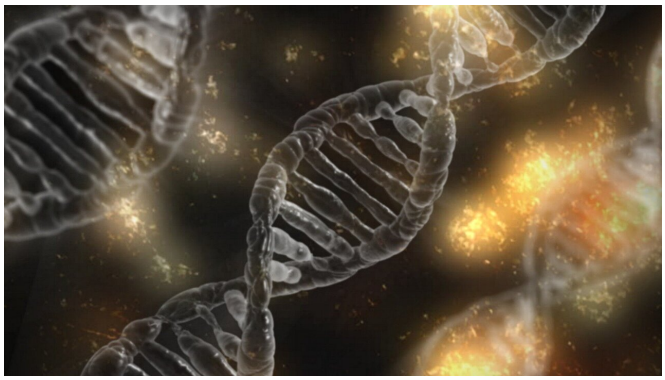
Q&A: Getting to the roots of fragile X syndrome

23 October 2020, by Kim Thurler



Credit: Pixabay/CC0 Public Domain

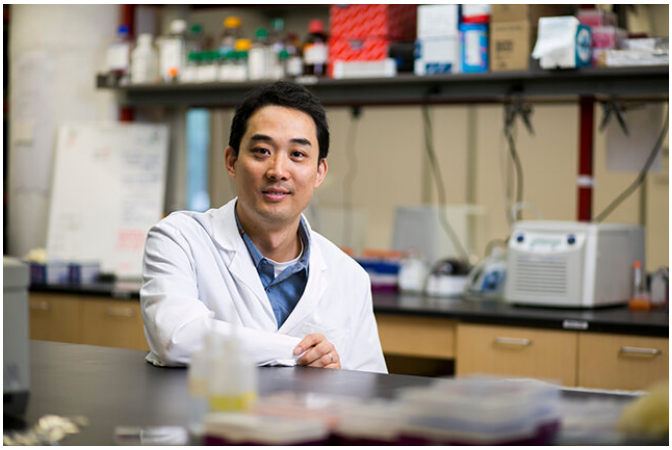
The cause of fragile X syndrome (FXS), the most common inherited intellectual disability, is easy to see in the lab. Under electron microscopy, an affected X chromosome exhibits a deformed tip that gives the disorder its name and pinpoints the causative gene malfunction. There's no cure for the disease, whose symptoms include learning deficits and hyperactivity and which has been linked with autism. FXS occurs in one in 4,000 to 7,000 males and one in 8,000 to 11,000 females in the United States.

Most research on FXS has focused on the brain's neurons, the cells that transmit electrical and chemical impulses. But for a decade Yongjie Yang, associate professor of neuroscience at Tufts University School of Medicine, has pursued a different path, investigating the involvement of glia cells, particularly astroglia, which support neuron function and make up more than half the brain. In the past month, he's published in the *Proceedings of the National Academy of Sciences* (*PNAS*) and *Glia*. Tufts Now spoke with Yang about his work.

Tufts Now: What do we know about FXS?

Yongjie Yang: Fragile X syndrome is caused by the mutation of a single gene, FMR1, that codes for the FMRP protein, which is found in all brain cells and is essential for normal cognitive development. The mutation doesn't actually change the genetic code. Instead it causes part of the gene, specifically the chemical bases CGG, to repeat. We all carry those repeats in different numbers. If you carry roughly 50 or fewer, your brain development will be normal, but if the repeats go beyond 200, you will have the full mutation and your brain will produce only 10 to 20 percent of the needed level of FMRP, especially if you're male. FXS was characterized in 1943 but the genetic mutation wasn't identified until 1991, almost half a century a later.

What is the relationship between autism spectrum disorder (ASD) and FXS?



Trials of fragile X syndrome treatments based on neuron studies have failed so far, says Yongjie Yang, associate professor. “Our glia/astroglia perspective gives a fresh view to search for new targets,” he says. Credit: Kelvin Ma

The two are intermingled. ASD is much more common, occurring in one in 54 children, according

to new estimates. It's believed that 1 to 6 percent of people with ASD have the FXS mutation, and that mutation accounts for the largest genetic subset of those with ASD. Many people with FXS are also autistic. FXS is a learning and intellectual disability, while ASD includes a wide range of social and communications challenges.

What are the key findings of your most recent research?

The study in *Glia* shows that some physical symptoms of FXS can be induced in mice by eliminating FMRP from astroglia alone. So in thinking about gene therapy for FXS, we need to consider glia cells, not just neurons. Our *PNAS* paper is exciting because it defines a unique, distinct FMRP-dependent pathway in mouse and human astroglia that regulates communications from astroglia to neurons through mGluR5, an important receptor for glutamate, the neurotransmitter that triggers brain activity. Interestingly, this regulation pathway isn't found in neurons. It's also the first study to demonstrate how overall protein expression is changed in FMR1-deficient astroglia. Unveiling astroglia-specific molecular mechanisms involved in FXS development could give us new targets for potential therapeutics.

What's next?

We want to better understand the pathophysiology of FXS and identify new avenues for drugs and other interventions to attenuate the effects of the disease. Of course gene therapy would be wonderful but it often takes a long, long time and carries a lot of risk. Most other studies have focused on the neuron side, and drug trials based on these studies have failed so far. Our glia/astroglia perspective gives a fresh view to search for new targets.

More information: Yuqin Men et al. Astroglial FMRP deficiency cell-autonomously up-regulates miR-128 and disrupts developmental astroglial mGluR5 signaling, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2014080117

Shan?Xue Jin et al. Astroglial FMRP modulates synaptic signaling and behavior phenotypes in FXS mouse model, *Glia* (2020). DOI: 10.1002/glia.23915

Provided by Tufts University