Schizophrenia gene mutation causes many changes in the mouse brain, new study shows

September 1 2023, by Leah Eisenstadt

Researchers studied the effects of a schizophrenia gene mutation in different regions of the mouse brain. Credit: Susanna Hamilton, Broad Communications

Researchers have identified common and rare gene mutations that increase risk for schizophrenia. Yet it's unclear what biological

mechanisms go awry in the brain to cause psychosis and other disabling symptoms, due in part to a lack of valid animal models to study in the lab.

Now, scientists in the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard and at MIT have taken a thorough, unbiased look at an animal model that carries a rare genetic mutation that greatly increases the risk of schizophrenia in humans.

The researchers examined multiple brain regions and cell types in mice lacking the Grin2a gene, which encodes a type of glutamate receptor involved in communication between neurons. They observed wide-ranging changes in gene expression, brain cell activity, cell signaling, synapse protein composition, and animal behavior. The findings are published in the journal *Neuron*.

The findings provide experimental evidence for two long-standing hypotheses that schizophrenia's symptoms arise from altered signaling by glutamate and dopamine, two neurotransmitters in the brain. Additionally the Grin2a-deficient mice had neurophysiological features resembling those observed in people with the disorder, including abnormal brain oscillations.

The researchers say the mouse model is a valuable new resource that will enable researchers to further explore the disorder's roots and probe for much-needed new therapeutic avenues.

"Very little is known about the neurobiological mechanisms that underlie schizophrenia, so having an animal model with human-genetic validity and clear-cut brain abnormalities could be transformative for the field," said study senior author Morgan Sheng, a core institute member at Broad, co-director of the Stanley Center for Psychiatric Research, and professor of neuroscience at MIT. "I find it remarkable that this animal

model lacking a single gene can mimic multiple facets of schizophrenia, revealing new mechanistic insights into this disabling condition."

"Finally, we have an animal model with human-genetic validity and robust neurobiological overlap with human patients that can help scientists learn how existing treatments work and potentially help identify new ones," said first author Zohreh Farsi, a staff scientist in the Sheng lab. "We hope others will utilize this rich data resource that we've shared for future mechanistic and therapeutics studies and to explore the roles of less studied mechanisms such as cholesterol dysregulation in schizophrenia pathophysiology."

New evidence for old hypotheses

A 2022 landmark genetic study led by Broad and other researchers identified rare mutations in 10 genes that strongly increase risk of schizophrenia. One of these is the GRIN2A gene, which encodes a subunit of a protein complex called the NMDA receptor.

This receptor binds to the neurotransmitter glutamate and scientists have long speculated that impaired glutamate signaling contributes to schizophrenia, but the biological role of the NMDA receptor in the disorder was still unclear.

In the current study, Farsi, Sheng, and colleagues set out to systematically characterize the effects of the Grin2a mutation in mice. In humans, the mutation effectively breaks one copy of the gene (a mechanism they recently confirmed), so the team generated a so-called "heterozygous" mouse model in which one copy of the Grin2a gene is disrupted, leaving one working copy.

The team took an unbiased, multidisciplinary approach to understand Grin2a's effects. Their analysis revealed changes in the expression of a

number of genes in different brain regions and at different ages in the mice, compared to mice with two working Grin2a copies and to those with none.

"We were surprised to see that just missing one copy of this gene can induce many changes at the RNA level, at the protein level, at the functional level, and at the behavioral level," said Farsi.

The team also found changes in several biochemical pathways, including a reduction in glutamate signaling, which is consistent with the glutamate hypothesis of schizophrenia.

Remarkably, their analysis also supported another long-standing hypothesis, centered on dopamine. Researchers have suspected that excessive dopamine signaling is partly to blame in schizophrenia, because medicines that block dopamine receptors are effective in reducing psychotic symptoms.

In a brain region called the striatum, the team found evidence for unrestrained dopamine signaling, including a striking increase in expression of the dopamine receptor gene Drd2, which is the target of most antipsychotic drugs. The scientists also found reduced levels of an enzyme that degrades dopamine, providing further evidence for dopamine's role in the disorder.

One mutation, many changes

To explore which cell types are involved, the researchers performed single nucleus RNA sequencing of different brain regions in Grin2a mutant mice, which revealed that in addition to neurons, other brain cells were affected in ways not frequently associated with schizophrenia. For example, genes related to cholesterol biosynthesis were more active in astrocytes in some brain regions. Changes in oligodendrocytes were also

prominent, pointing to altered myelination, a mechanism often overlooked in studies of psychiatric disorders.

At the brain network level, the researchers observed decreased activity of the prefrontal cortex and hyperactivity in the striatum and hippocampus, similar to what is seen in patients with schizophrenia, as well as abnormal locomotor patterns.

"The Grin2a mutation has disparate (even opposite) effects on different parts of the brain, which is unpredicted," said Sheng. "It illustrates the necessity of investigating gene-to-function at the level of the intact brain, to uncover systems-level effects like these that appear late in development."

The researchers say there is much more to learn from studying the Grin2a-mutant model.

"We've only scratched the surface of insights we can glean using this model," said Farsi. "By exploring how various antipsychotics work on Grin2a mutant mice, we might be able to tease apart the benefits of these drugs from the unwanted effects, so we can one day develop new drugs that specifically target the symptoms of this debilitating disorder."

Other researchers contributing to the work include Ally Nicollela, Sean Simmons, and Josh Levin of the Broad, who led the transcriptomic and single-nucleus RNA analysis; Sameer Aryal, Borislav Dejanovic, Hasmik Keshishian, and Steven Carr of the Broad, who led the proteomics experiments and analysis; and Robert Datta and Sherry Lin from Harvard Medical School, who analyzed behavioral measurements.

More information: Zohreh Farsi et al, Brain-region-specific changes in neurons and glia and dysregulation of dopamine signaling in Grin2a mutant mice, *Neuron* (2023). DOI: 10.1016/j.neuron.2023.08.004

Provided by Broad Institute of MIT and Harvard