Gene replacement therapy offers viable treatment option for fatal disease

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Lorson and his team are studying a subtype of SMA, spinal muscular atrophy with respiratory distress type 1, and have developed a gene replacement therapy that can be used to treat and control the disease in the future. Credit: Chris Lorson

Spinal muscular atrophy (SMA) is a disease that causes progressive degeneration in the nerve cells that control muscles, thereby causing muscle weakness and eventually death. SMA affects approximately 200,000 people in the U.S., often children. Now, researchers at the University of Missouri are studying a subtype of SMA, spinal muscular atrophy with respiratory distress type 1 (SMARD1), and have developed a gene replacement therapy that can be used to treat and control the disease in the future.

SMARD1 is a rare genetic condition with high mortality rate that develops primarily between the ages of six weeks and six months. The condition targets the spinal cord and leads to atrophy of body muscles and paralysis of the diaphragm, which is responsible for breathing. As the disease progresses, children with a SMARD1 diagnosis become paralyzed and require continuous artificial ventilation. The average life expectancy of a child diagnosed with SMARD1 is 13 months. Currently, there is no cure or effective treatment for this disease.

"Monogenic diseases like SMARD1, a disease that is caused by one gene, are ideal for gene therapy since the goal of the therapy is to replace the missing or defective gene," said Chris Lorson, an investigator in the Bond Life Sciences Center and a professor of veterinary pathobiology. "Our goals for this study were to develop a vector that would improve the outcomes of the disease and for the vector to be effective in a single dose."

Lorson and Monir Shababi, associate research professor in the Department of Veterinary Pathobiology in the MU College of Veterinary Medicine, developed a gene replacement therapy that was administered to infantile mice with a SMARD1 diagnosis. The therapy has the ability to cross the blood-brain barrier and directly targets motor neurons affected by SMARD1.

"One of the most remarkable aspects of this type of gene-replacement therapy is that it will last for an extended period of time," Lorson said. "The ability of the therapy to cross the blood-brain barrier, a protective barrier that typically prevents toxins or microbes from entering the brain, opens the door

for IV administration, allowing us to target motor neurons with a relatively non-invasive procedure."

The study determined that a low dose of the gene-replacement therapy led to significant improvements in muscle strength, protein expression in motor neurons and an extension in life span of the SMARD1 mouse model. The results of this study indicate that gene-replacement therapy is a potential treatment option for SMARD1.

With the results from this study, Lorson and his team are working to develop a most suitable delivery system for the gene replacement therapy; they want to determine the exact dose of the vector needed, when in the disease cycle the therapy will be most effective, and where in the body to administer for best outcomes.

More information: Monir Shababi et al. Rescue of a Mouse Model of Spinal Muscular Atrophy With Respiratory Distress Type 1 by AAV9-IGHMBP2 Is Dose Dependent, *Molecular Therapy* (2016). DOI: 10.1038/mt.2016.33