Press release

Rescuing human light-sensors in a common form of Leber congenital amaurosis

• Scientists successfully test new potential treatment for severe inherited childhood sight loss

• Tests were done using 3D mini-retinas grown with stem cells from a patient, as this ‘antisense’ treatment can’t be tested in animals

• Antisense treatment restored function to light-sensitive cells

• The treatment could one day be given by simple eye injection

Scientists at the UCL Institute of Ophthalmology have identified the mechanism behind a common inherited cause of severe sight loss in young children. The results also point to a potential new treatment that may be possible to deliver by simple injection to the eye. The research was funded by charities Fight for Sight, Moorfields Eye Charity and Guide Dogs, with support from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at Moorfields Eye Hospital.

Leber congenital amaurosis (LCA) is the name for a group of disorders that make up 5% of all inherited retinal dystrophies. These are conditions in which lightsensitive ‘photoreceptor’ cells in the layer of tissue at the back of the eye (the retina) degenerate and die, causing sight loss or blindness.

Up to 1 in 4 people with LCA have faults in the gene CEP290. Several syndromes, e.g. Senior-Loken syndrome, are linked to different faults in the same gene and can affect multiple parts of the body. But almost everyone with CEP290-LCA has a specific fault that only affects photoreceptors and, until now, we didn’t know why.

All of these disorders involve damage to sensors called cilia that stick out from the surface of most cells in the body like an antenna. They monitor the environment around them and can trigger a process of cell communication.

Cilia are vital for the body to work normally and research has shown that CEP290 protein is important for building them. But in CEP290-LCA the genetic fault leads to an unwanted instruction that tells the photoreceptor’s protein-making machinery to stop assembling CEP290 before it’s finished.

Photoreceptors have highly-specialised cilia made up of tightly-stacked discs (together called the ‘outer segment’). The discs are studded with molecules of protein called opsins that are pigments, meaning they absorb light.

When light hits an opsin it responds by changing shape. This sets off a chain of events in the photoreceptor that converts light into an electrical signal that can then be passed from eye to brain. Without an outer segment, photoreceptors are blind to light.

Previous reports have shown that skin cells (fibroblasts) from people with CEP290- LCA contain less than half the amount of full-length protein compared to healthy controls. But scientists have been unable to measure this in photoreceptors because it has not been possible to generate a CEP290-LCA animal model.

In this study, the research team, led by Professor Mike Cheetham at UCL Institute of Ophthalmology, was able to investigate the CEP290 fault in LCA retinal cells for the first time. They used induced pluripotent stem cells (iPSCs) generated from the skin cells of a patient with CEP290-LCA to grow 3D optic cups. The optic cup is a sheet of tissue that grows during eye development and goes on to become the layers of different cell types that make up the mature retina.

The team also tested a promising new way to treat CEP290-LCA using small engineered molecules known as ‘antisense morpholinos’. They have previously been shown in CEP290-LCA fibroblasts to prevent the premature stop instruction from being given, by changing which sections of the instructions are edited together (splicing). Here, the researchers designed an antisense morpholino, CEP290-MO, to target the LCA genetic fault.

Dr Amelia Lane is a research associate at UCL Institute of Ophthalmology and a first author on the study, which is published in the journal Cell Stem Cell. She says:

“We have been able to show that this CEP290-specific treatment restores normal splicing, increases protein and restores cilia numbers, structure and function in photoreceptors which we were able to make from CEP290-LCA patient cells. This is really encouraging because it’s the functional interaction between photoreceptor proteins that will be critical to whether the treatment can restore vision. CEP290 is not suitable for most current approaches to gene therapy but a recent study in normal mice showed that eye injection with the same class of molecule as CEP290- MO altered photoreceptor splicing and was relatively safe, so this could become a practical therapeutic option.”

Mike Cheetham is Professor of Molecular and Cell Biology at UCL Institute of Ophthalmology. He says:

“Our findings using stem cells grown into organoids in the lab provide direct evidence of tissue-specific differences how genes are used by cells that are likely to contribute to the relationship between genetic inheritance and the manifestation of symptoms that affect patients. It has been suggested that photoreceptors are more vulnerable to the CEP290-LCA fault than other cell types, but our results suggest instead that photoreceptors produce significantly less CEP290 than other cells. We think this may also apply to other genes but, importantly, we now have the means to correct this, and this understanding was only possible with stem cells derived from patients.”

Dr Dolores M Conroy is Director of Research at Fight for Sight. She says:

“Developing a treatment that could restore vision or slow slight loss is the top priority for research on inherited eye disorders as identified by patients, relatives, carers and health professionals in the Sight Loss and Vision Priority Setting Partnership and so these results are highly relevant as well as promising. However, we now need to translate these findings, using antisense therapy, into patients. In addition, this approach could be used to treat other inherited retinal disorders.”

Ends NOTES TO EDITORS Publication Parfitt et al., 2016, Cell Stem Cell 18, 1–13 http://dx.doi.org/10.1016/j.stem.2016.03.021 Fast facts • LCA affects between 1 in 30,000 and 1 in 81,000 people • The common LCA causative gene CEP290 is also known as LCA10, BBS14, JBTS5, NPHP6, MKS4 and SLSN6. • The work was also supported by the Rosetrees Trust, the London Project to Cure Blindness, the Special Trustees of Moorfields Eye Hospital, Wellcome Trust, National Institute for Health Research, (NIHR) Biomedical Research Centre (BRC) based at Moorfields Eye Hospital NHS Foundation Trust. Fight for Sight is the leading UK charity dedicated to funding pioneering research to prevent sight loss and treat eye disease. Fight for Sight is funding research at leading universities and hospitals throughout the UK. Major achievements to date include: saving the sight of thousands of premature babies through understanding and controlling levels of oxygen delivery; restoring sight by establishing the UK Corneal Transplant Service enabling over 52,000 corneal transplants to take place; providing the funding for the research leading to the world’s first clinical trial for choroideremia; bringing hope to children with inherited eye disease by co-funding the team responsible for the world’s first gene therapy clinical trial; and identifying new genes responsible for glaucoma, retinitis pigmentosa, keratoconus and other corneal disorders, and Nance-Horan syndrome. Fight for Sight’s current research programme is focusing on preventing and treating age-related macular degeneration, diabetic retinopathy, glaucoma, cataract and corneal disease. We are also funding research into the causes of childhood blindness and a large number of rare eye diseases. For more information, contact: Ade Deane-Pratt on 020 7264 3907 or ade@fightforsight.org.uk www.fightforsight.org.uk About UCL (University College London) UCL was founded in 1826. We were the first English university established after Oxford and Cambridge, the first to open up university education to those previously excluded from it, and the first to provide systematic teaching of law, architecture and medicine. We are among the world's top universities, as reflected by performance in a range of international rankings and tables. UCL currently has over 35,000 students from 150 countries and over 11,000 staff. Our annual income is more than £1 billion. www.ucl.ac.uk | Follow us on Twitter @uclnews | Watch our YouTube channel YouTube.com/UCLTV Moorfields Eye Hospital NHS Foundation Trust is one of the world’s leading eye hospitals, providing expertise in clinical care, research and education. Moorfields has provided excellence in eye care for more than 200 years and continues to be at the forefront of new breakthroughs and developments. Along with their academic partners at the UCL Institute of Ophthalmology, Moorfields is recognised as a leading centre of excellence in eye and vision research. Together, they form one of the largest ophthalmic research sites in the world.