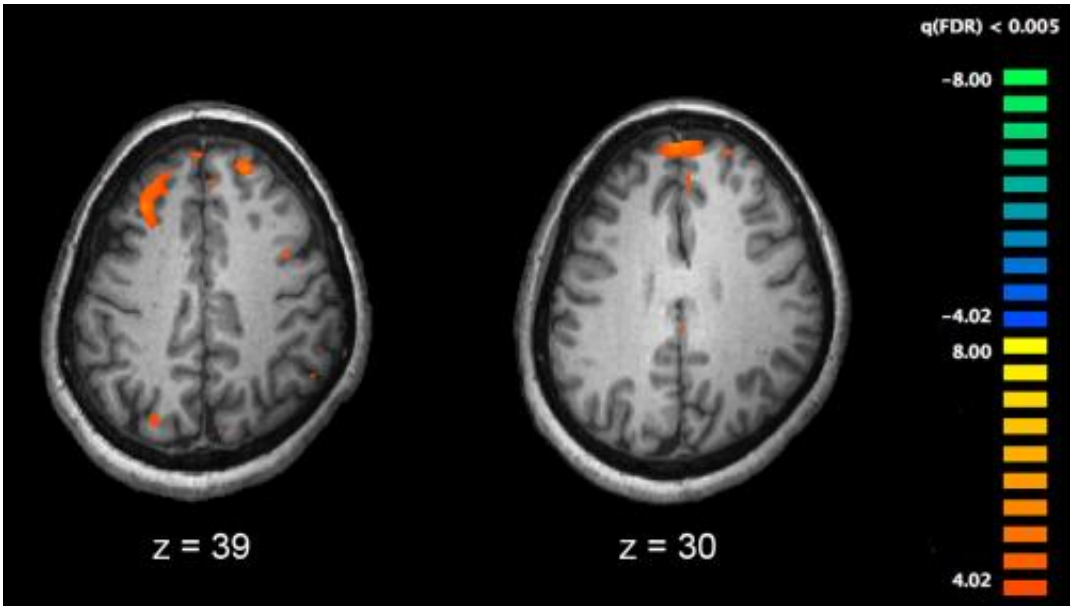
Schizophrenia-associated gene variation affects brain cell development

July 3 2014



Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Johns Hopkins researchers have begun to connect the dots between a schizophrenia-linked genetic variation and its effect on the developing brain. As they report July 3 in the journal *Cell Stem Cell*, their experiments show that the loss of a particular gene alters the skeletons of

developing brain cells, which in turn disrupts the orderly layers those cells would normally form.

"This is an important step toward understanding what physically happens in the developing brain that puts people at risk of schizophrenia," says Guo-li Ming, M.D., Ph.D., a professor of neurology and neuroscience in the Johns Hopkins University School of Medicine's Institute for Cell Engineering.

While no single genetic mutation is known to cause schizophrenia, so-called genomewide association studies have identified variations that are more common in people with the condition than in the general population. One of these is a missing piece from an area of the genome labeled 15q11.2. "While the deletion is linked to schizophrenia, having extra copies of this part of the genome raises the risk of autism," notes Ming.

For the new study, Ming's research group, along with that of her husband and collaborator, neurology and neuroscience professor Hongjun Song, Ph.D., used skin cells from people with schizophrenia who were missing part of 15q11.2 on one of their chromosomes. (Because everyone carries two copies of their genome, the patients each had an intact copy of 15q11.2 as well.)

The researchers grew the human skin cells in a dish and coaxed them to become induced pluripotent stem cells, and then to form neural progenitor cells, a kind of stem cell found in the developing brain.

"Normally, neural progenitors will form orderly rings when grown in a dish, but those with the deletion didn't," Ming says. To find out which of the four known genes in the missing piece of the genome were responsible for the change, the researchers engineered groups of progenitors that each produced less protein than normal from one of the

suspect genes. The crucial ingredient in ring formation turned out to be a gene called CYFIP1.

The team then altered the genomes of neural progenitors in mouse embryos so that they made less of the protein created by CYFIP1. The brain cells of the fetal mice turned out to have similar defects in structure to those in the dish-grown human cells. The reason, the team found, is that CYFIP1 plays a role in building the skeleton that gives shape to each cell, and its loss affects spots called adherens junctions where the skeletons of two neighboring cells connect.

Having less CYFIP1 protein also caused some neurons in the developing mice to end up in the wrong layer within the brain. "During development, new neurons get in place by 'climbing' the tendrils of neural progenitor cells," Ming says. "We think that disrupted adherens junctions don't provide a stable enough anchor for neural progenitors, so the 'rope' they form doesn't quite get new neurons to the right place."

The researchers say they also found that CYFIP1 is part of a complex of proteins called WAVE, which is key to building the cellular skeleton.

Many people with a CYFIP1 deletion do not get schizophrenia, so the team suspected the condition was more likely to arise in people with a second defect in the WAVE complex.

Analyzing data from genomewide association studies, they found a variation in the WAVE complex signaling gene ACTR2/Arp2 that, combined with the CYFIP1 deletion, increased the risk of schizophrenia more than either genetic change by itself.

In adding to science's understanding of schizophrenia, the study also shows how other mental illnesses might be similarly investigated, the researchers say. "Using induced pluripotent stem cells from people with

schizophrenia allowed us to see how their genes affected brain development," says Song. "Next, we'd like to investigate what effects remain in the mature brain."

Provided by Johns Hopkins University School of Medicine