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Clinical Features of the Metabolic Syndrome in Adolescents: Minor Role of the Trp64Arg β_3-Adrenergic Receptor Gene Variant

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ABSTRACT

Obesity and hypertension are increasing medical problems in adolescents. We evaluated the association between being overweight—particularly abdominal fat—and having hypertension and assessed the contribution of the Trp64Arg β_3-adrenergic receptor gene variant. In a population-based study, we determined family history, anthropometric variables, and arterial blood pressure of 934 high school students, out of whom we selected 121 normotensive and 54 hypertensive students. Biochemical measurements included circulating renin and angiotensin-converting enzyme activities, leptin, glucose, insulin and lipid levels, and β_3-adrenergic receptor genotypes. We used Mann-Whitney *U* test, χ^2-test, and Spearman rank-order correlation. In the total population, hypertension prevalence increased across the entire range of body mass index (BMI) percentiles. In the sample, hypertensive students showed higher BMI, waist-to-hip ratio, triglycerides, and insulin resistance and lower HDL-cholesterol than normotensive students did. Age- and sex-adjusted systolic arterial blood pressure was correlated with BMI, waist-to-hip ratio, insulin resistance, and leptin. Leptin was correlated with BMI and homeostasis model assessment method. We found no association among hypertension, BMI, and leptin levels with β_3-adrenergic receptor genotypes. Especially in girls, the waist-to-hip ratio was, however, suggestively higher in Arg64 variant carriers than in noncarriers, independent of hypertension. In fact, there was a significantly ($p < 0.01$) higher frequency of carriers of the Arg64 variant across the waist-to-hip ratio quartiles. In adolescents of European origin, hypertension is associated with an increased degree of obesity among other characteristics of the metabolic syndrome; the Trp64Arg variant of the β_3-adrenergic receptor gene may favor the central adiposity gain. **(*Pediatr Res* 55: 836–841, 2004)**

Abbreviations

β_3AR, β_3-adrenergic receptor
ABP, arterial blood pressure
BMI, body mass index
HOMA, homeostasis model assessment method
Trp64Arg, substitution of arginine for tryptophan at codon 64
WHR, waist-to-hip ratio

In many countries, last century's developments have led to lifestyle alterations characterized by increased caloric and fat intakes and reduction in physical activity along with a dramatic increase in metabolic syndrome–related diseases such as diabetes, dyslipidemias, hypertension, and obesity. Accordingly, obesity has become an important health problem in children and adolescents. Many of the above-mentioned outcomes associated with obesity—hypertension, type 2 diabetes mellitus, dyslipidemia, left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, and orthopedic problems that were previously thought of as adults' diseases—are now affecting children as well (1). Although prevention would be an optimum strategy, it may be difficult to identify children at risk of obesity and its comorbidities before they become overweight. Obesity is a complex disorder determined by an interplay of both environmental and genetic factors (2). The β_3AR is expressed in adipose tissue as an important lipolysis regulator, and a variant in this gene resulting from a substitution of arginine for tryptophan at codon 64 (Trp64Arg) has been identified (3–5). This allele seems to be associated with lower lipolytic activity of a selective β_3AR agonist in omental adipocytes (6). Modest associations between this variant and

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insulin resistance and obesity have been reported, but the inconsistencies among different studies have led some investigators to conclude that the Trp64Arg variant plays a small role in human obesity (7). In population-based studies, individuals may vary considerably with respect to other susceptibility genes and to exposure to other risk factors for obesity such as hypertension or insulin resistance. In addition, plasma leptin levels are strongly correlated with BMI, insulin resistance, and hypertension (8, 9). Still, little is known about the contribution of the Trp64Arg variant to these covariates in adolescents.

Thus, we studied the prevalence of obesity and hypertension in the total population of high school students at an inner city of our country. To account for the effects of the Trp64Arg variant of the β_3AR gene on clinical features of the metabolic syndrome, specifically the presence of central adiposity and hypertension, we studied a selected sample of normotensive and hypertensive adolescents from this high school–age population.

METHODS

Human subjects. In a country town (Chacabuco, Province of Buenos Aires), we interviewed the total high school student population consisting of 934 adolescents after written consent from their parents had been granted, in accordance with the procedures approved by the ethical committee of our institution. Under parental supervision, subjects responded to a questionnaire on medical history, physical activities, medication, and personal habits. Anthropometric assessment included measurement of height, weight, and waist and hip circumferences. Waist circumference was assessed in the standing position, midway between the highest point of the iliac crest and the lowest point of the costal margin in the mid-axillary line. Hip circumference was measured at the level of the femoral greater trochanter. Both measurements were taken by the same observer. Body height and weight were recorded in light clothing, and BMI was computed as weight in kilograms divided by height in meters squared. Resting ABP was measured after subjects had been sitting for at least 30 min. A mercury sphygmomanometer was used to measure blood pressure three times at the right arm by two investigators using cuffs with the appropriate length and width for the upper arm. We normalized BMI according to age and sex using the National Health and Nutrition Examination Survey located at the U.S. Centers for Disease Control and Prevention web site (www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm). Resting blood pressure was normalized as a Z score according to sex and age using the U.S. Task Force tables (10).

In addition, we selected and invited the participation of 220 adolescents who have systolic or diastolic blood pressures more than the 80th or less than the 20th percentiles based on a single set of measurements. One hundred seventy-five adolescents completed the study and underwent two additional blood pressure measurements on different days, biochemical analysis, and genotyping as described below. Adolescents with an average of systolic or diastolic blood pressure more than the 95th percentile and with no causes of secondary hypertension were considered essential hypertensives: 54 independent individuals met this criterion. Unfortunately, because there is no evidence-based definition that links specific levels of blood pressure with outcome, we used that "statistical" definition of hypertension.

Biochemical measurements. Blood was drawn from fasting subjects who were in a supine resting position for at least 30 min. All determinations of circulating components of the renin-angiotensin-aldosterone system were carried out in duplicate. Plasma renin activity was measured in a 1-mL plasma sample by means of a RIA kit based on angiotensin I production (Immunotech, Marseille, France). Aldosterone was quantified in 100 μL of serum by a standard RIA (Immunotech). Plasma glucose, insulin, uric acid, total cholesterol, HDL and LDL cholesterol, and triglycerides were measured by standard clinical laboratory techniques. We used the insulin-to-glucose ratio, the quantitative insulin sensitivity check index, and HOMA (fasting insulin in microunits per milliliter multiplied by fasting glucose in millimoles per liter divided by 22.5) as an estimation of insulin resistance (11–13). Because HOMA appeared to show stronger correlations with the Z score of systolic blood pressure ($r^- = 0.37$, $p < 0.05$) we used the HOMA index as indicator of insulin resistance. A commercial ELISA kit was used to measure plasma concentrations of leptin (Assay Designs, Inc, Ann Arbor, MI U.S.A.) in blood samples collected with sodium EDTA.

Genotype determination. Genomic DNA was extracted from white blood cells by a standard method as previously described (14). Genotyping for the Trp64Arg polymorphism was performed by hot-start PCR using molecular biology grade reagents from Sigma Chemical Co. (St. Louis, MO, U.S.A.) unless indicated, and a Stratagene Robocycler 96 thermal cycler (Stratagene, La Jolla, CA, U.S.A.). The PCR method, primers (Life Technologies, Rockville, MD, U.S.A.), and cleavage with *Bst*N1 were essentially as described by Walston *et al.* (3).

Statistical analyses. Quantitative data were analyzed with the Mann-Whitney *U* test or Student's *t* test (according to the nature of the distribution assessed by Shapiro-Wilk's test) and expressed as mean ± SD. Quantitative variable differences by sex according to genotypes were studied by two-way ANOVA model (Tukey's *post hoc* test). Genotype frequencies were analyzed by means of a χ^2 test. Correlations between variables were assessed by the Spearman rank-order correlation. Logistic regression was used for testing of multivariate associations among variables. We used the CSS/Statistica program package (StatSoft, Tulsa, OK, U.S.A.) to perform these analyses.

RESULTS

From a single set of measurements of ABP, irrespective of age and sex, the proportion of adolescents with elevated blood pressure was significantly higher for adolescents in the upper compared with the lower decile of BMI, with an increase in the frequency of systolic hypertension as BMI percentiles increased across the normal range (Fig. 1). The odds ratio of systolic hypertension in overweight adolescents (BMI > 90th percentile, 121 of 931 adolescents) is 3.42 (95% confidence interval, 2.20–5.32; $p < 0.0001$), independent of age and sex. Our data support the contention that the early clinical course of

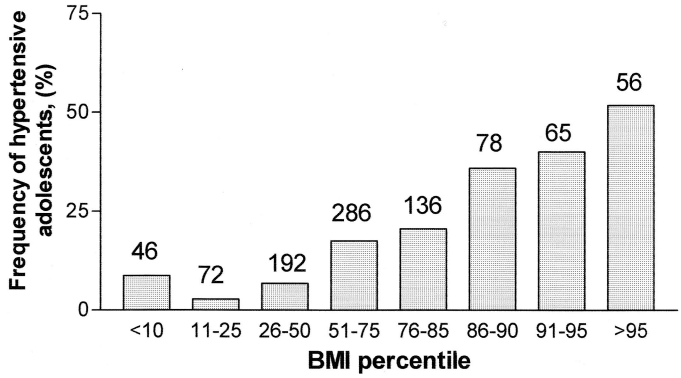

Figure 1. Distribution of BMI percentiles and the prevalence of hypertension within each percentile category based on a single set of ABP measurements. Values above bars indicate number of adolescents in each BMI category.

hypertension in these overweight adolescents appears to be characterized by systolic hypertension (data not shown). In addition, adolescents greater than the 90th percentile of BMI showed a higher heart rate compared with adolescents within lower percentiles (77.0 ± 11.4, *versus* 74.4 ± 11.8 beats/min, $p < 0.03$).

To further study the clinical characteristics of hypertensive adolescents, we compared two selected samples of adolescents basing our choice on their ABP as described in the "Methods." When compared with normotensive adolescents, hypertensive ones showed the clinical characteristics of the so-called metabolic syndrome because they had an increase in pulse pressure, BMI, WHR, plasma triglycerides, uric acid, insulin, and HOMA, and lower levels of plasma HDL (Table 1), even though none of them showed overt hyperglycemia or dyslipidemia, a fact which indicates they are neither diabetic nor dyslipidemic.

As expected in this total sample of 175 adolescents, univariate analysis showed that systolic blood pressure Z score correlated with BMI (Spearman ρ, 0.51; $p < 0.00001$), WHR (Spearman ρ, 0.24; $p < 0.002$), insulin resistance as estimated by HOMA (Spearman ρ, 0.35; $p < 0.00001$), and plasma leptin (Spearman ρ, 0.17; $p < 0.03$). In turn, leptin was correlated with BMI (Spearman ρ, 0.37; $p < 0.00001$) and HOMA (Spearman ρ, 0.25; $p < 0.001$).

β_3AR genotypes were similar to those described for other Caucasian populations (homozygous Trp64Trp, 85%; heterozygous Trp64Arg, 14.5%; and homozygous Arg64Arg, 0.5%) and seem to be in Hardy-Weinberg equilibrium by a visual inspection of the observed and expected frequency distributions.

No association was found among hypertension, BMI, and plasma leptin levels with β_3AR genotypes (data not shown). However, WHR was significantly higher in carriers of the Arg64 allele as compared with homozygous Trp64Trp, independent of hypertension (two-way ANOVA, $p < 0.04$; Fig. 2). Table 2 shows some clinical features of adolescents classified by β_3AR genotypes and sex. Female carriers of the Arg64 variant had a significantly ($p < 0.04$) higher WHR than female noncarriers, and there was a similar trend that did not reach statistical significance in boys. Accordingly, the frequencies of Arg64 carriers with respect to noncarriers were significantly (χ^2, $p < 0.01$) higher in the upper quartiles of the WHR (Table 3). In fact, using logistic regression analysis we found that the Arg64 variant may confer a 3-fold risk for central obesity (WHR > 0.80) independent of age, sex, hypertension, insulin resistance, or plasma leptin (odds ratio, 3.37; 95% confidence interval, 1.29–8.82).

In addition, when adolescents with a BMI higher than the 85th percentile were analyzed, carriers compared with noncarriers of the Arg64 variant showed a significant increase in fasting plasma glucose levels (97.8 ± 6.7 *versus* 87.7 ± 6.9 mg/dL, $n = 51$, $p < 0.002$) and serum uric acid (5.5 ± 1.1 *versus* 4.4 ± 1.1 mg/dL, $n = 51$, $p < 0.04$).

Finally, in a genotype-independent manner, boys showed higher systolic blood pressure levels ($p < 0.02$) and HOMA indices ($p < 0.01$) but lower plasma leptin concentrations ($p < 0.001$) than girls.

Table 1. *Clinical characteristics of hypertensive and normotensive adolescent subjects*

Clinical characteristics	Normotensives ($n = 121$)	Hypertensives ($n = 54$)
Age (y)	15 ± 2	15 ± 2
Sex (F/M)	71/50	22/32
Z score for systolic ABP	−0.17 ± 1.07	2.72 ± 1.11†
Z score for diastolic ABP	−0.37 ± 0.75	0.77 ± 0.79†
Pulse pressure (mm Hg)	47 ± 9	65 ± 12†
BMI (kg/m^2)	22 ± 3	25 ± 5†
WHR	0.80 ± 0.05	0.82 ± 0.06*
Triglycerides, mM (mg/dL)	1.01 ± 0.53 (89 ± 47)	1.16 ± 0.67 (103 ± 59)*
Total cholesterol, mM (mg/dL)	4.06 ± 0.72 (157 ± 28)	4.19 ± 0.70 (162 ± 27)
LDL, mM (mg/dL)	2.33 ± 0.59 (90 ± 23)	2.48 ± 0.62 (96 ± 24)
HDL, mM (mg/dL)	1.29 ± 0.26 (50 ± 10)	1.24 ± 0.21 (46 ± 8)*
Serum uric acid, μM (mg/dL)	233.9 ± 58.5 (4.0 ± 1.0)	269.0 ± 70.2 (4.6 ± 1.2)†
Plasma aldosterone, mM (ng/L)	2.580 ± 1.776 (93 ± 64)	2.358 ± 1.415 (85 ± 51)
Plasma renin activity, μg/L/h (ng/mL/h)	1.2 ± 2.5 (1.2 ± 2.5)	1.4 ± 2.8 (1.4 ± 2.8)
Plasma insulin, pM (μU/mL)	76.4 ± 34.7 (11 ± 5)	104.2 ± 69.5 (15 ± 10)†
Plasma glucose, mM (mg/dL)	4.94 ± 0.39 (89 ± 7)	4.94 ± 0.39 (89 ± 7)
HOMA index	2.28 ± 1.04	3.59 ± 2.31†

Results are expressed as mean ± SD.

* $p < 0.05$ (NS after Bonferroni's multiple-testing adjustment); † $p < 0.001$ ($p < 0.05$ after Bonferroni's multiple-testing adjustment).

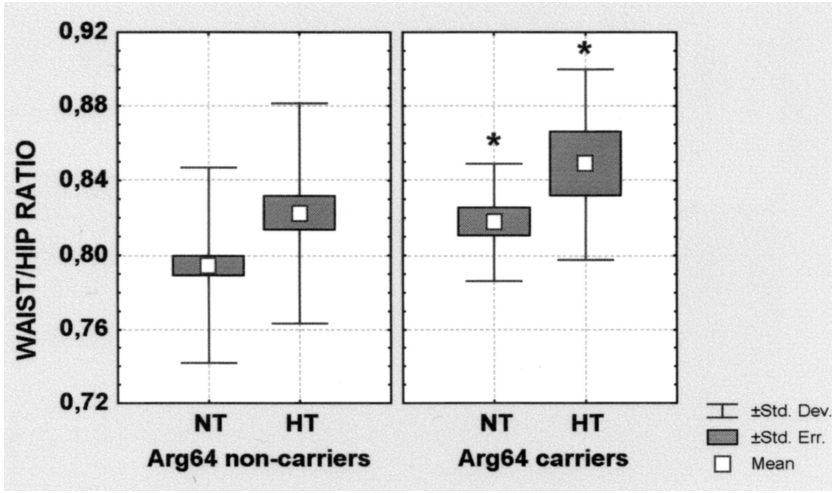

Figure 2. WHR in normotensive (*NT*) and hypertensive (*HT*) adolescents carrying or not carrying the Arg64 β_3AR gene variant. WHR was more in carriers of the Arg64 allele as compared with noncarriers, independent of hypertension (two-way ANOVA; *$p < 0.04$ compared with noncarriers in the same group, NS after Bonferroni's multiple-testing adjustment).

Table 2. *Characteristics of the population studied according to β_3AR genotypes and sex*

	Females		Males	
	Arg64 noncarriers	Arg64 carriers	Arg64 noncarriers	Arg64 carriers
Number of subjects	91	14	58	12
Age (y)	15.4 ± 1.5	15.1 ± 1.5	15.4 ± 1.6	15.5 ± 1.9
BMI (kg/m^2)	21.7 ± 3.8	21.7 ± 3.9	23.4 ± 4.4	23.3 ± 4.5
WHR	0.79 ± 0.05	0.82 ± 0.04*	0.82 ± 0.06	0.84 ± 0.04
Z score for systolic ABP	0.16 ± 1.33	0.50 ± 1.66	1.17 ± 1.94	1.10 ± 1.69
Z score for diastolic ABP	−0.15 ± 0.82	0.13 ± 0.82	0.02 ± 0.95	−0.15 ± 0.95
HOMA	2.42 ± 1.03	2.23 ± 1.00	2.86 ± 2.03	3.81 ± 2.28
Plasma leptin (ng/mL)	4.22 ± 4.16	3.96 ± 5.12	0.97 ± 1.72	1.74 ± 2.46

Results are expressed as mean ± SD.
* $p < 0.04$ in comparison with noncarriers of the Arg64 β_3AR gene variant (NS after Bonferroni's multiple-testing adjustment).

Table 3. *Frequencies (%) of Arg64 carriers and noncarriers according to quartiles of WHR*

	WHR quartiles			
	1st	2nd	3rd	4th
Arg64 carriers	7.7	15.4	34.6	42.3
Arg64 noncarriers	25.7	27.1	22.9	24.3

Frequencies of carriers and noncarriers of the Arg64 variant are differently distributed across the WHR quartiles ($p < 0.01$, χ^2 test).

DISCUSSION

Our data indicate that the prevalence of being overweight is approximately 13% in adolescents, a value that is in accordance with the increased prevalence and severity of being overweight in western countries, such as the United States (15). This increase in the prevalence of being overweight has led to an increase of the prevalence of related diseases such as type 2 diabetes and hypertension. We have focused our analysis on systolic hypertension, as most of the adolescents showed an elevation of their systolic but not diastolic ABP (data not shown). Thus, our results, based on a single set of ABP measurements, indicate that the risk of hypertension increases across the entire range of BMI values and is not defined by a single threshold effect. Similar results have been found by Rosner *et al.* (16), who reported a linear increase in the prevalence of hypertension in children regardless of race, sex, and age combinations as BMI increased across the normal range. Accordingly, similar results were reported by Sorof *et al.* (17), showing an increased prevalence of systolic hypertension (defined by a single measurement of ABP) as BMI percentile increased from the 5th to the 95th percentile and a 3-fold higher prevalence of hypertension in obese compared with nonobese adolescents. Fredman *et al.* (18) also reported that overweight children in the Bogalusa Heart Study were 4.5 times as likely to have elevated systolic ABP. In our study, the chance of being hypertensive in the overweight group, when compared with normotensive adolescents, was 3.4 times higher.

Although obesity-induced hypertension is likely to be caused by an overlap or combination of various factors, the link between obesity and hypertension may be mediated partly by sympathetic nervous system hyperactivity. This hypothesis was consistent with our findings that overweight adolescents have a significantly higher resting heart rate than lean ones. As shown by the Bogalusa Heart Study, a hyperdynamic cardiovascular state positively associated with several measures of obesity is a common finding (19).

To further characterize the clinical and genetic features of the metabolic syndrome in our adolescent population, we selected a sample whose blood pressure was below the 20th

and above the 80th percentile of systolic ABP from the total high school–age population. As expected, our results demonstrate that normotensive and hypertensive adolescents drawn from the same country community differ significantly in both degree and distribution of body fat accumulation. Hypertensive adolescents, compared with normotensive ones, were on average more obese and their body fat was more centrally distributed. Significant differences were observed for metabolic syndrome indicators such as insulin resistance, lower HDL cholesterol, and higher triglycerides. With respect to body fat distribution, a significant difference was seen in WHR. As expected, BMI and WHR were correlated with systolic ABP adjusted by age and sex. These results are consistent with a previous investigation (20) that demonstrated that both overall obesity and central distribution of body fat are independent risk factors for the development of hypertension. They are also consistent with the suggested role of intraabdominal fat in hypertension, because WHR has been previously shown to be one of the best anthropometric predictors of intraabdominal visceral fat (21, 22).

It has been suggested that genetic factors play a greater role in determining the degree of obesity in hypertensive than in nonhypertensive sibling pairs, indicating that, with respect to body fat distribution, these factors make hypertensive subjects more susceptible to the development of upper-body obesity, with heritability obesity estimates ranging from 17 to 36% (23).

A common latent factor mediating the clustering of obesity, hypertension, and diabetes was recently identified. Using multivariate genetic modeling, it was estimated that this common factor includes both genetic (59%) and environmental (41%) determinants (24). A good candidate might be the β_3AR gene, which is mainly expressed in adipose tissue and is an important regulator of lipolysis. In 1995, a variant of this gene resulting in a substitution of arginine for tryptophan at codon 64 (Trp64Arg) was identified (3–5). In our study, it is interesting that the Arg64 variant was more strongly associated with the indicator of abdominal fat (WHR) than it was with a global obesity measure such as BMI. However, the absolute amount of fat mass varies considerably even among individuals of the same height; previous studies provide evidence that single genes may have detectable effects on this phenotype (25).

On the other hand, we were not able to show any difference in Trp64Arg genotype frequencies between normotensive and hypertensive adolescents, despite the fact that the Arg64 variant was associated with abdominal fat. This might be owing to a lack of power of our study. But neither in the whole population nor in each sex group does Trp64Arg seem to influence ABP, suggesting that a lack of power is unlikely. To further test this controversial question, additional studies are warranted. Interestingly, leptin, which was correlated with systolic ABP in our study and may be the mediator in the increased sympathetic outflow observed in obesity-related hypertension, seems not to be affected by the presence of the Arg64 allele of the β_3AR gene. This lack of association was shown in both sexes despite the fact that female adolescents had significantly higher levels of plasma leptin than males did.

Previous studies of the effects of the Arg64 variant on obesity and insulin resistance have yielded largely inconsistent results. The initial studies, conducted in Pima Indians (3), French subjects (4), and Finns (5), suggested an association between the Arg64 variant and different aspects of the metabolic syndrome although, even in these studies, the effects were not large. The most convincing evidence for an effect of the Trp64Arg variant was reported in the Finnish study, in which subjects lacking the Arg64 variant were less likely than Arg64 carriers to have multiple features of the metabolic syndrome, including higher WHR, higher diastolic ABP, insulin resistance, and diabetes onset at a younger age (5).

More recent studies have provided additional support for a possible effect of the Arg64 variant on insulin resistance and obesity, although many inconsistencies remain to be solved. In Australians, the presence of the Arg64 variant was associated with higher BMI and diastolic ABP in women, but not in men (26). This is consistent with the present study, because only in girls of our young population have we found that adolescents carrying the Arg64 variant showed a significantly higher WHR than noncarrier adolescents. In other studies, no effect of the Trp64Arg variant could be detected on any of the measured phenotypes (7, 27, 28). Accordingly, we found no evidence of difference in insulin resistance between carriers and noncarriers of the Arg64 variant.

To date, several studies have directly assessed the functional properties of the Trp64Arg β_3AR gene variant. Candelore *et al.* (29) reported no differences in ligand binding or adenyl cyclase activation in Chinese hamster ovary cells overexpressing Trp64 or Arg64 β_3ARs. In contrast, Pietri-Rouxel *et al.* (30) showed decreased ligand-mediated maximal cAMP accumulation of the Arg64 in two different cell lines. On the other hand, Umekawa *et al.* (6) have shown that the Arg64 allele deteriorates lipolysis induced by β_3AR agonist in omental adipocytes. Conversely, Li and coworkers (31) detected no differences in rates of lipolysis in omental adipocytes of Caucasian subjects who were homozygous for the Trp64 compared with Trp64Arg heterozygotes, and Tataranni and coworkers (32) failed to detect differences among any of the three β_3AR genotypes and *in vivo* or *in vitro* measures of lipid metabolism in Pima Indians. Thus, the possibility should be considered that the Trp64Arg variant is a neutral polymorphism that is in linkage disequilibrium with some other mutation—perhaps in the β_3AR or a nearby gene—that influences obesity. An additional note of caution must be added: some differences we observed are of small significance, which can be lost if adjustments for multiple testing are applied.

CONCLUSIONS

In summary, the results of the present study suggest that, in adolescents of European origin, the presence of hypertension is associated with both an increased degree of adiposity and central distribution of body fat among other characteristics of the metabolic syndrome, and that genetic factors such as the Trp64Arg variant of the β_3AR gene, although with a minor effect, may favor this phenotype. In fact, it is noteworthy that in adolescents with a BMI greater than the 80th percentile,

subjects carrying the Arg64 variant of the β_3AR gene showed higher levels of plasma glucose and uric acid.

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