HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2015 June 22.

Published in final edited form as:

Obesity (Silver Spring). 2008 April ; 16(4): 902–904. doi:10.1038/oby.2007.126.

Association of the FTO Gene With BMI

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Abstract

Variants in the FTO gene have been strongly associated with obesity in a very large sample (38,759) of diabetic and control subjects. To replicate these findings, the previously reported SNP in the FTO gene (rs9939609, T/A) was genotyped in 5,607 subjects from five different Utah studies. The studies included a random sample of the Utah population, families selected for aggregation of extreme thinness, families selected for severe obesity, a series of unrelated severe obesity subjects, and families participating in a 25-year longitudinal study of cardiovascular disease and aging. Results show a strong significant increase in the rs9939609 A allele frequency with increasing BMI ($P < 0.0001$). In the longitudinal study, FTO genotypes were significantly associated with BMI at a baseline exam, a 2½-year follow-up exam and a 25-year follow-up exam using an additive genetic model. The mean genotype difference in BMI ranged from 1.3 to 2.1 kg/m^2 across exams. The genotype difference in BMI means was established in youth, and at-risk subjects under age 20 at baseline had a significantly larger 25-year BMI increase (10.0 for A/A; 9.7 for A/T, and 8.5 kg/m^2 for T/T, $P = 0.05$). We conclude that the BMI increases associated with FTO genotypes begin in youth and are maintained throughout adulthood.

Recently, variants in the FTO gene were strongly associated with obesity in 38,759 diabetic and control subjects (1). The associated SNP was identified from a genome-wide scan of 1,924 type 2 diabetes patients and 2,938 population controls. However, after adjustment for BMI, the association with diabetes disappeared, leading the authors to conclude that the increased risk for diabetes resulted from a strong association with high BMI. The association with BMI was also found in children as young as 7 years of age and persisted through the end of follow-up at age 11. An independent study of 8,000 subjects also showed highly significant associations with severe obesity in adults and with childhood obesity (2). Extensive replication of the FTO gene association is essential given the highly variable results reported for the *GAD2* and *INSIG2* genes (3–11). We have replicated the findings from both previous studies of the FTO gene in 5,607 subjects (ages 3–101 years) selected

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DISCLOSURE

The authors declared no conflict of interest.

for very wide extremes of obesity or thinness, with 37% of subjects having a BMI ≥ 35 kg/m^2.

For this report, subjects from five studies were genotyped. The first was a prospective family study of cardiovascular disease and aging (Utah Pedigree Study; *n* = 1,709 genotyped subjects in 98 multigeneration pedigrees) (12,13). Exams at baseline, 2½ years and 25 years are analyzed in this report. The second was a family study of severe obesity, in which multigeneration pedigrees were extended from nuclear families with two or more members with severe obesity (BMI ≥ 35 kg/m^2) (Obesity Pedigrees; *n* = 1,571 genotyped subjects) (14,15). The third study was a series of unrelated severely obese subjects enrolled in a case–control gastric bypass surgery study (Utah Obesity Study; *n* = 1,090 subjects genotyped) (16). In the fourth, a series of unrelated subjects were randomly recruited from the Utah population (Random subjects; *n* = 854 subjects genotyped) (5,17). The fifth study was a genetic study of leanness in small families selected for aggregation of thin sibpairs (BMI ≤ 20 kg/m^2 for males and ≤19 kg/m^2 for females) (Thin Pedigrees; *n* = 383 subjects genotyped). The term thin is used to describe these subjects, as the standard cutoff for underweight of 18.5 kg/m^2 was not used for this study.

Table 1 shows the subject characteristics of the five studies. More women than men participated in most studies and the mean age was usually in the early forties. The mean BMI ranged across the whole spectrum of underweight, normal weight, overweight, obesity, and severe obesity, and there was a wide range of BMI within each study. Thirty-seven percent (*N* = 2,062) of all subjects were severely obese and 6% (*N* = 353) were thin due to the selection criteria of three of the studies.

Figure 1 shows the allele frequency of the A allele of SNP rs9939609 (T/A) for each age- and gender-adjusted BMI unit and for categories of five BMI units for all subjects combined. There was a significant linear trend for increasing allele frequencies with increasing BMI ($P = 1 \times 10^{-10}$). The trend was significant if individual BMI unit categories or five-unit BMI categories are used and was significant for both males and females (not shown). Frequency of the A allele was 39.2% in the random subjects agreeing with the 39% frequency estimate in the study of Frayling *et al.* (1). The allele frequency ranged from 38.2 to 49.7% for the <20 vs. >50 kg/m^2 categories. Age-adjusted BMI means in the combined groups for females were 35.4, 34.4 and 33.2 kg/m^2 ($P = 3.7 \times 10^{-5}$), and for males were 32.3, 30.6 and 29.5 ($P = 4.4 \times 10^{-8}$) for A/A, A/T, and T/T genotypes. The variance in BMI explained by rs9939609 for all subjects combined was 0.7%.

The mean age-, gender-, and pedigree-adjusted BMI in the longitudinal Utah Pedigree Study differed significantly among genotypes for each of three exams (baseline, 2½-year, and 25-year follow-up, Table 2). In this cohort, BMI change over the 25-year follow-up also significantly differed among genotypes in subjects who were under age 20 at baseline (10.0 ± 0.53 kg/m^2 for A/A; 9.7 ± 0.45 kg/m^2 for A/T and 8.5 ± 0.51 kg/m^2 for T/T, $P = 0.050$) but not for subjects who were age 20 or older at baseline (4.5 ± 0.44 kg/m^2 for A/A; 4.6 ± 0.22 kg/m^2 for A/T and 4.2 ± 0.27 kg/m^2 for T/T, $P = 0.63$). The mean homozygote difference in BMI was 2.1 kg/m^2 at the 25-year follow-up, in the range of the BMI difference of 0.6–2.6 kg/m^2 seen in the study of Frayling *et al.* (1). Follow-up BMI (*P* =

0.02), but not baseline BMI ($P = 0.76$), showed a significant association with rs9939609, when a TDT test was performed in nuclear families derived from the larger pedigrees.

Analysis of glucose, insulin, hemoglobin A1c, lipids, and blood pressures with FTO genotypes showed nominal significance for HDL-C, glucose, and systolic blood pressure when adjusted for age and gender (Table 3). Excluding diabetic subjects from the glucose and insulin analyses did not change the significance levels (not shown). Further adjustment for BMI removed the glucose association and attenuated the significance for HDL-C and systolic blood pressure. After further adjustment for multiple comparisons, none of the variables remained significant.

Our series of subjects were selected specifically for either severe obesity or extreme leanness and also included random subjects and longitudinally followed subjects. The association of the A allele of the rs9939609 SNP in the FTO gene appeared to be consistently associated with all levels of BMI across the wide range of BMI values used in this analysis, providing further convincing evidence of the involvement of this gene in obesity. Frayling *et al.* did not find differences in weight or obesity in subjects at birth but found significant differences by age 7. Our data suggest that the additional weight gain due to this gene occurs primarily in childhood, as the youths under age 20 showed a significant association of the FTO gene with 25-year change in BMI but not the adults. However, our data also show that the BMI difference that occurs during youth persists into adulthood, as the 25-year cross-sectional differences in BMI were significant. The FTO gene appears to be associated with early-onset obesity.

We were not able to further define the function of the gene, as there were no significant associations of the gene with blood pressure, glucose, insulin, hemoglobin A1c, or lipids after adjustment for age, sex, BMI, and the number of the secondary hypothesis tests. HDL-C was the most significant variable using only age and sex adjustment, with lower HDL-C associated with the A allele of the FTO gene. Fasting glucose levels were higher in those with one or more A alleles prior to BMI adjustment. However, the 25-year change in glucose was not significantly different among FTO genotypes, and baseline glucose was not associated with FTO after adjustment for BMI. This may suggest that the increased glucose resulted from the increased BMI rather than contributing to the development of obesity.

The rs9939609 allele and genotype frequencies and the BMI differences among FTO genotypes were very similar among studies. Therefore, this work strongly confirms the conclusion that FTO is associated with increased BMI. Further, we show that a SNP in the FTO gene is associated with BMI in a 25-year longitudinal study and that the genotype-specific increase in BMI occurs in youth and young adulthood and is maintained throughout adulthood. While the study by Frayling *et al.* did not find SNPs that appeared to have functional significance, including rs9939609 (1), the study by Dina *et al.* provided evidence that three of the SNPs tested in their study were likely to be functional variants (2). One of these three variants, rs17817449, is in very high linkage disequilibrium with rs9939609 and had very similar allele frequencies in their severely obese subjects and controls to those in our severely obese and random subjects. It will be extremely important to determine the

function of FTO so that the physiological mechanisms leading to obesity may be understood and perhaps counteracted early in life.

Methods

Subjects were Whites. Blood was obtained in the sitting position after a 12-h overnight fast from which glucose, insulin, hemoglobin A1c levels, and lipids were measured. Insulin measurements were not available for the thin pedigree subjects or for nearly half of the random subjects. Hemoglobin A1c was only available in the Utah Obesity Study subjects. Blood pressure was measured by various automated devices using the correct cuff size for the subject's arm as determined by the arm circumference at mid-humerus. Subjects were genotyped for the rs9939609 of the FTO gene. Genotypes were in Hardy–Weinberg equilibrium for all the studies, except for the highly ascertained severe obesity subjects in the Utah Obesity Study ($P = 0.02$) who had an excess of the A allele. Subjects from all five studies were combined, and the frequency of the A allele was estimated for each individual BMI unit and also for BMI categories defined as <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50 kg/m^2 after adjusting BMI for age and gender. The midpoint of each category, or 17.5 and 52.5 kg/m^2 for the extremes, was used to plot the allele frequencies. Generalized estimating equations with an exchangeable correlation matrix were used to control for relatedness within pedigrees when estimating mean genotype effects in the longitudinal Utah Pedigree Study. Mean values and standard errors are presented except where indicated. TDT tests were performed using a family-based association test (18).

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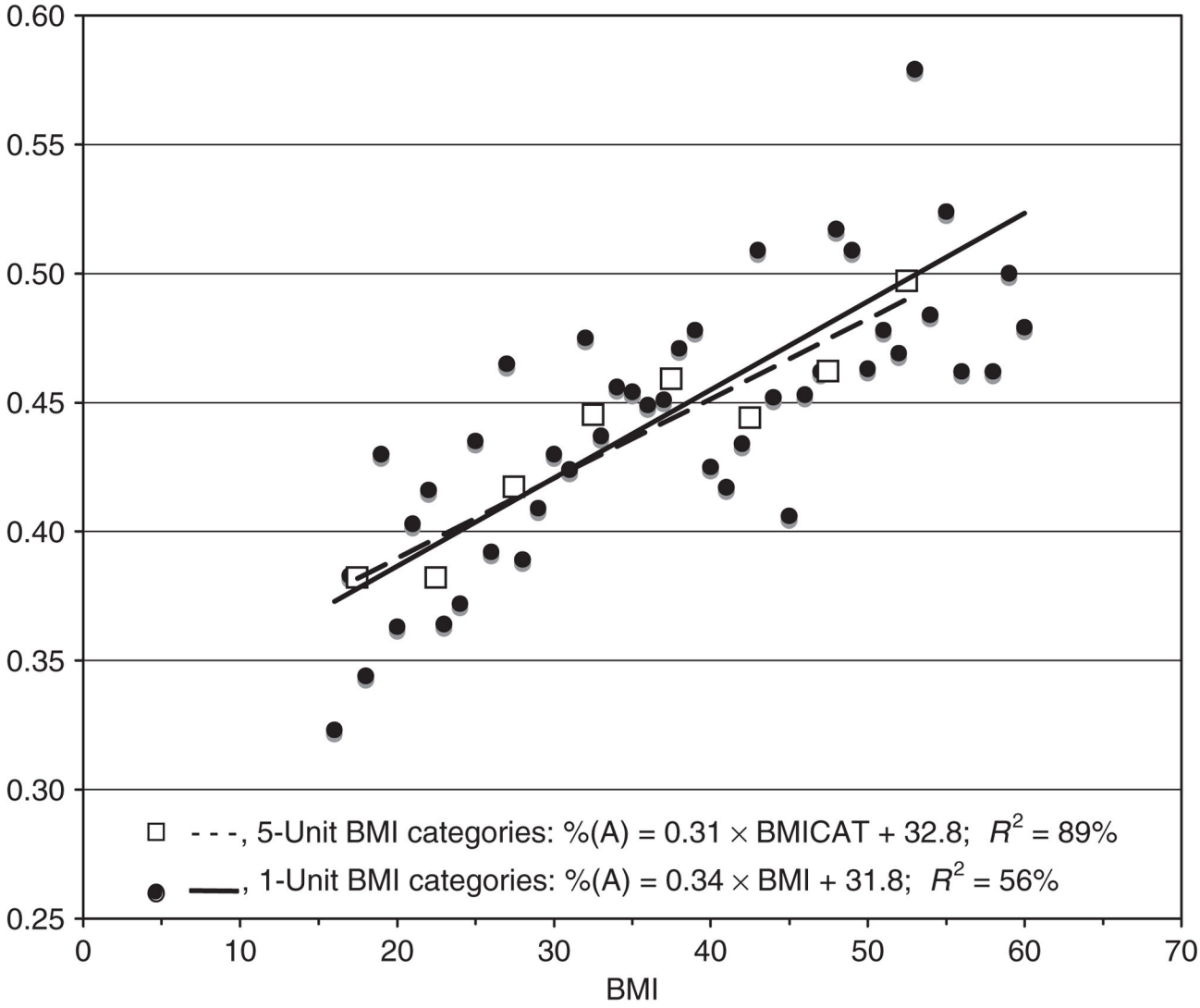

Figure 1.

Increase in allele frequency of the A allele of rs9939609 in the FTO gene with increasing BMI ($P = 1 \times 10^{-10}$ from a Mantel–Haenszel test for trend). Allele frequencies were estimated for each BMI unit or each 5-BMI unit after age and gender adjustment of BMI. Unweighted regression was used for the lines shown for each method.

Table 1

Study subject characteristics

Study groups (5,607)	Females (%)	Mean age ± s.d. (range)	Mean BMI ± s.d. (range)
Utah Pedigrees (1,709)	49	42.5 ± 20.3 (3–90)	27.5 ± 6.3 (13–56)
Obesity Pedigrees (1,571)	64	43.7 ± 17.7 (7–101)	34.8 ± 8.1 (17–82)
Thin Pedigrees (383)	56	37.8 ± 17.8 (11–90)	21.3 ± 3.7 (14–38)
Utah Obesity Study (1,090)	82	43.7 ± 11.4 (18–72)	46.1 ± 7.6 (33–92)
Random Subjects (854)	52	52.5 ± 8.5 (19–77)	27.6 ± 5.2 (17–51)

Table 2

Mean age- and gender-adjusted BMI (kg/m^2 ± s.e.m.) at three time points over 25 years in the Utah pedigree study for 947 subjects with data from all three exams

FTO genotypes	Exam 1 (baseline)	Exam 2 (2½ years)	Exam 3 (25 years)
A/A	23.6 ± 0.4	24.4 ± 0.4	29.9 ± 0.6
A/T	23.0 ± 0.2	23.8 ± 0.3	29.2 ± 0.4
T/T	22.3 ± 0.3	23.1 ± 0.3	27.8 ± 0.3
P (additive model)	0.013	0.016	0.007

Table 3

Clinical and biochemical variable associations with the FTO gene

Variable	*N*	Age- and gender-adjusted *P* value[a]	Age-, gender-, and BMI-adjusted *P* value[a]
Cholesterol	5,607	0.13	0.37
Triglycerides	5,607	0.37	0.67
HDL-C	5,607	0.005	0.03
Glucose	5,590	0.034	0.17
Insulin	4,049	0.27	0.25
HbA1c	863	0.73	0.25
SBP	5,191	0.014	0.03
DBP	5,191	0.38	0.83

[a] Additive genetic model for FTO. R^2 for rs9939609 vs. each variable was <0.2%.