**TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE**

**Genetic Associations of Obesity: The Fat-Mass and Obesity-Associated (FTO) Gene**

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**Introduction**

Obesity is a global epidemic and contributes to a myriad of medical conditions including cardiovascular disease, diabetes, and cancer. As with many other diseases, there is an increasing body of literature that links genetics to obesity. For example, several genes expressed in the hypothalamic region are involved in the regulation of appetite. To date, the strongest genome-wide association, as it relates to obesity, is located in introns 1 and 2 of the fat-mass and obesity-associated (FTO) gene located on chromosome 16q12.2. This relationship was first identified in a series of studies in 2007. Recently, several single-nucleotide polymorphisms (SNPs) of the FTO gene have been implicated in the risk of obesity and its complications. In this brief review, we will discuss new insights into the pathophysiological mechanism by which the FTO gene affects obesity and some clinical implications of its SNP variants.

**Mechanism**

In a landmark study using human adipose-derived progenitor cell cultures, Claussnitzer *et al.* attempted to elucidate the FTO variant associated with obesity, its upstream regulator, and its downstream target. To accomplish this goal, they incorporated a complex combination of epigenomics and comparative genomics using tissue samples from human subjects and mice. The authors were successful in identifying a causal FTO variant, a single nucleotide T-to-C variant, rs1421085, by using a phylogenetic module complexity analysis. This computer-based process is designed to identify genetic variations in noncoding regions of DNA that modulate gene expression by binding transcription factors. Under normal adipocyte differentiation, there is a programmed decreased expression of IRX3 and IRX5 by the repressor protein ARID5B. The variant FTO rs1421085 codes for an inactive ARID5B (and therefore there is increased production of IRX3 and IRX5). This change leads to a cell-autonomous shift in pre-adipocyte development from beige adipocytes, which are involved in energy-dissipating thermogenesis, to energy-storing white adipocytes involved in lipid storage, increased fat stores, and gain of body weight. In vitro, the group was able to edit the faulty ARID5B, and demonstrate that it was able to activate browning expression programs and increase adipocyte thermogenesis sevenfold.

**Clinical correlation**

Given the epidemic, it is imperative that we understand the genetic basis for obesity. There have been several recent studies that have examined the potential clinical implications if this thermogenesis pathway is disrupted in FTO gene variants.

1. **Non-alcoholic fatty liver disease (NAFLD).** It is already established that obese patients are at risk of developing NAFLD, though it is clear that not all obese patients have an affected liver. A study from China implicates overexpression of FTO mRNA as a potential cause, though the specific variant is not defined. Mouse models of NAFLD were compared to control mice. These mice were fed a high-fat diet, and subsequently demonstrated increased triglyceride levels as well as increased ALT and AST compared to normal mice. FTO mRNA and protein levels were found to be upregulated in NAFLD ($P<0.01$). Using isolated...
liver cells, expression of the *FTO* gene resulted in adipogenesis and subsequent steatosis via an oxidative stress mechanism.

2. **Colorectal adenomas.** These are established as the precursor lesion to colon cancers. While previous studies have shown conflicting results regarding the role of obesity in the development of adenomas, researchers recently demonstrated an increased risk of colorectal adenomas in patients who had specific *FTO* gene polymorphisms. This case–control study identified patients undergoing screening colonoscopy who either did (*n* = 321) or did not (*n* = 903) have histologically confirmed adenomas. Demographics were collected and genotyping was performed. Multivariate regression analysis controlling for multiple relevant confounders revealed that several *FTO* gene variants in African American participants were inversely associated with adenoma prevalence. This was observed in three different SNPs with differing base-pair variants (*rs17817449* T/G, *OR* = 0.54, 95% CI = 0.34–0.87; *rs8050136* C/A, *OR* = 0.54, 95% CI = 0.33–0.87; *rs9939609* T/A, *OR* = 0.57, 95% CI = 0.35–0.96). This result was not seen in the population as a whole or in the Caucasian cohort.

3. **Pancreatic cancer.** It is a relatively common GI malignancy, and is associated with high mortality. Some studies have implicated diabetes and obesity as risk factors for the development of pancreatic cancer. Investigators in Japan examined whether *FTO* gene variants were associated with pancreatic cancer. New diagnoses of pancreatic cancer over the period 2010–2012 were included as cases (*n* = 360). Controls were healthy patients without pancreatic cancer (*n* = 400) and matched to gender and age. All patients underwent genotype analysis of the *FTO* rs9939609 SNP. After multivariate analysis controlling for age, gender, BMI, smoking history, and diabetes, patients with the T/A variant (compared to the T/T homozygote) were significantly more likely to have developed pancreatic cancer (*OR* = 1.48, 95% CI = 1.07–2.04). Interestingly, this association persisted even when controlling for BMI, suggesting that the association between *FTO* rs9939609 and pancreatic cancer is independent of obesity. It is not clear if the risk associated with this *FTO* variant is relevant outside of East Asian populations; however, given the significant mortality of pancreatic cancer, this topic should be further studied.

4. **Bariatric surgery.** The use of weight loss surgery has been increasingly accepted as a valid method to reduce obesity and its long-term complications. Given the known associations between the *FTO* gene and obesity, it is important to examine what role variants in the gene may have on bariatric surgery outcomes. This question was recently addressed by Rodrigues et al. In a longitudinal study of 146 patients undergoing Roux-en-Y gastric bypass, researchers performed genotypic analysis of the *rs9939609* SNP and assessed its role in postoperative weight gain. Patients without the risk allele (TT) were compared to patients with one (TA) or two (AA) risk alleles. While the prevalence of patients with at least one risk allele is found in only 16% of the Caucasian population, 71.2% of patients undergoing bariatric surgery carried at least one risk allele. There was no difference in weight gain between the groups with and without the high-risk alleles at the end of 24 months. Beyond this, however, the groups began to diverge, with the patients with at least one risk allele having increased body weight and BMI at 36, 48, and 60 months following surgery compared with the TT patients. BMI was 5, 15, and 20% higher at these time points. The implications of this study are that the *FTO* gene may play an important role in the long-term outcomes of bariatric surgery, and perhaps a patient's genetic profile could be used prior to surgery to prognosticate their success.

**Conclusions**

While the genetics of obesity is complex, the *FTO* gene has been the most strongly associated with obesity thus far. Recently, researchers have begun to elucidate the underlying pathophysiology behind how this gene may act to increase the risk of obesity. Various SNPs may alter several downstream regulators of adipocyte differentiation and thermogenesis. Understanding this pathway has a variety of potential clinical implications. As summarized here, the *FTO* gene is associated with several significant gastrointestinal diseases, including NAFLD, colon adenomas, pancreatic cancer, and the success of bariatric surgery. Further investigation into this genetic locus may provide clues for potential therapeutic targets.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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