

The long-term effects of gene therapy in a novel mouse model of human MFRP-associated retinopathy.

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Abstract

Patients harboring homozygous c.498_499insC mutations in MFRP demonstrate hyperopia, microphthalmia, retinitis pigmentosa, retinal pigment epithelial (RPE) atrophy, variable degrees of foveal edema and optic disc drusen. The disease phenotype is variable however, with some patients maintaining good central vision and cone function till late in the disease. We developed a knock-in mouse model with the c.498_499insC mutation in Mfrp (Mfrp KI/KI) to understand the effects of these mutations in the retina. Our model shares many of the features of human clinical disease including reduced axial length, hyperopia, retinal degeneration, RPE atrophy and decreased electrophysiological responses. In addition, the eyes of these mice had a significantly greater refractive error ($p < 0.01$) when compared to age-matched wild type (WT) control animals. Administration of recombinant AAV (rAAV) mediated Mfrp-gene therapy significantly prevented thinning from retinal neurodegeneration ($p < 0.005$) and preserved retinal electrophysiology ($p < 0.001$) when treated eyes were compared to contralateral sham-treated control eyes. The Mfrp KI/KI mice will serve as a useful tool to model human disease and point to a potential gene therapeutic approach for patients with preserved vision and electrophysiological responses in MFRP-related retinopathy.

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