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Neuron Growth Pathway Linked to Schizophrenia

A gene strongly implicated in schizophrenia is essential for normal brain development and the growth of new neurons in the adult brain, according to new research by Howard Hughes Medical Institute (HHMI) scientists.

A research team led by HHMI investigator Li-Huei Tsai at the Massachusetts Institute of Technology found that a mutated form of the gene disrupts the growth and development of brain cells. Their findings may provide new targets for the development of novel drugs to treat schizophrenia.

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— Li-Huei Tsai

The researchers also showed that the gene DISC1 is part of the signaling pathway targeted by the mood stabilizer lithium. "For the first time, we have linked an evolutionarily conserved signaling pathway with schizophrenia," says Tsai. "The beauty of knowing that this is the signaling pathway is that researchers now have many new targets to aim for as they develop drugs to treat schizophrenia."

Tsai and her colleagues published their studies on March 20, 2009, in the journal *Cell*.

Schizophrenia is a common mental illness, affecting up to one percent of adults worldwide. Symptoms begin in late adolescence or early adulthood and can include delusions, hallucinations, paranoia, depression, and cognitive impairment.

Scientists have only just begun to unravel the complicated genetics of schizophrenia, says Tsai. Mutations in a variety of genes appear to increase risk for the disorder. In the early 1990s, researchers linked DISC1 to mental illnesses prevalent in a large Scottish family. Over five generations, many members of the family had developed schizophrenia, bipolar disorder, and other mood disorders. Each family member diagnosed with mental illness also carried a broken copy of the DISC1 gene. "DISC" stands for "disrupted

in schizophrenia.”

“Most people in the field consider DISC1 to be very important in schizophrenia and related disorders,” says Tsai.

When Tsai set out to understand DISC1’s role in brain development and how defects in the gene might lead to schizophrenia, she first studied the cells of embryonic mice to see where the protein was produced in abundance. She found large amounts of DISC1 in brain stem cells, which are crucial for proper brain growth.

Next, Tsai’s team examined DISC1 in the brain stem cells of adult mice. Also called neural progenitor cells, brain stem cells are active in only a few regions of the adult brain, including the hippocampus, a seahorse-shaped structure previously implicated in mood disorders. Throughout life, these cells continually grow, divide, and spin off new neurons, a process dubbed neurogenesis.

Tsai and her colleagues also found large amounts of DISC1 in the brain stem cells of adult mice. But when the scientists reduced the amount of DISC1 in those adult cells – simulating what occurs in people carrying a broken version of the gene – she found that the cells failed to grow and divide. “We show that this one gene product is clearly a key regulator of the proliferation of neural progenitors during embryonic brain development and adult neurogenesis,” says Tsai.

Furthermore, the researchers found that animals that had no DISC1 in their brain stem cells displayed behaviors that mimic schizophrenia in people. The mice skittered around their cages as if agitated, behavior considered a parallel to mania in people. When the mice were given a forced-swim test, which is commonly used by researchers to measure how antidepressant drugs affect the behavior of mice, the DISC1-deficient mice seemed depressed and did not swim for long. “When we downregulated DISC1 in the dentate gyrus, which is part of the hippocampus, the mice displayed abnormal behavior consistent with schizophrenia,” Tsai says.

Tsai and her colleagues then dissected the precise molecular role that DISC1 plays in brain stem cells. She found that the protein acts like lithium, a drug commonly prescribed as a mood stabilizer for patients with bipolar disorder. In particular, DISC1 inhibits the enzyme GSK3beta, the same enzyme inhibited by lithium. “Lithium is known to inhibit GSK3beta directly and indirectly, so it looks like DISC1 behaves like endogenous lithium,” says Tsai. Bipolar disorder and schizophrenia are often diagnosed together, and many psychiatrists consider the two disorders intimately linked, perhaps even lying along a spectrum.

In a final set of experiments, Tsai’s team depleted DISC1 activity in the brain stem cells of adult mice, and then treated the mice with a molecule that inhibits GSK3beta much like lithium does. The brain stem cells returned to normal, revving up production of new neurons. Further, the previously agitated and depressed animals recovered and began behaving normally.

“This drug-like small molecule completely reverses the deficiencies seen in the neural progenitor cells while alleviating the abnormal behavior in the mice,” says Tsai.

Tsai’s team also identified the key segment of the DISC1 protein that inhibits GSK3beta. Knowing the structure of this protein segment may help drug developers as they pursue better treatments for schizophrenia and related disorders, Tsai says. “We hope this information will lead to better treatments for schizophrenia, which are sorely needed.”

Tsai is now working with geneticists at the Stanley Center for Psychiatric Research in Cambridge, Massachusetts, where she holds a joint appointment, to identify additional variations in the DISC1 gene. “We need to get a handle on the genetics of schizophrenia,” says Tsai. “But now we know how DISC1 probably contributes to the disorder, which is a big step.”