

Hi, I'm Karmen Trzupek. And this is USH Talks. Today, I'm going to give you a very brief introduction to genetics. It is my hope that this overview will help you to understand how Usher Syndrome is inherited and provide a baseline for future topics in this series such as the role of genetic testing for families with Usher Syndrome and gene therapy.

The human body is made up of trillions of cells. Inside each cell is a nucleus, which contains chromosomes. Our chromosomes are like packages that contain our genes.

We all have about 22,000 genes housed in 23 pair of chromosomes. These genes determine complex bodily functions like the way the heart pumps blood or the structure and function of a cilia in the inner ear and [INAUDIBLE]. Our genes also determine traits like the color of our eyes.

This is a normal set of human chromosomes. The first 22 pair are numbered 1 through 22, so we call them autosomes, which means numbered chromosomes. The last pair of chromosomes are the sex-determined chromosomes, X and Y. Because this patient is a woman, she has two X chromosomes. Men have one X and one Y chromosome.

Some genetic diseases are linked to genes on the X chromosome. Usher Syndrome is not. Usher Syndrome is an autosomal recessive disease linked to genes on or the autosomes. As a result, men and women have an equal chance of developing Usher Syndrome.

In a recessive genetic disease, the condition results when someone inherits two genetic mutations-- one from their mother and one from their father. Someone who has one normal copy of the gene and one abnormal copy of the gene is called a carrier. Carriers of Usher Syndrome typically have normal hearing and normal vision.

When we look at a family history of Usher Syndrome, it often looks something like this. In this diagram or pedigree, circles are females, and squares are males. If the symbol is filled in, that person is affected.

Someone with Usher Syndrome may be the only one in their family affected. Or they may have an affected sibling as they do in this pedigree. But their parents, children, aunts, uncles, and cousins are typically not affected.

This family is a great example. Nancy and David Corderman have four children. Two of their kids have Usher Syndrome and two do not. No one else in their extended family is affected with Usher Syndrome.

This graph shows the number of genes known to be associated with retinal diseases. Of the 22,000 genes in the human body, we already know that almost 300 of them are involved in retinal disease. Of those, 15 genes appear

to be associated with Usher Syndrome.

These are the genes associated with Usher Syndrome type 1. Myosin VIIa is the most common gene associated with Usher Syndrome type 1. A little more than half of all patients with Usher Syndrome type 1 will have two mutations identified in the myosin VIIa gene.

Some subtypes of Usher Syndrome are more common in certain ethnic populations. USH1F, for example, is uncommon in the general population, but a very common cause of Usher Syndrome among people of Ashkenazi Jewish ancestry. In fact, almost 1 in 150 people of Ashkenazi Jewish ancestry are a carrier of Usher Syndrome type 1F.

USH1C is the most common cause of Usher Syndrome among the Acadian people of Louisiana. 1 in 70 individuals of Acadian ancestry living in Louisiana today is believed to be a carrier of Usher Syndrome type 1C. As a result, someone with Usher Syndrome will occasionally have an affected child.

Here's how that works. This man has Usher Syndrome type 1C. He has two copies of the USH1C mutation. So all of his children will inherit a mutation.

I'll say that again.

This man has Usher Syndrome type 1C. He has two copies of the USH1C mutation. So all of his children will inherit a mutation and be carriers. But if he marries a woman who is also of Acadian ancestry and she is a carrier of USH1C, there is a 50/50 chance that she will pass that on to any of their children. Any child who inherits two genetic mutations will be affected just like their father.

The USH2A gene is the most common gene associated with Usher Syndrome type 2. And because Usher Syndrome type 2 is more common than type 1 or type 3, this gene is the most common Usher Syndrome gene in the world. Usher Syndrome type 3 is very rare outside of Finnish and Ashkenazi Jewish populations.

We all meet and connect with people who share common backgrounds and interests. Sometimes a patient will ask me, what if I marry someone else with Usher Syndrome or someone with RP? Will all of our kids be affected?

In order for someone to be affected with Usher Syndrome, they must inherit two genetic mutations in the same gene. That means that if you have Usher Syndrome and your partner has RP, you likely have mutations in different genes. And your children will not develop either Usher Syndrome or RP. Similarly, if your partner has a different type of Usher Syndrome than you do, it's probably from a different gene.

As promised, I have given you a very brief glimpse of the genetics of Usher Syndrome. In a future talk, I will

address the role of genetic testing for patients with Usher Syndrome and the complexity of some genetic test results. Until then, this is Karmen Trzupsek for USH Talks.