Turning back the clock on a severe vision disorder

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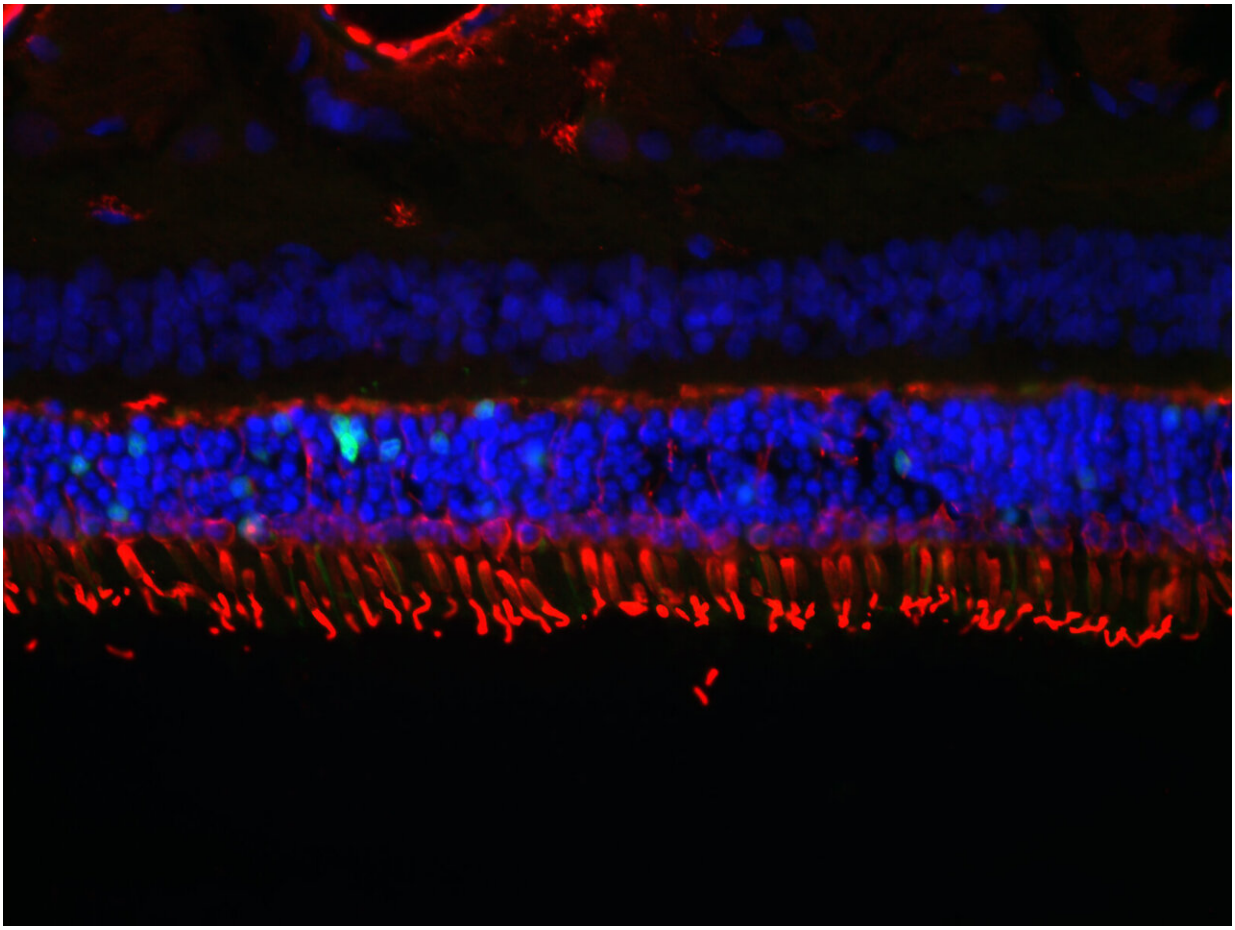

A mutation in the NPHP5 gene leads to a severe blinding disorder, Leber congenital amaurosis. Dogs with the condition that were treated with a gene therapy regrew normal, functional cone cells, labeled in red, that had previously failed to develop. The treatment led to a recovery of retinal function and vision. Credit: Gustavo Aguirre and William Beltran

Gustavo Aguirre and William Beltran, veterinary ophthalmologists and vision scientists at the University of Pennsylvania School of Veterinary Medicine, have studied a wide range of different retinal blinding disorders. But the one caused by mutations in the NPHP5 gene, leading to a form of Leber congenital amaurosis (LCA), is one of the most severe.

"Children with this disorder are not visual," says Aguirre. "They have a wandering, searching look on their faces and are usually diagnosed at a young age."

A nearly identical disease naturally occurs in dogs. In a new paper in the journal *Molecular Therapy*, Aguirre, Beltran, and colleagues at Penn and other institutions have demonstrated that a canine gene therapy can restore both normal structure and function to the retina's cone photoreceptor cells, which, in LCA patients, otherwise fail to develop normally. Delivering a normal copy of either the canine or human version of the NPHP5 gene restored vision in treated dogs.

"What's amazing is that you can take this disease in which cone cells have incompletely formed, and the therapy restores their function—they had no function whatsoever before—and recover their structure," says Aguirre.

"That plasticity is incredible and gives us a lot of hope," Beltran says.

LCA includes a wide range of inherited vision disorders characterized by blindness that strike in early childhood. The form of LCA associated with NPHP5 mutations is rare, affecting about 5,000 people worldwide. Known as a ciliopathy, it affects the cilia of cells of the retina. The cilia cells are antennalike structures on photoreceptor cells that translate the energy from light into visual signals.

In the NPHP5 disease, rod photoreceptor cells—those responsible for vision in low light—degenerate and progressively die early in the disease. Yet the cone photoreceptors, which enable color vision and, in the central retina, the perception of fine detail, while abnormal structurally, survive, albeit without function.

Aguirre and Beltran, together with colleagues and coauthors on the current work, Artur Cideciyan and Samuel Jacobson in Penn's Perelman School of Medicine, have found success with gene therapy approaches to treating a variety of inherited vision disorders. Often, they have aimed to treat early in the course of a retinal disease, before photoreceptor cells have died or entirely degenerated. But the fact that cone cells persisted in this form of LCA led the researchers to consider whether a therapy that targeted cones could not just stop but reverse the course of the disease.

Testing this approach, the team delivered retinal injections of adeno-associated viral vectors, a platform for ferrying the normal version of the NPHP5 gene, into one eye of each of nine five-week-old dogs with the vision disorder. Known as gene augmentation therapy, the injection is used to supply a healthy gene in disorders where the causative mutation leads to a defective or absent protein.

To determine the effectiveness of the treatment, the researchers used a technique called electroretinography, which measures the electrical response of photoreceptor cells to a light stimulus, as well as optical coherence tomography, which allows for the noninvasive imaging of fine cross sections of the retina. Both means of evaluating the experimental therapy rendered encouraging results. In the dogs' treated eyes, the outer segment of the cones regrew.

In addition, when the treated dogs were about six months old, their vision was tested using an obstacle-avoidance course. When their treated

eye was blindfolded, they had difficulty at navigating; however, when that eye was uncovered, their ability to avoid obstacles was notably improved.

"What's so appealing and so exciting here is that we're not just stopping a disease process, we're actually reverting a photoreceptor cell that is abnormal to become normal and function," says Beltran. "This disease in dogs very closely parallels the disease in humans, in quite specific terms, so there's a lot of support for the thought that a similar treatment approach could also help children."

Ongoing studies suggest that the treatment may be effective even when delivered at later stages of disease. With further support, the researchers hope to move the research along the path to a clinical trial in people.

More information: Gustavo D. Aguirre et al, Gene Therapy Reforms Photoreceptor Structure and Restores Vision in NPHP5-associated Leber Congenital Amaurosis, *Molecular Therapy* (2021). DOI: 10.1016/j.ymthe.2021.03.021

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