Researchers uncover Fragile X syndrome gene's role in shaping brain

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Researchers at UT Southwestern Medical Center have discovered how the genetic mutation that causes Fragile X syndrome, the most common form of inherited mental retardation, interferes with the "pruning" of nerve connections in the brain. Their findings appear in the April 29 issue of *Neuron*.

Soon after birth, the still-developing brain of a mammal produces too many nerve connections that create "noise" in the nervous system. The brain finds it hard to process these signals, like a person trying to have a conversation at a loud party. But as the brain matures and learning takes place, some nerve connections naturally become stronger while others weaken and die, leading to an adult with a properly wired brain.

Fragile X is caused by a mutation in a single gene, Fmr1, on the X chromosome. The gene codes for a protein called FMRP, which plays a role in learning and memory but whose full function is unknown. The protein's role in pruning nerve connections had been unclear.

"I think we've uncovered a core function for the gene involved in this disease, and if we can find other biochemical methods involved in nerve pruning, we might be able to help correct this," said Dr. Kimberly Huber, associate professor of neuroscience at UT Southwestern and senior author of the study.

In the current study, Dr. Huber and her colleagues examined nerve cells isolated from mice that had been engineered to lack the Fmr1 gene and,

therefore, did not produce FMRP protein. They then tested whether the lack of FMRP affected the functions of another protein called MEF2, which is known to be involved in pruning nerve connections.

The researchers found that nerve cells lacking FMRP were unable to respond to MEF2. Adding FMRP to the cells restored MEF2's normal function.

"We were massively activating the MEF2 gene in the cell, and it did absolutely nothing without FMRP," Dr. Huber said. Such an all-or-nothing requirement in a biochemical relationship is rare, she said.

The findings also raise questions about how the two proteins interact physically. MEF2 works in the nucleus of a cell, where it controls whether other genes are turned on or off. FMRP shuttles in and out of the cell's nucleus and into its main body.

"This opens up new ideas about how processes in the cell's nucleus, near its DNA, can affect the nerve connections, which are very far away at the other end of the cell," Dr. Huber said. "We think MEF2 is making messenger RNA [ribonucleic acid], which translates the genetic code of the DNA, and FMRP is binding to the RNA and either transporting it to the nerve connections and/or controlling how the RNA makes protein."

Further research will focus on the relationship between the proteins. For instance, one might directly control the other, or they might work together on a common target, Dr. Huber said.

"This work might not have clinical implications for quite a while," she said. "The goal for us as scientists is to understand how these genes relate to mechanisms that control the development of nerve connections."

Like other genetic diseases carried on the X chromosome, Fragile X

syndrome strikes boys more often and more severely than girls. Girls have two X chromosomes, so a normal gene on one chromosome can mitigate the effects of the disease if the gene on the other X chromosome is abnormal. Boys, however, have only one X chromosome, so if they inherit an abnormal gene on the X chromosome, they have no protection.

Provided by UT Southwestern Medical Center