GENETIC TESTING:
THE USH2A GENE

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The USH2A gene

- The *USH2A* gene is very large (73 exons)
- Defects (Mutations) in the USH2A gene are responsible for
  - 60-90% of the cases with Usher syndrome type II
  - 5-10% of the cases with non-syndromic retinitis pigmentosa
- The *USH2A* gene encodes at least 2 different USH2A proteins, also called Usherin
USH2A protein isoforms

**Isoform A**

- LamG/
- LamNT
- EGFLam
- FN3

**Isoform B**

- LamG/
- LamNT
- EGFLam
- FN3
- LamG
- FN3
- FN3

+ EX 71
From DNA to mRNA to Protein

DNA

exon

intron

transcription

Pre mRNA

splicing

mRNA

translation

Protein
DNA diagnostics – step 1

Normal

Early Stop

Code shift: Splice Defect, DNA missing, Additional DNA DNA missing no code shift

Shorter or no protein

Protein partly normal partly abnormal

Protein part missing
Change of 1 amino acid: effect?

Change in 1 Building block

Common in Usher syndrome cases and common in the general population
How to determine that these changes are likely to be deleterious?

- Big change in the chemical characteristics?
- Affects an amino acid that is conserved in evolution?
- Is predicted to change the structure of the protein
- Previously found in a person with Usher syndrome
- Very rare in the general population
- Guidelines by ACMG, expert evaluation teams
- Test family members
Testing family members

M = Mutation
N = Normal

Segregation with USH

No segregation with USH
Tests needed to prove the deleterious effect

Variants in non-coding DNA
Summary

- Protein coding regions of the USH2A gene and flanking regions are analyzed first in DNA diagnostics.
- DNA Changes that lead to the change of only 1 amino acid in the USH2A protein are often difficult to interpret.
- The ‘next step’ in DNA-diagnostics is the analysis and interpretation of variants in non-coding DNA.