The Genetics of Hearing Loss

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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

- Genetic
  - Nonsyndromic
  - Syndromic
  - Mitochondrial
  - X-Linked
- Environmental or Unknown Etiology
- Autosomal Dominant
- Autosomal Recessive
Human Karyotype
We inherit two copies of every gene, one from each parent.
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

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Gene(s)</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>Jervell and Lange-Nielsen</td>
<td>KCNQ1, KCNE1/IsK</td>
</tr>
<tr>
<td>Mitochondrial (MELAS/MERRF)</td>
<td>tRNA(^{leu(UUR)}), tRNA(^{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, USH1C, CDH23, PCDH15, SANS, USH2A, VLGR1, USH3</td>
</tr>
<tr>
<td>Waardenburg</td>
<td>PAX3, MITF, SLUG, EDN3, EDNRB, EDN3, SOX10</td>
</tr>
</tbody>
</table>

There are currently over 400 syndromes with associated hearing loss.
# Usher Syndrome

(3-6% of childhood deafness)

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing Loss</th>
<th>Vestibular System</th>
<th>Retinitis Pigmentosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Congenital profound</td>
<td>Congenital balance problems</td>
<td>Onset pre-puberty</td>
</tr>
<tr>
<td>Type II</td>
<td>Congenital mild-severe sloping</td>
<td>Normal</td>
<td>Onset in teens-20s</td>
</tr>
<tr>
<td>Type III</td>
<td>Progressive later onset</td>
<td>Progressive balance problems</td>
<td>Variable onset</td>
</tr>
<tr>
<td>Usher Type</td>
<td>Locus</td>
<td>Gene</td>
<td>Relative Incidence</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>USH1A</td>
<td>14q32</td>
<td>unknown</td>
<td>2%</td>
</tr>
<tr>
<td>USH1B</td>
<td>11q13.5</td>
<td>MYO7A</td>
<td>60%</td>
</tr>
<tr>
<td>USH1C</td>
<td>11p15.1</td>
<td>USH1C</td>
<td>5%</td>
</tr>
<tr>
<td>USH1D</td>
<td>10q</td>
<td>CDH23</td>
<td>10%</td>
</tr>
<tr>
<td>USH1E</td>
<td>21q</td>
<td>unknown</td>
<td>Rare</td>
</tr>
<tr>
<td>USH1F</td>
<td>10q21.1</td>
<td>PCDH15</td>
<td>Rare</td>
</tr>
<tr>
<td>USH1G</td>
<td>17q24-25</td>
<td>SANS</td>
<td>Rare</td>
</tr>
<tr>
<td>USH2A</td>
<td>1q41</td>
<td>USH2A (+51)</td>
<td>80%</td>
</tr>
<tr>
<td>USH2B</td>
<td>3p23-24.2</td>
<td>unknown</td>
<td>Rare</td>
</tr>
<tr>
<td>USH2C</td>
<td>5q14.3-q21.3</td>
<td>VLGR1</td>
<td>15%</td>
</tr>
<tr>
<td>USH3</td>
<td>3q21-q25</td>
<td>USH3</td>
<td>100%</td>
</tr>
</tbody>
</table>
Jervell & Lange-Nielsen Syndrome

- Incidence: 1/250,000
- Phenotype
  - Severe-profound congenital sensorineural hearing loss
  - Prolonged QT interval
  - Syncope
  - Arrhythmia
  - 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

Clinical Genetics

EKG

Ophthalmology

Management and Intervention

- Cochlear Implant
- Hearing Aids
- ASL

Genetic Counseling
Causes of Childhood Hearing Loss

Genetic
- Nonsyndromic
- Syndromic
- Autosomal Recessive
- Autosomal Dominant
- Mitochondrial
- X-Linked

Environmental or Unknown Etiology

Genetic

Nonsyndromic

Autosomal Recessive

Cx26
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**
- **Nonsense:** W24X, W44X, E47X, Q57X, Y65X, Y97X, Q124X, Y136X, W112X, W172X, C64X, Q80X, E147X
- **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
Connexin 26 Gene Sequence

ATGGATTGGGGCAGCAGGACGATCCTGGGGGGTGTGAACAGGGGATGTGAACA
AACACTCCACCAGCATTGGAAAGATCTGGGCTCACCCTCCTCTCTTC
ATTTTTTCGCATTATGATCCTCGTTGTGGCTGCAAAAGGAGGTGTGGGAGAATGGAGCAAGCCGACTTTTGTCTGCAACACCCCTGCAGCCA
GGCTGCAAGAACGTGTGCTACGATCAACTACTTTCCCCCATCTCCCCA
CATCCCGGTATGGGCCCCTGCAGCTGATCTTCGTGTCCAGCCCA
GCGCTCCCTAGTGCCCATGCACGCTGGCCTACCAGGAGACATGAGA
AGAAGAGGAAGGTTTCAATCAAGGGGGAGATAAAGAGTGTAATTTTAAG
GACATCGAGGAGATCAAAACCCAGGTCCCGCATCGAGAGGCT
CCCTGTGGGTGGGAACCTACACAAGCAGCATCTTCTTTCCGGGTTCATC
TTTCAAAGCCGCCCCTTCCATGTACGTCTCTATGTATGTATGCAGACGG
CTTCTCCATAGCAGCGGCTGGTAAGTGCAACGCCTGGGCCTTTGT
CCCAACACTGTGGGACTGCTTTTGTGTCCCGGGCCCACCGGAGAAGA
CTGTCTTTCACAGTGTTCATGATTGCACTGTCTGTGGAATTGGCATC
CTGCTGAAATCTGCACTGATTTGGTGTATTGGCTAATTAGATATTGTC
TCTGGGAAGGTCAAAAAAGCCAGTTAA
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

M34T/35delG | M34T/ M34T | M34T/ V37I | V37I/V37I

- Normal
- Mild
- Moderate
- Severe
- Profound
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:**

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biallelic mutations</td>
<td>20/101</td>
<td>20%</td>
</tr>
<tr>
<td>Heterozygous mutations</td>
<td>12/101</td>
<td>10%</td>
</tr>
<tr>
<td>No mutation detected</td>
<td>71/101</td>
<td>70%</td>
</tr>
</tbody>
</table>

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)

Progression of Cx26 Hearing Loss

Total = 100 patients

- Progressive: 19%
- Profound: 38%
- Stable: 43%
The Cochlea

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

Sound wave
Potassium Recycling in the Cochlea

Endolymph

K+ K+ K+ K+ K+ K+ K+

K+

K+

K+
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 absence of unrelated medical problems
Major Causes of Hearing Loss

- Genetic
  - Nonsyndromic
  - Syndromic
  - Autosomal Recessive
  - Autosomal Dominant
  - X-Linked
  - Mitochondrial

- Anatomical
- Traumas/Exposures
- Infections
- Drugs
- Unknown

~50 Genes

Cx26

~50 Genes
The longer the gene the more difficult and expensive to develop and perform a genetic test.
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
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”
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
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:
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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