

ORIGINAL ARTICLE

An Obesity-Associated *FTO* Gene Variant and Increased Energy Intake in Children

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ABSTRACT

BACKGROUND

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Variation in the fat mass and obesity-associated (*FTO*) gene has provided the most robust associations with common obesity to date. However, the role of *FTO* variants in modulating specific components of energy balance is unknown.

METHODS

We studied 2726 Scottish children, 4 to 10 years of age, who underwent genotyping for *FTO* variant rs9939609 and were measured for height and weight. A subsample of 97 children was examined for possible association of the *FTO* variant with adiposity, energy expenditure, and food intake.

RESULTS

In the total study group and the subsample, the A allele of rs9939609 was associated with increased weight ($P=0.003$ and $P=0.049$, respectively) and body-mass index ($P=0.003$ and $P=0.03$, respectively). In the intensively phenotyped subsample, the A allele was also associated with increased fat mass ($P=0.01$) but not with lean mass. Although total and resting energy expenditures were increased in children with the A allele ($P=0.009$ and $P=0.03$, respectively), resting energy expenditure was identical to that predicted for the age and weight of the child, indicating that there is no defect in metabolic adaptation to obesity in persons bearing the risk-associated allele. The A allele was associated with increased energy intake ($P=0.006$) independently of body weight. In contrast, the weight of food ingested by children who had the allele was similar to that in children who did not have the allele ($P=0.82$).

CONCLUSIONS

The *FTO* variant that confers a predisposition to obesity does not appear to be involved in the regulation of energy expenditure but may have a role in the control of food intake and food choice, suggesting a link to a hyperphagic phenotype or a preference for energy-dense foods.

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CHILDHOOD OBESITY IS A MAJOR PUBLIC health problem in most affluent countries, despite policies targeted toward reducing its prevalence. Impaired glucose tolerance and type 2 diabetes are currently being diagnosed in overweight children,^{1,2} along with associated risk factors for cardiovascular disease and the metabolic syndrome, conditions previously seen primarily in adults.³⁻⁵

Variation in the fat mass and obesity-associated (*FTO*) gene has been linked with obesity in a recent series of genomewide association studies.⁶⁻⁸ A number of single-nucleotide polymorphisms (SNPs) in tight linkage disequilibrium with rs9939609, and residing in the first intron of the *FTO* gene, have been associated with obesity in large populations of adults and children. These variants have also been shown to be associated with type 2 diabetes in an obesity-dependent manner.⁶⁻⁸ Expression of *FTO* in the arcuate nucleus in mice is regulated by fasting and feeding,⁹⁻¹¹ suggesting a potential role for this gene in central control of energy homeostasis. The protein encoded by *FTO* has recently been shown to have 2-oxoglutarate-dependent nucleic acid demethylase activity; however, it is not known whether the nucleic acid substrate of the protein is DNA or RNA, nor have the genes or gene products that might be regulated by this enzyme been identified.¹¹

In the present study, we examined the association between rs9939609 and both body weight and body-mass index (BMI) in a group of young Scottish schoolchildren. We also explored the role of rs9939609 in the control of energy expenditure and eating behavior in an intensively analyzed subsample of these children.

METHODS

SUBJECTS

Study participants were prepubertal schoolchildren, 4 to 10 years of age, from northeastern Scotland, most of whom were of European descent (95%). They were recruited from the Energy Balance Study, an investigation of phenotype-genotype associations in the maintenance of energy balance in children.¹²⁻¹⁴ Genomic DNA was isolated from saliva samples from all subjects after the parents or guardians had provided written informed consent and the children had provided assent. Approval for the Energy Balance Study

was granted by the Tayside Committee on Medical Research Ethics and the Fife Local Research Committee. The education department in each school authority (or district) and school head teachers (or principals) also gave their approval.

Genomic DNA from 2726 children was available for genotyping for association of the *FTO* gene variant of interest with overweight and obesity. A subsample of 97 children was available for evaluation of adiposity, energy expenditure, and eating behavior. These children were recruited from a subsample of the Energy Balance Study, prospectively enriched for variants of the peroxisome proliferator-activated receptor gene, *PPARG*.¹⁴

GENOTYPING

A SNP variant rs9939609 was genotyped with the use of an allelic discrimination assay (Custom TaqMan MGB, Applied Biosystems) with a 7700 detector (Applied Biosystems). The sequences of the assay components were as follows: forward primer, CTAGGTTTCCTTGCGACTGCT; reverse primer, ACCTATTAAAACCTTTAGAGTAACAGAGACTATCCA; probe 1, VIC-CATCACAAAATTCAC-BHQ, and probe 2, FAM-CATCACTAAATTCAC-BHQ.

ANTHROPOMETRIC MEASUREMENTS

Date of birth was ascertained. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. Standing height, without shoes, was measured (to the nearest 0.1 cm) with the use of a stadiometer (Leicester Stadiometer, Seca). Body weight, in light clothing, was measured (to the nearest 0.1 kg) with the use of a mechanical floor scale (Seca). Waist circumference (to the nearest 0.1 cm) was measured, in the standing position, midway between the iliac crest and the lower costal margin. Hip circumference (to the nearest 0.1 cm) was measured, in the standing position, at the maximum circumference over the buttocks. Anthropometric measurements included biceps, triceps, and subscapular and suprailiac skinfolds. The sum of the skinfold measurements was used to estimate fat and lean mass by means of Lohman's equations.^{15,16} All skinfold measurements were performed on the right side of the body by the same investigator.

MEASUREMENT OF FOOD INTAKE AT A TEST MEAL

The procedure for measurement of food intake at a test meal has been reported elsewhere.^{14,17} Briefly, on three occasions in school, 1.5 hours before

a test-meal lunch, children ingested a beverage or combination of food and beverage that varied in energy density: a no-energy control consisting of 250 ml of water (0 kJ), a low-energy combination of a 250-ml orange drink and 56-g muffin (783 kJ), and a high-energy combination of a 250-ml orange drink and 56-g muffin (1628 kJ). The amount of food subsequently consumed at the test meal was assessed by weighing the food items before and after eating. Energy and macronutrient intakes were assessed according to the manufacturers' information. In total, 76 children successfully completed all three tests and were included in this analysis.

ENERGY EXPENDITURE

The resting metabolic rate was assessed by indirect calorimetry, with the use of a ventilated hood (Deltatrac, Datex-Ohmeda) adapted for use with children. Measurements were performed when children were in a postprandial state, at the same time in the afternoon. The children's oxygen consumption and carbon dioxide output stabilized after approximately 4 minutes under the hood, and resting energy expenditure was measured for at least another 15 minutes. The mean of at least 10 stable values was used for analysis.

Total energy expenditure was measured by means of the doubly labeled water method over a period of 10 days. A preisotope urine sample was obtained on day 0 for estimation of the unenriched isotope ratios of ^{18}O and deuterium. After the sample was taken, the children were given an oral dose of labeled water ($^2\text{H}_2^{18}\text{O}$) in a low-calorie fruit juice. The juice was given at a dose of 0.15 g of 99% $^2\text{H}_2\text{O}$ (Sigma-Aldrich) per kilogram of body weight and 1.5 to 2.0 g of 10% H_2^{18}O (Goss Scientific Instruments) per kilogram of body weight. Urine samples were collected 4 hours after dosing and then once daily on days 1 through 5 and on day 10. Samples were frozen immediately after collection and returned to the laboratory after day 10. Urine samples were analyzed by isotope ratio mass spectrometry for enrichment of ^{18}O and deuterium. The fat mass was calculated on the assumption that 73% of lean body mass is water, as previously described.^{18,19}

STATISTICAL ANALYSIS

Data were analyzed with the use of SPSS software for Macintosh (version 16, SPSS), with the results

expressed as means \pm SE. Because of the low numbers of AA homozygotes, the genotype was analyzed with the use of the dominant-allele model, with the A allele being dominant. Quantitative traits (height, weight, BMI, waist and hip measurements, percent body fat, and energy expenditure) were analyzed with the use of univariate analysis of variance. Age and sex were incorporated as covariates when appropriate. Data on food intake were analyzed with the use of repeated-measures general linear modeling, with genotype included as a between-subject factor and age included as a covariate. Total energy intake was adjusted for body weight. Socioeconomic status (determined according to whether the child was entitled to receive free school meals) and sex were initially included as covariates in the model but were dropped by means of stepwise removal (removed if $P \geq 0.40$). Data on resting energy expenditure were analyzed with univariate analysis of variance with adjustment for lean body mass. Total energy expenditure and energy spent in activity were analyzed by univariate analysis of variance, with age, weight, and socioeconomic status included as covariates. The gaussian distribution was assessed with the use of the D'Agostino-Pearson omnibus normality test. Nonparametric analysis was performed by means of a Mann-Whitney U tests with GraphPad Prism software for Macintosh, version 4b (Graphpad Software). All reported P values are two sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

ALLELE FREQUENCIES

The allele frequencies of *FTO* rs9939609 for both the total group and the subsample are shown in Table 1. The frequency of the A allele was 0.385 for the total population and 0.381 for the subsample; it was in Hardy-Weinberg equilibrium in both groups ($P > 0.20$).

BMI AND GENOTYPE

The association of *FTO* rs9939609 with height, weight, and BMI was examined by means of univariate general linear modeling. In the total study group (Table 2), the A allele of rs9939609 was associated with significantly increased weight ($P = 0.003$) and BMI ($P = 0.003$). An allele-dose-dependent trend was observed for weight and

Table 1. *FTO* Genotype Frequencies and the Frequency of the A Allele in the Total Study Sample and the Subsample.*

Polymorphism rs9939609	Total Population (N=2726)		Subsample (N=97)	
	No. of Participants	Genotype Frequency	No. of Participants	Genotype Frequency
		%		%
TT	1016	37	36	37
AT	1322	49	48	50
AA	388	14	13	13
Frequency of A allele		0.385		0.381

* AA denotes homozygous carriers of the A allele, AT heterozygous carriers, and TT noncarriers.

Table 2. Association of the rs9939609 Variant of the *FTO* Gene with Height, Weight, and Body-Mass Index in the Total Study Group.*

Characteristic	No. of Participants	TT	AT	AA	P Value
Height	2423	1.25±0.002	1.25±0.002	1.26±0.003	0.17
Weight	2422	26.99±0.168	27.16±0.148	28.07±0.270	0.003
BMI†	2422	17.09±0.075	17.17±0.066	17.58±0.121	0.003

* Plus–minus values are means ±SE, with adjustment for age and sex (i.e., age and sex were included as covariates) after univariate analysis of variance. AA denotes homozygous carriers of the A allele, AT heterozygous carriers, and TT noncarriers.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

BMI. In the subsample of 97 children, similar increases in weight ($P=0.049$) and BMI ($P=0.03$) were associated with the A allele (Table 3).

ADIPOSIITY AND GENOTYPE

Children carrying the A allele had somewhat higher measures of waist and hip circumference than children who did not have the A allele, but the differences were not significant (Table 3). The A allele was also associated with significantly increased anthropometric skinfold values ($P=0.03$). Fat mass and lean mass were assessed with the use of both the skinfold data (with the use of the equations of Lohman) and the data for total body water (from the isotope-dilution studies). On the basis of the skinfold data, the children who carried the A allele had an estimated fat mass that was 1.78 kg greater than that of noncarriers ($P=0.01$) and an estimated lean mass that was less than 400 g greater than that of noncarriers ($P=0.46$). On the basis of the isotope-dilution data, the fat mass was 1.28 kg greater ($P=0.10$) and the lean mass less than 400 g greater ($P=0.58$) for carriers than for noncarriers.

ENERGY EXPENDITURE AND GENOTYPE

As assessed by indirect calorimetry, resting energy expenditure was 349 kJ greater in children who carried the A allele than in noncarriers ($P=0.03$) (Fig. 1A). This difference was similar to that predicted for resting energy expenditure with the use of Schofield's equations ($P=0.01$) (Fig. 1A),²⁰ which take body weight, age, and sex into consideration and are widely used to predict resting energy expenditure in children.^{20,21} In agreement with this observation, inclusion of body mass (weight) or lean body mass as a covariate in the regression model abolished the association between genotype and resting energy expenditure ($P>0.20$ in both cases). Total energy expenditure as measured on the basis of isotope dilution was also significantly greater in carriers of the A allele than in noncarriers, with a difference of 1160 kJ ($P=0.009$) (Fig. 1B). Subtraction of resting energy expenditure from total energy expenditure provides an estimate of the expenditure due to physical activity. Energy expenditure due to physical activity was also higher for carriers, with a difference of 1103 kJ ($P=0.02$). This measure of energy

Table 3. Association of the rs9939609 Variant of the *FTO* Gene with Anthropometric Measures in the Subsample.*

Anthropometric Measure	No. of Participants	TT	AT or AA	P Value
Height (m)	97	1.25±0.01	1.26±0.01	0.42
Weight (kg)	97	25.80±0.76	27.73±0.58	0.05
BMI†	97	16.36±0.33	17.26±0.25	0.03
Waist circumference (cm)	97	57.75±0.98	59.29±0.75	0.22
Hip circumference (cm)	97	65.39±0.86	67.47±0.66	0.06
Sum of skinfold values (cm)	95	30.58±2.97	39.15±2.29	0.03
Fat mass (kg)				
By Lohman's equations	95	6.26±0.55	8.04±0.43	0.01
By isotope dilution	71	8.21±0.58	9.49±0.46	0.10
Lean mass (kg)				
By Lohman's equations	95	19.50±0.39	19.88±0.30	0.45
By isotope dilution	71	17.79±0.57	18.21±0.46	0.58

* Plus-minus values are means ±SE, with adjustment for age and sex (i.e., age and sex were covariates) after univariate analysis of variance. AA denotes homozygous carriers of the A allele, AT heterozygous carriers, and TT noncarriers.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

expenditure related to activity was not correlated with the weight or BMI of the children when body weight was included as a covariate in the regression model.

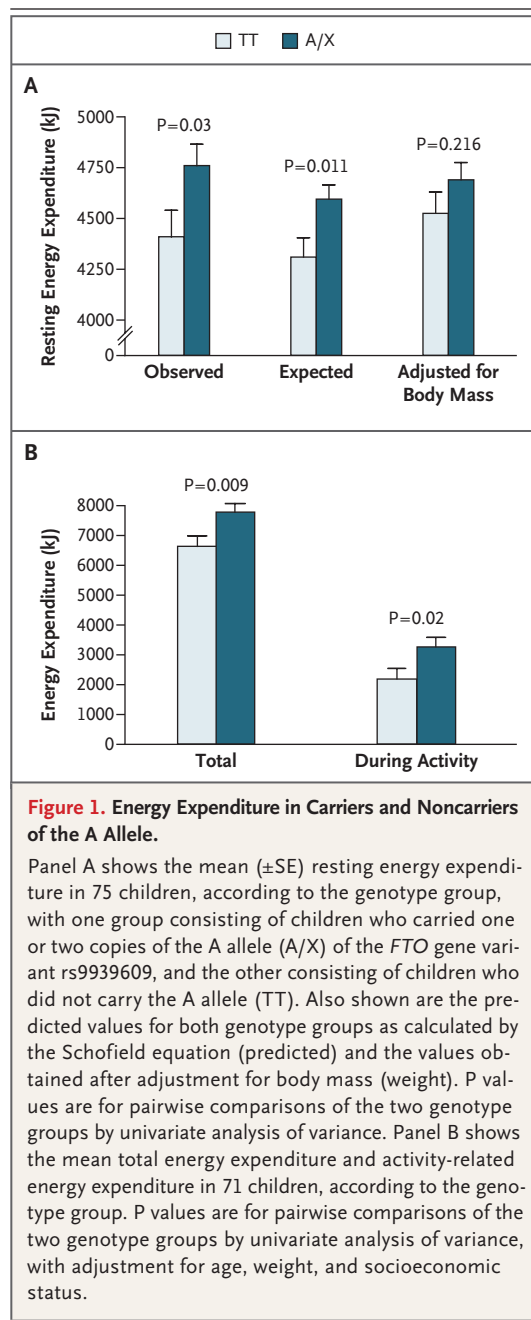
EATING BEHAVIOR AND GENOTYPE

Increased food intake at test meals (measured in kilojoules) was associated with the A allele. The presence of the rs9939609 variant was found to affect energy intake ($P=0.006$ by analysis of variance for the comparison of energy intake after the no-energy, low-energy, and high-energy premeal loads). After adjustment for age, the children who carried the A allele had significantly greater energy intake at the test meals that followed the control and low-energy loads than did noncarriers ($P=0.02$ and $P=0.002$, respectively) (Fig. 2A), with a similar trend with respect to the high-energy premeal load. These observations could not be explained by the presence of spurious outliers, since nonparametric analysis of total energy intake provided similar, if not stronger, results ($P=0.006$ for the control premeal load, $P=0.001$ for the low-energy load, and $P=0.03$ for the high-energy load by the Mann-Whitney U test). This increase in energy intake was independent of body mass, since these differences persisted when weight or lean body mass was included as a covariate in the regression model, and similar results were ob-

tained when energy intake was expressed as kilojoules of food ingested per kilogram of body weight ($P=0.005$ by analysis of variance and $P=0.025$ by the Mann-Whitney U test for the low-energy premeal load) (Fig. 2B). Interestingly, the total weight of food ingested was not markedly increased in carriers of the A allele as compared with noncarriers ($P=0.82$) (Fig. 2C), whereas the weights of individual macronutrients were consistently higher for carriers (Table 4), with 30% higher fat intake after the low-energy premeal load in the A allele carriers ($P=0.004$ by analysis of variance adjusted for body weight, and $P=0.003$ by the Mann-Whitney U test). Intake levels of the individual macronutrients did not differ significantly according to genotype, after adjustment for total energy intake. The energy density of the food ingested (kilojoules per gram of food ingested) after all three premeal loads tended to be higher among carriers of the A allele than among noncarriers, with 16% greater energy density of food ingested by carriers after the low-energy load ($P=0.03$ by analysis of variance and $P=0.03$ by the Mann-Whitney U test) (Fig. 2D).

DISCUSSION

The association of the *FTO* gene with human obesity is robust in populations of European de-



cent.⁶⁻⁸ The only negative studies published to date have involved non-European populations.^{22,23} Although the genetic architecture of the *FTO* locus has not been examined in great detail in either of these populations, evidence is emerging that rs9939609 may be in tight linkage disequilibrium with a causal variant in populations of European descent but that this linkage disequi-

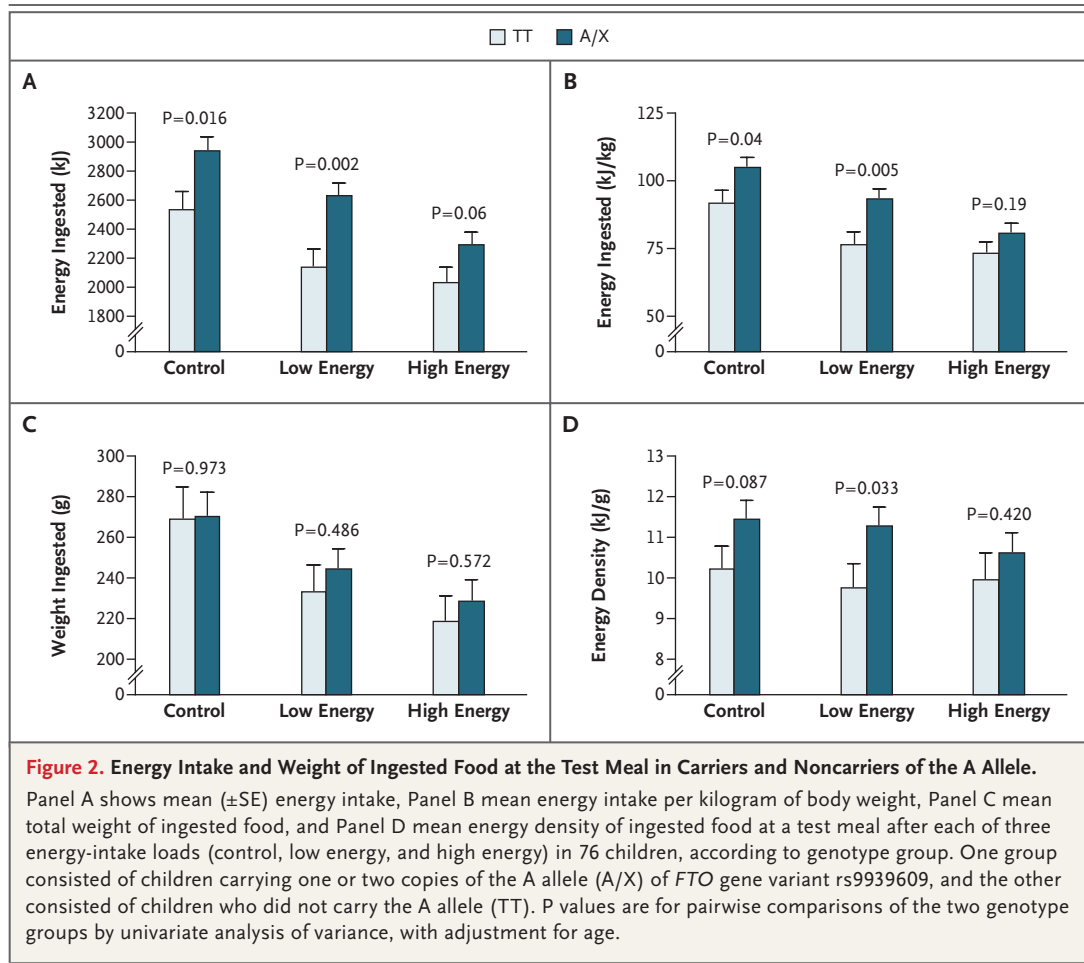
librium may break down in other ethnic and racial groups, such as blacks.²⁴

We confirmed the association of the *FTO* variant with BMI in a population of Scottish schoolchildren and then examined energy expenditure and eating in a subsample. The frequency of the A allele in the subsample (as well as the total study group) was consistent with the frequency reported in the initial association study.⁶ This reassured us that the use of the *FTO* genotype in the subsample, which had been enriched for the *PPARG* Pro12ala variant,¹⁴ was a valid approach. No interaction was observed between the *FTO* and *PPARG* variants for the association with height, weight, or BMI (data not shown).

The present data indicate that *FTO* SNP rs9939609 is associated with differences in BMI, with the presence of the A allele linked to a greater risk of increased BMI and increased values for specific measures of adiposity, such as the sum of skinfold values and total body water as assessed by isotope analysis. The skinfold approximation of the absolute amount of body fat was an underestimate, as previously reported in the literature,²⁵ and this underestimate is to be expected, considering that this method involves only a physical measure of subcutaneous fat, with no direct measurement of abdominal and intra-organ deposits. In agreement with a previous study, which used dual-energy x-ray absorptiometry (DEXA),⁶ the *FTO* genotype was associated with greater fat mass but not lean mass, as measured by both techniques used in our study.

This study indicates that there is no defect in the “output” side of energy balance, which constitutes energy expenditure. We did observe an increase in resting energy metabolism in the A allele carriers that was consistent with their increased body mass. In addition, we observed that the difference in total energy expenditure between the genotype groups was primarily a difference in activity-related expenditure, suggesting that the A allele is unlikely to be a marker of sedentary behavior. However, we do not know how this finding relates to the nature of the physical activity (i.e., exercise or other activity).²⁶

Most of our data suggest that the *FTO* gene influences the “input” side of the energy-balance equation, and this conclusion is supported by studies in rodents showing that the gene is expressed in the main regions of the brain that



control feeding and that its expression is regulated by food deprivation.⁹⁻¹¹ Another group of investigators, who used brain imaging in human subjects genotyped for the *FTO* alleles, found that the brains of subjects with the high-risk allele for the *FTO* gene were more resistant to the effects of insulin than were the brains of subjects without the high-risk allele.²⁷

Our study tested satiety by directly measuring food intake from a test meal after ingestion of one of three preloads, and the results show a robust effect of genotype on energy intake but not on the weight of food ingested. This increase in energy intake was independent of body weight. Thus, the children carrying the A allele ingested more energy-dense foods than did the children who were not carrying the A allele, indicating a preference for energy-dense foods. However, larger studies are required to confirm these observa-

tions and to examine the effect of being homozygous for the A allele as compared with being heterozygous.

Most monogenic obesity disorders directly affect eating behavior,²⁸ and our observations suggest that the *FTO* gene is not an exception. However, it is not yet clear whether *FTO* has a direct hypothalamic role in appetite regulation or has a systemic role in sensing food intake. In addition, it is possible that *RPGRIP1L* (the human orthologue of *Ftm*), a gene that encodes a molecular component of the basal body of cilia and that is coregulated by variation in the *FTO* locus, may have a role in the observed phenotype.⁹

In conclusion, variation within the *FTO* locus appears to confer a risk of obesity through increased energy intake, suggesting that moderate and controlled restriction of energy intake may prevent *FTO* genotype-associated obesity. This

Table 4. Association of the rs9939609 Variant of the *FTO* Gene with Macronutrient Intake in the Subsample.*

Macronutrient Intake and Premeal Energy Load	No. of Participants	TT	AT or AA	P Value		
				Adjusted for Age	Adjusted for Age and Body Weight	Adjusted for Age, Body Weight, and Total Energy Intake
Fat (g)		76				
Control		28.10±1.85	33.98±1.42	0.01	0.02	0.64
Low energy		23.19±1.80	30.14±1.41	0.003	0.004	0.71
High energy		21.55±1.46	25.47±1.14	0.04	0.04	0.34
Carbohydrate (g)		76				
Control		70.01±4.13	77.11±3.17	0.18	0.28	0.36
Low energy		60.09±3.81	69.84±2.99	0.05	0.10	0.53
High energy		58.76±3.88	62.01±3.04	0.51	0.75	0.10
Protein (g)		76				
Control		21.23±1.72	25.36±1.32	0.06	0.10	0.83
Low energy		18.57±1.53	22.55±1.20	0.04	0.08	0.71
High energy		16.60±1.34	20.57±1.05	0.02	0.04	0.24

* Plus-minus values are means ±SE, with adjustment, as shown, after univariate analysis of variance. AA denotes homozygous carriers of the A allele, AT heterozygous carriers, and TT noncarriers.

finding and its implications are especially important given the growing consensus that childhood obesity is a major predictor of cardiovascular morbidity and mortality in adulthood.^{29,30}

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No potential conflict of interest relevant to this article was reported.

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