Primary lipoprotein-lipase-activity deficiency: clinical investigation of a French Canadian population

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We examined 56 French Canadians, aged 1 week to 54 years, from eastern Quebec who were referred to the Laval University Lipid Research Centre and in whom coincidental finding (in 46% of the cases), abdominal pain (in 32%) or family screening (in 22%) led to the diagnosis of primary lipoprotein-lipase-activity deficiency (familial hyperchylomicronemia). Half of the patients had one or more of the following signs: lipemia retinalis, eruptive xanthomas, splenomegaly and hepatomegaly; the plasma triglyceride concentrations were significantly higher (greater than 40 mmol/L) among these patients than among those without clinical signs (mean 21.7 [standard deviation 13.5] mmol/L). The prevalence rate of this disorder was 30 times higher than the previously published rate and was highest in the counties of Charlevoix and Saguenay–Lac-St-Jean (200 and 100 cases per million respectively) because of the distinct demographic history of these areas. Because of a founder effect an autosomal recessive gene involved in lipoprotein-lipase expression or activation has probably been disseminated among this isolated French Canadian population.

Il s'agit ici de 56 Canadiens français, âgés de 1 semaine à 54 ans, en provenance de l'est du Québec, adressés au Centre de recherche sur les maladies lipidiques de l'université Laval et chez qui nous avons posé le diagnostic de déficit primitif en activité lipoprotéine-lipase (hyperchylomicronémie familiale). C'est une trouvaille fortuite dans 46% des cas; il y a eu douleur abdominale dans 32% des cas; les 22% restants sont découverts par le dépistage familial. Dans la moitié de ces sujets on observe au moins l'un des signes suivants: lipémie rétinienne, xanthome éruptif, splénomégalie et hépatomégalie. Chez eux la concentration plasmatique des triglycérides est nettement plus élevée (plus de 40 mmol/L) que chez ceux qui n'en présentent aucun (moyenne 21,7 [écart-type 13,5] mmol/L). Nous calculons un taux de morbidité de cette maladie qui est 30 fois le taux déjà publié; il est élevé surtout dans les comtés de Charlevoix et du Saguenay–Lac-St-Jean (soit respectivement 200 et 100 cas par million). Ceci s'expliquerait par l'histoire démographique de cette région. Dans sa population canadienne-française isolée un gène récessif autosomique jouant un rôle dans l'expression ou l'activation de la lipoprotéine-lipase se serait propagé par un effet de fondateur.

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Primary lipoprotein-lipase (LPL)-activity deficiency (hyperlipoproteinemia type I or familial hyperchylomicronemia) is a rare autosomal recessive disorder associated with elevated concentrations of plasma triglycerides, particularly chylomicrons, after fasting. Its prevalence has been

estimated to be 1 case per million population.[1] Although familial hyperchylomicronemia appears to be due to LPL-activity deficiency in most patients, it is also caused by other factors,[2,3] such as the absence of apoprotein CII (the LPL activator)[4,5] or the presence of an inherited plasma LPL inhibitor.[6] Moreover, various tissue lipase activities have also been reported.[7] The disorder usually appears during childhood and is marked by severe abdominal pain, with or without pancreatitis, high plasma chylomicron levels, with triglyceride levels greater than 12.0 mmol/L, lipemia retinalis, eruptive xanthomas, hepatomegaly and splenomegaly. The only treatment is to reduce the dietary intake of fat to less than 50 g/d in adults.[1]

We report our findings in a large number of French Canadians who presented with primary LPL-activity deficiency. Our objectives were to estimate the prevalence of this disorder in a well-defined population, to define the clinical manifestations and to evaluate their relation with plasma triglyceride concentrations.

Patients and methods

From September 1973 to June 1988, 56 French Canadians (30 males and 26 females) with hyperchylomicronemia from 38 different families were either referred directly to the Lipid Research Centre, Ste-Foy, PQ, which is a referral centre for lipid disorders detected in eastern Quebec, or were referred for full investigation after their condition had been diagnosed by the centre through family screening. At the time of referral some patients had been instructed to begin a low-fat diet or had decided to reduce the fat content of their diet. In some instances the disorder was diagnosed during a hospital stay because of pancreatitis.

All lipid values and signs reported in this paper are those observed at the first visit. Patients with secondary causes of hyperchylomicronemia were excluded from our study. None of the patients had diabetes, renal disease or chronic alcoholism. One woman was receiving therapy for Hashimoto's thyroiditis. At the time of evaluation her serum thyroxine and thyroid stimulating hormone levels were within normal limits.

Blood samples were collected in tubes containing 0.1% ethylenediaminetetraacetic acid after a fast of 12 to 14 hours. The tubes were immediately centrifuged at 1000 g for 10 minutes. Chylomicrons and very-low-density lipoprotein fractions were isolated through ultracentrifugation.[8,9] The infranatant was used to determine the levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol after selective precipitation of LDL by manganese chloride.[10] Lipid levels were analysed with the use of the Technicon AutoAnalyzer II (Technicon Instruments Corp., Tarrytown, New York).[11] Apoprotein B concentrations were measured by means of rocket immunoelectrophoresis.[12] The presence of apoprotein CII was determined by means of isoelectric focusing on polyacrylamide gels.[13]

Plasma samples were obtained 10 minutes after intravenous injection of heparin, 10 U/kg. In infants the lipolytic activity after heparin injection was not always measured at the first visit. The plasma samples were immediately frozen, lyophilized overnight and delipidated at 4°C with a solvent mixture of petroleum ether and ether (9:1) for measurement of the LPL and hepatic triglyceride lipase (h-TGL) activities. Incubation for enzyme activities was done with the use of artificial emulsions of substrates prepared with carbon-14-tagged triolein. Delipidated normal serum (containing apoprotein CII activator) or a mixture of albumin and lecithin was used to determine protamine-sensitive LPL and h-TGL activities.[14] In the two assays the release of free fatty acids was determined by means of liquid scintillation spectrometry. All analyses were done twice. Enzyme activities were expressed as nanomoles of fatty acids released per minute in 1 ml of heparinized plasma.

Results

The ages at the time of diagnosis of hyperchylomicronemia ranged from 1 week to 54 years; the mean age (and standard deviation [SD]) was 12.5 [12.5] years. LPL-activity deficiency was diagnosed later when the patients were referred to the Lipid Research Centre, and the mean age then was 20.5 (SD 13.9) years. Acute abdominal pain, with or without documented pancreatitis, was the reason for 18 patients to first seek medical care (Table I). In 26 patients hyperchylomicronemia was a coincidental finding during the investigation of other problems, such as epistaxis, trauma, tooth abscess, deafness, mononucleosis and asthma, as well as during routine blood analysis in three pregnant women. Five infants (aged 1 week to 6 months) had pallor without anemia (three infants), falsely high plasma bilirubin levels (461 mmol/L) without icterus (one infant) and hyperglycemia (serum glucose level 32 mmol/L) without glycosuria (one infant). These aberrant observations also led to the diagnosis of hyperchylomicronemia.

Table I — Circumstances that led to diagnosis of primary lipoprotein-lipase (LPL)-activity deficiency in 56 patients from eastern Quebec by age

	Circumstance; no. (and %) of patients		
Age, yr	Coincidental finding	Investigation of abdominal pain	Family screening
≤ 9	15 (50)	8 (27)	7 (23)
10–19	3 (25)	4 (33)	5 (42)
20–29	5 (56)	4 (44)	0
≥ 30	3 (60)	2 (40)	0
Total	26 (46)	18 (32)	12 (21)

Hepatosplenomegaly was the triggering element for diagnosis in another infant 9 months of age. Primary LPL-activity deficiency was diagnosed after family screening in 12 patients.

Many of the patients in whom other circumstances led to the diagnosis of LPL-activity deficiency had already experienced abdominal pain. The diagnosis was made before 1 year of age in 25% of the cases, before 10 years in 54% and before 20 years in 75%. The age at diagnosis and the reason for presentation were similar for male and female patients. Few patients had other clinical problems: one had gout, and another had high blood pressure. A 54-year-old patient had had a myocardial infarction at 50 years of age. Three women in whom the diagnosis was made during pregnancy delivered healthy term babies.

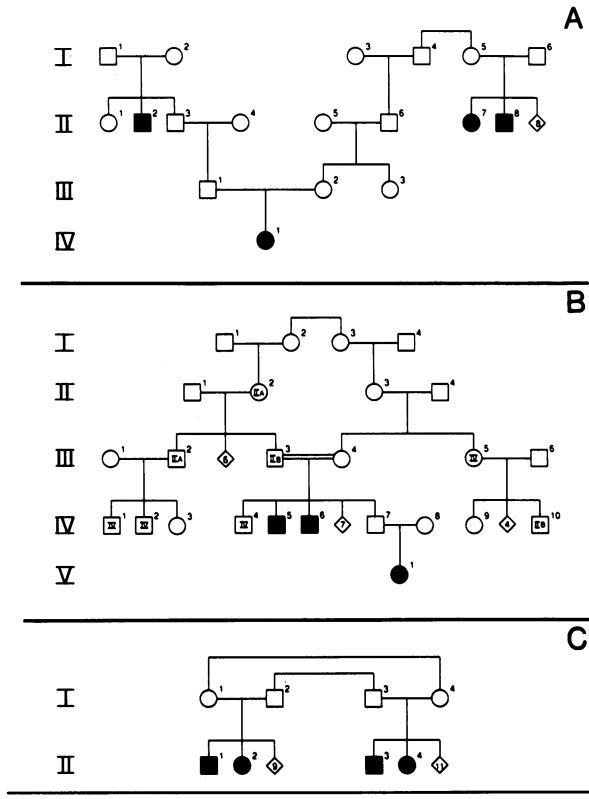

Fig. 1 — Pedigrees of three families in eastern Quebec, showing autosomal recessive inheritance of primary lipoprotein-lipase (LPL)-activity deficiency. Circles represent females and squares males; black circles and squares represent affected individuals. Roman numerals in squares and circles (B) indicate lipoprotein phenotypes. Double line indicates consanguinity.

Fig. 1 shows the pedigrees of three representative families affected by primary LPL-activity deficiency. These families were from the same area, and the patronyms were those of the few founding families of that area. Autosomal recessive inheritance was evident. Fig. 1A shows a child (IV-1) born of two normolipidemic parents (III-1 and III-2) whose relatives had hyperchylomicronemia (II-2, II-7 and II-8). Age and sex could not account for a dominant gene with variable expressivity. Fig. 1B illustrates a family with consanguinity (III-3 and III-4), as well as different lipoprotein phenotypes and premature cardiovascular disease (II-2, III-2, III-3 and III-5). Fig. 1C shows a family in which two male siblings from one family married two female siblings from another family, all of whom did not have clinical features of familial hyperchylomicronemia. However, each couple had two children with the disorder.

Splenomegaly was present in 21 patients (16 males), lipemia retinalis in 20 (12 males), hepatomegaly in 20 (15 males) and eruptive xanthomas in 6 (3 males). Half of the patients had one or more of these signs (Table II). Two patients had undergone splenectomy.

The mean plasma triglyceride concentrations were 78.7, 48.1, 46.9 and 40.4 mmol/L in patients who presented with eruptive xanthomas, hepatomegaly, lipemia retinalis and splenomegaly respectively. Patients without clinical signs had the lowest mean level (21.7 mmol/L). The differences in plasma triglyceride levels were statistically significant in patients who had eruptive xanthomas, hepatomegaly or lipemia retinalis, as compared with those who had no clinical signs. High plasma triglyceride concentrations (mean 50.7 [SD 63.5] mmol/L) were found in patients with splenomegaly and other signs of hyperchylomicronemia (15 patients) ($p = 0.02$). The mean concentration in the six patients with splenomegaly alone was comparable to that in those without clinical signs (16.7 [SD 8.3] v. 21.7 [SD 13.5] mmol/L).

Most of the patients came from eastern Quebec, near the St. Lawrence River (total population 2 million) (Fig. 2). This area represents the same area from which patients are referred to our clinic for various lipoprotein disorders. None of the patients came from the south shore of the St. Lawrence River east of Quebec City, even though

Table II — Mean plasma triglyceride levels (and standard deviation [SD]) by sign

Sign	No. (and %) of patients	Mean plasma triglyceride level (and SD), mmol/L	p value
None	26 (46)	21.7 (13.5)	–
Splenomegaly	21 (38)	40.4 (52.3)	NS*
Lipemia retinalis	20 (36)	46.9 (49.3)	< 0.02
Hepatomegaly	20 (36)	48.1 (58.8)	< 0.05
Eruptive xanthomas	6 (11)	78.7 (68.6)	< 0.01

*NS = not significant.

many patients from that area are seen at our clinic for other primary lipoprotein disorders. On a referral basis the prevalence of primary LPL-activity deficiency was 27 cases per million in eastern Quebec. However, in the counties of Charlevoix and Saguenay–Lac-St-Jean the prevalence rates were 200 and 100 cases per million respectively, as compared with the reported rate of 1 per million.[1] In the remaining part of eastern Quebec the prevalence rate was 19 cases per million (Table III). Prevalence rates were calculated according to the data from the 1981 *Census of Canada* report.[15]

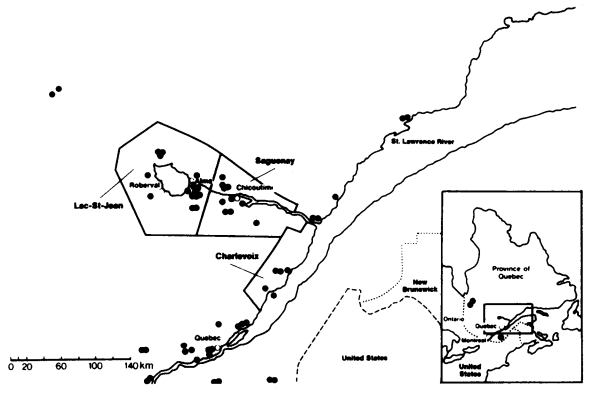

Fig. 2 — Geographic distribution of 56 patients with primary LPL-activity deficiency in eastern Quebec. Each black circle represents one patient; white circles represent major cities.

Large differences in the levels of plasma lipids, particularly triglycerides, were observed between the patients in our study and an unrelated control group living in the Saguenay–Lac-St-Jean area (Table IV). Moreover, there were large differences in the plasma lipid levels between the patients. There was no statistically significant difference between females and males in the levels, except for those of HDL-cholesterol. The total cholesterol:triglyceride ratios (weight:weight) were less than 0.10, less than 0.15 and less than 0.20 in 39%, 86% and 95% of the cases respectively. In three cases the ratios varied from 0.20 to 0.25: two patients were in hospital because of pancreatitis, and one had fasted for the 3 days previously because of bouts of abdominal pain.

In 65% of the patients the plasma triglyceride levels were from 11.3 to 33.8 mmol/L, and in 25% they were 33.9 mmol/L or greater (Fig. 3). Levels

Table III — Distribution of patients in Quebec by region

Region	No. of patients	Population* (approximate)	Estimated frequency of primary LPL-activity deficiency per million
Charlevoix	5	25 000	200
Saguenay–Lac-St-Jean	29	300 000	97
Quebec City	19	1 000 000	19
Other	3†	4 000 000	< 1

*Number of French Canadians, according to 1981 *Census of Canada* report.[15]
†Underestimate; patients from southern and western Quebec are usually referred to other clinics.

Table IV — Plasma lipid and apoprotein B concentrations in patients and control subjects by sex

Lipid/apoprotein	Females		Males		p value
	No. of subjects	Mean level (and SD)	No. of subjects	Mean level (and SD)	
Triglycerides, mmol/L					
Patients	26	25.89 (14.34)	30	35.75 (43.55)	NS
Controls	50	1.77 (0.78)	30	2.10 (1.08)	NS
Cholesterol, mmol/L					
Total					
Patients	26	7.27 (3.92)	30	7.66 (6.30)	NS
Controls	50	4.92 (0.92)	30	5.08 (1.11)	NS
Low-density lipoprotein (LDL)					
Patients	16	0.79 (0.43)	18	0.81 (0.37)	NS
Controls	50	3.10 (0.83)	30	3.32 (0.95)	NS
High-density lipoprotein					
Patients	19	0.36 (0.16)	20	0.27 (0.15)	< 0.05
Controls	50	1.32 (0.27)	30	1.14 (0.31)	< 0.01
Apoprotein B, g/L					
Total					
Patients	14	0.52 (0.23)	15	0.57 (0.43)	NS
Controls	50	0.83 (0.20)	30	0.92 (0.27)	NS
LDL					
Patients	14	0.33 (0.19)	15	0.38 (0.19)	NS
Controls	50	0.71 (0.18)	30	0.77 (0.24)	NS

below 11.3 mmol/L were observed in patients who were either in hospital at the time of the lipid analyses or were adhering to a strict low-fat diet.

LDL-cholesterol, apoprotein B and HDL-cholesterol levels were decreased. However, plasma cholesterol levels were significantly increased because of the presence of cholesterol in the chylomicrons. Profiles of the apoprotein C group were examined in 25 patients by means of isoelectric focusing in polyacrylamide gels; all of these patients had apoprotein CII.

LPL activity could not be detected in plasma obtained from 55 patients. All of these patients had normal plasma hepatic lipase activity (mean 21.9 [SD 17.1] nmol of fatty acids per minute in 1 ml heparinized plasma). LPL activity after heparin injection could not be determined in a 2-week-old infant with a plasma triglyceride level of 233.7 mmol/L after 3 hours of fasting. After the infant received a medium-chain triglyceride milk formula (Portagen; Mead Johnson Canada, Ottawa) for 6 months the plasma triglyceride level decreased to between 11.3 and 17.0 mmol/L. His older sister did not have LPL activity.

Discussion

Familial hyperchylomicronemia is a rare autosomal recessive metabolic disease. However, the large number of people with this disorder in eastern Quebec, the geographic distribution and the observation that only one ethnic group was affected can be explained by historic and demographic reasons.

At the time of the British conquest of Canada, in 1760, the population in Nouvelle France consisted of 70 000 descendants of the 8000 settlers who had migrated from Normandy, Brittany and the western provinces of France between 1608 and 1760.[16] Immigration from France was almost completely curtailed after that period. Intermarriage between French Canadians and other settlers, mostly from Britain, was very limited. Because of a high birth rate the total population of Quebec increased to 200 000 by 1800.[17] Thus, the small number of settlers and the high birth rate contributed to the transmission of gene defects. In the counties of Charlevoix and Saguenay–Lac-St-Jean this effect has probably been amplified because of the relative isolation of the settlers.

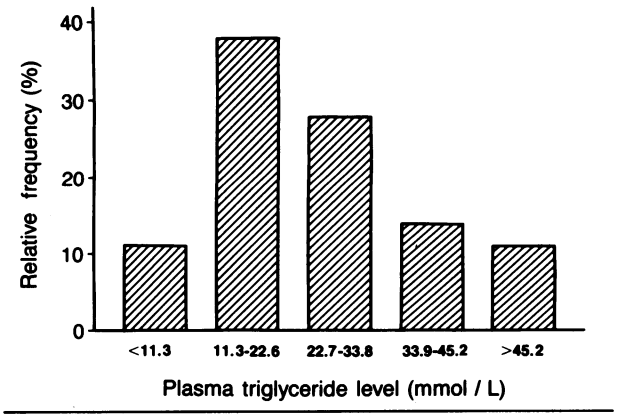

Fig. 3 — Relative frequency of plasma triglyceride levels at initial visit.

The population of Charlevoix originated from a small number of families who came from the Côte de Beaupré, a few kilometres east of Quebec City, in the 18th century. In the middle of the 19th century their descendants began migrating to the Saguenay–Lac-St-Jean area, and today they represent a large part of the population. In the 18th and 19th centuries the coefficient of consanguinity was high in these areas[18] ($f = 0.00956$ in Charlevoix; Gérard Bouchard: personal communication, 1988), although in 1985 it was reported to have decreased in Saguenay–Lac-St-Jean ($f = 0.00141$).[19] It is reasonable to assume that during this process the recessive LPL-gene defect was disseminated in the population. Indeed, the prevalence of homozygosity for LPL-activity deficiency is 200 per million population in Charlevoix, 200 times greater than that reported elsewhere.[1] The prevalence of heterozygosity for LPL-activity deficiency in eastern Quebec, excluding Charlevoix and Saguenay–Lac-St-Jean, has been determined on the basis of the Hardy–Weinberg equilibrium[20] and found to be 0.8 per 100 population. However, Charlevoix and Saguenay–Lac-St-Jean have prevalence rates of 2.8 and 2.3 per 100 respectively; these numbers are much higher than the rate of 0.2 per 100,[21] which was calculated on the basis of a disease prevalence of 1 case per million, and would probably be higher if they had been obtained after a systematic screening of the study population.

The frequency of heterozygosity in Saguenay remains at 2.3 per 100 if the degree of consanguinity of a control group is considered ($f = 0.00140$).[19] This suggests that genealogic studies would not show a higher frequency of consanguinous marriages among the patients in our study than among control subjects. This finding has also been shown for hereditary tyrosinemia and vitamin-D-deficiency rickets, both of which are autosomal recessive disorders found in the same area.[19] However, many of the patients in our study were related. We previously described a large family with four members who had LPL-activity deficiency;[22] this family was included in this report (Fig. 1B). Moreover, different phenotypes and premature ischemic heart disease were observed in other members of the family; this suggests familial combined hyperlipidemia.[21] A founding effect has also been observed among French Canadians affected by familial hypercholesterolemia, an autosomal dominant lipoprotein disorder.[23]

Whereas family screening and incidental findings led to the diagnosis of LPL-activity deficiency in over 50% of the patients, abdominal pain did so in only 35%, and in just one patient was the diagnosis suggested by clinical signs of hyperchylomicronemia. However, many of the patients

recalled having abdominal pain that they could prevent by avoiding fatty foods. The association of hyperchylomicronemia with acute pancreatitis and abdominal pain has been well established, but the precise mechanisms involved have yet to be determined.[1] A milky appearance of the plasma and false hyperbilirubinemia and hyperglycemia often triggered the clinical investigation in our study group. Other pseudoanomalies related to hyperchylomicronemia include pseudohyponatremia[24] and false elevation of the hemoglobin level.[25] Normal plasma and urinary amylase levels have been found in some patients with documented pancreatitis.[26] In addition, skin pallor in three infants prompted the parents to consult their physician; anemia was excluded and no other problems except hyperchylomicronemia were identified.

Physicians should check the appearance of the blood or the plasma in patients with acute abdominal pain. The presence of a creamy layer of chylomicrons can easily be detected in plasma stored overnight at 4°C; the plasma cholesterol:triglyceride ratio (mg:mg) in cases of familial hyperchylomicronemia is less than 0.20, or less than 0.50 in molar ratio.[1]

Primary LPL-activity deficiency is not restricted to a pediatric population.[27,28] Moreover, children with the disease are expected to reach adulthood. In our study 25% of the patients presented after 20 years of age, probably because they were more resistant to the clinical manifestations or they had learned to reduce their fat intake to avoid or relieve the abdominal pain. None of the patients showed signs of chronic pancreatitis, such as malabsorption or diabetes mellitus.

Although all of the patients knew they had some kind of lipid disorder related to the fat content of their diet, their lipid levels were similar to those published previously.[1] Clinical signs of hyperchylomicronemia were observed in patients with a mean plasma triglyceride concentration greater than 40 mmol/L. Eruptive xanthomas were less frequent than the other signs and were found in patients who had the highest mean plasma triglyceride concentrations. The prevalence rate of eruptive xanthomas was probably higher than the recorded rate, but because of the lability of this clinical sign it was not frequently observed at presentation. In addition, we found that splenomegaly may persist even when the plasma triglyceride levels decrease significantly and other signs disappear. None of the patients had evidence of hypersplenism.

A cardiovascular complication was observed in only one of the patients. The relative freedom from complications of atherosclerosis was probably due to the low age of the patients, the low LDL-cholesterol concentration, the low LDL:HDL cholesterol ratio or the nonatherogenic characteristics of large plasma lipoproteins such as chylomicrons.

The cause of primary LPL-activity deficiency is unknown. It is not likely due to the presence of a nonfunctional apoprotein CII, because lipase activity could not be detected after the addition of excessive amounts of normal apoprotein CII to the incubation mixture. Furthermore, apoprotein CII was found in the 25 patients tested for its presence. Nevertheless, the combination of LPL-activity deficiency and a nonfunctional apoprotein CII[29] cannot be ruled out. Thus, hyperchylomicronemia could be due to one or more of the following defects: the absence of an LPL enzyme,[1] a structurally altered LPL, no activation of apoprotein CII,[4,28] a selective tissue lipase deficiency[7] and the presence of a plasma LPL inhibitor.[6] A common metabolic defect is expected in eastern Quebec because of the genetic homogeneity of the population.

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Best, J.A.
Biehn, J.T., Jr.
Birkett, N.
Birmingham, L.
Blouin, A.G.
Blouin, D.
Boctor, M.A.
Bond, S.
Boone, J.E.
Bordage, G.
Brasher, P.
Brazeau, M.
Bridge, P.J.
Brisson, J.
Brown, N.E.
Brown, S.E.
Brownscombe, I.
Brunet, J.A.D.
Burge, F.I.
Busser, J.R.

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Cairns, J.A.
Capek, R.
Card, R.T.
Carson, G.D.
Carter, A.O.
Chan, K.
Chance, G.W.
Chappell, N.L.
Chisholm, A.W.
Churchill, B.M.
Churchill, D.N.
Clarfield, A.M.
Clayton, A.J.
Cockshott, W.P.
Cohen, M.
Connon, J.J.
Cudmore, D.W.

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Dales, R.
Daneman, D.
Dauphinee, W.D.
Deitel, M.
Del Greco, L.
Demianczuk, N.N.
Desgroseilliers, J.-P.
Devitt, J.E.
Dickinson, G.E.
Dionne, C.
Dodds, L.
Dolinsky, R.
Doran, T.A.
Dossetor, J.B.
Duperval, R.
Du Souich, B.P.

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Ehrlich, R.M.
Eliasiw, M.
Emerson, B.
Emmott, K.B.
English, M.J.M.
Esche, B.A.
Esplin, B.
Evans, C.E.