

# New study on promise of gene therapy for Leber congenital amaurosis

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Leber congenital amaurosis (LCA) is a congenital retinal dystrophy present in approximately 1 of 80,000 births. It is estimated that about 3,000 people in the United States are living with LCA and will likely become blind in their lifetimes. Recently, there has been progress in gene therapy for this condition. In a recent study published in the current issue of the *Journal of AAPOS*, the Official Publication of the American Association of Pediatric Ophthalmology and Strabismus, researchers from the University of Iowa Hospitals and Clinics, Iowa City, and The Hospital for Sick Children, Toronto, found that only a limited number of patients possess the exact genetic mutation necessary for a positive outcome from the therapy.

LCA and related early-onset retinal degenerations are caused by mutations in at least 15 genes. Based on a number of studies, LCE due to a mutation in the RPE65 gene may be treatable with a normal copy of the RPE65 gene.

Other [genetic mutations](#) will not respond to this therapy. Lead investigator Arlene Drack, MD, comments that "the interpretation of DNA variants is complex. Careful, accurate genetic diagnosis leads to effective treatment for patients, and avoids treating patients who cannot benefit from the current therapy."

Commenting on the article, JAAPOS Editor-in-Chief David G. Hunter, MD, PhD, stated, "It is a dream come true that many of our patients with Leber congenital amaurosis, who until now faced a lifetime of total blindness, now have a prospect of gaining sight. But in our enthusiasm to offer this novel treatment to patients, we have to be extremely careful to treat only those patients with the one molecular form that is amenable to [gene therapy](#) at present. Dr. Drack's article highlights this concern and provides a practical approach toward how this can be accomplished."

[Genetic testing](#) can detect changes from the norm in the [genetic code](#), but not all changes are cause for alarm. Some natural variations in the genome, called benign polymorphisms, are natural and do not cause disease. Because the therapy is so specific, it is vitally important that a multistep approach be used to ensure correct interpretation of variations found in the genome of patients. For example, an LCE patient may have benign polymorphisms in the RPE65 gene and true disease-causing mutations in some other, unidentified gene. If that patient is erroneously enrolled in the RPE65 gene replacement trial, there will be no benefit. Similarly, if a polymorphism is found in another LCA gene, patients may believe they are ineligible for the RPE65 trial and may miss out on a possible opportunity.

The authors analyzed 5 subjects and their families. Patient 1 was reported to have 2 disease-causing AIPL1 mutations. The family received incorrect prenatal counseling based on this result. The researchers found both variations to be benign ethnic polymorphisms. Case 2 had possible disease-causing mutations in RPE65, RPGRIP1, and CRB1; however, screening of family members revealed that only CRB1 variations were disease causing and the RPE65 change was a polymorphism found in 11% of African Americans. Case 3 had a diagnosis of CRB1-associated LCA, but this mutation was not disease causing; a true homozygous disease-causing mutation was later found in RDH12. Patient 4 had 3 mutations found in RPE65, but only 2 were disease causing. Patient 5 had a homozygous mutation in RPE65. Only Patients 4 and 5 would be eligible for clinical trials of RPE65 gene replacement, for which inclusion criteria are complex.

Writing in the article, Dr. Drack and colleagues state, "Gene therapy for patients with RPE65-associated LCA is now in clinical trials. Patients and families can be offered genetic testing, but results are complex and must be interpreted by

practitioners with experience in both clinical and molecular genetics to avoid either ineffective treatment or lack of treatment due to an erroneous genetic diagnosis."

In an accompanying editorial, Elise Héon, MD, The Hospital for Sick Children, Toronto, comments on the complexity of the genetic screening needed to isolate patients who can benefit from the gene therapy. She writes, "Ocular gene therapy is not available for all retinal dystrophies — only RPE65-related LCA. ...The article by Drack and colleagues nicely outlines how to screen for eligible patients and what to look for. This is timely and highlights important points relating this new era of ophthalmology: ocular gene therapy... The likely positive outcome of these trials highlights the critical contribution of the retinal clinician in identifying patients who can benefit from this remarkable therapy and in not misleading those who cannot."

**More information:** The article is "Which Leber congenital amaurosis patients are eligible for gene therapy trials?" by Arlene V. Drack, MD, Rebecca Johnston, BA, and Edwin M. Stone, MD, PhD. The editorial is "My child has Leber congenital amaurosis: Why is he/she not eligible for gene therapy trials?" by Elise Héon, MD. Both appeared in the Journal of AAPOS, December 2009, Volume 13, Issue 6.

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