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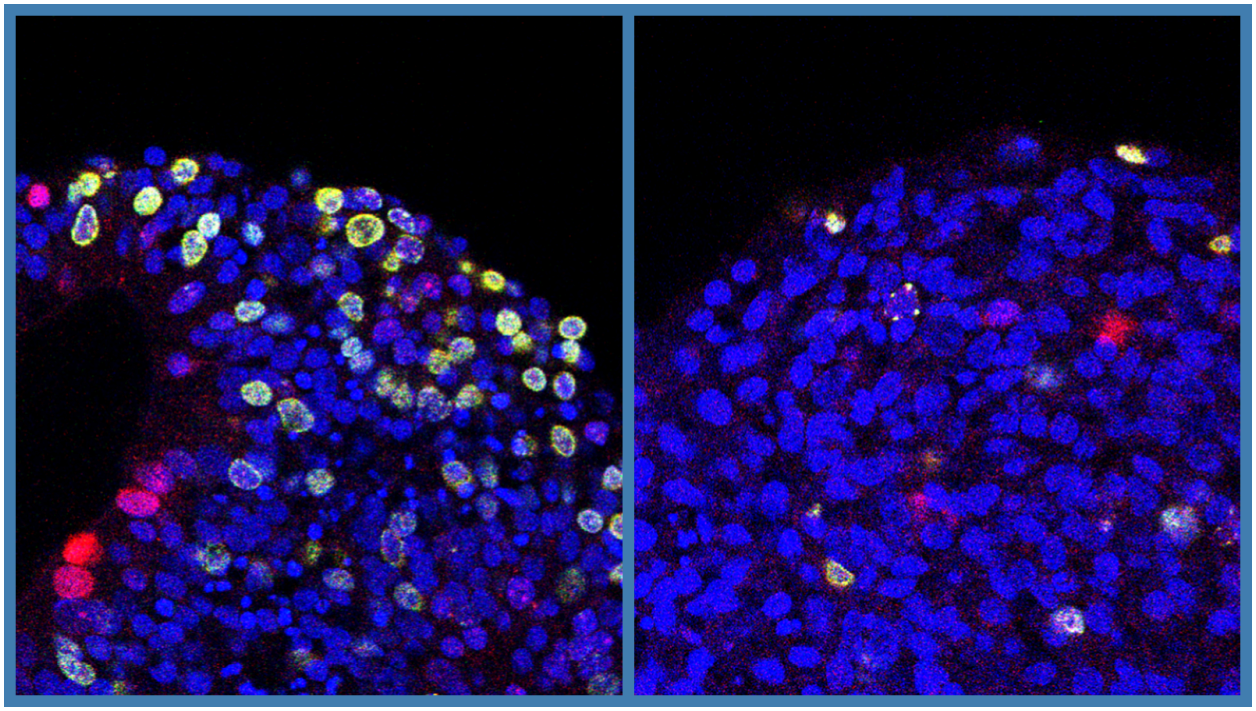
3-D Brain Cell Models Grown in Lab Shed Light on Mental Illness

A Q&A with neuroscientists Joseph Gogos and Bin Xu



Fluorescent labels reveal that a higher proportion of cells from 22q11.2 deletion syndrome patients (left) are stuck in an early phase of division (green), compared to cells from healthy individuals (right). (Gogos and Xu labs / Columbia's Zuckerman Institute).

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NEW YORK—*A missing chunk of a chromosome can result in significant problems in the human brain. What if snippets of DNA or certain medications could help undo these abnormalities?*

People born without the area known as 22q11.2 in their chromosomes experience a high risk of schizophrenia and suffer from memory impairments, social difficulties and mood-related symptoms. Human and mouse brain cells grown in the lab are now making it possible not only to discover what goes wrong in this condition, known as

22q11.2 deletion syndrome, but also to test both gene- and drug-based therapies that can help reverse these problems. This work is being done in the labs of Joseph Gogos, MD, PhD, a principal investigator at Columbia's Zuckerman Institute, and Bin Xu, an assistant professor of neurobiology at Columbia University's Irving Medical Center.

In a study published on August 1 in Nature Communications, *Drs. Gogos, Xu and colleagues across Columbia grew little brain-like balls of cells known as organoids, using cells donated by patients with 22q11.2 deletion syndrome and schizophrenia.*

We sat down with Dr. Xu as well as Dr. Gogos, who is also codirector of Columbia's Stavros Niarchos Foundation Center for Precision Psychiatry and Mental Health and a professor of physiology, neuroscience and psychiatry at Columbia's Vagelos College of Physicians and Surgeons, to talk about future directions in their research on 22q11.2 deletion syndrome.

How do the changes that result from 22q11.2 deletion syndrome compare to what prior work has found in schizophrenia?

Dr. Gogos: What we see in the 22q11.2 model lines up with previous studies of schizophrenia. Early brain cells, known as neural progenitor cells, don't grow or develop properly and often have trouble turning into mature neurons. This can lead to a smaller pool of brain cells and less-complex brain connections later in development, something that's been linked to cognitive and functional problems in schizophrenia.

Many past schizophrenia studies, though, have been complicated by genetic differences across patients, making it hard to pinpoint the causes of these abnormalities, and often yielding inconclusive results. With the 22q11.2 model, we can more clearly connect specific genetic changes to problems in brain development and function. Specifically, we found that a deficiency of the protein DGCR8, one of the roughly 40 genes in 22q11.2, plays a key role in the delayed development of cortical neurons, the cells underlying higher brain function. DGCR8 helps regulate how genes are turned on and off during brain development. This kind of information can help guide future studies and possibly new targeted treatments.

Interestingly, we also found that these developmental problems in 22q11.2 deletion models are very different from what's seen in autism models, where some of the same early brain cells actually mature too fast. This difference fits with large genetic studies showing that 22q11.2 deletions are strongly linked to schizophrenia risk, but not to autism.

What connections might we draw between the changes that result from 22q11.2 deletion and the symptoms in conditions such as schizophrenia?

Dr. Xu: Right now, it's still difficult to draw direct, one-to-one links between what we see in brain organoids and the symptoms people experience in schizophrenia, such as memory issues, learning challenges or hallucinations, as well as withdrawal or lack of motivation. That said, these cellular findings are important because they give us a window into early brain development, which is when things may start to go off track in conditions like 22q11.2 deletion syndrome and schizophrenia.

The changes in cell maturation, growth and connection we see likely cause early disruptions in how brain regions are built and wired together. These changes that may ripple through development and affect thinking and behavior later on.

Brain scans of people with the 22q11.2 deletion or schizophrenia have shown differences in brain structure, like changes in thickness and surface area in specific regions. Our organoid work suggests that these large-scale differences could stem from early problems with neural stem cell growth and neuron development.

We're still working to connect all the dots. Think of it like assembling a puzzle: organoids give us key pieces of how brain development might be disrupted, but we still need to understand how these pieces fit into the full picture of human symptoms. That's why the Stavros Niarchos Foundation Center for Precision Psychiatry combines this kind of research with studies in animals, patient data and eventually clinical research. This helps us build a stronger bridge between the lab and real-life outcomes.

Recently, you found that when it came to mice with a mutation mimicking 22q11.2 deletion syndrome, treating them with small DNA fragments improved their ability to navigate mazes and recognize other mice. What might be needed to see if such a gene therapy might have similar effects on people with this syndrome and schizophrenia?

Dr. Gogos: While many people think of schizophrenia mainly in terms of hallucinations or delusions, what's often overlooked are the cognitive symptoms like memory and attention problems, which can be just as serious. These cognitive deficits are often long-lasting, deeply impact day-to-day functioning and don't respond well to current treatments. So, if a therapy can improve memory or cognition in models of 22q11.2 deletion, there's real hope it could help address this unmet need in schizophrenia.

Of course, translating this to humans takes more work. We need to better understand the biology and test it carefully in multiple systems. It helps that we have cells derived directly from the neurons of patients with 22q11.2 deletion and schizophrenia.

We're currently testing these small DNA fragments to see if they reverse the effects we observe in organoids. In parallel, we're currently rapidly testing many compounds, including

FDA-approved drugs, to identify ones that can reverse the deficits seen with organoids grown from these cells. Promising candidates will then be validated in animal models of the 22q11.2 deletion to determine whether they also lead to behavioral and brain activity improvements. The ultimate goal is to identify compounds that can advance to clinical trials, offering new therapeutic options for individuals affected by the deletion.

For this study, you collaborated with colleagues across Columbia from many different fields. How were all these areas of expertise essential for this multidisciplinary study?

Dr. Xu: Psychiatrists identify and diagnose the patients who donate cells. Cell biologists ensure organoids grow and model brain development correctly. Biomedical engineers help develop culture protocols and imaging methods to study neurons. Data scientists analyze complex single-cell RNA data. Without combining these skills, we couldn't link patient biology with disease mechanisms in a meaningful way.

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The paper, "Aberrant pace of cortical neuron development in brain organoids from patients with 22q11.2 deletion syndrome-associated schizophrenia," was published in *Nature Communications* on August 1, 2025.

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The authors report no conflict of interest.