Obesity Associated Genetic Variation in FTO Is Associated with Diminished Satiety

Jane Wardle, Susan Carnell, Claire M. A. Haworth, I. Sadaf Farooqi, Stephen O’Rahilly, and Robert Plomin

Health Behaviour Research Centre (J.W., S.C.), Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom; Social, Genetic, and Developmental Psychiatry Centre (C.M.A.H., P.I.), Institute of Psychiatry, King’s College London, London SE5 8AF, United Kingdom; and University of Cambridge Metabolic Research Laboratories (I.S.F., S.O.), Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge CB2 2QQ, United Kingdom

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

<table>
<thead>
<tr>
<th>FTO genotype</th>
<th>TT (n = 1209)</th>
<th>AT (n = 1641)</th>
<th>AA (n = 487)</th>
<th>Group difference and ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>17.18 (16.74–17.60)</td>
<td>17.78 (17.41–18.14)</td>
<td>17.91 (17.25–18.58)</td>
<td>F_{(1,3354)} = 2.8; P = 0.059; ES = 0.002</td>
</tr>
<tr>
<td>BMI SD score</td>
<td>−0.123 (−0.194 to −0.052)</td>
<td>0.073 (0.012–0.134)</td>
<td>0.242 (0.131–0.354)</td>
<td>F_{(2,3256)} = 16.77; P &lt; 0.001; ES = 0.010</td>
</tr>
<tr>
<td>Waist</td>
<td>61.99 (61.54–62.44)</td>
<td>62.59 (62.19–62.98)</td>
<td>63.55 (62.83–64.26)</td>
<td>F_{(2,3400)} = 7.65; P &lt; 0.001; ES = 0.004</td>
</tr>
<tr>
<td>Waist SD score</td>
<td>0.702 (0.645–0.760)</td>
<td>0.802 (0.752–0.851)</td>
<td>0.997 (0.906–1.087)</td>
<td>F_{(2,3299)} = 14.68; P &lt; 0.001; ES = 0.009</td>
</tr>
<tr>
<td>Overweight/obese (%)</td>
<td>11.1</td>
<td>14.9</td>
<td>19.5</td>
<td>χ^2 = 20.77; P &lt; 0.001</td>
</tr>
<tr>
<td>CEBQ Satiety Responsiveness score (range 1–5)</td>
<td>2.666 (2.628–2.704)</td>
<td>2.654 (2.621–2.687)</td>
<td>2.551 (2.499–2.618)</td>
<td>F_{(2,3450)} = 4.79; P = 0.008; ES = 0.003</td>
</tr>
<tr>
<td>CEBQ Enjoyment of Food scores (1–5)</td>
<td>4.109 (4.068–4.149)</td>
<td>4.113 (4.078–4.148)</td>
<td>4.179 (4.115–4.243)</td>
<td>F_{(2,3450)} = 1.85; P = 0.157; ES = 0.001</td>
</tr>
</tbody>
</table>

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

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
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 $\pm$ 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 $\pm$ 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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Address all correspondence and requests for reprints to: Jane Wardle, Health Behavior Research Centre, University College London, Gower Street, London WC1E 6BT, United Kingdom. E-mail: j.wardle@ucl.ac.uk.

References


