usherkids uk

Genetics

Emily Rees
Genetic Counsellor, Cardiff

Usher Kids Family Info Day
10th October

Genetics Session

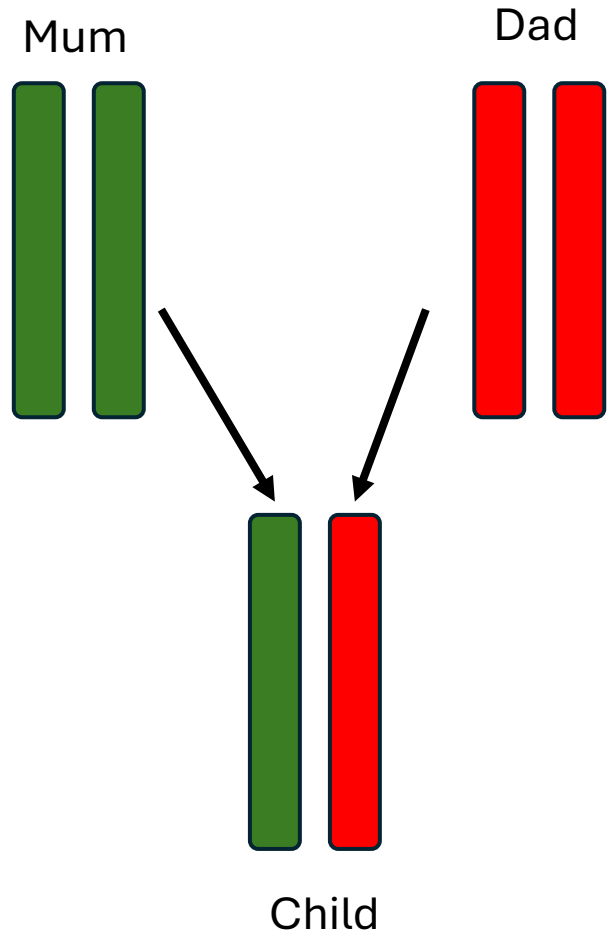
Emily Rees

Genetic Counsellor – AWMGS (Swansea)

Basic introduction to genetics

- Genes are sections of DNA that provide our body with instructions.
- We have over 20,000 genes, each have a key role within the body.
- Our genes are like a series of letters that our body reads.
- Most of our genes come in pairs, as we get one copy from each parent.





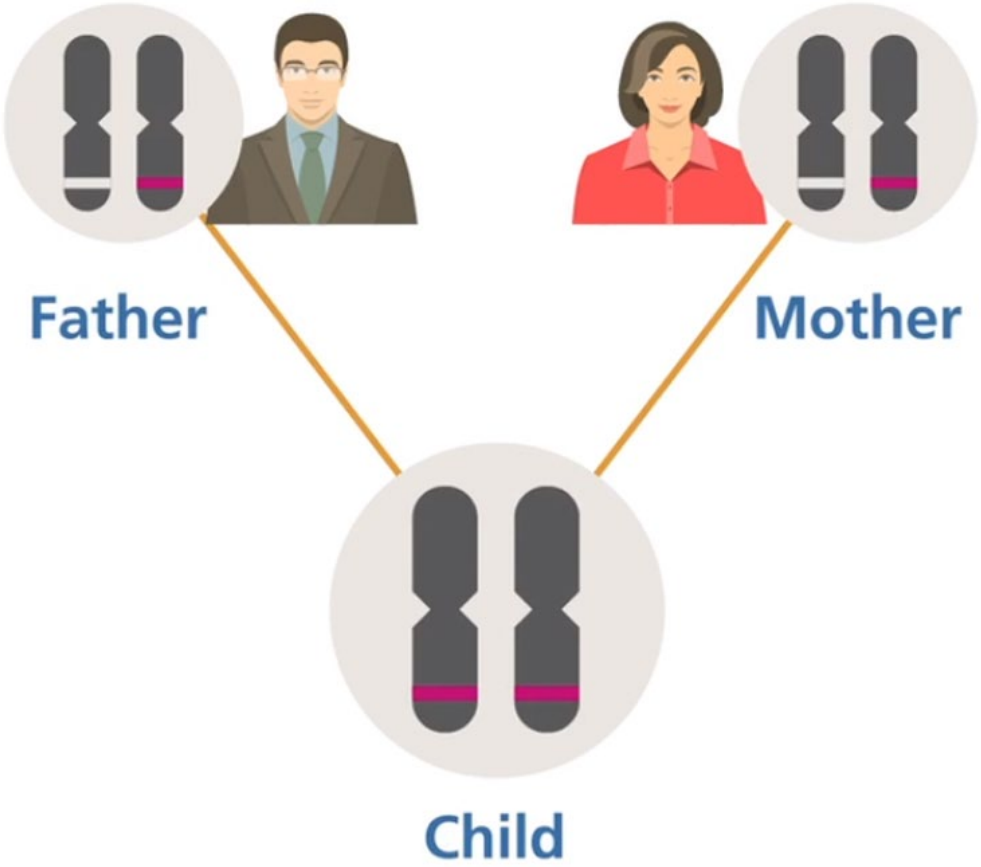
Inheritance pattern of Usher Syndrome

- Usher syndrome is inherited in an autosomal recessive pattern.

This means that both copies of a gene needs to be ‘non-working’ for someone to develop clinical features.

- This refers to a change/alteration/spelling mistake in the underlying code of the gene.
- The body can no longer read that gene and provide the instruction and therefore it becomes non-working.

- Recent review: 16 genes, involved in the function of inner hair cells and maintenance of photoreceptor cells in the retina.

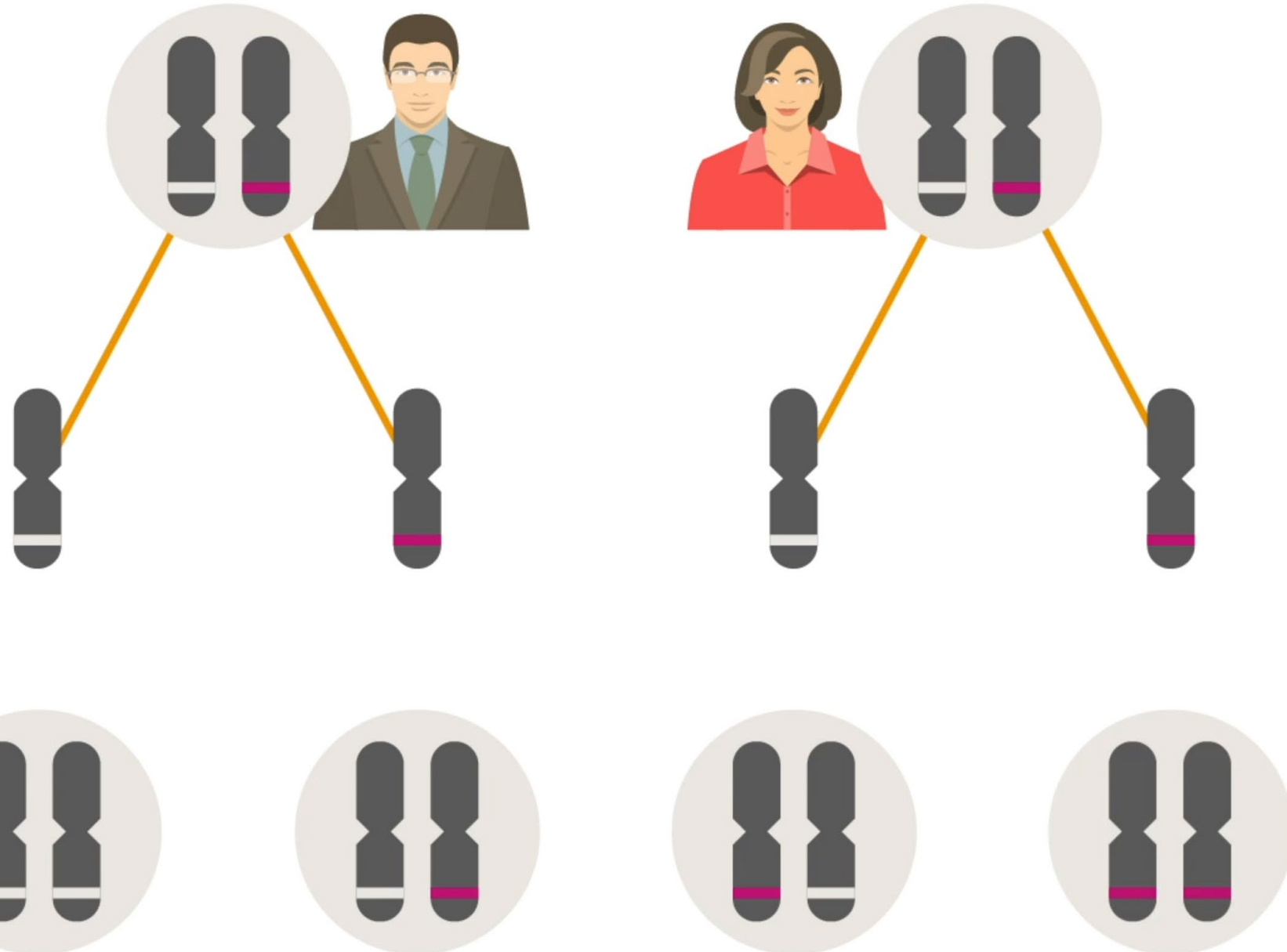


- Parents tend to be ‘carriers’ of autosomal recessive conditions.
- They have one working copy and one non-working copy.
- A carrier does not develop clinical symptoms due to having a working copy of the gene.
- Both parents must pass on both non-working copies.

Parents

Gametes

Conception



Autosomal recessive inheritance and future children

For a person with Usher Syndrome, they will pass on one copy of their non-working gene to any future children.

When they and their partner come to have children, we do not routinely offer their partner a carrier test. This is because being a carrier is rare.

There are some exceptions, for example, if their partner had a personal family history of Usher Syndrome or certain genes.

- Best to discuss this with your local Clinical Genetics.

Types of Usher Syndrome

- Classically Usher Syndrome is divided into 3 subtypes based on the severity, onset of hearing loss and presence of vestibular dysfunction:

USH I

Most prevalent form
- Congenital and profound hearing loss
- Early onset retinitis pigmentosa (RP) (childhood)
- Vestibular dysfunction

USH II

- Moderate to severe hearing loss from birth/early childhood
- Onset of RP tends to be in adolescence/early adulthood.
- The progression is less predicable.
- No vestibular dysfunction.

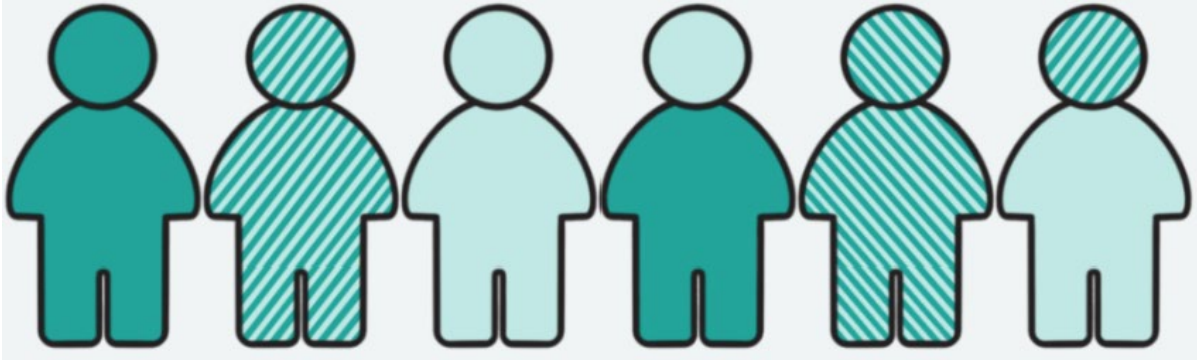
USH III

Least common form
- Symptoms can present at different ages and progress at varying rates.
- Progressive hearing loss in childhood/adolescence
- RP
- In some cases vestibular dysfunction.

Variable expressivity of Usher Syndrome

Expressivity: how a condition affects different people.

Many genetic conditions show different symptoms or severity in different people. This is called variable expressivity.



For Usher Syndrome

People (even in the same family) who carry same genetic alterations in the same gene, can experience significantly different timing, progression, and severity of vision loss, hearing impairment, and balance issues.

Genetic testing
- types of testing, report and possible results

Genetic testing for Usher Syndrome

Different pathways in which genetic testing can be offered:

- Hearing loss genetic testing
- Retinal dystrophy genetic testing

The initial testing tends to be a very broad genetic test, looking at lots of different genes associated with hearing loss/retinal dystrophies.

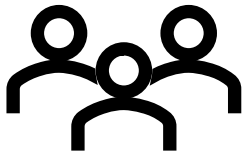
There are different types of broad genetic testing, depending on the pathway:

- Whole exome sequencing (WES), whole genome sequencing (WGS) and panel testing.

Carrier testing for parents

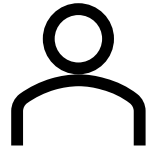
Initial genetic test:

Trio/duo testing



- Parental testing included as part of the analysis pathway.
- Likely that the laboratory would test the parents for the gene alterations found in their child, to help with interpretation.

Singleton testing



- Parental testing was not done.
- Parents are referred into Clinical Genetics to discuss carrier testing.
- Tends to be a shorter turn around time for results due a targeted test.
- Clinical Genetics can discuss carrier testing with you:

- If the timing is right?
- What would the information be helpful for?

RETINAL DYSTROPHY MUTATION ANALYSIS REPORT

NAME: [redacted]
DATE OF BIRTH:
SEX: Female
NHS No:
YOUR REF:
OUR REF: 10002008.712

ADDRESS: [redacted]

DATE: 17-Jul-2012

REASON FOR REFERRAL: [redacted] has gross motor delay, profound hearing loss and rod cone dystrophy and has been given a clinical diagnosis of Usher Type 1 syndrome. NGS analysis has been requested.

RESULTS:

NAME (DoB)	CLINICAL STATUS	RESULT
[redacted]	Usher Type I syndrome	**MYO7A** c.6025delG Heterozygous **MYO7A** c.4115T>G p.(Val1372Gly) Heterozygous **MYO7A** c.4589C>T p.(Ser1530Leu) Heterozygous **SEE COMMENTS**

COMMENTS: [redacted]'s DNA sample was screened for 105 genes associated with retinal dystrophy by next generation sequencing. Three heterozygous MYO7A changes c.6025delG, c.4115T>G p.(Val1372Gly) and c.4589C>T p.(Ser1530Leu) were identified (OMIM 276903), which have all been confirmed by Sanger sequencing.

c.6025delG has previously been reported as a homozygous and compound heterozygous mutation in Usher Type I patients (Gerber *et al*, 2006, Roux *et al*, 2011) and is predicted to disrupt normal translation of the MYO7A gene.

c.4115T>G p.(Val1372Gly) has not been previously reported in patients with Usher Type I patients nor has it been reported as a normal polymorphism*. The valine at 1372 is highly conserved across several species and *in silico* data indicates that this variant may have a detrimental effect on the MYO7A protein. c.4589C>T p.(Ser1530Leu) has previously been reported in patients with Usher type I syndrome; however it was considered to be benign (Roux *et al*, 2006; Neveling *et al*, 2012). The serine at position 1530 is not well-conserved across mammalian species and *in silico* analysis suggests that c.4589C>T p.(Ser1530Leu) is unlikely to have a damaging effect on the MYO7A protein.

[redacted] is therefore possibly a compound heterozygote for two MYO7A mutations, which may account for her clinical diagnosis of Usher Type I syndrome. However, in the absence of functional studies, the clinical significance of c.4115T>G p.(Val1372Gly) and c.4589C>T p.(Ser1530Leu) remains uncertain. In order to determine if these two changes are *in cis* or *in trans* with c.6025delG, we would recommend testing of [redacted] parents for these changes, if samples are available.

For a list of additional variants of unknown clinical significance, detected during this analysis, please refer to the technical report (10002008.712T).

NOTES: A total of 105 genes have been targeted using Agilent SureSelect Custom Design and sequenced on an ABI SOLiD 5500XL system. Please refer to the technical report (ref: 10002008.712T) for details of coverage and quality of data. Please note this method of analysis is not capable of detecting exonic or whole gene deletions. Mutation nomenclature follows HGVS guidelines (www.hgvs.org) with nucleotide 1 counted as the first nucleotide of translation initiation codon using Genbank accession numbers listed in the technical report (ref: 10002008.712T) and therefore nomenclature and exon numbering may differ from that given in the quoted literature. Reference sequence for MYO7A is NM_000260.3

REFS: Gerber et al (2006) USH1A Chronicle of a Slow Death Am.J.Hum.Genet. 78:357; Roux et al (2011) Four-Year Follow-up of Diagnostic Service in USH1 patients Invest. Ophthalmol. Vis. Sci. 52 :4063-4071 Roux et al (2006) Survey of the frequency of USH1 gene mutations in a cohort of Usher patients shows the importance of cadherin 23 and protocadherin 15 genes and establishes a detection rate of above 90% J Med Genet. Sep;43(9):763-8; Neveling et al (2012) Next-generation genetic testing for retinitis pigmentosa.Hum Mutat.Jun;33(6):963-72;
*http://evs.gs.washington.edu/EVS/ & http://www.ncbi.nlm.nih.gov/projects/SNP/

PREPARED & AUTHORISED:

Types of results

1. A genetic cause for the clinical symptoms is found.
2. A genetic cause is not identified.
3. Variant of uncertain significance (VUS) is found.
4. Incidental finding (IF) is found.

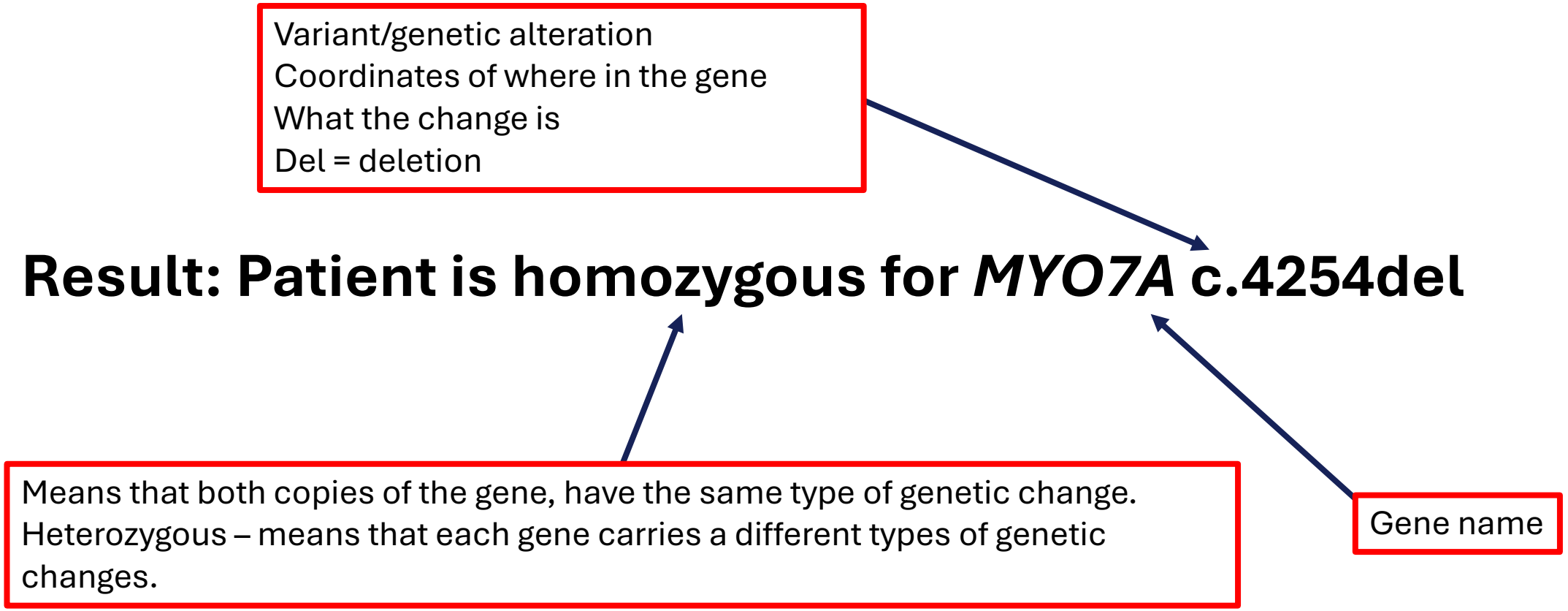
Variant of uncertain significance

A variant of uncertain significance is a variant/change that sits in the grey area. In other words, it could be causing the condition, but it also might not be, and we don't know for sure how significant it is.

How genetic changes are classified:



What information is on a genetic report



Navigating conversations

Managing the uncertainty

- Families are not alone in dealing with this,
- Hope that we better understand Usher Syndrome as our testing expands and we make more diagnoses

How to have these?

- Support from Clinical Genetics to help
- Having conversations during normal day to day activities
- Answer questions as they come, in an age-appropriate manner
- It is okay to not have all the answers
- Not alone in having to have these conversations