Summary for Family Day:
Diagnostics and Genetics of Usher Syndrome

#USH2018

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Speakers from Diagnostic Session

- Bill Kimberling (Omaha, US)
- Anne-Francoise Roux (Paris)
- Isabelle Audo (Paris)
- Adam Dubis (London)
- Aziz El Amraoui (Paris)
- Margaret Kenna (Boston, US)

- All additional speakers who touched on treatment based on a specific diagnosis
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 an effective treatment in the animal model
- Screen the human population to identify people who might benefit
  - Genetic testing
- Test the treatment in these people
  - Orphan diseases, small numbers, so build registries
# 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><strong>Type I</strong></td>
<td>Congenital profound</td>
<td>Congenital balance problems; absent responses</td>
<td>Onset pre-puberty</td>
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<tr>
<td><strong>Type II</strong></td>
<td>Congenital mild-severe sloping</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>
<tr>
<td>Locus name</td>
<td>Genome Locus</td>
<td>Gene name</td>
<td>Protein Product</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>USH1B</td>
<td>11q13.5</td>
<td>MYO7A</td>
<td>Myosin 7A</td>
</tr>
<tr>
<td>USH1C</td>
<td>11p15.1-p14</td>
<td>USH1C</td>
<td>Harmonin</td>
</tr>
<tr>
<td>USH1D</td>
<td>10q22-q22</td>
<td>CDH23</td>
<td>Cadherin 23</td>
</tr>
<tr>
<td>USH1E</td>
<td>21q21.1</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH1F</td>
<td>10q21.1</td>
<td>PCDH15</td>
<td>Protocadherin 15</td>
</tr>
<tr>
<td>USH1G</td>
<td>17q25.1</td>
<td>USH1G (SANS)</td>
<td>USH Type 1G protein</td>
</tr>
<tr>
<td>USH1J</td>
<td>15q25.1</td>
<td>CIB2 (may or may not be USH)</td>
<td>Calcium and integrin binding protein 2</td>
</tr>
<tr>
<td>USH2A</td>
<td>1q41</td>
<td>USH2A</td>
<td>Usherin</td>
</tr>
<tr>
<td>USH2C</td>
<td>5q13</td>
<td>ADGRV1</td>
<td>G protein-coupled receptor</td>
</tr>
<tr>
<td>USH2D</td>
<td>9q32-34</td>
<td>WHRN (DFNB31)</td>
<td>Cask-interacting protein</td>
</tr>
<tr>
<td>USH2A modifier</td>
<td>10q24.31</td>
<td>PDZD7</td>
<td>PDZD7</td>
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<tr>
<td>USH3A</td>
<td>3q21-q25</td>
<td>CLRN1</td>
<td>Clarin-1</td>
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<tr>
<td>USH3B</td>
<td>5q31.3</td>
<td>HARS</td>
<td></td>
</tr>
</tbody>
</table>
Which genotype?

GJB2 (Connexin 26)  
MYO7A (USH1B)
USH1B – atypical presentation

- 2 year old with 2 novel MYO7A mutations
- Better hearing than would be expected for the genotype
- Patient walked at 16 months
- Hearing loss progressed over several years into the profound range
- Patient received a cochlear implant at age 6
- Genetic testing key to making the diagnosis of USH1, not USH2
History- from Bill Kimberling’s talk

Timeline of Usher genetic testing

- Only research testing initially available
- Common mutations in single genes
- Many private, novel, denovo mutations
- Whole single genes
- Deafness sequencing panels
- Vision sequencing panels
- Usher specific panels
- Whole exome and whole genome
Why knowing the correct gene helps

- Better understanding of USH genes
  - How they interact
  - How they affect hearing and vision
  - Some mutations affect **ONLY** hearing **OR** vision
- If you change one gene, what will the other related genes do?
- Are there genes we still don’t know about?
- In some cases, such as USH2A, there are many different versions of the same gene
- Do you actually have USH?
Other genes that cause deafness and blindness

- Are these USHER genes?
- Is all deafness and blindness considered USH?
- Genes affecting the cilia
- Genes affecting microtubules
- What can we learn from other organ systems?
  - Gut (Matt Tyska, Nashville)
  - Skin (Fred Schwaller, Berlin)
  - Are other organs systems affected in USH?
Better genetic testing

- Find the second or even third mutation
- Deep intronic and splicing mutations
- Is it just simply dominant or recessive?
  - Could single mutations be disease causing?
- Two possible different genetic causes for hearing and vision loss?
- Can build registries based on most up to date knowledge of genetics and phenotype
How does knowing the gene help treatment?

- Treatment will be related to the gene and stage of USH
- When are the genes expressed?
- What type of mutation is present?
- Gene augmentation
- Gene replacement
- Gene modification
- Pharmacologic interventions
- Photoreceptor or retinal grafts
When to treat

- Confirm the gene(s) causing the clinical symptoms
- Different genes are expressed at different times in development
- When to intervene?
  - For the hearing loss?
  - For the vision loss?
- We can now test prenatally for the genes
  - Should we be treating the fetus?
Danke!
Thank you!