commentary

# The *FTO* (fat mass and obesity-associated) gene: big in adipocyte lipolysis?[1]

In the past year, genome-wide association studies have generated remarkable evidence that associates genetic variation at multiple regions of the genome with three quantitative traits that reflect obesity: increased body mass index (BMI), hip circumference, and weight. One of the strongest associations involves a variant residing at the *FTO* (for fat mass and obesity-associated) locus, designated the rs9939609 A-allele (1–3). In seven European populations, for example, this allele (frequency, 39%) was associated with a median increase in BMI of ~0.4 kg/m$^2$ ($P = 3 \times 10^{-35}$) plus an increased odds ratio (OR) of being overweight (OR = 1.18; 95% confidence interval = 1.13–1.24, $P = 1 \times 10^{-12}$) or obese (OR = 1.31; 95% confidence interval = 1.23–1.39, $P = 6 \times 10^{-16}$). Moreover, adults with two copies of the A-allele (~16%) weighed on average 3 kg more than those without the allele (1). These data have prompted a flurry of research into the biological function(s) of the *FTO* gene product(s). This research is considerably facilitated by prior cloning and annotation of the *FTO* gene in the course of investigating a mouse deletion syndrome that, in the heterozygous state, is manifested as fused toes and thymic hyperplasia (but not, as it happens, obesity) and as embryonic lethality in the homozygote state (4, 5).

In this issue of the *Journal of Lipid Research*, Wahlen, Sjolin, and Hoffstedt (6) report an association between the rs9939609 A-allele and variation in both the spontaneous release of glycerol from adipocytes in vitro ($P = 0.007$) and reduced plasma glycerol levels in vivo ($P = 0.037$). By way of biological support for the direct involvement of the *FTO* gene itself in obesity, they also show that *FTO* mRNA levels were higher in the adipose tissues taken from obese (BMI > 30 kg/m$^2$) compared with lean (BMI < 26 kg/m$^2$) women ($P = 0.002$) and that the expression of *FTO* is induced at an early stage of the adipocyte differentiation process. With these additional data, Wahlen, Sjolin, and Hoffstedt (6) suggest that *FTO* plays an important role in adipocyte lipolysis and that the association of the rs9939609 A-allele with obesity occurs, at least in part, through altered activity of this biochemical pathway. An important claim, so how might it fit into the bigger picture?

By analyzing purified adipocytes alongside intact adipose tissue, Wahlen, Sjolin, and Hoffstedt (6) show for the first time that *FTO* mRNA in subcutaneous adipose tissue is largely derived from fat cells per se, rather than from the microvascular cells and the other cell types that populate this tissue. Addressing the relationship between adipocyte ontology and *FTO* expression, they also show that cultured preadipocytes isolated from subcutaneous adipose tissue expressed higher levels of *FTO* mRNA at day 4 of their differentiation program compared with days 8 and 12 ($P = 0.004$). This intriguing observation raises such questions as whether the suppression of *FTO* expression aids the transformation of preadipocytes to fat-laden, mature adipocytes and, if so, by what mechanism.

The rs9939609 variant resides within the first intron of the *FTO* gene; therefore, the expectation is that the rs9939609 A-allele (or an associated variant in this intron) exerts its functional effect through the altered expression of *FTO* mRNA. However, Wahlen, Sjolin, and Hoffstedt (6) found no relationship between the *rs9939609* genotype and adipose tissue *FTO* mRNA levels in women when expression values were adjusted for the covariate BMI ($P = 0.21$). Although negative, this finding is of interest, because it might indicate that the influence of the *FTO* A-allele [or allele(s) in linkage disequilibrium] on spontaneous adipocyte lipolysis is mediated by an as yet unidentified *FTO* transcript; or indirectly through mechanisms such as appetite/satiety, endocrine, automatic nervous system, or exercise tolerance; or a combination of any/all of these. Regarding the first possibility, it is tantalizing that the rs9939609 A variant (and 40+ associated alleles) resides within an ~105 kb intron of arguably sufficient length to encode multiple isoforms of *FTO* mRNA, short transcripts that reduce the translation efficiency of *FTO* mRNA species, and even a novel small gene whose perturbed expression accounts for the association of the *rs9939609* A-allele with impaired spontaneous adipocyte lipolysis. It might also be pertinent that *FTO* has a very close neighbor, the primary cilia and centrosome gene *RPGRIP1L* (7), and that these two genes display very similar expression profiles (1). As such, it is conceivable that the first intron of *FTO* might contain *cis*-acting elements that affect the expression of not only *FTO* but also of *RPGRIP1* and that it is this that provides the mechanism for the association of the *rs9939609* A-allele [or allele(s) in linkage disequilibrium] with impaired adipocyte lipolysis and obesity-related traits.

Importantly, there are data to suggest that the *rs9939609* A-allele [or allele(s) in linkage disequilibrium] could influence adipocyte biological behavior via neural circuitry

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[1] See referenced article., *J. Lipid Res.* 2008, 49: 607–611.

(1, 8). Thus, *FTO* is most highly expressed in the brain, particularly in the hypothalamus, a functionally and neuroanatomically complex brain structure concerned with the regulation of arousal, appetite, temperature, autonomic function, and endocrine systems, among other things. Pertinently, mice fasted for 48 h display a specific reduction in *FTO* mRNA expression in the arcuate nucleus of the hypothalamus (8), which is thought to be one of the most important nuclei involved in appetite control (9).

In summary, it must be stressed that obesity is an etiologically complex state reflecting the outcome of variations in a number of biochemical, physiological, and behavioral systems, some causal but, no doubt, others compensatory. As such, the data of Wahlen, Sjolin, and Hoffstedt (6) will require confirmation in data sets of similar and differing ethnic origins, plus additional experimental data to help confirm and define more fully the role of *FTO* in adipocytes and elsewhere. This journal keenly awaits studies that define the identity of the causal allele or alleles within the first intron of *FTO* that confer susceptibility to obesity, as well as its/their molecular mode of action. Such studies might also include relating the substrate specificity of the putative nucleic acid demethylase activity of the *FTO* gene product (8) to both adipocyte and hypothalamic biochemistry and cell biology.

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