Researchers discover DNA variants significantly influence body fat distribution

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A new breakthrough from the Genetic Investigation of Anthropometric Traits consortium, which includes many public health researchers from the University of North Carolina at Chapel Hill, identifies multiple

genetic variants associated with how the body regulates and distributes body-fat tissue. The new findings broaden the understanding of how genes can predispose certain individuals to obesity.

The GIANT Consortium is a major international collaboration of more than 275 scientists that seeks to identify genetic sites that affect human body size and shape, including height and measures of obesity.

Kari E. North, professor of epidemiology at the University of North Carolina at Chapel Hill Gillings School of Global Public Health, is joint lead author of the new study, "Protein-Coding Variants Implicate Novel Genes Related to Lipid Homeostasis 1 Contributing to Body Fat Distribution," published February 18 in *Nature Genetics*.

Other co-authors from the UNC Gillings School include assistant professor Kristin Young, assistant professor Misa Graff, and postdoctoral fellow Heather Highland, all in the UNC Gillings School's department of epidemiology.

Identifying the genetic variants associated with obesity is central to developing targeted interventions that can reduce the risk of chronic illnesses, such as hypertension, type 2 diabetes, and heart disease, to which obesity contributes in significant ways. Genome-wide association studies previously identified 49 loci, or positions along a chromosome where the related genetic variants are located, that predispose individuals to a higher waist-to-hip ratio, which is a way to assess body-fat distribution. Lower values of WHR are associated with lower incidence of these diseases.

In this study, with a specific focus on coding variation, the team found 24 coding loci—15 common and nine rare—along the chromosomes of individuals that predispose to higher WHR. Further analysis revealed pathways and gene sets that influenced not only metabolism but also the

regulation of body fat tissue, bone growth and adiponectin, a hormone that controls glucose levels and breaks down fat.

The team also performed functional studies across other organisms and identified two genes that were associated with a significant increase in triglyceride levels and body fat across species.

"For the first time, we were able to examine, on a large scale, how low-frequency and rare variants influence body fat distribution," said Kari E. North. "These variants are rarer in the population, but the effects they have on individuals are much larger, possibly making them more clinically relevant."

Another major finding from this study is the importance of lipid metabolism to bodyfat distribution, which could lead to a better understanding of how obesity causes downstream diseases such as Type 2 diabetes and cardiovascular disease.

"A better understanding of the genetic underpinnings of body fat distribution may lead to better treatments for obesity and the cascade of downstream diseases obesity also impacts, for example type 2 diabetes and heart disease" North said.

More information: Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body-fat distribution, *Nature Genetics* (2019). DOI: 10.1038/s41588-018-0334-2

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