Usher Syndrome and Progressive Hearing Loss

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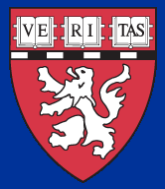
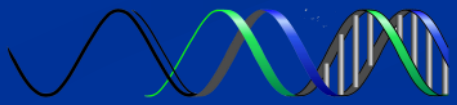


Harvard Medical School Center for Hereditary Deafness



Boston Children's Hospital

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 and 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

Incidence of Hearing Loss in Newborns

- Profound bilateral 1-2/1000 births
- Another 1-2/1000 with significant HL
- 33 babies born every day with significant permanent hearing loss
- >12,000 babies per year in the U.S.
- The most common congenital sensory impairment

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)

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

How to make the Usher Diagnosis

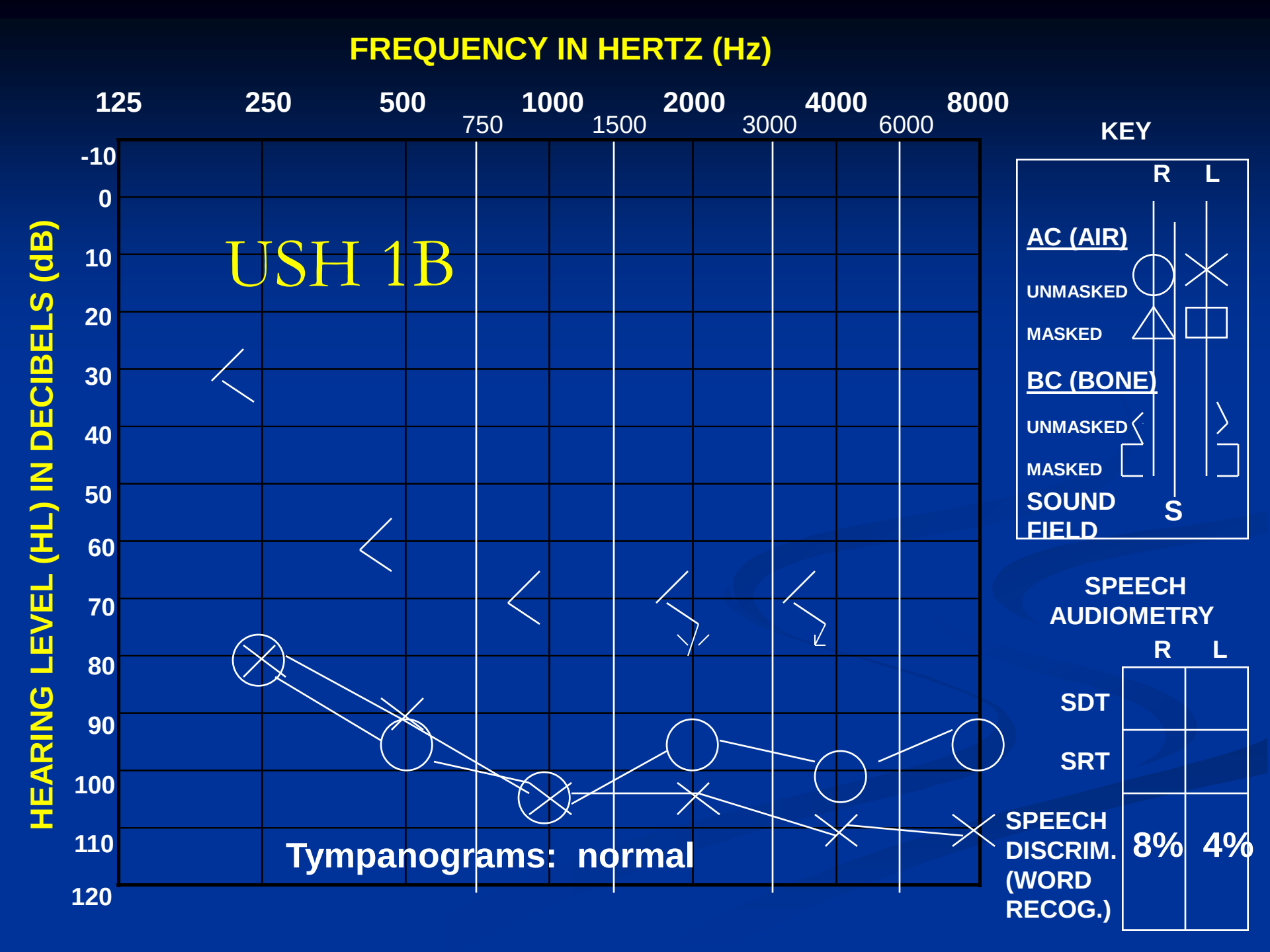
- Test the hearing
- Test the vision
- Test the balance
- Test the genes
- Test olfaction?
- Look at brain?

Audiologic Features

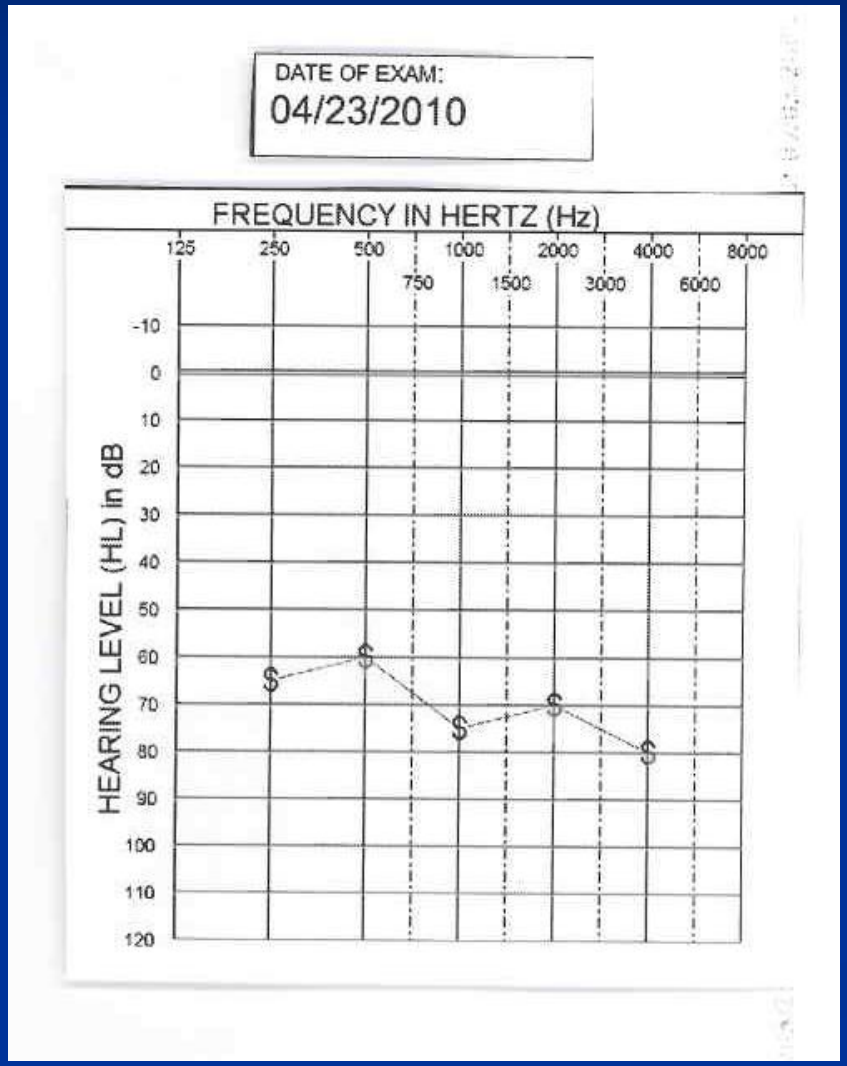
- USH 1 - bilateral congenital profound SNHL
- USH 2 - bilateral moderate SNHL; may progress
- USH 3 – May be of later onset, may progress
- **All patients initially appear non-syndromic except for the hearing loss**
- **Not all patients with mutations in the same Usher gene have the same presentation**

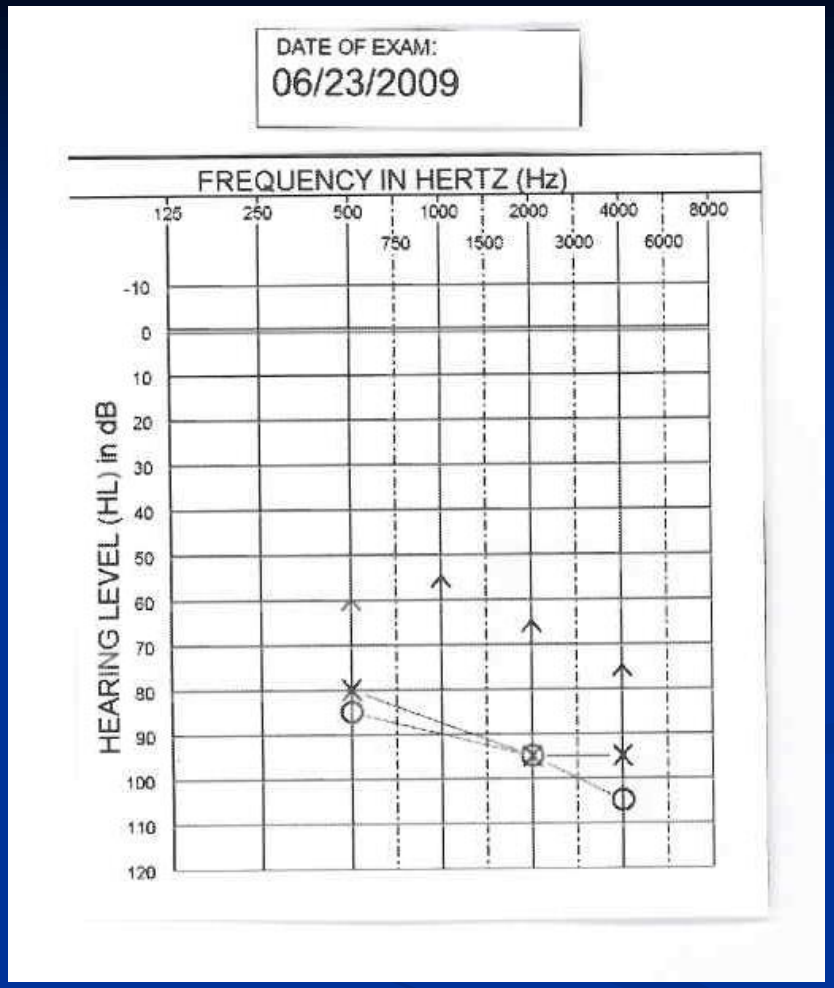
Usher Gene Phenotype

- Most genes cause congenital/childhood onset HL followed by RP
- USH2A also causes non-syndromic RP
- MYO7A, USH1C, CDH23, PCDH15, WHRN may cause hearing loss only
- Change in olfaction (sense of smell)
- Cognition
- Sperm motility
- Cerebral atrophy
- Ataxia
- Registry


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%

USH1B

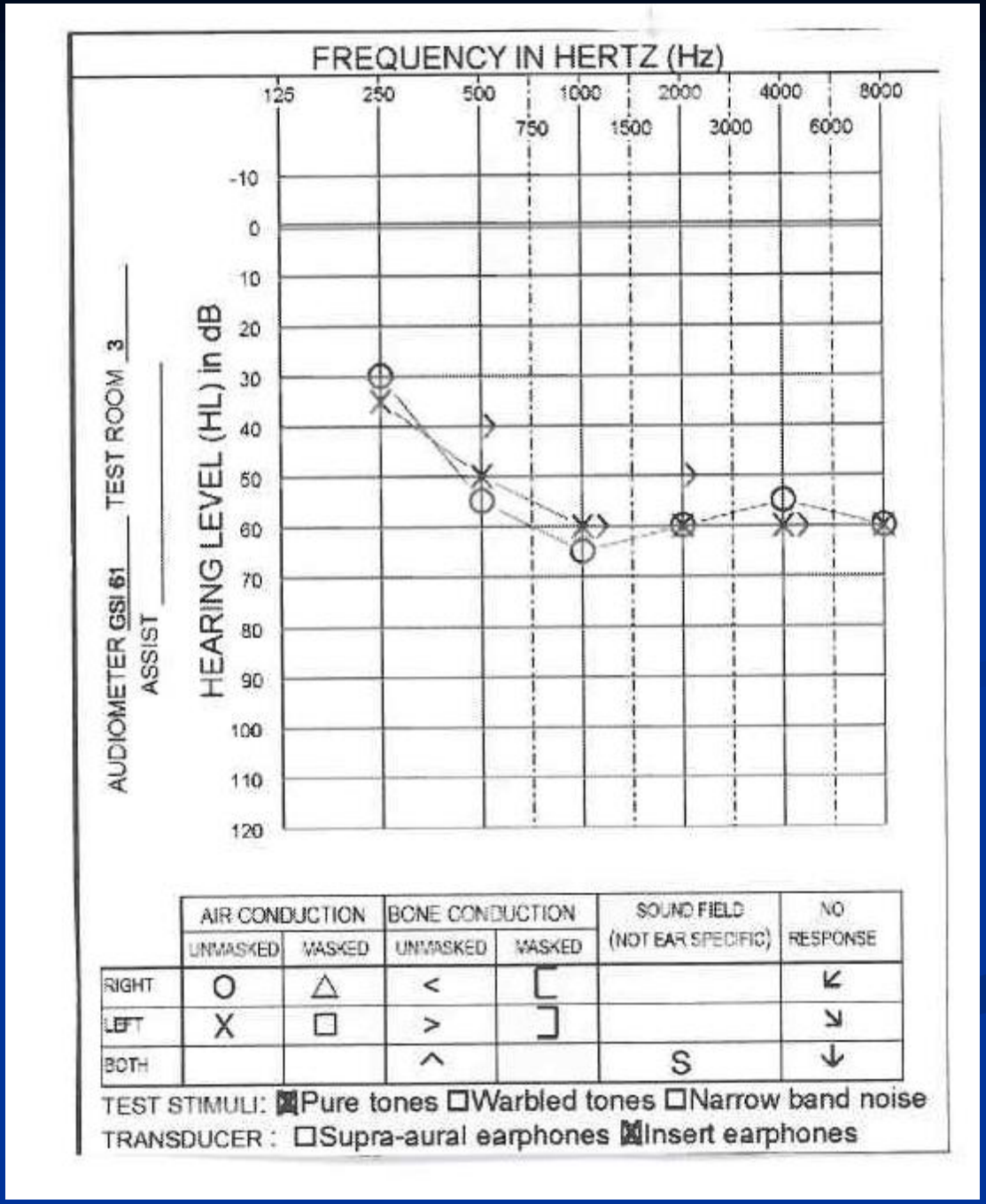




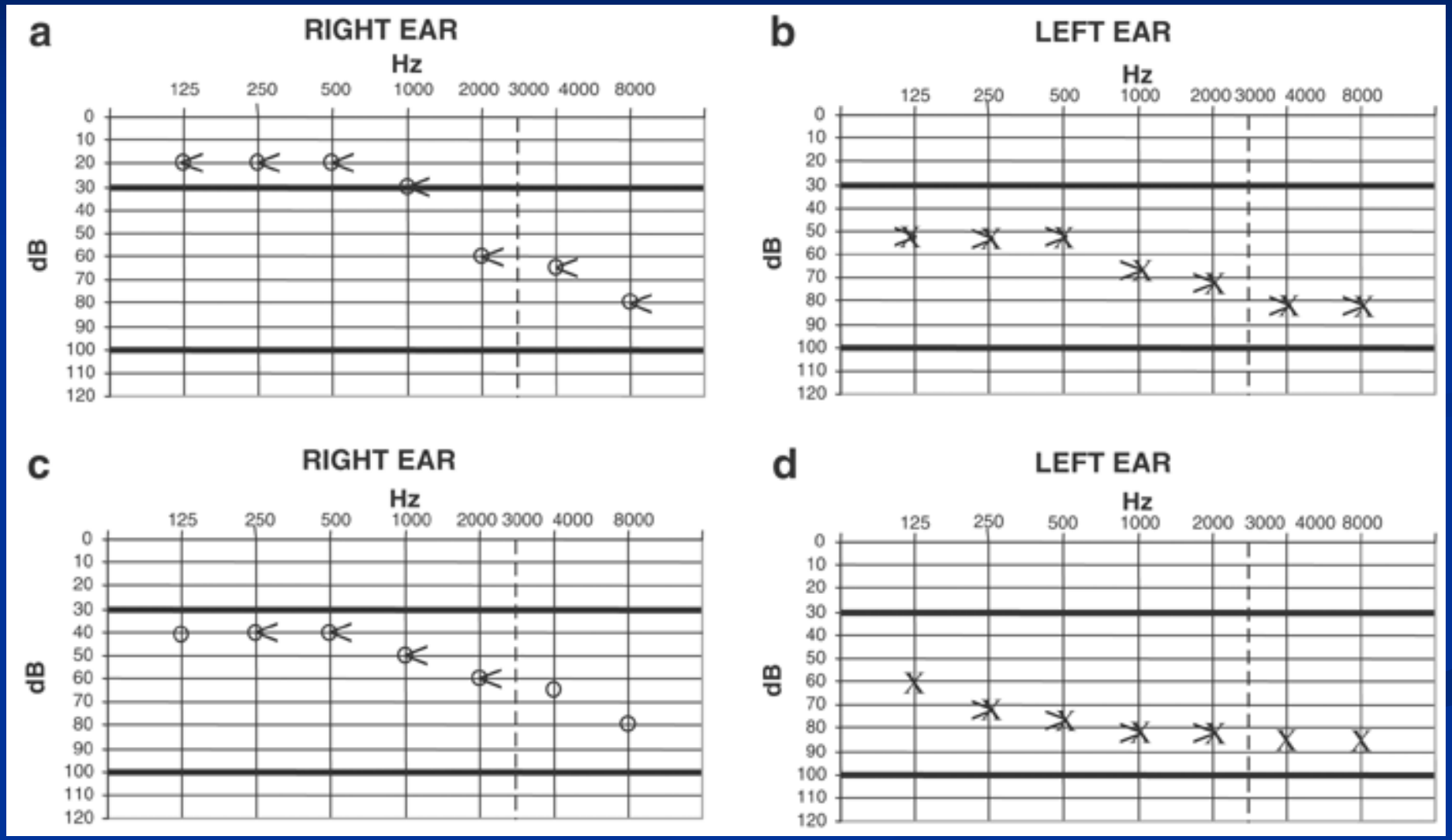
2 year old female
with 2 novel MYO7A
mutations

USH2A

8 year old male with USH2A and normal vision; ERG not done. Child's maternal grandmother and siblings have USH2 clinically, but child has a novel mutation, so unclear what effect this will have on his vision and ERG

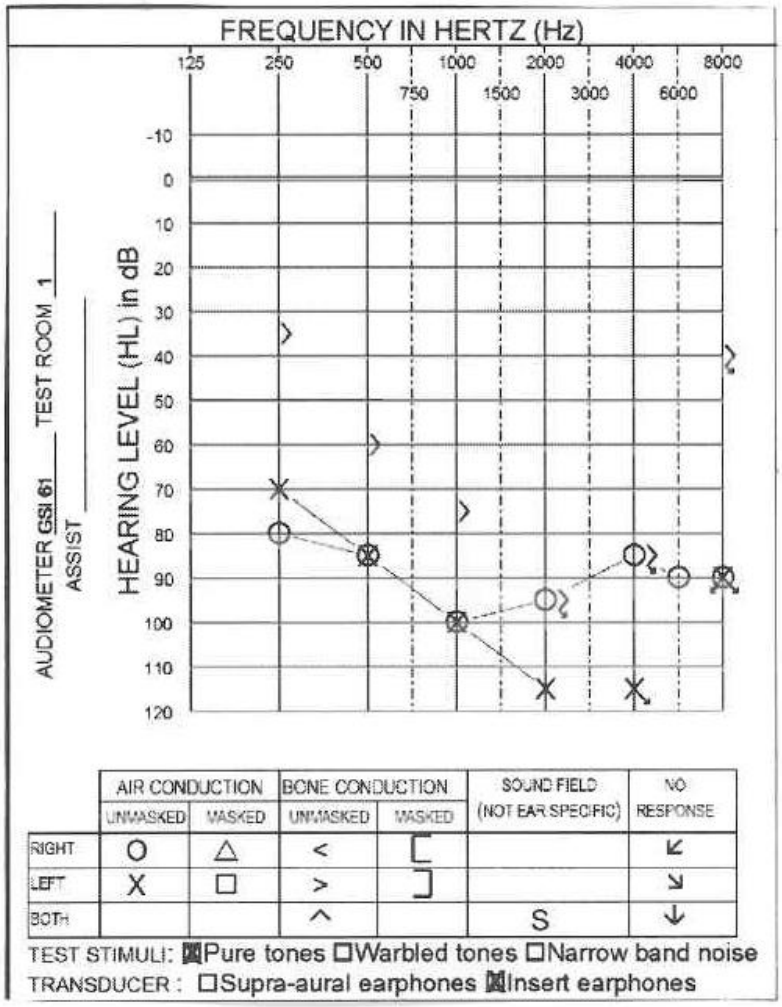


Adult with USH 2A who presented with "non-syndromic" RP

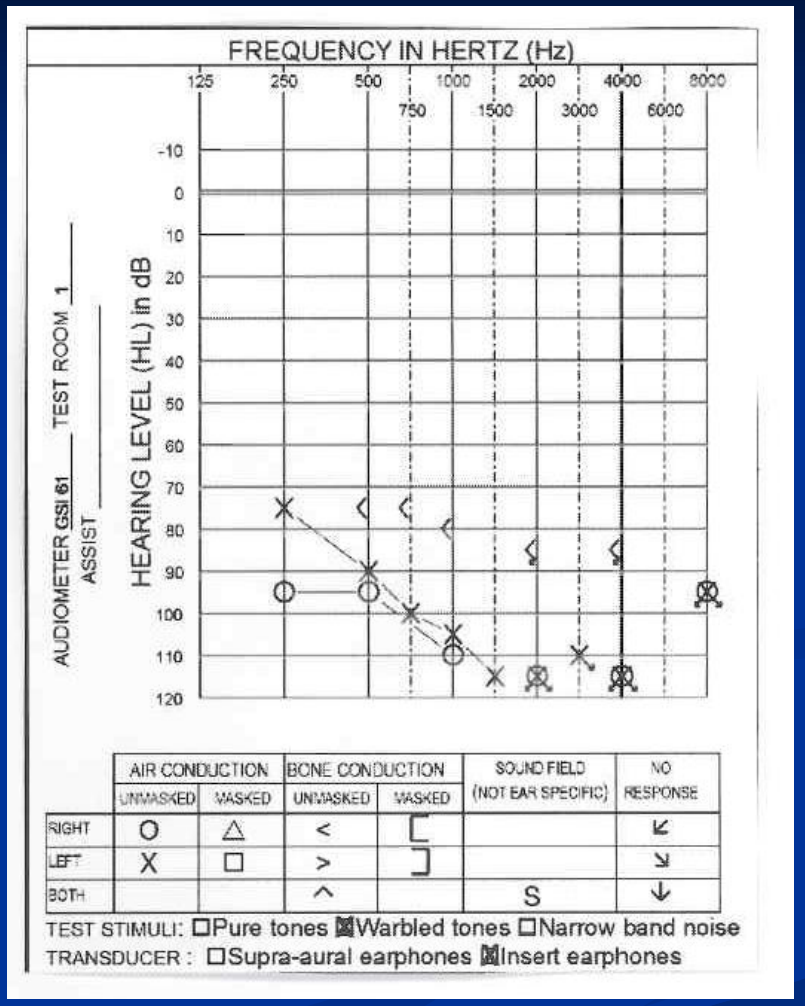


USH3

12/2/08



5/7/2010



14 year old female from Cape Verde with progressive SNHL and RP, and normal balance. Dad and Dad's brother with the same. Homozygous CLARIN1 mutations.

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

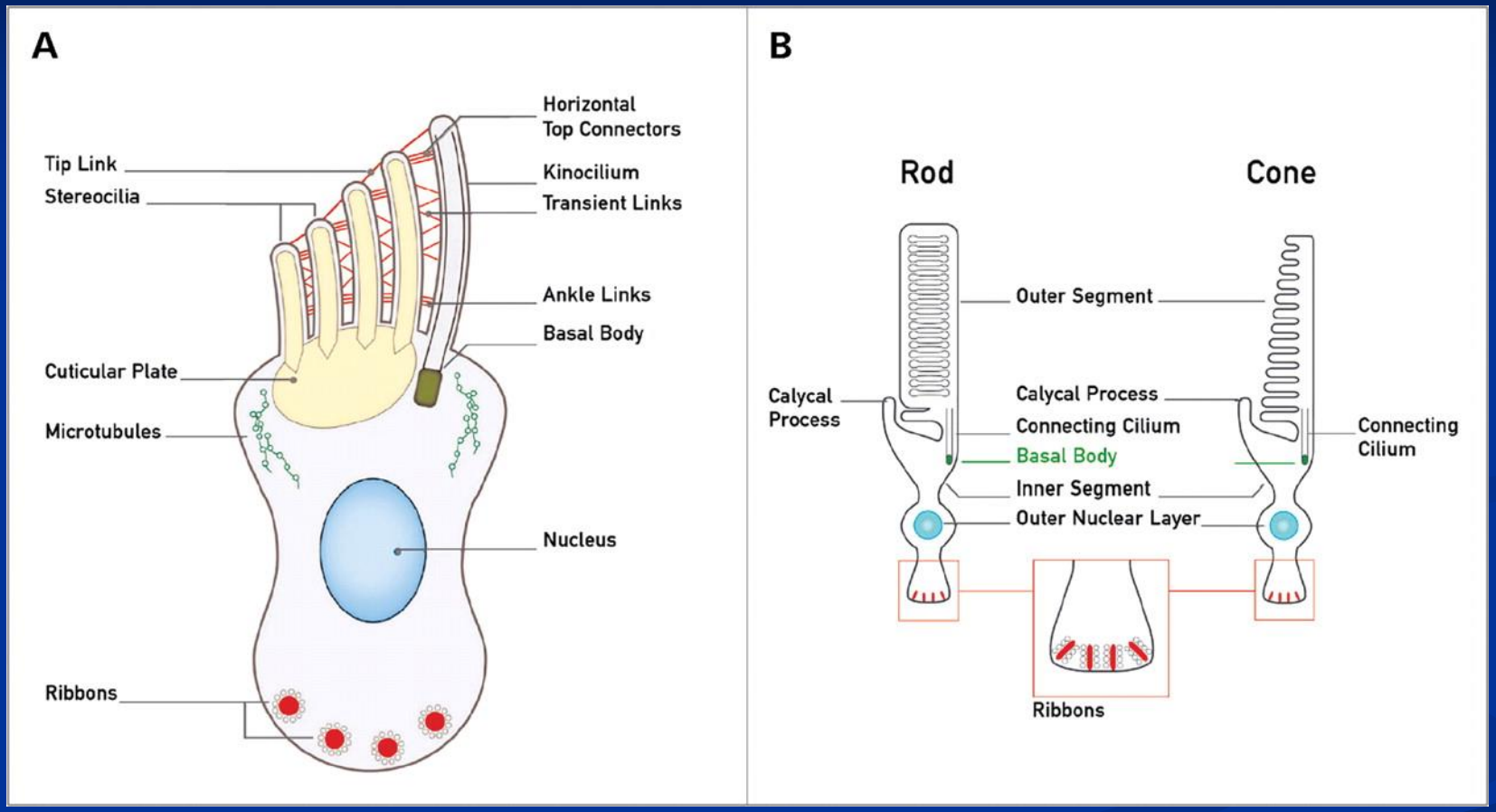
Kenna, Fulton, Hansen, Rehm, et al, 2010

How could the hearing loss progress

- Many genes
- Result in many proteins
- Many forms of each protein
- Interaction depends on many things besides just making the protein
- Environment

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	5q13	GRP98	G protein-coupled Receptor 98	
USH2D	9q32-34	DFNB31	Cask-interacting protein	
USH3A	3q21-q25	CLRN1	Clarin-1	
USH2A modifier	10q24.31	PDZD7	PDZD7	
USH3B	*5q31.3*	*HARS*		

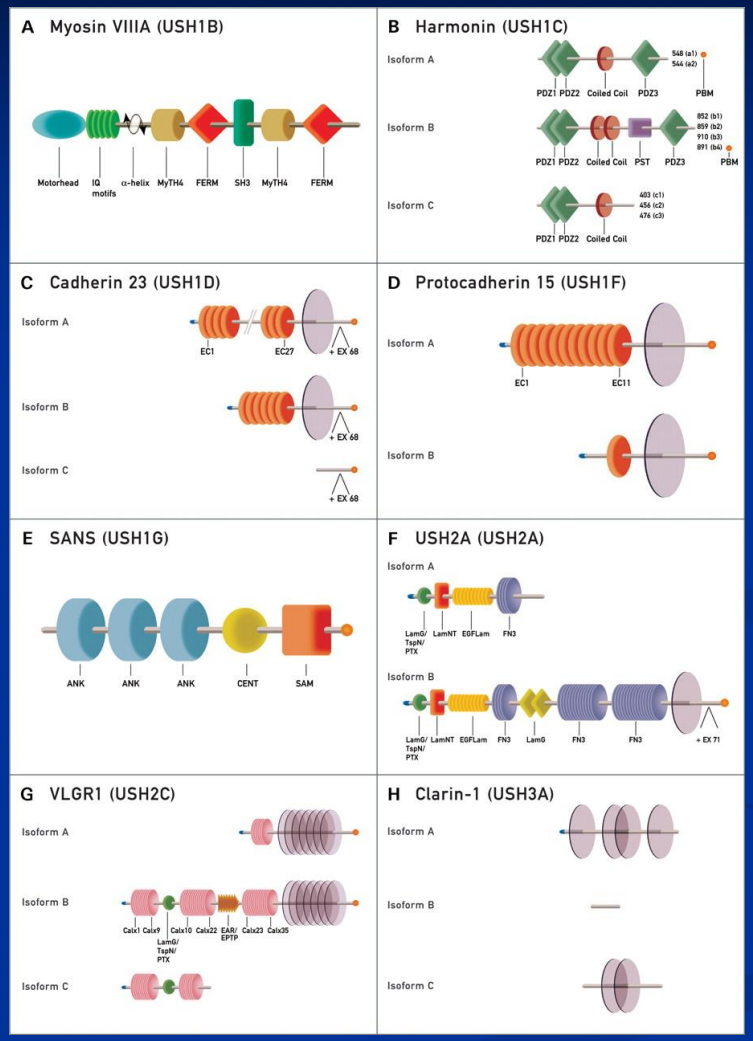
Diagram of the sensory cells in the inner ear and retina.



Kremer H et al. Hum. Mol. Genet. 2006;15:R262-R270

Human
Molecular Genetics

Outline of the Usher proteins and their different isoforms.



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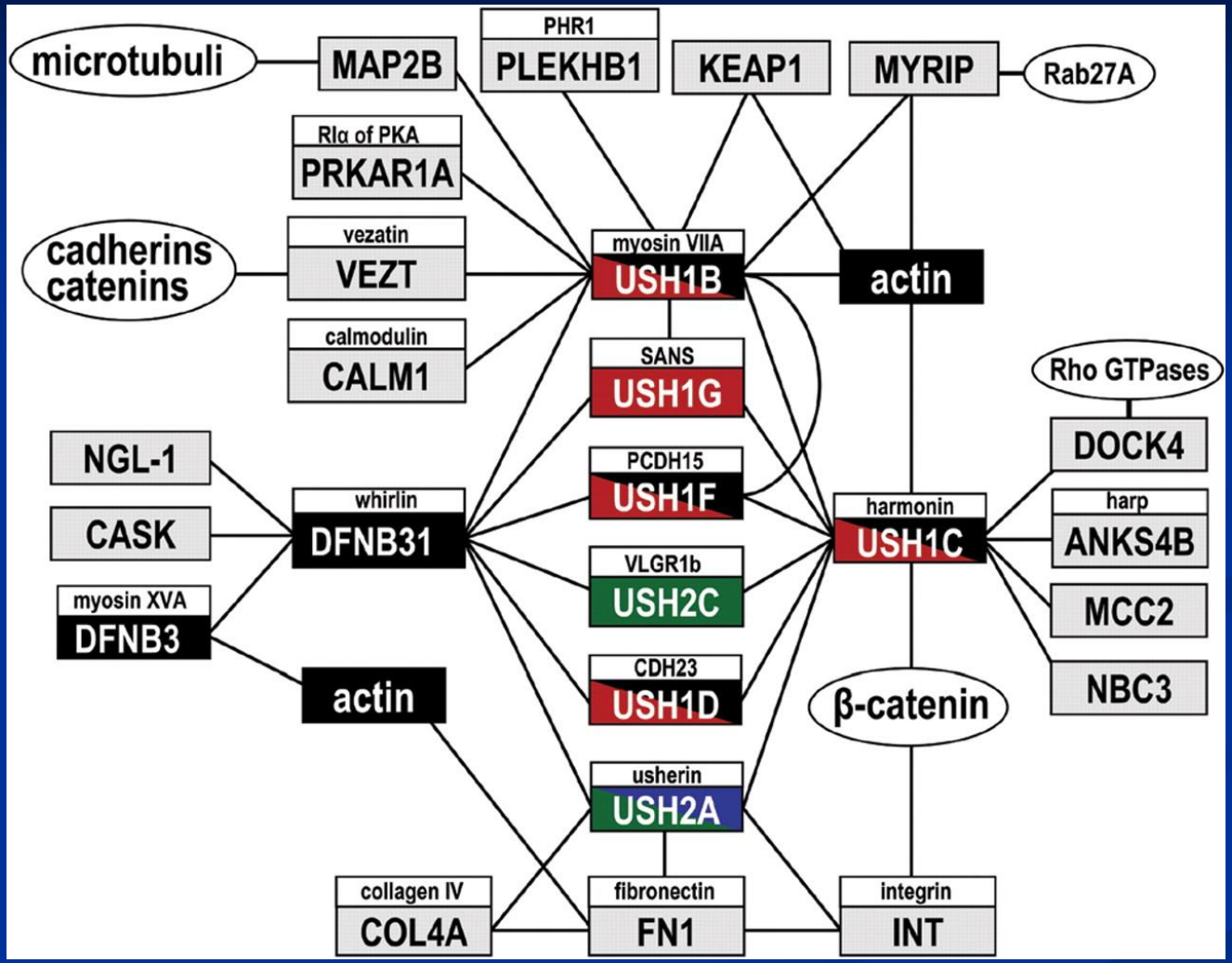
Human Molecular Genetics

The Usher protein network.



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Human Molecular Genetics

What else could be causing the hearing loss?

- CMV
- Other genetic
- Funny inner ear anatomy
- Other causes of hearing and vision loss
  - Prematurity
  - Alstrom syndrome
  - Two different causes for hearing loss and vision

Prenatal Infections

- TORCHES
- Toxoplasmosis 1:8000; 0-26% have HL, decreased if treated promptly
- Rubella (one reported case in 2006; but baby can get if mother vaccinated during pregnancy)
- CMV 1/100-200 births
- Herpes 1:2500-10,000, but HL very rare unless the baby has obvious systemic infection
- Syphilis 11/100,000 (2002)
- Inflammatory mediators pre/peri natal

Hearing Loss due to Perinatal Causes

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

Postnatally Acquired Infections

- Bacterial meningitis
  - Marked decrease since HIB, Prevnar®
  - N. meningitidis vaccination
- 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 hearing loss
- HIV
- EBV
- Ramsay-Hunt (Varicella zoster)
- Otitis media/cholesteatoma

Hearing Loss due to Postnatal Causes

- Trauma
- Head trauma
  - Sports
  - Altercations
  - MVA
  - Child abuse
- Noise
  - MP3
  - Hunting
- Radiation
- Surgery
- Autoimmune

Postnatally acquired causes of HL

- Ototoxicity
- Aminoglycosides
  - Mitochondrial genes confer increased susceptibility
  - Children with cystic fibrosis
  - Transplants
- Macrolides
  - Azithromycin, clarithromycin, erythromycin
- Diuretics
  - Furosemide (Lasix®)
- Retinoic acid
- Aspirin, acetaminophen with codeine, other

Children's Hospital Boston
300 Longwood Avenue, Boston, MA 02115
Telephone (617) 355-6461

REPORT OF AUDIOLOGICAL EVALUATION
DEPARTMENT OF OTOLARYNGOLOGY AND COMMUNICATION ENHANCEMENT

USE PLATE OR PRINT

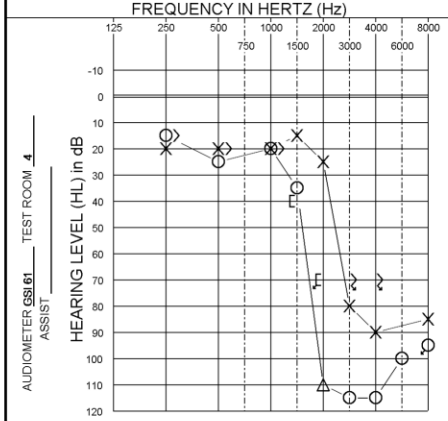
MRN: 111-11-11
NAME: PATIENT , CYSTICFIBROSIS
DOB: 12/ /1982
EN:

DATE OF EXAM: 10/19/2006
REFERRED BY: Inpatient
TESTED BY: Ellyn Zitzer, M.A., CCC-A

REFERRAL REASON

- ☐ History of middle ear problems.
- ☐ Speech-language concerns.
- ☒ Hearing concerns.
- ☐ Rule out hearing loss.
- ☐ Post-operative hearing test: Procedure _____ Date: _____
- ☐ Most recent hearing test: Results _____ Date: _____
- ☐ Newborn hearing screen: Pass/Refer _____
- ☒ Other: C/o hearing problems Right ear, H/O CF

FREQUENCY IN HERTZ (Hz)



	AIR CONDUCTION UNMASKED	AIR CONDUCTION MASKED	BONE CONDUCTION UNMASKED	BONE CONDUCTION MASKED	SOUND FIELD (NOT EAR SPECIFIC)	NO RESPONSE
RIGHT	O	△	<	[		↙
LEFT	X	□	>	]		↘
BOTH			^		S	↓

TEST STIMULI: ☒Pure tones ☐Warbled tones ☐Narrow band noise
TRANSDUCER: ☐Supra-aural earphones ☒Insert earphones

SPEECH AUDIOMETRY

	SRT (dBHL)	SAT (dBHL)	MASK	WORD RECOGNITION %	WORD RECOGNITION dBHL	WORD RECOGNITION MASK
R	25			88	65	
L	15			92	55	
BONE						
SF						

SPEECH AUDIOMETRY MATERIALS
SPEECH RECEPTION THRESHOLD (SRT): W2 Spondees
SPEECH AWARENESS THRESHOLD (SAT):
WORD RECOGNITION: CID W-22
☐Male ☒Live Voice
☒Female ☐Tape/CD

TEST METHODS FOR AUDIOGRAM

- ☒Conventional
- ☐Conditioned Play Audiometry
- ☐Visual Reinforcement Audiometry
- ☐Behavioral Observation Audiometry

RELIABILITY
- ☒Good
- ☐Fair
- ☐Poor

ACOUSTIC IMMITTANCE MEASURES

TYMPANOMETRY PROBE FREQ. 226 Hz

EAR	EQUIV CANAL VOL (cc)	PEAK PRESSURE (daPa)	STATIC ADMITTANCE (mmho)	GRADIENT (daPa)
RIGHT	0.9	-10	0.3	
LEFT	0.9	10	0.2	

ACOUSTIC REFLEX THRESHOLDS (dBHL)

PROBE EAR	STIM EAR (MODE)	500 Hz	1000 Hz	2000 Hz
RIGHT	RIGHT (IPSI)			
	LEFT (CONTRA)			
LEFT	LEFT (IPSI)			
	RIGHT (CONTRA)			

AUDIOMETRIC RESULTS:

RIGHT EAR:
- ☐ Normal hearing _____.
- ☒ normal-to-severe sensorineural hearing loss.

LEFT EAR:
- ☐ Normal hearing _____.
- ☒ normal-to-profound sensorineural hearing loss.

UNMASKED BONE (not ear-specific):
- ☐ Normal.
- ☐ Consistent with conductive component.
- ☐ Consistent with sensorineural component.

SOUND FIELD (Loudspeaker: not ear-specific):
- ☐ Normal hearing for at least one ear _____.
- ☐ _____degree of hearing loss for at least one ear (the better hearing ear if there is an ear difference).

INTERPRETATION OF TYMPANOMETRY:

	RIGHT EAR	LEFT EAR
Normal middle ear measures.	☒	☒
Negative middle ear pressure.	☐	☐
Low middle ear compliance peak with normal pressure.	☐	☐
Hypercompliant middle ear.	☐	☐
Flat tracing (poor middle ear compliance).	☐	☐
Large volume measure consistent with patent pressure equalization tube and/or non-intact eardrum.	☐	☐

OTHER TEST FINDINGS:

See above for speech audiometry hearing test results

COMMENTS & RECOMMENDATIONS:

Bilateral, significant, high frequency SNHL, greater in Right ear than Left ear. Advised patient to consider a trial with a hearing aid for the left ear. May also consider BiCros aid. Consult by ORL is recommended in light of present findings. Retest hearing as per medical management needs and communication interventions.

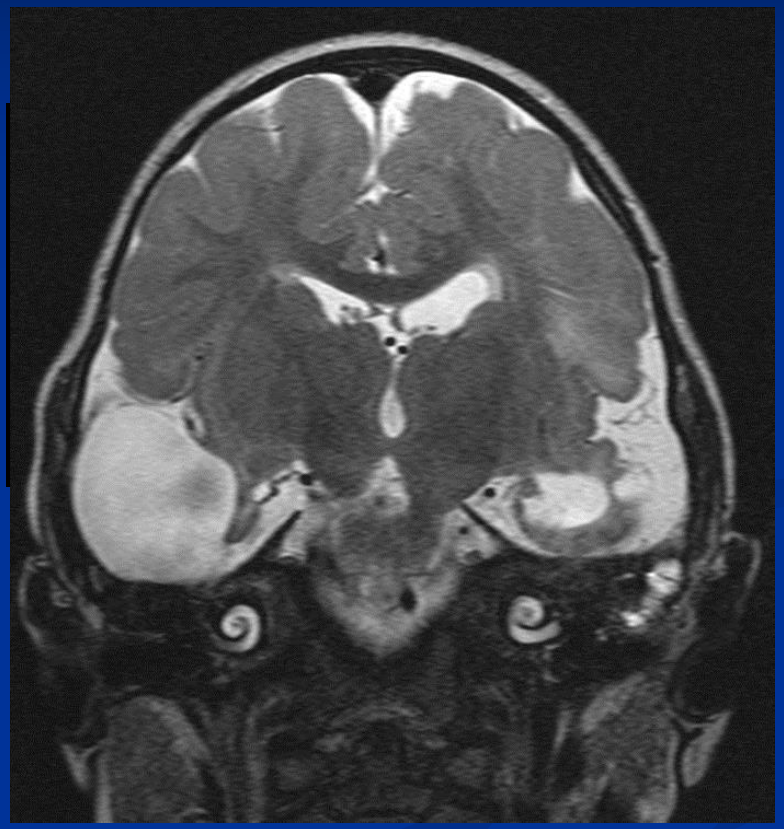
AUDIOLOGIST'S SIGNATURE: Ellyn Zitzer, MA, CCC-A

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

Radiological features

- Polymicrogyria
- Cerebral calcification
- White matter loss
- Ventricular dilatation
- Cystic changes
- Overall, abnormal in 54%



Genetics of Hearing Loss: Non-syndromic

- ~140 loci for Non-Syndromic HL
  - 70 recessive (DFNB)
  - 55 dominant (DFNA)
  - 5 X-linked (DFN)
  - 2 modifier (DFNM)
  - Several Mitochondrial (MTN)
  - 1 Y-linked (DFNY)
  - 1 Auditory neuropathy (AUN)

Van Camp G, Smith RJH. http://webho1.ua.ac.be/hhh 3.5.09

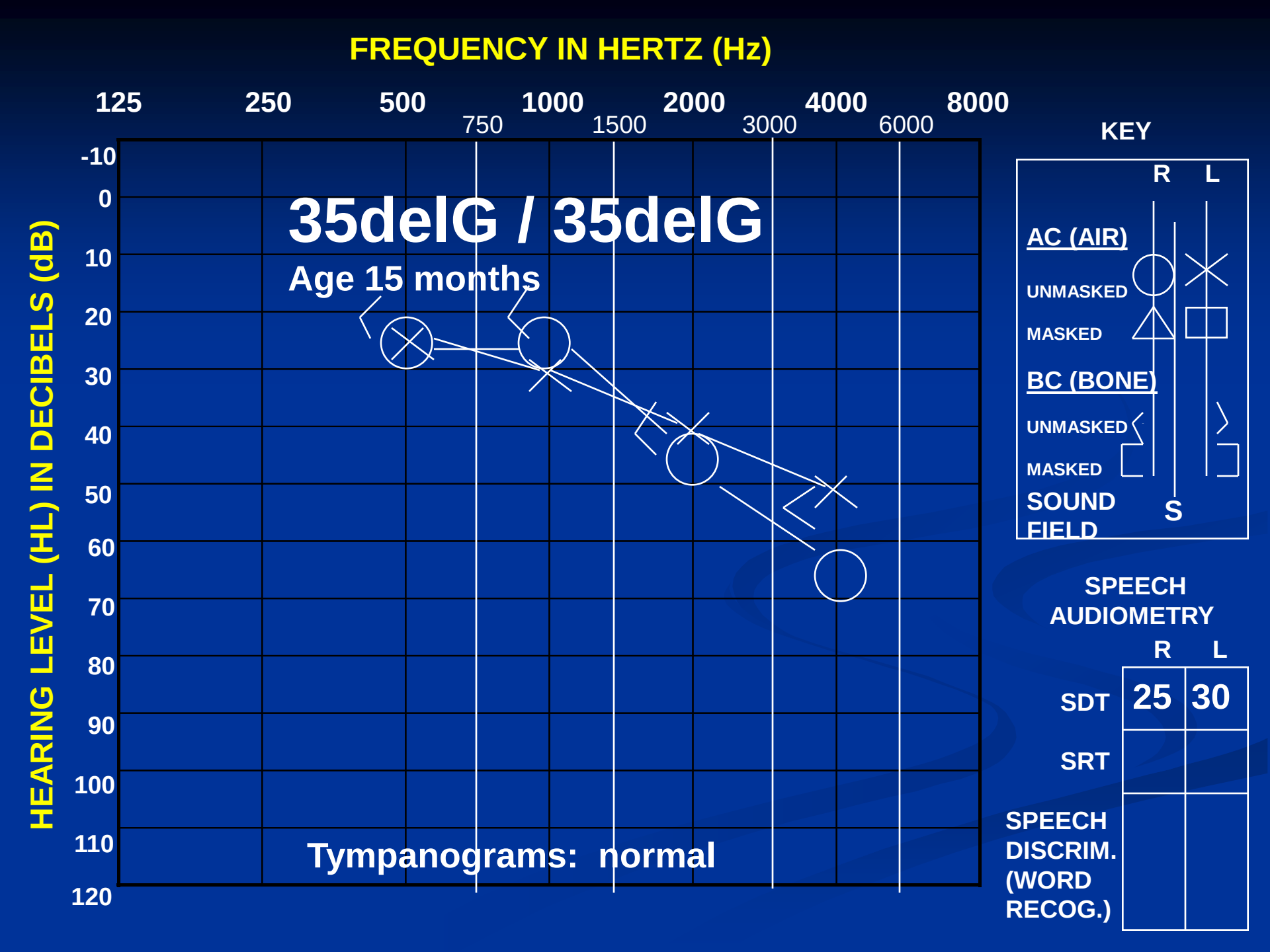
Syndromic Hearing Loss

Syndrome	**Inheritance**	**Prevalence****
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

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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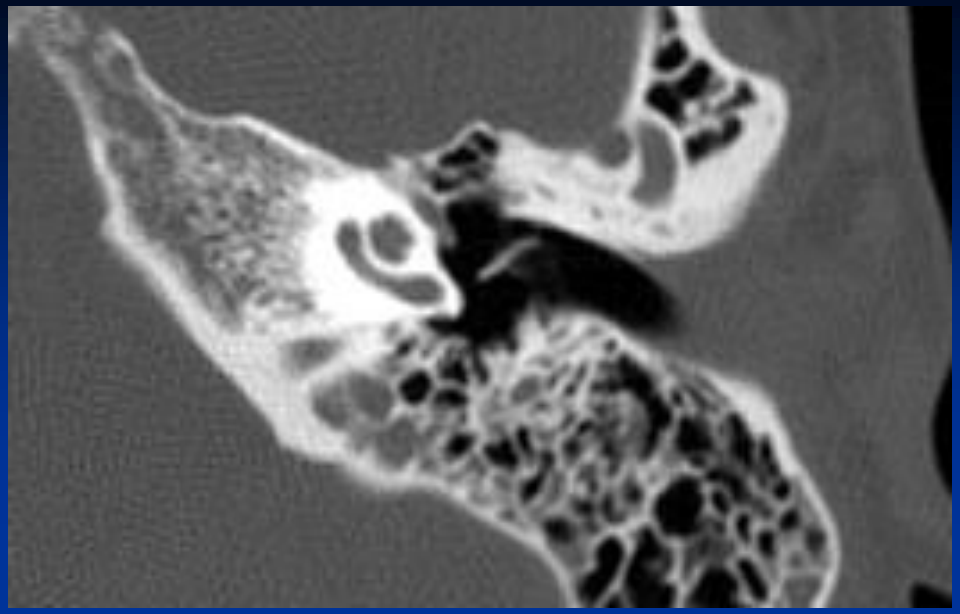
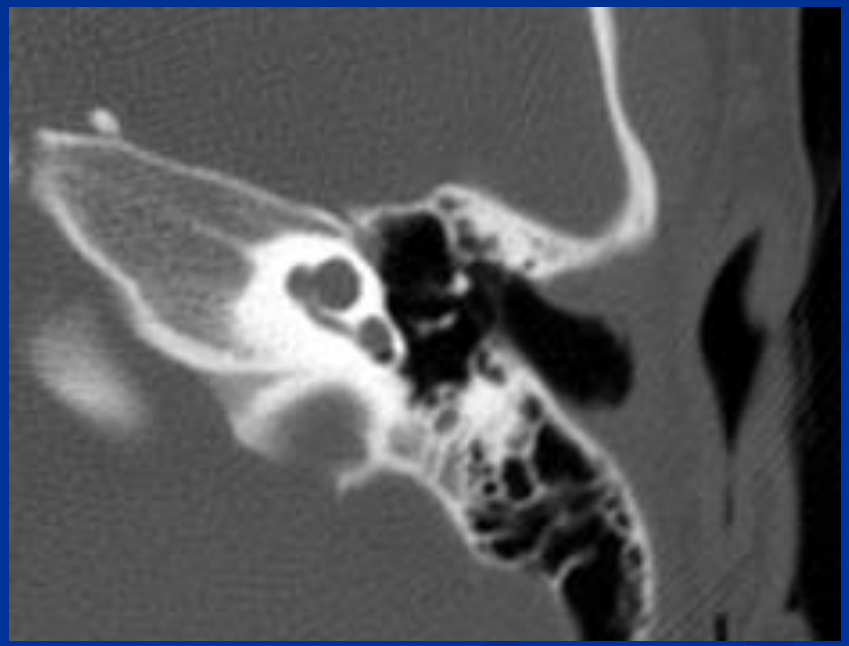
0
10
20
30
40
50
60
70
80
90
100
110
120
35delG / 35delG
Age 15 months
Tympanograms: normal
KEY
R
L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD
S
SPEECH AUDIOMETRY
R
L
SDT
25
30
SRT
SPEECH DISCRIM. (WORD RECOG.)

Pendred Syndrome

- 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
- SLC26A4 (PDS) causes both Pendred's Syndrome and recessive non-syndromic SNHL (DFNB4)





-Incomplete partition
-Modiolar deficiency
-“Mondini”

Testing for Usher Syndrome

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

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 non-profound losses if Cx26 (and possibly Cx30) negative and CT/MRI normal

Genetics of Hearing Loss

- 2 pathogenic mutations in a known USH gene
- 2 mutations of unclear significance in an USH gene (VUS)
- 1 pathogenic mutation and one VUS
- 1 pathogenic mutation in two different USH genes (digenic)
- Otochip®
- Otogenome®
- Otoscope®
- Insurance

OtoChip™ for Hearing Loss and Usher Syndrome

Nonsyndromic

Cx26 Testing

Aminoglycosides

Mitochondrial
- 12S rRNA
- tRNA ser

Family Hx

X-linked
- POU3F4

Dominant
- MYO6
- ACTG1
- DSPP
- TECTA
- EYA4
- MYO7A
- COL11A2
- POU4F3
- TMC1
- MYO1A
- DIAPH1
- WFS1
- GJB3
- KCNQ4
- GJB6
- DFNA5
- MYH9
- COCH
- TFCP2L3

No Family Hx

Recessive
- MYO7A
- MYO15
- PDS
- OTOF
- TMPRSS3
- TECTA
- GJB6
- CLDN14
- TMC1
- STRC
- TMIE
- CDH23
- USH1C
- OTOA
- MYO3A
- PCDH15
- WHRN
- ESPN
- MYO6
- PRES

Syndromic

Appropriate Gene(s)

Usher Syndrome
- MYO7A
- SANS
- USH1C
- USH2A
- CDH23
- VLGR1
- PCDH15
- USH3

JLNS
- KCNE1
- KCNQ1

19 genes - 430 amplicons
~70,000 bases

Treatment for the Hearing Loss

- Hearing Aids
- Cochlear implants
- Molecular therapy for the hearing loss
  - Gene therapy
  - Different size genes
  - Different viral vectors

Cochlear Implants

- Bilateral severe to profound
- Infants and young children
  - Early diagnosis of USH helps with decision making
- Progressive hearing loss
- Effect on balance

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
  - Patients may not understand that the cause of hearing loss could still be genetic

Summary

- If definitely USH, hearing loss 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

Thank you!