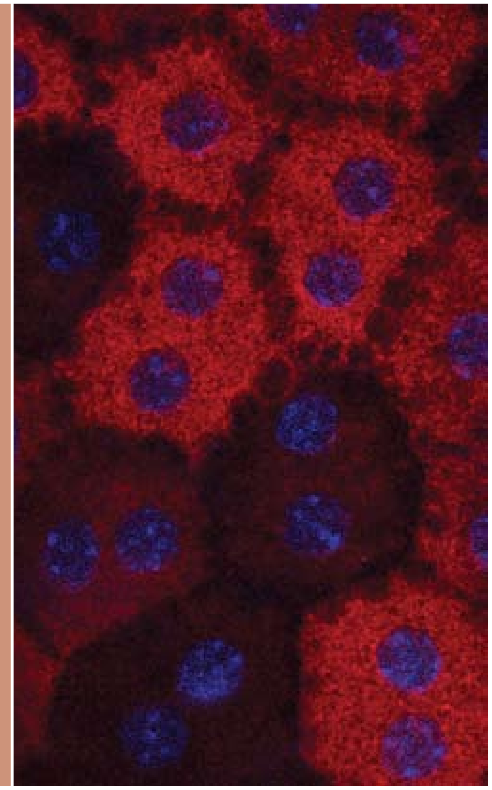
Society for Neuroscience

Vision and Gene Therapy

Vision loss and eye disease affect 3.6 million Americans and cost the United States $68 billion each year. However, advances in vision research are helping to combat some types of eye disease. An unexpected finding decades ago — the crucial role of vitamin A in the visual system — and the genetic revolution that began with the decoding of the human genome have combined to create one of the first success stories for gene therapy and hope for vision restoration in people.



Research & Discoveries chronicles examples of curiosity-driven research advances that are creating promise for the treatment of neurological and psychiatric disorders.

Basic research advances scientific knowledge and medical innovation by expanding understanding of the structure and function of molecules, genes, cells, systems, and complex behaviors. Clinical researchers exploit these findings and identify new applications that lead to medical treatments.

Basic research is largely funded by national agencies, such as the National Institutes of Health and the National Science Foundation in the United States. Continued investment in basic research is essential to ensuring discoveries that will inspire scientific pursuit and medical progress for future generations.

The Discovery

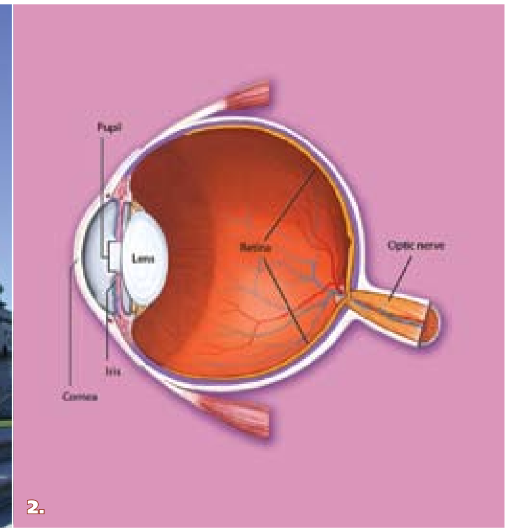
Research identifies the chemical and genetic bases of vision

In the 1930s, a researcher named George Wald discovered the vital role of vitamin A in the visual system, but the connection between diet and vision had been known for centuries. Ancient Egyptians recognized that night blindness could be a symptom of a poor diet. During World War I, researchers linked nutritional night blindness to deficiency of vitamin A, a newly discovered vitamin obtained from food.

Why does the lack of vitamin A impair vision? Researchers had previously isolated a purple pigment from rod photoreceptors, light-sensitive nerve cells in the retina that are important for night vision. Wald found that the pigment, rhodopsin, consisted of both a protein and a light-absorbing chemical related to vitamin A. He further identified a "visual cycle" that is essential for vision. First, light separates the vitamin A molecule from the protein and changes its shape, leading to initiation of neural signals from the eye to higher brain centers. Then, the vitamin A molecule is "recycled" — it is restored to its original shape and reunited with its protein partner. Research showed that the restoration of vitamin A is necessary for the eye's continual absorption of light. Wald's discovery earned him the Nobel Prize.

Genetics of Eye Disease

While research by Wald and others identified the basic mechanism of vision 70 years ago, the recent decoding of the human genome has helped determine how vision can be affected by disease. In the past 20 years, researchers have identified more than 400 genes that cause eye diseases. These inherited eye disorders comprise a major portion of all genetic diseases — nearly a fifth of all genes known to be related to any disease cause eye disorders. By shedding light on the genetic cause of disease, this research has opened the door to new treatment possibilities for disorders once believed to be permanent.



1. Briard dogs are prone to a condition that resembles Leber congenital amaurosis (LCA), a genetic form of blindness. Once treated with healthy copies of the *RPE65* gene, Briards that had been visually impaired showed improved vision. Today, Lancelot (shown) continues to see well after a single gene therapy treatment in 2000. Credit: Foundation Fighting Blindness

2. The cornea and lens help produce a clear image of the visual world on the retina, the sheet of nerve cells lining the back of the eye. The retina contains 125 million visual receptors that turn light into electrical signals that get transmitted to the brain via the optic nerve. Credit: © 2008 Society for Neuroscience, Illustration: Lydia V. Kibiuk, Baltimore, Maryland

3. Retinal photographs show how the eyes of a healthy patient (right) and an individual with Leber congenital amaurosis (LCA; left) differ. The LCA eye shows retinal thinning and abnormalities of the macula, which in the healthy eye is the central darkened spot. The LCA eye also shows reductions in vascular tissue, the eye's blood supply. Credit: Jean Bennett, MD, PhD, University of Pennsylvania

Cover Image Description: Image shows retinal pigment epithelial cells stained red by an RPE65 antibody. Mutation of the *RPE65* gene causes a genetic form of blindness (LCA2) that may be corrected by gene therapy. Credit: National Eye Institute, National Institutes of Health

New Application

Identifying a gene involved in childhood blindness

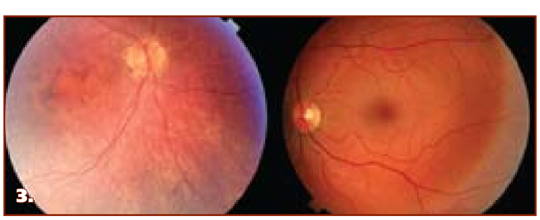
Leber congenital amaurosis (LCA) is a set of genetic eye diseases that affects infants and children. In fact, LCA is the most common cause of congenital vision loss in children. Infants with LCA are born with visual impairments that become more severe through adolescence, leading to complete blindness in adulthood.

To date, researchers have identified 13 gene mutations that can each result in LCA. One form of LCA is caused by a mutation in the gene RPE65, which is linked to vitamin A and the visual cycle. Researchers at the National Eye Institute identified *RPE65* in 1993, and shortly thereafter found that its mutation caused a form of LCA. Because it was the second gene found to be associated with LCA, the researchers named the specific disease caused by *RPE65* mutation LCA2.

How is *RPE65* important for vision? To answer this question, researchers generated mice that lacked the *RPE65* gene. They found that these mice had impaired vision because they were unable to recycle vitamin A in the visual cycle. Without the vitamin A molecule, rhodopsin could not be made, and without rhodopsin, rod photoreceptor cells could not respond to light, although they remained intact. Therefore, the research suggested that people with LCA2 may have all the machinery for vision — they just need a healthy copy of the *RPE65* gene to restart the visual cycle.

Hijacking a Virus

Researchers have developed ways to deliver healthy versions of affected genes to correct some genetic disorders. For *RPE65*, they used a virus to get the gene into photoreceptors. Viruses, like the flu or the common cold, take over a cell's machinery to reproduce their own genetic material and make more viruses. Researchers chose a virus that does not make people sick, removed its infective parts, and used it as a carrier for the healthy gene. After inserting the human *RPE65* gene, they prepared to test the modified virus — an *RPE65* gene therapy agent.



Health Implications

Gene therapy reverses a form of blindness

Research Helps Blind Dogs See

Before testing the gene therapy agent in humans, researchers needed to check its safety and effectiveness in animals. They found an appropriate animal model of LCA2 in Briard dogs, a breed that is prone to a condition that resembles LCA. Researchers injected the eyes of sick dogs with the modified virus that carried the *RPE65* gene. Once treated, dogs that had been visually impaired their whole lives behaved as if they could see more clearly, and their eyes responded to light. Dogs that had once bumped into objects in their paths were able to navigate through obstacle courses within weeks of treatment.

Translating Animal Research to Humans

In 2007, just 15 years after *RPE65* was cloned and 70 years after rhodopsin was discovered, three groups of researchers tested this gene therapy agent in humans with LCA2. Unlike most medications, which are secreted from the body and need to be taken regularly, most gene therapies last for extended periods of time, suggesting that just one treatment with *RPE65* gene therapy might result in long-lasting improvement.

In preliminary studies of young adults with LCA2, researchers reported that the gene therapy improved vision. After receiving treatment, two participants who had been unable to see a hand waving in front of them could see well enough to move around without help. One participant's vision improved so much that he was able to read small print with the help of a magnifying glass. Spearheaded by the National Eye Institute, the research was accomplished with support from public and private sources, both domestic and international.

These studies indicate a new direction in treating genetic eye diseases, including other forms of LCA. But their implications extend beyond the eye. Every day, research in labs across the world helps uncover basic biological and chemical processes, like George Wald's discovery of the visual cycle. With this knowledge as an important foundation, as researchers identify gene mutations that cause disease, they are increasingly able to treat them, potentially allowing clinicians to transition quickly from patient diagnosis to treatment.