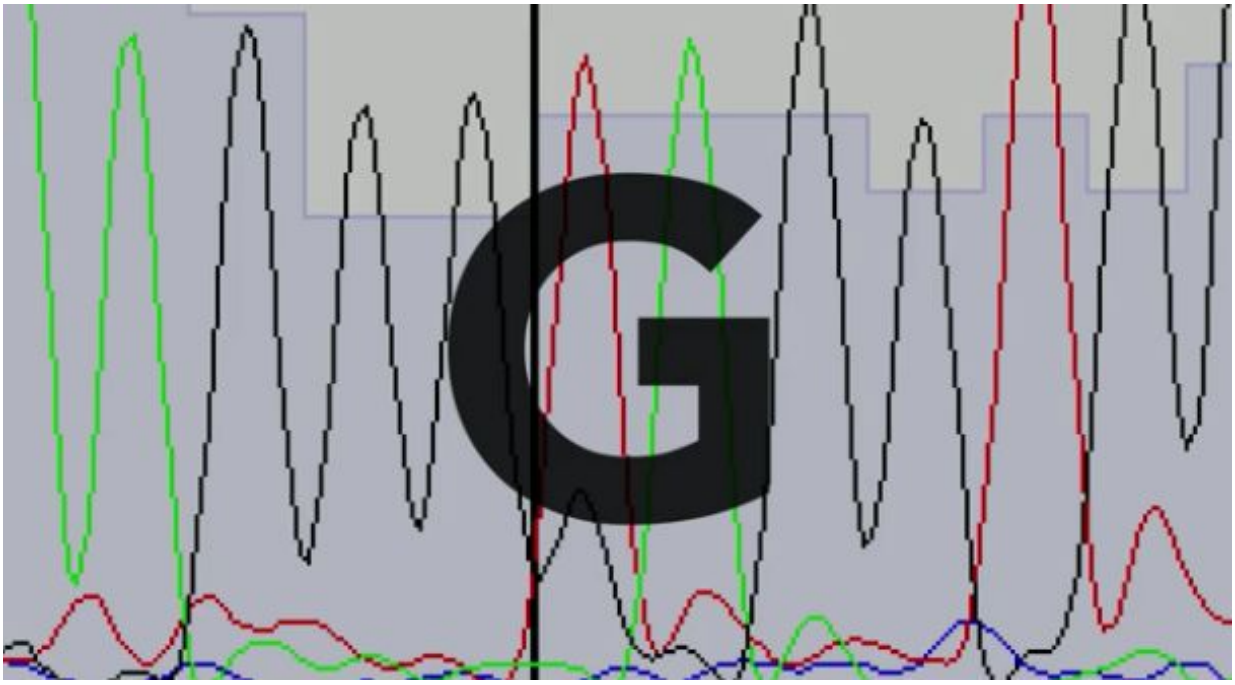
CRISPR used to repair blindness-causing genetic defect in patient-derived stem cells

January 27 2016



Columbia University Medical Center (CUMC) and University of Iowa scientists have used a new gene-editing technology called CRISPR, to repair a genetic mutation responsible for retinitis pigmentosa (RP), an inherited condition that causes the retina to degrade and leads to blindness in at least 1.5 million cases worldwide.

The study was published in *Scientific Reports*, and marks the first time researchers have replaced a defective gene associated with a sensory disease in stem cells that were derived from a patient's tissue.

"Our vision is to develop a personalized approach to treating eye disease ," says Stephen Tsang, MD, PhD, the László Z. Bitó Associate Professor of Ophthalmology and associate professor of Pathology & Cell Biology at CUMC, and one of the study's senior authors. "We still have some way to go, but we believe that the first therapeutic use of CRISPR will be to treat an eye disease. Here we have demonstrated that the initial steps are feasible."

In the study, the researchers created stem cells from a sample of skin that was taken from a patient with retinitis pigmentosa. As the patient-derived stem cells still harbored the disease-causing mutation, the teams used CRISPR to repair the defective gene. The stem cells can potentially be transformed into healthy retinal cells and transplanted back into the same patient to treat vision loss.

"The X-linked form of retinitis pigmentosa is an ideal candidate for a precision medicine approach because a common mutation accounts for 90% cases," Tsang explains. Using CRISPR —which is easily adaptable to diverse sequences of DNA, and allows for fast and accurate editing —scientists can take a patient's own cells and make pinpoint repairs specific to that individual's genome.

Because the corrections are made in cells derived from the patient's own tissue, doctors can re-transplant the cells with fewer fears of rejection by the immune system. Previous clinical trials have shown that generating retinal cells from embryonic stem cells and using them for transplantation is a safe and potentially effective procedure.

In this paper, the researchers targeted one of the most common variants

of retinitis pigmentosa, which is caused by a single mistake in a gene called RGPR. The composition of RGPR—which contains many repeats and tight-binding nucleotide pairs—make it a difficult gene to edit. The researchers say that preliminary success with RGPR is therefore promising for treating other forms of the condition caused by mutations in other genes.

The current treatment for retinitis pigmentosa recommended by the National Institutes of Health—consuming high doses of vitamin A—slows down vision loss but does not cure the disease.

Other types of gene therapies for retinitis pigmentosa are currently undergoing clinical trials. Unlike CRISPR-based methods, these therapies introduce stretches of DNA that supplement some of the activity of the defective gene, but do not directly correct the original mutation. Follow-up studies have shown that any gains in vision from these gene supplementation therapies wane over time.

A CRISPR-driven precision medicine approach to treating retinitis pigmentosa may improve upon current therapies and restore a patient's vision, because CRISPR, with its pinpoint accuracy can correct the fundamental genetic defect responsible for the disease. However, CRISPR technology has not yet been approved for use in humans.

Recently, another group has used CRISPR to ablate a disease-causing mutation in a rats with retinitis pigmentosa. This study hints at the promise for using CRISPR therapeutically in humans, and the CUMC and Iowa groups are now working to show that the technique does not introduce any unintended genetic modifications in human cells, and that the corrected cells are safe for transplantation.

Tsang and colleagues believe that the first clinical use of CRISPR could be for treating an eye disease because compared to other body parts, the

eye is easy to access for surgery, readily accepts new tissue, and can be noninvasively monitored.

More information: "Precision Medicine: Genetic Repair of Retinitis Pigmentosa in Patient-Derived Stem Cells" *Scientific Reports*, 2016.

Provided by Columbia University Medical Center