The β3-Adrenergic Receptor Gene Trp64Arg Mutation Is Overrepresented in Obese Women

Effects on Weight, BMI, Abdominal Fat, Blood Pressure, and Reproductive History in an Elderly Australian Population

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A tryptophan to arginine (Trp64Arg) mutation in the β3-adrenergic receptor (β3-AR) gene has been implicated in diabetes and obesity. We investigated the relationship of the β3-AR gene mutation with total body weight, BMI, central abdominal fat, blood pressure (BP), and reproductive history in 686 elderly subjects (429 women, 257 men; mean age 69.8 ± 6.9 [± SD] years) from a cross section of a normal population in Australia. About 14% of the test population were heterozygote carriers of the Trp64Arg mutation; however, significant effects on clinical parameters were only observed in women. The frequency of the mutation was significantly increased in obese women compared with lean women (BMI ≥27: 20% compared with BMI <27: 11%, P = 0.02). Significantly higher total body weight (67.5 ± 12.9 vs. 64.1 ± 12.2 kg, P = 0.03) and BMI (26.3 ± 4.7 vs. 25.1 ± 4.5 kg/m^2, P =0.03) was observed in heterozygote women compared with normal subjects (homozygous for tryptophan). Central abdominal fat was not significantly different, except in women under 70 years, where heterozygotes had 16% higher abdominal fat compared with normal subjects. Female heterozygotes had significantly higher diastolic BP, even after adjustment for age and BMI (88.9 ± 11.1 vs. 84.2 ± 10.8 mmHg, P = 0.003) and a longer reproductive life, with an earlier menarche (12.8 ± 1.3 vs. 13.4 ± 1.5 years, P = 0.006), a higher gravidity (4.4 ± 2.4 vs. 3.5 ± 2.1, P = 0.01), and higher parity (3.8 ± 2.0 vs. 3.0 ± 1.9, P = 0.005). Clearly, the β3-AR mutation has pleiotrophic effects on a number of physiological systems, including BMI, BP, and reproductive history, perhaps suggesting evolutionary reasons for its maintenance in the population. *Diabetes* 45:1358–1363, 1996

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ANCOVA, analysis of covariance; β3-AR, β3-adrenergic receptor; BP, blood pressure; DEXA, dual-energy X-ray absorptiometry; MAP, mean arterial pressure.

Obesity is a major risk factor for NIDDM and is associated with glucose intolerance, hypertension, and cardiovascular disease, particularly when the obesity is centrally distributed. While environmental factors contribute to obesity, there are also strong genetic influences on both total adiposity and body fat distribution (1–6). It has been suggested that a low rate of energy expenditure and reduced rates of fat oxidation may contribute to obesity (2). The β3-adrenergic receptor (β3-AR), which is expressed in brown adipose tissue of neonates and visceral adipocytes of adults, may contribute to the population variance in energy expenditure and body fat distribution (7–11). Recently, Walston, Widén, Clément, and colleagues (12–14) published studies on a physiologically significant missense mutation in codon 64 of the gene for the β3-AR with a replacement of tryptophan to arginine (Trp64Arg) in the receptor protein. Walston et al. (12) found a high frequency of this mutation in obese Pima Indians, and subjects homozygous for this mutation had an earlier onset of NIDDM and a tendency to a lower metabolic rate, despite similar total and central adiposity. Widén et al. (13) found that heterozygotes for the mutation also had an earlier onset of NIDDM. In addition, nondiabetic subjects with the mutation had a higher diastolic blood pressure (BP), increased glucose-stimulated insulin secretion, reduced insulin sensitivity, and an increased waist-to-hip ratio (in women only). Clément et al. (14) found that morbidly obese subjects with the mutation had an increased capacity to gain weight over a 20-year time period. Fujisawa et al. (15) observed a higher frequency of the Arg64 allele in Japanese and noted significantly increased BMI in the Arg/Arg homozygotes only. These results prompted us to further investigate the role of the β3-adrenergic receptor and its relationship to body fat distribution in an elderly general population.

This study was based on the hypotheses that the mutation would be functional in the general population, leading to increased weight, and that the mutation would be associated with significant differences in other biological variables, such as BP, through its effects on adrenergic receptors. Our analysis included possible environmental

TABLE 1
Frequency of the Trp64Arg mutation of the β3-AR gene in an Australian population

	Mutation homozygotes	Mutation heterozygotes	Wild type	Total
Women	2 (0.5)	59 (13.8)	368 (85.8)	429
Men	1 (0.4)	38 (14.8)	218 (84.8)	257
All	3 (0.4)	97 (14.1)	586 (85.4)	686

Data are *n* (%).

confounding influences, such as smoking (16), use of sex hormone replacement, and reproductive history because child bearing may exert lasting effects on body weight (17) and also influence subsequent incidence of NIDDM (18). We also measured central abdominal fat by dual-energy X-ray absorptiometry (DEXA) to investigate the hypothesis that the mutation was influencing carbohydrate metabolism through a preferential effect on abdominal adiposity.

RESEARCH DESIGN AND METHODS

Subjects. Of the Caucasian subjects, 686 (429 women, 257 men; mean age 69.8 ± 6.9 years) were randomly drawn from the original cohort population of an epidemiology study of 2,170 subjects (19,20). In 1989, all subjects over 60 years of age identified from a compulsory electoral roll in Dubbo, a town of ~32,000 people in rural Australia, were invited to participate in a study of cardiovascular endpoints and osteoporosis. Data collected included age, medications, past and present tobacco use, and reproductive history (age of menarche and menopause, gravidity, and parity). Height (m) and weight (kg) were measured by a nurse coordinator, and BMI was calculated as kg/m^2. Systolic and diastolic BP was measured on the right upper arm with the subject seated using phases I and V of the Korotkoff sounds, respectively. Mean arterial pressure (MAP) was calculated from the formula: MAP = diastolic pressure + 1/3 (diastolic pressure − systolic pressure).

Traditional measures of central fat, such as the waist-hip ratio, were not available. The measure of abdominal fat was taken from a spinal DEXA scan, which was derived from a standard window extending for 4 cm on either side of the first to fifth lumbar vertebrae. Fat mass is expressed as a percentage of the total tissue window measured. The coefficient of variation of this measurement as determined for dual scans performed on the same day in 60 people was 1.8%. To validate the anatomical and metabolic relevance of para-spinal abdominal fat, 9 men and 29 postmenopausal women with a mean age of 57 ± 8 years and BMI 26.7 ± 4.0 kg/m^2 were studied. Spinal DEXA abdominal fat correlated closely with measurements of percent central abdominal fat from whole-body DEXA scans (r = 0.93, P < 0.0001), fasting insulin (r = 0.53, P < 0.002), triglyceride levels (r = 0.48, P < 0.005), and insulin sensitivity (glucose disposal, μmol · kg^{-1} · min^{-1}, measured by euglycemic clamp, n = 18, F:M = 9:9, r = −0.77, P < 0.0005). Intra-abdominal fat area, measured by magnetic resonance imaging at the level of L3/4 in 10 subjects (F:M = 4:6), also correlated significantly with para-spinal abdominal fat (r = 0.85, P < 0.005) (D.G.P.C., unpublished observations). This measure of abdominal fat was considered an adequate and reproducible variable to test the hypothesis that the β3-AR mutation had a preferential effect on central abdominal fat.

DNA analysis. DNA was extracted from peripheral leukocytes by the standard phenol-chloroform procedure (21). The polymerase chain reaction of the DNA sequence flanking the polymorphic Bst-OI site (Promega, Madison, WI) was used to facilitate genotyping of subjects with primers 5'-CCAGTGGGCTGCCAGGGG-3' and 5'-GCCAGTGGCGCCCAACGG-3', as reported (14). Genotype was determined by ethidium-bromide-UVB illumination of the fragments separated on 3% agarose gels. Genotypic polymorphism was defined as homozygote for the mutation (absence of restriction site on both alleles), heterozygotes for the mutation, or wild type (presence of restriction site on both alleles).

Statistical analysis. The statistical assessment was based on several explicit hypotheses. Our analysis was based on testing the prior relationship of the β3-AR mutation to weight and BMI, in that the heterozygote genotype was expected to have increased weight and BMI (H_0 = no effect, H_1 = increase of weight and BMI in heterozygote genotype) (13,14). In testing an a priori hypothesis, a one-tailed unpaired t test was considered acceptable for the comparison of weight, BMI, and abdominal fat. Because men and women have different mean weights and different fat distributions, we considered the effect of the mutation separately in each sex. The individuals homozygous for the mutation were excluded from the analysis described below; however, adding these homozygous individuals to the group, designated heterozygote, did not alter the results in any substantial way.

We estimated statistical power based on the frequency of the mutation in other Caucasian populations and the standard deviation of the parameters in the Dubbo population. In the women genotyped, we had ~80% power to detect a difference in mean weight of 4 kg between genotypes using a single-sided test. Using two-tailed tests, we had 80% power to detect differences in systolic and diastolic BP of ~8 and 4 mmHg, respectively, and in central abdominal fat measured by DEXA (n = 375), we had 80% power to detect a difference of 3.5% fat. In men, we had 80% power to detect effects >5 kg weight (one-tailed test), 5 and 10 mmHg for diastolic and systolic BP, respectively, and 4.1% difference in central abdominal fat.

Exploratory statistics. Subsequent to genotyping, significant effects of the β3-AR genotype on other subject characteristics were tested using the χ^2 test, two-tailed unpaired t test, and analysis of covariance (ANCOVA) with appropriate covariates included in the model. Simple and multiple regression and Pearson's correlation were used where appropriate to estimate the relationship among variables and to estimate the contribution of the β3-AR genotype to the phenotypic variance in a trait. All data management and statistical computations were done with SuperANOVA (Abacus Concepts, Berkeley, CA). The results are presented as means ± SD. During the initial analysis, BMI and fat were found to be significantly negatively related to age (P = 0.0015 and 0.0008). The effect of the β3-AR genotype was therefore tested using adjusted and unadjusted variables. The clinical variables tested were diastolic and systolic blood pressure, a variable derived from these measures (mean arterial pressure), and para-spinal fat. Integer variables, such as age of menarche, gravidity, and parity, were tested using nonparametric ranking statistics (Mann-Whitney U test) but for simplicity, are presented as means ± SD.

RESULTS

Genotype frequencies. The frequencies of the Trp64Arg allele were 0.073, 0.078, and 0.075 in women, men, and all subjects, respectively, with the frequency of heterozygote carriers being 13.8, 14.8, and 14.1% in women, men, and all subjects, respectively (Table 1). Allele frequencies were consistent with the Hardy Weinberg equilibrium. Homozygous mutation was seen in two women and one man who were clinically unremarkable. Homozygous absence of

TABLE 2
Frequency of the Trp64Arg mutation of the β3-AR gene, according to BMI

	BMI <27		BMI ≥27		
	Heterozygotes	Wild type	Heterozygotes	Wild type	χ^2 P value
Women	32 (11.1)	257 (88.9)	27 (19.6)	111 (80.4)	0.02
Men	28 (15.7)	150 (84.3)	10 (12.8)	68 (87.2)	0.54

Data are *n* (%).

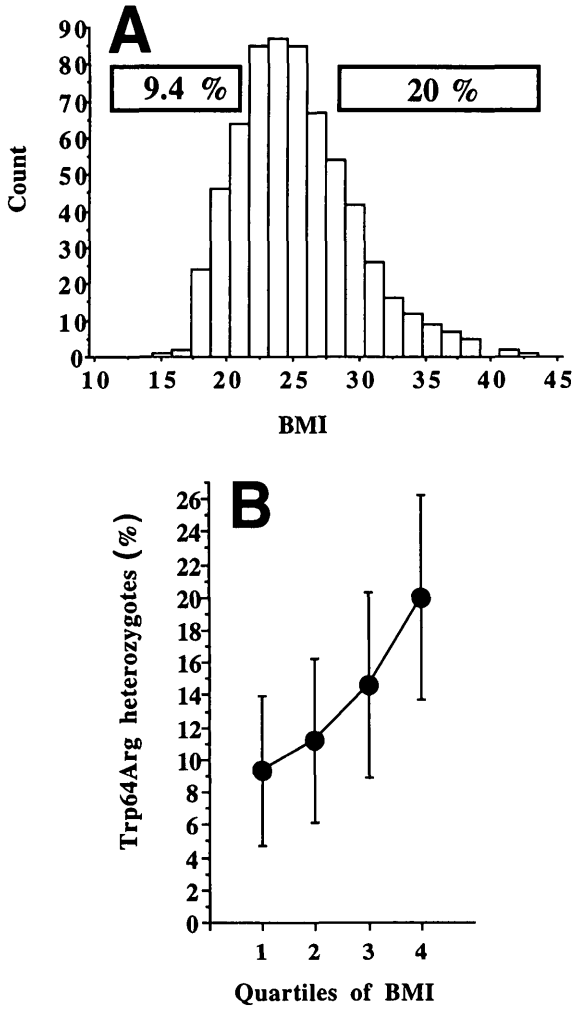

FIG. 1. *A*: **The distribution of BMI observed in women from the Dubbo study. The boxes indicate the frequency of heterozygotes for the β3-AR gene Trp64Arg mutation in the lower and upper quartiles of BMI.** *B*: **The frequency of heterozygous carriers of the Trp64Arg mutation shows a progressive increase across quartiles of BMI in the Dubbo study. The error bars represent the 95% CIs of the proportion of heterozygotes.**

the Trp64Arg mutation was arbitrarily defined as the wild type. The frequency of heterozygotes was significantly increased in overweight women (BMI <27, 11.1%; BMI ≥27, 19.6%, χ^2 *P* value = 0.02) but not men (BMI <27, 15.7%; BMI ≥27, 12.8%, *P* = 0.54) (Table 2). In women, the frequency of heterozygotes showed a progressive increase across quartiles of BMI, rising from 9.5 ± 5.5% (± 95% CI of the proportion) in the first quartile, 11.2 ± 6.0% in the second quartile, and 14.6 ± 6.8% in the third quartile to 20 ± 7.5% in last quartile of BMI (Fig. 1).

Body weight, BMI, and abdominal fat. In women, the heterozygote group had significantly higher weight and BMI compared with wild type (*P* = 0.03, Table 3). This effect was still significant after age adjustment. A larger difference in weight and BMI between the women heterozygote group compared with the wild type group was found when current smokers were excluded: weight, heterozygote, 67.8 ± 12.9 kg vs. wild type, 64.2 ± 11.8 kg (*P* = 0.02); BMI, heterozygote, 26.5 ± 4.7 kg/m^2 vs. wild type, 25.2 ± 4.5 kg/m^2 (*P* = 0.02). There was no significant effect of the β3-AR genotype on percent central abdominal fat either before or after age adjustment (Table 3). However, in 228 women under 70 years, abdominal fat in the heterozygote group was significantly higher compared with the wild type group (30.6 ± 5.7 vs. 26.4 ± 8.2%, *P* = 0.02). The mean difference in central fat between heterozygote and wild-type groups in the whole population was 1.4% (*P* = 0.3). If this represents the real effect of the β3-AR mutation on central fat, power calculations indicate that ~2,400 women need to be genotyped to exclude a real effect of this magnitude.

In men, significant differences in clinical parameters were not observed between β3-AR genotype groups. Adjustment of variables did not contribute to significant differences, and interaction models between the genotype and environmental variables did not reveal an effect of β3-AR genotype in men.

In women, there was a significant negative relationship between age and both weight (*P* = 0.0001) and abdominal fat (*P* = 0.0002), and the slope of these correlations differed according to β3-AR genotype: age vs. weight, heterozygote *r* = –0.858 and wild type *r* = –0.324; age and abdominal fat heterozygote: *r* = –0.611 and wild type *r* = –0.168. Paradoxically, both total weight and abdominal fat of the female heterozygote group decreased more rapidly with advancing age compared with the wild-type group. Again, no effect was observed in men.

Blood pressure. The heterozygote group had significantly higher diastolic BP (*P* = 0.01) and MAP (*P* = 0.02) compared with the wild type group (Table 3). There was a nonsignificant trend (*P* = 0.7) for a higher systolic BP in the heterozygote group with a mean difference of 5.2 mmHg. Because diastolic BP and MAP were significantly related to weight in women (*P* = 0.001, r^2 = 0.025; *P* = 0.004, r^2 = 0.02, respectively), the analysis was repeated after adjustment for weight, after which the β3-AR genotype was still significantly related to diastolic BP (*P* = 0.03) and MAP, explaining 1.3 and 1.2%, respectively, of the population variance. Similar results were obtained after adjustment for age and BMI, with the β3-AR mutation weakly related to diastolic BP (*P* = 0.04, r^2 = 0.012) but not systolic BP (*P* = 0.21).

In the wild type group, diastolic BP was strongly related to BMI (*P* = 0.0001), explaining 5.4% of the population variance with a positive slope (0.23), which was significantly different from that of the heterozygote group (*P* = 0.01). In the heterozygote group, there was no significant relationship between diastolic BP and BMI (*P* = 0.4). To determine if the mutation was modulating obesity-induced hypertension, subjects were divided into nonobese (BMI <27 kg/m^2) and obese (BMI ≥27 kg/m^2). In nonobese subjects, the diastolic BP, systolic BP, and MAP were all significantly elevated in the heterozygote group (*P* < 0.001), explaining 4.7, 3.3, and 5.1% of the phenotypic variance. In obese subjects, however, β3-AR genotype was not related to BP.

Reproductive history. An effect of the β3-AR mutation was observed on the age of menarche, with the heterozygote group having a significantly earlier age of menarche compared with the wild type (*P* = 0.006) (Table 4). Gravidity (*P* = 0.01) and parity (*P* = 0.005) were significantly increased in the heterozygote group,

TABLE 3
Body weight, height, BMI, and clinical characteristics of an Australian population, according to genotype of the β3-AR

	Women			Men		
	Heterozygotes	Wild type	*P* value	Heterozygotes	Wild type	*P* value
n	59	368	—	38	218	—
Weight (kg)						
Unadjusted	67.5 ± 12.9	64.1 ± 12.2	0.03	77.3 ± 12.6	78.1 ± 12.2	0.36
Adjusted for age	67.5 ± 11.9	64.1 ± 11.9	0.02	76.7 ± 11.9	78.2 ± 11.9	0.24
Height (cm)						
Unadjusted	160.0 ± 6.6	159.7 ± 6.1	0.36	174.3 ± 7.4	173.5 ± 6.7	0.27
Adjusted for age	160.0 ± 5.9	159.7 ± 5.9	0.35	174.0 ± 6.7	173.6 ± 6.7	0.35
BMI (kg/m^2)						
Unadjusted	26.3 ± 4.7	25.1 ± 4.5	0.03	25.4 ± 3.6	25.9 ± 3.6	0.23
Adjusted for age	26.3 ± 4.5	25.1 ± 4.5	0.03	25.3 ± 3.5	25.9 ± 3.5	0.16
Age (years)	70.1 ± 6.7	70.0 ± 7.5	0.98	68.2 ± 5.5	69.4 ± 6.1	0.22
Abdominal fat (%)						
Unadjusted	26.7 ± 9.0	25.3 ± 8.1	0.26	26.5 ± 8.0	26.0 ± 8.9	0.74
Adjusted for age	26.7 ± 8.1	25.3 ± 8.1	0.28	26.3 ± 8.9	26.0 ± 8.8	0.86
Systolic BP (mmHg)						
Unadjusted	146.0 ± 24.4	141.2 ± 19.8	0.11	142.9 ± 17.4	141.3 ± 20.0	0.64
Adjusted for age and BMI	145.0 ± 19.8	141.4 ± 19.8	0.21	143.3 ± 19.4	141.2 ± 19.3	0.53
Diastolic BP (mmHg)						
Unadjusted	88.2 ± 13.5	84.1 ± 10.7	0.01	85.9 ± 11.0	85.8 ± 11.2	0.94
Adjusted for age and BMI	88.9 ± 11.1	84.2 ± 10.8	0.003	86.0 ± 10.8	85.8 ± 10.7	0.91
MAP (mmHg)						
Unadjusted	107.5 ± 15.2	103.2 ± 12.0	0.02	104.9 ± 11.2	104.3 ± 12.9	0.77
Adjusted for age and BMI	107.8 ± 12.4	103.2 ± 12.1	0.01	105.1 ± 12.3	104.2 ± 12.3	0.69

Data are means ± SD. For weight, height, and BMI, *P* value determined by unpaired one-tailed *t* test; for all other data, *P* value determined by ANOVA or ANCOVA.

with the heterozygote group having about one child more than the wild type group.

Because the earlier menarche may be due to the β3-AR mutation's influence on BMI, we explored the relationship between current BMI and reproductive history in 429 subjects that were genotyped plus an additional 202 subjects for which reproductive history was available. Increasing BMI was significantly related to younger age of menarche ($P = 0.002$) and increased parity ($P = 0.004$) and gravidity ($P = 0.02$). Height alone was not significantly related to age of menarche ($P = 0.1$). Using multiple regression in the women that were genotyped, we found that age of menarche was related significantly to only β3-AR genotype ($P = 0.02$) and not BMI ($P = 0.1$).

DISCUSSION

In an elderly sample of the general Australian population, the frequency of the β3-AR mutation is similar to that reported in the U.S., Finland, and France (12–14). In this study, the mutation was significantly more frequent in overweight women, and in women, the mutation was associated with increased total body weight, elevated blood pressure, and earlier menarche. In fact, carriers of the mutation were twice as frequent in obese subjects as in lean subjects (9.4 vs. 20% heterozygotes), with a progressive increase in allele frequency across quartiles of BMI. This effect was not observed in other Caucasian studies. We may have observed this effect because of our demographic approach of taking an essentially unbiased population sample unrelated to obesity or because of the large size of the sample.

In addition to obvious effects on weight and obesity, the mutation has effects on blood pressure and reproductive history, independent of obesity. Only women aged under 70 years of age had increased central abdominal fat, and paradoxically, the age-related decline in weight tended to be greater in subjects with the mutation. If there is a significant effect on central abdominal fat, as measured by DEXA, then it is restricted to the less elderly or is of small effect. No significant clinical effects of the mutation were found in men, and there were no trends in the data to suggest an effect.

Impaired β3-AR activity may promote total body weight gain through reducing thermogenesis and basal energy expenditure and also by reducing lipolysis in both white and brown adipose tissue. In adults, however, there is very little brown fat, and β3-AR receptors are found predominantly in deep visceral adipose cells. It has been postulated, therefore, that weight gain associated with the Trp64Arg mutation may result predominantly in visceral obesity. Because men tend to have a higher intra-abdominal and lower peripheral fat mass than women, one might predict that the phenotypic expression of the β3-AR mutations would be greatest in men. Previous clinical studies, however, have demonstrated increased waist-to-hip ratio only in nondiabetic women (aged 50 ± 15 years), but it was not stated whether these women were all postmenopausal (13). We also found an effect of the mutation on central adiposity only in the less elderly women, with the heterozygote group having higher body weight and central abdominal fat. This may represent a real effect or a chance statistical finding. No effect on

TABLE 4
Reproductive characteristics of an Australian population, according to genotype of the β3-AR

	Heterozygotes	Wild type	*P* value
n	59	368	—
Age of menarche (years)	12.8 ± 1.3	13.4 ± 1.5	0.006
Gravidity	4.4 ± 2.4	3.5 ± 2.1	0.01
Parity	3.8 ± 2.0	3.0 ± 1.9	0.005
Age of menopause (years)	46.1 ± 7.9	46.6 ± 7.3	0.63

Data are means ± SD. *P* value: Mann-Whitney *U* test (menarche, gravidity, and parity), unpaired two-tailed *t* test (menopause).

central adiposity was seen in very elderly women (>70 years), which may be due to the reduced influence of the sympathetic nervous system on abdominal fat in the very elderly (22). Sympathetic activity increases with advancing age, obesity (23), and smoking (24). These factors may modulate the effect of the β3-AR mutation because the difference between heterozygotes and wild type was predominantly on weight in nonsmokers, blood pressure in nonobese subjects, and central fat in less elderly subjects. Studies of the effects of sex and age on β3-AR activity would be of interest.

Widén et al. (13) postulated that the increased diastolic BP in nondiabetic heterozygote subjects was secondary to increased visceral adiposity and associated insulin resistance. In this study, we did not measure insulin levels or insulin sensitivity; however, the effects of the mutation appeared to be independent of total and central adiposity, suggesting that the mutation was having a direct effect on vascular tone. These data suggest that in addition to regulating weight, the β3-AR mutation is a candidate gene for hypertension, independent of factors controlling weight.

This is the first study to suggest that the β3-AR mutation could influence menstrual history and fertility. Several decades ago, Post and White (25) noted that the menarche had occurred about one-half to three-quarters of a year earlier in women with adult-onset diabetes than in their nondiabetic siblings. The magnitude of this age difference is comparable to the difference in menarche between our heterozygote and wild type group of ~0.6 years. The timing of activation of the reproductive axis is believed to be due to a decline in central nervous system inhibitory tone and a decreased sensitivity to sex steroid feedback. There is substantial evidence that nutritional factors influence sexual maturation through their effect on adiposity (26). Moderately obese girls (20–30% over normal weight) have earlier menarche than normal weight girls (27). The β3-AR activity may therefore influence reproductive history through effects on childhood body mass but may also have direct effects at the level of the hypothalamus. As the presence of obesity during puberty has a high likelihood of persisting into adulthood (28), the Trp64Arg mutation may also influence adult weight through its effects during childhood. We have, however, no data relating to juvenile development of our subjects, and exploration of this observation should be tested in a younger cohort.

The significant differences in gravidity and parity imply that the β3-AR mutation may influence female fertility. This observation needs to be validated in other more direct studies. These parameters are obviously related and should be considered as one phenomenon. Earlier sexual development might allow for increased child bearing; alternatively, the increased parity in heterozygous subjects may reflect increased fertility. The mean number of offspring in our cohort was only 3.8 ± 2.0, suggesting that control of fertility was being practiced in the community. Our data suggest that a significant proportion of the increased weight in subjects with the β3-AR mutation may be from increased peripheral (gynecoid) fat, which is of interest because central obesity is often associated with late menarche and decreased fertility (29). Increased child bearing may in turn lead to increased adiposity later in adult life; however, because only 34 of our female subjects had never been pregnant, we were unable to determine the relationship between weight and β3-AR mutation in this subgroup. Further studies are needed to verify or reject a potential effect of the β3-AR gene variant on reproductive biology.

In contrast to the data in women, we found that the β3-AR mutation was not significantly related to any variable measured in men. While we cannot rule out effects in men, if the β3-AR mutation has an effect on these parameters in normal elderly men, the effect must be rather small. Compared with previous studies, our subjects were elderly, with a mean age of ~70 years. In men, more so than women, there is an age-related increase in central adiposity and insulin resistance (30), which may be partly due to a decreased sympathetic responsiveness of deep adipose tissue, particularly from a decreased expression of β3-AR (31). It is possible that in elderly men, further reduction of an already low tissue sympathetic responsiveness due to the presence of the β3-AR mutation does not have a significant metabolic effect. Our data suggest that the identification of genes regulating fat metabolism may be dependent on sex. These sex-specific effects need to be tested in other populations.

The "thrifty gene" hypothesis is frequently applied to subjects that appear to have genes for increased fat storage, which in a Westernized society, results in a high prevalence of obesity and NIDDM (32). The thrifty gene hypothesis largely supplanted an earlier alternative hypothesis that held that the high prevalence of diabetes- and obesity-related genes resulted from natural selection favoring genes, which conferred increased reproductive competence (32). The β3-AR data leads to a reconciliation of these two contrasting concepts of evolutionary causation: such diabetes- and obesity-related genes could simultaneously alter energy metabolism giving a thrifty phenotype and alter reproductive fitness through the effect of fat on reproductive ability. Genes, such as the β3-AR gene, which are involved in fat regulation, will remain in the population if they favorably influence reproductive competence, despite having negative effects, such as NIDDM, hypertension, and obesity, in later life. In conclusion, the β3-AR gene mutation is related to the control of body weight and is significantly more common in overweight women. The pleiotrophic effects of this mutation make it an ideal subject for physiological, epidemiological, and ethnobiological study in relation to the control of body weight.

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