

LOCHI

Aetiology
The ~~Genetic~~ Substudy

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What do I and my research group do?

I am a geneticist/molecular biologist interested in:

- **Identifying the causes hearing loss in children and adults**
- **Identifying people of high risk of developing hearing loss**
- **Understanding how the ear functions**
- **Improving the management of hearing loss**



What will I talk about?



- **Why include a study of aetiology?**
- **Causes of hearing loss in children**
- **Genes causing hearing loss in children**
- **Cytomegalovirus (CMV)**
- **Why do we ask for access to the child's Guthrie blood card**
- **Additional information, questions that you or parents/carers might have**
- **The consent and issues relating to ethics or the results of the aetiology study**

Why include a study of aetiology?

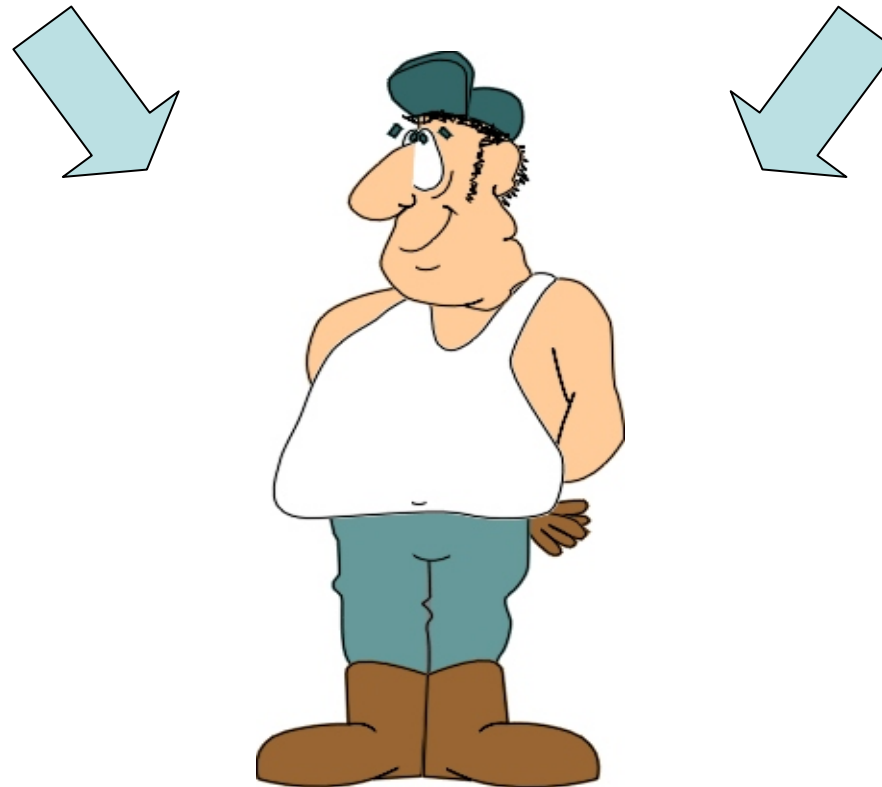
- It has become clear that hearing impairment isn't just one condition.
- We know that there are different underlying causes of hearing impairment.
- The aetiology of the hearing impairment might well be a factor when possible options for intervention and support are considered in the future.

Reasons for investigating the aetiology

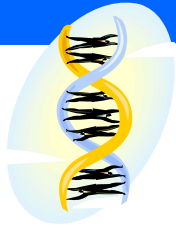
- **The outcome might to some extent depend on the underlying cause of the hearing impairment.**
- **But we don't know if this is the case!!**
- **The reason for a “genetic” sub-study to be added to the Outcome study is that we want to know if outcome is related to the aetiology of the hearing loss.**

What makes me me??

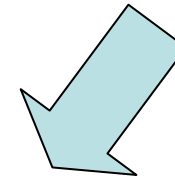
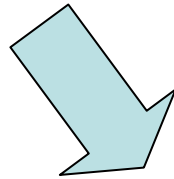
Genetic make up ↔ Environmental factors



What makes me deaf??



Genetic make up ↔ **Environmental factors**



Environmental causes of hearing loss

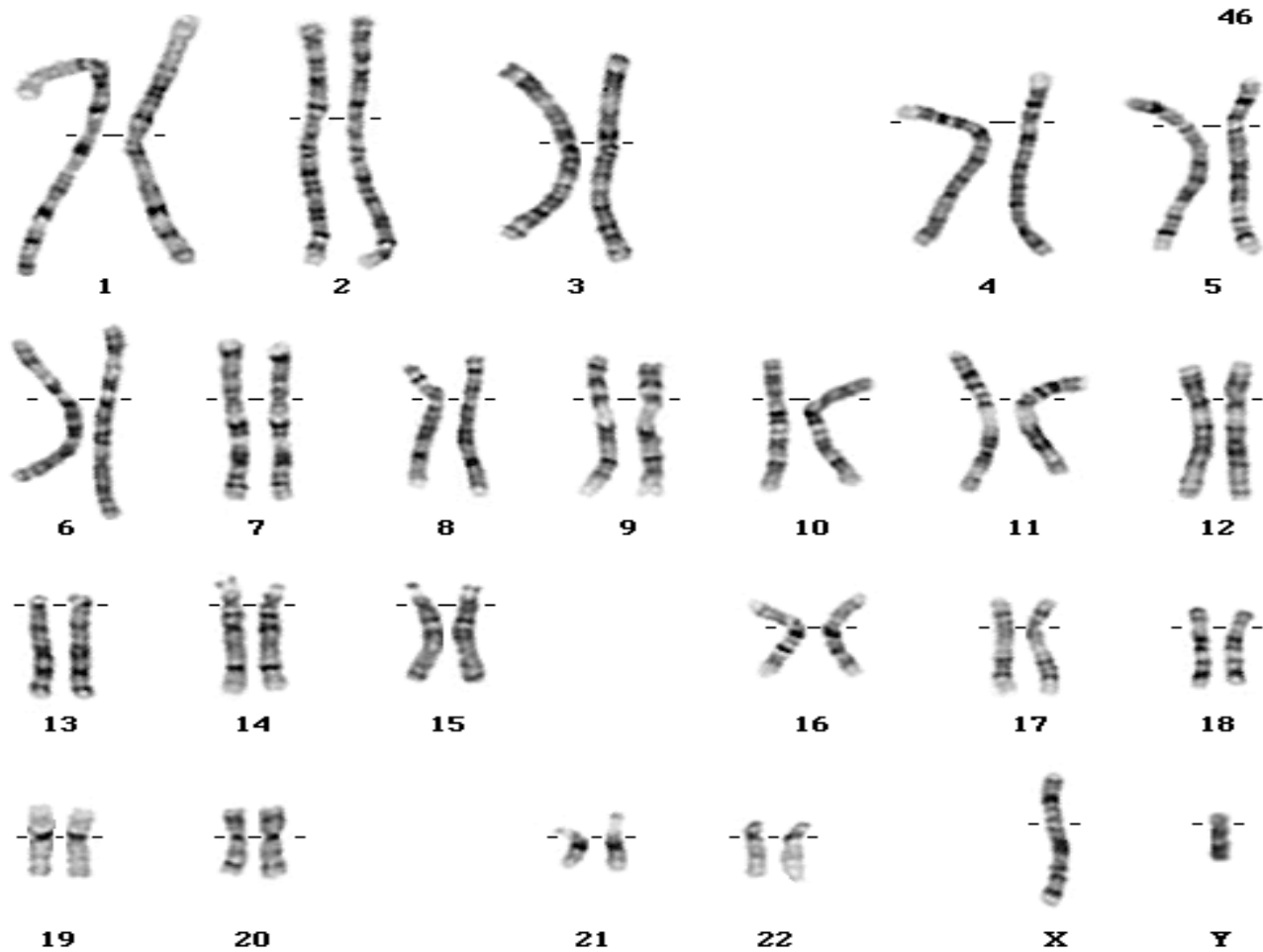
- **Viral infections:** Cytomegalovirus (CMV)
Rubella
- **Otitis media:** Infection and inflammation
- **Noise:** Industrial/walkmans (not common in young children!)
- **Prematurity:** Hypoxic damage
Hyperbilirubinemia (jaundice)
- **Antibiotics, ototoxic drugs:** Streptomycin, kanamycin, gentamycin, neomycin and other aminoglycosides; cisplatin

Are genetic causes of hearing loss common?

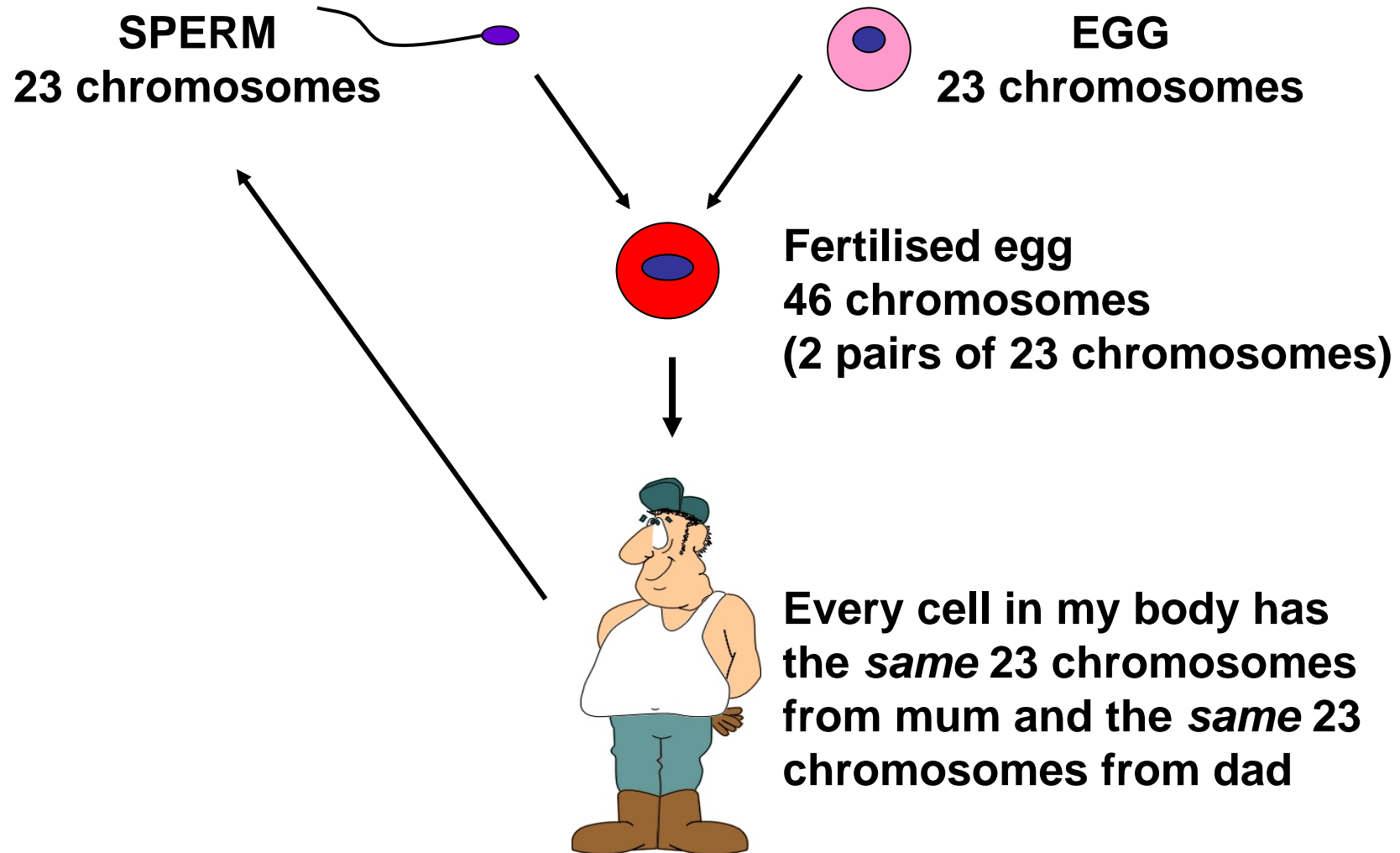
Genetic/inherited factors are the cause of deafness in 60-70% of children with a significant hearing loss.

Genetic factors also play a major role in later onset deafness and susceptibility to eg. noise or drugs.

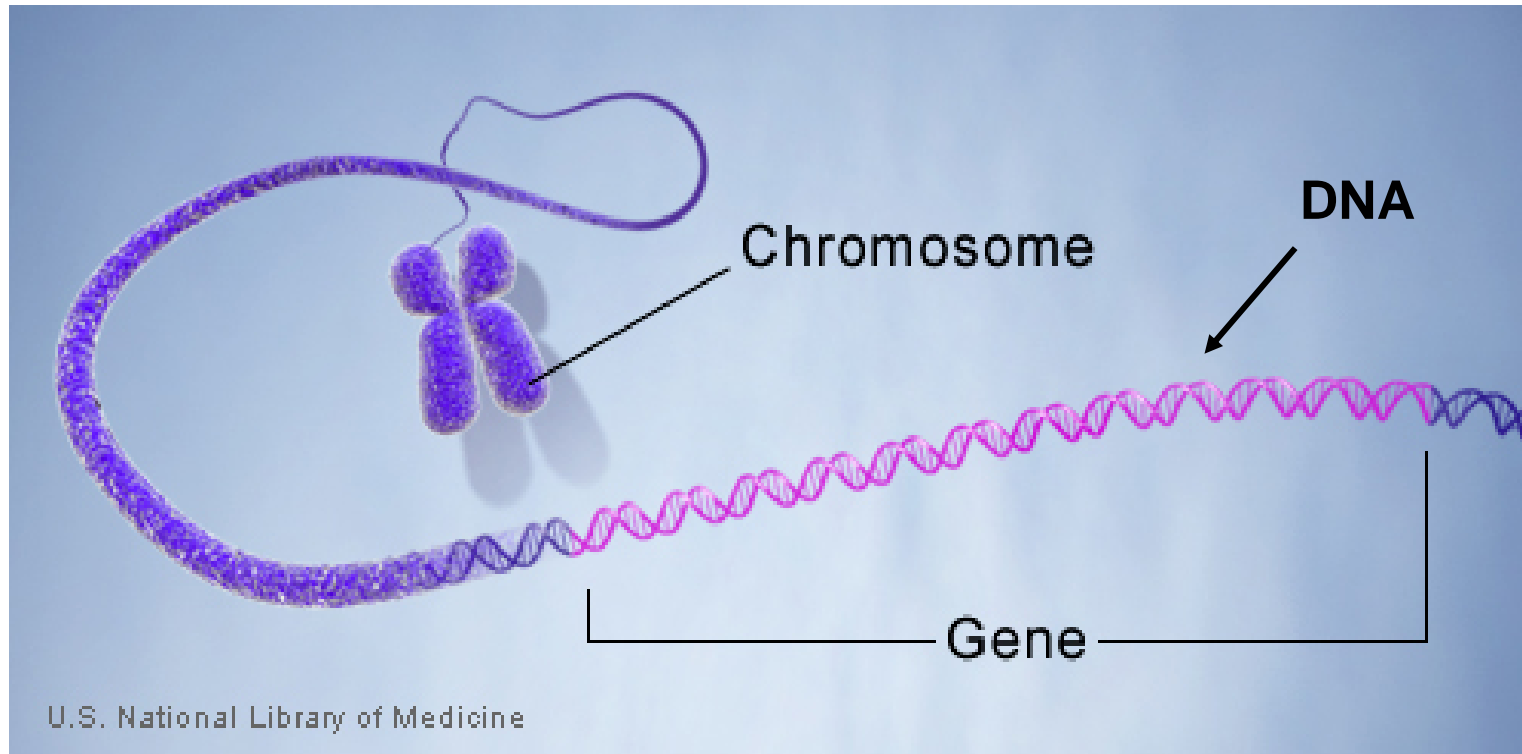
We have 23 chromosome pairs



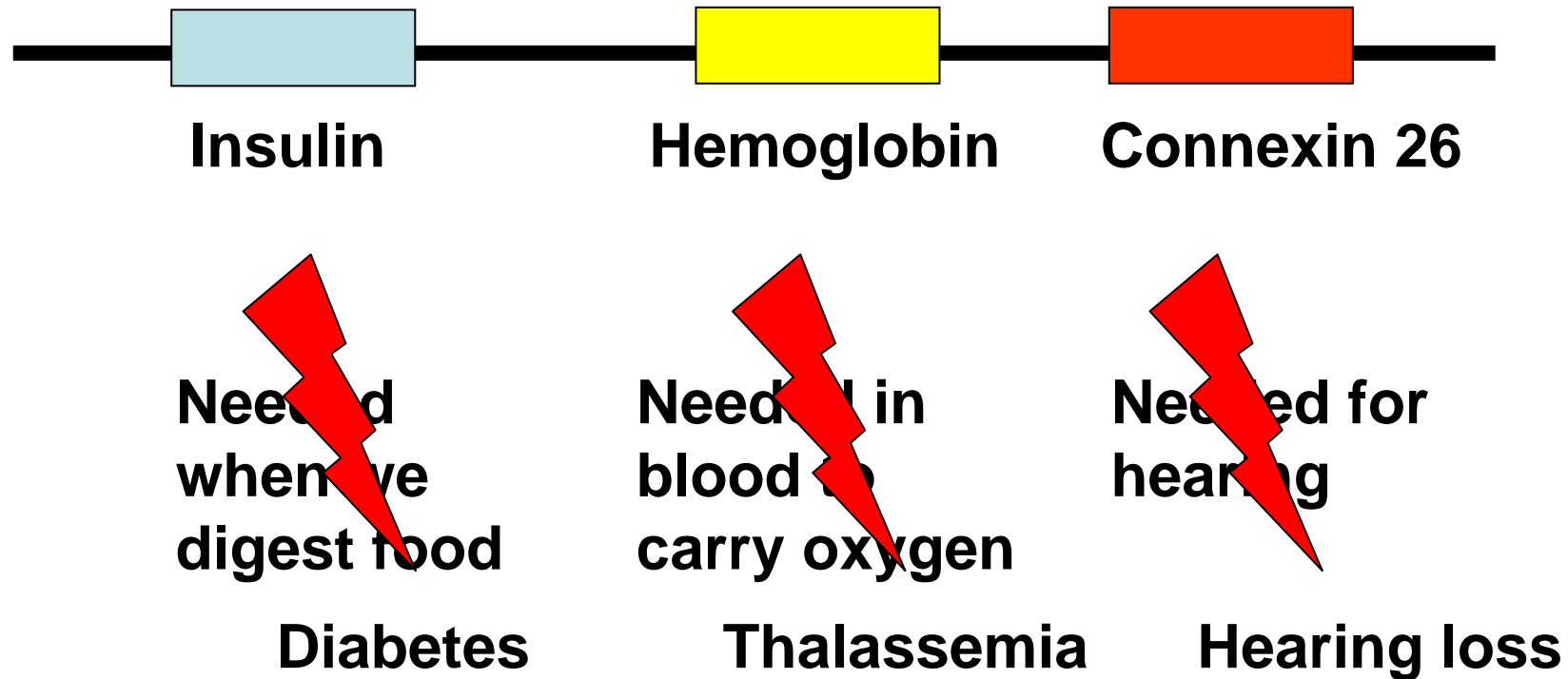
Where do our chromosomes come from?



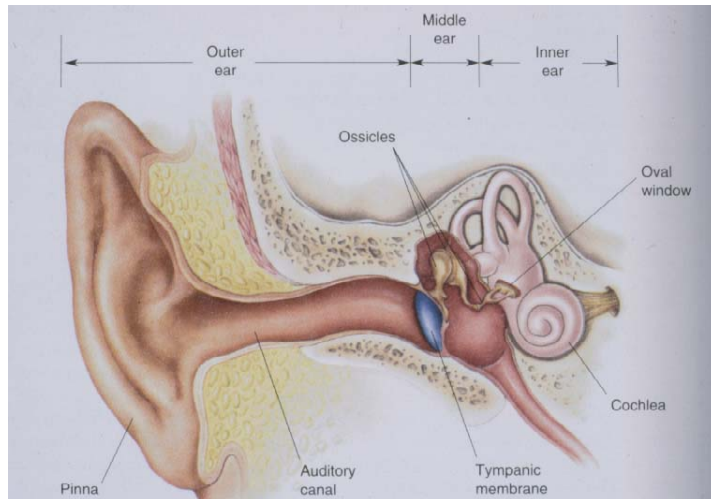
Chromosomes contain DNA & DNA codes for genes



Genes control many functions in the body



Genes and Hearing Loss



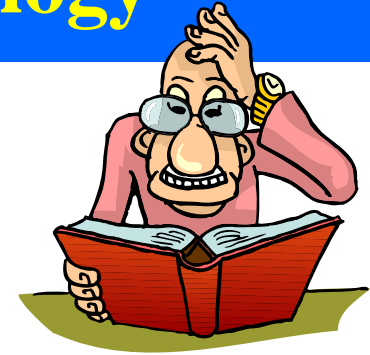
100-300 genes!



We know that changes (mutations) in many genes can cause hearing loss

We know some of these genes, but certainly not all of them

We usually don't know the aetiology



- We often don't know if a hearing loss is due to environmental or genetic factors.
- We usually can't tell which gene is mutated in a person with a genetic hearing loss.

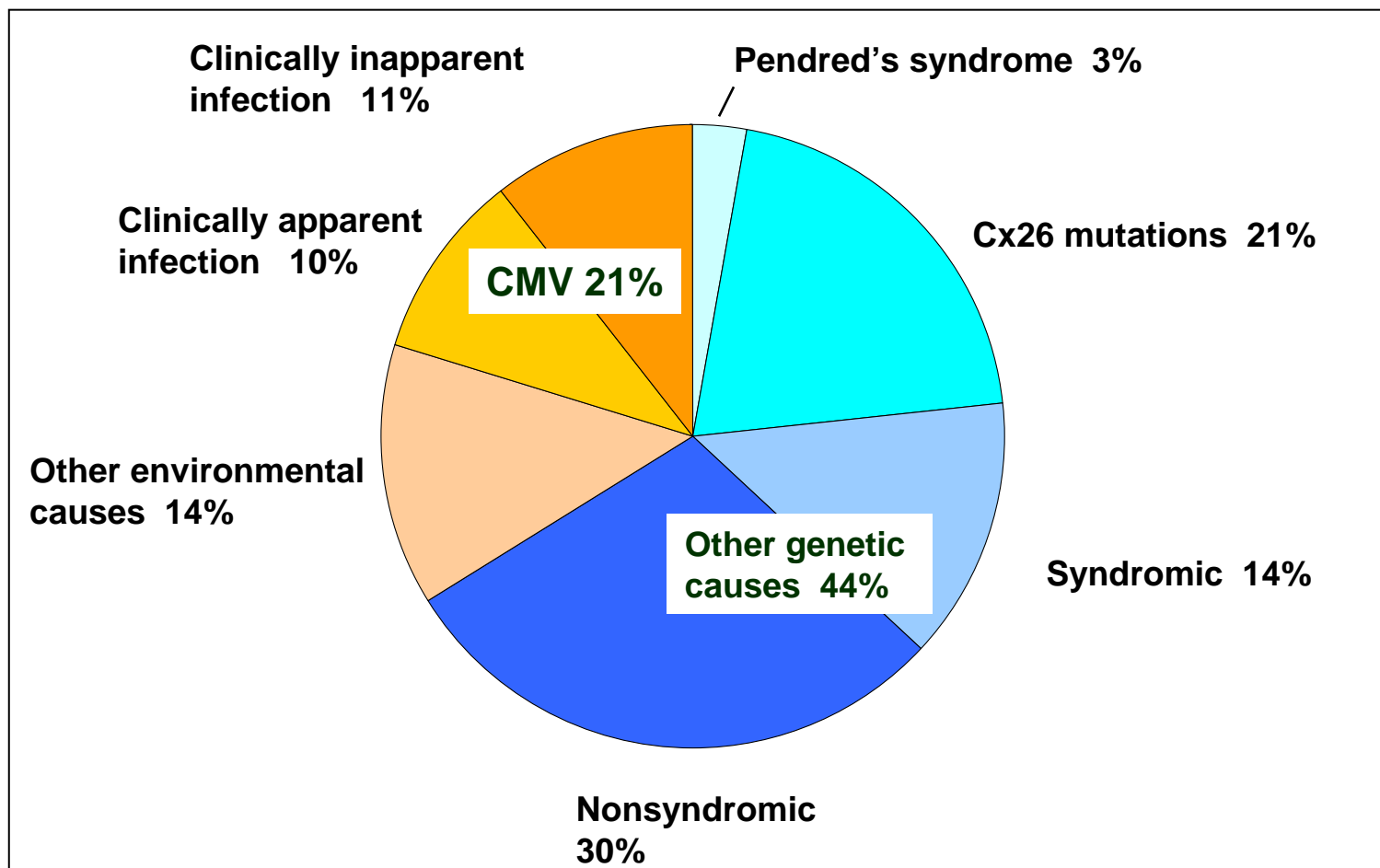
Why do we want to know the aetiology?

- **Currently, the main reason to determine the aetiology is to use the information in counselling:
“why is my child deaf?” and “what is the chance of having another child with hearing impairment”?**
- **In some cases it might be used in prenatal diagnosis.**
- **In the future it might influence intervention.**

Genes that cause hearing impairment

- I mentioned that many different genes can cause hearing loss: at least 100-300 different genes.
- We can't investigate all known "deafness" genes in all children with a hearing loss
- However, a few genes are relatively often causing hearing loss in children:
 - Connexin 26
 - Pendrin
 - A1555G mtDNA mutation (aminoglycoside ototoxicity)

Causes of hearing loss in children



Incidence at birth: 186 / 100,000.
Incidence at 4 years: 250 / 100,000

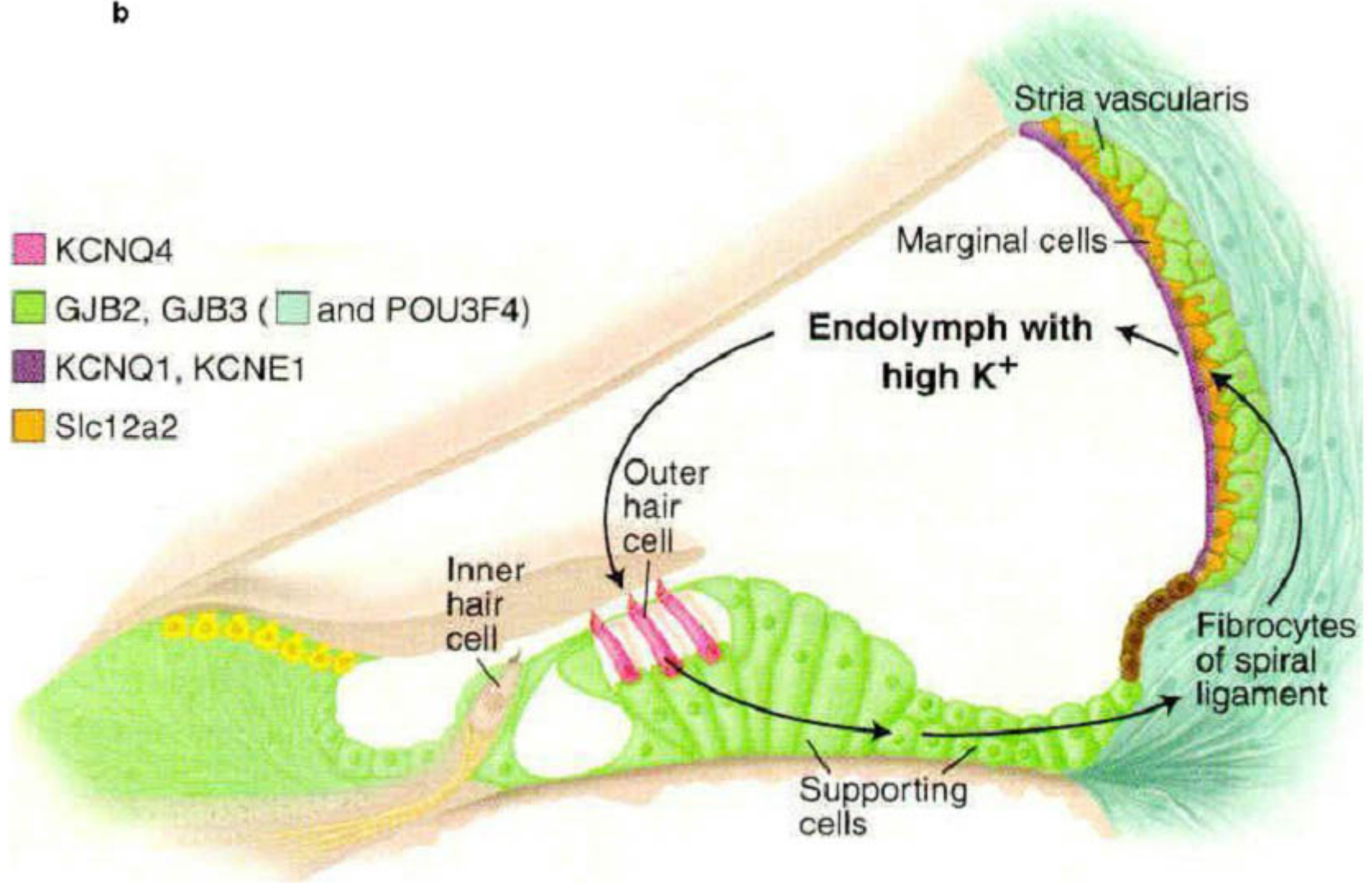
From: Morton and Nance, N Engl J Med 354: 2151-64 (2006)

The aetiology sub-study

- **The aim is to determine the underlying cause of deafness in a child if possible.**
- **More specifically we aim to determine if the hearing loss is due to these most common factors:**
 - **Mutations in the connexin 26 gene**
 - **Mutations in the pendrin gene**
 - **The A1555G mtDNA mutation**
 - **Cytomegalovirus infection during the pregnancy**

Connexin 26

b



Connexin 26

Mutations in connexin 26 account for 15-20% of all congenital deafness

The deafness is usually inherited as a recessive deafness

1 in 50 Australians is a carrier of a connexin 26 mutation

Many different mutations have been found in the connexin 26 gene

Common connexin 26 mutations

Caucasians

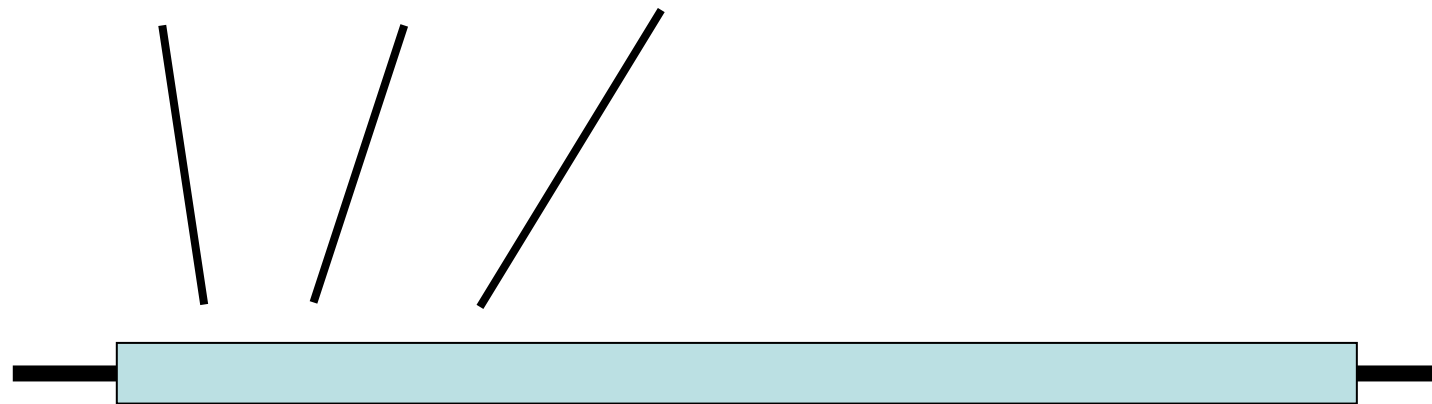
Asians

Ashkenazi Jews

35delG

V37I

167delT



Connexin 26 gene

Pendrin

Pendrin is a transporter of chloride and iodide

Mutations in the pendrin gene – also called SLC26A4 - can cause Pendred syndrome.

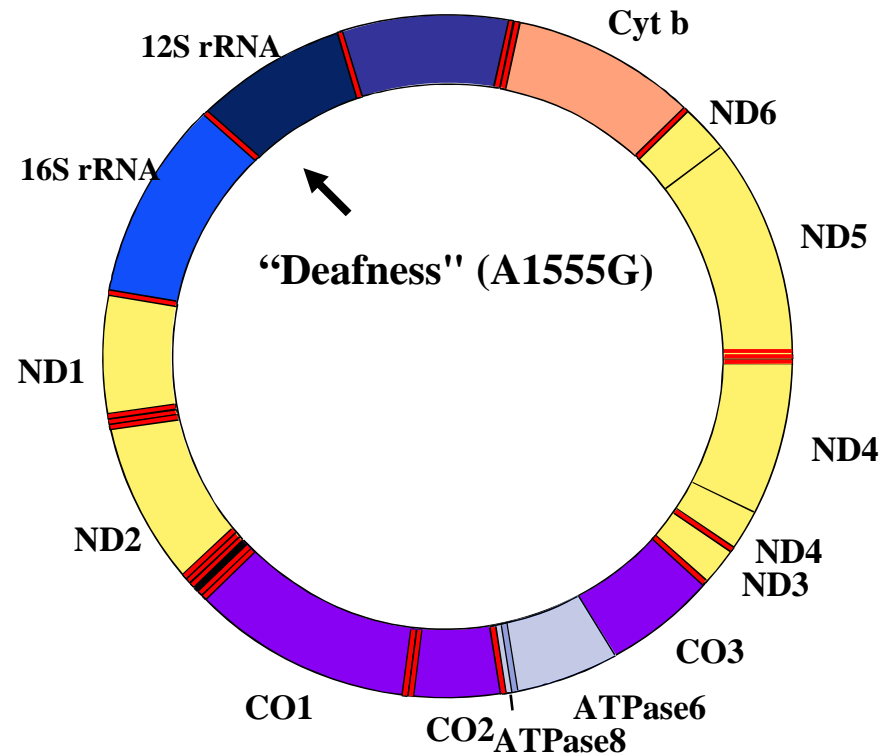
But they can also cause sensorineural hearing loss without goitre.

Often associated with temporal bone abnormalities such as Mondini dysplasia and/or Enlarged Vestibular Aqueduct.

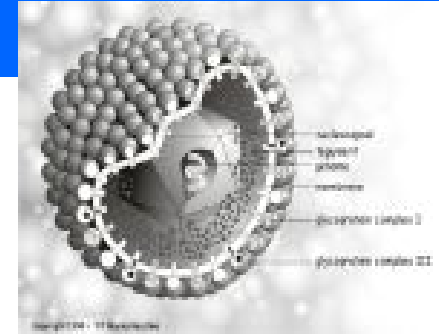
Accounts for 3-5% of congenital deafness.

The mitochondrial A1555G mutation

A “harmless” change in the mitochondrial DNA makes people much more susceptible to aminoglycoside induced hearing loss.



Cytomegalovirus (CMV)



- **A member of the herpes virus family**
- **CMV is found throughout all geographic locations and socioeconomic groups, and between 50% and 80% of adults in Australia are/have been infected.**
- **Most healthy people who are infected by CMV after birth have no symptoms.**
- **After infection, the virus remains latent in the body for the rest of the person's life.**

Cytomegalovirus (CMV)

- **Although it can be spread via sexual contact, it is most often transmitted through infected bodily fluids that come in contact with hands and then are absorbed through the nose or mouth of a susceptible person (eg. at childcare centres or schools).**

Cytomegalovirus (CMV) and hearing loss

- **CMV is the virus most frequently transmitted to a developing foetus.**
- **The incidence of primary CMV infection in pregnant women in the United States varies from 1% to 3%. Healthy pregnant women are not at special risk for disease from CMV infection. When infected with CMV, most women have no symptoms.**

Cytomegalovirus (CMV) and hearing loss

- **The developing foetuses may be at risk for congenital CMV disease if the mother has a primary CMV infection during the pregnancy.**
- **80% to 90% of children with congenital CMV disease will have complications within the first few years of life that may include hearing loss, vision impairment, and varying degrees of mental retardation.**

Cytomegalovirus (CMV) and hearing loss

- **CMV is a very common virus. Most of us have been infected by CMV. Although it can be spread by sexual contact, it is much more likely to spread via other routes.**
- **If CMV infection occurs during pregnancy the fetus/child might develop hearing loss**
- **We don't know the incidence of primary CMV infection in pregnant women in Australia**
- **We don't know the incidence of CMV-caused hearing impairment in Australia. This is one of the questions we also hope to answer.**

The aetiology sub-study

- **We will determine if the hearing loss is due to these most common factors:**
 - **Mutations in the connexin 26 gene**
 - **Mutations in the pendrin gene**
 - **The A1555G mtDNA mutation**
 - **Cytomegalovirus infection during the pregnancy**

What is needed to do the tests?

- **The study of the connexin 26, pendrin and A1555G genes can be done on any tissue sample from a child.**
- **Detection of the presence of CMV virus must be done on a sample taken at the time of birth. We do not know if the infection occurred during the pregnancy or after the birth if sample taken at a later time .**

What do we ask for?



- **We need a tissue sample from the child**
- **We ask for permission from the parent/guardian to access the child's Guthrie blood card.**
- **This is the blood that was taken following a heel prick shortly after birth to screen for a number of conditions.**
- **Guthrie blood spot cards are stored for a period of time according to your State's services protocol.**

Why the Guthrie blood card?

- **We don't have to get another tissue sample from the child.**
- **More importantly, it was taken at the time of birth and therefore allow us to determine if the child was infected with CMV during the pregnancy.**

Guthrie blood spots

- **It is important to tell the parents that the only use of the blood spots is to try to determine the cause of their child's hearing impairment, by testing for connexin 26, pendrin and the A1555G mtDNA mutation as well as for congenital CMV infection.**
- **We will not use the DNA in other tests. We can't determine paternity/maternity.**
- **We only use a small proportion of the blood. The rest will be available for future tests if needed/wanted.**

Additional information

- **Some children will already have had tests for genetic causes of hearing loss, especially for connexin 26 mutations. We are testing for additional factors. There will be very few children, if any, that will have had connexin 26, as well as pendrin, A1555G and CMV testing**
- **In some children the cause of their hearing loss has been determined, eg. by finding causative mutations in the connexin 26 gene. In that case we are still interested in accessing the Guthrie blood spot so that we can determine the true frequency of congenital CMV infections.**

Additional information

- **We will not be able to determine the cause of deafness in all children. In a large proportion of cases the hearing loss will be due to other genetic or environmental factors.**
- **We only need access to the Guthrie blood spot. No additional samples will be collected and no additional appointments are required.**

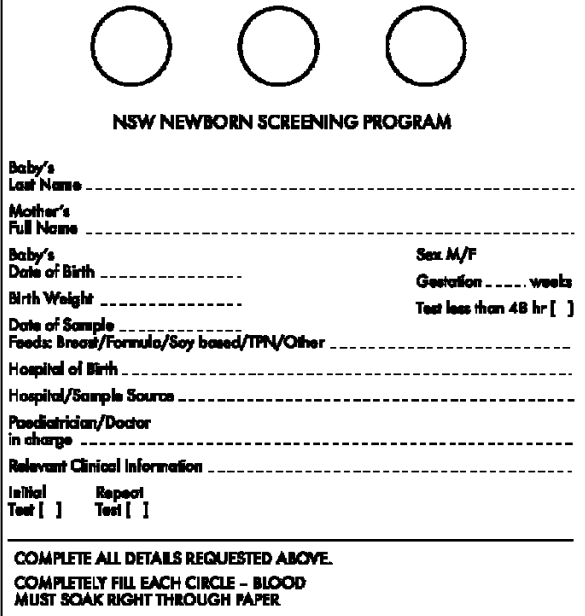
Additional information

- **The families do not have to take part in the Aetiology Substudy.**
- **If they want to be part of the study they must read and understand the information sheet and sign the consent form.**
- **The results of the Aetiology study will only be available to the individual families and the senior researchers. Names will not be used during analysis of the samples.**
- **There are no costs associated with participating in the genetic study**
- **The analyses will take many months to complete.**

The Consent

We cannot access the Guthrie blood cards without signed consent from the parents/guardians.

We also need information of when and where the child was born (to be able to find the Guthrie blood cards)



The form is titled "NSW NEWBORN SCREENING PROGRAM" and features three circles at the top for blood samples. It contains several fields for data entry, including: Baby's Last Name, Mother's Full Name, Baby's Date of Birth, Sex M/F, Birth Weight, Gestation (weeks), Date of Sample, Feeds (Breast/Formula/Soy based/TPN/Other), Hospital of Birth, Hospital/Sample Source, Paediatrician/Doctor in charge, and Relevant Clinical Information. At the bottom, there are checkboxes for "Initial Test" and "Repeat Test".

NSW NEWBORN SCREENING PROGRAM

Baby's Last Name

Mother's Full Name

Baby's Date of Birth Sex M/F

Birth Weight Gestation weeks

Date of Sample Test less than 48 hr []

Feeds: Breast/Formula/Soy based/TPN/Other

Hospital of Birth

Hospital/Sample Source

Paediatrician/Doctor in charge

Relevant Clinical Information

Initial Test [] Repeat Test []

**COMPLETE ALL DETAILS REQUESTED ABOVE.
COMPLETELY FILL EACH CIRCLE - BLOOD
MUST SOAK RIGHT THROUGH PAPER.**

Issues

Ethical conduct:

**Head of Department
Ethics and Research Department
Human Research Ethics Committee
The Royal Children's Hospital
Parkville, Melbourne 3052**

Telephone: (03) 9345 5044

Study: HREC Project Number 28055

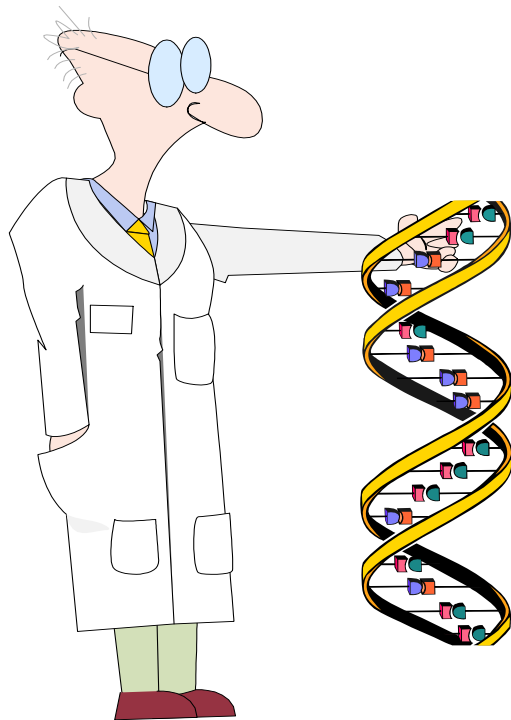
Issues relating to aetiology results

Discuss issues with:

**Dr Patricia Mutton
The Deafness Centre
Children's Hospital at Westmead
Sydney**

Telephone :02-9845 2139

We can also suggest other independent clinical geneticists or genetic counsellors at genetic services in Sydney, Brisbane or Melbourne.



Thanks for listening