Gene therapy successfully treats blindness

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Leber's congenital amaurosis (LCA) is a rare hereditary eye disease which occurs during infancy and causes severe vision loss and mostly affects night vision. It was Theodore Leber who first described the condition in 1869. LCA causes retinal degeneration resulting in vision impairment or loss of vision, with little or no change in the appearance of the eye. An infant may not be able to see objects and as he grows, there may be an inability to read and finally total blindness may occur by the time the individual is around 30–40 years of age. LCA is one of the most severe forms of congenital blindness[1–3]. Unfortunately, there is no treatment for LCA.

A recent study sponsored by the Centre for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia, USA, by Albert Maguire and his colleagues[1], bestows the foundation for gene-therapy approaches to the treatment of LCA and possibly other forms of retinal degeneration. According to Maguire, this is the first gene therapy trial for a non-lethal paediatric condition.

Today, more than 400 eye-disease genes have been identified, aided by the Human Genome Project. Till now, nine genes have been identified whose mutations lead to forms of LCA. Three other areas have been identified on human chromosomes in which an LCA gene resides, but has not been specifically identified. Mutations in the retinal pigment epithelium-specific 65 kDa protein gene (RPE65) cause LCA2, which accounts for 6% of the cases[3,4].

In 1997, scientists at the National Eye Institute, National Institutes of Health, US reported a mutation in the gene which resulted in LCA. Studies were then carried out in mice to figure out a way to fix these mutations. In 1998, Gregory Acland and Gustavo Aguirre at the Cornell University[5,6] came up with the same mutation, but this time it was observed in a breed of Briard dogs. In 2001, Maguire and his wife Jean Bennett used gene therapy to reverse blindness in a strain of Briard dogs with a defect in RPE65, suffering from congenital blindness. The dogs were treated sub-retinally with recombinant adeno-associated virus (AAV) carrying RPE65 complementary DNA (cDNA). Interestingly, by 2006, out of the 55 blind dogs used for the study, 90% began to see. It was time now to try the treatment on people.

Maguire and his colleagues[1] investigated the effect of recombinant AAV carrying RPE65, cDNA in LCA2 patients. The protein was administered sub-retinally in three patients – ages between 19 and 26, and short-term effects for 6 and 12 months were noted. These patients were enrolled in a clinical trial from September 2007 through January 2008. Each of these three patients had mutations in the gene which makes a protein needed by the retina for sensing light and sending images to the brain. Those without the gene gradually lose sight until they are blind in early adulthood.

A genetically engineered virus vector AAV2.hRPE65v2 (AAV), which carries a chicken beta actin (CBA), supplied by the Centre for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia, and current Good Manufacturing Practices were used[7] to carry RPE65 cDNA. The vector genome 1.5×10^{10} in a volume of 150 µl of phosphate-buffered saline supplemented with Pluronic F-68 NF Prill Poloxamer 188 was injected into the sub-retinal space following local or topical anaesthesia at the time of vitrectomy. Vitrectomy is the surgical removal of the vitreous, a normally clear, gel-like substance that fills the centre of the eye. The right eye for each patient was selected for the study.

A complete physical examination, ophthalmic examination, laboratory tests and vector bio-distribution and immune response were carried out in patients following surgery. Resolution of the localized retinal detachment was observed in 14 h. After surgery all three patients showed improvement in retinal function. They had improved vision in dim light. This was determined from detecting hand movements to reading lines on an eye chart. The patients also showed an improvement in pupillary light reflexes and visual acuity, which confirm increased sensitivity in the retina. However, since the AAV vector was not injected alone, researchers are skeptical about whether the improvement reflects expression of the protein encoded in the vector.

Since AAV brings about immune responses, people exposed to it may carry antibodies to AAV. Therefore, Maguire and his colleagues administered local and systemic corticosteroids and found that there was no inflammatory response[8]. Hence, no side effects or inflammation was reported following the procedure. Although one of the patients developed a hole in the retina, it did not affect his eyesight. Researchers relate the condition to surgery and not to the injected gene.

According to the study, a longer follow-up and many patients may be needed to ensure the safety and efficacy of the procedure and also to identify factors that influence the extent and duration of vision recovery. Yet the therapy can now be tried on other forms of retinitis pigmentosa, which strike several people.

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