Dominant Inheritance

Deaf × Hearing

Deaf Deaf Hearing Hearing
Recessive Inheritance

Hearing  X  Hearing

Deaf  Hearing  Hearing  Hearing
X-linked Inheritance

Hearing  

\[ \times \]  

Hearing  

Hearing  

Hearing  

Deaf
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
~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

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alport</td>
<td>COL4A5, COL4A3, Col4A4</td>
</tr>
<tr>
<td>Branchio-Oto-Renal</td>
<td>EYA1</td>
</tr>
<tr>
<td>Crouzon</td>
<td>FGF</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen</td>
<td>KCNQ1, KCNE1/IsK</td>
</tr>
<tr>
<td>Mitochondrial (MELAS, MERRF)</td>
<td>tRNA\textsuperscript{leu(UUR)}, tRNA\textsuperscript{lys}</td>
</tr>
<tr>
<td>Neurofibromatosis type II</td>
<td>NF2</td>
</tr>
<tr>
<td>Norrie</td>
<td>NDP</td>
</tr>
<tr>
<td>Osteogenesis Imperfecta</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Pendred</td>
<td>PDS</td>
</tr>
<tr>
<td>Stickler</td>
<td>COL2A1, COL11A2, COL11A1</td>
</tr>
<tr>
<td>Tranebjaerg-Mohr (DFN1)</td>
<td>DDP</td>
</tr>
<tr>
<td>Treacher Collins</td>
<td>TCOF1</td>
</tr>
<tr>
<td>Usher</td>
<td>MYO7A, USH2A, USH1C, CDH23</td>
</tr>
<tr>
<td>Waardenburg</td>
<td>PAX3, MITF, EDNRB, EDN3, SOX10</td>
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</tbody>
</table>
### Selected genetic syndromes with hearing loss

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incidence</th>
<th>Gene(s)</th>
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</thead>
<tbody>
<tr>
<td>Alport</td>
<td>1 in 5,000</td>
<td>COL4A3, COL4A4, COL4A5</td>
</tr>
<tr>
<td>Usher</td>
<td>1 in 23,000</td>
<td>MYO7A, USH1C, CDH23, USH2A</td>
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<tr>
<td>Jervell &amp; Lange-Nielsen</td>
<td>1 in 250,000</td>
<td>KCNQ1, KCNE1/ISK</td>
</tr>
<tr>
<td>Mitochondrial syndromes</td>
<td></td>
<td>tRNA-Leu, tRNA-Lys</td>
</tr>
<tr>
<td></td>
<td>(MERRF, MELAS, diabetes with deafness)</td>
<td></td>
</tr>
</tbody>
</table>
Pendred syndrome
1 in 7,500, autosomal recessive
Associated feature: late childhood/early adult onset goiter
Gene: PDS
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
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
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

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing loss</th>
<th>Vestibular loss</th>
<th>Vision loss</th>
<th>Min. # genes</th>
<th># genes Id’d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>congenital</td>
<td>absent</td>
<td>onset 1st</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>profound</td>
<td></td>
<td>decade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>congenital</td>
<td>normal</td>
<td>onset 1st</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>sloping</td>
<td></td>
<td>or 2nd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>progressive</td>
<td>variable</td>
<td>variable</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
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

Environmental

~50%

~50%

Genetic

30%

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

Jan2001
January, 2002
## Nonsyndromic Deafness Genes Cloned

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

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

Human-Mouse Homology Map

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
4) Mutation Analysis

Connexin 26 Gene

.. AGATGAGCA .. Hearing Deaf
.. AGATTAGCA .. Deaf

DFNB1

SGCG
GJB2
FGF9
SAP18
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 DSS210/DSS207 are $>10^{12}$. 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 $\approx 7$ centimorgans (cM).

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
Risk of deaf offspring

<table>
<thead>
<tr>
<th>Mating type</th>
<th>% Deaf offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>hearing x hearing</td>
<td>0.1%</td>
</tr>
<tr>
<td>hearing x deaf</td>
<td>7%</td>
</tr>
<tr>
<td>deaf x deaf</td>
<td>10%</td>
</tr>
</tbody>
</table>
deaf vs. Deaf
Additional Readings

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