

THE ROLE OF FAT MASS AND OBESITY ASSOCIATED GENE (FTO) IN SATIETY AND BINGE EATING DISORDER

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ABSTRACT

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Obesity is a major health problem and one of the biggest predictors of the development of chronic diseases. Variations in the Fat mass and obesity associated gene (FTO) have been shown to associate strongly with obesity. Among patients with severe obesity, there is a subpopulation that presents an eating disorder known as Binge Eating Disorder. Because of its expression in the hypothalamus, FTO could be associated with modulation of satiety and, perhaps, play a role in the genesis of BED, contributing to severe obesity. A search in PubMed was carried out with the following terms: Morbid Obesity AND FTO, FTO AND Satiety Response, Binge Eating Disorder AND FTO. No restriction on the date of publication, language or type of design was applied. Sixteen articles were found. Twelve were related to FTO and grade III obesity, and three were related to FTO and satiety. Ten studies were excluded. Thus, six articles were evaluated in this review. The scarce literature limits further conclusions about the potential impact of the associations with FTO in the treatment of obesity, but all articles included in this revision show association with at least one SNP of FTO. Further studies are required to clarify these associations, especially in relation to rs9939609 (A/T), because, up to this moment, it seems to be the one variant with greatest impact on obesity in humans.

Keywords: Obesity; FTO; satiety

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Obesity is one of the main health problems in the 21st Century. It is an established risk factor for conditions such as Type 2 diabetes mellitus, cardiovascular disease and cancer¹.

The prevalence of overweight and obesity has doubled in the last thirty years. In Brazil, a 2008/2009 survey of the Ministry of Health showed that 8.9% of the population is obese. In the South of the country, 10.1% of the male population and 15.1% of the female population is obese. Brazilian estimates point out that, in the year 2025, the country will have the fifth largest prevalence of obesity worldwide². Clinically, obesity is diagnosed in the presence of a body mass index (BMI) equal to or higher than 30 kg/m², in adults³.

Recent studies show associations of BMI with body fat and with the the "Fat mass and obesity associated" (FTO) gene⁴, located in chromosome 16q12.2^{5,6}. Variations in this gene (single-nucleotide polymorphisms – SNPs) were strongly associated with obesity and diabetes mellitus⁷. The association of FTO with human obesity has been shown in caucasian populations studies⁸⁻¹¹. Besides the association with BMI and higher risk for overweight and obesity, SNPs in FTO have been associated with obesity and body weight^{5,8,11}, leptin levels¹¹, subcutaneous fat^{5,8}, fat mass^{5,8,11} and waist circumference¹¹.

The messenger RNA (mRNA) of FTO is expressed in the hypothalamus¹², an area that is connected with appetite regulation; in rodents, FTO mRNA expression in the hypothalamus is modulated by acute food deprivation¹³. One recent study, in human adults, has found differences in the caloric intake, but no difference in the energy expenditure, showing that the FTO genotypes affect body weight mostly through caloric intake¹⁴.

Recent research shows that, among obese subjects, there is a subpopulation with similar characteristics that does not respond to the usual behavioral treatment for weight loss. This group presents an eating disorder known as Binge Eating Disorder (BED)¹⁵.

Binge eating is characterized by a very high intake of food within two hours, followed by a feeling of loss of control of what and how much it is eaten. According to DSM IV-TR, BED is diagnosed when episodes happen at least twice a week, for six months, associated to some characteristics of loss of control, and are not followed by compensatory behaviors (such as vomiting or use of laxatives)¹⁶.

Patient medical records indicate that they have an early onset of obesity, high BMIs, and poor response to dietary treatment; they also spend more time involved with their diets¹⁷. An estimated frequency of 5-30% (and in one extreme report, 50%) of BED among obese patients that look for help has been reported. In the general population, the prevalence of BED is of 2-3%. In Brazil, a prevalence of 15-22% has been reported in patients that look for help for weight loss¹⁸.

Due to its expression in the hypothalamus, FTO may be associated with satiety modulation and, consequently play a role in the genesis of BED, contributing to severe obesity and its complications.

This article sought to report the current knowledge on the association of polymorphisms of FTO with satiety in obese individuals.

METHODS

We conducted a search in Pubmed (National Center for Biotechnology Information, U.S. National Library of Medicine), with the following associated MESH terms: Obesity Morbid AND FTO, Satiety Response AND FTO, Binge eating disorder AND FTO. We set no restrictions as to the date of publication, language, age of the subjects in each study, or type of design.

The search and analysis strategies were of a structured review.

Were excluded from this review: studies that encompassed items not related to overweight and/or obesity, and those with patients who had undergone bariatric surgery or other surgery that could interfere with the gastrointestinal tract. Only studies with human subjects were included.

RESULTS

A total of 16 articles were found; of these, 12 were related to FTO and grade III obesity; 3 to FTO and satiety; and 1 to BED and FTO. Of the studies that correlated FTO and obesity, seven were excluded because the subjects had undergone bariatric surgery, and two were experimental animal studies. The article related to BED was excluded because it was in low-weight patients. Thus, 6 articles were evaluated in this review, as illustrated Figure 1: 3 case-control studies; 1 review, 1 cross-sectional study and 1 brief communication. All of the case-control studies looked for the association between the genes connected to

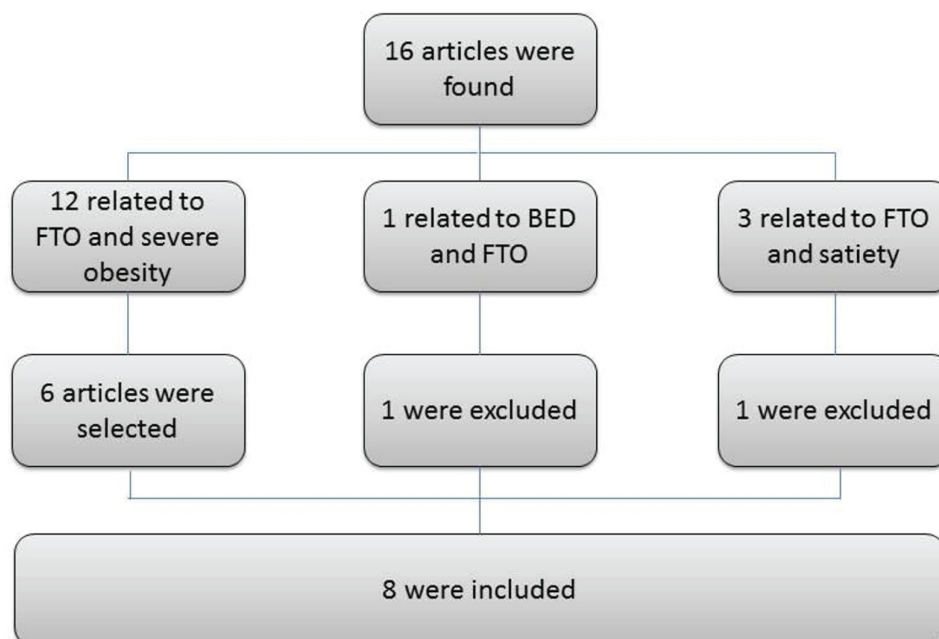


Figure 1: Article selection flowchart.

Table 1: Association of Obesity and FTO polymorphism.

Author/Year Journal/Qualis	Population	Objetive	Results
R Arlen Price (2008)¹⁹, <i>BMC Medical Genetics</i>	Women, BMI > 35kg/m ² (cases) Women, BMI < 25kg/m ² (controls)	Examine SNPs (rs1421085, rs17817449, rs9939609) to determine if the variability of FTO can be distinguished between cases of extreme obesity and normal weight control	There was association of obesity in all SNPs, the largest association observed with rs1421085
R. Attaoua (2009)²⁰, <i>Diabetes & Metabolism</i>	Thin women x obese women, all received three diets and after each diet there was blood collection. GTT for obese women	Investigate genetic association of FTO in obese women in the presence of IRS-2	There was association of FTO and obesity, as well as IRS-2. There was a correlation between insulin resistance and rs1421085
David Meyre (2009)²¹, <i>Nature Genetics</i>	Kids with obese Family, kids with normal weight, thin adults, morbid obese adults	Association of early onset genome (6 year old kids) and obese individuals, compared with individuals of the same age and normal weight	Evidence that obesity in childhood and adulthood have the same genetic background
Raquel Rodríguez-López (2010)²², <i>Endocrinología y Nutrición</i>	Patients with obesity before 16, patients with phenotype and Family history of obesity	Evaluate the association of variation of FTO gene, based on SNP rs1861868 and rs9939609, with hereditary predisposition to suffer from morbid obesity	There was an association of rs9939609 with severe obesity in the Spanish population

FTO: Fat Mass and Obesity associated, BMI: Body Mass Index, IRS-2: Insulin Receptor - 2, GTT: glucose tolerance test.

FTO and obesity. These articles described control groups of non-obese patients and obese patients (obesity level II and III). In the three articles, SNPs of FTO (rs1421085, rs1861868, rs9939609, rs17817449) were studied. In the study of Attaoua et al., a dietary intervention was carried out in order to provide the same nutritional environment. All studies showed associations between obesity and polymorphisms of FTO (table 1)^{19,20,22}.

The study by Meyre et al., shows gene associations (including FTO) in two life stages: childhood and adult obesity; it tested these associations in three scenarios: childhood obesity only, adult and childhood obesity, and adult obesity only. The study highlights the importance of these associations showing that obesity in childhood and adult life share the same genetic architecture²¹.

The study by den Hoed et al. evaluated individuals with an average BMI of 25 kg/m², who received balanced and standardized meals (27% protein, 45% carbohydrates, and 28% fat). After the test meals, hunger and satiety were evaluated through visual scales. In this article, five different SNPs were studied; one was FTO rs9939609. The authors found an association between the FTO rs9939609

polymorphism, lower satiety and lower postprandial hunger reduction²³.

The review article examined genes that contribute to obesity and eating behaviors in children and adolescents – FTO, PPARG and MC4R. The most frequent FTO SNP would be rs9939609, as seen in studies relating BMI and body fat to the SNP children and adolescents. A small number of studies conducted in children measured the indirect intake of energy associated with the FTO and confirmed the higher risk of obesity due to reduced satiety, preference for energy dense food and not for energy expenditure as suggested by the literature²⁴.

DISCUSSION

The present review shows how scarce are studies on FTO when associated with morbid obesity. In total only four SNPs in FTO were studied and not all showed positive associations. Of 4 studies that examined rs9939609, only one found association with obesity. Three studies examined rs1421085; one found an association with obesity and in one there was a correlated with insulin resistance¹⁹⁻²².

Price et al. found an association between obesity and several SNPs; among them, FTO rs1421085 showed the strongest association. This study included

only women, Attaoua et al. also studied only females and found, besides the association with obesity, a correlation of rs1421085 with insulin resistance. The relation of FTO with insulin resistance was also reported by Cecil^{20,24}.

The most studied SNP in FTO is rs9939609. Although just one study found an association with obesity in this review, there are in previous studies a description of decreased response to satiety in children and adolescents when rs9939609 is present, confirmed in other studies²⁵⁻²⁸. As Cecil, Frayling et al. also identified, rs9939609 carries an association with a higher Body Mass Index (BMI) in children and adults²⁹.

In individuals with normal weight or overweight, den Hoed found a variable, but significant, association between rs9939609 and postprandial response of hunger and satiety²³. These data suggest that the rs9939609 polymorphism is a predisposing factor to weight gain, but not mandatory.

A study related in a Spanish population demonstrated a relation of rs9939609 with severe obesity in childhood. Individuals with two SNPs (rs1861868 and rs9939609) had a 3.03% greater chance of developing severe obesity in adulthood. The impact of this and other eventual combinations of SNPs has not been properly evaluated to date²².

On the other hand, Liu et al. have not found associations of FTO rs9939609 with the caloric intake of the subjects in their review paper³⁰. Nevertheless, this study did show a correlation between satiety and the FTO rs9939609. Being a non-systematic review, Liu's findings have to be weighed in view of the obvious limitation.

Women are the largest population with overweight and obesity in Brazil²; this fact happens in most countries. In a study conducted in 2009, Cornes et al. analyzed rs9939609 and found an association with BMI in men and women, but with a stronger association in women⁴.

We notice that at different stages of life (childhood and adulthood) the association of FTO with obesity is similar. Meyere et al. confirm that obesity in both stages of life has the same genetics²¹.

We know the association of FTO with possible weight gain and increased BMI, waist circumference and insulin resistance, but we do not know where this influence begins and how FTO can be used to prevent obesity. Larder et al. reviewed studies of FTO in animal models and cell studies, and found no direct association with obesity-related mechanisms. There are still missing data to enable us to explain these relationships³¹.

All studies included in this review found positive associations between the FTO (and its various SNPs) and satiety and obesity. Unfortunately, the scarce literature limits further conclusions; the association exists, but it is not yet clear what real importance it carries to the problem of obesity, its mechanisms - particularly appetite modulation - and, eventually, its treatment.

FTO rs9939609 seems to be the one SNP with the greatest impact on obesity, it most likely influences body mass through some interference with satiety, but there are no data as to a clear relation of FTO with eating disorders. Further studies in humans will have to be designed and carried out in order to clarify this subject.

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Conflicts of interest

The authors declare no conflicts of interest.

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