Epigenetics drives weight differences between identical twins

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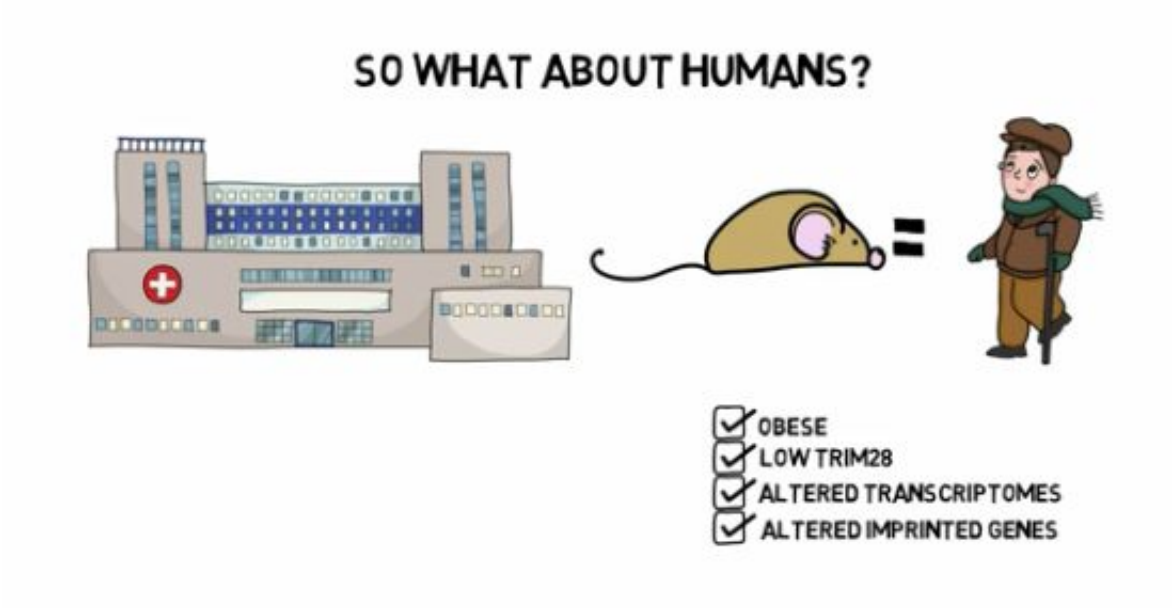

Having overweight parents significantly increases your risk of obesity, but the inheritance of specific mutations can't always explain why this is the case. In a study published January 28 in *Cell*, researchers show that differences in gene expression and not the DNA sequence play a key role in determining one's predisposition to obesity. In genetically identical mice and human twin pairs, epigenetic marks altered the activity of weight-control genes to produce distinct subpopulations of lean and obese individuals. The findings reveal a key role for an

epigenetic switch in explaining individual differences in obesity.

"We're interested in the mechanisms that can make identical twins come out not so identical, and how these mechanisms contribute to disease," says senior study author J. Andrew Pospisilik of the Max Planck Institute of Immunobiology and Epigenetics. "If twins can come out substantially different from one another, it means that each of us could have come out differently than how we did."

One clue came from a 2010 Genome Biology study (DOI: 10.1186/gb-2010-11-11-r111) showing that genetically identical mice sharing a mutation in a protein called Trim28 exhibit high variability in their body mass, suggesting that this protein might trigger epigenetic changes that contribute to individual variation in obesity.

To explore this idea, Pospisilik and his team generated large populations of Trim28-deficient mice that shared an identical genetic background and the same environmental conditions. These mice segregated into two distinct populations that showed striking differences in body mass. The Trim28-deficient obese mice showed impaired expression of epigenetically regulated "imprinted" genes, such as Nnat and Peg3, which alter growth and body weight.

To test whether these findings extend to humans, the researchers examined fat tissue samples from 22 lean and 18 obese pre-pubertal children who entered the clinic for elective surgery. Strikingly, obese children with Trim28-deficient tissue samples showed the same epigenetic changes observed in Trim28-deficient obese mice.

The researchers next analyzed publicly available datasets from genetically identical twin pairs, each comprising one obese and one lean individual. Compared with their lean counterparts, obese twins tended to show lower TRIM28 levels, as well as a reduction in the activity of

imprinted genes that control weight.

"The existence of strikingly different traits among genetically identical organisms has been heavily studied in insects and can explain the existence of castes such as worker and soldier ants or queen bees, for instance," Pospisilik says. "Our study demonstrates that this concept, known as polyphenism, also extends to mammals."

Although the evolutionary implications are not entirely clear, it is likely that such epigenetic changes, which can be inherited or modified by environmental factors, could allow a species to adapt to or survive extreme conditions. For example, starvation may produce epigenetic changes that trigger the emergence of a distinct subpopulation of individuals that develop substantial fat stores. "A switch-like mechanism to produce individuals with different traits without changing DNA provides a selective advantage at the population level," Pospisilik says. "Polyphenism allows an emergency or plan B version that gets the species through transient selective pressures."

In future studies, Pospisilik will continue to examine the underlying molecular mechanisms by which epigenetic changes contribute to individual variability in traits such as obesity. Because Trim28 deficiency also increases the risk of cancer and anxiety in mice, they will also examine the broader role of this protein in behavior and disease.

In the end, this research could have important clinical implications. "These findings set a new playing field for disease-associated epigenetic effects," Pospisilik says. "Previously, people would have thought that epigenetics can moderately increase or decrease traits of an organism, and that epigenetic therapies could then alter or combat these shifts. Our study shows that these shifts may not only occur along a continuum, but may also have areas of high stability. This suggests the possibility that we may be able to switch physiology to produce a state that is inherently

stable to stay lean or obese."

More information: *Cell*, Dalgaard et al.: "Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity"
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