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Advances in Inherited Retinal Disease

Inherited retinal diseases (IRDs) are a heterogeneous group of visually debilitating diseases caused by pathogenic variation in proteins critical to retinal function. The majority of IRDs are characterized by retinal degeneration, which can lead to significant vision impairment and blindness. Collectively, IRDs are estimated to affect more than 2 million people worldwide.

It is of interest that different genetic mutations may result in the same clinical disorder. Therefore, molecular genetic testing has become an important strategy to complement clinical findings and confirm or clarify a diagnosis. The advent of sophisticated testing technologies for genetic disorders has highlighted the need for awareness of human genetics and its relevance to personalized medicine in IRDs. The American Academy of Ophthalmology recommends genetic testing for all individuals with presumed or suspected IRDs for which a causative gene or genes have been identified.

Historically, genetic testing has been ordered and interpreted by IRD specialists and ocular genetic counselors at large academic research centers. Now however, genetic testing is relatively easily performed in ophthalmic clinics with INVITAE tests. A sample of saliva is taken, and over 250 genetic mutations are screened in the laboratory. The results take 2 t o3 weeks, and can confirm a variety of genetic disorders. The testing is free. While at the present time only one IRD is treatable (RP65) advances are being made with other mutations and it may be important for patients to have the necessary information about the genetic disorder that affects them.

At the present there are two methods used to treat IRDs. Viruses introduce their genetic material into the host cell, tricking the host's cellular machinery into using it as blueprints for viral proteins. Retroviruses go a stage further by having their genetic material copied into the genome of the host cell. We can exploit this by substituting a virus's genetic material with therapeutic DNA. A number of viruses have been used for human gene therapy, including retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus. Like the genetic material (DNA or RNA) in viruses, therapeutic DNA can be designed to simply serve as a temporary blueprint that is used to enter the host's genome, becoming a permanent part of the host's DNA in infected cells. Adeno associated viruses are most widely used in ophthalmology. Spark therapeutic's Luxturna, used to treat the RP65 form of Leber's congenital amaurosis, uses an adeno-associated virus to deliver the corrective gene.

A second method is CRISPR gene editing, which stands for "Clustered Regularly Interspersed Short Palindromic Repeats". This is a genetic engineering technique in molecular biology by which the genomes of living organisms may be modified. It is based on a simplified version of the bacterial CRISPR-Cas9 antiviral defense system. By delivering the Cas9 nuclease complexed with a synthetic guide RNA (gRNA) into a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or new ones added *in vivo*. The technique allows for the genomes to be edited *in vivo* with extremely high precision, cheaply, and with ease. Its use is just beginning.

There are a great many mutations that cause IRDs. There are over 130 different mutations that cause retinitis pigmentosa alone. In the future, these new therapies may be personalized to correct multiple specific genetic abnormalities that cause IRDs.

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To schedule an appointment at the Kentucky Lions Eye Center, please call 502-588-0588.