

Hello my name is Jacque Duncan and I'm a clinical professor of Ophthalmology at the University of California, San Francisco. I'm also the study chair for a clinical trial called the Rate of Progression of USH2A-related retinal degeneration. Or the RUSH2A study for short.

This is a longitudinal, natural history study of patients with mutations in the USH2A gene that will be coordinated by the JAEB center for Health Research Foundation and the Clinical Center Consortium, an initiative of the Clinical Research Institute of the Foundation Fighting Blindness.

As many of you already know, Usher syndrome is a leading cause of blindness and deafness, affecting between about 3 and 17 people per 100,000 in the United States, or between 10,000 and 55,000 people total in the US.

There are three types of Usher syndrome. They're distinguished by their onset and severity of hearing loss and retinal degeneration. And they've been associated with at least 11 genes and four loci. The gene most commonly associated with Usher syndrome type 2 is USH2A, which accounts for between 57 to 80% of patients with Usher syndrome type 2.

The USH2A gene is large. And its size exceeds the carrying capacity of many standard viral vectors that are currently used to deliver gene therapy. For this reason, investigators are working hard to develop other ways to deliver the USH2A gene to the retina, in addition to developing other non-gene specific treatments.

USH2A mutations may also cause retinitis pigmentosa with normal hearing at birth. And the USH2A gene may be the most common mutation in patients with autosomal recessive RP in the United States.

Suffice it to say, mutations in the USH2A gene are an important cause of retinal degeneration in patients with Usher syndrome type 2 and autosomal recessive RP.

The USH2A gene encodes a protein called usherin that is expressed in basement membranes in the inner ear and in the retina. Its function is not well understood, but it plays an important role in the development and maintenance of cells and their synaptic connections to other cells. Usherin is also expressed at the photoreceptor connecting cilium.

How do mutations in the USH2A gene affect the retina and cause vision loss? So far, there have been few limited studies reporting the natural history of retinal degeneration due to mutations in the USH2A gene. However, none of the earlier studies used current standard methods to measure retinal structure, such as OCT, or measured visual fields in a precise and quantitative way. Importantly, none of the prior studies included information from the patient's perspective obtained through standard questionnaires to provide patient-reported outcomes.

Natural history studies are important to prepare investigators to design clinical trials. It's essential to know how vision is affected in patients with USH2A mutations in order to determine what to measure and how much change we expect to see over time, in order to know whether a potential treatment improves the vision or decreases the rate of vision loss in the long run.

Currently, the FDA uses measures of visual acuity and visual field to determine if a potential treatment is safe and effective. These measures change very slowly in patients with Usher syndrome and RP. So we hope with this study to identify new, more sensitive, measures that are able to demonstrate a change in the rate of vision loss over shorter periods of time than standard measures.

The US Food and Drug Administration has an office of Orphan Product Development which funds research to develop treatments and cures for patients with diseases that affect fewer than 100,000 people in the United States. The FDA Office of Orphan Product Development issued a request for applications for studies that would describe the natural history of orphan diseases.

The Foundation Fighting Blindness Clinical Research Institute submitted a proposal in response to this request on October 15, 2016. That grant is currently under review. But the Foundation Fighting Blindness plans to support the infrastructure of the Clinical Consortium to conduct the trial, even if that grant does not receive funding.

The goal of the project is to describe the natural history of vision loss in patients with mutations in the USH2A gene and to define standard outcome measures in visual function and retinal structure in eyes with retinal degeneration associated with mutations in the USH2A gene. This project aims to identify new outcome measures that might reduce the time to demonstrate safety and efficacy of new treatments.

The Clinical Consortium represents a group of over 20 clinics in the United States, Canada, and Europe with expertise in the diagnosis and management of patients with retinal degenerations, including Usher syndrome. The clinics that plan to participate in the RUSH2A study are shown on this slide.

The executive committee for the Clinical Center Consortium comprises ophthalmologists, vision scientists, and clinical research specialists at academic institutions, including the National Eye Institute and the JAEB Center for Health Research.

The study proposes to measure patient demographics at baseline among patients who have already undergone genetic testing that has identified people with retinal degeneration associated with two disease-causing mutations in the USH2A gene. A committee of genetics experts will review the genetic test report for each paired participant. And in some cases of patients with retinitis pigmentosa, additional samples from parents or siblings will be

acquired to determine how the mutations were inherited and to confirm that they are likely to be disease-causing. Hearing and smell will also be tested at baseline.

There will be two cohorts, or groups, of patients. The first group of 100 patients will have vision that is 20/80 or better and they will be able to steadily look at things. This group will be seen at baseline and every year for four years. The second group of 20 patients will have vision of 20/100 or worse or will not be able to look at things steadily. They will only be seen once at the beginning of the study.

We hope and predict that about half the patients in the study will have Usher syndrome type 2 and the other half will have autosomal recessive RP due to mutations in the US2A gene.

The study will measure peripheral visual field using static perimetry with an analysis called the hill of vision that can measure vision and areas with reduced vision very precisely and quantitatively. The study will also measure retinal structure in the central retina or macula using OCT images. The ellipsoid zone, or EZ band, shows where the photo receptors remain and will be compared to visual field results.

The study will measure the patient experience of vision and hearing loss using patient-reported outcomes, or PROs. These include questionnaires about quality of life and visual function that gives insight into how vision and hearing loss affect patients' general well-being and their ability to perform activities of daily living, in addition to their independence and emotional state.

Thank you very much for this opportunity to tell you about the RUSH2A study. We are excited to begin this important study in 2017, which was featured in the Foundation Fighting Blindness newsletter last fall.

For information, please visit the Foundation Fighting Blindness website at www.fightblindness.org. Or contact Briana Jackson at the JAEB Center. Her email is bjackson@jaeb.org.

Thank you.