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Brain development switch could affect schizophrenia, other conditions

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An international team of scientists lead by researchers from Duke University and Johns Hopkins University have discovered a key "switch" in the brain that allows neurons to stop dividing so that these cells can migrate toward their final destinations in the brain.

The finding may be relevant to making early identification of people who go on to develop schizophrenia and other brain disorders.

"This work sheds light on what has been a big black box in neuroscience," said Nicholas Katsanis, Ph.D., co-senior author of the work and Jean and George Brumley Jr., MD, Professor of Developmental Biology, Professor of Pediatrics and Cell Biology. "It helps answer the question of what happens when neurons stop dividing and start moving along to populate the brain."

The study was published by *Nature* journal on April 6 in its advance online publication.

Katsanis predicts that, for perhaps 10 percent of psychiatric illness, the illness is primarily driven by defects in this switch system. "So we now have ways to interpret variation in humans, in a context that is relevant to their particular cases, to their physiology – that is where medicine will move next," Katsanis said.

Katsanis, who directs the Duke Center for Human Disease Modeling, and Akira Sawa, M.D., Ph.D., a Professor in the Department of

Psychiatry at Johns Hopkins, were introduced to each other by a clinical colleague who thought that Bardet-Biedl syndrome (BBS) proteins that are involved in transport duties within cells might have a role in schizophrenia. Katsanis is an expert in using BBS genetic mutations and proteins to learn more about other diseases. BBS is a complex genetic disease with autism-like symptoms, cognitive defects and depression. Sawa is an expert on DISC1, the protein named Disrupted in Schizophrenia 1, known to be a major susceptibility factor for schizophrenia and related disorders.

Together, they discovered that these proteins are involved in a key switch for neurons that is necessary for brain development. When DISC1 gains a phosphate group at a specific site, it recruits BBS1. When BBS1 is missing in this system, the team could observe defective neuron migration, while a model with no DISC1 at all leads to defects in both cell proliferation and migration.

We can now appreciate that some fraction of schizophrenia is truly developmentally regulated, Katsanis said.

"Even though the disease manifests itself after pubescence, scientists have suspected that the underpinnings are prenatal," he said. "We can greet this news with sadness or see it as an opportunity: we may have 20 years to help before a person starts experiencing symptoms, if we can develop techniques to use early enough."

The study also provides another example of how BBS proteins fit into neuroscience and provide another instance in which understanding of a rare phenotype (BBS) informs complex traits, like schizophrenia, profoundly, Katsanis said. "The trend in recent years has been to focus heavily on common disorders and to disregard disorders that might impact fewer people. Yet rare disorders continue to provide such important insights both into basic biological processes and complex

disease."

"With these findings, we have tools for interpretation in some schizophrenia cases," Katsanis said. About one in 100 children born go on to develop schizophrenia in early adulthood.

Now the scientists are engaged in medical re-sequencing of patients with psychiatric illness with a specific focus on the groups of proteins involved in the switch process. "We will be able to ask focused questions about the amount of variation that this particular system contributes to the complex landscape of genetic disease," Katsanis said.

Provided by Duke University Medical Center