RUSH2A Study: The Importance of Natural History Studies

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FOUNDATION FIGHTING BLINDNESS

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  - Consultant
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  - Consultant

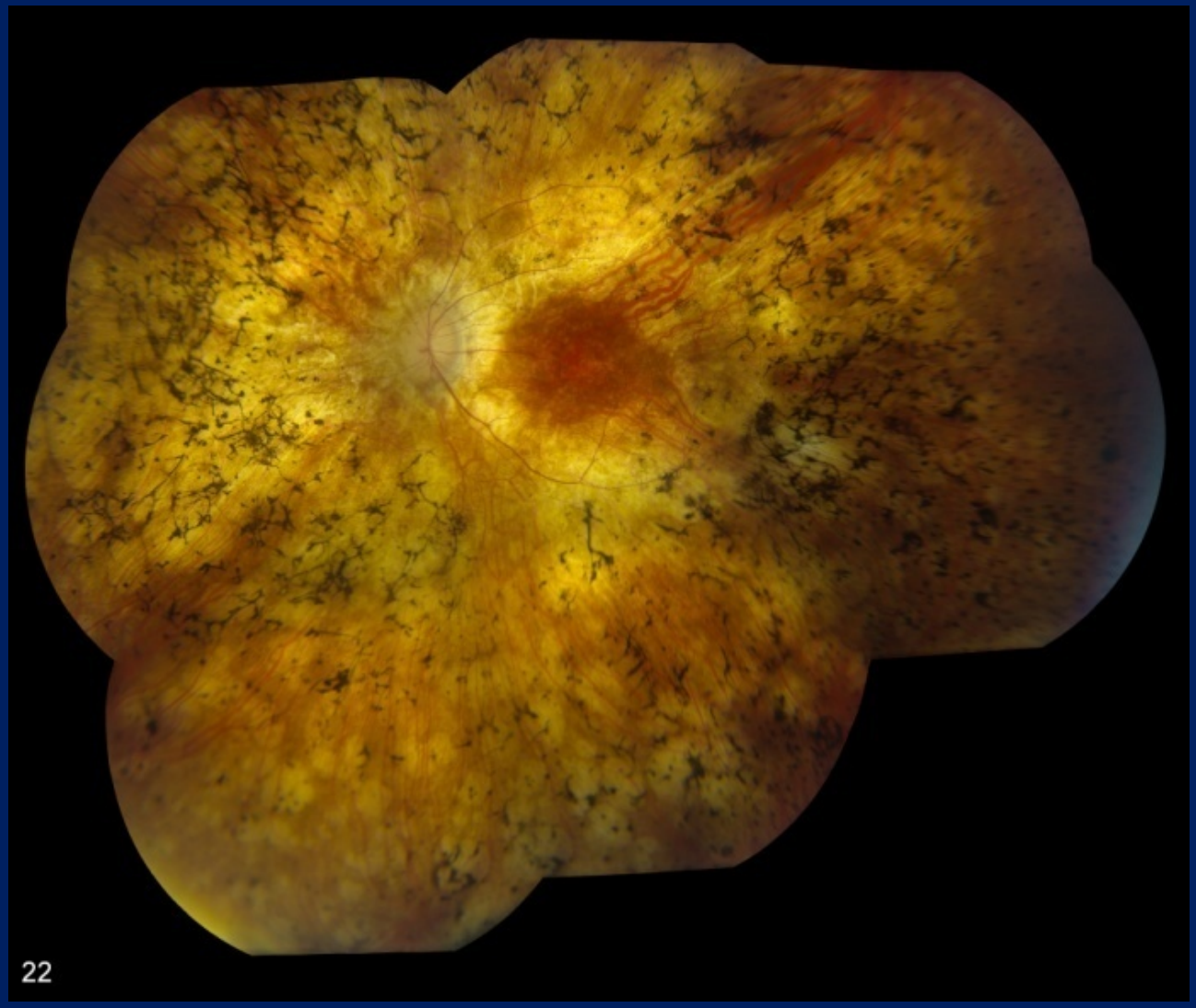
Usher Syndrome

- Prevalence is estimated at 1/30,000.
- Usher syndrome is the most common cause of hereditary combined deafness-blindness.
- Early onset hearing loss and RP (rod-cone dystrophy)
- Autosomal Recessive (AR)

Usher Syndrome Types

- Type 1 - (40%) Profound congenital sensorineural deafness, resultant speech impairment, vestibular symptoms.
  - Late milestones, walks later, severe
  - *MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *USH1G*
  - Ush 1B: Myocin 7A: UshStat (Sanofi gene therapy trial)
- Type 2 – (60%) Less severe hearing and RP, later onset
  - Meet milestones, usually normal hearing until mid-childhood
  - *USH2A*, *GPR98* and *DFNB31*
  - Ush2A: ProQR (antisense oligonucleotide therapy), Editas (CRISPR)
    - The most prevalent mutation in USH2A is the c.2299delG (exon 13)
- Type 3 – (<3%)
  - Finnish (40% of Finnish Usher syndrome pts, very rare in U.S.)
  - Aggressive/progressive
  - *CLRN1*

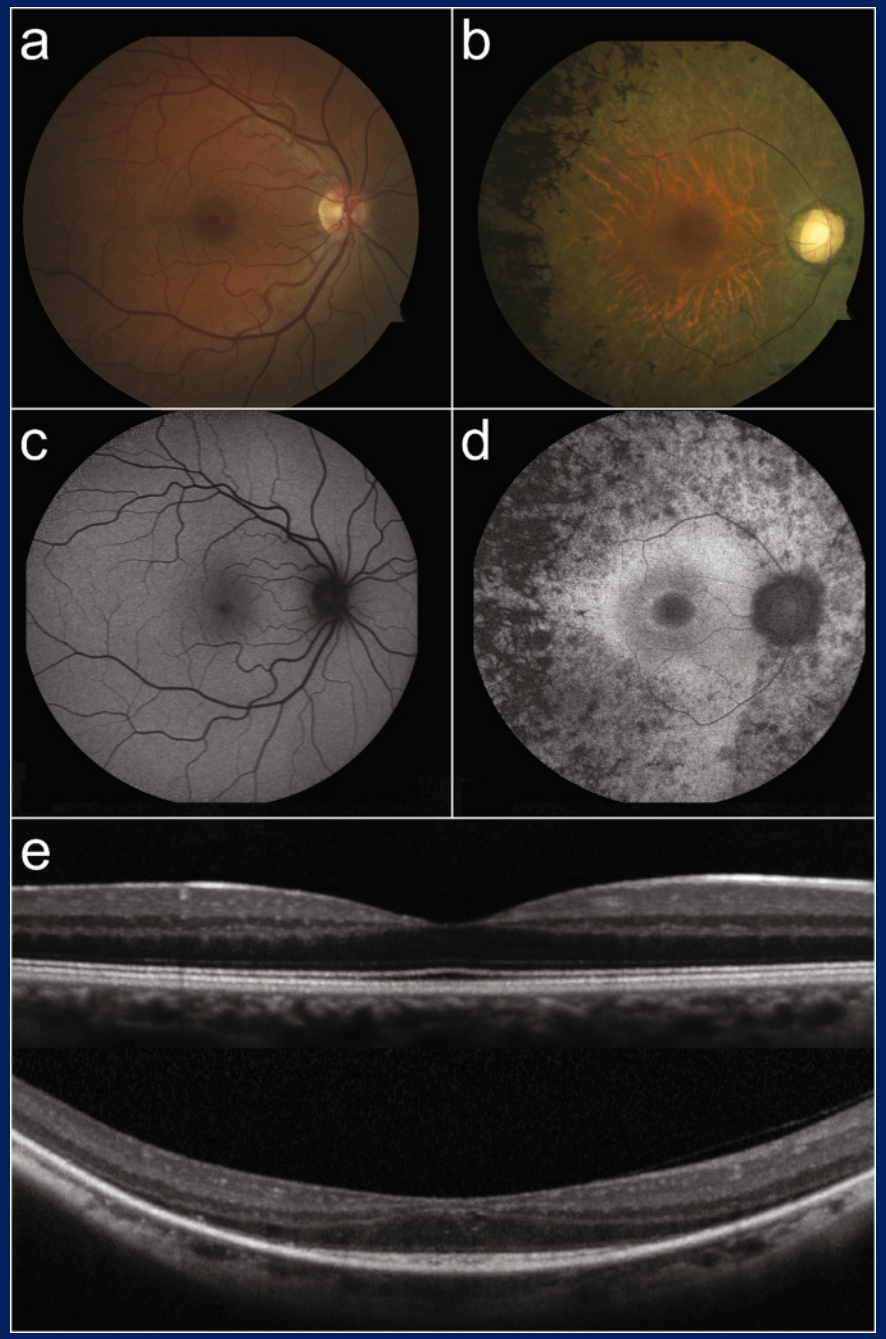
Ush2A associated retinal dystrophy



Ush2A phenotypes

- Usher Syndrome:
  - RP + hearing loss
- “Non-syndromic” Ush2A:
  - RP only (normal hearing)
  - RP may be less severe (residual cone responses)
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5593892/

Normal



NonsyndromicUsh2A

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5593892/

RUSH2A

- NCT03146078
- Rate of Progression in USH2A Related Retinal Degeneration
- Sponsor: JAEB Center
- Study Chair: Jacque Duncan, UCSF
- Collaborators:
  - Foundation Fighting Blindness
  - Duke University
  - Oregon Health and Science University

RUSH2A sites

UCSF
Vitreoretinal
Associates
Emory
Wilmer Eye Institute
NEI
MEEI
Kellogg Eye Center
Rutgers University
Columbia
Duke
OHSU

RUSH2A sites

Retina Foundation Southwest
Baylor
Moran Eye Center
Medical College of Wisconsin
Ghent University (Belgium)
Hospital for Sick Children (Toronto)
Institut de la Vision (Paris)
University of Tubingen (Germany)
Radboud University (Netherlands)
Moorfields (London)

Summary of RUSH2A

- To characterize the natural history of disease progression in patients with USH2A related retinal degeneration associated with congenital hearing loss (Usher syndrome type 2a) or non-syndromic retinitis pigmentosa (RP39).

Primary Study Objectives

- Characterize the natural history of retinal degeneration associated with biallelic pathogenic mutations in the USH2A gene over 4 years, as measured using:
  - Functional outcome measures (static perimetry, microperimetry, full-field stimulus threshold (FST), electroretinography (ERG), and visual acuity)
  - Structural outcome measures (spectral-domain optical coherence tomography (SD-OCT) ellipsoid zone (EZ) area)
- Investigate structure-function relationships for insights into the mechanisms of retinal degeneration by relating changes in SD-OCT EZ area to visual field progression in individuals with biallelic pathogenic mutations in the USH2A gene
- Assess for possible genotype, phenotype, and environmental risk factors with progression of the outcome measures at 4 years in individuals with biallelic pathogenic mutations in the USH2A gene

Primary Cohort: LONGITUDINAL STUDY

- Participants with:
  - Baseline visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better]
  - Stable fixation
  - Kinetic visual field III4e area 10° or more (on Octopus 900) in the study eye ("primary cohort") will be enrolled into the **longitudinal** natural history study

Secondary Cohort: CROSS SECTIONAL STUDY

- Participants with:
  - Baseline visual acuity ETDRS letter score of 53 or less [approximate Snellen equivalent 20/100 or worse]
  - or unstable fixation
  - or kinetic visual field III4e area less than 10°in the study eye ("secondary cohort") will be enrolled in the **cross-sectional** baseline study

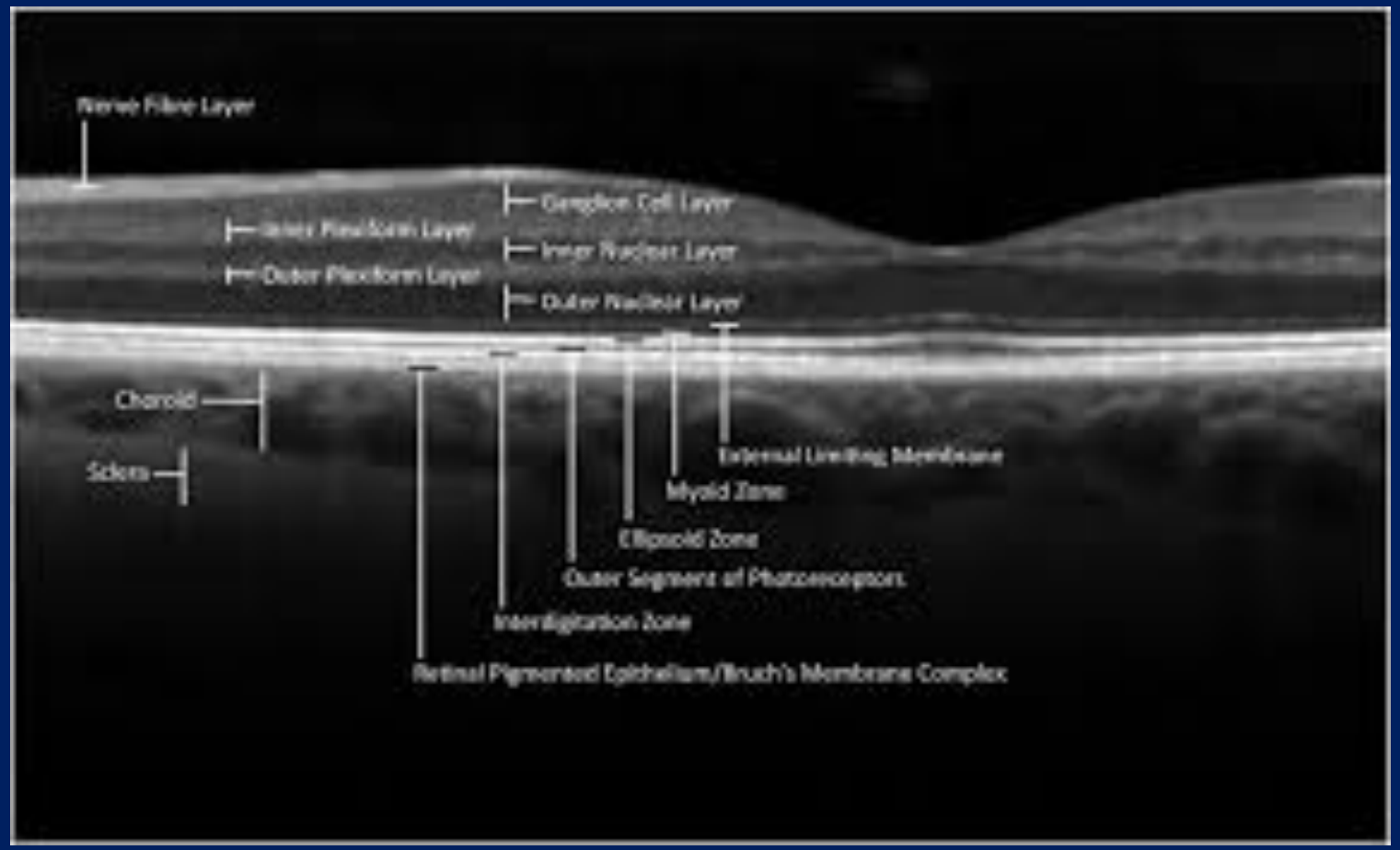
Primary Outcome Measures

- Change in Visual Field Sensitivity
- Change in Visual Acuity
- Change in Mean Retinal Sensitivity
- Change in EZ area
- Change in Rod- and cone-mediated retinal function - Measured by FST
- Change in Retinal function: Full-field ERG amplitudes and timing in response to rod- and cone-specific stimuli

EZ area on OCT – ellipsoid zone area

- Important to have reading center grade this in clinical trials (reduces bias, same methodology, reduces variability)

Ellipsoid Zone on OCT



Secondary Objectives

- Characterize baseline cross-sectional retinal degeneration associated with biallelic pathogenic mutations in the USH2A gene
- Investigate comorbidities associated with disease (baseline cross-sectional) and disease progression (longitudinal natural history study)
- Explore patient reported outcome (PRO) measures associated with disease (baseline cross-sectional) and disease progression (longitudinal natural history study)
- Evaluate variability and symmetry of left and right eye kinetic perimetry and SD-OCT outcomes at baseline and at 4 years

Inclusion Criteria

- Willing and able to complete the informed consent process
- Ability to return for all study visits over 48 months if in the natural history study
- Age ≥ 8 years
- At least 2 pathogenic or likely pathogenic mutations in USH2A gene from a clinically certified lab report

Ocular Inclusion Criteria

- Both eyes must meet all of the following:
- Clinical diagnosis of a rod-cone degeneration
- Clear ocular media and adequate pupil dilation to permit good quality photographic imaging
- Ability to perform kinetic and static perimetry reliably

Exclusion Criteria

- Mutations in genes that cause autosomal dominant RP, X-linked RP, or presence of biallelic mutations in autosomal recessive RP/retinal dystrophy genes other than USH2A
- Expected to enter experimental treatment trial at any time during this study
- History of more than 1 year of cumulative treatment, at any time, with an agent associated with pigmentary retinopathy (hydroxychloroquine, chloroquine, thioridazine, and deferoxamine)

Ocular Exclusion Criteria

- Current vitreous hemorrhage
- Current or any history of rhegmatogenous retinal detachment
- Current or any history of (e.g., prior to cataract or refractive surgery) spherical equivalent of the refractive error worse than -8 Diopters of myopia
- History of intraocular surgery (e.g., cataract surgery, vitrectomy, penetrating keratoplasty, or LASIK) within the last 3 months
- Current or any history of confirmed diagnosis of glaucoma (e.g., based on glaucoma visual field, nerve changes, or glaucoma filtering surgery)
- Current or any history of retinal vascular occlusion or proliferative diabetic retinopathy
- Expected to have cataract removal surgery during the study
- History or current evidence of ocular disease that, in the opinion of the investigator, may confound assessment of visual function
- History of treatment for retinitis pigmentosa that could affect the progression of retinal degeneration (including participation in a clinical trial within the last year or a retained drug delivery device)

RUSH2A Study Summary

- Study start date August 2017
- Expected completion January 2023
- Study ongoing, no longer recruiting
- Total enrollment: 137 patients:
  - 105 participants were enrolled in the primary cohort
  - 22 participants were enrolled in the secondary cohort
- More information on: www.clinicaltrials.gov

SECTION TWO

Importance of Natural History Studies

Why are natural history studies important?

- Information obtained from a natural history study can play an important role at every stage of drug development:
  - Drug discovery
  - Design of clinical studies
  - Support of marketing approval of a drug
  - Post-marketing
- Comprehensive knowledge of a disease can help sponsors design and conduct adequate and well-controlled clinical trials of adequate duration with clinically meaningful endpoints to support marketing applications for new drugs.

Uses of Natural History Study

- 1. Identifying the Patient Population
- 2. Identification or Development of Clinical Outcome Assessments
- 3. Identification or Development of Biomarkers
- 4. Design of Externally Controlled Studies: Use of Natural History Study Data

TYPES OF NATURAL HISTORY STUDIES

- Retrospective vs Prospective studies
- Cross-Sectional Studies and Longitudinal Natural History Studies
  - Cross-Sectional: data are collected from across a cohort of patients during a specified, limited time period
  - Longitudinal: data are collected from patients at several points over time

Considerations for patients involved in natural history trials

- NON-invasive trials
- Typically much less time intensive (often annual exams)
- May help increase chances of patients being recruited for future treatment trials
- Should not in any way prevent a patient from being involved in a future treatment trial (whereas involvement in one treatment trial may be an exclusion for involvement in another treatment trial)
- Patients MAY be withdrawn (although not ideal!) if necessary in order to join a treatment trial

Some examples of natural history IRD trials that have paved the way for treatment trials…

- PROGSTAR (Stargardt disease trial) – data used by Ophthotech for C3 inhibitor trial
- AGTC-sponsored Achromatopsia natural history trials – outcome measures optimized for treatment trials
- RUSH2A trial – will be useful for ongoing and soon to begin USH2A treatment trials (ProQR Therapeutics, Editas)

What can I do as a patient?

- Stay informed!
  - Organizations: Usher Syndrome Coalition, Foundation Fighting Blindness
  - Attend conferences/seminars
  - www.clinicaltrials.gov
  - Pubmed
- Talk to your doctor about diagnosis confirmation, genetic testing, and possible clinical trials
  - (ideally see an IRD specialist!)
- If a natural history trial is available for your condition – get involved!

Thank you!!