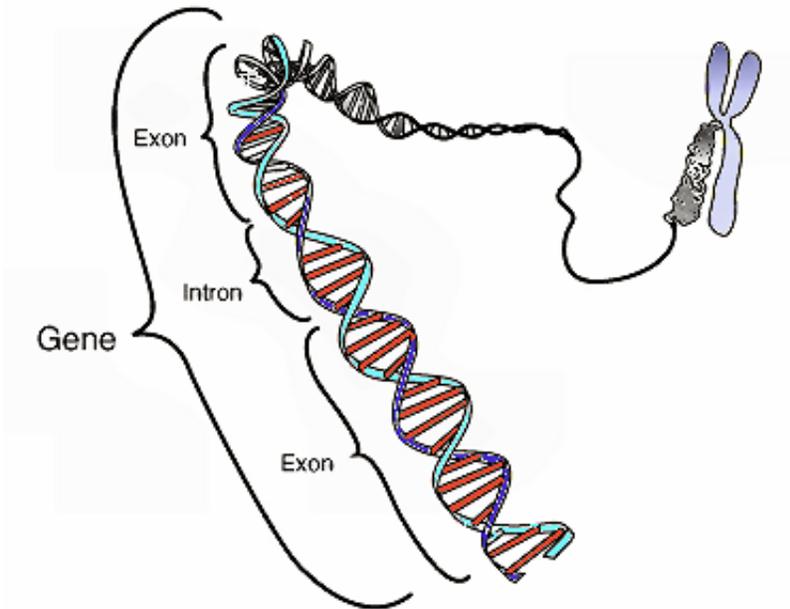


# Gene loss creates eating disorder-related behaviors in mice

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This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

Building on their discovery of a gene linked to eating disorders in humans, a team of researchers at the University of Iowa has now shown that loss of the gene in mice leads to several behavioral abnormalities that resemble behaviors seen in people with anorexia nervosa.

The team, led by Michael Lutter, MD, PhD, assistant professor of psychiatry in the UI Carver College of Medicine, found that mice that

lack the estrogen-related receptor alpha (ESRRA) gene are less motivated to seek out high-fat food when they are hungry and have abnormal social interactions. The effect was stronger in [female mice](#), which also showed increased obsessive-compulsive-like behaviors.

The study also shows that ESRRA levels are controlled by energy status in the mice. Restricting [calorie intake](#) to 60 percent of normal over several days significantly increased levels of ESRRA in the brains of normal mice.

"Decreased calorie intake usually motivates animals, including humans, to seek out high-calorie food. These findings suggest that loss of ESRRA activity may disrupt that response," Lutter says.

Anorexia nervosa and bulimia nervosa are common and severe mental illnesses. Lutter notes that although 50 to 70 percent of the risk of getting an [eating disorder](#) is inherited, identifying the genes that mediate this risk has proven difficult.

ESRRA is a transcription factor - a gene that turns on other genes. Lutter and his colleagues previously found that a mutation that reduces ESRRA activity is associated with an increased risk for eating disorders in human patients. Although ESRRA is expressed in many brain regions that are disrupted in anorexia, almost nothing was known about its function in the brain. In the new study, published online April 9 in the journal *Cell Reports*, Lutter's team manipulated ESRRA in mice to investigate the gene's role in behavior.

"This work identifies estrogen-related receptor alpha as one of the [genes](#) that is likely to contribute to the risk of getting [anorexia nervosa](#) or [bulimia nervosa](#)," Lutter says. "Clearly social factors, particularly the western ideal of thinness, contribute the remaining 'non-genetic' risk, and the increasing rate of eating disorders over the past several decades

is likely due to social factors, not genetics," he adds.

Through a series of experiments with genetically engineered mice, Lutter and his team showed that mice without the ESRRRA gene have [behavioral abnormalities](#) related to eating and social behavior. In particular, mice without ESRRRA show reduced effort to work for high-fat food when they are hungry. The mice also exhibited impaired social interaction and female mice without the gene show increased compulsive grooming, which may mimic obsessive-compulsive-type behavior in humans.

In order to refine their understanding of the effects of ESRRRA in the brain, the researchers selectively removed the gene from particular brain regions that have been associated with eating disorders. They found that removing the gene from the orbitofrontal cortex was associated with increased obsessive-compulsive-type behaviors in female mice, while loss of ESRRRA from the prefrontal cortex produced mice that were less willing to work to get [high-fat food](#) when they were hungry.

These new findings may point to particular neural circuits that could be targets to treat abnormal behaviors associated with eating disorders.

"Mouse models of human neuropsychiatric illnesses are useful for identifying cellular and molecular abnormalities that might contribute to illnesses like eating disorders," Lutter says. "They are also useful for screening new medications. We plan to start testing novel treatments for anorexia nervosa to see if they reverse behavioral problems in our [mice](#)."

**More information:** *Cell Reports*, Cut et al.: "Behavioral Disturbances in Estrogen-Related Receptor Alpha-Null Mice"

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