Polymorphisms $\text{FTO} \text{rs9939609}$, $\text{PPARG} \text{rs1801282}$ and $\text{ADIPOQ} \text{rs4632532}$ and rs182052 but not lifestyle are associated with obesity related-traits in Mexican children

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Abstract

Concerning the genetic factors of obesity, no consistent association between populations has been reported, which may be due to the frequency of polymorphisms, the lifestyle of studied populations and its interaction with other factors. We studied a possible association of polymorphisms $\text{FTO} \text{rs9939609}$, $\text{PPARG} \text{rs1801282}$, and $\text{ADIPOQ} \text{rs4632532}$ and rs182052 with obesity phenotypes in 215 Mexican children. Glucose, triglycerides, cholesterol, HDL and LDL were measured. In addition, weight, height, waist circumference and triceps skin thickness were recorded. High-energy diets and sedentary behavior were evaluated with a validated questionnaire. In contrast with other reports, only $\text{FTO} \text{rs9939609}$ was associated with obesity related-traits, including BMI ($p = 0.03$), waist circumference ($p = 0.02$), triceps skinfold ($p = 0.03$) and waist/height ratio ($p = 0.01$), and also with cholesterol levels ($p = 0.02$) and LDL ($p = 0.009$). Lower levels of triglycerides ($p=0.04$) were related with presence of $\text{PPARG} \text{rs1801282}$, while $\text{ADIPOQ} \text{rs4632532}$ showed an effect on HDL ($p = 0.03$) levels. On the other hand, diet, physical activity and screen time were not related with obesity. In summary, only $\text{FTO} \text{rs9939609}$ was associated with obesity related-traits, while $\text{PPARG} \text{rs1801282}$ and $\text{ADIPOQ} \text{rs4632532}$ were involved in lipid metabolism.

Keywords: Obesity, children; polymorphisms, energy intake, physical activity, lipid profile.

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Introduction

Obesity is a worldwide public health problem due to its association with chronic diseases, such as type 2 diabetes, hypertension, cardiovascular disorders and certain types of cancer. Obesity results from an interaction of social, psychological, genetic and environmental factors, like diet and physical exercise. The last National Health and Nutrition Survey found that the national prevalence of childhood overweight did not increase. However, in the Mexican state of Durango the childhood obesity raised from 22.9% in 2006 (Shamah-Levy and Villalpando-Hernández, 2007) to 37.5% in 2012 (Rivero-Vázquez, 2013), which might be the result of different genetic backgrounds of Mexico’s Northern populations (Silva-Zolezzi et al., 2009). Many studies have demonstrated that genetic factors have an important role in the development of obesity, although results are different depending on the population being evaluated.

One of the most studied genes, the $\text{PPARG}$ is a member of the nuclear hormone receptors super-family, which regulates transcription of genes involved in several biological functions, such as cell growth, adipocyte differentiation, metabolism of cholesterol and fatty acids, cell survival, ubiquitination and adaptive thermogenesis. $\text{PPARG}$ is activated by lipophilic hormones, fatty acids from the diet, and their metabolites (He, 2009). The Ala allele of the polymorphism Pro12Ala of $\text{PPARG}$ was associated with obesity in a population from Spain (OR = 2.36, $p = 0.03$) and from India (OR = 3.2, $p = 0.02$) (González-Sánchez et al., 2002; Bhatt et al., 2012), while the Pro allele was a risk factor for type 2 diabetes in a French population (OR = 1.37, $p = 0.04$) (Ghoussaini et al., 2005).
**Materials and Methods**

**Subjects**

Two hundred and fifteen Mexican mestizo children (108 males and 107 females, ranging from 6.1 to 12.3 years old), whose parents and grandparents were born in Mexico, were selected to participate in the study. Sampling was performed on ten public elementary schools from the bordering cities of Gómez Palacio and Lerdo, in the state of Durango, Mexico, between January and June 2012. The protocol was approved by the Ethics Committee of the Facultad de Medicina of the Universidad Autónoma de Coahuila, Mexico, and all parents signed an informed consent.

The BMI is an attempt to quantify the amount of tissue mass (muscle, fat, and bone) in an individual. It is defined as the body mass divided by the square of the body height, and is universally expressed in units of kg/m². The waist/height ratio is a better predictor of a person’s metabolic risk (Browning et al., 2010) and is defined as waist circumference (cm) divided by height (cm). Triceps skin-fold thickness is measured in the right arm with Lange calipers. All children were assessed and measurements were recorded according to an established protocol (Shamah-Levy and Villalpando-Hernández, 2007). The “overweight/obese” group was established using the age- and sex-specific BMI cutoff specified by the International Obesity Task Force (IOTF) (Cole et al., 2000) and by the World Health Organization (De Onis et al., 2007). Blood samples were drawn after overnight fasting. Total cholesterol, HDL (both by CHOD-PAP, Randox Laboratories Ltd. Ardmore, Crumlin, UK) and Triglyceride (Pointe Scientific Inc. Detroit, Michigan, US) levels were evaluated by enzymatic colorimetric methods. LDL levels were calculated using Friedewald’s formula. Glucose levels were measured by Glucose Oxidase method (Randox Laboratories Ltd. Ardmore, Crumlin, UK). Plasma glucose levels were measured within 2 hours after the sample was obtained and plasma samples were stored at –20°C until analysis for the other biochemical parameters.

Dietary information was obtained by a semi-quantitative food frequency questionnaire (FFQ) applied to mothers or caregivers by trained personnel. The questionnaire included 101 food items classified in 14 groups and was used by the National Institute of Public Health in The National Survey of Health and Nutrition 2006 (ENSANUT2006) (Shamah-Levy and Villalpando-Hernández, 2007). The interviewers asked about portions that were consumed by the children (times per week, times per day, and size) for each food item during the seven-day period prior to the interview. Dietary energy intake and source were calculated using the free specialized SNUIT software (Rivera-Dommarco et al., 2001). The number of hours per week that children engaged in intense physical activity were also asked, and recorded as Metabolic Equivalent (MET)/hour (a unit of MET represents a multiple of the oxygen consumed when at rest) which corresponds to 3.5 mL O₂/kg⁻¹·min⁻¹. For example, if a person exercising expends 10 METs, he/she is using 10 times the amount of oxygen consumed when at rest) (Ridley et al., 2008; Morales-Ruán et al., 2009). Energy intake was assessed considering plausible intake levels according to the methodology used for ENSANUT2006 (Rodriguez-Ramirez et al., 2009). Children with reported energy intake above 5 standard deviations (outliers) or below 25% of the recommended caloric intake (extreme malnutrition) were excluded from the obeseogenic environment analysis because these values are not biologically plausible (n=164). Atypical food consumptions were manually reviewed and when a clear mistake was detected or if the value was not plausible, the participant was excluded.

**Genotyping assays**

Genomic DNA was isolated from peripheral white blood cells (3mL blood in EDTA) using the salting out method (Lahiri and Nurnberger, 1991). Genotyping assays
were performed with TaqMan probes in the ABI Prism 7900HT sequence Detection System (Applied Biosystems, Foster City, CA, USA) using the probes C_1129864_10 for PPARG rs1801282, C_30090620_10 for FTO rs9939609, C_2412785_10 for ADIPOQ rs4632532 and C_27807233_10 for ADIPOQ rs182052 according to manufacturer’s instructions (Applied Biosystems).

Statistical analysis

The quantitative variables were reported as medians and interquartile ranges. Allele and genotype frequencies were estimated by direct gene counting. The Hardy-Weinberg equilibrium was estimated using a Chi-square test. All the analyses were performed considering the cutoffs for obesity established by IOTF. Logistic regression models adjusted for age and gender were used to test associations of each genotype with overweight/obesity. We also analyzed the effect of polymorphisms on several anthropometric (waist circumference, arm circumference, triceps skinfold thickness, waist circumference/height ratio) and metabolic parameters (glucose, triglycerides, cholesterol, HDL, LDL) using linear regressions under an additive model adjusted by gender and age. All quantitative traits were logarithmically transformed before statistical analysis because some variables did not follow a normal distribution. Association analyses were performed using the STATA 11.1 software. Statistical significance was considered at p-values < 0.05 for all comparisons.

Results

The prevalence of overweight/obesity in the 215 evaluated children was 43.72% and 39.07% based in the IOTF and WHO cutoffs, respectively (Table 1); no significant difference was observed in the association analysis using the different cutoffs. The obesogenic environment analysis showed that children consumed more fat and less protein than recommended (Casanueva and Kaufer, 2008). Also, screen time was above the limit established by the American Association of Pediatrics (2h/day), and triceps skinfold thickness was higher than the normal for the median age (Casaneuva et al., 2008). No significant associations were observed between obesogenic environment and obesity or related traits (data not shown).

Regarding the genetic background, we found a very high percentage of children with familiar history of obesity-related diseases such as diabetes mellitus (63.96%) and hypertension (59.90%). Some children had levels of biochemical parameters above the reference values (Internat-

| Variables               | n (%)     |
|-------------------------|-----------|
| **Gender**              |           |
| Male                    | 108 (50.23) |
| Female                  | 107 (49.77) |
| **IOTF cutoff**         |           |
| Normal weight           | 121 (56.28) |
| Overweight/Obesity      | 94 (43.72)  |
| **WHO cutoff**          |           |
| Normal weight           | 131 (60.93) |
| Overweight/Obesity      | 84 (39.07)  |
| **Median (Min-Max)**    |           |
| Age (years)             | 10.4 (6.10–12.30) |
| **Anthropometric**      |           |
| Waist circumference (cm)| 64.25 (48.95–96.85) |
| Arm circumference (cm)  | 21.95 (13.50–35.50) |
| Triceps (mm)            | 15.00 (5.50–28.00)  |
| Waist/height ratio      | 0.46 (0.35–0.63)   |
| **Obesogenic Environment** |       |
| Energy intake (kJ/d)    | 8837.62 (4235.32–19608.62) |
| Carbohydrates (%)       | 47.14 (21.37–73.14) |
| Protein (%)             | 13.81 (8.48–20.67)  |
| Fat (%)                 | 43.05 (20.18–64.52) |
| Physical activity (h/week)| 5 (1–6)  |
| Screen hours (h/week)   | 17 (2–32)    |

*n=164 children included. IOTF: International Obesity Task Force; WHO: World Health Organization.
The minor allele frequencies were 0.22 for PPARG rs1801282, 0.35 for FTO rs9939609, 0.61 for ADIPOQ rs4632532 and 0.63 for ADIPOQ rs182052, which are within range from those reported in other populations (Table 3). Genotype frequencies in all genes were in accordance with the Hardy-Weinberg equilibrium.

In respect to the association of genotypes with obesity, under an additive model, the OR was 1.25 (CI = 0.73 – 2.15) for PPARG rs1801282, 1.27 (CI = 0.82 – 1.98) for FTO rs9939609, 1.47 (CI = 0.78 – 2.74) for ADIPOQ rs4632532 and 1.43 (CI = 0.76 – 2.74) for ADIPOQ rs182052. A risk tendency was observed, although these values were not significant (Table 3). The association, however, was assessed under the codominant, dominant and recessive models and the risk trend was preserved (data not shown). The analysis of genotypes with obesity-related characteristics found that FTO was associated with BMI ($\beta = 0.46, p = 0.03$), waist circumference ($\beta = 0.03, p = 0.02$), triceps skinfold ($\beta = 0.08, p = 0.03$) and waist/height ratio ($\beta = 0.03, p = 0.01$) (Table 4). Additionally, FTO had an effect on total cholesterol ($\beta = 0.06, p = 0.02$) and LDL ($\beta = 0.12, p = 0.01$) levels, although the increase was modest; in contrast ADIPOQ rs4632532 and PPARG rs1801282 were associated with a slight decrease in levels of HDL ($\beta = -0.06, p = 0.03$) and triglycerides ($\beta = -0.11, p = 0.04$), respectively (Table 5).

Table 3 - Comparison of association of FTO rs9939609, PPARG2 rs1801282, and ADIPOQ rs4632532 and rs182052 with obesity in different populations.

| Polymorphism | Allelic Frequency | Model | OR | IC 95% | Population | Reference |
|--------------|------------------|-------|-----|--------|-----------|----------|
| PPARG rs1801282 | G = 0.09 | Additive | 2.36 | 1.10–5.05 | Caucasian | González-Sánchez, et al., 2002 |
| | G = 0.06 | Dominant | 2.85 | 1.07–7.62 | Caucasian | Morini, et al., 2008 |
| | G = 0.05 | Dominant | 0.64 | 0.42–0.76 | Chinese | Wang, et al., 2013 |
| | G = 0.11 | Recessive | 3.2 | 1.2–12.9 | Indian | Bhatt, et al., 2012 |
| | G = 0.22 | Additive | 1.25 | 0.73–2.15 | Mexican - Mestizo | This study |
| FTO rs9939609 | A = 0.19 | Additive | 1.41 | 1.15–1.76 | Mexican - Mestizo | León-Mimila, et al., 2013 |
| | A = 0.20 | Additive | 2.42 | 1.71–3.44 | Mexican - Mestizo | Villalobos-Camparán, et al., 2008 |
| | A = 0.12 | Additive | 1.29 | 1.11–1.49 | Chinese | Xi, et al., 2010 |
| | A = 0.42 | Additive | 1.27 | 1.20–1.34 | Caucasian | Andreasen, et al., 2008 |
| | A = 0.59 | Recessive | 1.97 | 1.29–3.00 | Caucasian | Luczynski, et al., 2012 |
| | A = 0.35 | Additive | 1.27 | 0.82–1.98 | Mexican - Mestizo | This study |
| ADIPOQ | rs4632532 | T = 0.48 | Codominant | Increase in BMI | Mexican - American | Richardson, et al., 2005 |
| | | T = 0.45 | Codominant | Increase in BMI | Hispano - American | Sutton, et al., 2005 |
| | | T = 0.61 | Additive | 1.47 | 0.78–2.74 | Mexican - Mestizo | This study |
| | rs182052 | G = 0.37 | Additive | 1.22 | 1.05–1.42 | Afroamerican | Bostrom, et al., 2008 |
| | | G = 0.48 | Codominant | Increase in BMI | Mexican - American | Richardson, et al., 2005 |
| | | G = 0.44 | Codominant | Increase in BMI | Hispano - American | Sutton, et al., 2005 |
| | | G = 0.63 | Additive | 1.43 | 0.76–2.74 | Mexican - Mestizo | This study |
related traits, while the obesogenic environment had no effect. The frequency of risk genotypes in \textit{FTO} rs9939609, \textit{PPARG} rs1801282, and \textit{ADIPOQ} rs4632532 and rs182052 was different from what has been reported in other populations. This was expected as a result, since studies show that there is variability in frequencies of polymorphisms in different populations of the same ethnicity (Table 3). In regard to the association of these genes with obesity, most studies report OR’s in the range of 1.2 to 2, similar to our results, indicating that these genes are of low penetrance and their contribution to the development of obesity is small. However, the presence of several genetic factors together with other factors could have a significant effect.

The presence of polymorphism \textit{FTO} rs9939609 was associated with an increment in BMI, waist circumference and waist/height ratio. Waist/height ratio measures the abdominal fat in any gender or age and is a better metabolic risk predictor than BMI (Browning \textit{et al.}, 2010; Kodama \textit{et al.}, 2012). This result is in agreement with other studies in different populations (León-Mimila \textit{et al.}, 2013; Luczynski \textit{et al.}, 2012; Villalobos-Comparán \textit{et al.}, 2008; Xi \textit{et al.}, 2010). We also found that the A allele increases the risk of alterations in the lipid profile (cholesterol and HDL levels), as reported by other groups (Villalobos-Comparán \textit{et al.}, 2008; Mascarenhas-Melo \textit{et al.}, 2013). This supports the suggested activity of FTO protein, in conjunction with C/EBP, as a co-activator of PPAR gamma, which is involved in adipocyte functions, such as lipid metabolism and differentiation (Wu \textit{et al.}, 2010).

The polymorphism \textit{PPARG} Pro12Ala (rs1801282) has been studied in different populations with contradictory results; in some studies Ala allele was associated with obesity (Bhatt \textit{et al.}, 2012; Morini \textit{et al.}, 2008), whereas in a Chinese population, it was reported as a protecting factor.

### Table 4 - Association of polymorphisms with obesity-related traits

| Measurements       | \textit{FTO} rs9939609 | \textit{PPARG} rs1801282 | \textit{ADIPOQ} rs4632532 | \textit{ADIPOQ} rs182052 |
|--------------------|------------------------|--------------------------|---------------------------|------------------------|
| \( \beta \) (CI 95%, P-value) | \(-0.004\) | \(-0.03\) | \(-0.004\) | \(-0.003\) |
| BMI                | \(0.46\)               | \(-0.005\)               | \(-0.005\)                | \(-0.003\)             |
| Waist circumference (cm) | \(-0.05\) | \(-0.04\) | \(-0.04\) | \(-0.04\) |
| Arm circumference (cm) | \(-0.002\) | \(-0.01\) | \(-0.002\) | \(-0.001\) |
| Triceps (mm)       | \(0.08\)               | \(-0.03\)                | \(-0.03\)                | \(-0.03\)             |
| Waist/height ratio | \(0.03\)               | \(-0.01\)                | \(-0.01\)                | \(-0.03\)             |

Linear regression was used to compare obesity measurements by genotype, using additive model adjusted for age and gender. Significant associations (\(p < 0.05\)) are indicated in bold. BMI: body mass index.

### Table 5 - Association of polymorphisms with biochemical parameters

| Parameter      | \textit{FTO} rs9939609 | \textit{PPARG} rs1801282 | \textit{ADIPOQ} rs4632532 | \textit{ADIPOQ} rs182052 |
|----------------|------------------------|--------------------------|---------------------------|------------------------|
| Glucose        | \(-0.01\) | \(-0.05\) | \(-0.02\) | \(-0.02\) |
| Cholesterol    | \(0.06\)               | \(-0.01\)                | \(-0.01\)                | \(-0.01\)             |
| Triglycerides  | \(0.07\)               | \(-0.11\)                | \(-0.04\)                | \(-0.04\)             |
| HDL            | \(-0.02\) | \(-0.05\) | \(-0.06\) | \(-0.05\) |
| LDL            | \(0.12\)               | \(0.04\)                | \(0.03\)                | \(0.02\)             |

Linear regression was used to compare biochemical measurements by genotype, using additive model adjusted for age, gender and body mass index. Significant associations (\(p < 0.05\)) are indicated in bold.
(Wang et al., 2013). In our study, we did not find an association under any model. However, this polymorphism showed a negative association with triglyceride level (β = −0.11, p = 0.04). This can be supported by in vitro evidence, which shows that allele Ala presents less affinity to DNA, and as a result, the ability to induce lipogenesis is decreased (Larsen et al., 2003). The different results reported for PPARG rs1801282 may be due to PPARG being a transcription factor that responds to the environment (high fatty acids diet) and shows epistasis with other polymorphisms in the same gene (rs2938392, rs1175542, rs1175544) and other genes (ADB3R). Therefore, specific features of the obesogenic environment may influence associations according to the population analyzed.

ADIPOQ rs4632532 showed an association with decreased HDL levels. The polymorphisms evaluated in this study are associated with obesity in Afro-Americans (Bostrom et al., 2008) and with increased BMI, waist circumference, fasting insulin levels and skin fold thickness in Mexicans living in USA (Richardson et al., 2006; Sutton et al., 2005). However, those studies did not find an association with HDL levels. Adiponectin participates in the beta-oxidation of fatty acids (Kadowaki and Yamauchi, 2005), so it is possible that the polymorphic gene impacts the transport of fatty acids (in HDL) into plasma. Accordingly, a positive correlation between HDL and adiponectin levels has been reported elsewhere (Mascarenhas-Melo et al., 2013). Although we did not measure plasma adiponectin, these studies support our results.

In addition to genetic factors, the obesogenic environment including diet, physical activity and screen time was evaluated, but no association was found between environmental factors and obesity or gain in anthropometric measurements. Similar results were found in the National Survey 2006 (Flores et al., 2009). This study presents inaccuracies in diet records of both obese and non-obese groups. Therefore, energy intake could have been wrongly associated with obesity. This imprecision is frequently caused by the use of questionnaires as tools for diet intake assessment. The use of dietary diaries could overcome the problem; however, that method becomes impractical when large populations are surveyed.

The findings of our study are important because there are only two other studies that show association of FTO rs9930609 with obesity or obesity-related traits and modified lipid profile in a Mexican population. In addition, the polymorphisms of PPARG rs1801282 and ADIPOQ rs4632532 were not assessed in those previous studies. However, limitations in our study include a small sample size and difficulty determining the obesogenic environment factors.

In conclusion, this study analyzed environment and genetic aspects of obesity and found significant associations between PPARG rs1801282 and triglycerides levels, ADIPOQ rs4632532 and HDL levels, and FTO rs9939609 with cholesterol, LDL and anthropometric measurements.

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