The Genetics of Hearing Loss

Heidi L. Rehm, Ph.D.

Harvard Medical School

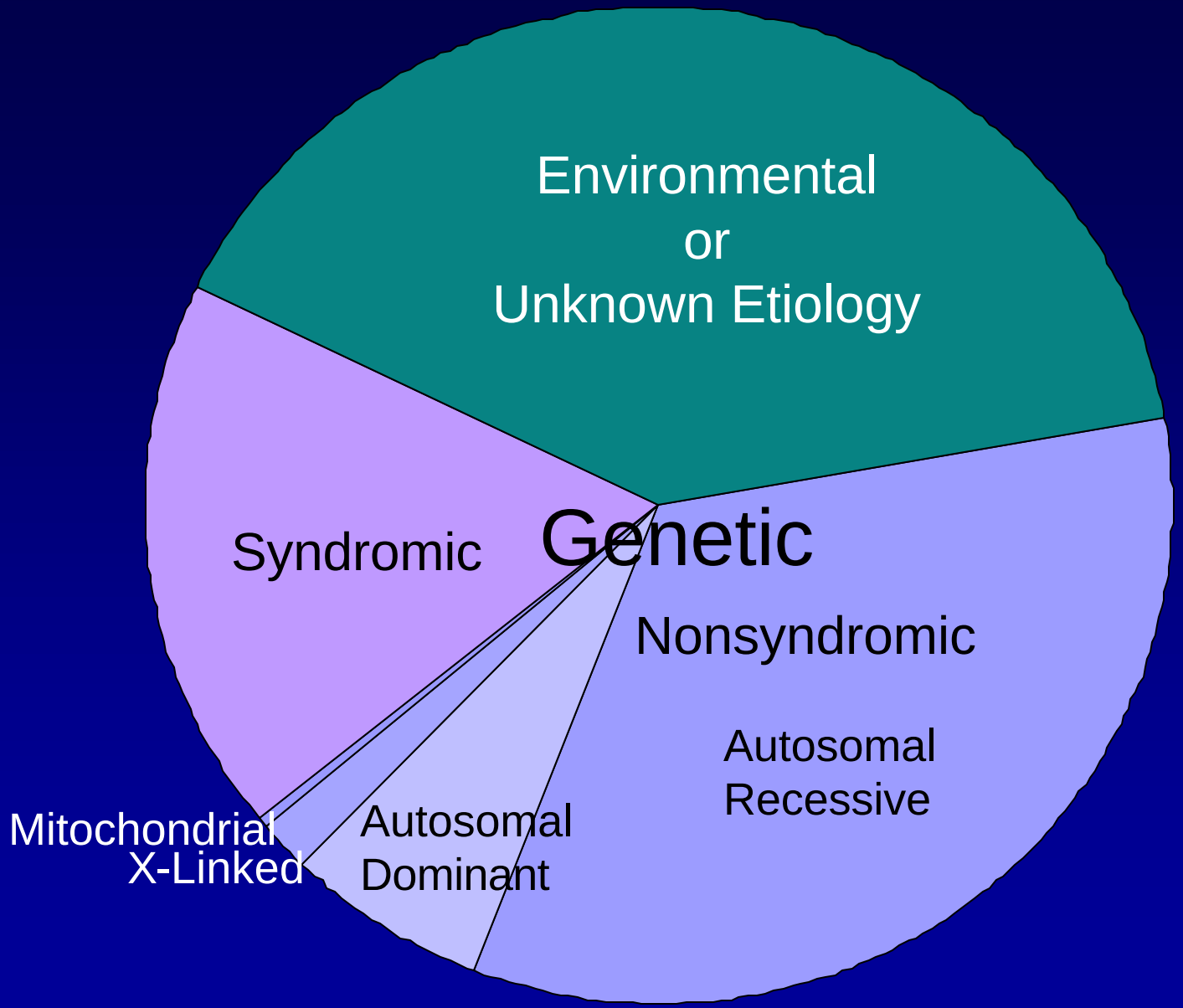
Boston, MA

Faculty Disclosure Information

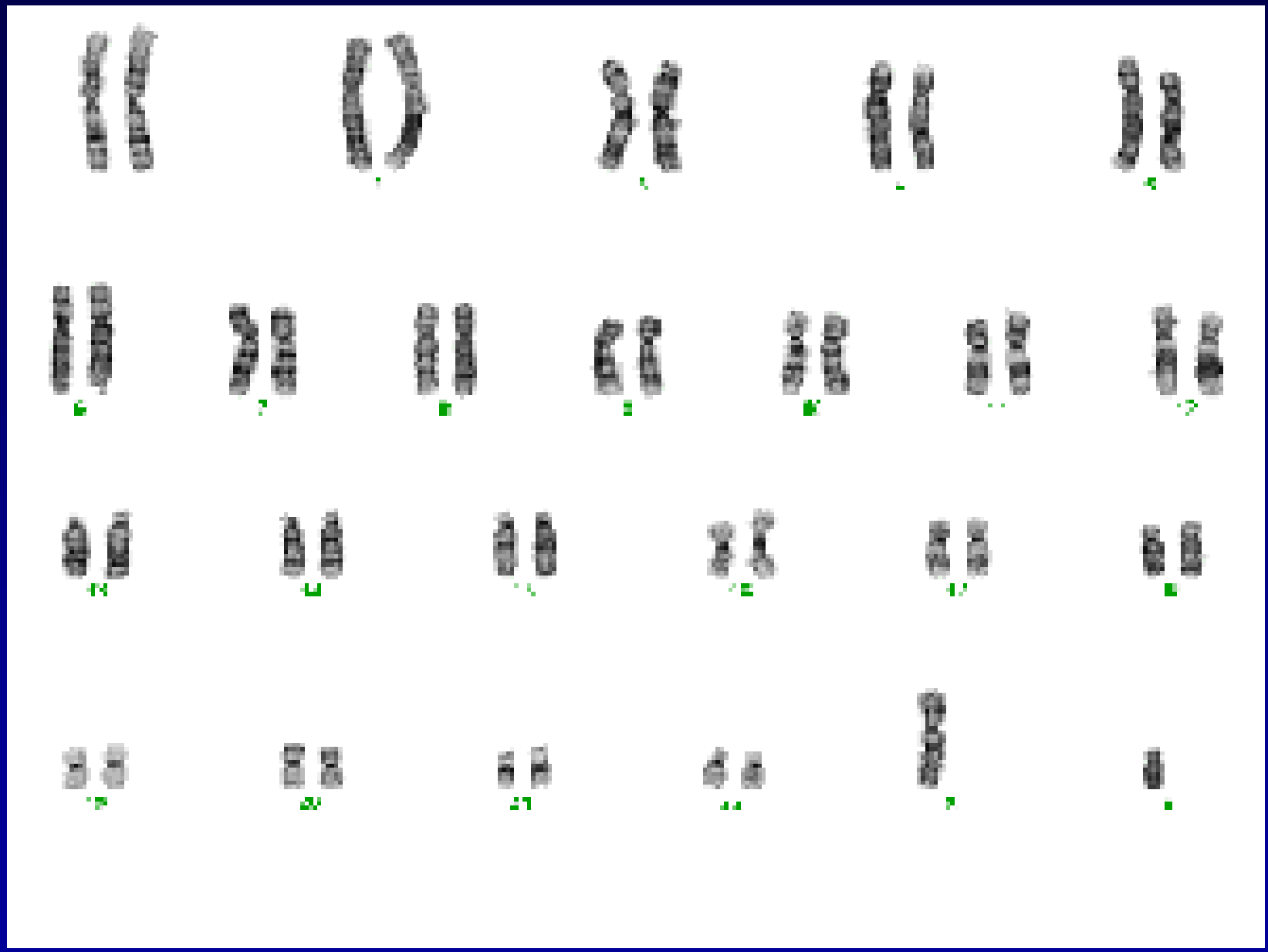
In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation

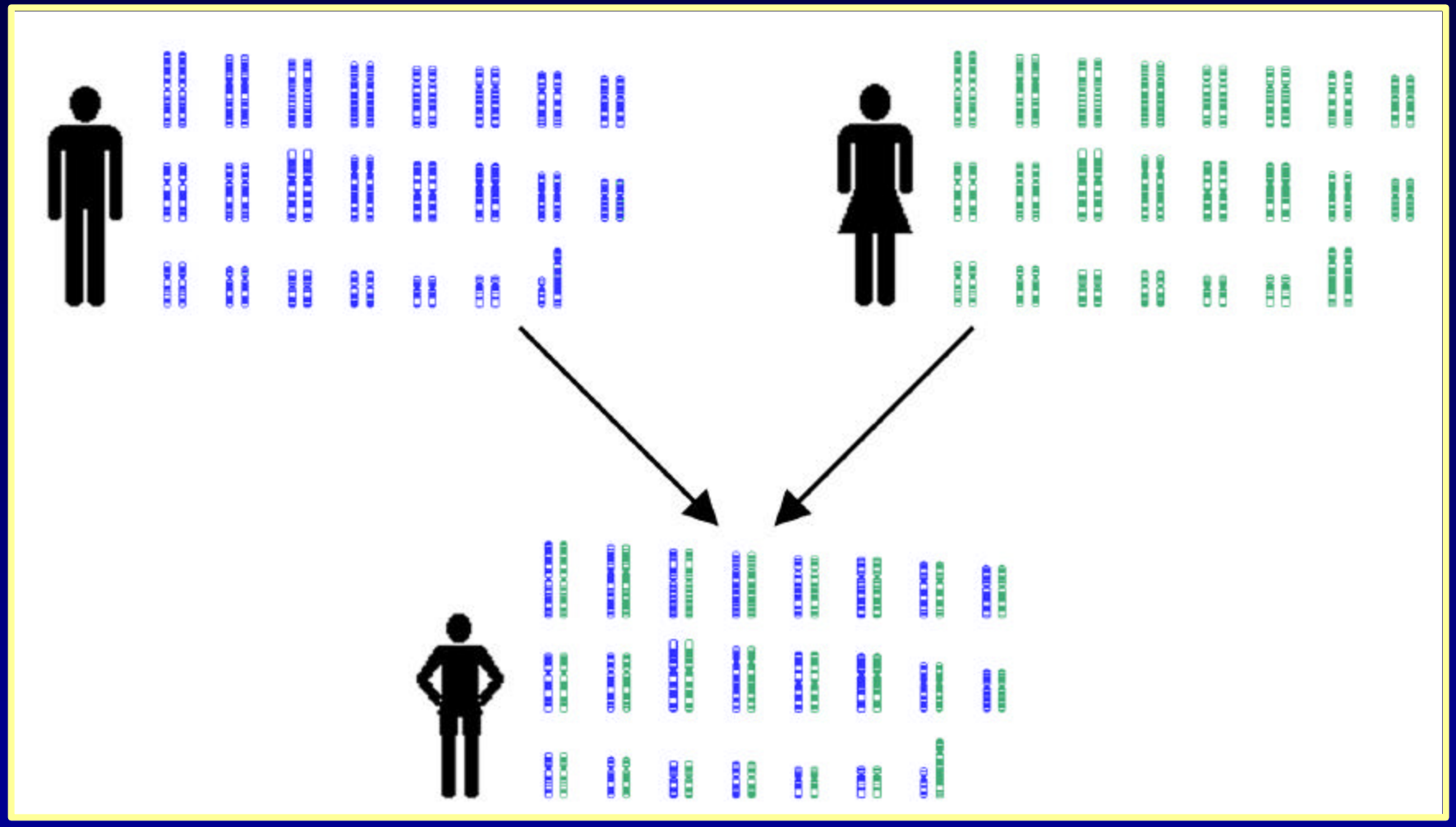
This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA or "off-label" uses of pharmaceuticals or devices.

Causes of Childhood Hearing Loss

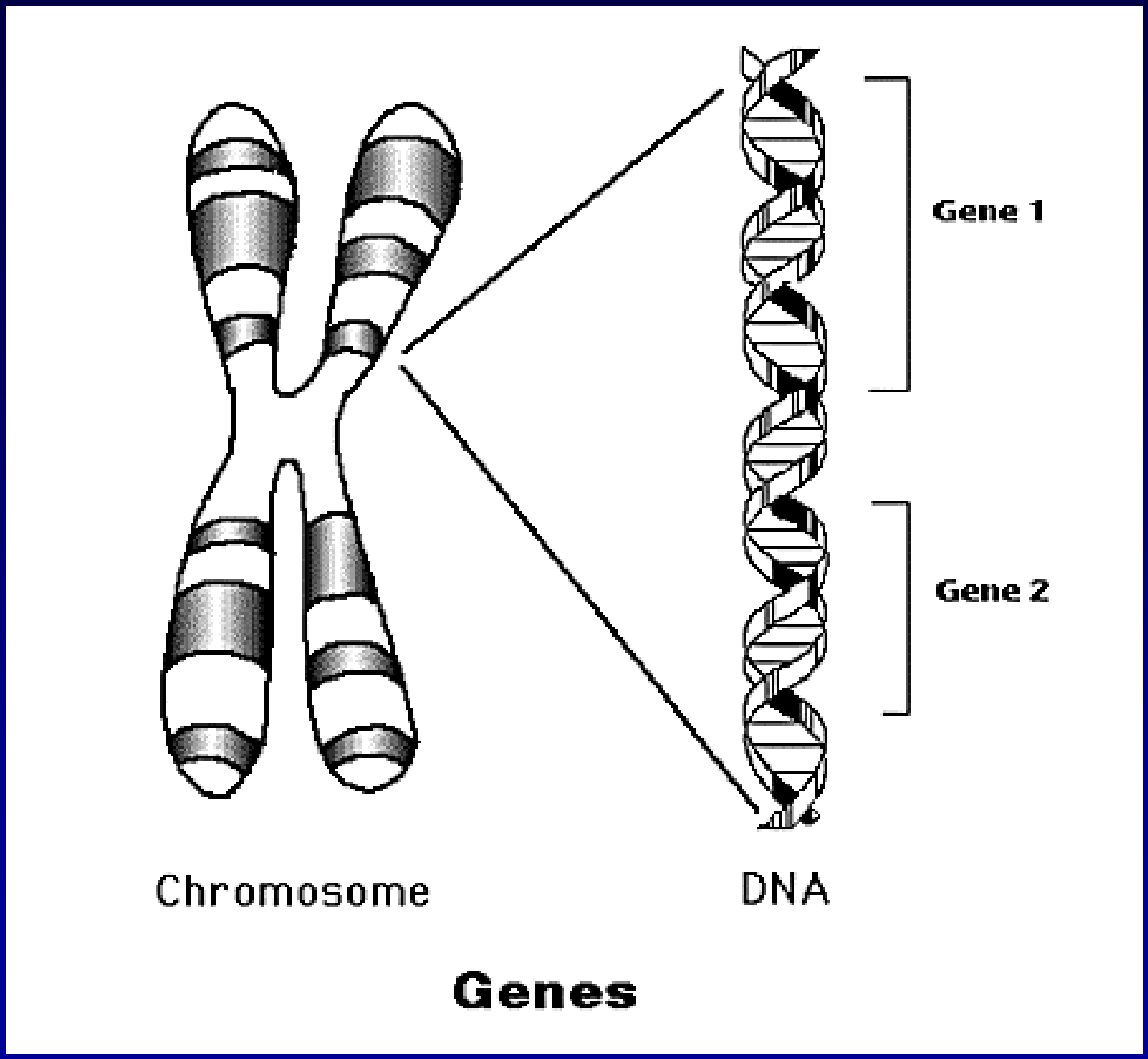


Human Karyotype





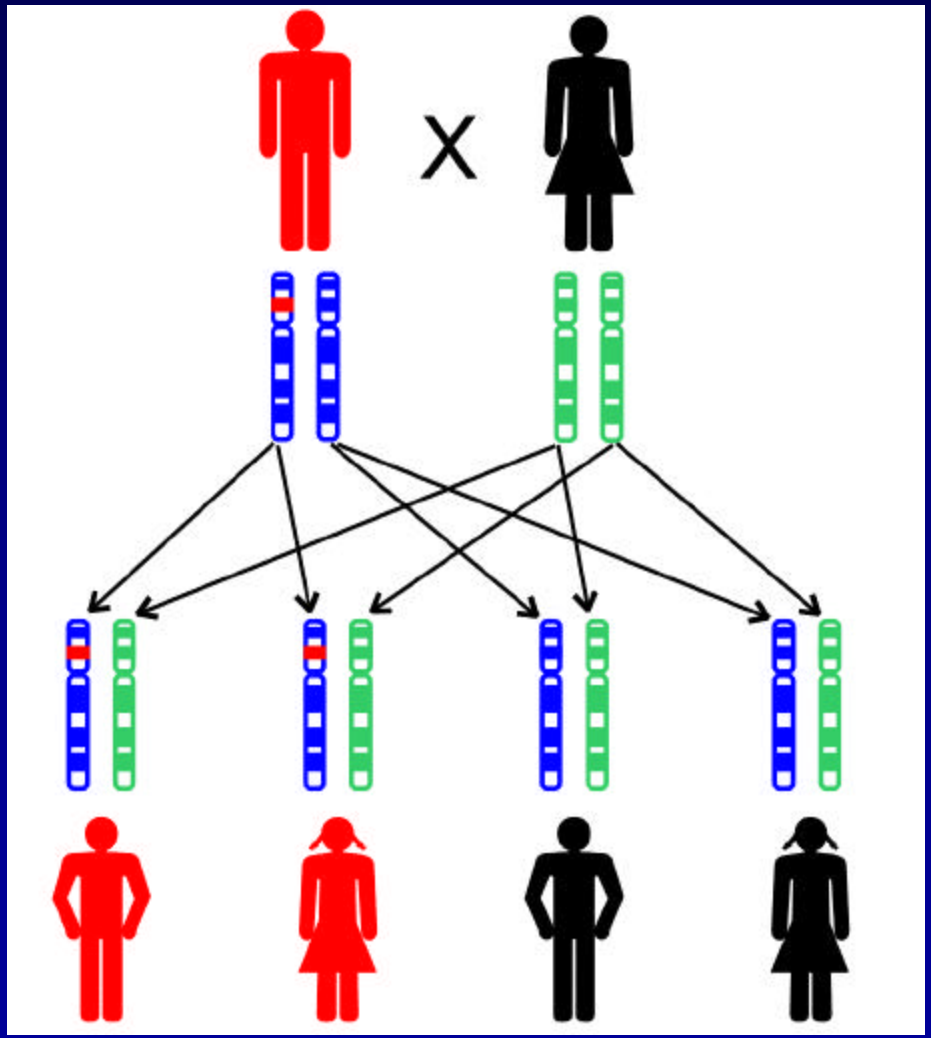
We inherit two copies of every gene, one from each parent.



http://www.accessexcellence.org/AB/GG/

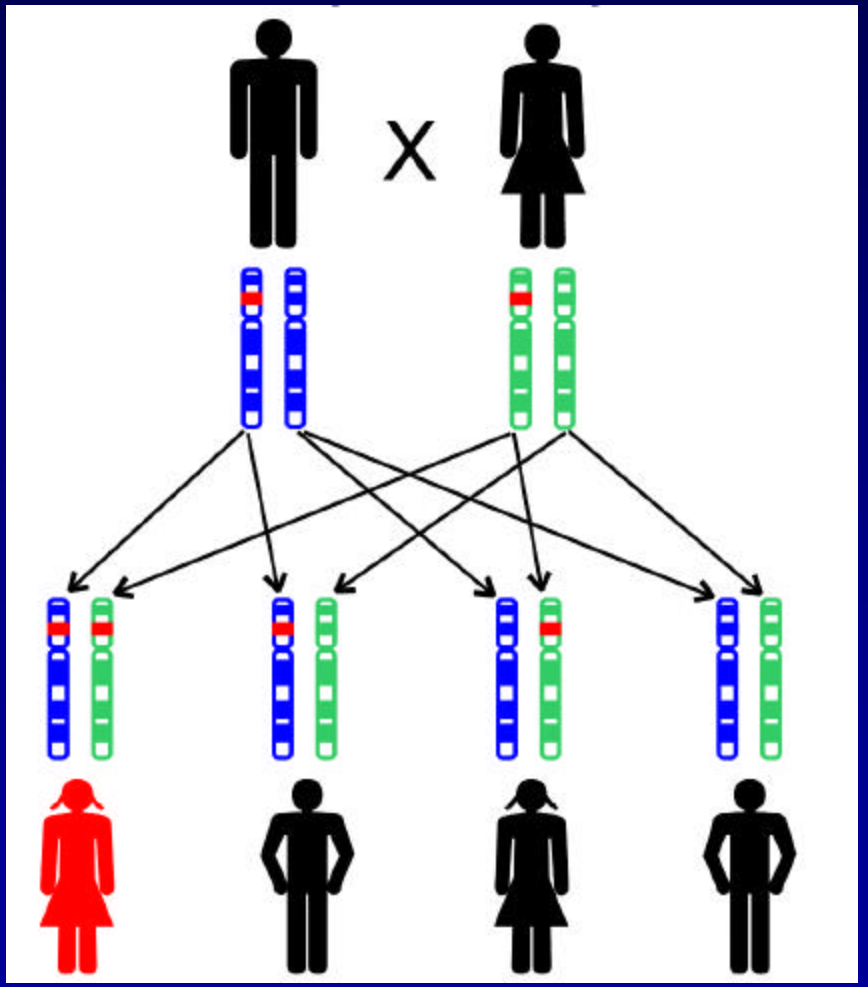
Dominant Mutations

- Dominant hearing loss can be caused by only one copy of a mutated gene
- Dominant hearing loss is seen in every generation
- If a parent has a dominant mutation, each child has a 50 % chance of inheriting it.



Autosomal Recessive Mutations

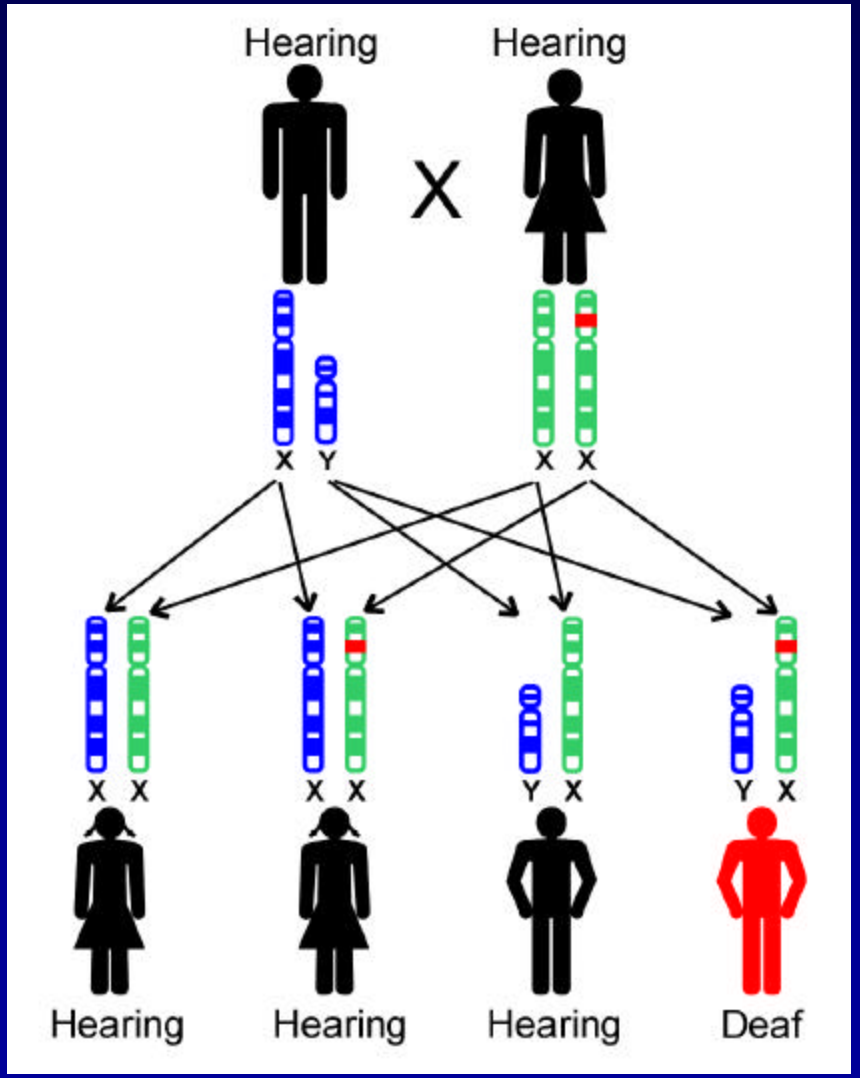
- For recessive hearing loss, both copies of a gene must be mutated to get hearing loss.
- Often, there is no family history of hearing loss.
- Each child will have a 25% chance of hearing loss.



A carrier is a person who carries one copy of a recessive mutation , but does not have hearing loss.

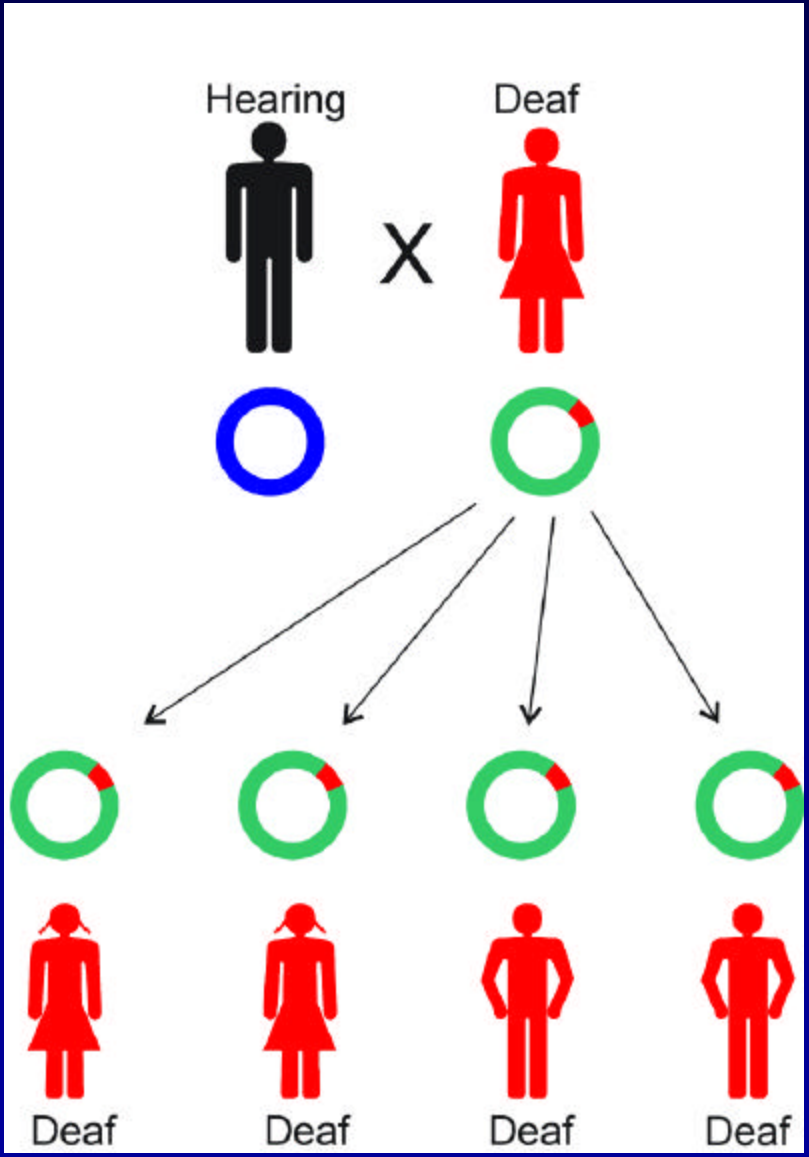
X-Linked Recessive Mutations

- Only males are affected.
- Each son will have a 50% chance of having hearing loss.
- Each daughter has a 50% chance of being a carrier.

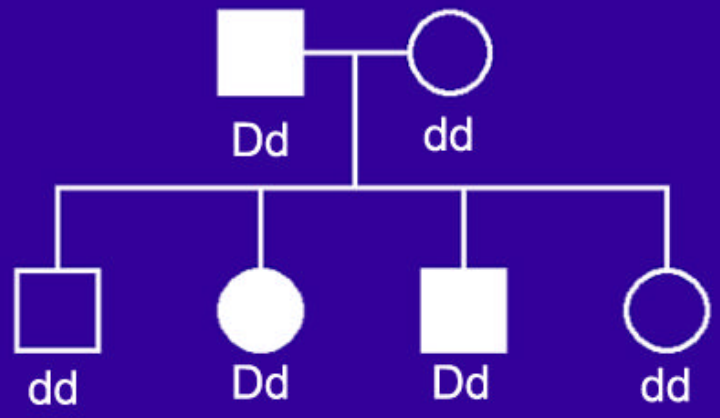


Mitochondrial Mutations

- Only the mother passes mitochondria to her children.
- All children will inherit a mitochondrial mutation from their mother.
- Mitochondrial mutations are often variable in their expression of hearing loss.

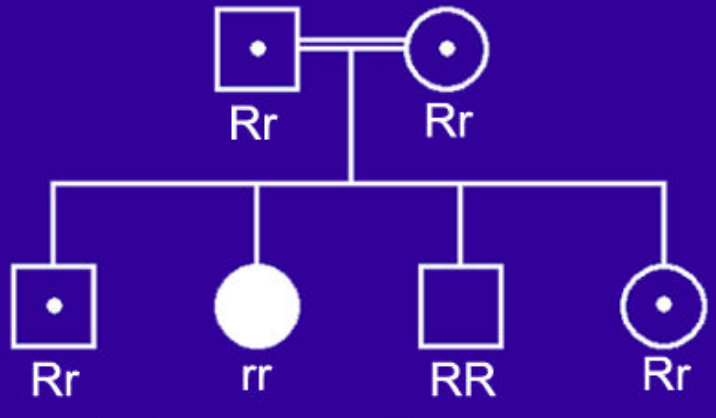


Modes of Inheritance



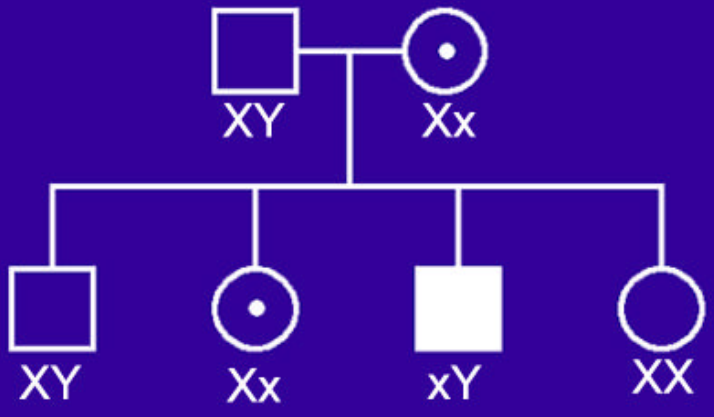
Autosomal Dominant

DFNA#

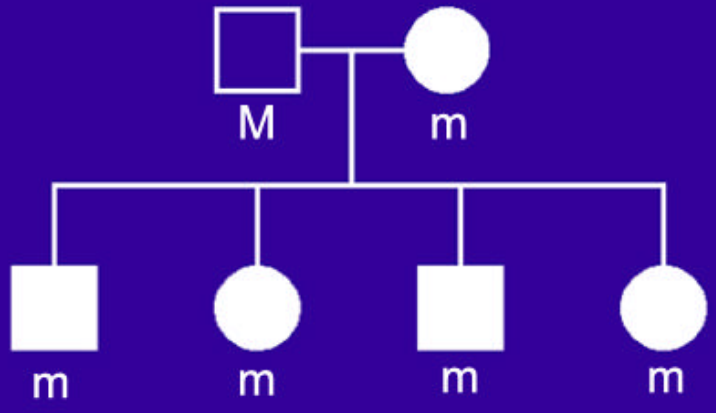


Autosomal Recessive

DFNB#

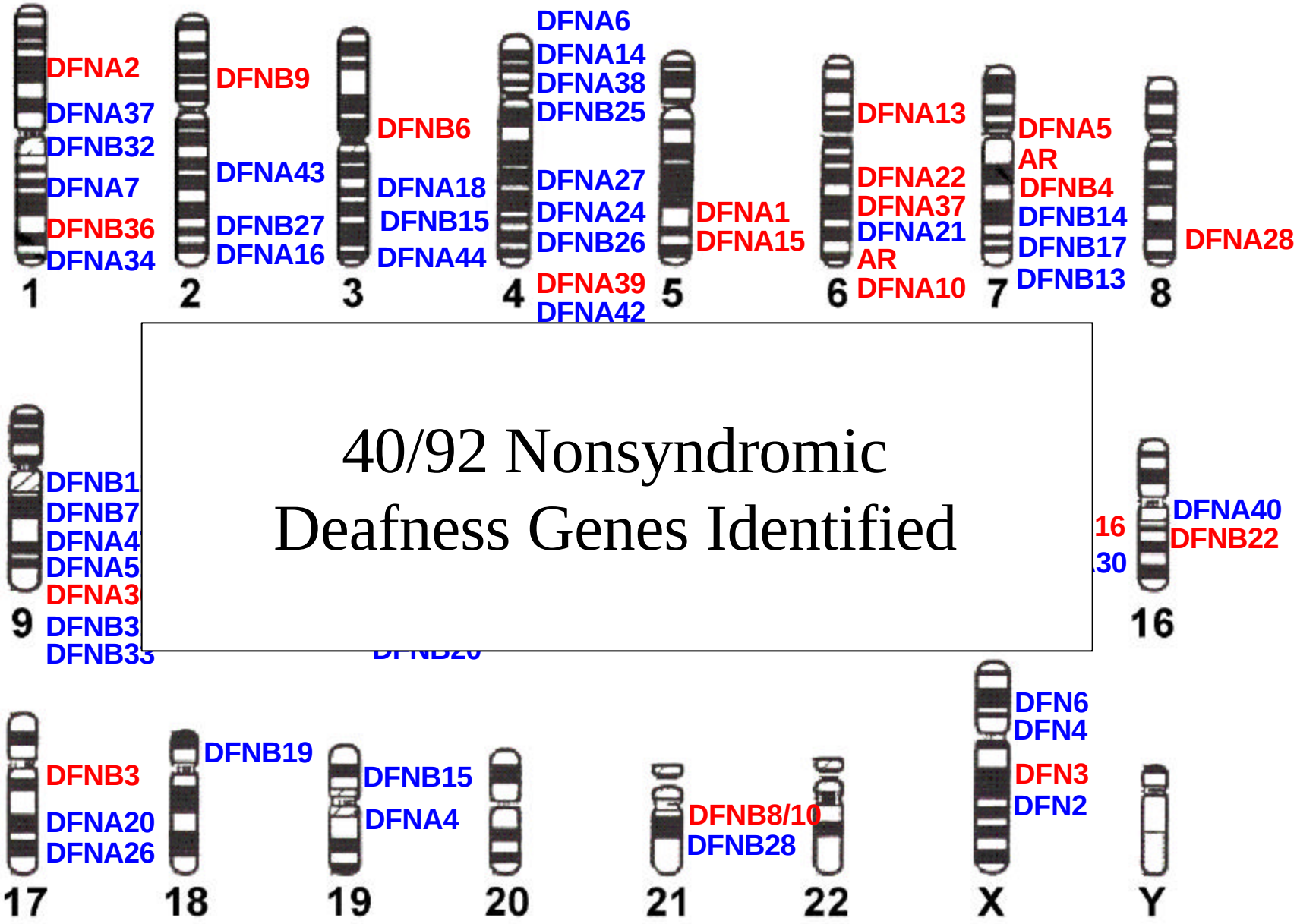


X-Linked DFN#



Mitochondrial

Nonsyndromic Deafness Genes in the Human Genome



40/92 Nonsyndromic Deafness Genes Identified

Syndromic Hearing Loss

Syndromes	Gene(s)
Alport	*COL4A5, COL4A3, COL4A4*
Branchio-Oto-Renal	*EYA1*
Jervell and Lange-Nielsen	*KCNQ1, KCNE1/IsK*
Mitochondrial (MELAS/MERRF)	$tRNA^{leu(UUR)}$, $tRNA^{lys}$
Neurofibromatosis type II	*NF2*
Norrie	*NDP*
Osteogenesis Imperfecta	*COL1A1, COL1A2*
Pendred	*PDS*
Stickler	*COL2A1, COL11A2, COL11A1*
Tranebjaerg-Mohr (DFN1)	*DDP*
Treacher Collins	*TCOF1*
Usher	*MYO7A, USH1C, CDH23, PCDH15, SANS, USH2A, VLGR1, USH3*
Waardenburg	*PAX3, MITF, SLUG, EDNRB, EDN3, SOX10*

There are currently over 400 syndromes with associated hearing loss.

Usher Syndrome

(3-6% of childhood deafness)

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

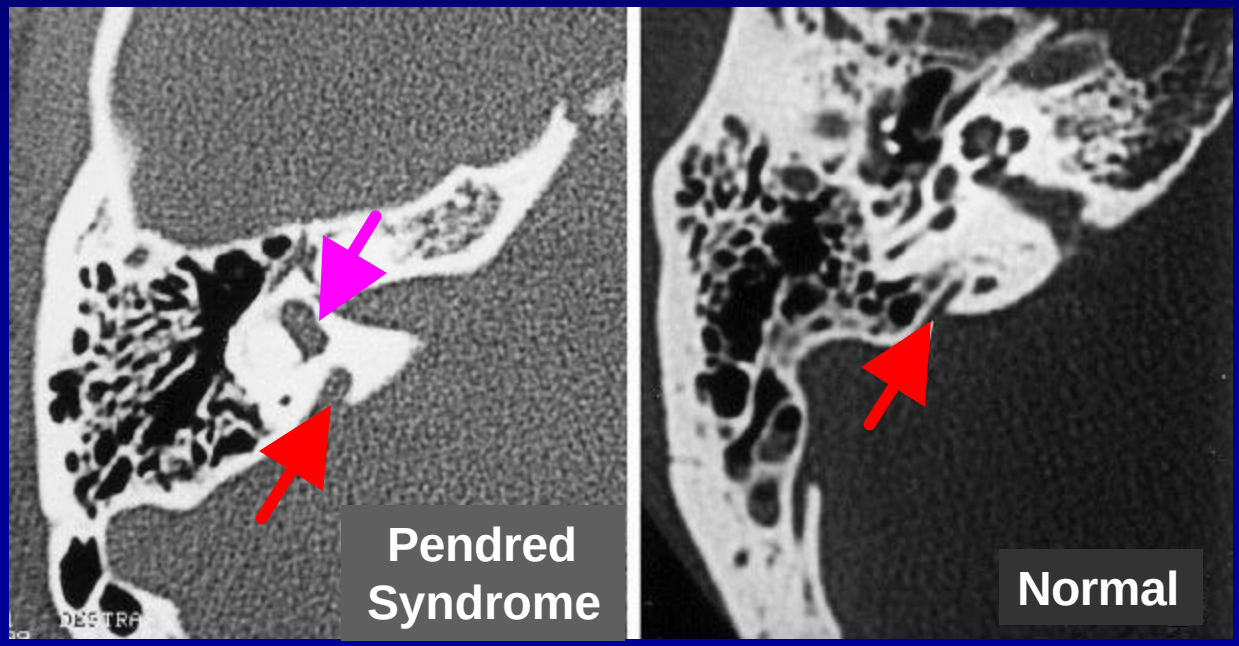
Usher Type	Locus	Gene	Relative Incidence
USH1A	14q32	unknown	2%
USH1B	11q13.5	*MYO7A*	60%
USH1C	11p15.1	*USH1C*	5%
USH1D	10q	*CDH23*	10%
USH1E	21q	unknown	Rare
USH1F	10q21.1	*PCDH15*	Rare
USH1G	17q24-25	*SANS*	Rare
USH2A	1q41	*USH2A (+51)*	80%
USH2B	3p23-24.2	unknown	Rare
USH2C	5q14.3-q21.3	*VLGR1*	15%
USH3	3q21-q25	*USH3*	100%

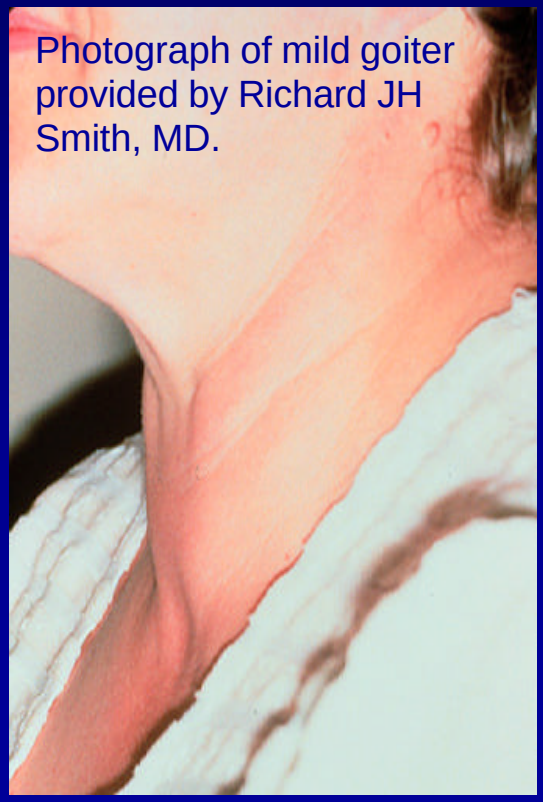
Jervell & Lange-Nielsen Syndrome

- Incidence: 1/250,000
- Phenotype
  - Severe-profound congenital sensorineural hearing loss
  - Prolonged QT interval
  - Syncope
  - Arrythmia
  - Sudden death
- Heart condition diagnosed by EKG and treatable with beta-blockers

DFNB4 Hearing Loss/Pendred Syndrome

- Congenital sensorineural hearing loss w/ EVA or Mondini
- ~20% with late onset goiter -> 10% hypothyroid
- Incidence: ~5% of congenital hearing loss
- Inheritance: Autosomal Recessive?



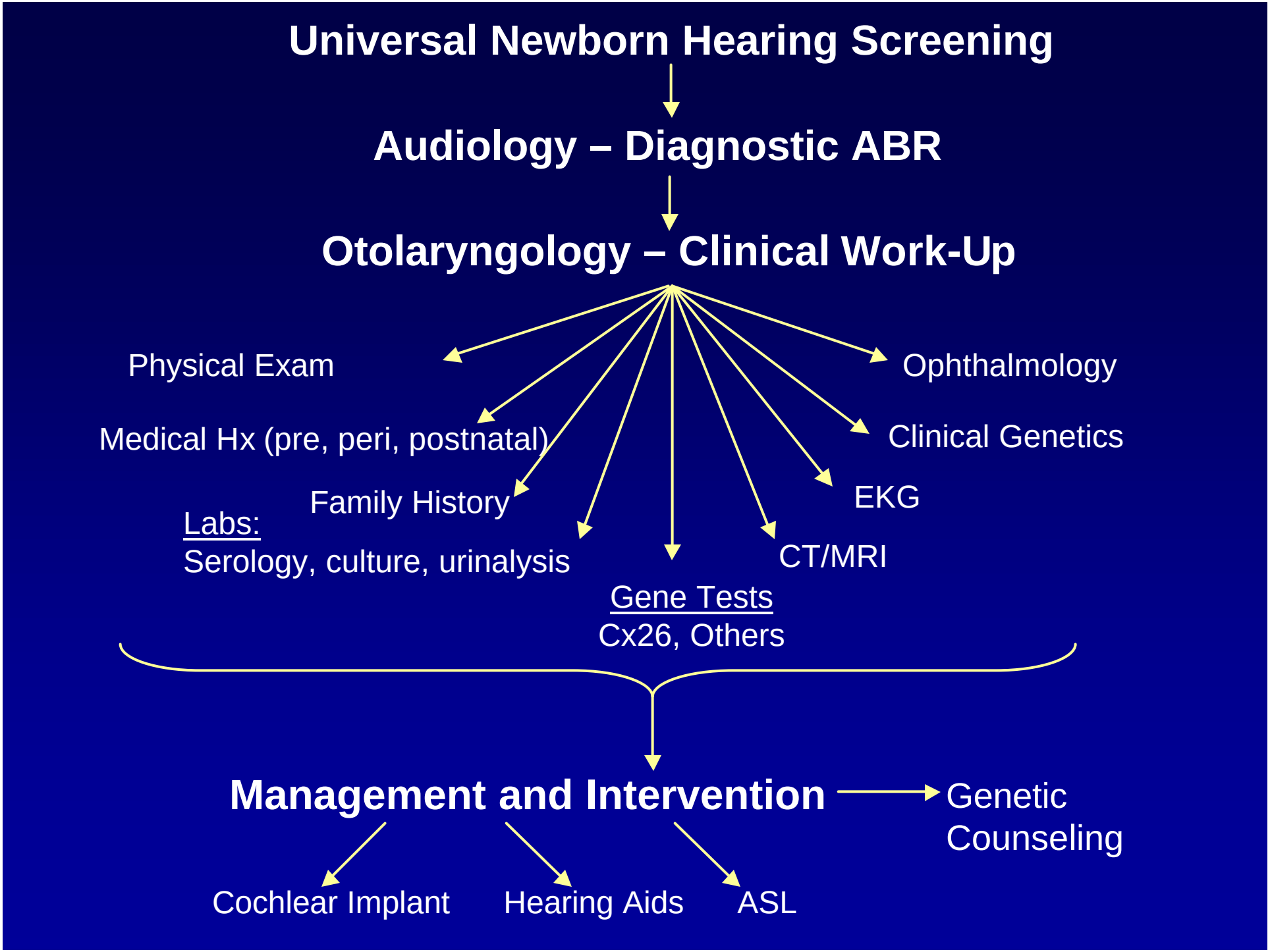


Photograph of mild goiter provided by Richard JH Smith, MD.

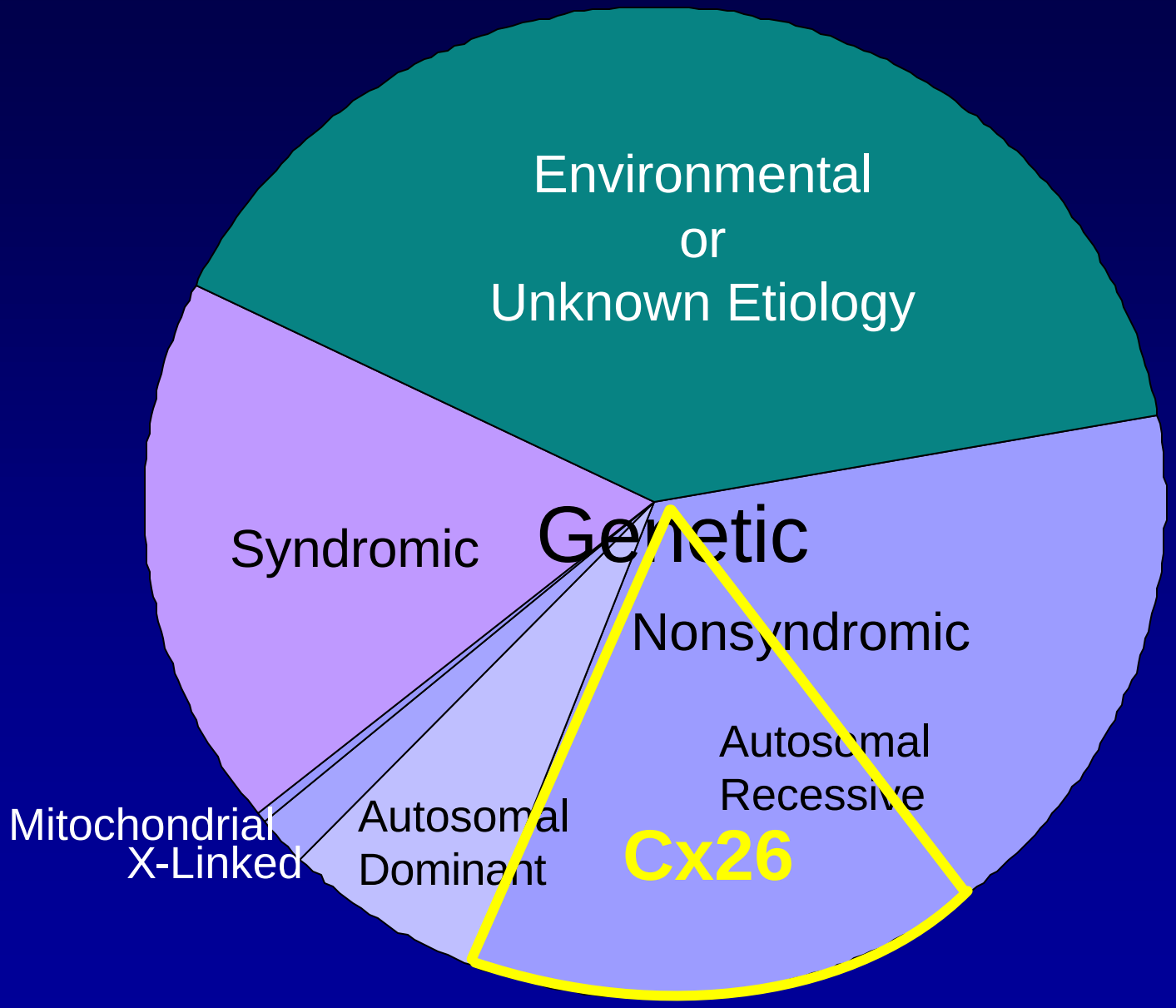
Hearing Loss and EVA

~30% of sporadic cases and ~90% of pts with family hx have mutations in the PDS gene.

Patients with 2 mutations will likely develop thyroid disease whereas those with only 1 or 0 mutations will likely not (Pryor et al. J Med Genet. 2005. 42(2):159-65)


Universal Newborn Hearing Screening
Audiology – Diagnostic ABR
Otolaryngology – Clinical Work-Up
Physical Exam
Medical Hx (pre, peri, postnatal)
Family History
Labs:
Serology, culture, urinalysis
Gene Tests
Cx26, Others
CT/MRI
EKG
Clinical Genetics
Ophthalmology
Management and Intervention
Genetic Counseling
Cochlear Implant
Hearing Aids
ASL

Causes of Childhood Hearing Loss



Should all Children with Hearing Loss have Cx26 Testing?

- Even cases that have an apparent explanation for hearing loss still may have Cx26 mutations
- Case A: Congenital syphilis
- Case B: CMV perinatal infection
- Case C: Prematurity
- Case D: Hyperbilirubinemia

GJB2 - Connexin 26

DFNB1 (Recessive) Mutations

Missense: M1V, T8M, G12V, K15T, S19T, I20T, R32C, M34T, V37I, A40E, A40G, G45E, E47K, W77R, V84L, L90P, V95M, H100Y, S113R, delE120, K122I, R127H, R143W, E147K, P175T, R184P, R184W, S199F, L214P, 05INS4, I203K, N206S, S139N, H100, E101G, L90V, M93I, 486INST, Q80R, I82M, S85P, A88S, L174R, L79P, Q80P, S19T, I20T, V27I+E114G, R32L, R165W

Nonsense: W24X, W44X, E47X, Q57X, Y65X, Y97X, Q124X, Y136X, W112X, W172X, C64X, Q80X, E147X

Frameshift: 31del14, 31del38, 35delG, 35insG, 51del12insA, 167delT, 176del16, 235delC, 269insT, 299delAT, 314del14, 333delAA, 290linsA, 310del14, 312del14, 509del14, 509insA, 515 del17, 631delGT, 504insAAGG, 515del17, 572delt, 645delTAGA, 302del3, 469delG

Splice Site: IVS1+1G>A

GJB6-D13S1830 (Cx30) Deletion

DFNA3 (Dominant) Mutations delE42, W44S/C, R75Q, D179N, R184Q, C202F, M163L

w/ Skin Disease G12R, S17F, D50N, N54K, G59A, D66H, R75W, R75Q

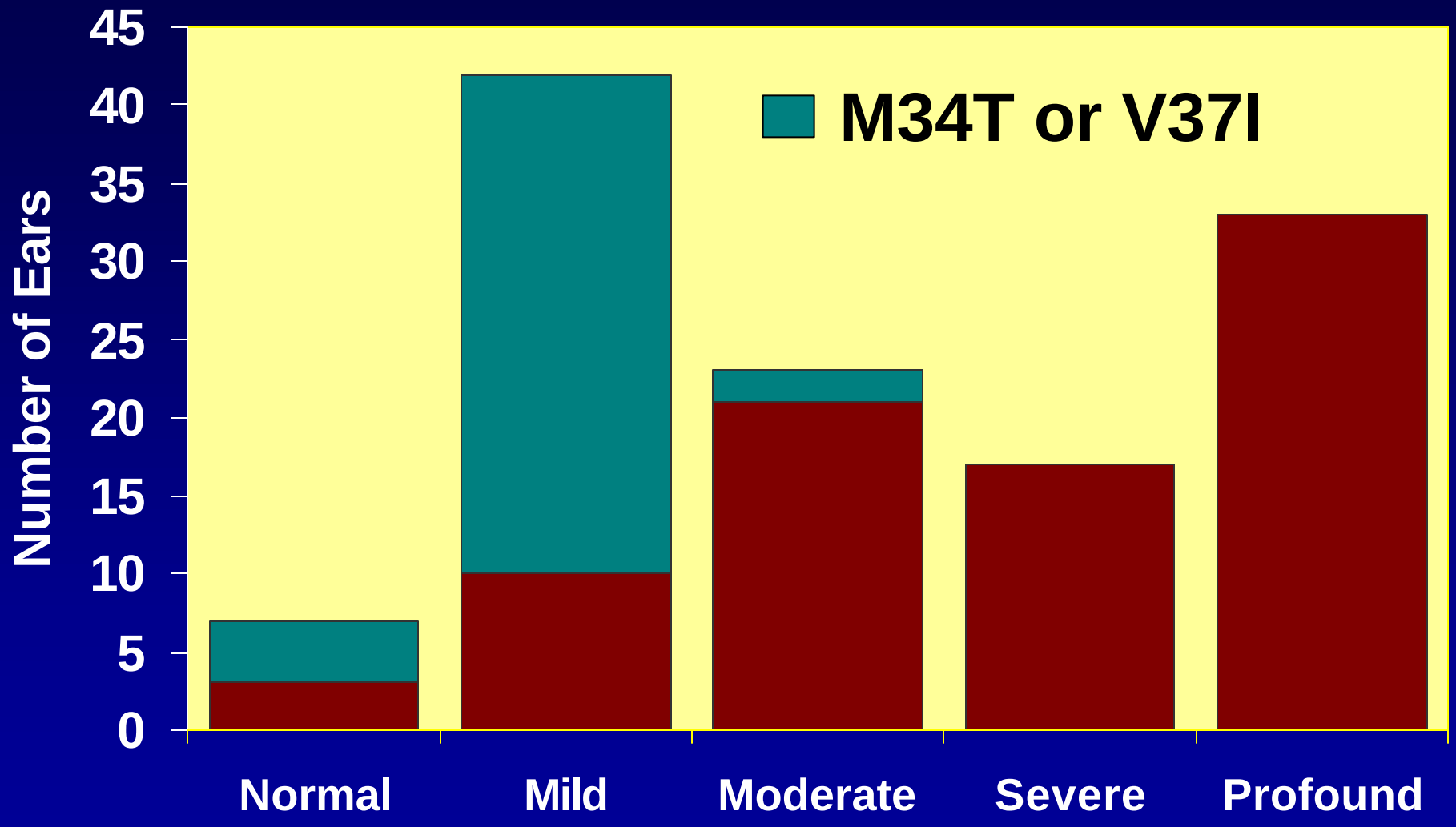
Unknown Significance H73R, R98Q, R127C, K224Q, IVS1, N54I, V84A, S85Y, 313delAA, 314delA, 360delG, T123N, E129K

Polymorphisms V27I, F83L, E114G, T123A, V153I, G160S, C169Y, I203T, Exon1 - 493del100, -3558T, -1C>T, I30I, A40A, R127H, S72C, Q80Q, L89L, R104R, I128I, V182V, V190V, 682C>T, 765C>T

Connexin 26 Gene Sequence

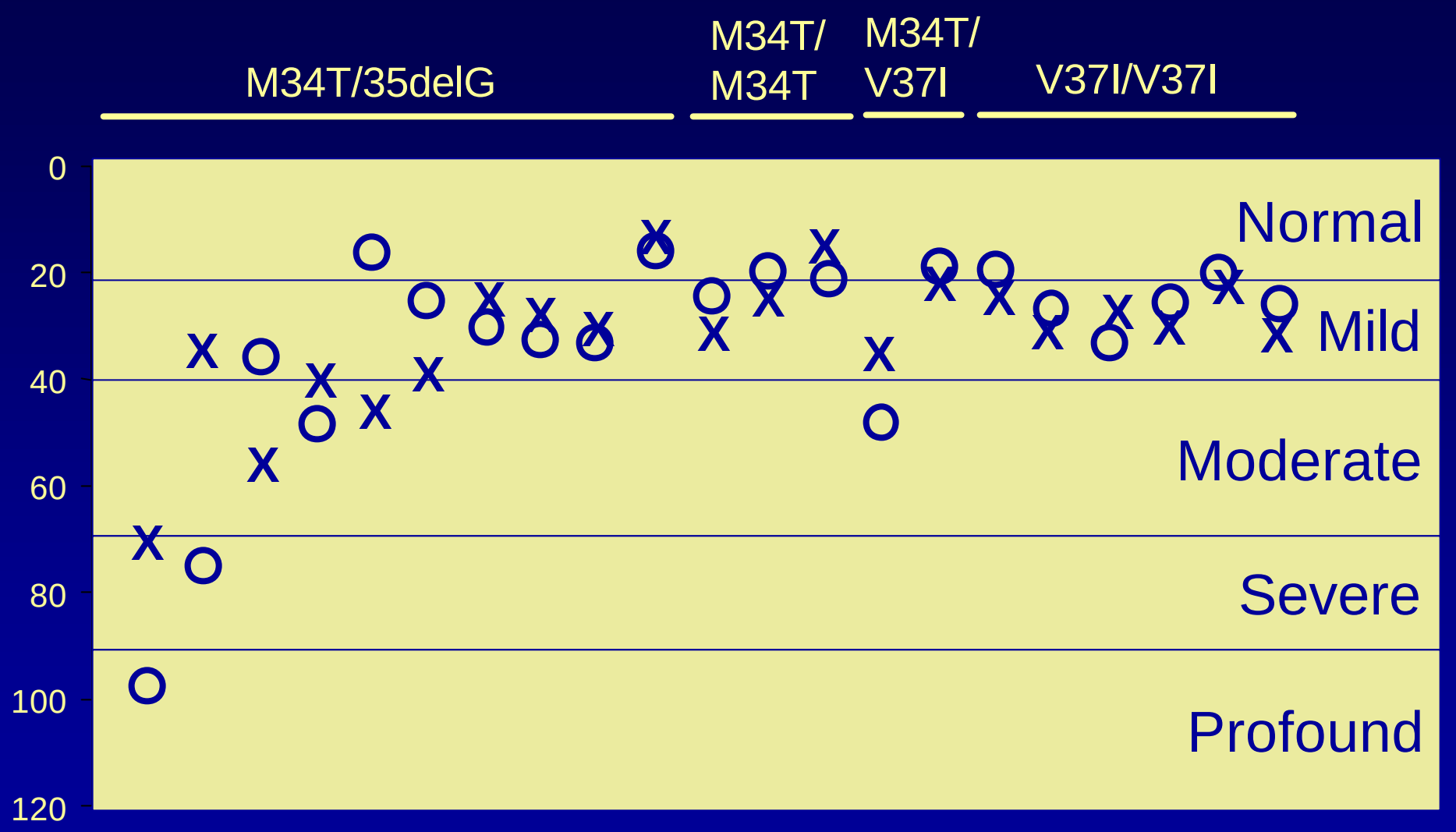
ATGGATTGGGGCACGCTGCAGACGATCCTGGGGGCTGTGAACA
AACACTCCACCAGCATTGGAAAGATCTGGCTCACCGTCCTCTTC
ATTTTTCGCATTATGATCCTCGTTGTGGCTGCAAAGGAGGTGTG
GGGAGATGAGCAGGCCGACTTTGTCTGCAACACCCTGCAGCCA
GGCTGCAAGAACGTGTGCTACGATCACTACTTCCCCATCTCCCA
CATCCGGCTATGGGCCCTGCAGCTGATCTTCGTGTCCAGCCCA
GCGCTCCTAGTGGCCATGCACGTGGCCTACCGGAGACATGAGA
AGAAGAGGAAGTTCATCAAGGGGGAGATAAAGAGTGAATTTAAG
GACATCGAGGAGATCAAAACCCAGAAGGTCCGCATCGAAGGCT
CCCTGTGGTGGACCTACACAAGCAGCATCTTCTTCCGGGTCATC
TTCGAAGCCGCCTTCATGTACGTCTTCTATGTCATGTACGACGG
CTTCTCCATGCAGCGGCTGGTGAAGTGCAACGCCTGGCCTTGT
CCCAACACTGTGGACTGCTTTGTGTCCCGGCCCACGGAGAAGA
CTGTCTTCACAGTGTTCATGATTGCAGTGTCTGGAATTTGCATC
CTGCTGAATGTCACTGAATTGTGTTATTTGCTAATTAGATATTGT
TCTGGGAAGTCAAAAAAGCCAGTTTAA

Hearing Loss Severity Associated with Biallelic Cx26 Mutations



Data from Children's Hospital Boston (Kenna and Rehm, 2005)

Pure Tone Averages for M34T and V37I Genotypes



Cx26 Gene Test Outcomes

1. **Two copies (homozygous) of a single mutation**

   e.g. 35delG/35delG

2. **Two different mutations (compound heterozygous)**

   e.g. 35delG/167delT

3. **No Cx26 mutations detected**

4. **Only one mutation detected (heterozygous)**

   e.g. 35delG/+

Cx26 Gene Testing at Children's Hospital Boston

Testing results from deaf probands:

Biallelic mutations:	20/101 (20%)
Heterozygous mutations:	12/101 (10%)
No mutation detected:	71/101 (70%)

Kenna and Rehm et al, 2000

Explanations for Deafness in an Individual with a Single Cx26 Mutation

- **The mutation may act dominantly**

  (There are at least six Cx26 mutations known to act dominantly.)

- **The Cx26 mutation is unrelated to the deafness**

  (The deafness may be caused by another gene mutation or a non-genetic cause.)

- **The test did not detect the second mutation**

  (There may be a mutation in a non-coding region.)

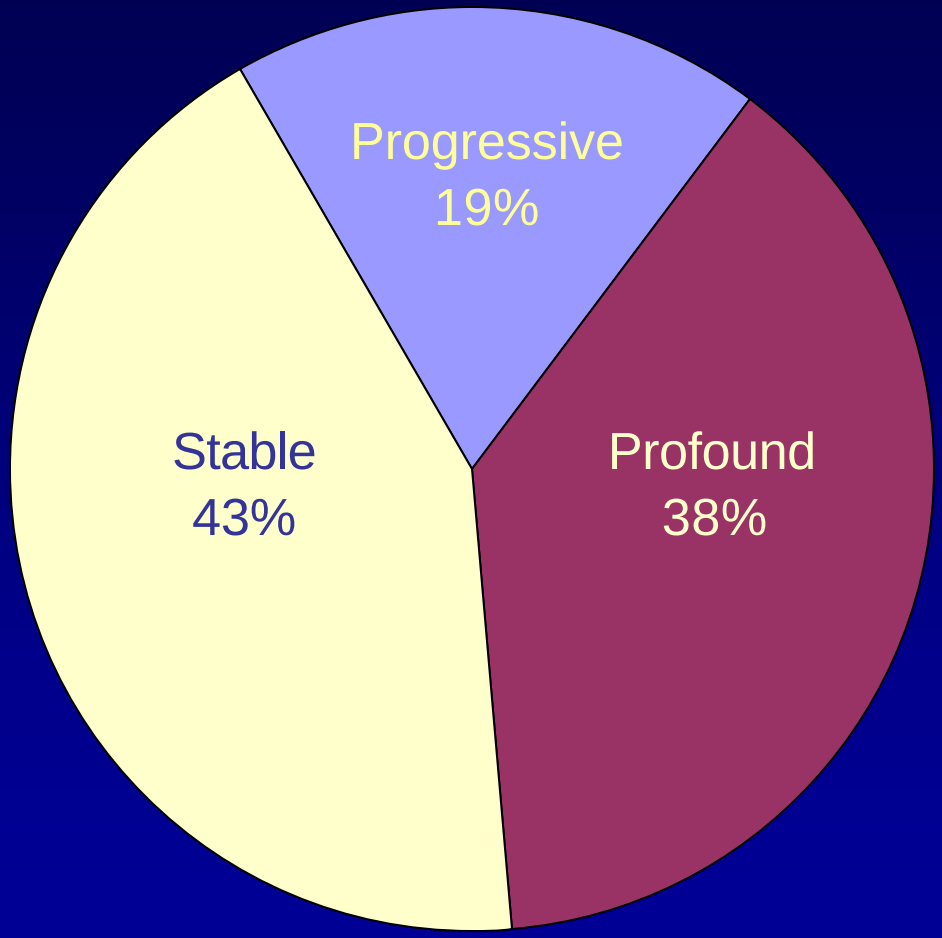
- **The genetic background of the patient may alter the mutations ability to cause deafness**

2 Cases of Delayed Onset Cx26 Deafness

- Two children who passed hearing screens later developed hearing loss
- Each was found to be have 2 mutations in the Cx26 gene (both were 35delG/35delG)
- **Child 1:** Diagnosed with profound deafness at age 15 months - (normal newborn ABR)
- **Child 2:** Diagnosed with severe hearing loss at age 9 months - (normal audiogram at 5 months)

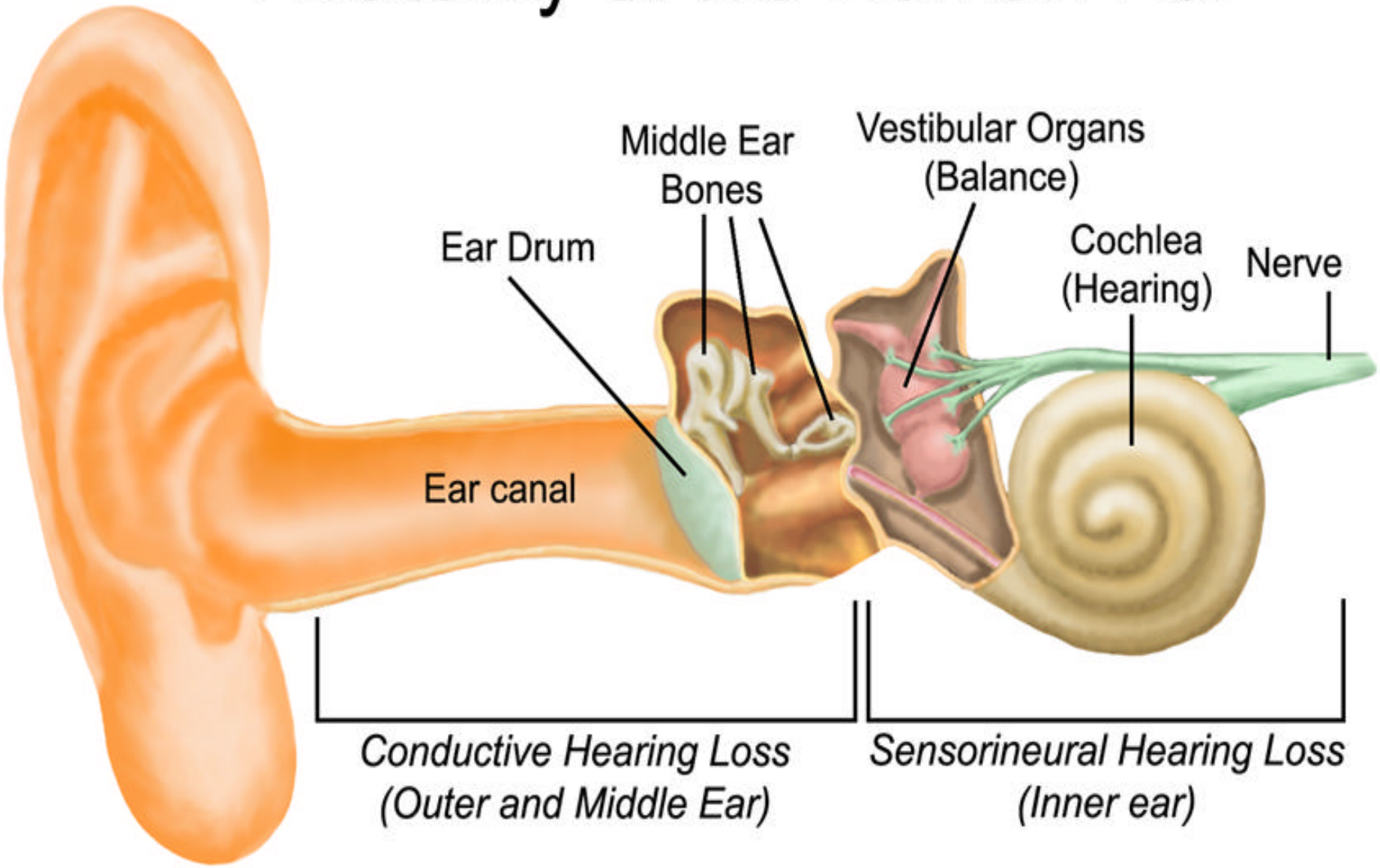
JAMA 284 (10):1245, 2000.

Progression of Cx26 Hearing Loss

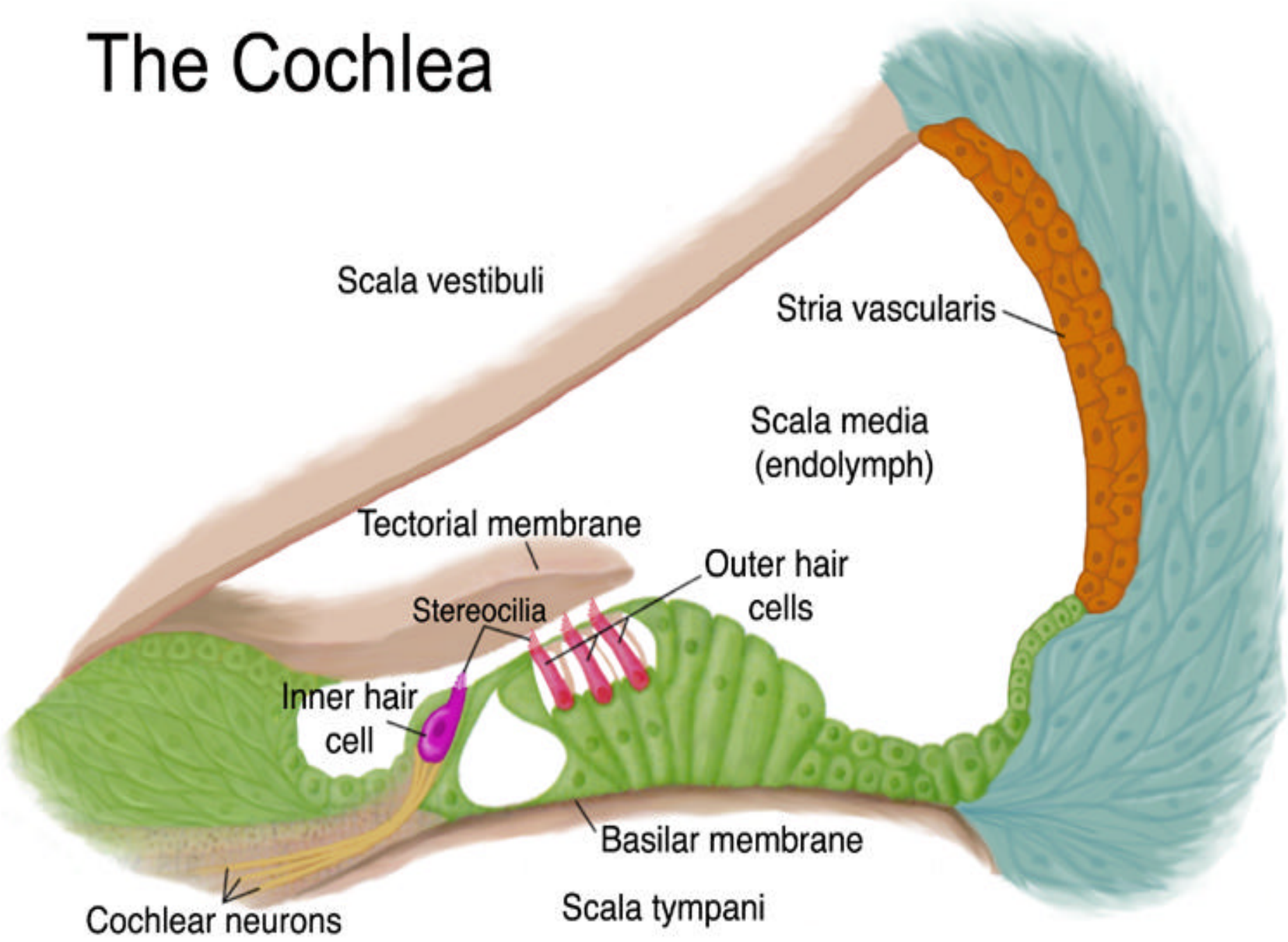


Total = 100 patients

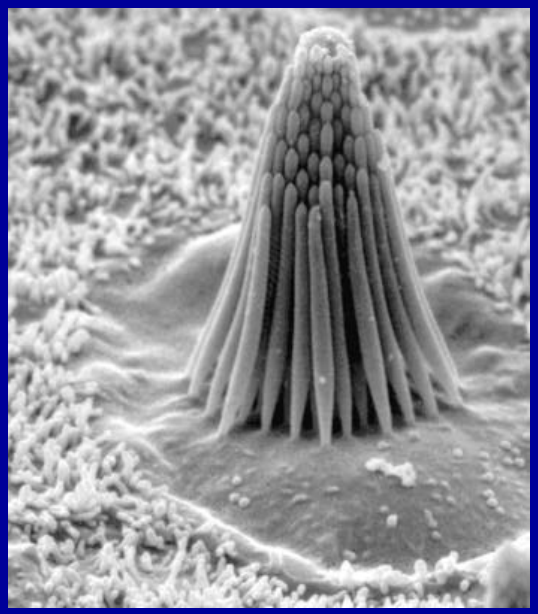
Anatomy of the Human Ear

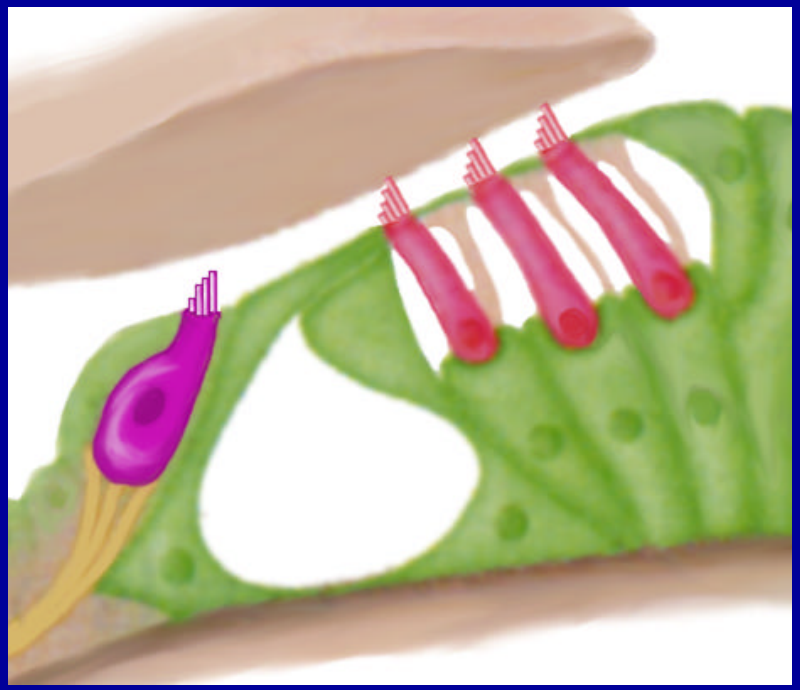


The Cochlea

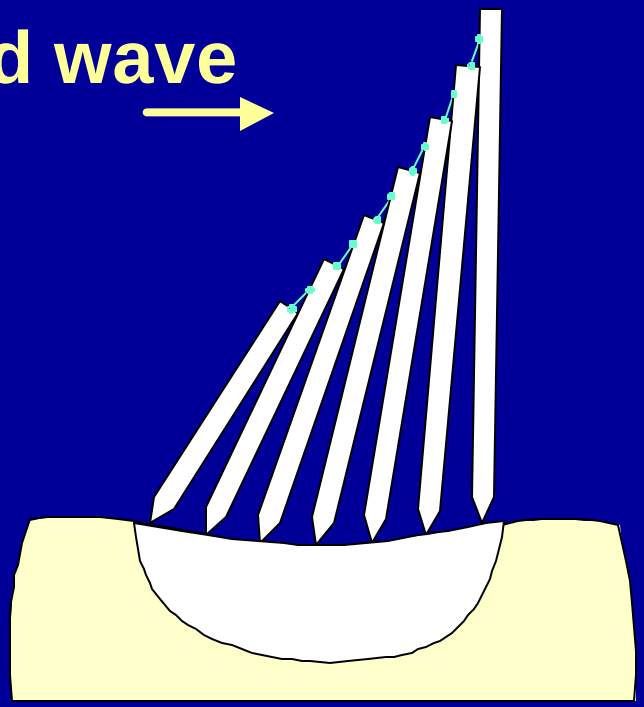

Scala vestibuli
Stria vascularis
Scala media
(endolymph)
Tectorial membrane
Outer hair
cells
Stereocilia
Inner hair
cell
Basilar membrane
Cochlear neurons
Scala tympani

Hair Cell Stimulation

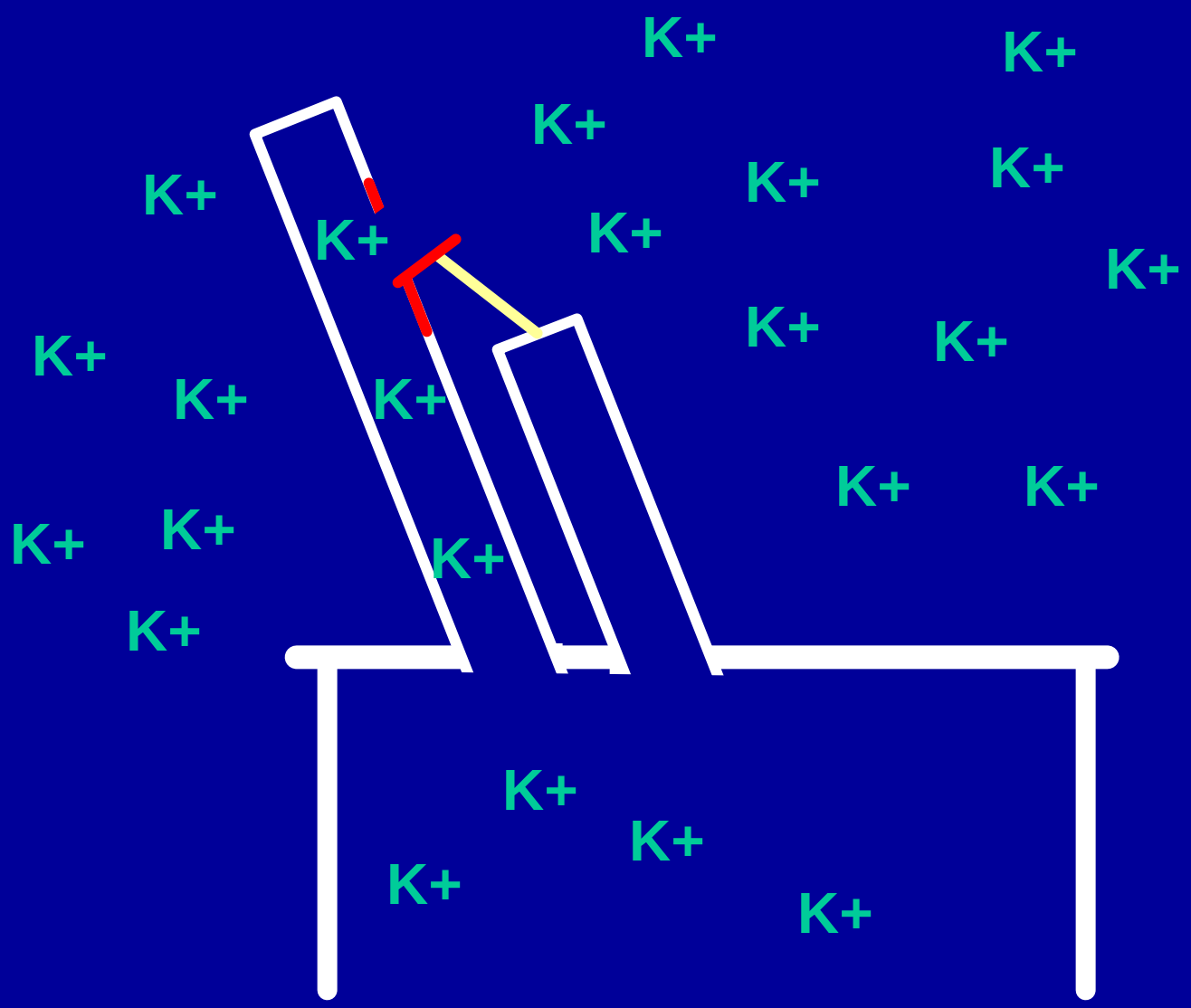


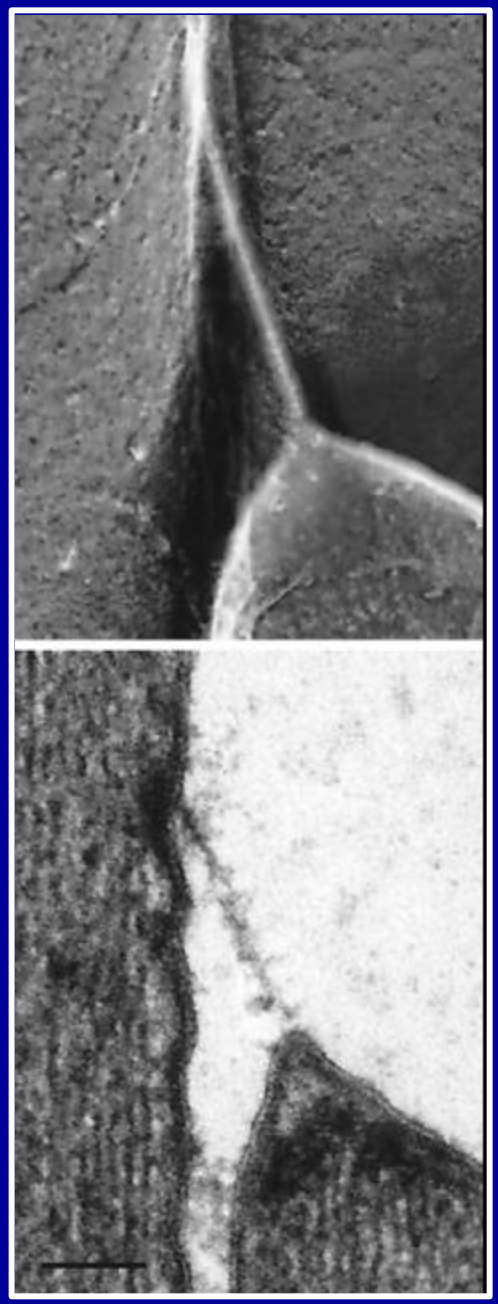


Sound wave

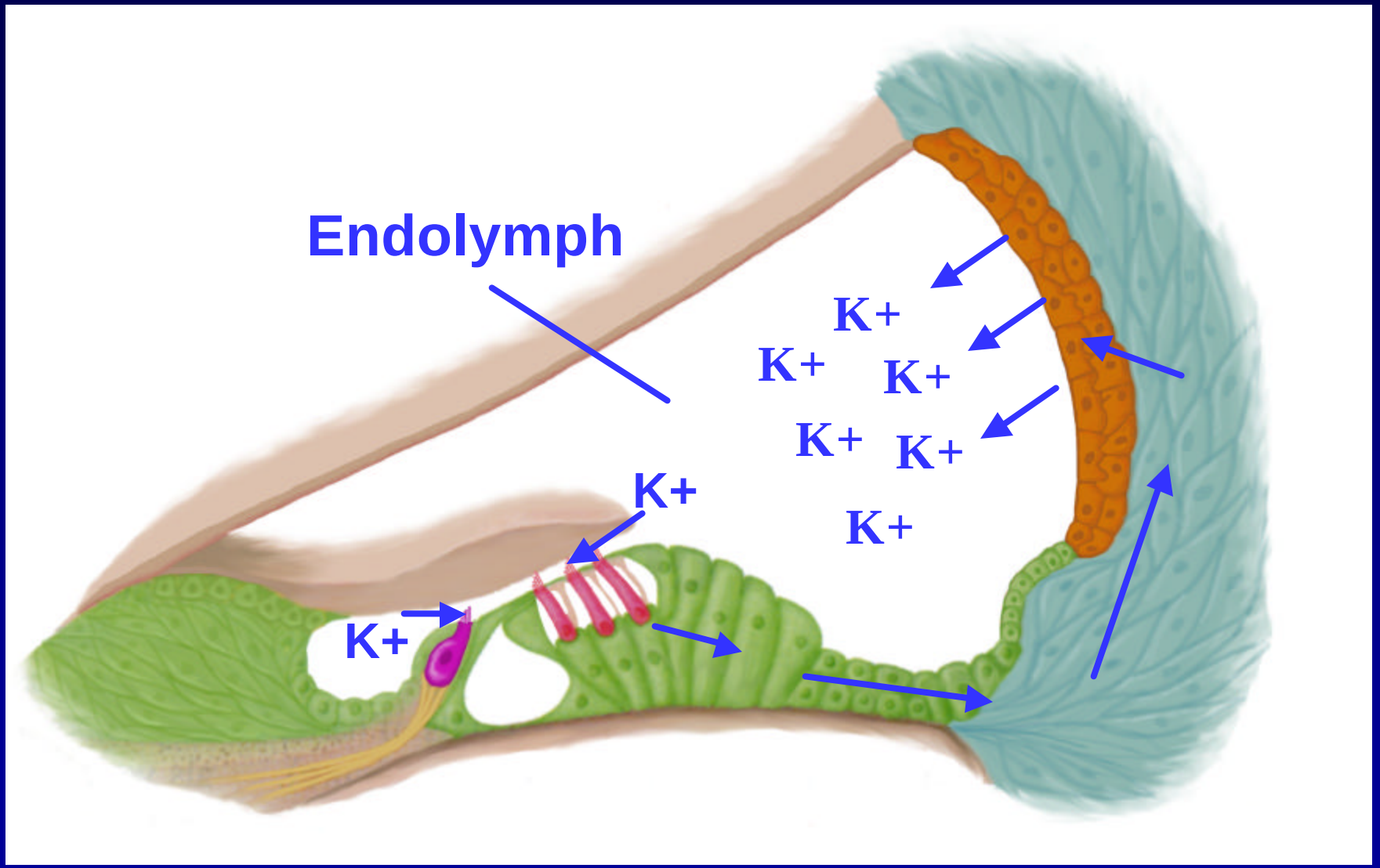


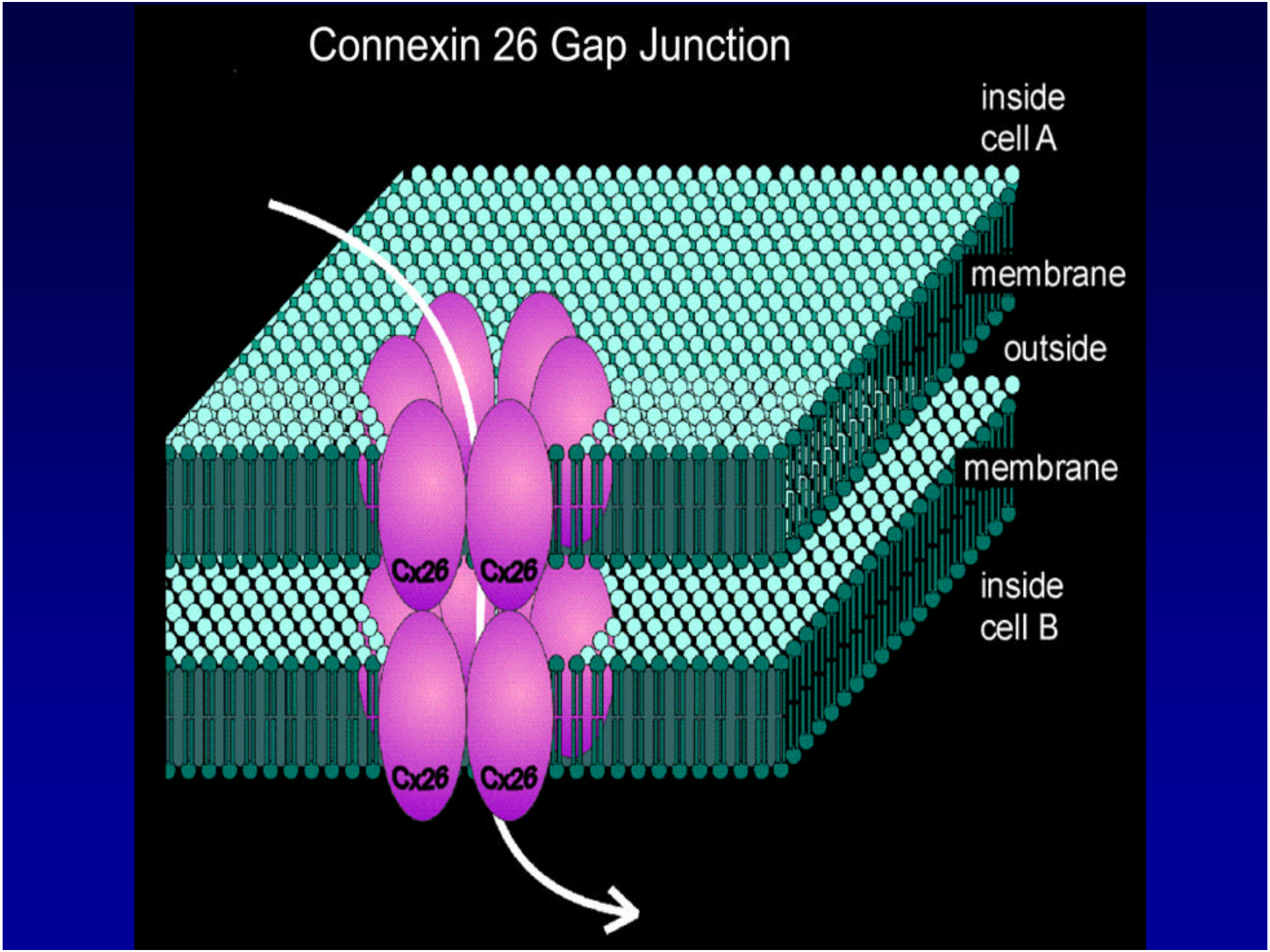
Hair Cell Transduction





Potassium Recycling in the Cochlea

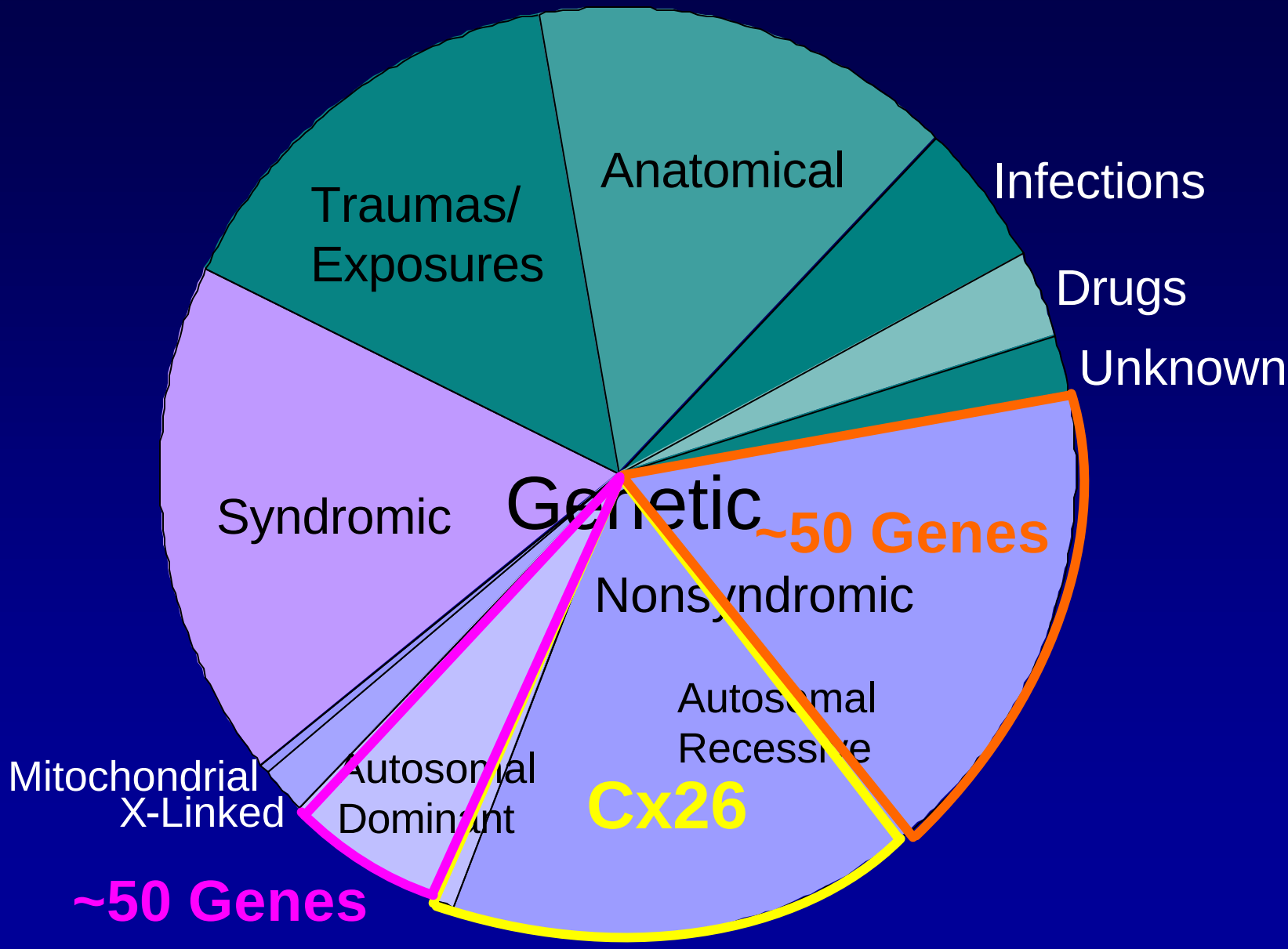


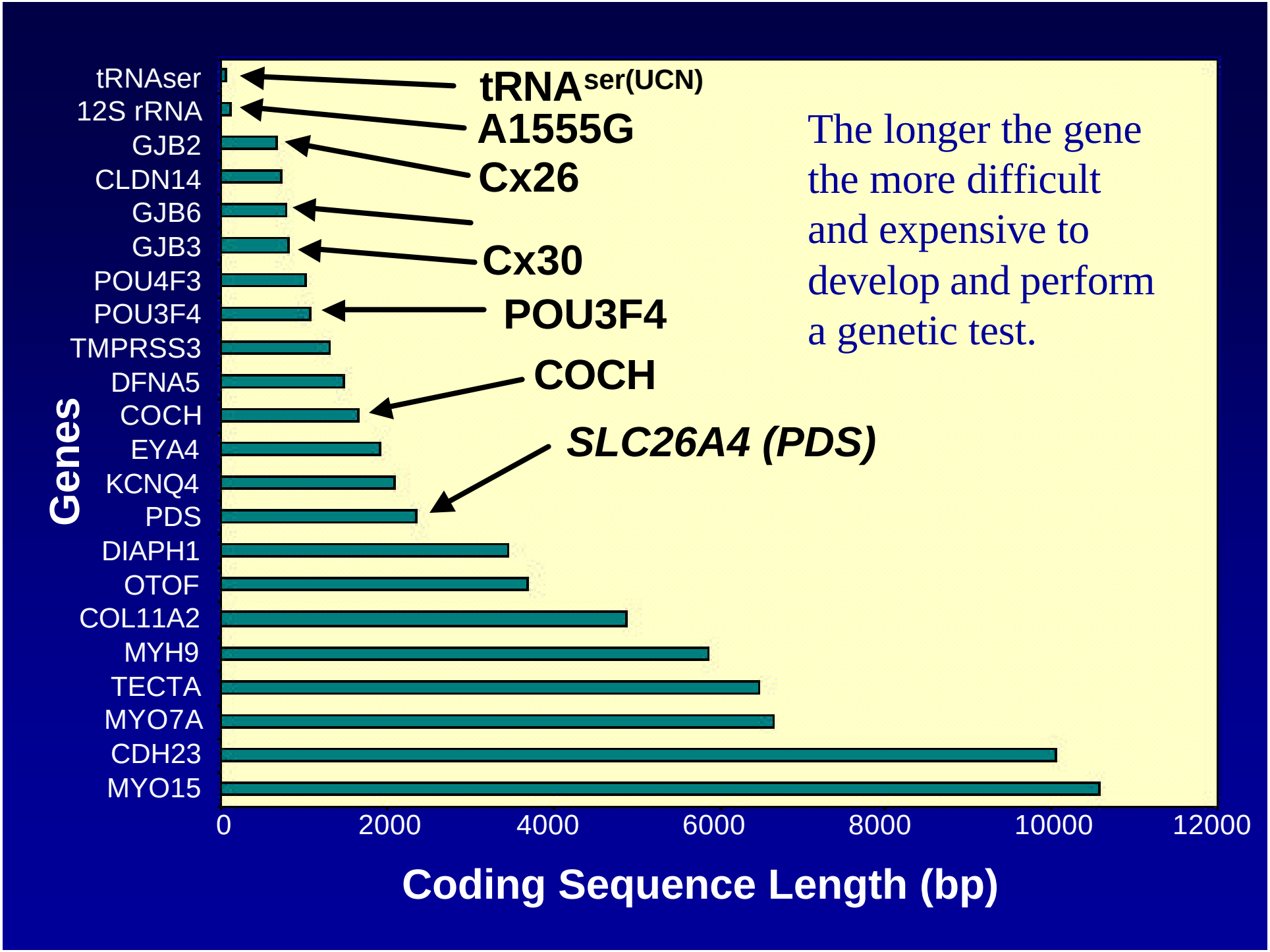

Connexin 26 Gap Junction
inside
cell A
membrane
outside
membrane
inside
cell B
Cx26
Cx26
Cx26
Cx26

Is Cx26 hearing loss always nonsyndromic??

Most likely, but that does not guarantee the absense of unrelated medical problems

Major Causes of Hearing Loss




tRNAser
12S rRNA
GJB2
CLDN14
GJB6
GJB3
POU4F3
POU3F4
TMPRSS3
DFNA5
COCH
EYA4
KCNQ4
PDS
DIAPH1
OTOF
COL11A2
MYH9
TECTA
MYO7A
CDH23
MYO15
Genes
tRNA ser(UCN) A1555G
Cx26
Cx30
POU3F4
COCH
SLC26A4 (PDS)
The longer the gene the more difficult and expensive to develop and perform a genetic test.
0
2000
4000
6000
8000
10000
12000
Coding Sequence Length (bp)

Benefits of Genetic Testing for Deafness

Genetic testing can:

- Aid in diagnosis and determining prognosis
- Eliminate the need for further clinical testing
- Help predict (or rule out) the onset of other clinical features of a syndrome (e.g. blindness in Usher syndrome)
- Help make more informed treatment decisions
- Aid in making reproductive choices
- Supply considerable “psychological” contentment

Genes and the Environment

Mitochondrial 12S rRNA gene

A1555G, C1494T, 961delCins(T)n mutations = increased risk of hearing loss from aminoglycoside antibiotics (i.e. gentimicin, tobramycin, amikacin)

Benefit of test: Prevent other family members with the mutation from being exposed to aminoglycosides

Note: Hearing loss due to these mutations can occur without aminoglycosides and aminoglycosides can cause hearing loss without these mutations.

Drawbacks of Genetic Testing for Deafness

Genetic testing may:

- Not always give clear answers or any answer
- Put a psychological burden on a parent or relative
- *Put an individual at risk for discrimination*
- Create ethical dilemmas associated with reproductive choices

Attitudes Towards Genetic Testing

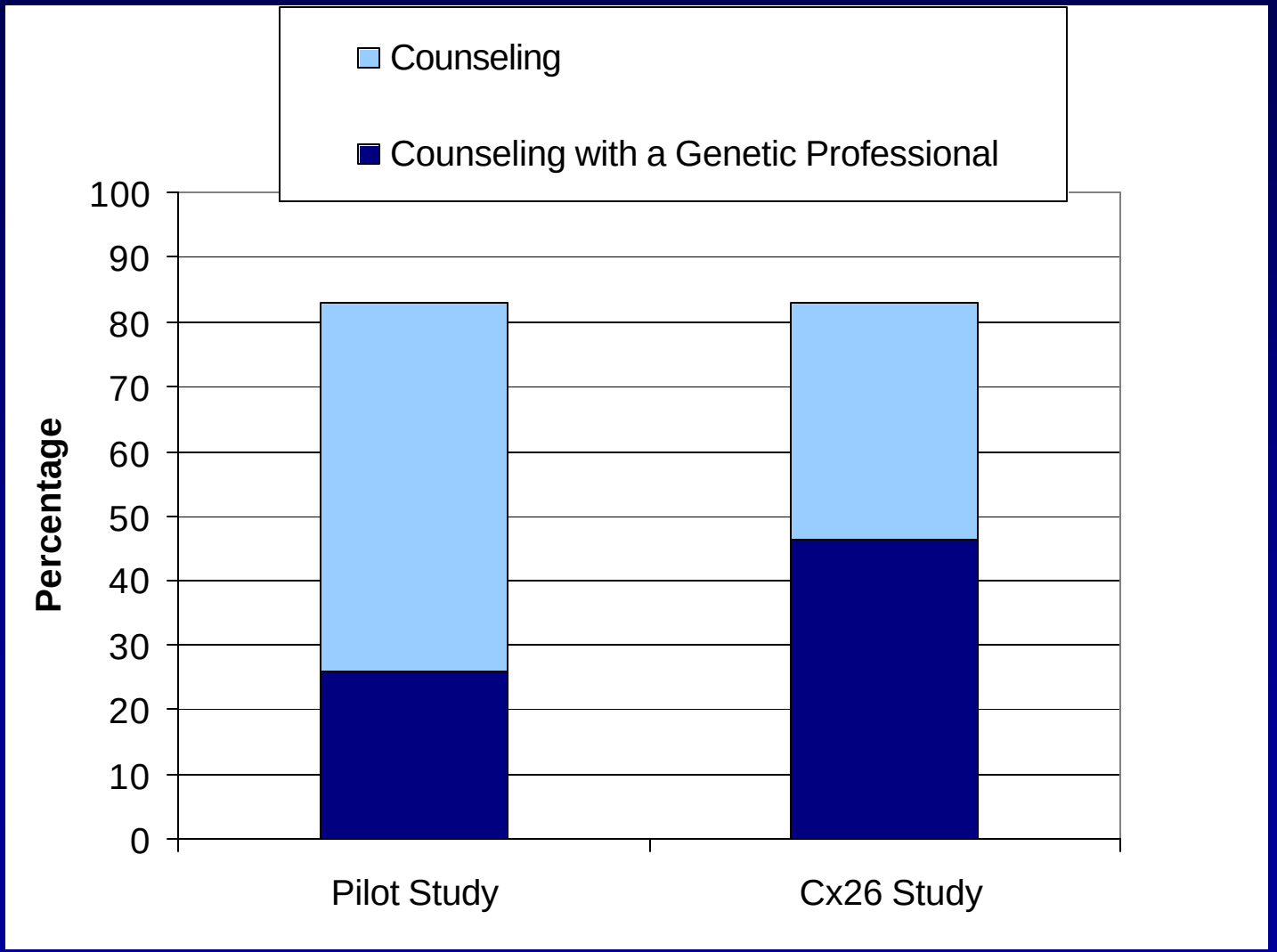
- Middleton et al. 1998, Attitudes of Deaf Adults toward Genetic Testing for Hereditary Deafness
  - 55% of “Deaf Nation” attendees thought genetic testing would do more harm than good, 46% thought its use devalued deaf people
- Brunger et al. 2000, Parental Attitudes toward Genetic Testing for Pediatric Deafness
  - 96% of parents of deaf children had positive attitude toward genetic testing
- Middleton et al. 2001, Prenatal Diagnosis for Inherited Deafness
  - 21% (deaf), 39% (HOH), 49% (hearing) would consider prenatal testing – 6%, 11% and 16% would consider terminating pregnancy

Genetic Counseling Study

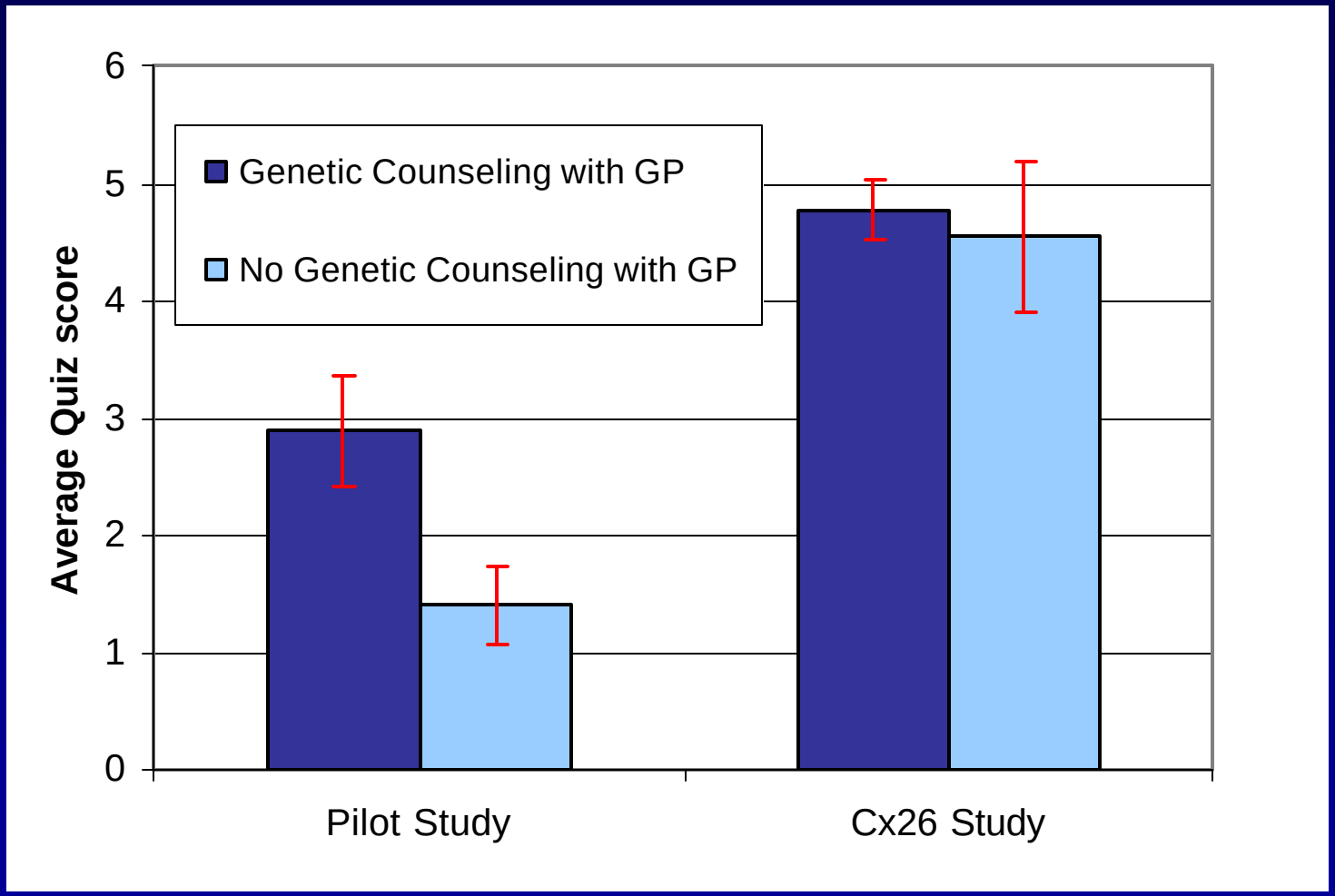
Brunger et al. 2000 found that all respondents had a poor understanding of genetics.

We are examining the extent to which families are receiving genetic counseling for hearing loss and how well they understand the genetics of hearing loss.

Did you have post-test genetic counseling and who provided it?



Relationship between Genetic Counseling with a Genetics Professional and Average Quiz Score



Quiz Question #6

There are many genes that cause hearing loss and tests are not yet available for all of these genes. Therefore, even if a person's current genetic test results are negative, the hearing loss may still be genetic. Were you aware of this fact?

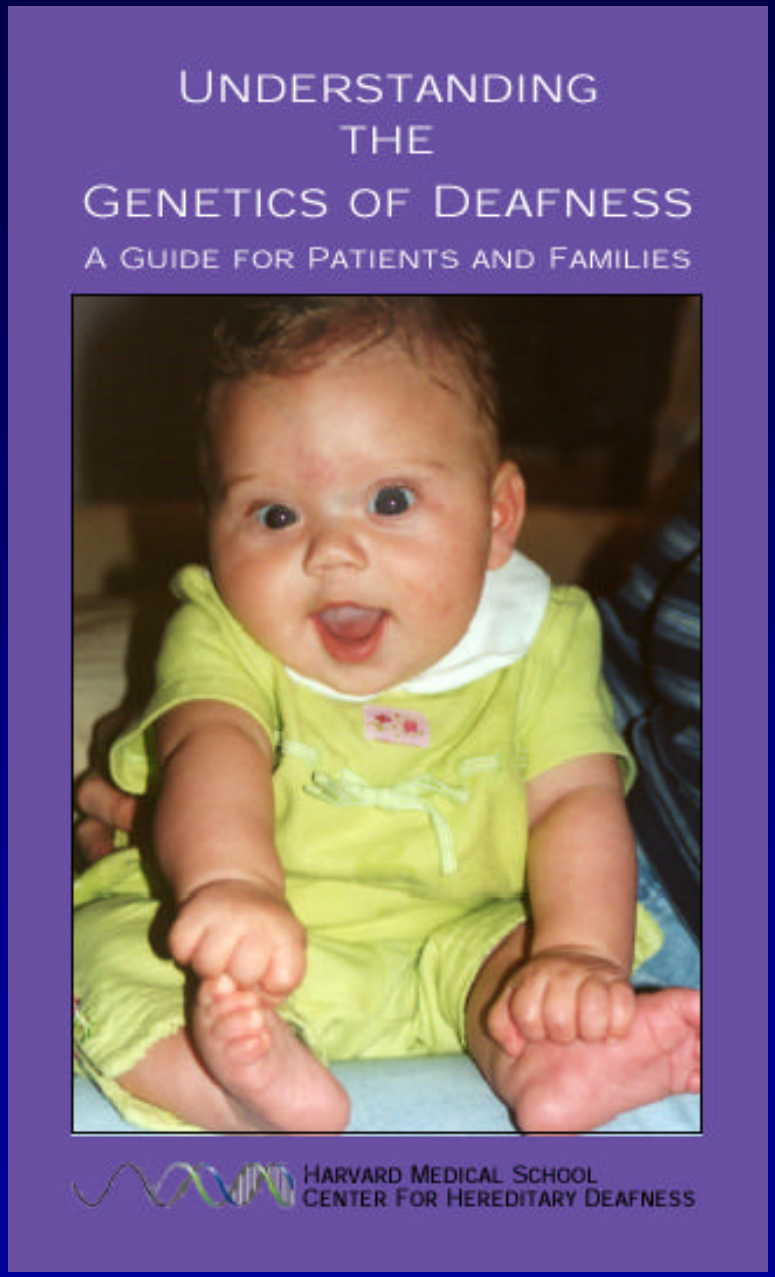
? Yes ? No

Pilot study - 34% said "No"
Cx26 Study – 22% said "No"

Take Home Message

Genetic counseling is equally if not more important for those families who are NEGATIVE for Cx26 and other tests

- Could still be genetic
- Recurrence risk 10-15%
- Follow for future testing



Version 2

Gene Test Cards:

Facts About Genetic Testing
Connexin 26 Test
Mitochondrial Tests
SLC26A4 (PDS) Test
COCH Test
Connexin 30 Deletion Test

http://hearing.harvard.edu

Common Causes of Hearing Loss

FOR PARENTS & FAMILIES

Department of Otolaryngology ? Children's Hospital Boston

HARVARD MEDICAL SCHOOL

Acknowledgements

Margaret A. Kenna, MD

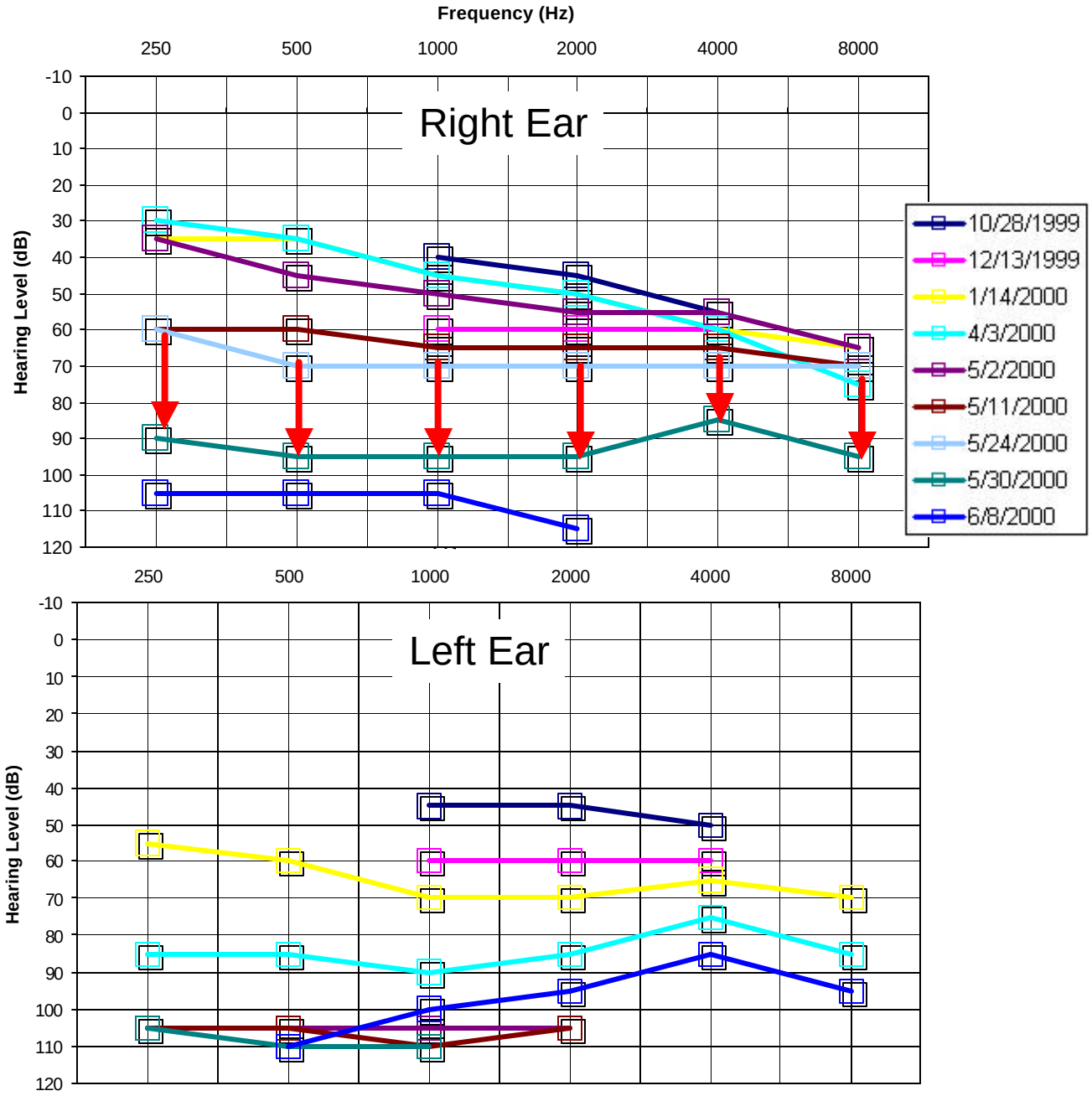
Anna Frangulov

Contact information:

http://hearing.harvard.edu

For booklets: hearing@hms.harvard.edu

For me: hrehm@hms.harvard.edu



7.5 year old girl discovered with moderate hearing loss during school exam

No newborn hearing screen was performed

5/27/00 – Patient reported sudden loss of hearing

Serial audiograms 6 days apart shows 25-30 dB

Cx26: 35delG/101del2