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***FTO* gains function**

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Abstract

Previous genome-wide association studies have identified a strong association between *FTO* and human obesity, although the mechanism by which *FTO* affects obesity remains unknown. A new study suggests that the obesity risk alleles are gain-of-function.

In 2007, a genome-wide association study identified the strongest association signal yet reported for an adiposity modifier gene¹, located in the first intron of *FTO* (also known as the fat mass and obesity-associated gene) (Fig. 1). Individuals homozygous for the *FTO* risk allele eat more² and are, on average, ~7 pounds heavier¹ than individuals homozygous for the protective allele. Individuals heterozygous for the risk allele are 3 pounds heavier on average, implying a dose-dependent effect¹. Although *FTO* was found to have demethylase activity³, this function provided no immediate clues as to the molecular-physiological mechanism by which this gene might affect adiposity.

Some studies have suggested that *FTO* exerts anorexigenic effects, as fasting (accompanied by an increased drive to eat) is associated with decreased hypothalamic *Fto* expression in mouse^{3,4}. However, mice segregating a null *Fto* allele are lean due to increased energy expenditure⁵. These mice also have higher postnatal mortality rates, generalized reduction in body size, hyperphagia and reduced body fat, suggesting that *Fto* may play a direct role in the development of adipose tissue. In contrast, mice homozygous for a dominant-negative *Fto* mutation that does not cause increased perinatal mortality or generalized reduction in body size display reduced fat mass, as well as increased energy expenditure without apparent changes in physical activity or food intake⁶. From these studies, it is not clear whether the susceptibility alleles in humans are hypermorphic or hypomorphic with regard to *FTO* function, whether the impact on obesity is conveyed entirely by effects in the brain or whether the effects on *FTO* expression differ by organ. On page 1086 of this issue, Roger Cox and colleagues report the first *in vivo* study that directly addresses the effects of systemic *Fto* overexpression on food intake and energy expenditure⁷.

***FTO* gain of function**

Church *et al.*⁷ created mice carrying one or two extra copies of a ubiquitously expressed *Fto* gene, resulting in *Fto* overexpression in all tissues tested, including white adipose tissue (overexpressed by ~1.5-fold and ~3-fold, respectively) and hypothalamus (overexpressed by ~2-fold and ~2.5-fold, respectively), with the highest levels of overexpression seen in muscle (~3-fold and ~10-fold, respectively). These mice displayed increased energy intake and increased adiposity in a dose-dependent manner, in agreement with the *FTO* dose-

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dependent differences in adiposity seen in humans¹. The authors also confirmed that *Fto*-null mice have reduced fat mass, as has been previously reported⁵. Taken together, these data suggest that increased *FTO* expression results in increased food intake, leading to increased adiposity. Thus, a gain-of-function effect is suggested for the implicated human allele.

Brain versus fat

Because *FTO* is ubiquitously expressed, it is not immediately apparent which organs are the primary mediators of the gene's effects on adiposity. *FTO* has been implicated in the regulation of lipolysis⁸. A number of contradictory reports found that *FTO* expression in human adipose tissue is negatively correlated or uncorrelated with *FTO* susceptibility alleles^{9,10}. Moreover, *FTO* expression is higher in the subcutaneous fat of obese individuals⁸ independent of *FTO* genotype status. Relevant to a possible primary role of *FTO* in adipose tissue, Church *et al.*⁷ now report that fasted mice overexpressing *Fto* have lower circulating concentrations of leptin per unit of fat mass than fasted control animals. Leptin is synthesized in fat and provides a signal to the hypothalamus and other parts of the brain regarding the size of fat stores. Absolute or relative leptin deficiency results in hyperphagia¹¹. Thus, it is possible that systemic *FTO* overexpression affects leptin expression or secretion from fat and thereby affects central nervous system-mediated control of food intake.

A number of reports have also implied a direct role for *FTO* in the central nervous system in mediating food intake^{3,4}. Overexpression of *Fto* in the arcuate nucleus, a hypothalamic region that plays a role in regulating food intake, decreases energy intake¹², an effect opposite to that reported by Church *et al.*⁷ in mice overexpressing *Fto* systemically.

The data described above suggest opposing effects of *FTO* upregulation on energy intake in fat versus brain that cannot be resolved using a transgenic animal with generalized *FTO* overexpression. The generalized extreme overexpressor model may not reflect the molecular physiology of obesity in humans segregating for *FTO* alleles that predispose to obesity; it is possible, for example, that the functional variant(s) in humans result in subtly reduced *FTO* expression in the brain and subtly increased expression in fat or other tissues.

What about RPGRIP1L?

The SNPs associated with adiposity are part of a linkage disequilibrium block that includes parts of *FTO* intron 1, exon 2 and part of intron 2 (Fig. 1). Because no functionally significant sequence variants have been found in exon 2, it seems likely that the functional SNP(s) alter a regulatory element that controls transcription. *RPGRIP1L*, the retinitis pigmentosa GTPase regulator-interacting protein-1 like gene, is located ~100 bp 5' of and in the opposite transcriptional orientation as *FTO* and may also account for some or all of the region's association with adiposity. *RPGRIP1L* is a component of the basal body of the primary cilium and might participate in human energy homeostasis by virtue of the obesity phenotypes in Bardet-Biedl and Alström syndromes, in which all implicated genes encode components of the primary cilium¹³. The leptin (LEPR) and melanin-concentrating hormone 1 (MCHR1) receptors (both involved in the regulation of feeding and energy balance) localize in the vicinity of neuronal cilia^{4,14,15}, which may affect leptin and/or MCH signaling. Hypothalamic *Rpgrip1l* expression, as with *Fto*, is decreased with fasting⁴, consistent with a role in energy homeostasis. In addition, *FTO* and *RPGRIP1L* are co-regulated by CUX1 from a site within the DNA region associated with obesity (Fig. 1)⁴. Therefore, the function of both *FTO* and *RPGRIP1L* may be affected in individuals carrying the obesity risk allele, which may also partly explain the strength of the association.

Thus, the molecular basis for the association of SNPs in intron 1 of *FTO* with adiposity in humans remains unknown. It is plausible that the locus contains elements that mediate the regulation of both *FTO* and *RPGRIP1L* (and, possibly, other more distant genes) and that this regulation involves the hypothalamus, adipocytes and possibly other cell types involved in the regulation of body weight. Tissue-specific underexpression and overexpression of both genes will be required to work out the complex molecular physiology of *FTO*-associated obesity. The effort is likely to be rewarded by identification of new regulators of body weight.

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Figure 1.

Genomic organization of the *FTO* locus on chromosome 16 (16q12.2, at 52.3–52.4 Mbp). rs9939609, in linkage disequilibrium (LD) with rs8050136, is associated with body mass index (BMI) and is located in a 47-kb LD block. *FTO* is an AlkB-like demethylase with a strong preference for 3-methylthymidine (3-metT) in single-stranded nucleic acids. *RPGRIP1L* is a component of the basal body of the cilium. The leptin (*LEPR*) and melanin-concentrating hormone 1 (*MCHR1*) receptors localize to neuronal cilia. *CUX1*, which binds at rs8050136, regulates *FTO* and *RPGRIP1L* expression from a site located in the region of association in intron 1 of *FTO*. Not drawn to scale. Black boxes indicate exons