

The FT0 genotype as a useful predictor of body weight maintenance: Initial data from a 5-year follow-up study

著者別名	中田 由夫, 田中 喜代次
journal or publication title	Metabolism : clinical and experimental
volume	63
number	7
page range	912-917
year	2014-07
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URL	http://hdl.handle.net/2241/00121918

doi: 10.1016/j.metabol.2014.03.013

1 **Title page**

2 Title

3 Is *FTO* genotype a useful predictor for body weight maintenance? Preliminary results of a
4 5-year follow-up study

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23 **Manuscript type:** Brief Reports

24 **Word Counts:** 1,765 (main text), 231 (abstract), 18 references, 2 tables

25

26 Conflicts of Interest

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

29

30 **Abstract**

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

34 **Materials/Methods:** One hundred twenty-eight Japanese women (BMI >25 kg/m²)
35 participated in a 14-week weight loss intervention between 2004 and 2006. Of the
36 participants, 62 consented to the 5-year follow-up measurement session. Of these women,
37 47 women who achieved a weight loss of at least 10% from their baseline values during the
38 14-week intervention were included in the analysis. Body weight, body fat, abdominal fat
39 assessed by CT scans, and metabolic risk factors (i.e., blood pressure, lipids, and glucose)
40 were measured at baseline, post-intervention, and at the 5-year follow-up.

41 **Results:** During the 5-year non-intervention period, increases in body weight, fat mass, total
42 abdominal fat, and subcutaneous abdominal fat were significantly greater in subjects with the
43 homozygous minor allele (AA genotype, n = 4; 8.5%) than in those with the homozygous
44 major allele (TT genotype, n = 31; 66.0%) or heterozygous allele (TA genotype, n = 12;
45 25.5%). In multiple regression analyses, the variation in rs9939609 was a significant and
46 independent predictor ($P < 0.001$) for regaining weight during the 5-year follow-up.

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

49 than women with the other genotypes.

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

51

52 **List of abbreviations**

53 AA: homozygous (adenine/adenine) allele

54 AC: abdominal circumference

55 BMI: body mass index

56 CT: computed tomography

57 DBP: diastolic blood pressures

58 SAF: subcutaneous abdominal fat

59 SBP: systolic blood pressures

60 TA: heterozygous (thymine/adenine) allele

61 TAF: total abdominal fat

62 TT: homozygous (thymine/thymine) allele

63 VAF: visceral abdominal fat

64

65 **Introduction**

66 Many studies [1-5] indicate that gene variants in the fat-mass and obesity-associated
67 (*FTO*) gene (primarily rs9939609) are associated with obesity traits. In our recent studies
68 [6-8], we showed significant associations between rs9939609 and BMI [7], metabolic
69 syndrome [6], and interventional weight loss [8] among the Japanese population. Until now,
70 however, there have been few studies investigating the associations between *FTO* genotype

71 and maintaining long-term body-weight loss after weight-loss intervention. In the present
72 study, we examined the association between rs9939609 and 5-year weight maintenance after
73 an initial 14-week weight loss intervention among middle-aged Japanese women. We
74 hypothesized that subjects with the homozygous minor allele (AA) of rs9939609 would be
75 more likely to increase their body weight than those with other genotypes during the 5 year
76 non-intervention period.

77

78 **Methods**

79 We recruited 128 Japanese women using the JASSO criterion of obesity of BMI > 25
80 kg/m² [9, 10] through advertisements in local newspapers to participate in a 14-week weight
81 loss intervention between 2004 and 2006. Of the participants, 124 women completed the
82 14-week intervention. Of these women, 62 women consented to a follow-up measurement
83 session at the end of a 5 year non-intervention period. In this study, because we focused on
84 maintaining the body weight change long-term after an intervention, we excluded 15 subjects
85 who did not achieve at least a 10% loss of weight [11] during the 14-week intervention.
86 Consequently, 47 subjects were included in the final analysis. The aim and design of this
87 study were explained to every subject before each gave her written, informed consent. This
88 study was conducted in accordance with the guidelines proposed in the Declaration of
89 Helsinki. The Ethical Committee of the University of Tsukuba reviewed and approved the

90 study protocol.

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

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

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

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

122

123 **Statistical analysis**

124 Values are expressed as the mean \pm standard deviation. Paired Student's *t* tests were
125 performed to test the significance of value changes measured at baseline, post-intervention,
126 and at the 5-year follow-up. We evaluated the differences among the genotypes by a
127 univariate ANOVA (PROC GLM in the SAS procedure) with adjustments for age, menstrual

128 status, and respective baseline values, when appropriate. Multiple regression analyses were
129 conducted to determine a combination of predictors for weight change. The
130 Hardy-Weinberg equilibrium was assessed using the χ^2 test. The data were analyzed with
131 the Statistical Analysis System (SAS), version 9.3 (SAS Institute Inc, Cary, NC, USA).

132

133 **Results**

134 The rs9939609 variant was in Hardy-Weinberg equilibrium ($P = 0.26$) and the minor allele
135 frequency was 0.213 (TT, $n = 31$, 66.0%; TA, $n = 12$, 25.5%; AA, $n = 4$, 8.5%). **Table 1**
136 shows subjects' characteristics at baseline, post-intervention, and at the 5-year follow-up
137 among the rs9939609 genotypes. At baseline, TAF and SAF were significantly greater in
138 subjects with the AA genotype than in those with the TT or TA genotypes. At the 5-year
139 follow-up, we obtained similar but clearer results, i.e., body weight, BMI, AC, fat mass, TAF,
140 and SAF were significantly greater in subjects with the AA genotype than in those with the
141 other genotypes. **Table 2** presents changes in measurement values from pre-intervention to
142 5-year follow-up and from post-intervention to 5-year follow-up by genotype group including
143 within-group analyses (paired t test) and group-difference analyses (ANOVA). In the
144 analyses comparing pre-intervention values with 5-year follow-up values, there was a trend
145 toward lower body fat-related values at the 5-year follow-up compared to pre-intervention in
146 all three groups. The decrease in fat mass was significantly smaller in subjects with the AA

147 genotype than in those with the TT or TA genotypes. The analyses of values from
148 post-intervention to 5-year follow-up showed most of the fat-related values of all three groups
149 had significantly increased at the 5-year follow-up. The increases in body weight, AC, fat
150 mass, TAF, and SAF were significantly greater in subjects with the AA genotype than in those
151 with the TT or TA genotypes. While significant increases were also observed in many of the
152 blood sample and blood pressure values during this period, no significant differences across
153 the genotypes were observed. In multiple regression analyses, the variation in rs9939609
154 was a significant and independent predictor ($P < 0.001$) for weight change during the 5-year
155 follow-up when age, menstrual status, and post-intervention body weight were included in the
156 model as adjusted values. The rs9939609 genotypes accounted for 19.3% (adjusted $R^2 =$
157 0.193) of the total body weight change variance.

158

159 **Discussion**

160 Our hypothesis is supported by the significantly greater increases in body weight, i.e.,
161 body fat, during the 5 years of non-intervention in subjects with the AA genotype than in
162 those with TT or TA genotypes. Previously, we reported that change in body fat during a
163 14-week lifestyle intervention tended to be smaller in subjects with AA genotype than in those
164 with other genotypes [8]. The results showed that AA genotype individuals may have more
165 difficulty reducing body fat than subjects with the other genotypes. On the other hand, the

166 previous study [8] also showed that all subjects, despite their genotype, decreased their body
167 weight significantly, and we concluded that the gene impact may not be great enough to
168 change body weight in response to a short-term intervention, and environmental and
169 behavioral factors may overcome the effects of genes on body-weight reduction. However,
170 the present study, over a much longer term, showed a notable association between *FTO*
171 genotype and body fat changes. Fredriksson et al. [15] indicated that the *FTO* gene may
172 participate in the central control of energy homeostasis. It is possible that the subjects with
173 the AA genotype in our study were unable to control the daily diet needed to maintain their
174 reduced body weight as well as the subjects with other genotypes could.

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

182 Our study did have limitations. First, sample size was small, and further research is
183 needed to confirm our results. However, the frequency for the A allele in this study (21.3%)
184 is similar to its frequency in the general Japanese population (21.5%) [6], suggesting this

185 study's subjects represent an unbiased population. Second, attendance rate at the 5-year
186 follow-up measurement session was low (50%). Mean body weight of all 47 subjects at the
187 5-year follow-up (61.5 ± 8.1 kg) was still lower ($P < 0.01$) than the mean pre-intervention
188 value (67.0 ± 8.6 kg), although it (61.5 ± 8.1 kg) was greater ($P < 0.01$) than the mean
189 post-intervention value (57.7 ± 7.3 kg). This suggests that the final analyses in the present
190 study included many subjects who suppressed body-weight rebound during the follow-up
191 period. This situation should be considered in the interpretation of our results. Third,
192 while the present study evaluated subjects' abdominal fat using a single-slice imaging
193 technique, a multiple-slice imaging technique might be better for detecting VAF change [18].

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

197

198 **Author Contributions**

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

203

204 **Acknowledgments and funding**

205 We thank Ms. Yukako Murotake for her support with this study. We are grateful to the
206 participants and staff members in the study. This study was supported by Meiji Yasuda Life
207 Foundation of Health and Welfare, and by Daiwa Securities Health Foundation.

208

209 **Conflict of interest**

210 The authors have nothing to declare.

211

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

	Baseline				Post-intervention				5-year follow up			
	TT	TA	AA	<i>P</i> ^a	TT	TA	AA	<i>P</i> ^a	TT	TA	AA	<i>P</i> ^a
	(n = 31)	(n = 12)	(n = 4)		(n = 31)	(n = 12)	(n = 4)		(n = 31)	(n = 12)	(n = 4)	
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 P^b	Changes from post-intervention to 5-year follow-up						Group difference P^c
	TT		TA		AA			TT		TA		AA		
	(n = 31)	P^a	(n = 12)	P^a	(n = 4)	P^a		(n = 31)	P^a	(n = 12)	P^a	(n = 4)	P^a	
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.