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ORIGINAL ARTICLE

Association between FTO gene rs9939609 and adiposity markers in Chilean children

Asociación entre el polimorfismo rs9939609 del gen *FTO* y marcadores de adiposidad en población infantil chilena

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What do we know about the subject matter of this study?

The rs9939609 variant of the FTO gene has been recognized worldwide for its association with obesity risk in different populations and ages according to the WHO classification, based on BMI or BMI percentile limits. Our group previously reported that the rs9939609 variant of the FTO gene was associated with a higher risk of increased BMI z-score in Chilean children.

What does this study contribute to what is already known?

Obesity is a pathological state characterized by excess body fat, specifically in the adipose tissue. This study shows the association between the presence of the polymorphism rs9939609 of the FTO gene and the increase of the general adiposity (% of fat mass) and central adiposity (waist circumference and waist/height ratio), in the pediatric population of Chile.

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Abstract

Obesity is considered a chronic inflammatory disease with an important genetic component. Although several studies have reported an association between the *FTO* (fat-mass associated gene) and adiposity in children, there is limited evidence in the Chilean population. **Objective:** To determine the association between the polymorphism rs9939609 of the *FTO* gene and markers of adiposity in Chilean children. **Patients and Method:** Cross-sectional study which included 361 children aged between 6 and 11 years (50% were girls). Between March and June 2008, clinical data and blood sample collection was carried out. The rs9939609 single-nucleotide polymorphism (SNP) of the *FTO* gene, was determined using the genomic DNA extracted from leukocytes, using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany).The adiposity markers included were body mass index (BMI), waist circumference (WC), body fat, and WC/H index; which were later compared adjusted by sex, age, and Tanner stage. Linear regression analyses were conducted to detect the association between the polymorphism and obesity markers. **Results:** After adjusting the models by age, sex, and Tanner stage, we found a significant association between the polymorphism and markers of adiposity. For each extra copy of the risk allele, we found an increase of 2.47 kg body weight (95% CI: 1.39-3.55); 1.06 kg/m^2 BMI (95% CI: 0.56-1.54); 2.55 cm WC, (95% CI: 1.26-3.85); and 1.98% body fat (95% CI: 0.78-3.19). When converting adiposity markers to z-score, we found that WC/height index shows the strongest association with the risk allele *FTO*. **Conclusion:** This study supports the association between the rs9939609 SNP of the *FTO* gene and overall and central adiposity markers in Chilean children.

Keywords:
Obesity;
FTO;
Genotype;
Children;
Body Mas Index

Introduction

Obesity is one of the preventable diseases, even though it is currently highly prevalent, affecting more than 600 million people in 2014[1] and is associated with the genesis and increased prevalence of chronic metabolic diseases[7]. For this reason, stopping the rise in obesity rates represents one of the nine global goals for preventing and controlling chronic non-communicable diseases that the World Health Organization (WHO) has set for 2025[8]. It has been estimated that the number of obese individuals will reach 1.12 billion by 2030[2,3].

In the child population, obesity is a serious and urgent public health problem. Its prevalence has increased significantly in children and adolescents, in both developed and developing countries[4]. In Chile, the increase in childhood obesity has been sustained since the late 1980s[33,34]. Currently, the prevalence of excess body weight presented in the pre-kindergarten, kindergarten, first, and ninth grade corresponds to 49.3%, 50.8%, 51.1%, and 44.5%, respectively[5,6]. This scenario confirms that childhood obesity represents a serious and urgent public health problem.

Among the main risk factors for the development of obesity are physical inactivity, sedentariness, the amount of energy intake, and the Western-type dietary pattern, all of which can be modified[9-11]. Potential non-modifiable risk factors include gender, age, ethnicity, as well as genetic polymorphisms.

Since 2007, after it was reported that the polymorphism rs9939609 of the *FTO* gene presents an association with body mass index (BMI)[14], the identification of single-nucleotide polymorphisms (SNP) genes associated with increased BMI has rapidly risen. By 2015, more than 97 genetic polymorphisms associated with increased BMI had been identified[12]. Recently, a meta-analysis summarized the existence of 738 SNPs associated with several obesity markers (waist circumference, body fat, visceral adipose tissue, etc.)[13].

Out of all the genetic variants studied, the variant rs9939609 of the *FTO* gene (fat mass and obesity-associated gene) is the one that has been mostly studied due to its recognized effect on increasing BMI and obesity risk, confirming its association in different adult and child populations worldwide[14-18].

Previously we reported that the variant rs9939609 of the *FTO* gene was associated with a higher risk of increased BMI in Chilean children, but its relationship with other adiposity markers was not evaluated[18]. The objective of this study was to investigate the association between the polymorphism rs9939609 of the *FTO* gene and markers of general and central adiposity in this Chilean child population.

Patients and Method

Cross-sectional study which included 361 children aged between 6 and 11 years from urban areas in the Biobío Region, Chile. Children suffering from any

chronic pathology were excluded. This study was approved by the Bioethics Committee of the University of Concepción. The parents or guardians of the children signed informed consent before the inclusion of their child in the study.

Anthropometric variables: obesity markers

Height was measured without shoes, using a wall-mounted stadiometer with an accuracy of 0.1 cm (Seca, model 208). The body weight was measured with light clothing and without shoes on a Tanita scale (model TBF-300) with an accuracy of 1 g. BMI was through body weight divided by height squared (kg/h^2). BMI z-score, based on age and sex, was calculated according to WHO definitions. Children were classified as normal (BMI ≥ 5 and < 85 percentile) or obese (BMI > 95 percentile) according to the international age and gender percentiles defined by the Center for Disease Control and Prevention (CDC)[19]. The waist circumference (WC) was measured between the lowest rib and the upper edge of the iliac crest, with a non-distensible tape measure (Seca, model 201) with an accuracy of 0.1 cm. Body composition was evaluated using a bioelectrical impedance analyzer (Tanita, TBF-300). All measurements were taken by trained nutritionists. To define the pubertal stage according to Tanner's criteria[20], children were examined by medical professionals.

Determination of allelic variation of the FTO gene

Between March and June 2008, the clinical data and blood samples were collected. The SNP polymorphism (rs9939609) of the *FTO* gene, was determined using genomic DNA extracted from leukocytes, using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's protocol. Polymerase chain reaction (PCR) amplifications were performed in using the Rotor-Gene 6500 real-time PCR cycler (Corbett Research, Sydney, Australia), using splitters previously described by Lopez-Bermejo et al.[21] (direct: 5'd AACTG GCTCTTGAATGAAATAGGATTCAGA 3' and inverse: 5' dAGAGTAACAGAGATCCAAGTG-CATCAC3 '), according to a previously standardized protocol[18].

Genotype identification was performed by comparison (confidence intervals, 95% CI) of fusion data with standard genotypes identified by sequencing analysis at the Department of Ecology, Faculty of Biological Sciences, Pontifical Catholic University of Chile. To confirm the existence of a single-stranded PCR product, we performed a 3% agarose gel electrophoresis. All sample analyses were performed in duplicates, with a 98% success rate in genotype determination.

Statistical analysis

The characteristics of the population studied are presented as mean and standard deviation (SD) for continuous variables, and as percentages for the categorical ones. Differences between genotypes were determined with regression analysis for continuous variables and with the Chi-square test for the categorical ones.

To identify the association between the *FTO* gene and obesity markers, we performed a linear regression analysis of BMI, waist circumference (WC), waist/height ratio, and % body fat. The SNP genotype rs9939609 of the *FTO* gene was encoded according to an additive genetic model (0 = TT - homozygous for the protective allele; 1 = AT - heterozygous for the risk allele; 2 = AA - homozygous for the risk allele), and subsequently, through linear regression analysis, we estimated the increase in the adiposity variable for each additional copy of the risk variant (allele A). These results are shown as average or beta coefficient with their respective 95% confidence intervals (95% CI).

To determine which adipose markers had the highest association with the *FTO* gene, all variables were standardized to z-score and, therefore, the results were presented as a standardized beta coefficient and their respective 95% CI, for each additional copy of the *FTO* gene risk allele.

All analyses were adjusted for confounding variables using three statistical models, Model 0 - unadjusted; Model 1 - adjusted for age and sex; Model 2 - adjusted by Model 1, but also by Tanner's stage. The Hardy-Weinberg principle of the *FTO* gene alleles was estimated through the Chi-square test in the STATA SE v14 software which was also used for all analyses. The significance level was defined as $p < 0.05$.

Results

The studied population comprises 361 Chilean children, in which anthropometric parameters were measured, and the SNP rs9939609 was genotyped in the *FTO* gene, finding that the respective allele frequency is distributed following the Hardy-Weinberg equilibrium (allele T = 0.649 and allele A = 0.351, $\chi^2 = 0.053$).

Table 1 describes the general characteristics of the population, which has 178 boys and 183 girls, aged between 6 and 11 years (average age: 8.51 ± 1.44). According to Tanner's stages, 79.8% of the children were in the pre-pubertal development stage. The average nutritional status showed a percentile 87.0 ± 16.6 with 66.8% of boys and 65.0% of girls obese. The risk variant in its heterozygous form (genotype TA) appears

Table 1. Population Characteristics

Socio-demographics	Number (%)
Total (n)	361 (100)
Girls, n (%)	183 (50.7)
Pre-pubertal, n (%)	288 (79.8)
Pubertal, n (%)	73 (20.2)
Normal, n (%)	123 (34.1)
Obese, n (%)	238 (65.9)
Variable	Media ± SD
Age (Years)	8.5 ± 1.4
Weight (kg)	37.0 ± 11.1
Height (cm)	131.5 ± 10.1
Waist Circumference (cm)	72.3 ± 11.4
BMI (kg/m2)	21.5 ± 4.0
BMI z score	1.5 ± 0.8
Percentile BMI	87.0 ± 16.6
Percentage fat	29.2 ± 9.0
Fat mass (kg)	12.1 ± 6.4
Lean mass (kg)	26.9 ± 5.4
Waist circumference / Height ratio	0.54 ± 0.06
Genotype FTO (rs9939609)	Number (%)
TT	184 (50.9)
TA	101 (27.9)
AA	76 (21.1)

Data is presented as media ± standar desviation for continuous variables and as percentage for discontinuos variables.

in 27.9% of the population and its homozygous form (genotype AA) in 21.1%.

Table 2 and Figure 1 show the results of the association between SNP rs9939609 of the *FTO* gene and the obesity variables. These results reveal that, in the model not adjusted for confounding variables, all obesity markers increased significantly for each extra copy of the risk allele (A) of the *FTO* gene. This increase was equivalent to 2.19 kg (95% CI 0.76, 3.61) for body weight; 2.28 kg/m^2 (95% CI 0.47, 1.51) for BMI; 2.28 cm (95% CI 0.81-0.75) for WC; and 1.93%, (95% CI 0.69, 3.17) for % fat mass. When the models were adjusted for confounding variables, model 1, age and sex, and models 2, age, sex and Tanner's stage, the magnitude of the association between the *FTO* gene and adiposity markers did not change and, generally, increased the statistical significance (Table 2).

In order to compare the strength of association of the obesity markers with the risk genotypes of the *FTO* gene, these were translated into z-score, expressing the measurement unit as standard deviation (SD) for each of them. These results indicate that in the most adjusted statistical model (model 2), the adiposity markers show the following classification of association with risk genotypes in *FTO* gene (decreasing order): (i) waist/height ratio (0.24 SD), (ii) waist circumference (0.22 SD), (iii) % fat mass; and, finally, (iv) BMI (0.19 SD) (Table 2 and Figure 2).

Table 2. Association between genotipe FTO (rs9939609) and adiposity markers

Variables	Genotype FTO rs9939609 (Media [IC 95%])			Effect of additive genetic model	p value
	TT	TA	AA		
Weight (kg)					
Model 0	36.6 (35.0 - 38.2)	38.0 (35.8 - 40.13)	41.2 (38.8 - 43.7)	2.19 (0.76 - 3.61)	0.003
Model 1	36.2 (35.0 - 37.4)	38.7 (37.1 - 40.3)	41.2 (39.4 - 43.1)	2.50 (1.41 - 3.57)	< 0.0001
Model 2	36.2 (35.0 - 37.4)	38.7 (37.1 - 40.3)	41.2 (39.3 - 43.1)	2.47 (1.39 - 3.55)	< 0.0001
IMC (kg/m2)					
Model 0	20.9 (20.3 - 21.4)	21.8 (20.0 - 22.5)	22.9 (21.0 - 23.9)	0.99 (0.47 - 1.51)	< 0.0001
Model 1	20.8 (20.3 - 21.3)	21.9 (21.2 - 22.6)	22.9 (22.1 - 23.7)	1.06 (0.57 - 1.54)	< 0.0001
Model 2	20.8 (21.2 - 21.3)	21.9(21.2 - 22.6)	22.9 (22.0 - 23.7)	1.06 (0.56 - 1.54)	< 0.0001
Waist circumference (cm)					
Model 0	70.8 (69.2 - 72.4)	72.6 (70.4 - 74.8)	75.5 (73.0 - 78.1)	2.28 (0.81 - 3.75)	< 0.0001
Model 1	70.5 (69.0 - 71.9)	73.2 (71.2 - 75.1)	75.6 (73.3 - 77.8)	2.56 (1.27 - 3.85)	< 0.0001
Model 2	70.5 (69.0 - 71.9)	73.2 (71.2 - 75.1)	75.6 (73.3 - 77.8)	2.55 (1.26 - 3.85)	< 0.0001
% Fat mass					
Model 0	28.1 (26.7 - 29.4)	29.2 (27.4 - 31.0)	32.2 (30.0 - 34.4)	1.93 (0.69 - 3.17)	0.002
Model 1	27.9 (26.6 - 29.2)	29.6 (27.8 - 31.3)	32.0 (29.9 - 34.1)	1.99 (0.78 - 3.19)	0.001
Model 2	27.9 (26.6 - 29.3)	29.6 (27.8 - 31.4)	32.0 (29.9 - 34.1)	1.98 (0.78 - 3.19)	0.001

Data is presented as media and its respective confidence interval, IC 95%, by each genotype. The additive genetic model indicates the increment media of adiposity variable for each additional copy of risk allele (A). The additive effect and its respective 95% IC was determinate by lineal regression. The analysis were adjusted by de following: Model 0 – non adjusted; Model 1 – adjusted by age, sex; Model 2 – adjusted by Model 1, but also by Tanner`s stage.

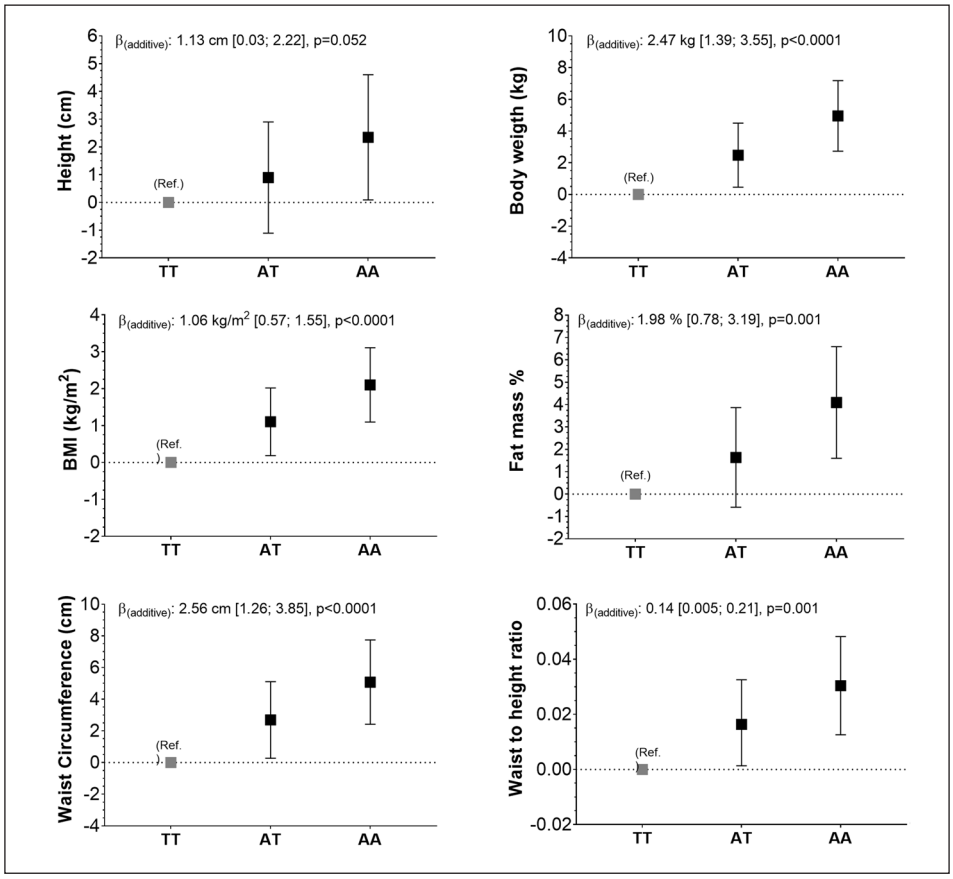

Figure 1. Association between genotype *FTO* (rs9939609) and adiposity markers. The results are presents as media and its respective 95% CI. The beta additive coefficient represents the increment of the variable for each additional copy of risk allele of FTO. The analysis was adjusted by age, sex and Tanner`s stage.

Discussion

In this study, the main result is that for each extra copy of the risk allele rs9939609 of the *FTO* gene, there was a greater probability of increasing the magnitude of the adiposity indicators studied (% body fat, WC, waist/height ratio, and BMI z-score).

These results indicate that the polymorphism rs9939609 of the *FTO* gene contributes to a higher level of obesity in Chilean children.

Previously, our research group had shown that rs9939609 of the *FTO* gene is associated with an increased risk of obesity, expressed as an Odds ratio[18], in this same cohort, comprised of boys and girls from 6 to 11 years of age, who come from an urban area and of social vulnerability state in the Biobío Region, Chile. However, this publication did not study other obesity indicators, nor did it include a statistical analysis to mitigate the influence of non-modifiable confounding factors (age, sex, Tanner's stage).

Several studies have shown that *FTO* is a gene of underlying susceptibility for polygenic obesity and that the influence of the *FTO* gene on BMI changes over life in European populations[22-24].

In this study, the association between rs9939609 polymorphism and obesity markers did not change, despite possible confounding factors (age, sex, or Tanner stages). The onset age of the association has been reported to be as early as 7 years or even earlier[25], which is consistent with our findings in this 6-11-year-

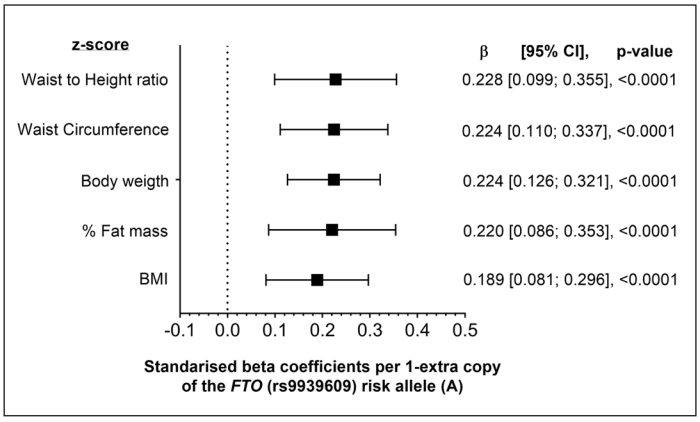

Figure 2. Association between genotype *FTO* (rs9939609) and adiposity markers standardized as z-score. Data are presented as coefficient beta standardized and its respective confidence intervals, 95% CI. This coefficient represent the increment of variables (adiposity variables) expressed as standard deviation by each additional copy of the risk allele of the *FTO*. The analysis were adjusted by age, sex and Tanner`s stage.

old population. The children in this study were mostly in a pre-pubertal stage (79.8%), while previous studies show variation in wider age ranges, throughout the first and also the second decade of life[23].

Besides that, the associations of *FTO* polymorphism with BMI and obesity were stronger in girls than in boys as has been previously reported[24,25], which was not observed in this study. These apparently contradictory results may be due to the low statistical power resulting from the small sample size, along with the relative predominance of a single Tanner stage (pre-pubertal). It is worth to mention that differences in the degree of exposure to obesogenic environments between populations in the different studies cannot be excluded either. In this context, it is essential to carry out new studies with a larger sample size, which allows a better exploration of the possible interactions between age, sex, and pubertal development.

In the Chilean adult population, the association between this *FTO* gene polymorphism and obesity variables has also been identified[26], but unlike in our work, there was no association with WC. This could indicate that the distribution of adiposity changes with age in subjects carrying the rs9939609 *FTO* gene polymorphism.

This fact is in line with a recent study, where researchers found that the association of BMI with different loci of genetic predisposition to obesity, changes throughout the development of the children in the Santiago Longitudinal Study (ELSOC). Specifically, it was observed that the highest association between core BMI-z and most loci occurs at age 10, except for *FTO*, which can reach its maximum effect up to age 16[27].

It is important to mention that several authors have shown that children who are carriers of the *FTO* risk variable, present low appetite regulation, and higher food intake[28-31]. In addition, a meta-analysis showed that dietary protein intake can modify the influence of *FTO* variants on BMI[32]. These findings provide new insight into the interrelationships between *FTO* gene variations, food intake, and obesity and may be useful in improving the design of intervention programs for children in the management of eating behaviors and excessive weight gain.

However, some limitations should be considered. Although the sample size provides sufficient statistical power to detect the overall association of the rs9939609 *FTO* gene polymorphism with obesity indicators, the sample size was not enough to perform stratified analysis by age, sex, or pubertal stage between the *FTO* gene genotype and adiposity indicators. Also, only the presence of the rs9939609 polymorphism in the first intron of the *FTO* gene was analyzed, and currently, it is known that the *FTO* gene is highly polymorphic as a whole, especially in introns 1 and 8[28].

Our analyses did not allow us to rule out the presence of other SNPs of the *FTO* gene in the analyzed population, and no background information on the children's lifestyles (eating habits, physical exercise, and others) was recorded, which could influence the association result that we report between the *FTO* gene and the obesity markers.

In conclusion, this study indicates the association of the *FTO* gene and its polymorphism rs9939609 with markers of general and central adiposity in the Chilean child population and provides evidence that this association is independent of some non-modifiable confounding factors (age, sex, Tanner stage). It would be interesting to carry out future studies to evaluate modifiable risk factors, such as eating behavior, physical exercise, and other lifestyle indicators of Chilean children carriers of this *FTO* gene polymorphism, and to determine how these behaviors or lifestyles affect the obesity markers in subjects carrying this genetic variant.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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