

# Rate of Progression in USH2A Related Retinal Degeneration: The RUSH2A Study

A Prospective, Longitudinal Natural History Study supported by the Clinical Center Consortium

Coordinated by the Jaeb Center for Health Research Foundation

An Initiative of the Clinical Research Institute of the Foundation Fighting Blindness



# Usher Syndrome

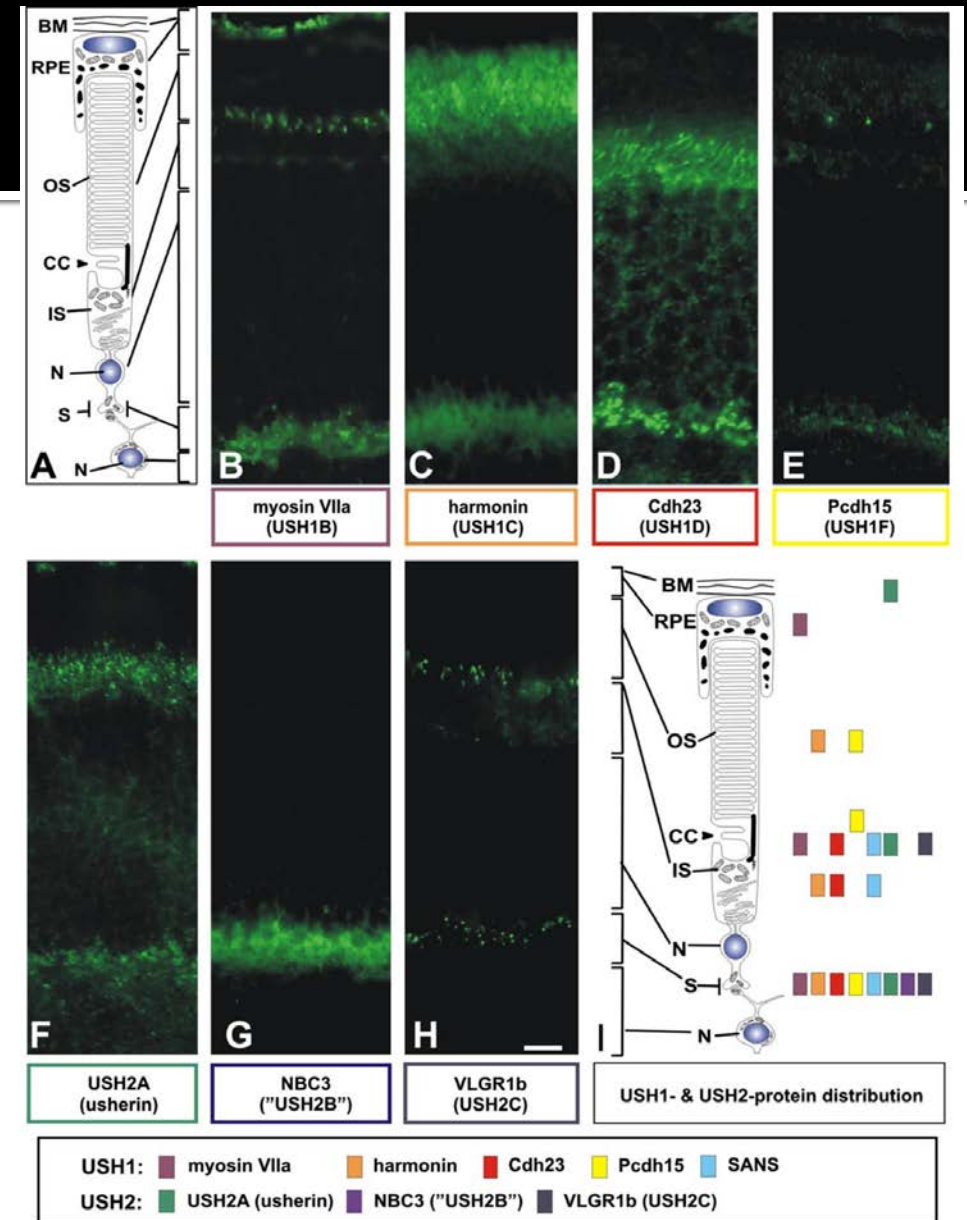
- Affects 3-16.7/100,000 in the US
- Roughly 10,000-55,000 people in the US
- 3 clinical types associated with at least 11 genes and 4 loci
- Usher syndrome type 2 is most commonly associated with mutations in the USH2A gene (57-79.3% of patients)

# USH2A

- Large gene
  - 790 kb spanning 72 exons with introns varying from 127 bp to 78 kb
  - Exceeds carrying capacity of standard viral vectors to deliver gene therapy
  - Other means of delivering USH2A are being developed, along with non-gene-specific treatments
- *USH2A* mutations may also cause RP with normal hearing at birth (RP39)
- *USH2A* mutations may represent the most common cause of autosomal recessive RP in the US
- *USH2A* is an important cause of photoreceptor degeneration

# USH2A

- Encodes a protein called usherin
- Component of basement membranes
- Found in the inner ear and the retina
- Function is not well understood but part of a protein complex that plays an important role in development and maintenance of cells and function of synapses
- Expressed at the connecting cilium



# Natural History of *USH2A*-related retinal degeneration

- Limited natural history data about *USH2A* related retinal degeneration
- None of the preceding studies used current standard methods to characterize patients
  - Spectral-domain optical coherence tomography (SD-OCT)
  - Static perimetry
  - Patient-reported outcomes (PROs)
- Natural History studies are critical for designing clinical trials
  - Identify more accurate, precise endpoints that are meaningful to physicians, patients and regulators
  - Development of improved endpoints may reduce study duration so trials don't take 5 years to demonstrate efficacy

# FDA-OOPD



- The US Food and Drug Administration Office of Orphan Product Development issued a Request for Applications to describe the natural history of orphan diseases
- The Foundation Fighting Blindness Clinical Research Institute worked with the Jaeb Center to submit a proposal that would support a 4 year natural history study of USH2A related retinal degeneration
- Currently under review; FFB will provide core and infrastructure support for consortium of clinics even if FDA-OOPD grant is not funded
- Goal:
  - Describe natural history
  - Define standard outcome measures of visual function and retinal structure in eyes with USH2A-related retinal degeneration
- New outcome measures could reduce the time required to demonstrate safety and efficacy

# Clinical Consortium of 20+ centers world-wide

Baylor, Houston, TX	Hospital for Sick Kids, Toronto, Canada
Columbia University, NY, NY	University of Michigan, Ann Arbor, MI
NEI, Bethesda, MD	Institut de la Vision, Paris, France
RFSW, Dallas, TX	Radboud University, Nijmegen, The Netherlands
Moorfield's Eye Hospital, London, England	University of Utah, Salt Lake City, UT
Scheie Eye Institute, Philadelphia, PA	Emory, Atlanta, GA
Medical College of Wisconsin, Milwaukee, WI	Wilmer Eye Institute, Baltimore, MD
Rutgers, Jersey City, NJ	Cincinnati Eye Institute, OH
UCSF, San Francisco, CA	Duke, Raleigh-Durham, NC
VRA, Gainesville, FL	Casey Eye Institute, Portland, OR
University of Tübingen, Germany	Ghent University, Belgium
MEEI, Boston, MA	



# Executive Committee: Ophthalmologists, vision scientists and clinical research specialists

- David Birch, PhD – Retina Foundation of the Southwest
- Jacque Duncan, MD – UCSF
- Mark Pennesi, MD, PhD – Casey Eye Institute
- Frederick Ferris, MD – National Eye Institute
- Maureen Maguire, PhD – Scheie Eye Institute, Jaeb Center
- Janet Cheetham, Pharm D – Foundation Fighting Blindness Clinical Research Institute
- Allison Ayala, MS – Jaeb Center
- Kristen Sheely, MS – Jaeb Center
- Adam Glassman, MS – Jaeb Center
- Briana Jackson, MS – Jaeb Center



# Baseline measures

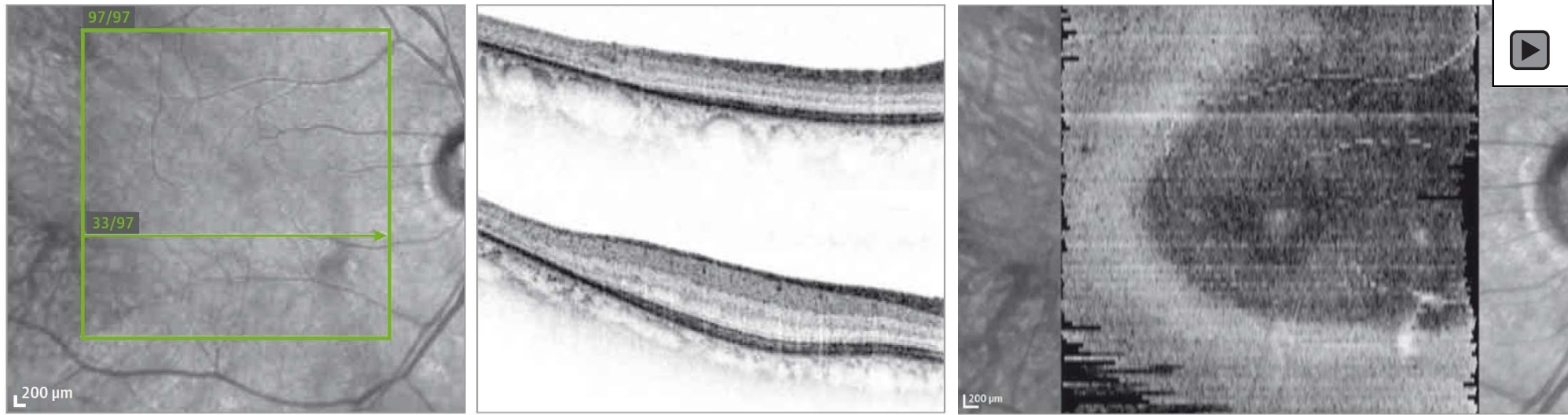
- Demographics: age, gender, family history, medical history
- Genetic evaluation of *USH2A* mutations: patients must already have had mutations identified, then committee of genetics experts will review and determine if mutations are likely pathogenic
- Audiograms
- Smell testing
- 2 cohorts:
  1. 100 patients with vision of 20/80 or better and stable fixation that will have exams every year for 4 years
  2. 20 patients with vision of 20/100 or worse or unstable fixation that will have exams only at baseline for cross-sectional study

# Outcome measures



- Static Perimetry: measure “hill of vision” using Visual Field Modeling Analysis software
- OCT images of macular structure: measure Ellipsoid zone (EZ) area

A EZ in B-scans



# Outcome measures

- Patient Reported Outcomes: Questionnaires to assess well being and impact of vision on activities
  - Quality of Life instruments
    - Monitor changes in patients' general well-being; may be related to visual outcome specifically
    - Address aspects such as independence and physical/ emotional state
    - Typical question: How concerned/satisfied...?
  - Visual Functioning Questionnaires
    - Rate the difficulty of daily visual activities
    - Activities may be selected for relevance/importance
    - Typical question: How difficult...?

## &lt; QUOTABLE &gt;



*“The eye is an approachable part of the brain.”*

Dr. José Sahel, a Professor of Ophthalmology and a renowned vision researcher, quoting his mentor Harvard’s Dr. John Dowling in *PittMed Magazine* (Summer 2016 issue).

### ⇒ WHAT'S INSIDE

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## FFB Clinical Consortium Launching Usher Syndrome Type 2A Patient Study

To maximize the chance that a therapy in development for a rare inherited retinal disease like retinitis pigmentosa (RP) will save or restore vision, researchers need a comprehensive understanding of how the condition affects patients. Several patient-related questions need to be answered before therapy developers can design and launch a clinical trial for the potential treatment. These questions include:

- When in a person’s life does the condition begin to cause significant vision loss?
- What cells in the retina are affected most (e.g., rods versus cones)?
- How do various gene mutations affect vision-loss severity and progression?
- What are the most effective methods for evaluating disease progression and changes in vision?

To address the need to better understand patients with rare, vision-robbing retinal diseases, the Foundation Fighting Blindness Clinical Research Institute (FFB-CRI) is establishing an international network of clinical experts — known as the FFB-CRI Clinical Consortium — to conduct robust

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natural history studies to identify, track, and document disease progression in retinal-degeneration patients. Depending on the condition, the studies could last from one to four years and involve dozens or hundreds of patients. The network will have approximately 20 clinical sites.

In addition, the Clinical Consortium will have available retinal-disease expertise and resources to conduct clinical trials of emerging therapies including: gene therapies, stem-cell treatments, and pharmaceuticals.

The consortium is benefitting from expert advice and scientific leadership from an executive committee, which includes: Jacque Duncan, M.D., University of California, San Francisco, who is serving as consortium chair; Rick Ferris, M.D., National Eye Institute; David Birch, Ph.D., Retina Foundation of the Southwest; and Mark Panessi, M.D., Ph.D., Oregon Health & Science University.

“The bottom line is that most inherited retinal diseases are quite uncommon, and we need more information about the affected patients,” says Janet Cheetham, Pharm.D., who is leading the consortium’s

See **TYPE 2A STUDY**, page 6

### TYPE 2A STUDY, continued from page 1

strategic development and study implementations. “The network will enable us to collect standardized natural history data that we’ll make available to treatment developers so they can launch well-designed human studies. Hopefully, making this patient information available will drive more companies and researchers to develop therapies for rare retinal diseases. We will also have the capacity to run all phases of clinical trials for potential therapies to assist companies and institutions in obtaining regulatory approval.”

The first patients to be studied by the Clinical Consortium will be those with RP and Usher syndrome (combined vision and hearing loss) caused by mutations in USH2A. Defects in the gene are a leading cause of inherited retinal disease; researchers estimate that USH2A mutations account for 30 to 40 percent of all Usher syndrome cases and 10 to 15 percent of all autosomal recessive RP. The USH2A natural history study will take place at approximately 20 clinical sites and follow more than 100 patients for four years.

“Our Clinical Consortium will

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play a uniquely valuable role in increasing the knowledge of retinal diseases in humans, and providing that information to industry to boost therapy development,” says Patricia Zilliox, Ph.D., Chief Drug Development Officer, CRI. “As a leading research-savvy nonprofit, we are strategically positioned to coordinate and invest in these critical natural history studies.”

ProgSTAR, FFB-CRI’s natural history study for people with Star-gardt disease, was conceived well before the Clinical Consortium was organized, but has served as a de facto pilot for it. Launched in 2013, the \$4.8 million, 250-patient ProgSTAR study will be completed in 2017.

“While we still have a lot of work to do in analyzing the data collected, we are very pleased with how well ProgSTAR has progressed thus far,” says Dr. Zilliox. “Our investigators were able to set up effective clinical centers, identify a large cohort of patients, and collect valuable imaging and functional data. ProgSTAR shows that our consortium concept can work well.”

# For more information, contact:

[www.fightblindness.org](http://www.fightblindness.org)

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- Foundation Fighting Blindness Clinical Research Institute
- Jaeb Center for Health Research Foundation
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