

# NCUS NEWSLETTER



Newsletter for the National Collaborative Usher Study • Issue 3 • Spring 2006

Hello again and welcome to any new readers of our newsletter. The Study is now into its third year of researching in depth into 200 UK families with Usher syndrome. During 2006 clinical investigations on vision, hearing and balance will be completed, but the work of the molecular geneticist continues until April 2007.

We know that many of you are keen to find out how the research is getting on in the meantime. If you want to hear about '**progress so far**' please put Saturday 24th June 2006 in your diary when we are holding a meeting at the Institute of Child Health, Guilford Street, London WC1N 1EH, from 1.30 in the Leolin Price lecture theatre. The aim of this meeting is to share some early findings and to explain the reasons for the tests which many of you have now experienced. All the researchers who have



My name is Louise Thomasson. I joined Sense as an Assistant Family Co-ordinator in December. My role is to visit families in their homes. We discuss the project and I then take family and medical

histories and collect blood samples. I studied genetics at university and have worked on a number of projects including prenatal genetics, kidney and bladder conditions in children and hereditary cancers. I have really enjoyed travelling up and down the country and meeting so many interesting people since I started working with Sense. Everyone has made me feel very welcome and been incredibly helpful.

been involved in the NCUS will be there to talk about their part of the work and answer your questions. However, and this is really important, it will not be possible to give information to individuals or relatives about specific results on any given family during this meeting.

Enclosed with this Newsletter is a return slip to attend the '**progress so far**' meeting on Saturday 24th June. Please send it as soon as you can to Liz Cook at Sense together with information about your communication needs and/or dietary needs.

Since Autumn 2005 two more colleagues have joined the NCUS team. Louise Thomasson is helping Liz Cook with recruitment and Polona Le Quesne, a molecular geneticist, is working on analysis. Louise who is with us until June has written on Genetic Counselling and Polona an article on Cells, genes and DNA.

**Mary Guest, Editor:** [mary.guest@sense.org.uk](mailto:mary.guest@sense.org.uk)

**Recruitment:** Liz Cook reports that 180 families are in the Study; she is keen to hear from others especially families with Usher Type 1. Blood samples from parents and siblings are now vital to the researchers. Please send them to Liz speedily. If you have not heard yet about clinical tests, you have not been forgotten, she and Melanie will be in touch.

**Liz Cook, Family Coordinator,  
National Collaborative Usher Study:**  
[liz.cook@sense.org.uk](mailto:liz.cook@sense.org.uk)

## *In this issue*

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# Let's look at hearing and some early results

NELL RANGESH

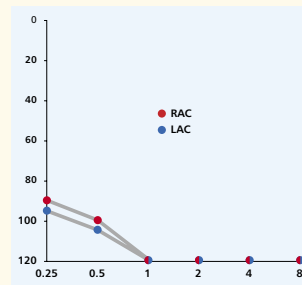
In the last newsletter we looked at tests for balance and how normal balance helps us to stand upright. In this article we look at hearing as well as some early patterns in hearing test results undertaken as part of the National Collaborative Usher Study.

In Usher syndrome hearing impairment is the first symptom and is caused by defective functioning of tiny cells (hair cells) in the hearing organ of the inner ear, called the cochlea. This prevents the sound energy that reaches the hair cells from being converted into electrical signals and sent to higher centres in the brain. The degree of hearing loss may depend on the severity and extent of damage to the cells, but people with Usher syndrome type 2, usually have a reasonable number of functioning hair cells and are able to use hearing aids to amplify the sound reaching the cochlea. Therefore, they can hear and learn to speak.

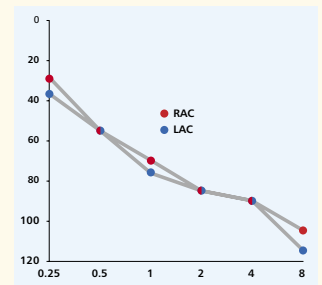
In type 1 Usher syndrome, the hearing loss is more severe and present from birth. As a consequence, it is difficult to hear and also difficult to learn to speak. In Usher syndrome type 3, there is not such a clear-cut pattern of changes. Hearing starts deteriorating much later and if hearing is adequate in the first two years of life, the youngster develops speech. To obtain an overall picture of hearing it is important to test not only the inner ear, but the mechanism through the outer ear canal and middle ear, as well as the inner ear and the nerve transmitting the signals from the inner ear into the brain. This nerve can be tested using computerised techniques that can pick up the minute electrical activity in the brain.

Puretone audiometry is still the main method of assessing hearing and provides a good

indication of hearing levels and progression (providing testing has been regular). On the audiogram the '0' line does not mean absence of sound but represents the baseline result of a large group of people with no hearing impairment. This standardisation allows comparison of audiograms across time, hospitals and even in different countries. The two audiograms shown below are patterns commonly seen in Usher syndrome. In type 3 Usher syndrome the audiogram pattern may resemble type 1 or 2.

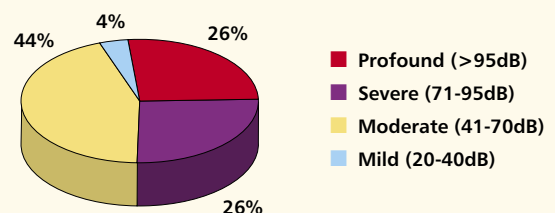


Type 1 Usher audiogram



Common Type 2 Usher audiogram

We, the researchers in the hearing and balance part of the Study, would like to thank all of you who have willingly subjected yourselves to a whole series of hearing and balance tests. We have audiogram data available on 106 people, 2% of you had a cold or ear infection or previous ear surgery and could not be included in the general analysis. This data is still very informative and allows us to gain an overall picture of people with Usher syndrome. The ear drum and middle ear was healthy in 84%.



Hearing Impairment in Usher syndrome

Two thirds of the group with profound loss (over 95decibels) is composed of people with Usher type1 where the hearing loss is expected to be more severe and present from birth. As can be seen only a small proportion of the total group had hearing levels better than 40 decibels (mild impairment)

We are working closely as a group to make this study a success and my Genetics and

Ophthalmology colleagues and I will soon be able to pool our findings and together with Sense provide more useful information to all of you. This study has been a learning experience for me in acquiring medical knowledge of Usher syndrome. More importantly it has been an eye opener to the strength and perseverance that you all have in your lives be it bungee jumping or coping with travel on the underground!

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## Hearing and balance testing

JANET CUMMING SHARES HER EXPERIENCE

When we arrived we were met by Dr. Nell Rangesh, who would be conducting the tests. The first thing she asked me was, had I booked an interpreter? I replied no, I've brought my husband!

Before each test, Dr. Rangesh explained very clearly exactly what she would be doing and what she wanted me to do. The first test began with watching Nell's finger move back and forth in front of my eyes. She then proceeded to turn my head to the left and then to the right with sudden movements to see how my eyes were reacting. The next test required me to be sat in what I called "The Electric Chair" luckily it wasn't plugged in! I was strapped in and had to wear a funny looking pair of goggles, fitted with a camera. These tests were all about following little red dots, turning horizontal lines into vertical lines and watching vertical black and white lines, while I was doing this, she was able to watch and record all of my eye movements. Dr. Rangesh asked me if I had had intra-ocular lenses implanted. I asked

her how she knew and she explained that it is possible to see a reflection when the infrared camera picks it up.

Nell had headphones on to listen to my response and was impressed to hear how well I spoke; I also made her laugh with what I was doing. It was like playing a computer game. The whole experience was very tiring but she made sure that I was all right and checking me, I told I was OK so we carried on. I was very interested in what was happening to me, and also I wanted to give researchers enough information to help them. The last test involved focusing at eye level on the wall as the chair rocked around which was difficult.

The next test was in a darkened soundproof room with electrodes on my head. I was asked to relax and sleep for 15 minutes; I had no trouble getting to sleep, while Nell and my hubby were chatting away. I was woken up within 10 minutes because I was very relaxed. I must have been tired after the first tests.

My hearing tests were relaxing with only having to press a button each time sound occurred but I had to do the ear pressure test 3 times because the results came out unexpectedly and I experienced dizziness as I did when I was younger from wearing hearing aids.

The test with warm then cold water in my ears was not to my liking although I was brave enough to go ahead. I felt disorientated. I remembered diving into the swimming pool and not knowing which way was up, I also

swam awkwardly, it was as if I didn't know which way to go and Dr Rangesh agreed that it was not good for me to swim under water.

I have enjoyed taking part in this study and I look forward to the result and to answer my question why me? This was mentioned in Issue 1. It has been a pleasure to help and gain a warm working relationship with Dr Zubin Saihan and Dr Nell Rangesh. I wish them luck.

*Editor: Thanks Janet.*

## Of cells, genes and DNA

DR POLONA LE QUESNE, YASMIN HUGHES

Many of you have kindly donated blood samples which are essential for genetic studies. In this issue we will explain what kind of information we can find from your blood sample and how it can help us understand the genetics of Usher syndrome.

### Cells contain DNA

The blood samples contain millions of cells and each cell carries a complete set of genetic information that is used to make up an individual human being (Figure 1). The genetic information comes in the form of DNA (deoxyribonucleic acid). The DNA in your blood cells is identical to the DNA in every cell of your body. To get hold of the DNA, the blood cells are treated with various chemicals that break the cells and purify the extracted DNA.

### The DNA code

The DNA is a double-helix of 3 billion letters (A, T, C and G) called nucleotides. At a first

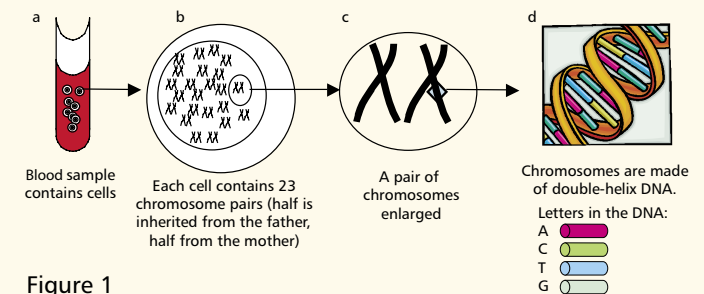


Figure 1

glance, these letters seem to be arranged meaninglessly, but if we speak the genetic language, letters (nucleotides) actually make words (codons) and words make sentences called genes. Genes carry instructions which tell cells how to produce the building blocks that make up our bodies (proteins) and how to perform special functions like hearing or vision. When a crucial part of the gene is misspelled, the message this particular gene is giving is altered and can cause a genetic disorder like Usher syndrome.

In previous studies, researchers have already identified nine genes that are involved in Usher

syndrome. However, in many cases, it is not clear what these changes are or how they cause Usher. For that reason we are currently analysing these nine genes in detail.

### *Evaluating the sequence differences*

After we have extracted the DNA from the blood cells, we determine the order of letters in the nine genes in a procedure called sequencing. Dr. Elene Haralambous explained more about sequencing in the autumn 2005 NCUS Newsletter. The order of letters (called the sequence) in the nine genes from Usher patients is then compared to the normal sequence. We check whether any letters in the genes are deleted, added, duplicated or changed. As an example, have a look at this sentence: "THE DOG ATE THE CAT". In the genetic language, all words are read in sets of three. Therefore, if the letter "E" in the first word is missing, we get the following nonsense sentence: "THD OGA TET HEC AT". In the same way, if our DNA sequence misses only one letter in a gene, the message this gene is giving is wrong and as a result, the cell will make a protein in the ears, eyes, heart or skin that cannot function properly. However, some of the differences we find are harmless, yet

others completely change the message of the gene and can be the cause of Usher. Therefore, all the differences we find must be studied carefully to find out whether they are indeed the ones that can cause the disorder rather than harmless varieties that do not change the message of the gene.

It must be mentioned that the DNA sequence of the nine genes we are analysing is much more complex than our simplified example. To make the reading and analysing of these genes experimentally possible, we divided them in 540 smaller parts. Each of these parts has on average 500 letters. In total, we are examining an estimated 200,000 DNA letters in each Usher patient. Approximately 50% of the letters have been analysed so far. During the course of the NCUS study, we have already found several differences in the DNA that explain Usher syndrome in some cases and we hope to discover the causes of Usher in many more families. However, the DNA with its 3 billion letters that carry the code for the building and functioning of our whole body is very complex and sometimes it takes a lot of research to get to the bottom of the problem.



Hi, my name is Polona Le Quesne. I joined the genetics team at the Institute of Child Health in December 2005 as a Research Fellow, replacing Dr. Elene Haralambous during her maternity leave. I am working together with Dr. Maria Bitner-Glindzicz and Research Assistant Yasmin Hughes. You can read more about our work in the article: "Of cells, genes and

DNA". I originally come from Slovenia where I studied veterinary medicine. After completing a veterinary degree I worked for four years in the Netherlands at Utrecht University where I was awarded my PhD in 2005. Since dogs, just like humans, suffer from numerous genetic disorders, I could quickly plug into my new job. I really enjoy working in the NCUS group.

POLONA

## Genetic Counselling

LOUISE THOMASSON, ASSISTANT FAMILY COORDINATOR

Families who have a genetic condition often want to learn more about it and discuss all the different aspects of the condition, including how it is inherited. The genetics healthcare team provides information and support to families with inherited conditions. The team consists of Clinical Geneticists, Clinical Nurse Specialists (both of whom are involved in medical aspects of genetics) and Genetic Counsellors. All three groups of people are specially trained professionals who are involved in the provision of genetic counselling. Most people who are seen by the genetics team are referred to the Genetics Service by their GP or hospital consultant, following a diagnosis. Other people request the service for advice when they find out that there is a genetic condition in their family.

The first meeting usually involves discussing your family history and drawing a family tree to establish your family history of the condition. A correct diagnosis is essential for genetic counselling to be effective, so test results of affected members of your family or further tests may be required. When the diagnosis has been made, the team can then tailor appointments to meet your family's specific needs.

Appointments will enable you to ask questions

about your family's specific condition. This is very useful for those families in which a new diagnosis has been made and there is no previous history. Sometimes people wonder how a condition can be genetic when no-one else in their family is affected, and so inheritance can be explained. Knowledge of how a condition is inherited leads to the understanding that the genetic condition could not have been avoided and that no-one is to blame. Genetic counselling can help you to understand the nature of the disease and what it means in practical terms, what to expect in terms of living with the condition, and options available for testing. You may be referred to other medical specialists and information of relevant support groups will be made available to you. Because of the nature of genetic conditions, there are often implications for other members of the family. In Usher syndrome risk to other hearing family members is often small. Family or individual sessions can be arranged to discuss this in more detail.

If you or any member of your family would like genetic counselling to discuss Usher syndrome, the first step is to speak to your GP or hospital consultant who will then be able to make a referral for you.

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## What is electrodiagnostic testing?

DR. ZUBIN SAIHAN

Did you know that your body is an electrical generator? Nerves and muscles all create electrical signals that deliver messages to and from your brain. Electrodiagnostic testing is a method of measuring changes in electrical activity in nerve or muscle. It can be used in

different parts of the body to test the function of nerves and muscles.

Electrical impulses travelling along nerves allow us to move muscles in our bodies. Sensory nerves from our eyes and ears also deliver

information regarding our surroundings to the brain for interpretation.

**Why is it useful?**

The electrodiagnostic testing that we do in people with retinal disease can tell us which cells in the retina are functioning normally or abnormally and can also give us additional information as to the location of these cells in the retina.

**How does it work?**

The retina is made up of many different types of cells. Two very important types are the cells that first 'sense' light that enters the eye called 'rods' and 'cones'. The rods and cones then pass information to other cells in the retina and ultimately to the brain where we interpret these signals as images.

We all start off life with millions of rods and cones, but with time these cells gradually reduce in number. In conditions such as RP the rods and cones can reduce in number quickly leading to problems such as loss of night vision and problems with central vision. Rods are responsible for night time vision and also help us to track moving objects. Cones are responsible for colour vision, which is better at

the centre of the retina. In the type of RP that we see in Usher syndrome the rods are usually more affected than the cones.

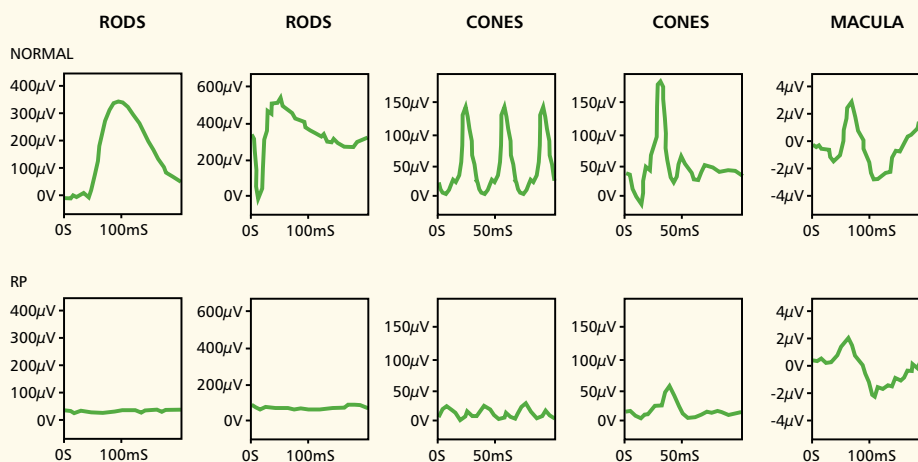
**How is it done?**

When light strikes the retina a series of very fast changes in electrical potential happen. These changes can be detected by recording the electrical current by placing electrodes at on or near the eye. We can plot the changing electrical potential of the retina with time (in milliseconds) called an electroretinogram (ERG). These signals are recorded as graphs. The shape of the graphs differs according to the type of light that is shone in to the retina and also which area of the retina is illuminated. The different peaks and troughs that we see can be attributed to the function of different cells in the retina under different conditions and can help us understand which parts of the retina are affected.

**What do the results look like?**

The images below represent the ERG's from a normal subject (above) and a person with RP (below).

Each peak and trough on the graphs represents a change in electrical activity of certain cells in the retina under different conditions. The two



images on the left are mainly from rods, the third and fourth images are mainly from cones whilst the fifth image represents macula (central retinal) function.

In the lower set of images all the traces appear flattened in comparison to the normal upper trace. The signal from the rods appears flatter (more severely affected) than those of the cones, as is most often the case in Usher syndrome. In this example the fifth trace from the RP subject shows that the function of the macula is preserved but somewhat reduced.

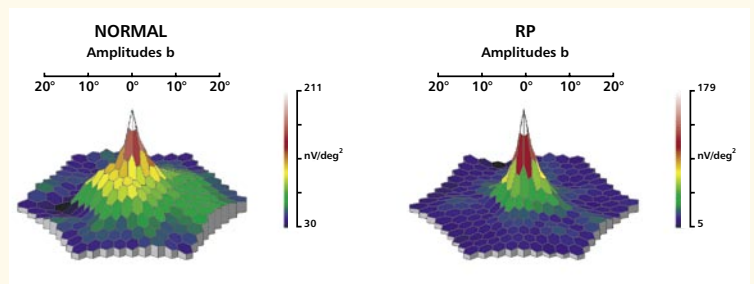
### Multifocal ERG

This type of ERG tests the electrical activity of the retina at different areas centred at the macula. It uses a computer program to test these small areas which represent 20-30 degrees of central vision.

The responses are plotted below. The response from a normal subject is shown on the left and from a subject with RP (on the right). It can

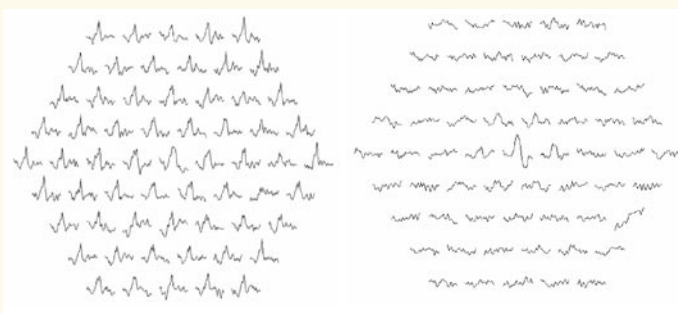
be seen that in the subject with RP the best electrical responses are seen centrally whilst the ones toward the periphery are less obvious.

These plots can also be represented graphically. From these plots it is clearer to see that the maximum responses are produced centrally both in normal eyes and those with RP. However, the responses fall off much quicker from the central point of testing in the eye with RP.



All the above electrical tests help by giving us objective measurements of retinal function; however they are only useful in a subset of people with RP and must really be interpreted alongside other tests. We must also realise that whilst electrical tests are helpful, the other tests such as the ability to read letters from a chart and visual field size are the ones where we can determine how well people with RP function on a day-to-day level.

(Thanks to A.Robson & M.Nevu from EDD department in Moorfields Eye Hospital for use of the images)



### Editor's note

We plan to send out the next issue of our NCUS Newsletter in Autumn 2006. If you have any news, letters or questions, please send them to Mary Guest by August 31st 2006. [mary.guest@sense.org.uk](mailto:mary.guest@sense.org.uk), Sense, 11-13 Clifton Terrace, Finsbury Park, London N4 3SR, Tel: 020 7272 7774 Text: 020 7272 9648

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