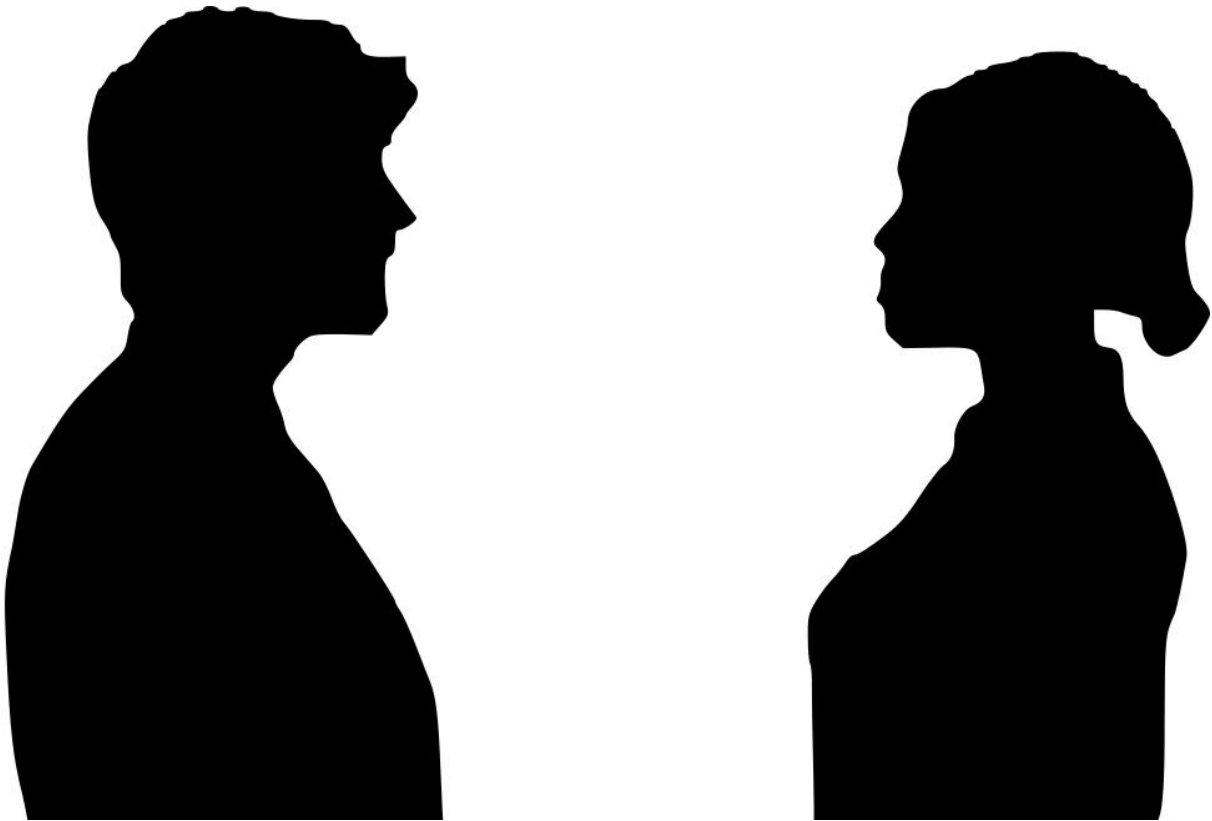


Genes that may predict complications from obesity differ between the sexes

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Obesity causes many health problems and worsens several chronic illnesses, including type 2 diabetes and cardiovascular disease. However, some obese people are more susceptible to complications than others.

Scientists have long been searching for genes linked to obesity that predispose people to such conditions, but zooming in on hundreds of leads to identify genes that may increase risk has been difficult.

In a new study published February 16, 2023, in *Nature Genetics* titled "Genetics of sexually dimorphic adipose distribution in humans," researchers from the University of Chicago characterized the impact of a genetic variant associated with a higher waist-to-hip ratio, a measure of abdominal fat, that is necessary for formation of fat cells in humans.

This variant is also associated with higher cholesterol and triglyceride blood levels in [women](#), but not men, and it contributes to excess fat accumulation as the result of diet in female mice, but not males, suggesting that similar [genes](#) might lead to different patterns of fat distribution and obesity-related disease risk for women.

"We think about obesity as a primary disease or the source of morbidity, but what obesity actually does is that it favors the appearance of cardiovascular and metabolic diseases like diabetes, heart attacks, and hypertension," said Marcelo Nobrega, MD, Ph.D., Professor of Human Genetics at UChicago and senior author of the study. "These are all related, but the baffling part is that not all [obese people](#) develop these kinds of complications."

Why distribution of fat matters

The distribution of fat on the body seems to play an important role in the development of disease. More fat deposited in the abdomen and around vital organs has been linked to increased insulin resistance and inflammation, and predicts a higher risk of [cardiovascular disease](#), kidney failure, and stroke. The amount of abdominal fat is commonly measured by the waist-to-hip ratio, which divides a person's waist measurement by hip measurement. Ratios of .99 or lower for men and

.90 or lower for women are considered healthy.

In the new research, Nobrega's team conducted several transcriptome-wide association studies (TWAS) that compared the genomes of hundreds of individuals to identify genes that are linked with obesity and a higher waist-to-hip ratio. The ratio is what is called a sexually dimorphic trait, meaning that it appears differently in males and females. Men and women naturally have different ratios, and the silhouette of an average man's body is different from that of a woman.

The [genetic analysis](#) found 91 genes that help regulate fat distribution primarily in women. Most of the genetic variants associated with these genes don't alter sequence of the genes that code for proteins—instead, they occur in noncoding regions that are believed to control where and how much a gene is expressed.

Interestingly, most of these variants are in a class of DNA elements called Alu repeats or retrotransposons, which are remnants of ancient viral infections that were integrated into the human genome and maintain hundreds of thousands of copies today, making up almost half of the noncoding human genome.

"We once assumed that most of these were archaeological sites of battles that happened in the past between our genome and that of viruses. But then over the years, people started to realize that a lot of these DNA sequences that came from viruses have actually become functional in the [human genome](#)," Nobrega said.

Jumping genes for metabolic health

These so-called "jumping genes" may have wired fat distribution patterns in humans, with implications for metabolic health in women. The researchers next focused on a gene called SNX10, which was most

strongly associated with the waist-to-hip ratio in women but not in men. They found that SNX10 controls the ability of adipocytes, or fat cells, to accumulate lipids and fat deposits. In a [mouse model](#), when the researchers knocked out SNX10 in the adipocytes, [female mice](#) did not become obese when fed a high-fat diet, while males did.

The team also searched the UK Biobank, a GWAS database containing more than 700,000 genomes, and found that not only is SNX10 linked to a higher waist-to-hip ratio in women, but it is also associated with higher levels of cholesterol and triglycerides, which are commonly associated with cardiovascular disease.

"We have now identified a gene, out of the hundreds of genes that are involved in fat accumulation or obesity, that may be more likely to cause disease complications and, interestingly, it does so primarily in women" Nobrega said. "That's what we were aiming for."

The next step, Nobrega said, is to dig into the biology of SNX10 and other genes like it to understand how it has these effects on the metabolism, and perhaps one day make it a target for treatment.

"We have too many genes associated with diseases, and one of the challenges is to sift through those and find ones that are most likely to be credible targets," he said. "Now, we think the road that led us to find SNX10 is a good way to identify other genes that are likely to be amenable to therapeutic development."

More information: Grace Hansen, Genetics of sexually dimorphic adipose distribution in humans, *Nature Genetics* (2023). [DOI: 10.1038/s41588-023-01306-0](https://doi.org/10.1038/s41588-023-01306-0).
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