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Gene Therapy Reforms Photoreceptor Structure and Restores Vision in NPHP5-associated Leber Congenital Amaurosis.

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The inherited childhood blindness caused by mutations in NPHP5, a form of Leber congenital amaurosis, results in abnormal development, dysfunction and degeneration of photoreceptors. A naturally occurring NPHP5 mutation in dogs leads to a phenotype that very nearly duplicates the human retinopathy in terms of the photoreceptors involved, spatial distribution of degeneration and the natural history of vision loss. We show that AAV-mediated NPHP5 gene augmentation of mutant canine retinas at the time of active degeneration and peak cell death stably restores photoreceptor structure, function, and vision with either the canine or human NPHP5 transgenes. Mutant cone photoreceptors, which failed to form outer segments during development, reform this structure after treatment. Degenerating rod photoreceptor outer segments are stabilized and develop normal structure. This process begins within 8 weeks following treatment, and remains stable throughout the 6 month post treatment period. In both photoreceptor cell classes mislocalization of rod and cone opsins is minimized or reversed. Retinal function and functional vision are restored. Efficacy of gene therapy in this large animal ciliopathy model of Leber congenital amaurosis provides a path for translation to human treatment.

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