

Researchers uncover mechanisms of common inherited mental retardation

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Dr. Kimberly Huber investigated how Fragile X syndrome affects communication between cells in the hippocampus, a region of the brain that is involved in learning and memory. Fragile X syndrome is the most common cause of inherited mental retardation and the most common genetic cause of autism. Credit: UT Southwestern Medical Center

Researchers at UT Southwestern Medical Center are uncovering how brain cells are affected in Fragile X syndrome, the most common cause of inherited mental retardation and the most common genetic cause of autism.

"I think we've discovered a core mechanism underlying Fragile X syndrome," said Dr. Kimberly Huber, assistant professor of neuroscience and senior author of a study appearing in Wednesday's edition of the *Journal of Neuroscience*.

Dr. Huber's research with mice focuses on how Fragile X syndrome affects communication between cells in the hippocampus, a region of the brain that is involved in learning and memory. Her findings show that two different chemical signals go awry in Fragile X syndrome, indicating that drugs that interact with these signals might be a

pathway to help treat the syndrome.

"The more we know about how signaling mechanisms in the brain lead to normal memory and learning, the better we can understand what goes wrong in conditions such as Fragile X syndrome," said Dr. Huber, who is a Southwestern Medical Foundation Scholar in Medical Research. "Our research is laying the groundwork for such understanding and indicates a new area for research."

Fragile X syndrome got its name because it affects a single gene, *Fmr1*, on the X chromosome. Under a microscope, the area around the gene looks narrower than normal, or "fragile." According to the Centers for Disease Control and Prevention, the syndrome, which mostly occurs in males, affects about one in every 4,000 white males in the U.S.

It often causes a distinct physical appearance including an elongated face with protruding ears, hyperflexible joints, and mental deficits ranging from mood disorders to severe mental retardation. Much of the current treatment focuses on behavioral therapy combined with medications to control mood and seizures.

Dr. Huber previously co-discovered that mice genetically engineered to lack *Fmr1* have a defective signaling system in the brain that controls learning in the hippocampus. This system relies on a chemical messenger called glutamate, which under normal circumstances causes nerve cells to make proteins and change their electrical firing patterns in response to learning situations. Without a properly working *Fmr1* gene, the glutamate signaling system malfunctions.

In 2007 she and colleagues at UT Southwestern found that acetylcholine, another specific signaling chemical, affects the same protein-making factory that glutamate does. This research appeared in the Oct. 24, 2007, issue of the *Journal of*

Neuroscience.

“We suggest that treatment that affects the acetylcholine system might be a supplement or alternative to drugs targeting the glutamate pathway,” Dr. Huber said.

In the current study, she and postdoctoral researcher Dr. Jennifer Ronesi investigated a protein, called Homer, which serves as a kind of structural support for the glutamate system. The Homer–glutamate support system is disconnected in Fragile X syndrome. Dr. Huber’s group discovered that this disconnection results in an inability of brain cells to make the new proteins important for learning and memory.

Source: UT Southwestern Medical Center

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