Title: *RPE65*-Related Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy *GeneReview* – Data Supporting Subretinal Gene Supplementation Therapy
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Data Supporting Subretinal Gene Supplementation Therapy

Among inherited retinal diseases, subretinal gene supplementation therapy for LCA has been investigated most extensively in *RPE65*-LCA/EOSRD (see Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview). Subretinal gene supplementation therapy for *RPE65*-LCA/EOSRD compensates for loss-of-function *RPE65* variants by providing a functional copy of the gene to cells that utilize it. Viral vectors (i.e, recombinant adeno-associated virus (AAV) vectors) have been used in clinical trials.

In preclinical testing over a ten-year period, multiple investigators using two different mouse models demonstrated that early subretinal delivery of viral vectors expressing wild-type *RPE65* to replace or supplement loss-of-function variants resulted in robust RPE65 expression and rescue of electroretinogram (ERG) responses and other measures of retinal function [Cideciyan 2010]. The mouse models were *Rpe65 -/-* knockout mice and *Rpe65*^{rd12} mice, a naturally occurring mouse with a missense variant in *Rpe65.* In another model, Briard dogs with a naturally occurring *RPE65* loss-of-function variant, subretinal injection of AAV2 vector demonstrated robust improvement in visual function sustained over many years [Acland et al 2001, Acland et al 2005, Cideciyan et al 2013].

References

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