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ORIGINAL ARTICLE

Combined effects of *FTO* rs9939609 and *MC4R* rs17782313 on obesity and BMI in Chinese Han populations

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Abstract Genetic variants of *FTO* and *MC4R* have been linked with obesity and *T2DM* in populations of Europeans. In this study, we have investigated the association of *FTO* rs9939609 and *MC4R* rs17782313 with obesity and *T2DM* in the Chinese population and analyzed the relationship between rs9939609 and rs17782313. 2351 individuals were recruited. We tested the rs9939609 and rs17782313 by sequences retrieval method. Clinical and biochemical characteristics were measured. The rs9939609 per-A allele and rs17782313 per-C allele increases of OR for obesity was 1.42 (95% CI 1.39–3.74) and 1.39 (95% CI 1.21–3.53).The genotypic OR for obesity was 1.92 (95% CI 1.81–4.67) for AA genotype, 1.71 (95% CI 1.47–4.54) for AT genotype, 1.87 (95% CI 1.72–4.00) for CC genotype, and 1.44 (95% CI 1.20–3.18) for CT genotype. BMI of participants carrying neither *FTO* nor *MC4R* risk allele was 25.9 ± 4.9, one risk allele was 26.4 ± 5.1, two risk alleles was 28.1 ± 5.5, and there or four risk alleles was 33.2 ± 6.3. We found no association between FTO and MC4R and the Chinese population with *T2DM* ($P > 0.05$). Our data support that the rs9939609 and rs17782313 are strongly associated with obesity and BMI. Their combined effects were significant in Chinese population. No association between FTO and MC4R and Chinese population with T2DM was found.

Keywords Gene polymorphism · Obesity · Type 2 diabetes · Chinese Han population

Introduction

Obesity is rapidly growing international health problem. It is a leading risk factor for multiple common diseases such as type 2 diabetes, heart diseases, and hypertension and has a strong genetic component [1]. Genetic factors play an important role in the development of obesity, but the underlying genetic causes are poorly understood [2]. The *FTO* gene was originally identified in mouse. Recent studies have revealed a strong association between common variants in the first introduction of *FTO* and obesity in the children and adults. Each rs9939609 an allele (chr16:52,378,028; dbSNP build 129) increased body weight by 1.2 kg in adult general populations and conferred a 31% higher risk of developing obesity [3]. *FTO* protein was found to be ubiquitously expressed in various tissues with relatively high levels in the hypothalamus and pancreatic islets [4]. *FTO* protein could, therefore, be a key link between central nervous system and energy balance. The *MC4R* gene, encoding the melanocortin 4 receptor, was the first locus at which mutations were associated with dominantly inherited morbid human obesity and was the commonest genetic cause of human obesity described before the era of genome-wide association (GWA) studies. The rs17782313 C allele (chr18:56, 002, 077; dbSNP build 129), located 188 kb downstream of *MC4R*, was similarly associated with obesity (OR = 1.30 [1.20–1.41]) in

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populations of European origin [5]. However, these associations need to be confirmed by further replication studies, particularly in other ethnic populations. Europeans and Chinese are different in their environmental risk, profiles, body composition, and genetic backgrounds. In this study, we have investigated the association of *FTO* and *MC4R* gene polymorphism with obesity and type 2 diabetes in the Chinese population and analyzed the relationship between *FTO* rs9939609 and *MC4R* rs17782313.

Research design and methods

We recruited 2,351 individuals aged 50–70 years (1,172 men and 1,179 women) which all were belonging to Han ethnicity from Hubei province of China, all their parents and grand parents self-identifying as Han, with no apparent consanguinity, through Physical Examination Center at ZhongNan Hospital of Wuhan University. This study had been reviewed and approved by Hubei ethics committee. The study subjects had been given informed consent to participate in the study by letters of advice. The experiment was divided into two groups, including obesity group (560 cases) and type 2 diabetes group (591cases) studies. The number of control subjects was 1,200, which of all clinical and biochemical characteristics were normal. Obesity was defined as BMI $\geq$ 28 kg/m^2, according to the Chinese criteria [6]. At the same time, the waist circumferences(male: WC $>$ 90 cm; female: WC $>$ 80 cm) were defined as central obesity [6].The patients were diagnosed *T2DM* based on 2003 American Diabetes Association criteria, expelled patients with type 1 diabetes, type 2 diabetes with diabetic ketoacidosis or hyperosmolar nonketotic diabetic coma, or with tumor, with severe liver or renal diseases.

Clinical measurements

Height and weight were measured with participants dressed in lightweight clothing without shoes. BMI was calculated as the weight in kilograms divided by the square of height in meters. Body fat percentage was assessed using dual energy X-ray absorptiometry. Waist circumference (in cm) was measured midway between the lowest Tib and the iliac crest to the nearest 0.1 cm after inhalation and exhalation. Fasting glucose was measured enzymatically on an automatic analyzer (Hitachi 7080). Fasting insulin was determined by radioimmunoassay (Linco Research, St. Charles, MO, USA). β-cell function (HOMA-B) and HOMA-IR was calculated using computer model (HOMA Calculator v2.2). HbA1C were measured by turbidometric immunoassay in red blood cells on the Hitachi 7080 analyzer. Blood total cholesterol, triglycerides, and LDL-C were also measured. Of the controls whose medical conditions were normal by done body examination in our department. We only extracted DNAs for genotyping.

Genotyping

Each subject donated 5 ml of blood sample for genomic DNA extraction. Genotyping conditions in our study were referring to a previous report [4]. The polymerase chain reaction (PCR) was performed on an automated DNA thermal cycler (Beijing Institute of Technology, China) with the primers of FTO rs9939609 (FP: 5′-AAGAG ATGATCTCAAATCTACTTTATGAGATA-3′ and RP: 5′-TTAGAGTAACAGAGACTATCCAAGTGCATCAT-3′, annealing temperature 54°C, 30 cycles and a 155 bp product) [4]. The primers of MC4R rs17782313 were designed using the primer5 software (FP: 5′-AGGAAA CAGCAGGGATAGGG-3′ and RP: 5′-TGCTGAGACAG GTTCAT AAAAAG-3′, annealing temperature 56°C, 30 cycles and a 407 bp product). The *MC4R* rs17782313 and *FTO* rs9939609 genotyped using sequences retrieval (SinoGenoMax Co.,Ltd).

Statistical analysis

Statistical analysis was performed using SPSS 11.5 for Windows. Genotype and allele frequencies were compared with the Hardy–Weinberg equilibrium model and then analyzed by χ^2 testing using contingency tables, respectively. Allelic and genotypic associations of the *FTO* rs9939609 and *MC4R* rs17782313 variant found significant were evaluated by computing odds ratios and 95% CIs. All data were presented as means $\pm$ SD. The clinical and biochemical characteristics with these genotypes were compared by one-way ANOVA. $P < 0.05$ was considered significant. All analyses were adjusted for sex, age, and geographical region.

Results

Effects of *FTO* and *MC4R* on obesity and BMI

The *MC4R* and *FTO* effects on the BMI were first investigated independently of each other. All the genotype and allele frequencies of *FTO* rs9939609 and *MC4R* rs17782313 are in agreement with the Hardy–Weinberg equilibrium ($P > 0.05$). All the frequencies were presented in Table 1.

Effects of the *FTO* rs9939609 on obesity and BMI (Table 1 and Table 2)

Genotype distribution were significantly different between obesity patients and controls ($P < 0.05$).The A allele and

Table 1 *FTO* rs9939609 and *MC4R* rs17782313 distributions in obesity and control groups

Groups	*n*	*FTO*(rs9939609)					*MC4R*(rs17782313)				
		Genotypes n(frequency)			Alleles n(frequency)		Genotypes n(frequency)			Alleles n(frequency)	
		AA	AT	TT	A	T	CC	CT	TT	C	T
Obesity	560	124 (22.1)	294 (52.5)	142 (25.4)	542 (48.4)	578 (51.6)	135 (24.1)	275 (49.1)	150 (26.8)	545 (48.7)	575 (51.3)
Controls	1200	205 (17.1)	545 (45.4)	450 (37.5)	955 (39.8)	1445 (60.2)	210 (17.5)	554 (46.2)	436 (36.3)	974 (40.6)	1426 (59.4)

Data are means (SD) for genotypic classes on unrelated individuals. FTO rs9939309: through Pearson χ^2 test, comparison of genotypes: obesity versus controls, $\chi^2 = 26.05$, $P < 0.05$; comparison of alleles: obesity vs. controls, $\chi^2 = 23.11$, $P < 0.05$; MC4R rs17782313: through Pearson χ^2 test, comparison of genotypes: obesity versus controls, $\chi^2 = 19.54$, $P < 0.05$; comparison of alleles: obesity versus controls, $\chi^2 = 19.52$, $P < 0.05$

Table 2 Obesity and type 2 diabetes studies

	FTO(rs9939609)				*MC4R*(rs17782313)			
	TT	AT	AA	P	TT	CT	CC	P
Obesity-related								
N	592	839	329		596	829	345	
BMI (kg/m^2)	26.9 ± 4.9	28.3 ± 4.6	30.1 ± 5.1	0.000073	25.2 ± 4.9	27.3 ± 5.1	28.9 ± 5.4	0.0033
Waist circumference (cm)	87.9 ± 16.1	89.3 ± 17.2	92.7 ± 16.4	0.00025	86.9 ± 16.7	88.5 ± 16.4	90.7 ± 17.2	0.04
Body fat (%)	28.2 ± 8.9	30.6 ± 9.3	31.5 ± 9.1	0.0032	28.8 ± 8.5	29.6 ± 8.4	31.3 ± 9.1	0.02
Type 2 diabetes								
N	886	723	182		912	712	167	
Fasting glucose(mmol/l)	5.69 ± 0.07	5.65 ± 0.04	5.52 ± 0.31	0.07	5.56 ± 0.11	5.54 ± 0.09	5.52 ± 0.25	0.11
Fasting insulin(pmol/l)	82.6(0.8)	79.4(1.6)	79.2(6.0)	0.19	85.6(0.8)	82.4(1.6)	82.2(6.0)	0.25
HOMA-B (%)	101.2(0.9)	101.5(1.7)	109.7(8.5)	0.85	103.1(0.8)	102.6(1.1)	106.2(6.9)	1.23
HOMA-IR	3.35(3.91)	3.42(2.72)	4.96(8.7)	0.28	3.38(4.11)	3.43(3.12)	4.87(5.7)	0.37
HBA1C (%)	6.01 ± 0.02	5.93 ± 0.06	5.94 ± 0.13	0.15	6.13 ± 0.02	5.98 ± 0.02	5.84 ± 0.23	0.18
TC(mmol/l)	4.46 ± 1.54	4.05 ± 1.50	4.41 ± 1.72	0.885	4.40 ± 1.51	4.09 ± 1.54	4.44 ± 1.75	0.889
TG(mmol/l)	2.32 ± 1.92	2.16 ± 1.31	2.11 ± 1.81	0.873	2.29 ± 1.91	2.18 ± 1.28	2.13 ± 1.82	0.878
LDL-C(mmol/l)	3.02 ± 2.02	3.21 ± 1.78	2.96 ± 1.84	0.456	3.11 ± 2.01	3.19 ± 1.75	2.91 ± 1.80	0.443

Data are geometric means (SD) or means ±SD unless otherwise indicated

AA genotype frequencies were all significantly higher in obesity patients than controls ($P < 0.05$). The A allele odds ratio for obesity was 1.42 (95% CI 1.39–3.74). The genotypic odds ratio for obesity was 1.92 (95% CI 1.81–4.67) for the AA genotype and 1.71 (95% CI 1.47–4.54) for the AT genotype.

Effects of the *MC4R* rs17782313 on obesity and BMI (Table 1 and Table 2)

Genotype distribution were also significantly different between obesity patients and controls ($P < 0.05$). We calculated the C allele and CC genotype frequencies were all significantly higher in obesity patients than controls ($P < 0.05$). The C allele odds ratio for obesity was 1.39 (95% CI 1.21–3.53).The genotypic odds ratio for obesity was 1.87 (95% CI 1.72–4.00) for the CC genotype and 1.44 (95% CI 1.20–3.18) for the CT genotype.

The combined effects of *FTO* rs9939609 and *MC4R* rs17782313 on obesity and BMI (Fig. 1)

In this study, we observed that BMI of participants simultaneously carrying the A and C alleles was significantly higher than carrying neither *FTO* nor *MC4R* risk allele ($\chi^2 = 29.78$, $P < 0.05$) and carrying alone the A or C alleles controls ($\chi^2 = 27.45$, $P < 0.05$). BMI of participants carrying neither *FTO* nor *MC4R* risk allele was 25.9 ± 4.9, carrying one risk allele was 26.4 ± 5.1, carrying two risk alleles was 28.1 ± 5.5 and carrying three or four risk alleles was 33.2 ± 6.3.

Effects of *FTO* and *MC4R* on type 2 diabetes (Table 2 and Table 3)

All the frequencies were presented in Table 3. We found no association between *FTO* and the Chinese population with *T2DM* ($P > 0.05$). The A allele and AA genotype frequencies were all no significant statistic differences in *T2DM* patients and controls ($P > 0.05$). Through the Pearson χ^2 test, no significant statistic differences were found of the three genotypes ($P > 0.05$) or the two alleles ($P > 0.05$) between the T2DM group and control group.

At the same time, no significant association between *MC4R* and the Chinese population with *T2DM* was observed ($P > 0.05$). The C allele and CC genotype frequencies were also no significant statistic differences in *T2DM* patients and controls ($P > 0.05$). Through Pearson χ^2 test, no significant statistic differences were found of the three genotypes ($P > 0.05$) or the two alleles ($P > 0.05$) between the *T2DM* group and control group.

Some factors may have something to do with insulin resistance (TC, TG, LDL-C). We measured some shown in Table 2. There was no significant difference between these clinical and biochemical characteristics and these genotypes compared by one-way ANOVA (Fisher test).

Discussion

Obesity is reaching epidemic proportions and has become a serious health problem as it contributes to the increasing burden of *T2DM*, heart disease, hypertension, and dyslipidemia [10]. Although numerous gene variants have been associated with obesity or obesity-related phenotypes, very few have been consistently replicated [11, 12]. Recently, several large-scale replication studies have provided the *FTO* and *MC4R* that they are major successes in the field of obesity genetics [7, 13]. Their role as genes predisposing to higher BMI, obesity [2–5, 7, 12–14], fat mass [1, 4, 7, 14, 15], *T2DM* risk [1, 7, 16–20] has then been confirmed mainly in many populations [21].

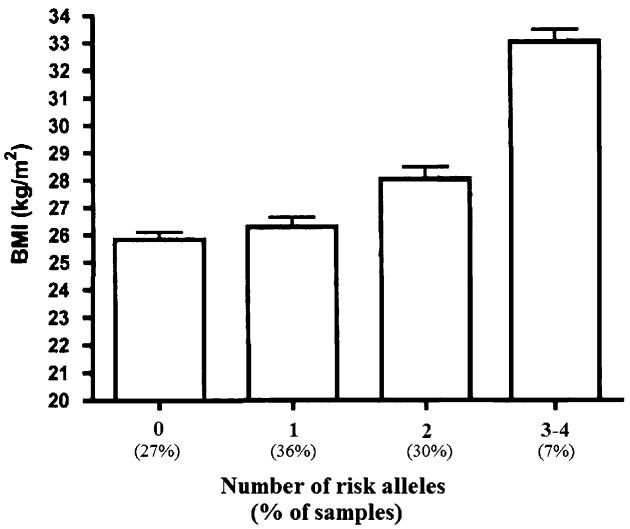

Fig. 1 BMI according to risk allele at rs9930609 and rs17782313. Data were expressed as means ± SE (*error bars*)

In this study, we demonstrated that the association between FTO and obesity is also present in the Chinese Han population. Our analysis demonstrated significant association of *FTO* and *MC4R* with BMI in Chinese population ($P < 0.05$). The combined effects of *FTO* and *MC4R* were significant in Chinese population. Their combined effects play an important role in fat mass, deposition, and obesity prevalence. BMI of participants carrying three or four risk alleles were heavier than carrying neither *FTO* nor *MC4R* risk allele ($P = 0.008$), carrying one risk allele ($P = 0.025$) and carrying two risk alleles ($P = 0.041$). The mechanism maybe their protein is a key link between central nervous system and energy balance. The *FTO* gene function is still unknown but based on the predicted structure, the *FTO* gene encodes a non-heme (FeII)-dioxygenase with a potential role in adaptation to hypoxia, lipolysis, or DNA methylation [22, 23]. The *FTO* protein is expressed in almost all tissues; at the cellular level, it has a nuclear localization [22]. The molecular mechanisms involved in the pathogenesis of obesity as well as the role of FTO in other complex disorders are unknown.

Interestingly, we found that the *FTO* rs9939609 A allele was more associated with obesity and BMI in women ($P = 0.008$ and 0.005, respectively) than in men ($P = 0.012$ and 0.009, respectively). In a previous study [24], the *FTO* variant rs9939609 showed association with obesity and BMI among girls ($P = 0.006$ and 0.004, respectively) but not among boys. Gender differences were also found in the associations of the *FTO* rs9939609 with obesity-related traits such as insulin sensitivity and plasma glucose. This suggests that *FTO* may have an important role for gender specific development of severe obesity and insulin resistance in children and adults. However, contrary to what was reported [8], the effects on obesity and BMI of *MC4R* rs17782313 C allele were similar in males ($P = 0.013$ and 0.011) and females ($P = 0.015$ and 0.012).

Type 2 diabetes is characterized by the presence of insulin resistance and pancreatic β-cell dysfunction, resulting from the interaction of genetic and environmental factors. In this study, the proportion of obese individuals was similar in both diabetic and nondiabetic individuals (37.8 and 33.5%, respectively), and this may explain that Chinese are at risk for type 2 disbetes at lower level of obesity, partly due to their increased predisposition to visceral adiposity and reduced pancreatic β-cell function [25].

Table 3 *FTO* rs9939609 and *MC4R* rs17782313 distributions in *T2DM* and control groups

Groups	*n*	*FTO*(rs9939609)					*MC4R*(rs17782313)				
		Genotypes n(frequency)			Alleles n(frequency)		Genotypes n(frequency)			Alleles n(frequency)	
		AA	AT	TT	A	T	CC	CT	TT	C	T
T2DM	591	57 (9.7)	240 (40.6)	294 (49.7)	354 (29.9)	828 (70.1)	50 (8.5)	237 (40.1)	304 (51.4)	337 (28.5)	845 (71.5)
Controls	1200	125 (10.4)	483 (40.3)	592 (49.3)	733 (30.5)	1667 (69.5)	117 (9.7)	475 (39.6)	608 (50.7)	709 (29.5)	1691 (70.5)

Data are means (SD) for genotypic classes on unrelated individuals. FTO rs9939309: through Pearson χ^2 test, comparison of genotypes: T2DM versus controls, $\chi^2 = 0.18$, $P > 0.05$; comparison of alleles: T2DM versus controls, $\chi 2 = 0.13$, $P > 0.05$; MC4R rs17782313: through Pearson χ^2 test, comparison of genotypes: T2DM versus controls, $\chi^2 = 0.90$, $P > 0.05$; comparison of alleles: T2DM versus controls, $\chi^2 = 0.41$, $P > 0.05$

The study did not observe that the increase in obesity associated with the specific FTO and MC4R alleles were also associated with type 2 diabetes in Chinese Han population. This is intriguing as obesity is usually shown as being a risk factor for type 2 diabetes. This is in contrast to the type 2 diabetic case subjects in the Welcome Trust Case Consortium and UK Type 2 Diabetes Genetic Consortium [26–28]. In accord with our study, Japanese population also yielded insignificant association of rs9939609 with type 2 diabetes [29]. The most probable reason was small size of the study for a genotyping study. A sample size of at least threefold of this study would be needed to detect the effect. Maybe these alleles not only cause obesity but also have a protective role on the development of type 2 diabetes. Maybe it is a double hit phenomenon. Maybe this is only observed in populations where these alleles are present in addition to inactivity (The Han population may be more active than other populations studied for instance). Therefore, our study is underpowered to detect such association. 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. 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 or type 2 diabetes susceptibility genes. Moreover, different genetic architecture between Chinese and other ethnic population is also a possible reason that these SNPs act differently in the Chinese population.

This study has some limitations: the single time point design of this study is a limitation of our research. Another limitation to this study was small size of the study for a genotyping study. Hence, our findings cannot be generalized to the greater Chinese community. Furthermore, it remains possible that the association observed was attributable to other genetic variant(s) in strong linkage disequilibrium with the FTO polymorphism.

In conclusion, we found that *FTO* and *MC4R* are major risk factors for obesity in the Chinese Han population, and their combined effects play an important role in fat mass deposition, obesity prevalence, and incidence. We did not observe a significant association of FTO genetic polymorphism with type 2 diabetic patients in the Chinese population, 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. However, even a gene were considered associated with obesity in some population, to enlarge the conclusion to all human population is arbitrary. And more, in the progress of obesity or diabetes, not only genetic factors, but there were also other factors such as environments or geographic reasons could interfere. All these factors had different impacts in each step of obesity or diabetes and they could impact each other. So whether a single gene could associate to obesity or diabetes or in which way is a complicated question. To solve this problem, we need long time work to get enough samples. *FTO* is a new gene reported in 2007 [6], by now, we have not give a perfect answer, for the researches among different nations were so few. From a population perspective, only the combined effect of the most potent genetic variants should be then considered. We need more assessing studies.

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