

Variants in the Fat Mass– and Obesity-Associated (*FTO*) Gene Are Not Associated With Obesity in a Chinese Han Population

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OBJECTIVE—Recently, genome-wide association studies have provided evidence that several common variants within the fat mass– and obesity-associated (*FTO*) gene were significantly associated with obesity in populations of European origin. However, their effects in other ethnic populations remain to be elucidated.

RESEARCH DESIGN AND METHODS—In this study, we examined the association between three *FTO* variants (rs8050136, rs9939609, and rs9930506) and obesity and related traits in a population-based study of 3,210 unrelated Chinese Han subjects from Shanghai and Beijing. In secondary analyses, we also tested for association with type 2 diabetes and related traits. Logistics regression and generalized linear models were used to test for additive and dominant effects of the risk alleles.

RESULTS—The minor allele frequencies of rs8050136, rs9939609, and rs9930506 in our population (0.12, 0.12, and 0.20, respectively) were substantially lower than those observed for populations of European descent (e.g., for CEU population of HapMap: 0.45, 0.48, and 0.45, respectively). Despite our study being sufficiently powered to detect effects similar to those previously reported, none of the *FTO* SNPs were found to be associated with obesity, overweight, BMI, waist circumference, or body fat percentage. In addition, none of the SNPs exhibited significant associations with fasting levels of plasma glucose, A1C, insulin, or β -cell function (estimated via homeostasis model assessment) under either an additive or a dominant model in the quantitative trait analyses. Analyses stratified by sex or geographical region did not change these observations.

CONCLUSIONS—Our data do not support that the *FTO* common variants are major contributors of obesity or type 2 diabetes in the Chinese Han population. *Diabetes* 57:264–268, 2008

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HOMA-B, homeostasis model assessment of β -cell function; HOMA-S, homeostasis model assessment of insulin sensitivity; LD, linkage disequilibrium; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

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Obesity is a leading risk factor for multiple common diseases such as type 2 diabetes, heart disease, and hypertension and has a strong genetic component (1–4). However, identification of genetic determinants of obesity has proven to be difficult in the past decades despite numerous studies and extensive efforts. Recently, as part of a genome-wide association study for type 2 diabetes, Frayling et al. (5) identified a common variant, rs9939609, in the *FTO* gene that was strongly associated with BMI and obesity in 1,924 case and 2,939 control subjects from the U.K. This association was further replicated in 13 cohorts including 38,758 individuals of European descent, showing that each additional copy of the rs9939609 A-allele was associated with 0.36 kg/m² increase in BMI and increased the risk of being obese by 32% (5). Subsequently, several nearby single nucleotide polymorphisms (SNPs) (rs1421085, rs1781449, rs8050136, and rs9930506) were also found to be significantly associated with an increased risk of obesity in white European populations (6,7). However, these associations need to be confirmed by further replication studies, particularly in other ethnic populations. Furthermore, the differences in risk allele frequencies and linkage disequilibrium (LD) structure across ethnicities can provide further insights to refine the association signal and identify the true risk variant. Therefore, this study aims to determine whether the previously identified *FTO* SNPs are associated with obesity and obesity-related phenotypes in a population-based Chinese Han cohort including 3,210 unrelated individuals from Beijing and Shanghai, China.

RESEARCH DESIGN AND METHODS

The study sample comprised 3,210 individuals (1,423 men and 1,787 women) from the Nutrition and Health of Aging Population in China, a population-based study among noninstitutionalized Chinese Han subjects aged 50–70 years in Beijing and Shanghai. The study design, methods, and measurements of this cohort study have been described in detail elsewhere (8). In brief, all participants attended a clinical examination that included standard anthropometric measurements and fasting plasma samples collection. Height and weight were measured with participants dressed in lightweight clothing without shoes, and BMI was calculated as weight in kilograms divided by the square of height in meters. Body fat percentage was assessed using dual-energy X-ray absorptiometry in a subpopulation comprising 1,139 participants (42% male) from Shanghai. Waist circumference (in centimeters) was measured midway between the lowest rib and the iliac crest to the nearest 0.1 cm after inhalation and exhalation. Glucose was measured enzymatically on an automatic analyzer (Hitachi 7080) with reagents purchased from Wako Pure Chemical Industries (Osaka, Japan). Fasting insulin was determined by radioimmunoassay (Linco Research, St. Charles, MO). A1C concentrations were measured by turbidometric immunoassay in red blood cells on the Hitachi 7080 Analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Homeostasis model assessment of insulin sensitivity (HOMA-S) and β -cell

TABLE 1
Characteristics of the study sample

	Male	Female	Whole population
<i>n</i> (%)	1,423 (44.3)	1,787 (55.7)	3,210
Age (years)	58.8 ± 5.9	58.4 ± 6.1	58.6 ± 6.0
BMI (kg/m ²)	24.0 (21.8–26.3)	24.5 (22.1–26.9)	24.2 (22.0–26.6)
Waist circumference (cm)	85.6 (78.0–92.7)	81.7 (74.9–89.0)	83.5 (76.0–90.8)
Body fat (%)	20.4 ± 5.4	32.5 ± 5.3	27.5 ± 8.0
Fasting glucose (mmol/l)	5.95 ± 1.89	5.74 ± 1.59	5.84 ± 1.74
A1C (%)	5.98 ± 1.14	6.00 ± 1.07	5.99 ± 1.10
Fasting insulin (pmol/l)	74.4 (52.8–102.0)	88.2 (64.8–119.4)	82.2 (59.4–112.2)
HOMA-B (%)	97.3 (73.1–125.0)	113.4 (87.2–142.6)	105.9 (80.6–135.2)
HOMA-S (%)	69.5 (51.1–96.6)	59.3 (44.6–81.1)	63.6 (47.1–86.9)
Overweight	37.3	38.7	38.0
Obese	12.4	16.6	14.8
IFG	29.9	25.4	27.4
Type 2 diabetes	14.6	12.1	13.2

Data are means ± SD, median (interquartile range), or percentages unless otherwise indicated. IFG, impaired fasting glucose.

function (HOMA-B) was estimated by the homeostasis model using Levy's computer model (9). Normal weight, overweight, and obesity were defined as BMI <24 kg/m², 24 ≤ BMI < 28 kg/m², and BMI ≥28 kg/m², respectively, according to the Chinese criteria (10). Diabetes was defined either by 1999 World Health Organization criteria (11) or self-report of being previously diagnosed as diabetic or treated with medication for diabetes confirmed by medical record review. Normal fasting glucose and impaired fasting glucose were defined as fasting glucose <5.6 mmol/l (100 mg/dl) and 5.6 mmol/l (100 mg/l) ≤ fasting glucose < 7.0 mmol/l (126 mg/l), respectively. Informed consent was obtained from all participants, and study protocols were approved by the institute review board of the Institute for Nutritional Sciences. Descriptive characteristics of the population are given in Table 1.

Genotyping. Genomic DNAs were extracted from peripheral blood leukocytes by a salting out procedure (<http://www.protocol-online.org/prot/Detailed/3171.html>). Genotyping was performed by the GenomeLab SNPstream Genotyping System (Beckman Coulter) according to protocol provided by the manufacturer. Since rs1421085 and rs1781449 are in strong LD with rs8050136 and rs9930506 ($r^2 = 1$), only rs9939609, rs9930506, and rs8050136 were genotyped in our population. The genotyping success rates were 99.5% (rs8050136), 97.2% (rs9930506), and 99.4% (rs9939609), and the estimated error rate of genotyping was 0.87% based on 12% duplicate samples for each SNP ($n = 384$). The genotypic distributions of the three SNPs are similar in Shanghai and Beijing ($P > 0.72$) and in men and women ($P > 0.43$) and did not deviate from Hardy-Weinberg equilibrium ($P > 0.16$ for all SNPs) (supplementary Table 1 [available in an online appendix at <http://diabetes.diabetesjournals.org>]).

Statistical analysis. Logistic regression was used to test for association between the three *FTO* SNPs and obesity, overweight, and type 2 diabetes. For quantitative traits, we applied generalized linear models. All analyses were adjusted for sex, age, geographical region (Shanghai/Beijing), and BMI (only for type 2 diabetes and related traits). Because of the low minor allele

frequencies (MAFs) (≤0.20) we tested for the additive and the dominant effects of the risk allele. BMI, waist circumference, insulin, HOMA-S, and HOMA-B were all log transformed before analysis, and data are presented as geometric means (SE) unless otherwise indicated. Since the SNP distribution was not different between geographical regions ($P > 0.72$), we pooled all 3,210 individuals for the association studies. All analyses were stratified by sex and geographical region as secondary analyses. LD patterns and comparison of allele and haplotype frequencies between CEU and HCB populations were estimated by Haploview, version 3.32 (<http://www.broad.mit.edu/mpg/haploview>). Power calculations were performed using Quanto software (<http://hydra.usc.edu/gxe/>). A likelihood ratio test was performed to assess Hardy-Weinberg equilibrium. Nominal two-sided P values are reported, and statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

We found no significant association between any of the three *FTO* SNPs and overweight or obesity under either an additive or dominant model (Table 2). Consistently, none of the SNPs were associated with any of the obesity-related quantitative traits (BMI, body fat percentage, and waist circumference) (Table 4). Also, for type 2 diabetes, impaired fasting glucose, and related quantitative traits (plasma glucose, A1C, insulin, and HOMA-B), we observed no significant associations with any of the *FTO* SNPs, although nominal associations of rs8050136 and rs9939609 with HOMA-S were found under an additive model (Table

TABLE 2
Associations of SNPs with obesity or overweight

SNP ID	Obese vs. normal				Obesity and overweight vs. normal			
	Additive model	<i>P</i>	Dominant model	<i>P</i>	Additive model	<i>P</i>	Dominant model	<i>P</i>
rs8050136								
Male	1.019 (0.704–1.475)	0.92	0.991 (0.648–1.516)	0.97	1.121 (0.893–1.406)	0.33	1.112 (0.856–1.443)	0.43
Female	1.091 (0.812–1.467)	0.56	1.093 (0.790–1.511)	0.59	0.977 (0.984–1.016)	0.83	0.971 (0.773–1.219)	0.80
All	1.070 (0.850–1.346)	0.57	1.062 (0.822–1.372)	0.65	1.043 (0.894–1.216)	0.60	1.032 (0.869–1.225)	0.72
rs9939609								
Male	0.909 (0.615–1.342)	0.63	0.885 (0.568–1.379)	0.59	0.979 (0.836–1.147)	0.80	1.027 (0.787–1.340)	0.84
Female	1.063 (0.785–1.440)	0.69	1.087 (0.784–1.505)	0.62	1.026 (0.813–1.297)	0.83	0.938 (0.745–1.182)	0.59
All	1.006 (0.793–1.275)	0.96	1.017 (0.784–1.320)	0.90	0.939 (0.757–1.165)	0.57	0.977 (0.821–1.163)	0.80
rs9930506								
Male	1.056 (0.785–1.422)	0.72	1.002 (0.801–1.255)	0.98	1.025 (0.849–1.239)	0.79	1.025 (0.818–1.286)	0.83
Female	1.000 (0.774–1.294)	1.00	1.023 (0.715–1.463)	0.90	0.914 (0.767–1.090)	0.32	0.885 (0.726–1.080)	0.23
All	1.024 (0.843–1.243)	0.81	0.984 (0.737–1.315)	0.91	0.964 (0.848–1.097)	0.58	0.945 (0.814–1.097)	0.46

Data are OR (95% CI) unless otherwise indicated. P values were adjusted for age, sex (where appropriate), and region.

TABLE 4
Associations between the genotypes of the three SNPs and obesity or type 2 diabetes-related quantitative traits

	rs8050136			rs9930609			rs9930506					
	CC	CA	AA	P_{additive}	TT	TA	AA	P_{additive}	AA	AG	GG	P_{additive}
Obesity related*												
BMI (kg/m ²)	24.1 (0.1)	24.2 (0.1)	24.4 (0.5)	0.36	24.1 (0.1)	24.3 (0.1)	23.9 (0.5)	0.70	24.2 (0.1)	24.1 (0.1)	24.4 (0.3)	0.74
Waist circumference (cm)	83.1 (0.2)	83.6 (0.4)	83.5 (1.4)	0.29	83.2 (0.2)	83.6 (0.4)	82.5 (1.5)	0.47	83.2 (0.2)	83.2 (0.3)	84.1 (1.0)	0.68
Body fat (%)†	26.4 ± 0.2	26.6 ± 0.3	27.0 ± 1.3	0.58	26.4 ± 0.2	26.5 ± 0.4	27.2 ± 1.4	0.64	26.4 ± 0.2	26.6 ± 0.3	26.4 ± 0.9	0.71
Type 2 diabetes related‡												
Glucose (mmol/l)	5.63 ± 0.03	5.58 ± 0.05	5.58 ± 0.05	0.15	5.69 ± 0.03	5.62 ± 0.06	5.32 ± 0.23	0.07	5.70 ± 0.03	5.61 ± 0.04	5.50 ± 0.13	0.02
AIC (%)	5.85 ± 0.02	5.83 ± 0.03	5.74 ± 0.12	0.35	5.87 ± 0.02	5.83 ± 0.04	5.74 ± 0.15	0.17	5.88 ± 0.02	5.84 ± 0.03	5.75 ± 0.09	0.08
Insulin (pmol/l)	79.6 (0.8)	78.0 (1.6)	72.7 (5.2)	0.17	79.6 (0.8)	77.4 (1.6)	76.2 (6.0)	0.20	78.9 (0.9)	79.8 (1.3)	75.7 (3.6)	0.98
HOMA-B (%)	103.4 (0.9)	101.8 (1.8)	104.4 (6.5)	0.55	103.2 (0.9)	102.1 (1.8)	108.7 (7.5)	0.88	102.5 (1.0)	109.2 (1.5)	102.2 (4.3)	0.41
HOMA-S (%)	65.7 (0.6)	68.1 (1.3)	73.1 (5.0)	0.03	65.7 (0.6)	68.7 (1.3)	69.9 (5.3)	0.03	66.1 (0.7)	66.4 (1.0)	71.4 (3.3)	0.28

Data are geometric means (SE) or means ± SE unless otherwise indicated. *Adjusted for age, sex, and region; †Assessed using dual-energy X-ray absorptiometry in a subpopulation comprising 1,139 participants (42% male) from Shanghai. ‡Adjusted for age, sex, region, and BMI; participants receiving anti-glucose treatment ($n = 232$) were excluded from the analyses.

3 and Table 4). Findings remained nonsignificant when stratified by sex or geographical region.

The MAFs observed in this study (0.12, 0.12, and 0.20 for rs8050136 A-allele, rs9939609 A-allele, and rs9930506 G-allele, respectively) were similar to those in the HapMap HCB sample (0.12, 0.12, and 0.19, respectively) and somewhat lower than in the HapMap JPT population (0.17, 0.17, and 0.24, respectively) but much lower than those in the HapMap CEU population (0.45, 0.45, and 0.48, respectively) and in the HapMap YRI population except rs9930506 (0.47, 0.52, and 0.18, respectively) (supplementary Table 1).

We compared the LD patterns among the three SNPs in the *FTO* gene among our population and those of HapMap HCB, JPT, CEU, and YRI (supplementary Fig. 1). All populations showed complete (HapMap HCB, JPT, and CEU) or almost complete (our population and that of HapMap YRI) between rs8050136 and rs9939609. Considerable variation in LD across the different ethnicities was observed between rs8050136/rs9939609 and rs9930506, with strongest LD in HapMap CEU ($r^2 = 0.83$), less in JPT ($r^2 = 0.65$) and HCB ($r^2 = 0.59$), and none in YRI ($r^2 < 0.05$). Our population ($r^2 = .40$), with more than 3,000 individuals, showed less LD between rs8050136/rs9939609 and rs9930506 than that for the much smaller HapMap HCB population. Besides significantly ($P < 2 \times 10^{-5}$) lower frequency of the risk alleles in the HCB population compared with that of the CEU population, the haplotype frequencies of the haplotype block formed by the three SNPs (rs8050136, rs9939609, and rs9930506) were also significantly different. More than 80% of the HCB population carries the haplotype of the common alleles (CTA), while only 52% of the CEU population carries this haplotype ($P = 1 \times 10^{-5}$). The haplotype of the risk alleles (AAG) is carried by only 12% of the CHB population and by 44% of the CEU population ($P = 6.5 \times 10^{-7}$). We further compared the LD structures among SNPs across intron 1 or the whole region of the *FTO* gene using HapMap HCB, JPT, CEU, and YRI data and found LD patterns similar to those observed in the small plots with only the three SNPs (data not shown).

Our study was powered at 80% to detect odds ratios (ORs) of ≥ 1.29 for obesity and ≥ 1.19 for overweight and standardized β s of ≥ 0.105 (Z score) per copy of the minor allele at a significance of 5% and an MAF $\geq 12\%$. Thus, both case-control and quantitative trait analyses had sufficient power to detect similar effect sizes, as previously reported by Frayling et al.

DISCUSSION

Numerous gene variants have been reported to be associated with obesity or obesity-related phenotypes, but very few have been replicated (12–15). Lack of replication has long been a big challenge in genetic association studies of obesity. Recently, several variants within the *FTO* gene have been suggested to be strongly associated with obesity in several populations of European origin, but their effects in other ethnic populations remain to be established. This study therefore aimed to test whether these variants (rs9939609, rs9930506, and rs8050136) in *FTO* were associated with obesity or type 2 diabetes in a Chinese population. However, we were unable to replicate the association between the three *FTO* SNPs and obesity or obesity-related phenotypes despite the fact that we had sufficient power to replicate the previously reported associations. Consistently, we also failed to find evidence for

TABLE 3
Associations of SNPs with type 2 diabetes and impaired fasting glucose (IFG)

SNP ID	Type 2 diabetes vs. normal				Type 2 diabetes and IFG vs. normal			
	Additive model	<i>P</i>	Dominant model	<i>P</i>	Additive model	<i>P</i>	Dominant model	<i>P</i>
rs8050136								
Male	0.885 (0.623–1.256)	0.49	0.894 (0.600–1.331)	0.58	0.990 (0.781–1.256)	0.93	1.025 (0.780–1.348)	0.86
Female	0.932 (0.665–1.305)	0.68	0.956 (0.663–1.377)	0.81	0.983 (0.786–1.229)	0.88	0.996 (0.781–1.269)	0.97
All	0.907 (0.712–1.156)	0.43	0.927 (0.708–1.212)	0.58	0.982 (0.835–1.155)	0.83	1.006 (0.840–1.206)	0.95
rs9939609								
Male	0.883 (0.621–1.257)	0.49	0.856 (0.571–1.285)	0.45	0.934 (0.731–1.193)	0.58	0.958 (0.724–1.266)	0.76
Female	0.915 (0.647–1.293)	0.61	0.919 (0.635–1.331)	0.66	0.972 (0.772–1.222)	0.81	0.970 (0.759–1.241)	0.81
All	0.901 (0.704–1.152)	0.40	0.893 (0.680–1.174)	0.42	0.946 (0.801–1.118)	0.52	0.959 (0.798–1.153)	0.66
rs9930506								
Male	0.920 (0.693–1.221)	0.56	0.863 (0.614–1.214)	0.40	0.879 (0.719–1.073)	0.21	0.846 (0.666–1.073)	0.17
Female	0.816 (0.610–1.091)	0.17	0.857 (0.620–1.184)	0.35	0.979 (0.811–1.181)	0.82	1.015 (0.821–1.255)	0.89
All	0.868 (0.709–1.063)	0.17	0.863 (0.682–1.090)	0.22	0.924 (0.808–1.059)	0.26	0.934 (0.798–1.094)	0.40

Data are OR (95% CI) unless otherwise indicated. *P* values were adjusted for age, sex (where appropriate), region, and BMI.

association with type 2 diabetes or most of the diabetes-related phenotypes in quantitative trait analyses.

Of interest are the substantial differences in MAFs and LD structure between our population, which were in line with those reported for the HCB HapMap population and those reported for white Europeans. While the *FTO* risk alleles are common in populations of European origin (MAF 0.45–0.48), they are relatively rare (MAF 0.12–0.20) in our population and the HapMap HCB population. Potentially, these population differences suggest an evolutionary divergence that might reflect a history of negative selection against the *FTO* risk alleles in the Chinese population. A phylogenetic reconstruction of the evolutionary relationships between haplotypes within the *FTO* gene could provide more insight into this hypothesis. Consistent with this notion, Scuteri et al. (6) were not able to replicate the association of rs9930506 with obesity in African Americans, in which the MAF was 0.21, comparable with 0.20 in our population and 0.18 in the HapMap YRI sample. However, it remains possible that other common variants in the *FTO* gene, particularly those with higher MAF, may contribute to the increased risk for obesity or type 2 diabetes in the Chinese population if *FTO* is a real obesity susceptibility gene, similar to the recent findings in the *TCF7L2* gene (16–18). Moreover, different genetic architecture between Chinese and other ethnic populations is also a possible reason that these SNPs act differently in the Chinese population. In contrast to populations of European ancestry, our population had moderate LD for the SNPs in the first intron or across the whole region of the *FTO* gene. For example, rs9930506 captures 17 SNPs ($r^2 > 0.8$) in the HapMap CEU population but did not capture any SNP in the region of the *FTO* gene in our population. If rs8050136, rs9939609, and rs9930506 are just proxy for an undiscovered causative variant, the variation in the extent and pattern of pairwise LD between these SNPs and the causal variant may change the power to detect the association between our population and the European populations studied in previous studies. Our findings, together with the negative results for rs9930506 in African Americans obtained by Scuteri et al. (6), suggest that the effects of all three SNPs in the *FTO* gene may be apparent only in populations with higher MAFs and stronger LD strength.

Taken together, despite our study being sufficiently powered, we found no evidence that the previously re-

ported common variants (rs8050136, rs9939609, and rs9930506) in the *FTO* gene increased risk of obesity and type 2 diabetes in a Chinese population. Different genetic architecture and allele frequencies in Chinese may contribute to the discrepancy between our data and previous findings in European populations. Further studies are warranted to examine whether other common variants in the *FTO* gene, particularly those with higher MAFs, contribute to the increased risk for obesity or type 2 diabetes in the Chinese population.

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