Understanding the Fat Gene
Obesity Common Variant FTO rs9939609

Muhammad Haris Lucky¹, Saeeda Baig², Zil-e-Rubab³

ABSTRACT

Obesity, attributable to the interaction of genetic makeup, lifestyle and environment factors are a multifactorial disease. However, not all people with similar genetics or same environmental setup become obese. Currently, extensive research is being conducted regarding increases in the prevalence of obesity, apparent in many societies, studying their eating habits and physical activity. Although, people with obesity have the equal distribution of body fat, yet they do not suffer from the same medical ailments. The recent identification of obesity-risk FTO variants rs9939609 associated with body mass index (BMI) and risk of obesity in multiple populations has led to the major success in the field of obesity genetics, making FTO the first locus unequivocally associated with adiposity. The role of FTO gene as a risk factor of obesity has also been identified by the Genome wide association which is entirely a new approach. The function of FTO gene was unknown, but recent investigation showed that the FTO gene regulates ghrelin a key mediator of ingestive behavior, which might explain a predisposition to increased food intake leading to obesity. People with rs9939609 variant of the FTO gene are at increased risk of obesity they have higher circulating levels of the hunger hormone ghrelin, and feel hungry soon after eating a meal. This review focuses on the genetics of FTO gene and the association of each additionally minor allele of (FTO) rs9939609 single nucleotide polymorphism (SNPs) with the risk of obesity.

KEY WORDS: FTO, SNPs, rs9939609, Lifestyle, Obesity.


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INTRODUCTION

Obesity: A Global problem

Obesity, in both children and adults, has reached to the extent of epidemic in multiple countries worldwide, with severe health problems and imposing an extensive economic burden on societies.\(^1\)\(^-\)\(^4\) Overweight and obesity, defined as body mass index (BMI) \(>25\) and \(\leq 30\), respectively, is associated with many chronic diseases and cancers\(^1\)\(^-\)\(^5\). Individuals belonging to both genders of all ages, any socioeconomic strata or ethnic groups are its victims. The population of overweight adults has reached upto 1 billion worldwide; of which 312 million are the obese adults and 10\% are overweight children.\(^6\)\(^,\)\(^7\) It is predicted to rise to 2.3 billion overweight and over 700 million obese adults by 2015 according to WHO. This epidemic has soared over the last three decades, this increase in global prevalence has been mainly driven by changes in lifestyle, which includes calorie excess and sedentary life style.\(^8\)\(^-\)\(^10\) Besides these environmental factors, genetic of a population are estimated to account for 40-90\% of the variation in BMI.\(^8\)\(^,\)\(^9\) Conversely, not everyone become obese in today's obeseogenic environment and studies suggest the involvement of genetics is in response to environmental influencers that lead to changes in adiposity.\(^11\)\(^,\)\(^12\) But obesity susceptibility loci could not be identified until 2007. In 2007, the intron 1 of (FTO) gene was identified as the obesity susceptibility locus in genome-wide association studies.\(^13\)\(^,\)\(^14\) Each additional minor allele of rs9939609 single nucleotide polymorphism (SNP) in FTO was found to be associated with the risk of obesity and increase in body weight. It was estimated that 40\%-70\% of the variation in obesity related phenotypes are genetic.\(^15\) FTO gene variants not only associated with human adiposity and metabolic disorder, but also with cancer.\(^16\) The objective of this review was to focus on the genetics of FTO gene and its rs9939609 (SNP) single nucleotide polymorphism.

DISCUSSION

The influential role of genes in obesity

Parental obesity is the strongest risk factor for childhood and adolescent obesity.\(^17\) If both parents are obese then the risk becomes particularly prominent.\(^18\) However, inheritance of obesity does not usually follow classic Mendelian patterns. A combination of genetic mutations, deletions and single nucleotide polymorphisms are all known to contribute to obesity. This can broadly be classified into three classes polygenic, monogenic or syndromic obesity.

Polygenic obesity: The majority cases are polygenic, result of multiple genes interact with a shifting environment. Each “Obesity gene” only makes a small contribution to phenotype, but collectively, inherited genetic variations play a major role in determining body mass and how the body maintains a balance between physical activity and nutrition. It arises when an individual’s genetic makeup is susceptible to an environment that promotes energy consumption over energy expenditure.\(^20\)

Monogenic obesity: That is the obesity associated with a single gene mutation. In these cases single gene variants are sufficient by themselves to cause obesity in food abundant societies. Patients with monogenic obesity usually show extremely severe phenotypes characterized by an early childhood obesity foundation, often linked with additional behavioral, developmental or endocrine disorders, like hyperphagia and hypogonadism. Monogenic obesity typically results in severe obesity as the main symptom.

Syndromic obesity: That includes some disorders with Mendelian inheritance, in which patients are clinically obese and are additionally characterized by mental retardation, dysmorphic features, and organ-specific developmental abnormalities. In fact Syndromic obesity, has many characteristics, of which obesity is one symptom.\(^19\)

Obesity contributing genes

How genes contribute to obesity lies in quite a few theories that are proposed to explain the genetic basis of human obesity.\(^21\)\(^,\)\(^22\) These include the thrifty gene hypothesis, the fetal programming hypothesis, the predation release hypothesis, the sedentary lifestyle hypothesis, the ethnic shift hypothesis, the increased reproductive fitness hypothesis, the assertive mating hypothesis and the complex hypothesis. But still an acceptable consensus in this field is
lacking and possibly due to the fact that complex genetic interactions influence the development of obesity. One of the facilitating explanations for the rapid rise in obesity is the difference between today’s environment and “energy thrifty genes” that multiplied in the past under different environmental conditions when food sources were rather limited. It has been argued that the thrifty genotype has been just part of a wider range of habits in which genes can favor fat accumulation in a given environment. The difference in how people respond to the same environmental conditions is an additional indication that genes play an important role in the development of obesity. This is also consistent with the concept that obesity results from genetic variation interacting with uneven environmental conditions. Recent advances in genetic epidemiological approaches have identified several genetic loci for obesity (see Table 1).

Table 1: Selected genes with variants associated with obesity

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Chromosome location</th>
<th>Gene product’s role in energy balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADIPOQ</td>
<td>Adipocyte-,C1q-, and collagen domain-containing</td>
<td>3q27</td>
<td>Produced by fat cells, adiponectin promotes energy expenditure</td>
</tr>
<tr>
<td>FTO</td>
<td>Fat mass-and obesity-associated gene</td>
<td>16p12.2</td>
<td>Promotes food intake</td>
</tr>
<tr>
<td>LEP</td>
<td>Leptin</td>
<td>7q31.3</td>
<td>Produced by fat cells</td>
</tr>
<tr>
<td>LEPR</td>
<td>Leptin receptor</td>
<td>1p31</td>
<td>When bound by leptin, inhibits appetite</td>
</tr>
<tr>
<td>INSLG2</td>
<td>Insulin-induced gene2</td>
<td>2q14.1</td>
<td>Regulation of cholesterol and fatty acid synthesis</td>
</tr>
<tr>
<td>MC4R</td>
<td>Melanocortin 4 receptor</td>
<td>18q22</td>
<td>When bound by alpha-melanocyte stimulating hormone, stimulates appetite</td>
</tr>
<tr>
<td>PCSK1</td>
<td>Proprotein convertase subtilisin/kexin type 1</td>
<td>5q15-q21</td>
<td>Regulates insulin biosynthesis</td>
</tr>
<tr>
<td>PPARC</td>
<td>Peroxisome proliferator-activated receptor gamma</td>
<td>3p25</td>
<td>Stimulates lipid uptake and development of fat tissue</td>
</tr>
</tbody>
</table>

FTO gene and obesity

The genetic contribution to common obesity was recognized initially through family, twin, and adoption studies. Twin studies have shown a comparatively high heritability ranging from 40%-77%. However, the search for obesity susceptibility genes has been a difficult task. Gene discovery in the last 15 years has been based on two extensive genetic epidemiological approaches (candidate gene and genome-wide linkage methods). Recently, genome-wide association studies have brought great information on obesity related genes. In their report, Frayling et al. showed association of 490,032 SNPs and their relationship to type 2 diabetes mellitus (T2DM) and 10 SNPs in intron 1 of FTO gene related to obesity. The predisposition to obesity conferred by this gene was not related to the regulation of energy expenditure, but was mainly accounted for the control of intake of food of high caloric density. The FTO gene rs9939609 obesity-risk allele has also been found to be associated with the loss of control over eating. Further analysis revealed an even stronger association between BMI and FTO intron 1. There is a strong association between SNPs of intron 1 of FTO and type 2 diabetes.

FTO gene risk allele (rs9939609)

FTO is a very large gene with nine exon span more than 400 kb on chromosome 16. FTO encodes a nuclear non-heme iron-and 2-oxoglutarate to succinate and the demethylation of 3-methylthymine and 3-methyluracil in DNA and RNA, respectively. Oxidative demethylation of alkylated acids is essential for maintenance of an intact genome. FTO is expressed ubiquitously in all fetal and adult tissues particularly in the hypothalamic arcuate nucleus, pituitary, heart, and liver. The arcuate nucleus is the site of synthesis of proopiomelanocortin (POMC) and its anorexigenic product α-melanocyte stimulating hormone and of orexigenic agouti-related peptide (AGRP) and neuropeptide Y (NPY) essential components of the appetite regulating system. The function of the FTO
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The SNP rs9939609, identified with the T to A missense mutation in the intron1on chromosome 16q12.2, is a common variant that is widely studied in different ethnic populations. The FTO gene has recently attracted much attention in obesity research. Previous genetic association-based studies have been shown that SNPs (rs9939609) in the FTO gene is associated with increased body mass index (BMI).

Table 2: Association between SNP of FTO gene (rs9939609) with Obesity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Age Range</th>
<th>Locus</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlos FF et al</td>
<td>Case-control</td>
<td>18-50 y</td>
<td>rs9939609</td>
<td>FTO gene locus rs9939609 are at higher risk for obesity in Portuguese population.</td>
</tr>
<tr>
<td>Rauhio A et al</td>
<td>Cross-sectional</td>
<td></td>
<td>rs9939609</td>
<td>FTO gene was associated with body weight.</td>
</tr>
<tr>
<td>Shahid A et al</td>
<td>Case-control</td>
<td>5-45 y</td>
<td>rs993960</td>
<td>FTO gene rs9939609 is associated with BMI and risk of obesity in adults Pakistani females.</td>
</tr>
<tr>
<td>Zhao XY et al</td>
<td>cohort</td>
<td>6-16 y</td>
<td>rs993960</td>
<td>Confirmation of the association of FTO rs9939609 with incidence and duration of obesity in children.</td>
</tr>
<tr>
<td>Lourenco BH et al</td>
<td>Population-based longitudinal study</td>
<td>&lt;10 y</td>
<td>rs9939609</td>
<td>The FTO gene rs9939609 was associated with increase in BMI</td>
</tr>
<tr>
<td>Da sliva et al</td>
<td>cohort</td>
<td>Birth till 8 y</td>
<td>rs9939609</td>
<td>FTO variants rs9939609 is associated with increased body mass and subcutaneous fat in Brazilian children.</td>
</tr>
<tr>
<td>Vasan SK et al</td>
<td>Cross-sectional</td>
<td>15-20 y</td>
<td>rs9939609</td>
<td>FTO (rs9939609) is associated with body fat distribution during early growth in Indian adolescents and may predispose to obesity and metabolic consequences in adulthood.</td>
</tr>
<tr>
<td>Shin-ya et al</td>
<td>Case-control</td>
<td></td>
<td>rs9939609</td>
<td>FTO rs9939609 polymorphism might have some impact on BMI in healthy subjects.</td>
</tr>
<tr>
<td>Xi B et al</td>
<td>Case-control</td>
<td>6-18 y</td>
<td>rs9939609</td>
<td>FTO polymorphism was associated with risk of central obesity in the Chinese children.</td>
</tr>
<tr>
<td>Albuquerque D et al</td>
<td>Case-control</td>
<td>6-12 y</td>
<td>rs9939609</td>
<td>FTO polymorphism was associated with anthropometric traits and risk of obesity in Portuguese children.</td>
</tr>
<tr>
<td>Lauria F et al</td>
<td>cohort</td>
<td>2-9 y</td>
<td>rs9939609</td>
<td>FTO rs9939609 polymorphism was associated with BMI overweight/obesity risk in European children.</td>
</tr>
<tr>
<td>Pyrzak et al</td>
<td>Case-control</td>
<td>6-16 y</td>
<td>rs9939609</td>
<td>FTO rs9939609 polymorphism was associated with BMI and the percent of fat content in children.</td>
</tr>
<tr>
<td>Sallman Almen M et</td>
<td>Case-control</td>
<td>6-18 y</td>
<td>rs9939609</td>
<td>FTO rs9939609 polymorphism was associated with BMI and the percent of fat content in children.</td>
</tr>
</tbody>
</table>
Since the FTO polymorphism is the most significant genetic factor for obesity to date, there is still has an urgent need to elucidate the exact mode of FTO risk alleles in regulating food intake or energy consumption.46

**Figure 1: Shows the association of rs9939609 FTO gene polymorphism with obesity related multiple disease.**

CONCLUSION

Obesity is caused by complex interactions between environment, behavior and genetic predisposition. The understanding of how genes influence the development of obesity has greatly improved in the recent years. This is mainly due to important technological advances such as genome-wide search for genes associated with obesity phenotypes, but the most prominent result being the discovery of the (rs9939609) FTO gene, which shows the association of FTO with BMI.

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