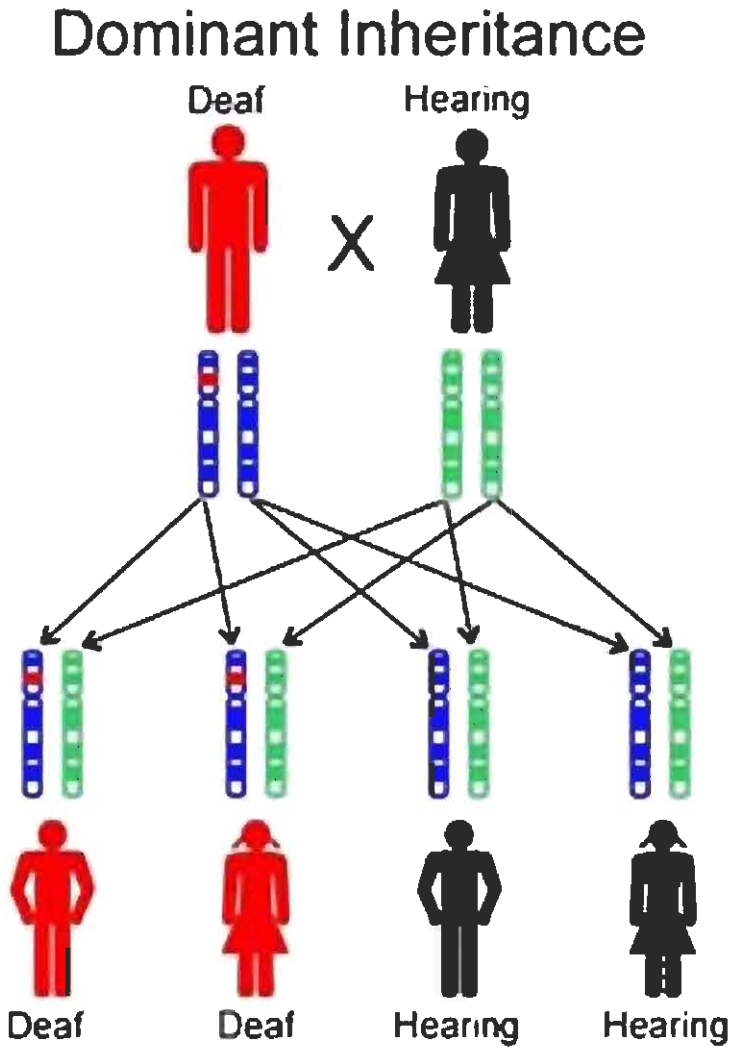
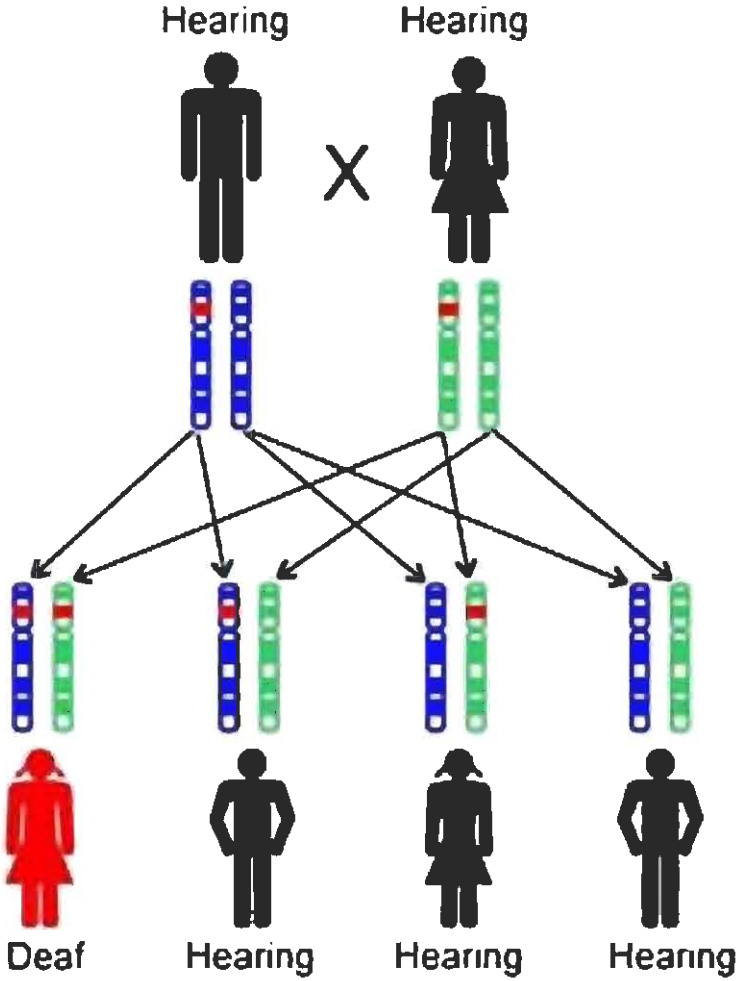
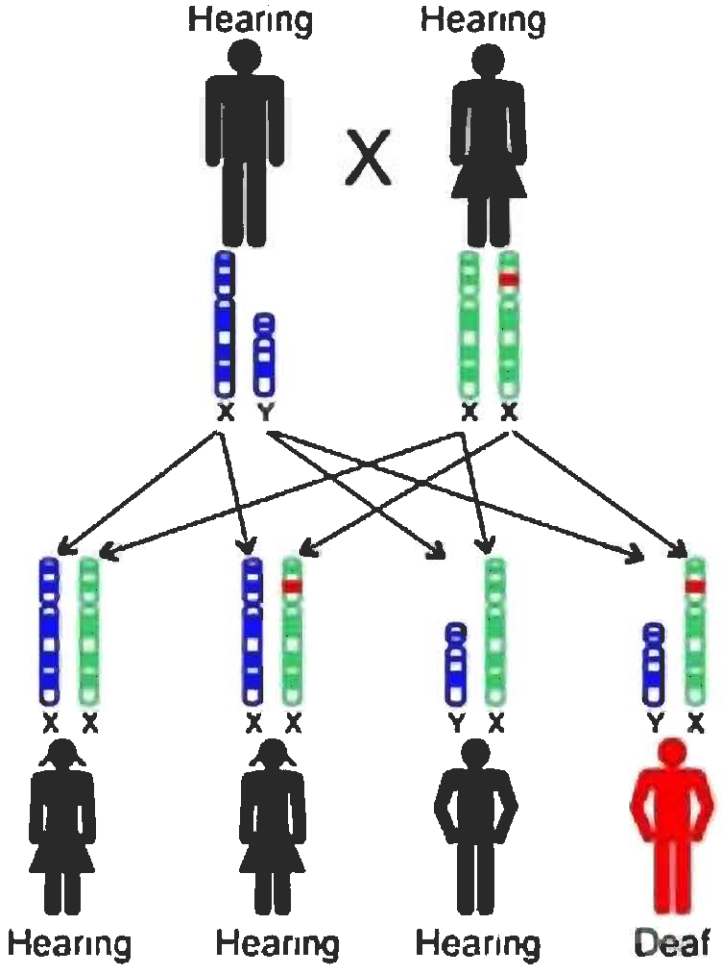


Harvard-MIT Division of Health Sciences and Technology
HST.730: Molecular Biology for the Auditory System
Prof. Anne Giersch

Recessive Inheritance



X-linked Inheritance



Early Childhood Hearing Loss

1 out of every 1,000 children is born deaf.

Approximately 1 out of every 300 children
has a hearing impairment
significant enough to affect speech
and language development, education,
and social development.

Prevalence of Hearing Impairment

- **28 million Americans**
- **2 million profoundly deaf**
- **1/1000 congenitally deaf**
- **1/3 impaired by age 65**
- **1/2 impaired by age 80**

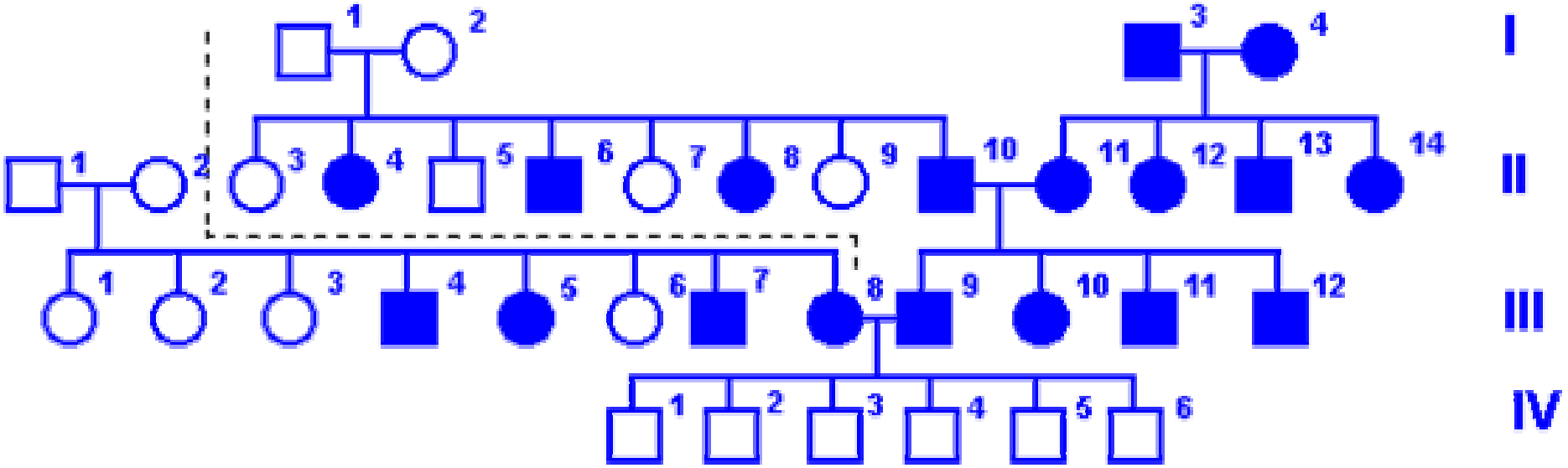
NIDCD National Strategic Research Plan, 1989

Genetic hearing loss may be…

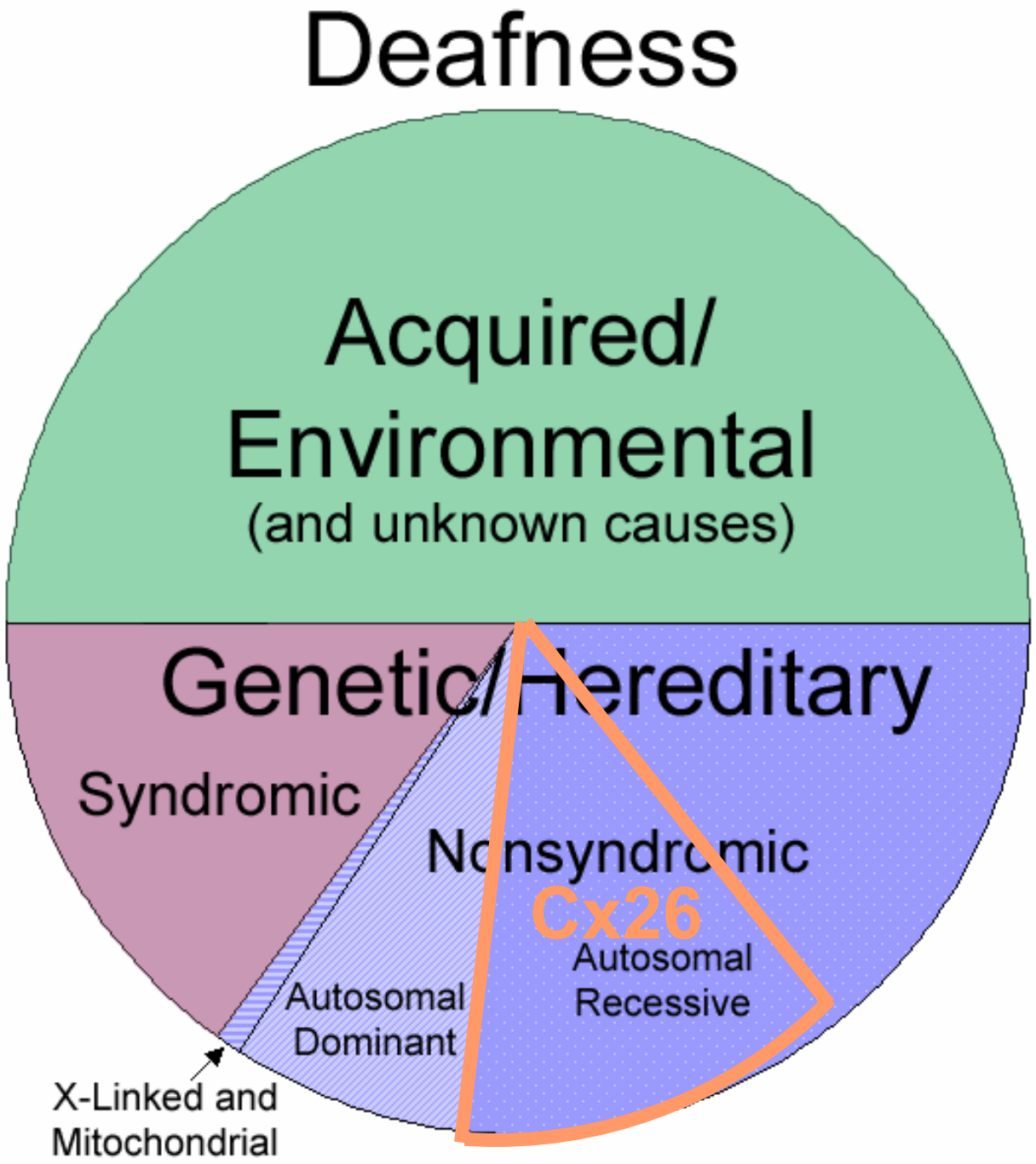
- Dominant, recessive, X-linked, mitochondrial, or chromosomal
- Congenital or have a post-natal onset (prelingual or postlingual)
- Stable or progressive
- Conductive, sensorineural or mixed
- An isolated finding or part of a syndrome

Obstacles to Studying Genetic Deafness

- Inaccessible to direct observation
- Located in the densest bone in the body
- Pathological studies are often much delayed
- Unparalleled genetic heterogeneity
- Deaf x deaf matings due to linguistic homogamy



http://www.people.virginia.edu/~rjh9u/gif/deafmute.gif


Deafness
Acquired/
Environmental
(and unknown causes)
Genetic/Hereditary
Syndromic
Nonsyndromic
Cx26
Autosomal
Recessive
Autosomal
Dominant
X-Linked and
Mitochondrial

~40% of early childhood hearing loss in the United States is caused by infectious or environmental factors.

Such factors include:

prenatal infections (toxoplasmosis, rubella, CMV, herpes, syphilis)

meningitis

low birth weight

prematurity

hyperbilirubinemia

ototoxic medications

mechanical ventilation

admission to neonatal ICU

Syndromic Hearing Loss

Syndrome	Gene
Alport	*COL4A5, COL4A3, Col4A4*
Branchio-Oto-Renal	*EYA1*
Crouzon	*FGF*
Jervell and Lange-Nielsen	*KCNQ1, KCNE1/lsK*
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, USH2A, USH1C, CDH23*
Waardenburg	*PAX3, MITF, EDNRB, EDN3, SOX10*

Selected genetic syndromes with hearing loss

Syndrome	Incidence	Gene(s)
Alport	1 in 5,000	COL4A3, COL4A4, COL4A5
Usher	1 in 23,000	MYO7A, USH1C, CDH23, USH2A
Jervell & Lange-Nielsen	1 in 250,000	KCNQ1, KCNE1/ISK
Mitochondrial syndromes (MERRF, MELAS, diabetes with deafness)		tRNA-Leu, tRNA-Lys

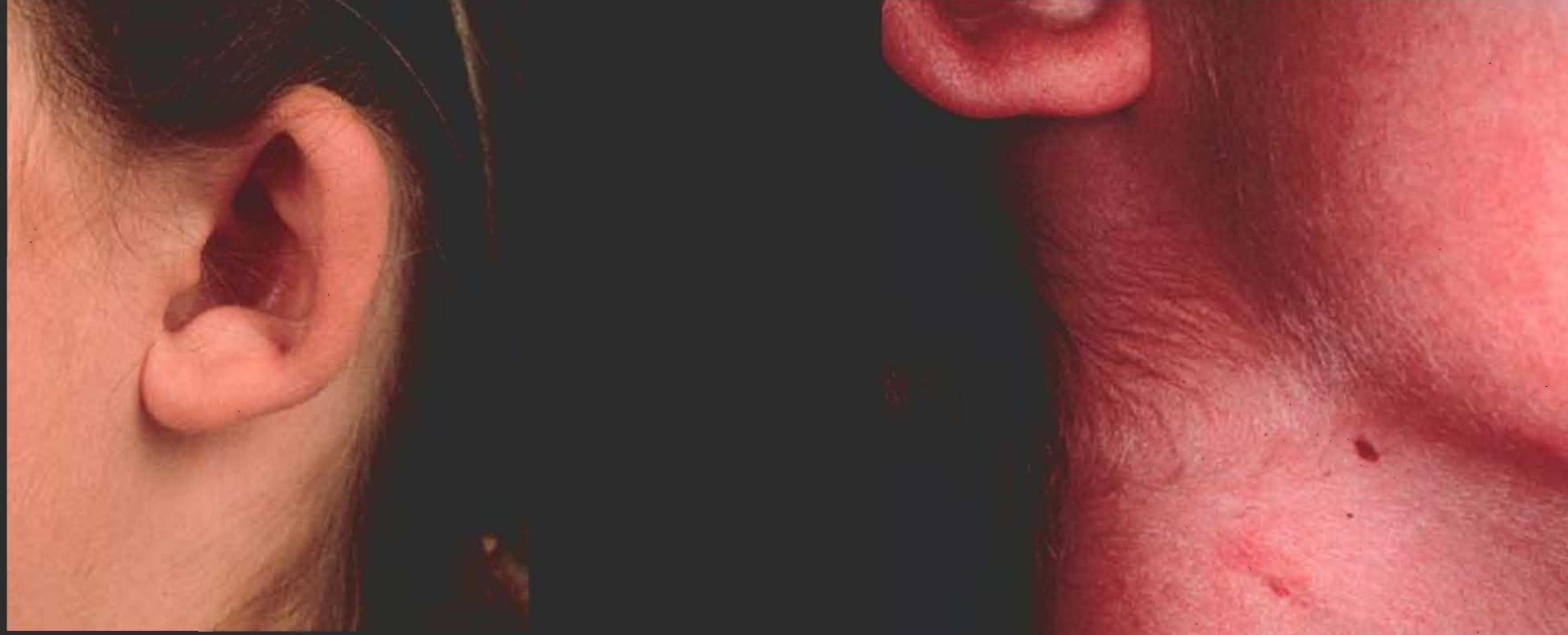
Pendred syndrome

1 in 7,500, autosomal recessive

Associated feature: late childhood/early adult onset goiter

Gene: PDS

photos from:
Richard JH Smith, MD



Branchio-oto-renal syndrome (BOR)

1 in 40,000, autosomal dominant

Associated features include: malformed pinnae, ear pits/tags, branchial fistulae or cysts, renal dysplasia/aplasia

Genes: EYA1;
second locus mapped, gene not yet identified

photos from:
Richard JH Smith, MD

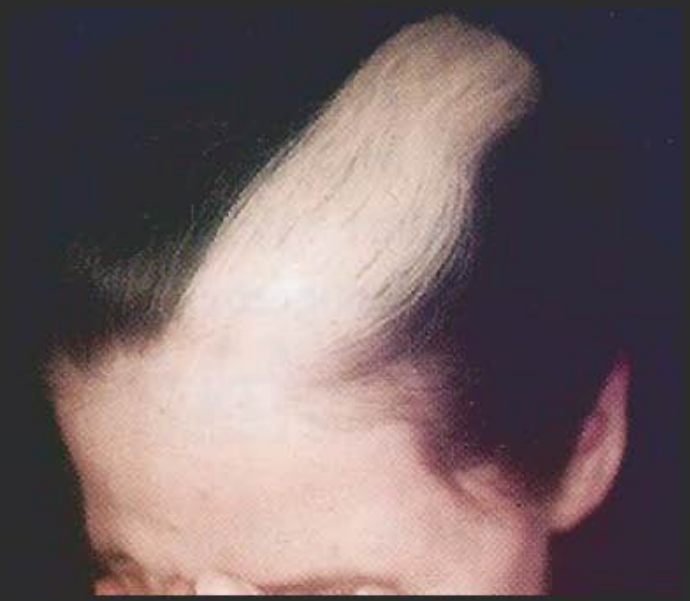
Waardenburg syndrome (WS)

1 in 42,000

Type 1/3: PAX3 (AD)

Type 2A: MITF (AD)

Type 4: SOX10 (AD); EDN3, EDNRB (AR)



photos from:
Richard JH Smith, MD (top right, top left)
V Sybert "Genetic Skin Disorders" (bottom right)

PAX3 at 2q35

See Ishikiriyama *et al*., 1989

Stickler syndrome

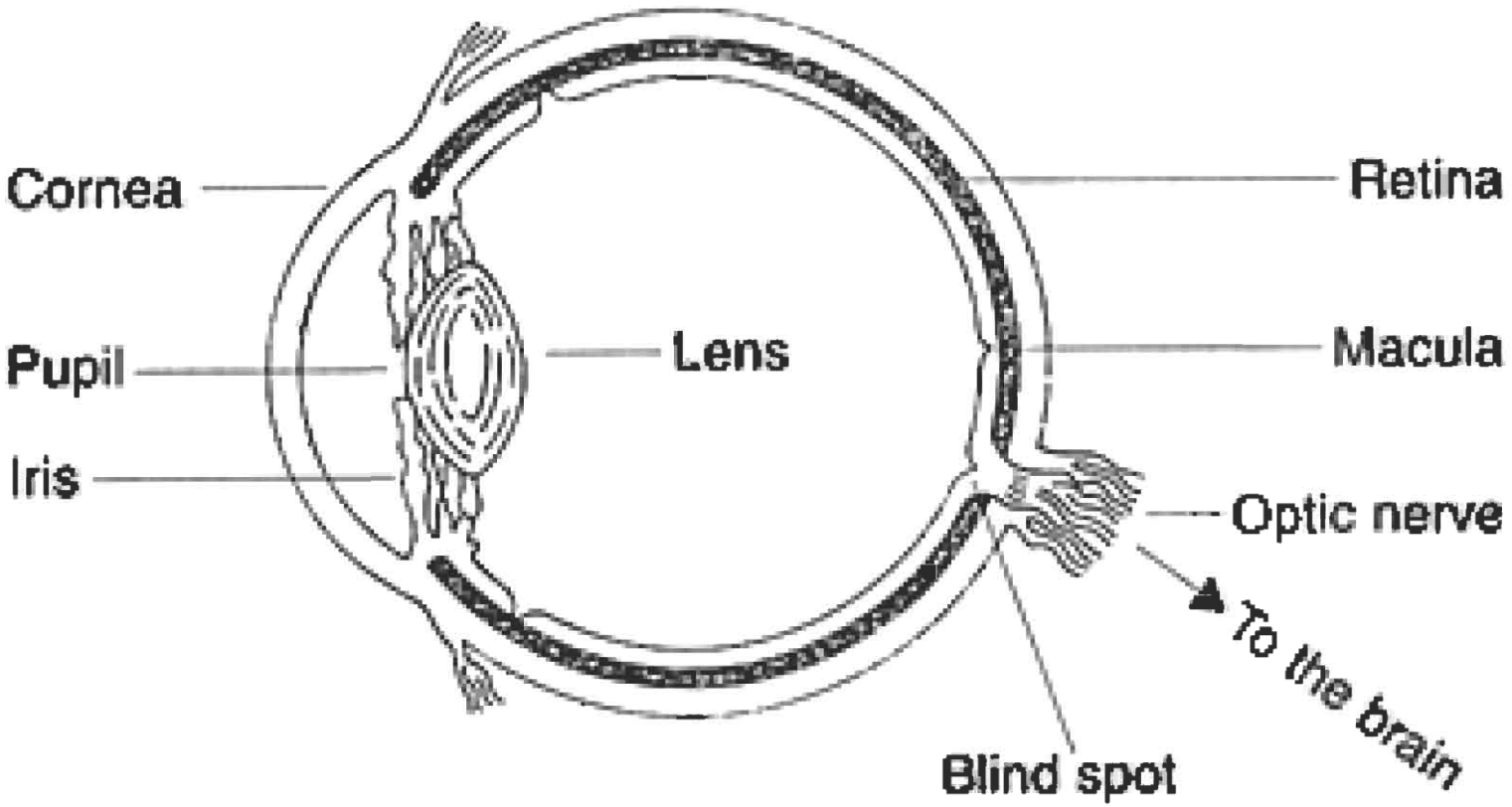
1 in 20,000, autosomal dominant

Type I: COL2A1 Type II: COL11A1 Type III: COL11A2

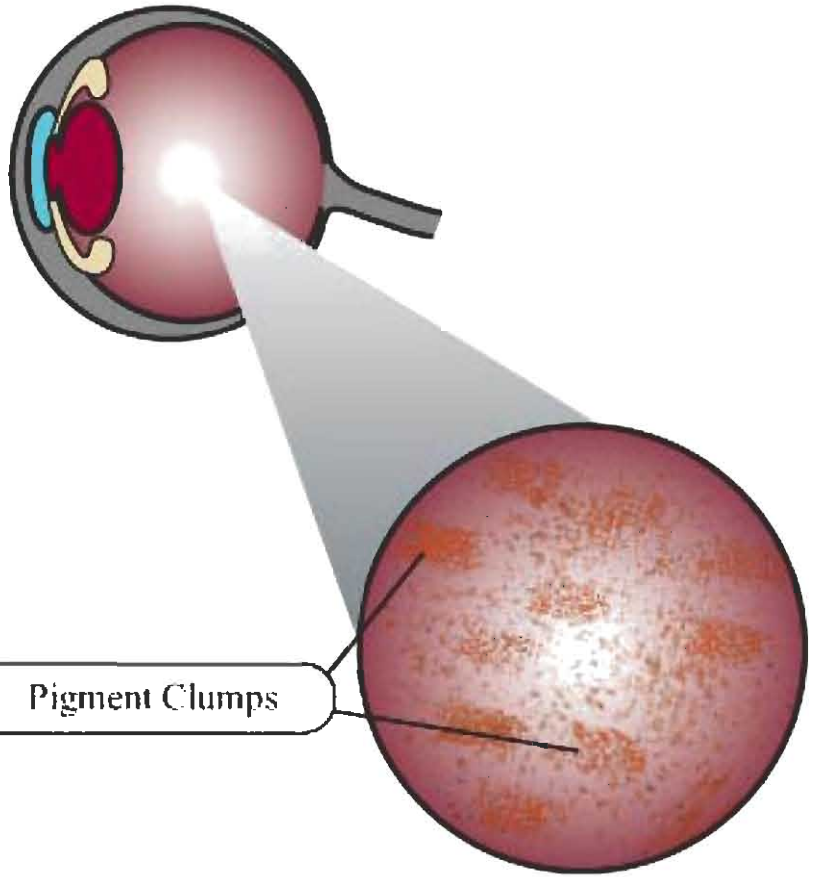
photos from: KL Jones, MD, Fourth Edition,
"Smith's Recognizable Patterns of Human Malformations."
Courtesy of Judith G Hall, MD

The Usher Syndromes

- C.H. Usher documented the association of deaf/blindness and its inheritance in an autosomal recessive fashion in 1914
- ~50% of the deaf/blind population has Usher syndrome
- Type I Usher Syndrome is three times more common than type II or III


Cornea
Pupil
Iris
Lens
Retina
Macula
Optic nerve
To the brain
Blind spot

Retinitis Pigmentosa



Signs and Symptoms - *Difficulty seeing in dim lighting, tendency to trip easily or bump into objects when in poor lighting, gradual loss of peripheral vision, loss of contrast sensitivity, eye fatigue (from straining to see)*

Clinical characteristics of the Usher syndromes

	Hearing loss	**Vestibular**	**Vision loss**	**Min. # genes**	**# genes Id'd**
Type I	congenital profound	absent	onset 1st decade	7	3
Type II	congenital sloping	normal	onset 1st or 2nd decade	3	1
Type III	progressive	variable	variable	1	0

Mitochondrial Deafness

- **Syndromic -** systemic neuromuscular syndromes, diabetes & deafness, PPK & deafness
- **Nonsyndromic -** A1555G 12S rRNA
  A7445G tRNAser
- **Ototoxic -** A1555G (12S rRNA)

Modifier Genes of Deafness

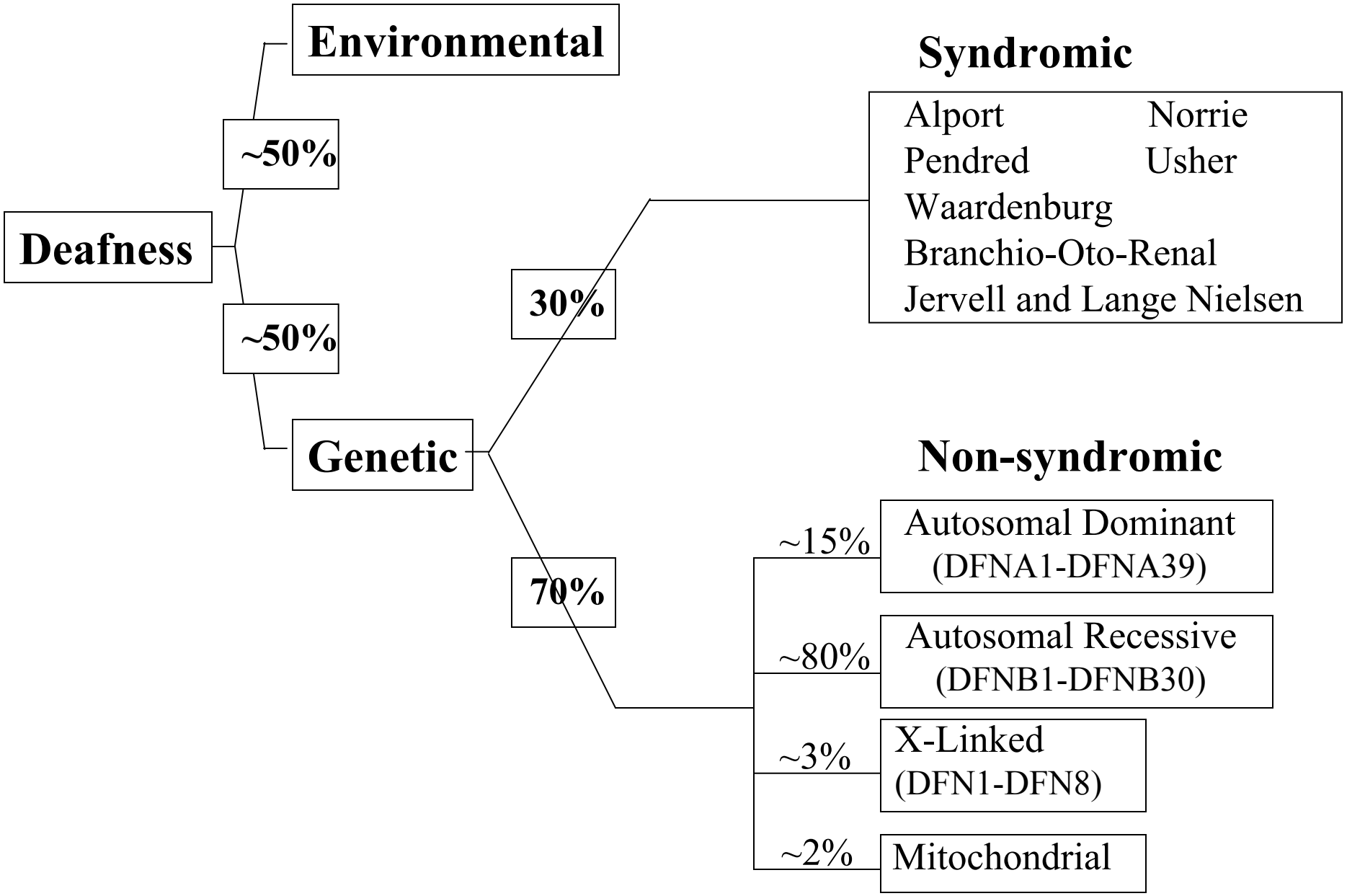
- Modifier gene: a particular allele of one gene affects the expression of a second gene and thereby modifies the phenotype

- Affect the age of onset, progression, severity, or penetrance of hearing loss

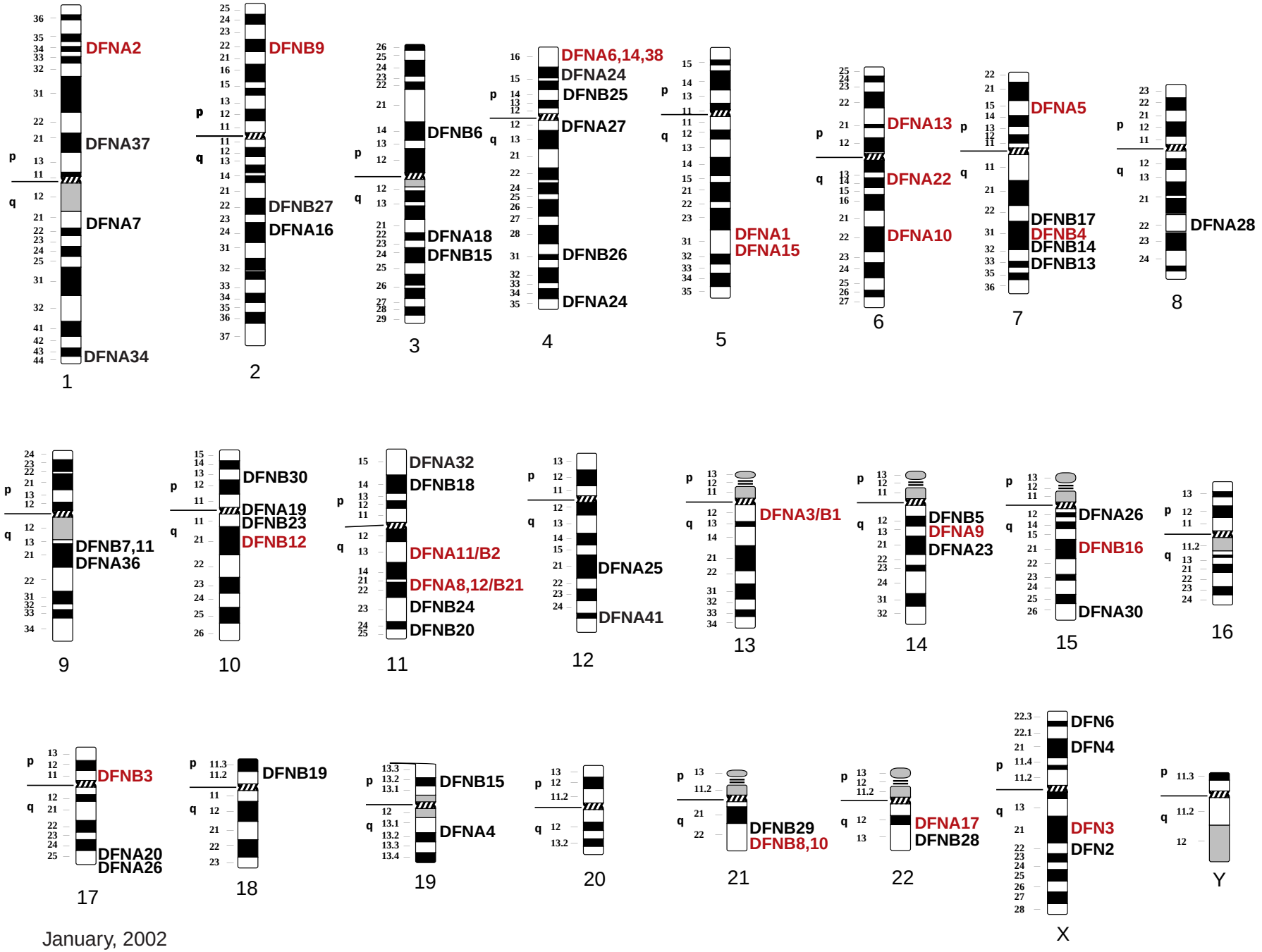
- May mediate normal or abnormal function; can prevent or worsen the hearing loss caused by the second gene

Deafness Modifier Genes

- *moth1* mutations prevents/worsens tubby mouse deafness (Ikeda et al . 1999)
- *mdfw* mouse locus prevents/worsens *deafwaddler* deafness (Noben-Trauth et al. 1997)
- A nuclear locus causes A1555G mitochondrial deafness in absence of aminoglycosides (Bykhovskaya et al. 2000)
- DFNM1 locus prevents DFNB26 deafness (Riazuddin et al. 2000)


Deafness
~50%
Environmental
~50%
Genetic
30%
Syndromic
Alport
Norrie
Pendred
Usher
Waardenburg
Branchio-Oto-Renal
Jervell and Lange Nielsen
70%
Non-syndromic
~15%
Autosomal Dominant
(DFNA1-DFNA39)
~80%
Autosomal Recessive
(DFNB1-DFNB30)
~3%
X-Linked
(DFN1-DFN8)
~2%
Mitochondrial

Jan2001



January, 2002

Nonsyndromic Deafness Genes Cloned

Locus	Gene (Protein)	Cloned
DFN3	*POU3F4* (POU3F4)	1995
DFNB1/A3	*GJB2* (connexin 26)	1997
DFNA11/B2	*MYO7A (*myosin VIIA)	1997
DFNA1	*DIAPH1* (diaphanous 1)	1997
DFNB4	*PDS* (pendrin)	1997
Near DFNA2	*GJB3* (connexin 31)	1998
DFNA5	*DFNA5* (DFNA5)	1998
DFNA9	*COCH* (COCH)	1998
DFNA15	*POU4F3* (POU4F3)	1998
DFNB3	*MYO15* (myosin XV)	1998
DFNA8/A12/B21	*TECTA* (α-tectorin)	1998
Near DFNA2	*KCNQ4* (KCNQ4)	1999
DFNB9	*OTOF* (otoferlin)	1999
Near DFNA3/B1	*GJB6* (connexin 30)	1999
DFNA13	*COL11A2* (collagen type XI α2)	1999
DFNB8/B10	*TMPRSS3* (serine protease 3)	2000
DFNA10	*EYA4* (EYA4)	2000
DFNB29	*CLDN14* (claudin-14)	2000
DFNA17	*MYO9* (myosin IX)	2000
DFNB12	*CHD23 (cadherin-23)*	2001

Autosomal Recessive

nonsyndromic hearing loss tends to be:

prelingual, stable, affecting all frequencies

Autosomal Dominant

nonsyndromic hearing loss tends to be:

postlingual, progressive, affecting a subset of frequencies

Gene Discovery Methods

Genetic Linkage

- Pedigree analysis of isolated populations

Tissue Specific Approaches

- Inner ear cDNA libraries
- Microarray expression profiling

Model System Approaches

- Mouse, fly, fish…

DFNA1 pedigree

See Lynch et al., Science 1997, 27b:1223

DFNB17 family from the Madras region of India

See American Journal of Medical Genetics 78:107–113 (1998), Grienwald et al.

Figure 1. Haplotype analysis showing selected markers in the Palestinian DFNB10 family (BT117)

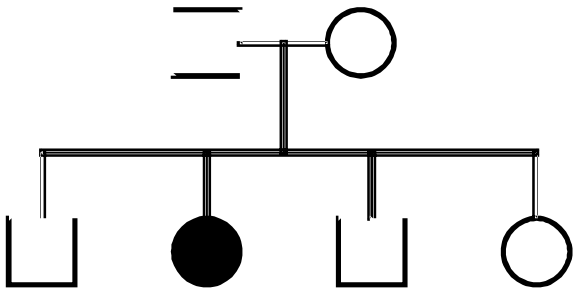
See Berry, et al, Genomics **68,** 22–29 (2000)

Human-Mouse Homology Map

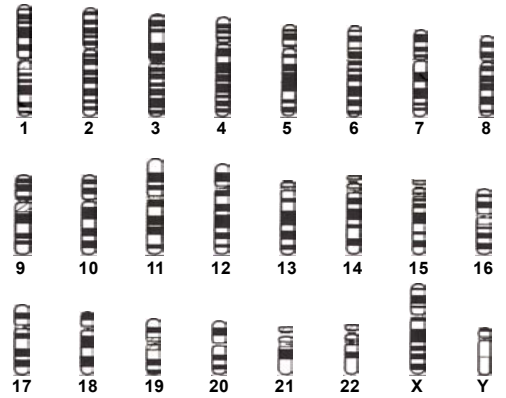
Figure 4–18 Conserved synteny between the human and mouse genomes.

See Molecular Biology of the Cell, Vol. 4, Alberts *et al.*

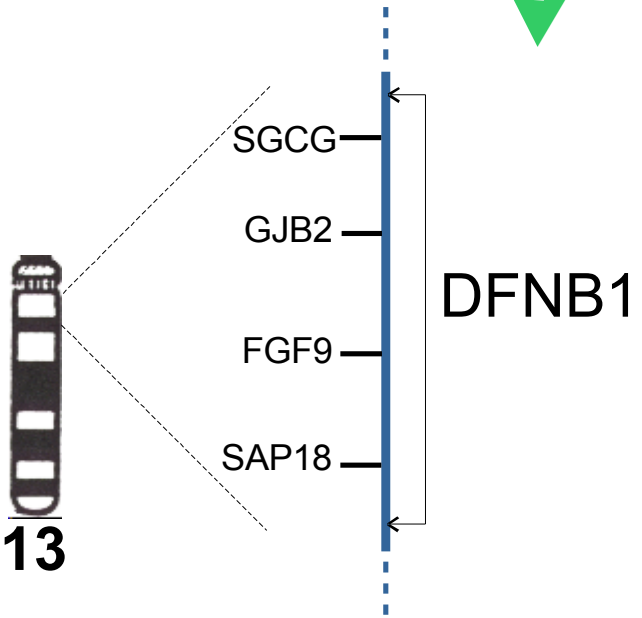
Gene/Mutation Identification



1) Family Discovery and Pedigree Construction



2) Linkage Analysis



3) Positional Cloning

Connexin 26 Gene

. . . A G A T G A G C A . . Hearing

. . . A G A T T A G C A . . Deaf

4) Mutation Analysis

FIG. 1. Linkage of deafness in the Monge kindred to markers on chromosome 5q31. Dark symbols indicate deaf persons; symbols with diagonal slashes represent deceased persons. The position of the "S.M." branch in the kindred is not certain. Genotypes of some deceased persons are suggested on the pedigree in brackets, but these inferred genotypes were not included in the statistical analysis. Boxes indicate the haplotypes apparently linked to deafness in each branch of the kindred. By multipoint analysis, odds in favor of linkage of deafness to the region between *IL9* and *D5S210/D5S207* are $>10^{12}$:1. Recombination events in persons A, C, E, and F indicate that the deafness gene lies above *GRL*; recombination events in persons B, D, and G indicate that the deafness gene lies below *IL9*. The distance between GRL and IL9 is ≈7 centimorgans (cM).

See Leon et. al, Proceedings of the National Academy of Science, 89 (1992)

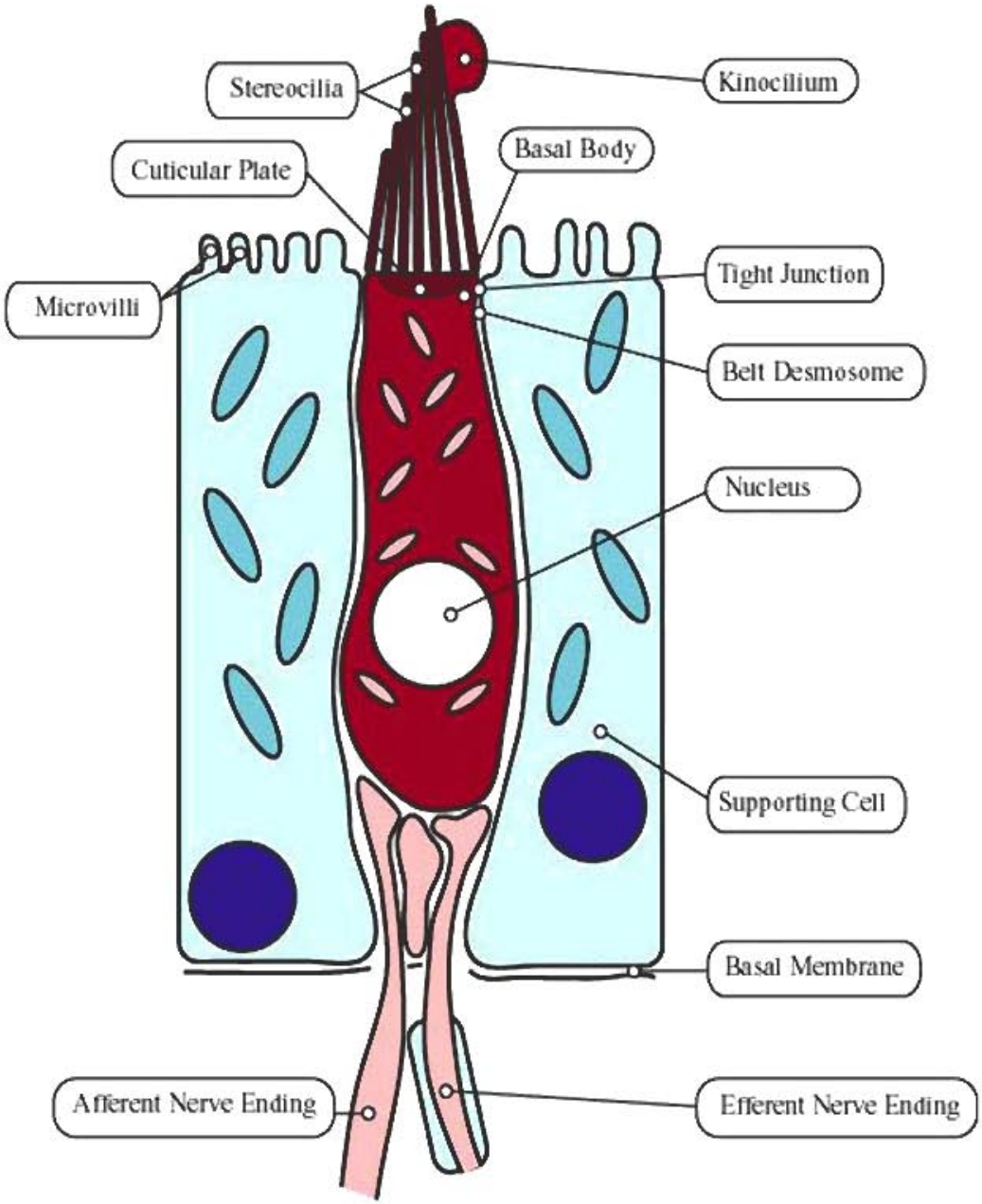
hDIAPH SSCP analysis and expression profile

See Lynch et al., Science 1997, 27b:1223

Mutations in the DFNA1 genomic and cDNA sequences

See Lynch et al., Science 1997, 27b:1223


human diaphonous 1


Stereocilia
Kinocilium
Cuticular Plate
Basal Body
Microvilli
Tight Junction
Belt Desmosome
Nucleus
Supporting Cell
Basal Membrane
Afferent Nerve Ending
Efferent Nerve Ending

Risk of deaf offspring

Mating type	**% Deaf offspring**
hearing x hearing	0.1%
hearing x deaf	7%
deaf x deaf	10%

deaf vs. Deaf

Additional Readings

Lynch et al., Science 1997, 27b:1223