Scientists identify rare gene variants which confer up to 6-fold increase in risk of obesity

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A study led by Medical Research Council (MRC) researchers has identified genetic variants in two genes that have some of the largest impacts on obesity risk discovered to date.

The discovery of rare variants in the genes BSN and APBA1 are some of the first obesity-related genes identified for which the increased risk of obesity is not observed until adulthood.

The study, published in *Nature Genetics*, was led by researchers at the MRC Epidemiology Unit and the MRC Metabolic Diseases Unit at the Institute of Metabolic Science, both based at the University of Cambridge.

The researchers used UK Biobank and other data to perform whole exome sequencing of body mass index (BMI) in over 500,000 individuals.

They found that genetic variants in the gene BSN, also known as Bassoon, can raise the risk of obesity as much as six times and was also associated with an increased risk of non-alcoholic fatty liver disease and of type 2 diabetes.

The Bassoon gene variants were found to affect 1 in 6,500 adults, so could affect about 10,000 people in the UK.

The brain's role in obesity

Obesity is a major public health concern as it is a significant risk factor for other serious diseases, including cardiovascular disease and type 2 diabetes, yet the genetic reasons why some people are more prone to weight gain are incompletely understood.

Previous research has identified several obesity-associated gene variants conferring large effects from childhood, acting through the leptin-melanocortin pathway in the brain, which plays a key role in appetite regulation.

However, while both BSN and APBA1 encode proteins found in the brain, they are not currently known to be involved in the leptin-melanocortin pathway. In addition, unlike the obesity genes previously identified, variants in BSN and APBA1 are not associated with childhood obesity.

This has led the researchers to believe that they may have uncovered a new biological mechanism for obesity, different to those we already know for previously identified obesity gene variants.

Based on published research and laboratory studies they report in this paper, which indicate that BSN and APBA1 play a role in the transmission of signals between brain cells, the researchers suggest that age-related neurodegeneration could be affecting appetite control.

Professor John Perry, study author and an MRC Investigator at the University of Cambridge, said, "These findings represent another example of the power of large-scale human population genetic studies to enhance our understanding of the biological basis of disease. The genetic variants we identify in BSN confer some of the largest effects on obesity, type 2 diabetes and fatty liver disease observed to date and highlight a new biological mechanism regulating appetite control."

The use of global data

The accessibility of large-scale databases such as UK Biobank has enabled researchers to search for rare gene variants that may be responsible for conditions including obesity.

For this study, the researchers worked closely with AstraZeneca to replicate their findings in existing cohorts using genetic data from individuals from Pakistan and Mexico. This is important as the researchers can now apply their findings beyond individuals of European

ancestry.

If the researchers can better understand the neural biology of obesity, it could present more potential drug targets to treat obesity in the future.

Dr. Slavé Petrovski, VP of the Center for Genomics Research at AstraZeneca, said, "Rigorous large-scale studies such as this are accelerating the pace at which we uncover new insights into human disease biology. By collaborating across academia and industry, leveraging global datasets for validation, and embedding a genomic approach to medicine more widely, we will continue to improve our understanding of disease—for the benefit of patients."

Professor Giles Yeo, study author based at the MRC Metabolic Diseases Unit, added, "We have identified two genes with variants that have the most profound impact on obesity risk at a population level we've ever seen, but perhaps more importantly, that the variation in Bassoon is linked to adult-onset and not childhood obesity. Thus these findings give us a new appreciation of the relationship between genetics, neurodevelopment and obesity."

More information: Protein-truncating variants in BSN are associated with severe adult-onset obesity, type 2 diabetes and fatty liver disease, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01694-x

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