Researchers use CRISPR engineering to prevent certain glaucoma in mice

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A University of Iowa-led team of researchers has used the gene editing method called CRISPR-Cas9 to disrupt a mutant gene that is responsible for some forms of glaucoma, one of the most common causes of irreversible blindness.

The study involves the elimination of the mutated myocilin protein from a mouse model of human glaucoma and cultured human cells through the

use of CRISPR-Cas9, which can alter DNA sequences and gene function. Mutations in myocilin are implicated in juvenile- and adult-onset primary open-angle glaucoma. In their experiments, researchers found that removing the mutated protein by disrupting the mutant myociln results in lowered intraocular pressure, which in turn prevents glaucomatous damage to the eye.

"As scientists we don't want to just discover a diseased gene, we want to understand what the gene does and, in this case, have a better understanding of glaucoma so that it can be more effectively treated," says Val Sheffield, MD, PhD, Carver Chair of Molecular Genetics at the University of Iowa and an investigator with the Wynn Institute for Vision Research at the University and senior author of the study. "No one knows what this gene does, except that its mutant form causes glaucoma."

The research is published online in the Oct. 2 issue of the journal, *Proceedings of the National Academy of Science*, or *PNAS*. It is the result of 24 years of collaboration between scientists at UI Carver College of Medicine, the Wynn Institute for Vision Research at the University of Iowa, and the North Texas Eye Research Institute at the UNT Health Science Center. Scientists from the McGovern Institute for Brain Research at the Massachusetts Institute of Technology also contributed to the study.

Glaucoma is a common vision and neurodegenerative disorder affecting 3 to 5 percent of people over the age of 40. An early precursor to the most common form of this disease known as primary open-angle glaucoma is high intraocular pressure - fluid pressure inside the eye - that damages retinal ganglion axons at the optic nerve and leads to death of retinal ganglion cells that carry the visual signals to the brain, which can cause blindness.

Myocilin is a protein found in the trabecular meshwork - a part of the eye that regulates intraocular pressure. A mutation in the myocilin gene can cause high intraocular pressure. Scientists found that genome editing using CRISPR-Cas9 to disrupt the mutant myocilin gene prevented production of the mutant protein, which prevented elevated intraocular pressure in mouse eyes, thus totally preventing this human form of glaucoma in mice. In addition, this same genome editing technology eliminated myocilin expression in perfusion cultured human eyes, that will translate into a unique new therapy to treat myocilin glaucoma in humans.

More information: Ankur Jain el al., "CRISPR-Cas9–based treatment of myocilin-associated glaucoma," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1706193114

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