

Mental health means new neurons?

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A gene strongly associated with schizophrenia and other neuropsychiatric disorders regulates the birth of new neurons in the adult brain, according to new research. [The study](#), published in *Cell* this week, supports a controversial theory linking diseases such as schizophrenia and depression to neurogenesis and provides new targets for the treatment of psychiatric conditions.

"This is the first time anybody has ever shown that this protein [coded by the gene] directly regulates the number of neural progenitors," said [Li-Huei Tsai](#), main author and neuroscientist at the Picower Institute of Learning and Memory at the Massachusetts Institute of Technology.

Previous studies have linked schizophrenia to disturbances in neurogenesis in a brain region called the hippocampus and suggested that anti-depressant medications such as Prozac work by stimulating hippocampal neurogenesis. The new findings link the gene, *DISC1*, to a well-studied signaling pathway that controls neurogenesis and the development of the nervous system.

"It really fits in with a lot of background information to suggest that hippocampal neurogenesis in particular is potentially a process which is going wrong in psychiatric illness," said [Ben Pickard](#), a medical geneticist at the University of Edinburgh who was not involved in the study.

Researchers first made the link between *DISC1* and psychiatric disorders [in 2001](#) -- a large Scottish family with a high incidence of schizophrenia and bipolar disorder displayed a specific translocation in the gene's sequence. Since then, Tsai and others have linked other mutations in the gene to psychiatric disorders. There have been suggestions that *DISC1* is involved in [early cortical development](#) and [integrating](#) newly produced neurons in the adult brain, but "because there were no sequence matches in the database," explained Pickard, "it was very hard to figure out what it does."

Tsai, who is a Howard Hughes Medical Institute investigator, and her colleagues showed that the *DISC1* protein interacts with a protein called GSK3-beta, muffling its effect. The role of GSK3-beta is to inhibit the function of the protein beta-catenin, which promotes stem cell proliferation. In essence, the job of *DISC1* is to inhibit the inhibition of neurogenesis. If a mutation in the gene is blocking the protein from doing its job, GSK3-beta is left exerting its inhibitory effect on neuronal growth, potentially causing different psychiatric illnesses. When the researchers silenced *DISC1* in the hippocampus of adult mice using RNA interference, the mice showed symptoms associated with schizophrenia and depression.

Interestingly, Pickard and Tsai noted that GSK3-beta is the molecular target of lithium, the most effective treatment available for bipolar disorder. Although the compound has been used for decades, how it works is largely unknown. Tsai's findings suggest that lithium's mechanism may involve stimulating neurogenesis. "One of the most exciting aspects of the study is the parallel between this one function and lithium," said Tsai.

That knowledge may also provide a genetic means of predicting which patients will respond to lithium. Indeed, the clear link the study makes between the genetics and the pathophysiology is "giving us clues as to why the medications might work in some people and not in others," said [David Porteous](#), a molecular geneticist also at the University of Edinburgh who was not involved in the present work, and who coauthored the original *DISC1* family study. "In that regard, it's not just a very good piece of science; it's also giving us a roadmap to what we should be doing next."

That will involve working out the fine details of how *DISC1* and GSK3-beta work together, and how other molecules are involved, Porteous said -- a project which Tsai's lab is now working on. Three years ago, Porteous, Pickard and others implicated *DISC1* in [another pathway](#) central to brain development. How the two interact may yield further clues to the molecular underpinnings of psychiatric illnesses. "We're starting to develop a kind of genetic network around the *DISC1* pathway," he said, which points to "targets for intervention in a much more rational fashion than what's been possible."