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Study may point to new treatment approach for ASD

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Using sophisticated genome mining and gene manipulation techniques, researchers at Vanderbilt University Medical Center (VUMC) have solved a mystery that could lead to a new treatment approach for autism spectrum disorder (ASD).

Their findings, reported last month in the *Journal of Neuroscience*, broke new ground: for the first time a variation in a gene called ITGB3 was

found to alter the supply of the neurotransmitter serotonin in a mouse model of ASD.

ASD occurs predominantly in boys. About a third of people with ASD have elevated blood levels of serotonin. Variations in ITGB3 and in the gene for the serotonin transporter (SERT), which regulates the serotonin supply, have previously been linked to the disorder.

ITGB3 is the gene for integrin subunit beta3, a receptor protein that, in platelets, plays a role in blood clotting. What role, if any, does it play in autism?

To find out, the researchers combed through Vanderbilt's DNA databank, BioVU, which links DNA samples to the electronic health record. They were looking for associations between a variation in ITGB3 that is commonly found in people with ASD and neuropsychiatric disorders.

They got two strong hits in males but not females: attention deficit hyperactivity disorder (ADHD) and ASD.

The researchers then turned to a mouse model that expressed the beta3 variant. They found male mice with beta3 variant, but not females, exhibited autistic-like behaviors and increased blood serotonin levels.

When they blocked an enzyme known to be activated by integrin beta3, brain serotonin function in the animals returned to normal, said Ana Carneiro, PhD, assistant professor of Pharmacology at Vanderbilt.

This suggests integrin beta3 may be a potential treatment target for autism, said Carneiro's colleague in the study, James Sutcliffe, PhD, associate professor of Molecular Physiology and Biophysics and of Psychiatry and Behavioral Sciences. But it also raises more questions.

Variations in ITGB3 are sufficient to affect serotonin signaling. "But what's causing the social deficits in autism?" Carneiro asked. "Is it a serotonin problem or is it an integrin problem?" Or, in some cases, is it both? Those are the next questions to be addressed.

SERT has long been linked to ASD. Anti-depressive drugs called selective serotonin reuptake inhibitors or SSRIs, which increase the brain's supply of serotonin by blocking SERT, can relieve some of the rigid-compulsive traits and social communication deficits that characterize ASD.

"Now we have a model that 'pheno-copies' multiple aspects of what we see in humans," she said. The hope is that the mouse model will help solve the mysteries of ASD, including why males are more likely to develop the disorder than females.

The latest findings are the culmination of more than a decade of painstaking work. In 2006 Sutcliffe and colleagues at Vanderbilt and the University of Chicago first reported that ITGB3 was associated with people with ASD who also had elevated blood levels of serotonin.

Two years later Carneiro and her colleagues, working in a separate lab at Vanderbilt, reported that integrin beta3 physically associates with and regulates SERT activity in platelets.

More information: Michael R. Dohn et al. The Gain-of-Function Integrin β3 Pro33 Variant Alters the Serotonin System in the Mouse Brain, *The Journal of Neuroscience* (2017). DOI: 10.1523/JNEUROSCI.1482-17.2017

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