ACHROMATOPSIA
Clinical overview
and
updates on clinical trial

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Achromatopsia

- Autosomal Recessive
- Prevalence of 1:30,000-50,000
- Mild congenital pendular nystagmus
- Protan (red), deutan (green), and tritan (blue) color defects
- Severe photophobia
- Decreased VA around 20/100-20/200
- ERG shows normal rod function and no cone function
- Can have normal fundus or classic foveal atrophy
- OCT with characteristic foveal photoreceptor atrophy
Anatomy overview
Macula
Between temporal arcades
6 mm or 4 DD in width
2 or more layers of ganglion cells
Inner plexiform layer

Outer plexiform layer

Pigment epithelium

Venule

Arteriole

Melanocytes

Nerve fiber layer

Ganglion cell layer

Inner nuclear layer

Outer nuclear layer

Cones and rods

Choroid

Sclera

100 µm
Photoreceptors

- Light sensitive cells found in the retina.
- Rods (93% of cells) and Cones (7%)
  - Rods: night vision, visual field
  - Cones: visual acuity, color vision

![Figure 8.4.2 Basic structure of rods and cones](image-url)
A graph showing the distribution of receptors (cones and rods) across different eccentricities in the eye. The graph is labeled with "cone peak" and "rod peak" indicating the areas of highest concentration for these photoreceptor types. The x-axis represents eccentricity in degrees (from temporal to nasal), and the y-axis shows receptor density in mm² x 10^3. The data is from Osterberg, 1935.
Achromatopsia foveal atrophy
lid taped up
very poor fixation
does not cover every
not a reliable test
CNGB3-Achromatopsia OCT
Genetics of Achromatopsia

- **CNGA3 or CNGB3**, Cyclic Nucleotide Gated Channel (Subtype A or Subtype B)
  - CNGA3 (25%)
  - CNGB3 (50%):
    - Most frequent mutation is Thr383fsx mutation (80%) – this frameshift mutation causes truncation of pore-forming loop and C-terminal cytoplasmic domain, and no intact CNGB3 is formed.

- GNAT2 (1%)

- PDE6C (1%)
Retinal Physiology

• Quick overview...
choroid
pigment epithelium
outer segments
inner segments
outer nuclear layer (ONL)
outer plexiform layer (OPL)
inner nuclear layer (INL)
inner plexiform layer (IPL)
ganglion cell layer (GCL)
Physiology of Photoreception: THE MAJOR PLAYERS

• Photoreceptor outer segment:
  – Phototransduction

• RPE cell:
  – Visual cycle
The Outer Segment: the light sensitive part of a photoreceptor

First step in phototransduction is activation of rhodopsin by light causes isomerization of 11-cis to all-trans
Cyclic Nucleotide Gated Channels

• CNG channels are localized to **plasma membrane of outer segment**

• Belong to superfamily of voltage-gated ion channels

• Play **pivotal role in phototransduction**:
  – CNGA1/B1: in rods
  – CNGA3/B3: in cones
CNGA3 versus CNGB3

- Two channel subunits, alpha and beta
- Alpha subunits are ion transporting structures
- Beta subunits modulate the behavior of alphas but do not function as channels by themselves
- CNGA3 and CNGB3 mutations involve inability to properly control or respond to altered levels of cGMP.
- cGMP level controls the opening of cyclic nucleotide gated-ion channels.
CNG channels localized to photoreceptor outer segment
Cyclic nucleotide gated channel
Light stimulation leads to hydrolysis of cGMP $\rightarrow$ CNG channel closure $\rightarrow$ reduction of inward Na$^+$ and Ca$^{2+}$ currents $\rightarrow$ membrane hyperpolarization
Physiology summary

- Achromatopsia involves mutations in genes that play critical roles in the way the retina electrically responds to light (PHOTOTRANSDUCTION).
- Achromatopsia involves mutations in CONE cells, which are clustered in the fovea, and are responsible for visual acuity and color vision.
Current management of achromatopsia in humans

• Tinted glasses (to minimize severe photosensitivity).
• Currently no approved treatment.
• Gene therapy studies underway...
CLINICAL TRIAL UPDATE

- Clinical and Genetic Characterization of Individuals With Achromatopsia
- NATURAL HISTORY TRIAL
- NIH grant (R24) to University of Florida and AGTC to co-sponsor a clinical trial on Achromatopsia
  - PI: Bill Hauswirth
  - Clinical PI’s:
    - Casey Eye Institute: Dick Weleber
    - Chicago, Lighthouse: Gerald Fishman
    - University of Florida: Christine Kay
    - Bascom Palmer: Byron Lam
    - Wisconsin: Joe Carroll (Adaptive Optics)
- Actively recruiting patients.
Population

• The study population will consist of up to 150 individuals at least 6 years of age with a clinical diagnosis of achromatopsia.
Protocol

**Study Duration:** Approximately 1.5 years per participant

**Objectives**
- Clinically characterize and genotype individuals with CNGB3-achromatopsia.
- Determine progression and stability of clinical measures
- Determine a subset of reliable endpoints and identify inclusion/exclusion criteria for future clinical trials

**Study Design:** Patients with mutations in both alleles of the *CNGB3* gene will be evaluated twice a year for up to 1.5 years by using a variety of non-invasive visual function tests to more fully characterize their clinical condition.
TESTING

- Genetic testing to confirm 2 CNGB3 mutations at Casey.
- Routine ophthalmic examination and visual acuity
- Color vision
- Reading speed (MNREAD)
- Microperimetry
- Two color dark adapted static perimetry (Octopus)
- Nystagmus testing on MP1S
- Light sensitivity testing (Octopus)
- Optical coherence tomography
- Fullfield and Multifocal Electroretinography
- Fundus photography
- Quality of life questionnaire
- Adaptive optics retinal imaging (Wisconsin)
Visual acuity

Figure 1 Electronic Visual Acuity Tester (EVA)
Figure 6 Example of an MNREAD chart. Actual charts are 11 by 14 inches.

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<th>M size</th>
<th>Snellen for 40cm (15 inches)</th>
<th>logMAR</th>
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<tr>
<td>1.3</td>
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My father asked me to help the two men carry the box inside.

Three of my friends had never been to a circus before today.

My grandfather has a large garden with fruit and vegetables.

He told a long story about ducks before his son went to bed.

My mother loves to hear the young girls sing in the morning.

The young boy held his hand high to ask questions in school.

My brother asked...
Farnsworth color testing
Microperimetry – assess function at particular anatomical location
Nystagmus testing on MP1S
LIGHT SENSITIVITY TESTING ON ESPION
Ganzfeld Electroretinogram

Burian-Allen contact lens electrode

DTL electrode
Multifocal ERG

- In 1990s Dr. Sutter created program to extract hundreds of focal ERGs from 1 electrical signal
- ERG activity in central 30 degrees tested
- Subject fixates on stimulus of hexagon pattern
- ERG tracings recorded
Imaging

- Spectral domain OCT
- Adaptive Optics

Carroll, Gray, Williams 2005
Retinal imaging with adaptive optics

Mina Chung, University of Rochester, Flaum Eye
Gene therapy for CNGB3 achromatopsia

• Plan to submit IND to FDA for gene therapy trial.
• Vector being chosen/optimized for preclinical testing.
• Shannon Boye to talk much more about Gene Therapy in next talk!
Surgical approach for gene therapy: VITRECTOMY
Vector delivery considerations

Can we get the vector to the cells we intend?

Will the immune system cooperate with us?

Is injecting under the retina ("subretinal injection") causing tissue damage?
Current gene therapy clinical trials

• Phase 1 trials:
  – Choroideremia: Oxford/Moorfields, (AAV2)
  – AMD: Genzyme (AAV2-sFLT01; intravitreal)
  – Stargardt: StarGen (Lentivirus)
  – Usher 1B: UshStat (Lentivirus)

• Phase 3: FIRST PHASE 3 trial for gene therapy:
  – RPE65-LCA: Ongoing at Iowa/Penn, (AAV2)