Powerful genetic regulator identified as risk factor for schizophrenia

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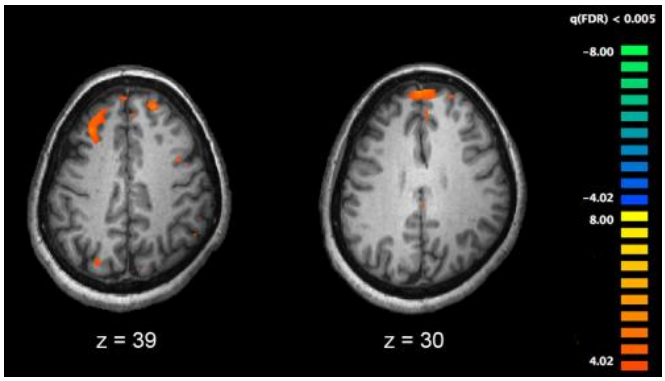

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

By turning skin cells into brain neurons, researchers at the Icahn School of Medicine at Mount Sinai have identified that certain tiny molecules aiding in gene expression, known as microRNAs (miRNAs), are under-expressed in the brains of the 14 schizophrenia patients they studied. Their findings, published online today in the journal *Cell Reports*, show that one of these molecules, a miRNA known as miR-9, is a risk factor that controls the activity of hundreds of genes.

The researchers, led by Kristen Brennand, PhD, Assistant Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai and Gang Fang, PhD, Assistant Professor in the Department of Genetics and Genomic Sciences, Icahn School of Medicine, found that miR-9 was significantly under-expressed in cells from four schizophrenic patients, compared to six control participants. The findings were replicated in a larger sample, from the National Institutes of Health, of ten childhood-onset schizophrenic patients and ten controls.

"Schizophrenia is a very complex disorder that is believed to be strongly genetically influenced—there are probably more than 1,000 genes contributing to its development, some or many of which will affect individual patients," says Kristen Brennand, PhD, Assistant Professor of Psychiatry, Icahn School of Medicine at Mount Sinai, and one of the study's lead authors. "The better we are able to fill in the pieces to this very difficult puzzle, the more we can think about treatment, and, better yet, prevention."

The genes controlled by miR-9 appear to play a role in the fetal development of neurons, and in where these neurons eventually settle in the brain. If these genes are not as active as they should be, the brain will likely be miswired, the authors suggest. miR-9 is only the second such powerful miRNA linked to the devastating psychiatric disorder, but researchers believe others may be involved.

Dr. Brennand also says that based on their findings, as well as those of other researchers in the field, many genes recently found to be linked to schizophrenia tend to be genes that are expressed during fetal development—even though schizophrenia usually becomes symptomatic in adulthood. "The idea that children are born with schizophrenia should take the pressure off of parents," she says. "This is a heritable disease that runs in families, and it's no one's fault that someone was born with this genetic risk."

Because the slow progress in decoding schizophrenia comes from the lack of live brain tissue to study, the research team combined expertise in stem cell biology, neurobiology, genomics, and systems biology to pioneer a new approach. They obtained skin samples from patients, reprogrammed them into induced

pluripotent stem cells, and then differentiated these cells into precise subtypes of human neurons.

"This has allowed us to begin to ask how and why neurons derived from schizophrenia patients differ from those derived from people who are unaffected by the disorder," Dr. Brennand says. "The goal of our research is to not just understand the genetic mechanisms contributing to schizophrenia, but ultimately to develop a screening platform that we can use to identify new therapeutics for the treatment of this debilitating disorder."

The team faced some challenges at the beginning of the project. "miR-9 was not the only miRNA that is differentially expressed in cells from schizophrenia patients compared to control participants," said Gang Fang PhD, an Assistant Professor in the Department of Genetics and Genomic Sciences and the other lead author of the study. "In fact, tens of miRNAs reached statistical significance and we wanted to identify a smaller number of key players.

We took a systems biology approach, where we integrated miRNA expression, gene expression, global gene regulatory networks, and proteomic data".

"This approach found evidence suggesting miR-9 has the most significant change of regulatory activity in addition to the expression change of itself," added Dr. Fang. "We hope this general approach will also help the discovery of additional genetic regulators of schizophrenia and other diseases."

D. Brennand and Dr. Fang highlight that their team's findings validate results of an earlier study published March 9 in *JAMA Psychiatry*, in which a genetic screen, taken from the blood of 35,000 schizophrenia patients, found either low expression or mutations in the hundreds of genes that miR-9 controls.

Provided by The Mount Sinai Hospital

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