UW-Madison: Multiple gene edits and computer simulations could help treat rare genetic diseases

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MADISON – The lab of Kris Saha at the University of Wisconsin-Madison has developed an innovative combination of gene-editing tools and computational simulations that can be used to develop new strategies for editing genes associated with genetic disorders.

In proof-of-concept experiments, the lab's researchers efficiently corrected multiple mutations responsible for a rare metabolic disorder, known as Pompe disease, in cells containing the disease-causing errors. They also used computer simulations to design the ideal gene-editing approach for treating human patients, a boon for rare disorders like Pompe disease that lack useful animal models.

Their promising platform advances the CRISPR genome-editing field and could lead to effective treatments for many diseases, not just Pompe disease.

"The exact mutations seen in the Pompe patients are not in an existing animal model, so we cannot do all of the preclinical studies that we would like to do in order to evaluate the safety and efficacy of different genome editing strategies," says Saha, a professor of biomedical engineering at UW-Madison's Wisconsin Institute for Discovery. "We need a way to think about how we go from patient material to a therapy without having to build an animal model, a process that takes months to years and hundreds of thousands of dollars."

Saha's team published its findings Dec. 8 in the journal Nature Communications.

In the first few months of life, an infant with Pompe disease becomes weaker and

weaker as glycogen builds up in their muscles, their cells unable to break the complex sugar down. Multiple mutations in a gene called GAA prevent their cells from correctly producing the proteins needed to make lysosomes, which turn glycogen into glucose, the fuel that powers cells. Left untreated, most patients with Pompe die within a year.

Developing effective therapies for such diseases can be difficult for a number of reasons. First, diseases like Pompe have no animal models in which to test treatments, a typical step in therapy development. And diseases like Pompe – and many other inherited diseases – are autosomal recessive, which means that mutations are present on both copies of a chromosome. Two sets of mutations require two successful gene-repair events for maximum effect. Further complicating the matter is the fact that many diseases are polygenic, resulting from mutations in two or more genes or multiple mutations spread across a single gene, as is the case for Pompe disease.

The Saha lab's new approach uses precise gene-editing tools to edit both faulty alleles simultaneously within individual cells to restore function. In its new report, the research team used induced pluripotent stem cells derived from Pompe patients to reproduce the exact GAA mutations that cause the disease and to approximate the resulting tissue pathology.

STORY CONTINUES AT https://news.wisc.edu/multiple-gene-edits-and-computer--simulations-could-help-treat-rare-genetic-diseases/