Usher Syndrome: When to Suspect it and How to Find It

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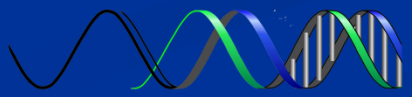

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Disclosure

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

This presentation is dedicated to our patients and their families, without whom I would have no reason to be here, and to my colleagues, without whom I could not be here

Why Study Diagnosis

- Many people are here to learn about potential therapies for Usher syndrome
- Our role as clinicians is to find these patients, so that they can benefit from new therapies
- And we have gotten much better at finding these patients at younger ages and with a more accurate diagnosis

Early Usher Diagnosis: Why Now?

- Universal newborn hearing screening, all 50 states and many countries
- Reliable tests to find the hearing loss
- Increasing clinical availability of genetic testing
- Increasing awareness that Usher not as rare as we thought
- Emerging laboratory work which can translate into the clinic means that we need to find the patients sooner

Incidence of SNHL in Children

- Hearing loss most common congenital sensory impairment
- Congenital 1-3/1000 live births with severe to profound SNHL
  - Another 1-2/1000 have milder or unilateral hearing loss
- Later onset/Acquired
  - 19.5% based on NHANES 2005-6 for ages 12-19 years
- May be the hearing loss manifestation of a **prenatal** occurrence: genetics, CMV, anatomic abnormalities

Incidence of congenital disorders detected by newborn screening in Massachusetts

Congenital hypothyroidism	1 in	3,800
Toxoplasmosis	1 in	8,000
PKU	1 in	12,000
Congenital adrenal hyperplasia	1 in	14,000
Biotinidase deficiency	1 in	32,000
Galactosemia	1 in	55,000
Maple syrup urine disease	1 in	157,000
Homocysteinuria	1 in	200,000

HEARING LOSS

1-2/1000 bilateral severe to profound

1-2/1000 milder bilateral or unilateral

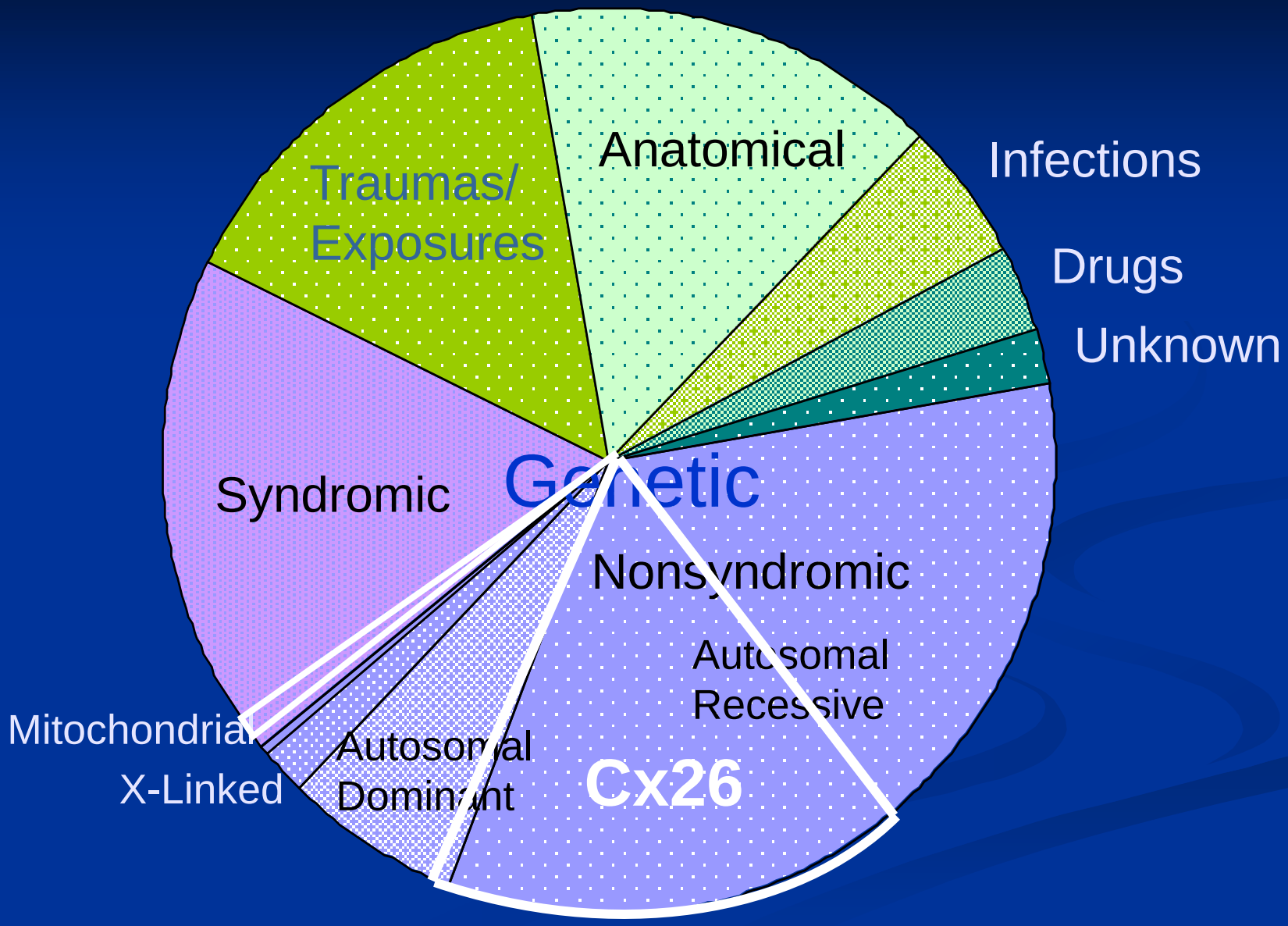
Why test hearing early?

- Effect of hearing loss on the development of speech and language
  - Academic achievement
  - Social and emotional development
- Age of detection of hearing loss
  - Presence of a “critical period” for auditory development
- Early establishment of language becomes even more critical if vision will change

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
- Test the treatment in these people
  - Orphan diseases, small numbers

Major Causes of Sensorineural Hearing Loss



New Era of Genetic Diagnosis in SNHL

- **1990: USH2A, Kimberling et al; 1998 Eudy et al**
- 1993: 1555A→G Mitochondrial gene for gentamicin ototoxicity
- **MYO7A: 1995 Weil et al**
- 1997: Identified Connexin 26 (GJB2) as the first non-syndromic autosomal recessive deafness gene, DFNB1
- 1998: Presence of large vestibular aqueducts in Pendrin syndrome (SLC26A4 [PDS] gene)

How Common is Usher Syndrome?

- Prevalence: 1/16-20,000 US; 3-6/100,000
- Estimated 16,000-45,000 individuals in the US with USH
- Up to 10 % of congenitally deaf children with USH1
- 3-6% of all congenitally hearing impaired children with USH1, 2, 3
- 0.6-28% HOH, deaf population
  - 1:6500 general population have genotype
- Carrier frequency 1/70 (varies by gene, mutation and population)

Why Does USH seem so rare?

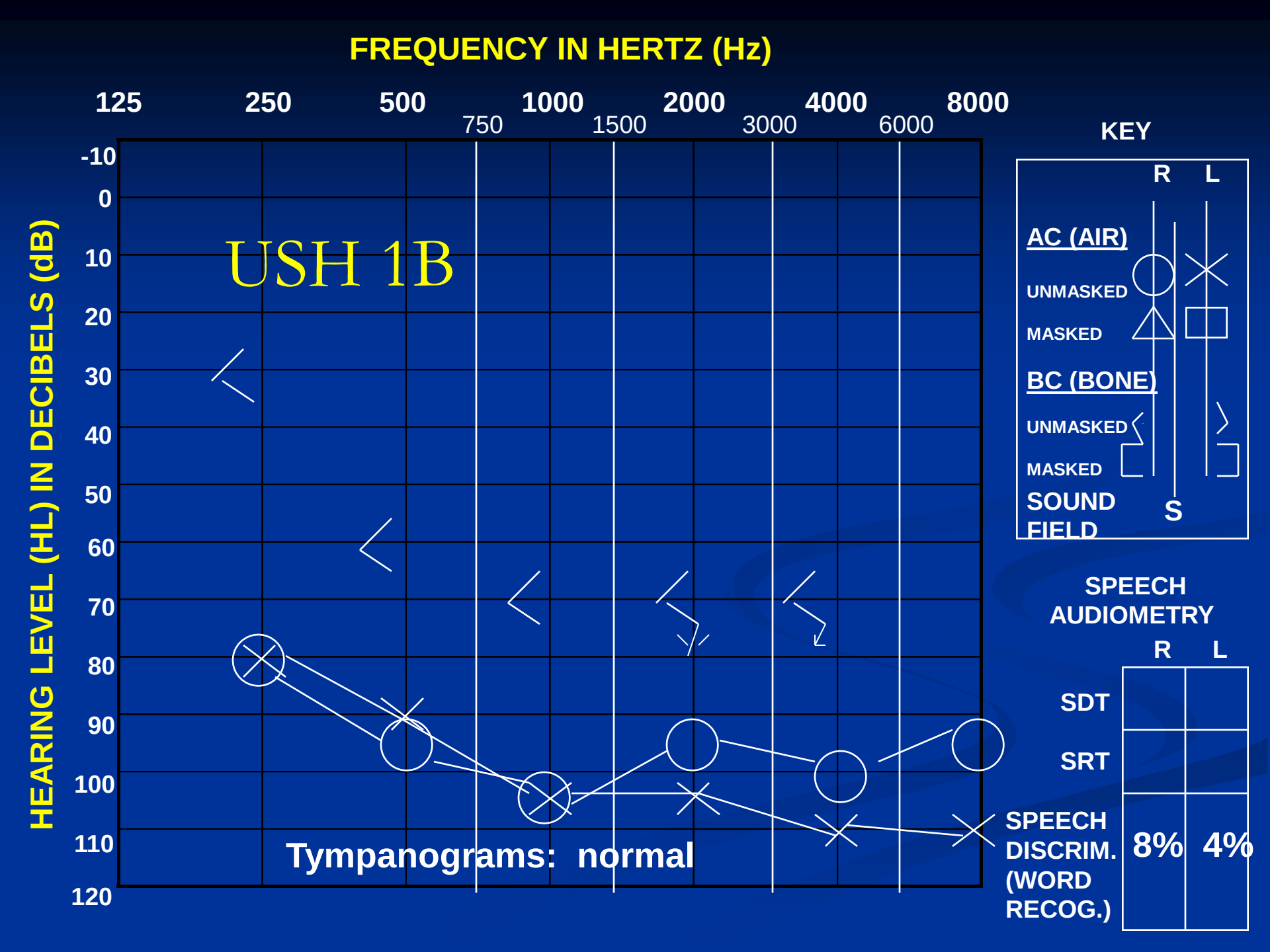
- Diagnosis still made late
  - Much later than Connexin 26
- Limited availability of genetic testing
  - Few clinical labs doing testing
  - Insurance does not always pay for testing
  - Physicians not always aware testing is available
- Heterogeneous presentation
- Later onset of visual loss than hearing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

Genetic Heterogeneity in "Non-Syndromic" Hearing Loss

- Many mutations cause a similar phenotype
- The same mutations may cause a very different phenotype
- Mutations in the same gene can cause both syndromic and non-syndromic HL
  - MYO7A (USH1B)
    - Recessive with RP
    - Dominant no RP
  - CDH23 (USH1D), USH1C, PCDH15 (USH1F) all have a recessive form without RP

Usher Syndrome

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


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
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SDT
SRT
SPEECH DISCRIM. (WORD RECOG.)
8%
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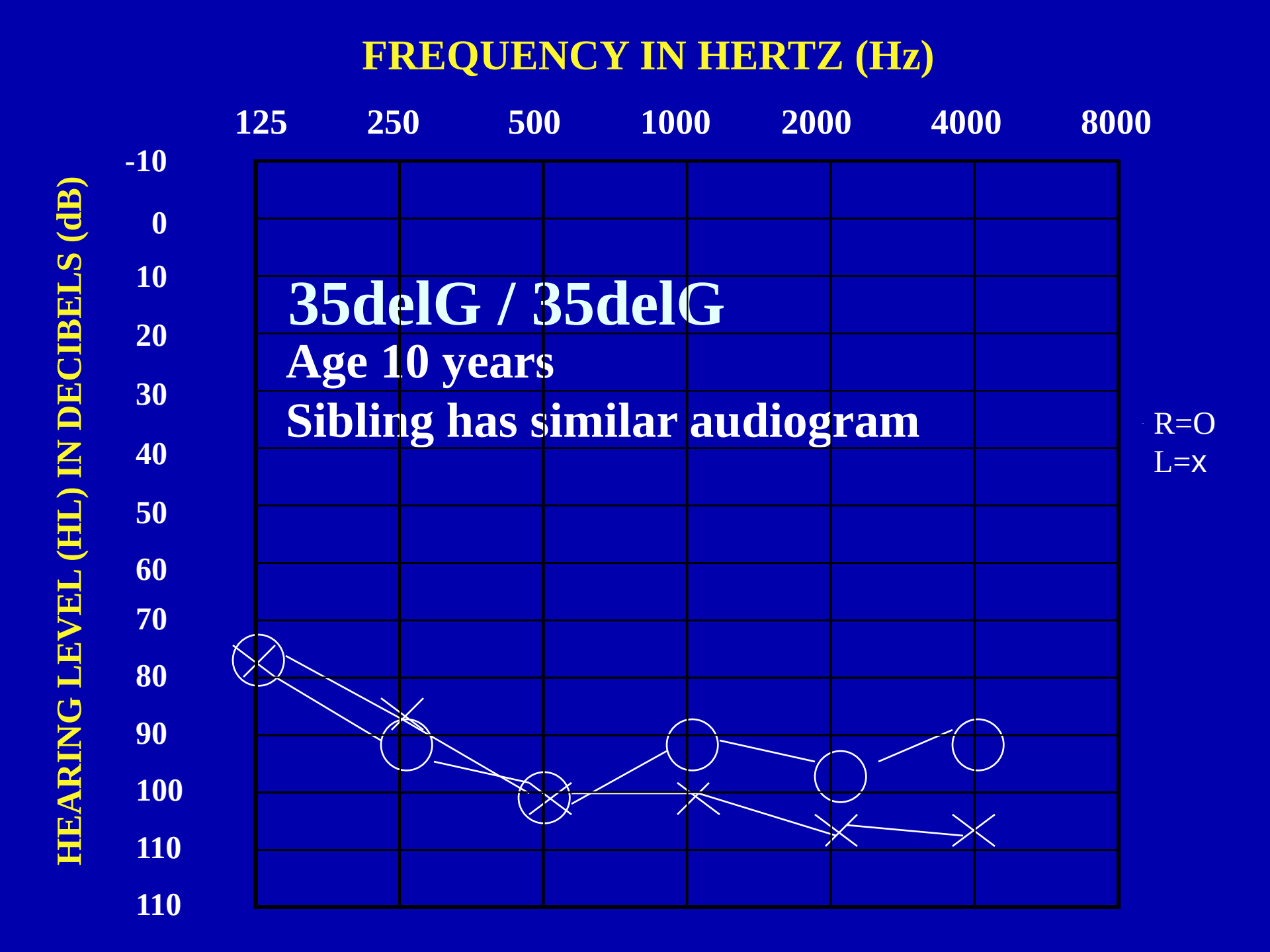
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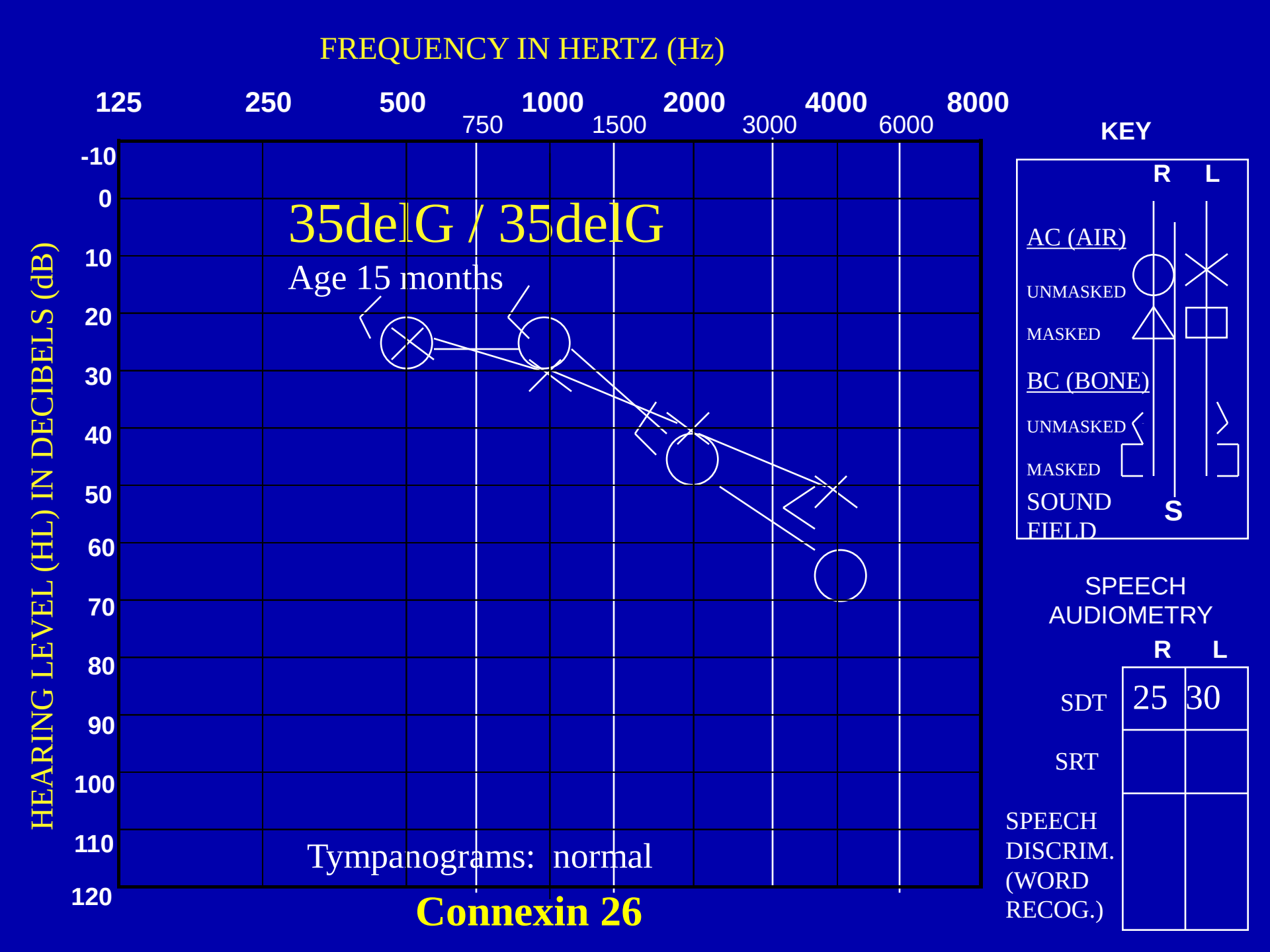
110
35delG / 35delG
Age 10 years
Sibling has similar audiogram
R=O
L=x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100
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120
35delG / 35delG
Age 15 months
Tympanograms: normal
Connexin 26
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
SPEECH AUDIOMETRY
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25
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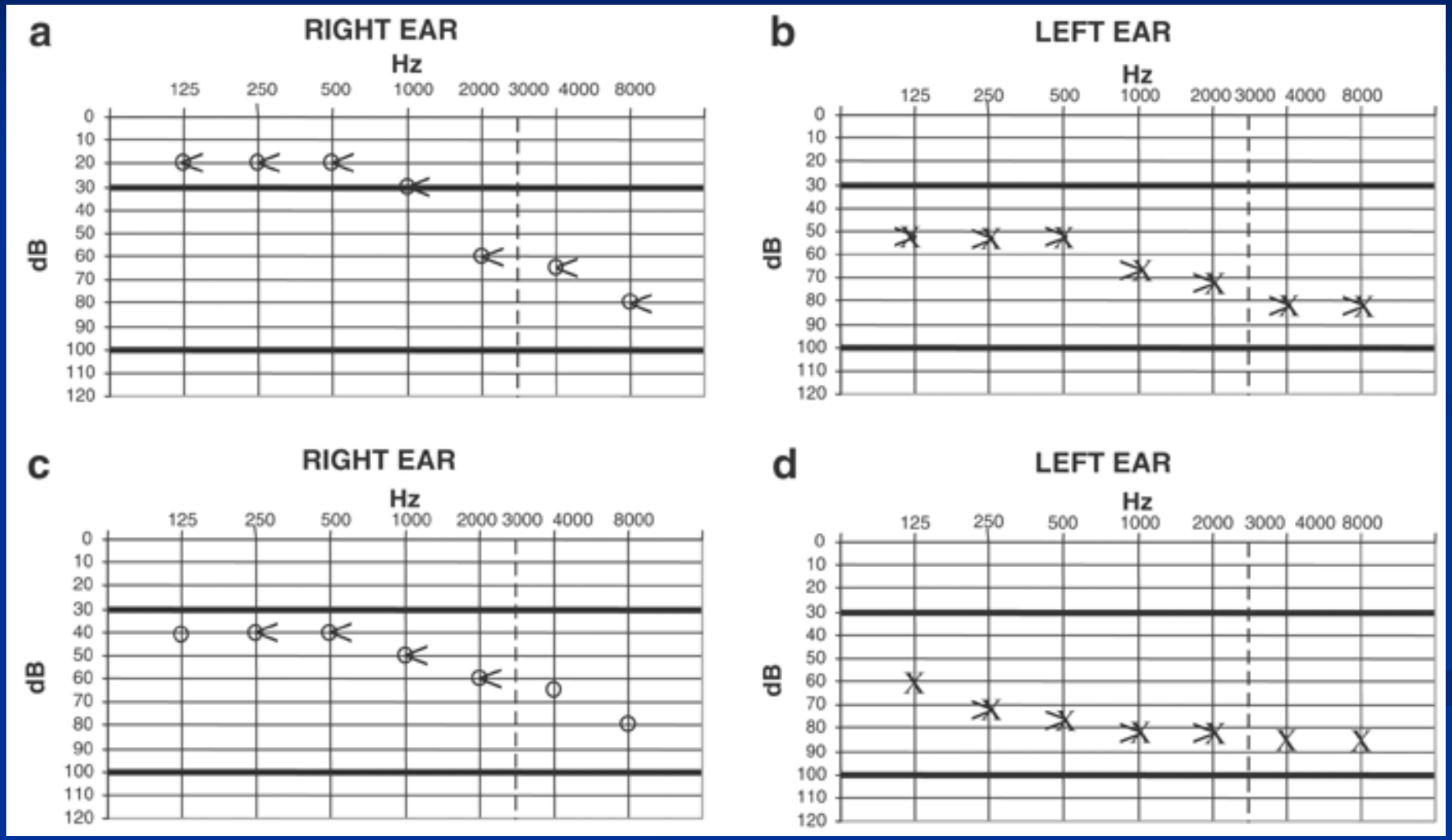
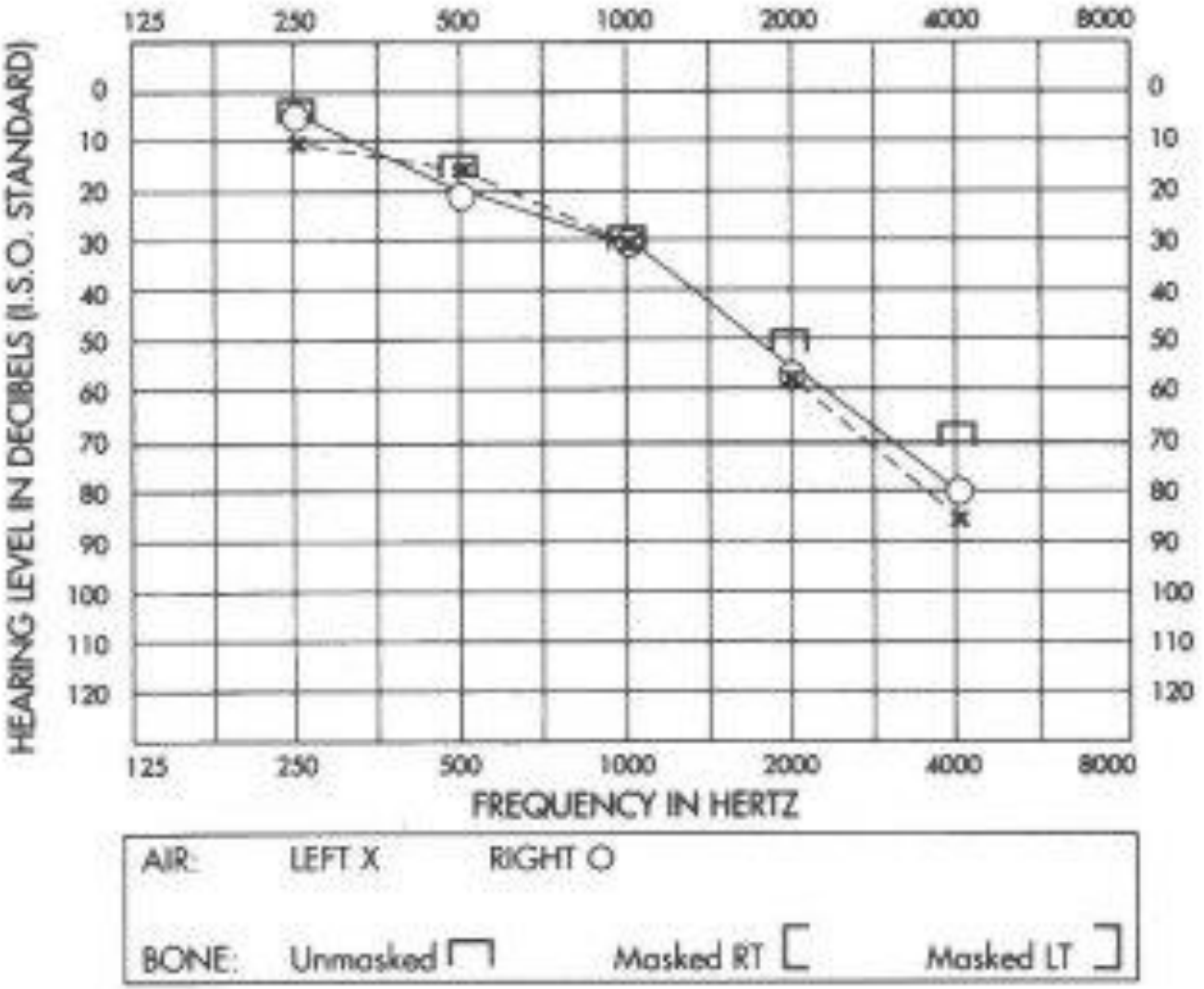
SRT
SPEECH DISCRIM. (WORD RECOG.)

Adult with USH 2A who presented with "non-syndromic" RP





An example of a mild to severe sensorineural hearing loss in both ears.

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)

Syndromic Hearing Loss

Syndrome	Inheritance	Prevalence**
Charge	AD	Common
Treacher-Collins	AD	Common
Pendred/LVAS	AR	Very common
Waardenburg	AD	Common
Usher	**AR**	**Common**
BOR Syndrome	AD	Common
Norrie Disease	XL, AR	Uncommon
Alport Syndrome	XL, AD, AR	Uncommon
Stickler Syndrome	AD	Uncommon
Jervell & Lange-Nielsen	AR	Rare

**relative to other syndromic forms of hearing loss

Locus name	Genome Location	Gene name	Gene 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	USH Type 1G protein
USH1H	15q22-23	USH1H	Unknown
USH 1 J	15q25.1	CIB2	Ca++ and integrin binding protein 2
USH 1K	10p11.21-q21.1	Unknown	Unknown
USH2A	1q41	USH2A	Usherin
USH2C	5q13	GRP98	G protein-coupled Receptor 98
USH2D	9q32-34	DFNB31	Cask-interacting protein
USH3A	3q21-q25	CLRN1	Clarin-1
USH2A modif	10q24.31	PDZD7	PDZD7
USH3B	*5q31.3*	*HARS*	
USH2J	17p11.2	MYO15A	

Vestibular Function in Usher Syndrome

- USH 1 associated with late walking and poor balance and are "areflexic"
  - Absence of response to cold caloric stimuli
  - Absence of post rotational nystagmus and abnormal VOR
  - Late walkers, average 20 months, but from "late normal" to >24 months
  - Although helps you suspect USH, not entirely reliable indicator
  - There are other causes for late walking, delayed milestones
- USH 2 – reportedly normal balance
- USH 3 – variable
- Balance in USH2 and USH3 not well studied

Vestibular Function

- Few labs are able to test children
- Limited norms for young children
- Each test evaluates a different part of the vestibular system
- Test are sometimes done in the dark, seem scary
- Tests may actually make the child dizzy
- Child may have trouble understanding the tests due to limitations of age, hearing and vision

Genetic Testing for Usher Syndrome

- Conservative approach
  - HL with retinal abnormalities (positive ERG test, DAT or pigmentary changes)
- Less conservative approach
  - Profound congenital hearing loss with delayed walking
- Even less conservative approach
  - Test infants and children with moderate to profound SNHL if Cx26 (and possibly Cx30) negative
  - Test infants and children with any degree of bilateral SNHL
- No matter which approach, need for genetic counseling

Interventions for the Hearing Loss

- Hearing aids
- Cochlear Implants
- Early diagnosis of bilateral severe to profound SNHL **AND** an early diagnosis of USH allows a decision for CI earlier
  - Early USH diagnosis may tip the scales towards CI in families who might have decided on manual communication in other circumstances

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!!

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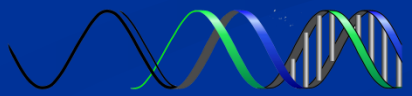

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