

Common Variation in the Fat Mass and Obesity-Associated (*FTO*) Gene Confers Risk of Obesity and Modulates BMI in the Chinese Population

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OBJECTIVE—Genetic variants in the fat mass and obesity-associated (*FTO*) gene have been linked with obesity and type 2 diabetes in European populations. We aimed to test the role of *FTO* genetic variants in obesity and type 2 diabetes in the Chinese population.

RESEARCH DESIGN AND METHODS—We genotyped 19 single-nucleotide polymorphisms (SNPs) spanning from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene. We analyzed their associations with obesity (638 case and 1,610 control subjects), type 2 diabetes (759 case and 784 control subjects), and obesity-related traits in non-diabetic subjects.

RESULTS—Among the 19 SNPs, the rs9939609 A allele was strongly associated with obesity ($P = 7.0 \times 10^{-4}$) and BMI ($P = 0.0024$) in the Chinese population. The odds ratio for obesity was 2.60 (95% CI 1.24–5.46) ($P = 0.011$) for the AA genotype and 1.32 (1.05–1.66) ($P = 0.018$) for the AT genotype compared with the TT genotype. Each additional copy of the rs9939609 A allele was associated with a BMI increase of ~ 0.37 kg/m². The rs9939609 A allele was substantially less common in the Chinese population than in the European population (12.6 vs. 45%). We did not find significant associations of the 19 SNPs with type 2 diabetes or other obesity-related traits.

CONCLUSIONS—Genetic variation in the *FTO* gene is strongly associated with obesity and BMI in the Chinese population. The risk variant is less common in the Chinese population, but its effect size on BMI is comparable with that in the European population. *Diabetes* 57:2245–2252, 2008

Obesity is strongly influenced by genetic factors, with an estimated heritability of $>60\%$ BMI (1,2). Genetic susceptibility to the common form of obesity appears to be polygenic. Although theoretical analyses emphasized the power of genetic association study in common polygenic diseases,

the search for genes conferring the risk of obesity has thus far not been very successful. A few reported associations with genes such as *GAD2*, *ENPP1*, and *INSIG2* also yielded inconsistent results in replication efforts (3–5).

Recently, several independent studies using different approaches reported strong associations of genetic variants in the fat mass and obesity-associated (*FTO*) gene with obesity in populations of European origin (6,7). Zeggini et al. (8) initially found the association of *FTO* genetic variants with type 2 diabetes in a genome-wide association study for type 2 diabetes. However, the association was abolished by adjustment for BMI, indicating that the association with type 2 diabetes was mediated through an effect of obesity (8). They replicated the associations (rs9939609) with obesity in a total of 38,759 individuals (6). Dina et al. (7) concurrently reported strong associations of single-nucleotide polymorphisms (SNPs) (rs1421085 and rs17817449) of the *FTO* gene with childhood and severe adult obesity. Two other genome-wide association studies (9,10) also independently reported the associations of nearby *FTO* genetic variants (rs9930506, rs8050136, rs7193144, rs1121980, and rs9939973) with obesity and obesity-related traits in European and Hispanic populations. All these SNPs fall in a region of strong linkage disequilibrium (LD) in intron 1 of the *FTO* gene (11). The effect of *FTO* genetic variants on common obesity is also substantial in the European population. Adults who are homozygous for the risk-conferring rs9939609 A allele weighed ~ 3 kg more and had a 1.67-fold increased odds ratio of obesity when compared with those without a risk allele (6). The calculated population-attributable risk is $\sim 22\%$ for common obesity in populations of European origin (6).

Reproducibility is essential for reported genetic associations, especially among populations of different ethnic backgrounds. However, studies in an Oceanic population (12), African Americans (10), Han Chinese (13), and Japanese (14) failed to detect associations between previously reported SNPs and obesity or obesity-related traits. Although the limited sample size and power of these studies is the most likely reason for the lack of association, there is emerging evidence showing that other *FTO* SNPs not in LD with rs9939609 may be the causative variant in non-European populations (15). In this study, we aimed to investigate the association of *FTO* genetic variants with obesity and type 2 diabetes in the Chinese population. Instead of testing only a few variants, we used a gene-based approach (16) by selecting potentially functional and common SNPs from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene. Their associations with obesity-related quantitative metabolic traits were also analyzed.

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RESEARCH DESIGN AND METHODS

We recruited 594 young obese case subjects from the bariatric surgery clinics of En Chu Kong General Hospital in Taiwan. Obesity was defined as BMI ≥ 30 kg/m². A total of 759 type 2 diabetic case subjects were recruited from the metabolic clinic of the National Taiwan University Hospital. Type 2 diabetes was diagnosed based on the criteria of the American Diabetes Association (17). We excluded diabetic patients with ages of onset <35 years.

We recruited 910 healthy nonobese control subjects from the health checkup service of the National Taiwan University Hospital and a community-based health screening program in Taiwan. Nonobesity was defined as BMI <30 kg/m². Among them, 784 were confirmed to be normal glucose tolerant after a 75-g oral glucose tolerance test.

The case-control association analysis for type 2 diabetes included the 759 type 2 diabetic case and 784 control subjects with normal fasting glucose and glucose tolerance. They were not matched for age, sex, or BMI. The case-control association analysis for obesity included 594 young obese case and 910 healthy nonobese control subjects. We further incorporated type 2 diabetic case subjects with available BMI data ($n = 744$) into the analysis. In total, 638 obese case subjects (594 young obese case and 44 obese type 2 diabetic case subjects) and 1,610 nonobese control subjects (910 healthy nonobese control and 700 nonobese type 2 diabetic case subjects) were used in the case-control association analysis for obesity. Association analysis for BMI was performed in all subjects with available BMI data. The association analyses for other obesity-related metabolic traits were performed in all nondiabetic subjects with available metabolic traits. Written informed consent was obtained from every participating subject, and the study was approved by the institutional review board of the National Taiwan University Hospital.

Clinical measurements. BMI was calculated as weight in kilograms divided by the square of height in meters. Plasma glucose was determined using a glucose oxidase autoanalyzer (Daikin Antsense II; Daikin, Osaka, Japan), and plasma insulin was measured using a radioimmunoassay (Abbott AxSYM; Abbott Diagnostics, Abbott Park, IL). Fasting total cholesterol, triglycerides, HDL and LDL cholesterol, and uric acid levels were measured using a dry-chemistry autoanalyzer (Fuji FDC-3000; Fuji Film, Tokyo, Japan). Serum high-sensitive C-reactive protein concentration was measured with a turbidimetric immunoassay utilizing an autoanalyzer (Toshiba TBA-120FR; Toshiba Medical Systems, Tokyo, Japan). The homeostasis model assessment of insulin resistance was calculated from fasting insulin concentration (mU/l) \times plasma glucose (mmol/l)/22.5 (18). The homeostasis model assessment of β -cell function was calculated as $20 \times$ fasting insulin (mU/l)/(fasting plasma glucose [mmol/l] - 3.5) (18).

Selection of SNPs and genotyping. We selected potentially functional and common SNPs from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene by using FASTSNP (Functional Analysis and Selection Tool for Single Nucleotide Polymorphism) software (19). The FASTSNP software is a web server that allows users to efficiently identify and prioritize SNPs according to their putative functional effects. The prioritization strategy is based on the priority proposed by Tabor et al. (20). All SNPs in the *FTO* gene with possible function effects are predicted as "intronic enhancers," which are intronic SNPs with a potential transcriptional factor binding site. We selected only SNPs with known minor allele frequencies >15% in the Chinese population. Twenty SNPs were selected. Among them, SNP rs1421092 is located in intron 1 of the *RPGRIP1L* gene. Other SNPs are located in intron 1 (rs11861870), intron 4 (rs2388405), intron 7 (rs2287142), intron 8 (rs16952730, rs16952777, rs4784338, rs1107355, rs12443572, rs13331869, rs12600060, rs16952987, rs918031, and rs1008400), and the 5' flanking region (rs1588413, rs11076022, rs11076023, rs12597712, rs2072518, and rs2075205) of the *FTO* gene. Because all *FTO* variants (rs7193144, rs8050136, rs9939609, rs9930506, rs1121980, and rs17817449) with known associations with obesity and type 2 diabetes in European populations (5–10) are <15% in the Chinese population and are in strong LD (mean $r^2 = 0.87$ and mean $D' = 1$) according to the HapMap Chinese in Beijing (CHB) databank (11), we additionally selected rs9939609 as a tag SNP capturing these SNPs. Genotyping was performed in a total of 21 SNPs using the GenomeLab SNPstream genotyping platform (Beckman Coulter, Fullerton, CA) and its accompanying SNPstream software suite. On average, 97.96% of attempted genotypes were successful, except for rs2388405 and rs2287142, in which genotyping failed in all samples. The concordance rate of genotyping duplication was 99.62%, based on 40 duplicate samples for each SNP. These 19 SNPs captured 96 of 407 alleles (23%), with frequencies >5% at an r^2 of 0.8 across a region of 419 kb containing the *FTO* gene from the HapMap CHB database (build 35 release) (11).

Statistical analyses. Genotype data of both case and control groups were used to estimate intermarker LD by pairwise D' and r^2 . We used the solid spine of the LD method implemented in the Haploview software (available at <http://www.broad.mit.edu/mpg/haploview/>) to define an LD block with an

extended spine of $D' > 0.8$ (21). To compare the LD structures of a 419-kb region containing the *FTO* gene between Chinese and European populations, we used the genotype data from the CHB (Han Chinese) and CEU (Centre d'Etude du Polymorphisme Humain, Utah residents of northern and western European ancestry) databases in the HapMap (build 35). The LD structures were visualized using the Haploview software.

A Hardy-Weinberg equilibrium test was performed for each SNP for the control group before marker-trait association analysis. The associations of each SNP with obesity and type 2 diabetes were estimated using logistic regression under a log-additive model implemented in the PLINK software (available at <http://pngu.mgh.harvard.edu/~purcell/plink/>) (22). We tested the model fit for disease association by comparing additive, dominant, and recessive models using logistic regression. Nominal two-sided P values were reported and were corrected for multiple testing by permutation for 10,000 times.

For quantitative trait analyses, all metabolic traits including BMI were logarithmically transformed and standardized to the Z score units. The associations of each SNP with metabolic traits and the per-allele effect size on metabolic traits were estimated using linear regression in an additive genetic model in PLINK. We tested the model fit for metabolic traits association by comparing additive, dominant, and recessive models using linear regression. Nominal two-sided P values were reported and were corrected for multiple testing by permutation for 10,000 times.

In the case-control association study for obesity and association analysis for quantitative metabolic traits, we combined samples from different study populations. We used the Cochran's Q test for heterogeneity and the I^2 statistics to estimate heterogeneity between study populations. Meta-analysis of obesity association for the combined samples was performed using the fixed-effects Cochran-Mantel-Haenszel method implemented in PLINK. The combined odds ratio and significance level was estimated using the study population as strata. For quantitative metabolic trait association analyses in the combined samples, we used inverse variance methods implemented in the Comprehensive Meta-Analysis Software version 2 (Biostat, Englewood, NJ) to estimate the combined effect size on BMI and significance level.

To provide an approximate estimate of the per-allele effect size in BMI units (kg/m²), we used the methods adopted by Frayling et al. (6). The Z score unit differences were translated into BMI units using the SD of BMI in the general Chinese population (3.01 kg/m² in healthy control subjects of this study).

The population-attributable risk fraction was estimated with data from the control group, calculated as follows: $1 - (1/p^2 OR_{\text{homo}} + 2p(1-p) OR_{\text{hetero}} + (1-p)^2)$, where p is the risk-allele frequency, OR_{homo} is the odds ratio for homozygotes, and OR_{hetero} is the odds ratio for heterozygotes. Power calculations were performed using a Genetic Power Calculator (available at <http://pngu.mgh.harvard.edu/~purcell/gpc/>) (23).

RESULTS

Basic demographic data, SNP information, and structure of LD. The baseline characteristics of participants are shown in Table 1. The basic information of the 19 genotyped SNPs is summarized in online appendix Table 1 (available at <http://dx.doi.org/10.2337/db08-0377>). Graphical representation of SNPs in relation to the exon-intron structure and the LD pattern between markers are depicted in Fig. 1. We compared the structures of LD across a 419-kb region containing the *FTO* gene using genotype data from the CHB and CEU HapMap samples. The LD structures across this region shared high similarity between the two populations (online appendix Fig. 1).

Association analysis of genetic variants of the *FTO* gene with obesity and BMI. The rs9939609 A allele was identified as the risk variant for obesity in populations of European ancestry (6). Among the 19 SNPs in this study, the rs9939609 A allele was strongly associated with obesity ($P = 7.0 \times 10^{-4}$) (Table 2) (Fig. 2). The per-A allele increase of odds ratio for obesity was 1.43 (95% CI 1.16–1.75) (Table 2 and online appendix Fig. 2). The association remained significant after correction for multiple testing. The genotypic odds ratio for obesity was 2.60 (1.24–5.46) ($P = 0.011$) for the AA genotype and 1.32 (1.05–1.66) ($P = 0.018$) for the AT genotype. The genetic model was best fit with an additive model ($P = 7.0 \times 10^{-4}$,

TABLE 1
Basic characteristics of the study subjects

	<i>n</i>	Male-to-female ratio	Age (years)	BMI (kg/m ²)
Obesity case-control study				
Case subjects	638	219:419	37.00 ± 0.56	38.86 ± 8.19
Control subjects	1,610	822:788	61.08 ± 0.33	24.04 ± 2.89
Type 2 diabetes case-control study				
Case subjects	759	381:378	60.03 ± 11.85	24.66 ± 3.40
Control subjects	784	438:346	63.37 ± 14.0	23.63 ± 3.08

Data are means ± SD, unless otherwise indicated.

0.0098, and 0.014 for additive, recessive, and dominant model, respectively). When different criteria for obesity were applied (24), the associations were also significant (allelic $P = 7.6 \times 10^{-4}$ for obesity defined as BMI ≥ 28 kg/m² and 0.0081 for BMI ≥ 27 kg/m²). The frequency of the rs9939609 A allele (12.6%) was substantially lower in our study than that of European populations (~45%) (6), corresponding to a lower population-attributable risk fraction of 8.7% in the Chinese population.

The rs9939609 A allele was also associated with increased BMI ($P = 0.0024$) (Fig. 2) and weight ($P = 0.0065$). In our study cohort, carriers with AA genotype ([means ± SD] BMI 31.52 ± 8.76 kg/m²) and AT genotype (28.75 ± 7.89 kg/m²) were heavier than those with TT genotypes (28.08 ± 8.45 kg/m²) ($P = 0.0088$ and 0.048, respectively) (Fig. 3). The genetic model was best fit with an additive genetic model ($P = 0.0024$, 0.0091, and 0.073 for additive, recessive, and

dominant models, respectively). Each additional copy of the rs9939609 A allele was associated with a BMI increase of a mean 0.124 Z score units, equivalent to ~0.37 kg/m² or 1.07 kg body wt for a person 1.7 m tall (online appendix Fig. 2). The extent of variance in BMI explained by rs9939609 was ~0.5% in the Chinese population.

There was no heterogeneity in the per-A allele increase of odds ratio for obesity and effect size on BMI among different study populations (online appendix Fig. 2). We did not detect any significant interaction between rs9939609 genotype and age or sex on the risk of obesity or BMI (data not shown).

Association analysis of genetic variants of the *FTO* gene with type 2 diabetes. We did not observe significant association between rs9939609 and type 2 diabetes. Two SNPs (rs16952777 and rs1107355) in LD block 1 were nominally associated with type 2 diabetes (Table 3). SNPs

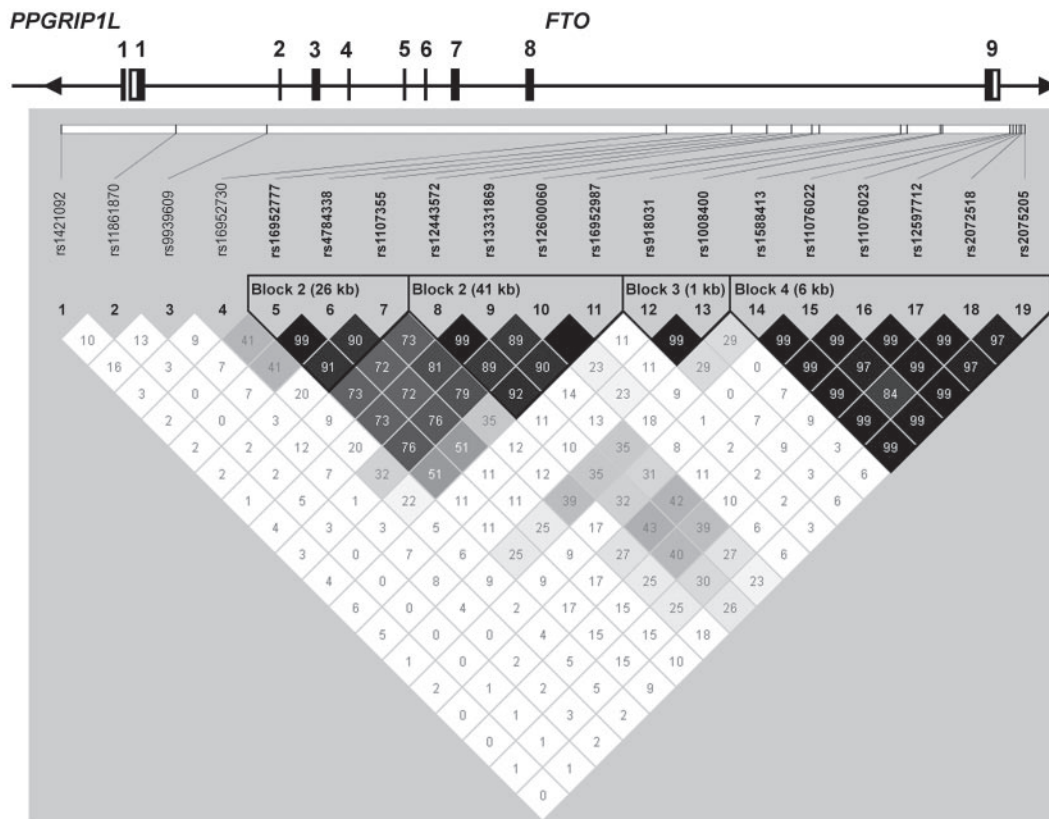


FIG. 1. Graphical representation of SNPs in relation to the exon-intron structure (upper part) and Haploview LD graph of the *FTO* gene (lower part). The exon regions are shown with filled rectangles and numbered in order. Pairwise LD coefficients $D' \times 100$ was shown in each cell (D' values of 1.0 were not shown). Alternative D' /logarithm of odds color scheme of Haploview was applied for LD color display (high logarithm of odds score and high D' in black; high logarithm of odds score and low D' in white; low logarithm of odds score and high D' in shades of gray; low logarithm of odds score and low D' in white).

TABLE 2
Association analysis of *FTO* sequence variants and obesity

No.	SNP name	Major/minor allele	Genotype distribution*		Genotypic P_{nominal}	MAF		Odds ratio for obesity (95% CI)	Allelic P_{nominal} (adjusted P) [†]	Allelic $P_{\text{permutated}}$ [‡]
			Case	Control		Case	Control			
1	rs1421092	G/A	(172:280:179)	(356:775:428)	0.018	0.494	0.476	1.08 (0.94–1.26)	0.26 (0.70)	0.96
2	rs11861870	T/C	(119:308:206)	(282:766:534)	0.81	0.432	0.421	1.04 (0.90–1.20)	0.60 (0.83)	1.0
3	rs9939609	T/A	(18:167:425)	(20:347:1158)	0.0028	0.166	0.126	1.43 (1.16–1.75)	7×10^{-4} (0.034)	0.0087
4	rs16952730	A/G	(52:268:310)	(136:651:784)	0.81	0.297	0.294	1.02 (0.87–1.19)	0.82 (0.69)	1.0
5	rs16952777	C/G	(142:313:159)	(342:786:425)	0.97	0.485	0.472	1.01 (0.88–1.17)	0.84 (0.32)	1.0
6	rs4784338	T/G	(41:315:165)	(338:785:432)	0.99	0.481	0.470	1.01 (0.87–1.16)	0.96 (0.27)	1.0
7	rs1107355	G/A	(74:312:228)	(273:756:542)	0.15	0.393	0.415	0.88 (0.76–1.02)	0.098 (0.42)	0.67
8	rs12443572	C/G	(12:171:426)	(50:443:1,047)	0.16	0.160	0.176	0.85 (0.70–1.03)	0.097 (0.55)	0.67
9	rs13331869	T/A	(11:166:44)	(47:436:1,046)	0.080	0.152	0.174	0.84 (0.69–1.02)	0.077 (0.33)	0.58
10	rs12600060	G/T	(119:323:168)	(307:766:462)	0.61	0.460	0.450	1.08 (0.93–1.25)	0.31 (0.84)	0.98
11	rs10952987	G/A	(80:299:249)	(208:707:647)	0.58	0.366	0.360	1.04 (0.89–1.21)	0.64 (0.73)	1.0
12	rs918031	T/C	(86:309:233)	(246:719:603)	0.38	0.383	0.386	0.97 (0.84–1.13)	0.68 (0.72)	1.0
13	rs1008400	C/T	(87:310:231)	(249:718:605)	0.34	0.385	0.387	0.97 (0.83–1.12)	0.65 (0.73)	1.0
14	rs1588413	C/T	(54:275:297)	(118:611:855)	0.029	0.306	0.268	1.23 (0.98–1.31)	0.011 (0.46)	0.12
15	rs11076022	G/A	(142:330:159)	(324:811:448)	0.28	0.486	0.462	1.13 (0.98–1.31)	0.10 (0.63)	0.68
16	rs11076023	T/A	(117:311:190)	(272:744:514)	0.31	0.441	0.422	1.11 (0.96–1.29)	0.16 (0.60)	0.85
17	rs12597712	C/G	(119:315:186)	(280:771:500)	0.40	0.446	0.429	1.11 (0.96–1.28)	0.16 (0.65)	0.86
18	rs2072518	G/A	(137:319:170)	(334:801:442)	0.65	0.474	0.466	1.07 (0.92–1.24)	0.36 (0.73)	0.99
19	rs2075205	A/T	(153:303:133)	(364:776:374)	0.36	0.483	0.503	0.91 (0.89–1.06)	0.22 (0.49)	0.93

*Genotype distributions are shown as the counts of three genotypes (aa, Aa, and AA). a, minor allele; A, major allele. [†]Adjusted for age, sex, and BMI. [‡]Permutation for 10,000 times. MAF, minor allele frequency. Bold indicates $P < 0.05$.

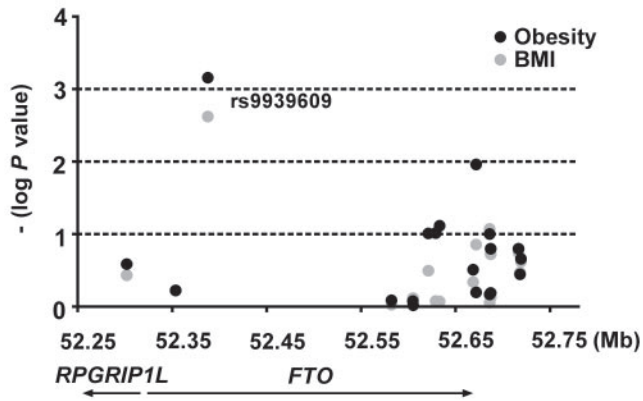


FIG. 2. Associations of SNPs near the *FTO* and *RPGRIP1L* gene regions of chromosome 16 with obesity and BMI in the Chinese population.

in the same block were also nominally associated with fasting glucose concentrations in nondiabetic subjects (online appendix Table 2). However, none of these associations remained significant after adjustment for multiple testing.

Association of *FTO* genetic variants with obesity-related metabolic traits. Results from the association analysis with other obesity-related metabolic traits are shown in online appendix Table 2. We did not observe significant association between rs9939609 and obesity-related metabolic traits, including fasting glucose, insulin, cholesterol, triglycerides, uric acid, C-reactive protein, and blood pressure. We found nine hypotheses with $P_{\text{nominal}} < 0.05$, but none of them remained significant after permutation testing. A borderline-significant association result was obtained between homeostasis model assessment of β -cell function and rs1421092 after permutation testing ($P_{\text{permuted}} = 0.054$).

DISCUSSION

Genetic polymorphisms of the *FTO* gene are the only genetic variants that have been reproducibly associated with obesity in populations of European ancestry

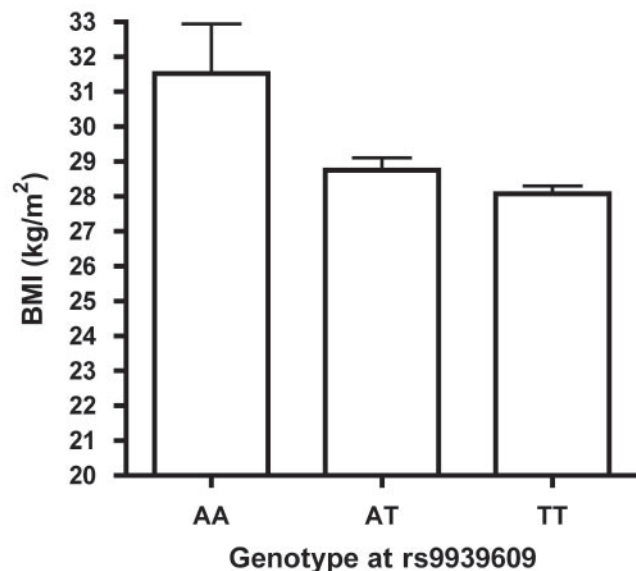


FIG. 3. BMI according to genotype at rs9939609. Data were expressed as means \pm SE (error bars).

(6,7,9,10). However, these associations were controversial in Asian populations. Li et al. (13) found no association of *FTO* variants with obesity and BMI in the Chinese population. Horikoshi et al. (14) also found no association of *FTO* variants with BMI in the Japanese population. In contrast, another group reported that rs9939609 was associated with BMI in the Japanese population (25). A recent study (26) also found strong associations of rs9939609 and other SNPs located in the intron 1 LD block with severe obesity in the Japanese population. In this study, we confirmed the strong association of *FTO* genetic variants with obesity and BMI in a Han Chinese population. This is one of the first studies that successfully replicated the association of *FTO* genetic polymorphisms with obesity in the Chinese population. Furthermore, we found that the effect size of the rs9939609 A allele on obesity risk and BMI are comparable with that in European populations (6,7). However, the risk allele was much less common in the Chinese population than in European populations (12.6 vs. 45%), leading to a lower population-attributable risk fraction (8.7 vs. 22%). Only $\sim 1.7\%$ of the Chinese population were homozygotes of the A allele, in contrast to 16% in European populations. The variance of BMI explained by rs9939609 was also lower ($\sim 0.5\%$) when compared with European populations ($\sim 1\%$). Previous analyses suggested that purifying selection (negative selection) has operated on the *FTO* gene since the divergence of chimpanzee and human (12). It will be of interest to reconstruct the phylogenetic relationship between *FTO* genetic variants and to explore possible adaptive evolution to environmental changes.

Li et al. (13) recently reported no association of *FTO* genetic polymorphism in the intron 1 block (rs9939609, rs8050136, and rs9930506) with obesity in the Chinese population. The reason for the discrepancy is not known. The sample size and design of the study by Li et al. was comparable with our study and was sufficiently powered. However, our study recruited mainly young obese case subjects. This approach may increase the genetic load and decrease the interference of environmental effects. It is also possible that unrecognized difference in population structure existed between two study populations. Li et al. also proposed that other *FTO* variants outside the intron 1 block might be associated with obesity. Therefore, instead of testing only few variants, we adopted a gene-based approach by selecting common and potential functional SNPs across the *FTO* and nearby *RPGRIP1L* gene. Although the coverage of *FTO* genetic variation was far from sufficient using this approach, the highest association signal appeared in the intron 1 of the *FTO* gene. Consistent with our findings, Hotta et al. (26) also found the highest association signals with severe obesity in the intron 1 block of the *FTO* gene. These data indicate that the underlying causative variant is located in the intron 1 block or is in strong LD with SNPs in the intron 1 block in the Chinese or Japanese populations, similar to the findings in European populations (6,7,9,10).

We did not detect an association of rs9939609 with type 2 diabetes in our study. Only nominal associations of two SNPs located in a nearby LD block were found with type 2 diabetes and fasting glucose. However, assuming an allele frequency of 12.5%, an allelic relative risk of 1.17 (8,27,28), and diabetes prevalence of 8% in the Chinese population in Taiwan, enrollment of $\sim 2,300$ case subjects would be necessary for the case-control study to have 80% power (23). A sample size of at least threefold of the present

TABLE 3
Association analysis of *FTO* sequence variants and type 2 diabetes

No.	SNP name	Major/ minor allele	Genotype distribution*		Genotypic P_{nominal}	MAF		Odds ratio for type 2 diabetes (95% CI)	Allelic P_{nominal} (adjusted P) [†]	Allelic $P_{\text{permutated}}$ [‡]
			Case	Control		Case	Control			
1	rs1421092	G/A	(178:356:219)	(164:376:208)	0.50	0.473	0.469	1.01 (0.88–1.18)	0.83 (0.92)	1.0
2	rs11861870	T/C	(136:358:259)	(131:377:256)	0.77	0.419	0.420	1.00 (0.86–1.15)	0.95 (0.80)	1.0
3	rs9939609	T/A	(11:172:55)	(10:166:550)	0.94	0.132	0.127	1.05 (0.84–1.31)	0.67 (0.86)	1.0
4	rs16952730	A/G	(61:316:380)	(71:314:371)	0.65	0.289	0.302	0.94 (0.80–1.10)	0.44 (0.64)	1.0
5	rs16952777	C/G	(154:366:219)	(180:384:188)	0.095	0.456	0.493	0.86 (0.75–0.99)	0.038 (0.056)	0.43
6	rs4784338	T/G	(153:370:220)	(175:378:194)	0.20	0.455	0.488	0.88 (0.76–1.01)	0.071 (0.14)	0.58
7	rs1107355	G/A	(115:369:270)	(146:369:246)	0.092	0.397	0.435	0.86 (0.74–0.98)	0.033 (0.044)	0.36
8	rs12443572	C/G	(19:216:50)	(23:214:50)	0.82	0.172	0.176	0.97 (0.77–1.18)	0.75 (0.61)	1.0
9	rs13331869	T/A	(16:211:499)	(23:214:501)	0.55	0.167	0.177	0.94 (0.77–1.14)	0.49 (0.49)	1.0
10	rs12600060	G/T	(157:354:223)	(139:379:218)	0.37	0.455	0.446	1.04 (0.89–1.20)	0.63 (0.71)	1.0
11	rs16952987	G/A	(96:350:308)	(101:339:311)	0.86	0.559	0.561	0.99 (0.86–1.16)	0.93 (0.99)	1.0
12	rs918031	T/C	(114:344:289)	(114:358:285)	0.88	0.483	0.486	0.99 (0.85–1.18)	0.86 (0.90)	1.0
13	rs1008400	C/T	(115:344:29)	(115:357:284)	0.86	0.383	0.387	0.98 (0.85–1.14)	0.82 (0.86)	1.0
14	rs1588413	C/T	(56:295:40)	(52:290:423)	0.78	0.269	0.259	1.05 (0.89–1.24)	0.52 (0.55)	1.0
15	rs11076022	G/A	(156:386:213)	(148:397:223)	0.79	0.462	0.453	1.04 (0.90–1.20)	0.61 (0.60)	0.87
16	rs11076023	T/A	(140:351:243)	(114:362:25)	0.21	0.430	0.405	1.11 (0.96–1.29)	0.15 (0.17)	0.93
17	rs12597712	C/G	(141:366:235)	(120:375:249)	0.33	0.437	0.413	1.10 (0.95–1.28)	0.19 (0.21)	0.91
18	rs2072518	G/A	(167:378:205)	(150:388:228)	0.35	0.475	0.450	1.10 (0.95–1.28)	0.18 (0.16)	0.99
19	rs2075205	A/T	(183:367:178)	(162:375:185)	0.48	0.503	0.485	1.07 (0.93–1.25)	0.31 (0.36)	1.0

*Genotype distributions are shown as the counts of three genotypes (aa, Aa, and AA). a, minor allele; A, major allele. [†]Adjusted for age, sex, and BMI. [‡]Permutation for 10,000 times. MAF, minor allele frequency. Bold indicates $P < 0.05$.

study would be needed to detect the effect. Therefore, our study is underpowered to detect such association. Furthermore, the type 2 diabetic case subjects in our study cohort was comprised of mostly nonobese subjects (mean BMI 24.66 kg/m²). This is in contrast to the type 2 diabetic case subjects in the Welcome Trust Case Control Consortium and U.K. Type 2 Diabetes Genetic Consortium (mean BMI 30.95 kg/m²) (8,27,28). The lower BMI of type 2 diabetic case subjects in our study would weaken the genetic contribution of *FTO* to type 2 diabetes. In accord with our study, two studies in Japanese and Chinese populations also yielded insignificant associations of rs9939609 with type 2 diabetes (13,25). Horikoshi et al. (14) reported a nominal association of rs8050316 with type 2 diabetes, but no association was found with rs9939609 in Japanese. The mean BMI of type 2 diabetic case subjects in these studies was similar to our study. Given the lower risk allele frequency and the relatively leaner body build of type 2 diabetic patients in the Chinese and Japanese population, larger sample size is needed to detect the association with type 2 diabetes, and the genetic contribution of *FTO* to type 2 diabetes may be of less importance in these populations.

We did not observe significant associations of obesity-related metabolic traits with SNPs near the *FTO* gene. Three studies (13,14,26) in Chinese and Japanese populations also failed to detect significant associations with obesity or type 2 diabetes-related metabolic traits including fasting glucose, insulin, lipids, and blood pressure. However, a meta-analysis in 17,037 Caucasians found significant associations of the *FTO* genotype with fasting glucose, insulin, triglycerides, and HDL cholesterol (29). Again, the most probable reason for lack of association in the Chinese and Japanese population is the lack of adequate power. A similar meta-analysis combining all studies in these populations may be needed to improve the power.

In summary, we confirmed the association of *FTO* genetic polymorphisms with obesity and BMI in the Chinese population. The risk allele is much less common in the Chinese population, but its effect size on obesity risk and BMI were comparable with those in European populations. We did not observe a significant association of *FTO* genetic polymorphism with type 2 diabetes, probably due to inadequate power. Given the lower risk allele frequency and the leaner body build of type 2 diabetic patients in the Chinese population, the genetic contribution of *FTO* gene to type 2 diabetes in the Chinese population may be less than that in European populations.

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