Brief Genetics Report

5′ Flanking Variants of Resistin Are Associated With Obesity

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Diabetes and obesity have long been known to be related. The recently characterized adipocyte hormone resistin (also called FIZZ3/ADSF) has been implicated as a molecular link between impaired glucose tolerance (IGT) and obesity in mice. A search for sequence variants at the human resistin locus identified nine single-nucleotide polymorphisms (SNPs) but no coding variants. An investigation into the association of these SNPs with diabetes and obesity revealed two 5′ flanking variants (g.-537 and g.-420), in strong linkage disequilibrium, that are associated with BMI. In nondiabetic individuals from the Quebec City area and the Saguenay-Lac-St-Jean region of Quebec, the g.-537 mutation (allelic frequency = 0.04) was significantly associated with an increase in BMI ($P = 0.03$ and $P = 0.01$, respectively). When the data from these two populations were combined and adjusted for age and sex, both the g.-537 (odds ratio [OR] 2.72, 95% CI 1.28–5.81) and the g.-420 variants (1.58, 1.06–2.35) were associated with an increased risk for a BMI ≥30 kg/m^2. In contrast, in case/control and family-based study populations from Scandinavia, we saw no effect on BMI with either of these promoter variants. No association was seen with diabetes in any of the population samples. *Diabetes* 51: 1629–1634, 2002

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IGT, impaired glucose tolerance; LD, linkage disequilibrium; OR, odds ratio; PPAR, peroxisome proliferator–activated receptor; QC, Quebec City; QTDT, quantitative transmission disequilibrium test; SLSJ, Saguenay-Lac-St-Jean; SNP, single-nucleotide polymorphism; TZD, thiazolidinedione.

Approximately 80% of type 2 diabetic subjects are overweight or obese. The growing rate of obesity (1,2) is thought to directly impact the increasing prevalence of type 2 diabetes in North America (3). Recently, the hormone resistin (accession no. NM_020415) has been postulated to play a role at the nexus of these two complex traits (4). Resistin belongs to a family of secreted peptides (5,6) that shares a cysteine-rich COOH-terminus and forms disulfide-linked homodimers (7). Resistin was identified in the mouse by screening differentiated adipocytes for genes repressed by the antidiabetic drug rosiglitazone, a member of the class of insulin-sensitizing drugs known as thiazolidinediones (TZDs), which are thought to target peroxisome proliferator–activated receptor (PPAR)-γ (rev. in 8). Mouse resistin is expressed exclusively in adipocytes (4,9) and inhibits their differentiation in culture (9). Circulating levels of resistin are increased after high-carbohydrate meals (9) and in genetically and diet-induced obesity (4). In mice fed a high-fat diet, anti-resistin antibodies improve blood glucose and insulin action (4). Human resistin is expressed only at low levels in adipose tissue (10,11), and its contribution to these disease states is unclear.

Previous work demonstrated that the Pro12Ala variant of PPAR-γ affects susceptibility to diabetes (12 and refs. therein). Because PPAR-γ is thought to be a target for TZDs, we reasoned that polymorphisms in the resistin gene, whose expression appears to be regulated by TZDs in mice (4,13,14), might show a similar association with these related disorders. Therefore, we examined resistin for coding and noncoding variants. In the polymorphism discovery phase of this study, all exons, the exon-intron boundaries, and 472 bp of the 5′ flanking region of resistin were resequenced in 45 individuals from two study populations (15,16) representing a sample of diabetic, obese, and control individuals. In this phase of the study, seven variants were found: one substitution in the 3′ UTR

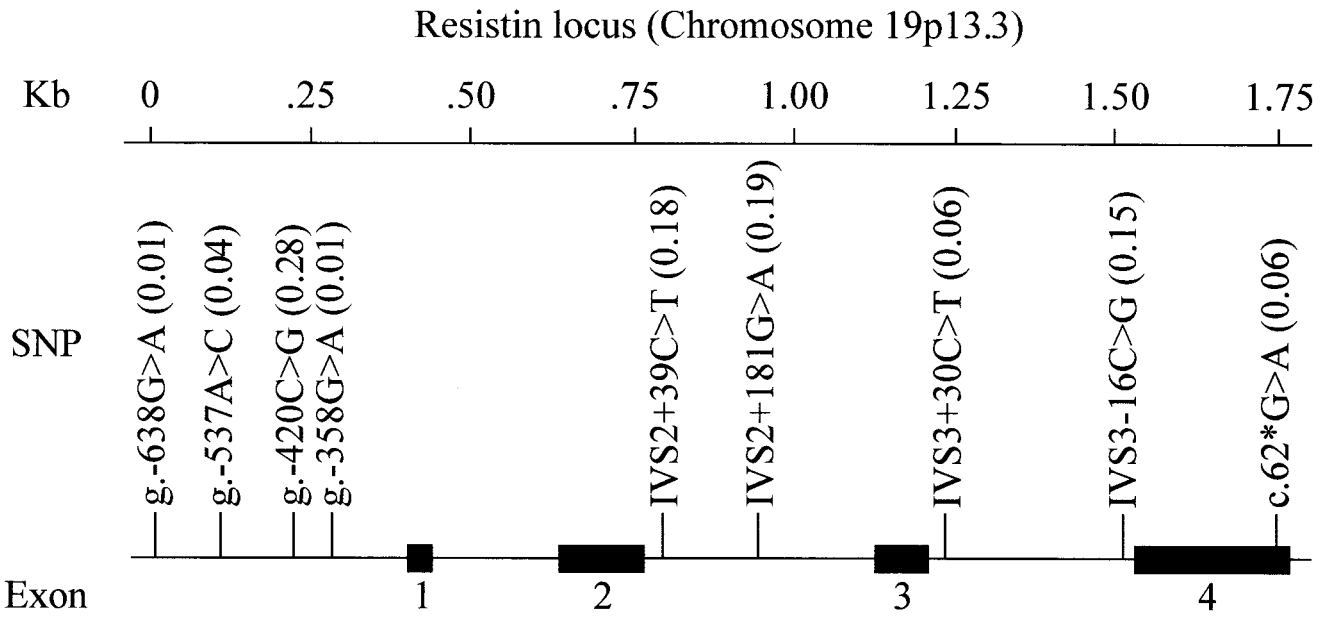

FIG. 1. SNPs in resistin. Schematic representation of the human resistin (FIZZ3) gene locus and exon structure and location of eight SNPs. Minor allele frequencies derived from all Quebec samples assayed are in parentheses (based on >300 samples for all SNPs except IVS3 + 30, which is based on 45 samples). SNP numbering is based on GenBank accession no. AF205952.

(c.*62G>A), two single-nucleotide polymorphisms (SNPs) in intron 2 (IVS2 + 39C>T and IVS2 + 181G>A), two SNPs in intron 3 (IVS3 + 30C>T and IVS3–16C>G), and two SNPs in the 5′ flanking region (g.-537A>C and g.-420C>G) (Fig. 1). Two polymorphisms were previously described (c.*62G>A and IVS2 + 39C>T) (17), and one (g.-420C>G) had been identified by the SNP Consortium (GenBank reference SNP no. 1862513). Because the two promoter polymorphisms are in close proximity, we elected to genotype them by sequencing genomic DNA. Two more rare 5′ flanking SNPs were identified in subsequent samples (g.-638G>A and g.-358G>A) (Fig. 1). These two SNPs appear to be in perfect linkage disequilibrium (LD), with the minor alleles present in the same 11 heterozygotes among 590 Quebec individuals.

As no coding variants were found and promoter variants are likely to play an important role in complex traits, we elected to first study the promoter SNPs for a possible relationship with diabetes or BMI. An association study was initiated to examine the two more common 5′ flanking SNPs (g.-537A>C and g.-420C>G) in a type 2 diabetic case/control sample from the Saguenay-Lac-St-Jean (SLSJ) region of Quebec and a population sample of men from the Quebec City (QC) area. Genotype distributions for these two variants did not differ significantly from Hardy-Weinberg equilibrium in either the QC or SLSJ case/control sample. In addition, allelic frequencies in these two study samples were not significantly different. To assess the association of the g.-537A>C and g.-420C>G polymorphisms with type 2 diabetes, we compared allele frequencies of these variants in the case/control study sample of diabetic and nondiabetic subjects recruited from the SLSJ area. As shown in Table 1, no difference in allele frequencies was observed between type 2 diabetic and nondiabetic subects. In a logistic regression model that included age and sex, neither the resistin g.-537A>C polymorphism nor the g.-420C>G polymorphism were significant contributors to diabetes (data not shown).

In the QC sample, an increase in BMI (30.4 vs. 29.2 kg/m^2, $P = 0.03$) was associated with the presence of the g.-420 G allele compared with the C/C genotype (Fig. 2*A*). Similarly, we found an association with the presence of the g.-537 C allele compared with the A/A genotype for BMI (31.8 vs. 29.7 kg/m^2), which was also significant ($P =$

TABLE 1
Genotype frequencies of 5′ flanking SNPs at the resistin locus

	Study sample 1 (SLSJ)				Study sample 2 (QC)		Study sample 3 (Scandanavia)			
	Diabetic subjects		Nondiabetic subjects		Nondiabetic subjects		Diabetic subjects		Nondiabetic subjects	
Variant	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese
−537										
AA	66 (91.7)	98 (91.6)	58 (86.6)	107 (94.6)	102 (88.7)	111 (95.7)	138 (96.5)	293 (94.8)	69 (95.8)	349 (95.9)
AC	6 (8.3)	8 (7.5)	9 (13.4)	5 (4.4)	13 (11.3)	5 (4.3)	5 (3.5)	16 (5.2)	3 (4.2)	15 (4.1)
CC		1 (0.9)		1 (0.9)						
−420										
CC	34 (47.2)	56 (52.3)	34 (50.7)	69 (61.1)	48 (41.7)	61 (52.6)	77 (54.2)	161 (51.9)	40 (55.6)	196 (54.3)
CG	36 (50.0)	42 (39.3)	29 (43.3)	40 (35.4)	56 (48.7)	44 (37.9)	52 (36.6)	118 (38.1)	25 (34.7)	131 (36.3)
GG	2 (2.8)	9 (8.4)	4 (6.0)	4 (3.5)	11 (9.6)	11 (9.5)	13 (9.2)	31 (10.0)	7 (9.7)	34 (9.4)

Percentage of each genotype is shown in parentheses.

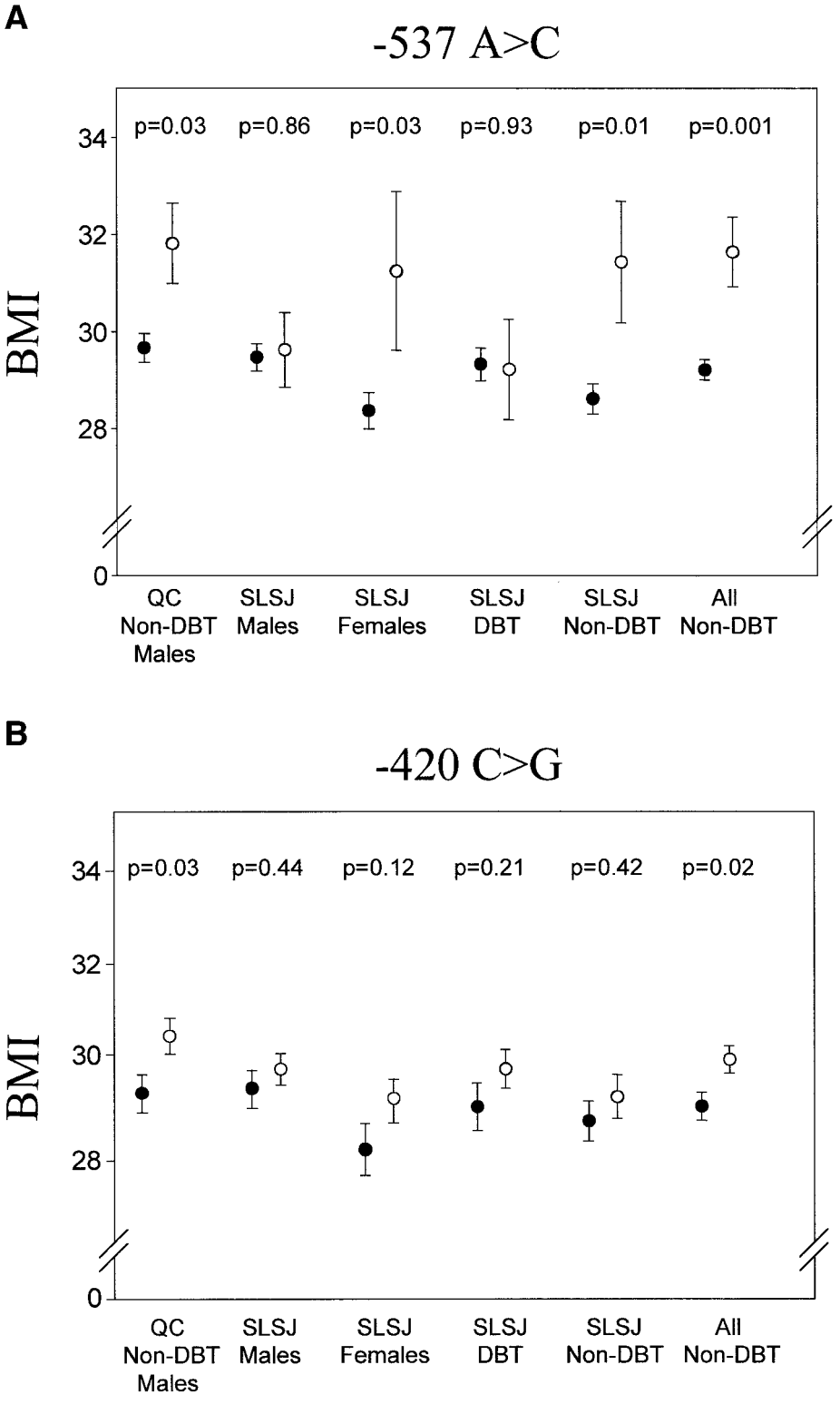

FIG. 2. Average BMI by genotype for g.-420 (*A*) and g.-537 (*B*). *A*: ●, CC genotype; ○, CG and GG genotypes combined. *B*: ●, AA genotype; ○, AC and CC genotypes combined. Error bars = SE of the mean. *P* values from Student's *t* test are shown above each comparison. DBT, diabetic; all non-DBT, all nondiabetic subjects from SLSJ combined with the QC samples.

0.03) (Fig. 2*B*), despite the low frequency (3.9%) of this allele. In addition, several indices of obesity were significantly associated with the G allele at g.-420: weight (92.8 vs. 87.9 kg, $P = 0.006$), body fat mass (27.8 vs. 25.4 kg, $P = 0.03$), and waist circumference (102.9 vs. 100.0 cm, $P = 0.04$) (Table 2). All of these same parameters were affected by the C allele at position g.-537. All differences remained statistically significant after adjustment for age (data not shown).

Because we observed an association of the g.-537 and

TABLE 2
Subjects' characteristics by genotype in the QC sample of nondiabetic men

Variable	−537			−420		
	A/A	A/C	*P*	C/C	C/G+G/G	*P*
Age (years)	42.5 ± 7.6 (212)	41.0 ± 8.6 (18)	0.43	43.1 ± 7.9 (109)	41.7 ± 7.4 (122)	0.17
BMI (kg/m^2)	26.3 ± 8.6 (213)	31.5 ± 7.3 (18)	0.01	25.4 ± 8.6 (109)	27.8 ± 8.5 (122)	0.03
Weight (kg)	89.8 ± 13.3 (213)	98.5 ± 12.7 (18)	0.008	87.9 ± 12.7 (109)	92.8 ± 13.6 (122)	0.006
Body fat mass (kg)	26.3 ± 8.6 (213)	31.5 ± 7.3 (18)	0.01	25.4 ± 8.6 (109)	27.8 ± 8.5 (122)	0.03
Waist circumference (cm)	101.0 ± 10.7 (212)	107.6 ± 10.1 (18)	0.01	100.0 ± 10.9 (108)	102.9 ± 10.5 (122)	0.04

Data are means ± SD (number of subjects).

c.-420 alleles with BMI in the QC sample, these alleles were analyzed in the SLSJ diabetic and nondiabetic subjects for their association with BMI. No association was observed between either of the polymorphisms and BMI in the whole study population (data not shown), but there was a statistically significant effect for carriers of the g.-537 C allele when only women were examined (P = 0.03) (Fig. 2*B*). Waist circumference was also significantly higher in these women (90.9 vs. 86.4 cm, P = 0.01). We also found a significantly higher BMI in carriers of the g.-537 C allele (P = 0.01), when only the nondiabetic subgroup of the SLSJ study population was examined (Fig. 2*A*). The most significant association of BMI and genotype was observed when combining all nondiabetic subjects from both studies, with both g.-420G and g.-537C significant at P = 0.017 and P = 0.001, respectively (Fig. 2*A* and *B*). All differences remained significant after adjustment for age (data not shown). In addition, in a family-based population sample from SLSJ that had some overlap with the case/control sample, a quantitative transmission disequilibrium test (QTDT) showed a significant contribution of the g.-537C allele to a higher BMI when age and sex were included in the model (P = 0.039). We note that as this family-based cohort contained some of the same individuals as the SLSJ case/control sample, this does not constitute an independent replication.

Using logistic regression analyses, we calculated odds ratios (ORs) for a BMI >30 kg/m^2. There was a strong agreement between the OR for the QC and the SLSJ study samples when only nondiabetic individuals were examined. For both of these groups, the OR was >1.5 for the g.-420G variant and >2.7 for the g.-537C variant (Table 3). Finally, for all nondiabetic subjects combined, the ORs for the G allele at g.-420C>G and the C allele at g.-537A>C are 1.58 (CI 1.06–2.35, P = 0.025) and 2.72 (1.28–5.81, P = 0.01), respectively, when age and sex are included in the model (Table 3).

The g.-420 G and the g.-537 C alleles are in significant LD with each other. In the 590 Quebec individuals studied thus far, the C allele at position g.-537 is present only in individuals bearing the G allele at position g.-420. We observed that the average BMI of those nondiabetic individuals possessing the C allele at position g.-537 (and thus possessing both variants) was higher than those possessing only the G allele at position g.-420 (P = 0.006).

It is possible that either of these 5′ polymorphisms may change a transcription factor binding site affecting resistin mRNA levels. A search for potential binding sites at positions g.-420 and g.-537 with MatInspector V2.2 (18) revealed several transcription factor motifs altered by these variant alleles (e.g., an AP1 site is destroyed by g.-537A>C). Although the precise mechanisms controlling resistin transcription remain to be elucidated, one report has implicated the β-adrenergic receptors and protein kinase A in decreased resistin expression (19).

We attempted to replicate our finding in Scandinavian study populations. There was no significant association between the two resistin promoter variants and obesity in these previously described (12) study populations, which included a diabetes case/control sample (Table 1), diabetic

TABLE 3
Logistic regression analyses for BMI >30 kg/m^2 for 5′ flanking SNPs at the resistin locus

Variant sample and phenotype	Individual variables	OR	Wald 95% CI	Wald adjusted *P* value
g.-420C				
SLSJ				
Diabetic subjects	Age, sex	1.26	0.69–2.32	0.45
Nondiabetic subjects	Age, sex	1.51	0.81–2.83	0.20
QC				
Nondiabetic subjects	Age	1.59	0.94–2.68	0.085
Combined				
Nondiabetic subjects	Age, sex	1.58	1.06–2.35	0.025
g.-537G				
SLSJ				
Diabetic subjects	Age, sex	1.00	0.33–3.00	0.99
Nondiabetic subjects	Age, sex	2.79	0.93–8.36	0.067
QC				
Nondiabetic subjects	Age	2.90	1.00–8.46	0.051
Combined				
Nondiabetic subjects	Age, sex	2.72	1.28–5.81	0.0097

trios, and normal glucose tolerant trios (QTDT, data not shown). In the case of g.-537, this may be because the rare allele had a frequency of 0.02 in the Scandinavian case/control sample, significantly lower than the 0.04 observed in Quebec ($P = 0.005$, Fisher's exact test) (Table 1). Three other alternatives may explain the lack of replication for the promoter variants: *1*) interacting loci or environmental conditions differ between these two populations and influence the phenotypic expression of the variants; *2*) resistin polymorphisms from Quebec are in LD with another functional variant in this or another gene, whereas the Scandinavian sample could be in linkage equilibrium with this other mutation; or *3*) the finding in the Quebec populations is spurious.

At present, very little is known about the function of resistin in humans, and the expression level in human adipose tissue remains controversial (10,11,20,21). However, Savage et al. (11) detected resistin more often in the fat of the morbidly obese than in normal control subjects, and McTernan et al. (20) found an increase in resistin in abdominal fat compared with thigh. Our results demonstrate an increased risk for higher BMI for carriers of two resistin promoter polymorphisms among French Canadians in Quebec. Interestingly, the observed effect appears to be strongest in nondiabetic subjects. In nondiabetic subjects, a change in the level of resistin may contribute to obesity, possibly as a result of misregulated transcription that has other physiological consequences in diabetic subjects. Alternatively, the basal or activated transcription of resistin in diabetic subjects may be different. Measuring levels of resistin in individuals with these variants could contribute to the characterization of the resistin promoter. The increased risk for obesity conferred by the resistin variants in these populations warrants additional studies in larger population samples.

RESEARCH DESIGN AND METHODS

Population samples. The diabetes case/control sample ($n = 359$, mean age 52.0 years) is described elsewhere (15). Briefly, the study population consisted of newly diagnosed type 2 diabetic subjects (1998 World Health Organization criteria) (22) from the SLSJ and age- and sex-matched control subjects (normal glucose tolerant). Some individuals were also enrolled in a family-based study of 79 families (424 individuals). The QC sample, comprised of 231 men (mean age 42.4 years) and selected for a wide range of adiposity, was previously described (16). Briefly, these subjects were sedentary, nonsmoking, and free of metabolic disorders requiring treatment, such as diabetes or hypertension. The Scandinavian case/control sample ($n = 968$, mean age 60.5 years) and family-based study populations are described elsewhere (12). Briefly, case subjects had either diabetes or severe IGT, and control subjects were matched for sex, age, and geographic location. The Scandinavian family-based study populations were based on trios in which offspring had either type 2 diabetes ($n = 126$), IGT ($n = 108$), impaired fasting glucose ($n = 99$), or normal glucose tolerance ($n = 379$). Patients gave informed consent, and research protocols were monitored by local institutional review boards.

Sequencing. Primer annealing temperatures were 56–60°C. PCR conditions were 50 ng genomic DNA, 1.25 units Qiagen HotStart *Taq* (Qiagen, Mississauga, Ontario, Canada) (1.5 mmol/l $MgCl_2$), 0.2 mmol/l dNTPs, and 0.4 μmol/l primers in a 50-μl reaction. PCR products were purified (Mulitiscreen; Millipore, Bedford, MA), and sequencing was performed using BigDye Terminator (version 2.0) and analyzed on ABI 3700 sequencers (Applied BioSystems, Foster City, CA). Data were processed using Sequencing Analysis software (version 3.6) and then aligned with Autoassembler 2.1 (Applied BioSystems). All exons, the exon-intron splicing boundaries, and the promoter of resistin were screened (see below for primers) by sequencing two Centre d'Etude du Polymorphisme Humain (CEPH) individuals and 45 individuals from SLSJ and QC, consisting of obese and nonobese patients (either nondiabetic or type 2 diabetic subjects). PCR products exhibited the expected lengths, consistent with the absence of deletions, duplications, or rearrangements.

Resistin sequencing primers. Primers were as follows: promoter F: tgtcattctcacccagagaca; promoter R: tgggctcagctaaccaaatc; exon 1–2F: gggacttattagccaagcca; exon 1–2R: tgggttggagtcaggtctgt. Intron 2F: gagaggatccaggaggtcg; intron 2R: aggtgacgctctggcact. Exon 3F: acagggctaggggaggatg; exon 3R: agtagaggctggacacggg. Exon 4F: cctcagcctcccagctca; exon 4R: agacgctagatcagtccctcc.

Statistical methods. Allele frequency and genotype distribution comparisons were assessed using the algorithms of Raymond and Rousset (23). Hardy-Weinberg analyses were performed based on Weir's algorithm (24), using Genetic Data Analysis (GDA) Version 1.0 (d12) by P.O. Lewis and D. Zaykin, available at http://lewis.eeb.uconn.edu/lewishome/gda.html.

Before analyses, distributions for BMI, weight, body fat mass, waist circumference, and abdominal adipose tissue (from computed tomography) were tested for skewness and kurtosis, and all variables were below one and four, respectively. Mean anthropometric values were compared between genotype classes using Student's t test. ANCOVA was used to adjust anthropometric variables for age. Logistic regression analyses were performed on the dependent variable, obesity, defined as BMI $\geq$30 kg/m^2 for obese versus BMI $<$30 kg/m^2 for nonobese subjects. ORs were adjusted for age and sex. Statistical analyses were performed with the SAS statistical package (SAS Institute, Cary, NC). All P values presented are nominal, as no corrections were made for multiple testing. The QTDTs were performed with the software QTDT version 2.2.1 (available at http://www.well.ox.ac.uk/asthma/QTDT), using an orthogonal association model (25).

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