Study uncovers gene that may strongly influence obesity

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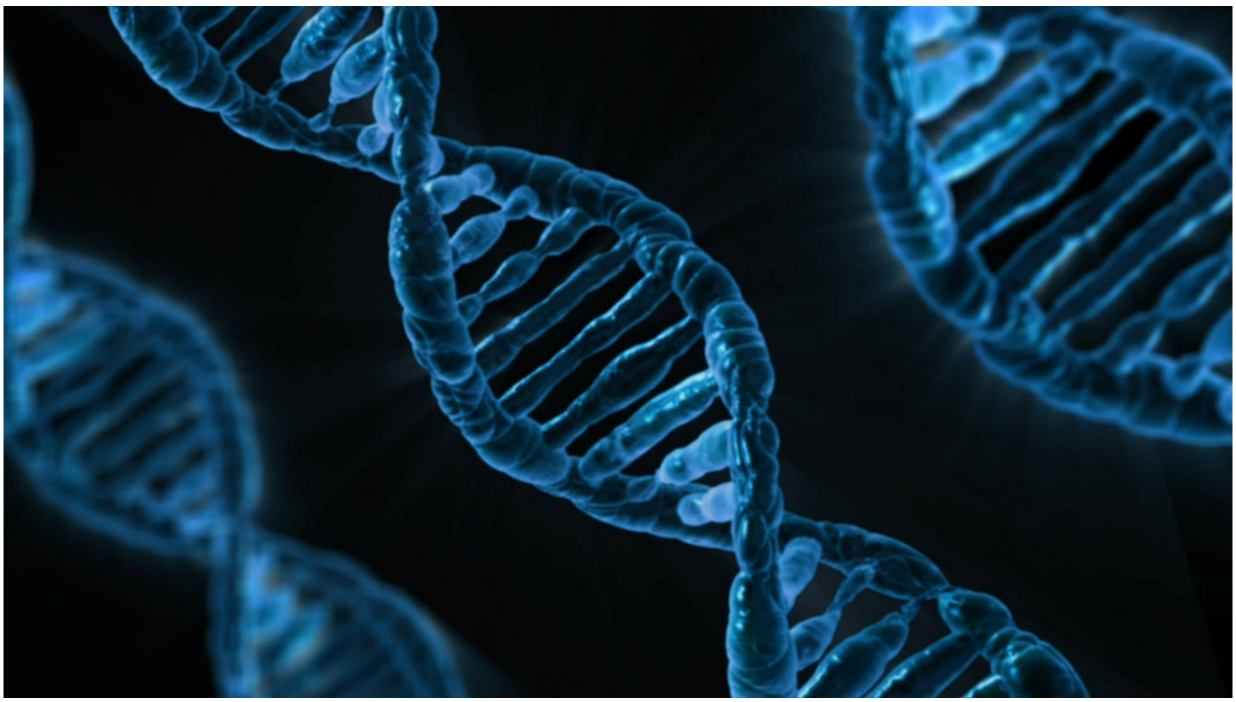

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A University of Toronto (U of T) study on fruit flies has uncovered a gene that could play a key role in obesity in humans.

The paper published online this month in *Genetics* examines a "foraging gene" humans share in common with the flies, which plays multiple roles and is found in similar places, such as the nervous system, in the muscle and in fat.

"What our study does is nails the gene for being very important for the traits of moving, feeding and fat storage," says University Professor Marla Sokolowski of the Department of Ecology & Evolutionary Biology (EEB) in U of T's Faculty of Arts & Science.

In nature, fruit flies called "rovers" with high amounts of the gene tend to move a lot, eat very little and stay lean, while flies with low amounts of for called "sitters" are the opposite. The foraging gene encodes a cell signalling molecule called a cGMP dependent protein kinase.

The same could apply to obesity in humans.

"When we say the foraging gene is the same, what we're saying is that when you look at the DNA sequences of the human and the fly there is a lot of similarity, enough that you can see it's the fly version of the gene that the human has," says Sokolowski.

"So you could imagine if you are a fly, preferences for sugar, the tendency to store a lot of fat and the tendency to move less could all be contributing to the likelihood of being more obese if you have low levels of this gene, or to be leaner if you have higher levels."

Such similarities between species are known as orthologs, meaning they are genes that evolved from a common ancestor eons ago.

When scientists first started mapping human genomes and comparing them to other organisms, they were shocked to discover humans don't have that many more genes than flies do.

Sokolowski says the research is another part of the puzzle, and the beginning of our understanding of how what was once considered "junk

DNA" is actually very important for regulating key characteristics such as behaviour and metabolism.

"No one has analyzed it in the way we have in flies, but it's a hint from the fly. The fly has been an excellent model organism to understand mammalian behaviour and metabolism, and so this work can point to places to look further in humans," says Sokolowski.

The study involved a technique called recombineering to manipulate DNA at the molecular level, so as to remove and then reinsert the gene in various doses to see the effects on behaviour and metabolism.

Lead author Aaron Allen was a PhD student in cell & systems biology at U of T when the work was done, and he was assisted by Sokolowski, fellow EEB student Ina Anreiter, and Oxford University collaborator Megan Neville, who taught Allen the technique.

"This kind of work is actually so cutting-edge that it takes a really good student to learn how to do this and then bring the technique back to the lab," says Sokolowski.

"To be able to take a gene of this large size and complexity and put it back in the fly so that it works is almost at the edge of what is possible."

Sokolowski says it's particularly interesting that one gene should have multiple roles in feeding and obesity in the body, a characteristic known as pleiotropy.

The next question would be how exactly it plays multiple roles. "Lots of genes have multiple roles, but the idea here is that this gene may be involved in the coordination of roles in traits important for feeding and obesity."

"We don't know much about pleiotropy, or how it happens, or how it's regulated at the level of the molecules. So this sets the groundwork to be able to look at that in detail."

More information: Aaron M. Allen et al, Feeding-Related Traits Are Affected by Dosage of theGene in, *Genetics* (2017). DOI: 10.1534/genetics.116.197939

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