Variants of the peroxisome proliferator-activated receptor γ- and β-adrenergic receptor genes are associated with measures of compensatory eating behaviors in young children[1–3]

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ABSTRACT

Background: Young children can regulate energy precisely in the short term, showing the potential for an innate compensation mechanism of eating behavior. However, data suggest that precise compensation is attenuated as a function of increasing adiposity, parental feeding style, and age. Common variation in candidate obesity genes may account for some of the individual variation observed in short-term energy compensation. Polymorphisms in the peroxisome proliferator-activated receptor γ (*PPARG*) and β-adrenergic receptor (*ADRB3*) genes have been linked to increased body mass index (BMI; in kg/m^2), obesity, and more recently dietary nutrients and preferences. In addition, common variation in *ADRB3* interacts with *PPARG* to modulate adult body weight.

Objective: This study investigated whether variants in these genes were associated with measurable effects on child eating behavior.

Design: Children ($n = 84$) aged 4–10 y were prospectively selected for variants of the *PPARG* locus (Pro12Ala, C1431T). Heights and weights were measured. Energy intake from a test meal was measured 90 min after ingestion of a no-energy (NE), low-energy (LE), or high-energy (HE) preload, and the compensation index (COMPX) was calculated.

Results: BMI differed significantly by gene model, whereby Pro12Ala was associated with a lower BMI. Poor COMPX was associated with the *PPARG* T1431 allele ($P = 0.009$). There was a significant interaction between COMPX and the *ADRB3* Trp64Arg variant in modulating compensation ($P = 0.003$), whereas the Arg64 allele was associated with good compensation ($P = 0.001$).

Conclusions: This is the first study to suggest that a genetic interaction involving *ADRB3* and *PPARG* variants influences eating behavior in children. *Am J Clin Nutr* 2007;86:167–73.

KEY WORDS Children, eating behavior, energy compensation, *PPARG* gene variants, BMI, body mass index

INTRODUCTION

Childhood obesity has increased in the United Kingdom (1). In Scotland 5.0% of boys and 7.2% of girls aged 4–10 y were obese, and 16.1% of boys and 20.9% of girls were overweight in 2003 (2), which confirms an exponential increase in the past decade. Causes of obesity are complex, but generally they result from a sustained imbalance of energy intake over expenditure, influenced by psychological, environmental, physiologic, and genetic factors. Genetic variation may influence the partitioning of energy metabolism, may predispose to site-specific adiposity, and may influence the experience of hunger, satiety, and other regulatory mechanisms for controlling food intake (3, 4).

The ability of persons to respond to hunger and satiety cues and to resist external cues to eat is encapsulated by a measure of short-term energy compensation (5–10). Individual differences in children's ability to regulate energy intake indicate that poor short-term energy regulation is associated with increased child age (6, 8), adiposity (11, 12), and restricted access to energy dense, highly palatable foods (11). These factors explain only part of the variance. Unexplained variation (between individuals) leads us to question the role of gene differences in short-term compensation (13–14).

One factor linking adiposity, food response, and appetite is the nuclear fatty acid receptor peroxisome proliferator-activated receptor γ (PPARγ) encoded by the *PPARG* gene (15). PPARγ is expressed in adipose tissue and is a key regulator of adiposity and energy balance. PPARγ is also a target for insulin-sensitizing drugs, known as thiazolidinediones (TZDs) (16). The TZD troglitazone appears to modulate appetite (17) and is mediated in part by PPARγ via regulation of leptin gene transcription (18). Notably, TZD activation of PPARγ results in down-regulation of the leptin gene (19). This association between PPARγ and leptin, a potent adiposity signal with a key role in modulating the central control of ingestive behavior, identifies *PPARG* as a candidate gene in mediating appetite.

Common variation of the *PPARG* gene has been linked to body mass index (BMI; in kg/m^2) and obesity in whites. The most

frequently studied *PPARG* variant is the praline-to-alanine substitution at codon 12 (Pro12Ala) (20), known to influence body weight regulation (21–24). Two additional variants, in linkage disequilibrium with Pro12Ala, are the C1431T variant in exon 6 of *PPARG* that is linked with susceptibility to cardiovascular disease (25, 26), leptin concentrations (27), and BMI (22, 28, 29) and the C−681G1 variant that resides in the PPARγ3 promoter region (30) and is implicated in bone growth (31) and increased height (22, 30). Diet-gene interactions among *PPARG* Pro12Ala, dietary carbohydrate (32), and fat (33–35) also suggest a *PPARG* role in modulating weight. In addition, the evidence for C1431T in modulating leptin concentrations further implicates *PPARG* in the control of appetite (27, 36).

This study investigated whether common *PPARG* gene variants are associated with short-term energy compensation, as a potential behavioral correlate of obesity. We hypothesized that *PPARG* variants associated with increased weight and BMI would be associated with low (poor) compensation (22). We also assessed the influence of the β-adrenergic receptor (*ADRB*) gene on eating, given their close link to *PPARG* function. *ADRB* subtypes are candidate obesity genes (37, 38), and *ADRB3* and *PPARG* variants interact to modulate adult body weight (39).

SUBJECTS AND METHODS

Subjects

Eighty-four prepubertal school children aged 4–10 y from 47 schools across northeastern Scotland participated in the study. The sample was largely white (95%). These children were initially recruited into a much larger study on the maintenance of energy balance (22) in which genomic DNA isolated from saliva was taken from 2454 children after child and parental consent. The 84 children in this study represent a subsample prospectively enriched for the Pro12Ala and C1431T variants of *PPARG*. Ethical approval for this work was granted by the Tayside Committee on Medical Research Ethics and the Fife Local Research Committee. The education department in each school authority and school head teachers also gave their approval.

DNA genotyping

DNA was prepared from mouthwash saliva pellets (40). Allelic discrimination by TaqMan assays was used to determine genotype. The probes and primers used to genotype the *PPARG* Pro12Ala, C1431T (29), and C−681G (22) variants were described previously. The reagents for the genotyping of the *ADRB3* Trp64Arg variant were as follows: forward primer, AGGCAACCTGCTGGTCATCGT; reverse primer, CATCAC-CAGGTCGGCTGCG; T allele probe, 5'FAM-CCATCGC-CTGGACTCCGAGACTCC-TAMRA; and C allele probe, 5'Tet-CCATCGCCCGGACTCCGAGACTCC-TAMRA.

All assays were performed with reagents supplied by Applied Biosystems (Foster City, CA) and with standard amplification conditions. Allelic discrimination was performed on an ABI7700 sequence detection system (Applied Biosystems).

Measurement of height and weight

Height and weight were measured on the morning of the first test condition. Standing height without shoes was measured to the nearest 0.1 cm with the use of a stadiometer (SECA, Bolton, United Kingdom). Body weight, with subjects wearing light clothing, was measured to the nearest 0.5 kg with a mechanical floor scale (SECA). BMI was calculated (2). Overweight and obesity were determined by the use of age- and sex-appropriate international cutoffs (41).

Procedure for measurement of compensation index

The procedure for measurement of compensation index (COMPX) was reported elsewhere (6). This method tests a person's ability to adjust energy intake at a test meal in response to the energy content of preloads. Briefly, children consumed either a no-energy (NE), low-energy (LE), or high-energy (HE) preload midmorning on 3 occasions at school, followed by a test-meal lunch 1.5 h later. The order of preload administration was partially randomized; the NE control preload was consistently administered as the first condition to familiarize children with the procedure and to act as a control condition. Tests were separated by at least 1 wk. Parents were instructed to provide their child with their habitual breakfast on the morning of each test and to record breakfast details.

Preloads and test meals

Three preloads were developed and designed to vary in energy density with minimal differences in sensory properties (6). The NE control (0 kJ) was 250 mL water. The LE preload (187 kcal, or 782.78 kJ) consisted of 250 mL orange drink (200 mL water + 50 mL low-energy orange still soft drink) and 56 g low-energy-dense muffins. The HE preload (389 kcal, or 1628.35 kJ) consisted of 250 mL orange drink (200 mL water + 50 mL low-energy orange still soft drink) with the addition of 15 g maltodextrin (Maxijul; SHS International Ltd, Liverpool, United Kingdom) and 56 g regular-energy-dense muffins. Each child was required to ingest 100% of the preload at each test.

Ninety minutes after preload, children were offered a self-selected test-meal lunch consisting of cold finger food (6). The meal was prepared in quantities in excess of what the children would normally be expected to consume, and the children were invited to eat and drink as much as they wanted. A maximum of 30 min was allotted for the lunch. The average group size on each test occasion was 4, and the children sat together to consume their lunch.

Assessment of food intake

Energy intake at the test meal was assessed by weighing the food items before and after lunch and then using the manufacturers' information to calculate the total amount of energy consumed. The precision of energy compensation was assessed by using the COMPX, which was calculated as the difference in energy intake from the test-meal lunch on any 2 occasions divided by the difference in the energy content of those preloads. The value was converted to a percentage [(change in energy intake at test meal/change between preload energy content) × 100] (11). A score of 100% represents precise (calorie for calorie) compensation. Values <100% reflect undercompensation; values >100% reflect overcompensation. Good COMPX was defined as >50%; poor COMPX was defined as <50%.

Data analyses

Genotype was analyzed with the use of dominant and codominant models, with multiple variants included in the models to test for interactions. Quantitative traits (weight, height, BMI) were

TABLE 1
Characteristics of the cohort[1]

Characteristics	Boys (n = 43)	Girls (n = 41)	Total (n = 84)
Age (y)	7.47 ± 1.20[2]	7.10 ± 0.92	7.29 ± 1.08
Height (m)	1.28 ± 0.08	1.27 ± 0.08	1.28 ± 0.08
Weight (kg)	28.2 ± 5.80	28.8 ± 7.16	28.5 ± 6.47
BMI (kg/m^2)	16.9 ± 2.04	17.8 ± 2.63	17.4 ± 2.37
Overweight (%)[3]	16.7	17.1	16.9
Obese (%)[3]	2.4	14.6	8.4

[1] There were no statistically significant differences between boys and girls in any of the variables.

[2] $\bar{x}$ ± SD (all such values).

[3] Overweight and obesity were determined by use of age- and sex-appropriate international cutoffs (41).

analyzed with the use of univariate general linear modeling. Age and sex were included as covariates in all models.

Energy intake and COMPX data were analyzed with the use of repeated measures analyses of variance, with age and sex as between-subject factors. Where significant main effects were obtained, post hoc multiple and pairwise comparisons with a Bonferroni correction factor were applied to determine the nature of the significance.

COMPX and genotype data were analyzed with the use of repeated measures general linear modeling, with genotypes as between-subject factors. Age and sex were used as covariates. Energy intake and genotype data were also analyzed in this way.

All data were analyzed by using SPSS for WINDOWS (version 12.0; SPSS, Chicago, IL). Results for mean COMPX and total energy intake are expressed as means ± SEM unless otherwise stated. Statistical significance was set at $P < 0.05$

RESULTS

Subject characteristics

Characteristics of the children are shown in **Table 1**. Forty-three boys and 41 girls with a mean age of 7.29 y participated in the study. In this sample, 16.7% of the boys and 17.1% of the girls were overweight and a further 2.4% of the boys and 14.6% of the girls were obese.

Allele frequencies

Allele frequencies of the 3 *PPARG* variants are described in **Table 2**. The sample was prospectively enriched for *PPARG* Ala12 and T1431 carriers (n = 84). The allele frequency of the Trp64Arg variant of the *ADRB3* gene is also described (Table 2).

BMI and genotype

The role of the individual variants was examined in relation to age, sex, height, weight, and BMI (**Table 3**). With the use of univariate general linear modeling, all 3 *PPARG* variants were included in the model. With the use of this 3-variant model, none of the variants were associated individually with BMI, although Pro12Ala just missed significance with BMI at $P = 0.066$. Pro12Ala was significantly associated with reduced weight ($P = 0.007$) and reduced height ($P = 0.003$), and C−681G was significantly associated with increased height (P for model 2 = 0.008; Table 3). There were no interactions among any of the 3

TABLE 2
Genotype frequencies for the cohort

Polymorphism	Genotype frequency		Allele frequency
	n	%	%
Pro12Ala			
Pro/Pro	41	48.8	
Pro/Ala	31	36.9	0.327
Ala/Ala	12	14.3	
C1431T			
C/C	31	36.9	
C/T	49	58.3	0.339
T/T	4	4.8	
C−681G			
C/C	36	42.9	
C/G	31	36.9	0.387
G/G	17	20.2	
Trp64Arg			
Trp/Trp	73	86.9	
Trp/Arg	11	13.1	0.065

variants. Examination of individual variants in isolation showed that *PPARG* Pro12Ala associated individually and significantly with reduced BMI ($P = 0.01$) and reduced weight ($P = 0.025$) but not height (P for model 1; Table 3). There were no significant associations with BMI, weight, and height for *PPARG* C1431T and C−681G when examined in isolation (P for model 1; Table 3).

When the *ADRB3* gene variant Trp64Arg was added into the model (P for model 3; Table 3), the effect of Pro12Ala on weight remained significant ($P = 0.023$). There was also an interaction between C1431T and Trp64Arg on weight ($P = 0.007$) but no separate individual effect of C1431T or Trp64Arg on weight. Examination of variants with regard to height showed separate effects of Pro12Ala ($P = 0.010$) and Trp64Arg ($P = 0.053$) on height (P for model 3; Table 3) and an interaction effect between Pro12Ala and C−681G ($P = 0.033$) and between C1431T and Trp64Arg ($P = 0.006$). Examination of the Trp64Arg variants in isolation showed no significant effects on BMI, weight, or height (P for model 1; Table 3).

Energy intake and COMPX

Analyses of energy intake from the test meal showed a main effect of preload ($P < 0.001$), which indicated that the children adjusted intake at lunch in response to preload energy content. Energy intake differed significantly by preload (NE: 3005 ± 84 kJ; LE: 2644 ± 78 kJ; HE: 2414 ± 71 kJ; $P < 0.001$). Total energy intake (energy from the test meal + preload) also differed significantly by preload ($P < 0.001$), indicating that, despite the adjustment in food intake at lunch after different preloads, this adjustment failed to accommodate precisely the energy content of the preloads. Thus, total energy intake increased by preload (NE: 3090 ± 122 kJ; LE: 3523 ± 113 kJ; HE: 4061 ± 105 kJ; $P < 0.001$). To determine the precision of energy compensation, COMPX was calculated and analyzed. COMPX scores showed low mean values for all preloads; however, this was subject to wide individual variation (**Table 4**). There were no main effects of preload, sex, or age on ability to compensate at the test meal. There was no correlation between COMPX and BMI, but BMI was positively correlated to energy intake for all preloads

TABLE 3
Association of variants of the peroxisome proliferator-activated receptor γ (*PPARG*) and β-adrenergic receptor (*ADRB3*) genes with height, weight, and BMI (*n* = 84)

	BMI				Weight				Height			
	Value[1]	*P* for model 1[2]	*P* for model 2[3]	*P* for model 3[4]	Value[1]	*P* for model 1[2]	*P* for model 2[3]	*P* for model 3[4]	Value[1]	*P* for model 1[2]	*P* for model 2[3]	*P* for model 3[4]
Pro12Ala												
Pro/Pro	18.09 ± 0.33				29.99 ± 0.76				1.28 ± 0.008			
Pro/Ala	16.54 ± 0.38				26.74 ± 0.89				1.27 ± 0.010			
Ala/Ala	16.99 ± 0.61	0.010	0.066	0.121	28.10 ± 1.41	0.025	0.007	0.023	1.29 ± 0.015	0.530	0.003	0.010
C1431T												
C/C	17.69 ± 0.39				29.27 ± 0.92				1.28 ± 0.01			
C/T	17.14 ± 0.31				28.03 ± 0.72				1.28 ± 0.007			
T/T	17.83 ± 1.10	0.503	0.587	0.351	29.28 ± 2.52	0.549	0.681	0.164	1.28 ± 0.026	0.999	0.891	0.433
C−681G												
C/C	17.78 ± 0.36				29.02 ± 0.84				1.27 ± 0.009			
C/G	17.06 ± 0.39				28.49 ± 0.92				1.29 ± 0.009			
G/G	17.06 ± 0.53	0.336	0.727	0.834	27.60 ± 1.23	0.637	0.231	0.657	1.27 ± 0.013	0.266	0.008	0.079
Trp64Arg												
Trp/Trp	17.33 ± 0.26				28.25 ± 0.58				1.27 ± 0.006			
Trp/Arg	17.63 ± 0.66	0.67		0.490	30.41 ± 1.50	0.183		0.123	1.30 ± 0.15	0.116		0.053

[1] Values are the estimated marginal $\bar{x}$ ± SEM adjusted for age and sex (ie, age and sex are covariates) after univariate general linear modeling.
[2] Model 1 includes variants, one by one, individually.
[3] Model 2 includes the 3 *PPARG* variants (Pro12Ala, C1431T, and C−681G).
[4] Model 3 includes all 4 gene variants (Pro12Ala, C1431T, C−681G, and Trp64Arg).

(NE: *r* = 0.37, *P* < 0.001; LE: *r* = 0.39, *P* < 0.001; HE: *r* = 0.32, *P* < 0.003).

COMPX and genotype

COMPX was associated with a gene model; a main effect of *PPARG* C1431T (*P* = 0.009) and *ADRB3* Trp64Arg (*P* = 0.001) was found for COMPX. We also tested this association adjusted for BMI, in addition to age- and sex-adjusted data, and the outcome was similar for *PPARG* C1431T (*P* = 0.02) and *ADBR3* Trp64Arg (*P* = 0.002). *PPARG* Pro12Ala and C−681G were removed from the model because they did not show any contribution to this phenotype (data not shown). The effect of preload was not significant, and there was no significant interaction between preload and genotype for either variant. The main effect of genotype indicated poor COMPX (<50%) with the presence of a T1431 allele (C1431T polymorphism), whereas good COMPX (>50%) was associated with the presence of an Arg allele (*ADRB3* polymorphism) (**Figures 1** and **2**). There was a significant interaction between Trp64Arg and C1431T in modulating COMPX (*P* = 0.003) whereby the presence of a T1431 allele ameliorated the effect of the Arg allele on

TABLE 4
Compensation index (COMPX) scores by preload for all cells (*n* = 84)[1]

	NE/LE	NE/HE	LE/HE
	%		
COMPX	46.2 ± 6.8	36.4 ± 3.7	27.3 ± 5.9
Range	(−73.8 to 203.2)	(−31.6 to 160.0)	(−75.5 to 170.8)

[1] All values are $\bar{x}$ ± SD; range in parentheses. Scores were calculated as (difference in energy intake between test meals after each preload) (difference in preload energy) × 100. NE, no-energy preload; LE, low-energy preload; HE, high-energy preload. No significant differences between COMPX scores by preload were found.

COMPX (**Table 5**). With the use of univariate general linear modeling, a regression model was performed on the interaction between C1431T and *ADRB3* gene variants for COMPX. In the resulting model for NE/HE COMPX, the overall contribution to the variance of the interaction model was 13.5%.

Energy intake and genotype

When the 4 genotypes (Pro12Ala, C1431T, C−681G, and Trp64Arg) were entered in the repeated measures model, energy intake from the test meal was associated with the gene model, with a main effect of C1431T (*P* = 0.016). However, this effect
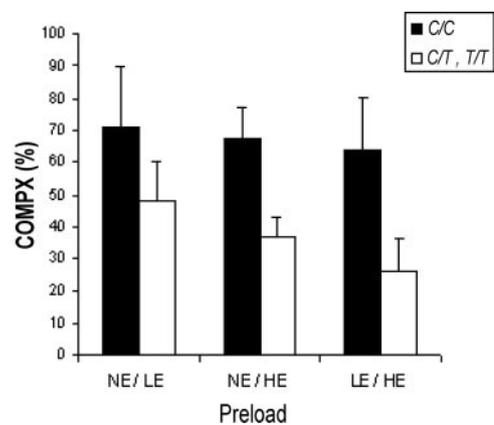
FIGURE 1. Mean (±SEM) energy compensation index (COMPX) after each preload [no-energy (NE), low-energy (LE), or high-energy (HE)] and a test meal in children carrying 1 copy (*C/T*) or 2 copies (*T/T*) of the *T* allele of the C1431T variant of the peroxisome-proliferator activated receptor γ gene and noncarriers (*C/C*). There was no genotype-by-condition interaction. Pairwise comparisons with Bonferroni adjustments between groups were as follows: *P* = 0.30 for NE/LE, *P* = 0.008 for NE/HE, and *P* = 0.05 for LE/HE.
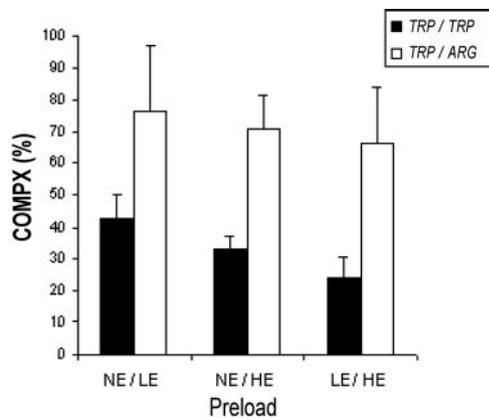
FIGURE 2. Mean (±SEM) energy compensation index (COMPX) after each preload condition and test meal [no-energy (NE), low-energy (LE), or high-energy (HE)] in children carrying 1 copy (*Trp/Arg*) of the *Arg* allele of the Trp64Arg variant of the β-adrenergic receptor gene and noncarriers (*Trp/Trp*). There were no persons carrying 2 copies of 64Arg. There was no genotype-by-condition interaction. Pairwise comparisons with Bonferroni adjustments between groups were as follows: $P = 0.14$ for NE/LE, $P = 0.001$ for NE/HE, and $P = 0.03$ for LE/HE.

was lost when nonsignificant genotypes (Pro12Ala, C−681G, and Trp64Arg) were removed from the model.

DISCUSSION

The aim of the present study was to determine whether common *PPARG* gene variants influence short-term energy compensation in children, an index of eating behavior control. This work represents a novel attempt to understand the influence of genes on a specific aspect of eating behavior and appetite control.

The data on overweight and obesity show that the children in this sample were representative of the larger cohort from which they were recruited (2) in terms of the percentage overweight. For obesity, the boys in the current sample had a lower prevalence (2.4%), whereas the girls had a higher prevalence (14.6%) compared with the main cohort (5.0% of boys and 7.2% of girls) (2). We did not measure entry to adiposity rebound but recognize it is a critical window and would advocate measuring this in future studies.

The data from the present study show clearly that *PPARG* Pro12Ala polymorphism is associated with lower BMI and weight, whereas C−681G was significantly associated with greater height. These findings were also present in the larger group from which these subjects were recruited (22). The data indicate that the *PPARG* Pro12Ala and C−681G variants display

TABLE 5
Effect of Trp64Arg and C1431T in modulating the compensation index (COMPX) with the presence of a T1431 allele[1]

Polymorphism	COMPX
CC + Trp/Trp (n = 27)	31.2 ± 6.0
CC + Trp/Arg (n = 3)	103.7 ± 18.4
CT/TT + Trp/Trp (n = 43)	35.7 ± 4.8
CT/TT + Trp/Arg (n = 8)	38.6 ± 11.1

[1] All values are $\bar{x}$ ± SD. Analyses of COMPX and genotype data used repeated-measures general linear modeling, with genotypes as between-subject factors. Age and sex were used as covariates. There was a significant interaction of Trp64Arg and C1431T on COMPX ($P = 0.003$).

an opposing interaction in terms of growth phenotype, with the G−681 variant associating with accelerated growth and the Pro12Ala variant linked to a deficient energy storage or utilization, leading to reduced growth. The current data also support previous studies in adults indicating that Pro12Ala is associated with protection from an increased BMI (21, 23, 29).

The data on energy compensation have shown that there is large interindividual variation in the ability to compensate at a test-meal lunch for energy ingested earlier in a preload snack. Children adjusted their energy intake in response to preloads in a dose-related manner, but overall the COMPX values showed relatively low values for accuracy for all preloads, indicting that the accuracy of energy compensation observed was poor. The individual variation in COMPX values were not explained by differences in sex or age. We have previously shown that younger children are on average better able to respond appropriately to the different energy contents of snacks given before lunch by adjusting food intake compared with older children (6). Other reports have shown that ability to compensate is also influenced by adiposity and degree of parental influence (11, 12). A major finding in this study was that genotype was a significant factor in ability to compensate. Thus, the COMPX score associated with the genotype of the person. The predominant *PPARG* single nucleotide polymorphism C1431T was associated with poor energy compensation, and this showed a significant interaction with the Trp64Arg variant of the β-3 adrenoreceptor. Poor COMPX (<50%) was associated with the presence of a T1431 allele (of C1431T polymorphism), whereas good COMPX (>50%) was associated with the presence of an Arg allele. Previous studies have shown an interaction between *ADRB3* and *PPARG* Pro12Ala variants in modulating adult body weight (38), probably because of linkage with C1431T, and the Trp64Arg variant was associated with carbohydrate preferences (42). Here, we suggest the presence of a genetic interaction between *ADRB*3 and *PPARG* variants in modulating energy compensation and a main effect of *PPARG* C1431T and *ADRB3*.

Interestingly, the role of *PPARG* T1431 in COMPX supports its reported association with increased BMI (29) and predisposition to cardiovascular disease (25, 26) in adults. We have also shown that this variant is associated with a small but nonsignificant increase in BMI in prepubertal children (22). In the current data, we showed no association between COMPX and child BMI; however, our children are young and will not yet express fully their *PPARG* genotype through currently developing phenotype. Thus, poor short-term energy compensation may well constitute a behavioral marker for positive energy balance later in life, as the child develops through adolescence and into adulthood. We have shown that the Pro12Ala variant is associated with lower BMI but is not associated with altered COMPX scores, which would support the notion that this Ala variant is directly associated with lower weight through modulation of energy utilization or storage, and would suggest that the mechanisms controlling eating behavior and weight gain are mediated by different genes or gene variants. In the future, we would want to test short-term COMPX effects on long-term weight gain in a longitudinal design and follow the T1431 carriers who display poor COMPX values at an early age into adulthood to determine their subsequent tendency to gain excess weight. The association of T1431 with poor satiety regulation could be explained in the context of leptin secretion and action, representing a plausible

mechanism by which this variant is associated with eating behavior. Indeed the T1431 allele has been shown to be associated with altered leptin concentrations (27, 36); however, we have not measured this factor in the current study. *PPARG* agonists are known to play a role in regulation of leptin production; eg, TZD activation of PPARγ results in down-regulation of the leptin gene (19). Low leptin concentrations in turn influence a number of neuroendocrine responses that function to conserve energy. Future analyses should include measurement of leptin concentrations to establish the strength of this link.

To date most research into the relation between specific genes and eating behavior has focused on single gene mutations and their role in appetite regulation pathways rather than on complex common gene variants. These single gene mutations, such as the leptin, leptin receptor, and melanocortin 4 receptor genes (43–47) are usually rare forms of genes that lead to severe obesity, due in part to a specific disruption or disruptions in the appetite regulatory pathway. So far, little data are available on complex common gene variants and eating behavior traits, but the potential for large interindividual variation in control of food intake that involves gene-gene and gene-environment interactions is likely. This is illustrated by recent data showing that *PPARG* variants interact with dietary nutrients in modulating body weight, suggesting that differential responses to dietary intake may depend on individual genotype (33–35).

The current study included a sample of persons who are largely white (95%). To check the possibility that ethnicity might have influenced the data analyses, we examined the white group ($n = 80$) separately in terms of allele frequency, genotype by BMI, and genotype and COMPX. The data for the white-only group were indistinguishable from the data presented here. Thus, it is unlikely that ethnic differences contributed significantly to observed gene effects. It is not yet clear how short-term markers of eating behavior predict long-term energy balance and the tendency to gain weight; hence, future follow-up studies would help elucidate our understanding of short-term energy regulation and energy balance in children.

In summary, the data presented here suggest that *PPARG* Pro12Ala is associated with protection from increased BMI and weight but is not associated with eating behavior specifically in terms of COMPX. *PPARG* T1431 may have a role in modulating COMPX in a manner concordant to its reported association with increased BMI in adults and children. It is acknowledged that common polymorphisms of the *PPARG* gene contribute significantly to human body weight, adiposity, and growth, and more recently data indicate that *PPARG* exerts modulatory effects of diet on body weight. However, this is the first study to report a relation between *PPARG* variants and energy compensation and supports the proposal that poor short-term energy compensation; hence, inability to regulate food intake may be a behavioral marker for future weight gain.

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