Medical Xpress

Batten disease may benefit from gene therapy

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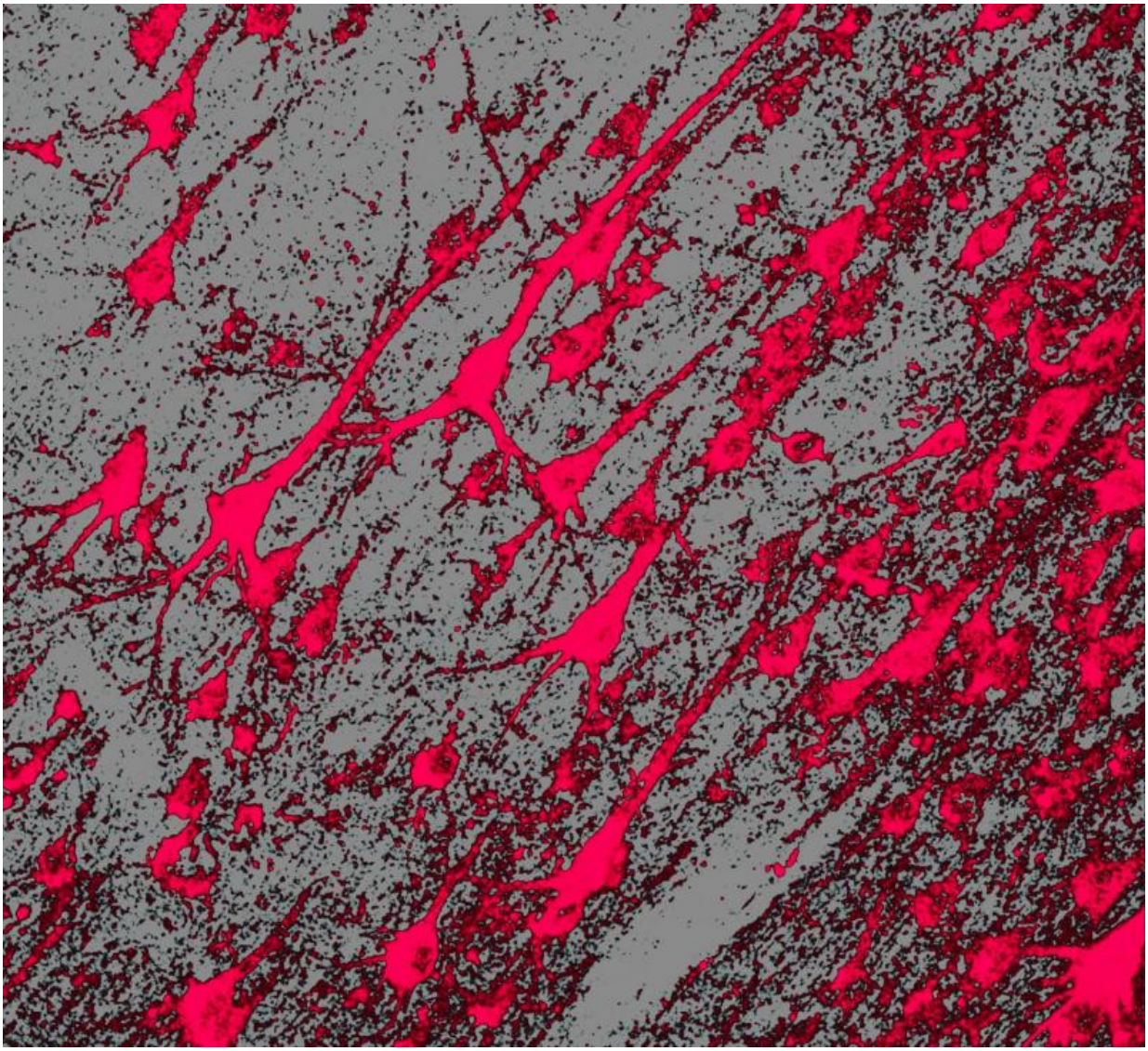

Injecting a shot of genes into the brain's ventricular plumbing system may be an effective long term method for treating Batten disease. Credit: Davidson lab, University of Pennsylvania, PA

In a study of dogs, scientists showed that a new way to deliver replacement genes may be effective at slowing the development of childhood Batten disease, a rare and fatal neurological disorder. The key may be to inject viruses that carry the codes for the gene products into the ventricles, which are fluid-filled compartments in the center of the brain that serve as a plumbing system. The study, published in *Science Translational Medicine*, was partially funded by the National Institutes of Health.

Batten disease is a lysosomal storage disorder, one of a group of diseases that causes problems with a cell's ability to breakdown specific molecules. Early symptoms may include vision loss, subtle changes in personality and behavior, slow learning, clumsiness, or stumbling. Eventually, the children become blind, bedridden and demented, and typically die within the first decade of their lives. Currently there are no effective treatments.

"Our study opens up the possibility of a one-and-done treatment for this form of Batten disease," said Beverly Davidson, Ph.D., director of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics at Children's Hospital of Philadelphia and the senior author of the study.

Working with scientists at the University of Missouri, Columbia, Davidson's team focused on the late infantile form of the disease that starts in children 2 to 4 years of age and is most often caused by mutations in the gene for the soluble lysosomal enzyme tripeptidyl peptidase 1 (TPP1), an enzyme which degrades proteins. They showed that if they treated dogs that have a similar disorder by injecting a safe virus containing the TPP1 gene code into the cerebrospinal fluid that fills ventricles, the dogs lived about twice as long as untreated dogs. Symptoms including problems with movement, pupil dilation and

making decisions were delayed or, in some cases, did not occur. The treatment, however, did not fully improve the dogs' vision suggesting that delivery to the eye itself may be necessary as well.

When the scientists inspected the dogs' brains, they found that the treatment reduced the damage normally caused by the disease. In comparison with untreated dogs, the treated dogs had less reactive glial cells and stored lipofuscins, fatty deposits that are hallmarks of Batten disease and similar disorders, called neuronal ceroid lipofuscinoses.

"Dr. Davidson and her team undertook a highly innovative approach for Batten disease gene therapy," said Jill Morris, Ph.D., program director at NIH's National Institute of Neurological Disorders and Stroke. "These results open up a promising path toward developing long-lasting treatments for Batten disease and similar lysosomal storage disorders."

Further inspections of the dogs' brains confirmed the scientists' hypothesis about how the therapy worked. The results suggested that parenchymal cells that line the ventricles and surface of the brain took up the injected genes from the cerebrospinal fluid and made more TPP1 protein. These cells then secreted the protein that, in turn, spread throughout the brain. Initial experiments showed the importance treating the dogs with the immunosuppressant, mycophenolate mofetil, before injecting the TPP1 gene. The immunosuppressant prevented the production of antibodies that accelerated TPP1 clearance from the cerebrospinal fluid.

"We saw profound effects from the gene therapy that, summed up, improved the dogs' health. We certainly hope that this approach will provide children suffering from this disorder similar benefits," said Dr. Davidson.

More information: Katz, Tecedor, Chen et al. "AAV gene transfer

delays disease onset in a TPP1-deficient canine model of the late infantile form of Batten disease," *Science Translational Medicine*, November 11, 2015. DOI: 10.10.1126/scitranslmed.aac6191

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