Unraveling Usher syndrome:
The role of genetic testing

Usher syndrome Family Conference
Seattle, 2016

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Potential Benefits of Genetic Testing

- Clarify uncertain diagnosis
- Predict disease progression
- Qualify for clinical treatment trial
- Enable testing of family members
- Aid research
Chromosomes

Normal female: 46,XX
Usher syndrome Inheritance: Autosomal Recessive

Unaffected "Carrier" Father

Unaffected "Carrier" Mother

Unaffected 1 in 4 chance

Unaffected "Carrier" 2 in 4 chance

Affected 1 in 4 chance
Recessive Inheritance
# Usher syndrome genes

<table>
<thead>
<tr>
<th>Total # of Mapped Genes</th>
<th>Identified Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>11 (12? 13?)</td>
</tr>
</tbody>
</table>

**Graph:**

**Mapped and Identified Retinal Disease Genes 1980 - 2014**
<table>
<thead>
<tr>
<th>Usher syndrome subtype</th>
<th>Gene Name</th>
<th>Relative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH1B</td>
<td>MYO7A</td>
<td>50-60%</td>
</tr>
<tr>
<td>USH1C</td>
<td>Ush1C</td>
<td>6-7%</td>
</tr>
<tr>
<td>USH1D</td>
<td>CDH23</td>
<td>15-20%</td>
</tr>
<tr>
<td>USH1E</td>
<td>?</td>
<td>Rare</td>
</tr>
<tr>
<td>USH1F</td>
<td>PCDH15</td>
<td>10-15%</td>
</tr>
<tr>
<td>USH1G</td>
<td>SANS</td>
<td>~7%</td>
</tr>
<tr>
<td>USH1H</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>USH1J</td>
<td>CIB2</td>
<td>?</td>
</tr>
<tr>
<td>USH1K</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Usher syndrome types II & III

<table>
<thead>
<tr>
<th>Usher syndrome subtype</th>
<th>Gene Name</th>
<th>Relative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH2A</td>
<td>Ush2A</td>
<td>~80%</td>
</tr>
<tr>
<td>USH2C</td>
<td>VLGR1 (GPR98)</td>
<td>~15%</td>
</tr>
<tr>
<td>USH2D</td>
<td>WHRN</td>
<td>~5%</td>
</tr>
<tr>
<td>USH1E</td>
<td>Unknown</td>
<td>Rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usher syndrome subtype</th>
<th>Gene Name</th>
<th>Relative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH3A</td>
<td>CLRN1</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>USH3B</td>
<td>HARS</td>
<td>Rare</td>
</tr>
</tbody>
</table>
UNRAVELING USH

AN USHER SYNDROME GENETIC TESTING INITIATIVE

A collaborative effort with Project Usher at the Stephen A. Wynn Institute for Vision Research to ensure everyone with Usher syndrome has access to genetic testing.
Participating in “Unraveling USH”

1. Meet with a physician or genetic counselor and ask them to order the test.
2. Work with provider to try to obtain insurance coverage for testing.
3. Add genetic test results to the International Usher syndrome registry.
Project Usher: 5 Goals

• Provide hope
• Provide accurate information
• Find the remaining genes
• Find cures
• Make genetic testing available to all
Genetic Testing Pipeline

Targeted testing: Most common Usher syndrome mutations

(+): 2 mutations found (4 months)

Done! ~50%

2nd mutation found (< 1 year)

(+): 1 mutation found Full gene sequencing

0 mutations found

Whole Exome Sequencing

Research for novel genes ~20%

(+): 2 mutations found (~1 year)

Done! ~20%

0 additional mutations found

Done! ~10%
Genetic Counseling & Test Coordination

1. Inherited Retinal Dystrophy Expert/Clinic
   • Usher syndrome coalition (usher-syndrome.org)
   • Foundation Fighting Blindness (blindness.org)

2. Genetic Counselor
   • By phone (informeddna.com)
   • In person (nsgc.org)

3. Local physician
   • Resources available at usher-syndrome.org
Clinical Trials: Who Will Benefit?

- Current clinical trials:
  - MYO7A

- Upcoming clinical trials:
  - Ush2A?
  - Ush1C?
  - CLRN1?

*Is genetic testing necessary for clinical trials that are NOT gene-based?*
What can genetic testing research teach us?

Underlying shared pathways
  • “Usher syndrome interactome”
  • Insights for treatment

Novel genes
  • ~80% of patients with Usher syndrome will test (+) for a known “US gene”

Modifiers of disease
  • PDZD7
What else can genetic testing research teach us?

What is an Usher syndrome gene?

- $ABHD12$?
- $PDZD7$?

What defines Usher syndrome?

- Shared genetic causes/ protein interactions?
- RP + HL +/- vestibular dysfunction, and nothing else?
  - What if a % of patients have Crohn’s disease/ IBD and have US from a “Classic” US gene?
Research article

**PDZD7** is a modifier of retinal disease and a contributor to digenic Usher syndrome

Clinical Annotation

A typical Usher syndrome panel test, using NGS, may identify 50-100 variants per patient.