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Is *FTO* genotype a useful predictor for body weight maintenance? Preliminary results of a 5-year follow-up study

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Conflicts of Interest

No author has any professional relationships with companies or manufactures who will benefit from the results of the present study. The authors declare no conflict of interest.

Abstract

Objective: We examined associations between the fat-mass and obesity-associated (*FTO*) gene (rs9939609) and any weight change over a 5-year period following a 14-week lifestyle intervention among middle-aged Japanese women.

Materials/Methods: One hundred twenty-eight Japanese women (BMI >25 kg/m^2) participated in a 14-week weight loss intervention between 2004 and 2006. Of the participants, 62 consented to the 5-year follow-up measurement session. Of these women, 47 women who achieved a weight loss of at least 10% from their baseline values during the 14-week intervention were included in the analysis. Body weight, body fat, abdominal fat assessed by CT scans, and metabolic risk factors (i.e., blood pressure, lipids, and glucose) were measured at baseline, post-intervention, and at the 5-year follow-up.

Results: During the 5-year non-intervention period, increases in body weight, fat mass, total abdominal fat, and subcutaneous abdominal fat were significantly greater in subjects with the homozygous minor allele (AA genotype, n = 4; 8.5%) than in those with the homozygous major allele (TT genotype, n = 31; 66.0%) or heterozygous allele (TA genotype, n = 12; 25.5%). In multiple regression analyses, the variation in rs9939609 was a significant and independent predictor (P <0.001) for regaining weight during the 5-year follow-up.

Conclusions: Our data suggest that Japanese women with the risk allele (AA) of rs9939609 may have more difficulty preventing fat gain from reoccurring after weight loss intervention

than women with the other genotypes.

Key words: Abdominal Obesity; Genotype; Lifestyle Intervention; Weight Loss

List of abbreviations

AA: homozygous (adenine/adenine) allele
AC: abdominal circumference
BMI: body mass index
CT: computed tomography
DBP: diastolic blood pressures
SAF: subcutaneous abdominal fat
SBP: systolic blood pressures
TA: heterozygous (thymine/adenine) allele
TAF: total abdominal fat
TT: homozygous (thymine/thymine) allele
VAF: visceral abdominal fat

Introduction

Many studies [1-5] indicate that gene variants in the fat-mass and obesity-associated (*FTO*) gene (primarily rs9939609) are associated with obesity traits. In our recent studies [6-8], we showed significant associations between rs9939609 and BMI [7], metabolic syndrome [6], and interventional weight loss [8] among the Japanese population. Until now, however, there have been few studies investigating the associations between *FTO* genotype and maintaining long-term body-weight loss after weight-loss intervention. In the present study, we examined the association between rs9939609 and 5-year weight maintenance after an initial 14-week weight loss intervention among middle-aged Japanese women. We hypothesized that subjects with the homozygous minor allele (AA) of rs9939609 would be more likely to increase their body weight than those with other genotypes during the 5 year non-intervention period.

Methods

We recruited 128 Japanese women using the JASSO criterion of obesity of BMI > 25 kg/m^2 [9, 10] through advertisements in local newspapers to participate in a 14-week weight loss intervention between 2004 and 2006. Of the participants, 124 women completed the 14-week intervention. Of these women, 62 women consented to a follow-up measurement session at the end of a 5 year non-intervention period. In this study, because we focused on maintaining the body weight change long-term after an intervention, we excluded 15 subjects who did not achieve at least a 10% loss of weight [11] during the 14-week intervention. Consequently, 47 subjects were included in the final analysis. The aim and design of this study were explained to every subject before each gave her written, informed consent. This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Ethical Committee of the University of Tsukuba reviewed and approved the study protocol.

The 14-week lifestyle intervention program was mainly comprised of dietary modifications with a physical activity program (90 minutes per session, 12 times in 14 weeks). Detailed descriptions of the program have been published elsewhere [12].

Anthropometric measurements were performed by a trained laboratory assistant at baseline, post-intervention, and at the 5-year follow-up. Body weight was measured once to the nearest 0.1 kg using a digital scale (TBF-551; Tanita, Tokyo, Japan), and height was measured once to the nearest 0.1 cm using a wall-mounted stadiometer (YG-200; Yagami, Nagoya, Japan) with the subjects in underwear and barefooted while fasting in the morning. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. AC was measured directly on the skin at the level of the umbilicus in the standing position. The AC measurements were taken in duplicate to the nearest 0.1 cm. Body composition, recorded as percentage fat mass, fat mass (kg), and fat-free mass (kg), was assessed by a bioelectrical impedance analysis (TBF-551; Tanita, Tokyo, Japan). We acquired CT images for each subject using a CT scanner (TSX-002A; Toshiba, Tokyo, Japan) in order to calculate TAF, VAF, and SAF areas. A single trained technician performed blinded image analyses to determine the TAF, VAF, and SAF areas using a computer software program (Fat Scan; N2 system, Osaka, Japan). Detailed descriptions of the CT methods have been published elsewhere [12].

Blood pressure and biochemical assays of blood were also measured at baseline, post-intervention, and at the 5-year follow-up. One trained nurse measured SBP and DBP of subjects at the right arm using a mercury manometer and a standard protocol after the subjects rested for at least 20 minutes in the sitting position. A blood sample was drawn from each subject after a 12-hour fast. Serum glucose and lipids were assayed by routine automated laboratory methods [13]. Low-density lipoprotein cholesterol was calculated according to Friedewald's formula [14].

Genomic DNA was prepared from the blood sample of each subject by using Genomix (Talent Srl, Trieste, Italy). The rs9939609 allele within the *FTO* gene was genotyped using the TaqMan probe (C_30090620_10; Applied Bio-systems, Foster City, CA, USA). To investigate the relationship between the measurement values and the rs9939609 genotype, subjects were assigned to one of 3 categories depending on their genotype: homozygous major allele, TT; heterozygous allele, TA; or homozygous minor allele, AA.

Statistical analysis

Values are expressed as the mean ± standard deviation. Paired Student's *t* tests were performed to test the significance of value changes measured at baseline, post-intervention, and at the 5-year follow-up. We evaluated the differences among the genotypes by a univariate ANOVA (PROC GLM in the SAS procedure) with adjustments for age, menstrual status, and respective baseline values, when appropriate. Multiple regression analyses were conducted to determine a combination of predictors for weight change. The Hardy-Weinberg equilibrium was assessed using the χ^2 test. The data were analyzed with the Statistical Analysis System (SAS), version 9.3 (SAS Institute Inc, Cary, NC, USA).

Results

The rs9939609 variant was in Hardy-Weinberg equilibrium (P = 0.26) and the minor allele frequency was 0.213 (TT, n = 31, 66.0%; TA, n = 12, 25.5%; AA, n = 4, 8.5%). **Table 1** shows subjects' characteristics at baseline, post-intervention, and at the 5-year follow-up among the rs9939609 genotypes. At baseline, TAF and SAF were significantly greater in subjects with the AA genotype than in those with the TT or TA genotypes. At the 5-year follow-up, we obtained similar but clearer results, i.e., body weight, BMI, AC, fat mass, TAF, and SAF were significantly greater in subjects with the AA genotype than in those with the other genotypes. **Table 2** presents changes in measurement values from pre-intervention to 5-year follow-up and from post-intervention to 5-year follow-up by genotype group including within-group analyses (paired t test) and group-difference analyses (ANOVA). In the analyses comparing pre-intervention values with 5-year follow-up values, there was a trend toward lower body fat-related values at the 5-year follow-up compared to pre-intervention in all three groups. The decrease in fat mass was significantly smaller in subjects with the AA genotype than in those with the TT or TA genotypes. The analyses of values from post-intervention to 5-year follow-up showed most of the fat-related values of all three groups had significantly increased at the 5-year follow-up. The increases in body weight, AC, fat mass, TAF, and SAF were significantly greater in subjects with the AA genotype than in those with the TT or TA genotypes. While significant increases were also observed in many of the blood sample and blood pressure values during this period, no significant differences across the genotypes were observed. In multiple regression analyses, the variation in rs9939609 was a significant and independent predictor (P <0.001) for weight change during the 5-year follow-up when age, menstrual status, and post-intervention body weight were included in the model as adjusted values. The rs9939609 genotypes accounted for 19.3% (adjusted R^2 = 0.193) of the total body weight change variance.

Discussion

Our hypothesis is supported by the significantly greater increases in body weight, i.e., body fat, during the 5 years of non-intervention in subjects with the AA genotype than in those with TT or TA genotypes. Previously, we reported that change in body fat during a 14-week lifestyle intervention tended to be smaller in subjects with AA genotype than in those with other genotypes [8]. The results showed that AA genotype individuals may have more difficulty reducing body fat than subjects with the other genotypes. On the other hand, the previous study [8] also showed that all subjects, despite their genotype, decreased their body weight significantly, and we concluded that the gene impact may not be great enough to change body weight in response to a short-term intervention, and environmental and behavioral factors may overcome the effects of genes on body-weight reduction. However, the present study, over a much longer term, showed a notable association between *FTO* genotype and body fat changes. Fredriksson et al. [15] indicated that the *FTO* gene may participate in the central control of energy homeostasis. It is possible that the subjects with the AA genotype in our study were unable to control the daily diet needed to maintain their reduced body weight as well as the subjects with other genotypes could.

Our results are consistent with other recent studies [16, 17]. Karra et al. [16] showed that AA carriers of rs9939609 have dysregulated circulating levels of the orexigenic hormone ghrelin and attenuated postprandial appetite reduction. Woehning et al. [17] showed that the AA carriers were more likely to regain weight during the weight maintenance period after a weight-loss intervention. If medical personnel could use genetic information for obesity therapy, they could provide a more effective intervention plan for their patients. *FTO* gene may be a useful predictor for body weight maintenance.

Our study did have limitations. First, sample size was small, and further research is needed to confirm our results. However, the frequency for the A allele in this study (21.3%) is similar to its frequency in the general Japanese population (21.5%) [6], suggesting this study's subjects represent an unbiased population. Second, attendance rate at the 5-year follow-up measurement session was low (50%). Mean body weight of all 47 subjects at the 5-year follow-up (61.5 ± 8.1 kg) was still lower (*P* <0.01) than the mean pre-intervention value (67.0 ± 8.6 kg), although it (61.5 ± 8.1 kg) was greater (*P* <0.01) than the mean post-intervention value (57.7 ± 7.3 kg). This suggests that the final analyses in the present study included many subjects who suppressed body-weight rebound during the follow-up period. This situation should be considered in the interpretation of our results. Third, while the present study evaluated subjects' abdominal fat using a single-slice imaging technique, a multiple-slice imaging technique might be better for detecting VAF change [18].

In conclusion, our data suggest that middle-aged Japanese women with the risk allele of rs9939609 may have more difficulty preventing fat gain from reoccurring after successfully achieving weight loss during an intervention than women with other genotypes.

Author Contributions

Contributions by each author are as follows: TM- manuscript writing, development of the study concept and design, data acquisition, and data analysis; YN and KH- manuscript revisions, data acquisition, and data analysis; KT- manuscript revisions, development of the study concept and design, and data acquisition.

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Conflict of interest

The authors have nothing to declare.

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Table 1. Comparisons of measurement values across genotypes of *FTO* rs9939609

	Baseline				Post-intervention				5-year follow up			
	TT (n = 31)	TA (n = 12)	AA (n = 4)	P [a]	TT (n = 31)	TA (n = 12)	AA (n = 4)	P [a]	TT (n = 31)	TA (n = 12)	AA (n = 4)	P [a]
Age, yr	55.1 ± 7.4	53.0 ± 5.2	46.3 ± 11.1	0.076	55.3 ± 7.5	53.4 ± 5.3	46.8 ± 11.1	0.096	60.3 ± 7.4	58.3 ± 5.5	51.3 ± 11.1	0.071
Height, cm	154.5 ± 5.0	155.9 ± 5.1	160.3 ± 3.8	0.373	154.5 ± 4.8	155.6 ± 5.2	160.0 ± 3.6	0.409	153.7 ± 5.0	154.9 ± 5.3	159.2 ± 3.8	0.548
Body weight, kg	65.0 ± 8.2	68.2 ± 8.2	78.2 ± 1.6	0.115	56.3 ± 6.9	58.9 ± 7.6	65.6 ± 3.5	0.306	59.7 ± 7.1	61.9 ± 8.0	74.5 ± 3.9	0.026
BMI, kg/m^2	27.2 ± 2.4	28.0 ± 2.2	30.5 ± 1.4	0.232	23.5 ± 2.0	24.3 ± 2.0	25.7 ± 1.9	0.526	25.2 ± 2.1	25.8 ± 2.6	29.4 ± 1.2	0.030
AC, cm	93.4 ± 7.0	93.1 ± 9.1	104.3 ± 4.2	0.137	84.5 ± 6.0	85.0 ± 8.7	93.2 ± 5.9	0.212	89.4 ± 5.7	89.5 ± 9.8	102.7 ± 4.4	<0.01
Percentage fat mass, %	36.5 ± 4.9	37.2 ± 4.8	45.0 ± 7.7	0.117	28.6 ± 4.4	28.9 ± 3.4	34.8 ± 3.9	0.143	32.7 ± 5.2	34.4 ± 4.6	43.6 ± 1.9	<0.01
Fat mass, kg	24.0 ± 6.8	25.4 ± 4.4	35.2 ± 5.8	0.078	16.3 ± 4.9	17.1 ± 3.6	22.8 ± 3.1	0.270	19.8 ± 5.1	21.5 ± 5.2	32.5 ± 1.9	<0.01
Fat-free mass, kg	41.0 ± 3.2	42.8 ± 6.1	43.1 ± 6.5	0.577	40.0 ± 3.0	41.8 ± 4.9	42.8 ± 3.0	0.327	40.0 ± 3.4	40.4 ± 3.9	42.0 ± 2.9	0.995
TAF area, cm^2	357 ± 70	359 ± 66	497 ± 31	<0.01	256 ± 67	263 ± 66	353 ± 44	0.146	280 ± 61	281 ± 93	427 ± 23	<0.01
VAF area, cm^2	107 ± 34	92 ± 26	118 ± 28	0.081	77 ± 23	67 ± 21	86 ± 38	0.321	69 ± 26	68 ± 34	81 ± 17	0.619
SAF area, cm^2	250 ± 71	267 ± 53	378 ± 23	0.024	179 ± 60	196 ± 51	267 ± 30	0.126	211 ± 58	213 ± 66	346 ± 12	<0.01
SBP, mmHg	123 ± 12	137 ± 24	139 ± 17	0.067	111 ± 13	123 ± 17	122 ± 18	0.033	120 ± 10	130 ± 16	136 ± 22	0.036
DBP, mmHg	80 ± 7	83 ± 10	87 ± 9	0.281	70 ± 8	75 ± 12	77 ± 9	0.230	77 ± 9	81 ± 13	82 ± 17	0.572
TC, mg/dl	239 ± 40	219 ± 30	228 ± 27	0.493	200 ± 38	206 ± 34	184 ± 32	0.791	219 ± 40	217 ± 36	212 ± 43	0.971
HDLC, mg/dl	60 ± 15	63 ± 13	57 ± 6	0.405	60 ± 12	64 ± 8	55 ± 5	0.206	64 ± 17	68 ± 12	55 ± 9	0.393
LDLC, mg/dl	153 ± 35	139 ± 27	147 ± 31	0.550	126 ± 32	128 ± 33	116 ± 30	0.935	136 ± 35	131 ± 31	138 ± 44	0.784
TG, mg/dl	136 ± 116	85 ± 33	120 ± 29	0.471	67 ± 25	69 ± 17	61 ± 10	0.916	94 ± 46	89 ± 40	96 ± 13	0.846
FPG, mg/dl	94 ± 8	107 ± 32	94 ± 8	0.174	88 ± 8	87 ± 6	91 ± 7	0.394	93 ± 8	98 ± 14	104 ± 9	0.104

Values are presented as the mean ± SD

AC, abdominal circumference; AA, homozygous minor allele carriers of rs9939609; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SAF, subcutaneous abdominal fat; SBP, systolic blood pressure; TA, heterozygous allele carriers of rs9939609; TAF, total abdominal fat; TC, total cholesterol; TG, triglycerides; TT, homozygous major allele carriers of rs9939609; VAF, visceral abdominal fat

[a] Values are adjusted for age and menstrual status except for age.

Table 2. Comparison of changes in values from pre-intervention to 5-year follow-up and post-intervention to 5-year follow-up across genotypes of *FTO* rs9939609

	Changes from pre-intervention to 5-year follow-up						Group difference	Changes from post-intervention to 5-year follow-up						Group difference
	TT (n = 31)	P^a	TA (n = 12)	P^a	AA (n = 4)	P^a	P^b	TT (n = 31)	P^a	TA (n = 12)	P^a	AA (n = 4)	P^a	P^c
Body weight, kg	-5.3 ± 4.3	<0.01	-6.2 ± 4.3	<0.01	-3.7 ± 2.4	0.056	0.099	3.4 ± 3.1	<0.01	3.0 ± 3.9	0.021	9.0 ± 3.3	0.013	<0.01
BMI, kg/m^2	-2.0 ± 1.8	<0.01	-2.2 ± 1.7	<0.01	-1.1 ± 0.9	0.088	0.095	1.7 ± 1.3	<0.01	1.5 ± 1.7	<0.01	3.8 ± 1.0	<0.01	<0.01
AC, cm	-4.0 ± 4.8	<0.01	-3.5 ± 5.7	0.056	-1.5 ± 2.8	0.364	0.111	4.9 ± 4.7	<0.01	4.5 ± 6.6	0.036	9.5 ± 1.5	<0.01	0.037
Percentage fat mass, %	-3.8 ± 5.1	<0.01	-2.8 ± 7.9	0.248	-1.4 ± 7.7	0.739	0.024	4.1 ± 4.5	<0.01	5.6 ± 4.4	<0.01	8.9 ± 3.1	0.011	0.034
Fat mass, kg	-4.3 ± 5.3	<0.01	-3.8 ± 5.8	0.043	-2.7 ± 6.6	0.477	0.025	3.4 ± 3.8	<0.01	4.4 ± 3.7	<0.01	9.7 ± 2.8	<0.01	<0.01
Fat-free mass, kg	-1.0 ± 2.1	<0.01	-2.4 ± 4.2	0.073	-1.0 ± 5.3	0.723	0.433	0.0 ± 1.6	0.978	-1.4 ± 2.4	0.069	-0.7 ± 2.4	0.578	0.192
TAF area, cm^2	-77 ± 68	<0.01	-77 ± 58	<0.01	-70 ± 37	0.032	0.238	24 ± 56	0.024	18 ± 64	0.354	74 ± 43	0.042	0.018
VAF area, cm^2	-38 ± 29	<0.01	-25 ± 28	0.014	-38 ± 27	0.068	0.749	-8 ± 24	0.067	1 ± 24	0.870	-5 ± 23	0.667	0.771
SAF area, cm^2	-39 ± 51	<0.01	-52 ± 37	<0.01	-32 ± 31	0.127	0.069	32 ± 45	<0.01	17 ± 44	0.217	79 ± 34	0.019	<0.01
SBP, mmHg	-3 ± 12	0.127	-7 ± 16	0.151	-3 ± 7	0.527	0.384	9 ± 12	<0.01	5 ± 12	0.193	14 ± 5	0.014	0.169
DBP, mmHg	-2 ± 9	0.138	-3 ± 12	0.495	-5 ± 10	0.439	0.959	7 ± 9	<0.01	5 ± 11	0.119	6 ± 8	0.241	0.957
TC, mg/dl	-21 ± 36	<0.01	-2 ± 29	0.855	-16 ± 35	0.439	0.749	19 ± 36	<0.01	12 ± 36	0.264	29 ± 26	0.111	0.761
HDLC, mg/dl	4 ± 8	0.013	5 ± 8	0.045	-2 ± 6	0.492	0.333	3 ± 14	0.193	4 ± 8	0.129	0 ± 8	1.000	0.747
LDLC, mg/dl	-16 ± 37	0.190	-8 ± 30	0.403	-9 ± 35	0.655	0.941	10 ± 35	0.101	4 ± 33	0.668	22 ± 24	0.166	0.636
TG, mg/dl	-42 ± 107	<0.01	4 ± 42	0.772	-24 ± 25	0.152	0.926	27 ± 44	<0.01	20 ± 35	0.069	36 ± 20	0.036	0.776
FPG, mg/dl	-1 ± 8	0.480	-8 ± 24	0.252	10 ± 4	0.017	0.077	5 ± 9	<0.01	12 ± 12	<0.01	13 ± 5	0.012	0.123

Values are presented as the mean ± SD

AC, abdominal circumference; AA, homozygous minor allele carriers of rs9939609; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SAF, subcutaneous abdominal fat; SBP, systolic blood pressure; TA, heterozygous allele carriers of rs9939609; TAF, total abdominal fat; TC, total cholesterol; TG, triglycerides; TT, homozygous major allele carriers of rs9939609; VAF, visceral abdominal fat

[a] Paired Student's *t* tests were performed to test the significance of changes in values.

[b] Values are adjusted for age, menstrual status, and pre-intervention values.

[c] Values are adjusted for age, menstrual status, and post-intervention values.