Rev Bras Cineantropom Hum

original article

DOI: http://dx.doi.org/10.5007/1980-0037.2016v18n3p259

FTO gene variant and association with overweight in Brazilian male students

Variante do gene FTO e associação com excesso de peso em estudantes brasileiros do sexo masculino

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Abstract – Obesity is considered a disease with multiple etiologies. Recent advances in technology have pointed candidate genes that are related to weight gain in several populations. However, in countries with ethnic miscegenation, such as Brazil, studies of this nature with students are still scarce. The aim of the present study was to compare anthropometric variables of Brazilian male students according to the genotypes of the rs9939609 of the FTO gene. In order to do so, 205 participants underwent body mass, height, waist circumference and skinfold thickness measurements. Body mass index (BMI), waist-to-height ratio and body fat percentage were calculated. Volunteers were characterized as overweight according to the BMI-for-age z-score. Participants were genotyped according to the single nucleotide polymorphism rs9939609 of the FTO gene (AA, AT and TT). ANOVA one-way with Bonferroni's *post hoc* was performed to compare genotypes and anthropometric variables. Odds Ratio was calculated to reveal increased chances of presenting higher body mass index z-score, waist-to-height ratio and body fat percentage. Participants homozygous for the A allele presented significantly higher values of BMI-for-age z-score (0.38±1.01 vs. -0.29±1.15), waist circumference (77.15±6.51 vs. 72.85±7.36 cm) and waist-to-height ratio (0.44±0.04 vs. 0.42±0.04) when compared to individuals with the TT genotype. The A allele of the rs9939609 of the FTO gene seems to influence in the adiposity of male students.

Key words: Anthropometry; Genetics; Overweight; Single nucleotide polymorphism; Students.

Resumo – *A obesidade é considerada doença com múltipla etiologia. Avanços recentes na tecnologia têm apontado genes candidatos que estão relacionados ao ganho de massa corporal em diversas populações. Entretanto, em países com miscigenação étnica, como o Brasil, estudos dessa natureza com escolares ainda são escassos. Objetivou-se comparar variáveis antropométricas em estudantes brasileiros do sexo masculino de acordo com os genótipos do rs9939609 do gene FTO. Para tanto, 205 participantes tiveram sua massa corporal, estatura, circunferência da cintura e dobras cutâneas medidos. Índice de massa corporal (IMC), relação cintura-estatura e percentual de gordura foram calculados. Os voluntários foram classificados como com excesso de peso de acordo com o escore-z de IMC por idade. Ademais, os participantes foram genotipados conforme o polimorfismo de nucleotídeo único rs9939609 do gene FTO (AA, AT e TT). ANOVA de uma entrada com post hoc de Bonferroni foi realizada para comparar as variáveis antropométricas entre os genótipos. Odds ratio foi calculada no intuito de revelar chances aumentadas de apresentar maior escore-z de IMC por idade, razão cintura-estatura e percentual de gordura. Os indivíduos homozigotos para o alelo A apresentaram valores significativamente mais altos para escore-z de IMC por idade (0,38±1,01 vs. -0,29±1,15), circunferência da cintura (77,15±6,51 vs. 72,85±7,36 cm) e relação cintura-estatura (0,44±0,04 vs. 0,42±0,04) quando comparados aos indivíduos com genótipo TT. O alelo A do rs9939609 do gene FTO parece influenciar a adiposidade de estudantes do sexo masculino.*

Palavras-chave: *Antropometria; Estudantes; Genética; Polimorfismo de nucleotídeo único; Sobrepeso.*

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Received: 18 August 2015
Accepted: 22 April 2016

INTRODUCTION

Obesity is considered a disease with multiple etiologies. It is usually a result of an unbalance between caloric intake and expenditure. However, its origins can be determined by factors related to metabolism, environment (eating habits and physical activity), psychological disorders and genetics[1].

The influence of genetics on excessive weight became more frequent in literature after the study published by Frayling et al.[2] They performed an association between 490,000 single nucleotide polymorphisms (SNPs) and the presence of type II diabetes in English adults. The results showed that the SNP rs9939609, of the FTO gene (Fat mass and obesity associated), situated on chromosome 16, was strongly associated to type II diabetes and increased body mass index (BMI). However, after statistical adjustments for BMI, the association between the SNP rs9939609 and type II diabetes lost its significance. Therefore, the authors concluded that the presence of diabetes in this population was due to elevated BMI values.

Afterwards, studies with SNPs from the FTO gene, especially the rs9939609, started to gain attention of researchers. In Chinese adults, Li et al.[3] observed that individual homozygous to the A allele presented significantly higher chances of being obese and developing type II diabetes. Legry et al.[4] referred an increased risk of 20.9% of being obese in French adults that carried the A allele when compared to individuals with the TT genotype.

In children and adolescents, literature also states that the A allele carriers of the rs9939609 of the FTO gene present increased chances of excessive weight. Dušátková et al.[5], studying 1443 adolescents aged 13 – 17.9 years from the Czech Republic, reported an increase of 40.0% of obesity in subjects that carried the A allele. In addition, Ruiz et al.[6], studying 752 adolescents, referred that the presence of the A allele was significantly associated with higher BMI, body fat percentage and waist circumference.

However, in countries with ethnic miscegenation, such as Brazil, studies of this nature with students are still scarce. Brazil's Northeastern region, in particular, has a mixed gene pool that is originated from Native Amerindians, Africans and Europeans. As of today, only eight studies involving the interaction of FTO and body adiposity using Brazilian populations have been published[7-12]. Only two of these studies involve children and adolescents[13,14].

In this scenario, the aim of the present study was to verify differences in anthropometric variables of Brazilian male students according to the different genotypes of the SNP rs9939609 of the FTO gene.

METHODOLOGICAL PROCEDURES

Sample and ethical procedures

Three high schools from the city of Petrolina, state of Pernambuco, Brazil, were randomly selected and all male students enrolled in the schools were invited to participate in the study. Only the ones who returned the

informed consent term signed by a parent (or himself if aged 18 or more) participated in the study. In total, 205 students, aged 14 to 20 years, participated (26.62%).

The present study was approved by the Ethics Committee of the Catholic University of Brasília (protocol number 195/2010) and all procedures were in accordance with the Declaration of Helsinki and the Resolution 466/2012 of the Brazilian National Health Council.

Sexual maturation

Initially, all participants informed their name, date of birth and age. Afterwards, sexual maturation was self-evaluated using Tanner's charts[15]. In order to do so, the participant was asked to look at drawings of the male reproductive organ and to indicate which picture better represented the stage they were in (stages 1 to 5).

Anthropometric evaluation

Anthropometric evaluation was performed by measurements of body mass, height, BMI, waist circumference, waist-to-height ratio and body fat percentage.

Body mass was measured with a digital scale (Wiso®, Brazil) and height was assessed with a portable stadiometer (Wiso®, Brazil). During both measurements the participants were without shoes and wore light clothes. BMI was calculated dividing body mass (kg) by the squared value of height (m^2). Overweight and obesity were characterized using the BMI-for-age z-scores defined by the World Health Organization[16]. Values between +1.00 and +1.99 were considered overweight and values higher than +2.00 were considered obese. Subjects aged 18 or older were characterized according to BMI values for adults (overweight between 25.00 and 29.99 kg/m^2 and obese above 30.00kg/m^2)[17]. Overweight and obese participants were grouped in the statistical analysis.

Waist circumference was measured with a non-extendible tape (CESCORF®, Brazil). The measurement was made between the last rib and the iliac crest. Values were considered high when equal or above the 90th percentile for age, according to Fernández et al.[18]. Waist-to-height ratio was calculated by dividing waist circumference (cm) by height (cm) and values were considered high when equal or above 0.50[19].

Triceps and calf skinfolds were measured according to Heyward and Stolarczyk[20] and body fat percentage was calculated using the equation created by Slaughter et al.[21] Values equal or higher than 20% were considered high.

DNA extraction and genotyping of the rs9939609

Blood samples were obtained from the antecubital vein by a trained professional. Three to five ml of blood was drawn in tubes containing EDTA anti-coagulant. DNA was obtained from peripheral blood leukocytes by using a DNA extraction kit according to the manufacturer's

recommendations (QIAamp DNA Blood Kits – QIAGEN, Germany)[22]. The extracted DNA was stored at -80°C for subsequent analysis.

The polymorphism in the human FTO gene (rs9939609) was determined by direct sequencing of a 182 bp Polimerase Chain Reaction (PCR) product amplified using a pair of specific primers: 5' - AACTGGCTCTTGAATGAAATAGGATTCAGA - 3' (sense) and 5' - AGAGTAACAGAGACTATCCAAGTGCAGTAC - 3' (antisense). Reaction tubes contained 100 ng DNA, 10 mmol/l Tris–HCl pH 8.3, 75 mmol/l KCl, 3.5 mmol/l MgCl2, 0.2 mmol/l dNTP, 20 pmol of each primer, 0.5 µg of ovalbumin and 1 U of Taq DNA polymerase (Invitrogen, Brazil) in a final volume of 25 µl. After 1 min of hot start at 80 °C and an initial denaturation for 5 min at 94 °C, the amplifications were performed using 35 cycles of 45 s at 94 °C, 45 s at 62 °C and 45 s at 72 °C followed by a final 10 min extension at 72 °C. Each PCR product was directly sequenced on a ABI PRISM 3700 DNA analyzer (Applied Biosystems®, USA), using the sense primer. Each sequence obtained was examined using the Staden software package (MRC®, United Kingdom), and confirmed by visual inspection.

Statistical Analysis

A descriptive analysis of the data was performed and values are expressed in relative frequency (%) and mean ± standard-deviation. The correction of the outliers was performed adding one unit to the extreme value[23]. Chi-Square test was performed to verify the balance between the genotypes of the rs9939609 of the FTO genes[24]. Statistical power *a priori* for the Chi-Square test was 93.3% (Power=0.933), considering and effect size of w=0.3 and an alpha of 5.0%.

A One-Way Analysis of Variance (ANOVA) with Bonferroni's *post hoc* was performed to verify the differences between the genotypes and the anthropometric variables. For this test the statistical power *a priori* was 90% (Power=0.90) considering an effect size of f=0.25, three groups (AA, AT and TT) and an alpha of 5.0%.

Finally, odds ratio was calculated using the Crosstabs option (confidence interval of 95%), with the aim of verifying if the individuals carrying the A allele had higher chances of presenting increased BMI-for-age z-score, waist circumference and waist-to-height ratio.

The level of significance adopted was 5.0% ($p<0.05$). Power was calculated using G*Power and statistical procedures were performed on the o Statistical Package for the Social Sciences (SPSS), version 15.0 for Windows®.

RESULTS

The main characteristics of the participants are shown in table 1. Of the 205 volunteers, 35 (17.1%) presented excessive weight according to their BMI-for-age z-score, 31 (15.1%) showed high body fat percentage values, 14 (6.8%) had increased waist-to-height ratio and only two (1.0%) volunteers presented elevated waist circumference.

Table 1. Sample's main characteristics (n=205).

Variables	Mean ± standard deviation
Age (years)	16.25 ± 1.27
Tanner's maturational stage	4.20 ± 0.63
Body mass (kg)	64.45 ± 12.34
Height (cm)	173.47 ± 6.62
Body mass index (kg/m²)	21.34 ± 3.52
BMI-for-age z-score	-0.04 ± 1.19
Waist circumference (cm)	74.22 ± 7.51
Waist-to-height ratio	0.43 ± 0.04
Triceps skinfold (mm)	8.89 ± 3.32
Calf skinfold (mm)	9.96 ± 4.01
Sum of skinfolds (mm)	18.85 ± 7.11
Body fat (%)	14.88 ± 5.27

BMI=body mass index.

Among the participants, 27 (13.2%) presented the AA genotype, 103 (50.2%) were heterozygous (AT) and 75 (36.6%) were TT allele carriers. Hardy-Weinberg's test revealed equilibrium between genotypes (X^2=0.82; p=0.36). The comparison between the anthropometric variables and the different genotypes of the rs9939609 of the FTO gene are shown in table 2. Participants homozygous for the A allele presented significantly higher values of BMI-for-age z-score, waist circumference and waist-to-height ratio when compared to TT allele carriers.

Table 2. Anthropometric variables according to the genotypes of the rs9939609 of the FTO gene (n=205). Values shown in mean ± standard deviation.

Variables	AA (n=27)	AT (n=103)	TT (n=75)
	Mean ± standard deviation		
Body mass (kg)	68.02 ± 10.14	65.53 ± 12.98	61.69 ± 11.74
Height (cm)	174.41 ± 7.16	173.69 ± 6.60	172.83 ± 6.48
BMI (kg/m²)	22.31 ± 2.77	21.64 ± 3.73	20.57 ± 3.34
BMI-for-age z-score	0.38 ± 1.01*	0.04 ± 1.22	-0.29 ± 1.15
Waist circumference (cm)	77.15 ± 6.51*	74.45 ± 7.69	72.85 ± 7.36
Waist-to-height ratio	0.44 ± 0.04*	0.43 ± 0.04	0.42 ± 0.04
Triceps skinfold (mm)	9.56 ± 3.46	9.03 ± 3.40	8.45 ± 3.14
Calf skinfold (mm)	11.00 ± 4.69	10.13 ± 3.88	9.34 ± 4.02
Sum of skinfolds (mm)	20.55 ± 7.71	19.15 ± 7.03	17.81 ± 6.95
Body fat (%)	16.14 ± 5.72	15.11 ± 5.21	14.10 ± 5.12

BMI=body mass index. *p≤0.05 to TT genotype.

Odds ratio revealed that carriers of the A allele of the rs9939609 of the FTO gene presented 1.83 more chances of having an increased BMI-for-age z-score when compared with individuals homozygous for the T allele. These chances were 1.48 and 1.49 times higher regarding waist-to-height ratio and body fat percentage, respectively. However, these increased chances did not reach statistical significance (X^2=2.15 for BMI-for-age z-score; X^2=0.52 for waist-to-height ratio; and X^2=0.90 for body fat percentage; p>0.05), as shown in table 3.

Table 3. Odds ratio for increased BMI-for-age z-score, body fat percentage and waist-to-height ratio according to the genotypes of the rs9939609 of the FTO gene (n=205).

n		Increased BMI-for-age z-score	
		Odds ratio	CI (95%)
75	TT	1	-
130	AA/AT	1.83	0.81 – 4.16
n		Increased body fat percentage	
		Odds ratio	CI (95%)
75	TT	1	-
130	AA/AT	1.49	0.65 – 3.44
n		Increased waist-to-height ratio	
		Odds ratio	CI (95%)
75	TT	1	-
130	AA/AT	1.48	0.45 – 4.89

CI=confidence interval.

DISCUSSION

In the present study, participants homozygous for the A allele of the rs9939609 of the gene FTO presented significantly higher values of BMI-for-age z-score, waist circumference and waist-to-height ratio when compared to those homozygous for the T allele. In addition, odds ratio showed that participants carrying the A allele presented more chances, although not statistically significant, of having increased values of BMI-for-age z-score, waist-to-height ratio and body fat percentage (83.0%, 48.0% and 49.0%, respectively).

Several studies have associated the presence of the A allele of the rs9939609 of the FTO gene with increased body adiposity. In the original study that first showed this association, Frayling et al.[2] observed that adults homozygous for the A allele presented higher body mass (3.0 kilos) and 67.0% more chances of being obese.

In children and adolescents, Ruiz et al.[6] reported higher BMI, body fat percentage and waist circumference in A allele carriers. Moreover, Dušátková et al.[5], in a similar design, reported 40.0% more chances of developing obesity in adolescents from the Czech Republic.

On the other hand, Bollepalli et al.[25] found no associations between the polymorphisms of the rs9939609 of the FTO gene and adiposity in African-American students aged 10-18 years. According to the authors, ethnic distinctions in metabolic risks factors could explain theses differences, since they found lower amounts of visceral fat in African-Americans when compared to non-Hispanic white students.

In Brazil, only two studies involving associations between the polymorphisms of the rs9939609 of the FTO gene and anthropometric profile in children and adolescents have been published. Lourenço et al.[14], in a longitudinal study with a mean duration of 4.6 years, evaluated 1,225 children with less than 10 years of age in the city of Acrelândia, situated in the Brazilian Amazon Rainforest region. The authors observed that the presence of the A allele was associated with an increase in BMI of 0.57 kg/

m^2 and a BMI-for-age z-score 0.25 unit higher when compared to children homozygous for the T allele.

Likewise, Silva et al.[13], following 348 children since birth until the age of 8, reported significantly higher values of BMI-for-age z-score, starting at the age of 4 in participants with the AA genotype. These differences were maintained until the age of 8. Moreover, the authors replicated these findings in 615 students aged 4 – 18 years and found significant differences in BMI-for-age z-score and subcutaneous fat in the participants that carried the A allele.

Although these above mentioned studies bring important information about the associations between the variants of the FTO gene and adiposity in Brazilian students, the present study innovates since it is the first to approach a more ethnically mixed population, such as the Brazilian Northeastern semi-arid region[26].

The mechanisms that explain why the polymorphisms of the rs9939609 of the FTO gene influence in the accumulation of body adiposity have not yet been elucidated[27]. However, Benedict et al.[28] found that FTO may facilitate weight gain by increasing grelin (hunger hormone) and decreasing leptine (saciety hormone) plasma levels. Finally, Almén et al.[29], on the other hand, suggested that the FTO gene could possibly influence in the methylation of other genes. According to the authors, one of these genes could be the TERF2IP, which is associated to the body's response to inflammatory processes. Finally, Merkestein et al.[30] described that FTO may influence weight gain by regulating adiponegenesis.

Even though the findings of the present study are important, they should be analyzed with caution. First, although the results showed statistically significant differences between the different genotypes of the rs9939609 of the FTO gene in Brazilian male students, it is not possible to describe the mechanisms that underlie these findings. Moreover, aspects regarding eating habits and exercise must be considered, since they directly influence the variables studied. The lack of control on the period of the day in which the measurements were performed can be considered as a limitation, since height and body mass can slightly change throughout a 24-h period. Lastly, the cross-sectional nature of the study does not allow establishing a cause-effect relationship among the variables studied.

CONCLUSIONS

The present study showed that the presence of the A allele of the rs9939609 of the FTO gene seems influence in the adiposity of male students, since the participants homozygous for the A allele presented higher values of BMI-for-age z-score, waist circumference and waist-to-height ratio. Moreover, the presence of the A allele reflected in higher, although not significant, chances of presenting increased BMI-for-age z-score, waist-to-height ratio and body fat percentage.

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