Yonago Acta medica 2012;55:29–40

Association of Gene Polymorphism of the Fat Mass and Obesity Associated Gene with Metabolic Syndrome: A Retrospective Cohort Study in Japanese Workers

Tomoka Kawajiri, Yoneatsu Osaki and Takuji Kishimoto

Division of Environmental and Preventive Medicine, Department of Social Medicine, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8503, Japan

To investigate whether gene polymorphism of the fat mass and obesity associated gene (FTO) is associated with metabolic syndrome (MS), we used two MS criteria, the National Cholesterol Education Program-Adult Treatment panel III (NCEP-ATPIII) definition in 2003 and the Japanese definition in 2005. Subjects were respectively 859 and 865 Japanese workers at a company in Shimane Prefecture, Japan. They were non-MS individuals in 1998 and had regular health checkups between 1998 and 2006. The Cox proportional hazard regression was used to predict MS. Three SNPs in the FTO, rs9939609, rs1121980 and rs1558902, were genotyped by the TaqMan PCR assay and a retrospective study was performed. The three SNPs in the FTO were significantly associated with body mass index, and rs1121980 and rs1558902 were associated with fasting plasma glucose. MS defined by the NCEP-ATPIII definition was significantly associated with additive and dominant models of rs9939609 and rs1121980, and the dominant model of rs1558902, even after adjusting for confounding factors such as age, sex and lifestyle. MS defined by the Japanese definition was significantly associated with the additive model of rs1121980 and additive and dominant models of rs1558902 in multivariate analysis. These results suggested that FTO gene polymorphisms, rs9939609, rs1121980 and rs1558902, were associated with an increased risk of MS among Japanese workers.

Key words: cohort study; fat mass and obesity associated gene; Japanese worker; metabolic syndrome; single nucleotide polymorphism

Metabolic syndrome (MS) is a cluster of risk factors for developing cardiovascular disease such as type 2 diabetes mellitus (T2DM), consisting of central obesity, high blood pressure, abnormal glucose tolerance and abnormal lipid profiles (Eckel et al., 2005; Grundy et al., 2005). The prevalence of MS has become increasingly common not only in Japan, but also in the world. It is because environmental factors contribute to the increased prevalence of MS, namely lifestyles (Fappa et al., 2008), and genetic factors are also related (Groop, 2000; Eckel et al., 2005).

Recently, part of a genome-wide association study found that several single nucleotide polymorphisms (SNPs) of the fat mass and obesity associated gene (FTO) were strongly associated with obesity and T2DM (Hinney et al., 2007; Scuteri et al., 2007).

Abbreviations: BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; FTO, fat mass and obesity associated gene; HDL, high density lipoprotein; MS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus

The human FTO is located on chromosome no.16 (16q12.2), which consists of 9 exons with an entire length of 410 kb (410,507 bp). The FTO encodes a 2-oxoglutarate-dependent nucleic acid demethylase and is widely expressed in many tissues, especially in the hypothalamus, which controls energy balance (Dina et al., 2007; Frayling et al., 2007). Studies in mice indicated that FTO mRNA levels were regulated by feeding and fasting (Gerken et al., 2007), and FTO knockout mice had postnatal growth delays, increased energy consumption and skinny body shapes (Fischer et al., 2009). Thus, the FTO may play an important role in controlling energy expenditure and may also be involved in energy homeostasis, but the exact function of the FTO and the mechanisms by which the FTO involves biological pathways remain unknown.

In previous genetic analyses, SNPs rs9939609, rs1121980 and rs1558902, located in intron1 of the FTO were strongly associated with obesity, BMI and MS in Caucasians and Hispanic Americans (Dina et al., 2007; Frayling et al., 2007; Hinney et al., 2007; Scuteri et al., 2007; Al-Attar et al., 2008; Andreasen et al., 2008; Sjögren et al., 2008; González-Sánchez et al., 2009), but not in African American, Oceanic or Chinese populations (Ohashi et al., 2007; Scuteri et al., 2007; Li et al., 2008). These reports suggest that the FTO is a race-specific gene. Studies in the Japanese failed to establish consistency in the association between FTO SNPs and obesity (Horikoshi et al., 2007; Omori et al., 2008; Hotta et al., 2010; Karasawa et al., 2010; Shimaoka et al., 2010). Concerning the Japanese, few reports indicated the association of FTO SNPs with MS, and some denied (Tabara et al., 2009; Shimaoka et al., 2010).

Therefore, in the present study, we analyzed the relationship between FTO SNPs, rs9939609, rs1121980 and rs1558902, and MS diagnosed by the NCEP-ATPIII and Japanese definitions among Japanese workers. To investigate the association in a more detailed manner than previous reports, a retrospective cohort study enrolling lifestyle factors as considerable variables was performed.

Materials and Methods

Subjects

Subjects consisted of 859 persons (486 males and 373 females) and 865 persons (498 males and 367 females) under the NCEP-ATPIII and Japanese definitions for MS, respectively. They were employees of an industry in the Izumo region of Shimane Prefecture in Japan who had consistently undergone health check-ups between 1998 and 2006 and were non-MS individuals in 1998. The average age (± SD) was 37.69 ± 8.74 years for the subjects under NCEP-ATPIII and 37.75 ± 8.72 years for those under the Japanese definition. A retrospective cohort study of the relationship between FTO polymorphism and the prevalence of MS for the period between 1998 and 2006 was performed. All subjects gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Tottori University (permission number, G63).

Subjects completed health check-ups consisting of measurements of the height, weight, body mass index (BMI), blood pressure (BP) and history taking (drinking, smoking, eating, exercise and sleeping habits). The BMI was calculated as the weight in kilogram divided by the square of the height in meter. Obesity was defined as a BMI ≥ 25.0 kg/m^2, as defined by the Japan Society of Obesity. Blood pressure was measured once on the health-check day in a sitting position with a standard sphygmomanometer. The first and fifth Korotkoff sounds were used to determine systolic BP and diastolic BP, respectively. Blood tests included high-density lipoprotein (HDL) cholesterol, triglycerides and fasting plasma glucose (FPG). Plasma glucose levels were determined by the hexokinase-G-6-PDH method (Wako, Tokyo, Japan.) We investigated lifestyles, alcohol drinking habits (no drinking, occasionally, nearly every day), cigarette smoking habits (no smoking, quit, smoking), eating habits (eat various food, consider balance slightly, rarely consider balance), exercise habits (frequently,

Table 1a. Clinical characteristics per genotype in rs9939609

		TT	TA	AA	TT + TA	TA + AA	All	*P* value*	*P* value†	*P* value‡
NCEP-ATPIII										
Number		570	251	38	821	570	859			
Age	(yr)	37.76 ± 8.59	37.32 ± 9.13	39.07 ± 8.56	37.63 ± 8.75	37.55 ± 9.06	37.69 ± 8.74	0.487	0.740	0.318
BMI	(kg/m²)	22.09 ± 2.98	22.54 ± 3.22	23.32 ± 3.52	22.23 ± 3.06	22.64 ± 3.26	22.28 ± 3.09	0.018	0.015	0.034
SBP	(mmHg)	115.29 ± 14.69	116.05 ± 15.58	116.95 ± 12.33	115.52 ± 14.96	116.17 ± 15.17	115.58 ± 14.85	0.672	0.411	0.563
DBP	(mmHg)	71.61 ± 10.54	71.92 ± 10.71	72.32 ± 11.36	71.7 ± 10.58	71.97 ± 10.77	71.73 ± 10.61	0.874	0.636	0.728
HDL-C	(mg/dL)	66.61 ± 17.26	65.39 ± 16.64	69.45 ± 14.38	66.24 ± 17.06	65.93 ± 16.39	66.38 ± 16.96	0.335	0.580	0.254
TG	(mg/dL)	95.96 ± 66.78	93.98 ± 59.06	89.63 ± 50.89	95.36 ± 64.48	93.4 ± 57.99	95.1 ± 63.93	0.795	0.580	0.590
FPG	(mg/dL)	95.66 ± 13.33	95.88 ± 17.28	96.55 ± 10.77	95.72 ± 14.64	95.97 ± 16.56	95.76 ± 14.49	0.924	0.768	0.730
Japanese definition										
Number		573	253	39	826	292	865			
Age	(yr)	37.79 ± 8.55	37.45 ± 9.13	39.1 ± 8.46	37.69 ± 8.73	37.67 ± 9.05	37.75 ± 8.72	0.533	0.841	0.322
BMI	(kg/m²)	22.14 ± 2.98	22.56 ± 3.05	23.42 ± 3.52	22.27 ± 3.01	22.67 ± 3.12	22.32 ± 3.04	0.013	0.015	0.021
SBP	(mmHg)	115.46 ± 14.72	116.08 ± 15.3	117.13 ± 12.22	115.65 ± 14.9	116.22 ± 14.91	115.71 ± 14.78	0.712	0.476	0.541
DBP	(mmHg)	71.72 ± 10.6	72.04 ± 10.67	72.62 ± 11.36	71.82 ± 10.62	72.12 ± 10.75	71.85 ± 10.65	0.833	0.606	0.648
HDL-C	(mg/dL)	66.16 ± 17.47	64.97 ± 16.98	68.64 ± 15.06	65.79 ± 17.32	65.46 ± 16.76	65.92 ± 17.23	0.396	0.573	0.313
TG	(mg/dL)	98.91 ± 72.86	96.39 ± 61.41	93.69 ± 56.26	98.14 ± 69.52	96.03 ± 60.66	97.94 ± 68.96	0.823	0.561	0.694
FPG	(mg/dL)	95.64 ± 13.17	95.99 ± 17.3	96.72 ± 10.68	95.75 ± 14.55	96.09 ± 16.56	95.79 ± 14.4	0.873	0.666	0.681

Data are numbers of subjects, divided into genotype groups, and values are mean ± SD.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high density lipoprotein-cholesterol; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III; SBP, systolic blood pressure; TG, triglyceride.
* Additive model (analysis of variance): comparison among 3 groups (TT versus TA versus AA).
† Dominant model (*t*-test): comparison of TT + TA with AA.
‡ Recessive model (*t*-test): comparison of TT with TA + AA.

sometimes, no exercise) and sleeping habits (sufficiency, usual, insufficiency).

Definition of metabolic syndrome

The NCEP-ATP III definition includes the presence of three or more of the following five criteria: central obesity (waist circumference ≥ 90 cm for males, ≥ 80 cm for females), elevated BP (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), elevated triglycerides (≥ 150 mg/dL), reduced HDL cholesterol (< 40 mg/dL for males, < 50 mg/dL for females), and elevated FPG (≥ 110 mg/dL). However, in this study, central obesity was defined as a BMI > 25 kg/m², as defined by the Japan Society of Obesity. A previous diagnosis of T2DM was considered to be evidence of an elevated FPG.

The Japanese definition includes the same five criteria as the NCEP-ATPIII definition, but raised triglycerides and/or reduced HDL cholesterol levels are regarded as a single dyslipidemia criterion. In addition, central obesity must be present as well as two or more of the other four factors. The Japanese definition includes: waist circumference ≥ 85 cm for males and ≥ 90 cm for females; systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg; triglycerides ≥ 150 mg/dL or HDL < 40 mg/dL in males and < 50 mg/dL in females; FPG ≥ 100 mg/dL. Central obesity was defined as a BMI > 25 kg/m², similar to the NCEP-ATP III definition. Furthermore, the Japanese definition stipulates that all subjects receiving pharmacological treatment for hypertension were considered to have elevated BP, all subjects receiving fibrates were considered to have elevated triglycerides levels, and all subjects previously diagnosed with T2DM were considered to have raised FPG.

Identification of FTO polymorphism

Peripheral blood samples, which had been collected for the health check-up in 1998 and remained after blood tests, were used for the identification of three SNPs rs9939609, rs1121980 and rs1558902 in the FTO. Genomic DNA was extracted from these samples using a QIAamp DNA Blood Kit

Table 1b. Lifestyle characteristics per genotypes in rs9939609

	TT	TA	AA	TT + TA	TA + AA	All	*P* value*	*P* value†	*P* value‡
NCEP-ATPIII									
Sex									
Male	321 (56.3)	147 (58.6)	18 (47.4)	468 (57.0)	165 (57.1)	486 (56.6)	0.421	0.828	0.241
Female	249 (43.7)	104 (41.4)	20 (52.6)	353 (43.0)	124 (42.9)	373 (43.4)			
Alchol drinking habit									
No drinking	252 (44.4)	101 (40.6)	22 (59.5)	353 (43.3)	123 (43.0)	375 (44.0)	0.300	0.914	0.149
Occasionally	178 (31.4)	83 (33.3)	8 (21.6)	261 (32.0)	91 (31.8)	269 (31.5)			
Nearly every day	137 (24.2)	65 (26.1)	7 (18.9)	202 (24.8)	72 (25.2)	209 (24.5)			
Smoking habit									
Never smoked	343 (60.3)	141 (56.2)	26 (68.4)	484 (59.0)	167 (57.8)	510 (59.4)	0.245	0.185	0.473
Ex-smokers	23 (4.0)	18 (7.2)	2 (5.3)	41 (5.0)	20 (6.9)	43 (5.0)			
Current smokers	203 (35.7)	92 (36.7)	10 (26.3)	295 (36.0)	102 (35.3)	305 (35.5)			
Balance of food									
Eat various food	227 (40.0)	108 (43.0)	15 (39.5)	335 (40.9)	123 (42.6)	350 (40.8)	0.899	0.658	0.982
Consider balance slightly	207 (36.4)	91 (36.3)	14 (36.8)	298 (36.4)	105 (36.3)	312 (36.4)			
Rarely consider balance	134 (23.6)	52 (20.7)	9 (23.7)	186 (22.7)	61 (21.1)	195 (22.8)			
Exercise habit									
Frequently	38 (6.7)	20 (8.0)	2 (5.3)	58 (7.1)	22 (7.6)	60 (7.0)	0.943	0.849	0.900
Sometimes	172 (30.2)	72 (28.7)	12 (31.6)	244 (29.8)	84 (29.1)	256 (29.8)			
No exercise	359 (63.1)	159 (63.3)	24 (63.2)	518 (63.2)	183 (63.3)	542 (63.2)			
Sleeping habit									
Sufficiently	93 (16.3)	48 (19.2)	7 (18.4)	141 (17.2)	55 (19.1)	148 (17.3)	0.671	0.502	0.526
Normal	411 (72.2)	176 (70.4)	29 (76.3)	587 (71.7)	205 (71.2)	616 (71.9)			
Insufficiently	65 (11.4)	26 (10.4)	2 (5.3)	91 (11.1)	28 (9.7)	93 (10.9)			
Japanese definition									
Sex									
Male	328 (57.2)	151 (59.7)	19 (48.7)	479 (58.0)	170 (55.8)	498 (57.6)	0.419	0.783	0.252
Female	245 (42.8)	102 (40.3)	20 (51.3)	347 (42.0)	122 (44.2)	367 (42.4)			
Alchol drinking habit									
No drinking	251 (44.0)	103 (41.0)	22 (57.9)	354 (43.1)	125 (44.3)	376 (43.8)	0.425	0.975	0.200
Occasionally	178 (31.2)	83 (33.1)	9 (23.7)	261 (31.8)	92 (31.1)	270 (31.4)			
Nearly every day	141 (24.7)	65 (25.9)	7 (18.4)	206 (25.1)	72 (24.6)	213 (24.8)			
Smoking habit									
Never smoked	340 (59.4)	140 (55.3)	27 (69.2)	480 (58.2)	167 (60.4)	507 (58.7)	0.134	0.118	0.369
Ex-smokers	24 (4.2)	20 (7.9)	2 (5.1)	44 (5.3)	22 (3.9)	46 (5.3)			
Current smokers	208 (36.4)	93 (36.8)	10 (25.6)	301 (36.5)	103 (35.7)	311 (36.0)			
Balance of food									
Eat various food	230 (40.3)	110 (43.5)	16 (41.0)	340 (41.3)	126 (43.2)	356 (41.3)	0.894	0.619	0.997
Consider balance slightly	207 (36.3)	91 (36.0)	14 (35.9)	298 (36.2)	105 (37.8)	312 (36.2)			
Rarely consider balance	134 (23.5)	52 (20.6)	9 (23.1)	186 (22.6)	61 (19.0)	195 (22.6)			
Exercise habit									
Frequently	39 (6.8)	19 (7.5)	2 (5.1)	58 (7.0)	21 (6.0)	60 (6.9)	0.965	0.897	0.895
Sometimes	171 (29.9)	71 (28.1)	12 (30.8)	242 (29.3)	83 (28.9)	254 (29.4)			
No exercise	362 (63.3)	163 (64.4)	25 (64.1)	525 (63.6)	188 (65.2)	550 (63.7)			
Sleeping habit									
Sufficiently	93 (16.3)	49 (19.4)	7 (17.9)	142 (17.2)	56 (15.8)	149 (17.3)	0.579	0.382	0.507
Normal	413 (72.2)	178 (70.6)	30 (76.9)	591 (71.7)	208 (70.2)	621 (72.0)			
Insufficiently	66 (11.5)	25 (9.9)	2 (5.1)	91 (11.0)	27 (9.3)	93 (10.8)			

( ), %.
NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III.
* Additive model.
† Dominant model.
‡ Recessive model (χ^2 test).

(Qiagen, Hilden, Germany). These SNPs were genotyped using TaqMan PCR methods with the following probes: C_30090620_10 for rs9939609, C_2031261_10 for rs1121980 and C_891711_10 for rs1558902 (Applied Biosystems, Foster City, CA).

Table 2a. Clinical characteristics per genotype in rs1121980

		GG	GA	AA	GG + GA	GA + AA	All	*P* value*	*P* value†	*P* value‡
NCEP-ATPIII										
Number		515	297	47	812	344	859			
Age	(yr)	37.72 ± 8.64	37.46 ± 8.94	38.83 ± 8.73	37.63 ± 8.75	37.65 ± 8.91	37.69 ± 8.74	0.607	0.910	0.360
BMI	(kg/m^2)	22.11 ± 2.95	22.38 ± 3.15	23.6 ± 3.74	22.21 ± 3.03	22.55 ± 3.26	22.28 ± 3.08	0.005	0.040	0.003
SBP	(mmHg)	115.56 ± 14.76	115.53 ± 15.46	116.13 ± 11.84	115.55 ± 15.01	115.62 ± 15	115.58 ± 14.85	0.967	0.960	0.796
DBP	(mmHg)	71.72 ± 10.47	71.89 ± 10.88	70.85 ± 10.53	71.78 ± 10.62	71.75 ± 10.83	71.73 ± 10.61	0.822	0.967	0.559
HDL-C	(mg/dL)	66.57 ± 17.21	65.87 ± 16.89	67.43 ± 14.67	66.32 ± 17.09	66.08 ± 16.59	66.38 ± 16.96	0.773	0.676	0.663
TG	(mg/dL)	95.15 ± 63.12	95.58 ± 66.43	91.64 ± 57.41	95.3 ± 64.31	95.04 ± 65.21	95.1 ± 63.93	0.926	0.981	0.703
FPG	(mg/dL)	95.7 ± 13.54	95.1 ± 9.47	100.57 ± 35.5	95.48 ± 12.21	95.85 ± 15.81	95.76 ± 14.48	0.055	0.884	0.019
Japanese definition										
Number		517	300	48	817	348	865			
Age	(yr)	37.75 ± 8.61	37.57 ± 8.93	38.85 ± 8.64	37.69 ± 8.72	37.75 ± 8.89	37.75 ± 8.72	0.640	0.997	0.368
BMI	(kg/m^2)	22.15 ± 2.96	22.4 ± 3.01	23.67 ± 3.73	22.24 ± 2.98	22.57 ± 3.15	22.32 ± 3.04	0.003	0.044	0.001
SBP	(mmHg)	115.76 ± 14.8	115.54 ± 15.22	116.29 ± 11.78	115.68 ± 14.95	115.64 ± 14.78	115.71 ± 14.78	0.942	0.910	0.781
DBP	(mmHg)	71.84 ± 10.56	72 ± 10.84	71.13 ± 10.6	71.9 ± 10.66	71.88 ± 10.8	71.85 ± 10.65	0.869	0.955	0.626
HDL-C	(mg/dL)	66.14 ± 17.41	65.4 ± 17.26	66.81 ± 15.13	65.87 ± 17.35	65.59 ± 16.97	65.92 ± 17.23	0.782	0.645	0.713
TG	(mg/dL)	97.86 ± 69.19	98.55 ± 69.94	94.9 ± 61.12	98.12 ± 69.42	98.05 ± 68.72	97.94 ± 68.96	0.943	0.970	0.753
FPG	(mg/dL)	95.64 ± 13.36	95.27 ± 9.64	100.63 ± 35.12	95.51 ± 12.12	96.01 ± 15.83	95.79 ± 14.4	0.053	0.717	0.017

Data are numbers of subjects, divided into genotype groups, and values are mean ± SD.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high density lipoprotein-cholesterol; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III; SBP, systolic blood pressure; TG, triglyceride.
* Additive model (analysis of variance): comparison among 3 groups (GG versus GA versus AA).
† Dominant model (*t*-test): comparison of GG + GA with AA.
‡ Recessive model (*t*-test): comparison of GG with GA + AA.

Statistical analysis

We used Student's *t*-test and analysis of variance to compare continuous variables and the χ^2 test to compare categorical variables. Quantitative variables were expressed as the mean ± SD. The hazard ratio and 95% confidence interval of each factor for incidence of MS were estimated by univariate and multivariate Cox proportional-hazards models adjusted for sex, age, smoking, drinking, exercise, eating and sleeping habits. The onset of metabolic syndrome was defined as the day of health checkup when an employee had a diagnosis of metabolic syndrome. Analysis was performed using PASW Statistics 18 (SPSS Japan, Tokyo). The significance level was set to *P* values of less than 0.05.

Results

The distributions of genotype and characteristics of study subjects are shown in Tables 1 to 3. The relative frequencies of TT homozygote, TA heterozygote and AA homozygote in rs9939609 were 66.4%, 29.2%, 4.4% and 66.2%, 29.3%, 4.5% according to the NCEP-ATP III and Japanese definitions, respectively. Those of GG, GA and AA in rs1121980 were 60.0%, 34.6%, 5.4% and 59.8%, 34.7%, 5.5% according to the NCEP-ATP III and Japanese definitions, respectively. Those of TT, TA and AA in rs1558902 were 66.6%, 29.1%, 4.3% and 66.5%, 29.1%, 4.4% according to the NCEP-ATP III and Japanese definitions, respectively.

In both the NCEP-ATP III and Japanese definitions, the three SNPs, rs9939609, rs1121980 and rs1558902, were significantly associated with the BMI, as shown in Tables 1a, 2a and 3a, but there was no association between genotypes and lifestyles, such as drinking, smoking, eating, exercise and sleeping habits. Moreover, for rs1121980 and rs1558902, there were significant differences on FPG (Tables 1b, 2b and 3b).

Results of univariate analyses of the hazard ratios for MS of gene polymorphism and the indices are shown in Table 4. According to the NCEP-ATP III definition, the hazard ratios of sex, age, additive

Table 2b. Lifestyle characteristics per genotypes in rs1121980

	GG	GA	AA	GG + GA	GA + AA	All	*P* value*	*P* value†	*P* value‡
NCEP-ATPIII									
Sex									
Male	297 (57.7)	165 (55.6)	24 (51.1)	462 (56.9)	189 (54.9)	486 (56.6)	0.619	0.429	0.433
Female	218 (42.3)	132 (44.4)	23 (48.9)	350 (43.1)	155 (45.1)	373 (43.4)			
Alchol drinking habit									
No drinking	216 (42.2)	132 (44.7)	27 (58.7)	348 (43.1)	159 (46.6)	375 (44.0)	0.111	0.205	0.092
Occasionally	160 (31.3)	100 (33.9)	9 (19.6)	260 (32.2)	109 (32.0)	269 (31.5)			
Nearly every day	136 (26.6)	63 (21.4)	10 (21.7)	199 (24.7)	73 (21.4)	209 (24.5)			
Smoking habit									
Never smoked	301 (58.6)	179 (60.3)	30 (63.8)	480 (59.2)	209 (60.8)	510 (59.4)	0.649	0.739	0.325
Ex-smokers	25 (4.9)	14 (4.7)	4 (8.5)	39 (4.8)	18 (5.2)	43 (5.0)			
Current smokers	188 (36.6)	104 (35.0)	13 (27.7)	292 (36.0)	117 (34.0)	305 (35.5)			
Balance of food									
Eat various food	209 (40.7)	123 (41.4)	18 (38.3)	332 (41.0)	141 (41.0)	350 (40.8)	0.621	0.983	0.285
Consider balance slightly	188 (36.6)	110 (37.0)	14 (29.8)	298 (36.8)	124 (36.0)	312 (36.4)			
Rarely consider balance	116 (22.6)	64 (21.5)	15 (31.9)	180 (22.2)	79 (23.0)	195 (22.8)			
Exercise habit									
Frequently	35 (6.8)	23 (7.7)	2 (4.3)	58 (7.2)	25 (7.3)	60 (7.0)	0.846	0.906	0.656
Sometimes	156 (30.4)	84 (28.3)	16 (34.0)	240 (29.6)	100 (29.1)	256 (29.8)			
No exercise	323 (62.8)	190 (64.0)	29 (61.7)	513 (63.3)	219 (63.7)	542 (63.2)			
Sleeping habit									
Sufficiently	87 (16.9)	51 (17.2)	10 (21.3)	138 (17.0)	61 (17.8)	148 (17.3)	0.609	0.948	0.286
Normal	371 (72.2)	210 (70.9)	35 (74.5)	581 (71.7)	245 (71.4)	616 (71.9)			
Insufficiently	56 (10.9)	35 (11.8)	2 (4.3)	91 (11.2)	37 (10.8)	93 (10.9)			
Japanese definition									
Sex									
Male	303 (58.6)	170 (56.7)	25 (52.1)	473 (57.9)	195 (56.0)	498 (57.6)	0.631	0.453	0.429
Female	214 (41.4)	130 (43.3)	23 (47.9)	344 (42.1)	153 (44.0)	367 (42.4)			
Alchol drinking habit									
No drinking	214 (41.6)	135 (45.3)	27 (57.4)	349 (43.0)	162 (47.0)	376 (43.8)	0.101	0.108	0.135
Occasionally	160 (31.1)	100 (33.6)	10 (21.3)	260 (32.0)	110 (31.9)	270 (31.4)			
Nearly every day	140 (27.2)	63 (21.1)	10 (21.3)	203 (25.0)	73 (21.2)	213 (24.8)			
Smoking habit									
Never smoked	298 (57.8)	178 (59.3)	31 (64.6)	476 (58.3)	209 (60.1)	507 (58.7)	0.630	0.635	0.319
Ex-smokers	26 (5.0)	16 (5.3)	4 (8.3)	42 (5.1)	20 (5.7)	46 (5.3)			
Current smokers	192 (37.2)	106 (35.3)	13 (27.1)	298 (36.5)	119 (34.2)	311 (36.0)			
Balance of food									
Eat various food	211 (41.0)	126 (42.0)	19 (39.6)	337 (41.3)	145 (41.7)	356 (41.3)	0.631	0.965	0.300
Consider balance slightly	188 (36.5)	110 (36.7)	14 (29.2)	298 (36.6)	124 (35.6)	312 (36.2)			
Rarely consider balance	116 (22.5)	64 (21.3)	15 (31.3)	180 (22.1)	79 (22.7)	195 (22.6)			
Exercise habit									
Frequently	36 (7.0)	22 (7.3)	2 (4.2)	58 (7.1)	24 (6.9)	60 (6.9)	0.851	0.873	0.656
Sometimes	155 (30.0)	83 (27.7)	16 (33.3)	238 (29.2)	99 (28.4)	254 (29.4)			
No exercise	325 (63.0)	195 (65.0)	30 (62.5)	520 (63.7)	225 (64.7)	550 (63.7)			
Sleeping habit									
Sufficiently	87 (16.9)	52 (17.4)	10 (20.8)	139 (17.1)	62 (17.9)	149 (17.3)	0.632	0.899	0.286
Normal	372 (72.1)	213 (71.2)	36 (75.0)	585 (71.8)	249 (71.8)	621 (72.0)			
Insufficiently	57 (11.0)	34 (11.4)	2 (4.2)	91 (11.2)	36 (10.4)	93 (10.8)			

( ), %.
NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III.
* Additive model.
† Dominant model.
‡ Recessive model (χ^2 test).

and dominant models of rs9939609 and rs1121980 and the dominant model of rs1558902 were significantly high. According to the Japanese definition, that of only sex was significantly high. In both definitions, drinking and smoking habits showed significantly high risks, but regarding balance of food,

Table 3a. Clinical characteristics per genotype in rs1558902

		TT	TA	AA	TT + TA	TA + AA	All	*P* value*	*P* value†	*P* value‡
NCEP-ATPIII										
Number		572	250	37	822	287	859			
Age	(yr)	37.73 ± 8.58	37.36 ± 9.14	39.41 ± 8.54	37.62 ± 8.75	37.62 ± 9.08	37.69 ± 8.74	0.407	0.864	0.224
BMI	(kg/m2)	22.08 ± 2.92	22.55 ± 3.25	23.58 ± 3.95	22.22 ± 3.03	22.68 ± 3.36	22.28 ± 3.08	0.005	0.008	0.009
SBP	(mmHg)	115.37 ± 14.78	115.86 ± 15.41	117.03 ± 12.14	115.52 ± 14.96	116.01 ± 15.01	115.58 ± 14.85	0.757	0.548	0.546
DBP	(mmHg)	71.62 ± 10.59	71.93 ± 10.6	72.16 ± 11.17	71.71 ± 10.59	71.96 ± 10.65	71.73 ± 10.61	0.899	0.658	0.801
HDL-C	(mg/dL)	66.73 ± 17.3	65.14 ± 16.45	69.3 ± 14.69	66.25 ± 17.05	65.67 ± 16.27	66.38 ± 16.96	0.262	0.389	0.285
TG	(mg/dL)	95.08 ± 63.8	95.72 ± 66.03	91.35 ± 51.67	95.27 ± 64.45	95.16 ± 64.29	95.1 ± 63.93	0.928	0.986	0.715
FPG	(mg/dL)	95.47 ± 13.07	95.36 ± 9.79	102.95 ± 39.64	95.44 ± 12.16	96.34 ± 16.96	95.76 ± 14.48	0.008	0.405	0.002
Japanese definition										
Number		575	252	38	827	290	865			
Age	(yr)	37.76 ± 8.55	37.48 ± 9.15	39.42 ± 8.43	37.67 ± 8.73	37.73 ± 9.06	37.75 ± 8.72	0.441	0.968	0.228
BMI	(kg/m2)	22.12 ± 2.92	22.56 ± 3.09	23.67 ± 3.94	22.26 ± 2.98	22.71 ± 3.23	22.32 ± 3.04	0.003	0.008	0.005
SBP	(mmHg)	115.54 ± 14.81	115.89 ± 15.14	117.21 ± 12.03	115.64 ± 14.9	116.06 ± 14.76	115.71 ± 14.78	0.777	0.622	0.523
DBP	(mmHg)	71.73 ± 10.66	72.05 ± 10.57	72.47 ± 11.19	71.83 ± 10.63	72.1 ± 10.63	71.85 ± 10.65	0.865	0.625	0.714
HDL-C	(mg/dL)	66.28 ± 17.52	64.71 ± 16.79	68.47 ± 15.36	65.8 ± 17.31	65.2 ± 16.63	65.92 ± 17.23	0.312	0.384	0.351
TG	(mg/dL)	98.02 ± 70.18	98.13 ± 68.03	95.47 ± 56.95	98.05 ± 69.49	97.78 ± 66.6	97.94 ± 68.96	0.975	0.962	0.822
FPG	(mg/dL)	95.45 ± 12.92	95.48 ± 9.92	102.95 ± 39.11	95.46 ± 12.08	96.46 ± 16.96	95.79 ± 14.4	0.007	0.332	0.002

Data are numbers of subjects, divided into genotype groups, and values are mean ± SD.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high density lipoprotein-cholesterol; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III; SBP, systolic blood pressure; TG, triglyceride.
* Additive model (analysis of variance): comparison among 3 groups (TT versus TA versus AA).
† Dominant model (*t*-test): comparison of TT + TA with AA.
‡ Recessive model (*t*-test): comparison of TT with TA + AA.

considering balance showed a significantly low risk.

After adjusting for age, sex and lifestyle (drinking, smoking, eating, exercise and sleeping habit), results of multivariate analysis are shown in Table 5. According to the NCEP-ATP III definition, results were almost the same as single variant analysis. But the hazard ratio was significantly higher in the additive model of rs1558902. In the Japanese definition, the additive model of rs1558902 was a significant high risk for MS.

Discussion

In the present study, a retrospective cohort study over 9 years was performed in Japanese workers to investigate the association of three SNPs, rs9939609, rs1121980 and rs1558902, in the FTO with the incidence of MS diagnosed by the NCEP-ATPIII and Japanese definitions.

The frequencies of genotypes and alleles in the FTO were similar to those in other studies in Japanese (Hotta et al., 2008; Shimaoka et al., 2010). In contrast, those of genotypes and alleles in other ethnic groups were remarkably different from those in Japanese. By the HapMap database (http://hapmap.ncbi.nlm.nih.gov/), the frequencies of the rs9939609 A allele were 0.14 in Chinese and Japanese, 0.45 in CEPH Europeans and 0.52 in Yorubans. Therefore, the effect and importance of genetic factors makes differences among ethnic groups.

According to the NCEP-ATPIII definition, the three SNPs in the FTO were significantly associated with BMI. Moreover, rs1121980 and rs1558902 were associated with FPG. These results were consistent with previous studies (Horikoshi et al., 2007; Hotta et al., 2008; Tabara et al., 2009; Hotta et al., 2010; Shimaoka et al., 2010). However, in both the NCEP-ATPIII and Japanese definitions, none of the three SNPs were associated with sex and lifestyle (drinking, smoking, eating, exercise and sleeping habit). The three SNPs clarified by not only univariate, but also multivariate analysis adjusting for age, sex and lifestyle were significantly associated with the incidence of MS diagnosed by the NCEP-ATPIII definition. By the Japanese definition, only rs1558902

Table 3b. Lifestyle characteristics per genotypes in rs1558902

	TT	TA	AA	TT + TA	TA + AA	All	P value*	P value†	P value‡
NCEP-ATPIII									
Sex									
Male	327 (57.2)	142 (56.8)	17 (45.9)	469 (57.1)	159 (55.4)	486 (56.6)	0.409	0.622	0.182
Female	245 (42.8)	108 (43.2)	20 (54.1)	353 (42.9)	128 (44.6)	373 (43.4)			
Alcohol drinking habit									
No drinking	246 (43.2)	107 (43.1)	22 (61.1)	353 (43.2)	129 (45.4)	375 (44.0)	0.274	0.718	0.098
Occasionally	179 (31.5)	83 (33.5)	7 (19.4)	262 (32.1)	90 (31.7)	269 (31.5)			
Nearly every day	144 (25.3)	58 (23.4)	7 (19.4)	202 (24.7)	65 (22.9)	209 (24.5)			
Smoking habit									
Never smoked	340 (59.5)	144 (57.6)	26 (70.3)	484 (59.0)	170 (59.2)	510 (59.4)	0.659	0.979	0.342
Ex-smokers	28 (4.9)	13 (5.2)	2 (5.4)	41 (5.0)	15 (5.2)	43 (5.0)			
Current smokers	203 (35.6)	93 (37.2)	9 (24.3)	296 (36.1)	102 (35.5)	305 (35.5)			
Balance of food									
Eat various food	227 (39.8)	108 (43.2)	15 (40.5)	335 (40.9)	123 (42.9)	350 (40.8)	0.890	0.641	0.970
Consider balance slightly	209 (36.7)	90 (36.0)	13 (35.1)	299 (36.5)	103 (35.9)	312 (36.4)			
Rarely consider balance	134 (23.5)	52 (20.8)	9 (24.3)	186 (22.7)	61 (21.3)	195 (22.8)			
Exercise habit									
Frequently	39 (6.8)	19 (7.6)	2 (5.4)	58 (7.1)	21 (7.3)	60 (7.0)	0.936	0.837	0.890
Sometimes	174 (30.5)	70 (28.0)	12 (32.4)	244 (29.7)	82 (28.6)	256 (29.8)			
No exercise	358 (62.7)	161 (64.4)	23 (62.2)	519 (63.2)	184 (64.1)	542 (63.2)			
Sleeping habit									
Sufficiently	94 (16.5)	48 (19.3)	6 (16.2)	142 (17.3)	54 (18.9)	148 (17.3)	0.675	0.673	0.520
Normal	414 (72.5)	173 (69.5)	29 (78.4)	587 (71.6)	202 (70.6)	616 (71.9)			
Insufficiently	63 (11.0)	28 (11.2)	2 (5.4)	91 (11.1)	30 (10.5)	93 (10.9)			
Japanese definition									
Sex									
Male	334 (58.1)	146 (57.9)	18 (47.4)	480 (58.0)	164 (56.6)	498 (57.6)	0.428	0.666	0.193
Female	241 (41.9)	106 (42.1)	20 (52.6)	347 (42.0)	126 (43.4)	367 (42.4)			
Alcohol drinking habit									
No drinking	245 (42.8)	109 (43.6)	22 (59.5)	354 (43.1)	131 (45.6)	376 (43.8)	0.328	0.560	0.143
Occasionally	179 (31.3)	83 (33.2)	8 (21.6)	262 (31.9)	91 (31.7)	270 (31.4)			
Nearly every day	148 (25.9)	58 (23.2)	7 (18.9)	206 (25.1)	65 (22.6)	213 (24.8)			
Smoking habit									
Never smoked	337 (58.7)	143 (56.7)	27 (71.1)	480 (58.1)	170 (58.6)	507 (58.7)	0.533	0.876	0.258
Ex-smokers	29 (5.1)	15 (6.0)	2 (5.3)	44 (5.3)	17 (5.9)	46 (5.3)			
Current smokers	208 (36.2)	94 (37.3)	9 (23.7)	302 (36.6)	103 (35.5)	311 (36.0)			
Balance of food									
Eat various food	230 (40.1)	110 (43.7)	16 (42.1)	340 (41.2)	230 (40.1)	356 (41.3)	0.877	0.597	0.966
Consider balance slightly	209 (36.5)	90 (35.7)	13 (34.2)	299 (36.2)	209 (36.5)	312 (36.2)			
Rarely consider balance	134 (23.4)	52 (20.6)	9 (23.7)	186 (22.5)	134 (23.4)	195 (22.6)			
Exercise habit									
Frequently	40 (7.0)	18 (7.1)	2 (5.3)	58 (7.0)	20 (6.9)	60 (6.9)	0.929	0.787	0.892
Sometimes	173 (30.1)	69 (27.4)	12 (31.6)	242 (29.3)	81 (27.9)	254 (29.4)			
No exercise	361 (62.9)	165 (65.5)	24 (63.2)	526 (63.7)	189 (65.2)	550 (63.7)			
Sleeping habit									
Sufficiently	94 (16.4)	49 (19.5)	6 (15.8)	143 (17.3)	55 (19.0)	149 (17.3)	0.618	0.586	0.486
Normal	416 (72.5)	175 (69.7)	30 (78.9)	591 (71.6)	205 (70.9)	621 (72.0)			
Insufficiently	64 (11.1)	27 (10.8)	2 (5.3)	91 (11.0)	29 (10.0)	93 (10.8)			

( ), %.
NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III.
* Additive model.
† Dominant model.
‡ Recessive model (χ^2 test).

was significantly associated with MS. Moreover, in rs1121980 and rs1558902, the hazard ratio for MS by the NCEP-ATPIII definition became higher as the number of risk alleles increased. Thus, it was suggested that the A allele at three SNPs is a risk allele and is at substantially increased risk of MS.

Table 4. Hazard ratios of gender, age and lifestyle for MS by genotype (univariate analysis)

			NCEP-ATPIII			Japanese definition		
			Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Sex	Female		1.00			1.00		
	Male		4.46	2.95–6.74	0.00	7.01	3.86–12.75	0
Age			1.02	1.00–1.04	0.02	1.01	0.99–1.03	0.53
rs9939609	Additive model	TT	1.00			1.00		
		TA	1.52	1.10–2.08	0.01	1.38	0.93–2.03	0.10
		AA	1.31	0.63–2.70	0.46	1.33	0.58–3.05	0.51
	Dominant model	TT	1.00			1.00		
		TA + AA	1.49	1.09–2.02	0.01	1.37	0.95–1.99	0.09
	Recessive model	TT + TA	1.00			1.00		
		AA	1.140	0.56–2.32	0.72	1.19	0.52–2.71	0.68
rs1121980	Additive model	GG	1.00			1.00		
		GA	1.57	1.14–2.16	0.01	1.19	0.80–1.74	0.39
		AA	1.78	0.92–3.41	0.08	1.82	0.93–3.55	0.07
	Dominant model	GG	1.00			1.00		
		GA + AA	1.60	1.17–2.16	0.00	1.27	0.88–1.83	0.2
	Recessive model	GG + GA	1.00			1.00		
		AA	1.520	0.80–2.89	0.20	1.7	0.89–3.26	0.11
rs1558902	Additive model	TT	1.00			1.00		
		TA	1.33	0.97–1.83	0.08	1.37	0.93–2.03	0.11
		AA	1.76	0.98–3.15	0.06	1.88	0.9–3.91	0.09
	Dominant model	TT	1.00			1.00		
		TA + AA	1.39	1.02–1.88	0.04	1.44	0.99–2.08	0.05
	Recessive model	AT + TT	1.00			1.00		
		AA	1.57	0.89–2.77	0.12	1.69	0.82–3.47	0.15
Alchol drinking habit	No drinking		1.00			1.00		
	Occasionally		1.70	1.16–2.49	0.01	1.37	0.87–2.15	0.18
	Nearly every day		2.36	1.62–3.45	0.00	1.99	1.28–3.10	0
Smoking habit	Never smoked		1.00			1.00		
	Ex-smokers		1.30	0.59–2.83	0.51	1.92	0.86–4.28	0.11
	Current smokers		2.81	2.05–3.85	0.00	2.92	1.98–4.30	0
Balance of food	Eat various food		1.00			1.00		
	Consider balance slightly		0.57	0.39–0.83	0.00	0.62	0.39–0.96	0.03
	Rarely consider balance		1.01	0.70–1.45	0.97	0.99	0.64–1.55	0.97
Exercise habit	Frequently		1.00			1.00		
	Sometimes		1.01	0.54–1.90	0.96	1.05	0.51–2.17	0.89
	No exercise		0.94	0.52–1.71	0.84	0.8	0.4–1.61	0.53
Sleeping habit	Sufficiently		1.00			1.00		
	Normal		0.75	0.52–1.10	0.14	0.96	0.60–1.55	0.88
	Insufficiently		0.68	0.38–1.22	0.20	0.83	0.40–1.71	0.6

CI, confidence interval; MS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III.

In the present study, we showed an association between SNPs FTO and MS diagnosed by the NCEP-ATP III and Japanese definitions which disagreed with the results of Shimaoka et al. (2010) and Tabara et al. (2009). However, according to the NCEP-ATP III definition used internationally, this study were consistent with the results of Sjögren et al. (2008) and Al-Attar et al. (2008) in Swedish, French, Inuit, and Chinese specific ethnic groups (Table 6). To investigate the importance of FTO SNPs in Japanese populations, further studies should be carried out in more extensive Japanese subjects.

The average of BMI in subjects was 22.3 ± 3.1 kg/m^2, which is close to the Japanese average of around 30 years of age. The hazard ratios of lifestyle for MS in univariate analysis were not significantly associated with food, exercise and sleeping habits. Lifestyle is known as a risk factor of MS, but an association with these habits was not found; however, we performed the investigation in 1998 and as for these lifestyles, we speculate the index easily changed during the 9 years between 1998 and

Table 5. Hazard ratios of gender, age and lifestyle for MS by genotype (multivariate analysis)

Genotype			NCEP-ATPIII			Japanese definition		
			Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
rs9939609	Additive model	TT	1.00			1.00		
		TA	1.48	1.07–2.04	0.02	1.35	0.91–2.00	0.13
		AA	1.48	0.72–3.07	0.29	1.54	0.66–3.57	0.32
	Dominant model	TT	1.00			1.00		
		TA + AA	1.48	1.08–2.02	0.01	1.37	0.94–2.00	0.10
	Recessive model	TT + TA	1.00			1.00		
		AA	1.29	0.63–2.63	0.49	1.38	0.60–3.18	0.44
rs1121980	Additive model	GG	1.00			1.00		
		GA	1.55	1.12–2.14	0.01	1.19	0.81–1.76	0.38
		AA	2.06	1.07–3.99	0.03	1.99	1.00–3.94	0.05
	Dominant model	GG	1.00			1.00		
		GA + AA	1.60	1.18–2.19	0.00	1.29	0.89–1.86	0.18
	Recessive model	GG + GA	1.00			1.00		
		AA	1.76	0.93–3.37	0.08	1.86	0.96–3.61	0.07
rs1558902	Additive model	TT	1.00			1.00		
		TA	1.35	0.98–1.86	0.07	1.37	0.93–2.04	0.12
		AA	1.88	1.04–3.40	0.04	2.24	1.07–4.72	0.03
	Dominant model	TT	1.00			1.00		
		TA + AA	1.41	1.04–1.92	0.03	1.47	1.01–2.13	0.05
	Recessive model	AT + TT	1.00			1.00		
		AA	1.67	0.94–2.97	0.08	2.01	0.97–4.17	0.06

Adjusted for sex, age and lifestyle (drinking, smoking, eating, exercise and sleeping habits).
CI, confidence interval; MS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III.

2006. Thus, lifestyles varied with the incidence of MS. According to alcohol and smoking habits, there were significant associations with MS. Lifestyle is the factor that is hard to be changed and it strongly affects the onset of MS.

It was reported that risk allele carriers were 3 kg heavier than non-carriers (Dina et al., 2007; Frayling et al., 2007). It has been reported that lifestyle alterations can reduce the risk of MS (Fappa et al., 2008), even in individuals carrying the MS-susceptibility variant of FTO. Therefore, genotyping SNPs of FTO in an individual may be effective for personalized preventive medicine in Japanese populations.

In the present study, we could not determine the mechanism of FTO SNPs affecting the prevalence of MS. So far, the function of the FTO was revealed gradually, and there was evidence that the FTO was involved in the development of obesity. FTO mRNA was widely expressed in fetal and adult tissues, especially in the brain, and in particular the hypothalamus, which is involved in energy balance (Dina et al., 2007; Frayling et al., 2007; Gerken et al., 2007). Moreover, several studies suggested that risk-allele carriers had greater food intake in human subjects (Cecil et al., 2008; Speakman et al., 2008), but not all (Tanofsky-Kraff et al., 2009). The risk-allele in human FTO may enhance the expression and/or activity of the FTO (Church et al., 2010). Thus, overexpression of the FTO may lead to increased food intake, resulting in obesity. However, the precise mechanism of how the FTO affects obesity and MS is not clear yet.

Most reports which have studied the relationship between polymorphism in the FTO and MS were analyzed using case-control or cross-sectional studies (Al-Attar et al., 2008; Tabara et al., 2009; Shimaoka et al., 2010) (Table 6). A retrospective cohort study among workers, not hospital-based, was employed in the present study. Although a cohort study was employed to reduce the effect of biases compared to the case-control study, some limitations remain. First, the relatively young subject population and healthy-worker effect due to selection of subjects after medical checkups at the time of employment may have decreased subjects with MS and affected the results of the study. Second, regarding the sam-

Table 6. Association of FTO genotype with MS

	Method	Subject	Definition of MS	SNP	Association
Present study	Cohort study	Japanese	Japanese definition	rs9939609	–
		(Izumo region, Shimane)		rs1121980	–
				rs1558902	+
			NCEP-ATPIII	rs9939609	+
				rs1121980	+
				rs1558902	+
Shimaoka et al., 2010	Cross-sectional study	Japanese	Japanese definition	rs9939609	–
		(Tanno-Sobetsu, Hokkaido)		rs1121980	–
				rs1558902	–
Tabara et al., 2009	Case-control study	Japanese	NCEP-ATPIII	rs9939609	–
		(Ehime)			
Sjögren et al., 2008	Cohort study	Swedish	Ordinal	rs9939609	+
			(reference to NCEP-ATPIII, IDF)		
Al-Attar et al., 2008	Meta-analysis	South Asian	IDF	rs9939609	+
		Chinese			–
		Oji-Cree			–
		Greenland Inuit			–
		South Asian	NCEP-ATPIII	rs9939609	–
		Chinese			–
		Oji-Cree			–
		Greenland Inuit			+

FTO, fat mass and obesity associated gene; IDF, International Diabetes Federation; MS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program-Adult Treatment panel III; SNP, single nucleotide polymorphism.

ple size, we could not recruit enough numbers of the risk A-allele homozygous genotype. Results presented above need to be further verified with increased numbers. Because we did not have the data of abdominal circumference of subjects, we used BMI for classification of Japanese metabolic syndrome in substitution for abdominal circumference. Since BMI ≥ 25 is a good surrogate measure of abdominal obesity among the Japanese population (Otsuka and Kawada, 2010), the effect of misclassification of the abdominal obesity to the study results is considered small.

In our results, we indicated that rs9939609, rs1121980 and rs1558902 in the FTO may be significantly associated with the incidence of MS diagnosed by the NCEP-ATP III in Japanese subjects, and by the Japanese definition the association applied to rs1558902. It is considered that there is the linkage disequilibrium between three SNPs assessed in the present study; however, we did not assessed statistically. SNPs may be an important risk factor for the future incidence of MS in the Japanese. Therefore, knowing earlier whether individuals are risk allele carriers may be useful in preventing MS in the future.

References

1 Al-Attar SA, Pollex RL, Ban MR, Young TK, Bjerregaard P, Anand SS, et al. Association between the FTO rs9939609 polymorphism and the metabolic syndrome in a non-Caucasian multi-ethnic sample. Cardiovasc Diabetol 2008;7:5.

2 Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 2008;57:95–101.

3 Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CNA. An obesity-associated *FTO* gene variant and increased energy intake in children. N Engl J Med 2008;359:2558–2566.

4 Church C, Moir L, McMurray F, Girard C, Banks GT, Teboul L, et al. Overexpression of *Fto* leads to increased food intake and results in obesity. Nat Genet 2010;42:1086–1093.

5 Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 2007;39:724–726.

6 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415–1428.

7 Fappa E, Yannakoulia M, Pitsavos C, Skoumas I, Valourdou S, Stefanadis C. Lifestyle intervention in the management of metabolic syndrome: could we improve adherence issues? Nutrition 2008;24:286–291.

8 Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Brüning JC, Rüther U. Inactivation of the Fto gene protects from obesity. Nature 2009;458:894–898.

9 Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889–894.

10 Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, et al. The obesity-associated *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 2007;318:1469–1472.

11 González-Sánchez, JL, Zabena C, Martínez-Larrad MT, Martínez-Calatrava MJ, Pérez-Barba M, Serrano-Ríos M. Variant rs9939609 in the FTO gene is associated with obesity in an adult population from Spain. Clin Endocrinol 2009;70:390–393.

12 Groop L. Genetics of the metabolic syndrome. Br J Nutr 2000;83(Suppl 1):S39–S48.

13 Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752.

14 Hinney A, Nguyen TT, Scherag A, Friedel S, Brönner G, Müller TD, et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS One 2007;2:e1361.

15 Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, et al. Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 2007;50:2461–2466.

16 Hotta K, Nakamura M, Nakamura T, Matsuo T, Nakata Y, Kamohara S, et al. Polymorphisms in NRXN3, TFAP2B, MSRA, LYPLAL1, FTO and MC4R and their effect on visceral fat area in the Japanese population. J Hum Genet 2010;55:738–742.

17 Hotta K, Nakata Y, Matsuko T, Kamohara S, Kotani K, Komatsu R, Itoh N, et al. Variations in the FTO gene are associated with severe obesity in the Japanese. J Hum Genet 2008;53:546–553.

18 Karasawa S, Daimon K, Sasaki S, Toriyama S, Oizumi T, Susa S, et al. Association of the common fat mass and obesity associated (FTO) gene polymorphism with obesity in a Japanese population. Endocr J 2010;57:293–301.

19 Li H, Wu Y, Loos RJ, Hu FB, Liu Y, Wang J, et al. Variants in the fat mass- and obesity-associated (*FTO*) gene are not associated with obesity in a Chinese Han population. Diabetes 2008;57:264–268.

20 Ohashi J, Naka I, Kimura R, Natsuhara K, Yamaguchi T, Furusawa T, et al. FTO polymorphism in oceanic populations. J Hum Genet 2007;52:1031–1035.

21 Omori S, Tanaka Y, Takahashi A, Hirose H, Kashiwagi A, Kaku K, et al. Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. Diabetes 2008;57:791–795.

22 Otsuka T, Kawada T. Validity of using body mass index as a surrogate measure of abdominal obesity. Circ J 2010;74:383.

23 Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 2007;3:e115.

24 Shimaoka I, Kamide K, Ohishi M, Katsuya T, Akasaka H, Saitoh S, et al. Association of gene polymorphism of the fat-mass and obesity-associated gene with insulin resistance in Japanese. Hyperten Res 2010;33:214–218.

25 Sjögren M, Lyssenko V, Jonsson A, Berglund G, Nilsson P, Groop L, Orho-Melander M. The search for putative unifying genetic factors for components of the metabolic syndrome. Diabetologia 2008;51:2242–2251.

26 Speakman JR, Rance KA, Johnstone AM. Polymorphisms of the *FTO* gene are associated with variation in energy intake, but not energy expenditure. Obesity 2008;16:1961–1965.

27 Tabara Y, Osawa H, Guo H, Kawamoto R, Onuma H, Shimizu I, et al. Prognostic significance of FTO genotype in the development of obesity in Japanese: the J-SHIPP study. Int J Obes 2009;33:1243–1248.

28 Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, et al. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nurtr 2009;90:1483–1488.

Received March 23, 2012; accepted May 7, 2012

Corresponding author: Yoneatsu Osaki, MD, PhD