





Interaction analysis of FTO and IRX3 genes with obesity and related metabolic disorders in an admixed Latin American population: a possible risk increases of body weight excess

Análisis de la interacción entre los genes FTO e IRX3 con obesidad y desórdenes metabólicos relacionados en una población mixta de América Latina: un posible aumento del riesgo de exceso de peso

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Abstract

Background:

Fat Mass and Obesity-related (FTO) has been one of the genes consistently related to common obesity. Single nucleotide polymorphisms (SNPs) in FTO have been linked with the IRX3 gene.

Aim:

This study was designed by testing the hypothesis that: i) common SNPs in FTO and IRX3 are associated with obesity and related disorders; ii) there is significant linkage disequilibrium between both genes.

Methods:

A cross-sectional study was carried out on the Colombian Caribbean Coast. Anthropometric and biochemical variables were measured, and obesity and metabolic disorders were diagnosed. Four SNPs were genotyped: 3 at FTO locus (rs17817449, rs8050136, rs9939609) and one at IRX3 locus (rs3751723). LD between these SNPs was estimated. A logistic regression model was applied to estimate associations.

Results:

A total of 792 subjects were included. FTO and IRX3 were not in LD ($D' \leq 0.03$; $R^2 \leq 0.03$). TT genotype (rs9939609) was found to be associated with waist circumference ($p = 0.04$; $\text{adj-}p = 0.01$), and IRX3 SNP with Body Weight Excess (BWE) ($OR = 1.06$, $\text{adj-}p = 0.03$). One FTO-IRX3 haplotype was associated with BWE (G-A-A-T, rs17817449-rs8050136-rs9939609-rs3751723; $OR = 0.67$, $p = 0.04$). The statistical significance of these relations continued after admixture adjustment for a three-hybrid population ($p = 0.03$).

Conclusions:

FTO was related to waist circumference, and IRX3 was associated with BWE in Latin American adults. This relation remained statistically significant after an adjustment for sex, age, and genetic ancestry was performed. Despite that these genes were not in LD, findings of a haplotype involving FTO-IRX3 suggest a gene-gene interaction associated with an increased risk of BWE.

Conflicts of interest:

Nothing

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Resumen

Introducción:

FTO (Fat Mass and Obesity-related) se ha relacionado de manera consistente con la obesidad. Recientemente, Polimorfismos de Nucleótido Único (SNP) en este gen se han relacionado con el gen IRX3.

Objetivo:

Probar la hipótesis de que: i) SNPs en FTO e IRX3 están asociados con la obesidad y trastornos relacionados; ii) existe desequilibrio de ligamiento (LD) significativo entre ambos genes.

Métodos:

se realizó un estudio transversal en la costa caribe colombiana. Se valoraron variables antropométricas y bioquímicas, la obesidad y trastornos metabólicos. Se genotipificaron 4 SNPs: 3 en FTO (rs17817449, rs8050136, rs9939609) y uno en IRX3 (rs3751723). Se estimó el LD entre estos SNPs. Se aplicó un modelo de regresión logística para estimar asociaciones.

Resultados:

Se incluyeron 792 sujetos. FTO e IRX3 no se encontraron en LD ($D' \leq 0.03$; $R2 \leq 0.03$). El genotipo TT (rs9939609) se encontró asociado con la circunferencia de la cintura ($p=0.04$; $\text{adj-}p=0.01$), y el SNP IRX3 con el Exceso de Peso (EP) ($OR=1.06$, $\text{adj-}p=0.03$). Se encontró un haplotipo FTO-IRX3 asociado con EP (G-A-A-T, rs17817449-rs8050136-rs9939609-rs3751723; $OR=0.67$, $p=0.04$). Esta asociación persistió después del ajuste para una población mixta ($p=0.03$).

Conclusiones:

FTO se encontró asociado con la circunferencia de la cintura e IRX3 con EP en adultos latinoamericanos. Estas asociaciones persistieron tras el ajuste por sexo, edad y ascendencia genética. Aunque estos genes no estaban en LD, los hallazgos de un haplotipo entre FTO-IRX3 sugieren una interacción gen-gen asociada con un mayor riesgo de EP.

Remark

1) Why was this study conducted?

The Latin American population has been exposed to significant racial mixing. In mixed populations such as this, understanding the genotype/phenotype interactions behind complex diseases such as obesity and obesity-related diseases remains a challenging task because genetic stratification represents a source of confounding bias. However, the diversity in this type of population is also an opportunity to discover associated genetic factors that could be useful in understanding complex diseases such as obesity. The present study provides evidence by testing the hypothesis that common Single Nucleotide Polymorphisms (SNPs) in FTO and IRX3 genes are associated with obesity and metabolic syndrome-related disorders; and that there is a significant interaction between both genes, when tested in a Latin American population in which a tri-hybrid genetic mixture has been previously described.

2) What were the most relevant results of the study?

Genetic variants in FTO gene were found to be unrelated to obesity or body weight, metabolic disorders (ie, hypertension, hyperglycemia, dyslipidemias, type 2 diabetes mellitus), and metabolic syndrome. On the other hand, IRX3 gene was found to be associated with excess body weight even after adjustment for genetic stratification.

3) What do these results contribute?

The findings of the current study showed no evidence of nonrandom segregation between the FTO and IRX3 SNPs in this sample of Latin American adults, possibly associated with the genetic substructure and the recent admixture process, which could be interfering with the measurement of intergenic applications. However, the design of other studies aimed at describing the role of the IRX3 gene and its product in energy metabolism appear to hold promise in understanding the real epidemic of excess body weight in populations with high genetic diversity.

Introduction

Obesity is a public health priority in almost every region worldwide¹. Its prevalence has continuously increased during the last three decades, shaping an epidemic pattern that has negatively impacted high-, middle- and low-income communities². As obesity prevalence increases, so do the frequency of metabolic disorders (e.g., dyslipidemias and high blood pressure, etc.), which share some pathophysiologic pathways³.

Genetic factors have been widely identified to be involved in obesity and the pathogenesis of obesity-related diseases, such as Diabetes Mellitus type 2, dyslipidemia, hypertension, and cardiovascular disease⁴. Among these, the Fat Mass and Obesity-related (*FTO*) has been one of the genes most consistently related to common obesity, according to findings from many Genome-Wide Association Studies (GWAS)^{5,6}. *FTO* gene plays an important role in regulating appetite and energy homeostasis⁷. In addition, some allelic variants have been strongly associated with fat deposition⁷. Despite that, the role of variations in the *FTO* chromosomal region and the protein FTO (a nuclear demethylase) on the cellular mechanisms responsible for the development of obesity has not been completely described^{8,9}.

Recent studies have shown that some allelic variants in *FTO* first intron might be influencing the transcription regulation of genes located near *loci*¹⁰. In this regard, Smemo *et al.*^{11,13}, and other authors have uncovered long-range functional connections between *FTO* first intron variants and the expression of the Iroquois Homeobox 3 (*IRX3*) gene^{12,13}. Furthermore, there is increasing

evidence that epistasis may play a role in disease risk, thus, the analysis of the relationship between these two genes could be particularly promissory since the activity of the *IRX3* protein has been associated with appetite control and obesity phenotype in animals ¹¹.

The Latin American population has been exposed to more significant racial admixture. In admixed populations like this, understanding the genotype/phenotype interactions behind complex diseases such as obesity and obesity-related diseases remains a challenging task because genetic stratification represents a source of bias brought about by confounding phenomena. However, the diversity in this type of population is also an opportunity to uncover associated genetic factors that might be helpful to understanding complex diseases such as obesity.

Based on those previous findings, some studies have been developed to analyze plausible linkage disequilibrium between *FTO* and *IRX3* SNPs ^{14,15}. Altogether, these results have revealed that this genomic interaction could be identified at the population level, which contributes to understanding the mechanisms of genetic predisposition to obesity and how genetic factors influence the current epidemic. Hence, the present study was designed to add evidence by testing the hypothesis that i) common SNPs in *FTO* and *IRX3* are associated with obesity and related disorders; ii) there is significant interaction between both genes. These hypotheses were tested on a Latin American population in which a tri-hybrid genetic admixing has been previously described ¹⁶.

Materials and Methods

Subjects

A cross-sectional study was carried out in Cartagena de Indias, a 1-million inhabitants city located on the Colombian Caribbean Coast ¹⁷. A sample of 792 subjects was employed to achieve 80% power of discrimination of genetic association with 2.5/3.5 (heterozygotes/homozygotes) odds ratio, assuming an outcome with 25% prevalence, 25% minor allele frequency, complete linkage disequilibrium ($D^2 = 1$), and 5% alpha-coefficient, according to calculations described by other authors, and as was applied in a previous work ¹⁸. Genetic Power Calculator software (<http://zzz.bwh.harvard.edu/gpc/cc2.html>) was used for this calculation ¹⁹.

Inclusion criteria included non-sibling subjects from both genders aging more than 18 years old who live in urban areas of Cartagena de Indias, a city located on the Colombian Caribbean Coast (an admixed population with a predominant European ancestry (~60%) due to Spaniard's colonization between XVI and XIX centuries) ²⁰. Siblings were initially identified by surnames comparison and then confirmed by telephone; therefore, first- and second-degree siblings were excluded for the analysis.

Those suffering from diseases that affect their body weight as primary endocrine disorders, genetic pathology, cancer, or surgical obesity treatment, as well as pregnant or breastfeeding, were also excluded. All subjects gave their informed consent to participate in the study, following the University of Cartagena ethics committee considerations. Subjects with missing data were excluded.

Participants were enrolled by trained medical staff in charge of performing an interview and physical examination focused on sociodemographic and clinical variables and the medical record of metabolic-related disorders (Figure 1).

Anthropometric variables

During the physical examination, anthropometric data were obtained. Height, weight, and waist circumference were recorded; all these measurements were obtained according to international diabetes guidelines for metabolic syndrome described by World Health Organization (WHO) ²¹. Height was measured in meters (m) using a stadiometer with the subject barefoot and straight. Weight was recorded in kilograms (Kg) through a calibrated bascule with the participant wearing light clothes without shoes. Body mass index (BMI)

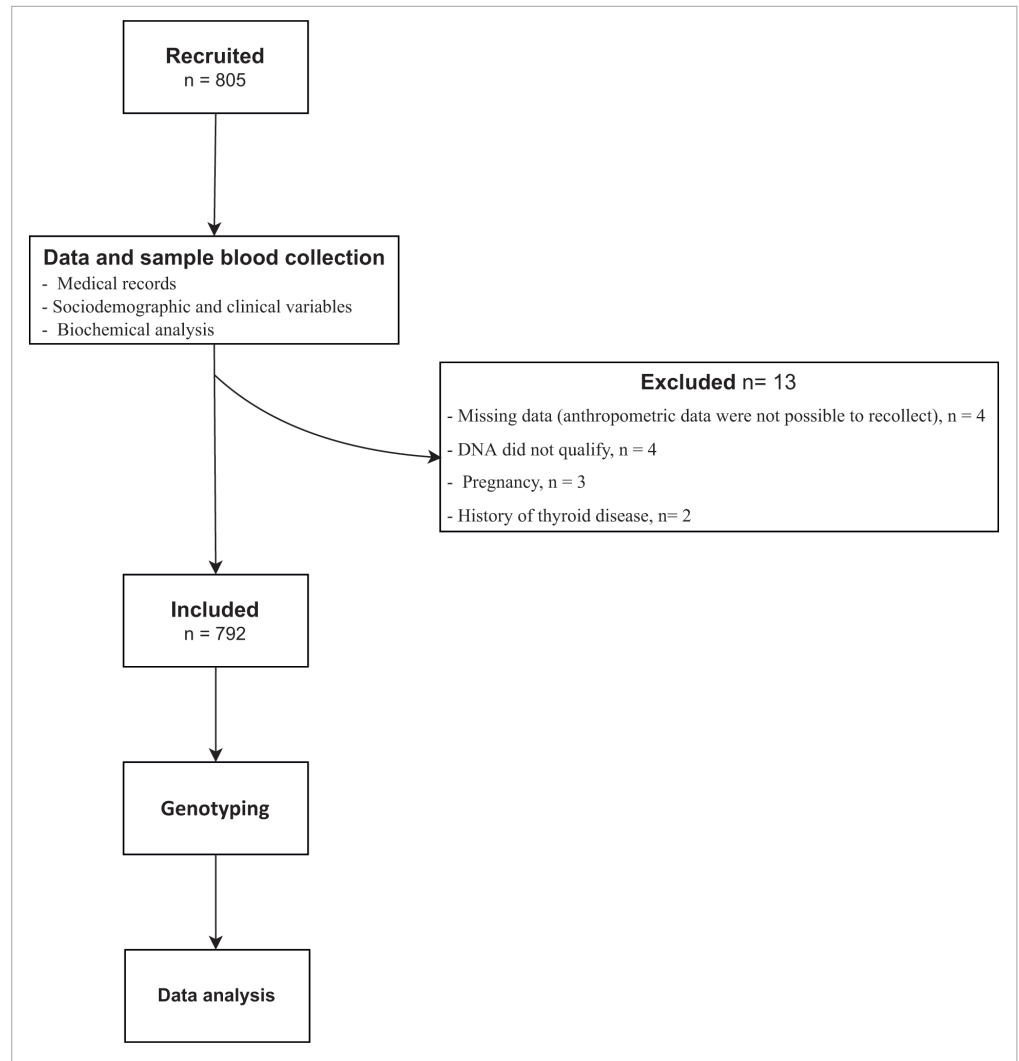


Figure 1. Flowchart for the enrollment of the study population

was calculated by dividing weight in Kg between the square of the height in meters (m²). An inelastic metric tape was used to measure the waist and hip circumference with a patient in a standing position, ensuring that the tape did not compress the skin. Blood pressure was measured using a sphygmomanometer following the 8th Joint National Committee (JNC8) ²².

Biochemical analysis. A whole-blood sample was collected from each one of the participants, who should have a fast of at least 8 hours. Serum concentrations of glucose, triglycerides (TG), and HDL cholesterol (HDLc) were measured through colorimetric assays at the UNIMOL laboratory at the University of Cartagena, following standard protocols.

Obesity and metabolic traits

Obesity was defined using the cut-off points for BMI suggested by the WHO ^{21,23}. Bodyweight excess (BWE) was defined as either overweight or obesity.

- Normal weight: BMI >18.5 and <25 Kg/m²
- Overweight: BMI ≥25 and <30 Kg/m²
- Obesity: BMI ≥30 Kg/m²

Hypertension or High Blood Pressure (HBP) was determined according to JNC8²²:

- Adults <60 years old: systolic ≥ 140 mmHg, diastolic ≥ 90 mmHg
- Adults ≥ 60 years old: systolic ≥ 150 mmHg, diastolic ≥ 90 mmHg

Metabolic syndrome and related conditions were defined through the Joint Interim Statement (JIS) criteria, considering the criteria described elsewhere^{22,24}.

- Abdominal obesity: waist circumference in men ≥ 90 cm and women ≥ 80 cm.
- Hyperglycemia: glucose impaired fasting ≥ 100 mg/dl or drug treatment for elevated glucose

Diabetes was determined through the American Diabetes Association (2018) criteria^{23,25}, considering the presence of the disease with fasting blood glucose values > 126 mg/dL or by HbA1c values $\geq 6.5\%$.

Genotyping

Common variants in *FTO* and *IRX3* were identified using 1,000 genome project reports. For this purpose, the bioinformatic resource *SNiPA* was used^{26,27}. SNPs with a minor allele frequency (MAF) ≥ 0.25 and correlation coefficient (R^2) = 1.0 were selected using data from populations with European ancestry. With this procedure, 3 variants were selected for *FTO*: rs9939609 (c.46-23525T>A), rs8050136 (c.46-27777C>A), rs17817449 (c.46-30685T>G) and only one for *IRX3*: rs3751723 (c.-235C>A), based on previous reports where the linkage disequilibrium between both genes was analyzed^{14,15,26,28}. These variants are proxies for several variants and have shown antecedents of genetic association with metabolic traits and obesity-related diseases²⁶.

SNPs were genotyped with quantitative polymerase chain reaction (qPCR) using Taqman probes (Thermo Fisher Scientific, Inc., Waltham, MA, USA). In addition, allelic discrimination and data were analyzed by StepOne Real-Time PCR Software (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

Statistics

Sociodemographic, anthropometric, biochemicals, and the other metabolic variables were described using the central tendency and frequency values as necessary, and the Lilliefors test was realized to verify the normality. Finally, mean values were compared using t-test and frequencies with Ji^2 or Fisher's exact test.

Allelic and genotype frequencies were described through direct count. Hardy-Weinberg Equilibrium was assessed through the inbreeding coefficient (F_{is}) values using Genetix 4.05 software. Linkage disequilibrium between the selected SNPs was estimated with the package *genetics* for R program 3.5.0²⁹; D' (*D prime*) and R^2 (*R-square*) were reported.

Associations between continuous traits and genotype distributions were analyzed using the analysis of variance (ANOVA) or the Kruskal Wallis test, where appropriate. Relations between categorical variables (metabolic traits), were determined with Ji^2 .

Additive genotype models were evaluated using generalized regression models. Haplotype models were also performed to estimate the association between *FTO* and *IRX3* SNPs with obesity and related outcomes. These models were adjusted by age, sex, and BMI, except for the bodyweight excess (overweight and obesity) analyses, where this last variable (BMI) was not employed due to collinearity. R program version 3.5.0., with the *genetics* and *PredictABEL* packages, was employed²⁹.

Associations were adjusted by genetic stratification assuming a three-hybrid substructure ($k=3$) using a Bayesian approach (Markov Chain Monte Carlo, or MCMC) with 100,000 replications using the STRAT software version 1.1 for DOS/Windows.

The three-hybrid admixture pattern applied is based on previous reports from Cartagena de Indias, where informative ancestry markers (AIMs) and the Y chromosome were used to describe local genetic substructure and ancestry distribution^{15,16,20,28}. In this study, 17 Y chromosome short tandem repeats (Y-STR; AmpFLSTR® Yfiler® PCR Amplification Kit, Thermo Fisher, Inc., USA) were used to confirm the admixture in sampled males²⁰

Results

General data

A total of 805 subjects were enrolled out, 13 were excluded (Figure 1). Finally, registers of 792 subjects (55.7% men and 44.3% women) were used in further analyses. The median age was 36 IQR: (28;52) years. Age ranges of included individuals were distributed according to population pyramid^{17,20}.

Anthropometric and serum biochemical variables

Median values for height, weight and BMI were 1.66 m IQR: (1.60;1.73), 71.3 Kg IQR: (60.7;81.5) and 25.6 Kg/m² IQR: (22.7;28.6), respectively. For the abdominal circumference median was 92 cm IQR: (84;99). Regarding blood pressure, the median values for systolic and diastolic pressure were 110 mmHg IQR: (110-120) and 74 mmHg IQR: (70;80) respectively.

Respecting biochemical variables, the median value for glycemia was 89.4 IQR: (78.6;104.4), serum concentration of triglycerides was 151.1 mg/dL IQR: (113.9;187.8), of HDL cholesterol was 46.0 mg/dL IQR: (39.2-51.8) and of total cholesterol was 183.3 mg/dL IQR: (160.4;205.4).

Metabolic traits

About 56.8% ($n=450/792$) of general population had excess of weight; Among this, 39.7% ($n=315/792$) had overweight and the 17.1% ($n=135/792$) had obesity.

HBP was found in 13.7% ($n=109/792$) of total sample. The frequency of hyperglycemia was 32.0% ($n=254/792$), and 17.1% ($n=136$) was diagnosed with type 2 Diabetes Mellitus (Glycemia ≥ 126 mg/dL, or drug treatment). More than a half of individuals had high serum concentrations of triglycerides (50.8%, $n=403/792$), 43.5% ($n=345/792$) low concentrations of HDL cholesterol and 38.7% ($n=307/792$) had high serum concentrations of total cholesterol. Metabolic syndrome was diagnosed in 31.9% ($n=253/792$) of population.

Genotyping

Genotyping assays were performed on the 792 subjects. Genotype distribution and F_{is} values for Hardy-Weinberg equilibrium are shown in Table 1.

Linkage Disequilibrium: association between alleles

FTO gen SNPs (rs9939609, rs17817449 and rs8050136) were not in LD with *IRX3* gen SNP (rs3751723) ($D' \leq 0.03$; $R^2 \leq 0.03$).

Genetic associations

Anthropometric variables were described through median and frequency values and were compared according to genotype distributions. In the *FTO* gene, for HDL cholesterol, TT homozygotes (rs9939609) shown lower values in comparison with AT+AA genotype ($p=0.037$), CC homozygotes (rs8050136) unlike AC+AA genotypes ($p=0.049$), and TT allele unlike GG+TT genotype ($p=0.036$) (Table 2). The statistical association between metabolic alterations and genotypes was not found (Table 3).

Table 1. Allelic frequencies and genotype distributions for *FTO* and *IRX3* genes

Gene	n	(%)	F_{is}	<i>p</i>
FTO				
rs9939609 (c.46-23525T>A)				
A	497	(31.4)	0.09	0.134
T	1087	(68.6)		
AA	89	(11.2)		
AT	319	(40.3)		
TT	384	(48.5)		
rs8050136 (c.46-27777C>A)				
A	481	(30.4)	0.08	0.205
C	1103	(69.6)		
AA	83	(10.5)		
AC	315	(39.8)		
CC	394	(49.7)		
rs17817449 (c.46-30685T>G)				
G	466	(29.4)	0.08	0.262
T	1118	(70.6)		
GG	78	(9.9)		
GT	310	(39.1)		
TT	404	(51.0)		
IRX3				
rs3751723 (c.-235C>A)				
T	394	(24.9)	0.04	0.09
G	1190	(75.1)		
TT	55	(7.0)		
GG	453	(57.2)		
GT	284	(35.8)		

F_{is} : inbreeding coefficient.

In the regression models where all SNPs were included as variables, TT genotype (rs9939609) was found to be associated with waist circumference ($p=0.04$; adj- $p=0.01$). *IRX3* SNP was found to be associated with BWE (OR= 1.06, adj- $p=0.03$) (Table 4). Also, one *FTO-IRX3* haplotype was found to be associated with BWE (G-A-A-T, rs17817449-rs8050136-rs9939609-rs3751723; OR= 0.67, $p=0.04$).

The additive model showed a significant association between excess weight and the SNP rs3751723 in *IRX3* gen (OR= 1.06, $p=0.024$), taking “G” as the risk allele. The statistical significance of these relations continued after admixture adjustment for a three-hybrid population ($p=0.03$) (Table 4). However, an additional analysis was performed, and statistical significance was not found (Table 5).

Discussion

In the current study, *FTO* and *IRX3* variations were assessed to find a genetic association with obesity and related disorders. Also, linkage disequilibrium between both genes was analyzed. According to our results, genetic variants in *FTO* were found to be unrelated to obesity or body weight, metabolic disorders (*i.e.*, HBP, Hyperglycemia, dyslipidemias, type 2 Diabetes Mellitus,) and metabolic syndrome. On the other hand, *IRX3* was found to be associated with body weight excess even after the adjustment by genetic stratification. Furthermore, despite previous reports, both genes were found to be in linkage equilibrium in this Latin American admixed population²⁸.

FTO has been repeatedly associated with obesity in European and Asian populations. In Latin America, Saldaña-Alvarez *et al*³⁰, published a genetic association study with the Mexican population where five SNPs in *FTO* (rs1121980, rs17817449, rs3751812, rs9930506, and rs17817449) were found to be related with obesity class II/III, while the SNP rs9930506 was associated with all obesity grades (I-III)^{29,30}. Similarly, the SNP rs17817449 in the *FTO* region was associated with glycemic traits in adults from one Colombian Andean city³¹. On the other hand, other studies have agreed with the current work. For instance, Mexican adults and children found no significant association between *FTO* and BMI ($\beta=0.187$, $p=0.143$), and a similar finding was reported for WC ($\beta=0.409$, $p=0.208$)³². Such discrepancies between Latin American studies show

Table 2. Median values of anthropometric and biochemistry parameters according to the genotype for FTO and IRX3 SNPs.

	FTO												
	rs9939609						rs8050136						
	AA	AT	TT	p	AT+TT	p	AC+CC	p	AC+AA	p			
BMI (Kg/m ²)	25.3	22.2-28	25.4	22.7-28.5	25.9	22.9-28.9	0.2	25.7	22.8-28.7	0.376	25.3	22.3-28.2	0.786
Waist Cir. (cm)	88.0	80.5-99	91.0	84.0-99.0	93.0	85-100	0.070	92.0	85.0-99.0	0.079	92.0	83.0-99.0	0.053
Blood Pressure													
Systolic (mmHg)	110.0	100.0-120.0	110.0	100.0-120.0	110.0	100.0-120.0	0.704	110.0	100.0-120.0	0.403	110	100.0-120.0	0.749
Diastolic (mmHg)	72.0	68.0-80.0	72.0	68.0-80.0	76.0	20.0-80.0	0.390	74.0	70.0-80.0	0.736	74.0	68.0-80.0	0.258
Serum concentrations													
Glucose (mg/dL)	89.10	75.7-99.7	89.0	78.6-103.6	89.5	79.6-105.3	0.793	89.5	79.0-104.8	0.510	89.0	78.2-103.0	0.697
Triglycerides	148.7	109.0-175.9	152.7	114.5-192.0	151.9	114.0-189.2	0.324	152.2	114.2-191.5	0.133	151.9	113.6-186.6	0.581
HDLc	46.3	37.5-51.6	46.8	40.6-53.7	45.1	38.9-51.0	0.051	45.9	39.5-51.9	0.639	46.5	39.8-53.5	0.037*
Totalc	175.9	159.0-197.9	184.0	162.5-205.5	183.9	160.1-207.4	0.453	184.0	160.9-206.4	0.212	182.8	161.1-204.0	0.786
	AA	AC	CC	p	AC+CC	p	AC+AA	p					
BMI (Kg/m ²)	25.3	22.2-28	25.4	22.7-28.2	25.9	22.9-28.9	0.301	25.6	22.2-28.7	0.512	25.4	22.4-28.2	0.123
Waist Cir. (cm)	90.0	81.5-99.0	91.00	83.0-99.0	92.0	85.0-100.0	0.310	92.0	84.0-99.0	0.321	91.0	83.0-99.0	0.151
Blood Pressure													
Systolic (mmHg)	110.0	100.0-120.0	110.0	100.5-120.0	110.0	100.0-120.0	0.846	110.0	100.0-120.0	0.989	110.0	100.0-120.0	0.591
Diastolic (mmHg)	78.0	70.0-81.0	72.0	68.0-80.0	76.0	70.0-80.0	0.324	74.0	70.0-80.0	0.319	74.0	68.0-80.0	
Serum concentrations													
Glucose (mg/dL)	91.0	76.1-103.4	88.7	78.3-103.2	89.6	79.8-105.2	0.875	89.1	79.0-104.4	0.971	88.9	78.0-103.2	0.620
Triglycerides	148.5	107.0-175.4	151.8	114.5-190.3	153.4	114.1-189.3	0.283	152.2	114.3-189.4	0.117	151.2	113.1-186.4	0.427
HDLc	46.5	37.7-52.6	46.5	40.3-53.7	45.1	38.9-50.7	0.122	45.7	39.5-51.7	0.911	46.5	39.7-53.5	0.049*
Totalc	175.4	159.0-198.3	184.0	161.0-205.4	185.0	160.9-206.2	0.508	184.1	160.9-206.2	0.247	182.1	160.0-203.8	0.605
	GG	GT	TT	p	GT+TT	p	GT+GG	p					
BMI (Kg/m ²)	25.3	22.2-28.0	25.3	22.4-28.2	25.9	22.9-28.9	0.232	25.6	22.8-28.7	0.470	25.3	22.3-28.2	0.088
Waist Cir. (cm)	89.5	81.2-98.7	91.0	83.0-99.0	92.0	85.0-100.0	0.196	92.0	84.0-99.0	0.304	91.0	83.0-99.0	0.081
Blood Pressure													
Systolic (mmHg)	100.0	100.0-120.0	110.0	100.0-120.0	110.0	100.0-120.0	0.841	110.0	100.0-120.0	0.613	110.0	100.0-120.0	0.913
Diastolic (mmHg)	76.0	68.5-80.0	74.0	68.0-80.0	76.0	70.0-80.0	0.499	74.0	70.0-90.0	0.823	74.0	68.0-80.0	0.311
Serum concentrations													
Glucose (mg/dL)	90.6	75.2-103.7	88.7	78.6-102.9	89.5	79.6-105.3	0.924	89.2	79.0-104.3	0.817	89.0	78.2-103.0	0.704
Triglycerides	145.2	100.5-177.4	150.7	114.4-187.5	154.0	114.3-192.6	0.135	152.2	114.4-189.2	0.071	149.0	112.3-185.4	0.152
HDLc	46.7	37.5-53.9	46.5	40.6-53.4	45.1	38.8-50.8	0.100	45.7	39.5-51.5	0.792	46.5	39.9-53.5	0.036*
Totalc	175.2	156.0-197.6	184.2	162.3-206.8	184.5	160.8-206.0	0.336	184.3	161.3-206.2	0.141	182.4	160.0-204.4	0.709
	TT	GT	GG	p	GT+GG	p	GT+TT	p					
BMI (Kg/m ²)	25.0	21.8-27.8	25.4	22.7-28.5	25.9	22.8-28.9	0.182	25.6	22.8-28.8	0.132	25.3	22.7-28.4	0.137
Waist Cir. (cm)	92.0	83.0-100.0	92.0	84.0-98.7	92.0	85.0-99.0	0.753	92.0	83.0-99.0	0.487	92.0	83.8-99.0	0.621
Blood Pressure													
Systolic (mmHg)	110.0	100.0-120.0	110.0	102.0-120.0	110.0	100.0-120.0	0.447	110.0	100.0-120.0	0.675	110.0	102.0-120.0	0.204
Diastolic (mmHg)	76.0	70.0-80.0	76.0	70.0-80.0	74.0	70.0-80.0	0.390	74.0	70.0-80.0	0.266	76.0	70.0-80.0	0.265
Serum concentrations													
Glucose (mg/dL)	90.0	81.0-109.2	90.0	77.0-105.1	88.8	78.9-103.4	0.735	89.4	78.0-104.2	0.435	90.0	78.0-105.5	0.751
Triglycerides	151.9	119.0-196.9	148.4	108.9-187.7	153.9	116.2-186.8	0.590	152.0	113.6-187.3	0.729	148.6	110.0-188.3	0.418
HDLc	45.9	39.4-51.0	46.1	38.9-52.8	45.7	39.7-51.4	0.966	46.0	39.2-52.2	0.874	46.1	38.9-52.3	0.882
Totalc	177.0	153.9-199.1	185.9	161.7-210.7	182.1	160.1-203.8	0.190	183.7	160.9-205.7	0.296	185.5	160.4-208.4	0.275

Data are median (1st quartile - 3rd quartile).

the complexity of genetic association analyses in admixed populations. Some of the non-significant results might be thought to be caused by the strictness in applying statistical procedures³³.

It is important to note that most Latin American communities are experiencing an intense nutrition transition. Under this phenomenon, a large proportion of inter-personal variability of BMI would be influenced by social and economic factors, such as urbanization and income, among others. It is plausible that the influence of socio-economic variables could have attenuated the impact of FTO genetic variations on the susceptibility to obesity. Similar interactions have been seen in other studies where the effect size and statistical significance are modified by environmental factors (e.g., dietary behaviors)^{34,35}.

The prevalence of body weight excess was associated with IRX3. A 10% increase in overweight or obesity frequency was found when rs3751723 genotype changed from GG to TT. This result coincides with recent studies from multiple populations in which the IRX3 genomic region has been related to anthropometric traits and obesity^{14,28,36}. Considering that this gene has been identified as a plausible effector for the influence of FTO on bodyweight¹⁰⁻¹³, the current genetic associations might be evidence supporting the biological role of IRX3 on weight control as it has been suggested in animal models^{12,13}. According to this, further studies focused on the cellular and physiologic mechanisms behind the role of this gene on the development of obesity are warrant.

Tabla 3. Allelic frequencies and genotype distributions for FTO and IRX3 genes

Gene	FTO																	
	rs9939609						rs8050136						rs17817449					
	AA	AT	TT	<i>p</i> AA vs AT+TT		TT vs A T+AA	AA	AC	CC	<i>p</i> AA vs AC+CC		CC vs AC+AA	GG	GT	TT	<i>p</i> GG vs GT+TT		TT vs GT+GG
Anthropometric and biochemical parameters																		
BMI																		
Normal weight	40 (44.9)	148 (46.4)	154 (40.1)				36 (43.4)	145 (46.0)	161 (40.9)				35 (44.9)	144 (46.5)	163 (40.4)			
Overweight	32 (36.0)	123 (38.6)	160 (41.7)				30 (36.1)	124 (39.4)	161 (40.9)				28 (35.9)	119 (38.4)	168 (41.6)			
Obese	17 (19.1)	48 (15.0)	70 (18.2)	0.441	0.708	0.232	17 (20.5)	46 (14.6)	72 (18.2)	0.514	0.621	0.385	15 (19.2)	47 (15.1)	73 (18.0)	0.484	0.731	0.256
Excess of weight	49 (55.1)	171 (43.6)	230 (59.9)				47 (56.6)	170 (54.0)	233 (59.1)				43 (45.1)	166 (43.5)	241 (59.6)			
WC																		
Abdominal Obesity	59 (66.3)	215 (67.4)	282 (73.4)				57 (68.7)	211 (67.0)	288 (73.1)				54 (69.2)	206 (66.4)	296 (73.3)			
Not altered	30 (33.7)	104 (32.6)	102 (26.6)	0.151	0.463	0.063	26 (31.3)	104 (33.0)	106 (26.9)	0.199	0.845	0.090	24 (30.8)	104 (33.6)	108 (26.7)	0.1399	0.946	0.064
BP																		
HBP	14 (15.7)	46 (14.4)	49 (12.7)				14 (16.9)	47 (14.9)	48 (12.2)				12 (15.4)	44 (14.2)	53 (13.1)			
Not altered	75 (84.3)	273 (85.6)	335 (87.3)	0.693	0.682	0.489	69 (83.1)	268 (85.1)	346 (87.8)	0.395	0.584	0.237	66 (84.6)	266 (85.8)	351 (86.9)	0.8342	0.791	0.664
Serum glucosa																		
Hyperglycemia	24 (27.0)	111 (34.8)	119 (30.0)				26 (31.3)	107 (34.0)	121 (30.7)				24 (30.8)	105 (33.9)	125 (30.9)			
Not altered	65 (73.0)	208 (65.2)	265 (70.0)	0.307	0.329	0.578	57 (68.7)	208 (66.0)	273 (69.3)	0.645	0.976	0.459	54 (69.2)	205 (66.1)	279 (69.1)	0.6843	0.895	0.535
Serum TG																		
HyperTG	44 (49.4)	164 (51.4)	195 (50.8)				40 (48.2)	159 (50.5)	204 (51.8)				37 (47.4)	154 (49.7)	212 (52.5)			
Not altered	45 (50.6)	155 (48.6)	189 (49.2)	0.945	0.859	1	43 (51.8)	156 (49.5)	190 (48.2)	0.824	0.687	0.667	41 (52.6)	157 (50.3)	192 (47.5)	0.6185	0.601	0.399
Serum HDLc																		
Low HDLc	43 (48.3)	130 (40.8)	172 (44.8)				40 (48.2)	127 (40.3)	178 (45.2)				38 (48.7)	185 (40.3)	182 (45.0)			
Not altered	46 (51.7)	189 (59.2)	212 (55.2)	0.353	0.397	0.544	43 (51.8)	188 (59.7)	216 (54.8)	0.288	0.433	0.400	40 (51.3)	125 (56.7)	222 (55.0)	0.2822	0.396	0.429
TC																		
Hight TC	59 (33.7)	188 (41.1)	238 (38.0)				29 (34.9)	129 (40.9)	149 (37.8)				25 (32.1)	130 (41.9)	152 (37.6)			
Not altered	30 (66.3)	131 (58.9)	146 (62.0)	0.414	0.355	0.731	54 (65.1)	186 (59.1)	245 (62.2)	0.523	0.524	0.638	53 (67.9)	180 (58.1)	252 (62.4)	0.2214	0.246	0.549
MetS																		
Yes	27 (30.3)	100 (31.3)	126 (32.8)				27 (32.5)	96 (30.5)	130 (33.0)				25 (32.0)	93 (30.0)	135 (33.4)			
No	62 (69.7)	219 (68.7)	258 (67.2)	0.864	0.822	0.665	56 (67.5)	219 (69.5)	264 (67.0)	0.769	1	0.579	53 (68.0)	217 (70.0)	269 (66.6)	0.624	1	0.406
Diabetes																		
Yes	13 (14.6)	59 (18.5)	64 (16.7)				14 (16.9)	56 (17.8)	66 (16.8)				13 (16.7)	55 (17.7)	68 (16.8)			
No	76 (85.4)	260 (81.5)	320 (83.3)	0.646	0.594	0.786	69 (83.1)	259 (82.2)	328 (83.2)	0.934	1	0.827	65 (83.3)	255 (82.3)	336 (83.2)	0.942	1	0.869

Data are numbers (%). **p* <0.05, Abbreviations: Abd. obesity - abdominal obesity, BMI - body mass index, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome, TG - triglycerides, WC - waist circumference.

Table 4. Association of FTO and IRX3 genes variants with metabolic disorders

Metabolic traits	FTO										IRX3									
	rs9939609					rs8050136					rs17817449					rs3751723				
	Beta coef.	OR	95% CI	p*	Adjusted p	Beta coef.	OR	95% CI	p*	Adjusted p	Beta coef.	OR	95% CI	p*	Adjusted p	Beta coef.	OR	95% CI	p*	Adjusted p
Weight excess	-0.036	0.96	0.91-1.01	0.156	0.225	-0.026	0.97	0.92-1.02	0.319	0.363	-0.036	0.96	0.91-1.01	0.167	0.194	0.057	1.06	1.00-1.12	0.039*	0.024
Abd. Obesity	-0.043	0.95	0.91-1.00	0.068	0.346	-0.035	0.96	0.92-1.01	0.141	0.152	-0.037	0.96	0.91-1.01	0.123	0.131	-0.007	0.99	0.94-1.04	0.764	0.057
HBP	0.015	1.01	0.98-1.05	0.394	0.124	0.024	1.02	0.98-1.06	0.175	0.076	0.011	1.01	0.97-1.04	0.547	0.323	-0.002	0.99	0.95-1.03	0.898	0.948
Hyperglycemia	-0.001	0.99	0.95-1.04	0.965	0.618	0.013	1.01	0.96-1.06	0.590	0.396	0.010	1.01	0.96-1.06	0.683	0.476	-0.011	0.98	0.93-1.04	0.657	0.722
Hyper TG	-0.002	0.99	0.94-1.05	0.925	0.879	-0.016	0.98	0.93-1.03	0.542	0.501	-0.026	0.97	0.92-1.02	0.328	0.304	0.043	1.04	0.98-1.10	0.124	0.254
Low HDLc	-0.001	0.99	0.94-1.05	0.958	0.709	-0.007	0.99	0.94-1.04	0.787	0.650	-0.005	0.99	0.94-1.04	0.829	0.664	-0.007	0.99	0.93-1.04	0.785	0.348
High Col	-0.004	0.99	0.94-1.04	0.859	0.798	0.001	1.00	0.95-1.05	0.952	0.824	-0.001	0.99	0.94-1.05	0.944	0.950	-0.007	0.99	0.94-1.04	0.790	0.940
MetS	-0.013	0.98	0.94-1.03	0.592	0.758	-0.010	0.98	0.94-1.03	0.678	0.760	-0.016	0.98	0.93-1.03	0.500	0.552	-0.003	0.99	0.94-1.04	0.889	0.499
Diabetes	-0.0009	0.99	0.96-1.03	0.961	0.663	0.003	1.00	0.96-1.04	0.843	0.646	0.002	1.00	0.96-1.04	0.889	0.705	-0.004	0.99	0.95-1.03	0.839	0.976

*p < 0.017 were considered as statistically significant (Bonferroni correction). † Admixture adjustment with Monte-Carlo-Markov Chain (k = 3). An additive model was assessed through a logistic regression where risk alleles were interpreted as the unit. Genetic variations in rs9939609 (AA = 2, AT = 1, and TT = 0), rs8050136 (AA = 2, AC = 1, and CC = 0), rs17817449 (GG = 2, GT = 1, and TT = 2) and rs3751723 (TT = 0, GT = 1, and GG = 2), were included as independent variables. Age, sex, and body mass index were included as confounding variables (except for the analysis of body weight excess in which only age and sex were used). An admixture adjustment was performed through a Monte-Carlo-Markov Chain where a three-hybrid genetic stratification was assumed. Abbreviations: Abd. obesity - abdominal obesity, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome.

In addition to the suspected central regulation of appetite, some authors have described an association of *IRX3* expression in adipocyte tissue with energy dissipation (through mitochondrial thermogenesis), and fat storage¹². This finding suggests that risk alleles in *IRX3* might be involved in obesity pathogenesis through several mechanisms and that rs3751723 could be linked to gene expression and adipocyte metabolism. If subjects with this genetic variation show a different expression profile and adipose tissue physiology might be an interesting focus in further researches.

Srivastrava et al.²⁸, reported linkage disequilibrium between both genes in a population from North India. Although a similar phenomenon is thought to be occurring in other groups, the findings from the current study showed no evidence of non-random segregation between the *FTO* and *IRX3* SNPs in this sample of Latin American adults. In this regard, the genetic sub-structure and recent admixture process remain concerning issues that could be interfering with the measurement of inter-gene regulations.

In conclusion, a genetic association between *IRX3* and body weight was found in Latin American adults. Furthermore, this relation persisted as statistically significant after an adjustment for sex, age, and genetic ancestry was performed. According to these results, it is plausible that *IRX3* gene expression might be involved in obesity prevalence in this population; hence, further studies aimed to describe the role of this gene and its product on energy metabolism seems to be promissory in the understanding of current body weight excess epidemic.

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