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Original Article

The Association of *FTO* SNP rs9939609 with Weight Gain at University

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Key Words
FTO · Genetics · Weight gain · Genetic test feedback · Young adult · University

Abstract
Aim: We tested the hypothesis that the obesity-associated FTO SNP rs9939609 would be associated with clinically significant weight gain (≥5% of initial body weight) in the first year of university; a time identified as high risk for weight gain. ***Methods:*** We collected anthropometric data from university students (n = 1,411, mean age: 22.4 ± 2.5 years, 49.1% male) at the beginning and end of the academic year. DNA was analysed for *FTO* rs9939609. Associations of *FTO* genotype with BMI at baseline were analysed using ANCOVA, and with risk of 5% weight gain over follow-up with logistic regression; both analyses adjusting for age and sex. The alpha level was reduced to 0.0125 to account for multiple testing. ***Results:*** Using an additive model, FTO status was not associated with higher BMI at baseline (22.2 vs. 21.9 kg/m^2, p = 0.059). Dropout was high but unrelated to genotype. Among the 310 (21.9%) completing follow-up, those with AT genotypes had twice the odds of ≥5% weight gain compared with TTs (OR = 2.05, 95% CI = 1.05–4.01, p = 0.036), but this was no longer significant after Bonferroni correction. There was a trend for AA carriers for ≥5% weight gain compared with TT carriers (p = 0.089), but sample size was small. ***Conclusion:*** This study provides nominal evidence for the genetic susceptibility hypothesis, but findings need to be replicated.

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Introduction

The behavioural susceptibility model of obesity proposes that individuals at higher genetic risk are more likely to overeat – and therefore gain weight – than their lower risk counterparts in situations of abundant food availability [1, 2]. This model is consistent with

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the changing population distribution of weight seen over the last few decades as the environment has become more 'obesogenic'; with weights at the lower end of the distribution staying fairly stable, while weights at the upper end have shown dramatic increases [3].

Multiple genes are associated with variation in weight in the population [4–6], with the strongest body of evidence for *FTO*, the first gene identified to be associated with 'common' obesity [7–9]. The SNP rs9939609, located on the first intron of the *FTO* gene, belongs to a cluster of 10 SNPs which have been associated with BMI early on [10].

Individuals who are homozygous for the higher-risk 'A' allele of SNP rs9939609 are on average 3 kg heavier, and have a 20% higher lifetime risk of becoming obese, than the lower risk 'TT' homozygotes [7–9]. FTO has been shown to be expressed in the hypothalamus and adjacent nuclei associated with feeding behaviour and food reward [11, 12], with gene expression modulated by food availability [13]. However, the mechanism whereby FTO exerts it effects is yet to be fully understood. The presence of FTO in the cell nucleus [11], its structure and resemblance to homologues involved in nucleic acid repair or modification, and the preferential binding to single-stranded RNA over double-stranded DNA of the FTO protein, suggested early on that it may be concerned with nucleic acid demethylation; which was recently confirmed [14]. Emerging evidence further suggests that the intronic SNP rs9939609 may influence BMI by increasing expression of *FTO* itself [15], or by forming long-range functional connections which increase the expression of other neighbouring genes such as *IRX3* [16] and *RPGRIP1L* [17].

In human studies, the A allele of *FTO* SNP rs9939609 has been associated with lower satiety responses and a higher propensity to eat when palatable food is supplied [1, 18, 19]; although evidence for overall increased energy intake is mixed [20–23]. With respect to weight loss, which could be used as a reverse longitudinal phenotype, FTO appears to have little influence on the success of lifestyle interventions aimed at weight loss [24–27]. However, to our knowledge, no study has specifically investigated whether *FTO* genotype moderates weight change following a move to a more obesogenic environment.

The transition from high school to university has been identified as a high-risk period for weight gain [28, 29]. It has been informally dubbed the 'Freshman 15', although most evidence indicates that average weight gain is closer to 5 lbs [30, 31], and may be even lower outside of the USA [29]. However, within this mean change, there is considerable individual variability, and to date there have been few pointers to the determinants of risk [30].

The present study used the 'freshman' context to test the genetic moderation hypothesis. Clinical studies assume a 5% weight loss beneficial [32]. However, by the same token, a 5% weight gain could therefore be considered clinically significant with respect to future health problems. We hypothesised that individuals carrying at least one higher-risk allele (AT, AA) would be more likely to experience a clinically significant weight gain (≥5% of initial weight) over the first year at university.

Material and Methods

Participants and Procedures

New students from a large UK university were recruited at the start of three consecutive academic years (October 2010, 2011, 2012). Follow-up anthropometric data were collected in the last week of May of each academic year. All interested individuals within the university aged between 18 and 30 years who were able to give informed consent were eligible.

The study was advertised by email, posters on campus, in halls of residence, and at the 'Welcome Fayre'; inviting students to take part in a study on genetic influences on weight gain. Interested participants were invited to come to the 'data collection stand' during the 2nd week of term. Here, a researcher explained the

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project in more detail, gave out information sheets and offered the opportunity to ask questions. Those willing to take part gave written consent. Ethical approval for the study was granted by the University College London Ethics Committee for non-NHS research (study no. 2471/002).

Sample Size

A power calculation conducted a priori using G*Power (version 3.1; Heinrich Heine University Düsseldorf, Germany) showed that a total sample size of n = 148 would be sufficient to detect a small effect (d = 0.25) on 5% weight gain with 95% power at the 5% significance level anticipating attrition of about 60% which is common in samples involving students [33].

Measures

Demographic information included age and sex. Anthropometric data were collected at study enrolment and at follow-up about 8 months later. Participants were asked to remove shoes, socks and outdoor clothes for weighing. Weight was measured to the nearest tenth of a kilogram with the TANITA scale (TBF-300 MA, Sindlfingen, Germany). Height was measured to the nearest centimetre using the Leicester Height Measure (Marsden Group, UK). BMI was calculated from weight and height (kg/m^2), and classified according to World Health Organization cut-off points (underweight/normal weight < 25.0 kg/m^2, overweight ≥25.0 to <30.0 kg/m^2, obese ≥30 kg/m^2) [17]. Participants could opt to receive a printout of their anthropometric results, and all chose to do so.

A saliva sample for DNA extraction was collected after enrolment by asking the participant to place some sugar on their tongue to stimulate saliva flow and then spit into a plastic tube to generate 1.5–2 ml of saliva. Saliva samples were coded with a unique identifier number immediately after collection so that they were anonymous but could be linked to the anthropometric data. DNA was isolated from saliva and analysed at The Institute of Metabolic Science, Cambridge, UK, as previously published [2].

Statistical Analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 20.0 (Chicago, IL, USA). Chi-square tests were performed to assess whether genotype frequencies were in Hardy-Weinberg equilibrium.

We used an additive model to explore the associations of *FTO* genotype with weight gain (TT vs. AT vs. AA) in all analyses. However, we also explored associations of genotype and weight gain in a dominant model (TT vs. AT/AA), in line with some previous studies [34, 35], and because the small sample size at follow-up meant that there were only very few participants with the AA genotype. The association of *FTO* genotype status with BMI at baseline was determined with Analysis of Covariance (ANCOVA), with age and sex as covariates. For the purpose of all analyses, age was dichotomized into 'younger' (18–20 years) and 'older' (age 21 years and over) because the strength of the FTO association with BMI has been shown to differ by age [36]. Bonferroni corrections were used to correct for multiple testing, and the alpha level to indicate significance was reduced to $\alpha = 0.0125$.

Weight change, both absolute (kg) and relative (percentage), was calculated for each participant. For binary analyses, we examined the proportion who gained ≥5% of their starting weight. The association between *FTO* gene status and 5% weight gain over follow-up period was investigated using binary logistic regression analyses adjusting for age (dichotomized) and sex.

Results

Participant Characteristics

In total, 1,518 students volunteered to take part. 107 (7.0%) had to be excluded for the following reasons: genotype could not be determined (5.8%, n = 89), missing anthropometric data (0.9%, n = 13) and no assigned ID so genotype data could not be matched to anthropometric data (0.04%, n = 5). The final baseline sample therefore consisted of 1,411 participants. Follow-up data were collected from 310 participants (21.9%). Anthropometric and demographic characteristics of those who were followed up were similar at baseline to the full sample (table 1).

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Table 1. Participant characteristics at baseline and follow-up

Participant characteristics	Baseline sample (N = 1,411)	Follow-up sample (N = 310)	p value
Baseline			
Mean height, m (SD)	1.70 (0.09)	1.71 (0.09)	0.865
Mean weight, kg (SD)	64.2 (12.0)	63.2 (2.6)	0.190
Mean BMI, kg/m^2 (SD)	22.0 (3.0)	21.6 (2.8)	0.061
Underweight/normal weight, n (%)	1,217 (86.3)	280 (90.3)	0.062
Overweight/obese, n (%)	194 (13.7)	30 (9.7)	
Sex			
Male, n (%)	693 (49.1)	148 (47.7)	0.707
Female, n (%)	718 (50.9)	162 (52.3)	
Mean age, years (SD)	20.4 (2.5)	20.3 (2.6)	0.570
18–20 years, n (%)	883 (62.6)	198 (63.9)	0.697
21–30 years, n (%)	528 (37.4)	112 (36.1)	
FTO status, n (%)			
TT	599 (42.5)	133 (42.9)	
AT	631 (44.7)	137 (44.2)	0.986
AA	181 (12.8)	40 (12.9)	
Follow-up			
Mean BMI, kg/m^2 (SD)	–	21.7 (2.9)	
Underweight/normal weight, % (n)	–	276 (89.0)	
Overweight/obese, % (n)	–	34 (11.0)	
Mean weight, kg (SD)	–	63.8 (11.6)	
Mean weight change, kg (SD)		0.54 (3.36)	
≥5% weight gain, % (n)			
No	–	255 (82.3)	
Yes	–	55 (17.7)	

Table 2. Participant characteristics by gender

Participant characteristics	Male	Female	p value (nominal)
Baseline			
Mean BMI, kg/m^2 (SD)	22.7 (2.5)	21.2 (2.9)	<0.001
Underweight/normal weight, % (n)	573 (82.7)	644 (89.7)	<0.001
Overweight/obese, % (n)	120 (17.3)	74 (10.3)	
Mean age, years (SD)	20.3 (2.4)	20.5 (2.5)	0.129
18–20 years, n (%)	450 (64.9)	433 (60.3)	0.072
21–30 years, n (%)	243 (35.1)	285 (39.7)	
FTO status, n (%)			
TT	290 (41.8)	309 (43.0)	0.648
AT	318 (45.9)	313 (43.6)	
AA	85 (12.3)	96 (13.4)	
Follow-up			
Mean BMI, kg/m^2 (SD)	22.5 (2.8)	22.7 (2.8)	<0.001
Underweight/normal weight, n (%)	129 (87.2)	147 (90.7)	0.316
Overweight/obese, n (%)	19 (12.8)	15 (9.3)	
≥5% weight gain, n (%)			
No	118 (79.7)	137 (84.6)	0.265
Yes	30 (20.3)	25 (15.4)	

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Table 3. Participant characteristics by *FTO* genotype

Participant characteristics	TT genotype	AT genotype	AA genotype	p value (nominal)
Baseline				
Mean BMI, kg/m^2 (SD)	21.7 (2.9)	22.1 (3.0)	22.0 (2.8)	0.082
Underweight/normal weight, n (%)	528 (88.1)	529 (83.8)	160 (88.4)	0.060
Overweight/obese, n (%)	71 (11.9)	102 (16.2)	21 (11.6)	
Sex				
Male n (%)	290 (41.8)	318 (45.9)	85 (12.3)	0.648
Female n (%)	309 (43.0)	313 (43.6)	96 (13.4)	
Mean age, years (SD)*	20.54 (2.6)[a]	20.40 (2.5)[a]	20.0 (2.2)[b]	0.027
18–20 years, n (%)	363 (41.1)	394 (44.6)	126 (14.3)	0.089
21–30 years, n (%)	236 (44.7)	237 (44.9)	55 (10.4)	
Follow-up				
Mean BMI, kg/m^2 (SD)	21.7 (2.8)	22.0 (2.9)	21.9 (3.4)	0.707
Underweight/normal weight, n (%)	121 (91.0)	119 (86.9)	36 (90.0)	0.545
Overweight/obese, n (%)	12 (9.0)	18 (13.1)	4 (10.0)	
≥5% weight gain, n (%)				
No	117 (88.0)	107 (78.1)	31 (77.5)	0.074
Yes	16 (12.0)	30 (21.9)	9 (22.5)	

*Means that do not share superscripts differ by $p < 0.05$.

At baseline, students' mean weight was 64.2 kg (SD = 12.0), height was 1.70 m (SD = 0.09) and BMI was 22.0 kg/m^2 (SD = 3.0). Only a very small proportion (6.4%; n = 91) of participants were classified as underweight (BMI < 18.5 kg/m^2); so they were grouped with normal-weight participants (79.8%, n = 1,126). Less than a quarter of the sample (13.7%, n = 194) were classified as overweight/obese. Mean age was 20.4 years at baseline (SD = 2.5 years), with 62.6% (n = 883) of the sample in the 18–20 age group and 37.4% (n = 528) being older. We also present descriptive data for males and females separately (table 2).

Baseline Differences in BMI by FTO *Genotype*

FTO was in Hardy-Weinberg equilibrium at baseline (χ^2 (2) = 0.54, p = 0.462) and at follow-up (χ^2 (2) = 0.28, p = 0.868).

Unadjusted differences in BMI by *FTO* genotype are presented in table 3. Using the additive model, the association between *FTO* genotype and BMI was not significant in adjusted analyses (p = 0.059); although there was a trend for those carrying the TT genotype to have a lower BMI than those carrying the AT genotype (21.8 kg/m^2 vs. 22.2 kg/m^2; Bonferroni-corrected p = 0.078). Age was significantly associated with BMI, with 'older' students having a higher BMI than 'younger' students (22.5 kg/m^2 vs. 21.6 kg/m^2, F (1, 1,406) = 30.55; Bonferroni-corrected p < 0.001). Sex was also significantly associated with BMI, with men having a higher BMI than women (22.8 kg/m^2 vs. 21.4 kg/m^2, F (1, 1,406) = 99.9; Bonferroni-corrected p < 0.001).

Assuming a dominant model, individuals carrying at least one A allele had a higher BMI than those with the lower-risk TT genotype; adjusting for age and sex (22.2 vs. 21.9 kg/m^2, F (1, 1407) = 5.66; p = 0.017). However, this finding remained no longer significant after applying the Bonferroni-corrected alpha level. The significant effects of age and gender were replicated (data not shown).

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Table 4. Multivariable predictors of 5% weight gain

Variable	OR	95% CI	p value (nominal)
FTO status			
TT	1		
AT	2.05	1.05–4.01	0.036
AA	2.24	0.88–5.70	0.089
Age			
21–30 years	1		
18–20 years	2.91	1.39–6.11	0.005
Sex			
Female	1		
Male	1.28	0.69–2.32	0.428

Weight Gain over Follow-Up by FTO *Genotype*

Attrition was high, with only 21.9% (n = 310) of the sample returning for follow-up weighing.

Weight change over the 8-month study period in those returning for follow-up was modest on average, but there was considerable variation (mean +0.54 kg, SD = 3.36 kg, range –12.60 to 14.40 kg). Just over half the students had gained weight (51.3%, n = 159), with 45.9% losing weight, and the remainder staying precisely stable. However, almost one in five of the total sample (17.7%; n = 55) had gained at least 5% of their initial body weight.

Using the additive model and adjusting for age and sex, *FTO* status was significantly associated with 5% weight gain at follow-up, with individuals carrying the AT genotype being about twice as likely to have gained at least 5% of their starting weight than participants carrying the TT genotype (OR 2.05, 95% CI 1.05–4.01; p = 0.036), and a trend for AA carriers to be more likely to have gained at least 5% of their starting weight than TT carriers (OR 2.24, 95% CI 0.88–5.70; p = 0.089). However, after applying Bonferroni correction, the former finding was no longer significant (table 3). Age was also a significant predictor of weight gain in the dominant model, with those between 18 and 20 years being more likely to have gained at least 5% of their starting weight than older participants using Bonferroni-corrected alpha levels (OR 2.91, 95% CI 1.39–6.11; p = 0.005). Sex was not a significant predictor of weight gain (p = 0.428) (table 4).

Using the dominant model, *FTO* status was also associated with a weight gain ≥ 5% in unadjusted analyses (p = 0.022), but, again, this finding remained no longer significant in adjusted analyses using the Bonferroni-corrected alpha level (OR 2.09, 95% CI 1.10–3.98; p = 0.024). Effects of age were replicated (data not shown).

Discussion

This is the first study to investigate the moderating effect of *FTO* gene status on weight gain over the medium term which is associated with a move into an environment that often provides greater freedom around eating behaviour than life within the parental home and abundant eating opportunities. Albeit only nominal and requiring replication in sufficiently large samples, the results showed that individuals with the higher-risk variants of the *FTO* gene were significantly more likely to experience significant weight gain (≥5% of their initial body weight) than those with the lower-risk genotype, with similar effects using additive and dominant models.

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Weight gain overall was modest (~0.5 kg); well below the anecdotal 'freshman 15', or the 5 lb observed in some US samples [28, 37]. However, younger students were more likely to gain ≥5% of their body weight than older students, suggesting that those who had recently transitioned from school to university were at greater risk than those who had either been at other universities or had taken on some other young adult role.

Although previous studies have investigated determinants of weight gain in student samples and found alcohol consumption, stress and high consumption of junk food to be significant predictors of weight gain [14, 37–40], none have taken the genetic perspective. Similarly, although some studies have investigated the effect of FTO in individuals attempting weight loss [24–27], none have focused on cohorts with low motivation to prevent weight gain. Evidence that FTO operates in part at least through effects on satiety responsiveness and food reward [2, 12, 41] suggests scope to evaluate interactions between genotype and environments with a highly palatable food supply and abundant eating opportunities; in particular, since emerging evidence suggests that genetics may also influence food choice [42].

The study had many limitations. Participant retention proved a challenge: despite personalized email reminders and small incentives to return for follow-up weighing, nearly 80% of the sample was lost to follow-up. This may have been, in part, due to the timing of follow-up weighing being scheduled at the end of the academic year when students were busy with exam preparations. Secondly, although it was presumed that all students had increased exposure to the obesogenic environment of university life, some students may have chosen to limit their exposure, for example by avoiding socialising in environments in which eating and drinking was involved. Some may have maintained the traditional diet of their home country (UCL has a high proportion of international students), and others may have taken advantage of opportunities to be physically active as part of university sports clubs; all of which would have limited the impact of any genetic predisposition to weight gain. Unfortunately, the current study did not assess whether students joined any sports clubs, or any other behavioural mediators, which limits the conclusions that can be drawn, but these could be investigated in future research. Thirdly, relatively few overweight and obese individuals took part in the study although the university in which the study was carried out has high academic standard and therefore may have had a lower prevalence of obesity given the established link between obesity and lower educational attainment (e.g. [43, 44]). It is therefore likely that the current findings provide a conservative estimate of the effects of FTO on weight gain in first-year university students. Since these results provided only nominal evidence for an association of *FTO* genotype with >5% weight gain, these findings will need to be replicated in sufficiently large samples.

Conclusion

Despite its limitations, this study provides nominal evidence that carriers of the higher-risk alleles of the *FTO* gene were more likely to gain significant amounts of weight as they moved into an environment known to carry an obesogenic risk than participants with the lower-risk TT genotype. Weight gain prevention programmes might benefit from including genetic information to raise awareness of personal risk of weight gain associated with move to an obesogenic environment.

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Disclosure Statement

The authors have no conflict of interest to declare.

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