Genetics of mental health yield surprising connections but no cures

A brother with schizophrenia. A mother with bipolar disorder. Families with a history of mental health conditions can often feel haunted by the chance they might also develop the condition. And many do. Even before candidate genes were named, mental health disorders were well known for they way they can carry through families. The path to finding these genes has uncovered some interesting connections between schizophrenia, autism, our immune systems and the delicate spaces where our brain cells connect and our personality is formed.

Siddhartha Mukherjee is a well known physician and author. He also has a strong family history of mental illness. Two of his uncles and at least one of his cousins had severe conditions that required significant care and sometimes institutionalization in their adulthoods. Mukherjee and his father traveled to Calcutta to visit his cousin, Moni who is institutionalized due to schizophrenia. He detailed their trip in the New Yorker:

> Moni is not the only member of the family with mental illness. Two of my father's four brothers suffered from various unravellings of the mind. Madness has been among the Mukherjees for generations, and at least part of my father's reluctance to accept Moni's diagnosis lies in a grim suspicion that something of the illness may be buried, like toxic waste, in himself.

More than 100 sites in the human genome have been linked to schizophrenia, making it difficult to pinpoint the physiological mechanisms that go awry in any particular individual or family who suffer from the disease. But in the last year, researchers have further studied a few of these genes linking them to the control mechanisms of the spaces between our neurons, called synapses. Some are also linked to autism and, surprisingly, our immune system.

MIT neuroscientists have shown that by mutating the SHANK3 gene in two different ways they can cause development of autism or schizophrenia-like conditions in mice. The SHANK3 gene makes a protein that acts as a scaffold in the synapses between neurons. It helps to hold and organize all the proteins in the synapse and work to create the electrochemical signals that move between them. From MIT News:

> [MIT neuroscientists Guoping] Feng wanted to find out how these two different mutations in the Shank3 gene could play a role in such different disorders. To do that, he and his colleagues engineered mice with each of the two mutations: The schizophrenia-related mutation results in a truncated version of the Shank3 protein, while the autism-linked mutation leads to a total loss of the Shank3 protein.

genome

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The two different mutations affected the

animals on a time scale that resembles thedevelopment of autism and schizophrenia in humans. Mice with the autism-like mutation developedproblems early in their development, while mice with the schizophrenia-like mutation weren't affected untillater in life. In humans, autism usually develops before the age of three while schizophrenia most oftenaffects people in young adulthood.

Another candidate gene is C4A. Its part of the major histocompatibility complex, a huge and complex set of genes that control immunity, cellular clean up, and organ transplant compatibility. The gene and its proteins are again linked to the spaces between neurons. In normal human development we start out with far too many neuronal connections. As we move through puberty thousands of extraneous connection are eliminated in a process called synaptic pruning. C4A and B are involved in picking which of our synapses stay and which go. Mukherjee writes about C4A in his New Yorker piece:

> Perhaps C4A, like the other immunological factors that Stevens had identified in synapse pruning, marks neuronal synapses destined to be eliminated during normal brain development. During the maturation of the brain, microglia recognize these factors as tags and engulf the tagged synapses. Variations in the C4A gene cause different amounts of the C4A protein to be expressed in the human brain. The overabundance of C4A protein in some people contributes to an excessively exuberant pruning of synapses—thereby decreasing the number of synapses in the brain, which would explain the well-established fact that schizophrenic patients tended to have fewer neuronal connections. That the symptoms of schizophrenia break loose during the second and third decades of life makes sense, in retrospect: adolescence and early adulthood are periods when synaptic pruning reaches a climax in the regions of the brain that govern planning and thinking.

It's possible that the pruning process is too rigorous or it doesn't stop when it should for people with schizophrenia. That could cause essential synapses to be destroyed and lead to the symptoms of the condition. That discovery is notable because its one of the first times scientists have been able to pinpoint how a gene known to be associated with schizophrenia might mechanistically be going wrong. Columbia

University geneticists Ryan Dhindrsa and David Goldstein write in a Nature comment [behind a paywall]:

> One of the main problems in deciphering the molecular basis of schizophrenia is that there is a near complete absence of clearly associated biological changes. However, schizophrenia is a strongly genetic disorder, and for decades many have believed that understanding the genetics involved might provide a way to begin to dissect the biology of the disease. Until now, following this line of reasoning has been a largely frustrating experience.

Studies like these show how much work there is to be done to understand all the genetic variations that cause the development of schizophrenia. For any one person who develops the condition there maybe a unique combination of those 108 identified loci that are at play. We may soon think of schizophrenia like we do cancers, where the genetic anomalies more than symptoms help us to describe a person's condition and identify potential treatments. This will likely not happen soon enough for Mukherjee's father to understand the mental health history in his family. But there is the potential that Mukherjee's daughters might.

Meredith Knight is a freelance science and health writer. Follow her on Twitter @meremereknight.