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Association of the *FTO* gene SNP rs17817449 with body fat distribution in Mexican women

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ABSTRACT. Polymorphisms in the *FTO* gene are associated with obesity, body mass index, hip circumference, and visceral and subcutaneous fat area. The objective of this study was to analyze the association of the *FTO* rs17817449 genetic variant (T>G polymorphism) with body fat distribution patterns in women. We included 65 women and 71 healthy subjects in this study. Anthropometric parameters were determined and laboratory studies were performed. The polymorphism was detected by a PCR-RFLP method. The groups were categorized by

type of body fat distribution: gynoid (N = 29) and android (N = 36). We found that the *FTO* gene polymorphism was not associated with body fat distribution according to the type of obesity (P > 0.05). The contribution of G and T alleles among groups indicated no statistically significant differences between the reference and gynoid group [P = 0.93; odds ratio (OR) = 0.97; 95% confidence interval (CI) = 0.46-2.02] and the reference and android group (P = 0.56; OR = 1.20; 95%CI = 0.54-2.82). Thorax circumference and thorax breast circumference were significantly different between the two groups (P = 0.009 and 0.021, respectively) with the genotype TT. We conclude that the *FTO* rs17817449 TT genotype predisposes individuals to fat deposition in the thoracic and breast region; individuals carrying this genotype had a decrease in thoracic and breast dimensions indirectly causing the gynoid phenotype in Mexican women.

Key words: FTO; rs17817449; Polymorphism; Mexican women; Body fat

INTRODUCTION

Obesity is a multifactorial disease that is a major public health problem in the world, and Mexico ranks second in adult obesity. The relative frequency of being overweight or obese in Mexican adults is 39.7 and 29.9%, respectively (Barquera et al., 2010). There are two patterns of body fat distribution: android obesity is characterized by fat deposition in the upper (central) body region, predominantly the abdomen; gynoid obesity is characterized by fat deposition mainly in the hips and thighs (Mirhosseini et al., 2012). Android obesity is an important factor associated with risk of cardiovascular disease, blood pressure levels, left ventricular mass, insulin resistance, and type 2 diabetes mellitus (Daniels et al., 2000).

Polymorphisms in the first intron of the fat mass and obesity-associated (*FTO*) gene (OMIM 610966) are associated with obesity, body mass index (BMI), hip circumference (Scuteri et al., 2007), and visceral and subcutaneous fat area (Haupt et al., 2008) in Europeans. However, these associations have not been replicated in other groups such as Chinese (Li et al., 2008), Japanese (Horikoshi et al., 2007), and Oceanic (Ohashi et al., 2007) populations. The allele G of the variant rs17817449 is strongly associated with obesity (Scuteri et al., 2007; Hinney et al., 2007). Villalobos-Comparán et al. (2008) reported that *FTO* gene polymorphisms are a major risk factor for class III obesity in the Mexican-Mestizo population, and expression of the *FTO* gene is upregulated in subcutaneous fat tissue of obese individuals. *FTO* gene variants are associated with body weight, BMI, and obesity, but not with patterns of body fat distribution. The aim of this study was to evaluate the association between the *FTO* rs17817449 variant (T>G) and body fat distribution patterns in Mexican women.

MATERIAL AND METHODS

This case-control study included 65 women referred from the reconstructive surgery service of the Instituto Jalisciense de Cirugía Reconstructiva "Dr. José Guerrerosantos", of Guadalajara, Jalisco, Mexico. The reference group included 71 healthy individuals from Guadalajara, Jalisco, Mexico. All participants signed an informed consent form. The study was

approved by the Ethics Committee of Instituto Jalisciense de Cirugía Reconstructiva "Dr. José Guerrerosantos", and was in adherence with the Declaration of Helsinki, and the Mexican regulations for health and research. Our inclusion criteria for the case group were the following: women 18-45 years old, healthy, without comorbidities, a body mass index (BMI) of 25-33 kg/m^2, and a waist circumference of 80-90 cm. These individuals were selected to clearly distinguish the gynoid or android type of fat distribution, and because they would undergo elective surgical procedures, mainly lipectomy and liposculpture, for aesthetic reasons.

Anthropometric parameters

Height, weight, and circumferences of waist, hip, thigh, leg, arm, thorax breast, and thorax were measured. Height was measured without shoes using a height meter (Seca 213 portable stadiometer). Weight was measured with a digital scale while subjects wore only light clothing (Tanita BC-558 digital floor scale). Waist circumference was measured at the smallest point between lower costal cartilage and 10th rib border; hip circumference was determined at the level of the greatest posterior protuberance of the buttocks corresponding anteriorly to the level of the symphysis pubis. Thigh circumference was measured on the left leg directly below the gluteal fold. Leg circumference was measured on the middle third of the tibia. Thorax breast was measured at the nipple level. Thoracic circumference was determined at the submammary line, corresponding to 5th-6th rib. All circumferences were determined using measuring tape. Anthropometric indices were calculated as follows: BMI = weight (kg)/height (m)^2; waist-to-hip ratio (WHR) = waist circumference/hip circumference. Gynoid fat distribution was defined as WHR $\leq$ 0.85, and android fat distribution as >0.85.

Biochemical analyses

Hemoglobin, urea, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were determined.

Genotyping

Genomic DNA was extracted from 10 mL peripheral venous blood, collected in EDTA using a salting-out method (Miller et al., 1988). The SNP variant rs17817449 was genotyped by a PCR-RFLP method. The primers were 5'-CGGTGAAGAGGAGGAGATTG-3' (forward) and 5'-CATCTCTGCCCCAGTTTCTC-3' (reverse) (Scott et al., 2010). The PCR cycling program consisted of an initial denaturation at 94°C for 5 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 57°C for 30 s, and extension at 72°C for 30 s, followed by a final elongation at 75°C for 5 min. PCR products were digested with *Alw*NI restriction enzyme at 37°C for 6 h. The G allele generated an undigested 223-bp product, whereas digestion of the T allele yielded two fragments of 123 and 100 bp.

Statistical analysis

Allele frequencies were determined by direct observations. The Hardy-Weinberg test was used to confirm independent segregation of the *FTO* alleles using the chi-square test. Dis-

tribution of genotypes in both groups was compared by chi-square or Fisher exact test. Non-parametric Kruskal-Wallis and Mann-Whitney U-tests were used to compare three or more groups. Statistical tests were performed using the SPSS v 18.0 software. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to estimate the association between genotypes and measurements. A $P < 0.05$ was considered to be statistically significant.

RESULTS

In total, 65 females were included in this study, categorized by the type of body fat distribution as gynoid (N = 29) or android (N = 36). The basic characteristics of the groups under study are summarized in Table 1. The results of biochemical analyses of each study group are shown in Table 2. The polymorphism was in Hardy-Weinberg equilibrium in the reference group. Genotype and allele frequencies of the *FTO* rs17817449 variant are shown in Table 3. Anthropometric measurements and biochemical analyzes were compared between genotypes (GG, GT, and TT) by using the Kruskal-Wallis test (Table 4). The Mann-Whitney U-test detected significant differences in measurements of thorax circumference (P = 0.009) and thorax breast (P = 0.021) between genotypes. We observed that the TT genotype was associated with statistically significantly decreased thoracic circumference (P = 0.01) and reduced thoracic breast circumference (P = 0.007) compared with the GT or GG genotypes. We observed that the TT genotype when compared with the GT or GG genotypes was associated with statistically significant differences in thoracic circumference (P = 0.01) and thoracic breast circumference (P = 0.007); therefore, the TT genotype appears to be associated with the deposition of body fat in the thoraco-mammary area.

Table 1. Descriptive characteristics by study group (means ± SD).

Clinical features/anthropometric measures	Total (N = 65)	Gynoid group (N = 29)	Android group (N = 36)
Age (years)	38.23 ± 9.95	38.31 ± 10.23	38.16 ± 9.86
Weight (kg)	82.79 ± 11.72	80.37 ± 13.79	84.69 ± 9.58
Height (m)	1.64 ± 0.67	1.64 ± 0.79	1.64 ± 0.79
Waist circumference (cm)	81.86 ± 15.12	67.52 ± 7.88	93.11 ± 8.31
Hip circumference (cm)	110.03 ± 10.52	96.86 ± 10.59	102.51 ± 9.91
Arm circumference (cm)	32.55 ± 10.77	33.936 ± 15.52	31.46 ± 4.40
Thigh circumference (cm)	62.05 ± 10.60	63.50 ± 14.22	60.91 ± 6.52
Leg circumferece (cm)	43.39 ± 7.96	42.24 ± 8.60	44.30 ± 7.41
Thorax breast circumference (cm)	96.73 ± 11.70	97.726 ± 13.10	95.95 ± 10.59
Thoracic circumference (cm)	90.8 ± 9.49	85.83 ± 7.11	94.84 ± 9.31
BMI (kg/cm^2)	30.58 ± 3.03	29.58 ± 2.88	31.37 ± 2.95
WHR (cm)	0.81 ± 0.11	0.69 ± 0.17	0.69 ± 0.17

BMI = body mass index; WHR = waist-to-hip ratio.

Table 2. Biochemical analysis by group (means ± SD).

Laboratory studies	Total (N = 65)	Gynoid (N = 29)	Android (N = 36)
Hb (mg/dL)	13.61 ± 1.05	13.67 ± 1.01	38.16 ± 9.86
Glucose (mg/dL)	85.53 ± 12.91	84.24 ± 12.6	86.54 ± 13.24
Urea (mg/dL)	28.78 ± 7.91	29.78 ± 8.80	28.00 ± 7.17
Creatinine (mg/dL)	0.77 ± 0.26	00.74 ± 0.26	0.79 ± 0.27
Cholesterol (mg/dL)	156.09 ± 21.53	157.25 ± 22.23	155.22 ± 21.26
HDL (mg/dL)	49.00 ± 9.98	50.00 ± 10.11	48.24 ± 9.95
Triglycerides (mg/dL)	102.50 ± 24.69	106.97 ± 28.64	99.00 ± 20.83
LDL (mg/dL)	90.30 ± 15.41	92.31 ± 16.71	88.73 ± 14.34

Hb = hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3. Genotype and allelic frequencies of the *FTO* rs17817449 SNP in Mexican women.

Frequencies	Group			HS *vs* Gynoid P value, OR (95%CI)	HS *vs* Android P value, OR (95%CI)
	HS [N = 71 (%)]	Gynoid [N = 29 (%)]	Android](N = 36 (%)]		
Genotype					
T/T	40 (56.3)	16 (55.2)	17 (47.2)		
G/T	22 (31.0)	10 (34.5)	15 (41.7)		
G/G	9 (12.7)	3 (10.3)	4 (11.1)		
Model					
Dominant					
GG	31	13	19	0.74, 1.25 (0.31-2.27)	0.81, 1.16 (0.33-4.06)
TT+GT	40	16	17		
Recesive					
TT	9	3	4	0.91, 0.95 (0.39-2.27)	0.37, 0.69 (0.31-1.55)
GG+GT	62	26	32		
Allele					
T	102	42	49		
G	40	16	23	0.93, 0.97 (0.46-2.02)	0.56, 1.20 (0.54-2.82)

HS = healthy subjects.

Table 4. Comparison of anthropometric measures and biochemical analysis per genotype (GG, GT and TT).

Variable	χ^2	P value (a two-tail)
Hemoglobin	0.61	0.73
Glucose	0.83	0.65
Urea	0.26	0.87
Creatinine	4.10	0.12
Cholesterol	0.74	0.69
HDL	3.99	0.13
Triglycerides	5.43	0.06
LDL	0.69	0.76
Weight	4.06	0.13
Height	3.49	0.17
Hip circumference	4.00	0.13
Waist circumference	1.27	0.52
Thigh circumference	5.12	0.07
Leg circumference	2.27	0.32
Arm circumference	3.44	0.17
Thorax breast circumference	9.34	0.009*
Thoracic circumference	7.70	0.021*
WHR	0.23	0.89
BMI	2.13	0.34

BMI = body mass index; WHR = waist-to-hip ratio. *P < 0.05.

DISCUSSION

In 2007, the *FTO* gene was identified in a genome-wide association study (GWAS) of type 2 diabetes (Frayling et al., 2007). At the same time, two independent teams using GWAS reported that the *FTO* gene is associated with obesity (Dina et al., 2007; Scuteri et al., 2007). The biological function of *FTO* is not known, but two studies have shown that the FTO protein is a 2-oxyglutarate-dependent demethylase of nucleic acids (Gerken et al., 2007; Sánchez-Pulido and Andrade-Navarro, 2007). However, its role in obesity is not well understood.

Several studies have identified genetic variants in the *FTO* gene that are associated with measures of adiposity in European populations. Recently, the analysis of *FTO* polymorphisms has been extended to different ethnic groups (Al-Attar et al., 2008). Several authors

have associated *FTO* gene variants with several metabolic conditions, but their results have been inconsistent. *FTO* gene variants are associated with measures of adiposity, predisposing individuals to obesity by increasing total fat mass in Hispanic Americans and to a lesser extend in African Americans (Wing et al., 2009). Villalobos-Comparán et al. (2008) reported that the single-nucleotide polymorphisms rs9939609, rs1421085, and rs17817449 in the *FTO* gene are associated with obesity, especially class III obesity, in the additive and dominant model (P = 0.0000004 and 0.000008, respectively) in the Mexican population.

Here, we have presented an association study of the *FTO* rs17817449 variant with the distribution pattern of body fat in Mexican women. We found that the *FTO* gene polymorphism is not associated with body fat distribution according to type of obesity (gynoid or android) when the polymorphism is examined in a dominant-recessive model. The contribution by G and T alleles, among groups, did not result in significant differences between the reference group and the gynoid type (P = 0.93; OR = 0.97; 95%CI = 0.46-2.02) nor between the reference group and the android type (P = 0.56; OR = 1.20; 95%CI = 0.54-2.82). Thorax circumference and thorax breast circumference measurements were statistically significant between groups (P = 0.009 and 0.021, respectively) and associated with the genotype TT. The mean of thoracic circumference in the gynoid group was 85.83 ± 7.11 cm, and that in the android group was 94.84 ± 9.31 cm; thus, the TT genotype may predispose its carriers to smaller breast and thoracic circumference. Although no differences were detected between the overweight android and gynoid distribution-type groups, breast and thoracic circumference are influenced by fat distribution; for example, increased fat deposition to the chest tends to result in the android type. Therefore, the *FOT* gene may be involved in the deposition of body fat in these areas. Also relevant to these observations is that G is a risk allele for obesity, which is supported by our observation that the T allele in its homozygous state was associated with a more benign phenotype (the gynoid pattern), which, when compared with the android pattern, has a decreased risk of obesity and other metabolic syndromes.

No significant differences were found in height, weight, BMI, WHR, or biochemical variables. These observations may reflect the selected study cohort, comprising individuals who were healthy enough to undergo a cosmetic surgical procedure. In addition, they may have received medication and preoperative monitoring of their health and the selection criteria were designed to obtain a homogeneous group with a BMI of >25 and <35 in order to observe the phenotypic characteristics of each group.

It is important to highlight the limitations of this study, which include small sample size and lack of data for *FTO* mRNA and protein expression. Therefore, further studies are required to confirm these results. In conclusion, we observed that the *FTO* rs17817449 TT genotype predisposes its carriers to fat deposition in the thoracic and breast region. Individuals carrying this genotype showed a decrease in thoracic and breast measures, which indirectly caused the gynoid phenotype in Mexican women.

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