Outline of Presentation

• Hearing Loss
  • Terminology, Types, Causes
  • Management

• Genetics of Hearing Loss
  • Syndromic, Non-Syndromic

• Testing Algorithm for Hearing Loss at Prevention Genetics
Deafness & Hearing Loss
TERMINOLOGY:

• **Hearing loss:**
  - Diminished sensitivity to sounds normally heard.
  - Severity is categorized according to the increase in volume above the usual level necessary before the listener can detect it.

• **Deafness:**
  - Inability to understand speech even in the presence of amplification.
    - *Profound deafness* - even the loudest sounds may not be detected.
    - *Total deafness* - no sounds are heard at all, regardless of amplification or method of production.
TERMINOLOGY:

- **Speech perception:**
  - Involves the perceived clarity of a sound rather than its amplitude.
  - These tests measure one's ability to understand speech, not merely to detect sound.
Types of Hearing Loss

Conductive

- Caused by diseases or obstructions in the outer or middle ear.
- Usually affects all frequencies of hearing evenly.
- Does not result in severe loss.
- Hearing aid / surgical intervention helps.
TYPES of HEARING LOSS

Sensorineural

- Results from damage to the delicate sensory hair cells of the inner ear or the nerves that supply it.
- Can range from mild to profound.
- Affect the person’s ability to hear certain frequencies more than others.
- Use of Hearing aid is sometimes impossible.
TYPES of HEARING LOSS

Mixed hearing loss:
- Combination of conductive and sensorineural loss
- Due to a problem in outer or middle & the inner ear.

Central hearing loss:
- From damage or impairment to nerves or nuclei of the CNS, either in pathways to the brain or in brain itself.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Hearing Threshold in Decibels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>26-40 dB</td>
</tr>
<tr>
<td>Moderate</td>
<td>41-55 dB</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>56-70 dB</td>
</tr>
<tr>
<td>Severe</td>
<td>71-90 dB</td>
</tr>
<tr>
<td>Profound</td>
<td>90 dB</td>
</tr>
</tbody>
</table>

Conversational speech is at approximately 50-60 dB HL (hearing level),
CAUSES of Hearing Loss

Prelingual

- Prolonged Loud Noise: 34%
- Infection/Injury: 17%
- Other: 17%
- Born with Hearing Loss: 4%
- Age: 28%
CAUSES of Hearing Loss in Adults

• Age: Presbycusis
  ▫ Degenerative changes in the ear with aging, that make them less able to respond to sound waves.

• Prolonged Loud Noise

• Infection/Injury
  ▫ Measles, Meningitis, Mumps, Syphilis

• Neurological Disorders
  ▫ Multiple Sclerosis, Strokes

• Chemicals
  ▫ Drugs/medications

• Genetics
  ▫ Syndromic
  ▫ Non-syndromic

Source: http://hcrp.georgetown.edu/agingsoociety/pdfs/hearing.pdf
CAUSES of Prelingual Hearing Loss

- Incidence at birth: 127 per 100,000
- Prevalence at 4 yrs: 270 per 100,000

MANAGEMENT of Hereditary Hearing Loss

GENETIC COUNSELING

TREATMENT
[Hearing aids, cochlear implantation, otologic surgery]

SPEECH THERAPIST / EDUCATOR FOR HEARING LOSS

GENETIC TESTING

Clinical Geneticist
Otorynologist
Ophthalmologist
Neurologist
Audiologist
Genetics of Hearing Loss
80 genes associated with prelingual hearing loss
Prelingual Deaf Children
1/500

Genetic
50%

Nonsyndromic
70%

Syndromic
30%

Genetics of Prelingual Hearing Loss

Different gene loci are labeled DFN (for DeaFNess); based on mode of inheritance

Nonsyndromic
70%

Autosomal recessive
75% - 85%

DFNB1
50%

[36 genes]

[26 genes]

DFNA

[3 genes]

Autosomal dominant
15% - 24%

Other DFNB
50%

X-linked
1% - 2%

DFNX

### NON-SYNDROMIC Hearing Loss

#### MITOCHONDRIAL INHERITENCE

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Severity</th>
<th>Penetranse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MT-RNR1</strong></td>
<td>961 different mutations</td>
<td></td>
<td>Highly variable, aminoglycoside induced</td>
</tr>
<tr>
<td></td>
<td>1494C&gt;T</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1555A&gt;G</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MT-TS1</strong></td>
<td>7445A&gt;G</td>
<td></td>
<td>Highly variable</td>
</tr>
<tr>
<td></td>
<td>7472insC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7510T&gt;C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7511T</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MT-CO1</strong></td>
<td>7444G&gt;A</td>
<td>Severe to profound</td>
<td>Complete, aminoglycoside associated; associated with MT-RNR1 1555A&gt;G</td>
</tr>
</tbody>
</table>

## SYNDROMIC Hearing Loss (30%)

- **Alport** (COL4A5)
- **Fabry** (GLA)
- **Nance** (POU3F4)
- **X-linked CMT** (GJB1)

  - **Usher** (10 genes - 379 exons)
  - **Waardenburg** (5 genes – 39 exons)
  - **Stickler** (5 genes – 258 exons)
  - **Perrault** (4 genes – 66 exons)
  - **Treacher Collins** (3 genes)
  - **Branchiootorenal** (3 genes)
  - **Jervell and Lange-Nielson** (KCNQ1 and KCNE1)
  - **Alport** (COL4A3, COL4A4 – 100 exons)
  - **Refsum Disease** (PEX7 and PHYH)
  - **Wolfram** (WFS1 and CISD2)
  - **Mohr-Tranebaerg** (TIMM8A)
  - **Pendred** (SLC26A4) with FOXI1 & KCNJ10 - Digenic
  - **Keratitis-Icthyosis-Deafness** (GJB2)
  - **Neurofibromatosis Type2** (NF2)
  - **Bartter** (BSND)
  - **Townes-Brooke** (SALL1)
  - **Alstrom** (ALMS1)
  - **Norrie** (NDP)
  - **Muckle-Wells** (NLRP3)
  - **Biotinidase deficiency** (BTD)

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**400 Syndromes associated with hearing loss.**
Mitochondrial Inheritance

Progressive myoclonic epilepsy, ataxia & hearing impairment
- MTTS1: 7512T->C

Maternally inherited diabetes & Deafness (MIDD)
- MTTL1: 3243A->G
- MTTK: 8296A->G
- MTTE: 14709T->C
GENETIC TESTING FOR HEARING LOSS AT PREVENTION GENETICS
10 years and 1000 genes later - Who We Are..

- Unsurpassed Quality
- Exceptional Customer Service
  (16 geneticists, 2 GCs, 3 Tech Reps)
- Lowest Prices and Quick TATs
  (40-50% lower, <20-40 days)
- Comprehensive genetic testing
  (>1000 genes)
Comprehensive Provider

- **Largest Sanger Sequencing menu in the US**
  - Over 1000 genes and growing every week

- **Next-Gen Sequencing Panels**
  - 60 panels covering 530 genes

- **Deletion/Duplication analysis via arrayCGH**
  - 833 genes

- **Affordable DNA Banking**
  - $98 (one-time fee) for a min. of 20 years storage
Exceptional Customer Service

“Exceptional Customer Service Comes From The People”

- Team of 16 highly experienced PhD level geneticists
  - Assigned specific gene portfolio to build expertise

- 2 Certified Genetic Counselors
  - Clinical counseling experience

- 3 Technical Product Representatives
  - Experienced in laboratory testing and development
Distinguishing Features

• Clear and Comprehensive Test Reports reviewed by two PhD geneticists

• Free Family Studies for up to 2 family members for VUS [variant of uncertain significance] identified

• Quick Turn around times

• Customized testing – single gene/panels
Genetic Testing Algorithm for Hearing Loss at PreventionGenetics

EVALUATION
Family history, Physical examination, Audiologic Workup

No Dx

GENETIC TESTING

Apparent syndromic phenotype
SYNDROMIC TESTING Single/Multi Gene

No apparent phenotype
TESTING FOR NONSYNDROMIC HEARING LOSS

Treatment
Genetic Testing for Hearing Loss at PreventionGenetics

Apparent syndromic phenotype

GENETIC TESTING

SYNDROMIC TESTING
Single/Multi Gene
WAARDENBURG SYNDROME

- Auditory-Pigmentary Disorder
  - Congenital SNHL
  - Hair Abnormalities [white forelock]
  - Eye Abnormalities [heterochromia]

WAARDENBURG SYNDROME

- **WS I:** Auditory-pigmentary abnormalities + dystopia canthorum (lateral displacement of the inner canthi)
  - Caused by mutations in *PAX3*

- **WS II:** Auditory-pigmentary abnormalities without dystopia canthorum
  - Mutations in *MITF, SNAI2 and SOX10*

- **WS III:** Type I with musculo-skeletal abnormalities of the upper limb (Klein-Waardenburg syndrome)
  - Caused by mutations in *PAX3*

- **WS IV:** Type II with Hirschsprung disease (Waardenburg-Shah syndrome)
  - Mutations in *EDNRB, EDN3 and SOX10*

# WAARDENBURG SYNDROME - Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WS I</td>
<td>Autosomal Dominant, <em>PAX3</em></td>
</tr>
<tr>
<td>WS IIA</td>
<td>Autosomal Dominant, <em>MITF</em></td>
</tr>
<tr>
<td>WS IID</td>
<td>Autosomal Recessive, <em>SNAI2</em></td>
</tr>
<tr>
<td>WS IIE</td>
<td>Autosomal Dominant, <em>SOX10</em></td>
</tr>
<tr>
<td>WS III</td>
<td>Dominant or Recessive, <em>PAX3</em></td>
</tr>
<tr>
<td>WS IVA</td>
<td>Autosomal Dominant, <em>EDNRB</em></td>
</tr>
<tr>
<td>WS IVB</td>
<td>Autosomal Recessive, <em>EDN3</em></td>
</tr>
<tr>
<td>WS IVC</td>
<td>Autosomal Dominant, <em>SOX10</em></td>
</tr>
</tbody>
</table>

Genetic Testing for Hearing Loss at PreventionGenetics

Apparent syndromic phenotype

SYNDROMIC TESTING
Single/Multi Gene

24 Syndromes..
61 genes..
1280 exons..

No apparent phenotype

TESTING FOR NONSYNDROMIC HEARING LOSS

Tier 1: Sanger Panel
- GJB2, GJB3, GJB6 – 7 exons

Tier 2: NextGen Panel
- Non-Syndromic Panel (50 genes)

GENETIC COUNSELING
# Genetic Testing for Hearing Loss at PreventionGenetics

## Non-Syndromic Hearing Loss

<table>
<thead>
<tr>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCDC50, CEACAM16, CIB2, CLDN14, COCH, CRYM, DFNB59, DIABLO, DIAPH1, ESRBB, EYA4, FGF3, FGFR3, GIPC3, GJB2, GJB3, GJB6, GPSM2, GRHL2, GRXCR1, HGF, ILDR1, KCNQ4, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MSRB3, MYH14, MYH9, MYO15A, MYO1A, MYO3A, MYO6, OTOA, OTOF, POU4F3, PRPS1, RDX, SERPINB6, SLC17A8, SLC26A5, SMPX, TECTA, TJP2, TMC1, TMIE, TMPRSS3, TPRN, TRIOBP</td>
</tr>
</tbody>
</table>
Contact Information

Website: www.PreventionGenetics.com

Clinical Email: ClinicalTesting@PreventionGenetics.com

Phone: 715-387-0484

Fax: 715-384-3661

Address: PreventionGenetics
3800 S. Business Park Ave.
Marshfield, WI 54449
Thank you