Finding the clues for better autism treatments

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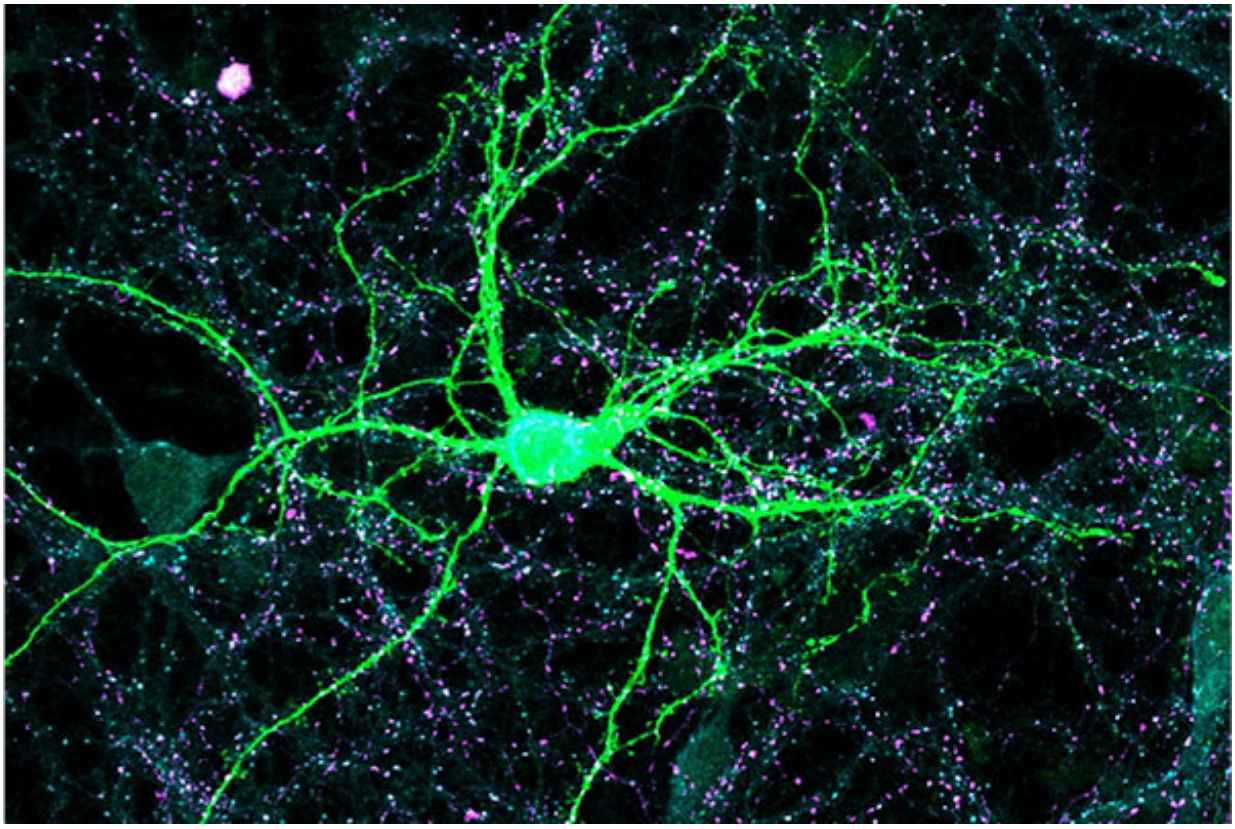

Credit: Medical University of South Carolina

As a researcher at Harvard Medical School, Christopher W. Cowan, Ph.D., used to watch autistic kids come onto campus to attend a special school.

They served as a reminder of why he was in his lab, teasing out clues to the possible causes and potential treatments for a disorder that affects one in 68 children. That image remains with him in his current lab at the Medical University of South Carolina, where he serves as the William E. Murray SmartState Endowed Chair in Neuroscience and vice-chairman of the Department of Neuroscience.

His latest study, published this week in *eLife*, sheds light on what might be going wrong in the regulation of genes that govern the brain's connectivity. "If we can identify the major players that cause brain development disorders, that creates therapeutic targets that pharmaceutical companies can use. They are desperate for new targets."

One potential target is the MEF2C gene, which is involved in muscle development and is highly expressed in the developing brain. Recent human genetic studies have shown that deletion or mutation of that gene is associated with a severe neurodevelopmental disorder with features of autism and intellectual disability.

Recent findings reveal that MEF2C is also linked to other brain-related disorders. The MEF2C gene is located at one of the 108 regions in the human genome associated with significant risk for schizophrenia, he said."Like autism, schizophrenia is a neurodevelopmental disorder - something goes wrong during brain development that gives rise to the later onset of symptoms. Both disorders are characterized by problems related to social interaction, language and often cognition.

The link between MEF2C and neurodevelopmental disorders is not surprising - it is enriched in parts of the developing brain important for cognition, social behaviors, sensory processing, motor control and language."

Led by MUSC postdoctoral fellow Adam Harrington, Ph.D., Cowan's

group wanted to look closer, because how exactly MEF2C functions in the developing brain is unclear.

First, they devised a way to delete MEF2C selectively in the developing mouse brain. They then studied the mutant mice in a chamber that allowed them to choose to socialize or interact with non-social items. "We noticed striking reductions in several social behaviors that are reminiscent of behaviors seen in autism. The deficient mice showed a robust decrease in social interaction with other animals."

The team had to get creative to study other symptoms, such as deficits in language and language development, which are difficult to test in mice. It turns out mice do "talk," but at ultrasonic frequencies beyond the 20 kilohertz that humans can hear.

Using special microphones, the researchers put male mice in the presence of sexually-receptive females - a socially-motivated scenario - and measured the amount and type of vocalizations. An isolated male mouse will emit one or two vocalizations in about five minutes. With a female present, that changes to around 1,000 calls. The MEF2C mutant mice generated about 80 percent fewer ultrasonic calls, and the structure of the calls was often very abnormal.

Dr. Christopher W. Cowan used special microphones to listen to mice interact. They speak at ultrasonic frequencies beyond what humans can hear. Credit: Sarah Pack

The researchers also monitored repetitive movements, another characteristic behavior that can be seen on the autism spectrum. "We noticed that the mutant mice were frequently jumping and rearing in the corners of their cages," he said. The researchers observed a 300 percent increase in this repetitive movement and increases in other stereotyped movements.

The mutant mice also had large deficits in learning and memory, Cowan said.The new findings go beyond autism, given that the researchers are

finding critical brain development roles for MEF2C. "An estimated 40 percent of autistics have co-occurring intellectual disabilities. People often associate autism with Rain Man or geniuses who are just socially awkward, but that's actually not the most common variety of autism."

MEF2C is a transcription factor, meaning that it works by regulating the expression of many other genes, Cowan explained. The research team found that a significant number of genes implicated in autism are abnormally expressed without MEF2C. Currently, there are hundreds of autism-linked genes, he said, but the fact that a single gene can influence so many different autism risk genes positions MEF2C as a central player in typical brain development.

"A disruption of this one gene has a profound effect," he said.

Not only did the researchers study the change in autism-like behaviors and the affected dysregulated genes, but they also looked at the impact of MEF2C on brain activity and the proper formation of brain connections. Cowan said his research supports one of the prevailing theories about the underlying cause of autism that points to an imbalance in the connections or synapses formed between brain cells.

"What we found was really striking," Cowan said. "Without MEF2C, there's a decrease in the connections that excite brain activity, and a big increase in connections that inhibit brain activity."

In the brain regions analyzed, these effects combined to cause a dramatic reduction in brain activity. This finding fits with the idea that neurodevelopmental disorders, like schizophrenia and autism, are likely caused by a disruption of the proper balance of synaptic connections in the brain, he said. One leading theory is that autism is caused by a change in synapse balance that produces hyperactivity of brain circuits. Cowan's findings suggest that decreasing brain activity also might

produce autism-related behaviors that co-occur with intellectual disability.

Researchers were able to "rescue" this effect in the mice by putting MEF2C back into the cells where it had been deleted, exploring the detailed mechanism of how this gene works.

"Our data strongly suggest that MEF2C in the brain is responding to patterns of activity. As the brain is forming and making these connections, the neurons become more and more activated. MEF2C is critical because it regulates downstream gene products that help to shape how the neurons will form, and refines their balance of connections. If you lose that balance, you get a completely abnormal set of connections."

Earlier studies by Cowan's team found that MEF2 family proteins play a key role in shaping how the brain forms its connections during development. "The chemical synapses formed between neurons during early brain development are thought to form very robustly, but they are pruned through late adolescence. MEF2 proteins, including MEF2C, appear to play an essential role in this important process."

One of the goals moving forward is to define the window of opportunity for reversibility. "My guess is that there is a period in early development that is crucial for MEF2C's function, but more research is needed to know that for sure."

Recent human sequencing studies suggest that a majority of what causes autism might be explained by genetic vulnerability, he said. "Most aspects of biology involve an interaction between genes and the environment. Environmental aspects are particularly complex and vary from individual to individual."

However, analysis of the influence of genetics has allowed researchers to

better define likely autism risk factors. "That's the ultimate goal, of course. If you can identify specific genetic causes of a developmental disorder and understand the function of those genes in development then you can potentially devise targeted therapies to improve patients' lives."

More information: Adam J Harrington et al, MEF2C regulates cortical inhibitory and excitatory synapses and behaviors relevant to neurodevelopmental disorders, *eLife* (2016). DOI: 10.7554/eLife.20059

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