

# Gene mutations from patients with debilitating seizure and movement disorder created in mice

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Mice genetically engineered to carry mutations that make the KCNMA1 ion channel more active (left) are hunched and immobilized after a stress test which triggers involuntary immobility; normal mice (middle) show typical mouse behavior, and those with a mutation causing reduced KCNMA1 ion channel activity appear restless. Credit: Cooper Roache and Andrea Meredith

Three genetic alterations associated with a rare seizure and a movement disorder primarily found in children were successfully mirrored in mice and their symptoms treated, in a new study from a University of Maryland School of Medicine (UMSOM) researcher, Andrea Meredith, Ph.D., Professor of Physiology and her collaborators.

The disorder—KCNMA1-linked channelopathy, named after the affected gene—is associated with involuntary collapsing episodes, in which patients slump over from loss of posture and muscle tone. Although these episodes are brief, they can occur hundreds of times per day, putting patients at risk of serious injury. The disorder can cause severe developmental delay and has been difficult to treat, with researchers lacking an explanation as to how this disease affects the brain and body.

"Most individuals with KCNMA1-linked channelopathy did not inherit the disorder from their parents," said Dr. Meredith, senior author of the paper. "Without this inheritance pattern, it is difficult to identify the major symptoms of the disorder and the KCNMA1 gene changes that produce these symptoms. Introducing patients' [mutations](#) into mice provides answers to these questions."

Dr. Meredith said that once they establish the mechanism behind these symptoms they will be ready to test therapies that can treat the disorder.

The findings were published online on July 12, 2022, in *eLife*.

Along with collapsing episodes, people who have mutations in the KCNMA1 gene can experience seizures and developmental delay. The manner in which genetic changes produce these symptoms is currently unknown. However, the researchers know that the KCNMA1 gene encodes an ion channel, which moves charged potassium through cells to produce electrical signals in neurons and muscles, controlling muscle movement. For KCNMA1 mutations found in patients, a single DNA letter is exchanged for another incorrect one. The researchers believe these KCNMA1 patient mutations change how ion channels function, which affects the brain's ability to control muscle movements.

To test this idea, the researchers genetically engineered several groups of

mice, in which each group carried one of three different KCNMA1 patient mutations, all associated with the disorder. Two of these mutations occur in about half of patients, while only one known patient carries the third mutation.

"In [neurological research](#), mouse disease models help us better identify specific aspects of brain activity that may cause seizures or movement problems in patients," said author Peter Crino, MD, Ph.D., the Dr. Richard and Kathryn Taylor Professor and Chair in UMSOM's Department of Neurology.

While none of the mice carrying KCNMA1 patient mutations had spontaneous seizures that occur in some patients, two of the mutations caused mice to develop them faster than healthy mice when given a seizure-inducing drug. These mice were then tested to see if they had a movement disorder. When stressed, these same mutant mice had a hunched posture and did not move for short time periods, similar to the slumping during the patients' collapsing episodes. However, mice carrying the third mutation did not develop seizures faster or move less than mice with normal ion channels when stressed.

Next, the researchers gave the group of mice with the most severe [movement disorder](#) a stimulant called dextroamphetamine, commonly prescribed as an ADHD medication. When the researchers tested the mice again after giving the stimulant, they stayed more active with fewer episodes of less mobility.

"Patients with the same KCNMA1 mutation also respond positively to stimulants," said Dr. Meredith. "Since this drug works to decrease the immobility episodes in mice, we can follow its effects to understand the mechanisms."

Because the [mutant mice](#) displayed the main symptoms of the disorder,

the researchers wanted to explore what was happening at a molecular level. The researchers first found that KCNMA1 patient mutations change how the ion channels behaved in cells that were in a dish. Next, the researchers recorded the electrical signals directly from mouse neurons. The two mutations that caused less movement in mice increased the ion channel current, causing the neurons to produce more electrical signals as compared to [mice](#) with normal [ion channels](#). The third mutation, which decreased [ion channel](#) current, did not show a difference in [electrical signals](#) in neurons. However, the researchers hypothesized that both types of changes in how the channels open may create the patient symptoms in a complex symphony of neuron and muscle miscommunication.

Dr. Meredith and her laboratory's findings have garnered interest for further drug validation. She is collaborating with researchers at the National Human Genome Research Institute to design a clinical trial evaluating stimulants to treat the KCNMA1-linked channelopathy disorder.

"We want to help as many patients as possible by identifying those that will respond to this treatment," said Dr. Meredith.

This clinical trial may further answer additional questions about how KCNMA1 mutations may cause the main patient symptoms.

"Animal models of disease serve as a cornerstone in understanding diseases and treatment," said Mark T. Gladwin, Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "Using modern molecular biology tools, Dr. Meredith and her team have created a mouse with a rare human disease that may help find new treatments. Finding treatments for children afflicted with rare diseases is a major focus of our scientific investigations."

**More information:** Su Mi Park et al, BK channel properties correlate with neurobehavioral severity in three KCNMA1-linked channelopathy mouse models, *eLife* (2022). [DOI: 10.7554/eLife.77953](https://doi.org/10.7554/eLife.77953)

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