Large-scale study to pinpoint genes linked to obesity

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It's not just diet and physical activity; your genes also determine how easily you lose or gain weight. In a study published in the January issue of *Nature Genetics*, researchers at the Icahn School of Medicine at Mount Sinai and other institutions of the Genetic Investigation of Anthropometric Traits (GIANT) consortium found 13 genes that carry variations associated with body mass index (BMI). This was the first large-scale study to pinpoint genetic variations that may directly impact

the function of the genes.

In the past decade, researchers in the GIANT consortium have performed genome-wide screens in hundreds of thousands of individuals to identify genetic variations associated with obesity and BMI. Until now, the genetic variations they identified were merely "flags" on the genome that highlighted DNA sequences of interest. In this new study, however, the consortium focused on a specific set of genetic variations that are likely to affect the function of genes and their proteins—an approach that expedited the discovery of the causal genes that affect body weight.

Led by Ruth Loos, PhD, professor at The Charles Bronfman Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai, and Joel Hirschhorn, MD, PhD, 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, the study was an international collaboration involving more than 250 research institutions. Genetic data from more than 700,000 individuals and 125 different studies were combined to form the largest genetic association study to date. The researchers identified 14 genetic variations in 13 genes, including a risky copy variation - a phenomenon in which sections of the genome are repeated - that causes carriers to weigh 15 pounds more, on average, than individuals who do not carry the variation. The gene is called MC4R and approximately 1 in 5,000 individuals carries this risk copy, which causes the gene not to produce any of the protein needed to inform the brain to stop eating. While this variant was identified two decades ago in individuals with extreme and early-onset obesity, the new study shows that it also affects body weight in the general population. Furthermore, the researchers identified two variants that may affect the function of a gene called GIPR. Approximately 1 in 400 individuals carries a protective copy of either variant and they tend to weigh an average of 4.5 pounds less than non-

carriers. Eight of the 13 genes identified were newly implicated in obesity and will require further follow-up to understand the mechanisms through which they affect body weight.

"Our study has identified genes that play a crucial role in the neuronal control of body weight. They act in the brain in pathways that may affect people's food intake, hunger, satiety, etc. Individuals who inherit these genetic variations may find it harder to eat less or stop eating, as compared to those who did not inherit these variations," said Dr. Loos. "It is also the first time a genetic association study for BMI identifies genes that act in pathways that affect energy expenditure and fat cell biology."

The investigators used computational analysis to further hone in on genes that likely play a key role in obesity. "By considering the genes as a group rather than one-by-one, we could highlight specific genes that both had strong support from genetics and that likely carry out functions that we predict to be important in controlling body weight," said Joel Hirschhorn, MD, PhD, Concordia Professor of Pediatrics and Professor of Genetics at Boston Children's Hospital and Harvard Medical School, Co-Director of the Metabolism Program at the Broad Institute and the GIANT consortium.

By knowing the genes and the biological pathways through which they work, researchers believe they are a few steps closer to understanding why some people gain weight more easily than others, which is critical for developing effective treatments.

"Our study has provided new potential targets for therapeutic interventions, and may even help personalize treatment for carriers of the genetic variations. While we are a few steps closer to understanding the biology of why some people gain or lose weight more easily than others, further research on each of the identified genes is needed to

understand the mechanisms trough which they act," noted Dr. Loos.

Other institutions involved in this study include the Eli and Edythe L. Broad Institute of the Massachusetts Institute of Technology and Harvard. Financial support for the international collaboration was provided in part by the National Institutes of Health.

More information: undefined undefined et al. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity, *Nature Genetics* (2017). DOI: 10.1038/s41588-017-0011-x

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