Study supports hypothesis that mitochondrial dysregulation is a contributor to the development of schizophrenia

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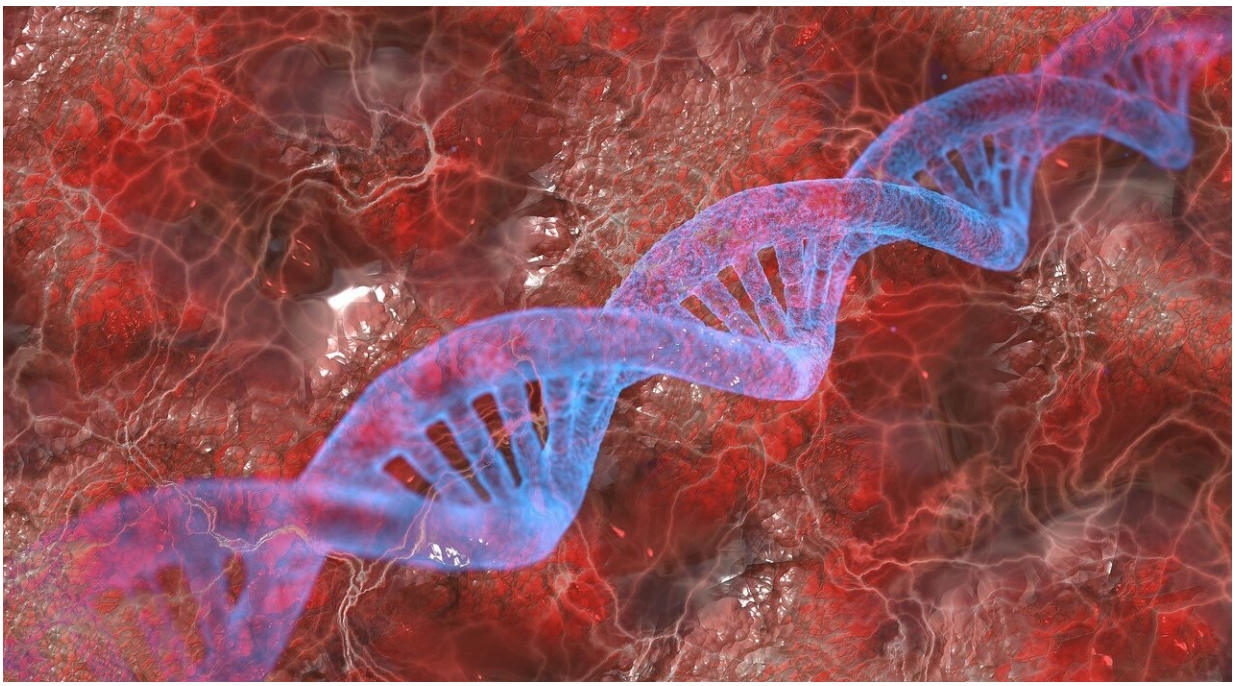

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Researchers at Rutgers and Emory University are gaining insights into how schizophrenia develops by studying the strongest-known genetic risk factor.

When a small portion of chromosome 3 is missing—known as 3q29 deletion syndrome—it increases the risk for schizophrenia by about 40-fold.

Researchers have now analyzed overlapping patterns of altered gene activity in two models of 3q29 deletion syndrome, including mice where the deletion has been engineered in using CRIPSR, and human brain organoids, or three-dimensional tissue cultures used to study disease. These two systems both exhibit impaired mitochondrial function. This dysfunction can cause energy shortfalls in the brain and result in psychiatric symptoms and disorders.

"Our data give strong support to the hypothesis that mitochondrial dysregulation is a contributor to the development of schizophrenia," said Jennifer Mulle, associate professor of psychiatry, neuroscience and cell biology at Rutgers Robert Wood Johnson Medical School and a co-senior author of the study published in *Science Advances*. "The interplay between mitochondrial dynamics and neuronal maturation is an important area for additional detailed and rigorous study."

Mulle, a member of the Center for Advanced Biotechnology and Medicine at Rutgers, and colleagues first showed that 3q29 deletion was a risk factor for schizophrenia in 2010. The findings converge with work on another genetic risk factor for schizophrenia, 22q11 deletion syndrome (or DiGeorge syndrome), which has also been found to involve disrupted mitochondrial function.

"For genetic variants associated with schizophrenia, we want to understand the primary pathology at the cellular level," said Ryan Purcell, assistant professor of cell biology at Emory University School of Medicine and co-lead author of the study. "This gives us a foothold, which may help cut through schizophrenia's polygenic complexity and better understand the neurobiology."

About one in 30,000 people are born with 3q29 deletion syndrome. In addition to increasing the risk for schizophrenia, 3q29 deletion can include intellectual disability, autism spectrum disorder and congenital heart defects. The effect of 3q29 deletion on schizophrenia risk is more than any single known gene variant, but the contributions of individual genes within the deletion are still being unraveled.

The finding that various schizophrenia-associated chromosomal deletions impair mitochondria runs counter to an expectation in the field that such mutations should alter proteins in the synapses that connect neurons. However, mitochondria are critical for energy-hungry synapses' function—so these models may not be in conflict.

It was also surprising that 3q29 cells have poorly functioning mitochondria because only one of the 22 genes in the deletion appears to encode a protein located in mitochondria. However, that gene or others within the interval may instead regulate the production or importation of mitochondrial proteins, the researchers said.

Mitochondria, which are found in every cell, produce energy from sugar or fat. Sometimes this process is aerobic (done with extra oxygen from inhaled air) and sometimes anaerobic (done without oxygen).

As a result of altered mitochondrial function, 3q29 cells lack metabolic flexibility, meaning their mitochondria have difficulty adapting to changes in sources of energy. This may interfere with neuronal development because maturing neurons need to switch to relying on aerobic energy production as they differentiate.

The results illustrate how 3q29 deletion affects the whole body, not just the brain: The effects on mitochondria are seen in kidney cells as well as in brain cells. Individuals with 3q29 deletion syndrome also tend to be smaller in size, possibly because of altered fat metabolism.

"Eventually, we want to understand which cellular changes like these are linked to specific clinical outcomes, which could help in designing more effective therapeutic strategies," Purcell said.

More information: Ryan Purcell et al, Cross-species analysis identifies mitochondrial dysregulation as a functional consequence of the schizophrenia-associated 3q29 deletion, *Science Advances* (2023). DOI: 10.1126/sciadv.adh0558. www.science.org/doi/10.1126/sciadv.adh0558

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