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Common Genomic Variation in *LMNA* Modulates Indexes of Obesity in Inuit*

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ABSTRACT

We discovered that rare mutations in *LMNA*, which encodes lamins A and C, underlie autosomal dominant Dunnigan-type familial partial lipodystrophy. Because familial partial lipodystrophy is an extreme example of genetically disturbed adipocyte differentiation, it is possible that common variation in *LMNA* is associated with obesity-related phenotypes. We subsequently discovered a common single nucleotide polymorphism (SNP) in *LMNA*, namely 1908C/T, which was associated with obesity-related traits in Canadian Oji-Cree. We now report association of this *LMNA* SNP with anthropometric indexes in 186 nondiabetic Canadian Inuit. We found that physical indexes of obesity, such as body mass index, waist circumference, waist to hip circumference ratio, subscapular skinfold thickness, and subscapular to triceps skinfold thickness ratio were each significantly higher among Inuit subjects with the *LMNA* 1908T allele than in subjects with the 1908C/1908C genotype. For each significantly associated obesity-related trait, the *LMNA* 1908C/T SNP genotype accounted for between approximately 10–100% of the attributable variation. The results indicate that common genetic variation in *LMNA* is an important determinant of obesity-related quantitative traits. (*J Clin Endocrinol Metab* **86:** 2747–2751, 2001)

AMONG THE INUIT (Eskimos) of Canada, obesity is now as prevalent as it is in the general North American population (1, 2). This new development probably reflects recent, rapid changes in physical activity, diet, and lifestyle (1, 2). Obesity in first nations people is believed to increase the risk for future development of chronic diseases, such as type 2 diabetes and hypertension (3). From a public health perspective, it is important to monitor and, if appropriate, to intervene in the changes in diet and physical activity to influence the development of obesity and associated adverse health effects. A more complete understanding of those endogenous, cultural, and environmental factors that contribute to obesity in aboriginal communities might be the first step toward developing an intervention program that uses both culturally and biologically appropriate strategies.

Obesity is a complex metabolic disorder with a strong genetic component (4). There are many candidate genes for obesity and its related phenotypes. Some genes are candidates for obesity because mutations in them cause rare genetic syndromes affecting adipocyte differentiation (4). For example, patients with autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD; OMIM 151660) are born with normal adipocyte distribution, but after puberty experience adipocyte degeneration in their extremities, trunk, and gluteal region (5–7). Subjects with FPLD have insulin resistance preceding the development of diabetes, which is often associated with dyslipidemia and atherosclerosis. Recently, we discovered that mutant *LMNA* underlies FPLD (8). The mechanisms through which *LMNA* mutations cause wasting of specific cell types and associated abnormal phenotypes are unknown. However, *LMNA* is clearly a candidate gene for adipose tissue metabolism.

In addition to the rare *LMNA* mutations in FPLD, we identified a common single nucleotide polymorphism (SNP) in exon 10 of *LMNA*, namely a silent C→T substitution at nt 1908 (1908C/T) (9), affecting the third base within codon 566, which is the last codon shared in common between lamin A and C before alternative splicing gives rise to the two distinct proteins (9). We previously showed that this SNP was associated with variation in obesity-related indexes in Canadian Oji-Cree, with the *LMNA* 1908T allele being associated with increased anthropometric measurements (9). We now report replication of this observation in an independent, genetically distinct aboriginal population, namely Canadian Inuit, suggesting that the impact of *LMNA* 1908T may extend to other populations at risk for obesity.

Subjects and Methods

Study subjects

The Northwest Territories are located above the 60th parallel of latitude and comprise one third of the landmass of Canada. In 1986 the population of the Northwest Territories was 52,000. Of these, 35% were Inuit (or Eskimos), 15% were Dene (or Athapaskan Indians), and 50% were predominantly migrants of European origin from other parts of Canada. The traditional Inuit territory extends from the Chukchi Peninsula Laboratories, Inc. in northeastern Asiatic Russia across Alaska and Northern Canada to Greenland. The present study involved residents of 8 communities from the Keewatin Region, mainly from the western shore of Hudson Bay between the 60th and 70th parallels of

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latitude (1, 2). These communities are included within a region that is now the self-governing jurisdiction called Nunavut.

Five hundred and sixteen randomly selected individuals, aged 18–80 yr, participated; of these, 281 (54.4%) reported themselves as being Inuit, 112 (21.7%) reported themselves as being of mixed ethnic background, 92 (17.8%) reported themselves as being of European background (white), and 31 (6.0%) reported themselves as being of an ethnic background other than Inuit, mixed, or white. At the time of the study these communities continued to adhere to a more traditional lifestyle, including the consumption of arctic fish at least three times per week. Blood samples were obtained with informed consent. The first exclusion criterion was self-reported non-Inuit ancestry. The second exclusion criterion was an inadequate blood sample for genetic determinations. This left 186 subjects (36.0% of the initial sample), who were similar to the nonincluded subjects in all measured traits (data not shown). The project was approved by the institutional review board of the University of Manitoba.

Clinical and anthropometric assessment

The survey consisted of an interviewer-administered questionnaire, clinical examination, and laboratory tests. The questionnaire was adapted from existing health survey protocols (1, 2). Standardized procedures were used in performing blood pressure and anthropometric measurements (1, 2). Field staff were trained by instructors from the Canada Heart Health Survey (1, 2). Subjects were measured without shoes in cotton examination gowns and underclothes. Each measurement was performed twice, and their average was used in the analysis. Height was measured to the nearest 0.1 cm using a tape measure with heels together and buttocks, back, shoulders, and head touching the wall. Weight was measured to the nearest 0.1 kg using a standard hospital balance beam scale (Health-O-Meter, Bridgeview, IL). Body mass index (BMI) was defined as weight (kilograms)/height (meters)^2. Waist and hip girths were measured with a tape measure, with the umbilicus and iliac crest serving as the anatomical landmarks, respectively. Large calipers (Cambridge Scientific Instruments, Cambridge, MD) were used to measure subscapular and triceps skinfold thickness. The waist to hip circumference ratio (WHR) and subscapular to triceps skinfold thickness ratio (STR) were derived for each subject. Concentrations of fasting plasma leptin were determined by quantitative enzyme-linked immunoabsorbent assay (Quantikine Human Leptin, R&D Systems, Inc., Minneapolis, MN). The leptin assay had a minimal detectable concentration of 0.5 ng/mL, a limit of linearity of 100 ng/mL, and an interassay coefficient of variation of 8.3%

Genetic analyses

The *LMNA* 1908C/T SNP genotype was determined from leukocyte DNA using amplification with primers LMNASNP1908F (5′-GCA AGA TAC ACC CAA GAG CC-3′) and LMNASNP1908R (5′-ACA CCT GGG TTC CCT GTT C-3′) over 30 amplification cycles and an annealing temperature of 60 C. The 1069-bp amplification product was then digested with *Pml*I and electrophoresed in 1.5% agarose gels. Digestion of the 1908C allele gave 2 fragments of 887 and 182 bp, whereas digestion of the 1908T allele gave a single fragment of 1069 bp.

Statistical analyses

Statistical analyses were performed using SAS statistical software, version 6.12, as previously described (9, 10). Between-sex and between-genotype differences in baseline clinical and biochemical traits were assessed using *t* tests with Bonferroni adjustment for multiple comparisons. Deviation of genotype frequencies from Hardy Weinberg equilibrium was assessed using χ^2 analysis. The association of *LMNA* genotype with quantitative traits was tested by ANOVA, using a general linear model, with levels of significance computed from the type III sums of squares. This approach is most appropriate for an unbalanced study design and reports significance after all covariates are taken into account.

The *LMNA* 1908C/T SNP genotype was introduced as a dichotomous variable in the analyses; subjects who carried at least one 1908T allele were compared with subjects who were homozygous for 1908C/1908C (*i.e.* a dominant model for 1908T). Although continuous dependent variables were not normally distributed, transformations resulted in variables with distributions that did not deviate significantly from normal by Wilk's test of normality. Logarithmic ($\log_e$) transformation of WHR, subscapular skinfold thickness, STR, and plasma leptin gave distributions that were not significantly different from normal. Inverse transformation for BMI, weight, and waist gave distributions that were not significantly different from normal. Square root transformation of triceps skinfold thickness gave a distribution that was not significantly different from normal. We also created a variable defined as the ratio of leptin to BMI (leptin/BMI ratio), as previously reported (9), to intrinsically correct for variation in leptin that was related to BMI. ANOVA was performed for weight, BMI, waist circumference, WHR, subscapular and triceps skinfold thickness, STR, plasma leptin, and leptin/BMI ratio using the transformed value for each as the dependent variable and the *LMNA* genotype, age, and sex as the independent variables. Confirmatory *post-hoc* analyses of between-genotype differences were conducted with the nonparametric Kruskal-Wallis χ^2 approximation test of the Wilcoxon rank sums for nontransformed variables, as previously reported (9). *Post-hoc* parametric analyses were also conducted for each sex separately, using *LMNA* genotype and age as independent variables. All parametric analyses were conducted using transformed variables, but untransformed mean values are shown in Tables 1 and 4.

When a new significant genotype-phenotype association was identified, the mean values for the trait were compared between genotypic classes using pairwise comparisons of least squares means. Least squares means are also called population marginal means and reflect means after adjustment for covariates used in the model. The percent contribution of the genotype to variation in the quantitative traits was estimated from partial regression coefficients obtained from multivariate regression analysis (with attributable variation defined as the ratio of the partial r^2 of the variable of interest divided by the partial r^2 for the whole model). A forward stepwise regression procedure was used to assist in the model building, with the *P* value for inclusion set at <0.15. The dependent variables in each regression analysis included transformed weight, BMI, waist circumference, WHR, subscapular and triceps skinfold, thickness, STR, leptin, and leptin/BMI ratio. The independent variables for each analysis included *LMNA* genotype, age, and sex.

TABLE 1. Baseline clinical and biochemical features (mean ± SD) for Inuit

	Overall (n = 186)	Male (n = 80)	Female (n = 106)	*P* value[a]
Age (yr)	36.3 ± 15.1	33.8 ± 15.3	38.1 ± 14.8	NS (0.06)
Wt (kg)	66.8 ± 12.6	69.8 ± 12.1	64.6 ± 12.6	<0.05
BMI (kg/m^2)	26.5 ± 4.4	25.5 ± 3.7	27.3 ± 4.8	<0.05
Waist (cm)	88.0 ± 12.0	87.6 ± 11.4	88.3 ± 12.4	NS (0.68)
WHR	0.87 ± 0.07	0.88 ± 0.07	0.86 ± 0.07	<0.05
Subscapular skinfold (mm)	21.0 ± 11.6	15.6 ± 8.6	25.0 ± 11.9	<0.0001
Triceps skinfold (mm)	21.1 ± 9.6	16.5 ± 9.2	24.5 ± 8.5	<0.0001
STR	1.11 ± 0.59	1.23 ± 0.81	1.02 ± 0.33	<0.005
Leptin (ng/mL)	11.6 ± 11.8	2.70 ± 3.35	17.3 ± 11.7	<0.0001
Leptin/BMI ratio	0.42 ± 0.39	0.11 ± 0.13	0.62 ± 0.37	<0.0001

[a] Bonferroni *P* values for between-sex differences using the *t* test.

Results

Clinical and biochemical attributes

The clinical and biochemical attributes of 186 adult Inuit subjects are shown in Table 1. None of the subjects had diabetes, muscular dystrophy, cardiomyopathy, or conduction system disease. None of the study subjects was taking oral hypoglycemic, antihypertensive, or antihyperlipidemic medications. We noted between-sex differences in most obesity-related traits (Table 1). Women were found to have higher BMI, subscapular and triceps skinfold thickness, plasma leptin concentration, and leptin/BMI ratio than men. In contrast, women had lower weight, WHR, and STR than men. Mean age and waist were not significantly different between the sexes. The observed 6-fold between-gender difference in plasma leptin concentration was particularly striking and was consistent with low adipose tissue mass in male Inuit.

Allele and genotype frequencies

The allele and genotype frequencies in the overall study sample and in each sex separately are shown in Table 2. None of the genotype frequencies deviated significantly from expectations of the Hardy-Weinberg equation. There were no significant differences between allele and genotype frequencies between the sexes.

Genotype-phenotype associations

In the 186 nondiabetic Inuit subjects, ANOVA (Table 3) revealed significant associations between *LMNA* 1908C/T SNP genotype and transformed weight, BMI, waist circumference, WHR, subscapular skinfold thickness, and STR (P = 0.016, 0.0031, 0.019, 0.024, 0.0036, and 0.029, respectively). These associations were each confirmed in an independent *post-hoc* nonparametric ANOVA (data not shown). There was no significant association of *LMNA* 1908C/T SNP genotype with triceps skinfold thickness, plasma leptin, or leptin/BMI ratio. Among nongenetic covariates, age was significantly associated with transformed BMI, waist circumference, and WHR, whereas sex was significantly associated with transformed weight, BMI, WHR, subscapular and triceps skinfold thickness, plasma leptin, and leptin/BMI ratio. When males and females were examined separately, there was no difference in the associations of quantitative traits with *LMNA* genotype (data not shown).

Pairwise comparisons showed significant between-genotype differences in least squares means of weight, BMI, waist circumference, WHR, subscapular skinfold thickness, and STR (Table 4; each $P < 0.05$, by Bonferroni test).

Multivariate regression analysis (Table 5) revealed that *LMNA* 1908C/T genotype accounted for 33.4%, 22.4%, 11.4%, 7.1%, 19.9%, and 100%, respectively, of the attributable variation in transformed weight, BMI, waist circumference, WHR, subscapular skinfold thickness, and STR (P = 0.007, 0.008, 0.016, 0.008, 0.0016, and 0.016, respectively). Sex accounted for 54.4%, 15.5%, 18.7%, 80.1%, 100%, 100%, and 100%, respectively, of the attributable variation in transformed weight, BMI, WHR, subscapular and triceps skinfold thicknesses, plasma leptin, and leptin/BMI ratio (P = 0.0008, 0.025, <0.005, <0.0001, <0.0001, <0.0001, and <0.0001, respectively).

TABLE 2. Allele and genotype frequencies for the *LMNA* 1908C/T SNP in Inuit

	n	Genotype frequency			Allele frequency	
		1908C/1908C	1908C/1908T	1908T/1908T	1908C	1908T
Total	186	0.226	0.586	0.188	0.519	0.481
Males	81	0.173	0.617	0.210	0.481	0.519
Females	105	0.267	0.562	0.171	0.548	0.452

TABLE 3. Summary of ANOVA for transformed quantitative traits in Inuit

	F value	*P* value
Dependent variable, weight; sources of variation:		
LMNA 1908C/T	5.89	0.016
Age	2.74	NS (0.09)
Sex	11.7	0.0008
Dependent variable, BMI; sources of variation:		
LMNA 1908C/T	8.98	0.0031
Age	13.31	0.0003
Sex	5.11	0.025
Dependent variable, waist circumference; sources of variation:		
LMNA 1908C/T	5.61	0.019
Age	39.3	<0.0001
Sex	0.06	NS (0.81)
Dependent variable, WHR; sources of variation:		
LMNA 1908C/T	5.16	0.024
Age	52.9	<0.0001
Sex	11.3	0.0009
Dependent variable, subscapular skinfold thickness; sources of variation:		
LMNA 1908C/T	8.70	0.0036
Age	1.79	NS (0.18)
Sex	41.7	<0.0001
Dependent variable, triceps skinfold thickness; sources of variation:		
LMNA 1908C/T	0.28	NS (0.59)
Age	0.60	NS (0.43)
Sex	38.35	<0.0001
Dependent variable, STR; sources of variation:		
LMNA 1908C/T	4.83	0.029
Age	1.08	NS (0.31)
Sex	0.06	NS (0.82)
Dependent variable, leptin; sources of variation:		
LMNA 1908C/T	0.85	NS (0.35)
Age	0.87	NS (0.35)
Sex	71.6	<0.0001
Dependent variable, leptin/BMI ratio; sources of variation:		
LMNA 1908C/T	0.14	NS (0.71)
Age	0.01	NS (0.92)
Sex	80.9	<0.0001

Discussion

We found that common *LMNA* 1908C/T SNP is associated with obesity-related anthropometric quantitative traits in Inuit. In particular, Inuit with the *LMNA* 1908T allele had

TABLE 4. Untransformed least squares mean ± SE of quantitative traits according to *LMNA* 1908C/T SNP genotype in Inuit

	1908C/1908C	1908C/1908T and 1908T/1908T	*P* value[a]
No.	42	144	
Wt (kg)	63.3 ± 1.9	68.4 ± 1.0	<0.05
BMI (kg/m^2)	24.8 ± 0.7	26.9 ± 0.4	<0.05
Waist circumference (cm)	84.6 ± 1.6	89.1 ± 0.91	<0.05
WHR	0.85 ± 0.01	0.87 ± 0.01	<0.05
Subscapular skinfold (mm)	16.7 ± 1.7	21.3 ± 0.9	<0.05
Triceps skinfold (mm)	20.1 ± 1.4	20.6 ± 0.8	NS
STR	0.96 ± 0.09	1.17 ± 0.05	<0.05
Leptin (ng/mL)	8.6 ± 1.8	10.5 ± 1.0	NS
Leptin/BMI ratio	0.34 ± 0.06	0.37 ± 0.03	NS

[a] Bonferroni adjusted *P* values for between-genotype differences using the *t* test.

TABLE 5. Summary of partial regression coefficients for transformed quantitative traits in Inuit

	Partial r^2	*P* value
Dependent variable, weight; sources of variation:		
LMNA 1908C/T	0.0372	0.007
Age	0.0136	NS (>0.10)
Sex	0.0607	0.0008
Model	0.1115	<0.0001
Dependent variable, BMI; sources of variation:		
LMNA 1908C/T	0.0349	0.008
Age	0.0970	<0.0001
Sex	0.0241	0.025
Model	0.1560	<0.0001
Dependent variable, waist circumference; sources of variation:		
LMNA 1908C/T	0.0257	0.016
Age	0.1999	<0.0001
Sex	0.0	NS (>0.15)
Model	0.2257	<0.0001
Dependent variable, WHR; sources of variation:		
LMNA 1908C/T	0.0208	0.008
Age	0.2159	<0.0001
Sex	0.0546	<0.005
Model	0.2913	<0.0001
Dependent variable, subscapular skinfold thickness; sources of variation:		
LMNA 1908C/T	0.0459	0.0016
Age	0.0	NS (>0.15)
Sex	0.1844	<0.0001
Model	0.2303	<0.0001
Dependent variable, triceps skinfold thickness; sources of variation:		
LMNA 1908C/T	0.0	NS (>0.15)
Age	0.0	NS (>0.15)
Sex	0.1890	<0.0001
Model	0.1890	<0.0001
Dependent variable, STR; sources of variation:		
LMNA 1908C/T	0.0333	0.016
Age	0.0	NS (>0.15)
Sex	0.0	NS (>0.15)
Model	0.0333	<0.0001
Dependent variable, leptin; sources of variation:		
LMNA 1908C/T	0.0	NS (>0.15)
Age	0.0	NS (>0.15)
Sex	0.3726	<0.0001
Model	0.3726	<0.0001
Dependent variable, leptin/BMI ratio; sources of variation:		
LMNA 1908C/T	0.0	NS (>0.15)
Age	0.0	NS (>0.15)
Sex	0.4080	<0.0001
Model	0.4080	<0.0001

significantly higher weight, BMI, waist circumference, WHR, subscapular skinfold thickness, and STR compared with Inuit who did not carry this allele. In addition, the *LMNA* genotype accounted for about 10% to almost 100% of the attributable variation in these traits in multivariate regression models. The findings are consistent with our previous observation of similar associations of the *LMNA* 1908T allele with increased obesity indexes in Oji-Cree. The replication of these results in samples taken from two independent, genetically distinct aboriginal populations suggests that the common *LMNA* 1908C/T SNP genotype may have a more general association with variation in indexes of obesity.

The widely expressed *LMNA* gene products, lamins A and C, are important elements of the nuclear lamina. Alternative splicing at exon 10 of *LMNA* gives rise to lamins A and C (11), which share sequence identity for the first 566 residues, but have distinctive C-termini (11). As the *LMNA* 1908C/T SNP is silent at the amino acid level, it is probable that the associations were the result of linkage disequilibrium with a functional variant elsewhere at this locus. However, we observed no other *LMNA* coding sequence variants in the Inuit, suggesting that this is unlikely. It is also possible that there was unmeasured variation within flanking noncoding regulatory sequences of *LMNA* or within a nearby gene on chromosome 1q21-q22, which we have not yet ruled out. Finally, it is possible that the *LMNA* 1908C/T SNP may mark a DNA change that has a functional molecular consequence. The affected residue is at the third base of *LMNA* codon 566, which is the last codon shared in common between lamin A and C before alternative splicing gives rise to the two distinct proteins (11). Although we are unaware of a precedent for a common SNP at a crucial site affecting message splicing, the proximity of this variant to such a focal nucleotide in *LMNA* might be more than coincidental, especially in light of the consistent phenotypic associations.

The mechanism underlying the association between common variation in *LMNA* and indexes of obesity is not clear. Lamins A and C are members of the intermediate filament multigene family and are present in most differentiated cells. Lamin A and C polymerize to form part of the nuclear lamina, a structural meshwork of 10-nm filaments on the nucleoplasmic side of the inner nuclear membrane (11). Lamins A and C form dimers through their rod domains. Variation that affects splicing of *LMNA* could have an effect on the ratio of lamin A to C isoforms in adipose tissue, which might have consequences for the development of adipocytes over time.

In the Oji-Cree sample, *LMNA* 1908T was associated not only with increased anthropometric indexes, but also with increased (by 18%) plasma leptin concentration (9). In the Inuit, we observed a consistent, but nonsignificant, increase in plasma leptin in carriers of *LMNA* 1908T compared with noncarriers (10.5 ± 1.0 *vs.* 8.6 ± 1.8 ng/mL; $P = 0.10$). The magnitude of this between-genotype difference (~20%) was the same as the magnitude of the between-genotype differ-

ence in plasma leptin observed in the much larger Oji-Cree sample (9). Our failure to detect an *LMNA* 1908C/T SNP genotype association with plasma leptin may simply have reflected a smaller sample size of the Inuit compared with the Oji-Cree (9). It is most probable that the differences in plasma leptin reflect variation in adipocyte mass rather than an independent effect of the *LMNA* variation.

Interestingly, sibling pair analyses performed in another North American aboriginal group, the Pima Indians, have suggested that there is a potential diabetes susceptibility locus on chromosome 1q (12). It would be of interest to determine whether variation in *LMNA*, possibly the 1908C/T variant itself, is associated with obesity-related end points in that aboriginal group and indeed in other aboriginal people. Of course, the *LMNA* 1908C/T variant may be in linkage disequilibrium with other variants at other nearby genes, such as *ARNT*, *RXR*, *CRP*, *CTSS*, or *CTSK*.

In conclusion, we report associations between the *LMNA* 1908C/T SNP and indexes of obesity in Canadian Inuit. The variation in these traits attributable to *LMNA* 1908C/T SNP ranged from approximately 10–100%, consistent with the idea that common variation in *LMNA* may be a more generally important contributor to variation in these traits. Further epidemiological and genetic studies of the *LMNA* gene locus and nearby SNPs are required to improve our understanding of the possible role of this potentially important gene in adipocyte biology and obesity.

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