Genetic Testing for Deafness

How it will impact your management of deaf and hard of hearing persons

Today’s goals are to review
- Where we are….
  - The importance of genetic testing for deafness
- Where we are going….
  - Initiatives to improve genetic testing
  - Initiatives to improve gene discovery
- Why we should get there….
  - Genetic testing and habilitation options for hearing loss

What do families want to know?
- What caused the hearing loss?
- Will the hearing loss progress?
- Is there anything else going on?
- How will my child do with hearing aids? With a CI?
- If I have other children, will they have hearing loss?
- When my child has children, will they have hearing loss?

Genetic testing can help you answer these questions.
In most developed countries, mutations in GJB2 are found in over half of cases.

In one-third of families like this, mutations will be found in GJB2.

Green et al. JAMA 281:2211-16, 1999
## Where we are….

### GJB2 - related deafness

- **Prelingual deafness**
- **Non-syndromic**
- Mild-to-profound hearing loss
- Generally no progressive (exception V37I)
- No vestibular abnormalities
- No radiographic abnormalities
- No sex bias
- In the USA, diagnosed in 1/3 of CI patients with congenital severe-to-profound deafness

<table>
<thead>
<tr>
<th>Genes</th>
<th>USA Labs</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>GJB2 (DFNB1, DFNA3)</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>GJB6 (DFNB1)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>SLC26A4 (DFNB4, PDS)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>EYA1 (BOR)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TECT4 (DFNB21, DFNA8/12)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>OTOF (DFNB9)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>KCNQ1 (DFNA2)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>POU3F4 (DFN3)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>WFS1 (DFNA6/14/38, DIDMOAD)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>MTRNR1 (A1555G)</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>MTTS1 (A7445G)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>MTTL1 (A3243G)</td>
<td>16</td>
<td>15</td>
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Where we are….

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### Example: A hearing couple have a deaf child, want to know why and want to know the chance of having another deaf child.

**GJB2 genotypes:**
- deaf child: 35delG/35delG
- mother: 35delG/normal
- father: 35delG/normal

**Recurrence chance:** 25%

**THEORETICAL ALTERNATIVE RESULTS:** If genetic testing is NOT offered the recurrence chance is 17%.

## GJB2 - related deafness

- we know the phenotype -

## GJB2 - related deafness

- we can predict the degree of hearing loss from the genotype -

### Component Scores (Z)

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<th>Value</th>
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<tr>
<td>Reading</td>
<td>0.2</td>
</tr>
<tr>
<td>Speech Perception</td>
<td>-0.6</td>
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</table>

### GJB2 status vs. reading ability

**Normal**

![Graph showing GJB2 status vs. reading ability]

### GJB2 - related deafness

- we can predict CI performance -

-2 -1.8 -1.6 -1.4 -1.2 -1.0 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

**Component Scores (Z)**

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![Graph showing component scores (Z)]

**Figure:** Snoeckx et al. JHG 77:945-57, 2005

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**ADNSHL**
- No single gene accounts for the majority of ADNSHL
- Audioprofiling
  - Clinical value: provide prognostic information to patient
  - Research value: prioritize genetic testing

**DFNA6 AUDIOPROFILING**

![Graph showing audioprofiling data for different frequencies and hearing levels for different samples.]

- **Daughter, 8 y**
- **Mother, 38 y**

**DFNA6 AUDIOPROFILING**

- **Family history +**
- **Family history -**

**WFS1 mutation screening**

- 77% of families
- 9% of sporadic cases

**A Large Pedigree Segregating ADNSHL**

Unable to localize the genetic cause.....

Consider this a nuclear family segregating recessive deafness and screen **GJB2**
A Large Pedigree Segregating ADNSHL

... and ARNSHL

Where we are going ....

- Clinical Diagnostics
  - AudioGene – computer driven
  - OtoSCOPE – new technologies

- Gene Discovery
  - OtoSCOPE + StereoCAPTURE

http://audiogene.eng.uiowa.edu/
OtoSCOPE (Otologic Sequence Capture of Pathogenic Exons)

- 57 genes: non-syndromic genes, microRNAs, mitochondrial mutations, Ushers
- Agilent solution-based capture and enrichment of all exons
- NEXT GEN sequencing

Sequencing Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence Output</td>
<td>32 million mappable reads per sample</td>
</tr>
<tr>
<td></td>
<td>2.2 billion mappable bases</td>
</tr>
<tr>
<td>Coverage Depth</td>
<td>&gt;700X depth of coverage per base</td>
</tr>
<tr>
<td>Target Enrichment</td>
<td>&gt;1,500X enrichment</td>
</tr>
<tr>
<td>% Targeted coding sequence coverage</td>
<td>97.8%</td>
</tr>
<tr>
<td>Sample</td>
<td>Status</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------</td>
</tr>
<tr>
<td>A1</td>
<td>Positive Control - COCH</td>
</tr>
<tr>
<td>A2</td>
<td>Positive Control - GJB2</td>
</tr>
<tr>
<td>A3</td>
<td>Biological replicate of A2</td>
</tr>
<tr>
<td>A4</td>
<td>Negative Control</td>
</tr>
<tr>
<td>A5</td>
<td>Unknown</td>
</tr>
<tr>
<td>A6</td>
<td>Unknown</td>
</tr>
<tr>
<td>A7</td>
<td>Unknown</td>
</tr>
<tr>
<td>A8</td>
<td>Unknown</td>
</tr>
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</table>

OtoSCOPE results compared favorably with Sanger sequencing.

**Subjects - Results**

**DIAGNOSTICS**

**Future Algorithm**

**RNAi**

**Why we should get there ...**

- Novel therapies for deafness
  - Genotype-specific therapies
  - Dependent on the specific (personal) type of hearing loss
  - Mechanism-specific therapies
    - Modify gene expression
    - RNAi
    - Medical therapy

**Prevention of hearing loss vs. correction of hearing loss**
DFNA2 – KCNQ4

- DFNA2 – KCNQ4 and GJB3
  - KCNQ4 – member of the KCNQ family of voltage-gated K+ channels
  - 4 KCNQ4 subunits aggregate to form functional channel
  - Mutant allele - only 1/16 of channels functional
  - One of the more frequently encountered ADNSHL loci

What do we need?

- Animal model
- Construct to suppress mutant allele
- Vector to deliver the construct to the appropriate cells
- Method to introduce the vector
- A lot of luck
Today’s goals were to review

• Where we are….
  – Genetic testing is important to deaf and hard-of-hearing persons and their families
  – Genetic testing may be valuable as a part of a CI evaluation

• Where we are going….
  – Several initiatives are ongoing to improve clinical diagnostics including AudioGene and OtoSCOPE
  – Hair bundle twist off > OtoSCOPE + StereoCAPTURE > mouse mutant = improved insight into biology of hearing and deafness

• Why we should get there….
  – Genotype-specific therapies will be developed to stop expression of dominant-negative alleles using RNAi