Hearing on the Horizon: Exploring the Multifaceted Dynamics of Hearing, from Genes to Patient Realities

INTERVIEW WITH: DR. DYLAN CHAN

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Dr. Dylan Chan *is a pediatric otolaryngologist, Director of the Children's Communication Center, and Professor in the Department of Otolaryngology—Head and Neck Surgery at UCSF. Dr. Chan specializes in ear, nose, and throat conditions, providing comprehensive, family-centered care for children with hearing impairments through advanced medical and surgical interventions like cochlear implants and ear canal reconstruction. His research seeks to understand how to support hearing and deafness, from basic science to health systems. In his lab, he studies the role of TMTC4, a hair-cell-specific human deafness, in hearing loss that happens due to changes in the Unfolded Protein Response. Clinically, since founding the UCSF Children's Communication Center in 2014, he has been dedicated to enhancing multidisciplinary care, community outreach, and the development of innovative ways to support hearing health for children.*

BSJ: How has your journey through medical school and graduate school molded your interest in pediatric otolaryngology?

DC: When I was growing up, I was always interested in going into medicine for the same reasons a lot of kids think about—wanting to become a doctor. However, I was also a musician and spent a lot of time playing classical piano and when I was in college, I was a double major in music as well as biochemistry with biophysics. Additionally, I was also very interested in neuroscience and neurodegenerative diseases. I wanted to identify the big problems in medicine and, at the time, there was very little that was understood about neurodegeneration, with diseases such as Alzheimer's and Parkinson's. When I entered medical school, I knew that I wanted to be a physician-scientist and was set on going into neuroscience. As a result I did my first couple of lab rotations in a structural biology lab studying Parkinson's. I spent another summer in a more molecular biology lab, studying Alzheimer's. For my third rotation, I was in a computational biology lab so I could learn techniques that would help me if I went back to the structural biology lab. It is an interesting thing when you think about it, because when you decide what to do for the next step, a lot of it is informed by what you have done before.

Right before I was about to start that third rotation, I had a bit of a crisis and questioned if this is really what I wanted to commit myself to doing long term. At the last minute, I decided to do my final rotation in a hearing research lab that one of my friends happened to rotate in the year before. I ended up really falling in love with hearing and the cochlea, and how the cells within the cochlea detect sound: it seemed like this magical biological system. And so, I ended up doing my PhD in this auditory physiology lab. That experience illustrates how you never know what you are going to do for your next step, but taking that leap can help you find what you truly care about.

I followed my PhD with a residency in otolaryngology, which covers everything from head and neck oncology, including laryngeal cancer, resections and reconstructions to voice surgery to taking care of kids or adults. One of the main things in otolaryngology is that we take care of hearing. During my residency it became obvious that what I cared most about in hearing is how we use hearing to communicate and how we rely on it to understand and produce speech. When I finished residency and was looking for faculty positions, I wanted to do it all– particularly a clinical practice taking care of kids with hearing loss. I still loved working in the lab and understanding how hearing and the inner ear functions, but I also wanted to have the opportunity to research how hearing healthcare can be better delivered to kids.

BSJ: In 2014, you established UCSF's Children's Communication Center. How have your experiences working with families of deaf and hard of hearing children inspired the research projects your lab addresses? Similarly, how does your background as both an MD and a PhD shape the questions you ask and the research you do on the subject?

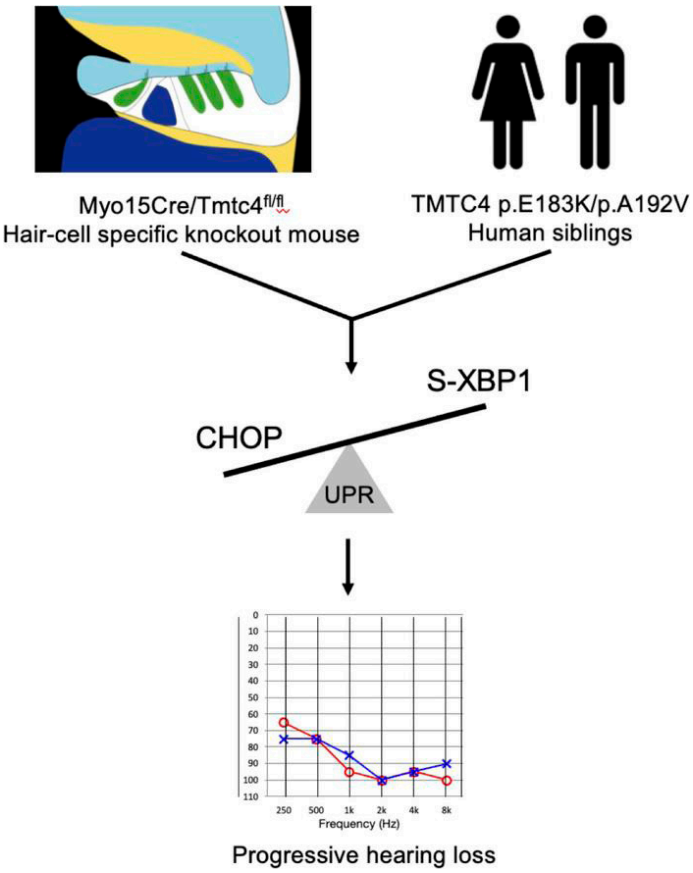

Figure 1: Graphical Abstract of TMTC4 is a hair cell–specific human deafness gene paper. Shows how a hair-cell specific knockout mouse (with postnatal onset deafness) was compared to a human family in which TMTC4 variants segregate with adult-onset progressive hearing loss. Using these instances TMTC4 variants showed a hypersensitivity of the UPR to apoptosis, this provides evidence that UPR is linked to progressive hearing loss and TMTC4 being a deafness gene in humans.[1]

DC: My initial experiences here at UCSF have played an enormous role in molding the work that my team and I do now. There is a big difference in training and learning how to do these things, when you are not primarily responsible for the people in front of you, or more broadly, the systems of care that bring them to you.

It was only when I started here at UCSF that I recognized how much it takes for the family to get to you and to even be able to be cared for by your team. We have people that are coming from six hours away that do not have transportation or people that do not speak English or others who do not understand how to navigate the medical system. Observing all of these things, right when I started, really helped me and others understand that the biggest problems in hearing healthcare right now are not how we do surgeries or the devices that we use. So, from the very beginning, our team was really focused on tackling this problem in multiple different ways.

One such way was through improving the coordination and multidisciplinary nature of care, and the other was to establish research and outreach programs that could help us to understand why these disparities happen and what kinds of interventions we could develop to address them. That is really how our big clinical research program has developed—it was a direct result of the challenges we observed.

BSJ: TMTC4 has been identified as a significant gene involved in hearing function, with its deletion or mutation linked directly to hearing loss. TMTC4 deletion causes overactivation of the unfolded protein response and your work demonstrated this strongly in mouse models. Has your group looked deeper into this genetic model? If so, in what ways?

DC: Whenever there is a genetic model of a disease or condition in mice, that genetic model often serves two different purposes. One purpose is that it can help you understand that specific gene and what it does. It can also be used as a way to understand more broadly the pathway that the gene is involved in. We focused on both of these. One of our interests is what TMTC4 is doing in the ear. We have done some work on that, both in our 2018 paper, as well as the most recent one, in terms of where the gene is functioning. It is active in the endoplasmic reticulum of cells in the ear, and it seems to be most active and expressed in the sensory hair cells of the inner ear, the cells that actually detect sound. And then we know a little bit about what TMTC is doing. It seems like it is interacting with this channel called SERCA, which manages calcium homeostasis, or transfer between the endoplasmic reticulum and the cytoplasm. We are interested in studying more deeply what TMTC4 does. On the human genetic side, we have identified a family where TMTC4 mutations seem to be directly causing hearing loss. That is an example of where we are trying to study the specific function of TMTC4 in these people. But it is more powerful to use this genetic model to see if TMTC4 deficiency causes rapidly progressive hearing loss. What would this tell us more broadly about how hearing loss happens in mice and in people? This is more powerful because so far, there have been two people in the entire world that have been identified with likely TMTC4 associated hearing loss. If we can say this genetic model of TMTC4 hearing loss demonstrates that the unfolded protein response and disorders of calcium regulation in hair cells are fundamental causes of hearing loss, then it opens up a much larger population of people that this is relevant for. Showing that TMTC4 is involved in calcium dynamics and the unfolded protein response allowed us to make the connection that the unfolded protein response and disorders of calcium regulation are generally involved in hearing loss, specifically in noise-induced hearing loss. In that way, we are able to then use the TMTC4 genetic model as an example of hearing loss that happens because of calcium dysregulation and the unfolded protein response. And so this model becomes relevant to everybody who has noise induced hearing loss.

BSJ: In your paper on the TMTC4 gene, you associated human hearing loss with TMTC4 missense variants. Genetics and gene engineering have been at the forefront of medical research, especially with CRISPR, but may not be fully accessible for some time. What are your thoughts on using gene therapies to not only tackle hearing loss from TMTC4, but more broadly health issues?

DC: Over the last year, the very first in human gene therapy trials for hearing loss have started. There is an article from the New York Times[3] about the companies that are specifically running human clinical trials with gene therapy for hearing loss due to deficiency of a gene called otoferlin. It is really important to understand that gene therapy is intended to address a genetic difference in the cells where it is relevant in that person. The goal

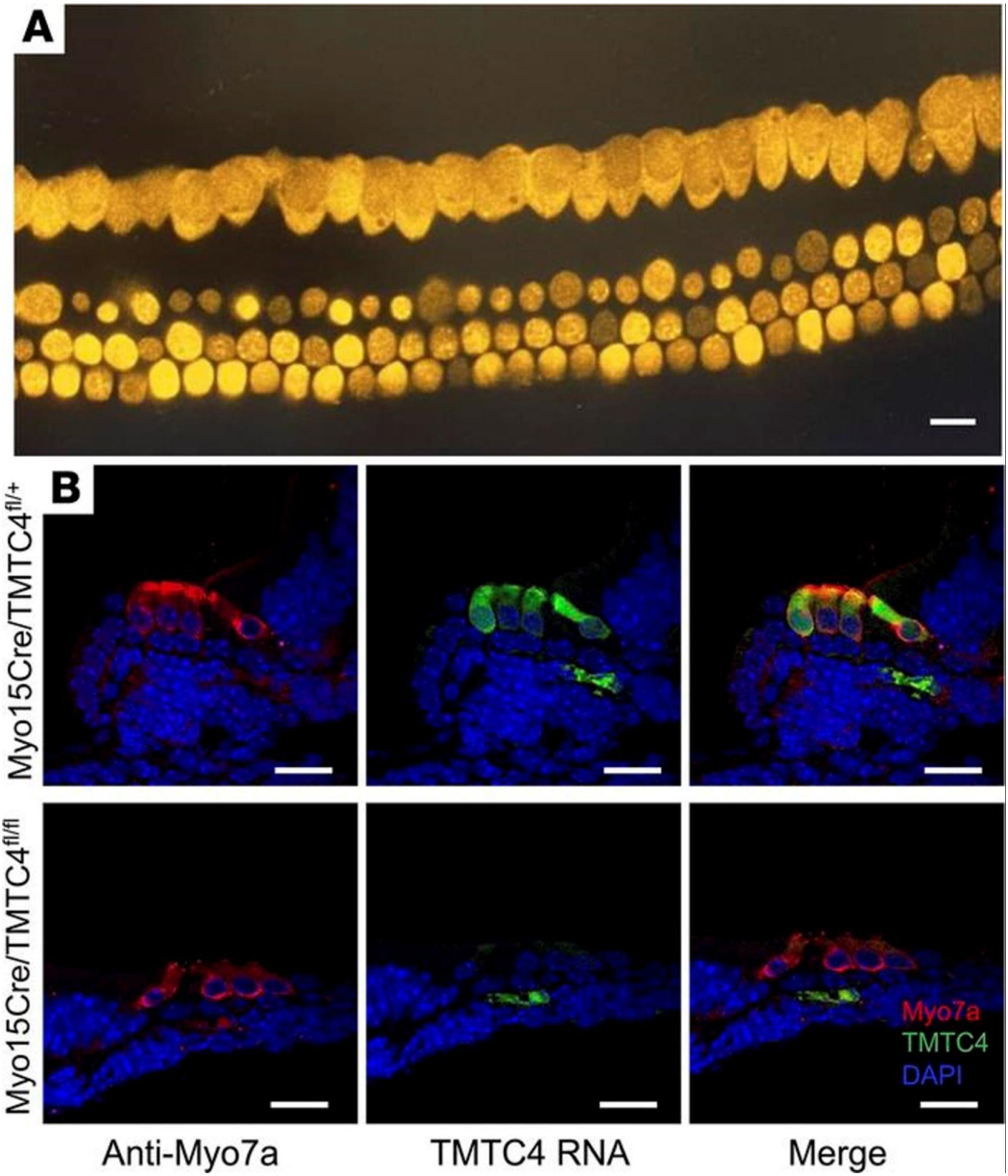

Figure 2: TMTC4 localization. These images highlight the specific patterns of TMTC4 expression in the cochleae of mice. a. Hair cells of a five-day-old mice cochlear explant indicating TMTC4 activity. b. Staining of hair cells in red and TMTC4 RNA in green. Contrasts presence of TMTC4 in both hair cells and surrounding areas in Myo15Cre/Tmtc4fl/+ mice and absence in hair cells of Myo15Cre/Tmtc4fl/fl conditional knockout (cKO) mice, demonstrating the effect of TMTC4 deletion.[1]

of gene therapy in the ear is to deliver a gene to the inner ear so that it specifically expresses a protein that replaces the function of a protein that is otherwise not there. In essence, it is not that different from any other molecular therapy for some kind of condition. For example, if you give insulin to a diabetic, it means that you are providing that person with a molecule that acts in cells that don't produce that molecule properly. In this way, gene therapy is not really doing anything that is radically different from how we typically treat conditions. The initial findings from these otoferlin gene therapy trials are suggesting that delivery of otoferlin into the cells of the inner ear is able to help those hair cells work better. But, I do not really think of it as fundamentally different from other ways that we think about addressing diseases and conditions. In particular, it is not altering anything in a heritable manner; even if this kind of gene therapy were to become widespread, there would still be just as many deaf babies born.

BSJ: Socio-demographic status is a major factor in the quality of medical care a person receives; as highlighted by your paper regarding socio-demographic influences on hearing quality of life.[1] Are there things you believe the public can do to improve hearing quality of life and medical care to those in more disadvantaged socio-demographics?

DC: This returns to the question of how to approach research in this field, or how PhD training informs the way we think about research. For a long time, even now, I think people consider socio-demographics and disparities research differently than how they do clinical or even basic science research. I would like for people to think about them as similar. People often think about socio-demographics as fixed characteristics that you can't develop interventions for. Often, people use the term "social determinants of health." The implication is that these socio-demographic factors determine a person's health.

This paper, and others like it, only describes the associations between those factors and health outcomes. Specifically, this paper looks at the associations with hearing-related quality of life. These seemingly fixed factors, like the language you speak at home, your ethnicity, or where you live, are often proxies for underlying elements that may actually be better understood and can be modified.

These studies are the very first level of description; they are things that we can easily measure and observe associations with in relation to health outcomes. Qualitative research sets the stage for us to ask the next question: "What is it about these factors that are really driving the differences in hearing-related quality of life, and how can we work to make it better?"

BSJ: How can studying socio-demographic influences on patients' quality of life and care be used to improve a medical practitioner's interactions with their patients on a daily basis?

DC: I mentioned the next stage of understanding this association. The best way to understand how these factors impact the outcome you're interested in, is to go out and engage with a diverse group of parents of kids that are hard of hearing. Ask them: "What is your identity? How is that affecting your perception of your child's hearing and your child's hearing related quality of life?"

We can do that from a research standpoint. There are rigorous ways of studying this so you can generate these root cause themes to understand this connection there. But this is something you can do as a medical practitioner as well.

I recently saw parents of a baby who was newly identified as deaf in the clinic and they were having trouble accepting this finding. The mom was worried about the child not being able to hear her voice. Obviously, that is a big quality of life issue for her. Once we got to that understanding, we spent a lot of time talking to her about all the different ways she can engage, communicate, and connect with her baby even though her baby was deaf. She could hold her baby, look at her baby, and communicate with her baby with sign language; there are so many ways a parent can communicate with their baby that is not through voice. There were also socio-demographic factors that played into her grief and processing of the situation.

Many quantitative research studies paint a superficial picture connecting socio-demographic factors and health outcomes. They can give a little bit of insight into who might be more at risk or how to approach these problems, but at the end of the day, the best way to address these challenges is to understand who your patients are and learn from them so that you can support them in a way that meets

Figure 3: Event with UCSF Children's Communication Center. This image depicts two UCSF staff interacting with a child in front of a diagram depicting degrees of hearing.

their needs. Learning who these families are and then applying that to support them in a way that is best for them.

BSJ: Considering the significance in understanding a patient's life story, how does the language we use in regards to hearing levels influence these perceptions? How do medical and scientific perspectives influence them?

DC: One idea that is important to think about as we talk about the topic of hearing loss as a medical condition is that we are trained, as practitioners and researchers, to "treat" it. I would like more people to be aware that there are a lot of complexities surrounding this terminology when talking about hearing in children.

The preferred language around hearing loss in children is evolving with the need to understand diversity, equity, and inclusion principles in this context. For example, rather than talking about "treating" hearing loss, we talk about interventions to support deaf and hard-of-hearing children. "Hearing loss" in itself is a tricky term, a more inclusive phrase could be "hearing levels," however that is a difficult term for many people, and even me, to get around.

Still, we usually refer to diagnosed children with the terms "deaf" or "hard of hearing" as opposed to "with hearing loss." This is because being "deaf" or "hard of hearing" is thought of as an identity for many people. There certainly is a culture of medicalization and ableism that pervades the space and we must try to distance ourselves from that, and understand that being deaf or hard of hearing can be an identity. Additionally, we must acknowledge there is tension between the idea of being deaf or hard of hearing as an identity and the terms as medical conditions.

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