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New Clues to Early Development of Schizophrenia

Stem cell studies published in Biological Psychiatry *open new opportunities for discovery*

Philadelphia, October 24, 2023 – Schizophrenia is a severe neuropsychiatric disease that remains poorly understood and treated. Schizophrenia onset is typically in adolescence or early adulthood, but its underlying causes are thought to involve neurodevelopmental abnormalities. Because human prenatal and postnatal brain tissue is exceedingly difficult to procure and therefore study, researchers have had limited opportunities to identify early disease mechanisms, especially during the critical prenatal period. Now, a pair of studies that appear in *Biological Psychiatry*, published by Elsevier, use new technology to study schizophrenia in models of early human brain development.

The first study used a unique approach involving three-dimensional brain organoids, which are known to recapitulate fetal brain development. The researchers, led by first author Ibrahim A. Akkouh, PhD, and senior author Srdjan Djurovic, PhD, both at Oslo University Hospital, collected skin cells from 14 patients with schizophrenia and 14 healthy controls and generated induced pluripotent stem cells (iPSCs), which they then manipulated to develop into brain-like cortical spheroids.

The organoids grown from patients and controls differed in their expression of thousands of genes – in line with the finding that the genetic influences on schizophrenia are many and very small. However, among the genes, those associated with neuronal axons stood out as a group.

Dr. Akkouh explained, *"We identified persistent axonal dysregulation as an early contribution to disease risk."*

Importantly, the researchers assessed organoid maturation at several time points, which enabled them to establish the persistent nature of the disturbances throughout development.

Dr. Akkouh added, *"Our findings provide novel and hitherto inaccessible insights into the molecular basis of schizophrenia during early brain development."*

In the second study, researchers led by Roy H. Perlis, PhD, at Harvard Medical School, focused on a particular genetic risk locus. The schizophrenia risk locus 15q11.2, a particular chromosomal region containing four genes, has a penetrance of over 10%, translating to a doubling of risk for schizophrenia among people carrying an unusual copy number of this genetic region. One gene in the locus, *CYFIP1*, has been associated with synaptic function in neurons and confers increased risk for neurodevelopmental disorders including schizophrenia and autism.

CYFIP1 is highly expressed in microglia, the brain's own immune cells, but its function there is unknown. Microglia are known to carry out synaptic pruning, in which they "eat" excess synaptic structures, a process critical to healthy brain development.

Dr. Perlis and colleagues collected blood cells from healthy volunteers and isolated iPSCs, which they then manipulated to differentiate into microglia-like cells. The researchers then used CRISPR technology to remove functional *CYFIP1* from the cells.

Dr. Perlis said of the work, *"Our findings suggest that changes in the behavior and function of microglia due to aberrant* CYFIP1 *function, such as through coding or copy number variants, could affect microglial processes such as synaptic pruning, homeostatic surveillance, and neuronal maintenance, which are critical for proper brain development and function. This could contribute to* CYFIP1*-related neurodevelopmental and psychiatric disorders resulting in part from microglia dysfunction. Among the specific disorders linked to variation in* CYFIP1 *are both autism and schizophrenia."*

John Krystal, MD, Editor of *Biological Psychiatry*, commented, *"The biology of schizophrenia is very complex and yet two themes represented by these two studies seem to be very important: the increased rate of elimination of glutamatergic synapses during development, and disturbances in the signaling properties of these glutamate synapses. These two disturbances could perturb circuit function in ways that are critical to development of symptoms and cognitive impairments associated with schizophrenia."*

Dr. Perlis added, *"More broadly, our findings highlight the importance of looking beyond neurons to understand risk genes. While finding risk loci may be the first step in understanding the role of genes in brain diseases, it's only a first step; figuring out the relevant cell type, and what those genes are doing, is absolutely critical in moving from association to – we hope – actual treatments."*

Notes for editors
The first article is "Longitudinal Transcriptomic Analysis of Human Cortical Spheroids Identifies Axonal Dysregulation in the Prenatal Brain as a Mediator of Genetic Risk for Schizophrenia," by Ibrahim Akkouh, Thor Ueland, Attila Szabo, Timothy Hughes, Olav B. Smeland, Ole A. Andreassen, Jordi Requena Osete, Srdjan Djurovic (https://doi.org/10.1016/j.biopsych.2023.08.017). It appears as an Article in Press in *Biological Psychiatry*, published by Elsevier.

The article is openly available at https://www.biologicalpsychiatryjournal.com/article/S0006-3223(23)01529-9/fulltext.

Copies of this paper are also available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@sobp.org. Journalists wishing to interview the authors may contact Srdjan Djurovic, PhD, at srdjan.djurovic@medisin.uio.no.

The second article is "Loss of Function in the Neurodevelopmental Disease and Schizophrenia-Associated Gene *CYFIP1* in Human Microglia-like Cells Supports a Functional Role in Synaptic Engulfment," by Steven D. Sheridan, Joy E. Horng, Hana Yeh, Liam McCrea, Jennifer Wang, Ting Fu, Roy H. Perlis (https://doi.org/10.1016/j.biopsych.2023.07.022). It appears as an Article in Press in *Biological Psychiatry*, published by Elsevier.

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@sobp.org. Journalists wishing to interview the authors may contact Roy H. Perlis, PhD, at +1 647-643-3080 or rperlis@mgh.harvard.edu.

The authors' affiliations and disclosures of financial and conflicts of interests are available in the article.

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The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

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