Obesity Associated Genetic Variation in *FTO* Is Associated with Diminished Satiety

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Context: Polymorphisms within the *FTO* gene have consistently been associated with obesity across multiple populations. However, to date, it is not known whether the association between genetic variation in *FTO* and obesity is mediated through effects on energy intake or energy expenditure.

Objective: Our objective was to examine the association between alleles of *FTO* known to increase obesity risk and measures of habitual appetitive behavior.

Methods: The intronic *FTO* single nucleotide polymorphism (rs9939609) was genotyped in 3337 United Kingdom children in whom measures of habitual appetitive behavior had been assessed using two scales (Satiety Responsiveness and Enjoyment of Food) from the Child Eating Behaviour Questionnaire, a psychometric tool that has been validated against objective measures of food intake. Associations of *FTO* genotype with indices of adiposity and appetite were assessed by ANOVA.

Results: As expected, the A allele was associated with increased adiposity in this cohort and in an independent case-control replication study of United Kingdom children of similar age. AA homozygotes had significantly reduced Satiety Responsiveness scores ($P = 0.008$, ANOVA). Mediation analysis indicated that the association of the AA genotype with increased adiposity was explained in part through effects on Satiety Responsiveness.

Conclusions: We have used a unique dataset to examine the relationship between a validated measure of children's habitual appetitive behavior and *FTO* obesity risk genotype and conclude that the commonest known risk allele for obesity is likely to exert at least some of its effects by influencing appetite. **(*J Clin Endocrinol Metab* 93: 3640–3643, 2008)**

Human obesity is a highly heritable trait, but it is not known whether the specific genetic variants underlying common forms of this condition predominantly influence the intake or expenditure of energy. Common intronic variants in the *FTO* gene have recently been strongly and replicably associated with higher body weight and adiposity (1–5), with individuals who are homozygous for the high-risk allele (AA) of rs9939609 weighing on average 3 kg more than those with two low-risk alleles (1). *Fto* mRNA is highly expressed in the hypothalamus (6), an area that is known to be involved in the regulation of appetite, and *fto* expression in the arcuate nucleus of the hypothalamus in rodents is modulated by acute food deprivation (7). These observations suggest that associations between *FTO* polymorphisms and weight may be due to differences in appetitive responses. This would be consistent with findings in monogenic obesity disorders, which are almost all characterized by an increased desire to eat (8).

We tested the hypothesis that children carrying the higher-risk *FTO* alleles have altered appetite in a sample of 3337 unrelated children aged 8–11 yr recruited as part of the Twins' Early Development Study (TEDS) (data from one child in each family). We have previously demonstrated that adiposity is highly heritable in this

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Abbreviations: BMI, Body mass index; CEBQ, Child Eating Behavior Questionnaire; CI, confidence interval; SCOOP-UK, Severe Childhood Onset Obesity Project United Kingdom; TEDS, Twins' Early Development Study.

TABLE 1. Association between *FTO* genotype, anthropometric, and appetitive measures in United Kingdom children from the TEDS cohort

	FTO genotype			
	TT (n = 1209)	AT (n = 1641)	AA (n = 487)	Group difference and ES
BMI	17.18 (16.74–17.60)	17.78 (17.41–18.14)	17.91 (17.25–18.58)	$F_{(1,3354)} = 2.8$; $P = 0.059$; ES = 0.002
BMI SD score	−0.123 (−0.194 to −0.502)	0.073 (0.012–0.134)	0.242 (0.131–0.354)	$F_{(2,3256)} = 16.77$; $P < 0.001$; ES = 0.010
Waist	61.99 (61.54–62.44)	62.59 (62.19–62.98)	63.55 (62.83–64.26)	$F_{(2,3402)} = 7.65$; $P < 0.001$; ES = 0.004
Waist SD score	0.702 (0.645–0.760)	0.802 (0.752–0.851)	0.997 (0.906–1.087)	$F_{(2,3299)} = 14.68$; $P < 0.001$; ES = 0.009
Overweight/obese (%)	11.1	14.9	19.5	$\chi^2 = 20.77$; $P < 0.001$
CEBQ Satiety Responsiveness score (range 1–5)	2.666 (2.628–2.704)	2.654 (2.621–2.687)	2.551 (2.499–2.618)	$F_{(2,3450)} = 4.79$; $P = 0.008$; ES = 0.003
CEBQ Enjoyment of Food scores (1–5)	4.109 (4.068–4.149)	4.113 (4.078–4.148)	4.179 (4.115–4.243)	$F_{(2,3450)} = 1.85$; $P = 0.157$; ES = 0.001

Means and 95% CI for anthropometric and appetitive measures with significance values and effect sizes (ES) for differences are shown.

cohort (9). To assess appetite in this large sample, we used a validated, parent-completed, psychometric measure (10–12).

Subjects and Methods

The main study population was recruited from TEDS, a population-based twin cohort whose anthropometric characteristics have been reported previously (9). Children's height, weight, and waist circumference were based on measurements taken by parents, which correlated highly with measurements taken by researchers in a subsample (9). Adiposity was indexed with body mass index (BMI) SD scores, and central adiposity with waist SD scores, using United Kingdom 1990 reference values (13). We used the International Obesity Task Force definitions of overweight and obesity.

rs9939609 was genotyped using a TaqMan assay that incorporates minor groove binding probe technology for allelic discrimination. The call rate was 98%, and the single nucleotide polymorphism was in Hardy-Weinberg equilibrium ($P = 0.729$).

Appetite was assessed using the Child Eating Behavior Questionnaire (CEBQ); a parent-completed, psychometric instrument that has been validated against behavioral measures of food intake and shows stability over time (10–12). We used two scales that assess underlying appetitive drivers of food intake, namely Satiety Responsiveness, a measure of the ease with which satiety is achieved (*e.g.* my child cannot eat a meal if he/she has had a snack just before), and Enjoyment of Food, a measure of the extent to which presentation of palatable foods provokes eating (*e.g.* my child loves food). Scores on these scales have been shown to be correlated with adiposity (14).

Associations between genotype adiposity and the two appetitive phenotypes were analyzed using ANOVA. To give an indication of the causal pathways, we assessed the mediating effect of the two appetitive phenotypes on the association between genotype and adiposity using the Sobel test (15, 16). We also carried out analysis of covariance including BMI SD scores to test whether *FTO* was associated with appetite independently of adiposity.

rs9939609 was also genotyped in a second United Kingdom Caucasian cohort, the Severe Childhood Onset Obesity Project United Kingdom (SCOOP-UK) which comprises 1000 United Kingdom Caucasian subjects with severe early-onset obesity of unknown etiology (536 females and 464 males; mean age, 10.7 ± 2.7 yr; mean BMI SD score = 3.5). Data were compared with published data from normal-weight United Kingdom children of the same age in the ALSPAC study (cohort characteristics summarized in Ref. 1).

Results

The rs9939609 genotype distribution in the TEDS sample (n = 3337) was similar to that reported in other population-based samples (AA = 14.6%; AT = 49.2%; TT = 36.2%) (1). As expected, we replicated the direction and magnitude of the known association between *FTO* and adiposity, with each additional copy of the A allele being associated with an increase of between 0.13 and 0.18 BMI SD scores (weight differences from 0.7–1.4 kg). We demonstrated similar effects for waist circumference, with increases of between 0.60 and 0.95 cm for each copy of the A allele (Table 1). Compared with children with the TT genotype, the odds of meeting the International Obesity Task Force criterion for pediatric overweight/obesity increased from 1.39 [95% confidence interval (CI), 1.11–1.75] for AT to 1.94 (95% CI, 1.45–2.59) for AA. This effect was replicated in an independent case-control study of 926 obese United Kingdom children (SCOOP-UK) compared with 4022 normal-weight controls from the ALSPAC cohort (Table 2).

In the TEDS sample, we examined scores on the CEBQ scales in relation to *FTO* genotype (Table 1 and Fig. 1). There was no

TABLE 2. *FTO* genotype in obese children from the SCOOP-UK cohort and normal weight control children from the ALSPAC cohort

		Genotype				
Weight	Total (n)	TT	AT	AA	Odds ratio (95% CI)	*P*
Normal	4022	1548	1878	596	1.76 (1.59–1.94)	9×10^{-28}
Obese	926	250	389	287		

A total of 1000 children from the SCOOP-UK cohort were genotyped, and 926 successful genotypes were obtained. Genotype results did not deviate significantly from Hardy-Weinberg equilibrium. We studied the association of *FTO* gene variation with the risk of being obese. We found that children homozygous for the A allele at rs9939609 were at substantially increased risk of being obese compared with those homozygous for the low-risk T allele (*P* value relates to the per A allele odds ratio).

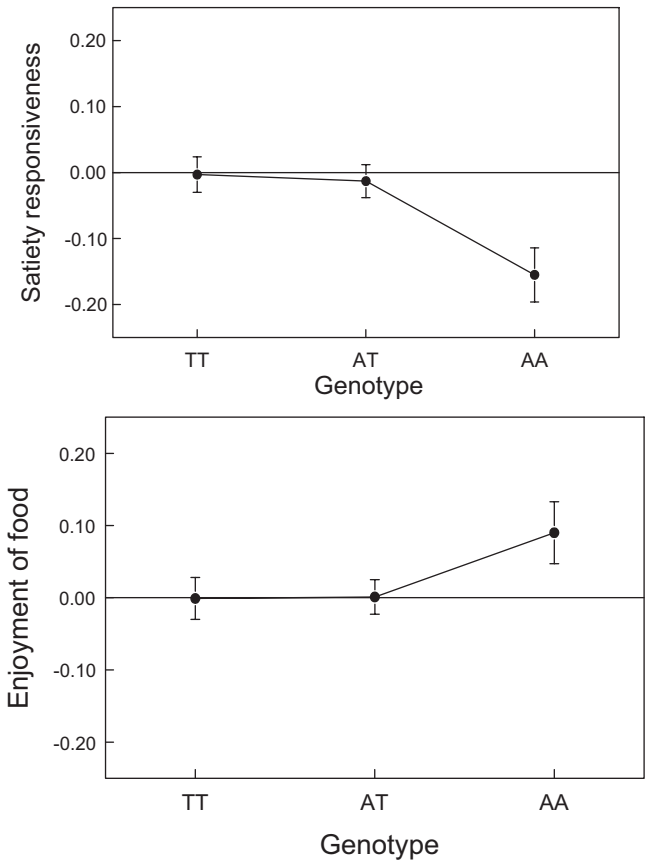

FIG. 1. *FTO* association results: SD scores for Satiety Responsiveness and Enjoyment of Food at age 8–11 yr. *Error bars* represent ±1 SE.

significant interaction between genotype and gender. Satiety Responsiveness was significantly lower in homozygotes for the A allele (2.55 *vs.* 2.65 in AT heterozygotes and 2.67 in TT homozygotes; $P = 0.008$). AA homozygotes also had the highest scores for Enjoyment of Food, but this did not reach statistical significance. In an analysis of covariance including *FTO*, gender, age, family socioeconomic status, and BMI SD score, the association between *FTO* and satiety responsiveness remained significant [$F_{(2,3105)} = 3.17$; $P = 0.04$; effect size = 0.002], but as expected, the effect size was reduced due to controlling for the known association of appetite and BMI.

Mediation analysis indicated that the effect of *FTO* genotype on BMI was significantly partially mediated by Satiety Responsiveness ($P < 0.05$). The extent of observed mediation is likely to be attenuated by error of measurement in the measure.

Discussion

Our finding of an increased risk of obesity associated with the AA genotype of *FTO* rs9939609 in two cohorts of United Kingdom children is in accordance with other studies in Caucasian cohorts (1–3). Possession of one copy of the A allele is sufficient to increase body weight by 1.5 kg in adults (1), and we were able to demonstrate a comparable effect in children. We also showed an equally strong effect for waist circumference. Together these studies provide robust support for the assertion that *FTO* represents the first common obesity susceptibility gene in Caucasian populations.

In the present study, we were uniquely able to examine the relationship between *FTO* genotype and measures of appetitive behavior in 3337 children recruited as part of the TEDS cohort. We showed that the obesity-linked *FTO* intronic single-nucleotide polymorphism rs9939609 was associated with impaired satiety responsiveness. Mediation analysis indicated that a proportion of the observed association between *FTO* genotype and BMI could be explained by effects on satiety responsiveness. The association between *FTO* genotype and satiety responsiveness remained significant after controlling for BMI SD score, consistent with the idea that *FTO* may have a direct effect on appetite, which in turn influences adiposity. However, given the cross-sectional nature of the phenotypic data, these analyses can only be indicative of the causal pathways.

Our findings are consistent with previous studies linking specific aspects of appetite to obesity. Schachter (17) first demonstrated that obese adults overeat compared with normal-weight controls under conditions of satiety but show no differences in food-deprived conditions; *i.e.* they are not simple overeaters, but less sensitive to satiety cues. The same effect has been observed in obese children (18). Importantly, several eating-behavior phenotypes, including aspects of appetite, have been shown to be heritable (19), and we have shown that Satiety Responsiveness and Enjoyment of Food are highly heritable (20). The results are also consistent with evidence that *fto* expression in the arcuate nucleus of the hypothalamus in rodents is modulated by acute food deprivation (7).

Despite the increased risk of obesity associated with heterozygosity for the A allele, we were unable to detect any effect of heterozygosity on appetite in this study. This may suggest that other obesogenic effects of the *FTO* A allele are operating in the heterozygotes or, more likely in our view, that the psychometric tool we used is insufficiently sensitive to detect the very small effects on cumulative energy intake that would be needed to result in the small increase in adiposity conveyed by heterozygosity for the risk allele.

These results need to be replicated in samples of other ages to determine whether the effect is also found in adults. *FTO* might of course influence other facets of energy balance, although recent results from the Quebec Family Study found no differences in resting energy expenditure between genotypes at the *FTO* locus (21).

The finding that individuals with two *FTO* A alleles have lower responsiveness to satiety cues, and that there is a significant indirect path between *FTO* genotype and BMI through satiety responsiveness, supports the hypothesis that the *FTO* association with BMI involves effects on appetite. Inter-individual differences in susceptibility to obesity may be determined in part by genetic variants impacting on satiety responsiveness that in turn influence the likelihood of overeating in environments where large portion sizes and multiple eating opportunities are the norm.

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References

1. **Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI** 2007 A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316:889–894
2. **Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougneres P, Kovacs P, Marre M, Balkau B, Cauchi S, Chevre JC, Froguel P** 2007 Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39:724–726
3. **Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orru M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR** 2007 Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 3:e115
4. **Hunt SC, Stone S, Xin Y, Scherer CA, Magness CL, Iadonato SP, Hopkins PN, Adams TD** 2008 Association of the FTO gene with BMI. Obesity (Silver Spring) 16:902–904
5. **Hinney A, Nguyen TT, Scherag A, Friedel S, Bronner G, Muller TD, Grallert H, Illig T, Wichmann HE, Rief W, Schafer H, Hebebrand J** 2007 Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS ONE 2:e1361
6. **Stratigopoulos G, Padilla S, Leduc CA, Watson E, Hattersley AT, McCarthy MI, Zeltser LM, Chung WK, Leibel RL** 2008 Regulation of Fto/Ftm gene expression in mice and humans. Am J Physiol Regul Integr Comp Physiol 294:R1185–R1196
7. **Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ** 2007 The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 318:1469–1472
8. **Farooqi IS, O'Rahilly S** 2005 Monogenic obesity in humans. Annu Rev Med 56:443–458
9. **Wardle J, Carnell S, Haworth CM, Plomin R** 2008 Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr 87:398–404
10. **Wardle J, Guthrie CA, Sanderson S, Rapoport L** 2001 Development of the Child Eating Behaviour Questionnaire. J Child Psychol Psychiatry 42:963–970
11. **Carnell S, Wardle J** 2007 Measuring behavioural susceptibility to obesity: validation of the Child Eating Behaviour Questionnaire. Appetite 48:104–113
12. **Ashcroft J, Semmler C, Carnell S, van Jaarsveld CH, Wardle J** 8 August 2007 Continuity and stability of eating behaviour traits in children. Eur J Clin Nutr 10.1038/sj.ejcn.1602855
13. **Cole TJ, Freeman JV, Preece MA** 1995 Body mass index reference curves for the UK, 1990. Arch Dis Child 73:25–29
14. **Carnell S, Wardle J** Appetite and adiposity in children: evidence for a behavioral susceptibility theory of obesity. Am J Clin Nutr 88:22–29
15. **Preacher KJ, Hayes AF** 2004 SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 36: 717–731
16. **MacKinnon DP, Fairchild AJ, Fritz MS** 2007 Mediation analysis. Annu Rev Psychol 58:593–614
17. **Schachter S** 1968 Obesity and eating. Internal and external cues differentially affect the eating behavior of obese and normal subjects. Science 161:751–756
18. **Jansen A, Theunissen N, Slechten K, Nederkoorn C, Boon B, Mulkens S, Roefs A** 2003 Overweight children overeat after exposure to food cues. Eat Behav 4:197–209
19. **Rankinen T, Bouchard C** 2006 Genetics of food intake and eating behavior phenotypes in humans. Annu Rev Nutr 26:413–434
20. **Carnell S, Haworth CM, Plomin R, Wardle J** 2008 Genetic influence on appetite in children. Int J Obes, in press
21. **Do R, Bailey SD, Desbiens K, Belisle A, Montpetit A, Bouchard C, Pérusse L, Vohl MC, Engert JC** 2008 Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study. Diabetes. 57:1147–1150