Rethinking genetic links to obesity: IRX3 is likely the 'fat gene'

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This is an image of a weight scale. Credit: CDC/Debora Cartagena

Mutations within the gene FTO have been implicated as the strongest genetic determinant of obesity risk in humans, but the mechanism behind this link remained unknown. Now, an international team of scientists has discovered that the obesity-associated elements within FTO interact with IRX3, a distant gene on the genome that appears to be the functional obesity gene. The FTO gene itself appears to have only a

peripheral effect on obesity. The study appears online March 12 in *Nature*.

"Our data strongly suggest that IRX3 controls body mass and regulates body composition," said senior study author Marcelo Nobrega, PhD, associate professor of human genetics at the University of Chicago. "Any association between FTO and obesity appears due to the influence of IRX3."

Mutations to introns (noncoding portions) of the gene FTO have been widely investigated after genome-wide association studies revealed a strong link between FTO and obesity and diabetes. Yet overexpressing or deleting FTO in animal models affects whole body mass and composition, not just fat, and experiments have failed to show that these obesity-linked introns affect the function of the FTO gene itself.

Hoping to explain these observations, Nobrega and his team mapped the behavior of promoters—regions of DNA that activate gene expression—located within one million base pairs on either side of the FTO gene. In adult mice brains, where FTO was thought to affect metabolic function, they discovered that the promoter that turns on FTO did not interact with obesity-associated FTO introns.

"Instead, we found that the promoter for IRX3, a gene several hundred thousand base pairs away, did interact with these introns, as well as a large number of other elements across the vast genetic distance we studied," said co-author Jose Luis Gomez-Skarmeta, PhD, a geneticist at the Andalusian Center of Developmental Biology in Sevilla, Spain. The researchers found a similar pattern of interactions in humans after analyzing data from the ENCODE project, which they confirmed with experiments on human cells.

Using data from 153 brain samples from individuals of European

ancestry, they discovered that the mutations to FTO introns that affected body weight are associated with IRX3 expression, but not FTO. Obesity-related FTO introns enhanced the expression of IRX3, functioning as regulatory elements. The FTO gene itself did not appear to play a role in this interaction.

"Regulatory elements are switches that turn genes on and off. What we've found is that the switches that control IRX3 are far away from the gene and actually inside the FTO gene", says Nobrega.

To verify the role of IRX3, the researchers engineered mice without the IRX3 gene. These mice were significantly leaner than their normal counterparts. They weighed about 30 percent less, primarily through reduced fat.

The decrease in weight gain occurred despite normal levels of food consumption and physical activity. When fed a high-fat diet, mice without IRX3 retained the same weight and fat levels as on normal diets. Normal mice fed a high-fat diet gained almost twice as much weight. Fat cells in IRX3-deficient mice were smaller, and increased levels of brown fat were observed. In addition, these mice were better able to process glucose.

"These mice are thin. They lose weight primarily through the loss of fat. But they are not runts," said co-author Chin-Chung Hui, PhD, professor of molecular genetics at the University of Toronto. "They are also completely resistant to high-fat diet-induced obesity. They have much better ability to handle glucose, and seem protected against diabetes."

The researchers also discovered that mice with altered IRX3 function in the hypothalamus, the portion of the brain known to regulate feeding behavior and energy expenditure, showed an identical pattern of leanness as mice which completely lacked IRX3. Hypothalamic function of

IRX3, therefore, appears to control body mass and composition in these animals, indicating that the genetic predisposition to obesity is wired in the brain.

IRX3 codes for a protein that regulates other genes, and is present both in and outside the brain, in organs and cells such as fat cells. Nobrega and his team are currently investigating how IRX3 interacts with genes and molecules that it regulates, and hope to identify targets for the development of novel therapies against obesity and diabetes.

"IRX3 is probably a master regulator of genetic programs in the cells where it is expressed," Nobrega said. "We're interested in what its targets are and what they alter. The goal is to identify downstream targets of IRX3 that become models for drug targeting."

More information: "Obesity-associated variants within FTO form long-range functional connections with IRX3," *Nature*, dx.doi.org/10.1038/nature13138

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