Leber’s Hereditary Optic Neuropathy

A summary of current information on LHON taken from the LHON Home Page website.
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Disclaimer

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Introduction

A summary of the current information on Leber's Hereditary Optic Neuropathy (LHON), also known as Leber's Optic Atrophy (LOA), Leber's Optic Neuropathy (LON) or Leber's Disease. It is often referred to as just Leber's for short.

It is important not to confuse LHON with other medical conditions, such as Leber Congenital Amaurosis, as Theodore Leber studied and named more than one disorder.

The aim of the website and this document is to present the information in a relatively non-technical way.

Although I've tried to keep these pages readable for people without a scientific background, the information is taken from scientific research and sometimes I have identified specific technical papers for those who want to read them. They are also informally reviewed by scientists researching into LHON in the UK. The LHON Links page also contains a great many references to scientific papers giving case reports and other research results which have contributed to this information.
Background

Leber's Hereditary Optic Neuropathy is a rare condition which can cause loss of central vision. It usually affects men, most commonly in the twenties or early thirties, but the symptoms can happen at any age, to men or women.

The disease was first described by the German eye specialist Theodore Leber in 1871.

The illness usually occurs in men, although some women can be affected.

There is no warning of the onset of the condition.

Once a member of a family is diagnosed as having Leber's Hereditary Optic Neuropathy (LHON) then other members of the family are known to be potential sufferers or carriers ("At risk").

Most people carrying one of the LHON genes do not lose any eyesight. There is at present no way of predicting whether or not an "at risk" person will develop symptoms of LHON. Not every "at risk" individual becomes a sufferer.

Only women can pass the problem on to their children, men are not known to pass on the disease.

Eyesight can deteriorate over a period of hours to months. Both eyes are typically involved, although to varying degrees. Very rarely eyesight may improve or recover.

Most LHON sufferers are registered (legally) blind, although many retain some useable eyesight, i.e. they can move around in familiar surroundings without any trouble but cannot drive a car or read without magnification aids.
Typically, sufferers cannot recognise people in the street, although they may be able to make out moving shapes as they approach. Ordinary eyeglasses or contact lenses are of no practical help as they alter the focusing of the eye.

There are many kinds of aid which can help someone affected by LHON.

Low Visual Aids to help with reading are available from the National Health Service and other sources.

Leber's Hereditary Optic Neuropathy was first described by Theodore Leber in the 19th century, but we only really started to understand the inheritance and cause of Leber's in the late 1980's. Since then researchers have learned a great deal about Mitochondria (the energy-providing parts of the cell), Mitochondrial Disorders and LHON.

Usually Leber's affects one eye first, so central vision is lost in that eye over a period of a few weeks. One or two months later, the second eye is affected in the same way. The time when someone is losing their eyesight is often called the 'acute' period. After a few more weeks, the eyesight stops getting worse.

Although that describes the most common pattern for Leber's, it can also affect someone very suddenly, or can affect them more gradually over a period of years.

Leber's is a genetic condition, that is, the root cause is a change in the affected person's DNA which leads to a problem with the body's mechanism for extracting energy from food. LHON is not caused by a germ, bug or virus and cannot be passed on to other people by contact like the 'Flu.

In a lot of cases, the change in DNA that leads to LHON is new, and did not exist in the person's grandparents, aunts or uncles. It is a normal part of the usual DNA copying process that the copying doesn't always make an exact copy, so a child's DNA will be very, very similar to his/her parents, but not absolutely letter-for-letter identical.
Once this change happens to DNA of a woman, it can be passed down through a family to her children, grandchildren and so on.

That is why we get a lot of cases of LHON around the world with no other family members affected, and we also get cases where many people are affected over several generations.

Not everyone in a family affected by Leber's will lose their eyesight, and we do not yet know how to tell who will get symptoms.

We do know that Leber's is inherited through a gene which is only passed on through the egg cell from the mother. Men cannot pass on Leber's Hereditary Optic Neuropathy to their children. Men with LHON do not pass it on to their children, whether boys or girls. A woman carrying one of the LHON genes will pass it on to all of her children, both boys and girls. This means that each of her children is at risk of developing symptoms of LHON. There are some detailed figures on this risk in the FAQ (Frequently Asked Questions) Section of this site.
Genes, DNA and Mitochondria

LHON is a Genetic Disorder - that means it is caused by a faulty Gene inside us, not a bug which can be caught like the common cold.

So what is a Gene?

For many years scientists talked about Genes but didn't actually know what a Gene physically looked like. They studied Genes by looking at the way certain things were passed down the generations of a family. If they saw that Blood Group was passed down from the parents, they said it must be controlled by a Gene. Anything passed down, or inherited, from the parents, was allocated a Gene so that we could study and analyze the way it was passed on.

Then came a huge breakthrough - we discovered that this mysterious thing called a 'Gene' actually does exist physically in the Human body. Every Human Gene is held as a chemical called DNA. Each piece of DNA can hold hundreds or even thousands of Genes.

Inheritance is controlled by this special Chemical called DNA. This is found in very tiny structures called Chromosomes, and most of these are grouped together into the Nucleus of each cell in the human body. This is the DNA which controls pretty much everything we normally think of as inherited - Sex, body shape, Blood Group, height, skin, hair eyes and so on.

Each cell has one Nucleus, that is one copy of the DNA which plays such a big part in who we are.
Each cell also has thousands of little structures called Mitochondria. (Pronounced Mite-oh-kon-dree-ah)

These structures are the 'power houses' of the cell. Each cell needs energy to do work, and it is the Mitochondria that provide the energy from the food we eat. Different kinds of cell do different kinds of work.

Nerve cells transmit information to and from the Brain.
Limb Muscle Cells use energy to contract and so move.
Heart Muscle Cells use energy to contract and pump the blood.
Retinal cells use energy to detect light.
Optic Nerve cells use energy to transmit those light impulses to the Brain.

All of these cells use the Mitochondria inside them to get their energy from the food given to them via the blood supply.

All of the Mitochondria in a human body come from the Egg cell of the person's Mother.

There is one thing very special about Mitochondria. The DNA which controls how Mitochondria work and how new Mitochondria are built is NOT held in the Nucleus. Every single one of the Mitochondria has its own little chromosome and its own special set of DNA.
We now know that Humans carry two separate sets of Genes held in two separate sets of DNA.

The Nuclear DNA

The Mitochondrial DNA.

Of the two, Mitochondrial DNA is much, much simpler. It only holds the information needed to build the Mitochondria and make them work. That is, it controls how good our Mitochondria are at getting energy out of our food.

But this is a crucial function - if a cell can't get enough energy, it can't work properly.

Now we come to LHON

Leber's Hereditary Optic Neuropathy is linked to a number of genes, all in the DNA of the structures called Mitochondria. These provide energy to the cells of the body. We believe that the particular gene changes linked to Leber's Hereditary Optic Neuropathy lower the amount of energy available to the cells of the optic nerve and retina. These cells are damaged and can even die because of this lack of energy. The damage to the optic nerve and retina is what causes the symptoms of Leber's.

Every person affected by LHON has a defect in the DNA of their Mitochondria. This defect means that the Mitochondria is a lot less efficient at getting energy out of food.
This defect may not be in the DNA of the person's mother. It could have happened while the egg or the embryo was developing. Scientists call this a 'spontaneous' case of Leber's and there is no family history of the condition.

Alternatively, the defect may have happened in the person's Mother, her Mother, Her Grandmother or many generations back. LHON may or may not be seen in the family tree, because not everyone with the defective Gene develops LHON.

In fact figures so far suggest that something like half the known cases of LHON have no family history and have come about from 'spontaneous' changes.

The On-line Mendelian Inheritance in Man (OMIM) web site provides a very technical review of current scientific knowledge on LHON at the O.M.I.M Leber's Hereditary Optic Neuropathy Section. This is fully documented with references to the formal scientific research papers. I have deliberately not included references to scientific papers in this site as it would make the site less readable for people without scientific training.
Is there a cure or treatment for LHON?

We do not yet have any proven treatment clinically available for Leber's Hereditary Optic Neuropathy. However there are some research projects underway looking into possible treatments.

At the moment, therapy for someone who has lost eyesight due to LHON concentrates on helping the person live with the condition. This involves rehabilitation, counselling, advice on low-vision aids, mobility help and so on.

Many people find that communicating with other families affected by LHON is very helpful. This also helps keep in touch with research going on around the world. See the LHON Community section of this site.

Study of possible treatments can be confused because a small number of people with LHON recover their eyesight without treatment, so individual cases of recovery do not prove that anything works as a general treatment. For information on the chance of recovery without treatment see the section on LHON Recovery

A 'Healthy' lifestyle and balanced diet rich in antioxidants (such as Vitamins A, C and E, Selenium and Zinc) can be recommended. Some Vitamins are poisonous if taken in large doses, so it is very important to consult your qualified physician before trying any treatment or food supplement.

Some advice on a healthy lifestyle can be found on the website NHS Choices - Food and Diet or US NIH Health Information site on Dieting

Avoid possible triggers such as smoking and drinking a lot of alcohol.

Vitamin B12

Injections of Hydroxycobalamin (a form of Vitamin B12) during the first few months after eyesight loss may help some people. It is thought that sometimes a deficiency of this vitamin may have triggered the symptoms. There is another form of Vitamin B12 called Cyanocobalamin. Many drug companies offering Cyanocobalamin as injection or tablets warn that someone carrying a LHON gene should not be treated with Cyanocobalamin as this may trigger sudden loss of eyesight.

This is also related to theories about the environmental triggers for LHON, especially
Smoking. Smokers have about 2.5 times the level of cyanide in their blood compared to non-smokers, and a higher level of Cyanocobalamin.

**Co-Enzyme Q10 (Ubiquinone)**

A diet supplement called Co-enzyme Q10 (sometimes called Ubiquinone) has been studied. Co-enzyme Q10 is part of the group of chemicals which turn food into energy in the Mitochondria. After some trials Co-Enzyme Q10 is not thought to be effective as a general treatment for LHON. Instead two synthetic drugs are being tested: Idebenone and EPI-743.

**Clinical Trials relating to LHON**

The US National Institute of Medicine sites Clinical Trials and Clinical Trial Feeds provide information and shows which clinical trials are currently recruiting subjects. Clinical Trial Feeds provides facilities for subscribing to updates made within the last 45 days.

The European Union Clinical Trials Register allows you to search for information on clinical trials in European Union (EU) member states and the European Economic Area (EEA) and clinical trials which are conducted outside the EU/EEA if they form part of a paediatric investigation plan (PIP). Again there is a facility to display any new or updated information, this time within the last 7 days.

There is also a trial by the North American Mitochondrial Disease Consortium of a new register of people affected by Mitochondrial diseases to help researchers by providing a database of people and tissue samples. The patient advisory body for this work is the United Mitochondrial Disease Foundation (UMDF).

**Idebenone**

Idebenone is a man-made chemical related to Co-Enzyme Q10 and performs the same function, helping Mitochondria provide energy to the cells. It is better then Co-Enzyme Q10 at moving from the bloodstream into the brain and Optic Nerve as the molecules are smaller.
When given as a drug it is taken daily by mouth in tablet form.

The aim of this is to increase the efficiency of energy (ATP) production in the mitochondria and provide anti-oxidant protection to the chemicals in the cell membrane.

Idebenone and related short-chain quinones are similar to, but different in structure to Co-enzyme Q10. This is thought to bypass the faulty Complex 1 part of the respiratory chain and link directly to Complex III. This would make it much more effective than Co-enzyme Q10 supplements if the LHON mutation had caused the cell to build a faulty Complex I.


Researchers in Newcastle-upon-Tyne, England and Munich, Germany are running formal clinical trials of Idebenone sponsored by the Swiss drug company Santhera.

The first trial has already completed. This looked at how effective Idebenone may be as a treatment for people in the ‘acute’ phase of LHON. That is, can Idebenone slow or even reverse the deterioration of eyesight when someone is first affected? The trial showed that a number of people regained some of their eyesight when treated with Idebenone. This means that Idebenone may protect the eyesight if given to someone who has started losing vision due to LHON in the last 2 or 3 months.

Researchers in Italy and Japan have tried using Idebenone on individual patients but there have been few general tests of it published yet. One Japanese study suggested that treatment with a combination of Idebenone, Vitamin B2 and Vitamin C could speed up the process when eyesight was recovering but did not seem to make more people recover.

Links relating to Idebenone Trials
EPI-743 Treatment

EPI-743 is a clinical trial code term for Alpha-tocotrienol-quinone. As with Idebenone, this is a synthetic chemical believed to improve the efficiency of the chemical pathways in the Mitochondria.

This drug is being developed by Edison Pharmaceuticals for the treatment of mitochondrial disorders and has shown promising results in patients with Leigh's Syndrome. There has also been a very small 5-patient trial at the Doheny Eye Institute, Los Angeles, CA, treating people with LHON. This is described in the scientific paper as a "clinical proof of principle".

5 patients were each treated, beginning within 90 days of onset, and in 4 of these the degradation of eyesight appeared to slow within 18 months, with some recovery in 2 out of 5. It is difficult to draw any conclusions from this, with such a small number of patients involved, and the chance of recovery without treatment, but EPI-743 seems a good prospect for further research and clinical trials.

This drug is also related to the chemicals which act inside the Mitochondria to release energy from food. Like Idebenone it is taken daily in tablet form.

Effect of EPI-743 on the Clinical Course of the Mitochondrial Disease Leber Hereditary Optic Neuropathy.  

Doheny Eye Institute, Department of Ophthalmology, USC-Keck School of Medicine, 1450 San Pablo St, Los Angeles, CA 90089-0228, USA. asadun@usc.edu


Acetyl-L-Carnitine

Like Co-enzyme Q10, this is synthesized inside the body unless someone has malnutrition, but can be taken as a food supplement. It does not form part of the mitochondrial respiratory
chain like Co-enzyme Q10. Instead it is part of the beta-oxidation process - the initial steps in deriving energy from Fatty Acids rather than carbohydrates.

There is no specific clinical trial evidence that taking Acetyl-L-Carnitine is useful to people carrying a LHON gene or already affected by LHON, but it may be possible to "encourage" the body tissues to derive more energy from Fatty Acids rather than the affected protein complexes of the Respiratory Chain.

**Other supplements/chemicals taken as possible mitochondrial "helpers"**

Acetyl-L-Carnitine is one of a short list of "vitamin co-factors" sometimes taken to try and "boost" the energy available to the body as a generalized "mitochondrial support" rather than a specific attempt at treatment for a disorder.

Also in this group of chemicals are:

- Co-enzyme Q10
- Folic Acid
- Vitamin B12
- Thiamine
- Riboflavin
- L-Arginine
- Creatine

Some nutrients are known to act as Anti-oxidants (electron acceptors) inside the body

- Vitamin C
- Menadiol

Some nutrients act as anti-oxidants by scavenging "Free Radicals" before they do damage

- Vitamin E
- Co-enzyme Q10
- Alpha-Linoic Acid
- Minocycline
- Cyclosporine A
- Clutathione

Dichloroacetate may be given to try and stimulate the respiratory chain function in mitochondria.
To repeat the warning above: Some vitamins or supplements are dangerous if taken in high doses. You should always consult your physician about trying any form of treatment, supplement or therapy.

For a discussion of the current status of possible LHON treatments see the paper

**Treatment of Leber hereditary optic neuropathy** Nancy J. Newman


**Gene Therapy**

Gene Therapy is a method of treatment that deals with the faulty gene in the Mitochondria of the affected person.

There are two forms of Gene Therapy being proposed at the moment.

1. Directly treating the individual with LHON.
2. Using In-Vitro Fertilisation (IVF) techniques to prevent a mother passing on mitochondria with LHON genes to her child.

**Gene Therapy to directly treat someone with LHON**

This type of therapy delivers 'healthy' copies of the mitochondrial genes to the cells of the person affected by LHON.

This means that the cells can make working copies of the proteins instead of relying on the LHON genes which tell the cell to make "unhealthy" or "Faulty" mitochondrial proteins.

Bascom Palmer Eye Institute, University of Miami, Florida, USA is investigating 'Allotropic' gene therapy. This means providing a working copy of the faulty Mitochondrial gene, but
placing this working copy in the Nucleus of the cell. This builds on gene therapy techniques developed for other genetic conditions which are related to genes held in the Nuclear DNA. They have already done a lot of work on animal models of LHON and are now carrying out some trials on Human patients.

Links relating to the Bascom Palmer Eye Institute

- Bascom Palmer LHON Research Review Article
- Bascom Palmer Preparatory Study Phase
- The Genetic House - Brian Aston's Treatment Blog

Researchers at the University of Florida have used a synthetic ND4 gene to prolong the life of experimental cells which contain the 11778 LHON mutation. This is not a treatment for people but shows that gene therapy could eventually be used to treat the effects of the LHON mutation.


Department of Ophthalmology, Neuro-Ophthalmology Service, University of Florida College of Medicine, Gainesville, FL 32610, USA.

Gene Therapy IVF so a mother does not pass on LHON genes to her child

This kind of gene therapy is to do with preventing passing on LHON genes to the next generation rather than treating the current generation.

it makes use of the fact that the LHON genes are in the Mitochondria of the mother and not in the cell nucleus.

All of the genes in the Mitochondria are to do with proteins used by the Mitochondria in releasing energy from food. The genes which control all of the things we usually think of as inherited - sex, body shape, skin, eye colour, blood type etc. - are in the cell nucleus.
Mitochondrial Replacement IVF is looking at techniques to make sure that the mother's genes in the Nucleus are passed on unchanged, but all of her mitochondria are 'healthy' ones from another person.

In one approach, the cell from the Mother is treated to replace the mitochondria, then the 'healthy' egg is fertilised and now common IVF techniques used to try and produce a child.

Alternatively, an egg from the mother and sperm from the father are used to produce a fertilised egg, then the mitochondria of the fertilised egg are replaced before it is allowed to develop into an embryo. Again the now standard IVF techniques are used to try and produce a child.

These are all experimental processes.

At the moment Mitochondrial Replacement IVF is illegal in the UK. This is because the Human Fertilisation and Embryology Authority (HFEA) regulations rule out any changes to the genes of a human egg cell. The HFEA are running a consultation exercise in the 3rd quarter of 2012, so they can recommend to the UK Government whether or not to amend the rules and allow this type of treatment for Mitochondrial Disorders.

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**Near Infra-red Light**

There is a clinical trial at the Medical College of Wisconsin testing the use of Light-Emitting Diodes (LEDs) producing Near Infra-Red Light as a therapy for LHON. They are working on a theory that the near infra-red energy will stimulate the mitochondria of the Retinal Ganglia Cells, helping to protect them from oxidative stress and so improve their chance of surviving the effects of the LHON genes.
Gene Therapy treating Leber Congenital Amaurosis

A group of researchers supported by the Foundation Fighting Blindness from Cornell University, University of Pennsylvania and the University of Florida have published an article in 'Nature Genetics' (May 2001) describing the use of gene therapy to treat dogs which have a form of Leber Congenital Amaurosis. The treatment involves injecting viruses carrying a 'healthy' form of the RPE65 gene into the eyes of affected dogs. After twelve weeks the treated dogs showed signs of improved retinal function. Leber's Congenital Amaurosis (LCA) was discovered by Leber but apart from that has no relation to LHON. LCA is caused by a mutation in the Nuclear DNA.

This is an important step in researching the treatment of LCA, but it is not yet a treatment used for humans.

It is important to understand that LCA is not the same disease as LHON.

In LHON the optic nerve is damaged rather than the retina, and different, mitochondrial, genes are involved.

It is encouraging that advances are being made in the possible use of gene therapy.
Where can I contact other families with LHON?

Leber's Hereditary Optic Neuropathy is a rare medical condition. A study in Finland gave the figure of affected people at 1 in 50,000. It is found around the world and studies have been published on people from countries such as:

- Argentina
- Australia
- Austria
- Belgium
- Borneo
- Brazil
- Bulgaria
- Cambodia
- Canada
- Chile
- China including Tibet
- Croatia
- Cuba
- Denmark
- Finland
- France
- Germany
- Greece
- Hungary
- India
- Indonesia
- Iran
- Ireland
- Italy
- Japan
- Malaya
- Mexico
- Netherlands
- New Zealand
- Norway
- Peru
- Philippines
- Poland
- Portugal
- Russia (Including Siberia)
- Senegal
- Serbia
- Slovakia
- South Korea
- Spain
- Sweden
- Switzerland
- Taiwan
- Thailand
- Turkey
- UK
- USA

This is just a list of countries taken from the Population Genetics section of the OMIM Article and various scientific papers describing cases of LHON. It does not mean LHON does not occur anywhere else. See the separate page LHON World for comments on "How Rare is LHON?"

This means that families affected by LHON can feel alone and isolated. They can talk to other people affected by blindness, but not those affected by LHON itself.

The Internet is now helping people to get together and share with others around the world. There are several places where people can contact others to discuss the impact of living with LHON. Many people find it very helpful to read the comments of others and share:
- Experiences
- Questions and Answers
- Feelings
- Treatment / Therapy views
- Research
- Ideas for coping with LHON
- Aids and helpful resources

Links to Internet LHON Communities

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<td><strong>LHON Members Yahoo group</strong></td>
<td>Although this is hosted on Yahoo, it can be used entirely through e-mail as well as on-line with a browser. It currently has 245 members. Activity varies as people e-mail questions, comments or information to the group. Open to those with LHON, their families, friends, medical practitioners Researchers.</td>
</tr>
<tr>
<td><strong>Leber's Hereditary Optic Neuropathy</strong></td>
<td>A Facebook Group which currently has around 900 members. A very helpful and active on-line community</td>
</tr>
<tr>
<td><strong>LHON to LHON</strong></td>
<td>A Facebook Group with around 60 members at the moment. This group is restricted to only people who have lost sight due to LHON. This allows things to be shared with a community who are all affected. Some people prefer this to the wider community of the other groups.</td>
</tr>
<tr>
<td><strong>Leber's Optic Neuropathy</strong></td>
<td>A Facebook Group with around 260 members at the moment.</td>
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<tr>
<td><strong>ASANOL</strong></td>
<td>La Asociación de Atrofia del Nervio óptico de Leber</td>
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<td>Spanish LHON association.</td>
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What is the cause of Leber Hereditary Optic Neuropathy?

LHON is a genetic condition, it cannot be passed from one person to another by a germ or bug like the common cold.

The underlying cause of LHON is a change in one or more Genes. The genes changed are ones which tell the body how to make chemicals that work together to release energy from the food we eat. The gene changes affect the structure of these chemicals and make them a lot less efficient at producing energy useable by the cells of the body.

The energy each cell in the body needs is produced and used in the form of a chemical called ATP. This is a high-energy 'fuel' used by the cell when it has to do some work.

The chemicals affected are called Protein Subunits or Protein Complexes. They link together, alongside 'helper' chemicals such as Co-enzyme Q10 and Cytochrome C, to form an energy-releasing mechanism called the Respiratory Chain.

The major symptom of LHON (for most people the only symptom) is loss of eyesight, especially the central vision where details and colours are sharpest.

The Respiratory Chain carries out a process called Oxidative Phosphorylation to make ATP - the fuel for the cell.

When someone is affected by a LHON gene, then at least one of the chemicals in the Respiratory Chain is a different shape. The change in shape makes it a lot less efficient at doing its job. A lot of energy is released as heat, and there are more wasteful 'by-products' of the reaction called Reactive Oxygen Species (ROS) or Free Radicals. These by-product chemicals can oxidise or damage any other chemical they touch inside the cell.

So a cell carrying a LHON gene is impaired in more than one way -

- It is getting a lot less fuel or energy to do its job
- It has more harmful by-products to deal with.
- It is generating more heat than normal

The eyesight is lost because cells at the back of the eye do not get enough energy to do their job. This lack of energy can be so large that the cells actually die. The affected cells are part of the nervous system responsible for transmitting vision from the eye back to the brain, known as the Optic Nerve.
One study has shown that a person affected by LHON may get 70% less energy from the food they use up - that is their cells are only getting about a third of the energy they need.

Light is getting into the eye, and hitting the light-sensitive layer or Retina at the back. The Retina is detecting the light and generating electrical signals, but the Optic Nerve is damaged so the nerve impulses cannot get back to the brain for processing.

**What causes the loss of energy?**
The energy available to each cell is produced by Mitochondria inside the cell. The mitochondria have their own separate piece of DNA inside them. This Mitochondrial DNA tells them how to build a small number of proteins used to generate energy from food. This DNA does not exist inside the cell Nucleus, only inside each Mitochondrion. There is a separate piece of DNA, or Gene, for each of the proteins used inside the Mitochondria.

A child receives all of his or her Mitochondria from the Mother, and normally the DNA of the child's Mitochondria is the same as that of the Mother. Sometimes there is a change in the DNA, known as a mutation. Mutations happen all the time as part of the process of copying DNA, but the vast majority of mutations have no impact on the function of the DNA at all.

Sometimes the change or mutation in the DNA does have a significant impact on the structure of the protein produced. It can stop the protein from working, or severely reduce how effective the protein is at doing its job.

That is what happens with someone affected by LHON.

A LHON suffer has mitochondria with a mutation in the Mitochondrial DNA. The mutation makes the protein much less efficient at producing energy, so the cells of that person are always suffering from a shortage of fuel.

If the Mitochondrial DNA has been affected by a LHON mutation in a girl, then the affected mitochondria will be passed on in her egg cells to all of her children. This will then start a family tree showing LHON being passed down the maternal line. If,
however, the mutation has happened in a boy, then he will not pass on his mitochondria to any of his children.

In a lot of cases, the mutation has only just happened, and the person has no family history of LHON. Studies have shown that about half of the cases of Leber's Hereditary Optic Neuropathy have no family history, and the mitochondria of both parents do not have LHON mutations. This means that the disorder has happened 'spontaneously' with a new mutation.

So why doesn't everyone with a LHON gene get affected?

The simple answer to this at the moment is that nobody knows. Carrying one of the LHON gene mutations does NOT mean that you are certain to develop Leber's Hereditary Optic Neuropathy. It just means that you are at risk of developing it.

There are two areas of research looking into this.

Are there environmental factors which trigger someone losing their eyesight?
Are there other genetic factors which make someone a higher risk of losing eyesight?
LHON Triggers
If someone is carrying a LHON gene, then various studies show that environmental factors increase the risk of developing symptoms and losing eyesight.

Smoking has been identified as a trigger for losing eyesight due to LHON both in men and women. Affected smokers also end up with worse eyesight than non-smokers.
Other likely triggers are:

Heavy use of Alcohol
Lack of Vitamin B12 (for example from extreme malnutrition or a digestive disorder)
Exposure to traces of poisons especially Cyanide based ones - see the Medscape article on Cyanide Toxicity.
Extreme stress affecting the body chemistry
Physical illness
Physical injury (Trauma)
Exposure to industrial chemicals such as n-Hexane (2,5-hexanedione).
Some medical treatments may also trigger it, such as
Ethambutol (used to treat Tuberculosis)
Cyanocobalamin (a form of Vitamin B12)
Sodium Nitroprusside (SNP). A powerful vasodilator used to treat extreme high blood pressure or to reduce bleeding during surgery.
Tadalafil (Viagra erectile dysfunction drug)
Erythromycin antibiotic (Mitochondrion. 2004 Jun;4(1):31-6.)
Telithromycin antibiotic.

A paper has linked LHON to Cocaine, Ecstasy and Telithromycin consumption. Telithromycin is an antibiotic with the brand name Ketek. (J Neurol. 2007 Feb;254(2):255-6. Epub 2007 Mar 2.)
A major factor triggering the damage to the Optic Nerve may be 'Free Radicals' or "Reactive Oxygen Species" (ROS) released inside the cells. These are a normal by-product of the chemical reactions going on, but can be increased by the environmental triggers mentioned above. These 'Free Radicals' are highly reactive and oxidise things which they touch, so the body has some chemical defences against them, known as Anti-Oxidants. You may have heard of some Anti-Oxidants such as:

- Vitamin A
- Vitamin C
- Vitamin E
- Selenium
- Zinc

Having a 'healthy' balanced diet which provides enough of these Anti-Oxidants is especially important for anyone at risk of developing LHON.
Are there foods to avoid if I am at risk of LHON?
Many years ago there was a theory that the LHON genes reduce the body's ability to deal with trace amounts of cyanide released when processing some foods. This came from one study which appeared to show that cells carrying a LHON gene had lower levels of an enzyme called Rhodanese, which cleans up the tiny amounts of cyanide produced in the mitochondria.

There are no documented cases of eyesight loss being triggered by eating particular foods.

There is a short list of foods that are relatively high in cyanide. Someone with a LHON gene might want to limit how much of these foods they eat.

- Almonds
- Apple Seeds (Pips)
- Apricot Seeds (stones/pits)
- Bamboo shoots
- Black Cherry seeds (stones/pits)
- Cassava root - uncooked (Tapioca) (The cyanide risk is removed by normal soaking & cooking)
- Lima Beans
- Millet Sprouts
- Peach Seeds (stones/pits)
- Sorghum
- Soy Beans
- Spinach

I stress that the level of cyanide in most of these foods is very, very small and should not cause a problem to anyone as part of a healthy, balanced diet. The only items that could cause toxicity problems if eaten in large amounts (for example over 100 in a short time) are Peach, Apricot or Cherry seeds, which are not normally eaten but thrown away.

See Agency for Toxic Substances & Disease Registry factsheet on Cyanide and the US EPA Toxicological Review on Hydrogen Cyanide and Cyanide Salts
Other Genetic Factors

Leber's Hereditary Optic Neuropathy has a strong sex-linked bias, that is, about 9 at-risk males develop symptoms for every 1 at-risk female. This has prompted researchers to try and find a second gene involved in damaging the eyesight. This second gene would be on one of the Sex Chromosomes in the Nucleus - the well-known X and Y Chromosomes.

The theory they are investigating is that someone carrying a LHON gene in their mitochondria must also have a defective gene on their Sex Chromosomes to trigger symptoms.

At present no studies have found any genes on the X/Y Chromosomes involved in LHON. Leber's Hereditary Optic Neuropathy is not a Chromosome X-Linked genetic disease like Haemophilia.

There is also a theory that more than one gene mutation is needed for someone to lose eyesight due to LHON, but the second gene is not on one of the sex chromosomes. There are 22 pairs of chromosomes in the Nucleus as well as the X and Y pair. This theory does not readily explain the sex bias in LHON patients, but could help explain why so many people can carry a LHON gene in their mitochondria without being affected.

The sex bias meaning a man carrying a LHON gene is more likely to lose eyesight than a woman carrying the same LHON gene may be explained by some factor other than something on the X and Y Chromosomes, but related to being male or female.

For example:

- Hormones and hormone levels in the body
- The difference in metabolism of fats and oils (lipids) between men and women
- Differences in body shape such as relative levels of fatty tissue in the body
- Differences in lifestyle such as relative numbers of smokers (although nowadays this is much less than in previous centuries)
A brief look inside Mitochondria

The Human Body is made up of billions of tiny structures called CELLS. Most cells are specialised to carry out specific functions for the body. For example there are skin cells, muscle cells, bone cells, blood cells and nerve cells. Cells do specific tasks, for example Red Blood Cells carry Oxygen around the body to where it is needed, and Nerve cells carry information as electrical impulses to and from the Brain.

Each cell is a complicated thing, but here is a simplified common structure.

- The cell has a boundary called the Cell Membrane.
- Most of the cell is filled with liquid and chemicals known as the Cytoplasm.
- The Cell Nucleus holds the Nuclear DNA gathered together into Nuclear Chromosomes.
- Spread throughout the cell are thousands of Mitochondria.

Each Body cell has thousands of tiny structures called Mitochondria inside it. One of these is called a Mitochondrion (pronounced Mite-Oh-Kon_Dre_oh). These structures are the ‘power houses’ of the cell - this is where the chemical reactions which release energy from food takes place.

The Nucleus is the main information centre of the cell. The Nuclear DNA controls how the cell will develop and how it will behave. It is the Nuclear DNA that makes a cell specialise and become a Red Blood Cell, a Nerve Cell etc.
DNA works mostly by controlling the production of chemicals called Proteins inside the cell. In a Red Blood Cell, the DNA drives the production of a protein called Haemoglobin. This protein attaches to Oxygen in the blood of the lungs and then releases it again in the blood of the body tissues.

Every cell in the body needs energy, both to survive and to do its job for the body. so every cell in the body is constantly using its mitochondria to process 'food' chemicals and release that energy.

Each Mitochondrion is like a tiny cell itself.

It is made up of two membranes, one inside the other. Think of it like a sausage with two skins. Embedded inside these membranes, and crossing between them, are the proteins that make a mitochondrion do its job. If you look inside a mitochondrion, there isn't much else to it! The membrane on the inside - known as the Inner Membrane - is actually bigger than the one on the outside and has little folds to expose more surface.

The chemicals used to derive energy from food are embedded into the membranes and the gap between them. These chemicals are a combination of proteins and protein-helpers called Co-Enzyme Q10 (ubiquinone) and Cytochrome C.
The mechanism for deriving energy from food is made up of five protein sub-units called Complex 1, Complex 2, Complex 3, Complex 4 and Complex 5. These all connect together with Ubiquinone (Co-Enzyme Q10) and Cytochrome C to form a chain embedded in the Inner Outer Membrane. This chain reacts with a chemical produced from food called NADH to build up a concentration of Hydrogen ions between the Inner and Outer Membranes. This concentration is used to create another chemical called ATP. ATP is the chemical that is moved around the cell and actually fuels the processes inside the cell.

The LHON Mutations

There are several changes or mutations in the Mitochondrial DNA thought to cause symptoms of Leber’s Heredity Optic Neuropathy, but almost every case (over 98 percent) is down to one of three mutations.
DNA is a chemical made up of incredibly long chains, but each chain is formed by combining only four different units called Bases. These are:

- Adenine (A)
- Cytosine (C)
- Guanine (G)
- Thymine (T)

So a Gene represented as a DNA Chain can be written down as a long sequence of letters representing these bases like this:

AATCCGAGGTACCCTTAGCAGCGATTTCCGGGAAATAAATTTTTTGGCCATTT........

...and so on...and on...and on!

The changes or mutations causing LHON are where the 'wrong' base has been put into the DNA, such as swapping an Adenine (A) for a Guanine (G).

Each mutation is identified by a code. The code tells us:

A letter showing the Base which is present in the 'normal' or un-mutated DNA

A number showing the position in the DNA Gene chain which has changed.

A letter showing the Base which is present in the mutated DNA.

The Three commonest LHON causing mutations are known as:

- G-11778-A
- G-3460-A
- T-14484-C

Sometimes these mutations are identified by geneticists using a code showing that they are Mitochondrial (MT) genes coding for Nicotinamide Dehydrogenase protein (ND) Complex Subunit, that is:

- MT-ND4-11778-A - accounts for about 50% of European cases and 95% of Asian.
- MT-ND1-3460-A - accounts for about 35% of European cases.
- MT-ND6-14484-C - accounts for about 15% of European cases.
Primary LHON Mutations in Europeans 1177834601448415%35%50%

But for most discussions of Leber's Hereditary Optic Neuropathy we just use the numbers 11778, 3460 and 14480.

The LHON mutation at 14459 is thought to cause the most severe symptoms, with Dystonia as well as sight loss, but is very rare.

Almost all cases of LHON are associated with mutations at locations 11778, 3460 or 14484.

There are a few cases associated with mutations at locations 14459 or 15257.

These 5 gene locations are known as "Primary" mutation sites, because we believe that a mutation here is enough to cause symptoms of LHON.

There are 3 more gene locations which are considered "Possible Primary" sites - which means there is some evidence that they can cause LHON on their own, but more is needed to confirm the situation.

There are about 9 other gene locations associated with LHON known as 'Secondary' mutation sites. These mutations are found along with one of the 'Primary' mutations, and may make the symptoms of LHON worse.
Quantitative triggers
A big word for a simple principle.

The trigger for losing eyesight may not be as simple as an on/off switch.

There may be something going on in the body that only triggers LHON symptoms when a certain level or threshold value is reached.

Every cell inside the body doesn't just have one Mitochondrion with one copy of mitochondrial DNA.

Each mitochondrion has more than one copy of DNA, and there are thousands of mitochondria in every cell.

We aren't born with all the cells we are ever going to have - the body is constantly getting rid of old cells and replacing them with new cells, tissues are growing and repairing themselves.

Similarly the mitochondria inside a cell can multiply in a similar way to early forms of bacteria. In fact when a cell divides to form two new cells, the mitochondria have to multiply otherwise every new generation would have fewer and fewer of them.

Two situations are possible when someone is carrying a LHON mitochondrial gene.

- All of the mitochondria have the same LHON gene. Scientists call this HOMEOPATHY. (all cells have the same stuff)
- Some of the mitochondria have the LHON gene and some don't have it. This is called HETEROPLASMY. (Some of the cells have different stuff)

Often when a doctor or researcher takes a blood sample to test for LHON, they will add this to the result of the test. That is, they may say "this person is Homeoplasmic with mutation 118812" or "This person is Heteroplasmic with gene 118812".
The first situation means all of the mitochondria found had the LHON gene, the second statement means that only a fraction or percentage of the mitochondria had the LHON gene, the rest were the usual, healthy gene. Often the usual, healthy gene is referred to as the "wild" gene.

A Homeoplasmic Cell where all of the mitochondria carry the same set of genes.

A Heteroplasmic Cell where some mitochondria carry a LHON gene and some don't.
As the mitochondria grow and divide, and the cells grow and divide, by chance some cells will end up with higher rates of LHON mutations than others.

It is possible that the cell begins life struggling along with some inefficient mitochondria. It may even trigger the creation of more mitochondria to try to get enough fuel, but if these are created by copying those with a LHON gene, it makes the cell's situation worse, not better. Inefficient processes and more damaging Free Radicals / Reactive Oxygen Species.

The Quantitative Trigger proposal is that there is a threshold situation where there are too many mitochondria carrying a LHON gene, and not enough carrying the healthy gene. The cell is "overwhelmed" by the mitochondria carrying the LHON genes. Once the threshold is reached the cell can't function any more and stops working or dies.
**LHON Symptoms**

The major symptom of Leber's Hereditary Optic Neuropathy is painless loss of central vision, known as a Central Scotoma. Although this can occur just in one eye, it usually occurs in both eyes (bilateral). The commonest way for someone to develop LHON is to start losing central vision in one eye, then the other. Vision loss happens over a period of a few months, known as the Acute phase.

Although vision loss can be very severe, with some patents reporting no light perception, someone affected by LHON is usually left with useable peripheral vision.

The amount of remaining vision left after the Acute phase varies from person to person. This vision is not in the centre, but around the edges of the visual field, and is known as Peripheral vision.

The centre of the visual field is where the eye is able to make out most detail, and differentiate between colours. The light focusing system in the eye also puts the sharpest image on the the centre. This means that someone with LHON will have trouble seeing details, at any distance, and is likely to have trouble differentiating colours.

At what age is the eyesight affected?

The loss of eyesight due to LHON can start at any age from 1 to over 70 years.

On average people first notice symptoms around the ages of 25 to 35.

Number of people first showing symptoms across the age range 1 to 70
Are there other symptoms of LHON?

A few people with LHON have also reported tremors, lack of co-ordination, weakness and numbness of arms and/or legs.

An Australian study has suggested that there may be a higher risk of Hearing impairment due to Auditory nerve function abnormalities in people carrying a LHON gene.

While Multiple Sclerosis appears to be more common in people with particular mitochondrial ancestry, there is no link to the LHON genes themselves.

Finnish and Japanese studies suggest that people with LHON are more likely to have heart rhythm problems (Wolff-Parkinson-White Syndrome or Lown-Ganong-Levine syndrome). While it is estimated that in the general population the incidence of Wolff-Parkinson-White syndrome is about 1 %, the incidence found in LHON patients was around 8 or 9 %. This means that 1 in 100 people are likely to have a heart rhythm syndrome, but about 1 in 10 people with a LHON gene are likely to have one of these syndromes.
Will the Eyesight keep getting worse?

LHON can affect the eyesight at any age from 1 to over 70 years.

On average people first notice symptoms around the ages of 25 to 35.

In most people the eyesight deteriorates in the few months after symptoms first appear, This is known as the 'Acute' phase. After a few months the eyesight becomes stable and does not get worse.

In some rare cases, eyesight has deteriorated slowly for up to two years or people lose their sight suddenly and rapidly.

Both eyes can be affected at the same time, but usually one eye shows symptoms first. The average time interval between the first and second eye being affected is about 2 months.

Once this initial eyesight loss is over, then people are usually left without central vision but have some peripheral vision "around the edges". This means that they can see relatively large objects but only by not looking directly at them.

Does the eyesight keep getting worse?

Number of people with worsening sight by month since start of symptoms

2 4 6 8 10 12 14 16 18 20 22 24
Will the Eyesight ever get better again?

Unfortunately, unless a treatment is found, the answer to this question for most people will be no. In most cases the eyesight gets worse for a couple of months, then stays the same for years.

A very small number of LHON patients will recover some of their eyesight even without any treatment. The chance of untreated recovery is different for each of the three main genetic defects as shown below.

When someone affected by LHON has had recovery of some eyesight, this has happened between one year and four years after the initial Acute phase.

A Japanese team studied people who lost sight due to the 11778 mutation and then recovered some sight. They found that the chance of sight recovery was higher in those who lost sight at a younger age.

Spontaneous Untreated Recovery

No Spontaneous Untreated Recovery
Untreated Recovery Rate for 11778 mutation: 4% (<1 in 20)

Untreated Recovery rate for 3460 mutation: 22% (< 1 in 4)

Untreated Recovery rate for 14484 mutation: 37% (< 2 in 5)
Can Women lose their eyesight as well as Men?

A girl who inherits a gene for Leber’s Hereditary Optic Neuropathy is much less likely to lose her eyesight due to LHON.

While a boy who inherits a LHON gene has about a 50 percent (5 out of 10) chance of being unaffected, the chance of being unaffected for a girl rises to 80 percent (8 out of 10).

However SMOKING drastically changes these figures - one recent large study showed that smoking reduces the chance of being unaffected to about 7 percent (less than 1 in 10). That is, someone who is carrying a LHON gene and smokes is increasing their risk of losing their eyesight to over 90 percent (9 out of 10), whether male or female.

In general, there are about 9 male cases of LHON in the world for every 1 female case.

What causes this difference?

There is no clear explanation for the difference in risk of developing LHON between Men and Women.

This is closely tied into the explanation of what triggers the symptoms of LHON in affected people.

The explanation could be in one or more of the following areas:

Environmental
The recent study which showed that smoking gives a 9 out of 10 chance of developing LHON symptoms for both men and women is strong evidence that environmental factors can be crucial, even over-riding any protective factor of hormones, fat metabolism etc. It may be that exposure to chemicals in tobacco, levels of alcohol intake and so on have been different for men and women in the populations studied.

**Biochemical / Hormonal**

It is possible that one or more of the biochemical differences between males and females protects women from developing the symptoms of LHON. These are controlled mainly by hormone levels, and the hormones may control this protection, directly or indirectly. A study carried out on cells outside the body (in vitro) showed that Estrogen (the main Female hormone) seems to provide a protective effect from the damage to the energy-releasing ability of mitochondria caused by a LHON gene. This could mean that female hormones keep cells with a LHON gene operating closer to normal.

**Genetics**

There may be a specific Nuclear Gene involved in triggering the symptoms of LHON as well as the inheritance of one of the LHON genes in someone's mitochondria.

With a disorder like Haemophilia, the gene responsible is sitting in the Nucleus on the Sex Chromosomes - the well known X and Y pair. In fact the gene sits only on the X chromosome, and the corresponding part is not present at all on the Y chromosome.

A Woman has two X chromosomes and a Man has one X and one Y.

As the Haemophilia gene sits on the X chromosome, a Woman will have two copies (one from her Father, one from her Mother), but a Man will only have one copy, on the X chromosome he inherits from his Mother.
A Woman has to inherit two copies of the faulty Haemophilia gene, one from her Father, and one from her Mother, to actually show symptoms of Haemophilia. If she only inherits one faulty Haemophilia gene and one 'working' gene then she will not show symptoms of Haemophilia - but she is a carrier.

Some researchers have studied the inheritance of Leber's Hereditary Optic Neuropathy to see if there is a second gene responsible for triggering symptoms, sitting on the X or Y chromosome like the Haemophilia gene. The results from these studies have identified possible genes on the X chromosome involved in producing LHON symptoms when combined with the 11778 Mitochondrial mutation.

The male/female ratio for people affected by LHON is different for the three main genes found in people of North European descent.
Ratio of Affected Males to Affected Females for 11778 Gene

Ratio of Affeted Males to Affected Females - 80% (1 in 5)

Ratio of Affected Males to Affected Females for 3460 Gene

Ratio of Affeted Males to Affected Females - 33 to 67 % (between 1 and 2 in 3 )

The ratio for this gene is not so precisely defined, it is somewhere around the 50/50 mark but tending towards more males then Females.

Ratio of Affected Males to Affected Females for 14484 Gene

Ratio of Affeted Males to Affected Females - 68 % ( 2 in 3 )
Is LHON in children different to LHON in adults?

Leber’s Hereditary Optic Neuropathy is often considered a disorder of adults, but some children are affected.

An Italian study in 2006 focused their attention on the clinical aspects of LHON in patients with onset in childhood.

Their findings support the view that patients with onset of LHON in childhood are more likely to recover eyesight, and ten to have better remaining eyesight than those who develop LHON as adults.

If a child has vision loss, especially in one eye only, and has no family history of vision loss, there seems to be a high rate of mis-diagnosis. LHON can be confused with Amblyoppia, Dominant Optic Atrophy or other forms of Optic Atrophy.

They took a sample of 56 previously studied LHON families (pedigrees) totalling 180 affected individuals. They could determine age of onset in 157 of these people and found 18 patients who had onset of LHON in childhood (up to and including 10 years old). From these 18, they recruited 14 patients for their study.

This study did not examine all 14 patients in childhood, but assessed all but one of them as teenagers / young adults.

The first point raised is that 11.5% of their LHON affected population experienced LHON symptoms before the age of 11 years.

The 14 childhood-onset patients were from 10 unrelated pedigrees, and no significant link was found between the LHON mutation carried and the likelihood of childhood onset.
9 patients from 6 different pedigrees carried the 11778 mutation.
4 patients from 3 different pedigrees carried the 3460 mutation.
1 patient carried the 3733 mutation.

Two of the families with the 11778 gene and one with the 3460 gene had more than one case of childhood-onset LHON.

8 of the 14 cases had been misdiagnosed as Amblyopia and 1 as Tapetoretinal degeneration the rest being those with a known family history of hereditary optic atrophy.

The male/female ratio was 12:2 that is, 86% male and 14% Female.

This is a very small sample size, but it is interesting that there appears to be a strong male bias in onset even before puberty.

The 14 patients were classified into 3 subgroups based on the clinical manifestations

Acute Bilateral – similar to adult manifestation
Acute Unilateral – Only one eye is affected, the other has subclinical features.
Slowly progressive – Vision loss takes more than two months.
Will my children be affected- will they lose eyesight due to LHON?

Probably not. Most people carrying a Leber's Hereditary Optic Neuropathy gene do not lose their eyesight. However anyone carrying one of these genes should reduce their risk by eating a healthy balanced diet and especially avoid smoking.

You should get advice from your doctor and experienced medical specialists. This site is intended to provide some background information in a non-technical way to help you.

A man affected by Leber's Hereditary Optic Neuropathy cannot pass it on to his children, whether they are boys or girls.

A woman who is carrying one of the LHON genes will pass on the gene to her children, boys or girls. This means that her children will be at risk of developing LHON. Her daughters will also pass on the risk to their children.

This does not mean that anyone in the family will definitely lose eyesight. Someone carrying a LHON gene has a risk of losing eyesight. At the moment we cannot predict which people at risk will actually lose any sight, but studies of large families have given us statistics on the risk of developing LHON symptoms.
This diagram shows three generations of a family - Parents, Children and Grandchildren.
At the top there is a couple where the woman is known to carry a LHON gene. They have three children, one boy and two girls.

All of the children have inherited their mitochondria from their mother, and are at risk of developing LHON.

The Son marries and has children, but they inherit their mitochondria from their mother, and so are not at risk of developing LHON.

One of the daughters marries and has her own children. She has one boy and one girl, who are both at risk of developing LHON.

Recent research has said that smoking is probably the biggest single thing affecting the risk of losing eyesight. Heavy smokers, whether male or female, can increase their risk to 90% or 9 out of 10. That is, of every 10 heavy smokers carrying a LHON gene, 9 of them will probably lose their eyesight.

Men are much more likely to lose eyesight than women - about 9 men to every 1 woman.
Of sons carrying the LHON gene, just over half will not lose their eyesight.

For daughters carrying the LHON gene, 90% or 9 out of 10, will not lose their eyesight.

Estimated risk for people carrying a LHON Gene

Ratio of Affected Males to Affected Females - 90% (1 in 10)
About 40% (4 out of 10) Men carrying a LHON gene are affected.

About 10% (1 out of 10) Women carrying a LHON gene are affected.
I don't know anyone else in my family with LHON

A lot of cases of LHON crop up where there is no known family history of LHON or blindness.

This could be because the LHON mutation has only just happened in the family, or it could be that the LHON gene is in the family history, that is, ancestors have been carrying the gene, but no-one has actually lost eyesight.

Because LHON is passed down through the mother, it is more difficult to trace back a family tree and find the ancestors, as the surnames keep changing due to marriages. Sometimes there are LHON cases in the same family but they are not close relatives, just distant cousins, and don't realise that they are related.

Sometimes there are relatives who have lost eyesight, but the cause was not diagnosed as LHON. In older generations blindness may have been put down to the effect of an illness like Measles or excessive alcohol intake, or just diagnosed as "Optic Atrophy of Unknown cause".

At the moment, almost half of LHON cases have no known family history.
These figures from OMIM were reported in the two papers below and so are around 20 years old.

How rare is Leber's Hereditary Optic Neuropathy?

Researchers have shown that most cases of LHON are from new, independent changes in the mitochondrial DNA, and are not being passed from generation to generation. There are a few large family trees identified around the world, but most people affected by LHON are not relatives of each other.

There are a few large pedigrees (family trees) where LHON has appeared in several generations. The largest known one is a family in Brazil. In a report after 8 years of study the family is described as 7 generations, with 328 family members of whom 38 were affected by LHON. This family carries the 11778 mutation and is Haplogroup J.

Three studies have produced figures for the number of LHON cases in the general population. The tale below shows the calculated ratio of LHON cases (showing symptoms) and then extrapolates that into an estimate for the number of cases in each country.

The figures have also been applied to the census populations of the EU and the USA.
<table>
<thead>
<tr>
<th>Country</th>
<th>Ratio</th>
<th>Population Size</th>
<th>Estimated number of cases (vision loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>1:31,000</td>
<td>60,000,000</td>
<td>about 2,000</td>
</tr>
<tr>
<td>Finland</td>
<td>1:50,000</td>
<td>5,400,000</td>
<td>about 100</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1:39,000</td>
<td>16,400,000</td>
<td>about 400</td>
</tr>
<tr>
<td>Europe (EU countries)</td>
<td>1: 50,000 - 1:30,000</td>
<td>495,000,000</td>
<td>about 10,000 - 16,000</td>
</tr>
<tr>
<td>USA</td>
<td>1: 50,000 - 1:30,000</td>
<td>291,000,000</td>
<td>about 6,000 - 10,000</td>
</tr>
</tbody>
</table>

Is Leber's Hereditary Optic Neuropathy found all over the world?

LHON is not a disease caused by a bug like the flu. It does not crop up in one place and then get spread as people travel.

As you'll see from the list of countries on the LHON Community page, LHON has been diagnosed and studied in many countries around the world. If a country is missing from the list, it does not mean that LHON does not occur there, just that I have not seen cases reported in the scientific journals yet.

The studies done include people of many ethnic backgrounds, confirmed by their Mitochondrial DNA analysis.

- African (including African-American)
- Asian (Including Han Chinese, Korean, Japanese, Malay, South East Asian, Thai, Tibetan)
- Amerindian
The study of Leber's Hereditary Optic Neuropathy and other Mitochondrial disorders has been going hand in hand with the study of population movement through genetics.

There are two pieces of DNA which are very useful to scientists study populations. The Y chromosome and the Mitochondrial DNA.

The Y chromosome is only passed down the male line, and the Mitochondrial DNA is only passed down the female line.

On the whole, Human DNA changes very slowly. It accumulates small changes, but certain parts of the Y chromosome, and certain parts of the Mitochondrial DNA, have stayed the same for tens of thousands of years.

Researchers have taken DNA samples from a vast number of people around the world, and they have found that the 7 billion people can be divided up into a surprisingly small number of groups, depending on the similarity of their Mitochondrial DNA.

The groups are identified by code letters, and some of these have been further sub-divided into sub-groups with letters and numbers.

Each unique pattern of Mitochondrial DNA is called a Haplotype, and the group of people with that DNA are a Haplogroup.

There is a whole area of study looking at these Mitochondrial haplogroups, how they are spread around the world now, and how this relates to the way human beings spread out of Africa to populate the rest of the world.
The map below shows a possible set of migrations of very early humans out of Africa.

The oldest Haplogroup found is L (L1, L2 & L3) found in Africa.

As humans migrated into the Middle East, some changes occurred which remained stable (conserved) and created two new Haplogroups, N and M.

Around 35,000 - 50,000 years ago, Humans migrated into Europe. While they were doing that, some new Haplogroups were formed, so the typical Mitochondrial groups found in Europe are I, J, K (Southern and Northern European mainland, UK) and H, S T, U, V, W, X (Northern Europe, Scandinavia)
What does someone with eyesight affected by LHON see?
It is difficult to give a simple answer to this. Eyesight varies from person to person, and for one person eyesight can vary from second to second! What someone sees also depends heavily on the quality of the lighting, the colours, the level of contrast in the image and so on. Seeing with damaged eyesight takes a lot of extra concentration, so feeling tired or ill can make a lot of difference as well.

This page tries to give some general guidance based on my experiences.

The centre of my vision is a constantly changing cloud of bright green, red, gold and yellow. I have vision at the edges, more in my left eye than my right.

Even at the edges, all images are slightly blurred and it is sometimes difficult to tell colours apart, especially red and green.

My visual acuity is less than 1/100 - in my left eye I can do some finger-counting and in my right I I can see a hand waving, but I can’t see an optician’s wall chart, let alone read the letters.

These two photos show what the impact of LHON can be on someone’s eyesight. Looking straight at someone, you cannot see their face or any detail.
Why can't ordinary spectacles / eyeglasses help?

How does eyesight work?

We see things because light bounces off them and passes into our eyes.

An eye works in much the same way as a camera.

The light passes through the transparent part at the front of the eye called the **CORNEA**. Behind the cornea is a circular shield called the **IRIS**. The iris is different colours in different people. (When we talk about the colour of someone's eyes, we are talking about the colour of their irises.)

There is a hole in the centre of the iris called the **PUPIL**. The light passes through this hole to get into the eye.

The size of the pupil changes to control how much light gets into the eye. Sometimes the light is too bright, so the pupil gets smaller and cuts down the light getting into the eye. If you go into a dark place, the pupil gets larger to let more light in.

The size of the pupil also depends on how interested you are in what you are looking at. If you are looking at someone or something very interesting, the pupil gets larger. This helps the eye **FOCUS** or concentrate on the interesting object.

An object **IN FOCUS** will have a sharp, clear image, that is you see it in detail without blurring. An object **OUT OF FOCUS** is blurred or fuzzy and can't be seen in detail.
The *LENS* is a transparent disk behind the pupil that can change shape slightly because it is attached to the eye by small muscles. This means the lens can alter while we are looking at things. When you change between looking at close objects and looking at distant objects, it is the lens in the eye that adjusts to keep the image sharp and detailed. The Cornea, Lens and Iris work together to keep a sharp image focused onto the back of the eye as much as possible.

Spectacles (eyeglasses) or contact lenses are usually worn to correct problems in this focusing system and get that sharp image from the light coming into the eye.

After passing through the cornea, the pupil and the lens, the light beams end up on the lining at the back of the eye. This is called the *RETINA*. The retina is like the film in an old style camera. The retina turns the light beams falling on it into electrical nerve signals. These nerve signals travel down the *OPTIC NERVE* to the brain.

(I'm not going to describe the detail of how the retina reacts to light, how we see colours or how the nerve signals are produced - all that is too complicated for this page!).

The retina does not work in the same way across the whole of the eyeball. Light coming from different places falls on different parts of the retina. If you look straight at something, the light will fall on the most central part of the retina. If you are looking at something 'out of the corner of your eye' then the light falls on the sides or edges of the retina.

The centre of the retina, called the *MACULA*, is the most sensitive to detail and to colour. This means that you get the most detail when you look directly at something. You can still see things even when you are not looking directly at them, but not in so much detail and you can't judge the colour so well.

When the eyesight is affected by Leber's Hereditary Optic Neuropathy, it is the retina and optic nerve that stop working properly. Some parts of the nerve may even die and so can't send the right signals to the brain any more.

At the back of the eye, concentrated in the centre, are lots of things called Retinal Ganglia Cells. These extend back and form part of the Optic Nerve. The eyesight loss from LHON seems to be because these cells stop working or even die.

The cornea, pupil and lens still work, but the light can't be converted into the right signals for the brain. The damage happens in the most sensitive part of the retina,
where the detailed vision and best colour vision normally sits. That is why people affected by Leber's lose the vision in the centre and can still see 'around the edges'.

Ordinary spectacles correct problems in the cornea or in the lens. They help the eye to focus the light onto the retina properly. When someone is affected by Leber's, the light is already being focused on the retina properly, but it isn't being converted into signals for the brain.

That is why ordinary spectacles can't help the symptoms of Leber's Hereditary Optic Neuropathy.

Most people with LHON have some useable vision, but this is around the edges of the visual field. This is often called 'peripheral vision'. It takes practice to use this vision, because we have to look away from something in order to try and see it.

This vision is using part of the eye away from the centre, so the image may not be as well focused. It will also be less detailed and with less ability to identify colours. It is common for people with a LHON gene to have colour weakness or colour blindness, especially between red and green.

Magnifiers and telescopes can help, because they make things look bigger to the eye. If you look at something through a magnifier or telescope you are using more of your retina to see it. If some of your retina is damaged and doesn't work properly, you can use some of the undamaged areas to try and see.

It is also very important for someone affected by LHON to work with good contrast material, in a suitable light.
What is Co-enzyme Q10?

Co-enzyme Q10 is an extremely important chemical throughout the human body. It is found in every cell in the body, especially in the mitochondria of the cells where food (carbohydrates and fatty acids) is being turned into energy for the cell (ATP).

The chemical structure of Co-enzyme Q10 is shown above. This is a simplified diagram of one Co-enzyme Q10 molecule.

I won't try to explain the detailed chemical structures and processes on this page. Instead I'm hoping to give some understanding of why this chemical is so important.

The molecule has two main features, which look a bit like a head and a tail.

The "head" is known as a Quinone ring. It's a special combination of carbon atoms in a ring, with two Oxygen atoms (O) and two Methyl groups (CH3) attached.

The "tail" or "side-chain" is 10 repeating structures called Isoprene units.

So in Q10 the "Q" stands for Quinone and the "10" is for the 10 Isoprene units in the chain.

Co-enzyme Q10 is found just about everywhere in the body, it is UBIQUITOUS, so it's often called Ubiquinone - the quinone found everywhere.
The "tail" or "side-chain" does not dissolve in water, but instead easily dissolves in fats or oils (fats and oils are known as lipids by scientists). This is important for many of the functions of Co-enzyme Q10, because the cell membranes and mitochondrial membranes are made up of a combination of lipids and proteins. Co-enzyme Q10 not only sits comfortably inside these membranes, it can do an important job helping to stabilize these membranes and keep them healthy.

The "head" or Quinone part of the molecule has two Oxygen atoms attached to it. Each of these can pick up a Hydrogen ion (proton) and then release it later on under the right conditions. This means that Co-enzyme Q10 can do a job of moving these Hydrogen ions and associated electrons across a membrane.

This change (or chemical reaction) runs in both directions, Co-enzyme Q10 can "pick up" Hydrogen (proton plus electron) in one place and then "put it down" in another, as the cell needs it. This is a crucial part of the respiratory chain in the mitochondria which turns food molecules into the fuel of the cell, ATP.

This 'juggling act' with Hydrogen means that Co-enzyme Q10 is an extremely powerful anti-oxidant. It not only reacts with free radicals itself, but we believe it also works with Vitamin C and Vitamin E to keep them functioning.

In the membranes of the Mitochondria Co-enzyme Q10 provides a crucial link from Complex I and Complex II to Complex III.
Embedded in the Mitochondrial membrane, Complexes I, II, III and IV pass electrons along and "pump" Hydrogen ions into the space between the Inner and Outer membrane. Complex V then uses that Hydrogen Gradient to create ATP, the fuel of the cell.

Co-enzyme Q10 may also be involved in other crucial functions such as:

- How cells handle chemical signals at the cell membrane
- Stimulating Cell growth
- Inhibiting programmed cell death (apoptosis)
- how genes are actioned (expressed) inside the cells.

**Where do humans get Co-enzyme Q10?**

We make Co-enzyme Q10 within our bodies as well as eating it whenever we eat animals. It is synthesized from an Amino Acid called Tyrosine, which is plentiful in a wide variety of common human foods.
Although some on-line sources imply Co-enzyme Q10 is an essential part of our food like a vitamin, anyone with a balanced diet is extremely unlikely to be deficient or need Co-enzyme Q10 supplements.

There are scientific studies going on to see if Co-enzyme Q10 diet supplements are useful as a therapy for some medical conditions such as Huntingdon's Disease or Friedrich's Ataxia. It may also help with side-effects of Statin treatment.

There does not seem to be any evidence that Co-enzyme Q10 is a useful therapy for Leber's Hereditary Optic Neuropathy. Instead, two synthetic drugs which perform similar functions to Co-enzyme Q10 are being clinically trialled.

**Patient Factsheet on Co-enzyme Q10**

**Biochemical functions of Co-enzyme Q10 (J Am Coll Nutr December 2001 vol. 20 no. 6 591-598 )**

**Idebenone and EPI-743**

The aim of these two drugs is to increase the efficiency of energy (ATP) production in the mitochondria and provide anti-oxidant protection to the chemicals in the cell membrane.

The difference in structure of Idebenone and related short-chain quinones is thought to bypass the faulty Complex 1 part of the respiratory chain and link directly to Complex III. This would make it much more effective than Co-enzyme Q10 supplements if the LHON mutation had caused the cell to build a faulty Complex I.