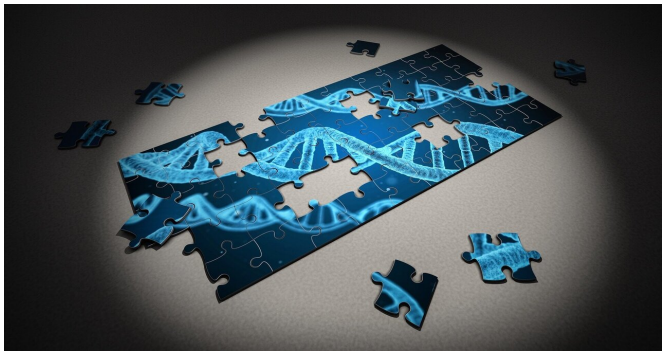
Expression of 'fat' genes correlate with metabolic, behavioral changes linked to obesity

3 June 2021



Credit: CC0 Public Domain

A collection of genetic variants influences the expression of obesity-associated genes in both the brain and fat tissue, according to a new study from researchers at the University of Chicago. The research team found that changes in the expression of the obesity-associated genes correlated with both metabolic and behavioral changes, suggesting that these variants produce combinatorial effects that increase the risk of obesity. The results, which scientists hope will lead to better understanding of the mechanisms that make some people more susceptible to obesity, were published June 4 in *Science*.

The strongest genetic association with obesity in humans corresponds to a group of genetic variants within a gene called FTO. Over 40% of humans have one copy of these variants and 16% have two copies, which increase their risk of becoming obese by 70%. Despite their prominent impact, the mechanisms by which these common variants lead to obesity remain unclear.

"Other research groups had shown that a single variant might influence the metabolism of fat cells, and how much fat they actually store, while our previous studies suggested variants in FTO influence the function of a portion of the brain called the hypothalamus, which contains neural circuitry known to regulate obesity," said senior author Marcelo Nóbrega, MD, Ph.D., Professor of Human Genetics at UChicago. "We were puzzled by this discrepancy and wanted to dissect the mechanism behind this FTO variant."

The authors first found that the genetic variants within the FTO gene physically interacted with two other genes, IRX3 and IRX5, suggesting that these genes mediated the risk to obesity.

"We engineered mice that lacked Irx3 and Irx5 and found that the mice were leaner," said co-author Ivy Aneas, Ph.D., a research associate professor in the Nóbrega group. "This provides additional evidence that these genes are connected to obesity risk."

Because it had previously been suggested that FTO variants could affect either fat tissue or the hypothalamus, the research team wanted to understand whether IRX3's and IRX5's expression was affected by the FTO variants in either tissue.

"We generated a mouse that lacked the obesity-associated region in FTO, allowing us to follow the animal's development over time and ask where and when these variants were potentially affecting Irx3 and Irx5 expression," said first author Débora R. Sobreira, Ph.D., post-doctoral researcher in the Nóbrega group.

The investigators found that the expression of Irx3 and Irx5 were reduced both in fat tissue and hypothalamus, but only at embryonic stages, not in adult tissue. Similar results were also seen in experiments in cultured human hypothalamic neurons.

While the research team had uncovered how the FTO variants affect IRX3 and IRX5 expression, they still wanted to know the effect of changing the expression of these genes. IRX3 and IRX5 were already known to regulate the metabolism of fat cells, suggesting one possible mechanism behind the obesity association. To understand the role of these genes in the hypothalamus, the researchers used the mice they had made that lacked Irx3 and asked whether these mice had different feeding behaviors.

"To our surprise, we found that these mice had a reduced preference for sweet foods, which had not been described before," said Nóbrega. "But we wanted to know: what does this mean for humans?"

Using data from 23andMe, a popular genetic testing service, the researchers found that the obesity-associated variants in FTO are also a strong predictor of sweet preference in humans.

"The final step was understanding the disparate metabolic and behavioral functions of these variants," said Nóbrega. "Work from Débora showed that this FTO genomic region actually contains multiple independent variants that are all inherited together, and they each affect the expression of IRX3 and IRX5 in fat tissue and the hypothalamus, leading to differences in both metabolism and food preference. Essentially, the adult obesity phenotype is a manifestation of multiple combinatorial effects established early during development."

To Nóbrega, the collaborative nature of this work was particularly important.

"Melina Claussnitzer of the Broad Institute of MIT and Harvard, who is also an author on this paper, had originally proposed a metabolic mechanism in fat tissue for a variant in the FTO gene while we and others had implicated the hypothalamus as a determinant of obesity risk," said Nóbrega. "This collaboration let us realize that in fact, everyone was right. We would not have solved this problem without our teaming up."

Future work will try to further understand the role of IRX3 and IRX5 in the brain.

"These genes are actually even more highly expressed outside of the hypothalamus than they are in the hypothalamus," said Nóbrega. "It wouldn't be surprising that other areas of the brain are also involved, and we are interested in understanding if there are additional new mechanisms that the FTO variants are involved in throughout other brain regions."

More information: "Extensive pleiotropism and allelic heterogeneity mediate metabolic effects of IRX3 and IRX5" *Science* (2021). science.sciencemag.org/cgi/doi … 1126/science.abf1008

Provided by University of Chicago Medical Center