Summary for Family Day: Diagnostics and Genetics of Usher Syndrome #USH2018

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Speakers from Diagnostic Session

- Bill Kimberling (Omaha, US)
- Anne-Francoise Roux (Paris)
- Isabelle Audo (Paris)
- Adam Dubis (London)
- Aziz El Amraoui (Paris)
- Margaret Kenna (Boston, US)
- All additional speakers who touched on treatment based on a specific diagnosis

Seven steps to treatment for an Inherited Disease (Bill Kimberling)

- Find the disease gene
- Correlate genotype with phenotype
- Find or develop animal models
- Elucidate the disease mechanism
- Find or develop an effective treatment in the animal model
- Screen the human population to identify people who might benefit
  - **Genetic testing**
- Test the treatment in these people
  - Orphan diseases, small numbers, so build registries

Usher Syndrome

(3-6% of childhood deafness)

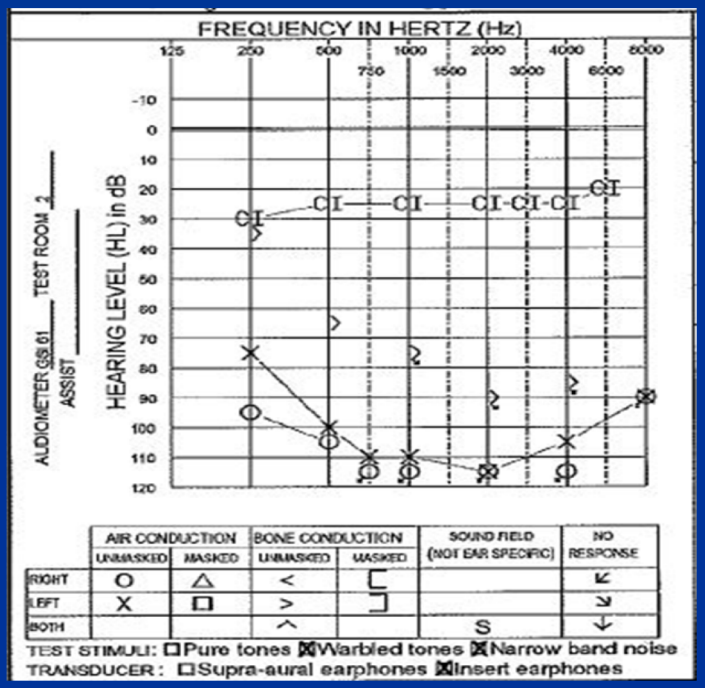
	Hearing Loss	Vestibular System	Retinitis Pigmentosa
Type I	Congenital profound	Congenital balance problems; absent responses	Onset pre-puberty
Type II	Congenital mild-severe sloping	Normal	Onset in teens-20s
Type III	Progressive later onset	Variable, often progressive balance problems	Variable onset

Usher Genes

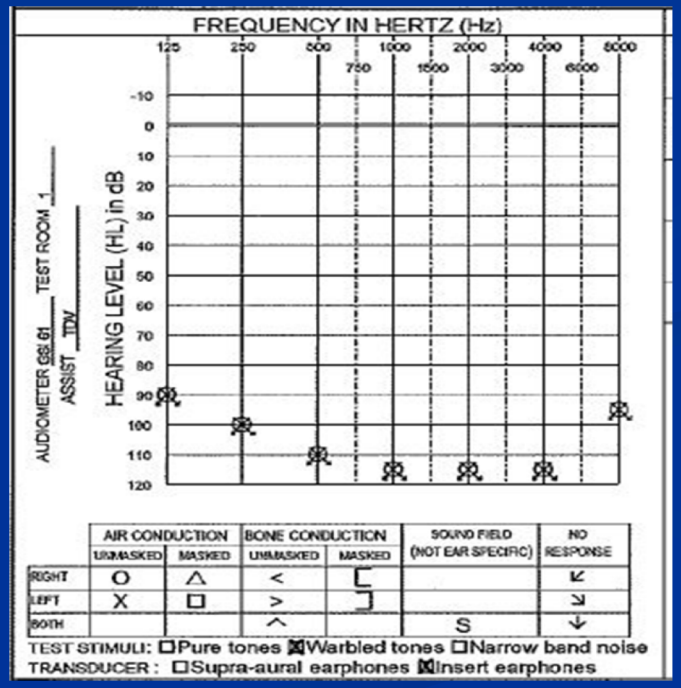
Locus name	Genome Locus	Gene name	Protein Product
USH1B	11q13.5	MYO7A	Myosin 7A
USH1C	11p15.1-p14	USH1C	Harmonin
USH1D	10q22-q22	CDH23	Cadherin 23
USH1E	21q21.1	Unknown	Unknown
USH1F	10q21.1	PCDH15	Protocadherin 15
USH1G	17q25.1	USH1G (SANS)	USH Type 1G protein
USH1J	15q25.1	CIB2 (may or may not be USH)	Calcium and integrin binding protein 2
USH2A	1q41	USH2A	Usherin
USH2C	5q13	ADGRV1	G protein-coupled receptor
USH2D	9q32-34	WHRN (DFNB31)	Cask-interacting protein
USH2A modifier	10q24.31	PDZD7	PDZD7
USH3A	3q21-q25	CLRN1	Clarin-1
USH3B	5q31.3	HARS	

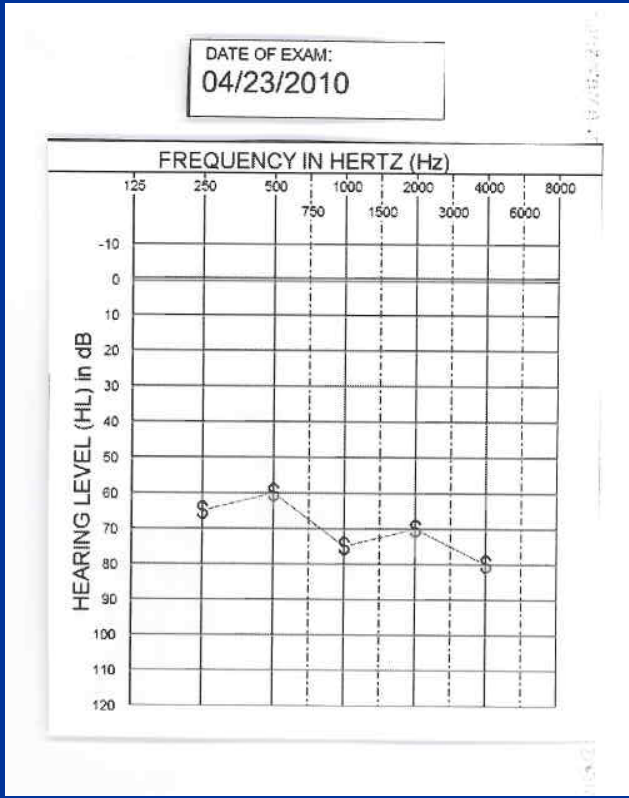
Which genotype?

GJB2 (Connexin 26)



MYO7A (USH1B)





USH1B –atypical presentation

-2 year old with 2 novel MYO7A mutations
-Better hearing than would be expected for the genotype
-Patient walked at 16 months
-Hearing loss progressed over several years into the profound range
-Patient received a cochlear implant at age 6
-Genetic testing key to making the diagnosis of USH1, not USH2

History- from Bill Kimberling's talk

In the past

Now

Timeline of Usher genetic testing

-Only research testing initially available
-Common mutations in single genes
-Many private, novel, denovo mutations
-Whole single genes
-Deafness sequencing panels
-Vision sequencing panels
-Usher specific panels
-Whole exome and whole genome

Why knowing the correct gene helps

- Better understanding of USH genes
  - How they interact
  - How they affect hearing and vision
  - Some mutations affect ONLY hearing OR vision
- If you change one gene, what will the other related genes do?
- Are there genes we still don't know about?
- In some cases, such as USH2A, there are many different versions of the same gene
- Do you actually have USH?

Other genes that cause deafness and blindness

- Are these USHER genes?
- Is all deafness and blindness considered USH?
- Genes affecting the cilia
- Genes affecting microtubules
- What can we learn from other organ systems?
  - Gut (Matt Tyska, Nashville)
  - Skin (Fred Schwaller, Berlin)
  - Are other organs systems affected in USH?

Better genetic testing

- Find the second or even third mutation
- Deep intronic and splicing mutations
- Is it just simply dominant or recessive?
  - Could single mutations be disease causing?
- Two possible different genetic causes for hearing and vision loss?
- Can build registries based on most up to date knowledge of genetics and phenotype

How does knowing the gene help treatment?

- Treatment will be related to the gene and stage of USH
- When are the genes expressed?
- What type of mutation is present?
- Gene augmentation
- Gene replacement
- Gene modification
- Pharmacologic interventions
- Photoreceptor or retinal grafts

When to treat

- Confirm the gene(s) causing the clinical symptoms
- Different genes are expressed at different times in development
- When to intervene?
  - For the hearing loss?
  - For the vision loss?
- We can now test prenatally for the genes
  - Should we be treating the fetus?

Danke!
Thank you!

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