Researchers discover potential treatment for rare degenerative disease

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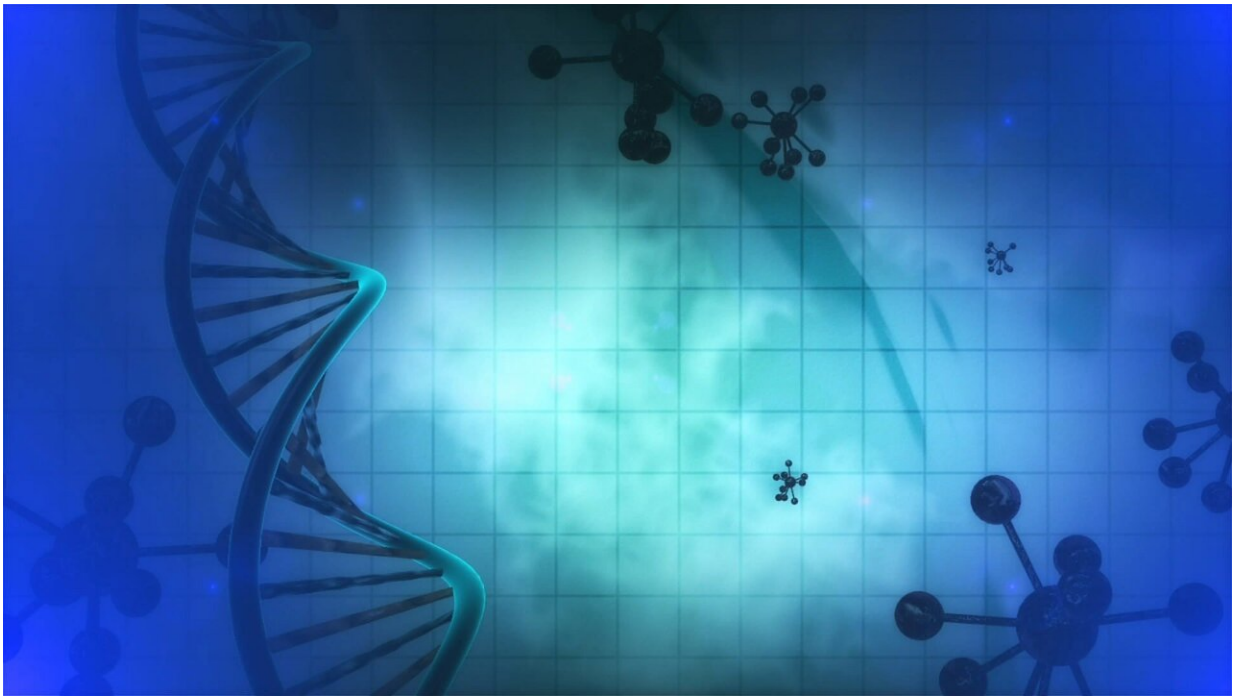

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Yale pharmacology professor Barbara Ehrlich and her team have uncovered a mechanism driving a rare, lethal disease called Wolfram Syndrome and also a potential treatment. Their findings appear in the July 6 edition of *Proceedings of the National Academy of Sciences*.

Wolfram Syndrome—a progressive degenerative disease that affects

about one in 500,000 people worldwide—is characterized by the onset of diabetes in childhood, and, in teen years, psychiatric symptoms, loss of vision, deafness, and incontinence. Most patients die in their 30s. There are no treatments.

The new study confirms that calcium inside the body's cells play a key role, and proposes a potential treatment involving two existing drugs.

Specifically, Ehrlich's team confirmed that when the protein Wolframin is lost in cells in the pancreas—the organ that produces insulin, which regulates blood sugar—"calcium signaling goes awry," Ehrlich said. This, the team found, results in reduced cell viability and lower insulin secretion, which, in turn, triggers the debilitating symptoms of the disease.

The researchers tested a number of compounds for their effectiveness in restoring calcium signaling and improving cell functions, and found two drugs that worked—ibudilast and a calpain inhibitor. Ibudilast has been approved for nearly 20 years to treat asthma in South Korea and Japan. It is now being tested in a number of clinical trials in the U.S., including for possible treatment of multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), and, in a trial underway at Yale, for COVID-19.

Some 99% of the body's calcium can be found in the bones and teeth. The other 1%—found in solution inside cells and bodily fluids—supports a variety of critical biological functions, said Ehrlich. It is this latter form of calcium that her lab has scrutinized in relation to Wolfram Syndrome. This fluid-based calcium is necessary for muscle contraction, nerve function, and insulin secretion, she said.

"Calcium is a signaling molecule," Ehrlich said. "It will signal, for instance, when insulin should be secreted."

Calcium signaling, in turn, is regulated by calcium-binding proteins, including neuronal calcium sensor-1 (NCS-1), a protein Ehrlich's lab has studied for the past 20 years. When a research group from Europe proposed that NCS-1 was involved in Wolfram Syndrome pathology, Ehrlich started investigating the disease.

"The first step was to better understand what the protein Wolframin does," said Tom T. Fischer, a medical student from Germany working in Ehrlich's lab. "In our cell model that is lacking Wolframin, we measured intracellular calcium and found that calcium signaling as well as calcium-dependent cell functions, particularly insulin secretion and cell viability, were disrupted."

They then tested a number of drug compounds and found that ibudilast and the calpain inhibitor restored intracellular calcium and cell functions, Fischer said.

With support from the Blavantik Fund for Innovation at Yale, Ehrlich's team will begin a mouse study within the next six months to further confirm the effectiveness of the drugs in correcting calcium signaling and preventing the progression of Wolfram Syndrome. If the results of the animal study show promise, the researchers said, they could move quickly into human trials.

Although Wolfram Syndrome is a rare disease caused by genetic mutations in a single gene, it is tied to a number of other diseases that could be viable targets for this treatment, including diabetes and bipolar disorder, the researchers said.

"Some people with bipolar disorder also have mutations in Wolframin," Ehrlich said. "This might be one of the first genetically identified mood disorders—and we will definitely be exploring this more."

More information: Lien D. Nguyen et al. Calpain inhibitor and ibudilast rescue β cell functions in a cellular model of Wolfram syndrome, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2007136117