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Study finds potential genetic link between epilepsy and neurodegenerative disorders

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A recent scientific discovery showed that mutations in prickle genes cause epilepsy, which in humans is a brain disorder characterized by repeated seizures over time. However, the mechanism responsible for generating prickle-associated seizures was unknown.

A new University of Iowa study, published online July 14 in the *Proceedings of the National Academy of Sciences*, reveals a novel pathway in the pathophysiology of epilepsy. UI researchers have identified the basic cellular mechanism that goes awry in prickle mutant flies, leading to the epilepsy-like seizures.

"This is to our knowledge the first direct genetic evidence demonstrating that mutations in the fly version of a known human epilepsy gene produce seizures through altered vesicle transport," says John Manak, senior author and associate professor of biology in the College of Liberal Arts and Sciences and pediatrics in the Carver College of Medicine.

Seizure suppression in flies

A neuron has an axon (nerve fiber) that projects from the cell body to different neurons, muscles, and glands. Information is transmitted along the axon to help a neuron function properly.

Manak and his fellow researchers show that seizure-prone prickle mutant flies have behavioral defects (such as uncoordinated gait) and

electrophysiological defects (problems in the electrical properties of biological cells) similar to other fly mutants used to study seizures. The researchers also show that altering the balance of two forms of the prickle gene disrupts neural information flow and causes epilepsy.

Further, they demonstrate that reducing either of two motor proteins responsible for directional movement of vesicles (small organelles within a cell that contain biologically important molecules) along tracks of structural proteins in axons can suppress the seizures.

"The reduction of either of two motor proteins, called Kinesins, fully suppressed the seizures in the prickle mutant flies," says Manak, faculty member in the Interdisciplinary Graduate Programs in Genetics, Molecular and Cellular Biology, and Health Informatics. "We were able to use two independent assays to show that we could suppress the seizures, effectively 'curing' the flies of their epileptic behaviors."

Genetic link between epilepsy and Alzheimer's

This new epilepsy pathway was previously shown to be involved in neurodegenerative diseases, including Alzheimer's and Parkinson's.

Manak and his colleagues note that two Alzheimer's-associated proteins, amyloid precursor protein and presenilin, are components of the same vesicle, and mutations in the genes encoding these proteins in flies affect vesicle transport in ways that are strikingly similar to how transport is impacted in prickle mutants.

"We are particularly excited because we may have stumbled upon one of the key genetic links between epilepsy and Alzheimer's, since both disorders are converging on the same pathway," Manak says. "This is not such a crazy idea. In fact, Dr. Jeff Noebels, a leading epilepsy researcher, has presented compelling evidence suggesting a link between

these disorders. Indeed, patients with inherited forms of Alzheimer's disease also present with epilepsy, and this has been documented in a number of published studies."

Manak adds, "If this connection is real, then drugs that have been developed to treat neurodegenerative disorders could potentially be screened for anti-seizure properties, and vice versa."

Manak's future research will involve treating seizure-prone flies with such drugs to see if he can suppress their seizures.

Provided by University of Iowa