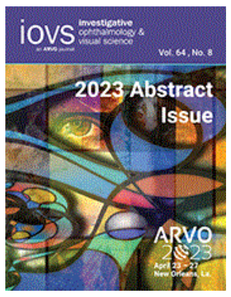

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‘Mini-PCDH15b’ gene therapy rescue visual deficits in a zebrafish retinopathy model of Usher syndrome type 1F

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Abstract

Purpose : Usher syndrome is a hereditary deafness and blindness caused by mutation of any of nine genes. Mutations in one gene, *PCDH15*, causes USH1F, manifesting as profound deafness and lack of balance at birth, and blindness developing over several decades. Treatment for USH1F is limited to cochlear implants, and there is no treatment for the blindness.

Gene addition therapy could be an attractive treatment; however, the PCDH15 coding sequence is too large to fit into a single AAV capsid. We engineered a mini-PCDH15 gene in which 5 of the 11 EC repeats were deleted but which demonstrated proper protein localization and rescue of hearing in mouse models of USH1F deafness. To test mini-PCDH15 gene therapy for blindness, we used a zebrafish USH1F mutant which exhibits PCDH15-associated retinopathy.

Methods : Using a transposon insertion strategy, we introduced mini-Pcdh15b, expressed under a photoreceptor-specific promoter, into *Pcdh15b*-mutant zebrafish. A stable transgenic line was generated. We assayed rescue of vision with electroretinogram (ERG) and optokinetic reflex (OKR) tests. We performed immunofluorescence (IF) and electron microscopy (EM) studies to localize the mini-Pcdh15b within photoreceptors, and compared results with untreated mutant fish.

Results : *Pcdh15b*-mutant zebrafish exhibit an early retinopathy, with defects in photoreceptor morphology and visual function. IF and EM of mutant photoreceptors revealed abnormal calyceal processes and distorted outer segments. In 7 dpf larvae, ERGs showed attenuated a- and b-wave amplitudes, and OKR responses were reduced.

Pcdh15b- mutant zebrafish expressing mini-Pcdh15b demonstrated rescue of vision to wild type levels, as assessed with ERG and OKR. With IF and immunogold SEM, strong mini-Pcdh15 signal was detected along calyceal processes of photoreceptors. Immunohistochemical and EM analysis showed robust rescue of photoreceptor morphology, comparable to that in normal larvae.

Conclusions : Mini-Pcdh15b expression restores vision in a zebrafish model of Usher 1F, and mediates expression and normal localization of Pcdh15b in photoreceptors, suggesting that a mini-PCDH15 gene therapy is a promising approach for the treatment of the progressive blindness in human Usher 1F. This work demonstrates that shortened versions of genes may be used to treat certain forms of vision loss for which the gene product is too large for AAV’s packaging limit.

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