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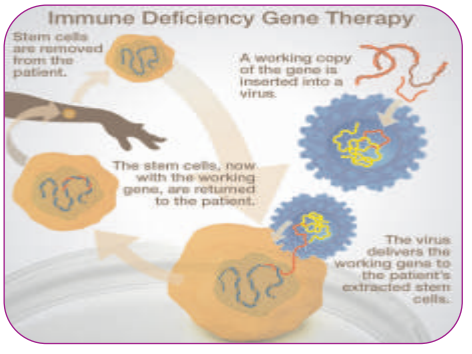
GENES AND GENE THERAPY

Rupa D. Vagga

WHAT ARE GENES?



Chromosomes contain the formula for bringing home the bacon thing. They are found in practically every phone's core and are produced using strands of DNA. Sections of DNA called "qualities" are the fixings, and chromosomes are the structures that contain every one of the qualities. Every quality adds a particular protein to the formula. Proteins manufacture, control and keep up your body. For example, they fabricate bones, they empower muscles to move, they control processing, and they keep your heart pulsating. It is considered 20,000 qualities in our cells that code for the greater part of our attributes. Your qualities make you what are, they choose practically every little thing about you.

Your genes are passed from one generation to the next via your children. We have 46 chromosomes in total; each child receives 23 chromosomes from its mother and 23 from its father. Unfortunately, genes can become damaged – just like a corrupt computer file. If this happens we can suffer illness or even pass this illness to the next generation.

Scientists have discovered that many retinal degenerative conditions are hereditary by studying the DNA from many members of the same family to see if there are any differences. In some cases a gene may not completely control a particular trait, but may partially control it. In this case, a combination of genes and environment may result in illness.

WHAT IS GENE THERAPY?

The theory behind gene therapy is to treat the disease by repairing the abnormal gene. This is achieved by replacing the disease causing faulty gene with a “normal” copy into an individual’s cells. The most successful method to deliver the gene to the cells is by using a virus that has been genetically modified to carry human DNA. The eye has proved to be an ideal organ for gene therapy as it is well protected from the body’s immune response, and these early successes will pave the way in the near future for treatments for both inherited and non-inherited forms of blindness.

In November 2012 a milestone was reached when Glybera®, which is for the treatment of a rare metabolic disorder known as lipoprotein lipase deficiency (LPLD), became the first gene therapy to be granted regulatory approval in Europe. Although this is not directly related to retinal research, it represents a huge step towards the development of registered and approved retinal gene therapies.

WHAT CONDITIONS CAN BENEFIT FROM GENE THERAPY?

Any condition where the faulty gene that is responsible for the disorder is known has the potential to benefit from gene therapy. Examples are forms of retinitis pigmentosa and Leber congential amaurosis. Other illnesses that are thought to be partially affected by genes and partially by our environment (e.g. lifestyle, exposure to sunlight) like age-related macular degeneration may also benefit from such a therapy in the future.

Blindness is only one disease which researchers are hoping gene therapy will cure. Others include severe combined immunodeficiency, haemophilia, Parkinson's disease, cancer and even HIV.

GENE THERAPY PROJECTS SUPPORTED BY FIGHTING BLINDNESS

Fighting Blindness realises the potential of gene therapy for the treatment of retinal degenerations and has a strong commitment to funding research in this area. Examples of some recently funded research projects are:

• 2012: Exploration of AAV-delivered gene therapies for Leber's hereditary optic neuropathy (LHON) – Professor Jane Farrar, Trinity College, Dublin. Read point 1 below for further explanation.
• 2011: Exploration of the candidacy of RPE65 in the etiology of adRP with choroidal involvement. – Prof Pete Humphries, Trinity College Dublin. Read point 2 below for further explanation.
• 2008: Development of gene and cell therapies for the treatment of retinal degeneration – Prof Robin Ali, Moorfields Hospital, London. Read point 3 below for further explanation.
• 2008: Clinical trials of gene therapy for retinitis pigmentosa – Prof Jane Farrar, Genable & Trinity College, Dublin.
• 2007: Optimal expansion and differentiation into photoreceptors of adult retinal stem cells from porcine pigmented ciliary epithelium – Dr Tiziana Cogliati, Queens University Belfast.
• 2006: On the molecular pathology of retinal degeneration caused by mutations within the IMPDH1 gene – Prof Pete Humphries, Trinity College Dublin.

1. Fighting Blindness continues to support gene therapy for Leber Hereditary Optic Neuropathy (LHON).

We are delighted to announce that Fighting Blindness will continue to support Irish research regarding the development of gene therapy for Leber hereditary optic neuropathy (LHON). Professor Jane Farrar and Dr. Naomi Chadderton of Trinity College, Dublin were recently successful in their application for funding through the joint funding scheme established by the Medical Research Charities Group (MRCG), which sees the Health Research Board match the funding invested into research by medical research charities in Ireland. Through this scheme, Fighting Blindness will directly invest €150,000 over the next three years towards this research and this will be matched by the Health Research Board.

Leber hereditary optic neuropathy (LHON) is a maternally inherited disorder affecting the mitochondrial DNA. Children inherit their mitochondrial DNA only from their mother, unlike nuclear DNA which comes from the mother and father. A woman carrying a LHON mutation will pass it to all of her children; men with the LHON gene never pass it to their children. Individuals with LHON experience fast, sudden, painless loss of vision in both eyes in their late teens or early 20s. Males are more commonly affected than females. The mitochondria are often referred to as the "powerhouses of the cell" because the mitochondria take in glucose and produce energy. In LHON, a mutation in the mitochondrial DNA leads to a loss of energy transfer to the optic nerve and a degeneration of the cells, resulting in loss of vision.

This investment will enable the continuation of the development of viral technology that will deliver a gene that provides energy back to the eye cells, preventing those cells from dying. We are extremely pleased that the scientific excellence of this project and urgent clinical necessity for the development of treatments for this disorder has been recognised by the Health Research Board and we are glad to be able to support this important project over the next three years.

2. Exploration of the candidacy of RPE65 in the etiology of adRP with choroidal involvement

Prof Humphries and his team have identified two families from Ireland who have autosomal dominant

retinitis pigmentosa. Autosomal dominant is one of several ways that a disorder can be passed down through families. If a disorder is autosomal dominant, it means that you only need to get the abnormal gene from one parent in order for you to inherit the disease. In the families in this study, members have a mutation on the RPE65 gene.

Up until this point, this particular gene has been associated with more rare conditions, so it is very interesting to discover that the mutation may be more common than previously suspected. There is evidence to show that it could cause up to 20% of cases with another condition called choroideremia.

Prof Humphries and his lab plan to use cultured cell lines to further their work. Cultured cells are cells of a single type (human, animal or plant) that have been adapted to grow continuously in a lab so that they can be used in research. The team will be closely examining mutant proteins in these cells as well as screening for further mutations in other cases of RP with choroidal involvement.

Prof Humphries is hopeful that these studies may reveal a new disease mechanism associated with RP and may also bear relevance to the design of future therapy opportunities. Fighting Blindness is glad to be able to support this important project as we learn more about the genetics of retinal degeneration's in Irish families and, importantly, progress towards the development of treatments.

3. Revolutionary gene therapy helps restore young man's sight

Fighting Blindness helped fund the world's first clinical trial to test a revolutionary gene therapy treatment which improved a young man's sight.

Professor Robin Ali pioneered the first ever successful trial of gene therapy for a form of blindness called Leber's Congenital Amaurosis.

The research conducted by Professor Robin Ali at University College London and Moorfields Eye Hospital in London brings hope to millions affected by eye diseases as a result of revolutionary gene therapy treatment.

Prof Ali treated a patient who has a rare genetic eye disease called Leber's Congenital Amaurosis (LCA). Steven Howarth, then 18, from Bolton, England, (pictured centre above with Prof Robin Ali, right, and Prof Michael Comer, left, Fighting Blindness Head of Research) had been left with extremely poor vision and completely unable to see in the dark.

Following the treatment, his sight improved sufficiently to be able to navigate a 'maze' in conditions similar to street lighting at night.

Prof Ali managed to replace the faulty 'RPE65' gene causing the condition with a normal gene. The therapy was delivered in a harmless virus or 'vector' which was injected into the back of the eye and spread to the cells.

As well as part-funding the UCL project, Fighting Blindness funds a similar project at Trinity College Dublin which is focused on developing a similar therapy but for a different type of gene, which causes Retinitis Pigmentosa – a condition leading to tunnel vision.

Professor Jane Farrar, of the Trinity College project, said: "This is great news. It shows that in principle gene-based medicines for the eye provide some hope for patients with many different forms of genetic eye disease".

Remarking on the discoveries, Professor Ali stated: "Appearing surprisingly that quality treatment can work in patients with eye ailment is an extremely huge point of reference. This trial sets up evidence of standard of quality treatment for acquired retinal infection and prepares for the improvement of quality treatment approaches for an expansive scope of eye issue.

"These outcomes give us incredible certainty that this method is protected and can convey genuine advantage to patients with hindered vision. While we're exceptionally amped up for the change in Steven's vision, underscore that quality treatment is as yet a test treatment not yet for the most part accessible to patients. The method will be tried in different patients with LCA and we likewise would like to start trials for different types of retinal illness later on."

The researchers believe the operation's success for Steven could be because his disease had not progressed to the same extent as the other two patients in the trial.

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• Wet AMD: http://clinicaltrials.gov/ct2/show/NCT01301443?term=retinostat&rank=2

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