Usher Syndrome
Genetics
Introduction

Usher syndrome is a genetic or inherited condition that affects hearing, vision and balance

The sight loss is caused by an eye condition known as retinitis pigmentosa (RP), which leads to a gradual and progressive reduction in vision.

The hearing loss is sensori-neural deafness – a problem with the inner ear or the auditory nerve. Usually a person with Usher experiences the hearing loss from birth.

Some types of Usher syndrome affect the development of the vestibular organs in the inner ear, which are responsible for balance and sense of space.

Congenital deafness and RP are rarely found together, and so most people who have both probably have Usher

Identification and diagnosis of Usher is improving all the time and early diagnosis is very important.

Diagnosis is usually done through hearing, and vision tests. Balance tests may also play a role in diagnosis.

Studies in the deaf population suggest an estimated incidence of Usher of 4 per 100,000 of that population. The latest genetic research suggests there may be more people with Usher than previously thought, with an estimated incidence of 15 per 100,000 live births.

More than 50 studies in schools for the deaf from around the world suggested three to six per cent of the deaf population have Usher syndrome. All of these studies focussed on deaf populations, particularly those with a profound hearing loss.

More recently, research into the genetics of Usher has suggested that 15-18 per cent of deaf and hard-of-hearing children have a genetic make up that suggests Usher syndrome, and that Usher in the general population is estimated at the rate of 1 in 6,500 births, or 15 per 100,000 live births.
Usher syndrome and lifestyle
People with Usher can achieve a great deal with the right support. A person’s sight and hearing loss will require changes to how they communicate, access information and explore the environment. The diagnosis of sight and hearing loss can have a significant emotional impact.

There is no cure for Usher syndrome but there are a number of steps people can take to protect their vision and hearing, as well as adjust to the emotional, communication and other day-to-day challenges Usher presents. With the research that is being done today, treatments may in the future slow down or stop further sight loss.

Usher general sub-types:
There are three clinical types of Usher syndrome, Usher one, Usher two and Usher three.

In the UK, Usher one and Usher two are the most common. However, we are finding increasing numbers of people with Usher who have experienced a progressive hearing loss from childhood. These people may have Usher type three.

Type one
People with Usher type one are profoundly deaf from birth and have balance problems.

The hearing loss associated with Usher often remains stable throughout a person’s life and is generally not helped by hearing aids. Most use sign language as their primary means of communication. However, recently children with Usher one are benefiting from cochlear implants, thereby allowing them to develop speech.

Most children with Usher type one usually begin to develop retinitis pigmentosa-related vision problems between the ages of 8-12 years old, with vision problems first noticed at night, followed by increasing difficulty with side (peripheral) vision. The vision continues to deteriorate.

Balance problems associated with Usher type one mean that children may be late in sitting up and walking.
Type two

Children with Usher two are born with moderate to severe hearing impairment and normal balance. The severity of their hearing impairment varies, but many, if not most, children can benefit from hearing aids. Children are likely to use speech to communicate.

The visual problems related to retinitis pigmentosa (RP) in Usher type 2 tend to progress more slowly than in Usher one and also tend to begin later, usually in the late teenage years. They may not even begin until the person is in their 30s or 40s.

The RP is variable from person to person, so it is impossible to predict how much sight and hearing someone might have at any given stage in life.

The person with Usher two is faced with continually adapting to two changing senses and the impact that a change in one sense has on their ability to use the other.

Type three

Children born with Usher three have normal hearing at birth. Their hearing worsens over time and may progress to profound hearing loss.

However, the rate at which hearing is lost can vary between individuals, even within the same family. Children may develop noticeable hearing problems by their teens and usually are using hearing aids by mid to late adulthood.

Vision problems usually begin during teenage years, starting with night blindness. The sight problems are more variable and this can mean that central vision is affected earlier.

As with Usher two, the RP is variable from person to person, so it is impossible to predict how much sight and hearing someone might have at any given stage in life.

Some people with Usher three will have near normal balance but some may develop problems later on.

As with Usher two, the person with Usher three is faced with continually adapting to two changing senses.

Usher three is rarer in the UK, so diagnosis is often delayed.
People with Usher type one have poor balance, and about half of all people with type three also develop balance problems over time. People with Usher type two may experience balance problems as a result of a combined sight and hearing loss.

There are therefore three broad types of Usher - types one, two and three. The age of onset, the extent and the progression of sight, vision and balance problems varies with each individual and each type. As genetic knowledge develops further sub-divisions and types may be suggested.
Usher genes

Background
Before we look at the details of Usher syndrome it is good to get an idea of what ‘genetics’ is and what some of the terms mean.

Q. What is genetics?
Genetics is the study of genes and how they are passed onto children from their parents.

Q. What is DNA?
DNA is a molecule that is responsible for the overall structure and function of an organism by the production of specific proteins. It is an ‘instruction booklet’ involving many codes (genetic information) that is read and followed; DNA is organized into thread-like strands called chromosomes. Each parent passes on their genetic information via DNA to their children.

Q. What is a gene?
A gene is a section of DNA that contains a specific protein or part of a protein that is responsible for/involves in a specific function. The gene allows a specific protein to be made in a specific cell type (cells in the eye, heart, lungs, etc) at a specific time. Genes control how our bodies work and determine some of the characteristics we will have such as eye colour. People inherit genes from both parents. Each individual has approximately 25,000 genes. A faulty version of a gene may cause a medical condition because the protein that is produced may be faulty or may not be produced at all, which may then affect a physical or behavioural characteristic of an individual.

Q. What is a protein?
Proteins are like machines that make all living cells function. Cells produce protein from the information they receive from genes (mentioned above) in the DNA sequence. There are different types of proteins that all have different functions, which are coded by different
genes. Proteins make up blood, muscles, tendons, skin, nerves and organs (NHS-genetics, 2012a).

Within each cell, there are thousands of different proteins that have different jobs; but they all work together to keep the cell alive and functioning.

Q. What is a mutation?
A mutation is when there is a change (variant) in the DNA sequence, that cause a change in the ‘instructions’ being given out producing proteins.

Mutations can have 3 consequences. One result could be a neutral effect, whereby the mutation still produces a functional protein. Another result could be a beneficial effect, whereby the mutation actually improves the protein’s function (these two effects can be classed as a polymorphism (see below)). The final result could be a detrimental one, whereby the mutation produces a protein that does not function properly or stops the production of a specific protein, which may result in a genetic disorder. The variant is the said to be pathogenic (see below).

<table>
<thead>
<tr>
<th>Mutation in gene</th>
<th>change in genetic code</th>
<th>faulty protein</th>
<th>dysfunctional cell</th>
<th>change in physical or behavioural characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example:</td>
<td></td>
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<tr>
<td>Mutation in Usher gene</td>
<td>change in genetic code</td>
<td>faulty photoreceptor and stereocilia protein</td>
<td>dysfunctional photoreceptor and stereocilia</td>
<td>disrupted visual cycle and hearing cycle = vision loss and deafness</td>
</tr>
</tbody>
</table>

Q. What is a polymorphism?
A polymorphism is a change in a DNA sequence that is common in a specific population of people. It is not disease causing (not pathogenic).

Q. What is pathogenicity?
Pathogenicity is the ability to cause disease.
Q. What is a variant?
Changes in the DNA sequence are called variants. Variants can be pathogenic or they could be neutral (this is when they would be called polymorphisms).

**What are the Usher genes?**
Currently there are a total of 9 genes that have been linked to Usher syndrome and they are often referred to as ‘the Usher genes’. The 9 genes are:
- Type one Usher syndrome: MY07A, USH1C, CDH23, PCHD15, SANS
- Type two Usher syndrome: USH2A, VLGR1, WHRN
- Type three Usher syndrome: USH3A

**Inheritance mode**
Inheritance mode is the way in which parents pass on specific genes to their children to produce specific characteristics. Examples include eye colour, height, facial features.

Usher syndrome is inherited, which means that it is passed from parents to their children through changed or mutated genes. Usher is autosomal recessive.

**Autosomal** means that both males and females can have the disorder and can pass along the disorder to a child.

**Recessive** means that a person must inherit a change in the same gene from each parent in order to have the disorder. If only one change is inherited, the child will be a carrier of Usher syndrome but will not develop the condition themselves.

**Carriers:**
A person with one changed gene does not have the disorder, but can pass either a changed or an unchanged gene on to his or her child. They are said to be a carrier because they ‘carry’ the gene with a mutation, but show no symptoms of the disorder.

Usually, parents who have normal hearing and vision do not know that they are carriers of an Usher syndrome gene mutation. Currently,
it is not possible to determine whether an individual who does not have a family history of Usher syndrome is a carrier. This may change as scientists learn more about the genes responsible for Usher syndrome.

If a ‘carrier mother’ and a ‘carrier father’ who each carry one copy of the same mutated gene (i.e. carriers of Usher syndrome) decide to have a child together then with each birth there is a:

- One in four chance of having a child with Usher syndrome.
- Two in four chance of having a child who is a carrier but does not have Usher syndrome.
- One in four chance of having a child who neither has Usher syndrome nor is a carrier.

The above image is taken from the National Institute of Health (NIH, 2008). It illustrates the inheritance pattern that occurs in autosomal recessive conditions.
Genetic test

What is a genetic test?
A genetic test is when an individual is checked to see if they are carrying a specific mutation in one of their genes and whether they are at risk of developing or passing on a particular genetic condition. Because this test is very specific, the individual must know what specific mutation they want to be tested for, and most importantly, whether that mutation does in fact cause a genetic condition. If it is not known whether a particular mutation causes a genetic condition, the mutation may not be harmful to the individual.

A genetic test usually requires a blood sample to be taken from the individual. Sophisticated equipment and techniques are then used to extract the DNA from the blood sample so the genetic information can be scanned. The individual’s DNA can be screened for the specific mutation in question (NHS genetics, 2012b; ORNL, 2010).

Genetic counselling

It is important to consider how the results of a genetic test might affect:

- your family
- your employment
- your insurance

Before individuals seek out genetic tests, they should first seek genetic counseling.

What is genetic counselling?

- It is a service provided by a specially trained professional (either a genetic counsellor or a clinical geneticist).
- It is important not to confuse genetic counselling with counselling therapy used for treating certain conditions such as depression and anxiety.
How to get an appointment with a genetic counsellor

If an individual would like to have genetic counselling, they should ask their GP for a referral. Sometimes the GP or hospital doctor may offer the referral themselves. A GP or hospital doctor will make a referral if:

There is a genetic condition that runs in the individual’s family and he/she would like to seek a professional for advice on the risks for themselves and their family (NHS Choices, 2012d).

The individual has a genetic condition and would like to seek additional, specialist information (NHS Choices, 2012d).

There may be a genetic condition that runs in the individual’s family and he/she would like to seek a professional for a genetic test and diagnosis (NHS Choices, 2012d).

An individual is pregnant and would like to seek a genetic counsellor for advice (NHS Choices, 2012d).

Another type of test carried out during pregnancy (ultrasound, blood test, etc) has indicated that the unborn child may have an increased risk of having a genetic condition (NHS Choices, 2012d).

The individual and their partner are close relatives and would like to have a baby (NHS Choices, 2012d).

The NHS have put together a leaflet on ‘Questions to ask’ as well as ‘Top Tips’ for before, during and after the appointment. They are as follows:

Preparing for your appointment

- Gather knowledge of your family history; any health conditions, particularly genetic conditions, which family members may have or have had.
- Write down your most important questions (NHS, 2012c).
- Write down details of your symptoms and any change observed (if the individual has not yet been clinically diagnosed with a genetic condition)(NHS, 2012c).
- Ask the hospital for an interpreter or any other form of communication support if you will need it during your appointment (NHS, 2012c).
• If you would like company during your appointment, ask a family member of friend to come with you (NHS, 2012c).

**What will happen at the appointment?**

The exact events that will happen at an appointment will depend on the reason why you have been referred to a genetic counsellor. However, there are general topics that are covered during a genetic counselling session and have been listed by the NHS (NHS choices, 2012b). These include:

• Explanation of isks, benefits and limitations of genetic counselling.
• Overview of the medical history of your family (family tree).
• Health conditions that run in your family and who is affected (inheritance pattern).
• Risk of developing a particular condition.
• Risk of passing on a genetic condition onto children i.e. inheritance pattern of the genetic condition and family planning.
• Support and advice for affected family members; this includes medical, psychological and social support.
• Arranging a genetic test to be carried out.
• Making or confirming a diagnosis from a genetic test.
• Support in understanding results from a genetic tests and their implication.
• What implications a positive and negative genetic test result can have on the individual and their family.
• Advice on how to progress after getting genetic test results.
• Answering your questions in regards to the condition diagnosed.

**Tips during your appointment**

• Always ask for further information if you are unclear about anything (NHS, 2012c).
• If there are any terms or words that you do not understand, ask the genetic counsellor to write it down and explain what it means (NHS, 2012c).
• Take notes for yourself or ask the family member or friend to take notes for you (NHS, 2012c).
• Go through your list of important questions that you may have made before your appointment, to make sure all your questions have been answered (NHS, 2012c).
• Go through what you have understood from your appointment to make sure you have not missed anything or misunderstood anything (NHS, 2012c).
• Make sure you ask what should happen next, when and how; write all these details down (NHS, 2012c).
• Ask who to contact if you have any more questions or problems as well as who to contact if you have not been given appointment dates for further tests (if applicable); write all these details down (NHS, 2012c).
• Ask for contact details of support groups as well as where to find further reliable information; write all these details down (NHS, 2012c).

**Tips after your appointment**

• Go over the notes you made during your appointment and add any additional notes you remember. Store these notes somewhere safe so you can refer to them when you need to (NHS, 2012c).
• Book any dates for further tests in your diary so you do not forget; if dates have not been given to you yet make sure you follow this up until you are given a date (NHS, 2012c).

**Usher and genetic tests**

Due to there being multiple genes associated with Usher Syndrome, genetic testing for this condition is not available on a widespread basis and diagnosis is usually done via clinical assessments of hearing, vision and balance (NIH, 2008).

The recent development of a test that can analyse more than 100 genes will allow experts to diagnose a range of conditions in the future, possibly including Usher Syndrome. This announcement was made by Professor Graeme Black who is the Professor of Genetics and Ophthalmology at Central Manchester University Hospital as well as the Director of the Biomedical Research Centre in Manchester.

Genetic testing is available for a few of the identified Usher genes and is available at a limited number of laboratories around the world (NIH, 2008). The best way to get reliable information about genetic testing for Usher Syndrome is to ask your genetic counsellor during
your appointment. Also, take a look at the NHS directory, which lists the genetic services they provide.

The National Center for Biotechnology Information’s website also has a list of gene tests for the different subtypes of Usher Syndrome and the laboratories (including details of the laboratory’s genetic counsellor) worldwide that provide the clinical tests (NCBI, 2012). The link for this webpage can be found in the ‘websites providing information’ section of this booklet.

Some research groups also provide genetic testing as part of their research. The NHS website has a page dedicated to clinical trials in genetics, also listing whether each study is recruiting patients or not. The link for this webpage can be found in the ‘websites providing information’ section of this booklet.

Regulation of genetic tests
Not all genetic tests have been assessed by the regulatory authorities. Caution must be taken when individuals seek out genetic tests, especially those not from well-known health organizations as well as ‘self-test’ kits. These may be dangerous because they may not be accurate and may discourage individuals from seeking professional advice to interpret the results but also to make further decisions in regards to their health and their family’s health (ORNL, 2010).

It is important to visit a genetic counsellor before taking a genetic test. During this session you can ask any specific questions you have regarding Usher syndrome and whether there are genetic tests available. Not only will the genetic counsellor be able to explain which genetic tests are suitable for you, they will also know which tests are safe and reliable.

Genetic counsellors can only provide you with information. The choice to pursue a genetic test is always down to the individual.

See below for NHS genetic services in the UK.
NHS genetics services

For information and contact details of local NHS genetic services, visit the Genetic Alliance website, which provides a directory of the UK NHS genetic services; details are listed in the ‘who to talk to’ section of this booklet:

You can also find a directory of UK NHS genetics services on the British Society for Human Genetics website; details are listed in the ‘who to talk to’ section of this booklet.

Contact details for these organisations can be found under the Further Information section.

It is important to keep in mind that even if an individual tests positive for a specific mutation, it is not certain that the specific mutation detected is responsible for the development of a specific genetic condition. Until this is certain, genetic tests cannot give confirmation diagnosis (NHS Choices, 2012b).
Further information:

If you would like specific advice, you should consult a clinical geneticist or genetic counsellor in your local NHS Regional Genetics Centre. To find out where that is, please contact either Genetic Alliance UK or The British Society for Human Genetics; details are listed below.

UK NHS genetic services in the UK:

Genetic Alliance UK:

- Has a list of NHS genetic services in the UK on their website, including contact details of regional services.
- Website link: http://www.geneticalliance.org.uk/services.htm
- Address: Genetic Alliance UK, Unit 4D, Leroy House, 436 Essex road, London N1 3QP, UK.
- Telephone: 02077043141
- Fax: 02075391447
- Email: contactus@geneticalliance.org.uk

The British Society for Human Genetics

- Has a directory of UK genetic centres in the UK on their website
- Website link: http://www.bshg.org.uk/genetic_centres/uk_genetic_centres.htm
- Address: The British Society for Human Genetics, Clinical Genetics Unit, Birmingham Women’s Hospital, Birmingham B15 2TG, UK.
- Telephone: 01216272634
- Fax: 01216236971
- Email: bshg@bshg.org.uk
Clinical trials in genetics

NHS

- The following link lists current ongoing clinical trials as well as their recruitment status:
  [http://www.nhs.uk/Conditions/Genetics/Pages/clinical-trial.aspx](http://www.nhs.uk/Conditions/Genetics/Pages/clinical-trial.aspx)

Organizations

Genetic alliance UK:

- Website: [http://www.geneticalliance.org.uk/](http://www.geneticalliance.org.uk/)
- Contact details are listed in the ‘UK NHS Genetic Services’ section.

UK Genetic Testing Network (UKGTN):

- Website: [http://www.ukgtn.nhs.uk/gtn/Home](http://www.ukgtn.nhs.uk/gtn/Home)
- Address: UK Genetic Testing Network, c/o NHS London, National Specialised Commissioning Team, 2nd Floor, Southside, 105 Victoria Street, London, SW1E 6QT.
- Telephone: 02079323969
- Fax: 02079323800
- Email: UKGTN.Enquiries@nsct.nhs.uk

The British Society for Human Genetics

- Website: [www.bshg.org.uk](http://www.bshg.org.uk)
- Contact details are listed in the ‘UK NHS Genetic Services’ section.
Informative leaflets and advice

Genetic Alliance

- This organization has a collection of patient leaflets on their website. Access these leaflets via the following link:
  http://www.geneticalliance.org.uk/publications_patients.htm

Human Genetics Commission

- Advice for those considering buying over-the-counter genetic tests can be found via the following link:
  http://www.hgc.gov.uk/Client/Content.asp?ContentId=793
- Further information on what to consider before taking a genetic test bought over-the-counter or on the internet can be found via the following link:
REFERENCES


This document was produced by:

Yemi Tadesse
Research Officer
Telephone: 02070149369
Email: yemi.tadesse@sense.org.uk
Sense, 101 Pentonville Road, London, N1 9LG.

Please do contact me if you have any queries.