**RPE65 Related Inherited Retinal Degeneration Gene Therapy Trials: Background and Current Status, Need for Genetic Testing, and Future Gene Therapies for Other Retinal Dystrophies**

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I. The Phase III *RPE65* subretinal gene therapy trial: what we have learned so far

a. Genetic testing is of the utmost importance in selecting patients for a gene replacement trial  
   i. Variability is high in the human genome—simply finding a change from the reported normal sequence does not prove that it is disease-causing  
   ii. For a recessive disease like *RPE65* LCA, 2 disease-causing mutations must be found, one on each allele, to prove disease causation  
      1. This may require parental DNA testing or other genetic tests  
   iii. All of us carry single disease-causing alleles for multiple disorders; patients with genetic eye disease are also often “carriers” of one or more recessive eye diseases in addition to the one they are actually affected with  
      1. Mistaking the carrier state for the diagnosis in an individual could invalidate the results of a gene therapy trial if the trial is relatively small  
   iv. Some diseases other than *RPE65* LCA for which this is an issue:  
      1. *ABCA4* Stargardt disease  
      2. Usher Syndrome

b. Which patients in your clinics might benefit from genetic testing and how should you get it for them?  
   i. Patients with nystagmus  
      1. *FRMD7* mutations may cause “motor” nystagmus with good vision
a. X-linked, but manifesting females are common
2. Albinism is one of the most common causes of nystagmus
   a. Many people have partial function of the albinism
genomes and therefore they do have some pigment,
pigmented nevi, and/or they tan
   i. Foveal hypoplasia on OCT may aid in
diagnosis however there is a wide range of
degree of hypoplasia
3. Missense mutations in the PAX6 gene may cause
nystagmus and foveal hypoplasia with only minimal
anomaly of the iris
ii. Patients with abnormal ERG
   1. These patients are the most likely to benefit from gene
   therapy in the near future, so genetic testing is vital
   2. The pattern of ERG abnormality may differentiate between
   LCA, achromatopsia, and congenital stationary night
   blindness
   a. These entities can have overlapping presentations
   in young children and ERG plus genetic testing is
   more accurate than clinical diagnosis alone
iii. Patients with hearing/vision loss
   1. Usher syndrome is the best known eye-ear genetic
disorder, but it is not the only one
   a. If ERG is normal, consider DOA (OPA1 mutations),
   Waardenburg, others
   2. Genetic testing often aids in diagnosis (Ko et al., e-poster,
   AAPOS 2015)
iv. Patients with optic nerve disorders
   1. ONH
   2. DOA
   3. others
v. Patients with pigment disorders
   1. Albinism
   2. Waardenburg syndrome
   3. others
vi. Patients with congenital cataracts
vii. Patients with congenital glaucoma
   1. CYP1B1
viii. Others
ix. Working up genetic or suspected genetic eye disease patients:
   1. Refer to a genetic eye disease specialist/service
   2. Order genetic testing and work with an medical geneticist
   or genetic counselor to interpret and discuss the results
   a. www.genetests.org (Genetests)
c. Subfoveal vs. extrafoveal surgery
   i. Subfoveal surgery has been associated with foveal holes in some patients (Maguire), however subfoveal surgery has the greatest chance to improve acuity
      1. A video of subfoveal surgery will be shown
   ii. The choroideremia subretinal gene replacement trial utilized subfoveal surgery out of necessity (ref)

d. Managing expectations in a clinical trial
   i. Parents’ expectations
   ii. Patients’ expectations

II. What animals models are teaching us about the possibility for future human clinical trials

a. Bardet Biedl Syndrome
   i. The protein products of multiple genes associate to form protein complexes. Introducing subretinal gene therapy in this type of disorder may be more nuanced than in the case of RPE65 (Seo S, Bhattarai S, Gratie D, Stone EM, Sheffield V, Mullins RF, Drack AV. Gene therapy in a mouse model of Bardet Biedl Syndrome type I. Invest Ophthalmol Vis Sci. 2013 Sep 11;54(9):6118-32. doi: 10.1167/iovs.13-11673)

b. Other lessons from animal models

III. What else is in the works

   i. www.clinicaltrials.gov
      1. gene therapy trial for ABCA4 (Stargardt)
      2. gene therapy trial for Usher syndrome
      3. medication trial for RPE65 LCA
         1. other gene therapy trials
   ii. Stem cell replacement therapies
      1. Induced pluripotent stem cells obviate the need for embryonic cells
   iii. Small molecule therapies