A Genealogical Study of Essential Hypertension with and without Obesity in French Canadians

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Abstract

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Objectives: To investigate genetic homogeneity in a set of hypertensive families and in subsets chosen for high and low prevalence of obesity; and to compare fasting insulin and lipids, ion transport, and water homeostasis in the obese and lean families.

Research Methods and Procedures: The study was carried out in a relative population isolate of the Saguenay/Lac St. Jean region in Canada. Genetic homogeneity was evaluated with the mean coefficients of kinship (ϕ) and inbreeding (F) computed with ascending genealogies. Serum insulin and lipids were measured after overnight fasting. Total body water was estimated with bioelectrical impedance. Sodium-lithium countertransport and sodium-potassium co-transport were determined in freshly isolated erythrocytes.

Results: F and ϕ were increased in hypertensive families compared with families selected at random. F and ϕ were further increased within the subsets of obese and lean families. In addition, fasting insulin, total body water, sodium-lithium countertransport, and sodium-potassium co-transport were higher in the obese than in the lean families. The two subsets of families did not differ by fasting lipids.

Discussion: In the Saguenay/Lac St. Jean population, the degree of genetic homogeneity was increased in families selected for hypertension, and it was further increased in subsets of hypertensive families with high and low prevalence of obesity. This suggests that hypertension in lean and obese individuals may represent, at least in part, separate genetic entities. Some of the extra genes shared in common within the subsets may contribute to their differences in body weight, insulin sensitivity, ion transport, and water homeostasis.

Key words: obesity-associated hypertension, kinship, inbreeding, ion transport, body water

Introduction

Susceptibility to essential hypertension is in part genetically determined (1). Heritable traits, such as augmented activities of ion transporters (2) and increased amount and central distribution of body fat (3), segregate with elevated blood pressure in families. These traits are believed to be intermediate phenotypes in the chain of pathophysiological events, leading from specific gene mutations to the development of the ultimate phenotype of essential hypertension (4). Different subsets of intermediate phenotypes may be present in individuals affected by the disease, suggesting that essential hypertension is a heterogenous group of disorders that develop due to different subsets of pathophysiological mechanisms. In addition, this phenotypic heterogeneity may be augmented by genetic heterogeneity, in which case the same pathophysiological mechanism may be determined by different genes located on the same or different chromosomes (5).

The heterogeneity of essential hypertension is negatively related to the power to identify its susceptibility genes (5). Thus, in the search for these genes, attempts are made to reduce disease heterogeneity. This can be achieved by either selecting subjects with clinically defined subsets of the

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disease or by drawing these subjects from a genetically isolated population. The basic assumption is that pathophysiological mechanisms contributing to the development of essential hypertension are shared among patients with a clinically defined subset of the disease and that, in genetically isolated populations, fewer genes are involved in the determination of these mechanisms (6).

In this study, we examined genetic hereterogeneity in hypertensive families with high or low prevalence of obesity (obese and lean families, respectively) selected from a geographically remote population of French origin living in the Saguenay/Lac St. Jean (SLSJ) region of the Canadian province of Quebec (7). The degree of genetic heterogeneity was evaluated by the coefficients of kinship and inbreeding computed with the use of ascending genealogies (8,9). We hypothesized that by selecting families with a high prevalence of specific subsets of essential hypertension, such as those with and without obesity, we could detect clusters of hypertensive families related to common ancestors characterized by increased kinship and inbreeding. This finding would attest to a greater share of common genes and thus, to greater genetic homogeneity existing within the clusters (10).

The genetic component of hypertension in obese and lean families was also evaluated with the sibling risk ratio (λ_S). λ_S of hypertension is defined as the ratio of the prevalence of hypertension in sibships to the prevalence of hypertension in the general population (6). λ_S provides an estimate of the strength of an underlying gene effect and the ease to detect it. $\lambda_S > 2$ is believed to indicate a significant genetic component (6).

The prevalence of obesity was chosen as a criterion to select the two subsets of hypertensive families for the following reasons. First, obesity is the leading risk factor for the development of essential hypertension (11). Second, hypertension in obese and non-obese individuals differs by several clinical features and hence, possibly also by a part of the pathophysiological mechanisms and genes involved in its pathogenesis. Thus, it has been shown that obese compared with non-obese hypertensive individuals exhibit higher renal sodium reabsorption, and perhaps in association with this functional change, higher total body water (TBW), plasma volume, and intracellular body water (11–13). They also demonstrate increased activity of specific sodium transporters (14,15). The activity of some of these transporters has been related to insulin or insulin resistance and the lipid effect on cell membranes (16).

Several lines of evidence suggest that some genetic determinants of obesity-associated hypertension may be specific to this form of the disease. Thus, significant familial cross-trait correlations between diastolic blood pressure and measures of upper-body obesity indicate that genes involved in the regulation of upper-body adiposity may also be involved in the control of blood pressure (17). Consistent with these findings, obesity has been associated with an augmented adipose-tissue expression of peptides that have been demonstrated to play a role in the regulation of both adiposity and blood pressure (18–20). Genes encoding such peptides as well as genes encoding peptides involved in their obesity-related regulatory pathways are believed to be the prime candidate genes of obesity-associated hypertension.

In this study, we compared fasting serum levels of insulin and lipids, TBW, sodium-lithium countertransport (Na^+/Li^+ CNT), and sodium-potassium co-transport (Na^+/K^+ CT) in obese and non-obese hypertensive individuals originating from obese and lean hypertensive families, respectively.

Research Methods and Procedures

The institutional ethics committee reviewed and approved this study. All subjects gave their informed consent. The families analyzed were selected from the geographically remote population living in the SLSJ region of Quebec (7). The initial habitation of this region occurred from 1838 to 1911, during which ~75% of 28,656 settlers came from the neighboring Charlevoix region (21). The settling of the Charlevoix region itself started in 1675. From 1675 to 1850, 599 founders of mostly French descent moved to this region from the Quebec City area (22). There has been relatively little migration into the SLSJ region since 1870, and the population has grown from 5200 in 1852 to 285,000 at present (23). The prevalence of several recessive disorders, including cystic fibrosis, tyrosinemia type I, and vitamin D-dependent rickets, is higher in SLSJ than in other populations (24). Because of the founder effect, limited allelic diversity exists among patients with these disorders. For example, a single homozygous mutation was identified in 80% of patients with hereditary tyrosinemia type I (25), and only three mutations were found in 94% of patients with cystic fibrosis (26).

The hypertensive families investigated here were selected on the basis of having at least two siblings presenting with early-onset (≤55 years) hypertension and dyslipidemia and without secondary hypertension, body mass index (BMI) >35 kg/m^2, diabetes mellitus, serum creatinine >180 mM, liver disease, malignancy, pregnancy, and substance abuse. Hypertension was defined as diastolic blood pressure >90 mm Hg on two occasions or currently taking antihypertensive medication with documented hypertension. In individuals older than 55 years, the onset of hypertension was determined from medical records. Dyslipidemia was defined as total cholesterol ≥5.2 mM, high-density lipoprotein cholesterol ≤0.9 mM, or currently taking lipid-lowering medication with documented dyslipidemia in the medical records. Dyslipidemia was added as a selection criterion to increase the clinical homogeneity of hypertension in the

selected families. When at least two siblings in a family satisfied all the above selection criteria, other siblings, not necessarily hypertensive, were also enrolled in the study. To ensure genetic homogeneity, only families with both parents of Catholic, French Canadian origin born in the SLSJ region were studied. Using these selection criteria, we collected 55 families with an average sibship size of 5.5 ± 2.6 siblings. From these families, clinically defined subsets of obese ($n = 15$) and lean ($n = 9$) families were selected on the basis of having either high (≥70%) or low (≤30%) prevalence of obesity (BMI ≥ 27 kg/m^2) among siblings within the family. For obese and lean families, the average sibship size was 5.2 ± 0.9 and 5.7 ± 0.9 siblings, respectively.

The genetic component of hypertension was evaluated with the λ_S, which is a ratio of the prevalence of hypertension in sibships to the prevalence of the disease in the general population (6). In this study, λ_S was determined for the entire set of 55 hypertensive families and for its subsets of 15 obese and 9 lean families. The following estimates were used in these calculations. The prevalence of hypertension in the SLSJ population is 19.2% (Cardiovascular Survey, Lac St. Jean-Chibougamau). The prevalence of obesity (BMI ≥ 27 kg/m^2) among Canadian men and women affected by hypertension is 52% and 49%, respectively (27).

In each study subject, a blood sample was drawn after overnight fasting to determine the plasma levels of glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Na^+/Li^+ CNT and Na^+/K^+ CT activities were measured in freshly isolated erythrocytes as described previously (28). The volume of TBW was measured by bioelectrical impedance analysis according to the manufacturer's instructions (RJL Systems, Inc., Clinton Township, MI). Before comparing the above variables in obese and lean families, they were adjusted for significant covariates, such as age, gender, and height, with linear regression.

The degree of genetic homogeneity was evaluated by coefficients of inbreeding (F) (8) and kinship (ϕ) (9), which were computed with ascending genealogies, as described previously (29,30). F is equal to the probability that the two genes an individual has at a given locus are identical by descent. ϕ is the probability that a gene taken at random from one individual is identical by common descent with a gene taken at the same locus from another individual. ϕ and F were determined using both ascending genealogies for 4 generations, with the 4th generation corresponding approximately to the generation that founded the colony in the SLSJ region, and 10 generations, with the 10th generation corresponding approximately to the generation that founded the population in the Charlevoix region. The number of generations was estimated on the basis of previous studies, suggesting that, on average, one generation in this population spans 30 years (31). Intergroup comparisons of F were carried out with Fisher's exact and Wilcoxon tests (32). The comparisons of ϕ were performed with a permutation test. Five thousand permutations under the null hypothesis were carried out (33). The groups were compared pair-wise.

Ascending genealogies were reconstructed with the BALSAC population register and the RETRO database. The BALSAC population register was constructed by linking the parish records of baptisms, marriages and deaths in the SLSJ region from 1840 to 1971 (34,35). The register now has been extended to the entire Province of Quebec (36). The RETRO database, a peripheral database of the BALSAC population register (37), contains information of ~137,000 marriages going back as far as the 16th century.

In addition to 55 families drawn for the presence of familial hypertension and dyslipidemia, F and ϕ were also computed in 100 control families that were selected randomly from families of 160,000 individuals born in the SLSJ region between 1950 and 1971 (mean year of birth, 1959). They were selected to represent the entire population of the SLSJ region (38). Any of the control families could be classified as hypertensive according to our selection criteria, because no clinical investigations have been carried out in these families and the prevalence of hypertension in the SLSJ population is 19.2% (Cardiovascular Survey, Lac St. Jean-Chibougamau).

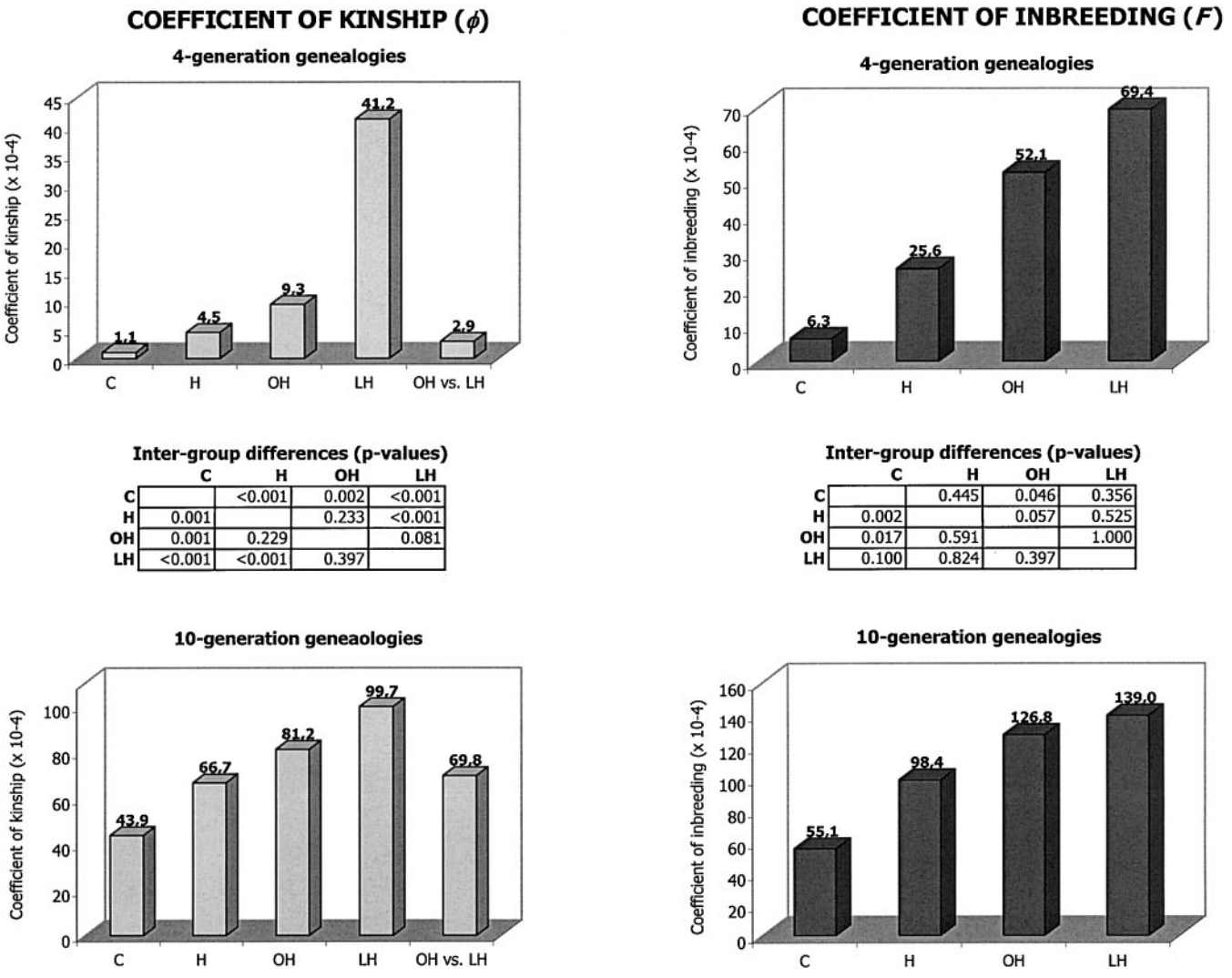
Results

Clinical Characteristics of 55 Hypertensive Families

Fifty-five hypertensive families comprising 225 hypertensive siblings (106 men and 119 women) were included in this study. On average, these individuals were 53.8 ± 7.4 years old and moderately overweight (BMI = 28.36 ± 0.30 kg/m^2). Their mean fasting triglycerides were within the normal range (2.32 ± 0.12 mM), whereas their average total cholesterol was borderline high (5.54 ± 0.07 mM). Fasting insulin, volume of TBW, Na^+/Li^+ CNT, and Na^+/K^+ CT activities were 120.3 ± 7.1 U/L, 35.0 ± 0.96 L, 384.3 ± 22.6 μM cells/h, and 278.8 ± 20.1 μM cells/h, respectively.

Analysis of Kinship and Inbreeding of Hypertensive and Control Families

Using ascending genealogies for 4 generations, both ϕ and F were approximately four times higher in the set of 55 hypertensive families than in the 100 control families (Figure 1). This difference was statistically significant for ϕ ($p < 0.001$) but not for F ($p = 0.455$; Figure 1). F and ϕ calculated with ascending genealogies for 10 generations were also higher in hypertensive than in control families (Figure 1). Although the differences were smaller in absolute values, they both reached a significant level ($p = 0.001$ for ϕ and $p = 0.002$ for F; Figure 1). These results suggest that the degree of kinship and the share of common genes



Inter-group differences (p-values)

	C	H	OH	LH
C		<0.001	0.002	<0.001
H	0.001		0.233	<0.001
OH	0.001	0.229		0.081
LH	<0.001	<0.001	0.397	

Inter-group differences (p-values)

	C	H	OH	LH
C		0.445	0.046	0.356
H	0.002		0.057	0.525
OH	0.017	0.591		1.000
LH	0.100	0.824	0.397	

Figure 1: Mean coefficient of kinship (ϕ, left panel) and inbreeding (F, right panel). Coefficients were computed using ascending genealogies for 4 and 10 generations, with the fourth generation being the one that founded the Saguenay/Lac St. Jean population, and with the 10th generation being the one that initially settled in the Charlevoix region. The coefficients were calculated for the groups of 100 control (C) and 55 hypertensive (H) families, as well as for the subsets of obese hypertensive (OH, $n = 15$) and lean hypertensive (LH, $n = 9$) families. ϕ was also calculated between the groups of OH and LH families (OH vs. LH). The statistical significance of the inter-group differences is shown in the tables between the figures. The p values for the computations including 4-generation genealogies appear in the upper matrix, and the p values for the computations including 10-generation genealogies are found in the lower matrix.

are greater among families selected for essential hypertension than among families selected at random.

Sibling Risk of Hypertension in All Hypertensive Families

When all 55 hypertensive families were analyzed, λ_S was estimated to be 3.89. This estimate was derived from the prevalence of hypertension in the sibships (74.75%) and from the prevalence of the disease in the SLSJ population (19.20%). λ_S 3.89 indicates an important role of genes in the development of hypertension in the examined set of families.

Clinical Characteristics of Obese and Lean Hypertensive Families

From the total of 55 hypertensive families, 15 obese and 9 lean families were identified. Obese hypertensive siblings from the obese families ($n = 60$) did not differ by gender, age, fasting lipids, and the percentage of individuals using blood pressure-lowering and lipid-lowering medications from non-obese hypertensive siblings ($n = 31$) originating from the lean families (Table 1). In contrast, the two groups of individuals differed by BMI (as expected), fasting insulin, volume of TBW, Na^+/Li^+CNT and Na^+/K^+CT. For all these variables, mean values were significantly greater in

Table 1. Characterization of obese and non-obese hypertensive individuals from obese and lean families, respectively

	Obese families		Lean families		*p* value
	%	*n*	%	*n*	χ^2 test
Men	48	60	32	31	NS
BP-lowering medication*	78	60	87	31	NS
Diuretics	27	60	26	31	NS
Lipid-lowering medication	42	60	29	31	NS
	Mean ± SEM	*n*	**Mean ± SEM**	*n*	*t* test
Age (years)	53.67 ± 0.85	60	53.80 ± 1.40	31	NS
BMI (kg/m^2)	31.75 ± 0.51	60	23.58 ± 0.42	31	2×10^{-21}
Cholesterol (mM)	5.62 ± 0.15	59	5.39 ± 0.20	29	NS
Triglycerides (mM)	2.38 ± 0.17	59	2.01 ± 0.26	29	NS
Insulin (U/L)	131.80 ± 8.53	48	86.19 ± 5.49	26	0.00003
Volume of TBW (L)	36.62 ± 0.50	53	30.22 ± 0.43	18	9×10^{-14}
Na^+/Li^+ CNT (μM/hour)	428.56 ± 24.61	31	292.65 ± 26.47	15	0.0006
Na^+/K^+ CT (μM/hour)	318.77 ± 23.88	33	219.53 ± 22.89	15	0.004

The variables included in the table are adjusted for significant covariates, such as age and gender. Volume of TBW is also adjusted for the significant effect of height.

BP, blood pressure; BMI, body mass index; TBW, total body water; Na^+/Li^+ CNT, sodium-lithium countertransport; Na^+/K^+ CT, sodium-potassium cotransport; NS, not significant.

* BP-lowering medication other than diuretics.

siblings from obese families than in siblings from lean families (Table 1). Furthermore, in the obese families, significant positive correlations were observed between volume of TBW and both Na^+/Li^+CNT and Na^+/K^+CT ($r = 0.57$, $p = 0.001$ and $r = 0.43$, $p = 0.02$, respectively). In contrast, these correlations were not significant in the lean families.

Analysis of Kinship and Inbreeding of Obese and Lean Hypertensive Families

Analysis of ascending genealogies for four generations showed that, compared with the whole set of 55 hypertensive families, ϕ was two times higher in the subset of 15 obese families ($p = 0.233$), and nine times higher in the subset of nine lean families ($p < 0.001$; Figure 1). Compared with the 100 control families, the differences were even greater. In the obese families, ϕ was increased eight times ($p = 0.002$), and in the lean families, it was increased 37 times ($p < 0.001$; Figure 1). A similar pattern was also observed for F, but the differences for the subset of lean families were less pronounced, and the only significant difference was between control and obese families ($p = 0.046$; Figure 1). This was mainly due to the fact that the subset of lean families included two families related at the level of first cousins and that this relationship is reflected only in ϕ but not in F. In addition, the data showed that ϕ computed between the subsets of lean and obese families was lower than that within the subsets (Figure 1). Analysis of ascending genealogies for 10 generations demonstrated similar results, but the differences were not as prominent (Figure 1). These data suggest that the degree of gene sharing, and hence genetic homogeneity, is increased in clinically defined subsets of hypertensive families with high and low prevalences of obesity. This finding, together with the observation that the level of kinship between the two clinically defined subsets of hypertensive families is lower than that within the subsets, indicates that essential hypertension with and without obesity may represent, at least in part, separate genetic entities.

Sibling Risk of Hypertension in Obese and Lean Hypertensive Families

In the subset of 15 obese families, λ_S of obesity-associated hypertension was estimated to be 8.66. This estimate was derived from the prevalence of obesity-associated hypertension in obese hypertensive families (83.11%) and from the prevalence of obesity-associated hypertension in the general population (9.60%). In the subset of nine lean families, λ_S of hypertension without obesity was estimated to be 6.25. This estimate was derived from the prevalence of

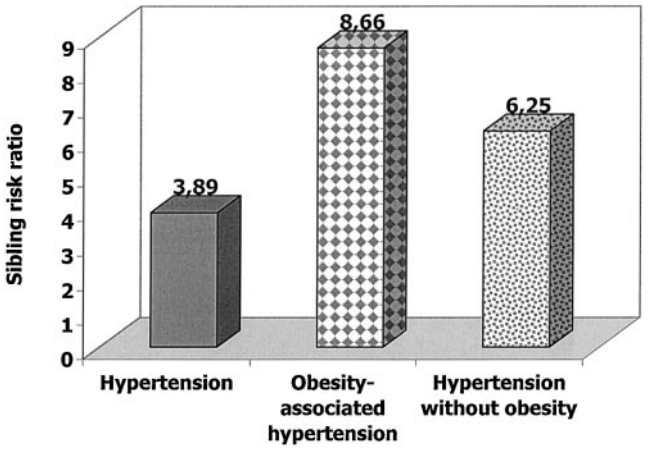


Figure 2: Sibling risk ratio (λ_S) of hypertension computed in all 55 hypertensive families, λ_S of obesity-associated hypertension calculated in 15 obese hypertensive families, and λ_S of hypertension without obesity computed in 9 lean hypertensive families.

hypertension without obesity in lean hypertensive families (60.00%) and from the prevalence of hypertension without obesity in the general population (9.60%). These results demonstrate that by selecting clinically defined subsets of hypertension, the strength of the genetic component of the disease and, thus, the probability of identifying its genes increases (Figure 2).

Discussion

The results of kinship and inbreeding analysis demonstrate that, in the French Canadian population of the SLSJ region, the degree of relatedness, and hence, the share of common genes, are increased among families selected for essential hypertension compared with families selected at random. This suggests that at least some of the extra genes shared in common by the hypertensive families may be involved in the pathogenesis of essential hypertension. Moreover, the data demonstrate that the degree of relatedness is further increased within but not between subsets of hypertensive families with high and low prevalence of obesity, indicating that hypertension with and without obesity may represent, at least in part, separate genetic entities. Analyses of kinship and inbreeding have been used previously to study both Mendelian and complex genetic traits. Thus, for example, it has been demonstrated, in the population we investigated here, that F and ϕ are higher in cystic fibrosis transmembrane conductance regulator mutation groups than in the general population (39). In the same population, it has also been shown that cases with a specific subset of late-onset Alzheimer's disease are more inbred than controls and that they are more closely related among themselves than to the controls. From this, the authors concluded that a recessive genetic element might be implicated in the pathogenesis of this form of Alzheimer's disease in the SLSJ region (40).

The investigations of λ_S carried out in this study indicate that genes play an important role in the development of hypertension in the examined set of families. They also indicate that the strength of the genetic component increases by selecting families with clinically defined subsets of hypertension. These epidemiological data are consistent with our results of the analyses of ascending genealogies.

This study indicates that subsets of hypertension with and without obesity may be separate genetic entities. This, in turn, suggests that at least part of the pathophysiological mechanisms and genes involved in the development of hypertension may be different in obese and non-obese individuals. In this study, hypertensive individuals from obese and lean families, respectively, differed in the amount of TBW and the activity of ion transporters. More specifically, the former demonstrated higher volumes of TBW, Na^+/Li^+CNT, and Na^+/K^+CT. These findings are consistent with previous investigations of obese and lean hypertensive individuals, demonstrating that the obese hypertensives have increased TBW, plasma volume, and intracellular water (12,13). They are also consistent with studies showing that Na^+/Li^+CNT is positively related to obesity (14). In addition, both Na^+/Li^+CNT and Na^+/K^+CT are considered to be predictors of hypertension (41), but it was demonstrated that the relationship between Na^+/Li^+CNT and blood pressure diminishes when adjusted for BMI (15). Consistent with these findings, in this study, Na^+/Li^+CNT was increased in obese, hypertensive individuals originating from obese families, whereas in non-obese hypertensive individuals from lean families, it was within the normal range (42).

Hypertension in obese compared with non-obese individuals is associated with increased renal sodium and water reabsorption (43). It has been suggested that an altered sodium transporter may be related to the difference (44). Supporting this possibility, although indirectly, a significant positive correlation between the amount of TBW and both Na^+/Li^+CNT and Na^+/K^+CT was observed in obese hypertensive families in this study.

The genetic basis of hypertension with and without obesity has been studied previously. In case of obesity-associated hypertension, it has been suggested that the disease may be determined, at least in part, by genes involved in the regulation of both adiposity and blood pressure. Thus, in families of French-Canadian origin not selected for a morbid condition, significant cross-trait correlations, indicating shared heritable factors, were observed between diastolic blood pressure and measures of upper body obesity (17). In another investigation, also involving French-Canadian families, in this case selected for the presence of familial dyslipidemic hypertension, siblings with and without hypertension originating from the same families differed in that the hypertensive siblings were more obese and their body fat was more centrally distributed. Familial correlations

suggested that this difference may be determined by genetic factors co-segregating with hypertension (3). In addition, candidate gene studies showed a genetic association or linkage with obesity-associated hypertension. These include investigations of tumor necrosis factor α (45), β3-adrenergic receptor (46,47), and G-protein β3 subunit (48) gene loci. The genetic basis of essential hypertension occurring in lean individuals also has been investigated. The HYPERGENE studies have implicated the angiotensinogen gene in the development of hypertension in individuals with BMI <27 kg/m^2 (49,50).

In summary, the results of this study suggest that, in a geographically remote population of French Canadian origin, the degree of genetic homogeneity increases with selecting clinically defined subsets of essential hypertension with and without obesity. They also indicate that at least some of the extra genes shared within these subsets may be involved in the determination of their differences in adiposity, water homeostasis, and the activities of ion transporters.

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References

1. **Pausova Z, Tremblay J, Hamet P.** Gene-environment interactions in hypertension. *Curr Hypertens Rep.* 1999;1:42–50.
2. **Williams RR, Hasstedt SJ, Hunt SC, et al.** Genetic traits related to hypertension and electrolyte metabolism. *Hypertension.* 1991;17(Suppl 1):I69–I73.
3. **Pausova Z, Gossard F, Gaudet D, et al.** Heritability estimates of obesity measures in siblings with and without hypertension. *Hypertension.* 2001;38:41–7.
4. **Williams GH, Hollenberg NK, Hopkins PM, Jeunemaitre X.** The role of intermediate phenotypes in essential hypertension: non-modulation as a model. *Endocr Res.* 1996;22:675–80.
5. **Schork NJ, Cardon LR, Xu X.** The future of genetic epidemiology. *Trends Genet.* 1998;14:266–72.
6. **Dracopoli NC, Haines LH, Korf BR, et al.** Overview of linkage analysis in complex traits. In: Dracopoli NC, Haines LH, Korf BR, et al., eds. *Current Protocols in Human Genetics*. New York, NY: John Wiley & Sons, Inc.; 1996, pp. 1.9.1–1.9.19.
7. **Gradie MI, Jorde LB, Bouchard G.** Genetic structure of the Saguenay, 1852–1911: evidence from migration and isonymy matrices. *Am J Phys Anthropol.* 1988;77:321–33.
8. **Wright S.** Coefficients of inbreeding and relationship. *Am Naturalist.* 1922;56:330–8.
9. **Malecot G.** *Les Mathematiques de l'hérédite.* Paris, France: Masson; 1948.
10. **Vogel F, Motulsky AG.** Consanguineous matings. In: Vogel F, Motulsky AG, eds. *Human Genetics: Problems and Approaches*. New York, NY: Springer-Verlag; 1979, pp. 414–23.
11. **Hall JE, Brands MW, Henegar JR.** Mechanisms of hypertension and kidney disease in obesity. *Ann N Y Acad Sci.* 1999;892:91–107.
12. **Raison J, Achimastos A, Bouthier J, London G, Safar M.** Intravascular volume, extracellular fluid volume, and total body water in obese and nonobese hypertensive patients. *Am J Cardiol.* 1983;51:165–70.
13. **Reisin E, Messerli FH, Ventura HO, Frohlich ED.** Renal haemodynamic studies in obesity hypertension. *J Hypertens.* 1987;5:397–400.
14. **Turner ST, Rebbeck TR, Sing CF.** Sodium-lithium countertransport and probability of hypertension in Caucasians 47 to 89 years old. *Hypertension.* 1992;20:841–50.
15. **Trevisan M, Strazzullo P, Cappuccio FP, et al.** Sodium-lithium countertransport and body fat distribution. *Life Sci.* 1992;51:687–93.
16. **West IC, Rutherford PA, Thomas TH.** Sodium-lithium countertransport: physiology and function. *J Hypertens.* 1998; 16:3–13.
17. **Rice T, Province M, Pérusse L, Bouchard C, Rao DC.** Cross-trait familial resemblance for body fat and blood pressure: familial correlations in the Québec family study. *Am J Hum Genet.* 1994;55:1019–29.
18. **Frederich RC Jr, Kahn BB, Peach MJ, Flier JS.** Tissue-specific nutritional regulation of angiotensinogen in adipose tissue. *Hypertension.* 1992;19:339–44.
19. **Engeli S, Negrel R, Sharma AM.** Physiology and pathophysiology of the adipose tissue renin-angiotensin system. *Hypertension.* 2000;35:1270–7.
20. **Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI.** Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest.* 1997;100:270–8.
21. **Gavreau D, Bourque M.** Mouvements migratoires et familles: le peuplement du Saguenay avant 1911. *Rev Hist Am Fr.* 1988;42:167–92.
22. **Jette R, Gauvreau D, Guerin M.** Aux origines d'une région: le peuplement fondateur de Charlevoix avant 1850. In: Bouchard G, De Braekeleer M, eds. *Histoire d'un Génome*. Québec, Canada: Presses de l'Université du Québec; 1991, pp. 75–106.
23. **Roy R, Bouchard G, Declos M.** La première génération de Saguenayens. In: Bouchard G, De Braekeleer M, eds. *Histoire d'un Génome*. Québec, Canada: Presses de l'Université du Québec; 1991, pp. 164–86.
24. **De Braekeleer M.** Hereditary disorders in Saguenay-Lac-St-Jean (Quebec, Canada). *Hum Hered.* 1991;41:141–6.
25. **Grompe M, St-Louis M, Demers S, Al-Dhalimy M, Leclerc B, Tanguay R.** A single mutation of the fumarylacetoacetate hydrolase gene in French Canadians with hereditary tyrosinemia type I. *N Engl J Med.* 1994;331:353–7.
26. **De Braekeleer M, Mari C, Verlingue C, et al.** Complete identification of cystic fibrosis transmembrane conductance regulator mutations in the CF population of Saguenay-Lac-Saint-Jean (Quebec, Canada). *Clin Genet.* 1998;53:44–6.
27. **Orlov SN, Pausova Z, Gossard F, et al.** Sibling resemblance of erythrocyte ion transporters in French-Canadian sibling-pairs affected with essential hypertension. *J Hypertens.* 2001; 17:1859–65.

28. **Tremblay M, Jomphe M, Vezina H .** Comparaison de structures patronymiques et génétiques dans la population québécoise: dans le patronyme. In: *Historie, Anthropologie at Société*. Paris, France: CNRS-Éditions; 2001, pp. 367–389.
29. **Couture P, Bovill EG, Demers C, et al.** Evidence of a founder effect for the protein C gene 3363 inserted C mutation in thrombophilic pedigrees of French origin. *Thromb Haemost.* 2001;86:1000–6.
30. **Tremblay M, Vezina H.** New estimates of intergenerational time intervals for the calculation of age and origin of mutations. *Am J Hum Genet.* 2000;66:651–8.
31. **Joffres MR, Hamet P, Rabkin SW, Gelskey D, Hogan K, Fodor G.** Prevalence, control and awareness of high blood pressure among Canadian adults. Canadian Heart Health Surveys Research Group. *CMAJ.* 1992;146:1997–2005.
32. **Daniel WW.** *Biostatistics: A Foundation for the Analysis in the Health Sciences*. New York, NY: Wiley and Sons; 1999, p. 755.
33. **Randles RH, Wolfe DA.** *Introduction to the Theory of Nonparametric Statistics*. Malabar FL: R.E. Krieger; 1991, p. 450.
34. **Bouchard G.** Current issues and new prospects for computerized record linkage in the province of Quebec. *Historical Methods.* 1992;25:67–73.
35. **Bouchard G, Roy R, Casgrain B, Hubert M.** Computer in human sciences: from family reconstitution to population reconstruction. In: Nissan E, Schmidt KM. eds. *From Information to Knowledge: Conceptual and Content Analysis by Computer*. Oxford, UK: Intellect; 1995, pp. 201–27.
36. **Bouchard G.** *Rapport Annuel du Project BALSAC 1999–2000.* Chicoutimi, Canada: Project BALSAC/IREP; 2000.
37. **Jomphe M, Casgrain B.** Base de données généalogiques RETRO: structure de données. In: *Project BALSAC/IREP, Document I-C-181*. Chicoutimi, Canada, Project BALSAC/IREP; 2000, p. 22.
38. **Heyer E, Tremblay M.** Variability of the genetic contribution of Quebec population founders associated with some deleterious genes. *Am J Hum Genet.* 1995;56:970–8.
39. **De Braekeleer M, Daigneault J, Allard C, Simard F, Aubin G.** Genealogy and geographical distribution of CFTR mutations in Saguenay Lac-Saint-Jean (Quebec, Canada). *Ann Hum Biol.* 1996;23:345–52.
40. **Vezina H, Heyer E, Fortier I, Oullette G, Robitaille Y, Gauvreau D.** A genealogical study of Alzheimer disease in the Saguenay region of Quebec. *Genet Epidemiol.* 1999;16:412–25.
41. **Turner ST, Sing CF.** Erythrocyte sodium transport and the probability of having hypertension. *J Hypertens.* 1996;14:829–37.
42. **Canessa ML, Adragna N, Solomon HS, Connolly TM, Tosteson DC.** Increased sodium-lithium counter-transport in red cells of patients with essential hypertension. *N Engl J Med.* 1980;302:772–6.
43. **Kikuchi K, Iimura O, Yamaji I, et al.** The pathophysiological role of water-sodium balance and renal dopaminergic activity in overweight patients with essential hypertension. *Am J Hypertens.* 1988;1:31–7.
44. **Hardman TC, Lant AF.** Controversies surrounding erythrocyte sodium-lithium countertransport. *J Hypertens.* 1996;14:695–703.
45. **Pausova Z, Deslauriers B, Gaudet D, et al.** Role of tumor necrosis factor-α gene locus in obesity and obesity-associated hypertension in French Canadians. *Hypertension.* 2000;36:14–9.
46. **Stunkard AJ, Sorensen TIA, Hanis C, et al.** An adoption study of human obesity. *N Engl J Med.* 1986;314:193–8.
47. **Strazzullo P, Iacone R, Siani A, et al.** Relationship of the Trp64Arg polymorphism of the β3-adrenoreceptor gene to central adiposity and high blood pressure. *J Hypertens.* 2001;19:399–406.
48. **Siffert W, Naber C, Walla M, Ritz E.** G-protein β3 subunit 825T allele and its potential association with obesity in hypertensive individuals. *J Hypertens.* 1999;17:1095–8.
49. **Jeunemaitre X, Soubrier F, Kotelevtsev Y, et al.** Molecular basis of human hypertension: role of angiotensinogen. *Cell.* 1992;71:169–78.
50. **Jeunemaitre X, Inoue I, Williams C, et al.** Haplotypes of angiotensinogen in essential hypertension. *Am J Hum Genet.* 1997;60:1448–60.