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The rs1477196 SNP of the *FTO* Gene is Associated with Primary Knee Osteoarthritis in a Female Population from Northern Mexico

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ABSTRACT

Background: Osteoarthritis is a frequent rheumatic disease. Some single-nucleotide polymorphisms of the gene associated with fat mass and obesity are associated with increased body mass index and knee osteoarthritis. **Objective:** The objective of this study was to analyze the association of single nucleotide polymorphism rs1477196 of the fat mass and obesity gene with primary knee osteoarthritis. **Methods:** This observational and cross-sectional study included 347 Mexican participants. We performed the genotypification analysis with TaqMan® probe C_2031262_10 for rs1477196 (Thermo Fisher Scientific). Multivariate analysis included covariables such as age, type 2 diabetes, obesity, and postmenopause. **Results:** Type 2 diabetes, obesity, and postmenopause were associated with primary knee osteoarthritis in female participants. We did not find an association between rs1477196 and obesity. In the codominant and dominant genetic models, rs1477196 was significantly associated with primary knee osteoarthritis only in the female group, including in the model adjusted by other covariables (odds ratio = 2.517; 1.035-6.123; p = 0.042 and odds ratio = 2.387; 1.054-5.407; p = 0.037, respectively). The interaction between rs1477196 and obesity was significantly associated with primary knee osteoarthritis in female participants (p = 0.039 and p = 0.043). **Conclusions:** Our findings suggest that the rs1477196 variant of the fat and obesity mass gene may be associated with the risk of primary knee osteoarthritis in women. (REV INVEST CLIN. 2024;76(1):37-44)

Keywords: Osteoarthritis. *FTO*. rs1477196.

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INTRODUCTION

Osteoarthritis (OA) is the most frequent rheumatic disease of the joints. It is caused by a series of biochemical, molecular, and mechanical factors that lead to a loss of balance between the synthesis and degradation of hyaline cartilage. OA is a frequent cause of pain and functional disability, mainly in the elderly population[1]. The etiology of the disease is multifactorial and may also include metabolic and inflammatory factors[2]. Some genetic factors may also explain susceptibility to OA. Different studies have evidenced risk loci for OA, including genome-wide association studies (GWASs) in which different single-nucleotide polymorphisms (SNPs) have been associated with the risk and progression of OA[3,4].

Obesity is a severe public health problem and has been identified as a risk factor in the pathogenesis of OA[5-7]. In adult and pediatric Latin populations, particularly among Mexican people, the highest frequencies of obesity worldwide have been observed[8]. Obesity is a risk factor for OA not only through the action of mechanical forces that overload the joints but also due to a variety of metabolically active adipokines that play a role as mediators of inflammation[9,10].

The genetic background of obesity has been widely studied[11,12]. In particular, the fat mass and obesity gene (*FTO* gene) has received particular attention for its association with obesity since the proteins it encodes have been related to adipogenesis[13]. In this way, different SNPs of the *FTO* gene have been associated with an increase in body mass index (BMI) and a greater risk of developing distinct types of cancer. However, its exact function has not yet been deciphered[14], particularly the rs9939609, rs9930506, rs1421085, rs8050136, rs1121980, and rs17817449 SNPs[13]. In addition, in the Mexican population, up to 15 variants of the *FTO* gene have been associated with indicators of overweight and obesity in a recessive genetic model[8].

This gene encodes a protein expressed in the hypothalamus that is involved in energy balance and adipose tissue. This protein has been strongly associated with BMI, body fat rate, waist and hip circumference, and energy consumption[15-17]. In this respect, Rampersaud et al. found that 26 variants of the *FTO* gene were associated with BMI. However, the authors suggested that the effect of this gene may be attenuated by physical activity[18]. The arcOGEN study showed that the SNP rs8044769 of the *FTO* gene was associated with OA in European women (p = 6.85E10−8), although this association was attenuated after adjustment for BMI[19]. This finding suggests that the effect of *FTO* on the risk of OA is through BMI. Some SNPs of the *FTO* gene have also been associated with intervertebral disc degeneration. Thus, this study found that the SNP rs1121980 had an allelic association with degenerative disc disease[20]. Other studies have found contradictory results for the association between the SNPs of the *FTO* gene and OA[21-23]. Recently, a meta-analysis described the association between the SNPs of the *FTO* gene and the risk for knee osteoarthritis (KOA) as significant, particularly in the European Caucasian and North American Caucasian populations[24].

The rs1477196 variant of the *FTO* gene has been widely studied in its association with the development of breast cancer, including the Mexican population[25,26]. In addition, this variant has been associated with obesity in a group of subjects with low levels of physical activity ($p < 0.0011$) but not with KOA[18].

This study analyzes the association of SNP rs1477196 of the *FTO* gene with primary knee OA in an adult population in northern Mexico.

MATERIAL AND METHODS

An observational cross-sectional study was conducted from January 2021 to June 2023. Through non-probabilistic convenience sampling, participants consisted of both sexes, were of Mexican Mestizo ethnicity, were aged 40 years or older, unrelated, and originated from and were residing in Torreón Coahuila, Mexico. All participants received clinical and radiographic examinations. A total of 183 subjects diagnosed with primary KOA and 164 non-KOA subjects were considered for participation in this study. The severity of KOA was classified following the radiological criteria of Kellgren and Lawrence[27].

All participants underwent a medical history, including anthropometric measurements and BMI. Covariates such as type 2 diabetes and postmenopausal status were also included in the study.

Subjects with intra-articular fractures, joint deformities, liver or kidney disease, oncological disease, risky work activities, treatment with chondromodulators, steroids, non-viable samples for analysis, incomplete files, and inflammatory, metabolic, infectious, or congenital OA were excluded from the study.

For DNA extraction, peripheral blood was collected from each subject, and the DTAB-CTAB method was used. To verify the purity of the DNA, 0.5 µL of extracted DNA was taken and placed in a microvolume spectrophotometer (Thermo NanoDrop 1000).

The genotyping assay used the TaqMan® probe was C_2031262_10 for the *FTO* gene rs1477196 (Thermo Fisher Scientific). Amplification was performed in a thermocycler (ABI PRISM 700 Sequence Detection System from Applied Biosystems in Foster City, CA, USA).

This study was approved by the Bioethics Committee of the Torreón Faculty of Medicine of the Autonomous University of Coahuila, with the number reference C.B/04-10-17, October 2017 and C.B/06-11-22, November 29, 2022. Informed consent was obtained from all participants.

Statistical Analysis

The descriptive analysis included means and standard deviation for quantitative variables and percentages for categorical variables. Hardy–Weinberg equilibrium (HWE) was performed using the Chi-square test. For comparison, bivariate analysis was performed using the Chi-square, Mann–Whitney U, or Kruskal–Wallis tests. In turn, binary logistic regression models adjusted for age, obesity, diabetes, and postmenopause status were used. We analyzed the interaction between obesity and genetic models of rs1477196 through binary logistic regression. We considered $p < 0.05$ and 95% confidence intervals as significant. Analyses were performed using the SPSS v.22 statistical package (IBM Corp., Armonk, NY, USA).

RESULTS

The study included 347 participants: 183 (52.7%) subjects with primary KOA and 164 (47.3%) without KOA. The female sex group had a frequency of 213 (61.4%) and the male sex group 134 (38.6%). Overall, the average age of participants was 59.5 ± 14.5 years; in subjects with primary KOA, the mean age was 66.8 ± 13.5 years, and in non-KOA subjects, 51.4 ± 11.0 years (p = 2.2E-23). The average BMI for primary KOA was 28.1 ± 4.2, and for the non-KOA group, 27.2 ± 4.0 (p = 0.029). For all participants, age was significantly associated with KOA (p = 4.5E-19); notably, unlike in male participants, obesity, type 2 diabetes, and postmenopause status were associated with KOA in female participants (Table 1).

The frequencies of the genotypes were consistent with the Hardy–Weinberg equilibrium: AA = 80 (23.1%); AG = 172 (49.6%); GG = 95 (27.4%), p = 0.89. However, no significant differences were observed for the AA, AG, and GG genotypes of rs1477196 between the study groups. Clinical covariates were not significantly associated with the rs1477196 genotypes. Likewise, the different genetic models did not show an association with these variables (Table 2).

No significant association of the different genetic models was observed between the study groups. Therefore, the participants were stratified by sex (Table 3). Notably, the codominant two and dominant genetic models were significantly associated with primary KOA in the female group, even in the model adjusted for other covariates (Table 4).

Finally, we evaluated the interaction between obesity and the different models studied; we proceeded to analyze the association in a binary logistic regression model, including additional covariates in models stratified by sex. The interaction of obesity with the codominant and dominant models remained significantly associated with primary KOA in female participants (Table 5).

DISCUSSION

Our results showed that in addition to age, postmenopause status, obesity, and type 2 diabetes were significantly associated with primary KOA, the latter particularly in female participants. These findings are consistent with some previously described. In this way, the relationship between menopause and OA has been widely studied, highlighting that the high prevalence of OA in menopause is due to estrogen

Table 1. Univariate analysis of the association between primary KOA, clinical characteristics, and rs1477196 of the *FTO* gene

	(n = 347)	KOA 183 (52.7%)	non-KOA 164 (47.3%)	p-value	OR	95% CI
Sex						
Female		62.3	60.4	0.712	1.032	0.873-1.220
Male		37.7	39.6			
Male	Age 60 years >	68.1	24.6	4.5E-7*	2.408	1.653-3.506
Female	Age 60 years >	71.9	21.2	1.4E-13*	2.737	2.012-3.723
Male	Type 2 diabetes	31.9	21.5	0.177	1.274	0.914-1.777
Female	Type 2 diabetes	36.8	13.1	0.00008*	1.676	1.338-2.099
Male	Obesity (BMI ≥ 30)	40.6	27.7	0.116	1.306	0.947-1.803
Female	Obesity (BMI ≥ 30)	33.3	19.2	0.020*	1,368	1.072-1.747
Female	Postmenopause	91.2	43.4	5.3E-14*	4.669	2.614-8.342
rs1477196 FTO gene						
Male	AA	17.4	24.6	0.232		
	AG	52.2	56.9			
	GG	30.4	18.5			
Female	AA	30.7	17.2	0.072		
	AG	43.0	50.5			
	GG	26.3	32.3			

*Chi-square test significant. KOA: knee osteoarthritis; OR: odds ratio; BMI: body mass index.

Table 2. Analysis of the association between the rs1477196 genotypes and the clinical characteristics of the participants

Genotypes (n = 347)	AA (%)	AG (%)	GG (%)	p-value
Obesity (BMI ≥ 30)	23.3	49.5	27.2	0.997*
Postmenopause	25.2	46.3	28.6	0.922*
Age > 60 years	25.9	46.4	27.7	0.410*
Type 2 diabetes	23.1	46.2	30.8	0.668*
KL-II	27.1	48.2	24.7	0.388*
KL-III	34.4	37.7	27.9	
KL-IV	11.4	51.4	37.1	

*Kruskal–Wallis test.
KL: Kellgren and Lawrence.

deficiency, which has been evidenced in animal and human studies[28].

Diabetes has been recognized individually or as a component of the metabolic syndrome as a risk factor for the development of OA. However, the findings have been inconsistent and controversial, requiring more studies to confirm the findings[29]. Obesity and being overweight are the most determining risk factors for developing KOA. Studies have shown that

Table 3. Analysis of the association of rs1477196 of the *FTO* gene with primary KOA in all participants

Genetic models (n = 347)	KOA (%)	non-KOA (%)	OR 95% CI	p-value
Codominant 1	47 (48.0)	32 (42.1)	1.108 (0.854-1.438)	0.442
AA/GG	51 (52.0)	44 (57.9)		
Codominant 2	47 (35.6)	33 (27.5)	1.189 (0.937-1.508)	0.167
AA/ AG	85 (64.4)	87 (72.5)		
Dominant	47 (25.7)	33 (20.1)	1.153 (0.927-1.435)	0.219
AA/ AG+GG	136 (74.3)	131 (79.9)		
Recessive	133 (72.7)	120 (73.2)	1.012 (0.810-1.264)	0.918
AA+AG/ GG	50 (27.3)	44 (26.8)		

KOA: knee osteoarthritis; OR: odds ratio.

Table 4. Binary logistic regression of the association between the rs1477196 polymorphism of the *FTO* gene and primary KOA stratified by sex

	Genetic models	KOA (%)	non-KOA (%)	OR 95% CI	p-value	Adjusted OR	Adjusted p-value
Male	Codominant 1	12 (36.4)	18 (57.1)	1.485 (0.901-2.447)	0.105	2.175 (0.697-6.791)	0.181
	AA/GG	21 (63.6)	12 (42.9)				
	Codominant 2	12 (25.0)	16 (30.2)	1.151 (0.707-1.872)	0.561	1.851 (0.657-5.216)	0.244
	AA/AG	36 (75.0)	37 (69.8)				
	Dominant	12 (17.4)	16 (24.6)	0.797 (0.502-1.266)	0.304	0.515 (0.194-1.366)	0.182
	AA/AG+GG	57 (82.6)	49 (75.4)				
	Recessive	48 (69.6)	53 (81.5)	1.339 (0.963-1.861)	0.108	1.528 (0.601-3.885)	0.373
	AA+AG/GG	21 (30.4)	12 (18.5)				
Female	Codominant 1	35 (53.8)	16 (33.3)	1.418 (1.033-1.947)	0.030*	2.308 (0.891-5.975)	0.085
	AA/GG	30 (46.2)	32 (66.7)				
	Codominant 2	35 (41.7)	17 (25.4)	1.360 (1.033-1.790)	0.036*	2.517 (1.035-6.123)	0.042†
	AA/AG	49 (58.3)	50 (74.6)				
	Dominant	35 (30.7)	17 (17.2)	1.372 (1.072-1.755)	0.022*	2.387 (1.054-5.407)	0.037†
	AA/AG+GG	79 (69.3)	82 (82.8)				
	Recessive	85 (74.6)	67 (67.7)	1.176 (0.872-1.586)	0.268	1.280 (0.621-2.639)	0.503
	AA+AG/GG	29 (25.4)	32 (32.3)				

*Significant unadjusted p value.
†Significant adjusted p value by type 2 diabetes, obesity, age, and postmenopause.
KOA: knee osteoarthritis; OR: odds ratio.

Table 5. Binary logistic regression analysis for the interaction of obesity with the rs1477196 codominant and dominant models in women with primary KOA

		p-value	OR	CI 95%	
Model 1 Female	Obesity	0.651	0.773	0.253	2.362
	Postmenopause	0.000*	5.383	2.110	13.731
	Age	0.002*	3.472	1.552	7.769
	Type 2 diabetes	0.289	1.554	0.688	3.507
	Dominant model rs1477196* Obesity	0.039*	1.615	1.025	2.544
Model 2 Female	Obesity	0.658	0.756	0.220	2.604
	Postmenopause	0.001*	6.557	2.067	20.798
	Age	0.019*	3.246	1.218	8.655
	Type 2 diabetes	0.622	1.275	0.485	3.355
	Codominant model 2 rs1477196* Obesity	0.043*	1.662	1.015	2.723
Model 3 Female	Postmenopause	0.021*	4.313	1.246	14.924
	Age	0.035*	3.448	1.088	10.922
	Type 2 diabetes	0.108	2.566	0.812	8.108
	Obesity	0.817	0.849	0.214	3.378
	Codominant model 1 rs1477196* Obesity	0.084	1.595	0.939	2.709

*Significance.

an increase of 5 units in body mass has been associated with a 35% increase in the risk of KOA[30]. Although the mechanism by which obesity develops is complex, *FTO* SNPs have been associated with increased BMI[13]. Furthermore, in the Mexican population, some variants of the *FTO* gene have been associated with indicators of obesity[8].

Adipogenesis and an increased food intake are possible mechanisms through which the proteins encoded by *FTO* act through modification in the activity of N6-methyladenosine (m6A)[31].

The association of *FTO* polymorphisms with OA has been controversial. A recent meta-analysis has shown that *FTO* gene polymorphisms were significantly associated with the risk of OA in the Caucasian population. However, it is notable that the rs1477196 variant was not included in this meta-analysis[24]. Wang et al. observed a significant interaction between rs8044769 *FTO* genotypes and BMI with the risk of KOA (p = 0.037) and a marginal interaction of the polymorphism with age (p = 0.062)[22]. Dai et al. did not demonstrate an association between rs8044769 and OA. Yau et al. conducted a genome-wide sequencing study in a North American Caucasian population. This study found significant associations with the loci rs143383 of GDF-5 and rs1558902 of *FTO* (OR = 1.10; CI = 1.02–1.18; p = 0.01)[21].

Our study's initial bivariate analysis showed no association of rs1477196 genotypes with KOA, BMI, and other covariables. Notably, our findings showed that, for female participants, the association of the SNP rs1477196 with KOA could be evidenced,

particularly with the codominant two and dominant genetic models, and this association remained significant after adjustment for covariates such as age, obesity, type 2 diabetes, and postmenopause status. Similarly, as obesity was associated with KOA in women, we analyzed whether there was any interaction between obesity and genetic models in this study group, and we observed that the association with primary KOA remained significant.

Our study shows weaknesses such as small sample size, selected participants being limited to a northern population, sampling limited to a hospital-based population, and subject characteristics such as diabetes and postmenopause status corroborated only by clinical history. We attempted to overcome these limitations by performing a stratified analysis to reduce the risk of false positives. We conducted a multivariate analysis adjusting for risk variables associated with OA, such as age, menopause, obesity, and type 2 diabetes, and through genotypes and genetic models of inheritance.

This is the first study in a population from northern Mexico to associate the rs1477196 variant of the *FTO* gene with primary KOA. Our findings suggest that the rs1477196 variant of the *FTO* gene may be related to the risk of KOA in women and possibly exert its effects through obesity and yet-unidentified mechanisms. These results contrast with what was reported in previously mentioned studies in other populations, in which variables such as menopause and diabetes were not included and the rs1477196 variant was not considered; however, we recognize that our findings cannot be generalized to other ethnic groups. Although we did not observe an association of this variant of the *FTO* gene with obesity in our study, we suggest studies be carried out with larger sample sizes compared to other populations, including different variants of the *FTO* gene, given that the discrepancies we found with other studies may be due to the genetic heterogeneity of the people studied.

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