MedicalXpress

New clues to molecular understanding of autism

September 12 2011

The first transgenic mouse model of a rare and severe type of autism called Timothy Syndrome is improving the scientific understanding of autism spectrum disorder in general and may help researchers design more targeted interventions and treatments.

The research is described in a paper published last week by scientists at the University at Buffalo and Stanford University in the Proceedings of the National Academy of Sciences.

The transgenic mouse developed at UB exhibits the repetitive physical behaviors, altered social behaviors and impaired communication abilities associated not just with Timothy Syndrome but with autism spectrum disorder in general.

The fact that this mouse exhibited so many behavioral parallels with humans diagnosed with autism was both surprising and encouraging, the researchers say.

"This animal and the syndrome that it is associated with, provides one of the best chances to understand the underlying mechanisms of autism," says Randall L. Rasmusson, PhD, professor of physiology and biophysics in the UB School of Medicine and Biomedical Sciences and co-author on the PNAS paper.

That's because the link between this genetic mutation and Timothy Syndrome (TS) is very strong.

"Most genetic mutations linked with autism increase the chances of having autism by a very small factor," Rasmusson explains. "In contrast, 75-80 percent of people with this Timothy Syndrome mutation have autism spectrum disorder."

The mutation alters a very well-known protein, the voltage-gated L-type calcium channel, causing it to affect how much calcium moves into cells and when.

"The fact that TS arises from such a well-defined alteration in a well-known ion channel gives us the opportunity to study the specifics of this one particular route to autism," he continues. "In understanding the specific, we hope to develop a better understanding of autism in general."

The UB scientists say that this research paves the way toward understanding autism on the molecular level, a critical component that has not yet been sufficiently explored.

"As long as autism is diagnosed by a set of behaviors, it will be an ill-defined condition," explains Rasmusson, who brings to the research a personal understanding of the condition's behavioral aspects, since his son is severely affected by autism spectrum disorder.

"Once we start to determine some definitive biomarkers, possibly, as this research suggests, calcium handling indicators, we will be able to appreciate the differences between how different individuals present with this condition," he says.

That understanding will have implications for treatments, too, because as the researchers point out, while 75 to 80 percent of patients with the mutation were diagnosed with autism, 20 percent did not.

"Once we determine how TS is related to being diagnosed with autism spectrum disorder, we have an opportunity to explore how that 20 percent of individuals manage to override the mutation's effect," says Glenna C.L. Bett, PhD, professor and vice chair of the Department of Gynecology-Obstetrics, professor of physiology and biophysics in the UB medical school and co-author on the PNAS paper. "Those mechanisms are likely to play a key role in developing interventional therapies for autism spectrum disorder."

The research also has the potential to help in modeling and understanding other psychiatric disorders, such as bipolar disorder and substance abuse and dependence.

Bett and Rasmusson were originally conducting research on calcium channels and their effects on heart function when they learned of research published in late 2004 showing that this single mutation in the L-type calcium channel could lead to Timothy Syndrome. At that point, they knew that developing a model of TS would be key to understanding the importance of this calcium channel not just in the heart but in other tissues, especially the brain.

"Cellular calcium activity is a dynamic process that can be modulated by behavior, drugs and the environment," Bett explains. "By understanding the Timothy Syndrome mutation and the consequences of altered calcium handling, we hope to develop a general understanding of the link between calcium and the molecular basis of brain function. Understanding this link will provide new avenues for pharmacological intervention."

Co-authors with Bett and Rasmusson are Patrick L. Bader, Mehrdad Faizi, Leo H. Kim, Scott F. Owen, Michael R. Tadross, Ronald W. Alfa, Richard W. Tsien and Mehrdad Shamloo, all of Stanford University.

Provided by University at Buffalo