The Trp64Arg Mutation of the β_3-Adrenergic Receptor Is Associated With Hyperglycemia and Current Body Mass Index in Jamaican Women

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The Trp64Arg mutation of the β_3-adrenergic receptor (β_3-AR) has been linked to earlier onset of non–insulin-dependent diabetes mellitus (NIDDM), insulin resistance, abdominal obesity, and an increased capacity to gain weight in some European and Japanese populations. We studied the prevalence of the mutation and its association with NIDDM and obesity in our population, in which both rates are high, especially in women. The frequency of the homozygous mutation was 1.53%, and of the Arg allele, 10.5%. Rates were similar in men and women. Significantly higher body mass index (BMI), weight, hip circumference, and fasting and postchallenge 2-hour blood glucose concentrations were associated with the presence of the Arg allele in women but not in men. The association with weight and hip measurements and with hyperglycemia was present only in women aged less than 55 years. In multivariate analysis, the mutation was associated with the BMI and sex in a model that also included age. The variation in fasting and 2-hour blood glucose levels was predicted by β_3-AR, gender, age, and BMI. These results suggest that the presence of the mutation contributes to obesity and hyperglycemia in our female population.

THE β_3-ADRENERGIC RECEPTORS (β_3-ARs) are G-protein–coupled receptors that span the cell membrane and are expressed in various fat depots, as well as in the gallbladder and colon. Stimulation by β-adrenergic agonists leads to increased lipolysis and thermogenesis.[1] The presence of uncoupling protein (UCP) in these depots was interpreted to indicate the presence of brown fat,[1] but there is recent evidence that UCP is also expressed in white adipose tissue.[2] The receptors have been implicated in the increased release of free fatty acids from visceral fat to the portal vein and the metabolic disturbances associated with upper-body fat.[3,4] Several studies have suggested that a mutation in codon 64 of the gene, which results in substitution of Trp by Arg in the first intracellular loop of the protein, is associated with the features of insulin resistance and a decreased resting metabolic rate,[5] earlier onset of non–insulin-dependent diabetes mellitus (NIDDM),[6] rapid weight gain in morbidity obese patients,[7] obesity and a low insulin sensitivity index,[8] and a decreased basal metabolic rate (BMR).[9] Other studies have found no association between the mutation and these indices of dysglycemia and obesity.[10]

Frequencies of the mutant allele have been reported to vary from 4% in Europeans to 31% and 37% in Pima Indians and Japanese, respectively.[5,10] A frequency of 12% was reported in African-Americans.[5] The number of individuals homozygous for the mutation is low, and in some studies no homozygotes were reported.[6,7] For several of the studies, the number of participants was small and phenotypic differences were often only of borderline significance.[10,11] In a group of elderly Australians (257 men and 429 women), the mutation was associated with the body weight, body mass index (BMI), and diastolic blood pressure only in women.[12]

NIDDM is a major cause of morbidity and mortality in our population, and obesity rates are especially high in women.[13] This study was performed to determine if the Trp64Arg mutation is associated with markers of obesity and/or diabetes.

SUBJECTS AND METHODS

Subjects were recruited as part of a survey aimed at determining the prevalence of hypertension and diabetes mellitus in a representative sample of Jamaica's population demographics. The sampling methodology was single-stage cluster sampling by probability proportionate to size.[14] All subjects were of predominantly African origin, and were defined as black by interviewer classification, self-categorization, and having three black grandparents.

Anthropometry

Subjects were invited to a local clinic at which the height, weight, and waist and hip circumferences were measured, and these measurements were used to derive the BMI and waist to hip ratio (WHR), respectively.

Blood Samples

Subjects who had fasted overnight underwent a 2-hour oral glucose tolerance test. At time 0, blood was drawn for estimation of fasting glucose, C-peptide, and insulin levels and preparation of genomic DNA. At 2 hours, samples were taken for glucose determinations. Buffy coats were prepared from 10 to 20 mL blood (EDTA anticoagulant) and stored at −70°C prior to DNA extraction. Glucose was estimated by the glucose oxidase method using an Abbott VP autoanalyzer (Chicago, IL). C-peptide and insulin levels were measured by enzyme-linked immunosorbent assays (Medgenix/Biosource, Fleurus, Belgium).

Genotyping

Genomic DNA was extracted from buffy coats by digestion with proteinase K followed by phenol extraction. Polymerase chain reaction (PCR) amplification of a 210-basepair fragment was made in a volume of 20 μL containing 140 ng DNA, 400 μmol/L of each dNTP, 1 mmol/L $MgCl_2$, 10% dimethyl sulfoxide, 1 μmol/L of each primer, and 0.5 U TAQ polymerase. Primers were as follows: upstream 5′-CGC-CCAATACCGCCAACAC-3′ and downstream 5′-CCACCAGGAGTC-CCATCACC-3′. The PCRs (model 9600, Perkin Elmer-Cetus, Norwalk, CT) were started with denaturation at 94°C for 5 minutes followed by 35 cycles of denaturation (94°C for 30 seconds), annealing

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(61°C for 30 seconds), extension (72°C for 30 seconds), followed by extension at 72°C for 10 minutes. The amplified product was digested with *Bst*N1 at 60°C overnight, and the fragments were resolved on a 2% agarose gel. The presence of the mutation eliminated a *Bst*N1 restriction site to yield the following: normal homozygote Trp/Trp, 97, 61 base pairs (bp); heterozygote Trp/Arg, 158, 97, 61 bp; and mutant homozygote Arg/Arg, 158 bps (smaller fragments were not resolvable). For confirmation, amplification and digestion were repeated on samples that were heterozygous or homozygous for the Arg allele. Products were then analyzed on a 3% Wide Range agarose gel (Sigma, St Louis, MO).

Statistical Analysis

Analyses were performed using the SPSS (SPSS, Chicago, IL) for Windows statistical package. Descriptive statistics including the mean ± SD were calculated. Differences were significant at P less than .05. Interactions between the polymorphism, obesity, and glycemic status, as well as the impact of gender, were assessed by ANOVA. Multiple regression analysis controlling for age and gender was used to evaluate the impact of the polymorphism on anthropometric variables and fasting and postchallenge serum glucose concentrations.

RESULTS

The study sample consisted of the first 586 subjects on whom genotyping was completed. There were no significant differences in anthropometric and glycemic variables compared with the parent population (Table 1).

Genotype and Allele Frequencies

Genotype and allele frequencies are shown in Table 2. Nine subjects were homozygous for the 64Arg mutation (four men and five women), and 105 were heterozygous (47 men and 58 women). The overall allelic frequency of the Arg allele in the population was 10.5%, and there was no difference in distribution between men and women. The alleles are in Hardy-Weinberg equilibrium.

Obesity and Dysglycemia

The subjects were of similar age, but there were significant differences in the mean values for measures of obesity and dysglycemia between men and women (Table 3). The women, who were significantly shorter, weighed the same as the men and therefore had a higher BMI. Waist and hip measurements were also significantly larger in women. Due to their larger hip measurements, women had a significantly lower WHR than men. Two-hour glucose levels and fasting insulin and C-peptide values were higher in women (Table 3). The women were twice as likely to develop diabetes (2-hour glucose > 11.1 mmol/L, odds ratio, 2.5; confidence interval, 1.01 to 6.63; $P = .03$) and four times more likely to be fat (BMI > 27 kg/m^2; odds ratio, 4.5; confidence interval, 2.96 to 6.75; $P = .001$) than the men.

Table 1. Characteristics of the Parent Population and Subset (mean ± SD)

Characteristic	Parent Population (N = 1,431)	Subset (n = 586)
Age (yr)	46.1 ± 13.9	46.4 ± 14.0
BMI (kg/m^2)	26.2 ± 6.1	25.6 ± 5.8
Weight (kg)	71.6 ± 16.3	69.9 ± 16.1
Height (cm)	165.4 ± 8.7	165.0 ± 8.6
WHR	0.81 ± 0.09	0.81 ± 0.07
Fasting glucose (mmol/L)	5.3 ± 1.98	5.4 ± 2.04
2-h glucose (mmol/L)	6.7 ± 3.16	6.8 ± 2.95
Fasting C-peptide (pmol/mL)	1.8 ± 1.89	2.6 ± 2.35
Fasting insulin (IU/L)	12.5 ± 18.4	15.9 ± 24.3

Table 2. Genotype and Allele Frequency of Trp64Arg in 586 Subjects (237 men and 349 women)

	Total		Men		Women	
	%	No.	%	No.	%	No.
Genotype	N = 586		n = 237		n = 349	
Trp/Trp	80.55	472	78.5	186	81.9	286
Trp/Arg	17.9	105	19.8	47	16.6	58
Arg/Arg	1.53	9	1.70	4	1.43	5
Allele	N = 1,172		n = 474		n = 698	
Trp	0.895	1,049	0.884	419	0.902	630
Arg	0.105	123	0.116	55	0.098	68

Effect of the β_3-AR Genotype

Due to the small number of mutant homozygotes, comparisons were made between carriers of the Arg allele and the wild-type, as well as between genotypes. There were differences that approached significance in BMI, weight, and hip measurements when all subjects were grouped by genotype and the presence or absence of the Arg allele (data not shown). In men, there were no significant differences in any anthropometric or glycemic status variables as a result of the polymorphism (Tables 4 and 5). However, among women, carriers of the Arg allele weighed more and had a significantly larger BMI and hip measurement. Carriers of the Arg allele had higher fasting and 2-hour blood glucose values. These differences were significant for the entire group (data not shown) and for women but, again, not for men (Tables 4 and 5).

To explore the gender relationship further, the women were divided into premenopausal (<55 years) and postmenopausal (>55 years) groups. Data for allele rather than genotype comparisons are shown, since there were no homozygotes among the older women. In the younger women, those with the Arg allele were heavier and had larger hips and significantly

Table 3. Anthropometry and Glycemic Status by Gender (mean ± SD)

Variable	Men (n = 237)	Women (n = 349)
Age (yr)	47.0 ± 15.1	45.9 ± 19.2
Weight (kg)	69.5 ± 13.4	70.3 ± 17.7
Height (m)	1.72 ± 0.07	1.6 ± 0.06†
BMI (kg/m^2)	23.3 ± 4.0	27.2 ± 6.4†
Hip (cm)	95.1 ± 8.2	102.5 ± 13.0†
Waist (cm)	79.7 ± 11.3	81.8 ± 12.7*
WHR	0.83 ± 0.07	0.79 ± 0.06†
2-h glucose (mmol/L)	6.2 ± 2.7	7.1 ± 0.31†
Fasting glucose (mmol/L)	5.4 ± 2.1	5.4 ± 1.9
Fasting insulin (IU/L)‡	9.4 ± 9.8 (n = 109)	20.9 ± 30.0† (n = 143)
Fasting C-peptide (pmol/L)‡	1.8 ± 1.8 (n = 65)	3.2 ± 2.5† (n = 58)

*$P = .038$.
†$P = .001$.
‡Insulin and C-peptide assays performed on subsets only.

Table 4. Anthropometric Variables According to β_3-AR Genotype and Carrier Status: Comparison of Mean Values for Trp/Trp Wild-Type to Heterozygous Trp/Arg and Homozygous Arg/Arg (mean ± SD)

Group	Genotype			P	P for Trend	Carrier Status (Trp/Arg, Arg/Arg)	P for Wild-Type v Carrier*
	Trp/Trp	Trp/Arg	Arg/Arg			Arg Carrier	
Men	n = 186	n = 47	n = 4			n = 51	
Age	46.5 ± 15.3	48.7 ± 14.3	49.2 ± 14.2	.64		48.8 ± 14.2	.34
BMI	23.3 ± 4.0	23.4 ± 4.0	23.0 ± 4.2	.97		23.4 ± 3.9	.88
Weight	69.5 ± 13.6	69.4 ± 13.2	67.1 ± 12.9	.93		69.3 ± 13.0	.90
Waist	79.6 ± 11.3	80.1 ± 11.8	76.9 ± 10.2	.86		79.8 ± 9.9	.52
Hip	95.1 ± 8.2	94.9 ± 8.2	95.4 ± 11.0	.99		95.0 ± 8.3	.95
WHR	0.83 ± 0.07	0.84 ± 0.08	0.81 ± 0.02	.52		0.81 ± 0.07	.70
Women	n = 269	n = 56	n = 5			n = 61	
Age	45.8 ± 13.4	46.5 ± 13.1	43.7 ± 9.4	.87		46.3 ± 12.8	.79
BMI	26.7 ± 6.1	29.1 ± 17.1	28.8 ± 7.2	.022	.013	29.1 ± 7.0	.009
Weight	69.3 ± 17.3	74.8 ± 19.3	77.3 ± 20.8	.07	.022	75.0 ± 19.3	.022
Waist	81.3 ± 12.3	84.2 ± 13.9	86.4 ± 19.3	.183	.066	84.4 ± 14.3	.07
Hip	101.7 ± 12.7	106.4 ± 13.7	106.5 ± 14.7	.034	.012	106.4 ± 13.7	.009
WHR	0.79 ± 0.06	0.79 ± 0.06	0.81 ± 0.1	.75		0.79 ± 0.06	.67

*P for comparison of heterozygous and homozygous mutants v wild-type subjects.

higher fasting and 2-hour postprandial blood glucose concentrations (Table 6). In the older women, higher blood glucose levels were not associated with the presence of the Arg allele. However, the BMI was higher in those with the mutation.

Regression Analysis

The contribution of the Trp64Arg polymorphism to the development of obesity and hyperglycemia was assessed by simple and multivariate linear regression analyses. Univariate analysis showed significant relationships between the mutation and fasting glucose ($P = .0122$, $R^2 = .011$) and 2-hour glucose ($P = .0069$, $R^2 = .013$). The relationship between the Arg polymorphism and BMI approached significance ($P = .0606$). Table 7 shows the relationships when other variables were included with the β_3-AR genotype in multivariate analyses. The polymorphism was associated with the BMI when sex was included in the model, and together, they accounted for 11% of the variance. In this model, age was not a significant contributor. Postchallenge blood glucose levels were associated with the polymorphism in a model including the BMI, itself an independent predictor of 2-hour glucose levels, age, and sex. Together, they explained 10% of the variance. When hip, waist, or WHR measurements replaced BMI in the model, the contribution of the polymorphism remained essentially the same (Table 7). In a similar model with fasting glucose as the dependent variable, β_3-AR, age, and BMI explained 4% of the variance (results not shown).

DISCUSSION

Our study shows that the substitution of Arg for Trp in codon 64 is present at an allelic frequency of 10.5%, and the homozygous genotype occurs at a frequency of 1.53% in a sample that is representative of the Jamaican population of predominantly African ancestry. This frequency is similar to the 12.0% reported by Walston et al,[5] who studied 49 African-Americans.

We also report that in women, the Trp64Arg mutation is associated with higher blood glucose levels and some measures of adiposity. In the entire group, the association with the BMI approached significance, while the relationship with the blood glucose level was significant. Analysis by gender revealed that the trends were driven by the women, and in fact, there were no significant relationships between the mutation and any of these variables in the male population. This sexual dimorphism is

Table 5. Glycemic Status According to β_3-AR Genotype and Carrier Status: Comparison of Mean Values for Trp/Trp Wild-Type to Heterozygous Trp/Arg and Homozygous Arg/Arg (mean ± SD)

Group	Genotype			P	P for Trend	Carrier Status (Trp/Arg, Arg/Arg)	P for Wild-Type v Carrier*
	Trp/Trp	Trp/Arg	Arg/Arg			Arg Carrier	
Men	n = 178	n = 46	n = 4			n = 50	
Fasting glucose (mmol/L)	5.4 ± 1.4	5.7 ± 3.9	4.5 ± 1.2	.48		5.57 ± 3.7	.54
2-h glucose (mmol/L)	6.1 ± 2.4	6.8 ± 3.6	6.1 ± 3.4	.38		6.7 ± 3.6	.19
Insulin (IU/L)	9.0 ± 8.2	11.3 ± 15.0	6.5 ± 0.4	.55		10.7 ± 14.1	.45
C-peptide (pmol/L)	1.7 ± 1.7	2.2 ± 2.29	1.8 ± 1.83	.63		2.18 ± 2.2	.37
Women	n = 270	n = 56	n = 5			n = 61	
Fasting glucose (mmol/L)	5.3 ± 1.4	6.1 ± 3.6	5.7 ± 0.7	.013	.007	6.1 ± 3.5	.003
2-h glucose	6.9 ± 2.6	8.3 ± 4.7	5.2 ± 1.5	.002	.049	8.0 ± 4.6	.008
Insulin (IU/L)	23.3 ± 33.8	14.7 ± 13.9	7.2 ± 2.6	.26		14.1 ± 13.5	.113
C-peptide (pmol/L)	3.2 ± 2.7	3.3 ± 2.0	2.5 ± 0.32	.92		3.2 ± 1.9	.99

*P for comparison of heterozygous and homozygous mutants v wild-type subjects.

Table 6. Effect of Age on the Relationship Between Trp64Arg Polymorphism and Measures of Obesity and Glycemic Status in Women (mean ± SD)

Variable	Age <55 Years (n = 248)			Age >55 Years (n = 82)		
	Trp Allele	Arg Allele	*P*	Trp Allele	Arg Allele	*P*
BMI (kg/m²)	27.1 ± 6.1	28.9 ± 6.9	.062	25.8 ± 6.1	29.4 ± 7.3	.048
Weight (kg)	70.9 ± 6.9	76.7 ± 7.0	.044	64.3 ± 17.4	69.4 ± 15.9	.103
Waist (cm)	81.4 ± 12.2	84.3 ± 14.7	.16	80.7 ± 12.7	84.9 ± 13.9	.253
Hip (cm)	102.7 ± 12.1	106.7 ± 13.7	.047	98.8 ± 13.7	105.2 ± 14.1	.103
WHR	0.79 ± 0.06	0.79 ± 0.06	.659	0.81 ± 0.08	0.81 ± 0.07	.097
Fasting glucose (mmol/L)	5.1 ± 1.2	6.1 ± 3.8	.001	5.7 ± 1.98	5.8 ± 1.60	.901
2-h glucose (mmol/L)	6.7 ± 2.3	7.9 ± 4.9	.013	7.6 ± 3.1	8.7 ± 3.8	.247

similar to that reported by Widen et al[6] and Kurabayashi et al.[12] Other studies have reported associations between markers of obesity and dysglycemia and the mutation in female cohorts.[10,14]

There was no difference in fasting insulin and C-peptide levels in subjects homozygous or heterozygous for Arg64. Widen et al[6] found that the mutation was associated with a significant increase in 2-hour insulin levels in normoglycemic subjects, but not with fasting serum insulin in either diabetics or nondiabetics. We did not measure 2-hour insulin levels in this study, but the higher fasting and 2-hour postchallenge blood glucose in subjects with the polymorphism are in keeping with a decreased sensitivity to insulin action.

β_3-ARs are expressed predominantly in visceral fat, where they have more marked lipolytic effects than in subcutaneous fat.[1] Some groups have reported an association of the mutation with central obesity and its sequelae.[6,15] We found an association with hip circumference—a proxy for peripheral/subcutaneous fat—but not with waist circumference or WHR. The relationship between fat depots, fat mass, and associated metabolic risk factors may differ between ethnic groups. Thus, for the same fat mass, African-American women had less visceral fat and yet were more insulin-resistant than white women.[16,17] One interpretation could be that subcutaneous fat per se is associated with more deleterious outcomes in black populations such that despite having less visceral fat, they develop the chronic cardiovascular diseases associated with obesity. On the other hand, given that fat distribution patterns differ among ethnic groups, it is also possible that the composition of the fat depots may differ and the β_3-AR may be of more importance in fat metabolism in our group of women.

When grouped by age (>55 years, postmenopausal), fasting and 2-hour glucose levels were different only in younger women. It is not possible to determine the contribution of age versus menopausal status, since we did not obtain menopausal histories. However, the mean age for onset of menopause in our population is 50 years (H. Fletcher, unpublished observations, October 1997). Together with the lack of an association in men, this indicates that there may be some interaction between estrogens and the gene(s) or gene product(s) in the regulation of glucose metabolism. This was not observed with measures of adiposity, since differences in the BMI were independent of age/menopausal status.

The findings suggest a role for the Trp64Arg polymorphism in the development of obesity and dysglycemia in Jamaican women, given that some measures of obesity and higher fasting and postprandial 2-hour glucose levels occur in the presence of the mutation. The observed effects could also be due to linkage disequilibrium of β_3-AR and gene(s) involved in fat and/or glucose metabolism. The mutation affects blood glucose levels and adiposity as assessed by the BMI. The effect of the mutation on glycemic status is independent of its effect on adiposity, since the effect remains significant in models controlling for BMI or other measures of adiposity. This suggests that to some extent, the polymorphism exerts its effect on the glycemic status independently of its effects on adiposity. This supports the notion that obesity and dysglycemia may occur independently of each other as a consequence of genetic predisposition and/or other environmental factors, and that one need not necessarily be a complication of the other.

Whether as a candidate or marker gene, the polymorphism

Table 7. Multivariate Linear Regression Analysis of the Relationship Between the β3-AR Trp64Arg Polymorphism and BMI and Blood Glucose Levels

Dependent Variable	B	CI	*P*	R^2
BMI				
Model 1				
Sex	3.88	2.98-4.81	.000	
β_3-AR	1.35	0.22-2.48	.0191	.114
2-h glucose				
Model 2				
Sex	0.646	0.14-1.15	.0125	
Age	0.045	0.03-0.06	.000	
BMI	0.086	0.04-0.12	.001	
β_3-AR	0.675	0.09-1.26	.0250	.103
Model 3				
Sex	0.864	0.39-1.34	.0040	
Age	0.041	0.02-0.06	.0000	
Waist	0.046	0.03-0.07	.0000	
β_3-AR	0.069	0.11-1.28	.0204	.112
Model 4				
Sex	0.695	0.192-1.19	.0068	
Age	0.046	0.029-0.06	.0000	
Hip	0.037	0.016-0.06	.0005	
β_3-AR	0.685	0.093-1.28	.0234	.096
Model 5				
Sex	1.19	0.70-1.69	.0000	
Age	0.035	0.02-0.05	.0001	
WHR	7.12	3.40-10.8	.0002	
β_3-AR	0.83	0.24-1.42	.0058	.100

NOTE. Model 1, stepwise regression analysis including sex, β_3-AR, and age as independent variables; models 2 to 5, the contribution of BMI, waist, hip, and WHR analyzed in separate models controlling for sex, age, and β_3-AR.

Abbreviations: B, regression coefficient; CI, confidence interval.

could explain part of the observed excess of obesity and diabetes found in the women. The small number of homozygotes does not allow any determination of a gene-dosage effect.

Reports on the relationship of this missense mutation to measures of obesity, insulin resistance, dyslipidema, BMR, NIDDM, and age of onset of NIDDM remain controversial.[10,18-22] Further studies on body composition, fat distribution, insulin sensitivity, and BMR in a larger number of individuals in this population should provide some answers.

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