NEWS

Rett syndrome gene involved in obesity and aggression

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The gene that causes Rett syndrome, a rare disorder on the autism spectrum that affects only females, may also play a key role in aggressive behavior and overeating in mice, according to a study published today in *Neuron*[1].

In 1999, **Huda Zoghbi** and her team first linked **mutations in MeCP2 to 95 percent** of Rett cases[2]. In the current study, her group selectively deleted the protein from a distinct brain region, a strategy that could be used to identify MeCP2's role in specific parts of the brain.

Girls who have Rett syndrome show symptoms within the first 18 months of life, beginning with delayed growth and speech, and progressing to mental retardation, impaired social behavior, seizures and stereotypic movements such as hand-wringing.

By their early 20s, they are often wheelchair-bound as a result of severe impairments in motor function. Mutations in the gene have also been seen in some cases of childhood schizophrenia and classic autism[3].

Researchers had previously developed animal models for Rett syndrome by creating mice that lack the MeCP2 gene. Those mice show a mix of Rett-like symptoms, including anxiety, motor dysfunction and impaired learning and memory.

In this study, Zoghbi and her colleagues developed mice that selectively lack the gene only in roughly a tenth of neurons within the hypothalamus. The hypothalamus is a brain region that regulates behavioral and physical responses to hunger and stress.

Unlike the other mouse models, these mutant mice are more aggressive in unfamiliar social situations, and tend to eat more.

“I think the most surprising thing is the important role of this protein in regulating feeding behavior ? that, and the aggression,” says Zoghbi, a Howard Hughes Medical Institute Investigator at the Baylor College of Medicine in Houston.

The mice do show some Rett-like features ? such as above-normal elevations of the stress hormone corticosterone ? but they do not have deficits in motor coordination or learning and memory, which are hallmarks of the disorder.

Master switch:

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Selective loss: Huda Zoghbi and her colleagues deleted MeCP2 (B) from a subset of neurons in the hypothalamus that express SIM1 (A).

Studying MeCP2?s role in Rett syndrome has been challenging for researchers because the protein is found throughout the brain and seems to control the **activation of thousands of other genes**.

The situation is further complicated because the defective MeCP2 is located on only one of two X chromosomes the girls possess; the other chromosome generally carries a healthy copy of the gene. Different brain cells selectively inactivate either the healthy or the defective copy of MeCP2, creating a ‘mosaic? effect.

Because the researchers are selectively deleting the gene only in defined regions, “In a sense this type of genetic study could mimic the mosaic scenario,” says **Josh Huang**, professor at Cold Spring Harbor Laboratory in New York.

Since the 1999 study, several groups have manipulated the gene in different ways to produce mouse models of Rett. Each model has an array of phenotypes, some of which overlap.

For instance, one team reported in 2006 that deleting the MeCP2 gene from select neurons in the mouse forebrain and midbrain triggers several Rett-like symptoms, including abnormal motor coordination, weight gain, and impaired learning and memory[4].

Zoghbi?s group focused on the hypothalamus because patients with mutations in MeCP2 tend to exhibit a constellation of symptoms ? difficulty sleeping, heightened anxiety, difficulty breathing, and elevated blood hormone responses to stress ? that implicate the brain region.

Because deletions of MeCP2 affect brain pathways involved in hunger, Zoghbi?s group is activating genes downstream of MeCP2 involved in feeding, such as the gene for brain-derived neurotrophic factor or BDNF, to test whether the mice regain normal feeding patterns.

The researchers are also selectively deleting MeCP2 from other regions in the brain to determine its relative contributions in other brain areas.

References:

1. Fyffe S.L. *et al. Neuron* **59**, 947-958 (2008) **Abstract ?**

2. Amir R.E. *et al. Nat. Genet.* **23**, 185-188 (1999) **PubMed ?**

3. Shibayama A. *et al. Am. J. Med. Genet. B Neuropsychiatr. Genet.* **128B**, 50-53 (2004) **PubMed ?**

4. Gemelli T. *et al. Biol. Psychiatry* **59**, 468-476 (2006) **PubMed ?**