Utilization of electroretinography and advanced retinal imaging to monitor development of retinal abnormalities in nonhuman primates with homozygous or heterozygous mutations in PDE6C

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Introduction

• The PDE6C gene is involved in the phototransduction pathway in cone cells of the retina. This gene encodes for phosphodiesterase-6-alpha enzyme, which hydrolyses cGMP to GMP.
• When this gene is mutated, it results in a condition known as achromatopsia. Those with achromatopsia have poor visual acuity, poor color vision, photophobia, and nystagmus.
• There is currently no cure for this disorder, but researchers are working on developing gene and cell therapies that might show some promise.

Electroretinography

Optical Coherence

Fundus Photography

therapies that might show some promise.

Specific aim 1: To determine when retinal abnormalities associated with a homozygous mutation in PDE6C appear in rhesus macaques and whether these abnormalities are stationary or progress over time.

Hypothesis

Rhesus macaques with the homozygous mutation will show reduced cone receptor function and macular abnormalities from birth and have slowly progressive macular disease over their lifetime. Also, rhesus macaques with the heterozygous mutations will show no discernible retinal abnormalities on electroretinography or retinal imaging.

Methods

Subjects

• 5 affected homozygous adult primates ranging from 4-13 years old with 5 age and sex-matched controls.
• 4 affected homozygous baby primates ranging from a few months to 4 years old with 4 age and sex-matched controls.
• 3 heterozygous primates ages 3 months, 4 months, and 12 years old.
• These primates were recruited from the California National Primate Research Center.

Electroretinography (ERG)

Spectral Domain Optical Coherence Tomography (SD-OCT)

Fundus Photography

Detects the retinal natural fluorophores located in the retinal pigment epithelium. This allows us to discern the quality of retinal metabolism and health.

Fluorescein Angiography

Statistical Analyses

Two-sample t-test

Results

ERG Measurements of Affected Babies vs. Controls

ERG Measurements of Affected Babies vs. Affected Adults

ERG boxplots comparing affected babies vs. controls and affected babies vs. affected adults.

Figure 4.

Figure 5.

Fundus autofluorescence of affected babies (left) and control babies (right).

Figure 6.

Fundus autofluorescence applications in retinal imaging.

Figure 7.

Fundus autofluorescence of affected babies (left) and control babies (right).

Figure 8.

Average foveal avascular zone (FAZ) for control babies (left): 3.22 mm²
Average foveal avascular zone (FAZ) for affected babies (right): 1.95 mm²
Sample size of the measurements for FAZ of control babies (n=2) were too few for meaningful statistical analyses

Discussion

1. Rhesus macaques with achromatopsia have reduced cone photoreceptor function and macular abnormalities from birth, implying that this disease is congenital. This is evident in the ERG data showing significantly decreased cone receptor activity in affected babies compared to control babies. The affected babies also seem to have unhealthy retinal pigment epithelium (RPE) cells compared to the controls as seen in the hypofluorescent and hyperfluorescent areas of the fundus autofluorescence. Certain layers of their retina are also significantly thinner compared to the controls in the OCT data.

2. There appears to be progression of the disease over time, although subtle. A decrease in cone function as babies become adults can be seen with the flicker test in the ERG. Significant thinning of some layers the retina can be appreciated in babies compared to adults.

3. We need a larger sample size of rhesus macaques with the heterozygous mutation to make any meaningful analyses or definitive conclusions on whether there is an intermediate phenotype of the disease. Some data were also missing in this cohort, resulting in their exclusion from the study and a sample size of only 2.

References


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