Faulty genomic pathway linked to schizophrenia developing in utero, study finds

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Credit: University at Buffalo

The skin cells of four adults with schizophrenia have provided an unprecedented "window" into how the disease began while they were still in the womb, according to a recent paper in *Schizophrenia Research*.

The paper was published online in January by researchers at the Jacobs School of Medicine and Biomedical Sciences at the University at

Buffalo in collaboration with the Icahn School of Medicine at Mount Sinai. It provides what the authors call the first proof of concept for their hypothesis that a common genomic pathway lies at the root of schizophrenia.

The researchers say the work is a first step toward the design of treatments that could be administered to pregnant mothers at high risk for bearing a child with schizophrenia, potentially preventing the disease before it begins.

Multiple mutations

"In the last 10 years, genetic investigations into schizophrenia have been plagued by an ever-increasing number of mutations found in patients with the disease," said Michal K. Stachowiak, PhD, senior author on the paper, and professor in the Department of Pathology and Anatomical Sciences in the Jacobs School of Medicine and Biomedical Sciences at UB.

PHOTO available here.

"We show for the first time that there is, indeed, a common, dysregulated gene pathway at work here," he said.

The authors gained insight into the early brain pathology of schizophrenia by using skin cells from four adults with schizophrenia and four adults without the disease that were reprogrammed back into induced pluripotent stem cells and then into neuronal progenitor cells.

"By studying induced pluripotent stem cells developed from different patients, we recreated the process that takes place during early brain development in utero, thus obtaining an unprecedented view of how this disease develops," said Stachowiak. "This work gives us an

unprecedented insight into those processes."

A central intersection point

The research provides what he calls proof of concept for the hypothesis he and his colleagues published in 2013. They proposed that a single genomic pathway, called the Integrative Nuclear FGFR 1 Signaling (INFS), is a central intersection point for multiple pathways involving more than 100 genes believed to be involved in schizophrenia.

"This research shows that there is a common dysregulated gene program that may be impacting more than 1,000 genes and that the great majority of those genes are targeted by the dysregulated nuclear FGFR1," Stachowiak said.

When even one of the many schizophrenia-linked genes undergoes mutation, by affecting the INFS it throws off the development of the brain as a whole, similar to the way that an entire orchestra can be affected by a musician playing just one wrong note, he said.

The next step in the research is to use these induced pluripotent stem cells to further study how the genome becomes dysregulated, allowing the disease to develop.

"We will utilize this strategy to grow cerebral organoids - mini-brains in a sense - to determine how this genomic dysregulation affects early brain development and to test potential preventive or corrective treatments," he said.

More information: S.T. Narla et al, Common developmental genome deprogramming in schizophrenia—Role of Integrative Nuclear FGFR1 Signaling (INFS), *Schizophrenia Research* (2017). DOI: 10.1016/j.schres.2016.12.012

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