NEWS

Autism-linked mutation alters neuronal network activity

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7 JUNE 2022

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Neurons that carry a disruptive mutation in SETD1A, a gene linked to autism and schizophrenia, show **atypical patterns of activity**, plus hyperactivity in a signaling pathway involved in learning and memory, a new study shows.

Dampening the signaling pathway using experimental drugs restored normal patterns of neuronal activity — offering clues for potential treatment strategies.

Rare mutations in **SETD1A** dramatically increase the **risk of developing schizophrenia**. Mutations in SETD1A have also been found in people with disrupted speech development and early-onset epilepsy, as well as in children with an **uncommon syndrome** characterized by developmental delay, intellectual disability and, in some cases, autism.

SETD1A is involved in remodeling chromatin, the complex of DNA and proteins that makes up chromosomes. Many autism-linked genes encode '**chromatin remodelers**,' which regulate the expression of other genes through epigenetic mechanisms, such as **the addition or removal of methyl tags** to the histone proteins around which DNA wraps.

"This study translates the area that we loosely call epigenetics into something that makes sense in the context of neuronal function — that's what I like about it," says **Adrian Harwood**, co-director of the Neuroscience and Mental Health Research Institute at Cardiff University in Wales, who was not involved in the research.

Previous studies used mouse models to investigate the consequences of loss-of-function mutations

— which destroy a protein or disrupt its activity — in SETD1A, but those results do not necessarily translate to people, says **Dirk Schubert**, assistant professor of cellular neurophysiology at Radboud University in Nijmegen, the Netherlands, who co-led the new work.

“As [a] chromatin modifier, SETD1A is regulating the expression of many genes,” Schubert says. “The consequences of distorted regulation of these gene expressions on brain development and neuronal-network function may be human-specific.”

So he and his team used CRISPR to edit skin cells from neurotypical people to carry a loss-of-function mutation in one copy of SETD1A. Then they reprogrammed the cells to develop into excitatory and inhibitory neurons and cultured them in special lab dishes fitted with electrodes to record the cells’ electrical signals.

After three weeks, both control cultures and those with mutated copies of SETD1A showed bursts of activity from cells firing at the same time — a sign that the neurons were connected to each other.

Compared with controls, neuronal networks in the SETD1A cultures were overactive, the researchers found. In these SETD1A cell lines, however, the network bursts — and the intervals between bursts — were shorter.

“The overall activity is similar to [that of] controls, but the network is differently organized,” says study investigator **Shan Wang**, a graduate student in Schubert’s lab and in the lab of co-lead investigator **Nael Nadif Kasri** at Radboud University.

Cultures that contained only excitatory neurons with a mutated copy of SETD1A showed the same network abnormalities as those observed in mixed cultures of excitatory and inhibitory neurons. And compared with controls, mature SETD1A neurons had larger cell bodies, as well as longer and more numerous dendritic branches, which receive signals from other brain cells.

These neurons also showed altered expression patterns of hundreds of genes, including many involved in synaptic function. Nearly 80 genes listed in **SFARI Gene** — a comprehensive list of genes linked to autism — overlapped with differentially expressed genes in SETD1A neurons, the researchers found. (SFARI Gene is funded by the Simons Foundation, *Spectrum*’s parent organization.)

Further analyses revealed that SETD1A neurons had increased levels of cyclic AMP and an enzyme called protein kinase A (PKA) — two components of a signaling network **involved in memory and learning** that appear to be dysregulated in **fragile X syndrome** and other neurodevelopmental conditions. Chemically inhibiting PKA in SETD1A cultures restored typical patterns of neuronal activity, including the network burst rate, the team found. The findings were published 3 May in *Cell Reports*.

“This is a highly novel study that uses a lot of top-of-the-line technologies,” says **S. Hossein Fatemi**, professor of psychiatry and neuroscience at the University of Minnesota in Minneapolis, who wasn’t involved in the research.

An important next step would be to see whether the findings generalize to cells derived from people with SETD1A-related conditions, Fatemi says.

Harwood notes that to prod skin cells to develop into neurons, the researchers used an accelerated differentiation approach that skips certain early stages of a neuron’s developmental program. “If you bypass a lot of it, you don’t know exactly what’s going on in the more natural condition.”

Despite this hastened development, the results are in line with earlier findings in mice with a **mutated copy of SETD1A**, says **Steven Kushner**, professor of neurobiological psychiatry at Columbia University, who was not involved in the study. “It’s reassuring that across multiple different model systems we’re seeing some of the same important cellular phenotypes.” The findings, he adds, also suggest a possible therapeutic target pathway.

The cyclic AMP signaling pathway could explain some aspects of SETD1A-related conditions, but it is likely not the only molecular pathway affected in people with mutations in SETD1A, Kasri says, adding that it may also be necessary or beneficial to reverse the epigenetic changes caused by SETD1A deficiency.

In the future, Kasri, Schubert and their colleagues plan to explore whether synaptic plasticity is impaired in neurons with a mutated copy of SETD1A. The team also aims to better understand how drugs that target the cyclic AMP signaling pathway can help restore typical network behavior in SETD1A neurons.

Cite this article: https://doi.org/10.53053/GWBL3471