Deletions in the 22q11 gene associated with autism and other behavioral diseases disrupt cellular and molecular mechanisms that ensure normal development of interneurons, according to recent research.

22q11 deletion syndrome affects 1 out of every 2,000-4,000 newborns. In addition to autism and other behavioral conditions, children with the disorder may also suffer from cleft palate, heart defects, immune system deficits, growth delay, kidney problems, hearing loss, and endocrine issues.

Writing in the Proceedings of the National Academy of Science, researchers at George Washington University in Washington, DC, show that deletions in 22q11.2 disrupt cortical circuit development in a mouse model. Early generated parvalbumin-expressing interneurons—which have relatively short axons and inhibit activity by other neurons—are made in the right numbers at their birthplace outside of the cortex, but don’t move properly into the cortex where they are needed to control circuit activity. That’s mainly because of diminished expression of activity of a key regulatory pathway for migration, the Cxcr4 cytokine receptor, the researchers conclude in their most recent study (Meechan et al., 2012).

In previous research, Meechan et al found that projection neurons—key cortical neurons with longer axons that go to more distant regions of the brain and have neurotransmitters causing more activity—were made in the right numbers at their birthplace outside of the cortex in a 22q11.2 mouse model (Meechan et al., 2009). This research showed that in cases of 22q11 deletion, “interneurons don’t get to the right spot, so the proper brain circuitry never develops,” says David R. Lynch, MD, PhD, Professor of Neurology at University of Pennsylvania in Philadelphia and attending physician at Children’s Hospital of Philadelphia. “It’s not a degenerative process.”

The team’s more recent findings are an important step forward, says lead author Anthony-Samuel LaMantia, PhD, Director of the GWU Institute for Biomedical Science. “We’ve identified a clear cellular target that causes change in brain circuitry,” LaMantia notes. “Now, with a mouse model and genetic tools, we can look more at developmental processes that occur before the brain is built and the behavior happens.”

The Study
The researchers examined mice with deletions of the region on chromosome 16 that is analogous to the 1.5 megabases missing in patients with 22q11 deletion syndrome, except for four genes. Researchers used a genetic marker to identify interneurons that travel to the cerebral cortex and distinguish them from those that don’t. They used microarrays on the interneurons that don’t make the trip to discern differences in Cxcr4 protein expression in those cells.

Since Cxcr4 was reduced in migrating interneurons, the researchers discerned that diminished Cxcr4 altered interneuron migration in the developing mouse cortex. “Thus, diminished 22q11.2 gene dosage disrupts cortical circuit development by modifying a critical molecular signaling pathway via Cxcr4 that regulates cortical interneuron migration and placement,” write Meechan et al.
A Piece of the Puzzle

The more recent paper is important because it identifies differences in the brains of patients with 22q11 deletion that can lead to behavioral and mental health disorders, says Dr. Lynch. The findings “may eventually help identify circuitry abnormality that we could selectively intervene upon,” he adds.

The researchers are working toward that goal. Next, they will try to find out how faulty signaling by Cxcr4 causes affected interneurons to lose their way and how that affects the building of brain structures. Dr. LaMantia says another aspect of research should address “whether Cxcr4-mediated change is specifically correlated with changes in behavior.”

Answers to these questions could identify a target for drug intervention. “Once we know why interneurons are in the wrong place, we can use that information and mouse models to see if drugs modify aberrant circuitry that drive behavioral changes,” says Dr. LaMantia. That knowledge could benefit human patients with 22q11 deletion, he adds.

The most recent findings by Meechan et al are important because the research “tells us the problem is with how the brain develops to begin with, not damage that happens afterwards,” notes Elizabeth McPherson, MD, Director of Medical Genetics at the Marshfield Clinic, headquartered in Marshfield, Wisconsin. “The more we understand about what’s different in the brains of people with 22q11 deletion, the closer we are to understanding why the majority have learning problems, and a significant number have mental health issues,” adds Dr. McPherson.

References
