Usher Syndrome: Connecting Genes to Disease

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Two main goals of this talk:

1. How do changes in genes cause disease?
   *making the connection between the various genetic mutations that cause Usher syndrome and the actual symptoms of Usher syndrome.

2. Why are so many different genes involved in Usher syndrome?
   *evidence that different Usher proteins work together to contribute to normal hearing and vision.
   *problems in any one of these proteins can result in the symptoms common to Usher syndrome.
How do changes in genes cause disease?
The DNA in human cells is organized into 23 pairs of chromosomes. One set of 23 is inherited from each parent.

Chromosomes 1-22 = autosomes. X and Y = sex chromosomes.
If we could look at the genomes of everyone in this room, our chromosomes would all appear very similar.

It is when we look at the information encoded in the DNA sequence that we can detect the many differences that lead to variation in our species: height, eye color, foot size, behavior, and the presence or absence of genetic disorders.
Usher genes are found on many autosomal chromosomes

One of every type of Usher gene (along with all the other genes on every chromosome in our individual genomes) is inherited from both parents.

In most cases, a disease-causing mutation must be present in *both* copies of a given Usher gene in order for disease symptoms to appear.
What does a “disease-causing mutation” look like?

At the DNA level, it simply looks like a difference in the sequence of molecules that form the genetic code.
DNA contains the blueprint for building functional molecules (mostly proteins).

Changes to the instructions can mean changes to the protein product.
If a mutation results in information being added or deleted from the code, the resulting protein will be affected:

- **Normal protein**
- **Information missing**
- **Information substituted**
- **Information added**

Changes in the shape or size of a protein will often affect its ability to occupy a particular space in the cell, interact with other molecules, or otherwise function normally.
Bella has Usher syndrome type 1B
Caused by mutations in the *MYO7A* gene

Bella and her family have given the Usher community support, exposure, and inspiration over the years. She has also, through her DNA, given us new information on mutations that cause Usher syndrome type 1B:

A *MYO7A* mutation previously identified in an Usher type 1B patient

A *MYO7A* mutation that had not been detected before in USH1B patients
How can we tell which mutations in Usher genes are going to cause disease?

*Prior knowledge of common disease-causing mutations can provide a starting point.

*Correlating the changes found in Usher genes with the incidence of disease in a particular family or population is sometimes possible.

*Animal model or cell culture can be used to study a particular human mutation for signs of disease causing behavior.

*Information about genetic changes that cause Usher syndrome in patients all over the world is VERY IMPORTANT!
Two main goals of this talk:

1. How do changes in genes cause disease?
   * making the connection between the various genetic mutations that cause Usher syndrome and the actual symptoms of Usher syndrome.

2. Why are so many different genes involved in Usher syndrome?
   * evidence that different Usher proteins work together to contribute to normal hearing and vision.
   * problems in any one of these proteins can result in the symptoms common to Usher syndrome.
Hair cells of the inner ear and photoreceptors in the retina are responsible for receiving environmental information and relaying it to the brain through intermediate cell networks.

Although the type of environmental signal is different (sound vs. light), the basic job of these cells—receiving, converting, and passing on the signal—is the same. In addition to having some cellular structures in common, these cells would use similar molecular tool kits to achieve their respective functions. **Usher proteins appear to be key components of these tool kits.**
Why are there so many ‘types’ of Usher syndrome? Because there are so many Usher genes.

Each known Usher gene encodes a distinct protein with its own functional significance...

<table>
<thead>
<tr>
<th>Usher type</th>
<th>Human gene</th>
<th>Protein: potential function</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH1B</td>
<td>MYO7A</td>
<td>MyosinV11A: motor activity</td>
</tr>
<tr>
<td>USH1C</td>
<td>USH1C</td>
<td>Harmonin: scaffold</td>
</tr>
<tr>
<td>USH1D</td>
<td>CDH23</td>
<td>Cadherin: calcium dependent adhesion</td>
</tr>
<tr>
<td>USH1E</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH1F</td>
<td>PCDH15</td>
<td>Protocadherin15: adhesion, signaling</td>
</tr>
<tr>
<td>USH1G</td>
<td>USH1G</td>
<td>SANS: membrane associated scaffold</td>
</tr>
<tr>
<td>USH1H</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH1J</td>
<td>CIB2</td>
<td>Calcium-and integrin-binding protein</td>
</tr>
<tr>
<td>USH2A</td>
<td>USH2A</td>
<td>Usherin: Laminin-like transmembrane protein</td>
</tr>
<tr>
<td>USH2C</td>
<td>GPR98</td>
<td>Gpr98: G-protein coupled receptor, signaling</td>
</tr>
<tr>
<td>USH2D</td>
<td>CIP98</td>
<td>Whirlin: scaffold</td>
</tr>
<tr>
<td>USH3A</td>
<td>CLRN1</td>
<td>Clarin1: 4-pass transmembrane protein</td>
</tr>
<tr>
<td>USH3B</td>
<td>HARS</td>
<td>Histidyl t-RNA synthetase</td>
</tr>
</tbody>
</table>
...however, all Usher mutations give similar disease symptoms.

Disease symptoms in humans can be observed through clinical tests.

Evidence of the defects resulting from Usher gene mutations can be observed at the cellular and molecular level in animal models:

Cochlear hair cells from mice with defects in Usher type 1 genes show that the hair bundles are poorly formed.

Brown et al, 2008
So why ARE so many different genes involved in Usher syndrome?

Usher proteins work together to form and maintain this important sensory structure. Losing function in any one of the 11 known Usher genes leads to hearing impairment along with retinal degeneration.

Some other mutations in these same Usher genes lead to hearing impairments alone, without vision problems.
What about the retina?

Many Usher proteins localize to the region around the connecting cilium, a structure that serves as a converyer belt between two distinct parts of the photoreceptor cell. It is thought that Usher proteins might be involved in loading cargo for transport up the connecting cilium. However, there are many unanswered questions about this process. It’s not clear that all Usher proteins are involved, or even present in this area.
There are many other cell types in the retina beyond photoreceptors. Usher proteins have been detected in several of these other retinal cell populations as well.

*Usher proteins may be required in more than one retinal cell type.

*Alternatively, they may be present in multiple cell types, but only necessary in one (e.g., the photoreceptor).

*Usher proteins may work together to carry out molecular functions in these cells. They may also work alone, or with different partners than those that have been identified in hair cells.

*The difference in time of onset of vision loss between different types of Usher might help us decipher what roles these proteins play in retinal cells.

*Targeting the right cell type at the right time is important information for developing gene therapies.
To augment the study of human mutations and their clinical presentations, researchers like me use animals or cultured cells in the laboratory to learn more about how these proteins behave in living, functional sensory cells.

Analysis of Usher proteins in the ear has been fairly straightforward in model animals. Differences in the retinal cell structure and behavior between human and non-primate retinas present some research challenges, but we are working on solutions!
In the Westerfield lab, we use zebrafish to study how Usher proteins function in normal hearing and vision. Our studies have shown that:

In the retina:

• Some Usher proteins are found in retinal cells other than photoreceptors. Usher proteins in these cells are important for forming connections between photoreceptors and other retinal cells.
* Fish with defects in Usher proteins found at these locations don’t see well, and some experience retinal degeneration.

In the ear:

* Similar to their ‘cargo loading’ role described in the photoreceptors, some Usher proteins appear to be involved in moving cargo from place to place in zebrafish hair cells.

* Usher proteins that don’t form properly due to mutations accumulate and cause stress in the cell. We are currently testing to see whether we can see signs of cell stress preceding sensory cell death in these Usher models.
THANK YOU FOR YOUR ATTENTION!

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http://www.usher-syndrome.org/index.cfm/event/blog