

## **Symptoms, causes and treatment options of different IRDs**

While all IRDs affect the retina and visual function, the symptoms, onset, progression and cause of each varies. Here, we will give an overview of the different symptoms of the different IRDs in a PDF format that you can easily download. In our “Focus On” section on this website, you can find out more about certain diseases as this Toolkit develops.

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## **Usher syndrome**

Usher syndrome is a syndromic IRD that affects both hearing and vision. The symptoms of Usher syndrome consist of hearing loss (found at an early age), vision loss caused by a condition called retinitis pigmentosa (RP), and sometimes balance problems.

While people with IRDs do have a higher risk of developing hearing issues late in life than the general population, Usher syndrome is characterised by hearing loss early-on in life. You can find more information on Usher Syndrome in our “Focus on: Usher Syndrome” section ([link](#))

## **Leber Congenital Amaurosis**

Leber congenital amaurosis (LCA) appears at birth or in very young children. It is an inherited disease that can result in quite severe vision loss. The level of vision loss varies between individuals; some people affected can have little or no light perception. Both rod and cone cells are affected by the mutations and both will degenerate and die.

## **Retinitis Pigmentosa**

Retinitis pigmentosa (RP) is a term used to describe a group of diseases where vision loss gradually worsens due to progressive photoreceptor degeneration, resulting in legal blindness. Onset of the disease can vary widely, with some people starting to notice changes as children while others are diagnosed in adulthood. In general, RP affects both eyes similarly.

The early symptoms noticed by people with RP usually include difficulties with seeing in dim light and moving between bright or dark environments, along with a gradual loss of peripheral vision. These symptoms are due to the initial degeneration of the rod cells, which are responsible for seeing in dim light and are more concentrated at the edges of the retina. In the later stages of the disease, the disease can affect cones cells in the centre of the retina, resulting in loss of central vision and colour vision. This video gives an insight into loss of peripheral vision due to RP. Video showing loss of peripheral vision with RP:

<https://www.youtube.com/watch?v=-abLJJAmB54>

While visual function will get progressively worse with time in people with RP, the rate of progression and the extent of vision loss can be very different between individuals affected, even varying between people from the same family. For this reason, it is very difficult to know how quickly or slowly the disease will progress in an affected individual.

### *What is the cause of RP and how is it inherited?*

RP is one of the most complicated genetic conditions of all, and over 50 different genes have been identified to be causative for various forms of RP. There are various inheritance patterns for RP, including autosomal dominant (30-40%), autosomal recessive (50-60%) and X-linked (5-15%). Approximately 50% of RP patients will have a history of at least one other family member being affected. Half of patients will not have a family history of the condition. While their RP is still caused by a gene alteration, it might not be possible to determine the inheritance pattern in these patients.

The autosomal dominant form of disease tends to follow a milder course with maintenance of preserved vision well into late middle age. The X-linked form is the most severe and central vision may be lost by the third decade. RP is a genetic disease, but cases with no family history also commonly occur. If a family member is diagnosed with RP, it is strongly advised that other members of the family also have an eye exam by an eye doctor (ophthalmologist) who is specially trained to detect retinal diseases.

### *What treatments are available for RP?*

Maximising the remaining vision that an individual has is a crucial first step to take. There are many new low vision aids including telescopic and magnifying lenses. The wide range of assistive technologies for people with visual impairments provides plenty of choice for users at all stages of sight loss, and this technology has also removed many barriers to education and employment.

There are, as of yet, no proven or effective cures for RP, although research in this area has accelerated and potential therapies are in clinical trial stage. The term RP represents an extremely large and varied group of diseases, as scientists have now identified more than 200 genes that can have mutations causing RP.

Typically, each person with RP only has a mutation in a single pair of genes. Gene therapy to replace defective genes by inserting healthy genes into the retina via harmless viruses is being explored in clinical trials for a small number of RP genes. Emerging gene therapy treatments are designed to specifically target the gene responsible for the individual patient's form of RP. Therefore, the importance of ensuring access to genetic testing to establish which form of RP a family or individual is affected by cannot be overemphasised.

Another research area currently being explored is that of drug treatments which aim to preserve the function of the rod and cone photoreceptor cells, thereby keeping them alive for longer. Many of these drugs are re-purposed drugs, which may have already been approved for a different disease and are now being tested for their effectiveness in RP. It is estimated that as few as 5% of cone cells need to be preserved by such a treatment in order to have a significant impact on quality of life by the maintenance of a small but very useful amount of central vision.

Gene therapy and drug therapies hold huge promise to treat individuals at an early to mid-stage of disease progression, where there are still some viable rod and cone cells present.

Information about clinical trials that are currently being conducted worldwide can be found on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and can be searched by condition and trial location.

### *Stem Cell Technology*

Stem cell technology holds great potential to replace retinal cells that have already died due to degeneration. Scientists are currently working on replacing two different cell types by stem cell therapy - retinal pigment epithelium (RPE) cells and photoreceptor cells. RPE cells are a special type of cell that support the photoreceptor cells, but are not responsible for “seeing”, therefore it is hoped that replacement of RPE cells will help the retina function better, prevent further vision loss, and help nourish surviving retinal cells. This cell type would need to be replaced in time to help support a retina that is still working. Efforts at transplanting stem cell-derived photoreceptor cells are at an even earlier stage of research, however a number of recent animal studies have shown the potential to restore function in the eye, which may pave the way for human studies in the future.

### *Retina Implants*

Retinal implants are a form of biomedical technology currently being developed for use by people affected by retinitis pigmentosa. A number of these implants have shown success in delivering a form of artificial vision to individuals with total vision loss due to RP. When all or most of the photoreceptor cells have died, they can theoretically be replaced by an electronic microchip that brings a visual image to the remaining cells of the retina. These microchips electronically signal the remaining retinal cells which pass the signal down the optic nerve for processing as a visual image by the brain. At the moment, these devices do not restore natural vision, but can be very useful in improving mobility, by allowing an individual to see a difference in light and dark to the point where they can tell how to walk through a doorway. A number of devices are now on the market in certain regions.

### *See your Eye Doctor!*

Despite the lack of current treatments for RP, it is still very important to continue to have regular eye check-ups. This is because people with RP are still at risk for other kinds of eye problems that can affect the general population and may be treatable. RP patients tend to develop cataracts at an earlier age than the non-RP population and can do very well from cataract surgery, although the visual outcome obviously depends on the severity of the retinal degeneration. Regular visits to your eye doctor can also make you aware of current advances as we learn more about RP.

## **Choroideremia**

Choroideremia primarily occurs in men as it is caused by a genetic defect on the X-chromosome. Women can be carriers of choroideremia but rarely experience full symptoms. The first symptom of choroideremia is problems with seeing in low light (night-blindness), which is usually seen in childhood. As the disease progresses, peripheral vision deteriorates first and people with choroideremia may develop tunnel vision. By late adulthood, the remaining central vision is lost.

Choroideremia is a rare disease, affecting an estimated 1 in 50,000 people.

Choroideremia is sometimes misdiagnosed as other retinal conditions such as RP due to the similarity of symptoms. However, the family inheritance pattern of mainly males being affected and the characteristic pattern of the back of the eye help with diagnosis.

### *What is the cause of choroideremia and how is it inherited?*

Unlike some other retinal degenerations, such as RP, cases of choroideremia are due to mutations in just one gene, known as *CHM*. The *CHM* gene makes an essential protein called REP-1, which is involved in escorting essential nutrients between cells in the back of the eye. However, about 20% of patients with a clinical diagnosis of choroideremia have been found not to have a mutation in the *CHM* gene.

Choroideremia is genetically passed through families by an X-linked pattern of inheritance. The *CHM* gene is located on the X chromosome. Females have two X chromosomes, but generally only one of the chromosomes will carry a faulty copy of the gene and the other functioning copy will compensate. Therefore, females are carriers of the condition, but do not generally display the severe symptoms of the disease. In women, one or other of the two X chromosomes is randomly inactivated in every cell. Usually, in female carriers of X-linked disease genes, including *CHM*, this results in 50% of the retinal cells working on the altered *CHM* gene and the other 50% working on the normal copy of the *CHM* gene. These women will have very subtle, if any, symptoms of the disease. Inactivation, however, in some women may be skewed in favour of either the normal or the altered *CHM* gene copy. If more than 50% of the normal *CHM* copy is inactivated, the carrier female will have more symptoms. In rare, extreme cases of skewed inactivation the carrier female might be almost as severely affected as a male. Because males only have one X chromosome, they will become affected by the condition if they receive a faulty copy of the gene. Affected males cannot pass on the disease to their sons, because they pass on their Y chromosome. Men with choroideremia will pass on the disease gene to all of their daughters, who then become carriers of the gene.

If a family member is diagnosed with choroideremia, it is strongly advised that other members of the family also have an eye exam by an eye doctor (ophthalmologist) who is specially trained to detect retinal diseases.

### *What treatments are available?*

For an individual affected by choroideremia, maximising the remaining vision that an individual has is a crucial first step to take, and there are many new low vision aids including telescopic and magnifying lenses. The wide range of assistive technologies for people with visual impairments provides plenty of choice for users at all stages of sight loss, and this technology has also removed many barriers to education and employment.

At this time, there are no treatments available for choroideremia. However, in recent years there have been momentous leaps made in clinical research and development. Over the past twenty years, researchers have identified the causative *CHM* gene, explored gene therapy in mouse models of disease and performed necessary safety tests of this treatment approach. This has culminated in the authorisation of a small number of gene therapy clinical trials in people with choroideremia. In these gene therapy trials, the researchers engineer a small, non-toxic virus to deliver the correct version of the *CHM* gene into the light-sensing photoreceptor cells in the retina. The patient's retina is first detached and then the virus is injected underneath using a very fine needle. Early results from this trial have been positive, no safety issues have been reported and, in some cases, improvements in vision have been observed. The safety and effectiveness of this treatment is being monitored as a priority and there is great hope that a treatment will emerge in the future. Information about clinical trials that are currently being conducted worldwide can be found on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and can be searched by condition and trial location.

### **Juvenile Macular Degeneration**

Juvenile macular degeneration is the term used to describe a series of inherited eye disorders that affect children and young adults. Juvenile macular degeneration is different from age-related macular degeneration, which occurs as part of the body's natural aging process. Juvenile macular degeneration is sometimes called macular dystrophy.

Macular degeneration is a deterioration or breakdown of the eye's macula. The macula is a small area in the centre of the retina — the light-sensitive tissue lining the back of the eye. The macula is the part of the retina that is responsible for your central vision, allowing you to see fine details clearly. The macula makes up only a small part of the retina, yet it is much more sensitive to detail than the rest of the retina (called the peripheral retina). The macula is what allows you to thread a needle, read small print, and read street signs. The peripheral retina gives you side (or peripheral) vision. If someone is standing off to one side of your vision, your peripheral retina helps you know that person is there by allowing you to see their general shape.

The most common form of juvenile macular degeneration is Stargardt disease. Other types of juvenile macular degeneration include Best's disease (also called Best's vitelliform retinal dystrophy), and juvenile retinoschisis. All of these diseases are rare and cause central vision loss. Unfortunately, there is no treatment available to prevent vision loss.

Information about clinical trials that are currently being conducted worldwide can be found on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and can be searched by condition and trial location.

## **Stargardt Disease**

Stargardt disease, also referred to as ‘fundus flavimaculatus’, affects the functional, central area of the retina called the macula. It is the most common form of inherited juvenile macular degeneration. The macula is rich in cone cells, which give us colour vision and central vision for tasks such as reading. It is usually first diagnosed in the teenage years when decreased central vision is experienced. The progression of Stargardt disease varies between individuals. However, while central vision is lost, peripheral vision can often be preserved as this is reliant on rod cells rather than cone cells.

### *Stargardt Disease Symptoms*

Usually, both eyes are affected to a similar extent. The initial symptom experienced is usually difficulty reading as central vision is impaired. This can be followed by the appearance of blind spots in the visual field that may increase with time. While it is usual for an individual with Stargardt disease to completely lose their sight, the disease can progress slowly and be degenerative. However, it is difficult to predict progression in the future as the disease can vary considerably between individuals, even affected members of the same family.

The following videos address living with Stargardt disease: from Fighting Blindness

<https://www.youtube.com/watch?v=DkKck3zdcyk> and from MDF Australia

[https://www.youtube.com/watch?v=3\\_8ByHoKQzg](https://www.youtube.com/watch?v=3_8ByHoKQzg)

### *What is the cause of Stargardt disease and how is it inherited?*

Stargardt disease is estimated to affect between 1 in 8,000 to 10,000 people worldwide. The majority of people with Stargardt disease have the recessive form of disease, involving mutations in the *ABCA4* gene, which provides instructions to make the *ABCA4* protein.

If there is a faulty *ABCA4* gene, it leads to the build-up of a toxic waste product known as A2E in the retinal pigment epithelium (RPE) and this can lead to macular degeneration and progressive loss of vision.

A very rare form of Stargardt disease may be caused by mutations in the *ELOVL4* gene, which follows an autosomal dominant form of inheritance. Mutations in the *ELOVL4* gene can make dysfunctional *ELOVL4* protein clumps that can interfere with photoreceptor cell functions leading to cell death.

If a family member is diagnosed with Stargardt disease, it is strongly advised that other members of the family also have an eye exam by an eye doctor (ophthalmologist) who is specially trained to detect retinal diseases.

#### *What treatments are available?*

At present, there are no effective treatments for Stargardt disease. There is research to suggest that UV sunlight can increase the toxicity of the waste products accumulating in the retina, therefore, it is recommended that people with Stargardt disease wear UV screening sunglasses when out in direct sunlight. Recent evidence also suggests that taking extra vitamin A, such as in a vitamin supplement, may have a negative effect on the condition and should be avoided.

Gene therapy is currently being explored for the recessive form of Stargardt disease caused by *ABCA4* gene mutations. The idea behind gene therapy is that a “normal” copy of the *ABCA4* gene can be engineered in the laboratory. This can then be injected into the eye of an affected individual, delivering the correct copy of the gene and therefore stopping the degeneration of the sight of the individual. This safety and effectiveness of this treatment approach is currently being evaluated in early-stage clinical trials conducted in people with this form of Stargardt disease

Stem cells are amazing cells that are produced in the body and have the remarkable potential to develop into many different cell types in the body during early life and growth. A number of groups worldwide are currently manipulating stem cells from various origins in order to produce retinal pigment epithelial (RPE) and these cells have been injected into a number of patients. The transplantation of these functional cells into patients may prevent the death of the remaining photoreceptors and may, therefore, help Stargardt patients avoid further sight loss. These early stage clinical trials are currently on-going. Efforts at transplanting stem cell-derived photoreceptor cells are at an even earlier stage of research, but a number of recent animal studies have shown the potential to restore function in the eye, which may pave the way for human studies in the future.

Another interesting approach that is currently being studied as a therapy involves research into a modified form of vitamin A, called deuterated vitamin A. The researchers hope that this may help slow the accumulation of A2E by blocking its formation downstream in the visual cycle. They are currently testing the safety of this approach. Please note however that recent evidence suggests that taking extra “normal” vitamin A, such as in a vitamin supplement from a health shop, may have a negative effect on the condition and should be avoided as this can increase toxic levels of A2E.

Despite the lack of current treatments for Stargardt disease, general eye check-ups are important. This is because people with Stargardt disease are still at risk for other kinds of eye problems that can affect the general population and may be treatable. Regular visits to your eye doctor can also make you aware of current advances and new treatments as we learn more about the condition.

Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.



## **Best Disease**

### *What Is Best Disease?*

Best disease, also known as vitelliform macular dystrophy, is an inherited form of retinal degeneration affecting the portion of the retina known as the macula. The macula is the central part of the retina containing the photoreceptor cells known as cone cells, which are responsible for fine visual detail and colour perception. Best disease is usually diagnosed during the teenage years, but vision does not generally deteriorate until later in life. The progression of visual loss varies between individuals but side or peripheral vision usually remains unaffected. Therefore, people with Best disease do not generally have issues with independent mobility.

### *What are the symptoms of Best disease?*

The first symptoms of Best disease can vary from person to person but always involves the central vision. In the initial stages, a fatty yellow pigment builds up in the cells underneath the macula. Over time, the abnormal accumulation of this substance can damage the cone cells located in the macula, leading to a blurring or distortion of central vision. Best disease generally doesn't affect peripheral or side vision. It does not always affect both eyes equally and clearer vision is sometimes retained in one eye.

### *What is the cause of Best disease and how is it inherited?*

Best disease is a genetic disease and is caused by mutations in the *BEST1* gene which produces the protein Bestrophin-1. Best disease is passed down through families by an autosomal dominant pattern of inheritance. In this pattern of inheritance, an affected person has a mutated *BEST1* gene paired with a normal copy of the *BEST1* gene. When the affected person has children with an unaffected partner, there is a 50 percent chance that the affected parent will pass the mutated *BEST1* gene to each child. The unaffected partner will only pass normal copies of *BEST1* genes. A child who does not have a mutated *BEST1* gene will not have the disease and cannot then pass the disease to his or her children. Owing to the variable expression of the *BEST1*-mutated gene, some people who have the mutation may have very mild, or in rare cases, no symptoms.

### *What treatments are available?*

Currently, there is no treatment for Best disease. Genetic research identified the *BEST1* gene as causative for Best disease in 1998 and researchers are now working on understanding the function of this gene in the retina. Recently, there have been encouraging gene therapy studies in preclinical models of Best disease. These findings mark the first clear steps to developing a therapy that could prevent vision loss. Using this approach, which has proven to be safe in other retinal conditions, researchers engineer small, non-toxic viruses to deliver the correct version of the *BEST1* gene to the retina. Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.

## **Juvenile X-linked Retinoschisis**

Juvenile X-linked retinoschisis is a rare genetic disease of the retina and primarily affects boys and young men. Retinoschisis is a condition in which an area of the retina (the tissue lining the inside of the back of the eye that transmits visual signals to the optic nerve and brain) has separated into two layers. The part of the retina that is affected by retinoschisis will have poorer vision, however very few people with retinoschisis lose all of their vision.

Affected boys are usually diagnosed while at primary/middle school when poor vision and difficulty with reading become more apparent, but occasionally the disease is diagnosed in young infants. Most boys with retinoschisis present with a mild decrease in central vision that may be subtle and not perceptible. They may continue to lose vision into their teens. Once they are adults, their vision often stabilises until they are in their 50s or 60s. Retinoschisis patients are more susceptible to retinal detachment and eye haemorrhage (bleeding) than other people and they should have regular examinations with an eye doctor. When detected early, a complicating retinal detachment can be treated surgically.

### *What is the cause of retinoschisis and how is it inherited?*

The exact prevalence of retinoschisis is currently unknown, but it is thought to affect between one in 5,000 to 20,000 people, and is therefore a rare condition. X-linked retinoschisis is usually caused by mutations (defects) in the *RS1 (retinoschisin 1)* gene, which is located, as the name suggests, on the X chromosome. Men have only one X chromosome, while women have two. Therefore, because women almost always have another functioning X chromosome, they typically retain normal vision, even as carriers. However, in rare circumstances, due to the phenomenon of 'non-random X chromosome inactivation' some female carriers may have symptoms. Men, on the other hand, will develop sub-optimal vision if they have an affected X chromosome. Affected males cannot pass on the disease to their sons, because they pass on their Y chromosome. Men who have retinoschisis must pass on the disease gene to all of their daughters who in turn become carriers of the condition.

### *What treatments are available?*

Maximising an individual's remaining vision is a crucial first step to take, and there are many new low vision aids including telescopic and magnifying lenses.

Currently, there are no medical or surgical treatments available for retinoschisis. Glasses may improve the overall quality of vision in a patient with retinoschisis who is also near-sighted or far-sighted but will not repair the nerve tissue damage from the retinoschisis.

In 1997, researchers identified mutations in the *RS1* gene on the X chromosome that cause retinoschisis. Scientists then studied the gene to determine its function in the retina and this work has greatly enhanced efforts to develop treatments for this condition. A number of groups

worldwide are now working on developing gene therapies for retinoschisis. These innovative therapies aim to deliver healthy copies of the *RS1* gene by a non-toxic virus, therefore replacing defective copies at the back of the eye.

General eye check-ups are important for people with retinoschisis, as these men and boys are still at risk for other kinds of eye problems that can affect the general population and may be treatable. They are also more vulnerable to retinal detachments and haemorrhages. Regular visits to your eye doctor can also make you aware of current advances as we learn more about retinoschisis.

Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.

### **Leber Hereditary Optic Neuropathy**

Leber hereditary optic neuropathy (LHON) is a genetic disease that leads to sudden vision loss during young adult life. Men are more likely to be affected than women. LHON is a disorder caused by mutations in the genetic code of the mitochondria, which are small subunits that reside within the cell. Mitochondria are also known as the “powerhouses of the cell” as they constantly convert energy locked in our food into energy that the cell can use.

Our eyes are our most energy hungry organs and a lack of energy production can lead to degeneration and death of retinal ganglion cells (RGCs), which are the nerve cells that communicate visual information to the brain. Loss of these cells leads to subsequent degeneration of the optic nerve and visual loss. However, it is worth noting that a significant percentage of people who possess a mutation that causes LHON do not develop any features of the disorder.

Loss of vision due to LHON does not cause any eye pain, but it is quite an alarming experience as the loss of central vision presents suddenly and can progress quite quickly, leaving only peripheral vision. This means that the majority of people with LHON retain independent mobility but cannot focus on anything straight ahead or see fine detail.

#### *What are the symptoms of LHON?*

Affected individuals do not usually present any symptoms until they develop visual blurring affecting their central vision. These vision problems may begin in one eye or both simultaneously. If one eye is affected, then similar symptoms appear in the other eye on average eight weeks later.

Over time, the vision in both eyes worsens with a severe loss of sharpness and a fading of colour vision. The vision loss mainly affects central vision, which is needed for tasks such as reading, driving and recognising faces. In a small percentage of cases, the central vision loss can improve; but in most cases loss of vision is permanent.

The severity of symptoms may vary from one affected individual to another, even within the same family, due to a ‘dosage’ effect. This is due to the fact that we have many mitochondria in each cell.

In one individual, if only a small proportion of mitochondria in each cell have the mutation, symptoms will be mild. In another individual, if a higher proportion of mitochondria in each cell carry the mutation, symptoms will be more severe.

*What is the cause of LHON and how is it inherited?*

LHON follows a mitochondrial pattern of inheritance, which is also known as maternal inheritance. Only egg cells and not sperm cells contribute mitochondria to a developing embryo, therefore only females can pass mitochondrial conditions to their children. Fathers affected by LHON or carrying LHON mutations do not pass the condition to their children.

Often, people who develop LHON have no family history of the condition. However, it is currently impossible to predict which members of a family who carry a mutation will eventually develop vision loss. More than 50% of men and more than 85% of women with a mitochondrial mutation will never experience vision loss. LHON is a very rare condition. Research has revealed that three particular mutations in mitochondrial genes account for between 85% – 90% of cases of LHON.

Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.

## **Cone-Rod Dystrophies**

Cone-rod dystrophies refer to a group of inherited diseases that affect the photoreceptor (light sensing) cells that are responsible for capturing images from the visual field. These cells line the back of the eye in the region known as the retina. Cone cells are present throughout the retina but are concentrated in the central region (the macula). They are useful for central (reading) vision. Rod cells are present throughout the retina except for the very centre and they help with night vision.

In contrast to typical RP (known as the rod-cone dystrophies), which results from the loss of rod cells and later the cone cells, cone-rod dystrophies reflect the opposite sequence of events, where cone cells are primarily first affected with later loss of rods.

### *What are the symptoms of cone-rod dystrophy?*

The cone cells are initially involved, as previously mentioned, and difficulty with the clarity of vision, colour vision problems and light sensitivity can be some of the earliest symptoms experienced. This is followed by a progressive loss of rod cells, which leads to night blindness and loss of side (peripheral) vision. The age of onset, progression and severity of cone-rod dystrophies can vary greatly from one person to another, even among individuals with the same type of cone-rod dystrophy. It is therefore very difficult to predict what an individual's vision will be like at a specific time in the future. Some forms of cone-rod dystrophy are inherited; other forms appear to occur spontaneously for no apparent reason (sporadically).

Cone-rod dystrophies have many similarities to RP following varied inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked.

### *What treatments are available?*

Maximising an individual's remaining vision is a crucial first step to take. There are many new low vision aids, including telescopic and magnifying lenses, providing plenty of choice for users at all stages of sight loss. This technology has also removed many barriers to education and employment.

There are, currently, no proven or effective cures for cone-rod dystrophies. However, scientists have identified more than 20 genes that can have mutations which cause these conditions. It is likely that many more mutations in many more genes will be identified in the coming years.

Despite the lack of current treatments for cone-rod dystrophies, general eye check-ups are important. People with these conditions are still at risk for other kinds of eye problems that can affect the general population and may be treatable. Patients with cone rod dystrophies tend to develop cataracts at an earlier age than the overall population. Regular visits to your eye doctor can also make you aware of current advances as we learn more about these conditions. Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.

## **Achromatopsia**

Achromatopsia is a rare hereditary vision disorder affecting the cone photoreceptor cells, resulting in an absence of colour vision along with additional visual problems. There are two main types of cells in the retina responsible for capturing the visual field; the rod cells and the cone cells. We use our rod cells at night time and in low light, but they are not sensitive to colour and do not provide detailed vision. We use our cone cells in bright light. They are responsible for our colour vision and for our central, reading vision. Genetic changes or mutations in genes that function in cone cells are responsible for achromatopsia. Individuals with achromatopsia have reduced visual acuity and are completely or almost fully colour blind; however, the condition is not progressive and it does not lead to blindness.

### *What are the symptoms of achromatopsia?*

The condition is often first noticed in a young child by their parents, as children with achromatopsia may dislike bright lights and often avoid the daylight (known as photophobia). Nystagmus is another symptom of the condition, where their eyes may involuntarily move and “dance”. Judging from their behaviour some parents may notice that their child’s vision may be reduced or blurred. However, most children with achromatopsia have no problem with mobility or getting around.

### *What is the cause of achromatopsia and how is it inherited?*

To date, mutations in one of five genes are known to cause achromatopsia. The condition is inherited in an autosomal recessive manner, which means that an affected individual inherits a mutated copy of an achromatopsia-linked gene from both parents. Most often, the parents of an individual with achromatopsia each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

### *What treatments are available?*

The vision of people with achromatopsia decreases as the levels of light increase. In regular home lighting indoors, or outdoors just after dawn or just before dusk, some people with achromatopsia adapt to their reduced level of visual function without resorting to tinted lenses. Instead, they use visual strategies such as squinting or shielding their eyes or they position themselves in favourable light. Others sometimes wear medium tinted lenses in such settings. However, in full sunlight outdoors, or in very bright indoor spaces, almost all people with achromatopsia use very dark tinted lenses in order to function with a reasonable amount of vision, since they do not possess functioning cone photoreceptors needed in order to see well in these types of settings. Two of the most common genes linked to the condition (*CNGB3* and *CNGA3*) account for 75% of achromatopsia cases, making this condition potentially amenable to gene therapy. Based on a number of successful results in animal models of achromatopsia, a number of groups have initiated human gene therapy clinical trials. These trials plan to deliver a “normal” copy of the mutated gene back to retina, in theory restoring cone function and visual function. Information about clinical trials that are currently being conducted worldwide can be found on <http://www.ClinicalTrials.gov> and can be searched by condition and trial location.

## **Gyrate Atrophy**

Gyrate atrophy is an autosomal recessive dystrophy caused by mutations in the gene for ornithine aminotransferase (OAT), located on chromosome 10. Originally thought to be a subtype of choroideremia, the disorder is the result of ten-fold elevations of plasma ornithine, which is toxic to the RPE and choroid. Patients with gyrate atrophy have hyperpigmented fundi, with lobular loss of the RPE and choroid.

The finding of generalised hyperpigmentation of the remaining RPE helps to clinically distinguish gyrate atrophy from choroideremia. In the early stages, patients have large, geographic peripheral paving-stone-like areas of atrophy of the RPE and choriocapillaris, which gradually coalesce to form a characteristic scalloped border at the junction of normal and abnormal RPE.

Affected patients usually develop night blindness during the first decade of life and experience progressive loss of visual field and visual acuity later in the disease course. The clinical diagnosis can be confirmed by measuring serum or plasma ornithine levels; molecular confirmation can be obtained by mutational analysis of the *OAT* gene. Occasionally, older patients present with an uncommon syndrome of peripheral chorioretinal atrophy that closely mimics gyrate atrophy; normal plasma ornithine levels in such patients exclude the diagnosis.

### *What treatments are available?*

Although dietary restriction of arginine has been used to treat some gyrate atrophy patients, the diet is very difficult to maintain and must be monitored by paediatricians with experience in metabolic disease. Vitamin B6 treatment lowers the plasma ornithine levels in a small percentage of gyrate atrophy patients.

Whether such a reduction improves the long-term visual outcome is unknown, but, unlike arginine restriction, vitamin supplementation is relatively easy to administer. Long-term vitamin therapy should be considered only for patients whose ornithine levels can be shown to drop in response to treatment.

## **Kearns-Sayre syndrome**

Kearns-Sayre syndrome is a condition that affects many parts of the body, especially the eyes. The features of Kearns-Sayre syndrome usually appear before the age of 20 years, and the condition is diagnosed by a few characteristic signs and symptoms.

### *What are the symptoms of Kearns-Sayre Syndrome?*

People with Kearns-Sayre syndrome have progressive external ophthalmoplegia, which is weakness or paralysis of the eye muscles that impairs eye movement and causes drooping eyelids (ptosis). Affected individuals also have an eye condition called pigmentary retinopathy, which results from degeneration of the retina that gives it a speckled and streaked appearance. The retinopathy may cause loss of vision.

People with Kearns-Sayre syndrome can often have abnormalities of the electrical signals that control the heartbeat (cardiac conduction defects), problems with coordination and balance that cause unsteadiness while walking (ataxia), or abnormally high levels of protein in the fluid that surrounds and protects the brain and spinal cord (the cerebrospinal fluid or CSF). They may also experience muscle weakness in their limbs, deafness, kidney problems, or a deterioration of cognitive functions (dementia). Affected individuals often have short stature. In addition, diabetes mellitus is occasionally seen in people with Kearns-Sayre syndrome.

When the muscle cells of affected individuals are stained and viewed under a microscope, these cells usually appear abnormal. The abnormal muscle cells contain an excess of structures called mitochondria and are known as ragged-red fibers.

A related condition called ophthalmoplegia-plus may be diagnosed if an individual has many of the signs and symptoms of Kearns-Sayre syndrome but not all the criteria are met.