Global Impact and Screening Strategy for Deafness Genes in Individuals with CI

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Disclosures

No conflicts of interest to disclose in relation to this presentation.

Grant support: NIH/NIDCD
Second largest medical Center in USA

Serving a diverse patient population from the South Eastern United States to Latin America and the Caribbean.
University of Miami Ear Institute

- Center for Hereditary Deafness
- Cochlear Implant Program
- Skull Base Treatment Center
- Clinical Audiology
- Hearing Aid Center
- The Center for Advanced Treatment of Meniere's Disease and Balance Disorders
- Facial Nerve Disorders
- Microsurgery Training Center (RMSB)
- Barton G CI Family Resource Center
Gene Identification

- Extremely heterogeneous with at least >800 genes involved
- Only >100 identified genes with diverse function
- 2-3 genes accounting for major component of human deafness
- 20-60% patients identified to have mutations in known genes
The discovery that genes at only 2-3 loci account for a major component of human deafness suggested to us that the sequential screening of DNA samples from probands in multiplex sibships for mutations at selected candidate loci would be an effective strategy for identifying new genes for hereditary deafness. And mutations


The Lancet

Relation between choice of partner and high frequency of connexin-26 deafness

Walter E Nance, MD, Xue-Zhong Liu, MD, Arti Pandya, MD

**THE LANCET**

**Volume 356, Issue 9228, 5 August 2000, Pages 500–501**

**Hypothesis**

Reserve for future genomic tech available

**Identify new Deafness genes**

**Determine Phenotypic Frequencies & Distribution of Mutant Alleles.**

**Sequential Screening of Non syndromic**

**Screen for MYO7A**

**Screen for USH2A**

**Screening for MYO7A**

**Screen for other Human/mouse cloned genes**

**Multiplex**

**Simplex**

**Screen for Cx26 & Mitochondrial Mutations**

**Screen for other connexin mutations**

**Cx26 Het**

**Mit- Cx26-**

**Cx26+**

**Mit+**

**Mit+ Cx26+**

**Mit-Cx26-**

**Cx26 het**

**Non-syndromic**
### Sequencing technology

<table>
<thead>
<tr>
<th>Year</th>
<th>Technology Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 yrs</td>
<td>Sanger sequencing</td>
<td>DNA sequencing by direct sequencing of individual genes</td>
</tr>
<tr>
<td>3 yrs</td>
<td>Next Generation Sequencing (NGS)</td>
<td>Mutigene SNP mutation chips-selected number of mutations in a small number of genes</td>
</tr>
<tr>
<td>5 yrs</td>
<td>Third generation Sequencing</td>
<td>500 genes identified in clinical setting</td>
</tr>
<tr>
<td>3 yrs</td>
<td>NGS in widespread use across research setting</td>
<td>Whole genome sequencing by third generation sequencing technology</td>
</tr>
<tr>
<td>10 yrs</td>
<td>Whole genome sequencing by third generation sequencing technology</td>
<td>Whole genome sequencing by third generation sequencing technology</td>
</tr>
</tbody>
</table>

### Timeline of developments in genetic screening for hearing loss

- **2010/2011**: 60-70 known genes associated with hearing loss.
- **2012**: Developments in the speed/cost of sequencing enable knowledge in the field of genetic hearing loss to proceed at a rapid pace.
- **2013**: Potentially all 500 genes involved with hearing loss identified.
- **2014-2015**: Sequence all 20,000-25,000 genes in the genome may be possible a reasonable cost. Identify all conditions with a genetic basis - issue for all services within the NHS.

### Knowledge of genetic hearing loss

Screening methods available for genes causing hearing loss in USA:

- **Sanger sequencing; DNA Array; NGS**
Treatment of Hearing Loss

- Ultimate goal is to customize HL treatment based on the particular mutation
- Prevention and early treatment of HL
  - Prior to giving known ototoxic drugs, screen for pre-disposing mutations (e.g. m.A1555G)
  - Early rehab w/ HA or CI and speech therapy
  - More predictable response to CI or ABI
- Gene therapy
- Stem cells
- Preimplantation genetic diagnosis
Multidisciplinary collaboration effort

DNA sample collection, population-based cohort data, gene mapping, & whole exome sequencing

Clinical Management & Diagnosis
- diagnosis, counseling, personalized sequence profile

In vitro and in vivo therapeutic Gene/cell/drug-based studies

MiamiOtoGenomic Diagnostic and Therapeutic Platform
Multidisciplinary collaborations & integrate biomedical research and medicine

Department of Otolaryngology

Ear Institute
Hearing Loss Clinics (Clinical Services, clinical research)

Division of Audiology
Cochlear implant research Labs

Miami Otogenetic Center
HIHG-iPSc

Department of Biology

ECHO

CI Program
HIHG

Department of Human Genetics
The Miami Hearing Loss Clinic

Molecular Genetic Lab
Liu's Research Group - 2014
The University of Miami Miller School of Medicine

Gene Function Lab

The Miami Hereditary Hearing Loss Clinic

CHD
Case Presentation

- 10 y/o boy with congenital profound HL
- CI when 3 y/o, but outcome was poor
- USH1B with MYO7A mutations 2010
- Autism 2010
- Using implant more for environment contact and preparing worsening eye-sight deteriorates
For 7 Cutler Bay Siblings Born Deaf from genetic etiology, Sweet Sounds

Most families would take the buzz of four kids chirping away over homework for granted, but for the Guillou children, sound was never heard until recently. NBC 6’s Keith Jones reports. (Published Monday, Nov 25, 2013)
Therapeutic Strategies for genetic deafness

Blood Sample
Tumor tissue

Skin Biopsy

Genetic Testing

Establish Cell Lines
iPSC

Create Transplantable Cells

Evaluate Mutations

Therapy

Test Efficacy of Gene and Drug Therapies

Stem cell based
iPSC

Virus based therapies

AAV
Lenti
HSV

Genome based therapies

iPSC

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Etiology of Hearing Loss
Increasing Importance in Cochlear Implantation

Vivero et al, *Int J of Ped Otol* 2010

Vivero… Liu, *Int J of Ped Otol* 2010

- There are differences in auditory performance that are not attributable to age at implantation or auditory training.
- In DFNB1, cochlear nerve and spiral ganglion cells are preserved and this suggests the potential for excellent performance.
- Most common identified etiology of congenital deafness in children receiving CI (18-40%).
- Positive GJB2 screening results establish an etiologic diagnosis and provide prognostic, genetic, and therapeutic information.
- Better speech performance/preservation of central cognition function from different countries.
CI in Cx26 Related Deafness

n=31 of 44 Pediatric CI recipients (10/98 – 4/05)


- Mean duration of follow-up: 32 months (12-102)
- 1 Med-el, 2 Clarion, 28 Nucleus-24
- Verbal comprehension score:
  - **DFNB1**: 80%
  - **Non-DFNB1**: 64% (p<0.001)
- Expressive language score
  - **DFNB1**: 75%
  - **Non-DFNB1**: 65% (p=0.04)
- DFNB1 patients show higher scores in Language Development tests, and faster and more uniform gains on speech perception tests than non-DFNB1 patients
Language Skills

- DFNB1 children who use cochlear implants show greater gains in expressive language than non-DFNB1 children, independent of age at implantation and duration of implant use.
CI in Usher Syndrome

• Most common deaf-blind disorder

• 7% in congenital deaf patients with CI

• Virtually all members of the deaf community view the visual impairment as a devastating handicap

• ERG for early diagnosis, genetic tests available now

• Studies showing the best perceptive results found in children implanted before 9 y/o

Genetic variants in the peripheral auditory system significantly affect cochlear implant performance

Etiologic diagnosis INCLUDING neural vs sensory genetic defect is the biggest predictor of post-implant performance (18%). Further work: would different CI programming/rehab work better for neural defects?

Shearer, 2017

**The Neural Partition**
- **Spiral Ganglion Function:** AIFM1, DIAPH3, DFNB59, MT-RNR1, OPA1
- **Function Unknown:** TMPRSS3, TRPM1

**The Sensory Partition**
- **Organ of Corti:** 85 known genes
- **Synaptic Function:** CABP2, CACNA1D, OTOF, SLC17A8

<table>
<thead>
<tr>
<th>Total n</th>
<th>Azbio n</th>
<th>Avg Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>155</td>
<td>119</td>
</tr>
<tr>
<td>Neural-Genetic</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Sensory-Genetic</td>
<td>12</td>
<td>9</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation(s)</th>
<th>Frequency in patients (%)</th>
<th>Occurrence in the gene (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GJB2</strong></td>
<td>35delC</td>
<td>25.4</td>
<td>Up to 88</td>
</tr>
<tr>
<td></td>
<td>W44C</td>
<td>0.38</td>
<td>0-3.6</td>
</tr>
<tr>
<td></td>
<td>L90P</td>
<td>0.29</td>
<td>0-1.47</td>
</tr>
<tr>
<td><strong>SLC26A4</strong></td>
<td>L236P</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>T416P</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td><strong>MT-RNR1</strong></td>
<td>1555A&gt;G</td>
<td>0-3.6</td>
<td>37.6-100</td>
</tr>
<tr>
<td></td>
<td>7444G&gt;A</td>
<td>1.6-1.84</td>
<td></td>
</tr>
<tr>
<td><strong>GJB6</strong></td>
<td>309 kb deletion</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>309 kb deletion</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digenic with GJB2</td>
<td>16-21</td>
<td></td>
</tr>
</tbody>
</table>
A custom capture panel of 180 known deafness genes with a target size of approximately 1MB (Agilent Sure Select DNA Design). These results prove the accuracy and reliability of the custom capture experiment.

Identifying Causative Gene VARIANTS for Hearing Loss Using a Target Enrichment/Next Generation Strategy – MiamiOtoGenes (MOG)

Tekin et al, 2015; Yan et al, 2016
Ethnic-Based Sequential Screening Strategy to diagnose genetic deafness and to identifying new genes.

**Probands/Pedigrees**

- Screen GJB2, SLC2CA4, MTRN1

  **Pathogenic Variants**

  - **YES**
    - Homozygous or Compound Heterozygous
      - **YES**
        - Stop
      - **NO**
        - Targeted Sequence All Deafness Genes (MiamiOtoGenes Panel)

  - **NO**

**Screen Repository**

**In vitro and In vivo Studies**

**Whole Exome Sequencing**

- **Novel new genes**
- **Screen Repository**

**Sanger Sequencing**

- Population/Ethnic based Genechips
- CapitalBioMiamiArray

**MiamiOtoGenes (MOG)** used for identification of the remaining cases.

**Molecular Epidemiology**

**Confirm pathogenic Variants CLIA Lab**

**Miami Clinical Otogenic Program**
Who should be offered genetic screening in CI patients?

1) Expert opinion by the members of the International Pediatric Otolaryngology Group (IPOG), 2016. After audio, comprehensive genetic testing has highest diagnostic yield of any test for SNHL (62% agree)

2) Non-syndromic children with unilateral HL should NOT be offered genetic testing with initial workup (62% agree)

3) Identification of HL caused from the peripheral auditory system
Conclusions

- Genetic deafness affects 50% of all individuals with hearing loss
- >70% genetic deafness is nonsyndromic
- Connexin 26 is the most common etiology
- Usually CI given good to excellent outcomes are favorable. An appropriate management algorithm facilitates effective patient care
- Learn to recognize syndromes and their special considerations
- CI team will need to become increasingly familiar with available tests and their interpretation in order to use them effectively and counsel patients regarding prognosis and treatment