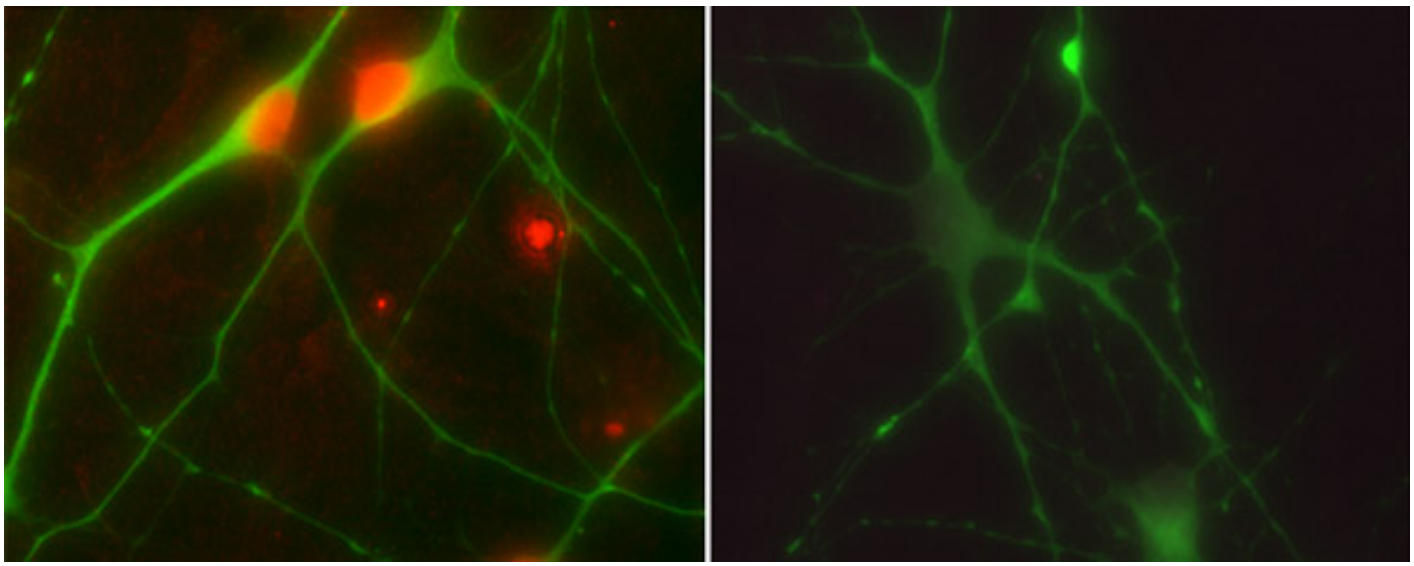
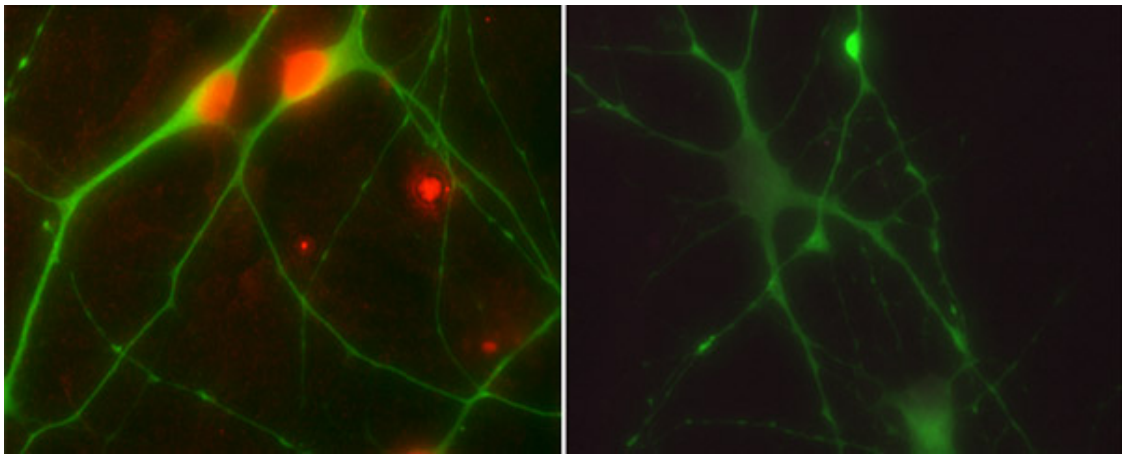
NEWS

Growth factor rescues neurons made from boys with Rett

BY **KATIE MOISSE**

18 NOVEMBER 2014





Mutant model: Neurons made from a boy with Rett syndrome (right) lack the MeCP2 protein (red, left).

Neurons derived from the skin cells of boys with Rett syndrome can help screen potential treatments for the disorder, suggest unpublished results presented yesterday at the **2014 Society for Neuroscience annual meeting** in Washington, D.C.

Rett syndrome is a developmental disorder caused by mutations in the **MeCP2** gene, located on the X chromosome. The mutations abolish the MeCP2 protein, which is necessary for normal neuronal function.

The disorder affects girls almost exclusively, as MeCP2 mutations are usually fatal in boys. But some boys have rare mutations that cause mild symptoms. Because girls have two X chromosomes, only some of their cells express the mutated copy of the gene. By studying cells from boys with Rett, the researchers avoid the time-consuming search for only mutant cells.

In the new study, researchers used skin cells from two boys with Rett syndrome to create so-called induced pluripotent stem cells. One of the boys has a nonsense mutation, which prematurely stops MeCP2 production. The other boy has a missense mutation that changes the amino acid sequence; it also blocks MeCP2's expression.

The researchers coaxed the stem cells to become neurons and let them **mature in the presence of star-shaped support cells called astrocytes**. This environment enables neurons to form connections, called **synapses**, with each other.

As expected, these neurons all lack MeCP2. They also form fewer synapses and show impaired excitatory signaling, meaning they fire less frequently than control neurons do. The controls are neurons derived from the boys' fathers, who are genetically similar but carry a normal version of MeCP2.

"We have established a system for people to get mature neurons in a reproducible and fast fashion," says **Xin Tang**, who did the work as a graduate student in **Gong Chen's** lab at Pennsylvania State University. "It opens a lot of possibilities."

The researchers used the cells to test the effects of insulin-like growth factor, or IGF. This hormone **eases symptoms in a mouse model of Rett** syndrome and is being tested in **children with Rett** as well as **other autism-related disorders**. IGF normalizes excitatory signaling in the cells.

Treatment with brain-derived neurotrophic factor (BDNF), another growth factor, has similar effects. Compounds that stimulate BDNF production have been shown to **improve symptoms in a mouse model of Rett syndrome**.

Neither IGF nor BDNF has any effect on the control neurons, suggesting that they target defects caused by MeCP2 loss. Introducing normal MeCP2 into the mutant neurons also normalizes signaling. The researchers plan to use the cells to screen other candidate drugs.

*For more reports from the 2014 Society for Neuroscience annual meeting, please **click here**.*