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ADRB2 gene variants, dual-energy x-ray absorptiometry body composition, and hypertension in Tobago men of African descent

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Abstract

Classic tissue effects of β_2-adrenergic receptor activation include skeletal muscle glycogenolysis and vascular smooth muscle relaxation, factors relevant to obesity and hypertension, respectively. In a population-based study, we examined 2 common amino acid substitutions in the β_2-adrenergic receptor gene (*ADRB2*) in relation to body composition and blood pressure. A cross-sectional analysis of 1893 African-descent men living in Tobago and participating in a prostate cancer screening study was performed. Body mass index, waist circumference, blood pressure, dual-energy x-ray absorptiometry body composition, and *ADRB2* (Arg16Gly; Gln27Glu) genotype were determined. Twenty-six percent were obese (body mass index $\geq$30 kg/m^2), and 50% were hypertensive. *ADRB2* Arg16Gly and Gln27Glu alleles were in linkage disequilibrium (D' = 0.96, r^2 = 0.15). *ADRB2* 16Gly-containing and 27Glu-containing genotypes were equally frequent in low, medium, and high tertiles of percentage of body fat mass (16Gly-containing genotypes: 73.4%, 74.4%, and 74.5%, P_{trend} = .66; 27Glu-containing genotypes: 27.6%, 23.8%, and 25.4%, P_{trend} = .39) and in normal blood pressure, prehypertensive, and hypertensive men (16Gly-containing genotypes: 73.4%, 72.8%, and 74.4%, P_{trend} = .61; 27Glu-containing genotypes: 25.6%, 24.1%, and 26.7%, P_{trend} = .50). In a high-obesity and high–hypertension risk population with ancestry in common with African Americans, genetic variation defined by 2 common *ADRB2* amino acid substitutions was not associated with body composition or hypertension.

1. Introduction

Interacting with diet and physical activity, genetic factors contribute to obesity and hypertension.[1-3] Frequently studied candidate genes include the leptin [4], catecholamine [5], and peroxisome proliferators–activated receptors [6] and genes in the renin-angiotensin system.[7] Stimulating β-adrenergic receptor function promotes lipolysis in fat cells. [2,8] The β_2-adrenergic receptor gene (*ADRB2*) attracts interest because catecholamine activation of the β_2-adrenergic receptor regulates skeletal muscle glycogenolysis and vascular smooth muscle relaxation.[9,10] The *ADRB2* single nucleotide polymorphisms most often studied in human populations substitute glycine for arginine at codon 16 (Arg16Gly) and glutamic acid for glutamine at codon 27 (Gln27Glu) [11].

Despite numerous published studies, the connection, if any, between *ADRB2* Arg16Gly or Gln27Glu genotype and metabolic phenotypes, including obesity and hypertension, is tentative. Results from early recombinant cell culture experiments [12], for example, launched a long-standing hypothesis asserting that the *ADRB2* 16Gly variant promoted obesity and hypertension by causing receptor down-regulation and physiologic desensitization in response to chronic agonist stimulation [13]. However, subsequent human experiments showed agonist-induced desensitization only in persons with the *ADRB2* 16Arg variant [13-15]. A 2008 meta-analysis examined obesity risk in relation to *ADRB2* codon 16 variation (13 studies with 6825 subjects) and in relation to *ADRB2* codon 27 variation (28 studies with 14 450 subjects) [11]. Random effects meta-regression analysis showed statistically insignificant obesity risks in

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relation to 16Arg-containing genotype (odds ratio [OR], 1.02; 95% confidence interval [CI], 0.89-1.18) and in relation to 27Glu-containing genotype (OR, 1.11; 95% CI, 0.98-1.27). However, meta-analysis restricted to Asian (7 studies with 3575 subjects), Pacific Island (1 study with 1020 subjects), and native South American populations (1 study with 149 subjects) showed statistically significant association between 27Glu-containing genotype and obesity (OR, 1.46; 95% CI, 1.02-2.10). One study [16] with African American subjects, but not a second [17], showed association between obesity measures and *ADRB2* genotype.

We defined a large population on the Caribbean island of Tobago with ancestry in common with African Americans, determined *ADRB2* Arg16Gly and Gln27Glu genotypes, measured blood pressure, and used dual-energy x-ray absorptiometry (DEXA) to estimate body composition. Analyses examined *ADRB2* genotypes in relation to body composition and hypertension.

2. Materials and methods

2.1. Study sample

Between September 1997 and September 2007, the Tobago Prostate Study used public service announcements, flyers, local health care workers, and word of mouth to solicit 40- to 79-year-old men in Tobago for participation in a study of periodic prostate cancer screening [18]. The study excluded nonambulatory, terminally ill, or cognitively impaired men. Participants signed written informed consent. The Institutional Review Boards of the University of Pittsburgh and Tobago Division of Health and Social Services approved the research protocol.

The Tobago Prostate Study enrolled 3837 men. Standardized entry questionnaires provided demographic and basic cancer risk factor information. To support studies of obesity, hypertension, diabetes, and musculoskeletal health, men enrolling or returning after January 2004 also completed a detailed standardized staff-administered health history questionnaire. We defined, for the current analysis, a race-eligible study group that consisted of 3363 (87.6% of 3837) men reporting 4 grandparents of African descent (when data were not missing) or self-reporting black or African race (when grandparents' data were missing).

Procedures included periodic musculoskeletal tests (DEXA and/or quantitative computed tomography) and, for the subset of men who completed the health history questionnaire and accepted musculoskeletal testing, genetic tests. Information from DEXA was available for 2766 (82.2%) and health history questionnaires for 2170 (64.5%) of 3363 race-eligible men and *ADRB2* Arg16Gly and/or Gln27Glu genotypes for 1890 (92.2%) of 2049 race-eligible men with both health history questionnaires and DEXA. Data analyses included 1893 (1888 with DEXA) *ADRB2* genotyped men with health history questionnaires affirming 4 grandparents of African descent. When compared against the group of men not available for the health history questionnaire (n = 1193), n = 12 missing grandparents' race on health history questionnaire, or not otherwise genotyped (n = 265), the 1893 men included in analyses enrolled at younger age (median, 52 vs 56 years, P (Wilcoxon) < .0001). Genotyped and nongenotyped race-eligible men available for the health questionnaire had statistically similar body mass index (BMI), waist circumference, hypertension prevalence, and body composition (percentage of body fat).

ADRB2 Arg16Gly (rs1042713) and Gln27Glu (rs1042714) genotype determinations used a TaqMan allelic discrimination assay performed on an Applied Biosystems (Foster City, CA) 7900HT Fast Real-Time PCR System. Call rates for the *ADRB2* Arg16Gly and Gln27Glu polymorphisms were 97.0% and 94.5%, respectively. *ADRB2* Arg16Gly, Gln27Glu, and both Arg16Gly and Gln27Glu genotypes were available for 1790 (94.6%), 1800 (95.1%), and 1697 (89.6%) men included in data analyses, respectively. Genotype distributions for *ADRB2* Arg16Gly and Gln27Glu satisfied Hardy-Weinberg equilibrium conditions ($P > .05$). Allele frequencies (16Gly, 49.6%; standard error, 0.8% and 27Glu, 13.9%; standard error, 0.6%) estimated for the 1893 men included in data analyses agreed with values reported by the International HapMap Project (www.hapmap.org) for the Yoruba population (50.0% and 17.5%, respectively). *ADRB2* Arg16Gly and Gln27Glu alleles were in linkage disequilibrium ($D' = 0.96$, $r^2 = 0.15$).

2.2. Outcome measurements

Outcome measurements included height (measured without shoes to the nearest 0.1 cm on a wall-mounted stadiometer), weight (measured without shoes to the nearest 0.1 kg on a balance beam scale), BMI (calculated as weight in kilograms divided by height in meters squared), and waist circumference (measured in centimeters at the umbilicus with an inelastic tape measure). Percentage of body fat was acquired on a Hologic QDR 4500W DEXA operated in array beam mode and analyzed with QDR software version 8.26a (Hologic, Bedford, MA). After seating and resting subjects for 5 minutes, technicians selected an appropriate cuff size and used an automated OMRON HEM705CP sphygmomanometer (Omron Healthcare, Vernon Hills, IL) to obtain 3 consecutive blood pressure measurements.

2.3. Statistical analysis

Using the second and third measurements, if available, or any 2 available measurements otherwise, analyses calculated average values for systolic (SBP) and diastolic blood pressure (DBP). Using these measurements, we classified subjects into 3 mutually exclusive hypertension categories: hypertension (SBP >140 mm Hg or DBP >90 mm Hg or current antihypertensive medication use), prehypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg and current antihypertensive medication nonuse), and normal (SBP <120 mm Hg and DBP <80 mm Hg and current

Table 1
Body composition measures (means ± SDs) according to *ADRB2* genotype, restricted to subjects with 4 grandparents of African descent

Body composition measure	Arg16Gly				Gln27Glu			
	Arg/Arg	Arg/Gly	Gly/Gly	*P* value[a]	Gln/Gln	Gln/Glu	Glu/Glu	*P* value[a]
All men								
n[b]	462-465	871-875	446-449		1335-1339	418-421	39	
Height (cm)	175.8 ± 7.1	175.0 ± 6.9	174.5 ± 6.6	.0181	174.8 ± 6.8	175.5 ± 7.2	175.8 ± 6.6	.1393
Weight (kg)	85.1 ± 15.2	84.9 ± 17.1	82.7 ± 15.6	.0363	84.6 ± 16.2	84.8 ± 17.5	84.2 ± 14.6	.9683
Waist circumference (cm)	93.6 ± 12.8	93.4 ± 11.2	91.9 ± 11.3	.0488	93.3 ± 11.6	93.0 ± 11.4	92.3 ± 9.0	.7723
BMI (kg/m^2)	27.5 ± 4.5	27.7 ± 5.2	27.1 ± 4.7	.1678	27.7 ± 4.9	27.5 ± 5.2	27.2 ± 4.0	.6617
Total body fat (%)[c]	20.9 ± 6.4	21.2 ± 6.3	20.6 ± 6.2	.2247	21.2 ± 6.3	20.9 ± 6.5	21.5 ± 6.1	.6474
Obese men (BMI ≥30 kg/m^2)								
n[b]	128-130	213-215	109-110		345-349	107-108	9	
Height (cm)	174.8 ± 6.6	175.4 ± 6.3	174.1 ± 6.8	.2514	174.6 ± 6.2	175.3 ± 7.4	177.8 ± 7.0	.2361
Weight (kg)	101.2 ± 12.4	105.0 ± 17.4	101.4 ± 13.0	.0369	103.0 ± 14.8	104.3 ± 18.2	103.0 ± 8.1	.7522
Waist circumference (cm)	105.5 ± 9.8	106.5 ± 9.1	104.9 ± 8.2	.3028	106.0 ± 9.4	105.9 ± 8.3	102.5 ± 3.1	.5298
BMI (kg/m^2)	33.1 ± 3.1	34.1 ± 5.4	33.4 ± 3.4	.0863	33.8 ± 4.5	33.9 ± 5.0	32.6 ± 1.4	.7302
Total body fat (%)[c]	25.8 ± 5.2	26.6 ± 4.7	26.0 ± 4.3	.3408	26.2 ± 4.7	26.5 ± 4.9	26.2 ± 3.8	.8005

[a] Statistical significance (analysis of variance) of differences in mean values across genotype categories.
[b] Sample numbers vary because of missing attribute data.
[c] Total body (except head) fat mass expressed as a percentage of total body (except head) mass.

antihypertensive medication nonuse). Sixty-two (3.3%) men were not classified because of missing blood pressure measurements (n = 6) and/or missing or inconsistent self-reports of antihypertensive medication use (n = 61). The BMI classification used the World Health Organization cut points (underweight, <18.5 kg/m^2; normal weight, 18.5-24.9 kg/m^2; overweight, 25-29.9 kg/m^2; and obese, ≥30 kg/m^2).

Statistical analyses (SAS 9.2; SAS Institute, Cary, NC) used conventional methods (χ^2 or Fisher exact tests for discrete data and *t* tests, analysis of variance, or Wilcoxon rank sum tests for continuous data) to evaluate the significance of group differences. Haplotype-based analyses used the Expectation-Maximization algorithm implemented in SAS Genetics (PROC HAPLOTYPE) to estimate group-level haplotype frequencies and to generate subject-level haplotype probability weights.[1] Expectation-Maximization algorithm refers to a statistical genetic method commonly used to estimate haplotype frequencies from genotype data where gametic phase is ambiguous for individuals who are heterozygous at more than one locus [19]. We then used simple linear regression (implemented in SAS PROC GENMOD with normal probability distribution and identity link function) to estimate independent associations between the haplotype probability weights and continuous outcomes (BMI and total body percentage of body fat) and logistic regression (implemented in SAS PROC LOGISTIC) to estimate independent associations between the haplotype probability weights and binary outcomes (hypertension or prehypertension vs normal blood pressure).

We used Quanto (Version 1.2.4; http://hydra.usc.edu/GxE) to estimate the statistical power of studies designed to detect genetic effects on a continuous outcome with 6.3-unit population standard distribution (corresponding to the value observed for percentage of body fat) under an additive model tested at $\alpha = .05$ (2-sided). For polymorphisms with 0.50 and 0.14 minor allele frequencies (corresponding to the values observed for Arg16Gly and Gln27Glu), a study genotyping 1850 unrelated subjects detects (at 80% power) per allele effects of 0.6 and 0.9 units, respectively.

3. Results

Study men had a mean age of 58.9 years (SD, 10.4 years). More than half (50.5%) were hypertensive, 32.4% were prehypertensive, 43.9% were overweight, and 25.6% were obese. One (16.5%) in 6 self-reported a physician diagnosis of diabetes.

Genotype frequencies were 26.0% Arg/Arg, 48.9% Arg/Gly, and 25.1% Gly/Gly at codon 16 (n = 1790) and 74.4% Gln/Gln, 23.4% Gln/Glu, and 2.2% Glu/Gly at codon 27 (n = 1800). The prevalence of obesity (BMI ≥30 kg/m^2) did not vary according to genotype (28.0% of 465, 24.6% of 873, and 24.5% of 449 men with the codon 16 Arg/Arg, Arg/Gly, and Gly/Gly genotype, $P = .3562$, and 26.1% of 1338, 25.7% of 420, and 23.1% of 39 men with the codon 27 Gln/Gln, Gln/Glu, and Glu/Glu genotype, $P = .9085$). Height, weight, and waist circumference were slightly higher in men with a 16Arg allele (Table 1). Arg16Gly associations with height, weight, and waist circumference reached statistical significance ($P = .0181$, .0363, and .0488, respectively). Otherwise, weight, waist circumference, BMI, and percentage of body fat were unrelated to *ADRB2* genotype (Table 1). In the obese subset, body measurements did not vary in any systematic or meaningful way with respect to *ADRB2* genotype (Table 1).

ADRB2 16Gly-containing and 27Glu-containing genotypes were equally frequent in low, medium, and high tertiles

[1] http://support.sas.com/documentation/cdl/en/geneug/59659/HTML/default/geneug_haplotype_sect021.htm.

Table 2
ADRB2 genotype and body composition, restricted to subjects with 4 grandparents of African descent

ADRB2 genotype	Percentage of total body fat[a]						
	Low tertile n = 629		Middle tertile n = 630		High tertile n = 629		
	n	%	n	%	n	%	
Arg16Gly							
Arg/Arg	158	26.6	153	25.6	151	25.5	P_{global} = .76
Arg/Gly	279	47.0	294	49.2	301	50.7	
Gly/Gly	157	26.4	151	25.2	141	23.8	
Arg/Gly or Gly/Gly	436	73.4	445	74.4	442	74.5	P_{trend} = .66
Gln27Glu							
Gln/Gln	424	72.4	454	76.2	457	74.6	P_{global} = .24
Gln/Glu	146	24.9	135	22.6	140	22.8	
Glu/Glu	16	2.7	7	1.2	16	2.6	
Gln/Glu or Glu/Glu	162	27.6	142	23.8	156	25.4	P_{trend} = .39

[a] Percentage of total body fat (total body [except head] fat mass expressed as a percentage of total body [except head] mass). Low tertile: 4.769 to 18.764; middle tertile, 18.765 to 23.745; and high tertile, 23.746 to 44.352.

of percentage of body fat (Table 2; 16Gly-containing genotypes: 73.4%, 74.4%, and 74.5%, P_{trend} = .66; 27Glu-containing genotypes: 27.6%, 23.8%, and 25.4%, P_{trend} = .39) and in normal blood pressure, prehypertensive, and hypertensive men (Table 3; 16Gly-containing genotypes: 73.4%, 72.8%, and 74.4%, P_{trend} = .61; 27Glu-containing genotypes: 25.6%, 24.1%, and 26.7%, P_{trend} = .50). In men not taking antihypertensive medication, systolic, diastolic, and mean arterial blood pressure values were unrelated to *ADRB2* genotype (data not shown).

Estimated *ADRB2* Arg16Gly Gln27Glu haplotype frequencies were Arg-Gln 50.0% (standard error, 0.8%), Gly-Gln 36.0% (standard error, 0.8%), Gly-Glu 13.6% (standard error, 0.6%), and Arg-Glu 0.3% (standard error, 0.1%). Fig. 1 uses box plots to summarize BMI and percentage of body fat distributions in men classified according to most probable haplotype combination. In linear models, the less common Gly-Gln and Gly-Glu haplotypes associated with lower BMI and lower percentage of body fat (Table 4). In obese men, one or both haplotypes associated with higher percentage of body fat and lower waist circumference (Table 4). However, none of these associations, including the apparent interaction between haplotype and obesity grouping (data not shown), was statistically significant. Finally, logistic regression did not show statistically significant *ADRB2* haplotype associations with either prehypertension or hypertension (data not shown).

4. Discussion

Mediating fat cell lipolysis [2,8] and vascular smooth muscle relaxation [10], *ADRB2* gene variants that code for functionally altered receptors could promote weight gain or high blood pressure. In a study of 1893 Tobago men of African ancestry, however, we observed no significant body composition or blood pressure associations with the 2 most commonly studied *ADRB2* gene variants.

Different investigations have reached different conclusions about the significance of *ADRB2* genotype in relation to obesity and related phenotypes [11,20-22]. Variability related to sex may explain inconsistencies in the published literature. Some authors, including Corbalan et al [23] and González Sánchez et al [24], suggest that *ADRB2* genotype determines not obesity, but obese subtype, perhaps in only one sex group. For example, in a Spanish clinic-based study with 40 men and 199 women, Corbalan et al [23] compared the *ADRB2* Gln27Glu genotypes of subjects with either abdominal obesity (BMI >30 kg/m^2 and waist-to-hip ratio >0.85) or normal body mass (BMI <25 kg/m^2 and waist-to-hip ratio <0.85). In men, but not women, 27Glu-containing genotypes were more frequent in the group with abdominal obesity. In a Spanish population-based study with 319 white men and 347 white women, González Sánchez et al [24] noted a statistically nonsignificant trend in men (but not women) between *ADRB2* Gln27Glu genotype and obesity prevalence (20.0% of 130, 27.7% of 155, and 29.4% of 34 men with the codon 27 Gln/Gln, Gln/Glu, and Glu/Glu

Table 3
ADRB2 genotype and hypertension, restricted to subjects with 4 grandparents of African descent

ADRB2 genotype	Normal blood pressure n = 314		Prehypertensive n = 593		Hypertensive n = 924		
	n	%	n	%	n	%	
Arg16Gly							
Arg/Arg	79	26.6	153	27.2	223	25.6	P_{global} = .94
Arg/Gly	143	48.2	274	48.8	423	48.6	
Gly/Gly	75	25.2	135	24.0	225	25.8	
Arg/Gly or Gly/Gly	218	73.4	409	72.8	648	74.4	P_{trend} = .61
Gln27Glu							
Gln/Gln	218	74.4	432	75.9	646	73.3	P_{global} = .73
Gln/Glu	71	24.2	125	22.0	217	24.6	
Glu/Glu	4	1.4	12	2.1	18	2.1	
Gln/Glu or Glu/Glu	75	25.6	137	24.1	235	26.7	P_{trend} = .50

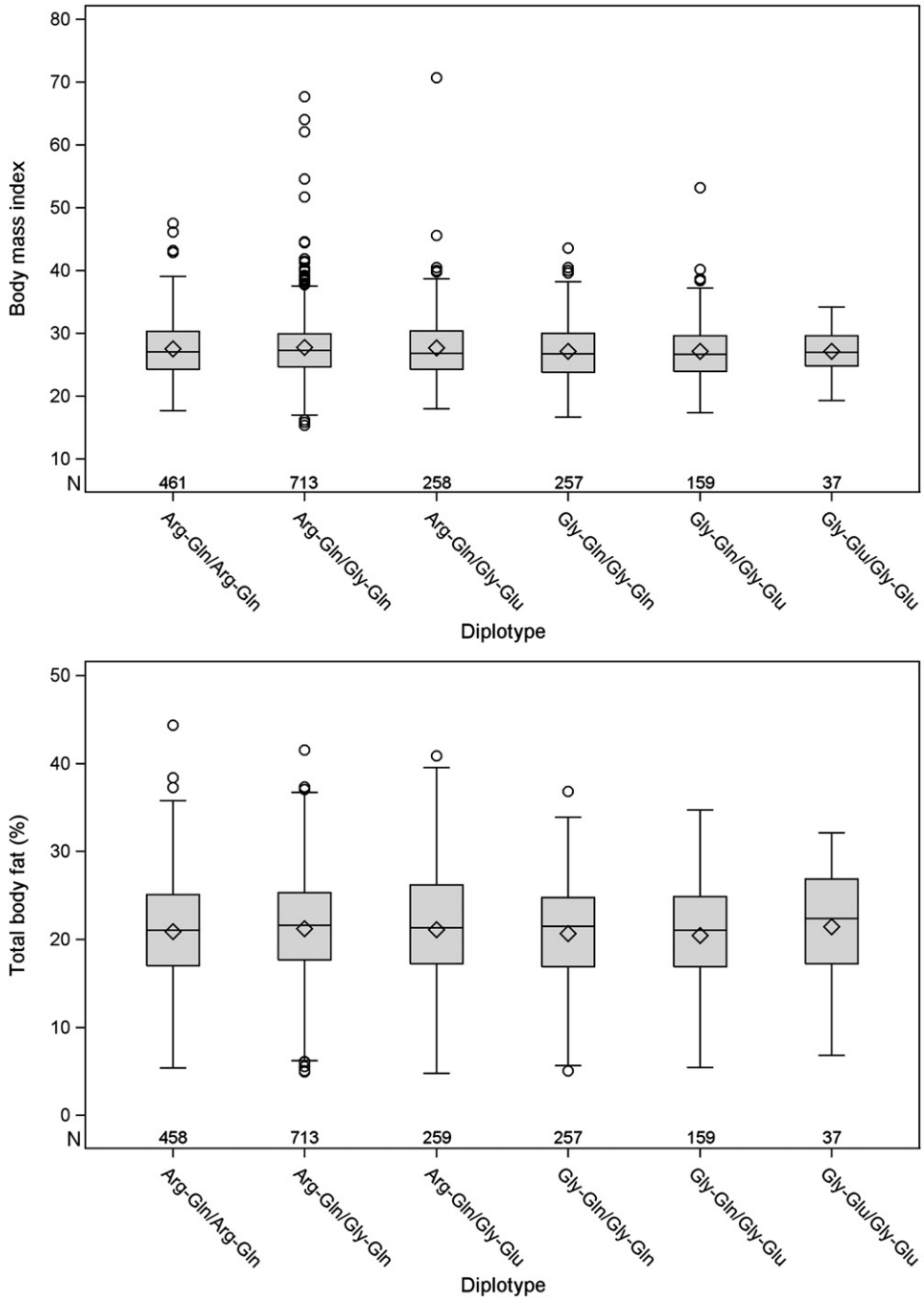

Fig. 1. Box plots showing BMI (upper figure) and DEXA-determined percentage of body fat (lower figure) in men subgrouped according to diplotype (most probable *ADRB2* Arg16Gly Gln27Glu haplotype combination). The number in each subgroup appears above the diplotype label. Analyses exclude 6 men with an Arg-Glu haplotype-containing diplotype. The line segment and diamond symbol within each box identify the median and mean, respectively. The lower and upper borders of each box identify the 25th and 75th percentiles, respectively. The lower whisker extends to the minimum observation greater than or equal to the 25th percentile minus 1.5 times the interquartile range. The upper whisker extends to the maximum observation less than or equal to the 75th percentile plus 1.5 times the interquartile range. Open circle symbols identify individual observations less than the 25th percentile minus 1.5 times the interquartile range or greater than the 75th percentile plus 1.5 times the interquartile range.

genotype, respectively, $P = .2572$). In the obese subset, men with the rare Glu/Glu genotype had significantly higher mean BMI (34.1 kg/m^2, n = 10) than men with either the Gln/Glu (31.9 kg/m^2, n = 46, $P = .013$) or Gln/Gln genotype (32.0 kg/m^2, n = 26, $P = .023$). To support specific association with abdominal obesity, González Sánchez et al [24] noted that obese men with the rare Glu/Glu genotype also had significantly higher mean sagittal abdominal diameter (27.8 cm, n = 10) than obese men with either the Gln/Glu (24.9 cm, n = 46, $P = .037$) or Gln/Gln genotype

Table 4
Estimated difference (Δ; and 95% CI) in body composition measure between men homozygous for a specified haplotype relative to men homozygous for the Arg-Gln haplotype

Body composition measure	n	Gly-Gln			Gly-Glu		
		Δ	95% CI	*P* value	Δ	95% CI	*P* value
BMI (kg/m^2)	1890	−0.36	−1.06, 0.34	.3109	−0.59	−1.56, 0.39	.2370
Total body fat %[a]	1888	−0.29	−1.19, 0.60	.5198	−0.54	−1.79, 0.70	.3923
Total body fat %[a], in obese men	479	0.00	−1.31, 1.31	.9989	0.51	−1.35, 2.37	.5916
Waist circumference (cm), in obese men	481	−0.42	−2.93, 2.10	.7458	−1.29	−4.88, 2.30	.4819

[a] Total body (except head) fat mass expressed as a percentage of total body (except head) mass.

(24.9 cm, n = 26, *P* = .062). Among obese women, sagittal abdominal diameter was not related to *ADRB2* Gln27Gly genotype. In agreement with González Sánchez et al, we observed no statistical association between obesity prevalence and *ADRB2* genotype. Among obese Afro-Caribbean men, BMI, waist circumference, and body fat values were unrelated to *ADRB2* genotype (Table 1). Simply, our results do not support a relationship, specifically in obese men, between *ADRB2* genotype and obesity subtype.

Excluding persons treated for high blood lipids, high blood pressure, or diabetes, Meirhaeghe et al [25] studied a population-based sample of 836 35- to 64-year-old urban-dwelling persons from northern France (419 men and 417 women; 14.2% obese overall) and observed sex-specific associations between *ADRB2* genotype and body composition. Body weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio mean values were significantly higher in men with the codon 16 Arg/Arg genotype than men with either the Arg/Gly or Gly/Gly genotype and significantly higher in men with the codon 27 Glu/Glu genotype than men with either the Gln/Glu or Gln/Gln genotype. In women, differences were not statistically significant. Observing linkage disequilibrium between 16Arg and 27Gln, Meirhaeghe et al [25] compared, in men, body composition measures according to combined genotypes at Arg16Gly and Gln27Gly. With the Gly-Glu haplotype serving as reference, higher body weight, BMI, and waist-to-hip ratio associated with the Arg-Gln haplotype, not with the Gly-Gln haplotype. In Afro-Caribbean men, body weight and waist circumference were slightly higher in men with a 16Arg allele (Arg/Arg or Arg/Gly genotype) than men without a 16Arg allele (Gly/Gly genotype; Table 1). However, BMI and percentage of body fat did not vary according to Arg16Gly genotype. Body weight, waist circumference, BMI, and percentage of body fat were completely independent of Gln27Glu genotype.

Only 2 studies [16,17] to date have included a meaningful number of African Americans. The Insulin Resistance and Atherosclerosis Family Study [16] genotyped 272 African Americans and 720 Hispanic Americans from 18 and 45 families, respectively, and used single-slice computed tomography to measure visceral and subcutaneous fat. Obesity measures associated with Gln27Glu, specifically the Glu/Glu genotype, but not with Arg16Gly genotype. High visceral fat area associated with the Glu/Glu genotype, even after control for BMI. Results for men and women and for African and Hispanic Americans were statistically indistinguishable. The Heritage Family Study included 274 African Americans (31.8% obese) and 502 whites (19.3% obese) and used underwater weighing to measure fat mass, single-slice computed tomography to measure visceral and subcutaneous fat, and skin calipers to measure skin-fold thickness [17]. In white obese (BMI ≥30 kg/m^2) subjects only, the Heritage Family Study observed *lower* fat mass in obese white men with 27Glu-containing genotypes and lower fat mass in obese white women with 16Gly-containing genotypes. In African American subjects, the Heritage Family Study did not report any statistically significant cross-sectional associations between *ADRB2* genotype and any body composition measure.

One study of *ADRB2* genotype included Afro-Caribbeans recruited from primary care clinics located on St Vincent [26]. The case group included 136 patients (19.9% men) with high blood pressure (DBP >95 mm Hg or antihypertensive medication use) and family history of hypertension. The control group included 81 patients (46.9% men) with normal blood pressure (DBP <85 mm Hg and antihypertensive medication nonuse) and no family history of hypertension. The 16Gly allele was much more frequent in the case group (84.6% vs 66.7%, *P* = .000014). Our community-based study of 1893 Afro-Caribbean men from Tobago included 318 and 537 persons who satisfied the St Vincent case and control definitions. In Tobago, 16Gly was also more frequent in cases (51.9% vs 48.4%). However, the difference was not statistically significant (*P* [allele χ^2] = .1655). In the St Vincent study, genotype frequencies in both the case and control groups violated Hardy-Weinberg equilibrium. The control frequency (66.7%) of the putative risk allele (16Gly) in St Vincent was high when compared against reference frequencies in the HapMap Yoruba (50.0%) and Tobago populations (49.6%). Therefore, selection bias and genotyping error plausibly explain the anomalous St Vincent results.

Our study participants volunteered for prostate cancer screening, in many instances survived a variable duration after study entry, and agreed to extra visits that included measurements, such as DEXA. Therefore, absence of meaningful association between *ADRB2* genotype and body composition could occur if these study selection factors preferentially excluded men with certain genotype-

phenotype combinations. However, selection bias deriving from factors related to initial study participation can be discounted to the extent that the Tobago Prostate Study, as a whole, enrolled a high proportion (60%) of age-eligible men (approximately 5000) living in Tobago. To address possible survival bias, we compared the 1661 and 232 men who had body composition measurements after study entry and coincident with study entry, respectively, and found statistically similar relationships between *ADRB2* genotype and body composition (data not shown). Finally, study procedures captured a reasonable proportion (1893 of 3363, 56.3%) of race-eligible Tobago Prostate Study enrollees.

Results from some studies suggest specific *ADRB2* association with regional fat distribution [16,23-25]. Our primary body composition measures, BMI and DEXA-derived percentage of body fat, do not distinguish between visceral and subcutaneous fat. However, our data set included waist circumference, an indirect measure of central obesity. Waist circumference and *ADRB2* genotype were statistically independent (Table 1). When compared against criterion methods, such as total body water measured by isotope dilution, the Hologic QDR 4500W DEXA operated in array beam mode underestimates fat mass and percentage of body fat by 10% [27]. Unless related to genotype, this systematic measurement error should not bias associations observed between genotype and body composition.

Finally, we evaluated only 2 *ADRB2* genetic variants. These variants change the amino acid sequence of the β_2-adrenergic receptor protein. However, these changes are not generally believed to alter agonist binding or signal transduction [13]. The Arg16Gly and Gln27Glu variants may affect function secondarily, perhaps through agonist-induced receptor protein down-regulation or linkage disequilibrium with other less common but more influential variants [13].

In a large racially homogenous population of men with black African ancestry and high prevalence of obesity and hypertension, single-variant and haplotype-based analyses did not show meaningful or consistent association between *ADRB2* Arg16Gly and Gln27Glu variation and phenotypes related to obesity and hypertension.

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