

Research at a Glance

Dual AAV system enables Cas9-mediated correction of metabolic liver disease in newborn experimental model

What's known:

A deficiency of the enzyme ornithine transcarbamylase (OTC) in humans causes life-threatening hyperammonemic crises. The OTC gene enables the body to make an enzyme that is a critical player in the urea cycle, a process that ensures excess nitrogen is excreted by the kidneys. Left unchecked, accumulating nitrogen becomes a toxic form of ammonia. Infants with OTC deficiency can suffer their first metabolic crisis as newborns. Up to 50 percent die or sustain severe brain injury, and survivors typically need a liver transplant by age 1. Gene therapy could cure OTC deficiency, but currently used viruses, such as adeno-associated virus (AAV), are not optimal in the neonatal setting.

What's new:

The research team led by Children's National Health System and the University of Pennsylvania reasoned that the newborn liver may be an ideal setting for AAV-mediated gene correction using CRISPR-Cas9 gene editing. They intravenously infused two-day-old mice with partial OTC deficiency two AAVs, one expressing Cas9 and the other expressing a guide RNA and the donor OTC DNA. This resulted in correction of the mutation in 10 percent of liver cells and increased survival in mice challenged with a high-protein diet, which normally exacerbates disease. After consuming a high-protein diet for one week, the treated newborns had a 40 percent reduction in ammonia compared with the untreated group. The correction appears to last long term. The study "provides evidence for efficacy of gene editing in neonatal onset OTC deficiency," says Mark L. Batshaw, M.D., Physician-In-Chief and Chief Academic Officer at Children's National, and a study co-author. "This study provides convincing evidence for efficacy of *in vivo* genome editing in an authentic animal model of a lethal human metabolic disease," the research team concludes.

Questions for future research:

- Q:** More than 400 mutations can cause OTC deficiency, and each would require a separate gene-editing approach. Is it possible instead to insert the OTC genome using CRISPR-Cas9 to correct the disorder irrespective of the mutation?
- Q:** Will such gene editing also work in adult animal models of the OTC disorder?
- Q:** Do these encouraging results in animals translate to efficacy in infants?

Source: "A dual AAV system enables the Cas9-mediated correction of a metabolic liver disease in newborn mice." Yang, Y., L. Wang, P. Bell, D. McMenamin, Z. He, J. White, H. Yu, C. Xu, H. Morizono, K. Musunuru, M.L. Batshaw and J.M. Wilson. Published Feb. 1, 2016 by Nature Biotechnology.

