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Letter

G-protein β3 Subunit Gene Splice Variant and Body Fat Distribution in Nunavut Inuit

Robert A. Hegele,[1,4] Carol Anderson,[1] T. Kue Young,[2] and Philip W. Connelly[3]

[1]*Robarts Research Institute and Department of Medicine, University of Western Ontario, London, Ontario, Canada N6A5K8;* [2]*Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada R3E0W2;* [3]*Departments of Medicine and Biochemistry, St. Michael's Hospital and University of Toronto, Toronto, Ontario, Canada M5B1A6*

The *GNB3* 825T allele encodes a product that has enhanced activation of heterotrimeric G proteins in vitro and could play a role in adipogenesis. We therefore evaluated the possibility that the *GNB3* 825T allele was associated with obesity in a sample of 213 healthy Canadian Inuit. We found that body weight, body mass index, waist girth, hip girth, subscapular skinfold thickness, and triceps skinfold thickness were significantly higher in subjects with the *GNB3* 825T/T genotype than in subjects with other genotypes. Furthermore, two anthropometric ratios, namely that of waist to hip circumference and that of subscapular to triceps skinfold thickness, were not significantly different across genotypes. This suggested that the increased deposition of fat in subjects with the *GNB3* 825T/T genotype was generalized and not localized to particular subregions. There was no association of this genetic variation with blood pressure. The *GNB3* 825T/T genotype accounted for between 1.6% and 3.3% of the total variation (≤13% of attributable variation) of the obesity-related traits. The potential for a genetic marker of obesity creates opportunities for future studies in the Inuit, not just to confirm the associations, but also to examine prospectively the influence of interventions and possible relationships between *GNB3* 825T and longer term complications of obesity.

There is a growing prevalence of obesity and its complications within many Canadian aboriginal communities (MacMillan et al. 1996). Among the Inuit (Eskimos) of Canada, obesity is now as prevalent as it is in the general North American population (Young 1996a,b). This is a relatively new development, and is probably the result of recent, rapid changes in physical activity, diet, and lifestyle in the Inuit (Young 1996). In addition, some aspects of obesity in the Inuit are unique, for example, obesity is more prevalent among Inuit women (Young 1996a,b). Obesity is believed to increase the risk for the development of chronic diseases, such as hypertension and diabetes, in these people (Young and Sevenhuysen 1989). From a public health perspective, it is important to monitor and, if appropriate, to effect changes in diet and physical activity in order to prevent obesity and associated adverse health effects. A fuller understanding of those endogenous, cultural, and environmental factors that have contributed to obesity in aboriginal communities might be the first step toward developing an intervention program that utilizes both culturally and biologically appropriate strategies.

In most human populations, obesity is considered to have manifold genetic and nongenetic causes (Comuzzie and Allison 1998). One set of candidate genes for obesity is the heterotrimeric G proteins, which are key components of intracellular signal transduction and play a focal role in adipogenesis (Malbon 1997; Comuzzie and Allison 1998). Mice with a disrupted gene for the Giα2 subunit are deficient in total body adipocyte mass (Su et al. 1993). Furthermore, increased expression of Giα2 results in hyperplasia and lipid accumulation within adipocytes (Moxham et al. 1993). The Giα2 subunit interacts with other heterotrimeric G-protein subunits, such as the β3 subunit (Siffert et al. 1998), which is encoded by the *GNB3* gene.

A common C → T change at nucleotide 825 of the *GNB3* gene activates a cryptic splice site that results in alternative splicing of exon 9 (Siffert et al. 1998). The product of the *GNB3* 825T is 41 amino acids smaller than the wild-type 825C allele product (Siffert et al. 1998). The *GNB3* 825T allele product has enhanced activation of heterotrimeric G proteins in vitro (Siffert et al. 1998). The *GNB3* 825T allele has been variably associated with hypertension (Benjafield et al. 1998; Hegele et al. 1998; Schunkert et al. 1998; Siffert 1998a,b; Siffert et al. 1998). Some of the associations might have been secondary to obesity (Siffert 1998a,b). Because of the potential role of G proteins in obesity and because of their association with a related phenotype, we examined the possibility that the *GNB3* 825T allele was associated with obesity in a sample of healthy Canadian Inuit.

RESULTS

Baseline Clinical Features

Sufficient clinical information and DNA for all analyses were obtained from 213 subjects. The baseline clinical and anthropometric attributes of the study sample

[4]Corresponding author.
E-MAIL robert.hegele@rri.on.ca; FAX (519) 663-3789.

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are shown in Table 1. Fifteen subjects (6.5% of the total sample) were hypertensive.

Allele and Genotype Frequencie

The frequencies of the *GNB3* 825T and 825C alleles in the overall study sample were 0.504 and 0.496, respectively. The frequencies were 0.225, 0.535, and 0.239, respectively, for the 825C/C, 825T/C, and 825T/T genotypes in the overall study sample. There was no deviation of the observed genotype frequencies from those predicted from the Hardy–Weinberg equation.

Genetic Associations with Obesity Phenotypes: Regression Analysis

Results of regression analysis for all anthropometric traits are shown in Table 2. Gender was a significant determinant of weight, the ratio of waist to hip circumference (WHR), subscapular skinfold thickness, and triceps skinfold thickness. Age was a significant determinant of all traits except triceps skinfold thickness. The genotype was not a significant source of variation in regression models that included a codominant or dominant effect for *GNB3* 825T. However, at a nominal $P \leq 0.05$, the recessive effect for *GNB3* 825T was significant for all obesity-related traits, except for WHR and the ratio of subscapular to triceps skinfold thickness (STR). A recessive effect of *GNB3* 825T accounted for between 1.6% and 3.3% of the total variation (≤13% of the attributable variation) in weight, body mass index (BMI), waist girth, hip girth, subscapular skinfold thickness, and triceps skinfold thickness, as estimated from partial regression coefficients.

Because the regression model indicated that the genetic association was most significant for a recessive influence of *GNB3* 825T, the mean (±S.D.) for each obesity-related trait was compared between the groups of individuals with the *GNB3* 825T/T genotype and those with either the 825C/T or 825C/C genotypes. The mean values for the entire sample were compared according to *GNB3* genotype class.

Table 1. Baseline Quantitative Features of 213 Canadian Inuit

	Mean ± S.D.	Range
Age (years)	36.6 ± 15.1	18.0–78.0
Females (%)	57.4	
Weight (kg)	67.0 ± 13.1	41.0–118.0
BMI (kg/m^2)	26.7 ± 4.4	20.0–39.0
Waist girth (cm)	88.5 ± 12.2	67.0–131.0
Hip girth (cm)	101.1 ± 8.6	83.0–124.0
WHR	0.87 ± 0.07	0.73–1.15
Subscapular skinfold (mm)	20.9 ± 9.4	4.0–54.0
Triceps skinfold (mm)	20.7 ± 11.4	6.0–59.0
STR	1.10 ± 0.58	0.21–4.71
Blood pressure (mmHg)		
systolic	119.8 ± 16.5	82.0–189.0
diastolic	75.6 ± 10.3	52.0–103.0

Genetic Associations with Obesity Phenotypes: Pairwise Comparisons

Pairwise comparisons, with Bonferroni adjustment for multiple tests, showed that subjects with the *GNB3* 825T/T genotype had significantly higher BMI, waist girth, hip girth, triceps skinfold thickness, and subscapular skinfold thickness than subjects with the other genotypes (Table 3). However, the weight, WHR, and STR did not differ among genotype classes, suggesting that it is generally the absolute value of the anthropometric measurements, rather than the derived ratios, were significantly higher in subjects with the *GNB3* 825T/T genotype. A post hoc analysis found that there was no significant interaction between genotype and gender for any phenotype (data not shown).

Pairwise comparisons in females alone, with Bonferroni adjustment for multiple tests, showed that female subjects with the *GNB3* 825T/T genotype had significantly higher hip girth and triceps skinfold thickness than female subjects with the other genotypes (data not shown). Consistent with the observations in the overall sample, weight, BMI, waist girth, and subscapular skinfold thickness were all higher in female subjects with the *GNB3* 825T/T genotype, although these differences were not significant after adjustment for multiple comparisons (data not shown).

Pairwise comparisons in males alone, with Bonferroni adjustment for multiple tests, showed no significant between-genotype differences for any anthropometric measure (data not shown). Consistent with the observations in the overall sample, and in the female subgroup, weight, BMI, waist girth, hip girth, triceps skinfold thickness, and subscapular skinfold thickness, were all higher in male subjects with the *GNB3* 825T/T genotype, although these differences were not significant after adjustment for multiple comparisons (data not shown).

There was no association of *GNB3* genotype with either log systolic or log diastolic blood pressure within the overall sample, and the male and female subgroups, under any model of inheritance (data not shown). Furthermore, there was no significant between-genotype difference in the proportion of subjects with hypertension (Table 1).

DISCUSSION

The regression analysis and pairwise testing both showed that BMI, waist girth, hip girth, subscapular skinfold thickness, and triceps skinfold thickness were

Table 2. Sources of Variation for Quantitative Traits in Canadian Inuit from Stepwise Regression Analysis

Covariate	Partial r^2	Pr>F[a]	Partial r^2	Pr>F[a]	Partial r^2	Pr>F[a]
	Weight		BMI			
Sex	0.095	<0.0001		N.S. (>0.15)		
Age	0.029	0.010	0.088	<0.0001		
GNB3 825T recessive	**0.019**	**0.034**	**0.030**	**0.008**		
	Waist girth		Hip girth		WHR	
Sex	0.017	0.035		N.S. (>0.15)	0.094	<0.0001
Age	0.189	<0.0001	0.098	<0.0001	0.171	<0.0001
GNB3 825T recessive	**0.021**	**0.021**	**0.037**	**0.003**		N.S. (>0.15)
	Subscapular skinfold		Triceps skinfold		STR	
Sex	0.133	<0.0001	0.143	<0.0001		N.S. (>0.15)
Age	0.015	0.061		N.S. (>0.15)	0.011	0.14
GNB3 825T recessive	**0.016**	**0.052**	**0.017**	**0.047**		N.S. (>0.15)
	Systolic blood pressure		Diastolic blood pressure			
Sex	0.085	<0.0001	0.062	0.0002		
Age	0.131	0.0002		N.S. (>0.15)		
GNB3 825T recessive		N.S. (>0.15)		N.S. (>0.15)		

[a](Pr>F), Probability of a greater *F*-value from linear regression. Significant associations with the genetic marker are shown in boldface type.

significantly higher in subjects with the *GNB3* 825T/T genotype compared to subjects with the other two genotypes. Furthermore, the two ratios, namely WHR and STR, were not significantly different among genotypes. This suggests that the degree of increased fat deposition is similar in the waist and hip depots and in the subscapular and triceps depots among *GNB3* 825T/T subjects when compared to subjects with the other genotypes. This generalized increase in fat deposition is reflected in significantly increased BMI, which represents body weight that has been corrected for height, among *GNB3* 825T/T subjects when compared to subjects with the other genotypes.

Table 3. Mean (± S.D.) Quantitative Phenotypes in Canadian Inuit According to *GNB3* 825T Genotype

	825C/C plus 825C/T	825T/T	Bonferroni $P < 0.05$[a]
Number	162	51	
Weight (kg)	66.5 ± 13.0	68.7 ± 13.5	no
BMI (kg/m^2}	26.3 ± 4.3	27.9 ± 4.6	yes
Waist girth (cm)	87.6 ± 12.0	91.2 ± 12.7	yes
Hip girth (cm)	100.2 ± 8.3	103.9 ± 9.1	yes
WHR	0.87 ± 0.07	0.88 ± 0.06	no
Subscapular skinfold (mm)	19.7 ± 11.1	24.3 ± 11.8	yes
Triceps skinfold (mm)	19.9 ± 9.2	24.3 ± 9.6	yes
STR	1.12 ± 0.64	1.05 ± 0.36	no
Blood pressure (mmHg)			
systolic	120 ± 17.0	119 ± 14.6	no
diastolic	75.5 ± 10.4	75.9 ± 10.0	no
Percent with hypertension	6.2	8.8	no

[a]Bonferroni-adjusted probability of a significant difference between the means of the two genotype classes.

Examining the genders separately indicated that these relationships were consistent for both men and women. However, pairwise comparisons indicated that only the mean hip girth and triceps skinfold thickness were significantly different between genotypes in females, with males showing nonsignificant but consistent trends for each obesity-related trait. Given that: (1) the trends for between-genotype differences for each of the obesity-related traits were similar in both genders and (2) that the genotype–gender interaction term was not significant for any obesity-related trait, it is most likely that failure of the pairwise comparisons to reach a nominal significance for these traits in the subgroups divided by gender was simply due to a relatively small number of subjects in the subgroups. Larger study samples of both men and women taken from Inuit and other ethnic groups would be required to determine if such generalizations can be made.

There is evidence from other experimental systems that favors a role for G proteins in adipogenesis and adipocyte metabolism. For example, increased signaling by pertussis toxin-sensitive G proteins has been shown to stimulate adipogenesis (Moxham et al. 1993). Furthermore, increased expression of the Gαi2 in murine embryonic stem cells has been shown to promote terminal differentiation of adipocytes (Su et al. 1993). Such examples demonstrate the principle that variation in G-protein-mediated intracellular signaling could have a role in adipocyte biology and possibly human obesity. The shorter product of the *GNB3* 825T allele is associated with enhanced activation of

heterotrimeric G proteins compared with the product of the 825C allele (Siffert et al. 1998).

It is of interest that heterozygotes for *GNB3* 825T were phenotypically more like homozygotes for 825C/C than homozygotes for 825T/T. This suggests that a single copy of the 825C allele is sufficient to attenuate a possible deleterious influence of the 825T allele. Because the G proteins function as hetero-oligimers (Siffert 1998a,b; Siffert et al. 1998), there is the potential to proliferate many scenarios that could explain the apparent recessive influence of the *GNB3* 825T allele. It is fairly certain that the complexity of all the possible protein–protein interactions, regulatory mechanisms, and terminal effects of G proteins will tend to obfuscate efforts to understand the actual mechanism underlying the association with obesity at the cellular level.

We found no association with blood pressure in this study sample, although admittedly, the prevalence of hypertension is very low in this group. The association of the *GNB3* 825T variant with hypertension has been inconsistent (Benjafield et al. 1998; Hegele et al. 1998; Schunkert et al. 1998; Siffert et al. 1998). Given the present observations, it is possible that the more proximal association is with obesity and generalized fat deposition and that the associations with hypertension may be secondary to obesity (Siffert 1998a,b).

As is typical in association studies, we cannot exclude the possibility of population stratification artifacts. Historically little European or other ethnic admixture exists among selfdescribed Inuit individuals of the Far North. Also, the frequencies of some typical European genetic markers, such as factor V Leiden, *HFE* Y282, and *MTHFR* 677T, are either absent or very low among the Inuit (Hegele et al. 1997a,b). In addition, there has been a proven in vitro functional impact of the *GNB3* 825T allele product. In light of these facts, the associations are more likely due to a functional impact of *GNB3* 825T, although we cannot definitively rule out linkage disequilibrium between 825T and another functional site in *GNB3* or another closely linked gene. There is no known candidate gene for obesity in the vicinity of the *GNB3* locus on chromosome 12p13 (Siffert et al. 1998).

Other studies have shown that factors such as education, income, fluency in the Inuit language, and less time spent on the land are associated with obesity among the Inuit (Young 1996a,b). In general, Inuit men tend to show the pattern observed in developing societies, where obesity is more prevalent among those with higher socioeconomic status. However, Inuit women are more characteristic of developed societies, where obesity is associated with a lower socioeconomic status (Young 1996). The different gender roles in a rapidly modernizing population are most likely responsible for this phenomenon. Despite the apparent gender-related differences in the ecological and epidemiological determinants, observations made from this study suggest that the influence of *GNB3* 825T can be seen in both genders.

Obesity in the Inuit now appears to be as prevalent as in non-Inuit populations (Young 1996a,b). Interestingly, other studies on the Inuit have shown that blood pressure and one or more of the plasma lipid variables show a positive association with obesity, but plasma glucose or insulin shows no significant change (Young 1996a,b). This observation suggests that the Inuit may experience a specific type of selective insulin resistance, which may be the underlying mechanism for several of the chronic complications of obesity. From a public health perspective, it is important to monitor and ameliorate the impact of changing diet and physical activity on the prevalence of obesity and associated health effects in these people. A genetic marker may prove to be helpful for prospective studies of obesity in the Inuit.

METHODS

Study Subjects

The Northwest Territories are located above the 60th parallel of latitude and comprise one-third of the land mass of Canada. In 1986, the population of the Northwest Territories was 52,000. Of these, 35% were Inuit (Eskimos), 15% were Dene (Athapaskan Indians), and 50% were predominantly migrants of European origin from other parts of Canada. The traditional Inuit territory extends from the Chukchi Peninsula in northeastern Asiatic Russia, across Alaska and northern Canada, to Greenland. The present study involved residents of eight communities from the Keewatin region, mainly from the western shore of Hudson Bay between the 60th and 70th parallels of latitude (Young 1996a,b). These communities are included within a region that is now the self-governing jurisdiction called Nunavut.

A total of 516 randomly selected individuals, aged 18–80, participated; of these, 281 reported themselves as being Inuit, 112 reported themselves as being of mixed ethnic background, 92 reported themselves as being of European background (white), and 31 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 a self-reported non-Inuit ancestry. The second exclusion criterion was an inadequate blood sample for genetic determinations. With these exclusions, 213 subjects remained. The project was approved by the Institutional Review Boards of the Universities of Manitoba and Toronto.

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 (Young 1996a,b). Standardized procedures were used in performing blood pressure and anthropometric measurements (Young 1996a,b). Two blood pressure measurements

were taken at least 10 min apart after resting, using an appropriate cuff size of a standard mercury sphygmomanometer. Anthropometry consisted of measurements of the subscapular and triceps skinfold thicknesses, waist and hip girths, and height and weight. Field staff were trained by instructors from the Canada Heart Health Survey (Young 1996). Large calipers (Cambridge Scientific Instruments, Cambridge, MD) were used for skinfold thickness measurements.

Subjects were measured without shoes in cotton examination gowns and underclothes. Each measurement was performed twice and the 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). BMI was defined as weight/height^2 (kg/m^2). Waist and hip girths were measured with a tape measure, with the umbilicus and iliac crest serving as the anatomical landmarks, respectively.

Genetic Analyses

Genotypes for *GNB3* nucleotide 825 were determined using primers, amplification conditions, digestion with *Bse*DI (Fermentas), and electrophoresis as described (Siffert et al. 1998; Hegele et al. 1998). The phenotyping and genotyping were carried out at least 4 years apart, and the individual performing the genotyping had only anonymous numerical identifiers for the DNA samples. After the genotyping was completed, the results were merged with the phenotypes in a database for subsequent statistical testing.

Statistical Analysis

The distribution of each anthropometric variable was significantly non-normal in this data set. Therefore, for parametric statistical analyses, each variable was transformed and subjected to analysis of normality. Waist girth, WHR, subscapular skinfold thickness, STR, and both systolic and diastolic blood pressure were each transformed using the logarithm base 10. Hip girth, BMI, and weight were each inverse transformed. The triceps skinfold thickness was square-root transformed. The transformed variables were used for statistical analyses, but the nontransformed values are presented in Tables 1 and 3.

The significance of deviations of observed genotype frequencies from those predicted by the Hardy–Weinberg equation was evaluated with χ^2 analysis. χ^2 analysis was also used to assess between-group differences in proportions of alleles and genotypes.

Multivariate regression analysis in Statistical Analysis Software (SAS) version 6.12 (SAS Institute, Cary, NC) was used to determine the sources of variation for transformed anthropometric traits. A stepwise regression procedure was used to assist in the model building, with the *P* value for inclusion set at ≤0.15. The dependent variables were transformed weight, BMI, waist girth, hip girth, WHR, subscapular skinfold thickness, triceps skinfold thickness, and STR. The independent variables in the model for each analysis included *GNB3* genotype with assumption of a recessive effect of *GNB3* 825T on each phenotype. This was done by setting the *GNB3* genotype variable at zero for 825C/C and 825T/C subjects and at one for 825T/T subjects. *GNB3* was the only genetic variable studied for association with obesity. Age and gender were also included as independent variables. Both dominant and codominant models of inheritance were also tested in separate regression analyses. The partial correlation coefficient in each regression was used to estimate the proportion of variation in the dependent variable that was due to each significantly associated independent variable.

We also used similar regression models to test for association of *GNB3* codon 825 genotype with log systolic and log diastolic blood pressure, using age, gender, and BMI as independent covariates in each model.

In separate post hoc analyses, we included in each regression model an interaction term comprised of *GNB3* 825T/T genotype and gender to more formally evaluate if the associations of *GNB3* genotype with the phenotypes were gender-specific.

For those quantitative traits that showed a significant association with *GNB3* genotype, assuming a recessive effect of 825T, we subsequently performed pairwise comparisons of least squares means of the 825C/C plus 825C/T genotype class and the 825T/T genotype class. We used the Bonferroni method to adjust for multiple pairwise comparisons, with a Bonferroni adjusted $P \leq 0.05$ set as the nominal level of significance for pairwise comparisons.

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