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OBESITY

BMI-associated genetic variants in *FTO* mastermind *IRX3* expression

The introns of the *FTO* gene contain long-range *IRX3* enhancers, shows a recent study published in *Nature*. The new findings challenge the established view of *FTO* as the major genetic factor associated with risks of obesity and type 2 diabetes mellitus (T2DM).

Genetic variants in introns 1 and 2 of *FTO* have been associated with the risks of obesity and T2DM, but the functional link mediating this association was unclear. The hypothesis that enhancers within *FTO* are in fact *IRX3* enhancers had been previously suggested; in this new study, "we were able to directly test this hypothesis in multiple ways," says senior researcher Marcelo Nóbrega (University of Chicago).

Nóbrega and colleagues used chromatin conformation capture techniques to investigate how the intronic regions of *FTO* interact with other genomic regions in mice, humans and zebrafish. The researchers uncovered a direct interaction between BMI-associated *FTO* noncoding sequences and *IRX3*. They also found that BMI-associated single nucleotide polymorphisms in *FTO* introns were associated with the expression of *IRX3*, not *FTO*, in human brain samples. Finally, the team observed that *Irx3*-deficient mice are 20–30% leaner and have higher metabolic rates than wild-type mice.

"We are interested in understanding what genetic programs are regulated by IRX3 in the brain and other tissues, and how these programs regulate various aspects of metabolism," comments Nóbrega. "Our hope is that once we understand the mechanisms by which IRX3 controls metabolism we may identify targets for therapeutic development."

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Original article Smemo, S. *et al.* Obesity-associated variants within *FTO* form long-range functional connections with *IRX3*. *Nature* doi:10.1038/nature13138