Usher Syndrome: Why a definite diagnosis matters

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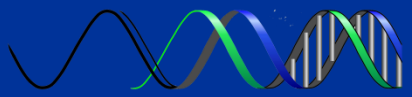

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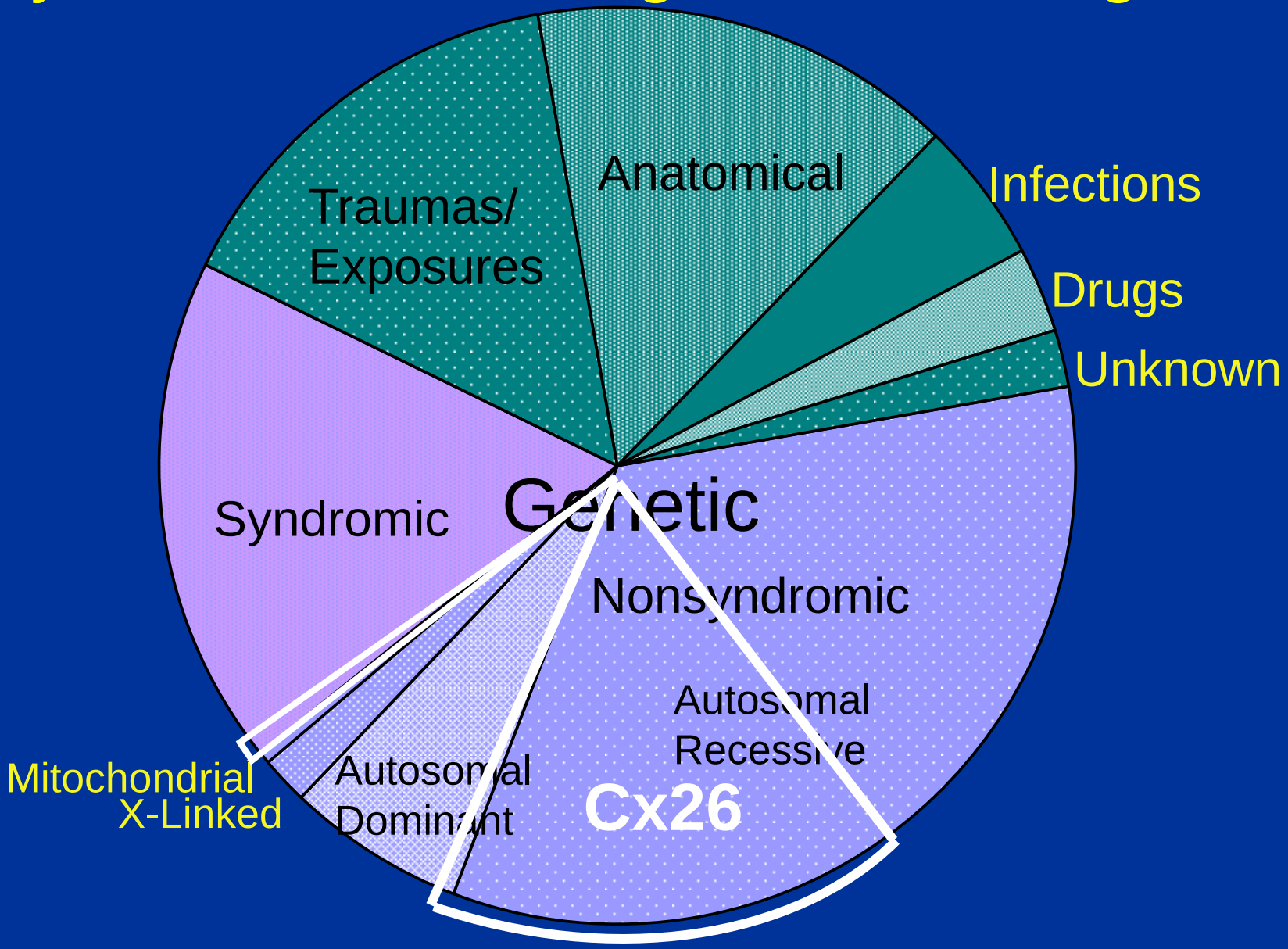
Disclosure

I have no actual or potential conflicts of interest in relation to this program/presentation

Hearing Loss at Birth

- News is overwhelming
- Often the diagnosis is hard to believe, as you can’t see it or touch it
- Many tests are needed to confirm the diagnosis
- Many interventions are needed to insure the child develops good speech and language

Major Causes of Congenital Hearing Loss



Genetic causes of hearing loss

- Over 50% of hearing loss is genetic
- 75% of genetic hearing loss is recessive
- Most parents say that there is no childhood onset hearing loss in their family (which is usually true of a recessive disease)
- So how could it be genetic?
- And even if we can figure out the genetic cause, what can we do about it? If we can't do anything about it, why bother to look?

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 building registries might help

Some syndromes easier to diagnose

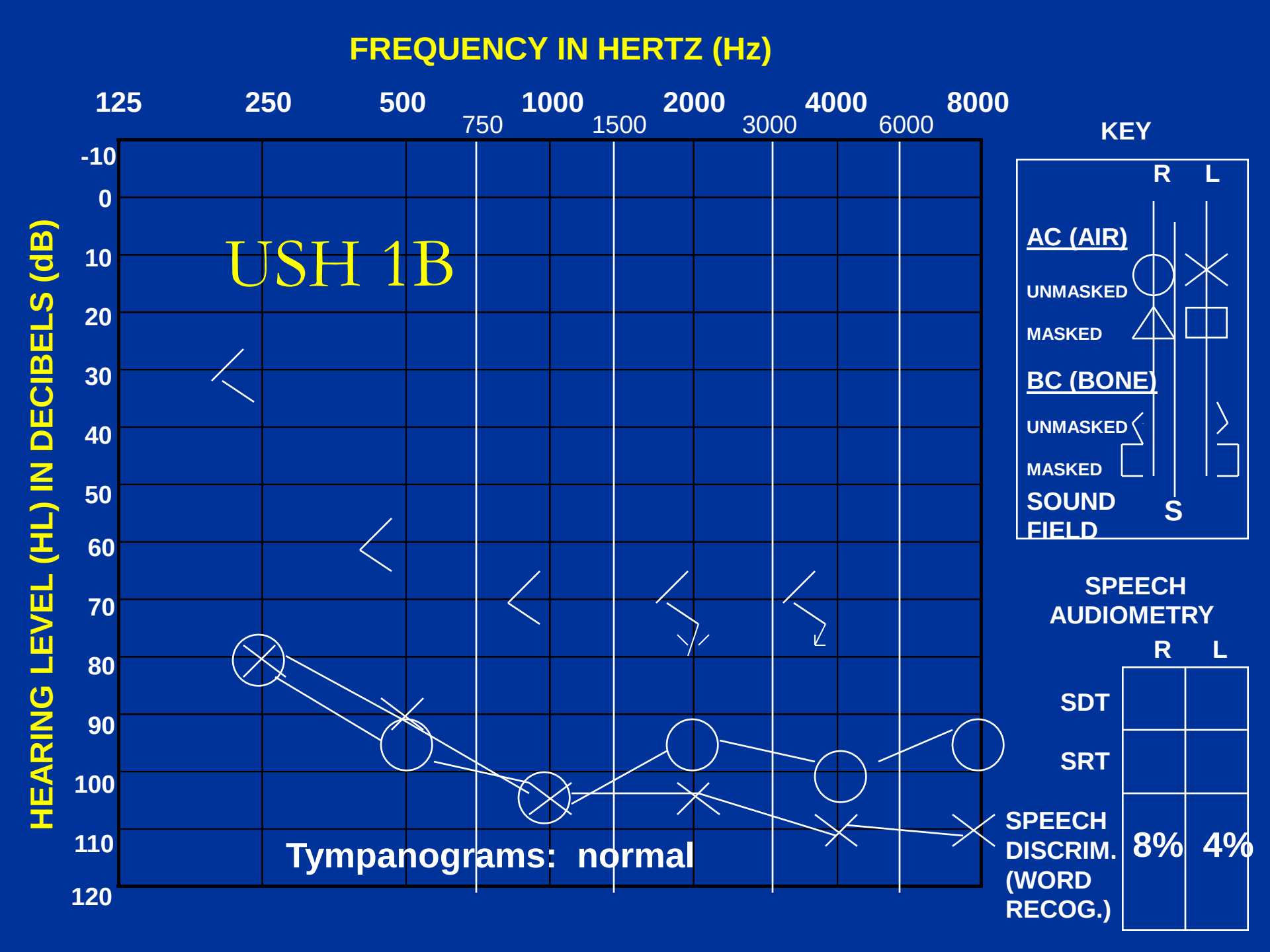
- Pendred's syndrome: patients have enlarged vestibular aqueduct on CT or MRI
  - SLC26A4 (PDS) gene test available
- Jervell and Lange-Nielsen (Long QT) diagnose by EKG
- Stickler, Waardenburg, BOR, Treacher-Collins have characteristic physical or non-genetic lab findings
- Usher patients look normal

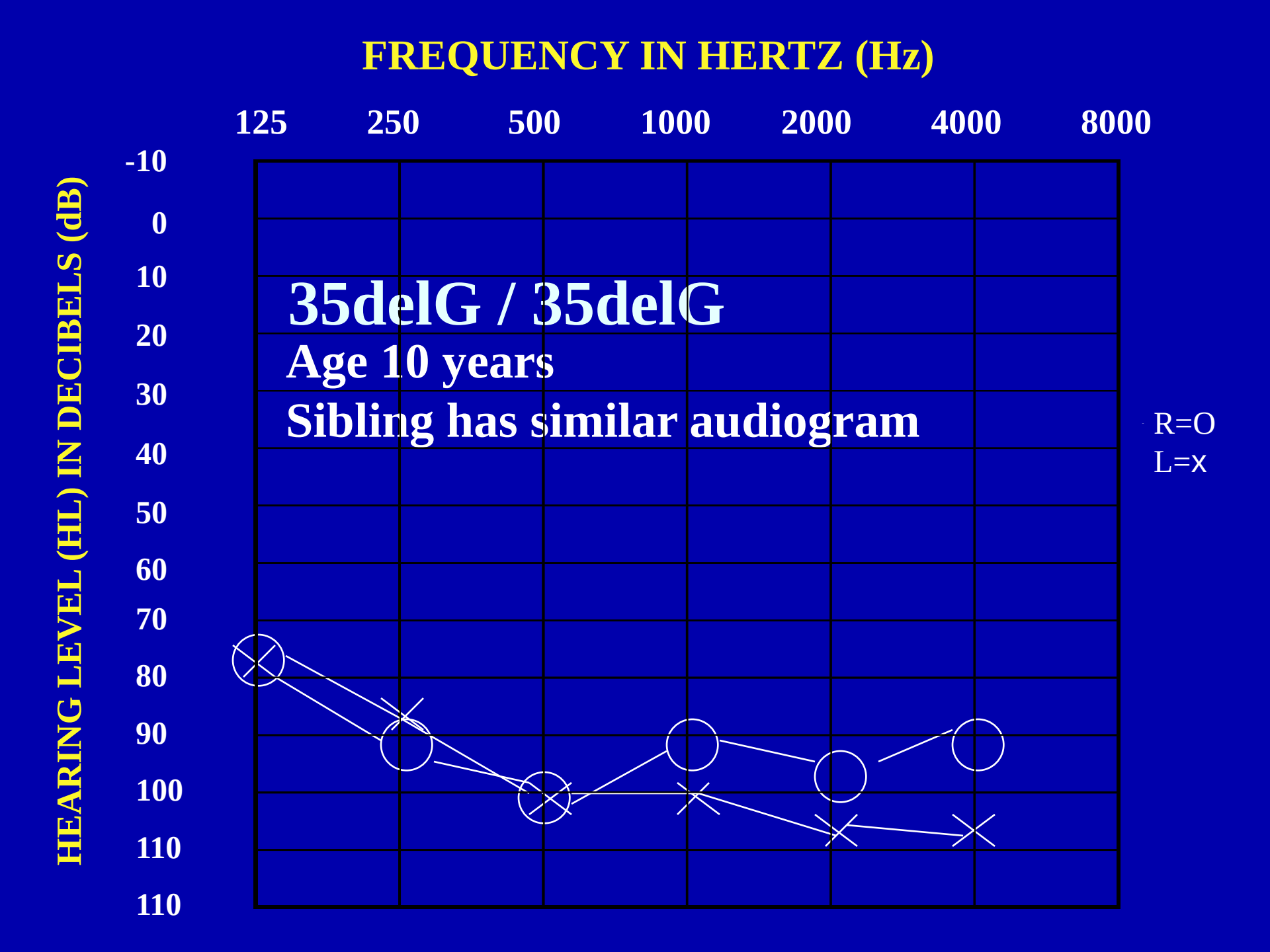
Why Does USH seem so rare?

- Diagnosis still made late
  - Much later than Connexin 26
- Limited availability of genetic testing
  - Few clinical labs doing testing
  - Insurance does not always pay for testing
  - Physicians not always aware testing is available
- Heterogeneous presentation
- Later onset of visual loss than hearing loss
- Retinal findings difficult to determine on physical exam in young children
- Prevalence of balance abnormalities poorly studied

Why figure out the genetics?

- All of the non-syndromic patients look the same early on
- No distinguishing facial features
- No characteristic audiograms (many audiograms look the same)
- Varying management depending on the gene(s)
- Varying outcomes depending on the gene(s)


FREQUENCY IN HERTZ (Hz)
125
250
500
750
1000
1500
2000
3000
4000
6000
8000
HEARING LEVEL (HL) IN DECIBELS (dB)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
USH 1B
Tympanograms: normal
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
SPEECH AUDIOMETRY
R
L
SDT
SRT
SPEECH DISCRIM. (WORD RECOG.)
8%
4%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70
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110
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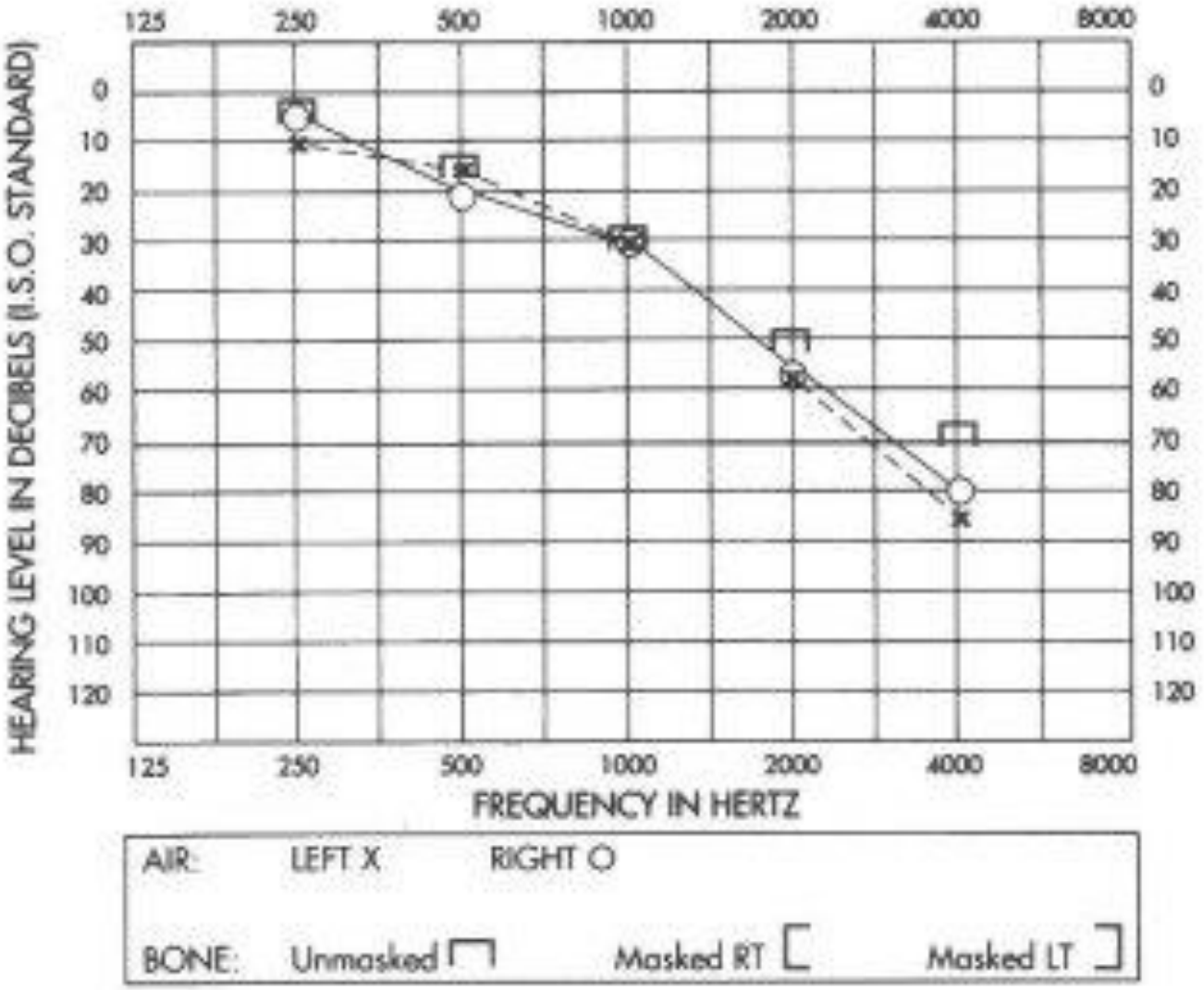
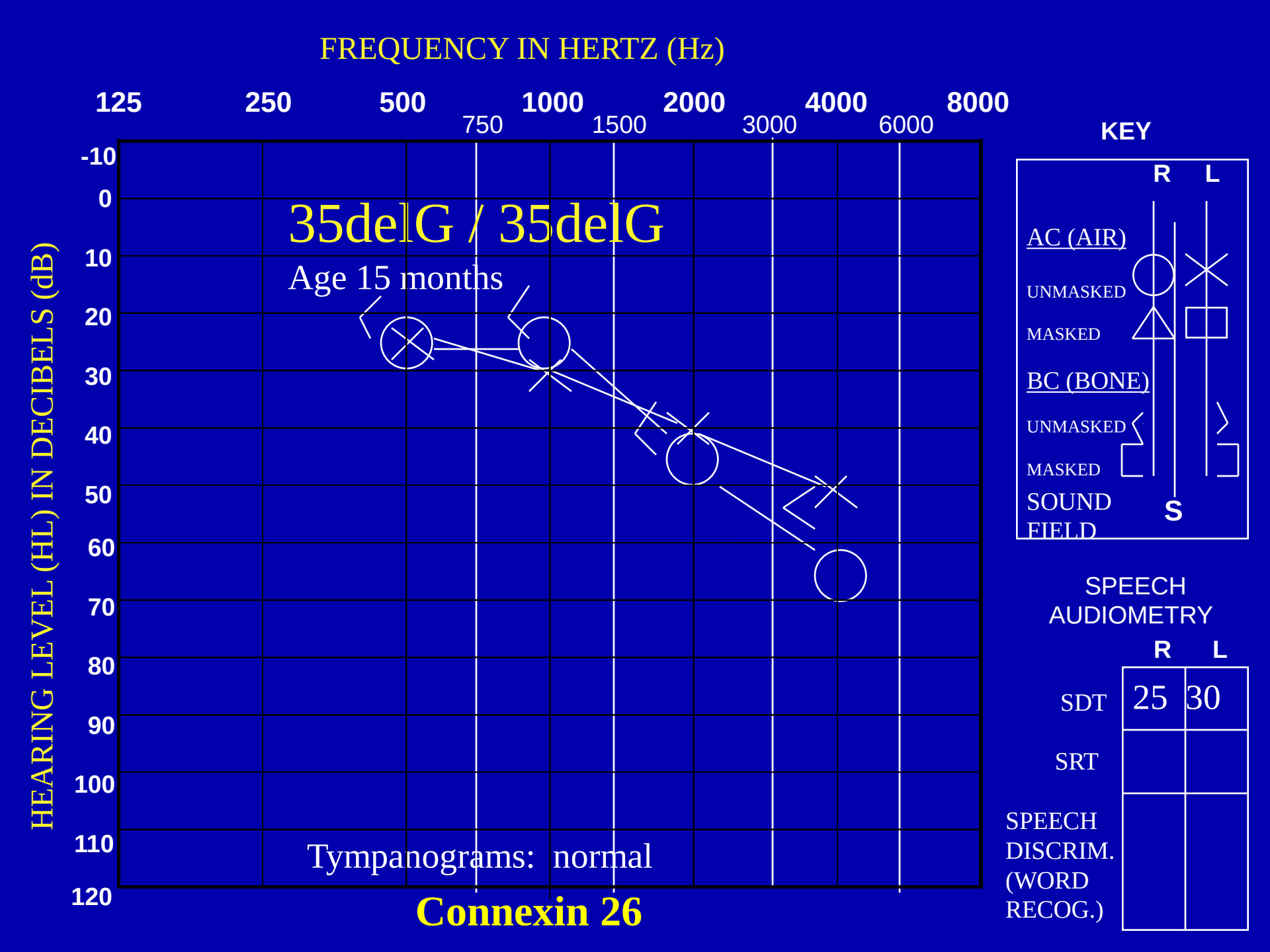
35delG / 35delG
Age 10 years
Sibling has similar audiogram
R=O
L=x

USH 2A



An example of a mild to severe sensorineural hearing loss in both ears.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35delG / 35delG
Age 15 months
Tympanograms: normal
Connexin 26
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
SPEECH AUDIOMETRY
R
L
SDT
25
30
SRT
SPEECH DISCRIM. (WORD RECOG.)

Incidence of Usher Syndrome

- 3-6.2/100,000 general population
- 3-6% of all children with hearing loss
  - Up to 10% of all congenitally deaf children
- 50% of deaf-blind adults
- 0.6-28% deaf population
- Still late diagnosis
  - Limited availability of genetic testing
  - Heterogeneous presentation
  - Later onset of visual loss than hearing loss
  - Retinal findings difficult to determine

How Common is Usher Syndrome?

- A rare disease is considered to be less than 200,000 Americans
- Estimated 16,000-45,000 individuals in the US with USH
- Carrier frequency for one copy of an USH gene is 1/70 (varies by gene, mutation and population)

First rule out non-Usher diagnoses

- Congenital CMV, toxoplasmosis, syphilis
  - Congenital infectious causes
- Auditory dyssynchrony…probably not USH
  - Although may be genetic, vision not usually involved
- Anatomical abnormalities…probably not USH
  - USH patients usually have normal CT and MRI
- Other genetic causes..Cx26 is the most common recessive genetic cause of SNHL
- Occasionally find more than one cause

What are other causes of both hearing and vision loss?

- Alström: progressive vision and hearing loss, cardiomyopathy, obesity, type 2 diabetes, short stature, acanthosis nigricans
- Norrie Disease-blindness in male infants and progressive hearing loss
- Mitochondrial diseases
- Congenital rubella
- Congenital cytomegalovirus
- Extreme prematurity
- Two different causes for hearing and vision loss

Genetic causes of later onset and progressive HL

- Dominant genes associated with presbycusis
- GJB2 (Connexin 26): 50% progression rate
- SLC26A4 (PDS): Associated with enlarged vestibular aqueduct
- Turner's syndrome (XO): mid-frequency dip
- Otosclerosis: later onset and progressive
- **Usher's syndrome, types 2 and 3 esp.**
- Mitochondrial genes: may cause HL with or without aminoglycosides

Testing for Usher Syndrome

- Clinical diagnosis
  - Hearing loss
  - RP
    - Electroretinography
  - Balance
  - ??/olfaction, cognition
- Genetic diagnosis
  - Single gene testing
  - Multiple gene testing

Why pursue genetic testing for USH?

- Recessive syndrome so usually no family history
- Find out what caused the hearing loss
  - Symptoms alone cannot exclude the diagnosis
    - Balance, age at walking
    - Vision, “normal” eye exam
    - Degree of hearing loss
- Find out what did not cause the hearing loss
- Plan for the future, for other children
- Talk to others with same condition
- If find a definite genetic cause
  - Can apply current therapy
  - May qualify for future therapy/research

Why not pursue genetic testing for Usher Syndrome

- Usher diagnosis seems unlikely
  - Normal balance and vision so must not be Usher
  - No one in the family has it
- We aren't planning to have any more children
- Expensive and maybe insurance won’t cover
- Results will be inconclusive
- No intervention that makes it better or stops progression
- Anxiety
  - Fear of the unknown
  - Fear of the known
  - Parents or patients think they are not smart enough to understand the testing or the results

What if people do not want to get tested?

- If adults, explain why/why not and let them decide
- If parents, trickier.
  - If no standard intervention then testing elective
  - Once interventions are established that improve/stabilize condition then makes it a thornier question

Genetic Testing for Usher Syndrome

- Conservative approach:
  - HL with retinal abnormalities (positive ERG test or pigmentary changes)
- Less conservative approach:
  - Profound congenital hearing loss with delayed walking
- Even less conservative approach
  - Test children with bilateral hearing loss if Cx26/30 negative and CT/MRI normal

Genetic Testing

- Selected mutations or genes
- NGS
- Whole exome
- Whole genome
- Who will pay for it
- Who will order it
- Who will explain it

Future Directions

- Phenotype-genotype correlation
  - Hearing
  - Balance
  - Why deaf before blind?
  - Other clinical findings; olfaction, brain size and development
  - Response to therapy
  - Vestibular, CI, hearing aids
  - Other interventions: Vit A, Omega 3, light protection

Thank You!

Our entire planning committee, esp. Krista
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NIDCD-first Cx26 studies
NIDCD, NEI , National Center for Advancing Translational Science, this Symposium
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Dept. of Otolaryngology and Communication Enhancement

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