

**(Margaret Kenna) Is this on? Can you hear me? Thank you. My name is Margaret Kenna, I am a pediatric ear, nose and throat doctor in Boston.**

And I get to do this, and I'm really privileged to be here, because we diagnose babies with hearing loss at birth. And so because of that I've learned a lot about the causes of hearing loss in young children, and this is certainly one of them. But before I get going I want to thank the planning committee. Gwen and I are the US version, but really it's the people here in Germany that did all the work as everybody has said, and we really appreciate it. I also want to thank the interpreters.

When we did this in Boston, we were still looking for interpreters an hour before the conference started, and I know how much work this is, all the different types of interpretation and translation and access. I know this is a lot of work, and I've been watching interpreters and reading written text, and it's, they are really good! So anyway, thank you very much for that. (applause)

And finally, and of course without the patients and the families there would be no reason for us to be here. I've been to many of the other family conferences. We are going to need a bigger room the next time we do that, so it's

MARGARET KENNA

all good. So I'm going to just summarize very briefly some of the information that was presented in the first day about the diagnostic part of Usher syndrome. And obviously as many of the previous speakers just said, without the diagnosis you wouldn't all know each other. And when we come to clinical trials or treatments, you won't know that you are eligible. So there is a whole bunch of reasons to do this.

Many of the speakers on the first day, including Dr. Kimberling who was part of the team that discovered the very first Usher gene, Myosin 7A - and I'm assuming he is in here someplace - and then many of the other people that are listed here talked about different aspects in the genetics of Usher syndrome. Many other people talked about treatments or the way the different genes work together. So the truth is, this is really from everybody in the last two days.

So, Bill Kimberling, as I just mentioned, really came up years ago with seven steps to treatment for an inherited disease. And when he did this, we weren't very far down this pathway. And it was really starting with finding and the genes that cause a particular disease. We are very far down that path now with Usher syndrome. There are other genes that we don't know about, and the way the genes work we are not completely sure about, but I think one of the things that is really key and that Rebecca just alluded to is: get your genotype done if you can. Figure out what the gene is. Make sure you actually have, if that's the case, Usher syndrome.

MARGARET KENNA

There are a lot of other things that cause hearing loss and vision impairment, and so having a correct diagnosis, whatever the diagnosis is, really matters. Everybody knows there are at least three types of Usher syndrome, but as Rebecca alluded to, some of the presentations are rather atypical for what we know from this little box up here.

So it's entirely possible to have Usher syndrome type I and look like you have type II or have type II and have type I, or have Usher syndrome III and look like type I. So there is a lot to be learned based on the genotype. And there also is a wide variation in the way patients present. So this is the reason we get testing. These are the known genes, but almost certainly there are other genes that are also an underlying reason to have Usher syndrome or genes that interact with these genes.

And depending on how you play with the genes or what you do to the genes really may result in the clinical changes that we are all talking about and hoping for. So here is the other reason we need genetic testing. These are two of my patients. The one on the left, GJB2, that is Connexin 26, this child presented as deaf. The patient on the right, MYO7A, USH1B presented as deaf - same hearing test. And looking at a baby, when they present they look exactly the same. For us to figure out what to do with them, we have to do genetic testing.

This is a patient with MYO7A USH1B. This patient has a profound hearing loss this is a patient with USH1B, MYO7A,

MARGARET KENNA

this patient does not have a profound hearing loss, at least not at the beginning. And so both of these patients have mutations in the same gene, but they didn't have the same mutations, and their clinical presentation wasn't the same. And actually the second patient here, this patient walked on time, her balance is pretty good, she wore hearing aids for years, and then her hearing loss progressed, and now she has cochlear implants. So same gene, different mutations, very important to figure this out.

Bill Kimberling talked a lot about the history of genetic testing, and there are probably people in this room without research testing. And if they only have one gene and they are not entirely sure, all these other things now that are available, common mutation testing came next, followed by single genes, followed by deafness panels, where we have 120 or 30 or 60 genes, vision panels that are similar. What we probably need is a combined vision and hearing loss panel, so we are not missing anybody.

And then now we are talking a lot about testing whole exomes, that is the protein part of the DNA, and then whole DNA testing. So things are progressing really rapidly, but each step has the good news and the other news. And it's the other news that we have to be careful about. So why knowing? Why does this matter? And when you call the insurance company in the United States, they say exactly what our first speaker said: why do you have to do this, how is it going to change, why should we pay for it? Well, to get a diagnosis helps a lot. And then once there are

MARGARET KENNA

interventions that will also help. We also want to know how the genes interact, how they affect both hearing and vision and balance and things that we are not really looking at very hard, but we should be. And some genes only affect the hearing or the vision, not both. Or some mutations in the same gene. And if you change this gene over here, it's like those little toys you push this box and the other boxes move, like what happens over here. So anything that we do to intervene we have to make sure it doesn't make things worse. Other genes we don't know about, Almost certainly there are genes we don't know about.

And so for example USH2A, which is a really big gene and one of the common causes of Usher syndrome. There are a lot of different versions of USH2A. Which ones do you treat? Which ones do you worry about? How do they look clinically? So, and finally, do you actually have USH? And I know that sounds kind of silly, but there are people who do have vision impairment and hearing loss, but they don't have the clinical diagnosis of Usher. And that would guide them down a different pathway.

And this really gets to talking about what we consider Usher syndrome. It's a particular type of vision impairment, a particular type of hearing loss, and there may be other things. So what else can we learn from other people about when they study cilia, which are the little cells, the little hairs - they are not really hairs - but maybe there are other genes that have to do with cilia, microtubules. We actually heard from two other really excellent speak-

*MARGARET KENNA*

ers in the last two days - Matt Tyska from Nashville who talked about the gut. Well, how does that affect the ears or the vision? But the system in the gut that he is looking at is very reminiscent of what's going on with Usher syndrome.

So maybe there is something that we can learn from that. And then Fred Schwaller from Berlin talked about the skin. And once again, lots of similarities. So there are other organ systems that we can learn from, and maybe they are even involved in Usher syndrome. So the other thing is better genetic testing. Anne-Françoise Roux talked about finding the second mutation or even the third mutation and how that affects the diagnosis and then the interventions.

Are the mutations in places in the DNA that we haven't looked? Like in the introns, which is part of how the DNA gets transcribed, or in the splicing which turns out different types of genes, so different versions of the gene. Is it really dominant or is it recessive? So are there to possible causes for the hearing loss or the vision impairment? That happens. I know that sounds rare, but it's not that rare once you begin to look.

And then, of course, most important and as everybody before me mentioned, we need registries, we need to be able to find the patients and families so that we can do better networking, - although we are doing a pretty good job of that - and then better treatment as things come down the road. How will knowing the genes really help?

MARGARET KENNA

Well, where are the genes expressed they don't all start out at the beginning. What type in mutation is present? What kind of intervention is it going to be making the genes bigger, better, smaller, different, replacing them, are there going to be medications?

Yesterday there was a very eloquent speaker on using something called Baclofen, which is something we use for tight muscles. And maybe it will help with vision and hearing. So I think we don't know, but without knowing the genes, and when the genes express themselves we won't know what to do. And then when to treat? So say you assume you know the gene, and we know that when the genes are expressed at different times. So when do you do something about it? When do you do something about the hearing loss? When do you do something about the vision impairment? And if it turns out there are GI symptoms, when to do something about that? And we can test prenatally now for genes.

I have patients or parents coming to me, and their baby is not born yet, and they know the baby is going to have something that affects their hearing or their vision. And they want to know what that's going to turn out like. And is there something they can do before the baby is born? So these are tricky questions, they are ethically tricky questions, and yet they are very exciting questions. And it's sort of what all of these people, the families and the patients and the science folks together, are going to figure out. So anyway, thank you very much. (applause)