

This plain-language summary (or PLS) describes a paper on Leber congenital amaurosis 10 that was published in a medical journal called “*Retina*”.

Title of the paper:

Leber congenital amaurosis due to *CEP290* mutations – severe vision impairment with a high unmet medical need: a review

Author and journal details:

Bart P. Leroy, David G. Birch, Jacque L. Duncan, Byron L. Lam, Robert K. Koeneke, Fernanda B. O. Porto, Stephen R. Russell, Aniz Girach.

Retina 2021;doi:10.1097/IAE.0000000000003133. Online ahead of print.

What does this paper report on?

- The authors of this paper reviewed what scientists know about the genetic eye disease called **Leber congenital amaurosis 10 (also known as LCA10)**. They looked at the scientific articles on this subject that have been published in high-quality medical journals

Why was this research needed?

- Tying together separate pieces of scientific evidence about a disease can help us to understand the disease better. It also helps identify where there may be areas of care for people with the disease that need to be improved. We call these gaps “unmet medical needs”
- Bringing evidence together in this way is especially important for rare diseases as it improves awareness among healthcare professionals of the needs of people living with the disease

The authors of the paper are expert eye doctors working at specialist centers in Belgium, Brazil, Canada, and the USA; one of the authors is an employee of ProQR Therapeutics.

This PLS has been developed in collaboration with Bart Leroy (an author on the original paper), Francesca Diodati and Matthew Carr, with medical writing assistance provided by ApotheCom. The review paper and this PLS were sponsored by ProQR Therapeutics.

What did the research look at?

The review focused on LCA10, and examined:

- Causes of the disease
- Diagnosis of the disease
- The impact it has on individuals and families
- Potential treatments that are being investigated by researchers

This PLS provides a summary of what the authors found. It also contains additional background information on protein production and on clinical research phases to provide context to what the authors report on. This supplementary information is displayed in Explainer 1 and Explainer 2 at the end of this PLS.

Key points

- The review gathered information about LCA10 that has been published in medical journals
- It found unmet medical needs in three key areas: challenges around achieving an accurate diagnosis; managing the impact of LCA10 on the individual and family; and lack of treatment options
- Two investigational treatments for LCA10 are currently being explored in clinical trials

What do we know about LCA10?

Leber congenital amaurosis 10 (LCA10)

LCA10 is the most common subtype of LCA

Leber congenital amaurosis (LCA)

LCA is a family of closely related diseases, each with mutations in specific genes; LCA is one of the most severe types of IRD

Inherited retinal diseases (IRDs)

IRDs are a large group of diseases that are passed down from parents to child and affect the cells at the back of the eye

"Leber" is the name of the man who first discovered this group of diseases.

"Congenital" means present at birth

"Amaurosis" means blindness

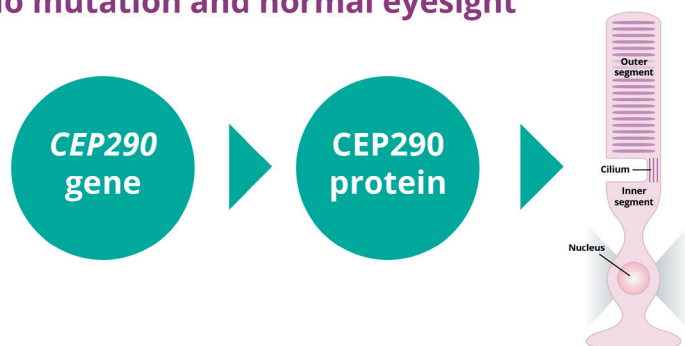
LCA is rare: **only 1 in 30,000** newborns are affected

LCA10 causes severe vision loss that typically occurs early in childhood; the extent of the loss varies between individuals. Other signs of LCA10 include repeated poking of the eyes, an inability to follow light or objects with the eyes, and repetitive involuntary eye movements also known as nystagmus.

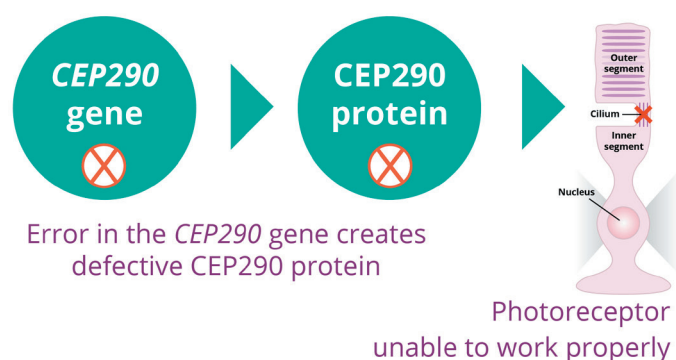
What causes LCA10?

- LCA10 is caused by a defect in a protein known as "CEP290", which is needed by light-sensing cells known as "photoreceptors" in a region at the back of the eye called the "retina"
- Photoreceptors translate images into electrical signals that then get passed on from the eye to the brain
- The CEP290 protein is located in an important central region of the photoreceptor known as the "cilium"
- All the instructions for making the CEP290 protein are held in a specific *CEP290 gene*
- In people with LCA10, there are errors (or "mutations") in both copies of the *CEP290 gene* that alters the instructions; and this disrupts the protein-making process causing the photoreceptors to stop working properly and then die (see also Explainer 1 at the end of this PLS)

No mutation and normal eyesight



LCA10 and vision loss



Children with LCA10 have normal photoreceptors when they are born. The photoreceptor loss due to the *CEP290* mutation occurs over time in early childhood. This may create a useful opportunity for treatment.

What are the unmet medical needs in LCA10?

Need 1 – Correct diagnosis is important but identifying LCA10 is challenging

- Early and accurate diagnosis is critical to allow patients and their families to be given the appropriate support
- It can be difficult for physicians to recognize LCA10 because other diseases can cause similar symptoms
- There are not enough specialist training programs for medical professionals on diagnosing inherited diseases affecting the retina
- Genetic testing in LCA can provide a more specific diagnosis. However, use of genetic testing by physicians is relatively low

38% of people with an IRD have not had a genetic test

Need 2 – Early vision loss has a significant effect on health-related quality of life

Health-related quality of life is a measure of how much a person's health problems affect their life. It assesses, for example, how able they are to engage in work, social, and family activities, whether they can take care of themselves, whether they are anxious or depressed, or whether they live with pain or discomfort.

Although there are no studies in LCA10 specifically, more general studies of childhood vision loss have found that:



It reduces quality of life: children with low vision have a 36% lower quality of life than children of the same age with no vision disability



It affects early development that can limit other areas such as understanding and movement



It causes lifelong psychological effects: individuals with early vision loss may suffer depression and feelings of worthlessness into adulthood



It impacts the child's family and alters how that family functions



It causes parental stress: 75% of parents of visually impaired children report moderate to very severe anxiety

More than **70%** of individuals with an IRD and their parents are frustrated by the lack of awareness and support for their condition

Need 3 – No treatments are available for LCA10

The LCA family of diseases has been considered incurable since their discovery back in 1869. However, advances in our understanding of genetics and of the biology of the retina have been made more recently.

In 2017, a gene therapy became available for LCA; however, this is for a different type of LCA known as “LCA2”. But there are still no treatments for LCA10.

Developing an effective treatment for LCA10 may be more difficult than for LCA2:

- Use of LCA2 gene therapy technology may not be suitable for LCA10
- The vision loss in LCA10 is more severe and occurs earlier than in LCA2. This means that there is a shorter “therapeutic window” – this window is the stretch of time that a treatment could restore vision before too much sight loss or loss of retinal tissue has occurred

However, scientists have discovered that photoreceptors in a region of the retina may be preserved in LCA10, even in people with severe vision loss. This suggests a potential opportunity for improving vision if a suitable treatment can be developed.

Which potential treatments are being developed for LCA10?

There are two investigational therapies being explored in LCA10: a type of RNA therapy called “sepfarsen” and a gene therapy known as “EDIT-101” (see also Explainer 2 at the end of this PLS).

Sepfarsen (also known as “QR-110”)

This is a type of RNA therapy known as an “antisense oligonucleotide (or AON)”. Like all genes, the *CEP290* gene is written in DNA. To translate this into a protein, it first has to be transcribed into RNA. First, a near-carbon copy of DNA, called pre-mRNA, is made. This then has to be modified into mature mRNA by a process known as splicing, before it can be translated into protein. In LCA10, a frequent mutation or error in the *CEP290* gene gets copied into the pre-mRNA. This error leads to an abnormal mature mRNA that makes no protein. Sepfarsen works as a patch, by making sure that the pre-mRNA is spliced correctly even though it contains an error, into the proper mature mRNA, which then gets translated into correct CEP290 protein. Sepfarsen is used for one specific mutation that can occur in the *CEP290* gene, but not all mutations in this gene..

The first study in people (a Phase 1-2 study in 11 children and adults with LCA10 with severe vision loss) has been completed. Results from up to 12 months of sepfarsen treatment have been reported. Sepfarsen led to:

- Meaningful and lasting improvements in vision
- Significant improvements in visual sensitivity to light
- Improvements in ability to navigate a way through a mobility course

The safety profile of sepfarsen in this study was considered manageable. In particular, cataracts (a clouding of the lens of the eye that affects vision) occurred in some participants as an unwanted effect of the treatment; cataracts are also common with other treatments injected into the eye.

Participants from the Phase 1-2 study have been enrolled into an extension study to provide long-term data. Results are expected in early 2021. A separate Phase 2-3 study has completed recruitment; early results from this study are due in 2022.*

*This is the status as of March 2021; this information has been updated since publication of the paper by Leroy *et al.*

RNA therapy is different from gene therapy and has several advantages, for example:

- It targets the temporary RNA molecules rather than the permanent DNA so may reduce the risk of causing permanent unwanted effects
- It can be injected into the fluid inside the eyeball (the “vitreous”), which means that the procedure is more straightforward than for gene therapy and that the treatment can reach all areas of the retina

EDIT-101 (also known as “AGN-151587”)

This is a type of gene therapy. It works by correcting the mutation in the DNA. EDIT-101 is used for one specific mutation that can occur in the *CEP290* gene, but not all mutations in this gene. Little is known about how effective this therapy is, or which unwanted effects it is associated with. The first study in people (a Phase 1-2 study in children and adults with LCA10) is currently recruiting participants; results are expected in 2024.

What were the authors’ conclusions?

- **Currently, no treatments are available for people with LCA10**
- **There is a great demand for treatments for LCA10, due to the severity and early onset of vision loss in this disease**
- **Two potential therapies for LCA10 are being investigated in clinical studies and the results of these studies are eagerly awaited**

Where can I learn more?

Organizations for people living with LCA10 include:

- Foundation Fighting Blindness www.fightingblindness.org
- Prevent Blindness www.preventblindness.org
- National Organization for Rare Disorders www.rarediseases.org

Information on clinical trials in LCA10 can be found at: www.clinicaltrials.gov and www.clinicaltrialsregister.eu

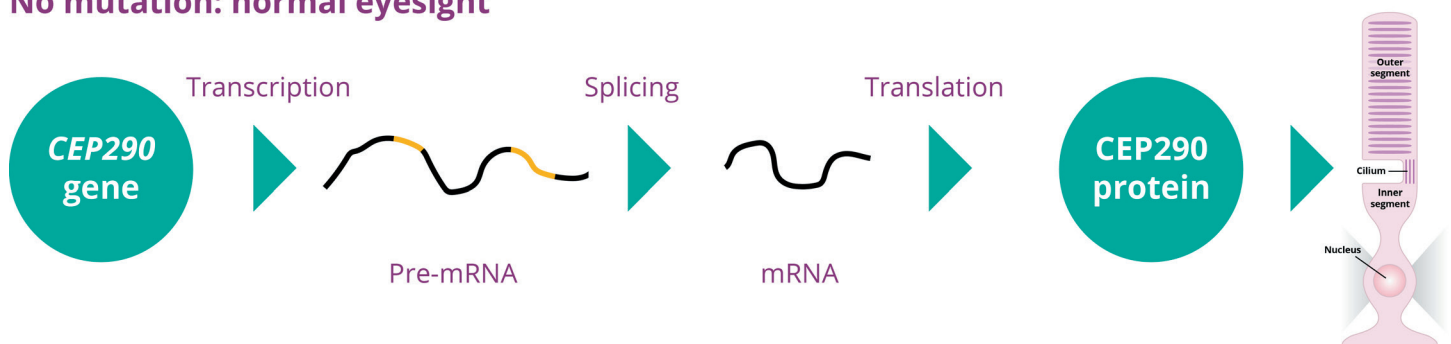
The full paper on unmet medical needs in LCA10 can be accessed here: https://journals.lww.com/retinajournal/Abstract/9000/Leber_Congenital_Amaurosis_Due_to_CEP290_Mutations.95553.aspx

Explainer 1: How the CEP290 protein is made in photoreceptors

The instructions for making the CEP290 protein are held in the *CEP290* gene as coiled lengths of genetic material called “DNA” tightly wrapped up in the nucleus of the photoreceptor.

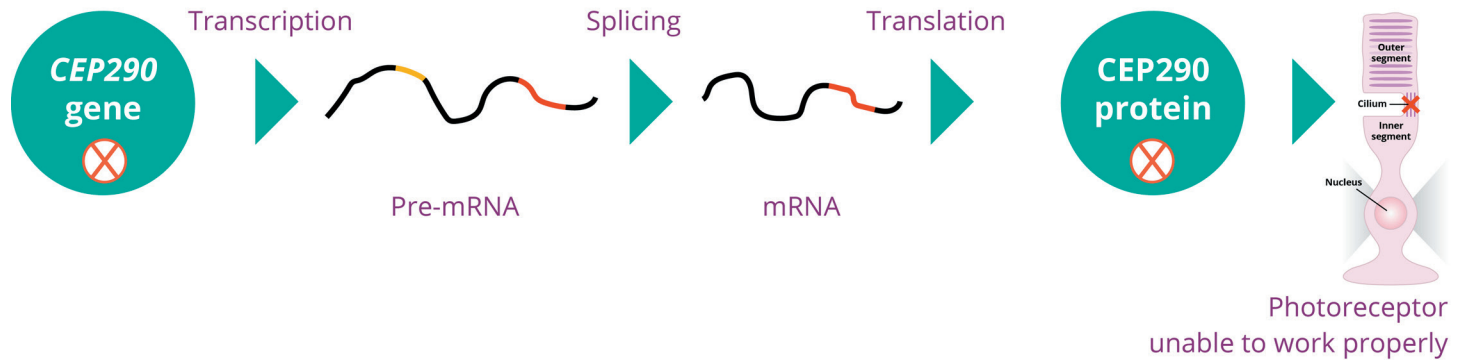
1. To make the CEP290 protein, the DNA unwraps and a new length of RNA is made. This process is called “transcription”. RNA is genetic material similar to DNA but is a short, temporary thread of genetic material. The new length of RNA is called “pre-mRNA” and contains a copy of the genetic instructions held in the DNA
2. Unwanted sections of this pre-mRNA thread (shown in orange in the diagram below) are then chopped off (or “spliced”) to make a shorter mRNA molecule
3. The mRNA then builds the protein, in a process called “translation”, following the genetic instructions that it holds

No mutation: normal eyesight



In LCA10, a specific, frequent mutation in the *CEP290* gene (shown in red in the diagram below) is carried over to the pre-mRNA during transcription. This change in the genetic instructions disrupts the splicing process, and an extra piece of unwanted genetic information is left in. This, in turn, creates errors in the instructions that the mRNA tries to follow during translation, which stops the CEP290 protein from being made correctly.

LCA10: vision loss



It is like adding a nonsense word into an instruction that stops you from fully understanding what you are being told to do. For example:

*“Count to ten and then jump four times” becomes “Count to ten and then **cook** jump four times”*

Explainer 2: How potential new treatments are investigated

All treatments must pass through a set pathway of research studies before they can be approved for use and doctors can prescribe them for people. The steps are:

- **Preclinical studies** to test the concept in the laboratory; does not involve people
- **Phase 1 clinical studies** to learn how safe the treatment is in people; they usually involve people who do not have the disease (known as “healthy volunteers”)
- **Phase 2 clinical studies** to learn how safe the treatment is, and how good it is at treating the disease at different doses; they involve only a small number of people with the disease
- **Phase 3 clinical studies** to understand more about how well the treatment works balanced against the side effects it produces; they involve a larger number of people with the disease

Sometimes, the steps can be combined if there are only a small number of participants who could be enrolled.

While treatments are in this pathway, they are called “investigational treatments”. This means that researchers are still learning about their safety profile and how well they might treat the disease in question, and the treatments have not yet been approved for use outside of a clinical study.