Hearing Loss in Infants and Children: Could it be Usher Syndrome?

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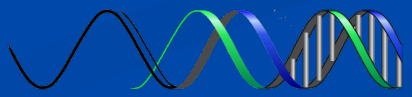
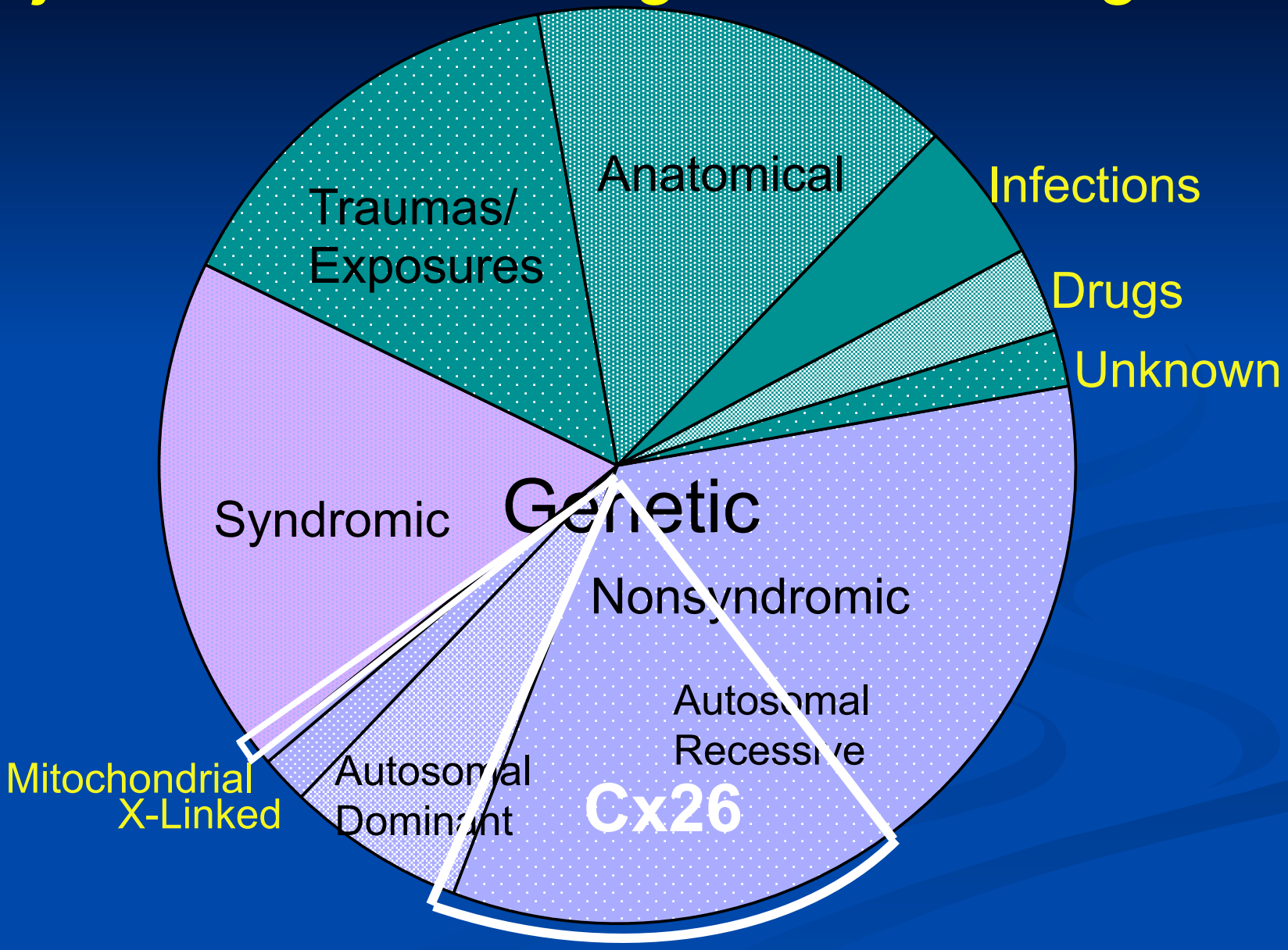


Boston Children's Hospital

Suspecting a diagnosis of Usher Syndrome

- Before universal newborn hearing screening (UNHS) and genetic testing, USH diagnosis usually made by ophthalmologists when vision started to change
- UNHS gives otolaryngologists an opportunity to make an earlier USH diagnosis
  - Need to work with ophthalmology and clinical genetics
  - Need access to genetic testing and ERG
  - Need to know what to do next

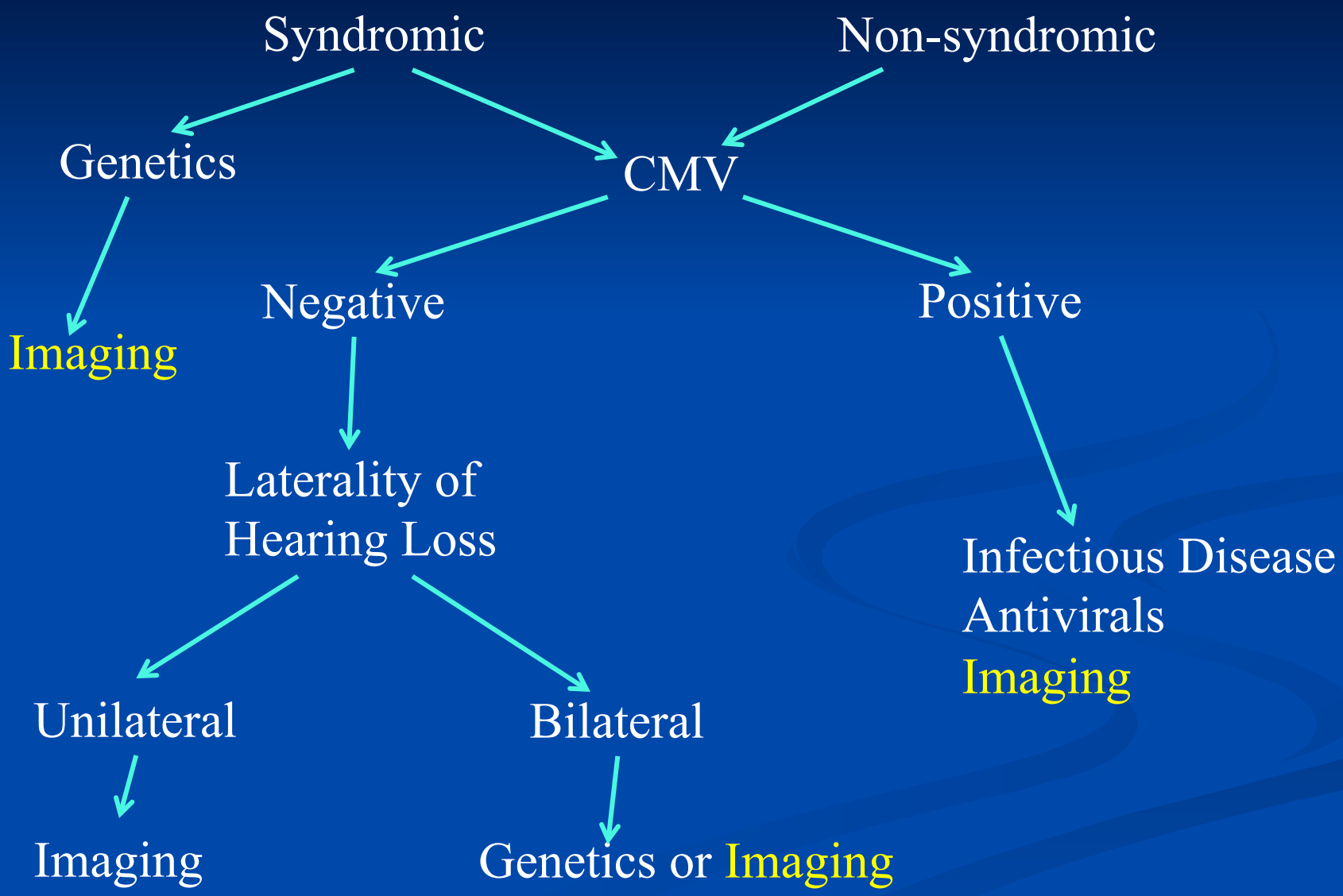
Major Causes of Congenital Hearing Loss



First rule out non-Usher diagnoses

- Congenital CMV, toxoplasmosis, syphilis
- Auditory dyssynchrony…probably not USH
- Anatomical abnormalities…probably not USH
- Other genetic causes..Cx26
- Occasionally find more than one cause

Confirmed diagnosis of SNHL in Newborn



Hearing Loss Due to **Prenatal** Causes

- Genetics
- Abnormal inner ear anatomy
- Infections – CMV, toxoplasmosis, syphilis
- Maternal, placental factors
  - Fetal Alcohol exposure
  - Twin-twin transfusion
  - Chorioamnionitis
  - Ototoxic drugs

Epidemiology of CMV

- 1% of all live births
- 10-15% of babies with congenital CMV are symptomatic
  - 75% of these will have CNS symptoms
  - 65% of these will have SNHL
- Of asymptomatic babies 5-10% develop SNHL
- Over 50% have progressive hearing loss

Hearing Loss due to Perinatal Causes

- NICU
  - PPHN
  - Ototoxicity
  - Sepsis
- Hyperbilirubinemia
- ECMO
- Ototoxicity
- Sepsis
- Extreme prematurity
  - Auditory dyssynchrony

Postnatally Acquired: Infections

- Bacterial meningitis
  - Group B strep (perinatal)
  - Marked decrease since HIB, Prevnar®, PCV13
  - N. meningitidis vaccination: MCV4, MPSV4
- Parvovirus B-19 (Fifth's disease)
  - Associated with autoimmune hearing loss
- Mumps (2007, 800/100,000 US)
- Measles (2005, <1/1,000,000)
- Lyme - Facial nerve dysfunction more common than SNHL
- HIV
- EBV
- HSV
- Ramsay-Hunt (Varicella zoster)
- Otitis media/cholesteatoma

Hearing Loss due to Postnatal Causes

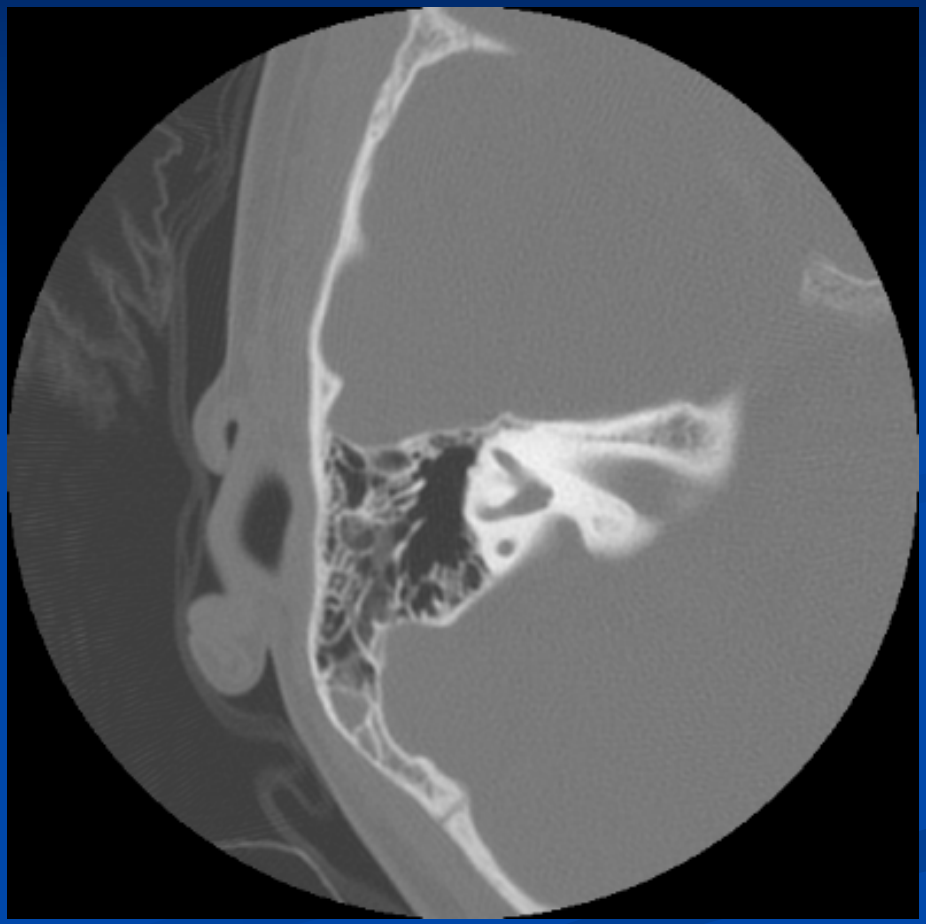
- Head trauma
  - Sports
  - Altercations
  - MVA
  - Child abuse
- Noise
  - **Noise in the NICU????**
  - MP3
  - Recreational other than MP3
  - Musical instruments: violin, rock music
  - Hunting, car repair
- Radiation
- Surgery
- Autoimmune

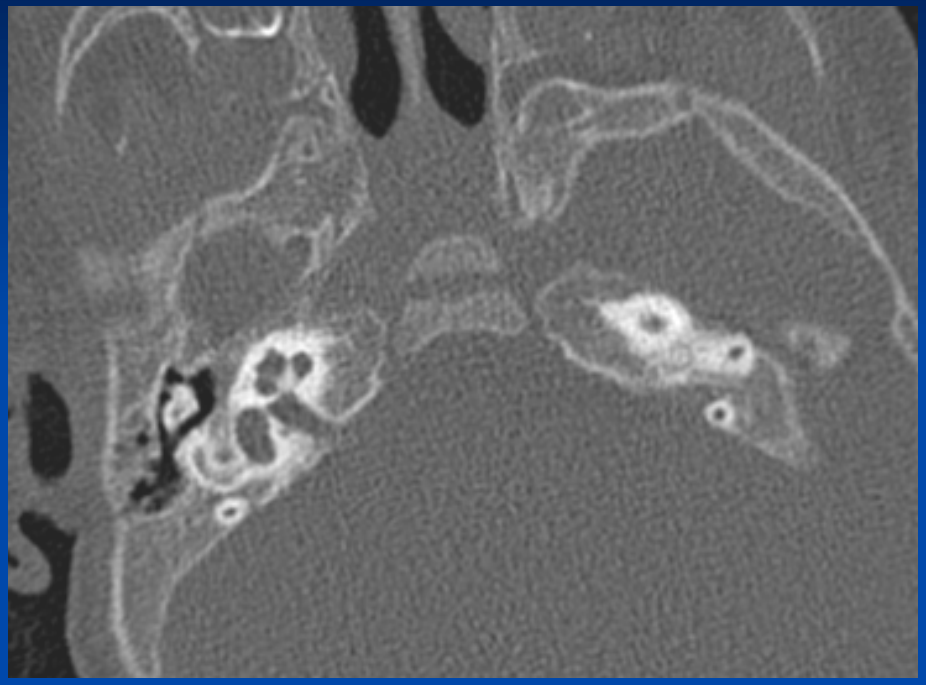
T-bone abnormalities with Hearing Loss

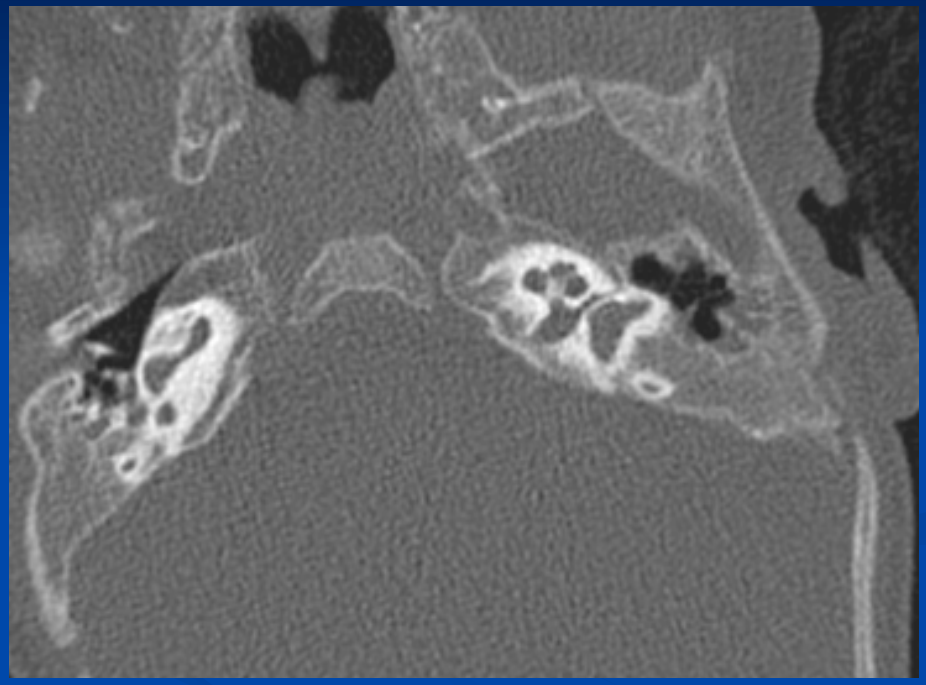
- Hearing loss
  - may present at birth or later, and is often fluctuating or progressive
  - May present after head trauma
  - Hearing loss is often mixed
- Enlarged vestibular aqueduct
- Superior semicircular canal dehiscence
- Ossification: bacterial meningitis, autoimmune
- Narrow cochlear aperture (cochlear stenosis)
- Narrow internal auditory canal
  - Associated with hypoplastic auditory nerve
- Dysplastic and/or small cochleas

Enlarged Vestibular Aqueduct

- Most common radiographic abnormality with SNHL
- Associated with fluctuating/progressive hearing loss
- HL often mixed
- About 10% of AU EVA associated with full Pendred syndrome







-CT absent eighth nerve AU
-Infant failed UNHS

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

- Find the disease gene
  - Initial discovery of the gene
  - In a particular patient
- 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

Genetics of Hearing Loss

- Loci (genes) for Non-Syndromic HL
  - 71 (39) recessive (DFNB)
  - 54 (25) dominant (DFNA)
  - 5 (3) X-linked (DFNX)
  - 2 modifier (DFNM)
  - Several Mitochondrial (MTN)
  - 1 Y-linked (DFNY)
  - 1 (1) Auditory neuropathy (AUNA1)
- Syndromic hearing loss: hundreds of genes (loci/genes)
  - Waardenburg (9/6) (dominant)
  - Branchio-oto-renal (4/3)(dominant)
  - Pendred (3/3) (recessive)
  - Usher (13/10) (recessive)
  - CHARGE (2/2) (dominant)
  - Alport (2/3) (dominant, recessive, x-l;inked)
  - Jervell and Lange Nielsen (2) recessive
  - Norrie (1/1) recessive
  - Stickler (3/3) dominant
  - Treacher Collins (1/1) dominant

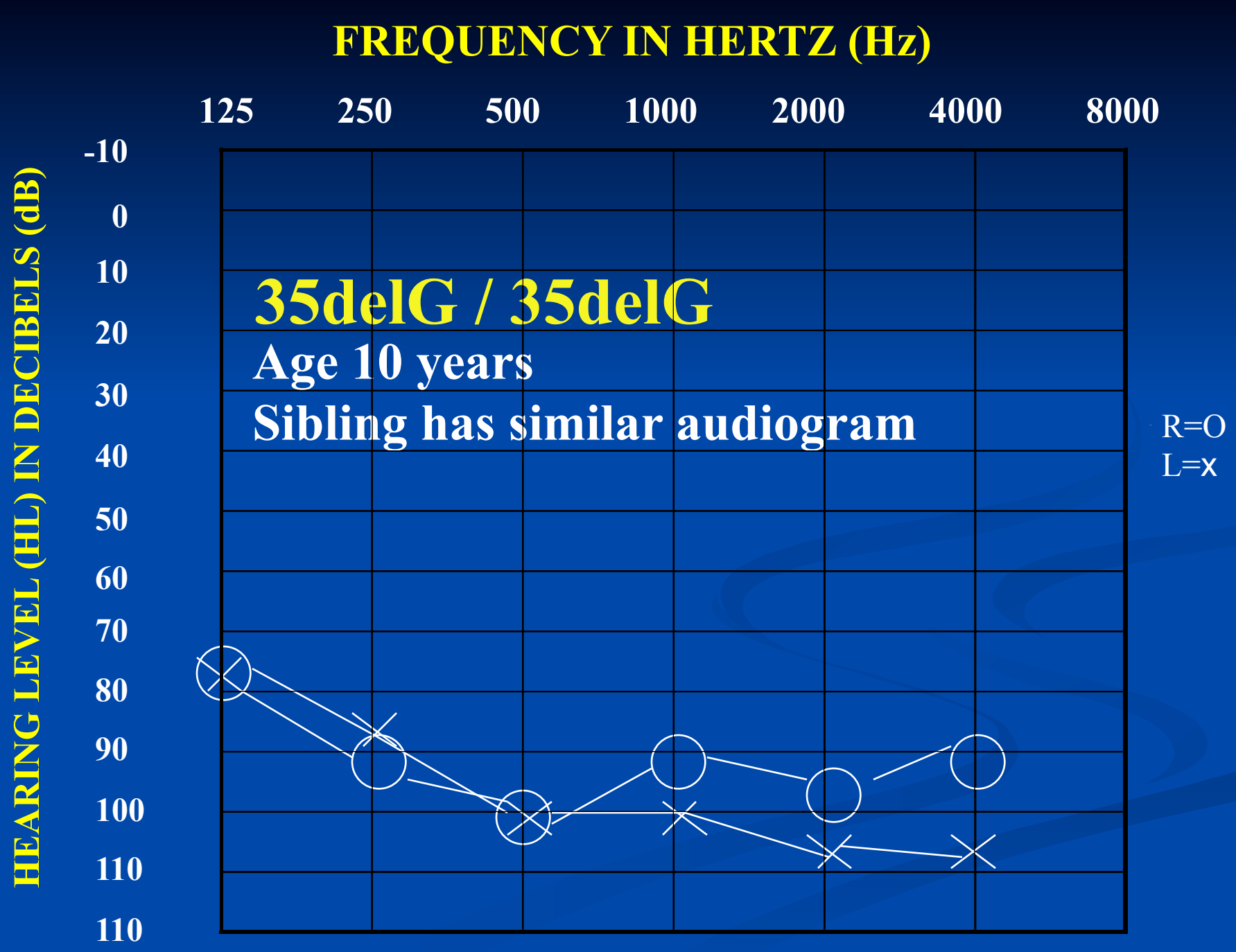
Van Camp G, Smith RJH.
http://hereditaryhearingloss.org 8.21.2012

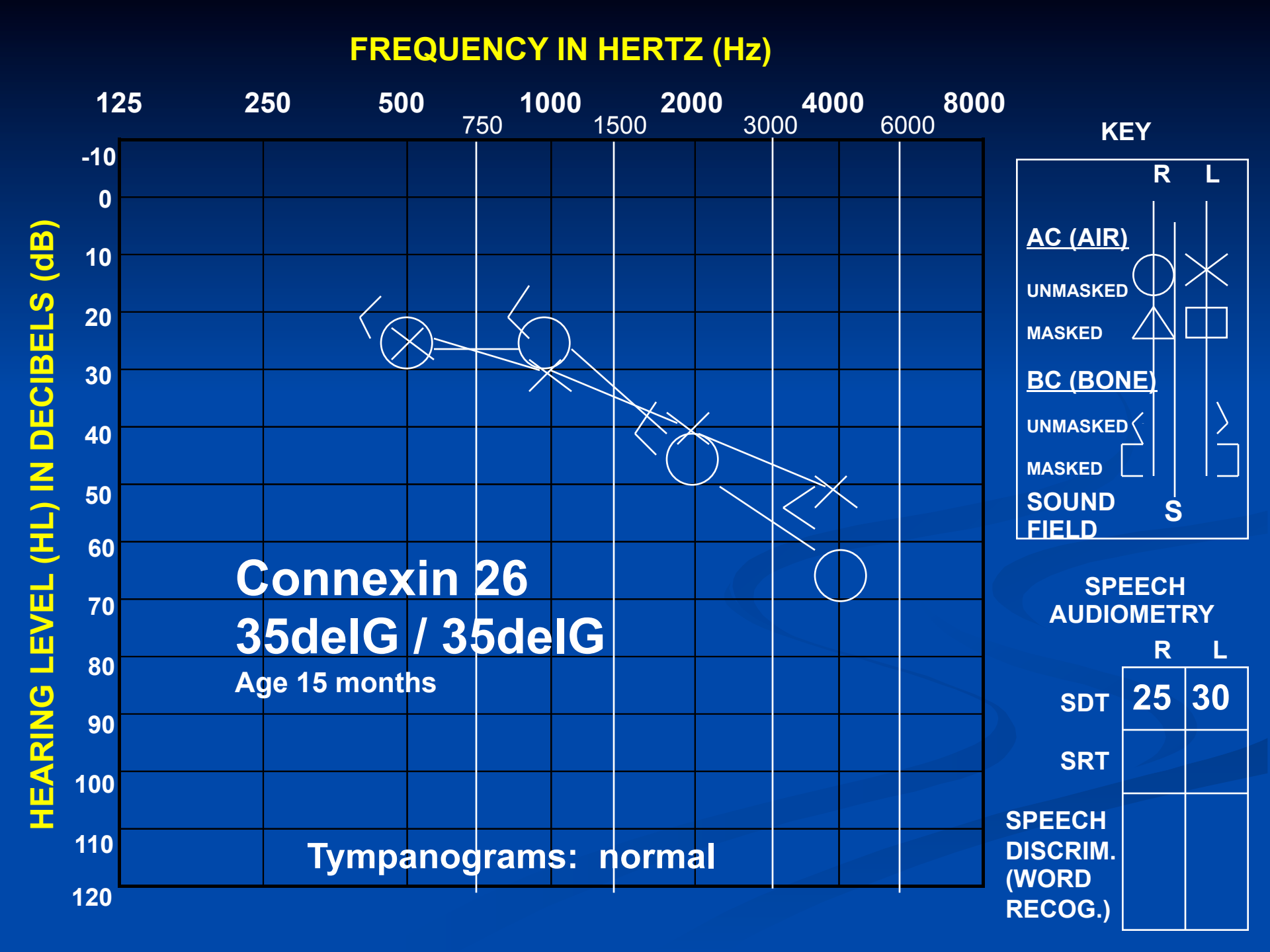
Genetic causes of later onset and progressive HL

- 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

GJB2 (Connexin 26)

- Most common genetic cause of hearing loss
- DFNB1: locus name
- GJB2 (gap junction beta 2): name of gene
- Connexin 26: name of protein
- Phenotype
  - Usually congenital SNHL
  - Recessive (10% of mutations dominant)
  - ~50% with severe to profound hearing loss (>75dB HL)
  - Generally no other physical or radiographic findings (except for pts with PPK or KID syndrome)
  - Hearing loss worsens up to 50% of the time


FREQUENCY IN HERTZ (Hz)
125
250
500
1000
2000
4000
8000
HEARING LEVEL (HL) IN DECIBELS (dB)
-10
0
10
20
30
40
50
60
70
80
90
100
110
110
35delG / 35delG
Age 10 years
Sibling has similar audiogram
R=O
L=x


FREQUENCY IN HERTZ (Hz)
125
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750
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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
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
Connexin 26
35delG / 35delG
Age 15 months
Tympanograms: normal
SPEECH AUDIOMETRY
R
L
SDT
25
30
SRT
SPEECH DISCRIM. (WORD RECOG.)

Pendred Syndrome

- Most common genetic cause after Cx26
- Enlarged vestibular aqueducts
  - 10-20% of pts with AU EVA have PDS
- Goiter resulting from abnormal organification of iodine in the thyroid
  - If have Pendred syndrome, will have abnormal perchlorate washout studies but euthyroid labs
- Mutations in SLC26A4 (PDS) cause both Pendred Syndrome and recessive non-syndromic SNHL (DFNB4)

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

Locus name	Genome Location	Gene name	Gene Protein Product	Animal Model
USH1B	11q13.5	MYO7A	Myosin 7A	Shaker 1/Mariner
USH1C	11p15.1-p14	USH1C	Harmonin	Deaf circler
USH1D	10q22-q22	CDH23	Cadherin 23	Waltzer/deaf waddler
USH1E	21q21.1	Unknown	Unknown	none
USH1F	10q21.1	PCDH15	Protocadherin 15	Ames waltzer
USH1G	17q25.1	USH1G	Usher Syndrome Type 1G protein	
USH1H	15q22-23	USH1H	Unknown	
USH 1K	10p11.21-q21.1	Unknown	Unknown	
USH2A	1q41	USH2A	Usherin	
USH2C	5q14.3	VLGR1	G protein-coupled Receptor 98	
USH2D	9q32-34	DFNB31 (WHRN)	Cask-interacting protein	
USH3A	3q21-q25	CLRN1	Clarin-1	
USH2A modifier	10q24.31	PDZD7	PDZD7	
USH3B	*5q31.3*	*HARS*		

How Common is Usher Syndrome

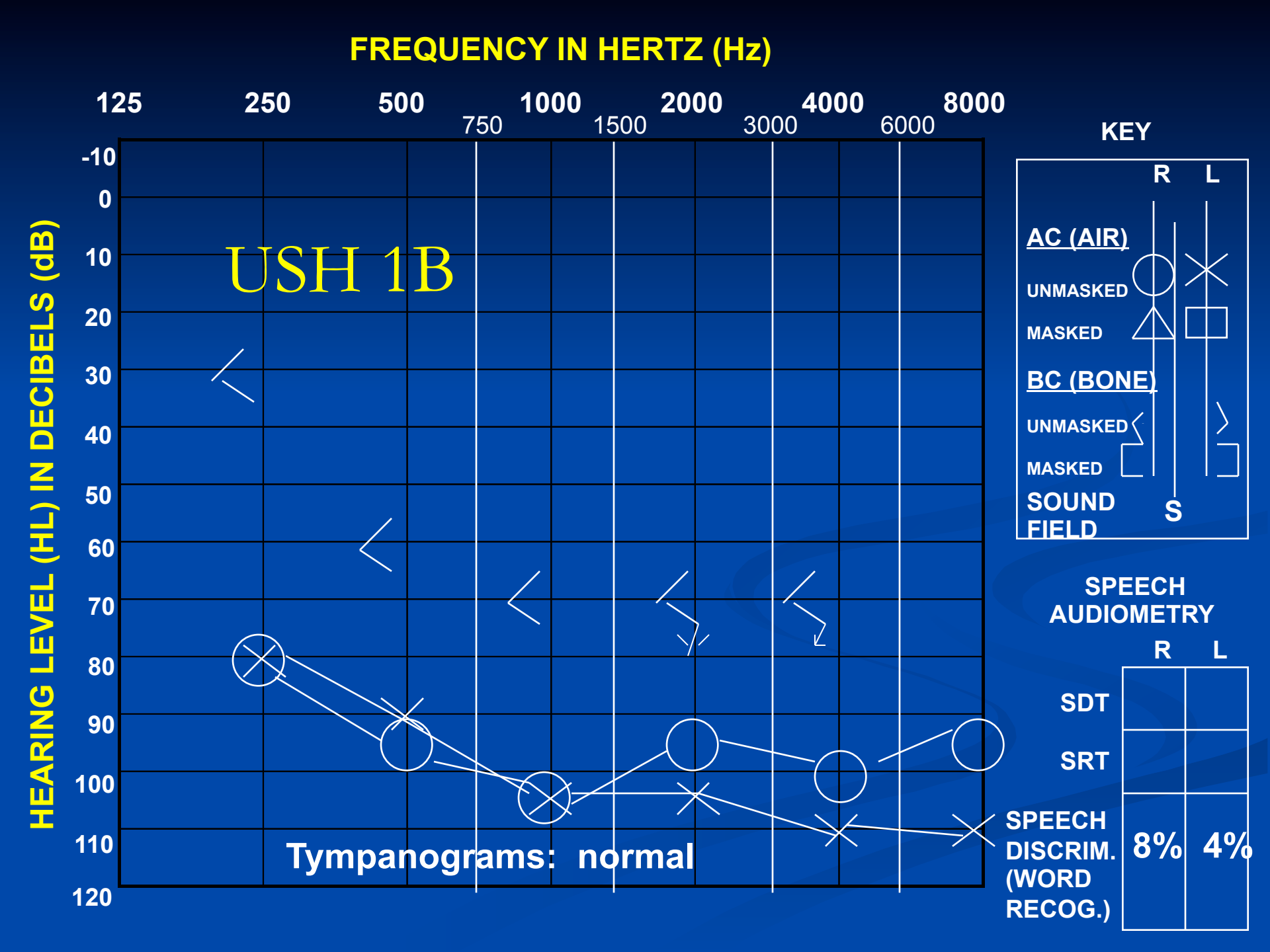
- Prevalence: 1/16-20,000 US
  - With more genes more common
- Estimated 16,000-25,000 individuals in the US with USH
- Up to 10 % of congenitally deaf children with USH1
- 3-6% of all congenitally hearing impaired children with USH1, 2, 3
- Carrier frequency 1/70 (varies by gene, mutation and population)

How to make the Usher Diagnosis

- Test the hearing
- Test the vision
- Test the balance
- Test the genes
- Test olfaction?
- Look at brain?

Audiologic Features

- USH 1 - bilateral congenital profound SNHL
- USH 2 - bilateral moderate SNHL; may progress
- USH 3 – May be of later onset, may progress
- **All patients initially appear non-syndromic except for the hearing loss**
- **Not all patients with mutations in the same Usher gene have the same presentation**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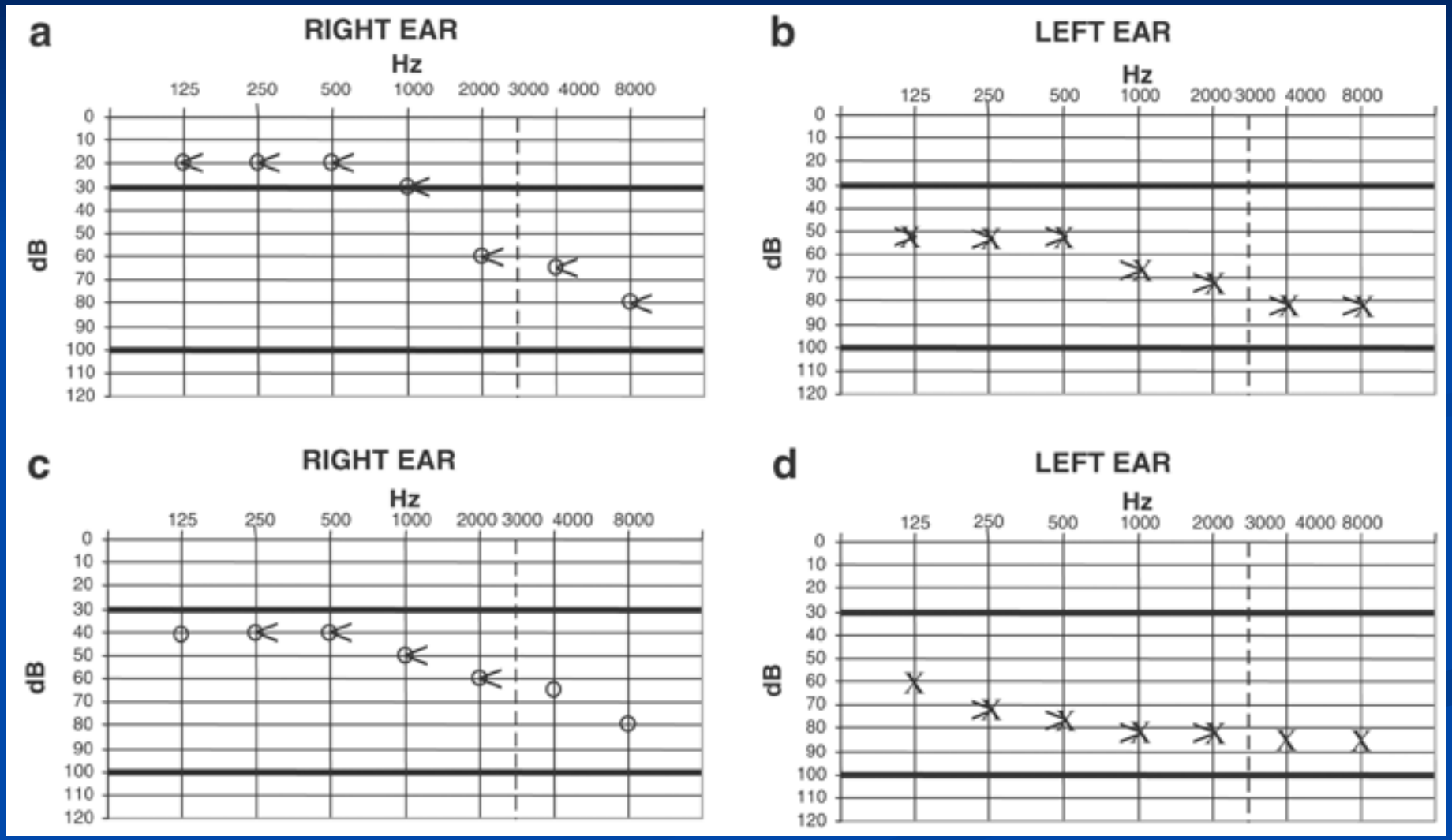
100
110
120
USH 1B
Tympanograms: normal
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
SPEECH AUDIOMETRY
R
L
SDT
SRT
SPEECH DISCRIM. (WORD RECOG.)
8%
4%

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



Usher Gene Phenotype

- Most genes cause congenital/childhood onset SNHL followed by RP
- USH2A also causes non-syndromic RP
- MYO7A, USH1C, CDH23, PCDH15, WHRN may cause hearing loss only
- USH1K reported in association with hyperinsulinism, cognitive impairment and non-autoimmune diabetes
- Change in olfaction (sense of smell)
- Cognition
- Sperm motility
- Cerebral atrophy
- Ataxia
- Registry

Routine Eye Exams in Children with SNHL: Can you diagnose Usher Syndrome?

- 16 children
- All have two pathogenic USH mutations
- "Routine" eye exams did not pick up USH in any patients who were pre-symptomatic (i.e. not night blind)
- 9/16 had diagnosis made by genetic testing; youngest was 8 months
- Age of walking not entirely predictive of USH 1 patients, and was normal in USH 2 and USH 3

Kenna, Fulton, Hansen, Rehm, et al, 2010

Testing for Usher Syndrome

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

Why Pursue Usher Testing: Hearing Loss

- USH 1 - bilateral congenital profound SNHL
- USH 2 - bilateral moderate SNHL; may progress
- USH 3 – May be of later onset, may progress
- **All patients initially appear non-syndromic except for the hearing loss**
- **Eye exams are frequently non-diagnostic or falsely reassuring**
- **Not all patients with mutations in Usher genes will have the same presentation**
  - **Hearing loss may be milder than expected**
  - **USH 1: MYO7A, USH1C, CDH23, PCDH15, DFNB31; some with hearing loss only**
  - **DFNA11-MYO7A: Dominant non-syndromic hearing loss**

Why pursue genetic testing for Usher Syndrome?

- 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
- Plan 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

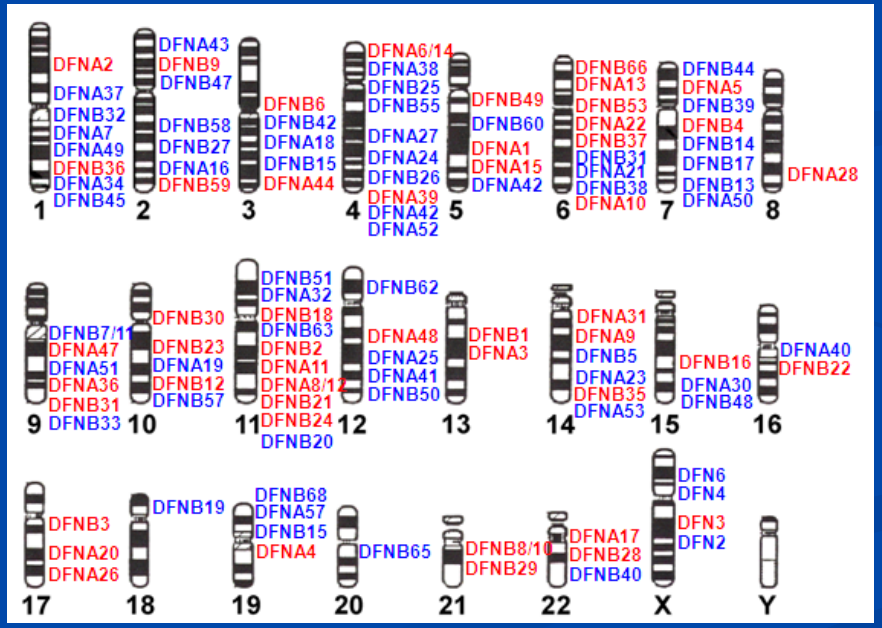
- Usher diagnosis seems unlikely
  - Normal balance and vision so must not be Usher
  - No one in the family has it
- We aren't planning to have any more children
- Expensive and maybe insurance won’t cover
- Results will be inconclusive
- No intervention that makes it better or stops progression
- Anxiety
  - 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 elective
  - Once interventions are established that improve/ stabilize condition then makes it a thornier question

OtoGenome Test

- 71 genes for nonsyndromic hearing loss as well as a subset of syndromic genes that can mimic NSNHL (e.g. Usher, Pendred, JLNS, BOR)
- Detection of all variant types (substitutions, indels, CNVs)
- Technology: pooled barcoded samples, custom Agilent SureSelect capture, Illumina HiSeq, BWA/GATK alignment, minimum 20X coverage with Sanger fill-in and confirmation of variants



Usher Genes on Otogenome™

- *MYO7A* at 11q13.5
- *USH1C* at 11p15.1
- *CDH23* at 10q21-q22
- *PCDH15* at 10q21-q22
- *USH1G* (*SANS*) at 17q24-q25
- *USH2A* at 1q41
- *GPR98* (*VLGR1*) at 5q14
- *PDZD7* at 10q24.31
- *DFNB31* (*WHRN*) at 9q32-34
- *CLRN1* (*USH3A*) at 3q21-q25

New Hearing Loss Gene Chips

- Otogenome™
  - 71 genes for nonsyndromic hearing loss (NSNHL) and several syndromic genes (Usher, Pendred, JLNS, BOR) that can mimic NSNHL early on
  - http://pcpgm.partners.org/lmm/tests/hearing-loss/OtoGenome
- OtoSeq™
  - 23 genes
  - Designed to detect mutations in the most common genes causing early onset Non-syndromic SNHL, Usher and Pendred Syndrome
  - www.cchmc.org/hearing-loss
- OtoScope™
  - 66 genes for Non-syndromic SNHL, Usher Syndrome and Pendred syndrome
  - http://www.healthcare.uiowa.edu/labs/morl/

What do results mean?

- 2 pathogenic mutations in a known USH gene
- 2 mutations of unclear significance in an USH gene (variant of unknown significance=VUS)
- 1 pathogenic mutation and one VUS
- 1 pathogenic mutation in two different USH genes (digenic)

Who Needs Genetic Counseling

- Families/patients being tested for hearing loss genes (pre-testing)
- Families/patients being given genetic results
- There may be a greater need for genetic counseling when test results are negative or inconclusive
  - Patients may not understand that the cause of hearing loss could still be genetic

Summary

- If definitely USH, hearing loss and vision can progress
- If not certain USH, try and confirm a diagnosis
- Rarely, could be more than one diagnosis
- Manage the hearing loss according to degree
- Manage the diagnosis according to what makes sense
- Match USH genetic results to possible clinical trials

THANKS!

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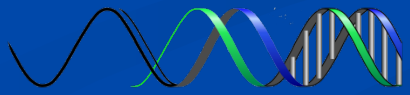

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