Hare, N. Quercia, D. Zackon and E. A. Shoubbridge, "Pedigree analysis of French-Canadian families with T1448C Leber's hereditary optic neuropathy," *Neurology*, Vol. 50 1998: 417-422.

⁴⁶ N. Howell, R. J. Oostra, P. A. Bolhuis *et al*, "Sequence analysis of the mitochondrial genomes from Dutch pedigrees with Leber hereditary optic neuropathy" *American Journal of Human Genetics*, Vol. 72, #6, 2003: 1460-1469. A-M. Laberge, M. Jomphe, L. Houde, H. Vézina, M. Tremblay *et al*, "A 'Fille du Roy' Introduced the T14484C Leber Hereditary Optic Neuropathy Mutations in French Canadians," *The American Journal of Human Genetics*, Vol. 77, #2, 2005: 313-317. Catherine Suret's story and an account of Leber's in the author's family will follow in a future edition of *MHH*.

⁴⁷ P. Yu-Wai-Man and P. F. Chinnery, "Leber Hereditary Optic Neuropathy," *Gene Reviews*, University of Washington, Seattle. Initial Posting: Oct. 26, 2000; Last Update: March 10, 2008.

⁴⁸ A. Grenier, J. H Dussault, C. Laberge and J. Morissette, "Maladies congénitales et héréditaires; l'importance d'un dépistage précoce," *Le Clinicien*, Vol. 3, 1988: 57-69.

⁴⁹ S. Lyonnet, D. Melle and M. DeBraekeleer *et al*, "Time and space clusters of the French-Canadian M1V phenylketonuria mutation in France" *American Journal of Human Genetics* Vol. 51, #1, 1992: 191-196.

⁵⁰ R. Rozen, A. Mascisch, M. Lambert, R. Laframboise and C. R. Scriver, "Mutation profiles of phenylketonuria in Quebec populations: evidence of stratification and novel mutations," *American Journal of Human Genetics*, Vol. 55, #2, 1994: 321-326.

⁵¹ J. Mathieu, M. DeBraekeleer and C. Prevost, "Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint-Jean area (Quebec, Canada)," *Neurology*, Vol. 40, #5, 1990: 839-842.

Fragile X syndrome

This is an X-linked disorder, which is more common in men than women since males have only one X chromosome while women have an extra one to compensate. It is characterized by mental retardation and a particular appearance including large ears. Prevalence of male carriers was estimated to be one in 813 based on screening of 10,000 Quebec males.⁵²

Familial hypercholesterolaemia

This autosomal dominant disorder (mainly caused by a mutation in the LDL-receptor gene) markedly increases the risk of premature atherosclerosis. Adults have tendinous xanthomas (nodes on tendons). It's about twice as frequent among French Canadians (one in 270) as in the rest of the western world (one in 500). Frequencies are highest in Gaspésie (one in 167), Saguenay-Lac-Saint Jean (one in 122), and Côte Nord (one in 81).⁵³ Molecular (DNA) testing can be diagnostically useful in French-Canadian patients. The recommended treatment is a low-cholesterol diet and healthy lifestyle behaviors.

Familial hyperchylomicronaemia (lipoprotein lipase (LPL) deficiency)

This autosomal recessive disease is characterized by abdominal pain, pancreatitis, eruptive xanthomas (nodes) and visceromegaly (enlargement of the internal organs of the abdomen) caused by LPL deficiency. The carrier rate of LPL deficiency in Quebec is one in 139, but it is higher in eastern (one in 85) than in western (one in 219) Quebec.⁵⁴ Treatment includes a diet very low in long-chain fat.

Hereditary hemochromatosis (HHC)

This autosomal recessive disorder causes iron accumulation in tissues, leading to cirrhosis, diabetes, cardiomyopathy, arthropathy, and hypogonadism. It may be more severe and of earlier onset in Saguenay-Lac-Saint-Jean.⁵⁵ Regular phlebotomies (letting of blood) can reduce symptoms and prevent complications.

Cystic fibrosis (CF)

This autosomal recessive disorder causes pulmonary symptoms such as chronic cough and recurrent infections, pancreatic illness, and congenital bilateral agenesis of the vas deferens (failure of the tube connecting the testes and urethra to develop). It occurs in one in 902 residents of Saguenay/Lac-Saint-Jean with a carrier frequency of one in fifteen.⁵⁶ Supportive treatment is given.

The BRCA1 and BRCA2 hereditary breast cancer genes

Mutations of BRCA1 and BRCA2 are associated with a higher lifetime risk of developing breast cancer and/or ovarian cancer. In French Canadians, 41 of 97 of the breast and ovarian cancer families were associated with one out of eight founder mutations in BRCA1 or BRCA2. In French-Canadian women with ovarian cancer unselected for family history, founder heritable mutations were identified in eight of 99 cases of invasive carcinomas (five in BRCA1 and three in BRCA2).⁵⁷ Founder mutations were found in four of 127 unselected French-Canadian women

⁵² C. Dombrowski, S. Levesque, M. L. Morel, P. Rouillard, K. Morgan and F. Rousseau, "Premutation and intermediate-size FMR1 alleles in 10572 males from the general population: loss of an AGG interruption in a late event in the generation of fragile X syndrome alleles," *Human Molecular Genetics*, Vol. 11, #4, 2002: 371-378.

⁵³ M. C. Vohl, S. Moorjani, M. Roy *et al*, "Geographic distribution of French-Canadian low-density lipoprotein receptor gene mutations in the Province of Quebec," *Clinical Genetics*, Vol. 52, #1, 1997: 1-6. L. R. Simard, J. Viel, M. Lambert, G. Paradis, E. Levy, E. E. Delvin and G. A. Mitchell, "The delta>15 Kb deletion French Canadian founder mutation in familial hypercholesterolemia: rapid polymerase chain reaction-based diagnostic assay and prevalence in Quebec," *Clinical Genetics*, Vol. 65, #3, 2004: 202-208; published online Jan. 30, 2004.

⁵⁴ C. Dionne, C. Gagné, P. Julien *et al*, "Genealogy and regional distribution of lipoprotein lipase deficiency in French Canadians of Quebec," *Human Biology*, Vol. 65, #1, 1993: 29-39.

⁵⁵ S. R. Rivard, C. Mura, H. Simard *et al*, "Mutation analysis in the HFE gene of patients with hereditary hemochromatosis in Saguenay-Lac-Saint-Jean (Quebec, Canada)," *British Journal of Haematology*, Vol. 108, #4, 2000: 854-858.

⁵⁶ J. Daigneault, G. Aubin, F. Simard and M. DeBraekeleer, "Incidence of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada)," *Human Biology*, Vol. 64, #1, 1992: 115-119.

with breast cancer, all in BRCA2.⁵⁸ In early-onset cases of breast cancer (age 40 or younger), eight of 61 French-Canadian women carried a founder mutation (half in BRCA1 and half in BRCA2).⁵⁹ Those with BRCA1 and 2 mutations can be offered surveillance, prophylactic mastectomy and/or oophorectomy (removal of the ovaries), and chemo-prevention.⁶⁰

Beta-thalassaemia

This disorder causes anemia through the defective production of hemoglobin. In French Canada, this autosomal recessive disease may have originated in the Languedoc region of Southern France. The carrier frequency is around 3% of the world population, but it is most frequent in the Mediterranean, Middle East, and some parts of Asia where it is thought to provide some protection from malaria. In Portneuf County, southwest of Quebec City, beta-thalassaemia minor is found in about 1.03% of the population.⁶¹ Carrier screening has been provided in Montréal since 1980. The only cure is bone marrow transplant. Supportive treatment includes regular blood transfusions.

X-linked hereditary neuropathy or X-linked Charcot-Marie-Tooth disease

A variety of neuropathies are thought to originate in founder effect. (For details see footnotes 62-68.)^{62,63,64,65,66,67,68}

A sampling of studies linking other disorders and French-Canadian genetics

Tourette Syndrome and related psychiatric disorders: Mérette *et al* (2000) studied a large French-Canadian family in the Charlevoix region and found statistically significant evidence for genetic linkage with Tourette Syndrome.⁶⁹

⁵⁷ P. N. Tonin, A. M. Mes-Mason, P. A. Futreal *et al*, "Founder BRAC1 and BRAC2 mutations in French-Canadian breast and ovarian cancer families," *American Journal of Human Genetics*, Vol. 63, #5, 1998: 1341-1351.

⁵⁸ P. O. Chappuis, N. Hamel, A. J. Paradis *et al*, "Prevalence of founder BRAC1 and BRAC2 mutations in unselected French-Canadian women with breast cancer," *Clinical Genetics*, Vol. 59, #6, 2001: 418-423.

⁵⁹ P. N. Tonin, C. Perret, J. A. Lambert *et al*, "Founder BRAC1 and BRAC2 mutations in early-onset French-Canadian breast cancer cases unselected for family history," *International Journal of Cancer*, Vol. 95, #3, 2001: 189-193.

⁶⁰ R. Calderon-Margalit and O. Paltiel, "Prevention of breast cancer in women who carry BRAC1 and BRAC2 mutations: a critical review of the literature," *International Journal of Cancer*, Vol. 112, #3, 2004: 357-364.

⁶¹ C. Prevost, R. Laframboise, M. Bardanis *et al*, "The beta-thalassaemia gene in French-Canadian reappearance in Portneuf County," *Union Medical Canada*, Vol. 118, #3, 1988: 241, 243-244.

⁶² N. Dupré, L. Cossette, C. K. Hand, J. P. Bouchard, G. A. Rouleau and J. Puymirat, "A founder mutation in French-Canadian families with X-linked hereditary neuropathy," *Canadian Journal of Neurological Science*, Vol. 28, #1, 2001: 51-55.

⁶³ J. Couture, A. Mitri, R. Lagacé *et al*, "A germline mutation at the extreme 3' end of the APC gene results in a severe desmoid phenotype and is associated with overexpression of beta-catenin in the desmoid tumor," *Clinical Genetics*, Vol. 57, #3, 2000: 205-212.

⁶⁴ P. Cossette, L. Liu, K. Brisebois *et al*, "Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy," *National Genetics*, Vol. 31, #2, 2002: 184-189.

⁶⁵ M. Faucher, J. L. Antil, M. A. Rodrigue *et al*, "Founder TIGR/myocilin mutations for glaucoma in the Quebec population," *Human Molecular Genetics*, Vol. 11, #18, 2002: 2077-2090.

⁶⁶ A. Desautels, G. Turecki, J. Monplaisir, A. Sequeira, A. Verner and G. A. Rouleau, "Identifications of a major susceptibility locus of restless legs syndrome on chromosome 12q," *American Journal of Human Genetics*, Vol. 69, #6, 2001: 1266-1270.

⁶⁷ C. A. Drouin and P. Rioux, "Érythrokratoderme atypique surdité, neurosensorielle, diarrhée congénitale chronique et élévation des acides gras et longues chaînes (C26): un nouveau syndrome neurocutané?" *Annual Dermatology Venereology*, Vol. 127, 2000: 4596.

⁶⁸ C. Laprise, L. P. Boulet, J. Morissette, E. Winstall and V. Raymond, "Evidence for association and linkage between atopy, airway, hyper-responsiveness, and the beta subunit Glu237Gly variant of the high-affinity receptor for immunoglobulin E in the French-Canadian population," *Immunogenetics*, Vol. 51, #8-9, 2000: 695-702.

Hypertension: Hamett *et al*⁷⁰ researched early-onset hypertension and/or dyslipidemia at Saguenay/Lac Saint-Jean and found a link to the founder effect.

Lynch syndrome: Chong *et al*⁷¹ studied this autosomal dominant colorectal cancer syndrome and found some linkage to founder-effect mutations.

Glaucoma: Faucher *et al*⁷² suggest the French Canadians have probably inherited six mutations associated with glaucoma from seven to ten Québec settlers.

Malignant hyperthermia (MH): This rare, potentially fatal disorder, first reported in 1960, is brought on by certain types of general anesthesia (all volatile anesthetics), nearly all gas anesthetics, and the neuromuscular blocking agent succinylcholine. A genetic link was ascertained for this autosomal dominant condition in the early 1990s, and further studies have revealed complex genetic pathways involving six genes, but it is mostly linked to the ryanodine receptor gene (*RYR1*). This disorder is related to central core disease (CCD), an autosomal dominant disorder characterized by both MH symptoms and myopathy (muscular disorders). It is difficult to diagnose and is best-anticipated through family history. An attack in progress can be mitigated with dantrolene sodium, but attacks can be avoided altogether by use of alternate anesthetics.⁷³ In 1992, seven at-risk families were studied in Abitibi-Témiscamingue (in west Quebec along its border with Ontario). Genealogical studies showed no common ancestor in the colonization of Abitibi-Témiscamingue but common ancestors were found around the ninth generation.⁷⁴

All the disorders discussed in this article do not exhaust the literature linking various disorders to French-Canadian founder effect. Québec's unique history of few founders plus relative isolation for generations has made it a laboratory for genetic studies. These studies have advanced the science of genetics and have led to a better understanding of many diseases, and for French Canadians they have enhanced the awareness of patients and doctors so that timely intervention is now available for several of these tragic afflictions.

Impact on Americans of French-Canadian descent

Do not despair. Our gene pool has enlarged in modern times rendering these disorders less of a threat in most areas. We must, however, remain vigilant. Although the frequency of several of these French-Canadian disorders is significantly high, universal screening in Quebec is currently offered to newborns for only phenylketonuria, tyrosinaemia type I, and congenital hypothyroidism. Voluntary screening of urine and targeted carrier-screening programs are available for certain other newborn errors in metabolism. Nevertheless, much remains to be done as to genetic screening, public education, and health care management.⁷⁵

General awareness of founder effect disorders among the 7.5 million French Canadians of Québec is spotty. How much less are they recognized among Americans of French-Canadian and Acadian descent by their doctors? Since over 2.3 million Americans report French-Canadian ancestry,⁷⁶ it is in our best interest to record genetic disorders in our families as we record other genealogical information and to seek genetic counseling, as needed. In Québec,

⁶⁹ C. Mérette, A. Brassard, A. Potvin, H. Bouvier, F. Rousseau *et al*, "Significant Linkage for Tourette Syndrome in a Large French-Canadian Family," *American Journal of Human Genetics*, Vol. 67, #4, Oct. 2000: 1008-1013.

⁷⁰ P. Hamet, E. Merlo, O. Seda, U. Broeckel, J. Tremblay *et al*, "Quantitative Founder-Effect Analysis of French Canadian Families Identifies Specific Loci Contributing to Metabolic Phenotypes of Hypertension," *American Journal of Human Genetics*, Vol. 76, #5, 2005: 815-832.

⁷¹ G. Chong, J. Jarry, V. Marcus, I. Thiffault, S. Winocour *et al*, "High frequency of exon deletions and putative founder effects in French-Canadian Lynch syndrome families," *Human Mutation*, Vol. 30, #8, May 20, 2009: E797-E812.

⁷² M. Faucher, J-L. Anctil, M-A. Rodrigue, M. A. Duchesne, D. Bergeron *et al*, "Founder TIGR/myocilin mutations for glaucoma in the Québec population," *Human Molecular Genetics*, Vol. 11, #18, 2002: 2077-2090.

⁷³ J.F. Hernandez, J.A. Secrest, L. Hill, and S.J. McClarty "Scientific Advances in the Genetic Understanding and Diagnosis of Malignant Hyperthermia," *Journal of PeriAnesthesia Nursing*, Vol. 24, #1, 2009: 19-34. http://en.wikipedia.org/wiki/Malignant_hyperthermia

⁷⁴ M. Bachand, N. Vachon, M. Boisvert, F.M. Mayer, and D. Chartrand "Clinical reassessment of malignant hyperthermia in Abitibi-Témiscamingue," *Canadian Journal of Anesthesia*, Vol. 44, #7, 1997: 696-701.

⁷⁵ Laberg *et al*, 2005.

⁷⁶ A. Brittingham and G. P. de la Cruz (US Census Bureau) Ancestry 2000 Brief. June 2004. Report #C2KBR-35.

these genetic diseases are studied by the Quebec Network of Genetic Medicine (QNGM),⁷⁷ and they are mapped at Génome Québec, which promotes the research and development of genomics in the province. In this Internet age, it is hoped that awareness of these disorders and their interventions will spread to all areas of Canada and the United States where French Canadians and their descendants now live.

⁷⁷ C. Scriver "Community Genetics and Dignity in Diversity in the Quebec Network of Genetic Medicine," *Community Genetics*, Vol. 9, #3, 2006: 142-152.