Largest ever genome-wide study strengthens genetic link to obesity

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

There are many reasons why people gain different amounts of weight and why fat becomes stored in different parts of their bodies. Now researchers are homing in on genetic reasons. Their findings, part of the largest genome-wide study to date, were published in two companion papers today in the journal *Nature*.

By analyzing genetic samples from more than 300,000 individuals to study obesity and body fat distribution, researchers in the international Genetic Investigation of Anthropometric Traits (GIANT) Consortium completed the largest study of genetic variation to date, and found over 140 locations across the genome that play roles in various obesity traits.

By applying novel computational methods to the genetic results, they discovered new biological pathways that are important in controlling body weight and fat distribution.

This work is the first step toward finding individual genes that play key roles in body shape and size. The proteins these genes help produce could become targets for future drug development.

Obesity is a global public health burden that affects millions of people. Yet, there are no long-term treatments.

Waist-to-hip ratios key for health risk

One paper focused on where fat is stored in the body, one determinant of health risk. One of the observable traits linked to the genetic locations was waist-to-hip circumference ratio. People with waistlines larger than hip circumferences have more belly fat surrounding their abdominal organs. This makes them more likely to have metabolic conditions, such as type-2 diabetes, and cardiovascular problems than do people with body fat concentrated more in the hip area or distributed equally throughout the body.

"We need to know these genetic locations because different fat depots pose different health risks," says Karen Mohlke, Ph.D., professor of genetics at the University of North Carolina School of Medicine and senior author of the paper that examined waist-to-hip ratio of fat distribution. "If we can figure out which genes influence where fat is deposited, it could help us understand the biology that leads to various health conditions, such as insulin resistance/diabetes, metabolic syndrome, and heart disease."

The genetic locations associated with fat depots are associated with genes previously identified as being important for the creation of adipose tissue. Researchers also determined that 19 of the fat distribution genetic locations had a stronger effect in women; one had a stronger effect in men.

"By finding genetic variants that play an important role in influencing body fat distribution and the ways in which fat distribution differs between men and women, we hope to zoom in on the crucial

underlying biological processes," says Cecilia Lindgren, Ph.D., senior author and scholar in residence at the Broad Institute of MIT and Harvard and a professor at the University of Oxford.

BMI linked to genetic factors and new biology

In the *Nature* paper focusing on body mass index (BMI), researchers identified 97 genome-wide regions that influence obesity, a finding that tripled the number of previously known regions.

"Our work clearly shows that predisposition to obesity and increased BMI is not due to a single gene or genetic change," says Elizabeth Speliotes, M.D., Ph.D., M.P.H., assistant professor of internal medicine, assistant professor of computational medicine and bioinformatics at the University of Michigan Health System and senior author of the BMI paper.

"The large number of genes makes it less likely that one solution to beat obesity will work for everyone and opens the door to possible ways we could use genetic clues to help defeat obesity," she says.

Further, the researchers found that the genetic locations associated with BMI are likely involved in neural processes, specifically brain signaling, that control appetite and energy use.

"Using novel computational methods, we have pointed to new biological pathways that act in the brain to regulate overall obesity, and also to a different set of pathways related to fat distribution that regulate key metabolic processes," says senior author Joel Hirschhorn, M.D., Ph.D., Concordia professor of pediatrics and professor of genetics at Boston Children's Hospital and Harvard Medical School, and co-director of the Broad Institute Metabolism Program.

Once better understood, these mechanisms may not only help to explain why not all of those who are obese develop related metabolic diseases, such as diabetes and high cholesterol, but could lead to possible ways to treat obesity or prevent metabolic diseases in those who are already obese.

The researchers note that while some genes involved in obesity could already have been implicated in other aspects of human health, others could be part of novel pathways that are not yet understood. A better understanding of their functions related to body fat and obesity could provide a better picture of the roles these genes play in a variety of diseases.

"Finding the genes that increase risk of obesity is only the end of the beginning," says senior author Ruth Loos, Ph.D., professor of preventive medicine at Mt. Sinai Hospital, and director of the Genetics of Obesity and related Metabolic Traits Program in the Charles Bronfman Institute for Personalized Medicine.

"A major challenge now is learning about the function of these genetic variations and how they indeed increase people's susceptibility to gain weight," Loos says. "This will be the critical next step, which will require input from scientists with a range of expertise, before our new findings can be used towards targeted obesity prevention or treatment strategies."

More information: New genetic loci link adipose and insulin biology to body fat distribution, dx.doi.org/10.1038/nature14132

Genetic studies of body mass index yield new insights for obesity biology, dx.doi.org/10.1038/nature14177

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