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Association of *FTO*, *ABCA1*, *ADRB3*, and *PPARG* variants with obesity, type 2 diabetes, and metabolic syndrome in a Northwest Mexican adult population

Jorge Velazquez-Roman [a], Uriel A. Angulo-Zamudio [a], Nidia León-Sicairos [a,b], Julio Medina-Serrano [c,d], Nora DeLira-Bustillos [c], Hugo Villamil-Ramírez [e], Samuel Canizales-Quinteros [e], Luis Macías-Kauffer [e], Abraham Campos-Romero [f], Jonathan Alcántar-Fernández [f], Adrian Canizalez-Roman [a,g,*]

[a] School of Medicine, CIASaP, Autonomous University of Sinaloa, 80246 Culiacan, Sinaloa, Mexico
[b] Pediatric Hospital of Sinaloa, 80200 Culiacan, Sinaloa, Mexico
[c] Programa de Maestría en Ciencias en Biomedicina Molecular, UAS, 80246 Culiacan, Sinaloa, Mexico
[d] Coordinación de Planeación y Enlace Institucional, Órgano de Operación Administrativa Desconcentrada (OOAD) de Sinaloa, Instituto Mexicano del Seguro Social (IMSS), Culiacan Sinaloa, Mexico
[e] Unidad de Genómica de Poblaciones Aplicada a la Salud, Facultad de Química, UNAM/INMEGEN, Mexico City, Mexico
[f] Salud Digna A.C., 80000 Culiacán, Sinaloa, Mexico
[g] The Women's Hospital, Secretariat of Health, 80020 Culiacan, Sinaloa, Mexico

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ABSTRACT

Aim: To identify associations among allelic variants of the genes *FTO*, *ABCA1*, *ADRB3*, and *PPARG* with anthropometric and biochemical traits, metabolic diseases (obesity, T2D or metabolic syndrome) in an adult population from Northwest Mexico.

Methods: Blood samples were collected from 846 subjects including 266 normal weight subjects, 285 with obesity, and 295 with T2D. Of the 846 persons in the study, 365 presented metabolic syndrome diagnostic criteria. Anthropometric and biochemical traits were recorded and 4 single nucleotide polymorphisms (SNPs): *FTO* rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele were genotyped by real-time PCR.

Results: *FTO* rs9939609 A-allele was significantly associated with obesity (p: 8.3×10^{-4}), and metabolic syndrome (p: 0.001), but no individual SNPs were significantly associated with T2D. Finally, the cumulative risk of the four SNPs was significantly associated with obesity (p: 1.95×10^{-4}).

Conclusion: Associations in *FTO, ABCA, ADRB3*, and *PPARG* SNPs presented in this study with obesity and metabolic syndrome could represent a risk for developing metabolic diseases in Northwest Mexican adult subjects.

1. Introduction

Non-communicable diseases related to metabolism, such as obesity, type 2 diabetes (T2D), and metabolic syndrome are a major global public health problem of the 21st century, with obesity being particularly important because it is the most frequent. The worldwide prevalence of obesity has increased considerably in recent years in adults and children; nearly 40% of adults are classed as overweight and 10–15% are obese.[1] In Mexico, the prevalence of non-communicable diseases is continuously increasing. According to the 2018 National Health and Nutrition Survey in the Mexican population, the prevalence of adults classified as overweight and obese was 75.2% (71.3% in 2012), whereas the prevalence of T2D was 10.3% (9.2% in 2012).[2]

Various environmental factors are associated with obesity, T2D, and metabolic syndrome including those related to lifestyle (diet or level of activity), gut microbiota and its composition, and genetic alterations as

* Corresponding author at: Autonomous University of Sinaloa, School of Medicine, CIASAP, 80246 Culiacan, Sinaloa, Mexico.
E-mail address: canizalez@uas.edu.mx (A. Canizalez-Roman).

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single nucleotide polymorphisms (SNPs).[3,4] The advent of genome-wide association studies (GWAS) has led to revelations of numerous SNPs being associated with differences in anthropometrical or biochemical traits, or associated with metabolic diseases. However, genetic variation identified to date explains only a small fraction (5–10%) of genetic variance. More than 120 genes have been demonstrated to be associated with obesity, predominantly in European populations.[5] Fat mass and obesity-associated gene (*FTO*) variants are some of the most studied SNPs globally, and have a strong association with obesity. SNPs in *ABCA1* and *PPARG* have also been linked with metabolic diseases. *ABCA1* is highly expressed in the liver and adipose tissues, and its expression is important in mobilizing adipose tissue cholesterol for transport to the liver for excretion, whereas *PPARG* is related to adipogenesis regulation. In contrast, *ADBR3* is a beta-adrenergic receptor which could participate in the development of metabolic diseases, such as T2D (participating in insulin sensitivity) or obesity (control of fatty acid storage and release in adipose tissue).[6]

Alleles from *FTO*, *ABCA1, ADRB3*, and *PPARG* have been associated with obesity in some Mexican populations, predominantly those from Central Mexico.[7,8] Due to nutritional differences among Northwest of Mexico and Central Mexico subjects (higher consumption of red meat and simple carbohydrates in Northwest of Mexico[2]) and the important participation of *FTO*, *ABCA1*, *ADBR3*, and *PPARG* in the development of metabolic diseases (obesity, T2D, and metabolic syndrome) in several populations, the study of these allelic variants in Northwest Mexican adult population is important to assess their contribution to these phenotypes. The aim of this work was to identify associations among *FTO* rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele with metabolic diseases such as obesity, T2D, or metabolic syndrome in a population from Northwest Mexico.

2. Materials and methods

2.1. Population-based study

Sample size was estimated for the association between *FTO* rs9939609 and obesity in a cases-control design considering an additive model with an allele frequency of 0.23, the frequency reported in individuals of Mexican Ancestry in Los Angeles from the 1000 genomes project, with the Genetic Association Study Power Calculator, with alpha set at 0.05. For a power of 80%, 250 normal weight and 250 obese subjects were required to detect an allelic odds ratio of 1.35. Blood samples were taken from 846 Mexican subjects aged older than 30 years who were recruited from different municipalities of Sinaloa (most of them were from Culiacan municipally) a state located in Northwest Mexico. A nested case–control analysis was performed including normal weight subjects and people with obesity, T2D, or metabolic syndrome.

The classification of obesity was based on World Health Organization (WHO) criteria: class I obesity was defined as body mass index (BMI) $\geq$30 and <35 kg/m^2; class II as BMI $\geq$35 and <40 kg/m^2; and class III as BMI $\geq$40 kg/m^2. Normal weight subjects were defined as BMI >18.5 and <25 kg/m^2.[1] Classification of T2D was according to American Diabetes Association criteria: fasting plasma glucose $\geq$126 mg/dL, glucose at any time of the day $\geq$200 mg/dL or glycated hemoglobin (HbA1c) $\geq$6.5%.[10] Metabolic syndrome was classified on the basis of the Adult Treatment Panel III (ATP III) and the American Heart Association/National Heart, Lung and Blood Institute Scientific Statement, and considered present if a patient had any three of the following: waist circumference, female >88 cm and male >102 cm; blood pressure, systolic <130 mmHg and diastolic <85 mmHg; HDL cholesterol, female <40 mg/dL and male <50 mg/dL; triglycerides >150 mg/dL; and glucose >100 mg/dL.[11,12]

Prior to blood samples being taken, the subjects were informed about the investigation and signed informed consent agreeing to participate in the study. The study was approved by the Ethics Committee of The Women's Hospital of Sinaloa, Secretariat of Health No. 202009-07.

2.2. Anthropometric and biochemical parameters

Anthropometric measurements, including height, weight, and waist and hip circumferences, were collected following the procedures previously described.[9] BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-hip ratio (WHR) was calculated by dividing waist circumference with hip circumference. Blood pressure was measured using the digital blood pressure monitor HEM-907 XL (Omron, Osaka, Japan) following WHO standards.[10] Glucose, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and creatinine levels were analyzed by a clinical laboratory (Salud Digna A.C.) based on Mexican official standards.

2.3. Genotyping

Genomic DNA was isolated from peripheral white blood cells using a commercial kit based on the salt fractionation method (QIAmp 96 DNA Blood Kit; Qiagen, Hilden, Germany) according to the manufacturer's instructions. The amount and purity of DNA extracted from the samples was evaluated using the Nanodrop 2000 (ThermoFisher Scientific, Massachusetts, BA, USA). SNPs rs9939609 (*FTO*), rs9282541 (*ABCA1)*, rs4994 (*ADRB3)* and rs1801282 (*PPARG*) were genotyped using TaqMan probes (Applied Biosystems, Foster City, CA, USA) and a LightCycler® 96 instrument II (Roche, Rotkreuz, Switzerland). Approximately 5% of the samples were duplicated and the genotype in all cases was concordant.

2.4. Statistical analyses

The descriptive characteristics of the study participants were presented as mean ± standard deviation (SD) and Mann-Whitney *U* test was used to analyze the differences between the groups. All associations were tested using logistic regression, adjusting for age; sex and locality to obesity and metabolic syndrome analyses and addition of BMI in T2D, all tests were under an additive model. Additionally, we constructed a genetic risk score, in which SNPs of rs9939609 (*FTO*), rs9282541 (*ABCA1)*, rs4994 (*ADRB3)* and rs1801282 (*PPARG*) were included.[11,12] Bonferroni correction was applied to avoid alpha 1 error, thus p value $\leq$0.003 was used for declaring significant association. All statistical analyses were performed using SPSS (version 20.0; Chicago, IL, USA). Deviation from Hardy–Weinberg equilibrium was not observed for any SNPs in any group ($p > 0.05$).

3. Results

3.1. Characteristics of the study population

The study population comprised 846 individuals from Sinaloa state. Of these, 266 were classified as normal weight, 285 with obesity (without T2D), and 295 with T2D. Of all the subjects with obesity and T2D, 62% (365 people) were classified with metabolic syndrome. The biochemical and anthropometrical parameters measured in the study participants are shown in Table 1. Most parameters including age, weight, BMI, waist circumference, hip circumference, arterial pressure, total cholesterol, and glucose, were significantly higher in subjects with obesity and T2D in comparison with normal weight subjects ($p < 3 \times 10^{-06}$; Table 1). Moreover, most of anthropometric and biochemical traits were higher in subjects with metabolic syndrome in comparison with those without (Table 2).

3.2. Association of allelic variants of FTO, ABCA1, ADRB3, and PPARG with metabolic diseases

FTO rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele were analyzed for associations with obesity, T2D, or metabolic syndrome (Tables 3 and 4). The

Table 1
Comparison of anthropometric and biochemical traits among study groups.

Traits	Normal weight $n = 266$	Subjects with obesity $n = 285$		Subjects with diabetes $n = 295$	
	Mean (SD)	Mean (SD)	p value	Mean (SD)	p value
Age (years)	39.66 ± 10.15	43.60 ± 10.64	3×10^{-06}*	57.67 ± 9.80	0.0×10^{-36}*
Height (m)	1.65 ± 0.09	1.62 ± 0.08	1.15×10^{-4} *	1.59 ± 0.08	5.4×10^{-16}*
Weight (kg)	63.90 ± 10.34	90.10 ± 17.68	0.0×10^{-36}*	78.36 ± 15.43	1.8×10^{-31}*
BMI (kg/m^2)	23.05 ± 2.36	33.96 ± 5.74	0.0×10^{-36}*	30.98 ± 5.96	0.0×10^{-36}*
Waist circumference (cm)	79.73 ± 9.14	105.83 ± 15.50	0.0×10^{-36}*	102.84 ± 12.36	0.0×10^{-36}*
Hip circumference (cm)	97.64 ± 5.97	119.10 ± 61.13	0.0×10^{-36}*	108.26 ± 12.58	1.5×10^{-28}*
WHR	0.8081 ± 0.105	0.904 ± 0.132	9.7×10^{-31}*	0.94 ± 0.091	0.0×10^{-36}*
Diastolic pressure (mm/Hg)	71.026 ± 10.22	78.9 ± 11.90	1.4×10^{-20}*	75.92 ± 9.95	7.3×10^{-34}*
Systolic pressure (mm/Hg)	111.57 ± 14.12	128.24 ± 44.81	3.7×10^{-18}*	131.29 ± 19.61	1.1×10^{-08}*
Cholesterol (mg/dL)	194.72 ± 84.12	180.42 ± 46.72	0.037	184.67 ± 46.93	0.075
LDL (mg/dL)	125.85 ± 44.82	118.42 ± 37.48	0.19	110.34 ± 42.42	3.3×10^{-04}*
HDL (mg/dL)	52.62 ± 18.37	38.31 ± 14.44	8.7×10^{-24}*	39.04 ± 14.10	4.5×10^{-19}*
Glucose (mg/dL)	93 07 ± 13.94	90.62 ± 13.54	0.042	172.64 ± 85.92	0.0×10^{-36}*
Triglycerides (mg/dL)	111.34 ± 0.77.71	155.37 ± 79.59	3.7×10^{-18}*	179.67 ± 127.0	5.1×10^{-19}*
Creatinine (mg/dL)	0.728 ± 0.20	0.904 ± 0.132	3.3×10^{-10}*	0.94 ± 0.091	0.351

Abbreviations: m, meters; cm, centimeters; kg, kilograms; mm, millimeters; Hg, mercury; mg, milligrams; dL, deciliters, WHR, waist-hip ratio; SD, standard deviation. Mean and standard deviation were obtained by means of a frequency analysis. Normal values: BMI, 20–25 kg/m^2; blood pressure, 120/80 mm/Hg; cholesterol, <200 mg/dL; LDL, <130 mg/dL; HDL, >50 mg/dL in women, >40 mg/dL in men; triglycerides, <150 mg/dL; glucose, <100 mg/dL; creatinine, 0.7–1.3 mg/dL.

* Statistical significance vs. normal weight group. Bonferroni correction was applied to avoid alpha 1 error, thus p value ≤0.003 was used for declaring significant association.

Table 2
Comparison of anthropometric and biochemical traits among subjects with and without metabolic syndrome.

Traits	Subjects without metabolic syndrome	Subjects with metabolic syndrome	
	$n = 481$	$n = 365$	
	Mean (SD)	Mean (SD)	p value
Age (years)	43.69 ± 12.75	52.05 ± 11.28	4.4×10^{-23}*
Height (m)	1.66 ± 47.4	1.63 ± 9.76	7.6×10^{-11}*
Weight (kg)	72.43 ± 17.15	84.90 ± 17.26	4.08×10^{-24} *
BMI (kg/m^2)	25.12 ± 6.12	33.07 ± 5.87	0.0×10^{-36}*
Waist circumference (cm)	89.17 ± 15.8	106.38 ± 13.33	0.0×10^{-36}*
Hip circumference (cm)	105.3 ± 48.04	112.89 ± 13.08	4.6×10^{-36}*
WHR	0.8504 ± 0.129	0.941 ± 0.097	3.8×10^{-35}*
Diastolic pressure (mm/Hg)	72.34 ± 10.22	79.48 ± 11.12	2×10^{-36}*
Systolic pressure (mm/Hg)	117.97 ± 36.21	132.14 ± 18.9	4.4×10^{-19}*
Cholesterol (mg/dL)	184.25 ± 69.10	189.23 ± 49.03	0.026
LDL (mg/dL)	117.71 ± 42.69	118.24 ± 41.24	0.604
HDL (mg/dL)	48.98 ± 18.11	35.30 ± 11.30	2.09×10^{-36}*
Glucose (mg/dL)	100.06 ± 41.05	146.20 ± 79.15	1.7×10^{-33}*
Triglycerides (mg/dL)	109.04 ± 62.06	203.49 ± 118.66	0.0×10^{-36}*
Creatinine (mg/dL)	1.65 ± 0.30	0.732 ± 0.600	0.001*

Abbreviations: m, meters; cm, centimeters; kg, kilograms; mm, millimeters; Hg, mercury; mg, milligrams; dL, deciliters, WHR, waist-hip ratio; SD, standard deviation. Mean and standard deviation were obtained by means of a frequency analysis. Normal values: BMI, 20–25 kg/m2; blood pressure, 120/80 mm/Hg; cholesterol, <200 mg/dL; LDL, <130 mg/dL; HDL, >50 mg/dL in women, >40 mg/dL in men; triglycerides, <150 mg/dL; glucose, <100 mg/dL; creatinine, 0.7–1.3 mg/dL.

* Statistical significance vs. non- metabolic syndrome subjects. Bonferroni correction was applied to avoid alpha 1 error, thus p value ≤0.003 was used for declaring significant association.

presence of *FTO* rs9939609 A-allele was significantly associated with obesity, having an allelic frequency of 30.1% for the A-allele (OR: 1.60, 95% CI: 1.21–2.1, p: 0.001) (Table 3). In addition, the presence of this SNP was significantly associated with metabolic syndrome in study individuals (OR: 1.511, 95% CI: 1.19–1.90, p: 8.3×10^4; Table 4), but was not associated with T2D (Table 3). Moreover, the presence of *PPARG* rs1801282 G-allele was significantly associated with obesity; the allelic frequency was 10.7% for the G-allele (OR: 1.56, 95% CI: 0.48–3.4, p: 0.036), however this association was lost when Bonferroni correction was applied. Similarly, this SNP was not associated with T2D and metabolic syndrome, Table 3. The SNPs *ABCA1* rs9282541 A-allele and *ADRB3* rs4994 G-allele were not associated with any metabolic diseases (obesity, T2D and metabolic syndrome) the study population (Tables 3 and 4).

3.3. Genetic risk score analyses

The cumulative risk effect of multiple SNPs was investigated to determine association with metabolic diseases (Table 5). The presence of all four SNPs together (*FTO* rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele) was significantly associated with obesity (OR: 1.27, 95% CI: 1.20–1.44, p: 1.95×10^{-4}). However, before of apply the Bonferroni correction the presence of 4 SNPs were associated with T2D (OR: 1.36, 95% CI: 1.02–1.81, p: 0.033), and metabolic syndrome (OR: 1.25, 95% CI: 1.17–1.65, p: 0.044), Table 5.

4. Discussion

This study demonstrated that allelic variants of the genes *FTO* rs9939609 A-allele was associated with obesity and metabolic syndrome and the presence of all four SNPs together was associated with obesity. However, the individual presences of SNPs (*ABCA1*, *ADRB3*, and *PPARG)* were not associated with metabolic diseases in Northwest Mexican adult population.

The presence of SNPs may be associated with metabolic diseases such as obesity, T2D, and metabolic syndrome, obesity is the most important of the aforementioned. Obesity is a serious public health problem in Mexico; more than 40% of the population have obesity, with Sinaloa state is within 10 most affected.[2] In the current study, *FTO* rs9939609 A-allele was associated with obesity. The frequency of *FTO* in this study was higher in comparison with children and adults from Mexico City.[13]

Several studies have reported associations of *FTO* variants with

Table 3
Association of multiple SNPs with obesity and diabetes.

Gene/SNP	Condition	Genotype, n (%)					Additive model	
		n	TT	TA	AA	A-Allele frequency (%)	Odds ratio (95%, CI)	*P* value
	Normal weight	265	165 (62.2)	88 (33.8)	12 (4.5)	21.1		
FTO rs9939609	Obesity	277	134 (48.3)	117 (43.1)	25 (9.0)	30.1	1.60 (1.21–2.1)	8.3×10^{-4}*
	Diabetes	258	144 (55.8)	97 (37.6)	17 (6.6)	25.3	1.27 (0.68–2.3)	0.446
Gene/SNP	Condition	n	GG	GA	AA	A-Allele frequency (%)	Odds ratio (95%, CI)	*P* value
	Normal weight	278	259 (93.2)	18 (6.5)	0	3		
ABCA1 rs9282541	Obesity	299	267 (89.3)	31 (10.4)	1 (0.3)	5.5	1.52 (0.83–2.7)	0.168
	Diabetes	295	268 (90.8)	27 (9.15)	1 (0.3)	4.9	2.37 (0.79–7.0)	0.122
Gene/SNP	Condition	n	AA	AG	GG	G-Allele frequency (%)	Odds ratio (95%, CI)	*P* value
	Normal weight	278	213 (76.6)	61 (21.94)	4 (1.4)	12.4		
ADRB3 rs4994	Obesity	296	222 (75.0)	68 (22.9)	5 (1.6)	13.1	1.15 (0.81–1.6)	0.423
	Diabetes	293	221 (75.4)	67 (22.8)	5 (1.7)	13.1	1.16 (0.55–2.4)	0.688
Gene/SNP	Condition	n	CC	CG	GG	G-Allele frequency (%)	Odds ratio (95%, CI)	*P* value
	Normal weight	270	239 (88.5)	30 (11.1)	1 (0.4)	5.9		
PPARG rs1801282	Obesity	297	239 (80.5)	52 (17.5)	6 (2.0)	10.7	1.56 (1.03–2.3)	0.036
	Diabetes	291	257 (88.3)	32 (10.9)	1 (0.3)	5.8	1.28 (0.48–3.4)	0.615

Abbreviations: CI, confidence index. *p* values and odds ratios were calculated using a logistic regression; *p* values were adjusted for obesity with gender, age, and locality, while in diabetes they were adjusted with gender, age, locality, and BMI, using an additive model. Bonferroni correction was applied to avoid alpha 1 error, thus p value $\leq$0.003 was used for declaring significant association.
* Statistical significance.

Table 4
Association of multiple SNPs with metabolic syndrome.

Gene	SNP	Risk allele	Odds ratio (95%, CI)	*p* Value
FTO	rs9939609	A	1.538 (1.19–1.90)	0.001*
ABCA1	rs9282541	A	1.088 (0.61–1.91)	0.771
ADRB3	rs4994	G	1.011(0.74–1.37)	0.946
PPARG	rs1801282	G	1.111 (0.76–1.61)	0.581

Abbreviations: SNP, single nucleotide polymorphism; CI, confidence index. *p* values and odds ratio were calculated using a logistic regression; *p* values were adjusted for gender, age, and locality, using an additive model; patients were classified with metabolic syndrome based on the criteria of Adult Treatment Panel III (ATP III) and American Heart Association/National Heart, Lung and Blood Institute Scientific Statement, people with metabolic syndrome were compared with those without it. Bonferroni correction was applied to avoid alpha 1 error, thus *p* value $\leq$0.003 was used for declaring significant association. *P*-values were tested under an additive model.
* Statistical significance.

Table 5
Association of a genetic risk score of SNP with metabolic diseases.

Metabolic disease	Odds ratio (95%, CI)	*p* Value
Obesity	1.27 (1.12–1.44)	1.95×10^{-4}*
Diabetes	1.36 (1.02–1.81)	0.033
Metabolic syndrome	1.25 (1.17–1.65)	0.044

Abbreviation: CI, confidence index. Genetic risk score was calculated through the sum of the odds ratio of the alleles; for statistical significance a linear regression was used; the obesity and metabolic syndrome groups were adjusted for age, gender, and locality, while the diabetes group was adjusted by age, gender, location, and BMI. Genetic risk score weighted was used. $p < 0.05$ was taken as significant. Bonferroni correction was applied to avoid alpha 1 error, thus p value $\leq$0.003 was used for declaring significant association. *Statistical significance.

obesity in Mexican subjects. Villalobos-Comparan et al. (2008) found a significant association among *FTO* rs9939609 and obesity, particularly in class III obesity, and identified an A-allelic frequency of 21.1 with obesity class I/II and 31.1 with obesity class III[14]; these results are in agreement with those of the current study. This SNP is not only associated with obesity in Mexican adults, but also with obesity in Mexican American, Mexican mestizo children, and Maya children.[13,15–17] Genetic variants of *FTO* associated with obesity have also been reported in populations of other countries, such as Asia (e.g. China, and Japan), Europe (e.g., Spain and Germany), and Africa.[18–20] The association of *FTO* gene variants with obesity could be due to the multiple effects of this gene in humans such as in control of satiety, in increasing white adipocytes, and in stimulating adipogenesis, as previously mentioned. On the other hand, recent studies has been associated than the effects of the *FTO* gene on obesity could be influence by the expression of *IRX3* gene.[21]

The only SNP associated with metabolic syndrome in this study was *FTO* rs9939609 A-allele. In contrast to other studies in which *FTO* was associated with some components of metabolic syndrome,[22,23] in the current study it was analyzed as a disease based on the ATP III and American Heart Association/National Heart, Lung and Blood Institute Scientific Statement and not only with some parameters related to metabolic syndrome. Cruz et al. (2010) also analyzed metabolic syndrome as a disease, and reported that the presence of *ADRB3* rs4994 but not *FTO* rs9939609 was associated with metabolic syndrome in subjects from Mexico City.[24] Nevertheless, *FTO* also has been associated with metabolic syndrome in others population as Egyptians and Turks.[25,26]

On the other hand, no associations were found among *ABCA1*, *ADRB3*, and *PPARG* with metabolic diseases, the lack of associations of SNPs depends of different factors such as: *i*) the genetic variability of study population, through time, the human has migrated, adapted to different diets, lifestyles, and they have to mixed with different races and ethnicities, fact that has resulted in population with high genetic variety with different susceptibility to SNPs.[27,28] *ii*) Sample size, larger the sample is higher probabilities to found association between the SNP and metabolic diseases, inclusive several studies have concluded that with larger sample size, they could found associations.[29–31]

Metabolic diseases have been related not only with one gene; in fact they have been classified as poly-gene disease. The multi-variant effects, especially gene-gene interactions, are considered as important components of the genetic architecture influencing susceptibility to common human diseases.[32] There are some works than demonstrate the importance of study the interaction gene-gene in these diseases. Huerta-Chagoya et al., (2020) they did a polygenic risk scores from 103 SNPs previously reported and associated with dyslipidemia and T2D, and identified that in T2D, the overall genetic variance explained by the 27 T2D-related genetic variants was 0.1%[33] Hernández-Tobías et al. (2016), also found that from 11 polymorphisms only the multi-allelic combination of PPARG-LYPLAL1 were associated with obesity and being overweight in Mexican adolescent females.[34] On the other hand,

Soung Yj et al. (2016) reported the influence of combination of SNPs *BBS9, ADCY8* and *KCNK9* on visceral a fat, and *MLLT10, DNAJC* and *EBLN1*on subcutaneous.[35] Dong SS et al., (2017) also showed than the effect of two SNPs (*WNT4-WNT5A*) could affect the BMI of Chinese population.[36] Heid IM et al., (2010) reported in a Meta-analyze that 13 SNPs (*RSPO3, VEGFA, TBX15-WARS2, NFE2L3, GRB14, DNM3-PIGC, ITPR2-SSPN, LY86, HOXC13, ADAMTS9, ZNRF3-KREMEN1, NISCH-STAB1*and *CPEB4SNP*) located in different chromosomes presented important effect on changes in WHR and modulates fat distribution.[37]

In this study four SNPs were analyzed located on different chromosomes; the cumulative risk of the four SNPs was significantly associated with obesity in Mexican subjects, regardless of whether individual SNPs did not exhibited associations (e.g. *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele). There are studies than matched with our results. Liu S et al., (2016), searched the association of 657 common SNPs with obesity in 2137 African American, of them *NEGR1*, *ADCY3*, *TMEM18*, *TFAP2B*, *BDNF*, *NRXN3*, *FTO* and *MC4R* were associated with obesity, other 57 were marginally significant, but they lost the association after the Bonferroni correction.[38] Knuppel S et al., (2013), evaluated association among obesity and 41 candidate SNPs, of them two combination of 6 SNPs were associated with waist circumference and 15 combination of three SNPs with BMI in Germany subjects.[39] Srivastava A et al., (2016), searched association among 55 SNPs and obesity in 480 North Indian populations, they found that the interaction of *FTO* rs9939609 with *TCF7L2* rs7903146 and *FTO* rs9939609 and *IRX3* rs3751723 were associated with increase of BMI.[40]

On the other hand, gene-gene interaction and cumulative risk are useful tool to analyze the effect of several SNPs, this tool has not only been used to associate SNPs with metabolic diseases, but have also been used to others diseases.[41] Analysis of the possible effect of multiple SNPs together instead of individually is important because most metabolic diseases are polygenic. Thus, the effect of one SNP is probably not associated with a determined population, but in combination with other genetics variants it could increase susceptibility to some diseases, as observed in this study. Because of that, more researches are needed in which genetic variants and its impact in a network models should be studied.

The strength of this study is the associations of *FTO* rs9939609 A-allele with obesity and metabolic syndrome and the 4 SNPs with obesity, because this supports the concept about the study of network models of genes. The limitation of this study was the sample size and the low statistic power than we got, thus the marginal association of single SNPs with the metabolic diseases. Other was the stratification of population, because the data did not adjust by ethnic mix.

To the best of our knowledge, this is the first report in which *FTO* rs9939609 A-allele is associated with Mexican subjects classified as having metabolic syndrome on the basis of international standards (ATP III and American Heart Association/National Heart, Lung and Blood Institute Scientific Statement), rather than only being associated with a few parameters related to metabolic syndrome, as in other studies. Moreover, the cumulative risk of *FTO* rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele were associated for the first time with obesity in a Mexican subjects.

5. Conclusions

This study provides the evidence that the individual presence of *FTO* rs9939609 A-allele could participate in development of obesity or metabolic syndrome. Additionally, our cumulative risk analysis supports the influence of *FTO* rs9939609 A-allele, *ABCA1* rs9282541 A-allele, *ADRB3* rs4994 G-allele, and *PPARG* rs1801282 G-allele as a genetic risk factor in obesity. Lastly, this study shows evidence of the importance of studying network models of genes in metabolic diseases, which could help to decrease the burden of these diseases and its complications in Mexico.

CRediT authorship contribution statement

Jorge Velazquez-Roman: Data curation, Writing-Original draft preparation, conceptualization; Uriel A. Angulo-Zamudio: Visualization, Investigation, Methodology; Julio Medina-Serranod and Nora DeLira-Bustillo: Formal analysis, Data curation; Hugo Villamil-Ramírez and Samuel Canizales-Quinteros: Writing- Reviewing and Editing; Nidia Leon-Sicairos: Supervision and Reviewing; Abraham Campos-Romerog and Jonathan Alcántar-Fernández: Software, Validation and Reviewing; Adrian Canizalez-Roman: Writing-Original draft preparation, conceptualization, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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