Usher Syndrome and Progressive Hearing Loss

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Seven steps to treatment for an Inherited Disease (Bill Kimberling)

- Find the disease gene
- **Correlate genotype with phenotype**
- Find or develop animal models
- Elucidate the disease mechanism
- Find or develop and effective treatment in the animal model
- Screen the human population to identify people who might benefit
- Test the treatment in these people
  - Orphan diseases, small numbers
Incidence of Hearing Loss in Newborns

- Profound bilateral 1-2/1000 births
- Another 1-2/1000 with significant HL
- 33 babies born every day with significant permanent hearing loss
- >12,000 babies per year in the U.S.
- The most common congenital sensory impairment
How Common is Usher Syndrome

- Prevalence: 1/16-20,000 US
  - With more genes more common
- Estimated 16,000-25,000 individuals in the US with USH
- Up to 10% of congenitally deaf children with USH1
- 3-6% of all congenitally hearing impaired children with USH1, 2, 3
- Carrier frequency 1/70 (varies by gene, mutation and population)
# Usher Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing Loss</th>
<th>Vestibular System</th>
<th>Retinitis Pigmentosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Congenital profound</td>
<td>Congenital balance problems; absent caloric responses</td>
<td>Onset pre-puberty</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>Congenital mild-severe sloping; progressive</td>
<td>Normal</td>
<td>Onset in teens-20s</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Progressive later onset</td>
<td>Variable, often progressive balance problems</td>
<td>Variable onset</td>
</tr>
</tbody>
</table>
How to make the Usher Diagnosis

- Test the hearing
- Test the vision
- Test the balance
- Test the genes
- Test olfaction?
- Look at brain?
Audiologic Features

- **USH 1** - bilateral congenital profound SNHL
- **USH 2** - bilateral moderate SNHL; may progress
- **USH 3** – May be of later onset, may progress
- All patients initially appear non-syndromic except for the hearing loss
- Not all patients with mutations in the same Usher gene have the same presentation
Usher Gene Phenotype

- Most genes cause congenital/childhood onset HL followed by RP
- USH2A also causes non-syndromic RP
- MYO7A, USH1C, CDH23, PCDH15, WHRN may cause hearing loss only
- Change in olfaction (sense of smell)
- Cognition
- Sperm motility
- Cerebral atrophy
- Ataxia
- Registry
FREQUENCY IN Hertz (Hz)

HEARING LEVEL (HL) IN Decibels (dB)

Tympanograms: normal

USH 1B

KEY

AC (Air)
Unmasked
Masked
BC (Bone)
Unmasked
Masked
SOUND FIELD

SPEECH AUDIOMETRY

SDT
SRT
SPEECH DISCRIM. (WORD RECOG.)

R L

8% 4%
2 year old female with 2 novel MYO7A mutations
8 year old male with USH2A and normal vision; ERG not done. Child’s maternal grandmother and siblings have USH2 clinically, but child has a novel mutation, so unclear what effect this will have on his vision and ERG
Adult with USH 2A who presented with “non-syndromic” RP
14 year old female from Cape Verde with progressive SNHL and RP, and normal balance. Dad and Dad’s brother with the same. Homozygous CLARIN1 mutations.
Routine Eye Exams in Children with SNHL: Can you diagnose Usher Syndrome?

- 16 children
- All have two pathogenic USH mutations
- “Routine” eye exams did not pick up USH in any patients who were pre-symptomatic (i.e. not night blind)
- 9/16 had diagnosis made by genetic testing; youngest was 8 months
- Age of walking not entirely predictive of USH 1 patients, and was normal in USH 2 and USH 3

Kenna, Fulton, Hansen, Rehm, et al, 2010
How could the hearing loss progress

- Many genes
- Result in many proteins
- Many forms of each protein
- Interaction depends on many things besides just making the protein
- Environment
<table>
<thead>
<tr>
<th>Locus name</th>
<th>Genome Location</th>
<th>Gene name</th>
<th>Gene Protein Product</th>
<th>Animal Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH1B</td>
<td>11q13.5</td>
<td>MYO7A</td>
<td>Myosin 7A</td>
<td>Shaker 1/Mariner</td>
</tr>
<tr>
<td>USH1C</td>
<td>11p15.1-p14</td>
<td>USH1C</td>
<td>Harmonin</td>
<td>Deaf circler</td>
</tr>
<tr>
<td>USH1D</td>
<td>10q22-q22</td>
<td>CDH23</td>
<td>Cadherin 23</td>
<td>Waltzer/deaf waddler</td>
</tr>
<tr>
<td>USH1E</td>
<td>21q21.1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>none</td>
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<tr>
<td>USH1F</td>
<td>10q21.1</td>
<td>PCDH15</td>
<td>Protocadherin 15</td>
<td>Ames waltzer</td>
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<tr>
<td>USH1G</td>
<td>17q25.1</td>
<td>USH1G</td>
<td>Usher Syndrome Type 1G protein</td>
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</tr>
<tr>
<td>USH1H</td>
<td>15q22-23</td>
<td>USH1H</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>USH1K</td>
<td>10p11.21-q21.1</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>USH2A</td>
<td>1q41</td>
<td>USH2A</td>
<td>Usherin</td>
<td></td>
</tr>
<tr>
<td>USH2C</td>
<td>5q13</td>
<td>GRP98</td>
<td>G protein-coupled Receptor 98</td>
<td></td>
</tr>
<tr>
<td>USH2D</td>
<td>9q32-34</td>
<td>DFNB31</td>
<td>Cask-interacting protein</td>
<td></td>
</tr>
<tr>
<td>USH3A</td>
<td>3q21-q25</td>
<td>CLRN1</td>
<td>Clarin-1</td>
<td></td>
</tr>
<tr>
<td>USH2A modifier</td>
<td>10q24.31</td>
<td>PDZD7</td>
<td>PDZD7</td>
<td></td>
</tr>
<tr>
<td>USH3B</td>
<td>5q31.3</td>
<td>HARS</td>
<td></td>
<td></td>
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</table>
Diagram of the sensory cells in the inner ear and retina.

Outline of the Usher proteins and their different isoforms.

The Usher protein network.

What else could be causing the hearing loss?

- CMV
- Other genetic
- Funny inner ear anatomy
- Other causes of hearing and vision loss
  - Prematurity
  - Alstrom syndrome
  - Two different causes for hearing loss and vision
Prenatal Infections

- TORCHES
- Toxoplasmosis 1:8000; 0-26% have HL, decreased if treated promptly
- Rubella (one reported case in 2006; but baby can get if mother vaccinated during pregnancy)
- CMV 1/100-200 births
- Herpes 1:2500-10,000, but HL very rare unless the baby has obvious systemic infection
- Syphilis 11/100,000 (2002)
- Inflammatory mediators pre/peri natal
Hearing Loss due to Perinatal Causes

- NICU
  - PPHN
  - Ototoxicity
  - Sepsis
- Hyperbilirubinemia
- ECMO
- Ototoxicity
- Sepsis
- Extreme prematurity
  - Auditory dyssynchrony
Postnatally Acquired Infections

- **Bacterial meningitis**
  - Marked decrease since HIB, Prevnar®
  - N. meningitidis vaccination

- **Parvovirus B-19 (Fifth’s disease)**
  - Associated with autoimmune hearing loss

- **Mumps** (2007, 800/100,000 US)

- **Measles** (2005, <1/1,000,000)

- **Lyme** - Facial nerve dysfunction more common than hearing loss

- **HIV**

- **EBV**

- **Ramsay-Hunt (Varicella zoster)**

- **Otitis media/cholesteatoma**
Hearing Loss due to Postnatal Causes

- Trauma
- Head trauma
  - Sports
  - Altercations
  - MVA
  - Child abuse
- Noise
  - MP3
  - Hunting
- Radiation
- Surgery
- Autoimmune
Postnatally acquired causes of HL

- **Ototoxicity**
- **Aminoglycosides**
  - Mitochondrial genes confer increased susceptibility
  - Children with cystic fibrosis
  - Transplants
- **Macrolides**
  - Azithromycin, clarithromycin, erythromycin
- **Diuretics**
  - Furosemide (Lasix®)
- **Retinoic acid**
- **Aspirin, acetaminophen with codeine, other**
Bilateral, significant, high frequency SNHL, greater in Right ear than Left ear. Advised patient to consider a trial with a hearing aid for the left ear. May also consider BiCros aid. Consult by ORL is recommended in light of present findings. Retest hearing as per medical management needs and communication interventions.
Epidemiology of CMV

- 1% of all live births
- 10-15% of babies with congenital CMV are symptomatic
  - 75% of these will have CNS symptoms
  - 65% of these will have SNHL
- Of asymptomatic babies 5-10% develop SNHL
- Over 50% have progressive hearing loss
Radiological features

- Polymicrogyria
- Cerebral calcification
- White matter loss
- Ventricular dilatation
- Cystic changes
- Overall, abnormal in 54%
Genetics of Hearing Loss: Non-syndromic

- ~140 loci for Non-Syndromic HL
  - 70 recessive (DFNB)
  - 55 dominant (DFNA)
  - 5 X-linked (DFN)
  - 2 modifier (DFNM)
  - Several Mitochondrial (MTN)
  - 1 Y-linked (DFNY)
  - 1 Auditory neuropathy (AUN)

Van Camp G, Smith RJH. [http://webho1.ua.ac.be/hhh](http://webho1.ua.ac.be/hhh) 3.5.09
# Syndromic Hearing Loss

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Prevalence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treacher-Collins</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Pendred/LVAS</td>
<td>AR</td>
<td>Very common</td>
</tr>
<tr>
<td>Waardenburg</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Usher</td>
<td>AR</td>
<td>Common</td>
</tr>
<tr>
<td>BOR Syndrome</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Norrie Disease</td>
<td>XL, AR</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alport Syndrome</td>
<td>XL, AD, AR</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Stickler Syndrome</td>
<td>AD</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Jervell &amp; Lange-Nielsen</td>
<td>AR</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Relative to other syndromic forms of hearing loss**
Genetic causes of later onset and progressive HL

- Dominant genes associated with presbycusis
- GJB2 (Connexin 26): 50% progression rate
- SLC26A4 (PDS): Associated with enlarged vestibular aqueduct
- Turner’s syndrome (XO): mid-frequency dip
- Otosclerosis: later onset and progressive
- Usher’s syndrome, types 2 and 3 esp.
- Mitochondrial genes: may cause HL with or without aminoglycosides
35delG / 35delG
Age 15 months

Tympanograms: normal
Pendred Syndrome

- Enlarged vestibular aqueducts
  - 10-20% of pts with AU EVA have PDS

- Goiter resulting from abnormal organification of iodine in the thyroid
  - If have Pendred syndrome, will have abnormal perchlorate washout studies but euthyroid labs

- SLC26A4 (PDS) causes both Pendred’s Syndrome and recessive non-syndromic SNHL (DFNB4)
- Incomplete partition
- Modiolar deficiency
- "Mondini"
Testing for Usher Syndrome

- **Clinical diagnosis**
  - Hearing loss
  - RP
    - Electroretinography
  - Balance
  - ??/olfaction, cognition

- **Genetic diagnosis**
  - Single gene testing
  - Multiple gene testing
Genetic Testing for Usher Syndrome

- **Conservative approach:**
  - HL with retinal abnormalities (positive ERG test or pigmentary changes)

- **Less conservative approach:**
  - Profound congenital hearing loss with delayed walking

- **Even less conservative approach**
  - Test children with non-profound losses if Cx26 (and possibly Cx30) negative and CT/MRI normal
Genetics of Hearing Loss

- 2 pathogenic mutations in a known USH gene
- 2 mutations of unclear significance in an USH gene (VUS)
- 1 pathogenic mutation and one VUS
- 1 pathogenic mutation in two different USH genes (digenic)
- Otochip®
- Otogenome®
- Otoscope®
- Insurance
Treatment for the Hearing Loss

- Hearing Aids
- Cochlear implants
- Molecular therapy for the hearing loss
  - Gene therapy
  - Different size genes
  - Different viral vectors
Cochlear Implants

- Bilateral severe to profound
- Infants and young children
  - Early diagnosis of USH helps with decision making
- Progressive hearing loss
- Effect on balance
Who Needs Genetic Counseling

- Families/patients being tested for hearing loss genes (pre-testing)
- Families/patients being given genetic results
- There may be a greater need for genetic counseling when test results are negative
  - Patients may not understand that the cause of hearing loss could still be genetic
Summary

- If definitely USH, hearing loss can progress
- If not certain USH, try and confirm a diagnosis
- Rarely, could be more than one diagnosis
- Manage the hearing loss according to degree
- Manage the diagnosis according to what makes sense
Thank you!