Alterations in human gene TRPC5 cause obesity and postpartum depression, scientists discover

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Researchers at Baylor College of Medicine, the University of Cambridge and collaborating institutions have discovered that alterations in the

human gene TRPC5 cause obesity and postpartum depression.

Taken together, their studies in cells, animal models and humans showed that TRPC5 acts on distinct neuronal populations in the hypothalamus, a brain region that regulates multiple innate behaviors including feeding, anxiety, socialization and maternal care. The findings, published in the journal *Cell*, identify TRPC5 as a diagnostic marker of obesity and postpartum depression as well as potential therapeutic strategies to treat these conditions.

"Our investigation into the role of TRPC5 in obesity and postpartum depression began with the finding that the X chromosomes of two unrelated boys with intense food-seeking behavior, severe obesity and other altered behaviors were missing a small piece that included this gene," said co-corresponding author Dr. Sadaf Farooqi, professor of metabolism and medicine at the University of Cambridge.

"Their mothers had obesity, anxiety and postpartum depression. We found that they were carriers—one of their two X chromosomes was missing the TRPC5 gene."

Obesity and postpartum depression are significant global health problems. According to the World Health Organization, obesity has more than doubled in adults since 1990, and quadrupled in adolescents.

Postpartum depression occurs in 10 to 15% of mothers and is associated with significant maternal health problems. Globally, postpartum depression remains a major cause of death by suicide in women at a time when maternal mortality due to infections and hemorrhage has declined.

The brain connection

"Previous studies had shown that disrupting gene Trpc5 in the brain

causes obesity due to increased food intake and reduced energy expenditure in mice," said co-corresponding author Dr. Yong Xu, professor of pediatrics—nutrition and associate director for basic sciences at the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine.

In the current study, the Xu lab and the Farooqi lab collaborated to investigate the role of TRPC5 in obesity and postpartum depression. By combining the individual expertise of each lab—basic and genetic animal studies in the Xu lab and human genetics and clinical studies in the Farooqi lab—the team was able to show that TRPC5 is an important regulator of obesity, postpartum depression and other human behaviors.

To investigate the mechanisms underlying the characteristics observed in people with a defective TRPC5 gene, the researchers generated a mouse model that carries a defective variant of this human gene.

Male mice with this mutation gained weight on a high-fat diet and showed anxiety, increased arousal and reduced sociability. Female mice carrying the mutation exhibited depression-like behavior after giving birth and impaired maternal-offspring interactions. Intriguingly, virgin female mice carrying the mutation did not show depression-like behavior.

"These studies show that the characteristics and behaviors seen in humans with a defective TRPC5 gene were also present in our mouse model and establish that TRPC5 regulates a spectrum of innate behaviors across mammalian species," Xu said.

Digging deeper into the mechanisms mediating the actions of this gene, the researchers found that the gene's actions seem to involve at least two different types of brain cells, Pomc neurons and oxytocin neurons, both in the hypothalamus.

Pomc neurons in the arcuate nucleus of the hypothalamus help regulate body weight by reducing food intake, and about 90% of these cells express Trpc5. The team discovered that genetic disruption of Trpc5 impaired the ability of Pomc neurons to reduce appetite in mice.

The team also discovered high levels of Trpc5 expression in oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVH) in mice. This specific group of neurons in the brain is known to regulate energy balance in the body and the response to stress, emotion and social behaviors including mother-infant bonding.

"Removing the Trpc5 gene from PVH oxytocin neurons in mice caused severe overeating and obesity in both sexes and postpartum depressive behavior and reduced maternal care in females," Xu said.

"On the other hand, overexpressing the functional gene in the neurons of mice carrying a defective gene improved these conditions. Together, the results show that these genetically encoded innate maternal behaviors are mediated by Trpc5 on oxytocin neurons."

"Our findings not only provide a better understanding of the genetic basis and neural mechanisms involved in obesity and postpartum depression but also have direct clinical implications by advancing the diagnostic practice of these two different human diseases," Farooqi said. "Our work supports screening for TRPC5 to provide a clinical diagnosis for these conditions."

In addition, the discovery of the key role TRPC5 plays in these conditions suggests that strategies directed at this protein can potentially lead to new treatments.

The authors propose that as overeating and obesity of TRPC5 deficiency is mediated by impaired activation of Pomc neurons, this disorder may

be treatable with an MC4R agonist drug licensed for the treatment of genetic obesity syndromes.

Oxytocin receptor agonists or gene therapy to restore TRPC5 expression in specific areas of the hypothalamus are potential therapeutic strategies for people with postpartum depression.

More information: Loss of Transient Receptor Potential Channel 5 Causes Obesity and Postpartum Depression, *Cell* (2024). DOI: 10.1016/j.cell.2024.06.001.
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