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Different mutations in a single gene can wreak many types of havoc in brain cells

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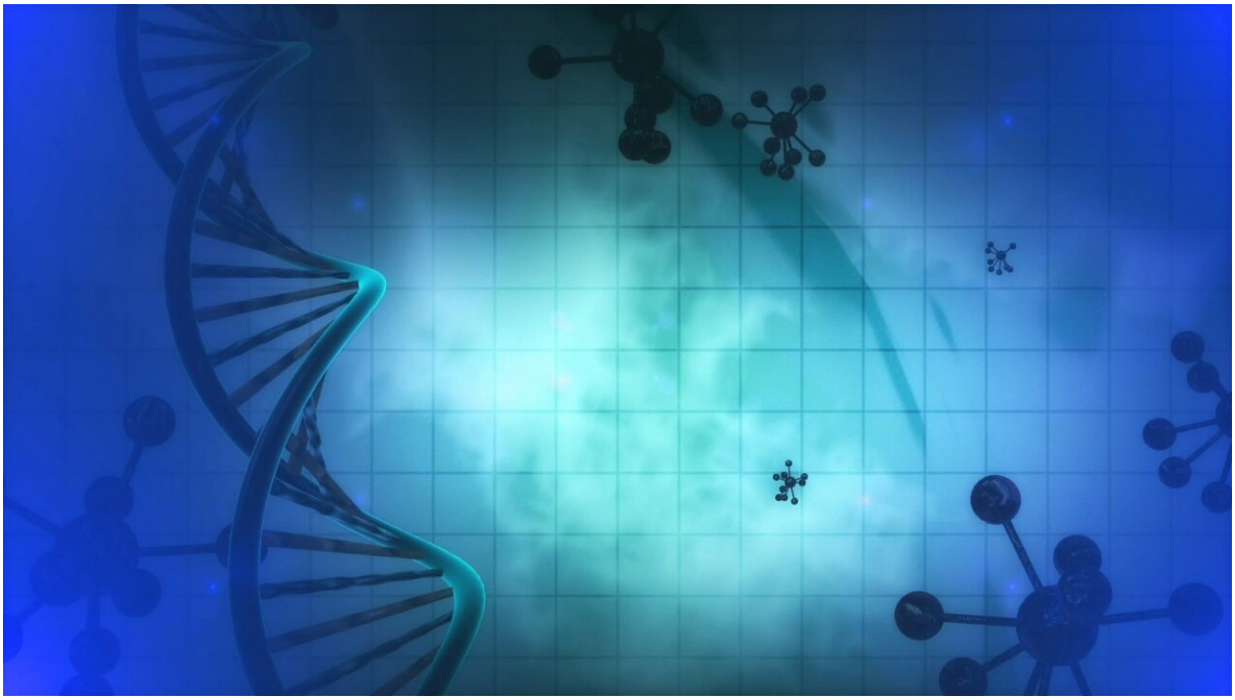

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Mount Sinai researchers have found that different mutations in a single gene can have myriad effects on a person's health, suggesting that gene therapies may need to do more than just replenish the missing or dysfunctional protein the gene is supposed to encode, according to a study published in *Nature Genetics* in November.

"You have to fully understand the mutation to understand how to fix it," said Kristen Brennand, Ph.D., Associate Professor of Genetics and Genomic Sciences, Neuroscience, and Psychiatry at the Icahn School of Medicine at Mount Sinai, and together with Gang Fang, Ph.D., Associate Professor of Genetics and Genomic Sciences, one of the lead authors of the study. The two researchers "have been collaborating for seven years on multiple projects that combine our complementary expertise in biology and informatics," said Dr. Fang.

The collaboration originated from Dr. Brennand's interest in the function of the gene neurexin-1, or NRXN1, in psychiatric disorders and Dr. Fang's technology expertise in the use of sophisticated techniques for analyzing different forms of individual genes. Much of the work was led by Shijia Zhu, Ph.D., formerly a postdoctoral fellow in Dr. Fang's lab, and Erin Flaherty, Ph.D., a former graduate student in Dr. Brennand's lab.

Patients with schizophrenia, autism, and bipolar disorder sometimes carry mutations in NRXN1. Until now, NRXN1 "had largely been studied only in mice. And, from the mouse studies, we know there are over 300 splice isoforms," said Dr. Brennand. "That means that this one gene makes 300 different proteins in the mouse."

The team set out to understand how NRXN1 functions in typical human neurons, and how different mutations might impact cellular function.

Dr. Brennand and her team started with skin samples from several patients at The Mount Sinai Hospital who had mental health diagnoses and carried mutated forms of the gene. They used these samples, as well as samples from participants without these diagnoses, to culture human induced pluripotent stem cells (hiPSCs)—cells with the ability to grow into any cell in the body.

The cells were then induced to grow into neurons. In the cells that came from patients with mutations in NRXN1, the scientists noted differences in the shape and electrical activity of the neurons as well as the rates at which they matured.

But that wasn't all. All people have two copies of the gene. If there is a mutation, it is usually only in one of those copies. The normal, unmutated gene still produces the healthy protein, but the mutated copy is unable to produce any protein, meaning the individual produces less of the protein than is necessary for normal function. The researchers figured that introducing more of the healthy protein would rescue the neurons, but this wasn't always the case.

Some of the mutations cause the second copy of the gene to produce a separate, mutated version of the protein. The researchers found that these mutated proteins may interfere with the action of the healthy protein. The team found that even cells that could produce enough of the healthy protein that they should have functioned normally would suffer if they were also exposed to a mutant form of the protein—and different mutations led to different problems.

"Functionally, these mutant proteins seem to have a dominant negative effect," said Dr. Brennand. "Overexpression of a single mutant protein in healthy neurons is enough to cause them to fire irregularly."

The study was small, and the gene variants the team studied are rare. In the future it will be important to tease out exactly how the variants impact function: do developmental perturbations lead to later differences in activity or vice versa? But both Dr. Brennand and Dr. Fang emphasized that the overall message is crucial for anyone hoping to use genetics to personalize medicine.

"I went into this really naively, thinking that all patients with deletions in

this gene would probably show the same effect," she said. "What we learned is that if you want to move towards precision medicine, it matters not just what genes are impacted, but how they're mutated as well."

More information: Erin Flaherty et al, Neuronal impact of patient-specific aberrant NRXN1α splicing, *Nature Genetics* (2019). DOI: 10.1038/s41588-019-0539-z

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