Associations between uncoupling protein 2, body composition, and resting energy expenditure in lean and obese African American, white, and Asian children¹⁻³

Jack A Yanovski, Adam L Diament, Kera N Sovik, Tuc T Nguyen, Hongze Li, Nancy G Sebring, and Craig H Warden

ABSTRACT

Background: Little is known about genes that affect childhood body weight.

Objective: The objective of this study was to examine the association between alleles of the mitochondrial uncoupling protein 2 (UCP2) gene and obesity because UCP2 may influence energy expenditure.

Design: We related UCP2 genotype to body composition and resting energy expenditure in 105 children aged 6–10 y. Overweight children and nonoverweight children of overweight parents were genotyped for a 45–base pair deletion/insertion (del/ins) in the 3′-untranslated region of exon 8 and for an exon 4 C to T transition.

Results: Eighty-nine children were genotyped for the exon 8 allele: 50 children had del/del, 33 had del/ins, and 6 had ins/ins. Mean (±SD) body mass index (BMI; in kg/m²) was greater for children with del/ins (24.1 ± 5.9) than for children with del/del (20.4 ± 4.8; P < 0.001). BMI of ins/ins children (23.7 ± 7.8) was not significantly different from that of del/ins children. A greater BMI in del/ins children was independent of race and sex. Body composition was also different according to UCP2 genotype. All body circumferences and skinfold thicknesses examined were significantly greater in del/ins than in del/del children. Body fat mass as determined by dual-energy X-ray absorptiometry was also greater in del/ins than in del/del children (P < 0.005). For 104 children genotyped at exon 4, no significant differences in BMI or body composition were found among the 3 exon 4 genotypes. Neither resting energy expenditure nor respiratory quotient were different according to UCP2 exon 4 or exon 8 genotype.

Conclusions: The exon 8 ins/del polymorphism of UCP2 appears to be associated with childhood-onset obesity. The UCP2/UCP3 genetic locus may play a role in childhood body weight.

KEY WORDS Body mass index, weight, obesity, polymorphism, genetics, childhood

INTRODUCTION

Body weight in humans appears to be a trait with strong genetic determinants; heritability is estimated to be between 50% and 85% for adult body weight (1–4). Because obesity is presumed to develop when there is an imbalance between energy intake and energy expenditure, candidate genes for body weight regulation include those that might be important for the regulation of energy expenditure, such as those that may affect thermogenesis. Therefore, the uncoupling proteins (UCPs), which may translocate protons into the mitochondrial matrix, resulting in heat generation without ATP synthesis (5), have been examined for associations with body weight. UCP1, found predominantly in brown adipose tissue and important for shivering thermogenesis in rodents, has been linked in adults to the amount of weight lost during dieting (6) but has not been strongly linked to adult or child body weight (7–11). The human genetic locus containing the recently cloned UCP2 and UCP3 [11q13 (12–16)] genes has been linked to several factors that are believed to be relevant for the regulation of body weight in adults. Adult resting energy expenditure (REE) (17–19), weight gain (8), and possibly percentage body fat (18) have all been found to have genetic linkage to the UCP2/UCP3 locus. In one study, a higher prevalence of a heterozygous polymorphism altering the UCP3 exon 6-splice donor site that truncates the terminal 37 amino acids of UCP3 was found in severely obese than in lean African American subjects. This same study found that those with this polymorphism had lower basal fat oxidation rates than did those with the more common allele (20). However, other studies in adults did not find a significant link

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²Supported by the Office of Research on Minority Health, the National Institutes of Health, and NIH HD-00641 (JAY) and by NIH DK-52581 and HL-35773 (CHW and ALD). JAY and NGS are Commissioned Officers in the US Public Health Service.

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Received May 5, 1999. Accepted for publication November 5, 1999.
between the UCP2/UCP3 locus and obesity, insulin resistance, or REE (21–28). Few previous studies determined linkage of the UCP2/UCP3 locus to body weight in childhood, and little is known about the genes that predispose individuals to become overweight in childhood.

Two independent risk factors for obesity in adulthood are body mass index (BMI; in kg/m²) of school-age children and BMI of the children's parents (29). Children aged 6–10 y with a BMI greater than the 85th percentile for age and sex have a relative risk of adult obesity that is 8.8-fold greater than that of children with a lower BMI. Irrespective of their own BMIs, 6–10-y-old children with 2 overweight parents have a relative risk of adult obesity that is 5-fold greater than that of children with 2 normal-weight parents (29). The results of a recent study suggested that REE may differ between lean and overweight children only when the children are grouped according to the degree of their parents' obesity (30). We hypothesized that children whose BMIs were already greater than the 95th percentile by age 6–10 y were likely to have genetic factors predisposing them to obesity that were distinct from those that might cause later obesity in the relatively lean children of overweight parents. We further hypothesized that alterations in genes that may regulate energy economy, such as the UCP2 gene, would be more likely to contribute to childhood-onset obesity than to obesity that occurs only in adulthood. Therefore, we investigated the association of UCP2 polymorphisms with body weight, body composition, and REE in overweight children and in nonoverweight children with obese parents.

**TABLE 1**
Study subjects grouped by exon 8 deletion (del)/insertion (ins) genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>del/del</th>
<th>del/ins</th>
<th>ins/ins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(n = 50)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>8.3 ± 1.3</td>
<td>8.6 ± 1.2</td>
<td>8.3 ± 1.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>36.5 ± 11.4</td>
<td>46.6 ± 16.7</td>
<td>47.5 ± 33.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>134.2 ± 9.6</td>
<td>136.6 ± 9.7</td>
<td>139.4 ± 14.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.4 ± 4.8</td>
<td>24.1 ± 5.9</td>
<td>23.7 ± 7.8</td>
</tr>
<tr>
<td>SD score</td>
<td>2.0 ± 2.5</td>
<td>3.3 ± 2.8</td>
<td>3.1 ± 3.2</td>
</tr>
<tr>
<td>Percentage overweight (%)</td>
<td>37.7 ± 33.0</td>
<td>56.3 ± 38.9</td>
<td>49.7 ± 44.4</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>10</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>African American</td>
<td>30</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>White</td>
<td>60</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>Bone age (y)</td>
<td>9.0 ± 1.7</td>
<td>9.4 ± 2.0</td>
<td>9.8 ± 2.7</td>
</tr>
<tr>
<td>Boy's testis volume (mL)</td>
<td>2.4 ± 1.1</td>
<td>2.7 ± 1.6</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td>Girls' breast development (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner stage 1</td>
<td>75</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Tanner stage 2</td>
<td>25</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Pubic hair (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner stage 1</td>
<td>81</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>Tanner stage 2</td>
<td>13</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Tanner stage 3</td>
<td>6</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Girls' plasma estradiol (pmol/L)</td>
<td>40.0 ± 32.7</td>
<td>34.5 ± 18.7</td>
<td>36.2 ± 13.2</td>
</tr>
<tr>
<td>Boys' plasma testosterone (nmol/L)</td>
<td>0.43 ± 0.20</td>
<td>0.49 ± 0.23</td>
<td>0.38 ± 0.07</td>
</tr>
<tr>
<td>Plasma dehydroepiandrosterone sulfate (µmol/L)</td>
<td>1.27 ± 0.98</td>
<td>1.43 ± 1.16</td>
<td>1.74 ± 0.99</td>
</tr>
</tbody>
</table>

1-2: ± SD. 2-4: Significantly different from del/del: 2 P < 0.001, 3 P < 0.05, 4 P < 0.005. 5: Defined as the percentage by which a BMI is greater than the 50th percentile for age, sex, and race (31).

**SUBJECTS AND METHODS**

**Subjects**

Subjects were recruited through notices mailed to children aged 6–10 y in the Montgomery County, MD, school district and, in the case of overweight children, by referral from local physicians. We studied a total of 105 African American, Asian, and white children aged 6–10 y (63 girls and 42 boys) for whom we obtained samples for genomic DNA analysis (Tables 1 and 2). The children were recruited for studies of physiology and metabolism in 3 groups: 58 overweight children [BMI greater than the 95th percentile for age, sex, and race (31)] who did not have a discernable medical cause of their obesity, 32 children with a BMI between the 15th and 95th percentiles and for whom both parents and grandparents, and all the white children had white parents and grandparents. For analysis, only one child from each family was studied. All subjects were free of significant medical disease. All had normal results of physical examinations and normal hepatic, renal, and thyroid function. Each subject underwent a detailed medical history and was examined for clinical signs of adrenarche or!gandarche. The study was approved by the...
National Institutes of Health Intramural Clinical Research Subpanel. Each child gave written assent to participate in the study and one parent gave written consent.

Protocol

The subjects were studied in the morning ≈12 h after their last meal. Anthropometric measurements were obtained as recommended (33). These measurements included weight, height, skinfold thicknesses, and body circumferences (obtained with a flexible, nonstretching tape measure). Waist circumference was measured around the buttocks at the maximum circumference. The waist circumference divided by the hip circumference was calculated to determine the waist-to-hip ratio. Height was measured (3 times) with a stadiometer (Holtain Ltd, Crymych, United Kingdom) calibrated before each height measurement to the nearest 1 mm. Weight was obtained to the nearest 0.1 kg by using a calibrated digital scale (Scale-Tronix, Wheaton, IL). A roentgenogram of the left hand and wrist for bone maturation was also obtained (34).

Body composition (by using dual-energy X-ray absorptiometry [DXA]) and REE were measured at the National Institutes of Health Warren Grant Magnuson Clinical Center as described previously (35). The subjects were at bed rest for 4 h before measurement of REE and had nothing to eat or drink except water after midnight on the day of the study. The subjects were awake, lay supine in bed, and watched noncommercial children’s television shows during measurement. Oxygen consumption (\(\hat{V}O_2\)) and carbon dioxide production (\(\hat{V}CO_2\)) were measured at 1-min intervals by respiratory exchange by using a ventilated hood system (DeltaTrac; SensorMedics, Yorba Linda, CA). REE was calculated from the rates of \(\hat{V}O_2\) and \(\hat{V}CO_2\) (36). Breath-by-breath measurements of \(\hat{V}O_2\) and \(\hat{V}CO_2\) were automatically averaged and recorded at 1-min intervals for ≥15 min until > 10 min with a CV in energy expenditure of < 5% was achieved. The mean of the energy expenditure and respiratory quotient (RQ) measurements was determined for each subject and used for further analysis. All subjects had blood samples drawn after an overnight fast. Total testosterone, estradiol, and dehydroepiandrosterone sulfate were measured at Covance Laboratories (Vienna, VA) as described previously (37, 38).

Genomic DNA was isolated from peripheral blood leukocytes and amplified by the polymerase chain reaction (PCR). For exon 8, a sense primer (hUCP2e8f, 5’ CAG TGA GGG AAG TGG GAG G 3’) and an antisense primer (hUCP2e8r, 5’ GGG GCA GGA CGA AGA TTC 3’) that flank the region containing a 45–base pair (bp) insertion/deletion in the 3‘-untranslated region (UTR) of exon 8 of the UCP2 gene were used as described previously (17). These PCR primers produce either 457- or 412-bp products, depending on whether the insert is present. Subjects were identified on the basis of PCR products as being either homozygous for the 3‘-UTR exon 8 deletion (del/del), heterozygous (ins/del), or homozygous for the 3‘-UTR exon 8 insertion (ins/ins) for exon 4, the sense
primer Ex4F1 (5’TGG CTG CCA TCT TCC TGG TCC CCC 3’) and antisense primer Ex4R1 (5’GGC CCA ACG CCT TGC TCC 3’) were used to amplify genomic DNA. A second set of PCR primers (Ex4A/VF: 5’GGG CCA GTG CGA CCT ACA G 3’ and Ex4A/VR: 5’ATG CGG ACA GAG GCA AAG C 3’) were then used to introduce an EciI restriction site that produces 167-bp (for T) or 151-bp products (for C), allowing subjects to be identified as having the homozygous C/C, heterozygous C/T, or homozygous T/T genotype (39).

**Data analysis**

Parametric data were analyzed by using SUPERANOVA 1.11 and STATVIEW 4.5 (Abacus Concepts, Inc, Berkeley, CA). Anthropometric and DXA body-composition results from all 3 genotypes were compared by using analysis of variance (ANOVA). Logarithmic transformation was performed before analysis for all anthropometric circumference measurements, for plasma dehydroepiandrosterone sulfate, and for DXA lean body mass and body fat mass measurements (determined by DXA). Significant results by ANOVA were followed by post hoc Fisher’s protected least-significant-difference tests. All tests were two-tailed. Sex, race, and UCP2 polymorphism status were factors for analyses of BMI and percentage body fat as determined by DXA. Lean body mass of the trunk and percentage fat mass of the arm and trunk could not be successfully normalized by transformation and were compared by using the nonparametric Mann-Whitney U test. Statistical results were interpreted with Bonferroni adjustment for multiple comparisons. Nominal P values are reported. Categorical data were examined by using contingency-table analysis. The presence of linkage disequilibrium between exon 4 and exon 8 alleles was tested by using the chi-square statistic. There were 88 children with results available from both exon 4 and exon 8 polymorphisms for this analysis. Analysis of covariance, with the log of lean body mass as determined by DXA, the log of body fat mass as determined by DXA, and sex as the covariates, was performed to evaluate the effect of UCP2 genotype on the log of REE. Because some study participants had evidence of early puberty or adrenarche, analyses were also performed by using evidence of production of pubertal or adrenarchal sex hormones as a factor. The presence of puberty or adrenarche, either at physical examination (presence of axillary or pubic hair or a Tanner stage > 1) or by laboratory testing [estradiol > 36.7 pmol/L (15 pg/mL), testosterone > 0.7 mmol/L, and dehydroepiandrosterone sulfate > 0.95 μmol/L (35 μg/dL)], these hormone cutoff points represent the mean + 2 SDs for each hormone in the assays used for children aged < 6 y (40–42). There were no significant differences between results for children with and children without evidence of early puberty or adrenarche; therefore, results for the entire group of 105 children are presented.

**RESULTS**

Genotypes were obtained in 89 children for the exon 8 ins/del allele (Table 1), including 50 children with homozygous 45-bp deletion alleles in the 3’UTR of exon 8 of UCP2 (del/del), 33 children heterozygous for the insertion allele (ins/del), and 6 children with homozygous insertions (ins/ins). Because so few ins/ins children were identified, there was insufficient power to determine significance of differences found in ins/ins subjects. For the 104 children genotyped at exon 4 (Table 2), 42 had the C/C, 47 had the T/C, and 15 had the T/T genotypes. In the 88 children for whom genotypes at both exons were available, polymorphisms in exons 4 and 8 were in linkage disequilibrium (Table 3).

For both exon 4 and exon 8 polymorphisms, sex and racial distributions were not significantly different in each group, and the groups were also not significantly different in age, bone age, pubertal maturation, or plasma adrenal and gonadal hormones (Tables 1 and 2). However, weight and BMI were significantly greater in children with the del/ins genotype than in those with the del/del genotype (Table 1). These effects were confirmed when BMI was expressed either as an SD score or as a percentage of overweight children (Table 1) and the effects on BMI and DXA body fat mass were independent of race (Figure 1) and sex (P < 0.01, ANOVA). BMI was not significantly different for children with different exon 4 genotypes (T/T: 24.2 ± 7.0, T/C: 22.1 ± 5.7, and C/C: 21.9 ± 5.3; P = 0.12, ANOVA; Table 2).

Body composition was also different according to UCP2 exon 8 genotype. Anthropometric measurements were significantly greater in del/ins than in del/del children for all circumferences and skinfold thicknesses examined (Table 4). Waist-to-hip ratio was the only anthropometric variable that was not significantly different among the groups, and similar results were found for all 3 racial groups studied (Figure 1). These results were confirmed by DXA (Figure 2): Body fat mass and percentage of total body mass that was fat were significantly greater in del/ins than in del/del children, independent of race and sex. As expected given their greater body fat mass, del/ins children had a significantly greater total lean body mass than did del/del children. There were no significant differences in body composition, assessed either by DXA or by anthropometry, for children with the 3 exon 4 genotypes (Table 5).

In analyses using lean body mass, body fat mass, and sex as covariates, REE was not significantly different according to exon 4 or exon 8 genotype (Figure 3). RQ was also not significantly different among groups (exon 8: del/del, 0.87 ± 0.04; del/ins, 0.86 ± 0.05; ins/ins, 0.88 ± 0.05; exon 4: C/C, 0.85 ± 0.04; T/C, 0.87 ± 0.04; T/T, 0.86 ± 0.04).

**DISCUSSION**

We found a significant association between an allelic variant in the 3’UTR of UCP2 exon 8 and measures of obesity in this small sample of children. Children with the del/ins genotype had a significantly greater BMI than did those with the del/del genotype. Body fat measurements, determined either by anthropometry or by DXA, were also greater in children with the del/ins genotype.
Although too few ins/ins children were identified to enable significant increases in any measured variable to be detected, results for ins/ins children were generally similar to results for del/ins children. To our knowledge, these findings are the first linking any gene locus relevant for energy expenditure to body weight regulation in childhood. By contrast, as others have reported in adults and children (17, 23, 43), we found no significant associations between UCP2 exon 4 allelic variation and BMI or body composition. Thus, it appears that the exon 4 Ala to Val variant at amino acid 55 is of little or no importance for regulation of child or adult body weight. Although there was some concordance between the exon 8 and exon 4 variants (Table 3), the C/T genotype was fairly evenly divided between those with the del/del genotype (19% of subjects) and those with the del/ins genotype (29% of subjects).

![FIGURE 1. BMI, percentage overweight, waist circumference, total body fat mass as measured by dual-energy X-ray absorptiometry (DXA), and total percentage body fat as measured by DXA in African American, white, and Asian subjects. *Significantly different from del/del, P < 0.05; for BMIs of Asian subjects, P = 0.07. There were no Asian subjects and only one African American subject with the ins/ins genotype. Percentage overweight is defined as the percentage by which BMI exceeds the 50th percentile for age, sex, and race (31).](https://academic.oup.com/ajcn/article-abstract/71/6/1405/4729371)

![FIGURE 2. Regional body composition as measured by dual-energy X-ray absorptiometry. *P < 0.05, **P < 0.005, ***P < 0.001.](https://academic.oup.com/ajcn/article-abstract/71/6/1405/4729371)
We found an association of perhaps explaining why the 
2
Fat mass (kg)
2
examined. These findings suggest that a gene either within or 
type with BMI and body fat mass in all 3 racial subgroups 
or energy expenditure to the 
childhood measures of body adiposity.

2

Skinfold thickness (mm)

Waist-to-hip ratio 0.86

Circumference (cm)

Sum of 4 skinfolds 56.6

Subscapular 15.8

Biceps 10.2

Axilla 28.3 ± 4.8

Calf 30.0 ± 3.6

Triceps 20.8

Neck 29.9 ± 3.3

Upper arm 24.8 ± 5.1

Forearm 21.1 ± 2.7

Calf 30.0 ± 3.6

Hip 78.1 ± 11.2

Waist 67.2 ± 12.1

Hip 78.1 ± 11.2

Waist 67.2 ± 12.1

Upper arm 24.8 ± 5.1

Forearm 21.1 ± 2.7

Axilla 28.3 ± 4.8

Chest 75.5 ± 11.5

Table 5

Body composition according to exon 4 genotype

<table>
<thead>
<tr>
<th>Circumference (cm)</th>
<th>C/C (n = 42)</th>
<th>C/T (n = 47)</th>
<th>T/T (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>29.9 ± 3.3</td>
<td>29.9 ± 3.0</td>
<td>31.2 ± 4.5</td>
</tr>
<tr>
<td>Upper arm</td>
<td>24.8 ± 5.1</td>
<td>25.1 ± 5.5</td>
<td>27.3 ± 6.2</td>
</tr>
<tr>
<td>Forearm</td>
<td>21.1 ± 2.7</td>
<td>21.3 ± 3.1</td>
<td>22.1 ± 3.5</td>
</tr>
<tr>
<td>Axilla</td>
<td>28.3 ± 4.8</td>
<td>28.6 ± 5.2</td>
<td>30.8 ± 6.1</td>
</tr>
<tr>
<td>Chest</td>
<td>75.5 ± 11.5</td>
<td>76.4 ± 11.3</td>
<td>80.9 ± 14.3</td>
</tr>
<tr>
<td>Waist</td>
<td>67.2 ± 12.1</td>
<td>68.6 ± 12.4</td>
<td>74.1 ± 16.7</td>
</tr>
<tr>
<td>Hip</td>
<td>78.1 ± 11.2</td>
<td>79.6 ± 12.3</td>
<td>83.3 ± 14.3</td>
</tr>
<tr>
<td>Thigh</td>
<td>42.5 ± 7.3</td>
<td>43.7 ± 7.8</td>
<td>47.7 ± 9.5</td>
</tr>
<tr>
<td>Calf</td>
<td>30.0 ± 3.6</td>
<td>31.2 ± 5.1</td>
<td>32.6 ± 5.9</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.86 ± 0.05</td>
<td>0.86 ± 0.05</td>
<td>0.88 ± 0.06</td>
</tr>
</tbody>
</table>

Skinfold thickness (mm)

Triceps 20.8 ± 8.2

Biceps 10.2 ± 4.3

Subscapular 15.8 ± 8.9

Suprailiac 18.4 ± 8.9

Sum of 4 skinfolds 56.6 ± 26.6

Lean mass (kg)2

Fat mass (kg)3

Percentage fat mass (%)2

3 ± SD.

Determined by dual-energy X-ray absorptiometry.

Perhaps explaining why the C/T genotype was not associated with childhood measures of body adiposity.

Some previous studies in adults found linkage of body weight or energy expenditure to the UCP2/UCP3 locus in distinct subpopulations (17, 20). We found an association of UCP2 genotype with BMI and body fat mass in all 3 racial subgroups examined. These findings suggest that a gene either within or close to the UCP2/UCP3 locus may be an important determinant of body weight in children.

At present, little is known about the effect of the exon 8 insertion variant on UCP2 function. The ins/del polymorphism has been hypothesized to influence UCP2 protein amounts by altering messenger RNA (mRNA) concentrations or translation rates. In a study of muscle biopsy specimens from Pima Indians, UCP2 mRNA (50) was not significantly different in 10 of muscle biopsy specimens from Pima Indians, and energy expenditure to the adult metabolic rate (17), it may be necessary to study considerably larger samples to enable changes in energy expenditure or RQ related to this UCP2 variant in childhood to be detected, where the variability of measurements is often higher than that observed in adults.

We chose to compare normal-weight children who had overweight parents with children who were already overweight before adolescence because we hypothesized that the genetic determinants of pediatric- and adult-onset obesity would be different. We believe that the results of the present study validate this approach. It can be anticipated that other genetic factors involved in pediatric weight regulation can be uncovered through such comparisons.

FIGURE 3. Resting energy expenditure was not significantly different in children with different exon 8 or exon 4 polymorphisms.
In conclusion, we found that a genetic variant of UCP2 appears to be associated with childhood-onset obesity. These findings suggest that the UCP2/UCP3 genetic locus may be involved in determining childhood body weight.

REFERENCES