FACULTÉ DE MÉDECINE

LA DÉFICIENCE EN LIPOPROTÉINE LIPASE CHEZ LES CANADIENS FRANÇAIS: ÉTUDE SPATIALE, GÉNÉTIQUE ET GÉNÉALOGIQUE.

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RÉSUMÉ

La déficience en lipoprotéine lipase est une maladie autosomale récessive qui a atteint une forte prévalence dans la population canadienne-française de l'est du Québec. Au Saguenay-Lac-St-Jean, région isolée géographiquement du nord est de la province du Québec, la prévalence est estimée à 1/6382 habitants et le taux de porteurs à 1/46. Cette prévalence élevée semble être le résultat de l'immigration de porteurs venant de Charlevoix couplé à de l'endogamie.

Une étude spatiale et généalogique réalisée à partir des patients identifiés au Centre de Recherches sur les maladies lipidiques du Centre Hospitalier de l'Université Laval avait montré qu'il y avait plus d'une mutation dans le génome canadien-français. Depuis lors, deux mutations, M-188 et M-207, ont été décrites dans cette population. Alors que la M-188 est principalement retrouvée dans la région de la Mauricie-Trois-Rivières, la M-207 se rencontre surtout dans la partie nord-est du Québec (Saguenay-Lac-St-Jean, Charlevoix). Ces deux mutations ont été introduites dans le bassin génétique canadien-français par des immigrants venant de France au 17^{è} siècle. L'analyse de ces généalogies montre aussi que la mutation 207 serait vraisemblablement d'origine française et que la mutation 188 serait possiblement d'origine écossaise.

Carole Dionne

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Marc De Braekeleer

SUMMARY

Lipoprotein lipase deficiency is an autosomal recessive disorder which has a high prevalence in the French Canadian population of eastern Quebec. In Saguenay-Lac-St-Jean, a region geographically isolated in northeastern Quebec, the prevalence is estimated at 1/6382 inhabitants and the carrier rate at 1/46. This high prevalence appears to be the result of immigration of carriers from Charlevoix and endogamy.

A spatial and genealogical study on patients ascertained at the "Centre de Recherches sur les maladies lipidiques" of the "Centre Hospitalier de l'Université Laval" had previously shown that more than one mutation segregated in the French Canadian of population of Quebec. Since then, two mutations, M-188 and M-207, have been described in this population. M-207 is mainly found in northeastern Quebec (Saguenay-Lac-St-Jean, Charlevoix) whereas M-188 is more prevalent in the Mauricie-Trois-Rivières region.

These two mutations were introduced in the French Canadian genetic pool by migrants coming from France in the 17th century. The analysis of these genealogies also showed that M-207 appears to be of French origin while M-188 is likely to have a Scottish origin.

AVANT-PROPOS

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INTRODUCTION GÉNÉRALE

La déficience en lipoprotéine lipase est une maladie rare qui se caractérise par une accumulation massive de chylomicrons dans le plasma et qui correspond à une élévation de la concentration des triglycérides plasmatiques (Brunzell 1986; Brunzell 1989). La fréquence mondiale est évaluée à moins de un cas par million d'habitants (Brunzell 1989; Nikkilä 1983). C'est une maladie héréditaire autosomale récessive dont la fréquence des porteurs est estimée à 1/500 dans la population générale (Ma 1991; Nikkilä 1983). Cette maladie a été décrite chez les Blancs, les Noirs et les Asiatiques (Brunzell 1989; Rane et al. 1984). Les deux sexes sont affectés également (Brunzell 1989; Gagné et al. 1989; Rane et al. 1984).

La fréquence la plus élevée rapportée dans le monde se rencontre dans certaines régions de la province du Québec au Canada (Gagné et al. 1989). Ceci a motivé la mise sur pied d'un groupe collaboratif pluridisciplinaire de recherche concernant la déficience en lipoprotéine lipase. Ce groupe comprend des chercheurs de quatre universités; à savoir l'Université de Washington à Seattle, l'Université de la Colombie Britannique à Vancouver, l'Université Laval et l'Université du Québec à Chicoutimi. Les recherches qui sont menées actuellement essaient de mieux connaître la biochimie, la physiopathologie, la biologie moléculaire et l'épidémiologie génétique de cette maladie. Ce mémoire s'inscrit donc dans le cadre de ces recherches qui ont pour but de mieux connaître la problématique de la déficience en lipoprotéine lipase au Québec.

CHAPITRE I

LA MALADIE ET LES OBJECTIFS DE RECHERCHE

I.1 LA MALADIE

I.1.1 Historique

Le syndrome clinique associé avec un plasma lactescent dans l'enfance a été décrit pour la première fois en 1932 par Bürger et Grütz chez un jeune garçon issu d'un mariage consanguin. Cette maladie fut d'abord appelée *lipémie familiale idiopathique* , à cause de la nature familiale du désordre, puis *hyperlipémie essentielle* et *lipémie induite par les gras* et finalement *hyperlipoprotéinémie du type I.* C'est en 1960 que la déficience en lipoprotéine lipase a été notée comme étant une cause de chylomicronémie familiale chez les enfants (Brunzell 1989).

I.1.2 Age d'apparition des symptômes

La déficience en LPL se manifeste habituellement dans l'enfance (Brunzell 1989). L'affection débute dans 50% des cas avant l'âge de deux ans et en règle générale avant 10 ans (Guyot et al.1986; Ménage et De Gennes 1971). Le plus jeune malade à avoir été diagnostiqué est probablement un enfant de cinq jours (Kondo et al. 1985). Les sujets atteints de ce désordre familial se situent à l'intérieur d'une grande catégorie d'âge (1 semaine à 54 ans), ce qui indique que cette maladie n'est pas restreinte à la population en âge pédiatrique (Gagné et al. 1989; Sadan et al. 1977; Hoeg et al. 1983; Brunzell 1989). Les enfants atteints de cette maladie atteindront l'âge adulte. De plus, 25% de ces

patients ont consulté après l'âge de 20 ans probablement parce qu'ils sont plus résistants aux manifestations cliniques de l'hyperchylomicronémie familiale ou parce qu'ils avaient appris à réduire leur consommation de gras pour éviter ou traiter la douleur abdominale (Gagné et al. 1989).

I.1.3 Manifestations cliniques

Le syndrome clinique de la déficience primaire en lipoprotéine lipase peut être décelé tôt dans l'enfance et se présente d'abord avec des douleurs abdominales (Langlois et al 1989); c'est d'ailleurs le symptôme le plus commun (75% des cas) (Rane et al. 1984]). De plus, elles sont très souvent le motif de consultation. Le mécanisme des crises abdominales douloureuses est peu clair lorsqu'il n'existe pas de pancréatite; il pourrait s'agir d'un blocage du canal thoracique par des embolies de chylomicrons, d'embolies graisseuses dans le pancréas ou de l'accumulation toxique d'acide gras par l'hydrolyse des triglycérides par la lipase pancréatique, voire de la distension du foie et de la rate par des dépôts lipidiques (Guyot et al. 1986). La douleur abdominale est habituellement localisée au milieu de l'épigastre et irradie dans le dos. Elle peut aussi être présente dans le quadrant supérieur droit ou gauche de l'abdomen ou encore dans le milieu antérieur de la cage thoracique. L'intensité de cette douleur est variable; elle peut être légère, modérée ou même sévère (Brunzell 1989).

De plus, les patients présentent un plasma lactescent (Langlois et al. 1989) et un niveau de chylomicrons élevés avec des triglycérides au dessus de 12.0 mmol/L (Gagné et al. 1989) qui sont associés à des signes

cliniques typiques tels que la lipémia rétinalis et les xanthomes éruptifs. Ces derniers sont des petites lésions jaunes sous forme de papules correspondant à des dépôts de lipides dans la peau. Ils sont localisés sur les fesses, les genoux, à la surface du muscle extenseur des bras et peuvent même être généralisés. On observe aussi de l'hépatomégalie qui est habituellement décelée dans les formes modérées et graves d'hypertriglycéridémie et de la splénomégalie qui est moins fréquente (Brunzell 1989). Des pertes de mémoire et de la dépression ont aussi été rapportées chez certains patients ayant une hyperchylomicronémie (Brunzell 1989). Enfin, la sévérité des symptômes est proportionnelle à la concentration plasmatique en chylomicrons (Agarwal et al. 1985)

I.1.4 Physiologie

Les symptômes cliniques de la déficience en LPL familiale sont la conséquence d'une accumulation des chylomicrons dans le sang due à la déficience en lipoprotéine lipase (Kern et al. 1990). La lipoprotéine lipase (LPL; triaglycero-protéine acylhydrolase, EC 3.1.134) qui est une glycoprotéine constituée de 448 acides aminés est synthétisée par de nombreux tissus parenchymateux, incluant les tissus adipeux, musculaires et cardiaques (Auwerx et al.1989; Bergeron et al.1991a; Langlois et al. 1989; Brunzell 1989). Son activité biologique réside toutefois à la surface luminale des capillaires sanguins où elle s'accroche à l'héparan sulfate des protéoglycans de l'endothélium et catalyse l'hydrolyse des triglycérides transportés par les chylomicrons et les lipoprotéines de très basse densité (VLDL). L'apolipoprotéine C-II présente à la surface des chylomicrons et des VLDL sert de cofacteur essentiel à cette hydrolyse des triglycérides. Cette activité lipolytique

constitue l'étape limitante du catabolisme intravasculaire des triglycérides et du transfert de ces acides gras vers les tissus périphériques; elle est également essentielle à la maturation de l'ensemble des lipoprotéines plasmatiques (Bergeron et al. 1991a; Brunzell 1989).

I.1.5 Diagnostic

Cette maladie est souvent diagnostiquée accidentellement dans l'enfance à cause d'épisodes de douleurs abdominales répétitives et d' attaques récidivantes de pancréatite (Agarwal et al. 1985). Plus de 30% des cas des déficiences en LPL sont trouvés par hasard lors d'investigations de problèmes médicaux non reliés à la maladie (Gagné et al. 1989; Bergeron et al. 1991b). Le diagnostic est basé sur une activité enzymatique basse ou absente dans un test qui a exclu les autres enzymes lipolytiques et qui contient du plasma normal ou de l'apoC-II, un activateur nécessaire de l'enzyme (Brunzell 1989). Chez ces patients, l'activité de la LPL dans le plasma est faible ou absente après une injection intraveineuse de 60 unités d'héparine par kg de poids (Brunzell 1989; Gagné et al. 1989).

I.1.6 Traitement

Le traitement de cette maladie repose sur un régime pauvre en graisses qui permet de supprimer les symptômes et de normaliser le bilan lipidique (Guyot et al. 1986; Nocton et al. 1966). L'apport en gras alimentaire permis est de 10-20 gr/jour avec une consommation adéquate en acides gras essentiels (Agarwal et al. 1985). Cependant la

tolérance est variable selon les individus, ce qui est à rapprocher de l'expression également variable de l'affection. La tolérance aux hydrates de carbones est très bonne, permettant de fournir 60 à 70% de la ration calorique sous cette forme (Guyot et al. 1986). Pour améliorer la réponse thérapeutique et afin d'éviter la surcharge calorique on peut remplacer une partie des calories provenant des graisses par des triglycérides à chaîne moyenne (MCT) (Agarwal et al. 1985). Leur absorption digestive n'est pas dépendante des chylomicrons; cela représente donc un moyen appréciable d'augmenter l'apport calorique chez les patients. Avec un tel régime tous ces troubles sont au moins partiellement réversibles (Guyot et al. 1986). La restriction en gras est habituellement suffisante pour garder le patient asymptomatique. Par exemple le volume de la rate peut redevenir normal à l'intérieur d'une semaine de régime et les xanthomes éruptifs peuvent disparaître dans l'intervalle d'une semaine à plusieurs mois. Si les xanthomes persistent ou récidivent ils sont une indication que la thérapie est inadéquate. Les médicaments disponibles pour abaisser les triglycérides dans le sang ne sont pas efficaces (Brunzell 1989).

I.1.7 Évolution de la maladie

L'évolution de la maladie est dominée par le risque de complications telles que pancréatite aigüe, anémie et atteinte osseuse par envahissement du tissu hématopoïétique médullaire et par récidive de douleurs abdominales (Guyot et al. 1986; Frederickson et al. 1977). Si la diète restrictive est maintenue tout au long de la vie le pronostic final sera excellent (Rane et al. 1884; Frederickson et al. 1977). Tous les auteurs étaient unanimes à dire que le risque athéromateux était nul car les chylomicrons, qui sont les lipoprotéines les plus volumineuses,

seraient trop gros pour infiltrer la paroi artérielle. Cependant les études récentes chez les familles atteintes d'hyperlipoprotéinémie de type I suggèrent que cet enzyme puisse être impliqué dans l'expression phénotypique de dyslipoprotéinémies potentiellement athérogènes chez les hétérozygotes (Bergeron et al. 1991a).

I.1.8 Biologie moléculaire

Le gène de la LPL humaine, présent en une seule copie, est localisé dans la bande p22 du chromosome 8. D'une longueur approximative de 30 kilobases, il contient 10 exons (Bergeron et al. 1991a, Ma et al. 1991). Plusieurs mutations ont maintenant été décrites dans ce gène (Tableau I). Elles ont été décrites chez les malades atteints de déficience en LPL d'origine ethnique très variée (Français, Canadiens-français, Anglais, Écossais, Irlandais, Allemands, Hollandais, Japonais, Malais, Noirs Américains, etc.).

Plus particulièrement au Québec, deux mutations ont été décrites: la M-188 (Monsalve et al. 1990) et la M-207 (Ma et al. 1991).

I.2 OBJECTIFS DE RECHERCHE

I.2.1 Objectif général

Mieux connaître l'épidémiologique génétique de la déficience en lipoprotéine lipase chez les Canadiens-français du Québec.

I.2.2 Objectifs spécifiques

Déterminer l'origine et la distribution de la déficience en lipoprotéine lipase chez les Canadiens français.

Déterminer l'origine et la distribution de la M-188 chez les Canadiens français.

Déterminer l'origine et la distribution de la M-207 chez les Canadiens français.

TABLEAU I

MUTATIONS DANS LE GENE DE LA LPL ASSOCIÉES À UNE ANOMALIE DE L'EXPRESSION DE L'ACTIVITÉ

Exon	Anomalies	Références
Intron 2	Perte du site d'épissage 3'	Gotoda et al. 1990; Hata et al. 1990
Exon 3	Tyr ^{61} —>codon de terminaison	Gotoda et al.1990
Exon 3	Gln ^{106} —>codon de terminaison	Emi et al.1990
Exon 3	Insertion de GGGCT	Henderson et al. 1990
Exon 3-4-5	Deletion 6 kb	Langlois et al.1989
Exon 4	Gly ^{142} —>Glu	Ameis et al.1991
Exon 5	Pro ^{157} —>Arg	Bruin et al. 1990
Exon 5	Ala ^{176} —>Thr	Beg et al. 1990
Exon 5	Gly ^{188} —>Glu	Monsalve et al. 1990
Exon 5	Ile ^{194} —>Thr	Henderson et al. 1991
Exon 5	Pro ^{207} —>Leu	Ma et al. 1991
Exon 6	Arg ^{243} —>His	Dichek et al. 1991
Exon 6	Ser ^{244} —>Thr	Hata et al. 1990
Exon 6	Tyr ^{262} —> codon de terminaison	Funke et al. 1990
Exon 6	Insertion 2 kb	Devlin et al. 1990
Exon 9	Ser ^{447} —> codon de terminaison	Bergeron et al. 1991a

Ref: Bergeron et al. 1991a; Hayden et al. 1991

CHAPITRE II

EFFET FONDATEUR DE L'HYPERCHYLOMICRONÉMIE FAMILIALE CHEZ LES CANADIENS FRANÇAIS DU QUÉBEC.

(FOUNDER EFFECT IN FAMILIAL HYPERCHYLOMICRONEMIA AMONG FRENCH CANADADIANS OF QUEBEC).

* Marc De Braekeleer, Carole Dionne, Claude Gagné, Pierre Julien, Daniel Brun, M. R. Ven Murthy, Paul-J. Lupien. Founder Effect in Familial Hyperchylomicronemia among French Canadians of Quebec. Hum Hered 1991; 41: 168-173.

II.1 RÉSUMÉ

L'hyperchylomicronémie familiale est une maladie qui a atteint une forte prévalence dans la population canadienne-française de l'est du Québec. Les lieux de naissance de 58 porteurs identifiés suite à la naissance d'un enfant atteint sont concentrés dans 3 régions du Québec. Aucun fondateur commun à ces 58 porteurs obligatoires n'a été identifié par reconstitution généalogique.

Trois noyaux fondateurs, un par région, ont été identifiés; certains de ces fondateurs ont été retrouvés dans 2 régions différentes. Ces résultats suggèrent fortement que plus d'une mutation est présente dans la population canadienne-française et qu'elles y ont été introduites par des immigrants français au 17e siècle.

Le Perche qui est une région située entre Paris et la Normandie semble être le centre de diffusion le plus probable d'au moins une mutation présente dans la population canadienne-française actuelle du Québec.

II.2 ABSTRACT

Familial hyperchylomicronemia has reached a high prevalence in the French Canadian population of eastern Quebec. The birth places of 58 carriers identified through the birth of one affected child clustered in three regions. The genealogies of these 58 individuals showed that no founder was common to all of them. Three sets of founders were found, one for each region, with little overlapping between two regions.

These results strongly suggest that more than one mutation, introduced by the French migrants in the 17th century, are segregating in the French Canadian population. Perche, a region situated between Paris and Normandy, appeared to be the most likely putative centre of diffusion of at least one mutation in the lipoprotein lipase gene segregating in the modern day French Canadian population of Quebec.

II.3 INTRODUCTION

Familial hyperchylomicronemia [primary lipoprotein lipase (LPL) activity deficiency, type I hyperlipoproteinemia] is a rare autosomal recessive disorder characterized by massive accumulation of chylomicra in the plasma of fasting patients [1]. Elevated concentrations of triglycerides are due to defective plasma LPL activity, the enzyme responsible for the hydrolysis of the triglycerides of chylomicra and very-low-density lipoproteins. Brunzell et al. [2] identified a number of LPL- deficient variants including absence of LPL enzyme and activity, presence of an inactive and structurally modified LPL enzyme, presence of plasma LPL enzyme with defective binding to endothelium [3], selective tissue lipase deficiency [4], presence of an inherited plasma LPL inhibitor [5] , and lack of LPL activity due to apoprotein CII deficiency [6]. In the French Canadian population of Quebec, a defect in the LPL enzyme and not in its activator, the apoprotein CII, was shown to be responsible for the observed hyperchylomicronemia [7].

The prevalence of familial hyperchylomicronemia in the general population was estimated at 1 case per million [1]. However, we recently identified 56 cases of familial hyperchylomicronemia in eastern Quebec and described the related clinical manifestations such as abdominal pains, pancreatitis, lipemia retinalis, eruptive xanthomas, hepatomegaly and splenomegaly [7]. The incidence in this Quebec population was shown to be 30 times higher than previously published [7]. We hypothesized that a unique mutant gene spread in the French Canadian population due to a founder effect.

We now report a genealogical study based on 43 cases of familial hyperchylomicronemia distributed in 29 families found in this Quebec population. Detailed genealogical studies led us to conclude that the LPL deficiency was introduced by at least three founders and suggest that more than one gene defect may underlie the familial hyperchylomicronemia disorder observed in this population.

II.4 MATERIAL AND METHODS

The genealogical studies were carried out in 43 hyperchylomicronemic patients from 29 different French Canadian families living in the province of Quebec. These patients were evaluated and are being regularly followed at the Lipid Research Centre of the "Centre hospitalier de l'Université Laval". Detailed clinical data related to this population were previously published [7,8]. Blood samples were obtained after a 12-hour fasting period for lipid and lipoprotein analyses and showed the presence of chylomicra with a mean plasma triglyceride level well above 10 mmol/l. The diagnosis of familial hyperchylomicronemia was confirmed after determination of plasma LPL activity measured 10 and 20 min before and after intravenous injection of 60 IU/kg of heparin as previously described [9].

All 29 families were contacted and asked to fill a questionnaire regarding their date and place of birth, the date and place of birth of their parents and grandparents as well as the date and place of marriage of their parents and grandparents.

The genealogies of the 29 probands were reconstructed using various sources. For those who were born in the Saguenay-Lac-St-Jean

(SLSJ) region, the genealogies were reconstructed using the computerized population register maintained at SOREP [10,11]. This stage allowed occasional reconstructions as far as the middle of the 19th century. The genealogical reconstruction was then pursued manually, using several marriage repositories of Quebec [see, for example, ref. 12-14]. Other sources included the 'Fichier Loiselle' which contains more than 410,000 marriage records from various parishes in Quebec and the 'Fichier Jetté' which contains more than 140,000 marriage records from the origins of Quebec in the 17th century to 1825. Genealogical dictionaries were also consulted; these are the *Dictionnaire généalogique des familles du Québec*, which contains all civic records of all individuals having lived in Quebec from the origins of the French colony to 1730 [15], and the 'Dictionnaire généalogique des familles canadiennes', which includes civic records of individuals who lived in Quebec from the origins to 1800 [16]. The genealogies of the probands not living in the SLSJ region were reconstructed manually using the same sources. The genealogies were reconstructed to an average depth of 12 generations, allowing recognition of the founders of the French Canadian population in Europe, mainly in France, in the 17th century. When necessary, the concerned parishes were contacted by phone to obtain further information regarding particular marriages.

The genealogies were then recorded in a computerized genealogical database (BELGE developed at SOREP). Each record contains a set of three numbers (ego, father, mother), the sex of the individual, his date and place of marriage, and his status (e.g. affected, carrier).

The genealogies were analysed using MEDIC4-BELGE (software developed at SOREP), which calculates inbreeding and kinship

coefficients, and PED-BELGE (also developed at SOREP), which, based on an algorithm determining the closest relationship between individuals at each generation, identifies the most likely founders in a set of families whith a given disorder [11,17]. The most likely paths of descent of the gene were determined using PED-DESC (developed at SOREP) and the pedigrees drawn using PEDIGREE/DRAW developed at the Southwest Foundation for Biomedical Research in San Antonio, Tex., USA [18].

II.5 RESULTS

Figure 1 shows the spatial distribution of the birthplaces of the 58 heterozygote parents. Most of the carriers were born in northeastern Quebec (SLSJ and Charlevoix). Five carriers were born in three different municipalities located within a radius of 20 km in Beauce whereas an other set of 5 carriers was born in the Trois-Rivières region (Mauricie).

No single founder was found to be common to all carriers. A group of 11 founders, born in the 17th century, was shown to be common to all carriers born in SLSJ, Charlevoix, the Quebec City area and Portneuf (figure 1). One founder was born in Switzerland and, of the remaining 10, 8 were born in Perche, a small region of France situated between Paris and Normandy.

A set of 109 founders common to the 5 carriers born in Beauce was found. It included all founders common to the carriers born in northeast Quebec. The remaining founders mainly originated from Perche and Normandy whereas 2 founders were of Acadian origin. A couple who got married in 1767 in St-François de Beauce was also found to be common to all 5 carriers born in Beauce (figure 2).

Nineteen founders were found to be common to all 3 carriers born in the Trois-Rivières region as well as 1 carrier born in the Bois-Francs region (figure 1). Five founders originated from Perche and 3 from Saintonge, another region of France.

II.6 DISCUSSION

Hyperchylomicronemia is a very rare autosomal recessive disorder which has a high prevalence in eastern Quebec and, more particularly, in Charlevoix and SLSJ [7]. It was postulated that a founder effect might explain the presence of this disorder in French Canadians [7]. Therefore, a genealogical reconstruction was attempted to test this hypothesis.

However, genealogical reconstruction has its limits. Cases of adoption and non-paternity should be considered; depending upon the sources, it was occasionally possible to identify such cases. As an example, it was not unusual for the priest in the 17th or 18th century to indicate on the baptism record whether the child was legitimate or not.

An additional limit of the genealogical reconstruction is the reliability of the sources. The familial links were usually identified through several sources and, whenever any differences were found, the priest or his secretary was asked by phone to read the original marriage record kept in the parish.

Finally, the genealogical reconstruction is usually limited by its lack of completeness. Indeed, although all available sources have been consulted, a few marriage records could not be found. There are several

explanations including the inaccessibility of the marriage records of a particular parish, the destruction of the original record or a change in the surname, which was common practice in Quebec in the 17th and 18th centuries. Therefore, when interpreting the results we have to keep in mind that the gene may have been transmitted through a missing genealogical link. However, with the exception of the maternal side of a patient whose genealogy could not be reconstructed beyond the 4th generation, and was not included in the analysis, only a few marriages were not found, all of them beyond the 6th generation.

Our results strongly suggest that more than one mutation is present in the French Canadian population. Although it cannot be excluded that only one mutation segregates in this population, it seems that at least one mutation is segregating in the population of northeastern Quebec and that a different mutation is present in the Trois-Rivières population. Since the set of founders common to all the carriers born in Beauce included all founders common to the carriers from northeast Quebec, the mutation(s) present in Beauce could be identical to the one(s) found in northeast Quebec.

Our results also suggest that the mutations present in the French Canadian population were introduced in the province of Quebec by French immigrants in the 17th century. Indeed, from the origins of the French colony to 1763, year of the take-over by the English, some 25,000 individuals came to Quebec. However, a large number of them did not settle in the colony and it is estimated that only 8,500 persons, including 1,600 women, settled permanently and founded the French Canadian population [19-21]. Because of its relative cultural and linguistic isolation, it is believed that the present French Canadian

population is mostly derived from that founding nucleus [21,22]. Studies on the places of origin in Europe of the founders of the French Canadian population also showed that only 4.1% were not from France. Among those from France, for example, 13.2% came from Normandy, 13.0% from Paris and Ile de France, 8.9% from Poitou, 8.0% from Aunis, 4.8% from Saintonge and 2.6% from Perche [19-21]. Among the 139 founders (11 for northeast Quebec + 109 for Beauce + 19 for Trois-Rivières) of hyperchylomicronemia, 21 (15.1%) came from Normandy, 9 (6.5%) from Paris, 6 (4.3%) from Poitou, 8 (5.8%) from Aunis and Saintonge each, and 34 (24.5%) from Perche. Although it remains to be seen if such a distribution is not the consequence of differential fertility, these results suggest that Perche was a putative center of diffusion in the 17th century for at least one mutation in the LPL gene in the French Canadian population. A similar conclusion was already reached for one mutation of phenylketonuria (PKU) segregating in the present French Canadian population of Quebec [De Braekeleer et al., submitted]. It must be noted that 15 of the founders of the PKU mutation originating from Perche were also amongst the founders of hyperchylomicronemia.

Molecular studies are underway in an attempt to identify the mutation(s) in the LPL gene which is (are) segregating in the French Canadian population. They should give us clues to the accuracy of the conclusions drawn from the genealogical reconstruction.

II.7 ACKNOWLEDGEMENTS

This work was supported by research grants from the 'Fondation de l'Université du Québec à Chicoutimi', the Quebec Heart Foundation and Parke-Davis Canada. P.J. is a career scientist of the 'Fonds de la

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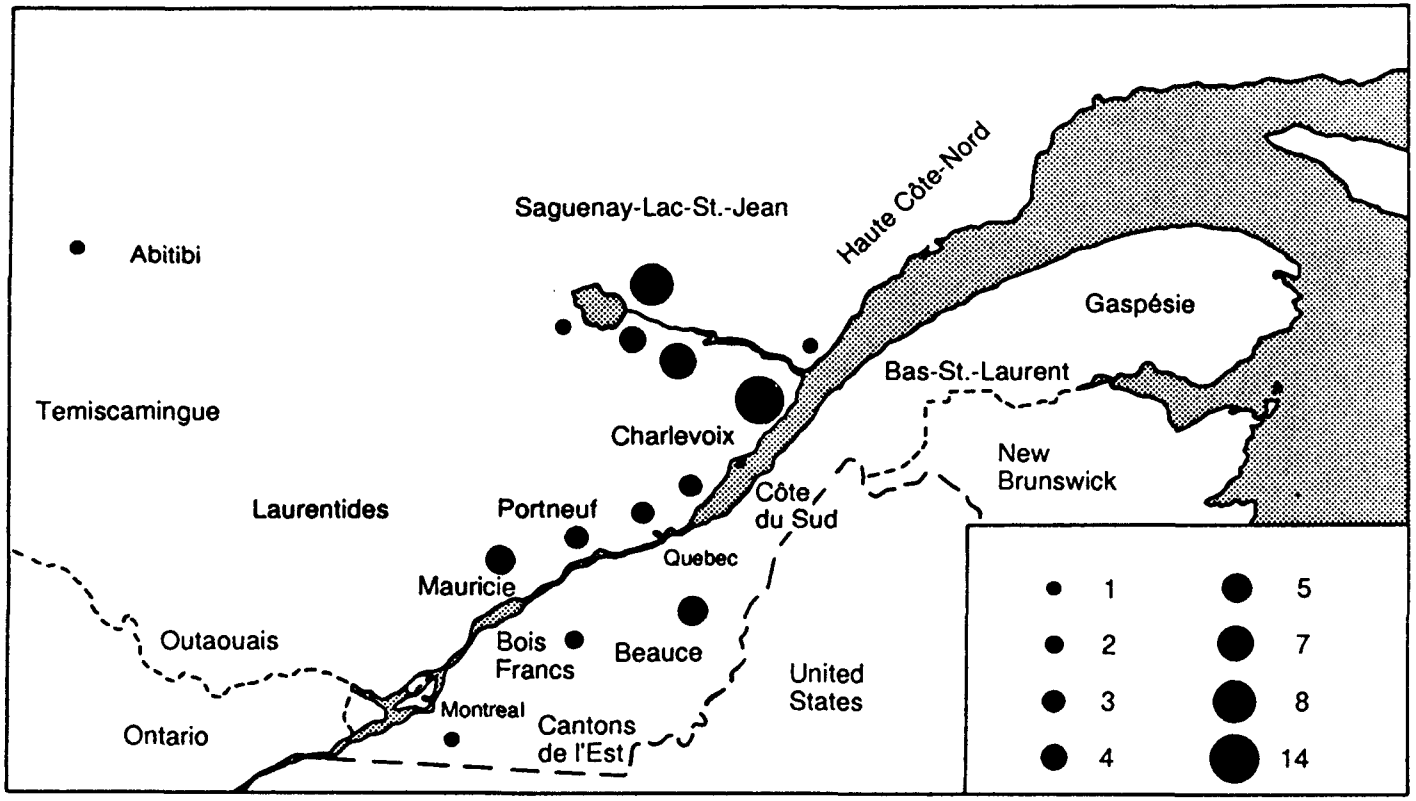
II.9 FIGURES

Figure II.1 : Geographic distribution of the birthplaces of the 58 obligate carriers of an LPL gene deficiency in the province of Quebec.


Saguenay-Lac-St.-Jean
Haute Côte-Nord
Abitibi
Gaspésie
Bas-St.-Laurent
Temiscamingue
Charlevoix
New
Brunswick
Laurentides
Portneuf
Côte
du Sud
Quebec
Mauricie
Outaouais
Bois
Francs
Beauce
United
States
Montreal
Ontario
Cantons
de l'Est
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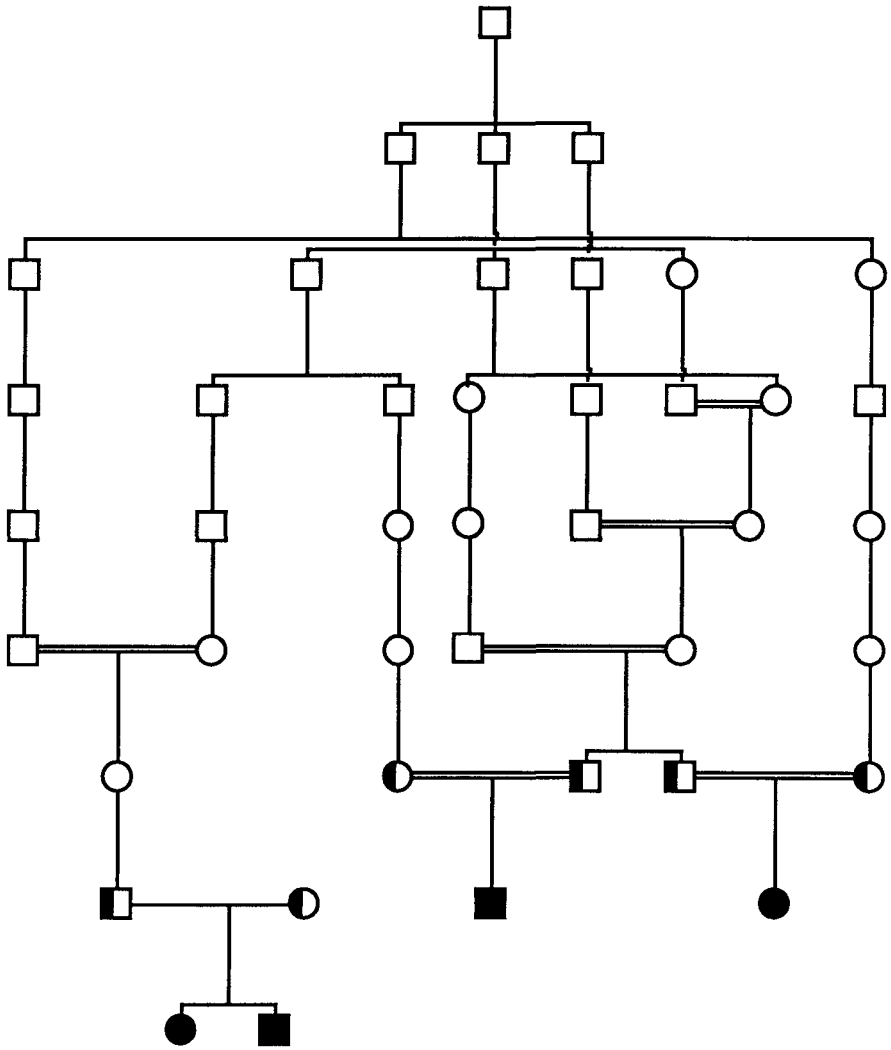
FigureII.2 : Genealogical reconstruction of the 5 obligate carriers of an LPL gene deficiency born in the Beauce region showing a common ancestor couple at the 6th generation.



CHAPITRE III

EPIDÉMIOLOGIE GÉNÉTIQUE DU DÉFICIT EN LIPOPROTÉINE LIPASE AU SAGUENAY-LAC-ST-JEAN (QUÉBEC, CANADA).

(GENETIC EPIDEMIOLOGY OF LIPOPROTEIN LIPASE DEFICIENCY IN SAGUENAY-LAC-ST-JEAN (QUEBEC,CANADA)).

* C. Dionne, C. Gagné, P. Julien, M.R.V. Murthy, M. Lambert, G. Roederer, J. Davignon, M.R. Hayden, P.J. Lupien, M. De Braekeleer. GENETIC EPIDEMIOLOGY OF LIPOPROTEIN LIPASE DEFICIENCY IN SAGUENAY-LAC-ST-JEAN (QUEBEC, CANADA).1991; Accepté pour publication dans: ANNALES DE GÉNÉTIQUE (PARIS).

III.1 RÉSUMÉ

L'hyperchylomicronémie familiale due à un déficit d'activité en lipoprotéine lipase (hyperlipoprotéinémie de type I) est une maladie autosomale récessive dont la prévalence est estimée à un cas par million. Trente-quatre personnes atteintes d'hyperlipoprotéinémie de type I sont connues au Saguenay-Lac-St-Jean (SLSJ), une région isolée géographiquement du Québec. La prévalence a été estimée à 1/6382 habitants et le taux de porteurs à 1/46 dans cette région. Le coefficient moyen de consanguinité était légèrement augmenté dans le groupe cible par rapport à 3 groupes témoins. Le coefficient moyen de parenté était 15,1 fois plus élevé dans le groupe malade que dans les groupes témoins. La prévalence élevée de l'hyperchylomicronémie familiale au SLSJ semble être le résultat de l'émigration de porteurs venant de Charlevoix, une autre région isolée du Québec, vers le SLSJ. L'endogamie a aussi joué un rôle important dans l'augmentation de la prévalence de type I au SLSJ.

III.2 ABSTRACT

Familial hyperchylomicronemia due to the lipoprotein lipase (LPL) activity deficiency (Type I hyperlipoproteinemia) is an autosomal recessive disorder with a prevalence estimated at one case per million. Thirty-four type I individuals are known in Saguenay-Lac-St-Jean (SLSJ), a geographically isolated region of Quebec. The prevalence of type I and LPL deficient heterozygotes in this region was estimated at 1/6382 and 1/46 inhabitants respectively. The mean inbreeding coefficient was slightly elevated in the type I group compared with three control groups. The mean kinship coefficient was 15.1 times higher in the type I group than in the control groups. The high prevalence of type I in SLSJ appears to be the result of the emigration of carriers of LPL deficiency from Charlevoix, another isolated region of Quebec to the SLSJ region. Endogamy also played a crucial role in increasing the prevalence of type I in SLSJ.

III.3 INTRODUCTION

Saguenay-Lac-St-Jean (SLSJ) is a geographically isolated region located 200 kilometers northeast of Quebec City (Figure 1). The region under study has been described in full detail elsewhere [De Braekeleer and Larochelle 1990; De Braekeleer 1991]. Primary lipoprotein lipase (LPL) activity deficiency (Type I hyperlipoproteinemia) is a rare autosomal recessive disorder resulting in massive hyperchylomicronemia [Brunzell 1989]. The prevalence of familial hyperchylomicronemia in the general population is estimated at one case per million [Brunzell 1989]. In the past few years, it became evident that the prevalence of LPL deficiency was much higher in eastern Quebec (27 cases per million) than in the general population [Gagné et al 1989]. The prevalence in Saguenay-Lac-St-Jean was estimated at 200 cases per million [Gagné et al 1989]. Furthermore, a founder effect was suggested [Gagné et al 1989; De Braekeleer et al 1991].

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

III.4 MATERIAL AND METHODS

Data regarding the patients and their families was obtained from the attending physicians. Most of the patients were followed at the Lipid Research Centre of the Centre Hospitalier de l'Université Laval; the remaining were seen at the Ste-Justine Hospital or the Clinical

Research Institute in Montreal. Detailed clinical data related to this French Canadian population have previously been published [Gagné et al 1977; Gagné et al 1989].

Blood samples were obtained after a 12-hour fasting period for lipid and lipoprotein analyses and showed the presence of chylomicrons with plasma triglyceride levels above 10 mmoles/L [Gagné et al 1989]. Diagnosis of familial hyperchylomicronemia was confirmed after determination of plasma LPL activity measured 10 and 20 minutes before and after I.V. injection of 60 IU/Kg of heparin, as previously described [Brun et al 1989]. Birthdates of the affected individuals were extracted from the patient files whereas their birthplaces were obtained from the families. The prevalence was calculated by dividing the total number of patients by the whole population of SLSJ. The carrier rate was estimated using the Hardy-Weinberg equilibrium law. The places of residence of the parents (obligate carriers) of type I individuals in Saguenay-Lac-St-Jean at the time of birth of the latters were obtained from the families, as were the places of residence of the grandparents of the type I individuals at the time of birth of the obligate carriers.

Three control groups matched on the date and place of marriage of the obligate carrier couples married in SLSJ as well as the husband's occupation were created using the SLSJ population register developed and maintained at SOREP (Interuniversity Centre for Research on Populations), as previously described in detail elsewhere [De Braekeleer and Larochelle 1990]. They were used in the study of consanguinity, kinship and endogamy, as previously described [De Braekeleer and Larochelle 1990].

III.5 RESULTS

A total of 34 individuals, including one adopted, affected with LPL deficiency and distributed in 23 families lived in SLSJ on December 31st 1990. The prevalence of LPL deficiency was calculated to be 34/285,000 or 1/6,382 inhabitants. The carrier rate was estimated to be 1/46 inhabitants.

Twenty-five obligate heterozygote couples, ascertained through the birth of at least an individual affected with LPL deficiency, got married in SLSJ. These couples had a total of 36 LPL deficient children. Two of them were born in Quebec city, one near Montreal, and the remaining 33 in SLSJ. The places of residence of the parents at the time of birth of these 34 type I individuals were distributed in 15 of the 66 municipalities within SLSJ. It should be noted that 17 LPL deficient patients belonging to 9 different families were born in a small area situated east of Lac-St-Jean. This area is identified by an shaded ellipse in figure 1.

Figure 2 shows the spatial distribution of the places of residence of the parents at the time of birth of the obligate carriers of LPL deficiency. Forty-nine places were distributed in 21 of the 66 municipalities within SLSJ whereas one place of residence was located outside this region. The Monte Carlo simulations showed 5 municipalities (identified by an asterisk in figure 2) to have a higher number of places of residence than expected on the basis of their relative contribution to the whole SLSJ population ($p<0.05$). Again a cluster of birth places of obligate carriers was observed in the eastern part of Lac-St-Jean (identified in figure 1).

The parents of individuals affected with LPL deficiency and those of control children were equally likely to have been born in the SLSJ region or outside (chi-square=0.00, p=1.00). Among the parents born in SLSJ, parents of affected children and parents of control children were equally likely to have been born in the same municipality, in contiguous municipalities or in non-contiguous municipalities (chi-square = 3.17, p = 0.20).

The mean coefficients of inbreeding and kinship of the LPL deficiency and control groups are given in table I. The mean coefficient of inbreeding was found to be 5.3 times higher in the LPL deficiency group than the average value of the mean coefficients of inbreeding of the three control groups. This increase was mainly due to one marriage between second-degree cousins. The mean kinship coefficient was found to be 15.1 times higher in the LPL deficient group than the average value of the mean kinship coefficients of the three control groups pooled together. Two probands were related as aunt-nephew, two as double first-degree cousins, two as first-degree cousins once removed, and ten as second-degree cousins.

III.6 DISCUSSION

The prevalence of familial hyperchylomicronemia in the general population is estimated to be 1/1,000,000 and the carrier rate to be 1/500 inhabitants [Brunzell 1989]. Both prevalence and carrier rate are much higher in SLSJ. However, the values calculated in this region must be considered as minimal estimations. Indeed, Gagné et al (1989) reported that in 26 of 56 patients followed at the Lipid Research Centre,

hyperchylomicronemia was a coincidental finding in the clinical and laboratory investigation of various symptoms not related to type I. Therefore, one can ask how many type I patients have never been diagnosed and/or seen in a specialized lipid clinic. Hypothetically, if 30% of the patients are not refered to the lipid clinics, the prevalence of type I and the carrier rate in SLSJ could be as high as 1/5868 and 1/38 respectively.

The birth places of the patients and their parents (obligate carriers) clustered in an area located east of Lac-St-Jean (figure 1). Such a result could be the consequence of non random mating. Indeed, the closest relationships were found between probands born in this particular area; a sibship exchange was even documented. No type I patients and obligate carriers were born in the eastern part of SLSJ known as Bas-Saguenay (figure 2). This isolated subregion has a high mean coefficient of inbreeding and kinship (De Braekeleer 1991; De Braekeleer and Ross 1991). Also, no type I cases have been identified in the extreme western part of Lac-St-Jean. This area was settled mainly by immigrants coming from various regions of Western Quebec whereas the remaining part of the SLSJ region was developed by individuals coming from eastern Quebec and more particularly from Charlevoix, an isolated county situated on the north shore of the St-Lawrence river (figure 1) (Gauvreau et al 1991; Bouchard 1988). Indeed, from 1838 to 1911, 50% of the 28,656 immigrants to SLSJ came from Charlevoix (Gauvreau et al 1991). It should be noted that the carrier rate in Charlevoix is estimated to be 1/35 (Gagné et al 1989). Moreover, the surnames of the obligate carriers identified so far in SLSJ are the same as those found in Charlevoix.

Two mutations have now been described in the French Canadian population of Quebec; these are the M-188 mostly distributed in western Quebec and the M-207 predominantly found in eastern Quebec (Monsalve et al 1990; Ma et al 1991). Ongoing studies show that the frequency of M-207 mutation is very high in Charlevoix and in SLSJ. The high prevalence of type I in SLSJ is therefore the result of the emigration of carriers of the M-207 mutation from Charlevoix to the SLSJ region. Endogamy also played a crucial role in increasing the prevalence of type I in SLSJ.

III.7 ACKNOWLEDGEMENTS

This work was supported by research grants from the 'Fondation de l'Université du Quebec à Chicoutimi', the Quebec Heart and Stroke Foundation and Parke-Davis Canada. P.J. is a career scientist of the 'Fonds de la Recherche en Santé du Quebec'.

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Davignon J., Lupien P.J., Brunzell J.D., Hayden M.R. - A missense mutation at codon 188 of the human lipoprotein lipase gene is a frequent cause of lipoprotein lipase deficiency in persons of different ancestries. J. Clin. Invest., 1990, 86, 728-734.

III.9 TABLE

Table III.1

Mean coefficients of inbreeding and kinship in lipoprotein lipase deficiency and control groups in Saguenay-Lac-St-Jean.

Group	Mean coefficient of inbreeding $(\times 10^{-4})$	Mean coefficient of kinship $(\times 10^{-4})$
LPL deficiency	8.22	26.36
Controls 1	2.57	1.28
Controls 2	2.06	0.90
Controls 3	0.00	3.05

III.10 FIGURES

Figure III.1: Localization of Saguenay-Lac-St-Jean and Charlevoix within the province of Quebec.

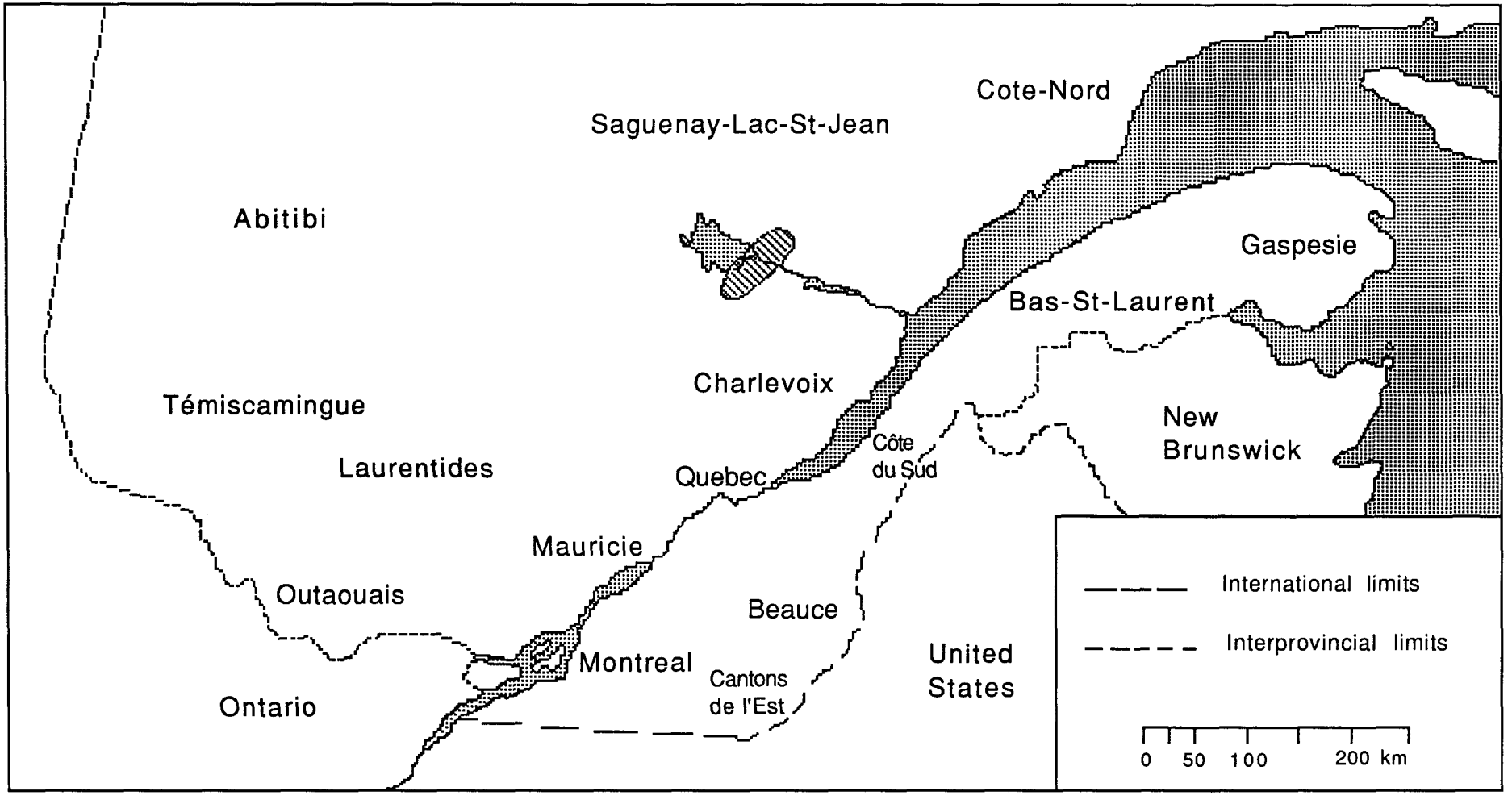
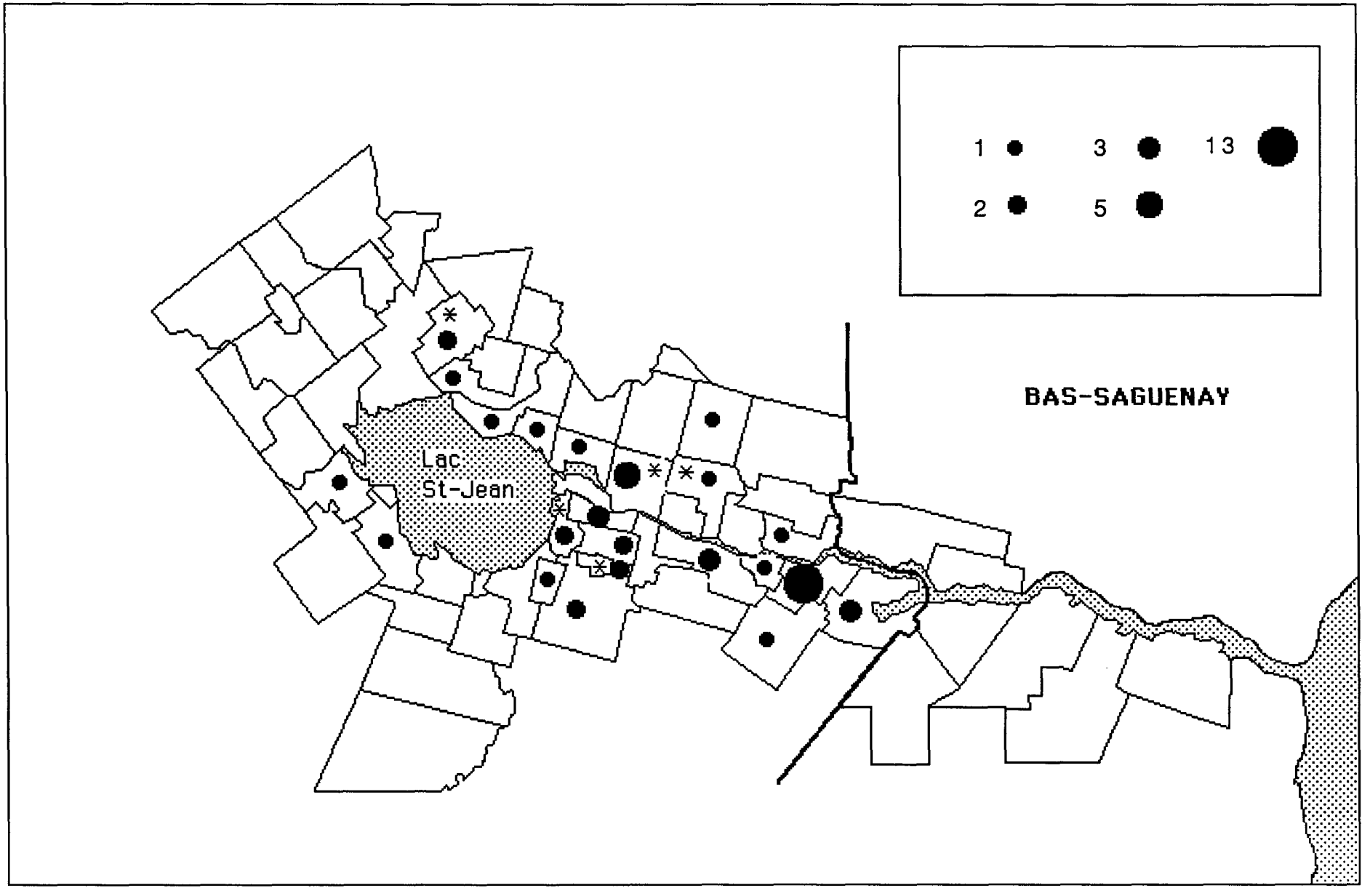

Cote-Nord
Saguenay-Lac-St-Jean
Abitibi
Gaspesie
Bas-St-Laurent
Charlevoix
Témiscamingue
New
Brunswick
Côte
du Sud
Laurentides
Quebec
Mauricie
Outaouais
Beauce
Montreal
Cantons
de l'Est
United
States
Ontario
International limits
Interprovincial limits
0 50 100 200 km

Figure III.2: Spatial distribution of the places of residence of the parents at the time of birth of the obligate carriers of lipoprotein lipase deficiency in Saguenay-Lac-St-Jean.
An * indicates a municipality with a number of places of residence higher than expected ($p<0.05$).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CHAPITRE IV

ÉTUDE SPATIALE ET GÉNÉALOGIQUE DE LA DÉFICIENCE EN LIPOPROTÉINE LIPASE CHEZ LES CANADIENS FRANÇAIS DU QUÉBEC.

(A STUDY OF THE GENEALOGY AND REGIONAL DISTRIBUTION OF LIPOPROTEIN LIPASE DEFICIENCY IN FRENCH-CANADIANS OF QUEBEC).

* Carole Dionne, Claude Gagné, Pierre Julien, M.R.Ven Murthy, Ghyslaine Roederer, Jean Davignon, Marie Lambert, D. Chitayat, R. Ma, H. Henderson, Michael R. Hayden, Paul J. Lupien, Marc De Braekeleer. A STUDY OF THE GENEALOGY AND REGIONAL DISTRIBUTION OF LIPOPROTEIN LIPASE DEFICIENCY IN FRENCH-CANADIANS OF QUEBEC. 1991, pour être soumis à J. MED. GENET.

IV.1 RÉSUMÉ

La déficience en lipoprotéine lipase (LPL) est une maladie autosomale récessive provoquant de l'hyperchylomicronémie qui a une prévalence élevée dans la population canadienne française du Québec. Les bases moléculaires de la déficience en LPL ont été définies et l'on sait que deux mutations, M-188 et M-207, ont une distribution géographique particulière. Ces deux mutations comptent pour 95% des allèles mutants. Le taux de porteurs de la M-188 était le plus élevé dans l'ouest du Québec (1/326) mais celui de la M-207 était beaucoup plus haut dans l'est de la province (1/85). La reconstitution généalogique a montré que ces deux mutations ont été introduites dans la population canadienne française par des immigrants venant de la France au 17è siècle. La mutation M-188 a vraisemblablement une origine écossaise alors que la M-207 semble être d'origine française.

IV.2 ABSTRACT

Lipoprotein lipase (LPL) deficiency, an autosomal recessive disorder causing chylomicronemia, has a high prevalence in the French Canadian population of Quebec. The molecular basis of LPL deficiency has been defined and two major mutations are now shown to have an uneven geographic distribution. Two mutations, one at residue 188 (M-188) and the other at residue 207 (M-207), have now been described and account for 95% of the mutant alleles. The carrier rate of M-188 was highest in western Quebec (1/326), but that of M-207 was much higher in the eastern part of the province (1/85). Genealogical reconstruction has revealed that both mutations were introduced in the French Canadian population by migrants from France in the 17th century. M-188 is likely to have a Scottish ancestor while M-207 appears to be of French origin.

Key words: LPL deficiency - chylomicronemia - French Canadian - population genetics - epidemiology - regional distribution.

IV.3 INTRODUCTION

Familial chylomicronemia due to lipoprotein lipase (LPL) deficiency (type I hyperlipoproteinemia) is an autosomal recessive disorder which has a prevalence estimated at one per million [1]. However, its prevalence is much higher in the French-Canadian population of Quebec, more particularly in the eastern part of the province [2,3]. Indeed, in 1988, the prevalence was calculated to be 1/10,345 in Saguenay-Lac-St-Jean, 1/5,000 in Charlevoix, and 1/52,632 in the Quebec city area [2].

A founder effect was suggested to explain the high prevalence of LPL deficiency in eastern Quebec [2,3]. More recently, as more patients have come to our attention, the prevalence in Saguenay-Lac-St-Jean was recalculated to be 1/8,382, and the carrier rate to be 1/47 inhabitants [Dionne et al, submitted]. Several mutations in the LPL gene have now been identified (reviewed in [4,15]). However, with the exception of the M-188 mutation and a 2kb insertion which have been found in patients of different ethnic origins, most of the mutations were reported in unique families (reviewed in [4,15]).

Recently, we reported the results of a geographical and genealogical study based on 43 type I patients distributed in 29 French Canadian families followed at the Lipid Research Centre of the Centre Hospitalier de l'Université Laval (CHUL) in Ste-Foy [3]. Although the birth places of the obligate carriers were scattered in the province of Quebec, three geographical clusters were identified: the Trois-Rivières-Mauricie region, the Saguenay-Lac-St-Jean and Charlevoix regions, and

the Beauce region. The results also suggested that more than one mutation in the LPL gene introduced by French immigrants in the 17th century were segregating in the French-Canadian population [3]. We now know two separate mutations underlying LPL deficiency in the French Canadian families of Quebec; these are the M-188 [5] and the M-207 [6]. Recently additional type I homozygotes and heterozygotes were identified at different lipid clinics.

The present study was aimed at analyzing the geographical distribution and determining the prevalence of these two mutations in Quebec. The genealogies of the carriers of these mutations were also analyzed to identify the probable founders for each mutant allele.

IV.4 MATERIAL AND METHODS

Eighty four French Canadian patients with type I hyperlipoproteinemia distributed in 60 families have been ascertained in the province of Quebec. Furthermore, 10 of 110 dyslipidemic patients with no known family history of chylomicronemia were found to be heterozygotes for a LPL gene mutation.

Data regarding the patients and their families were obtained from the attending physicians. Most of the patients were followed at the Lipid Research Center of the Centre hospitalier de l'Université Laval (CHUL); the remaining were seen at the Ste-Justine Hospital, the Clinical Research Institute in Montreal and the Montreal Children's Hospital. Detailed clinical data related to this French Canadian population were previously published [2,7].

Blood samples were obtained after a 12-hour fasting period for lipid and lipoprotein analyses and showed the presence of chylomicrons with plasma triglyceride levels above 10 mmoles/L [2]. Diagnosis of familial hyperchylomicronemia was confirmed after determination of plasma LPL activity measured 10 and 20 minutes before and after an I.V. injection of 60 IU/Kg of heparin, as previously described [8].

Birthdates of the affected individuals were extracted from the patients files. All families were contacted and asked to fill a questionnaire regarding their date and place of birth, the date and place of birth of their parents and grandparents as well as the date and place of marriage of their parents and grandparents.

The prevalence of type I hyperlipoproteinemia for each administrative region of Quebec was calculated by dividing the total number of patients in each region by the whole population of that given region. The size of the population for each administrative region in 1985 was obtained from Statistics Quebec. The carrier rate for each region was estimated using Hardy-Weinberg equilibrium calculations.

The genealogies of all the probands were reconstructed using various sources such as computerized population registers, marriage repositories and genealogical dictionaries to an average depth of 12 generations, allowing the recognition of the founders of the French Canadian population in Europe in the 17th century [3,9]. They were then recorded in a computerized genealogical database (BELGE developed at UQAC) and analyzed using various programs, notably PED-BELGE (also developed at UQAC) which, based on an algorithm, determines the closest relationship between individuals at each generation, and identifies the

most likely founders in a set of families with a given disorder [9]. A founder was defined as an individual born outside Quebec (usually in France) who contributed to the genealogy. The methodology of genealogical reconstruction and analysis has been described in full detail elsewhere [3,9].

IV.5 RESULTS

Among the eighty-four type I patients of French Canadian origin who were born and lived in Quebec, 59 (70%) lived in eastern Quebec, which region accounts for 26.3% of the whole population of the province (Table 1). Therefore, the carrier rate of LPL deficiency was estimated to be 1/139 in the whole province but 1/85 in eastern Quebec. The highest carrier rate was found in the administrative region 02 (Saguenay-Lac-St-Jean) with a value of 1/47 (Table 1).

Sixty-eight of the 84 type I patients have now been characterized at the molecular level. Eleven patients were shown to be homozygotes for the M-188 mutation; all of them were born in western Quebec, more particularly in the administrative regions of Montreal and Trois-Rivières (Table 1). Of the 43 type I homozygotes for M-207 mutation, 38 were born in eastern Quebec, including 24 in SLSJ (region 02) (Table 1). Ten type I patients were found to be genetic compounds M-188-207. One patient was shown to carry neither the M-188 mutation nor the M-207 mutation whereas three other patients were found to carry either the M-188 mutation or the M-207 mutation and another still uncharacterized mutation (Table 1). The carrier rate for the M-188 mutation was estimated to be 1/334 in the French Canadian population of Quebec, the highest rate having been found in the Trois-Rivières administrative

region (1/169). The carrier rate for the M-207 mutation was calculated to be 1/211 for the whole province, but 1/67 in the region 02 (SLSJ).

Furthermore, molecular studies done on 110 dyslipidemic patients not closely related to the type I individuals showed three of them to be heterozygotes for the M-188 mutation and seven for the M-207 mutation. Two carriers of the M-188 mutation came from the Trois-Rivières region and one from the Quebec region whereas six of the seven M-207 carriers originated in eastern Quebec.

Figure 1 shows the spatial distribution of the birth places of 126 carriers so far identified. They include 116 obligate carriers ascertained through the birth of a child with LPL deficiency and the 10 carriers found during the screening of dyslipidemic patients. Although 60 type I nuclear families were known, the information regarding the birth places was only available for 116 of the 120 obligate carriers. Indeed, one type I individual was adopted and another was lost to follow-up.

The great majority of carriers of the M-207 mutation were born in eastern Quebec, and more particularly in the regions located north of the St-Lawrence River. Most of the M-188 carriers were born in the Montreal and the Trois-Rivières-Mauricie regions (western Quebec). It should be noted that only two M-207 carriers and no M-188 carriers were born in the eastern part of the province, south of the St-Lawrence river (Côte du Sud, Bas St-Laurent, Gaspésie) (Figure 1). Eighteen carriers for whom no DNA was available were born in the Charlevoix and SLSJ regions (Figure 1). It is most likely that these individuals are also carriers of the M-207 mutation.

Of the 108 heterozygotes who were characterized at the DNA level, five were found not to carry either the M-207 or the M-188 mutation. These five individuals were born in eastern Quebec; therefore, at least a third mutation segregates in eastern Quebec. Of the 26 heterozygotes carriers of the M-188 mutation, genealogical reconstruction was attempted for 22 who provided the necessary family data. However this reconstruction was only completed in 14 cases. Indeed in four families, two from Montreal and two from Trois-Rivières there were too many missing genealogical links to allow the genetic analysis. Close inbreeding was found in three families from the Montreal region; there were two marriages between first-degree cousins and one between second-degree cousins. No close inbreeding was found in the other families in which a patient was a true M-188 homozygote. The genetic analysis allowed the recognition of four founders (two couples) in the 17th century common to all 14 genealogies. There was no ancestor born in Quebec, common to all 14 carriers. All four founders emigrated from France; two of them were of French origin, born in Perche, a 17th century province located in the western part of France while the other two were of unknown origin, possibly of Scottish descent (Figure 2).

The genealogies of 72 of the 77 carriers of the M-207 mutation were successfully completed to an average depth of 12 generations. Close inbreeding was found in two individuals homozygous for the M-207 mutation; it consisted of one marriage between second-degree cousins and one between second-degree cousins once removed. Sixteen founders in the 17th century were found to be common to all 72 genealogies. Again, there was no ancestor born in Quebec common to all 72 carriers. All 16 founders emigrated from France. Ten were born in Perche, two in

Poitou, one in Normandie, one in Aunis whereas the origin of the remaining two founders is not known (Figure 2).

IV.6 DISCUSSION

Our results show that M-188 and M-207 account for 24% (26/108) and 71% (77/108) respectively of mutant LPL alleles in the French-Canadian population. Still 5% (5/108) of the mutant alleles has yet to be characterized. The genetic analysis of the genealogies of the carriers for whom no mutation has been defined show no ancestor to be common to all five. Therefore, it is postulated that at least three and possibly four mutations segregate in this population, as suggested by Ma et al. [6]. Furthermore, one of these carriers is of Amerindian origin although admixture was noted among his ancestors in the 18th century.

The geographical distribution of the birth places of the carriers of both mutations so far identified is highly uneven, with the M-188 being much more prevalent in western Quebec and the M-207 in eastern Quebec. It is doubtful that such a result is the consequence of an ascertainement bias since all the referral lipid centres in the province of Quebec participated in this study.

The carrier rates of the M-188 and M-207 mutations in each administrative region must be considered as minimal values. Indeed, if we take into account the fact that more than 30% of the type I cases are coincidental findings in the clinical and laboratory investigation of various symptoms not related to type I [2], these carrier rates could be at least significantly higher than the present estimates.

Since the administrative regions sometimes include large population sizes and quite different subregions, the calculated carrier rates may not be representative of the real frequencies of these mutations in smaller areas. As an example, 10 type I patients including seven homozygotes for the M-207 mutation are known in Charlevoix, a 30,000 inhabitant region located east of Quebec, on the north shore of the St-Lawrence river and belonging to the Quebec administrative region (region 03) (Figure 1). The carrier rates of LPL deficiency and M-207 in Charlevoix have then been estimated at 1/27 and 1/33 respectively. Moreover, since the three remaining type I patients for whom no DNA is available are most likely to be homozygotes for the M-207 mutation, the carrier rate of this mutation could be as high as 1/24 in this region.

No common ancestor born in Quebec was found in the genealogies of all the M-188 carriers nor those of all the M-207 carriers. This means that both mutations are not indigeneous to the French Canadian population but were introduced in its gene pool by immigrants. From the origins of the French colony to 1763, year of the takeover by the English, approximately 25,000 individuals came mainly from France to Quebec. However, a large number of them did not settle in the colony; it is estimated that only 8,500 persons who migrated mainly from the western provinces of France settled permanently and founded the French Canadian population [11-13]. Because of its relative cultural and linguistic isolation, it is believed that the present French Canadian population is mostly derived from that founding nucleus [13-14].

Four founders common to all the 14 M-188 carriers were identified. Since this mutation appears to be rare in the non French Canadian population, it is probable that this mutation was introduced in

the French Canadian gene pool by one of these four early settlers. Whether this founder was of French or possibly Scottish origin remains unknown. Although all the four founders emigrated from France, M-188 has not been so far reported in France but it has been found in patients of English and Irish descent [5]. Most of the genealogies of modern-day French Canadians from eastern and western Quebec can be traced back to these four founders. In fact, as early as 1730, these founders already had a very large number of descendants. Furthermore, these founders are also recognized as the possible origins for other autosomal recessive disorders common in eastern Quebec [10]. It is also possible that M-188 was introduced by several carriers in the French Canadian gene pool. Since M-188 appears to be a very old mutation carried on the same haplotype regardless of the ancestral origin (English, German, Polish, Indian, etc.) of the patients [5], this question could remain unanswered.

Fourteen of the 16 founders of the M-207, which is on the same DNA haplotype in all the carriers [6], were born in the western provinces of France, including 10 (62.5%) in Perche. Since Perche only contributed 217 of the 8,500 founders (2.6%) of the French Canadian population, it appears to be the likely center of diffusion of M-207 in the French-Canadian population. However, one century after the initial settlement in North America, the founders originating from Perche had a very large number of descendants. Indeed, among the 50 more fertile settler couples, 14 came from Perche [10,13]. As a consequence, founders from Perche are over represented in all the autosomal recessive disorders studied so far (17-43%) [10]. Final confirmation depends on the detection of the M-207 in the French population. Analysis of families from and around Perche will determine whether the M-207 found in the French Canadian population originated from that French region.

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IV.9 TABLE

Table IV.1 : Distribution of the birth places of the type I individuals by genotype and carrier rates by administrative regions of Quebec. Eastern Quebec includes administrative regions 01, 02, 03, and 09.

Administrative regions	Nr of homo 188-188	Nr of homo 207-207	Nr of comp 188-207	Nr of comp 188-?	Nr of comp 207-?	Nr of comp ?-?	Nr of Type I without DNA	Estimated c.r. 188	Estimated c. r. 207	LPL deficiency c.r.
01 Bas St-Laurent Gaspésie	0	0	0	0	0	0	0			
02 Saguenay-Lac-Saint-Jean	0	24	1	0	1	0	9	1/341	1/67	1/47
03 Quebec	0	14	2	1	1	1	3	1/364	1/153	1/110
04 Trois-Rivières	5	1	1	0	0	0	0	1/169	1/292	1/127
05 Estrie	0	0	0	0	0	0	0			
06 Montréal	6	4	5	0	0	0	1	1/356	1/393	1/241
07 Outaouais	0	0	0	0	0	0	0			
08 Abitibi-Témiscamingue	0	0	0	0	0	0	2			1/140
09 Côte-Nord	0	0	1	0	0	0	1	1/202	1/202	1/117
10 Nouveau-Quebec	0	0	0	0	0	0	0			
Eastern Quebec	0	38	4	1	2	1	13	1/359	1/121	1/85
Western Quebec	11	5	6	0	0	0	3	1/326	1/405	1/219
Whole Quebec	11	43	10	1	2	1	16	1/334	1/211	1/139

Nr = number; homo = homozygotes; c.r = carrier rate; comp = compounds

IV.10 FIGURES

Figure IV.1: Spatial distribution of the birthplaces of the lipoprotein lipase deficiency carriers by type of mutation.

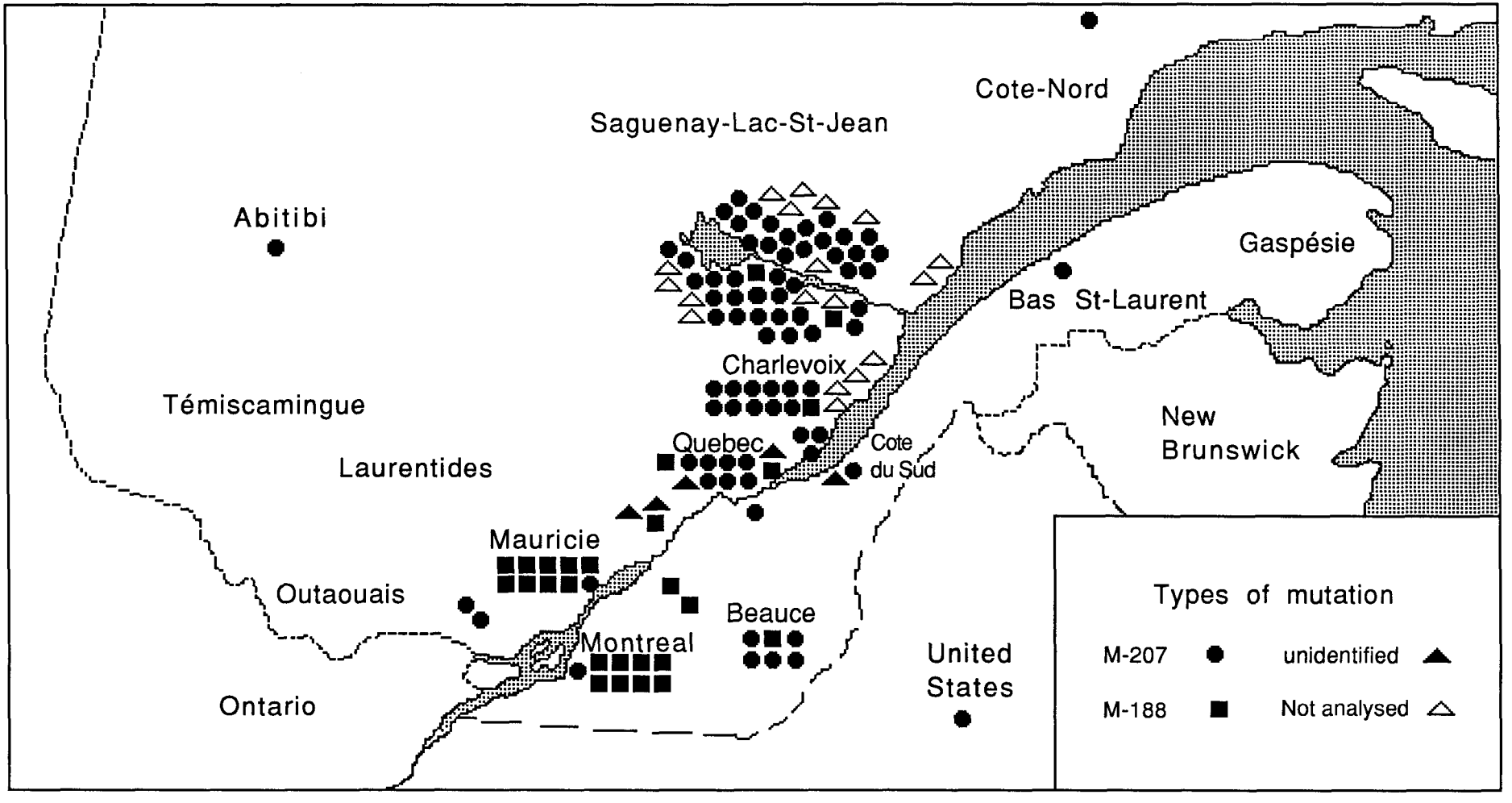
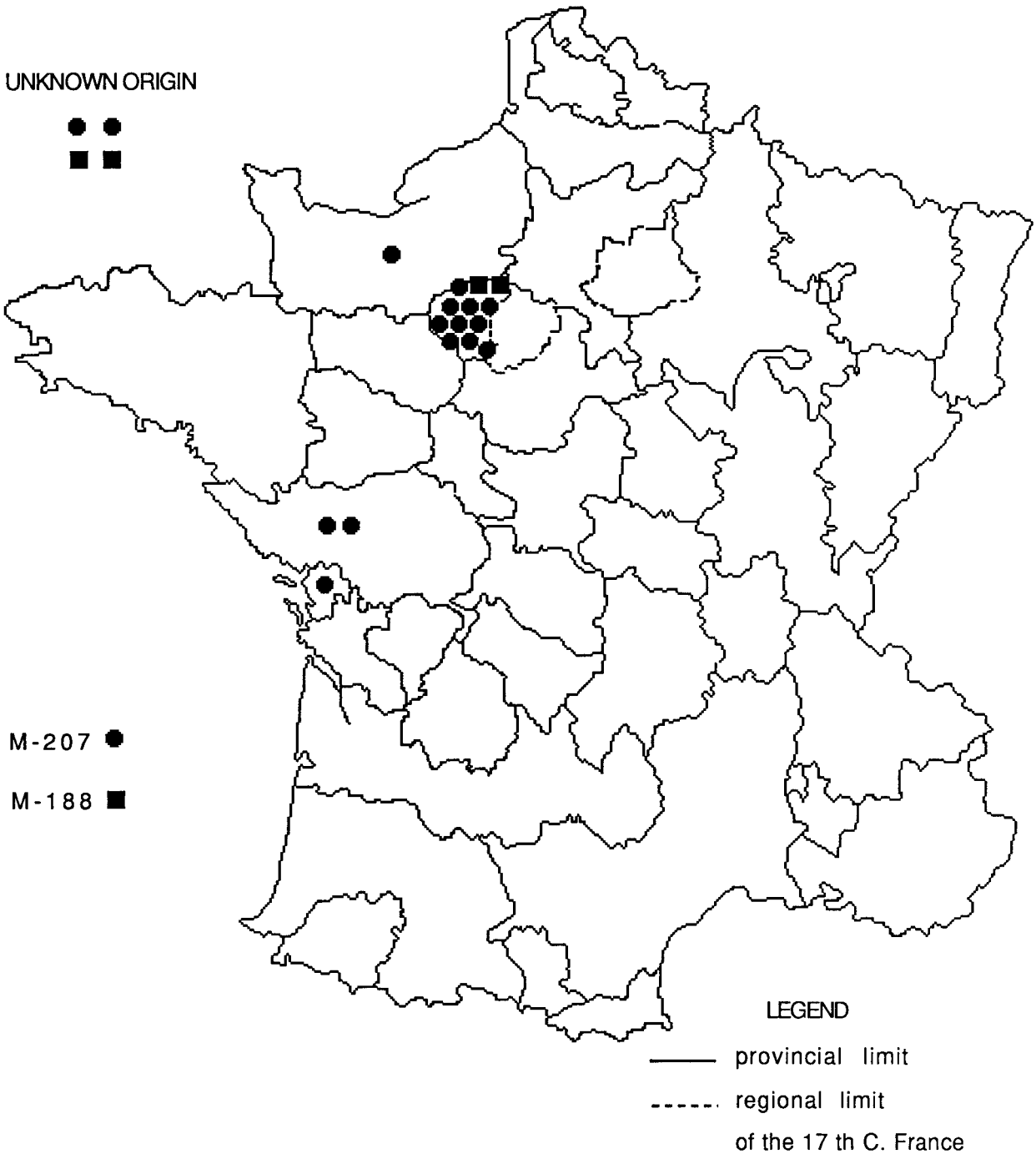

Cote-Nord
Saguenay-Lac-St-Jean
Abitibi
Gaspésie
Bas St-Laurent
Charlevoix
Témiscamingue
New
Brunswick
Quebec
Cote
du Sud
Laurentides
Mauricie
Outaouais
Beauce
Montreal
United
States
Ontario
Types of mutation
M-207
unidentified
M-188
Not analysed

Figure IV.2: Geographical distribution of the places of origin in the 17th century France of the founders of M-207 and M-188.


UNKNOWN ORIGIN
M-207
M-188
LEGEND
provincial limit
regional limit
of the 17 th C. France

CONCLUSION

Cette recherche a permis de confirmer et de développer nos connaissances à propos de l'épidémiologie génétique de la déficience en lipoprotéine lipase au Québec. Ce mémoire a surtout essayé de mieux cerner l'origine de cette maladie autosomale récessive dans la population canadienne française ainsi que sa distribution géographique.

La déficience en lipoprotéine lipase est particulièrement fréquente dans l'est de la province du Québec. Cette prévalence élevée est due à un effet fondateur suivi vraisemblablement d'une dérive génétique. Cette maladie a été introduite dans la population canadienne française par des immigrants venus d'Europe, principalement de France, aux 17è et 18è siècles.

L'étude réalisée au Saguenay-Lac-St-Jean a permis de confirmer cette fréquence élevée du gène. En effet le coefficient moyen de consanguinité n'était que marginalement plus élevé que dans des groupes contrôles alors que le coefficient moyen de parenté était plus élevé. De plus, la probabilité d'avoir un enfant atteint de la déficience en lipoprotéine lipase dans cette région était indépendante de la distance entre les lieux de naissance de ses parents.

Durant le cheminement de ma maîtrise, deux mutations dans le gène de la lipoprotéine lipase comptant pour 95% des allèles mutants ont été identifiées; il s'agit de la M-207 et M-188. La première est principalement rencontrée dans les régions du nord-est du Québec, la prévalence la plus élevée ayant été trouvée dans le comté de Charlevoix. Cette mutation a été amenée au Québec par des immigrants venant du

nord-ouest de la France. La M-188 est plus fréquente dans l'ouest du Québec, notammemt dans la région de Trois-Rivières-Mauricie; elle a également été amenée par des immigrants venus de France mais son origine pourrait être écossaise.

Ce mémoire s'inscrivant dans un effort pluridisciplinaire afin de mieux connaître la problématique de la déficience en lipoprotéine lipase au Québec, plusieurs axes de recherches sont maintenant développés. Il s'agit notamment d'identifier la (les) mutation(s) présente(s) sur les 5% d'allèles mutants restants mais surtout de savoir si le fait d'être porteur d'une mutation dans le gène de la lipoprotéine lipase peut être un facteur de risque de certaines maladies cardio-vasculaires.

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