Retinal Gene Therapy Stimulates Cortical Responses in Dogs with Congenital Blindness

By Gina Shaw

ARTICLE IN BRIEF:

✔ Gene therapy corrected the defective retinal and visual pathway responses to light in dogs deficient in *RPE65* — a mutation that causes a congenital form of blindness called Leber congenital amaurosis.

Retinal gene therapy can restore the sight of dogs with an unusual genetic mutation causing congenital blindness, according to a new study led by researchers at the University of Pennsylvania.

Dr. Byron Lam: "What we have learned about the treatment method, using the adeno-associated virus as the agent for transferring the gene, will help us to treat other types of retinal dystrophies."

Published June 26 in the open-access online journal *Public Library of Science Medicine*, the study reports that dogs born with *RPE65* gene mutations — the mutation that causes the congenital human blindness known as Leber congenital amaurosis (LCA) — showed dramatic improvement in visual cortical responses following retinal gene therapy.

Leber congenital amaurosis is a rare autosomal recessive disorder, often confused with other conditions such as early onset retinitis pigmentosa and cortical blindness. Approximately 3,000 people in the United States have the condition.

Study Protocols

Principal investigator Geoffrey K. Aguirre, MD, PhD, assistant professor in the department of neurology and the Center for Cognitive Neuroscience at the University of Pennsylvania, and colleagues used functional MRI to assess light-induced brain activity in *RPE65*-mutant dogs before and after gene therapy.

Eight dogs were included in the experiment — two normal animals and six *RPE65*-mutant dogs. Therapy was delivered by subretinal injection of adeno-associated viral vector carrying the wild-type *RPE65*. One of the mutant dogs received a subtherapeutic dose, serving as a treatment control.

All of the dogs, including one treated at four years of age, showed rapid and permanent recovery in their cortical responses to light stimulation. This suggests that even in patients lacking the early visual experience — thought to be a prerequisite for the development of a functioning visual cortex — gene therapy might still restore vision.

"If you don't have any afferent visual input, then your visual cortex may be less likely to develop normally," explained neuro-ophthalmologist Byron Lam, MD, professor of ophthalmology at the University of Miami Miller School of Medicine Bascom Palmer Eye Institute, who was not involved with the study.

"So the concern was that even if you could rescue retinal function with gene therapy, the cortex might not be normal enough to interpret the visual signals received. This paper convincingly shows that in dogs, gene therapy rescues retinal function and, once you've done that, signals are getting through, being received, and processed in the visual cortex."

The study also assessed human patients with LCA with both structural and functional MRI. Investigators observed that the optic nerve diameter and the visual cortical structure were similar to that of normal individuals, and that although the visual cortex of LCA patients did not respond to dim light, it responded to bright light in much the same way as normally sighted individuals.

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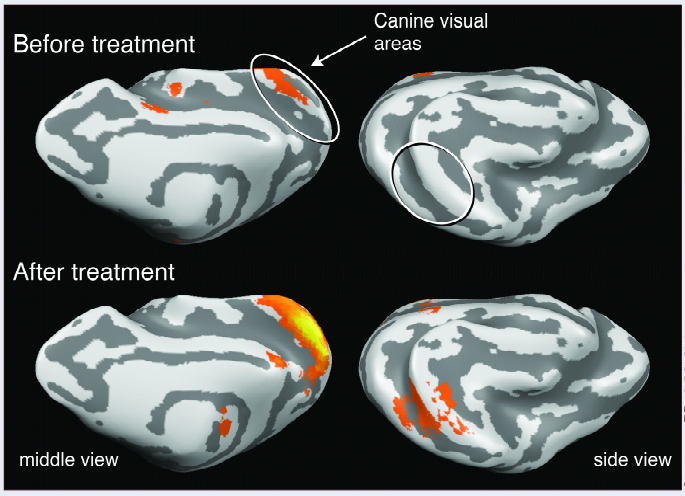
Early Human Trials

Phase 1 human trials for *RPE65* mutation gene therapy are set to start soon in the US, led by Samuel Jacobson, MD, one of the investigators on the dog study. The first human trial of the therapy began in May in the UK, where a team at London's Moorfields Eye Hospital implanted the gene therapy vector in a dozen young adults with LCA, who had developed the condition as children.

"We have data from the dog trials to help guide human trials, but it's still not as easy as it seems," Dr. Lam told *Neurology Today*. "First, you have to determine the optimal time to treat. In addition, because it is a gene therapy, there is concern about safety in humans, which still needs to be worked out over the next several years."

Application to Other Eye Conditions

Dr. Lam suggested that this body of research could also apply to a condition like retinitis pigmentosa (RP), which is much more prevalent than LCA. "Some 50 percent of RP patients have recessive disease," he said. "So as with the *RPE65* mutation, which is also a recessive condition—perhaps with those patients who have later-onset retinal degeneration, maybe you have a larger window to intervene."



Courtesy: PLoS Medicine

Cortical responses in RPE65-mutant dogs before and after treatment compared to normal treatment. Areas of cortical activation to visual stimulation are shown in red and yellow on the inflated cortical surface from medial and lateral views. Shades of gray indicated gyral (light) and sulcal (dark) cortex, and the position of three sulci are marked for reference.

"The problem with LCA and all these recessive retinal degenerations is that the genotype is extremely heterogeneous," said Dr. Lam. There are multiple genes involved in LCA —14 have been identified so far, according to the Foundation Fighting Blindness — and within each gene, a change in a single codon can cause the disease, he added.

"What we have learned about the treatment method, using the adeno-associated virus as the agent for transferring the gene, will help us to treat other types of retinal dystrophies," Dr. Lam said. "We now also understand the natural course of the disease much better. This study tells us that even if you intervene in dogs that are a few years old, you can help their vision. That's quite helpful, because retinal degeneration starts early and is rather progressive."

But he cautioned that much more remains to be understood. "This is an important paper, but it's important to recognize that we don't have enough data on humans being treated with gene therapy for this mutation," he says. "We don't have enough testing in humans to say that the human visual cortex is intact. The title of the paper ["Canine and Human Visual Cortex Intact and Responsive Despite Early Retinal Blindness from *RPE65* Mutation"] does say that, but I think it's a matter of degree. Is it 60 percent intact, 80 percent, or 100 percent [intact]? That's not completely understood. But this is an exciting paper and a promising area of research." ■

Reference:

- Aguirre GK, Kamaromy AM, Jacobson SG, et al. Canine and human visual cortex intact and responsive despite early retinal blindness from *RPE65* mutation. *PLoS Med* 2007; 4:1117-11128.