Gene Therapy Improves Sight of Four Patients

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In what eye researchers are hailing as a major advance, gene therapy has partially restored the sight of four young adults born with severe blindness. In two small studies, the patients' ability to sense light improved, and two can now read several lines of an eye chart. All are still legally blind, but the same treatment could potentially prevent this type of blindness in babies.

The four patients have a disease called Leber congenital amaurosis (LCA), an inherited disorder affecting about 3000 Americans that begins at birth and leads to complete blindness by age 40. Researchers blame one form of the disease on a mutation in a gene called retinal pigment epithelium 65 (RPE65). The protein encoded by the gene helps convert vitamin A into a form used by the retina's light-sensing cells (rods and cones) to make rhodopsin, a pigment that absorbs light. Without rhodopsin, these photoreceptor cells eventually die. In 2001, researchers reported that giving retina cells a working copy of RPE65 restored photoreceptor function in blind Briard dogs with the RPE65 mutation. After a gene-therapy injection, the dogs could avoid objects and walk through a maze (*Science*NOW, 27 April 2001).

Now researchers have tested the treatment in six patients ages 17 to 26 with the RPE65 defect. At Children's Hospital of Philadelphia, University of Pennsylvania (Penn) gene-therapy researcher Jean Bennett's team injected one eye of each patient with a harmless virus modified to carry the RPE65 gene. The gene therapy did not appear to cause side effects. (One patient's retina developed a small hole, but it didn't affect vision.) A few weeks later, a test based on pupil constriction showed that the patients could detect three times more light. Two patients who could see only hand motions before were able to read several lines of an eye chart. And one patient was able to navigate an obstacle course efficiently for the first time.

In a similar safety study at University College London, Robin Ali's team saw improvement in only one of three patients--the one with the most intact retinal tissue, an 18-year-old, Ali says. He was no better at reading an eye chart, but his light perception improved 100-fold. In a video before treatment, he stumbles

through a simulated night street scene, bumping into walls several times in 77 seconds. Six months after the injection, he breezes through in 14 seconds. "It's more than we could have hoped for," Ali says. Both teams reported their findings online yesterday in the *New England Journal of Medicine* and presented them yesterday and today at the annual meeting of the Association for Research in Vision and Ophthalmology in Fort Lauderdale, Florida.

Although these studies were only designed to test safety, the results are "exciting," says Paul Sieving, director of the National Eye Institute (NEI). "There is certainly a suggestion of efficacy." NEI is funding a third study based on the same gene therapy at Penn and at the University of Florida that also has "very encouraging" results, says principal investigator Samuel Jacobson of Penn, but it is not yet ready for publication.

The London and Philadelphia teams are now planning to treat younger LCA patients, who have better preserved retinas and so could benefit even more. Eventually, in order to prevent blindness altogether, "you need to treat babies," says neurobiologist Dean Bok of the University of California, Los Angeles.

Meanwhile, researchers are thinking about gene-therapy trials for other inherited retinal diseases as well as for more common disorders such as macular degeneration. If the LCA findings hold up, "it will open the floodgates for therapies for other diseases," says eye-disease geneticist Stephen Daiger of the University of Texas Health Science Center in Houston.