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New study solidifies role of DISC1 in risk for schizophrenia and other mental illness

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Johns Hopkins researchers report the discovery of a molecular switch that regulates the behavior of a protein that, when altered, is already known to increase human susceptibility to schizophrenia and mood disorders.

The findings, published online in the journal *Nature*, expand the possibility of creating biomarkers that can better diagnose those with mental illnesses and track their treatment.

Building on previous studies at Hopkins, the new research further offers clues to why the Disrupted In Schizophrenia gene (DISC1) and its protein product plays so many distinct roles in the development and functioning of the brain.

The scientific team was led by Akira Sawa, M.D., Ph.D., a professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. They found one specific protein modification that governs DISC1's two most important functions: regulation of new neuron production in the cerebral cortex, or thinking part of the brain, and the programmed migration of these neurons, essential in the formation of the brain's architecture. If the switch malfunctions — if it allows too many new neurons or there's not enough migration, for example — the brain may not develop properly, leaving it ripe to develop mental illness.

Sawa says the switch appears to change the function of DISC1 from its

role in building new neurons to its role in neuron migration. This change occurs, he says, when the protein is modified through a biochemical process called phosphorylation, or attachment of a phosphate to the protein.

"It seems that just one specific protein modification is a key determinant that accounts for the two most important functions of this molecule," Sawa says.

The discovery is important because, Sawa says, having a means of identifying and tracking this molecular switch may strengthen diagnostic efforts, which currently rely mostly on patient behavior.

To find the switch, Sawa's team used mass spectrometry to look at tissue samples. Using an antibody they generated, Sawa's team realized that some of the protein had been modified and some had not. They then determined that the unmodified DISC1 and not the modified version was needed to regulate new neurons. The reverse was true for neural cell migration: the modified version of DISC1 bound to other proteins involved in facilitating cell movement, but not the unmodified one.

The researchers validated their findings by using their antibody which can specifically detect this protein modification in mouse models. They used the antibody to probe the brains of fetal mice at embryonic day 14, when neurons are being generated. Results showed that unmodified DISC1 was the predominant form of the protein. At day 18, when the mouse brain neurons typically are migrating, the team found mostly modified DISC1. This led the researchers to conclude that the modification acts a switch to determine whether DISC1 is involved in neurogenesis or cell migration.

Sawa says these findings are likely to be similar in humans, because mouse models of schizophrenia closely mimic some key biological

processes of human schizophrenia.

Sawa's team has already developed a version of the antibody that can be used to look at human brain tissue to test for the presence of the protein there.

Provided by Johns Hopkins Medical Institutions

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