Genetic Hearing Loss

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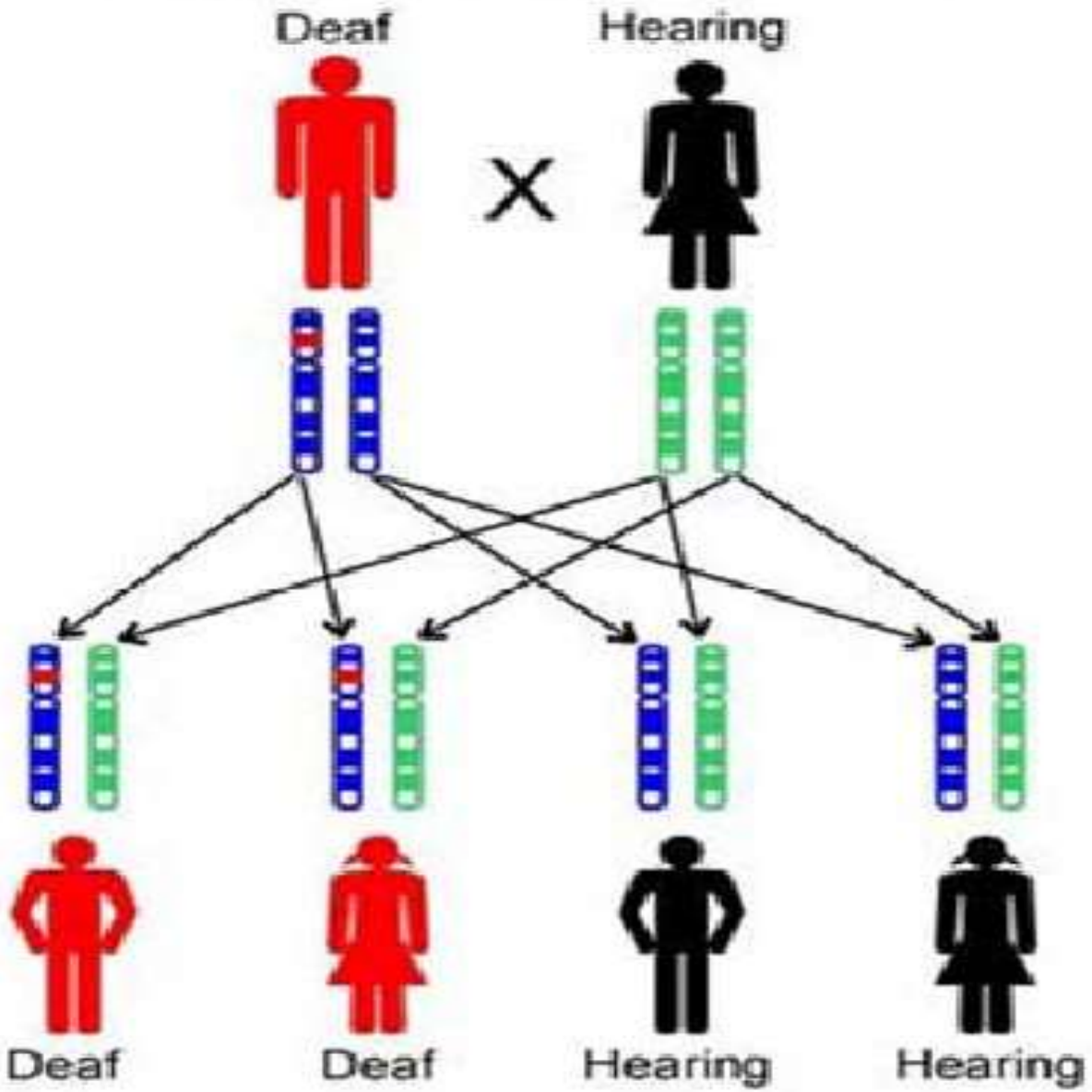
Grand Rounds Presentation
March 2004

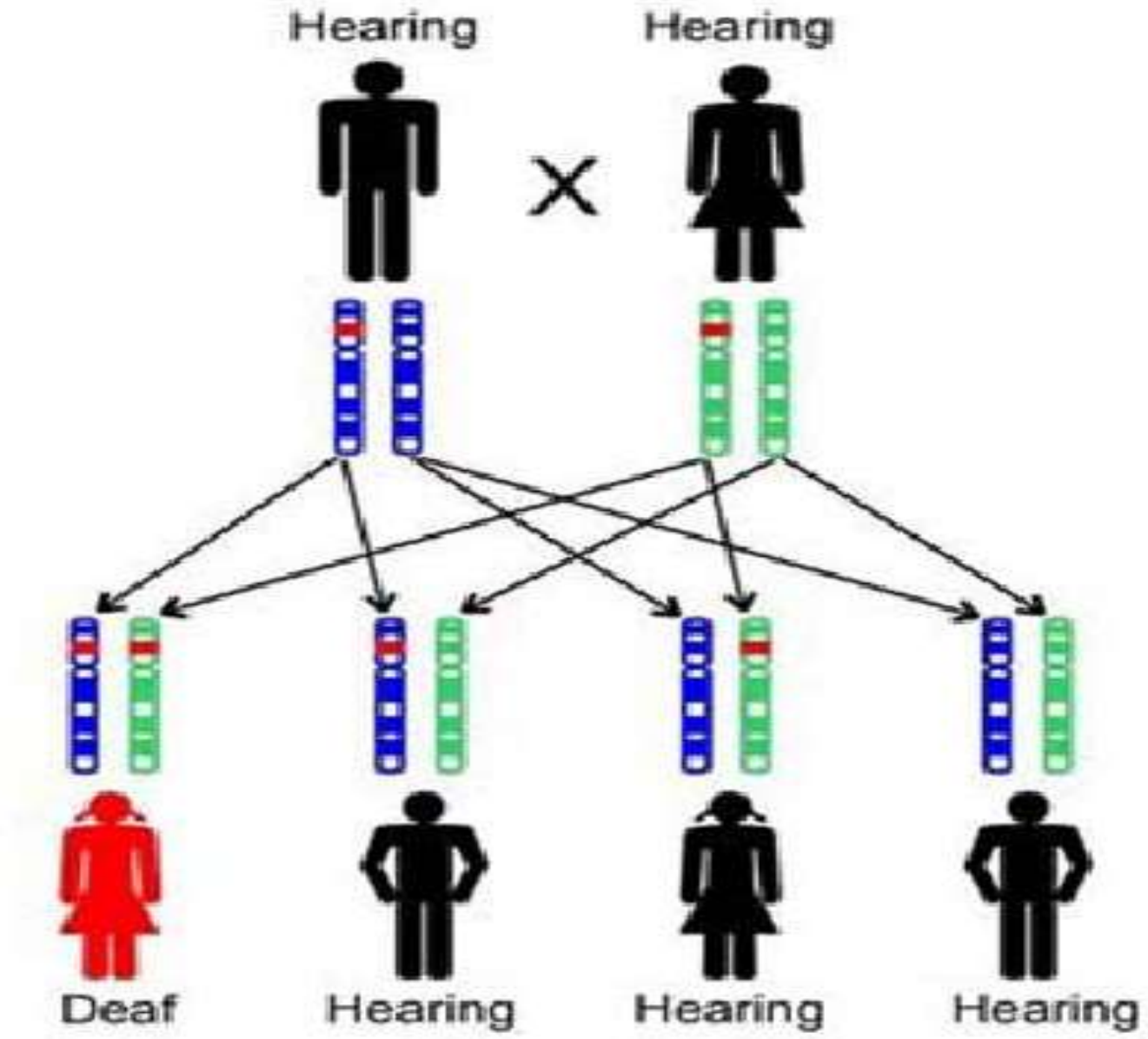
Epidemiology

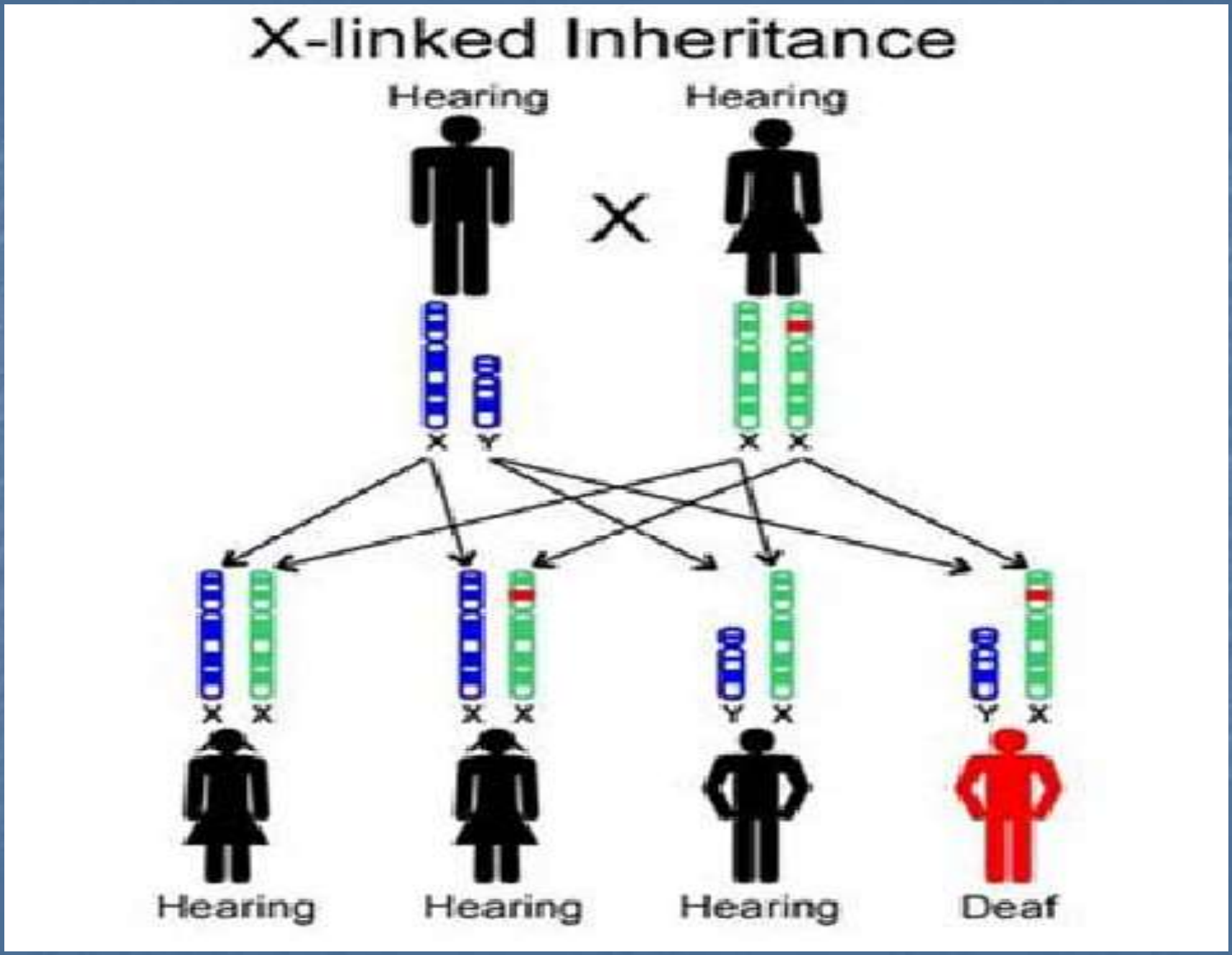
- Hearing loss occurs in 1 out of every 1,000 births
- 50 % are hereditary
- Syndromic vs. nonsyndromic
  - 30% syndromic
  - 70% nonsyndromic
- Autosomal dominant vs. autosomal recessive vs. x-linked vs. mitochondrion

Dominant Inheritance



Recessive Inheritance




X-linked Inheritance
Hearing
Hearing
X
X
Y
X
X
X
X
X
X
Y
Y
X
Hearing
Hearing
Hearing
Deaf

Methods

- Linkage mapping
- Mouse model
- Difficulties:
  - Families too small for linkage analysis
  - Assortive mating introducing various genes into one single pedigree
  - Incomplete penetrance

Syndromic deafness

- Has other abnormalities
- About 20-30% of genetic hearing loss
- Two syndromes can be caused by different mutations of the same gene
- Mutations of more than one gene can cause the same clinical phenotype

Alport syndrome

- At least 1% of congenital hearing loss
- X-linked inheritance (80%), autosomal recessive as well as dominant
- Sensorineural hearing loss: mostly affect high tone
- Renal dysfunction
  - Microscopic hematuria
  - Man are more severely affected than woman
  - Onset in early childhood and progress to renal failure in adulthood
  - increased risk of developing anti-GBM nephritis after renal transplantation

Alport syndrome

- Ocular abnormalities
  - Lenticulus
  - Retina flecks
- Defective collagen type 4 causes abnormalities in the basement membrane
- 3 genes: *COL4A5, COL4A3, COL4A4*
- These collagens found in the basilar membrane, parts of the spiral ligament, and stria vascularis
- Exact mechanism of hearing loss is unknown

Branchio-oto-renal syndrome

- 2% of profoundly deaf children
- Autosomal dominant disorder
- Otologic anomalies:
  - variable hearing loss (sensorineural, conductive or mixed)
  - malformed pinna, preauricular pits
- Branchial derived abnormalities: cyst, cleft, fistula
- Renal malformation: renal dysplasia with anomalies of the collecting system, renal agenesis
- Sometimes with lacrimal duct abnormalities: aplasia, stenosis
- *EYA1* gene mutation – knockout-mice showed no ears and kidneys because apoptotic regression of the organ primordia

Jervell and Lange-Nielsen syndrome

- Autosomal recessive
- 0.25% of profound congenital hearing loss
- Prolonged QT interval, sudden syncopal attacks
- Severe to profound sensorineural hearing loss
- 2 genes identified:
  - *KVLQT1*: expressed in the stria vascularis of mouse inner ear
  - *KCNE1*
  - Both gene products form subunits of a potassium channel involved in endolymph homeostasis

Norrie syndrome

- X-linked inheritance
- Ocular symptoms with congenital blindness: pseudotumor of the retina, retinal hyperplasia, hypoplasia and necrosis of the inner layer of the retina, cataracts, phthisis bulbi
- Progressive sensorineural hearing loss
- Mental deficiency
- *Norrin* gene: encodes a protein related to mucins

Pendred Syndrome

- Most common form of syndromal deafness- 4-10 %
- Autosomal recessive disorder
- Sensorineural hearing loss
  - bilateral, severe to profound, and sloping in the higher frequencies
  - incomplete partition of the cochlear

Pendred syndrome

- Vestibular dysfunction:
  - enlargement of the vestibular aqueducts, the endolymphatic sac and duct
- Thyroid goiter:
  - usually euthyroid, can be hypothyroid
  - defective organic binding of iodine
  - positive potassium perchlorate discharge test

Pendred syndrome

- *PDS* gene mutations:
  - on chromosome 7q31
  - encodes pendrin: an anion transporter in inner ear, thyroid, kidney
- *PDS* knockout mouse:
  - complete deaf
  - endolymph-containing spaces enlargement
  - inner and outer hair cell degeneration
  - no thyroid abnormality

Stickler syndrome

- Autosomal dominant
- Variable sensorineural hearing loss
- Ocular symptoms: progressive myopia, resulting in retina detachment and blindness
- Arthropathy: premature degenerative changes in various joints
- Orofacial features: midface hypoplasia
- Three genes: *COL2A1, COL11A1, COL11A2*
  - Associated with defective collagen protein
  - Each gene mutation corresponding to a phenotype

Treacher-collins syndrome

- Autosomal dominant with variable expression
- Conductive hearing loss
- Craniofacial abnormalities:
  - Coloboma of the lower lids, micrognathia, microtia, hypoplasia of zygomatic arches, macrostomia, slanting of the lateral canthi
- *TCOF1* gene:
  - Involved in nucleolar-cytoplasmic transport
  - mutation results in premature termination of the protein product

Usher syndrome

- Autosomal recessive disorder
- Sensorineural hearing loss
- Progressive loss of sight due to retinitis pigmentosa
- Three different clinical types
- 11 loci and 6 genes have been identified

Usher syndrome

- Type 1:
  - Profound congenital deafness, absent vestibular response, onset of retinitis pigmentosa in the first decade of life
- Type 2:
  - Sloping congenital deafness, normal vestibular response, onset of retinitis pigmentosa in first or second decade of life
- Type 3:
  - Progressive hearing loss, variable vestibular response, variable onset of retinitis pigmentosa

Type	Locus name	gene
I	USH1A	unknown
	USH1B	*MYO7A*
	USH1C	*USH1C*
	USH1D	*CDH23*
	USH1E	unknown
	USH1F	*PCDH15*
	USH1G	unknown
II	USH2A	*USH2A*
	USH2B	unknown
	USH2C	unknown
III	USH3	*USH3*

Usher syndrome

- *MYO7A*: encodes for myosin 7A, molecular motor for hair cells
- *USH1C*: encodes for harmonin, bundling protein in stereocilia
- *CDH23*: encodes cadherin 23, an adhesion molecule may be important for crosslinking of stereocilia, also may be involved in maintaining the ionic composition of the endolymph
- Myosin 7A, harmonin, and cadherin 23 form a transient functional complex in stereocilia

Waardenburg syndrome

- About 2% of congenital hearing loss
- Usually autosomal dominant
- Dystonia canthorum
- Pigmentary abnormalities of hair, iris and skin
- Sensorineural hearing loss
- 4 clinical subtypes

Waardenburg syndrome

- Type 1:
  - With dystopia canthorum
  - Penetrance for hearing loss 36% to 58%
  - Wide confluent eyebrow, high broad nasal root, heterochromia irides, brilliant blue eyes, premature gray of hair, eyelashes, or eyebrows, white forelock, vestibular dysfunction
- Type 2:
  - like type 1 but without dystopia canthorum
  - Hearing loss penetrance as high as 87%

Waardenburg syndrome

- Type 3 (Klein-Waardenburg syndrome):
  - Type 1 clinical features + hypoplastic muscles and contractures of the upper limbs
- Type 4 (Shah-Waardenburg syndrome):
  - Type 2 clinical features + Hirschsprung's disease
- Five genes on five chromosomes have been identified

Waardenburg syndrome

- Type 1 and type 3:
  - all associated with *PAX3* gene mutation
- Type 2:
  - Associated with dominant mutations of *MITF* gene
  - Associated with homozygous deletion of *SLUG* gene
  - MITF was found to activate the *SLUG* gene

Waardenburg syndrome

- Type 4:
  - *EDNRB* gene – encodes endothelin-b receptor, development of two neural crest derived-cell lineages, epidermal melanocytes and enteric neurons
  - *EDN3* gene – encodes endothelin-3, ligand for the endothelin-b receptor
  - *SOX10* gene – encodes transcription factor

Non-syndromic deafness

- About 70-80% of hereditary hearing loss
- Autosomal dominant (15%):
  - 41 loci (DFNA) and 20 genes identified
  - Usually postlingual onset, progressive
  - Severity from moderate to severe
  - Majority of the hearing loss in middle, high or all frequencies
- Autosomal recessive (80%):
  - 33 loci (DFNB) and 21 genes identified
  - Usually prelingual onset, non-progressive
  - Severity from severe to profound
  - All frequencies affected
- X-linked (2-3%):
  - 4 loci (DFN) and 1 gene identified
  - Either high or all frequencies affected

Non-syndromic deafness

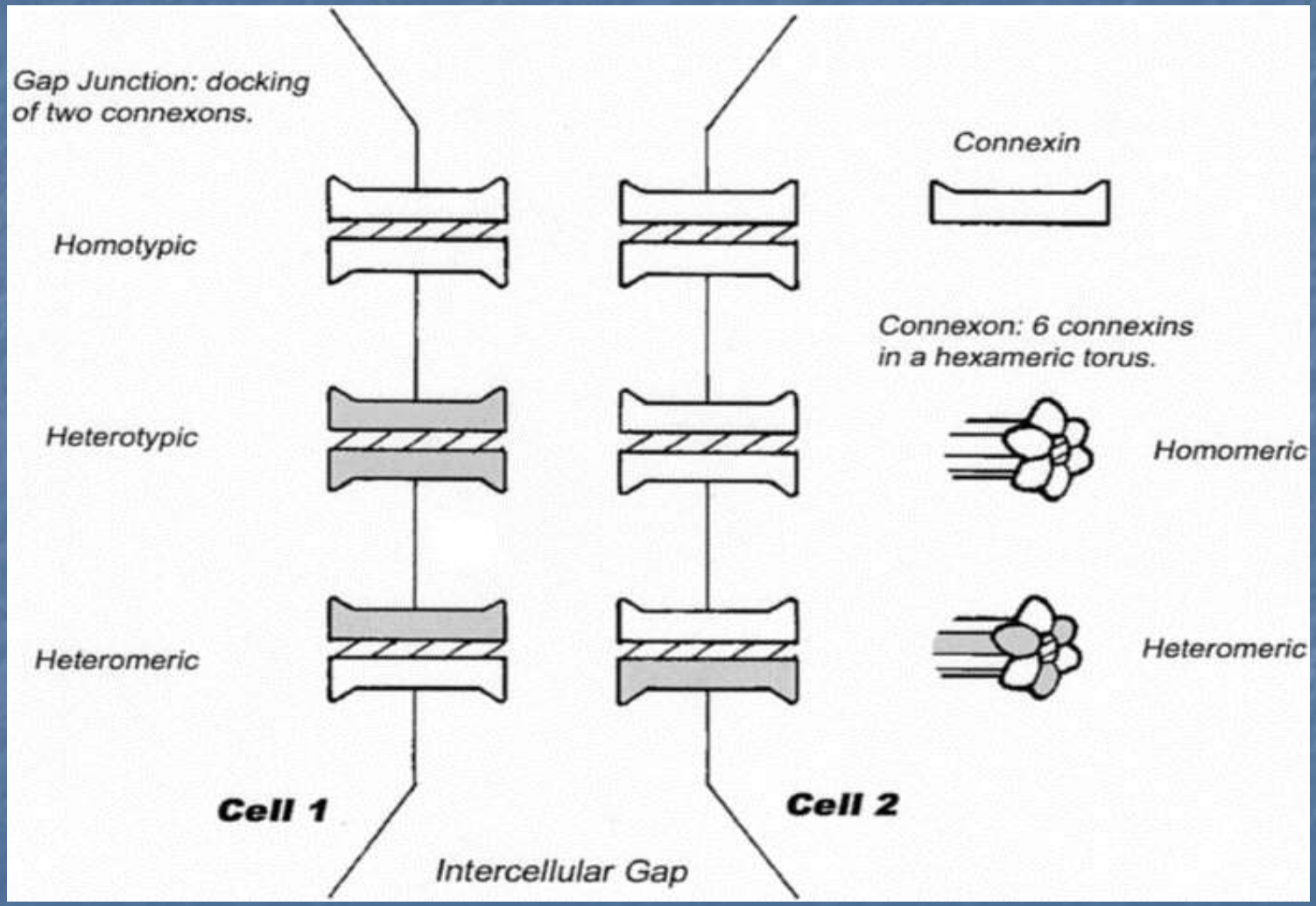
- Identified genes encode:
  - Unconventional myosin and cytoskeleton proteins
  - Extracellular matrix proteins
  - Channel and gap junction components
  - Transcription factors
  - Proteins with unknown functions
- More than one gene found in the same loci (DFNA2 and DFNA3)
- Some genes cause autosomal dominant and autosomal recessive hearing loss
- Some genes cause non-syndromic and syndromic hearing loss

Ion homeostasis

- Potassium recycling to maintain high potassium concentration in endolymph
- *KCNQ4*: encodes a potassium channel
- *SLC26A4*: encodes an anion transporter, pendrin
- 4 gap junction genes: *GJB2, GJB3, DJB6, GJA1*
  - Encode connexin proteins
  - Function of gap junctions: molecular pores connecting two adjacent cells allowing small molecules and metabolites exchange

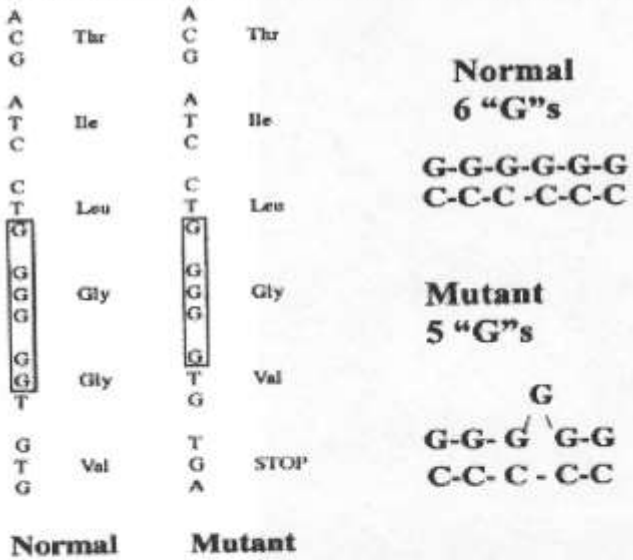
GJB2 (Gap Junction Beta 2)

- The first non-syndromic sensorineural deafness gene to be discovered
- On chromosome 13q11
- 50% of recessive non-syndromic hearing loss
- Encodes connexin 26
  - Expressed in stria vascularis, basement membrane, limbus, spiral prominence of cochlea
  - Recycling of potassium back to the endolymph after stimulation of the sensory hair cell
- 80 recessive and 6 dominant mutations
- 35delG mutation
  - One guanosine residue deletion from nucleotide position 35
  - Results in protein truncation
  - High prevalence in Caucasian population
  - Screening test available


Gap Junction: docking of two connexons.
Homotypic
Heterotypic
Heteromeric
Cell 1
Cell 2
Intercellular Gap
Connexin
Connexon: 6 connexins in a hexameric torus.
Homomeric
Heteromeric

Otolaryngologic Clinics of North America
Volume 35 • Number 4 • August 2002

Fig. 2. The "common" 35delG mutation arises from loss of a guanosine residue at nucleotide position 35 of GJB2 and results in a shift in reading frame that produces premature protein truncation.



Transcription factors

- *POU3F4*
  - X-linked mixed hearing loss
  - Stapes fixation causing conductive hearing loss
  - Increased perilymphatic pressure
  - Causing the typical "gusher" during stapes footplate surgery – stapes-gusher syndrome
- *POU4F3*
  - Autosomal dominant hearing loss
  - Knockout mice fail to develop hair cells with subsequent loss of spiral and vestibular ganglia
- *EYA4*
- *TFCP2L3*

Cytoskeleton proteins

- Associated with actin-rich stereocilia of hair cells
- Myosin: actin-dependent molecular motor proteins
  - *MYH9*
  - *MYO3A, MYO6, MYO7A, MYO15* – all have vestibular dysfunction
- Otoferlin: calcium triggered synaptic vesicle trafficking
  - *OTOF*
  - one particular mutation accounts for 4.4% of recessive prelingual hearing loss negative for *GJB2* mutation
- Actin-polymerization protein: *HDIA1*
- Harmonin: organize multiprotein complexes in specific domains (tight junction, synaptic junction)
  - *USH1C* (also in Usher type 1c)
- Cadherin: important for stereocilia organization
  - *CDH23* (also in Usher type 1d)

Extracellular matrix components

- *TECTA*
  - Encodes alpha tectorin- component of the tectorial membrane
  - Knockout mice with detachment of tectorial membrane from the cochlear epithelium
- *COL11A2*
  - Encodes collage type XI polypeptide subunit 2
  - Knockout mice with atypical and disorganized collagen fibrils of the tectorial membrane
- *COCH*
  - Encodes COCH (coagulation factor C homologue) protein
  - Expressed in cochlear and vestibular organs
  - Associated with vestibular problems

Unknown function genes

- *WFS1*
  - Dominant sensorineural hearing loss
  - Responsible for 75% of low frequency nonsyndromic progressive hearing
  - Responsible for up to 90% of cases of Wolfram syndrome, a recessive disorder with diabetes mellitus, diabetes insipidus, optic atrophy, and deafness

Mitochondrial disorders

- 2-10 mitochondrial chromosomes in each mitochondrion
- Transmitted only through mothers
- With syndromic hearing loss
  - Associated with systemic neuromuscular syndromes: such as Kearns-Sayre syndrome, MELAS, MERRF
  - Also in families with diabetes and sensorineural hearing loss
  - Associated with skin condition: palmoplantar keratoderma
- With non-syndromic hearing loss
- With aminoglycoside ototoxic hearing loss
  - A1555G mutation in the 12S ribosomal RNA gene
  - Maternally transmitted predisposition to aminoglycoside ototoxicity
  - Accounts for 15% of all aminoglycoside induced deafness

Evaluation

- History
  - Prenatal: infection, medication
  - Perinatal: risk factors
  - Postnatal: infection, speech and language milestones
  - Family:
    - hearing loss in first and second degree relatives
    - Hearing loss occurred before age 30
    - Consanguinity or common origin from ethnically isolated areas

Evaluation

- Physical exam: features of syndromic hearing loss
  - Hair color: white forelock, premature graying
  - Facial shape
  - Skull shape
  - Eye: color, position, intercanthal distance, cataracts, retinal findings
  - Ear: preauricular pit, skin tags, shape and size of pinna, abnormality of EAC and TM
  - Oral cavity: cleft
  - Neck: brachial anomalies, thyroid enlargement
  - Skin: hyper/ hypopigmentation, café-au-lait spots
  - Digits: number, size, shape
  - Neurological exam: gait, balance

Evaluation

- Audiologic evaluation
- Lab testing: based on history and physical exam
  - Torch titers
  - CBC and electrolytes
  - Urinalysis
  - thyroid function test (perchlorate discharge test)
  - EKG
- Radiological study:
  - CT temporal bone is the test of choice
    - Dilated vestibular aqueduct (>1.5mm at middle third or >2mm anywhere along its length)
    - Mondini malformation
    - Semicircular canal absence or dysplasia
    - Internal auditory canal narrowing or dilation
  - Renal ultrasound

Genetic screening

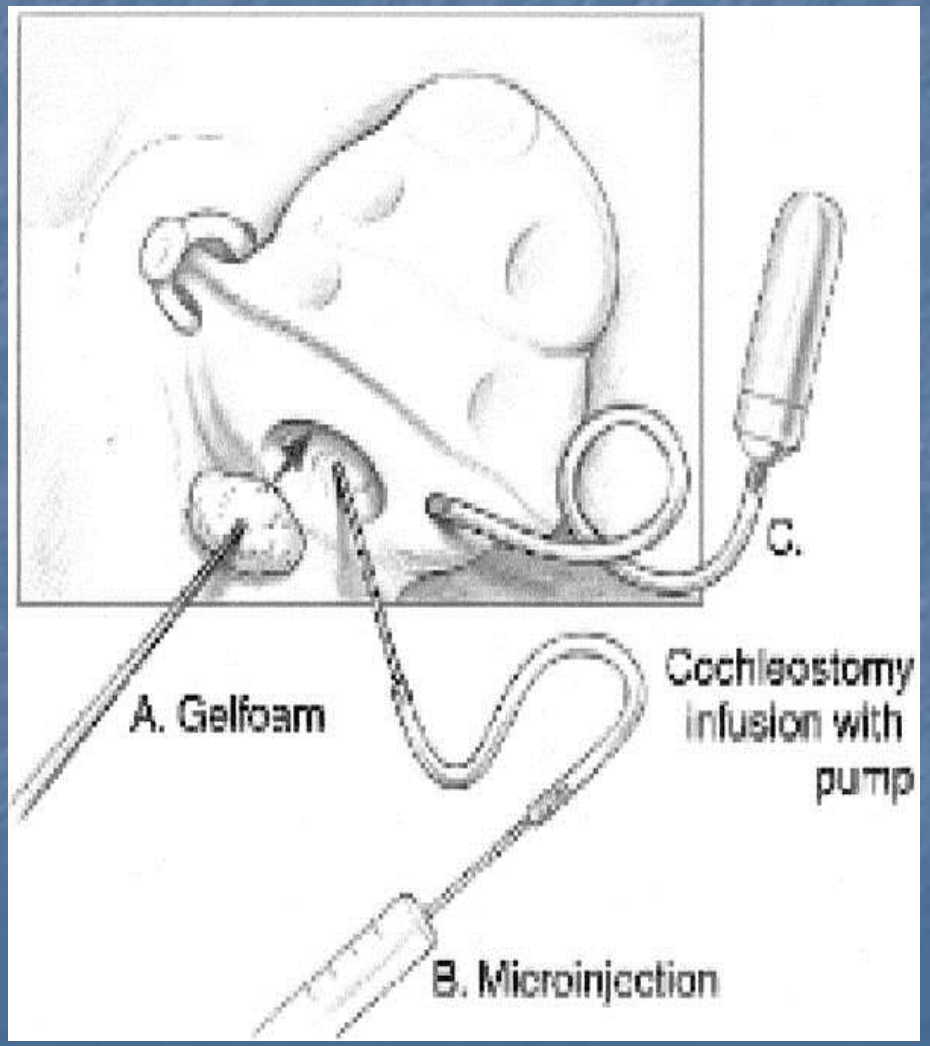
- GJB2
  - most common cause of severe to profound nonsyndromic recessive deafness
  - High prevalence of 35delG mutation
  - Small size of *GJB2* gene
- SLC26A4- most common cause of Mondini dysplasia or dilated vestibular aqueduct syndrome
- EYA1- 30-40% of families with a branchio-oto-renal phenotype

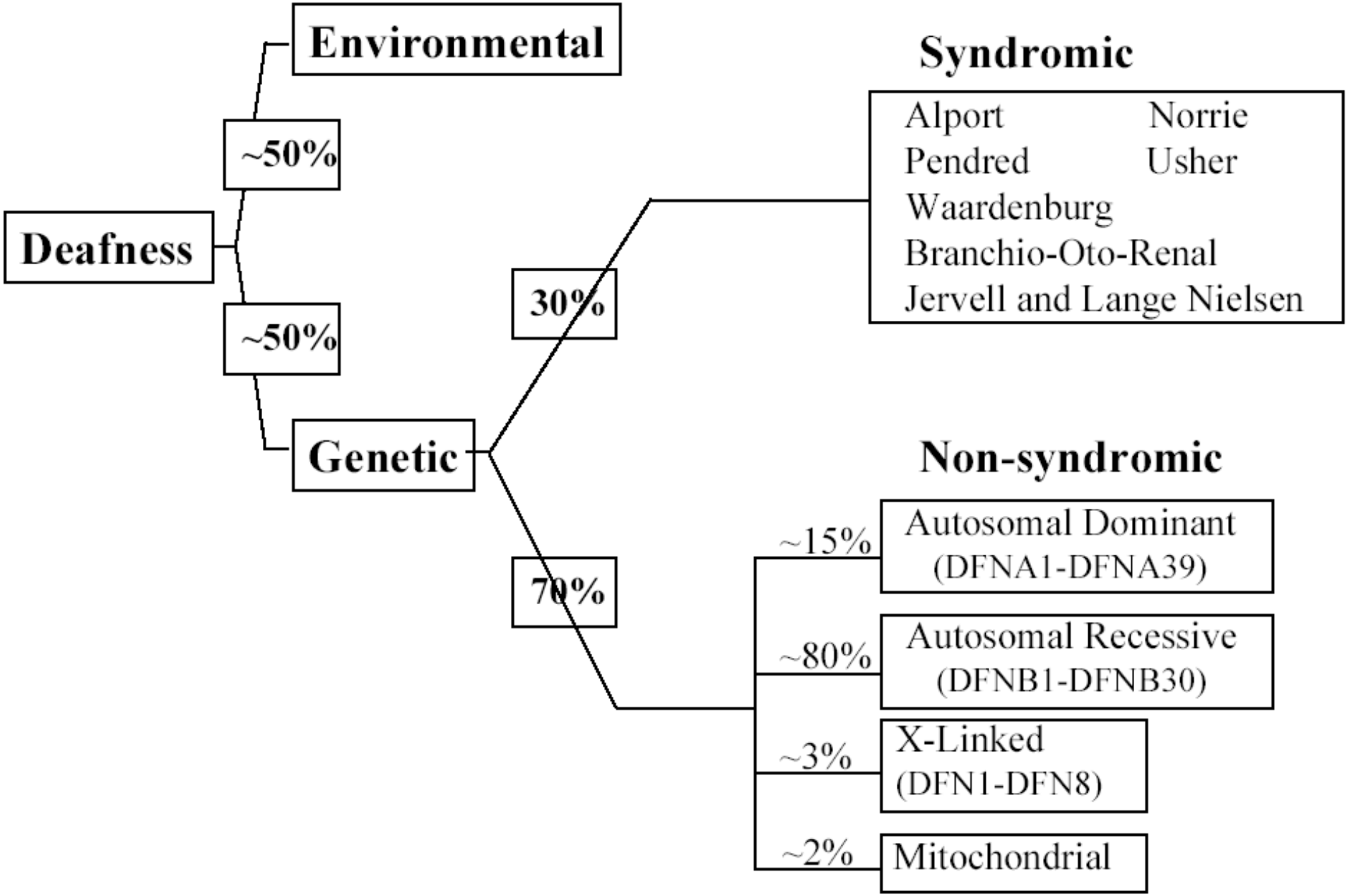
Genetic counseling

- Goal:
  - Cause of deafness
  - Other medical implication
  - Chance of recurrence in future children
  - Implications for other family members
  - Assist family in making choices that are appropriate for them
- Team approach including clinical/medical geneticist, genetic counselor, social worker, psychologists
- Consent need to be obtained for genetic testing

Cochlear gene therapy

- Adenoid associated virus as vector
- Routes of delivery
- Safety concern
  - Hearing loss
  - Regional and distal dissemination




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

Resources for hereditary hearing loss

- Hereditary hearing loss home page http://www.uia.ac.be/dnalab/hhh
- Online Mendelian Inheritance in Man www.ncbi.nlm.nih.gov/Omim

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