Team sheds light on genetic mutations in autism disorders

January 20 2015

Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

Recent research has linked autism with a lack of "pruning" in developing brain connections, but a new Dartmouth study suggests instead it is the excessive growth of new connections that causes sensory overload in people with the disorder.

The results, which have broad implications for understanding the neurobiological basis of autism spectrum disorders, appear in *The Journal of Neuroscience*.

"We've been working on understanding how dysfunction of the gene Pten, which is known to cause some cases of autism, effects neuronal development, and I believe our findings represent the best understanding in science today for how an autism candidate gene changes the functional characteristics of developing neurons," says senior author Bryan Luikart, an assistant professor of Physiology and Neurobiology in the Geisel School of Medicine at Dartmouth.

Mutations in the gene Pten are among the most common single-gene mutations that cause autism and a group of interrelated syndromes. People with these diseases have increased chances of having autism, intellectual disability and epilepsy. Luikart's team is investigating the neurobiological basis of the complex symptoms of autism by modeling genetic changes associated with autism in humans in neurons of mice. For their new study, the researchers generated a model in which they injected retroviruses into the brains of developing mice to both knockout the Pten gene and to label the knockout neurons with a fluorescent marker. This allowed them to study how turning off the gene alters the structural and electrical development of the neurons. They found that knocking out the Pten gene caused overt overgrowth of the neurons, which resulted in an increase in the number of excitatory synapses, or the connections that transmit signals from a nerve cell to another cell. The ultimate result of this is that the neurons become hyperactive.

Recent media coverage has surrounded the idea that autism is associated with a lack of "pruning" or refinement of excitatory synapses later in development. But the Dartmouth study argues against this, saying it is not a failure of "pruning" that results in the ultimate increase in excitatory synapses, but an increase in new production of excitatory

synapses. Further, they found a tight interrelationship between the structural and functional changes produced by the Pten gene knockout.

"The broader implication for this is that mutations in the gene Pten in humans likely result in an increased developmental proliferation of excitatory synaptic connections," Luikart says. "This may result in a given sensory experience stimulating neurons or even whole brain regions that would never be excited in a normal brain. Conceptually, this could be the neurobiological basis for the inappropriate responses to sensory stimulation that is often characteristic of patients with autism."

Provided by Dartmouth College