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CASE REPORT

Association of the common rs9939609 variant of *FTO* gene with polycystic ovary syndrome in Chinese women

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Abstract Variations in the fat mass and obesity-associated (*FTO*) gene have recently been associated with obesity and type 2 diabetes mellitus among different ethnic populations. Given that the phenotype of polycystic ovary syndrome (PCOS) overlaps with obesity and type 2 diabetes, we hypothesize that the common rs9939609 variant of *FTO* gene is related to PCOS susceptibility. We performed a case–control association study on 215 women with PCOS, using 227 healthy women as the control. We examined the association between rs9939609 variant and PCOS susceptibility, as well as between PCOS and obesity-related parameters in Chinese women. We observed significant differences in the allelic and genotypic distributions between PCOS patients and the control group. The A allele was significantly more frequent among PCOS patients than in the control population (15.1% vs. 9.9%; A allele vs. T allele, OR = 1.62, $P = 0.019$). The A allele carrier genotype (AA and AT) frequencies were also significantly greater in PCOS patients than in the controls (28% vs. 19%; AT and TT vs. TT genotype, OR = 1·61, $P = 0.035$). In logistic regression, the strength of this association was attenuated after adjustment for body mass index (BMI) (A allele vs. T allele, OR = 1.39, $P = 0.286$; AT and TT genotypes vs. TT genotype, OR = 1.40, $P = 0.312$). However, we did not find any significant associations of rs9939609 variant with obesity-related traits. In conclusions, the rs9939609 variant in the FTO gene is associated with PCOS susceptibility in the Chinese population, probably because of its effect on BMI.

Keywords *FTO* · Single nucleotide polymorphism · Polycystic ovary syndrome

Abbreviations

BMI	Body mass index
FTO	Fat mass and obesity-associated gene
HWE	Hardy–Weinberg equilibrium
HOMA-IR	Homeostasis model assessment-insulin resistance
MAF	Minor allele frequency
OGTT	Glucose tolerance test
OR [95% CI]	Odds ratio with 95% confidence interval
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone-binding globulin
SNP	Single nucleotide polymorphism

Introduction

Polycystic ovary syndrome (PCOS) is a disorder characterized by signs and symptoms of oligo- or amenorrhea, polycystic ovaries, and hyperandrogenism. It frequently coexists with obesity and type 2 diabetes mellitus [1–3]. It is reported that approximately 50% of PCOS women are

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overweight or obese, and most of them exhibit abdominal fat distribution similar to the fat distribution seen in most healthy obese women [4]. This implies that obesity is an important factor in the etiology of PCOS [3, 5]. The evidence from family-based and unrelated association studies suggests that obesity and PCOS have a significant inherited basis, pointing to a shared genetic predisposition in contributing to their co-occurrence [6, 7].

Recently, a number of studies have reported remarkably strong, replicable associations of genetic variants in the fat mass and obesity-associated gene (*FTO*) among obese European populations [8–10]. Subsequently, this finding was replicated in different study samples of different ethnicities, including those in East Asia [11–16]. Studies also showed that the FTO variants, including the common rs9939609 variant, were strongly associated with obesity-related traits (e.g., body fat distribution, decreased insulin sensitivity, and HDL-cholesterol) [10, 11].

The human *FTO* gene is located in chromosome 16q12.2 and expressed in a wide range of tissues, including the adipose tissue and specific areas of the brain and muscles [9, 12], suggesting its potential role in body weight regulation. Recently, Barber et al. [17] found that the *FTO* gene variants (rs9939609), by its association with body mass index (BMI), are also associated with PCOS status in women from the UK. Additionally, Attaoua et al. [18] found that other variants of the *FTO* gene (rs1421085), independent of BMI, were strongly associated with glucose intolerance in Caucasian women. However, data regarding these associations with PCOS in Asian population have yet to be established.

In the current study, we aim to investigate the genotypes of the rs9939609 polymorphism of *FTO* in Chinese PCOS patients, and to examine the association between the rs9939609 variant and PCOS susceptibility. We will also analyze its role in obesity-related traits (BMI, waist–hip ratio, glucose and insulin levels, and insulin resistance) in all the participants, as well as PCOS related traits in affected subjects.

Materials and methods subjects

A total of 215 PCOS individuals between 15 and 36 years of age and 227 healthy control women of the same age range were included in our study. All subjects were unrelated Han Chinese living in Shanghai. None of them were on hypoglycemic agents or hormonal therapy (including oral contraceptives) for at least 3 months prior to testing.

All patients were not pregnant and recruited (Jan 2004 to Jun 2008) from the specialized outpatient clinic for obesity in Ruijin Hospital. They all had a confirmed diagnosis of PCOS according to the criteria of Rotterdam Revised 2003 (2 out of 3): (i) oligomenorrhea or amenorrhea for at least 6 months; (ii) clinical and/or biochemical signs of hyperandrogenism; (iii) polycystic ovaries (the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter) and/or increased ovarian volume (>10 ml) and exclusion of congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumor, hyperprolactinemia and thyroid dysfunction [2, 19].

Among the 227 healthy controls, 127 females (first control group) recruited from the Department of Gynecology and Obstetrics in Ruijin Hospital were of proven fertile in a pre-natal examination. They have a normal menstrual cycle and ovarian morphology, and no family history of abnormal menses or hirsutism. The other 100 females (second control group) were recruited from a community-based health screening program in an urban district of Shanghai, and among this second group 33 volunteers had their serum sex hormone levels measured. None of the control group had evidence of acne, hirsutism, alopecia, or any other endocrine dysfunction. All subjects gave informed consent. This study was approved by the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine.

Clinical and biochemical measurements

For the PCOS patients and second control group, the height, weight, waist and hip circumference, and seated blood pressure were measured by the same observer; and for the first control group, anthropometric parameters were obtained from the record of pre-natal examination. BMI was calculated as weight (kg) divided by height square (m). Obesity was defined as BMI $\geq$ 28 kg/m^2 [20]. Ultrasonography was performed in the early follicular phase (third–fifth) of a spontaneous or progestin-induced menstrual cycle. The 75-g glucose tolerance test (OGTT) was performed between 0700 and 0800 h after an overnight fasting. Venous blood samples were collected during fasting and at 2-h after the glucose load. Laboratory examinations used were according to those described in another study [21]. The formula of Vermeulen et al. [22] (http://www.issam.ch/freetesto.htm) was used to calculate free testosterone from total testosterone. Homeostasis model assessment-insulin resistance (HOMA-IR) was used to estimate insulin resistance as fasting insulin (μIU/ml) × fasting glucose (mmol/l)/22.5.

Genotyping analysis

Genomic DNA was extracted from the peripheral blood leukocytes of the PCOS and control subjects according to the

manufacturer's instructions for a commercially available kit (Qiagen, Hilden, Germany), quantified by spectrophotometer, and then stored at −20°C. Single nucleotide polymorphism (SNP) rs9939609 (A/T) of *FTO* was genotyped directly by sequencing analysis. The forward primer (5′-CAAAACTG GCTCTTGAATGAA-3′) and the reverse primer (5′-TGTCCA AACAGTAGGTCAGGA-3′) were designed for PCR amplification reaction. PCR was performed at a volume of 50 μl containing 1.5 mM $MgCl_2$, 10 mM dNTP, 20 ng genomic DNA, 5 pmol of each primer, and 2.5 U Taq DNA polymerase (Shenergy Biocolor, Shanghai, China). The PCR amplification consisted of 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 1 min. The PCR products were purified using a gel extraction kit (Qiagen, Hilden, Germany) and sequenced on the ABI 3700 automated sequencer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Unless denoted otherwise, categorical data are described as percentages and continuous data are described as means ± SD. Student *t*-tests were used to compare clinical characteristics between women with and without PCOS, as well as PCOS or obesity-related parameters between rs9939609 genotypes. Abnormally distributed continuous variables (i.e., HOMA-IR, serum SHBG) were log transformed before analysis. *P*-values < 0.05 were considered significant. Analyses were performed using software package SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Associations of rs9939609 variant with the presence/absence of PCOS, as well as Hardy–Weinberg equilibrium (HWE), were conducted using the DeFinetti program online (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The strength of association was estimated by the odds ratio with 95% confidence interval (OR [95% CI]). We also performed multiple logistic regressions to detect the associations of rs9939609 variant with PCOS by adjusting for age and BMI. Power calculations were performed using the Quanto v.1.2.3 (log additive model) (http://hydra.usc.euc/GxE/). Assuming a population with a 2.2% prevalence of PCOS [23], a minor allele frequency of 12% in China, and a type I error of 0.05 with two-sided, we had 67.5% power to detect an effect with a per-minor allele relative risk of PCOS of 1.6 associated with the presence of rs9939609 SNP.

Results

Clinical characteristics

The clinical and biochemical characteristics of all the patients and healthy controls are shown in Table 1. As expected, the PCOS patients had a greater BMI and waist–hip ratio than those in the healthy controls (28.0 ± 6.1 vs. 20.8 ± 3.3, $P < 0.001$ and 0.86 ± 0.09 vs. 0.79 ± 0.05,

Table 1 Clinical characteristics of PCOS patients and healthy control women

Clinical characteristics	All PCOS ($n = 215$)	Control ($n = 227$)	*P* value
Age	21.7 ± 5.5	27.5 ± 4.8	<0.001
BMI	28.0 ± 6.1	20.8 ± 3.3	<0.001
Waist–hip ratio	0.86 ± 0.09	0.79 ± 0.05	0.003
Obesity[a]	110(51.2%)	7(3.1%)	<0.001
FSH (mIU/ml)	5.17 ± 2.43	4.58 ± 2.72[c]	0.279
LH (mIU/ml)	7.57 ± 5.61	3.48 ± 1.34[c]	<0.001
Total testosterone (ng/dl)	91.5 ± 42.1	29.9 ± 16.9[c]	<0.001
SHBG (nmol/l)[b]	33.5(19.4, 64.6)	55.4(47.7, 74.7)[c]	<0.001
Free testosterone (ng/dl)[b]	1.54(1.05,1.68)	0.33(0.19,0.46)	<0.001
Fasting glucose (mmol/l)	4.9 ± 0.6	4.5 ± 0.8	<0.001
2-h glucose (mmol/l)	6.8 ± 1.8	6.3 ± 1.7	0.028
Fasting insulin (μIU/ml)	16.8 ± 14.1	8.9 ± 6.6	<0.001
2-h insulin(μIU/ml)	137.4 ± 115.7	94.6 ± 83.5	0.001
HOMA-IR (μIU mol/l^2)[b]	2.78(1.79, 4.77)	1.44(0.69, 2.52)	<0.001

[a] Data are presented as *n* (%)

[b] Data are presented as median (range); other data are presented as means ± SD

[c] Data were from 33 healthy volunteers

Abbreviations: *PCOS* polycystic ovary syndrome, *BMI* body mass index, *SHBG* sex hormone-binding globulin, *HOMA-IR* homeostasis model assessment-insulin resistance

$P = 0.003$, respectively). With significantly higher levels of LH and serum total testosterone, and lower levels of SHBG (all $P < 0.001$), the sex hormonal profile in PCOS patients also differed from the profile in the control group. The results of OGTT revealed that the PCOS group had higher levels of serum fasting and 2-h glucose, insulin, and HOMA-IR than the control group (all $P < 0.05$).

Association between *FTO* rs9939609 variant and PCOS

The genotype distribution of all the participants was 76.4% TT, 22.2% AT, and 1.4% AA for the *FTO* rs9939609 variant. The overall minor allele frequency (MAF) was 12.4%, which was similar to those in the HapMap-HCB sample (12.2%), but much lower than those in the HapMap-CEU population (45%). The observed genotype distributions were consistent with HWE, both in patients and controls ($P = 0.963$, $P = 0.361$, respectively). Genotype distributions and association tests for rs9939609 SNP between patients and controls are shown in Table 2.

Significant differences in allelic and genotypic distributions according to PCOS were observed. The A allele was significantly more frequent in all PCOS patients than in the controls (15.1% vs. 9.9%; A allele vs. T allele, OR, 1.62 [95% CI 1.08–2.43], $P = 0.019$); and the A allele carrier genotype (AA and AT genotypes) frequencies were also significantly greater in PCOS patients compared to the controls (28% vs.19%; AT and TT vs. TT genotype, OR, 1.61 [95% CI 1.03–2.51], $P = 0.035$). The A allele of rs9939609 is estimated to have a population attributable risk percent of 6.72% for PCOS in Chinese women. However, the strength of association was attenuated after adjustment for BMI (A allele vs. T allele, OR, 1.39 [95% CI 0.76–2.52], $P = 0.286$; AT and TT genotypes vs. TT genotype, OR, 1.40 [95% CI 0.73–2.68], $P = 0.312$).

For further study, the patients were divided into obese PCOS (BMI = 32.9 ± 4.1 kg/m^2) and non-obese PCOS (BMI = 23.1 ± 3.3 kg/m^2) subgroups. Association analyses were conducted separately between the two subgroups and the control. The A allele (MAF) in obese and non-obese PCOS patients was 16.4% and 14.9%, respectively, with only the obese group significantly associated with PCOS as compared to the healthy controls (A allele vs. T allele, $P = 0.016$ for obese patients; $P = 0.065$, non-obese patients) (Table 3).

Table 3 Association of the *FTO* rs9939609 variant with obese and non-obese PCOS

Group	*n*	TT	AT + AA	*P* value[a]	OR[a] [95%CI]
Control	227	183(80.6%)	44(19.4%)		
Obese PCOS	110	77(70.0%)	33(30.0%)	0.016	1.78 [1.11–2.85]
Non-obese PCOS	97	70(72.2%)	27(27.8%)	0.065	1.60 [0.97–2.64]

[a] Compared with healthy control women. The rs9939609 variant was shown with the exact count of each genotype in PCOS and healthy controls. ORs were given for the minor allele as risk factor of PCOS. *P*-values < 0.05 were considered significant. Abbreviations see Tables 1 and 2

Association study of *FTO* rs9939609 genotypes with disease-related traits

For the small number of AA genotype in our study, we combined the AA and AT genotype as a dominant model to analyze the associations between the rs9939609 genotype with obesity or PCOS related parameters. We failed to find any significant associations of clinical parameters related to obesity such as BMI, waist–hip ratio, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, and HOMA-IR with *FTO* rs9939609 in either the healthy controls or PCOS patients. Nor did we detect any significant association of PCOS-related traits such as total testosterone, serum SHBG, or free testosterone in all PCOS patients.

Discussion

In the current study, we found a significant association between *FTO* rs9939609 variant with PCOS status in

Table 2 Association of the *FTO* rs9939609 variant with PCOS

	PCOS (215)	Controls (227)	OR [95% CI]	*P* value	BMI adjusted *P* value
Genotype					
TT	155	183	1.61 [1.03–2.51]	0.035	0.312
AT + AA	55 + 5	43 + 1			
A allele (%) (MAF)	15.1	9.9	1.62 [1.08–2.43]	0.019	0.286

The rs9939609 variant was shown with A allele and the exact count of each genotype in PCOS and healthy controls. OR was given for the minor allele as risk factor of PCOS. *P*-values < 0.05 were considered significant

Abbreviations: *FTO* fat mass and obesity-related gene, *MAF* minor allele frequency, *OR [95% CI]* odds ratios [95% confidence interval)

Chinese Han subjects, and the association was abolished after adjustment for BMI. This association is most evident in obese PCOS patients, although no significant association between *FTO* genotype and BMI was found in our studied subjects. These findings are consistent with the study of the UK population by Barber et al. They performed a case–control association study in 463 PCOS patients and 1,336 controls with UK British/Irish origin [17]. They detected a significant association between *FTO* genotype and PCOS status, and this association is also attenuated after adjustment for BMI.

Associations of *FTO* genotypes with obesity in European populations have been repeatedly confirmed since their initial disclosure [8–12]. However, these associations are controversial in Asian populations [15, 24–26]. Li et al. [24] found no association of polymorphism in the intron 1 block (rs9939609, rs8050136, and rs9930506) of *FTO* with obesity and BMI in Chinese population. However, in a Han Chinese population, Chang et al. [15] confirmed the strong association of *FTO* genetic variants with obesity and BMI, in which the MAF was 12.6%, similar to those in Li's (12%), and HapMap-HCB sample (12.2%); they showed that the effect of rs9939609 A allele on obesity risk and BMI were comparable with that of European populations [9, 12]. The different protocols used in the two Chinese studies may explain the contrary results. In Li's study, obese was defined as BMI $\geq$ 28 kg/m^2 and participants were obese adults aged 50–70 years; and the obesity status of this age group is more likely to be influenced by environmental factors [27]. While in Chang's study, obese was defined as BMI $\geq$ 30 kg/m^2 and participants were mainly young obese subjects, a group that would have increased genetic load and decreased interference of environmental effects, thus increasing the power of detection. These data, combined with similar results from the study of the Singapore population, provides strong support that rs9939609 variants in the *FTO* gene are associated with BMI in Chinese Han population [16].

In this study, we detected significant association between *FTO* rs9939609 variant and PCOS status, and this association was attenuated after adjustment for BMI, similar to the relationship between *FTO* variation and predisposition to type 2 diabetes mellitus [8]. It seems likely that the effect of rs9939609 on PCOS risk is also through an effect on BMI. Although we are unable to demonstrate the association between *FTO* rs9939609 variant and BMI, this could be due to inadequate power; evidence shows that the case–control association is far weaker when restricted to the non-obese PCOS patients.

The function of FTO protein and the involved biological pathways is still unknown, as is the mechanism by which the rs9939609 variant affects body size and predicts the risk of PCOS. Studies in rodent show that the FTO gene is expressed in the main regions of the brain that control feeding, and that its expression is regulated by food deprivation [28–30]. In addition, Cecil et al. [31] recently found that the risk allele of rs9939609 was associated with increased energy intake, suggesting *FTO* variant may affect body size by influencing the "input" side of the energy-balance equation.

In conclusion, our results demonstrate that the common rs9939609 variant in the *FTO* gene is associated with PCOS, and this association is probably mediated by adiposity. Further association studies of *FTO* variants with PCOS in other ethnic populations are necessary to corroborate our findings and those of Barber's. More in-depth studies are required to elucidate the biological role and mechanisms of *FTO* variants with respect to body weight and obesity, which would help explain how they influence PCOS susceptibility.

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