Variations in the FTO gene are associated with severe obesity in the Japanese

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Abstract Variations in the fat-mass and obesity-associated gene (FTO) are associated with the obesity phenotype in many Caucasian populations. This association with the obesity phenotype is not clear in the Japanese. To investigate the relationship between the FTO gene and obesity in the Japanese, we genotyped single nucleotide polymorphisms (SNPs) in the FTO genes from severely obese subjects [n = 927, body mass index (BMI) ≥ 30 kg/m2] and normal-weight control subjects (n = 1,527, BMI < 25 kg/m2).

A case-control association analysis revealed that 15 SNPs, including rs9939609 and rs1121980, in a linkage disequilibrium (LD) block of approximately 50 kb demonstrated significant associations with obesity; rs1558902 was most significantly associated with obesity. P value in additive mode was 0.0000041, and odds ratio (OR) adjusted for age and gender was 1.41 [95% confidential interval (CI) = 1.22–1.62]. Obesity-associated phenotypes, which include the level of plasma glucose, hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and blood pressure were not associated with the...
rs1558902 genotype. Thus, the SNPs in the \( FTO \) gene were found to be associated with obesity, i.e., severe obesity, in the Japanese.

**Keywords**  Fat-mass and obesity-associated gene · Obesity · Japanese population · Association · SNP

**Introduction**

Obesity is the most common nutritional disorder in developed countries, and it is a major risk factor for hypertension, cardiovascular disease, and type 2 diabetes (Kopelman 2000; Wilson et al. 2003). Genetic and environmental factors contribute to obesity development (Maes et al. 1997; Barsh et al. 2000; Rankinen et al. 2006). Recent progress in single nucleotide polymorphism (SNP) genotyping techniques has enabled genome-wide association studies on common diseases (Herbert et al. 2006; Frayling et al. 2007; Scuteri et al. 2007; The Wellcome Trust Case Control Consortium 2007; Hinney et al. 2007). Using a large-scale case-control association study, we found that secretogranin III (SCG3) (Tanabe et al. 2007) and myotubularin-related protein 9 (MTMR9) (Yanagiya et al. 2007) are involved in susceptibility to the obesity phenotype. Genome-wide association studies have shown that the fat-mass and obesity-associated gene (\( FTO \)) is also associated with the obesity phenotype (Frayling et al. 2007; Scuteri et al. 2007; Hinney et al. 2007). This association was also found in many Caucasian and Hispanic American populations (Frayling et al. 2007; Scuteri et al. 2007; Dina et al. 2007; Field et al. 2007; Andreasen et al. 2008; Wåhlén et al. 2008; Peeters et al. 2008), whereas it was not found in the Chinese Han population (Li et al. 2008). Among Japanese, body mass index (BMI) was higher in subjects who had the A allele of rs9939609, similar to that observed in Caucasians; however, this finding was not significant (Horikoshi et al. 2007). Another group reported that rs9939609 was associated with BMI in the Japanese (Omori et al. 2008). Thus, the association of SNPs in the \( FTO \) gene with obesity in the Japanese remains controversial.

To investigate the relationship between the \( FTO \) gene and obesity in the Japanese, we performed a case-control association study using patients with severe adult obesity (BMI \( \geq 30 \text{ kg/m}^2 \)) and normal-weight controls (BMI \( < 25 \text{ kg/m}^2 \)); we found that SNPs in intron 1 of the \( FTO \) gene were associated with severe adult obesity.

**Materials and methods**

**Study subjects**

The sample size for severely obese Japanese subjects (BMI \( \geq 30 \text{ kg/m}^2 \)) was 927 (male:female ratio 419:508, age 48.7 ± 14.2 years, BMI 34.2 ± 5.4 kg/m\(^2\)), whereas that for Japanese normal weight controls (BMI < 25 kg/m\(^2\)) was 1,527 (male:female ratio 685:842, age 48.1 ± 16.5 years, BMI 21.7 ± 2.1 kg/m\(^2\)). The severely obese subjects were recruited from among outpatients of medical institutes. Patients with secondary obesity and obesity-related hereditary disorders were not included, and neither were patients with medication-induced obesity. The normal-weight controls were recruited from among subjects who had undergone a medical examination for screening of common diseases. Clinical features of the subjects are illustrated in Table 1. Additionally, 1,604 subjects were recruited (male:female ratio 803:801, age 48.7 ± 16.9 years, BMI 22.66 ± 3.16 kg/m\(^2\)) from the Japanese general population. Each subject provided written informed consent, and the protocol was approved by the ethics committee of each institution and that of RIKEN.

**DNA preparation and SNP genotyping**

Genomic DNA was prepared from the blood sample of each subject by using the Genomix (Talent Srl, Trieste, Italy). We searched for dbsSNPs with minor allele frequencies (MAF) > 0.10 in the \( FTO \) gene of Japanese people. We selected 90 SNPs and were able to construct Invader probes (Third Wave Technologies, Madison, WI)
for them (Supplementary Table 1). SNPs were genotyped using Invader assays as described previously (Ohnishi et al. 2001; Takei et al. 2002). Nine SNPs (rs9937053, rs9939973, rs9940128, rs7193144, rs8043757, rs9923233, rs9926289, rs9939609, and rs9930506) reported in a previous genome-wide association study (Scuteri et al. 2007) were genotyped using TaqMan probes (C__29910458_10, C__29910458_10, C__29819994_10; Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Genotype or allele frequencies were compared between cases and controls in three different modes. In the first mode, i.e., the additive mode, $\chi^2$ test was performed according to Sladek et al. (Sladek et al. 2007). In the second mode, i.e., the minor allele recessive mode, frequencies of the homozygous genotype for the minor allele were compared using a $2 \times 2$ contingency table. In the third mode, i.e., the minor allele dominant mode, frequencies of the homozygous genotype for the major allele were compared using a $2 \times 2$ contingency table. A test of independence was performed using Pearson’s $\chi^2$ method. $P$ values were corrected by Bonferroni adjustment and $P < 0.00017$ [0.05/99 (total SNP number)/3 (number of modes)] was considered significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated using Woolf’s method. We coded genotypes as 0, 1, and 2, depending on the number of copies of the risk alleles. OR adjusted for age and gender was calculated using multiple logistic regression with genotypes, age, and gender as independent variables. Hardy–Weinberg equilibrium was assessed using the $\chi^2$ test (Nielsen et al. 1998). Haplotype blocks were determined using Haplovew (Barrett et al. 2005).

Table 1

|                | Obese   | Control | $P$ value |
|----------------|---------|---------|-----------|
| Gender (M/F)   | 419/508 | 658/842 | 0.049     |
| Age (year)     | 49.1 ± 14.2 | 48.2 ± 16.5 | 0.009     |
| Body mass index (kg/m²) | 34.50 ± 5.39 | 21.65 ± 2.08 | <0.000001 |
| Glucose (mg/dl) | 129.2 ± 49.6 | 97.7 ± 23.9 | <0.000001 |
| HbA1c (%)      | 6.5 ± 1.8  | 5.1 ± 0.6 | <0.000001 |
| Total cholesterol (mg/dl) | 209.9 ± 37.9 | 201.2 ± 36.4 | <0.000001 |
| Triglycerides (mg/dl) | 153.2 ± 99.5 | 104.0 ± 73.2 | <0.000001 |
| High-density lipoprotein cholesterol (mg/dl) | 53.1 ± 18.9 | 65.1 ± 15.7 | <0.000001 |
| Systolic blood pressure (mmHg) | 136.4 ± 18.1 | 123.4 ± 17.8 | <0.000001 |
| Diastolic blood pressure (mmHg) | 83.8 ± 12.0  | 76.0 ± 11.1 | <0.000001 |

$P$ values were analyzed using Mann–Whitney $U$ test. Data are mean ± standard deviation

Results

Case-control association studies

We searched for dbSNPs with MAF > 0.10 in the FTO gene. By using Invader and TaqMan assay, we successfully genotyped 99 SNPs spanning the FTO gene (Supplementary Table 1). Using these SNPs, we performed tests of independence between the phenotype and genotypes of obesity at each SNP by using severely obese subjects (BMI ≥ 30 kg/m²) and normal weight controls (BMI < 25 kg/m²). For each SNP, the lowest P value among the three different modes was selected as the minimum P value. All SNPs, including rs1421084, were in Hardy–Weinberg equilibrium ($P > 0.01$) (Supplementary Table 1).

The power of the test was calculated by Monte Carlo method with different MAFs and different effect sizes. Effect of the risk allele on penetrance was assumed to be multiplicative; i.e., the penetrances for three genotypes were assumed to be $a$, $ar$, and $ar^2$, respectively, where $a$ and $r$ denote the lowest penetrance and genotype relative risk, respectively. Supplementary Table 2 shows the calculated values of the power of the test with different MAFs and different genotype relative risks ($r$). The lowest penetrance ($a$) was calculated for each gender by assuming the affection rates of 2.3% for men and 3.4% for women (Yoshikie et al. 2002). Genotype relative risk ($r$) was assumed to be

![Image of Table 1](https://via.placeholder.com/150)
the same for both genders. Supplementary Table 2 shows that the test has significant power at relative high risk allele frequency when genotype relative risk is >1.7.

As shown in Fig. 1 and Supplementary Table 1, 15 SNPs demonstrated significant associations with the obesity phenotype; the threshold of significance using Bonferroni correction was $P < 0.00017$. These SNPs included rs9939609 (Frayling et al. 2007) and rs1121980 (Hinney et al. 2007) that were reported to be significantly associated with the obesity phenotype in the Caucasian population, as determined by genome-wide association studies; rs9930506 (Scuteri et al. 2007) showed marginal association with obesity in the Japanese. Linkage disequilibrium (LD) analysis revealed that these 15 SNPs were in almost complete LD ($D' > 0.98$, $r^2 > 0.80$) and were located within the same LD block of approximately 50 kb (Fig. 1). The most significant association was observed for rs1558902 [additive mode, $P = 0.0000041$ and allele-specific OR (95% CI) adjusted for age and gender was 1.41 (1.22–1.62)]. The minor alleles of rs9939609 (MAF = 0.24) and rs1121980 (MAF = 0.26) were significantly more frequent in the obese group than in the normal-weight control group [additive mode, $P = 0.000012$ and $P = 0.000051$, respectively], and ORs were 1.38 (95% CI = 1.20–1.59) and 1.33 (95% CI = 1.16–1.52), respectively (Table 2, Supplementary Table 1). The MAF of both SNPs in the control group was 0.18; this was consistent with data obtained from the haplotype map of the human genome (HapMap) (Supplementary Table 1). Our data indicated that the SNPs in the FTO gene were associated with severe obesity in the Japanese.

Analysis of various quantitative phenotypes with rs1558902

To investigate whether the genotypes of SNP rs1558902 are associated with the phenotypes of metabolic disorders, we compared the following among the different genotypes in the cases, controls, and combined groups: ANOVA results, BMI, levels of fasting plasma glucose, hemoglobin A1c (HbA1c), total cholesterol, triglycerides, HDL cholesterol, and blood pressure. As rs1558902 showed the most significant association with obesity and its call rate was the highest, we analyzed various quantitative phenotypes by using this SNP. The quantitative phenotypes regarding BMI and the levels of fasting plasma glucose, HbA1c, total cholesterol, triglycerides, HDL cholesterol, and blood pressure were not found to be significantly associated with the genotypes at rs1558902 in either the case or control group (Table 3). Although there was no significant difference in BMI values among genotypes in either the control or case group, the direction of the difference (AA $>$ AT $>$ TT) was in accordance with the association between the qualitative obesity phenotype and the genotype shown.

Finally, we examined the BMI distribution of rs1558902 in the Japanese general population and found that rs1558902 genotype was significantly associated with BMI.

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**Fig. 1** Linkage disequilibrium (LD) mapping, polymorphisms, and $P$ values obtained in the test of independence between the phenotype and genotypes of obesity at various single nucleotide polymorphisms (SNPs) in the fat-mass and obesity-associated gene (FTO) gene. $P$ values are expressed as negative logarithm of the minimum $P$ values obtained in the three models (additive, minor allele dominant, and minor allele recessive modes). LD coefficients ($D'$) between each pair of SNPs were calculated and are displayed as a strand in the LD blocks. Minor allele frequencies of all SNPs used in this analysis are $\geq 10\%$. The genomic structure is shown in the upper. The gray bar marks the LD block associated with obesity.

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## Table 2

Associations of single nucleotide polymorphisms (SNPs) in the fat-mass and obesity-associated gene (*FTO*) gene with obesity existing in the 50-kb linkage disequilibrium (LD) block

| dbsNP ID | Allele | Genotype | Case | Control | Additive mode | Recessive mode | Dominant mode |
|----------|--------|----------|------|---------|---------------|----------------|---------------|
|          |        |          | OR (95% CI) | χ² | P value | OR (95% CI) | χ² | P value | OR (95% CI) | χ² | P value |
|          |        |          |      |        |      |      |      |        |      |        |       |
| rs9937053 | A/G    | 59 360 494 913 | 63 414 773 1250 | 1.31 (1.13–1.51) | 12.3 | 0.00047 | 2.0 | 0.16 | 1.30 (0.90–1.88) | 13.0 | 0.00031 |
| rs9939973 | A/G    | 61 367 496 924 | 75 504 941 1520 | 1.32 (1.15–1.51) | 15.7 | 0.000077a | 3.0 | 0.081 | 1.36 (0.96–1.93) | 16.1 | 0.000061a |
| rs9940128 | A/G    | 60 366 498 924 | 75 500 941 1516 | 1.31 (1.15–1.50) | 15.2 | 0.00010a | 2.6 | 0.11 | 1.33 (0.94–1.89) | 15.9 | 0.000068a |
| rs1421085 | C/T    | 49 338 537 924 | 57 443 1019 1519 | 1.38 (1.20–1.59) | 19.6 | 0.000011a | 3.3 | 0.068 | 1.44 (0.97–2.12) | 20.0 | 0.000078a |
| rs1558902 | A/T    | 48 341 536 925 | 52 449 1021 1522 | 1.41 (1.22–1.62) | 21.2 | 0.0000041a | 4.6 | 0.032 | 1.55 (1.04–2.31) | 20.8 | 0.000052a |
| rs1121980 | A/G    | 61 367 499 927 | 73 504 947 1524 | 1.33 (1.16–1.52) | 16.5 | 0.000051a | 3.6 | 0.059 | 1.40 (0.99–1.99) | 16.5 | 0.000050a |
| rs7193144 | C/T    | 49 339 532 920 | 55 447 1014 1516 | 1.39 (1.21–1.61) | 20.4 | 0.0000067a | 4.0 | 0.044 | 1.49 (1.01–2.22) | 20.3 | 0.0000067a |
| rs8043757 | T/A    | 48 319 541 908 | 54 436 1027 1517 | 1.36 (1.18–1.57) | 17.4 | 0.000037a | 4.2 | 0.040 | 1.51 (1.02–2.25) | 16.4 | 0.000052a |
| rs8050136 | A/C    | 51 336 538 925 | 56 450 1018 1524 | 1.38 (1.20–1.59) | 19.4 | 0.000012a | 4.7 | 0.031 | 1.53 (1.04–2.26) | 18.5 | 0.000017a |
| rs3751812 | T/G    | 51 340 534 925 | 55 458 1013 1526 | 1.38 (1.20–1.59) | 19.6 | 0.000099a | 5.0 | 0.024 | 1.56 (1.06–2.31) | 18.5 | 0.000017a |
| rs9923233 | C/G    | 51 335 533 919 | 55 449 1010 1514 | 1.38 (1.20–1.60) | 19.8 | 0.0000093a | 5.0 | 0.025 | 1.56 (1.06–2.30) | 18.7 | 0.000015a |
| rs9926289 | A/G    | 50 323 531 904 | 56 425 993 1474 | 1.37 (1.19–1.58) | 18.7 | 0.000020a | 3.9 | 0.047 | 1.48 (1.00–2.29) | 18.1 | 0.000021a |
| rs9939609 | A/T    | 51 334 534 919 | 56 443 1005 1504 | 1.38 (1.20–1.59) | 19.5 | 0.000012a | 4.5 | 0.034 | 1.52 (1.03–2.24) | 18.7 | 0.000015a |
| rs7185735 | G/A    | 51 340 536 927 | 55 455 1014 1524 | 1.38 (1.20–1.59) | 19.9 | 0.0000089a | 5.0 | 0.025 | 1.55 (1.05–2.30) | 18.8 | 0.000014a |
| rs9913494 | G/C    | 64 363 494 921 | 71 504 942 1517 | 1.35 (1.18–1.55) | 18.4 | 0.000018a | 5.6 | 0.018 | 1.52 (1.07–2.15) | 16.9 | 0.000039a |
| rs17819964 | T/C   | 62 361 500 923 | 68 524 930 1522 | 1.30 (1.14–1.49) | 13.5 | 0.00022 | 5.8 | 0.016 | 1.54 (1.08–2.19) | 11.4 | 0.00075 |
| rs9930506 | G/A    | 67 365 488 920 | 82 521 913 1516 | 1.28 (1.12–1.46) | 12.8 | 0.00038 | 3.5 | 0.061 | 1.37 (0.98–1.92) | 12.1 | 0.00051 |
| rs9932754 | C/T    | 66 368 491 925 | 78 525 919 1522 | 1.29 (1.13–1.48) | 13.6 | 0.00023 | 4.2 | 0.040 | 1.42 (1.01–2.00) | 12.6 | 0.00040 |
| rs9922619 | T/G    | 66 368 489 923 | 78 529 919 1526 | 1.29 (1.13–1.48) | 13.5 | 0.00024 | 4.3 | 0.038 | 1.43 (1.02–2.01) | 12.3 | 0.00044 |
| rs7204609 | C/T    | 134 418 373 925 | 273 717 529 1519 | 0.83 (0.73–0.93) | 9.68 | 0.0022 | 5.0 | 0.025 | 0.77 (0.62–0.97) | 7.5 | 0.0063 |
| rs12149832 | A/G   | 53 349 525 927 | 62 480 982 1524 | 1.33 (1.15–1.53) | 15.2 | 0.000098a | 3.5 | 0.061 | 1.43 (0.98–2.08) | 14.8 | 0.00012a |

The odds ratio (OR) for each SNP was adjusted simultaneously for age and gender using additive model.

CI: confidence interval, χ²: chi-square

a Significant P value (P < 0.00017)
Discussion

Recent genome-wide association studies have shown that the *FTO* gene is associated with obesity (Frayling et al. 2007; Scuteri et al. 2007; Hinney et al. 2007). The associations between variations in the *FTO* gene and the obesity phenotype have been observed in many Caucasian subjects (Frayling et al. 2007; Scuteri et al. 2007; Dina et al. 2007; Field et al. 2007; Andreasen et al. 2008; Wahlén et al. 2008; Peeters et al. 2008). However, these associations were controversial with regard to Asian subjects (Horikoshi et al. 2007; Li et al. 2008; Omori et al. 2008). BMI values did not significantly differ among the genotypes in the general population of Chinese and Japanese (Horikoshi et al. 2007; Li et al. 2008). We performed a case-control association study with regard to severe obesity and found that the SNPs in the *FTO* gene were significantly associated with severe obesity. Although the SNPs demonstrated the most significant association in the Japanese, which was different from that in Caucasians, the significantly associated SNPs existed in a similar block as that in Caucasians. Therefore, the *FTO* gene could also contribute to the development of severe obesity in the Japanese.

BMI was modestly different among rs1558902 genotypes in the general population in this study; rs9939609 was not significantly associated with BMI in the general population (AA 23.22 ± 3.14 vs AT 22.79 ± 3.25 vs TT 22.58 ± 3.13, P = 0.063). In the Japanese population, rs1558902 may be more tightly associated with BMI than rs9939609. The National Nutrition Survey of Japan reported that the prevalence of subjects with a BMI of
The significant SNPs were located in intron 1 of the FTO gene. The rs1558902 and other significant SNPs, for example, rs9939609 and rs1121980, would affect transcriptional activity of the FTO gene, although further investigation is necessary. The precise mechanism by which the FTO gene leads to obesity development is unclear (Gerken et al. 2007; Sanchez-Pulido et al. 2007). However, the FTO gene is expressed in the hypothalamus and regulated by fasting and leptin (Frayling et al. 2007; Gerken et al. 2007). Using large-scale case-control association studies, we determined that the SGC3 (Tanabe et al. 2007) and MTMR9 (Yanagiya et al. 2007) genes are involved in susceptibility to the obesity phenotype. These two genes are expressed in the hypothalamus. Genetic studies in mice have suggested that mutations in several genes, such as those encoding leptin, proopiomelanocortin, and melanocortin-4 receptor, are implicated in a monogenic form of inherited obesity (Barsh et al. 2000; Rankinen et al. 2006). Such mutations have also been reported in obese humans. As most such genes are expressed in the hypothalamus and have been indicated to play important roles in the regulation of food intake, genes expressed in the hypothalamus are likely to be good candidates for susceptibility to obesity.

In summary, we have identified the genetic variations in the FTO gene that may influence the risk of severe obesity in the Japanese.

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