The Rett gene -- a rogue activator

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In 1999, when Dr. Huda Zoghbi and her Baylor College of Medicine colleagues identified a mutation of the gene MeCP2 as the culprit in Rett syndrome, a neurodevelopmental disorder, the discovery was only the prelude to understanding a symphony of neurological missteps.

Unraveling the story of MeCP2 demonstrates the finicky nature of neurons that work best when the recipe for the proteins affecting them is followed exactly. Zoghbi and her collaborators describe the role MeCP2 plays in the brain in a report that appears in the current issue of the journal *Science*.

“Whether you lose the protein or gain too much, the symptoms in the brain overlap quite a bit,” said Zoghbi, who is a BCM professor of pediatrics, neurology, neuroscience, molecular and human genetics and a Howard Hughes Medical Institute investigator. “The brain is very sensitive to its physiological equilibrium.”

Yet the brain or neurons in it can demonstrate a problem with only a limited range of symptoms – autism, seizures or mental retardation.

“The symptoms are those of an unhappy neuron,” said Zoghbi. Yet as the MeCP2 studies show, these symptoms can have different causes. That fact may mean that what outwardly appears to be the same disease could have very different beginnings and require wholly different treatments.

Zoghbi and her colleagues found that MeCP2 is a key regulator that can turn on and off genes that govern activities in the neurons of the

hypothalamus. While MeCP2 can turn off a gene, it is more likely to turn it on.

As infants, girls with Rett syndrome seem normal for at least six months. Between the ages of 6 and 18 months, however, their development stops and they begin to regress, losing the ability to talk. Then they begin to have problems walking and keeping their balance and develop typical hand-wringing behavior. Many of their symptoms mirror those of autism. Zoghbi's laboratory was the first to identify a mutation in the MeCP2 gene that results in too little of this protein, causing girls to develop Rett. Boys who suffer from a disorder linked to an excess of MeCP2 have impaired motor function, seizures and mental retardation with autism-like behavior.

In trying to find out how the alterations in MeCP2 affect the brain, the scientists began their studies in the hypothalamus because symptoms of Rett syndrome such as anxiety, sleep disturbance and slowed growth can all be attributed to problems in that part of the brain. Previous studies of the whole brain proved inconclusive, and by targeting a very specific area of the brain, Zoghbi and her collaborators hoped to zero in on the problem.

"Loss of function of the MeCP2 gene causes Rett syndrome," said Maria Chahrour, a BCM graduate student and first author of the report. Doubling or tripling MeCP2 levels causes other neurological disorders. To better understand the protein, the scientists decided to study mice that either lacked MeCP2 or had too much of it.

They dissected the hypothalamus in both kinds of mice and looked at changes in the genes compared to the same genes in normal mice.

"There are thousands of genes changed by MeCP2," said Chahrour. In both the mice who had no MeCP2 and those who had too much of the

dysfunctional gene, they found changes in expression of thousands of genes. Surprisingly, they found that in at least 85 percent of the genes, MeCP2 turned the gene on. In fact, they found that it associates with CREB1, another gene tasked with turning on genes.

Interestingly, although the two diseases share many features, having no protein versus having too much caused opposite effects on gene expression, suggesting again that “the symptoms are those of an unhappy neuron,” said Zoghbi. Yet as the MeCP2 studies show, these symptoms can have different causes. That fact may mean that what outwardly appears to be the same disease could have very different beginnings and require wholly different treatments.

“Because MeCP2 regulates thousands of genes, it does not make sense to target each of them individually in designing treatments,” Chahrour said. “We are going to have to find a therapeutic strategy that can bypass MeCP2 and restore the normal order in the brain,” she said.

Source: Baylor College of Medicine