

Genetic variants that protect against obesity could aid new weight loss medicines

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Around four million people in the UK carry genetic variants that protect them from obesity, type 2 diabetes and heart disease, suggests new research from the University of Cambridge. The team say the discovery could lead to the development of new drugs that help people lose weight.

Scientists have known for several years that genes can influence a person's weight. One of the genes that is known to play a key role in regulating weight is MC4R, which codes for the melanocortin 4 receptor. This receptor acts like a switch in the brain to suppress appetite. People who have genetic variants that disrupt this receptor gain weight easily.

Now, in a study published today in the journal *Cell*, researchers have shown that other genetic variants in the MC4R gene that increase the activity of this brain receptor can protect people from becoming overweight, a finding that could lead to the development of new medicines that 'copy' the protective effect of these genetic variants to achieve or maintain weight-loss.

A team led by Professors Sadaf Farooqi and Nick Wareham and Dr. Claudia Langenberg at the Wellcome Trust-MRC Institute of Metabolic Science in Cambridge looked at the MC4R gene in half a million volunteers from the UK population who have taken part in the UK Biobank study, finding 61 distinct naturally-occurring genetic variants. While some of these genetic variants predisposed people to become obese, other variants provided protection against obesity and some of its major complications, such as type 2 diabetes and [heart disease](#).

To investigate the reasons for this mystery, Professor Farooqi's team,

who previously showed that MC4R works in the brain as a 'switch' to tell us to stop eating after a meal, studied the function of these genetic variants in a number of laboratory experiments. They found that MC4R gene variants linked to higher obesity risk stopped the gene from working, whereas variants that offered protection against obesity kept the gene 'switched on'.

Around six per cent of study participants carried genetic variants that caused the receptor to remain 'switched on'. People with these variants would eat less, which could explain their lower weight. People with two copies of these particular variants (1 in over 1,000 people) were on average 2.5 kg lighter than people without the variants and had a 50% lower risk of type 2 diabetes and heart disease.

"This study drives home the fact that genetics plays a major role in why some people are obese—and that some people are fortunate enough to have genes that protect them from obesity," says Professor Farooqi of the University of Cambridge Metabolic Research Laboratories.

The discovery adds to recent work by the team which showed that some slim people have a genetic advantage when it comes to maintaining their weight.

"It doesn't mean that we can't influence our weight by watching what we eat, but it does mean the odds are stacked against some people and in favour of others," added Professor Farooqi.

When the researchers looked in detail at the genetic variants in laboratory experiments, they found that MC4R can send signals through a pathway—known as the beta-arrestin pathway—that had not previously been linked to weight regulation. Genetic variants that sent signals preferentially through this pathway were the ones driving the association with protection against obesity and its complications and, importantly,

were also associated with lower blood pressure. Designing drugs that mimic the effect of the protective variants in MC4R could provide new, safer weight loss therapies.

"A powerful emerging concept is that genetic variants that protect against disease can be used as models for the development of medicines that are more effective and safer," said Dr. Luca Lotta, Senior Clinical Investigator at the Medical Research Council Epidemiology Unit and joint lead author of the study. "Our findings may pave the way for a new generation of [weight](#) loss therapies that activate MC4R preferentially via the beta-arrestin pathway."

"Our work would not have been possible without the unique blend of expertise in large-scale genetic epidemiology analysis and laboratory experiments at the Institute of Metabolic Science," says Professor Wareham, Director of the MRC Epidemiology Unit and Co-Director of the Institute.

"Genetic studies of thousands of people and a functional understanding of the mechanisms behind protective genetic variants can really help us inform the development of a new generation of medicines for common diseases like obesity and diabetes that affect millions of people globally."

More information: Lotta, LA, Mokrosiski, J et al. Human gain-of-function MC4R variants show signaling bias and protect against obesity. *Cell*; 18 April 2019; [DOI: 10.1016/j.cell.2019.03.044](https://doi.org/10.1016/j.cell.2019.03.044)

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