Commentary

MOLECULAR METABOLISM

Human obesity: FTO, IRX3, or both?[a]

Jonathan Cedernaes*, Christian Benedict

Until recently, evidence was lacking for an enhanced gene expression of the fat mass and obesity (*FTO*) gene in humans who carry obesity-susceptible genetic variants in *FTO*. By using a data set of 153 cerebellar brain samples from individuals of European ancestry, Smemo and colleagues have now demonstrated that carriers of common single nucleotide polymorphisms in the *FTO* gene exhibit a higher cerebellar expression of the homeobox gene *IRX3* [1]. They further demonstrated that the obesity-associated noncoding sequences within *FTO* are functionally connected, at megabase distances, with *IRX3*. In contrast, in this study of cerebellar samples, *FTO* gene expression did not differ between *FTO* genotypes. Additional genetic experiments revealed that global *Irx3* deficiency led to a ~30% body weight reduction in mice [1]. At first glance, these findings argue against a contribution of increased central nervous system *FTO* expression to obesity in carriers of common obesity susceptible single nucleotide polymorphisms (SNPs) within *FTO*, as previously suggested by findings from genetic animal studies (systematically reviewed in Ref. [2]). Instead, these results suggest that overexpression of *IRX3* as a functional long-range target of obesity-associated variants within *FTO* might drive weight gain and the development of overweight and obesity in carriers of common single nucleotide polymorphisms in the *FTO* gene. However, some important points require more detailed discussion. It should be borne in mind that the studied brain region — the cerebellum — is not primarily involved in food intake or appetite regulation. This is however certainly the case for the brainstem and the hypothalamus, and it was in this latter region that Smemo and colleagues found *Irx3* expression to play a role for the metabolic parameters regulated by this gene [1]. *Fto* is however also highly expressed in especially the hypothalamus and its arcuate, paraventricular, dorsomedial and ventromedial nuclei [3], all of which are recognized to be much more highly involved in the regulation of appetite and energy metabolism than the cerebellum. It is possible that *FTO* expression in humans in *e.g.* these regions of the hypothalamus, and/or brainstem — regions in which *Fto* expression in animal models furthermore has been shown to be implicated in feeding condition and regulation of energy expenditure (systematically reviewed in Ref. [2]) — could be differentially regulated depending on *FTO* genotype. These data suggest that the function of *Fto* expression may function in a site dependently manner, as global overexpression of *Fto* has been shown to cause hyperphagia [4]. Other studies however suggest that *Fto* protein and gene expression in the brain at least in mice is uniform across *e.g.* the cerebellum and hypothalamus — furthermore being unaffected by short-term fasting [5]. Against this background, further studies are needed where human brain samples covering extra-cerebellar brain regions are utilized — *e.g.* prefrontal brain regions involved in the inhibitory control of food intake [6] — until the conclusion can be drawn as to the role of the *FTO* gene expression in relation to *FTO* polymorphisms.

Interestingly, a dynamic phenotype depending on *FTO* genotype is also supported in humans by studies using functional magnetic resonance imaging (fMRI). For instance, in a study of healthy participants utilizing fMRI to examine the brain response post-glucose ingestion, Heni and colleagues found significant *FTO*-genotype dependent differences in the prefrontal cortex [7], a brain region highly involved in inhibitory control, comprising that on food intake [6]. Moreover, another fMRI study found that homozygous carriers of the common *FTO* rs9939609 risk *A* allele exhibited an altered brain response to postprandially suppressing circulating acyl-ghrelin when exposed to food cues [8], especially in regions coupled with reward and appetite regulation. In contrast to these studies following behavioral or physiological interventions, the cerebellar *IRX3* and *FTO* expression in the study of Smemo and colleagues was only studied under basal conditions [1], which furthermore could also be related to the post-mortem analysis, as opposed to an in vivo or near real-time acute change. A hypothesis could therefore be that such differential effects may be evident for *FTO* expression depending on its polymorphism under more dynamic settings, such as following food cue exposure or longer dietary interventions, which would also be supported by the aforementioned animal studies and human brain imaging studies.

Another finding of the study by Smemo and colleagues warrants additional attention. Although no differences in central nervous system FTO gene expression between FTO genotypes in the cerebellum were found, there was indeed inter-individual variance in the FTO expression in this examined brain region [1]. Previous studies in mice have shown that the CNS expression of *Fto* can be weakened by exercise protocols [9]. This may also explain why population-based studies have shown that regular exercise attenuates the strength of the association between genetic variants in *FTO* and human obesity [10]. Thus, the findings described by Smemo et al. [5], albeit intriguing, do not provide conclusive evidence against a contribution of central nervous system *FTO* expression to the risk to develop obesity in carriers of common obesity-susceptible genetic variants within *FTO*. It cannot be ruled out

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Department of Neuroscience, Uppsala University, Box 593, 751 24 Uppsala, Sweden

*Corresponding author. Tel.: +46 184714102; fax: +46 18511540. E-mail: jonathan.cedernaes@neuro.uu.se (J. Cedernaes).

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that the differences in central nervous system *FTO* expression between human *FTO* risk allele carriers and non-carriers might have been masked by inter-individual differences in lifestyles, *e.g.* engagement in regular exercise activities.

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