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Variant rs9939609 in the *FTO* gene is associated with body mass index among Chinese children

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Abstract

Background: Fat-mass and obesity-associated (*FTO*) gene is a gene located in chromosome region 16q12.2. Genetic variants in *FTO* are associated with the obesity phenotype in European and Hispanic populations. However, this association still remains controversial in Asian population. We aimed to test the association of *FTO* genetic variants with obesity and obesity-related metabolic traits among children living in Beijing, China.

Methods: We genotyped *FTO* variants rs9939609 in 670 children (332 girls and 338 boys) aged 8-11 years living in Beijing, and analyzed its association with obesity and obesity-related metabolic traits. Overweight and obesity were defined by age- and sex-specific BMI reference for Chinese children. Obesity-related metabolic traits included fasting plasma glucose, lipid profiles, leptin, ghrelin, adiponectin and blood pressures.

Results: The frequency of rs9939609 A allele was 12.2%, which was 21.9% for the heterozygote and 1.2% for the homozygote of the A allele. The obesity prevalence among the carriers of AA/AT genotypes was significantly higher than that among those with TT genotype (36.4% vs. 22.6%, $P = 0.004$). Compared to the carrier of TT genotype, the likelihood of obesity was 1.79 (95% confidence interval (95% CI) 1.20-2.67, $P = 0.004$) for the carrier of AA/AT genotype, after adjustment of sex, age and puberty stages. The BMI Z-score of children with AA/AT genotype were significantly higher than that of their counterparts with the TT genotype (1.1 ± 0.1 vs. 0.8 ± 0.1 , $P = 0.02$). The concentration of triglyceride was 1.03 ± 0.52 mmol/L among TT carrier and 1.13 ± 0.68 mmol/L among AA/AT carrier ($P = 0.045$). While, the concentrations of adiponectin were 18.0 ± 0.4 μ g/ml among carriers of TT and 16.2 ± 0.7 μ g/ml among subjects with AA/AT genotype ($P = 0.03$). The level of glucose marginally increased in the AA/AT genotype subjects (4.67 ± 0.40 mmol/L vs. 4.60 ± 0.35 mmol/L, $P = 0.08$). The evidence of association was reduced after adjustment for BMI ($P = 0.38$ for triglyceride, $P = 0.20$ for adiponectin and glucose). There was weak evidence of association between rs9939609 and other obesity-related metabolic traits including total cholesterol (3.92 ± 0.03 mmol/L vs. 4.02 ± 0.05 mmol/L, $P = 0.10$), insulin (2.69 ± 1.77 ng/ml vs. 3.12 ± 2.91 ng/ml, $P = 0.14$), and insulin resistance (HOMA-IR 0.56 ± 0.03 vs. 0.66 ± 0.05 , $P = 0.10$).

Conclusions: Genetic variation in the *FTO* gene associates with obesity in Chinese children.

Background

Obesity is a consequence of unhealthy lifestyle combined with genetic susceptibility. Recent genome-wide association (GWA) studies identified a group of loci associated with obesity. Among those genes, *FTO* explained the largest variation of BMI and obesity [1,2]. Frayling et al. first reported the association of *FTO* genetic variants with obesity [1]. Subsequently, the association with BMI and obesity was unequivocally

replicated in European and Hispanic populations in both children and adults [3-8].

However, these associations were controversial with regard to Asian populations [9-18]. Chang et al. [9] reported that rs9939609 was associated with BMI in the Chinese population living in Taiwan, China. Tan et al. [10] also found associations of rs9939609 and other SNPs located in the intron 1 LD block with obesity in the Chinese and Malays lived in Singapore. Omori S and Hotta K [11,12] found strong associations of *FTO* variants with BMI in the Japanese population. Cha et al. [13] confirmed the strong association of *FTO* genetic variants with BMI in a Korean population. Ng et al. found association of *FTO*

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variants with BMI in East Asians but the association of *FTO* and BMI was weaker in Asians as compared to the Europeans [14]. In contrast, the first study of the association between *FTO* and BMI among Chinese population in mainland China [15] found no association of *FTO* variants with obesity and BMI in the Chinese adults aged 50-70 years living in Beijing and Shanghai. Meanwhile, Horikoshi *et al.* [16] also found no association of *FTO* variants with BMI in the Japanese population. The rs9939609 A allele frequency was lower in Chinese and Japanese compared to that in Europeans, which was assumed to be one reason of the controversial findings. Recently, Li X *et al.* [17] found that rs9939609 SNP was strongly associated with risk of obesity and newly diagnosed type 2 diabetes in the Chinese adults and Xi *et al.* [18] confirmed that *FTO* rs9939609 variant was strongly associated with BMI and the risk of obesity in Chinese children and adolescents in Beijing.

The purpose of this study is to replicate the associations of *FTO* rs9939609 with obesity and obesity-related metabolic traits in Chinese children.

Methods

Study participants

This is a cross-sectional study conducted in 2005. Two districts, Dongcheng and Chongwen, were randomly selected in downtown Beijing, China. Ten primary schools were randomly selected from the two districts. Han students of the third and fourth grade in the selected schools were asked to voluntarily participate in the study. In this study, we restrict our analysis to Han nationality to minimize the probably effect from population stratification.

A total of 1126 Han students aged 8-11 years and/or their legal guardians were invited and 674 agreed to participate and signed the informed consent form, with a participation rate of 59.9%. All the 674 Han students were enrolled and voluntarily attended a clinical examination that included standardized anthropometric measurements and fasting plasma samples collection. A total of 670 students were successfully isolated genomic DNA and genotyped *FTO* rs9939609 genotypes. No significant differences were found of age, sex, weight, height and BMI between the students who participated and who did not.

The study protocol was approved by the Ethical Committee of the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. All study participants and/or legal guardians provided written informed consent.

Anthropometric and laboratory methods

Anthropometric measurements included weight, height, waist circumference, hip circumference, subscapular

skinfold thickness, suprailiac skinfold thickness, systolic (SBP) and diastolic blood pressures (DBP). All anthropometric measurements were taken in accordance with WHO standards [19] by the trained investigators in the schools. Anthropometric measurements for each participant were taken after an overnight fast while the subject wore light clothing and no shoes.

Height was determined using a standard steel strip stadiometer and was measured to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg using a digital electronic scale (Seca, model 890, Hamburg). Waist circumference was measured mid-way between the lower rib margin and the iliac crest with flexible anthropometric tape. Hip circumference was measured at the point over the buttocks yielding the maximum circumference. The waist circumference and hip circumference were measured twice to the nearest 0.1 cm. If the variation between these two measurements was greater than 2 cm, a third measurement was taken and the mean was calculated by using the two closest measurements. The BMI Z-score, based on age and sex, was calculated according to the method recommended by WHO [20] using the WHO growth reference for children aged 5-17 years [21].

Skinfolds were lifted vertically and then measuring its thickness with Harpenden Skinfold Caliper. The subscapular skinfold was measured below the tip of the scapula. The suprailiac skinfold was measured immediately above the crest of the ilium, and the fold was lifted at a slight angle to the vertical along the normal fold line. The skinfolds were measured twice to the nearest 0.2 mm. If the variation between these two measurements was greater than 0.5 mm, a third measurement was taken and the mean was calculated by using the two closest measurements.

Blood pressure was measured in the supine position using a mercury sphygmomanometer by trained nurses. Subjects took at least a 10-min rest before the measurement was taken. Three measurements were taken from all the subjects at 2-min intervals, and the average of the last two measurements was used. These were recorded to the nearest 2 mmHg.

Bioelectrical impedance analysis (BIA) method was used to assess the body composition. A four terminal impedance plethysmograph (RJL2System 101 USA, 50 kHz, 800 μ A) was used to measure electrical impedance, resistance (R) and reactance (Xc), according to the instructions provided by the manufacturer. Fat free mass (FFM), fat mass and percent body fat were calculated using the prediction equations suggested by Deurenberg *et al.* [22].

Pubertal staging criteria and definitions used were the 5 stages of pubic hair growth, breast development, and genital development described by Marshall and Tanner

known as Tanner staging [23,24]. Data were collected by physicians during the physical examination.

Blood samples were taken in the morning after an overnight fasting. Plasma glucose was determined by a glucose-oxidase method (Osaka, Japan). Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL) were determined by enzymatic methods using commercial kits (Fuji Film, Tokyo, Japan). The intra and inter coefficient variations (CV) were less than 16% for all these tests. Serum insulin concentrations were determined by radioimmunoassay (RIA) (Human Insulin Specific RIA kit, Linco Research, St Louis, MO, USA). The intra and inter coefficient variations were 7.2% and 15.1%, respectively. Leptin and adiponectin serum concentrations were assayed by sensitive/specific RIA as follows: leptin by a highly sensitive RIA (Human Leptin RIA Kit, Linco Research, St Louis, MO, USA), the intra and inter coefficient variations were 9.3% and 14.5%, respectively; Total adiponectin were determined by competitive radioimmunoassay (Human Adiponectin Specific RIA kit, Linco Research, St Louis, MO, USA), the intra and inter coefficient variations were 7.5% and 15.8%, respectively. Total ghrelin concentrations were determined by radioimmunoassay (RIA) kit (Human Ghrelin (Total) RIA Kit, Linco Research, St. Charles, MO, USA), and the intra and inter coefficient variations were 6.6% and 12.6%, respectively.

Insulin resistance was measured by the homeostasis model assessment (HOMA). HOMA insulin resistance index (HOMA-IR) was calculated as [Plasma glucose (GLU, mmol/L) × serum insulin (mIU/L)]/22.5. HOMA insulin sensitivity index (HOMA-ISI) was calculated as 1/(GLU × serum insulin).

Definition of obesity

The age- and sex-specific BMI reference developed by Working Group on Obesity in China (WGOC) was used for defining the overweight and obesity [25]. The 85th and the 95th percentiles were used as cut-off points for defining overweight and obesity, respectively. In present study, overweight included obesity.

Genotyping

Genomic DNA was isolated from whole blood, using the QIAmp Blood kit (Qiagen). The rs9939609 SNP of the *FTO* gene was selected. This polymorphism was genotyped by allelic discrimination assays using a TaqMan probe allelic discrimination (Applied Biosystems). Fluorescence was visualized through an ABI 7900 HT fast real-time PCR system (Applied Biosystems). The genotyping success rate was 99.4%, and genotype distribution was in Hardy-Weinberg equilibrium

($P = 0.4732$). To assess genotyping reproducibility, a random 10% selection of samples was re-genotyped with 100% concordance.

Statistical analysis

A likelihood ratio test was performed to assess Hardy-Weinberg equilibrium. Based on the minor allele frequency of 0.12, a prevalence of 0.25 and a significance level at 0.05, our study was powered at 44% to detect odds ratios (OR) of 1.15 for obesity. Logistic regression analysis was performed to compare the likelihood of overweight and obesity between the carriers of TT genotype and the carrier of AA/AT genotype. Association of *FTO* rs9939609 with obesity-related measures and obesity-related metabolic traits were performed with General Linear Model, using sex, age and puberty stages as covariates. Triglyceride, insulin and leptin were natural logarithm transformed before analysis. When the associations between *FTO* rs9939609 and obesity-related metabolic traits were significant, BMI was further adjusted.

Results

Characteristics of subjects

The characteristics of the subjects are given in Table 1. A total of 670 children aged 9.3 ± 0.8 years (332 girls and 338 boys) completed the study.

The rs9939609 A allele frequency of the study population was 12.2%. The frequency of heterozygote and homozygote of the A allele was 21.9% and 1.2%, respectively. No significant differences in the genotypic distributions were found between boys and girls.

Association of *FTO* rs9939609 with overweight and obesity

The prevalence of obesity among the carriers of AA/AT genotypes was significantly higher than that among those with TT genotype (36.4% vs. 22.6%, $P = 0.004$). Compared to the carrier of TT genotype, the likelihood of obesity was 1.79 (95% confidence interval (95% CI) 1.20-2.67) for the carrier of AA/AT genotype, after adjustment of sex, age and puberty stages, Table 2.

Table 1 Characteristics of the study objects

Characteristics	Total
N	670
Age (years)	9.3 ± 0.8 (8-11)
Girl (%)	49.6
BMI (kg/m^2)	19.1 ± 3.9
BMI Z-score	0.8 ± 0.7
Overweight and obesity (%)	43.6
Obesity (%)	25.8

Data are means \pm SD, or percentages.

Table 2 Associations of the *FTO* variant with overweight and obesity¹

	Overweight and obesity			Obesity		
	Prevalence (%)	OR (95% CI)	P	Prevalence (%)	OR (95% CI)	P
TT ²	41.5	1.00		22.6	1.00	
AA/AT	50.7	1.32 (0.91-1.92)	0.15	36.4	1.79 (1.20-2.67)	0.004

¹ Logistic regression analyses, adjusted age, sex and puberty stage;

² Carriers with the TT genotype are used as the reference group.

FTO rs9939609 and obesity-related measures

Compared with the TT genotype, the weight, BMI, BMI Z-score and waist-to-hip ratio (WHR) of carriers with the AA/AT genotype were significantly higher than those with TT genotype, Table 3. Carrier with the AA/AT genotype also had significant higher subscapular skinfold thickness, suprailiac skinfold thickness, body fat and lean body mass as shown in Table 3. The height and percent body fat were not significantly different between the children with TT and AA/AT genotype.

FTO rs9939609 and obesity-related metabolic traits

The concentration of triglyceride was found obviously higher in the children with AA/AT than carriers with TT genotype (1.13 ± 0.68 mmol/L vs. 1.03 ± 0.52 mmol/L, *P* = 0.045). While, the adiponectin levels in subjects with AA/AT genotype were obviously lower than subjects with the TT genotype (16.2 ± 0.7 µg/ml vs. 18.0 ± 0.4 µg/ml, *P* = 0.03). We also found marginally increasing level of glucose in the AA/AT genotype subjects (4.67 ± 0.40 mmol/L vs. 4.60 ± 0.35 mmol/L, *P* = 0.08). The evidence of association was reduced after further adjustment for BMI (*P* = 0.38 for triglyceride, *P* = 0.20 for adiponectin and glucose). There was weak

Table 3 Association of rs9939609 with obesity-related measures¹

	TT	AA/AT	P
N	515	155	
Weight (kg)	38.1 (0.4)	40.1 (0.8)	0.02
Height (cm)	141.0 (0.3)	141.7 (0.6)	0.30
BMI (kg/m ²)	18.9 (0.2)	19.8 (0.3)	0.01
BMI Z-score	0.8 (0.1)	1.1 (0.1)	0.02
WHR	0.85 (0.003)	0.86 (0.01)	0.02
Suprailiac skinfold (mm)	18.1 (0.3)	19.5 (0.6)	0.04
Subscapular skinfold (mm)	16.5 (0.5)	19.3 (0.9)	0.003
Fat free mass (kg)	27.5 (0.3)	28.7 (0.5)	0.02
Fat mass (kg)	10.6 (0.2)	11.4 (0.4)	0.049
Percent body fat (%)	27.1 (0.2)	27.5 (0.4)	0.29

Abbreviation: BMI, body mass index; BMI Z-score, body mass index Z-score; WHR, waist to hip ratio.

¹ Data are age, sex and puberty stage adjusted mean ± standard error, using General Linear Regression Model.

evidence of association between rs9939609 and other obesity-related metabolic traits including TC (3.92 ± 0.03 mmol/L vs. 4.02 ± 0.05 mmol/L, *P* = 0.10), insulin (2.69 ± 1.77 ng/ml vs. 3.12 ± 2.91 ng/ml, *P* = 0.14), and insulin resistance (HOMA-IR 0.56 ± 0.03 vs. 0.66 ± 0.05, *P* = 0.10), Table 4.

Discussion

In this study, we confirmed the strong association of *FTO* SNP rs9939609 with obesity and BMI among Chinese children, in accord with the recent finding of Xi et al. [18]. The obesity prevalence and BMI of AA/AT genotype carriers were significantly higher than that of their counterparts with the TT genotype. Similar to the results reported by Li H (12%), Chang (12.6%) and the results described in HapMap for Han Chinese population (HCB) [9,15], the rs9939609 A allele frequency was substantially lower in our study as compared with the European populations (12.2 vs. 45%), and did not deviate from Hardy-Weinberg equilibrium (*P* = 0.47). Only 1.2% of the Chinese population were homozygote of the A allele, in contrast to 16% in European populations.

In our study, the associations of rs9939609 with obesity were significant among Chinese children. While, among the first study about the association between rs9939609 and BMI among Chinese adults in mainland China, Li H et al. [15] reported no association of *FTO* genetic polymorphism in the intron 1 block (rs9939609, rs8050136, and rs9930506) with obesity in the Chinese

Table 4 Association of rs9939609 with obesity-related metabolic traits¹

	TT	AA/AT	P	P (adjusted) ²
GLU (mmol/L)	4.60 (0.35)	4.66 (0.40)	0.08	0.20
LogTG	-0.08 (0.02)	0.03 (0.04)	0.045	0.38
TC (mmol/L)	3.92 (0.03)	4.02 (0.05)	0.10	
LDL (mmol/L)	2.24 (0.03)	2.31 (0.05)	0.28	
HDL (mmol/L)	1.41 (0.01)	1.43 (0.02)	0.40	
Loginsulin	0.68 (0.04)	0.80 (0.07)	0.14	
Logleptin	0.57 (0.08)	0.63 (0.15)	0.76	
Adiponectin (µg/ml)	18.0 (0.4)	16.2 (0.7)	0.03	0.20
Ghrelin (ng/ml)	3.72 (0.08)	3.89 (0.15)	0.30	
SBP (mmHg)	104.8 (0.4)	105.9 (0.8)	0.21	
DBP (mmHg)	67.9 (0.3)	67.8 (0.6)	0.91	
HOMA-IR	0.56 (0.03)	0.66 (0.05)	0.10	
HOMA-ISI	0.16 (0.01)	0.14 (0.02)	0.26	

Abbreviation: GLU, fasting glucose; LogTG, natural logarithm-transformed triglyceride; TC, total cholesterol; LDL, low-density lipoprotein-cholesterol; HDL, high-density lipoprotein-cholesterol; Loginsulin, log-transformed insulin; Logleptin, natural logarithm-transformed leptin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance index; HOMA-ISI, homeostasis model assessment of insulin sensitivity index.

¹ Data are age, sex and puberty stage adjusted mean ± standard error, using General Linear Regression Model.

² Further adjusted BMI.

adults. Several meta-analysis studies demonstrated significant association of *FTO* and BMI in Asian adults, although their risk allele frequency and effect size were lower compared with Europeans [14,26]. Several other studies also found positive association between *FTO* rs9939609 and the risk of obesity (OR = 1.43, OR = 1.38 and OR = 1.39 respectively) in the East Asian adults [9,12,26]. Recently, Li X et al. [17] found that the A allele was strongly associated with obesity and overweight in Chinese adults (OR = 1.45, 95% CI 1.10-1.90). Meanwhile, Xi et al. [18] firstly confirmed the significant associations of rs9939609 variant with BMI and the risk of obesity in Chinese children and adolescents in Beijing, China. Our study further confirmed the positive association for this variant in Chinese children. Although the effect size estimate of 1.79 seems larger in our study, it does not mean that the effect size is bigger than those reported in Asian adults because the 95% confidence intervals for 1.79 are wide (95% CI 1.20-2.67) and encompass the previously reported estimates. In addition, the effect size of *FTO* rs9939609 on the risk of obesity observed in our study was similar to the effects reported by Frayling et al. in UK children aged 11 years (OR per-A allele = 1.35, 95% CI 1.14-1.61) [3] and Hinney et al. in German children and adolescents (OR = 1.57, 95% CI 1.30-1.90) [27], although the minor allele frequency of rs9939609 SNP was lower in Chinese than in European populations.

The reason for the different results among Chinese populations might be the ages of studied population. Our study recruited children aged 8-11 years; the subjects aged 6-18 years in Xi's study [18] and 45 years in Li X's study [17], all being younger than the study population in Li H's study who were 50-70 years [15]. The approach among young population may increase the genetic load and decrease the interference of environmental effects. Qi et al. reported that the association between rs9939609 and BMI in elderly men decreased [28]. Some studies also suggest that genetic effects influencing obesity may alter throughout life and decrease with older age [29-31]. The interference of environmental effects increases with older age and may exert stronger influences on later BMI. Loos's study also showed that the association between *FTO* and BMI was higher in children than in adults [32]. This discrepancy might be due to inability of BMI to capture adiposity as successfully in older people as in younger people. Aging is characterized by lean body mass loss and adipose tissue increase without weight gain that may not be captured by BMI, and traditional adiposity measures lose their predictive ability in the elderly [33-35].

We also confirmed the finding of Freathy et al. [36] that *FTO* genotype was associated with metabolic traits to an extent consistent with its effect on BMI, which

were reduced after adjustment for BMI. Those results implied that the association of *FTO* genotype with plasma triglyceride and adiponectin may be mediated through obesity. In accord with Zabena's report [37], no association between serum leptin levels and rs9939609 genotypes was detected. In according with several studies [10,16,38,39] in Chinese and Japanese populations, there was weak evidence of association between rs9939609 and obesity-related metabolic traits including TC, insulin, and insulin resistance. This may be due to the minor allele frequency in the Chinese Han population and other Asians was much smaller than that in the European population. A larger sample size is needed to achieve sufficient power under a smaller minor allele frequency. Our study only obtained 44% power to detect the association between *FTO* genotype and obesity. It would require more power to detect the associations between *FTO* genotype and other obesity-related metabolic traits.

The limitations of the present study should be noticed. The first is the small sample size and limited statistic power, though it seems to be sufficient to detect the significant association between *FTO* and obesity, it may be not sufficient to detect the association between *FTO* and some obesity-related metabolic traits if it did exist, which need further research. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, overweight and obese students and/or who pay more attention to health may be more likely to participate. However, we can still infer similar conclusions except that students carrier specific genotype would be more prefer to the study, which was not the case by now. Therefore, we do not consider the selection bias as a major limitation. Moreover, using a single genetic variant of given gene (*FTO* rs9939609) in present study was also a limitation, which may be in linkage disequilibrium with polymorphisms of other nearby genes that actually contributed to the development of obesity.

Conclusions

In summary, we replicated that the genetic variation in the *FTO* gene associates with obesity in the Chinese children. More replication studies about the association between the *FTO* gene and obesity-related metabolic traits were guaranteed among larger Chinese population.

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Authors' contributions

HF and YL coordinated the DNA sample collection and genotyping, carried out statistical analyses and drafted the manuscript. SD carried out the field work including sample and data collection. GM, XH, QZ and AL were

involved in the project design and helped draft the manuscript. GM supervised the progress of the study and finalized the manuscript critically. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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