Fragile X proteins involved in proper neuron development

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Prominent characteristics of the syndrome include an elongated face, large or protruding ears, and low muscle tone. Credit: Wikipedia

Fragile X syndrome is the most common inherited intellectual disability and the greatest single genetic contributor to autism. Unlocking the mechanisms behind fragile X could make important revelations about the brain.

In a new study published June 4 in the journal *Cell Reports*, researchers from the University of Wisconsin-Madison Waisman Center and Department of Neuroscience show that two proteins implicated in fragile X play a crucial role in the proper development of neurons in mice. They also show that while the two proteins act through distinct mechanisms in the formation of new neurons—which send, receive and process information in the brain—they also share some duties.

'This is the first demonstration of the additive function of fragile X proteins in neuronal development,' says study corresponding author and Waisman Center and Department of Neuroscience Professor Xinyu Zhao.

Relatively little is known about the underlying mechanisms that lead to the cognitive and learning deficits in fragile X syndrome, Zhao says, making it difficult to devise effective therapies. She studies the two fragile X proteins, FMRP and FXR2P, because doing so could yield new information that ultimately leads to treatment for fragile X and other disorders marked by defects in neuronal development, like autism and schizophrenia.

For instance, while FXR2P has been shown to be important in autism, the function of the protein and its contribution to fragile X syndrome has been unclear, Zhao says.

Fragile X is a genetic condition that affects one in 4,000 males and one in 8,000 females. It's linked to a mutation in the gene that makes the FMRP protein, located on the X chromosome. Up to a third of people with fragile X also have autism.

Children with the syndrome are more prone to attention deficit disorder and a diagnosis on the autism spectrum; display physical features such as flat feet, a prominent jaw and forehead, and a long and narrow face, and may have anxiety.

Additionally, an estimated one in 250 women and one in 500 men carry a 'premutation' on the gene that makes FMRP protein, which renders the gene unstable. Carriers can pass it on to future generations and are at greater risk for a Parkinson's disease-like disorder called fragile X-associated tremor/ataxia syndrome. They may also be more prone to stress and other challenges.

In a previous study, Zhao's team showed that both FMRP and FXR2P are integral for new neuron production in adult mice and are important for learning and cognition. In the current study, the research team looked at the function of the proteins in the maturation of newly formed adult neurons.

The researchers found that mice lacking the FXR2P protein had impaired performance in learning and memory tasks. Using techniques to study newly formed neurons in the brain, the team also found these mice had neurons that did not mature properly. The neurons were also less well connected to other neurons that form important circuits in the brain compared to mice with the protein.

The team also highlighted a new interaction between the FXR2P protein and a specific neuronal receptor, a protein charged with receiving messages and passing along information, and showed that the two work together for proper neuronal development. Additionally, it revealed that FXR2P and FMRP work together in regulating this receptor's activity and the maturation of neurons.

'The findings suggest that fostering new nerve cell development during the postnatal period may have therapeutic potential for people with fragile X syndrome and other neurological disorders,' says Zhao.

Her research group will continue to study these proteins and the role they play in neural development and fragile X syndrome—work that's likely to influence other fields of inquiry in autism and beyond. The lab will also work toward translating the findings in mice into human therapies. It is far more challenging to study brain development in people, so mice serve as a model for these studies.

'If we can find a way to reactivate the FMRP gene, we may be able to treat the disease,' says Zhao.

Provided by University of Wisconsin-Madison