

## Gene Therapy for X-Linked Retinitis Pigmentosa

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Retinitis Pigmentosa (RP) is a group of heterogeneous genetic disorders with a worldwide prevalence of 1 in 4000 individuals [1]. RP can be inherited in autosomal, X-linked or mitochondrial format. X-linked RP (XLRP) is one of the most severe forms of retinopathies, accounting for about 10-20% of all RP cases. Mutations in the Retinitis Pigmentosa Gtpase Regulator (*RPGR*) gene are the major cause of XLRP, accounting for 70 to 80% of affected XLRP cases [2]. The initially identified *RPGR* (*RPGR<sup>ex1-19</sup>*) contains 19 exons and encodes for a predicted 90 KDa protein [3]. A subsequent study identified a large C-terminal exon, called ORF15, in the major functional form (*RPGR<sup>ORF15</sup>*). The exon ORF15 encodes a repetitive glycine and glutamic acid-rich domain with a evolutionary conserved basic C-terminal domain, and harbors a high frequency of reading-frameshift and premature stop mutations, producing truncated proteins of varying length [4]. More than 300 *RPGR* mutations have been reported, most causing XLRP, a few causing human cone-rod, cone, or macular dystrophies, or syndromal forms of XLRP with primary ciliary dyskinesia and hearing loss [5].

*RPGR* is predominantly expressed in connecting cilia of photoreceptors, but expression has been reported in photoreceptor outer segments in some species. In mammalian and non-mammalian cell lines, *RPGR* localizes in centrosome of non-ciliated cells, and in basal body of ciliated cells [6]. Knock-down of *RPGR* in human retinal pigmented epithelium hTERT-RPE1 cell line caused defects in cilia genesis, suggesting *RPGR* has a role in the initial steps of cilia formation and/or stability [7]. Zebrafish embryos with *RPGR* knock-down by morpholino injection exhibited developmental defects ranging from small eyes to convergent extension defects, consistent with many other ciliary disorders [8]. *RPGR* Knock-out mouse model showed a slow degeneration of photoreceptors, with features resembling a cone-rod dystrophy, along with partial mislocalization of cone opsins [9]. There are two naturally occurring dog models: canine X-linked Progressive Retinal Atrophy (XLPRA) 1 has a 5-base pair deletion in *RPGR* exon ORF15, XLPRA 2 carries a 2-base deletion in exon ORF15 [10]. The XLPRA1 mutation results in a shorter frameshift and immediate premature stop codon, showing a slow degeneration phenotype in which rod and cone photoreceptors start to degenerate at about 6 months old; the XLPRA2 mutation leads to a long frameshift with 34 C-terminal basic residues. The XLPRA2 show a faster degeneration along with disorganized and disoriented photoreceptor outer segments. The above *RPGR* mouse and dog models provide a platform for testing preclinical therapies.

Gene therapy in the retina holds great promise in treating retinitis pigmentosa. Several factors make the retina amenable to the gene-replacement therapy, including relatively easy accessibility, immune privilege, and non-invasive safe evaluation of therapeutic effects [11]. The commonly used vectors for retinal gene delivery are recombinant Adeno-Associated Viruses (AAV), which have shown consistent success in targeting to the retinal pigment epithelial and photoreceptor cells. Recently Dr Aguirre and his collaborators at the School of Veterinary Medicine, University of Pennsylvania, reported that gene therapy rescued retinal degeneration phenotype in *RPGR* mutant dog models by over-expression of human *RPGR<sup>ORF15</sup>* in XLPRA dog photoreceptor cells with Adeno-Associated Virus (AAV) 2/5 vector under the control of either a human IRBP or GRK1 promoters [12]. The treatment was more effective when human *RPGR<sup>ORF15</sup>* was driven by hIRBP promoter

rather than GRK1 promoter. Since it is thought that over-expression of *RPGR<sup>ORF15</sup>* will cause toxicity in photoreceptors, ideally future *RPGR* gene therapy in RP patients will use human *RPGR* promoter to regulate *RPGR* expression. We have recently characterized the human *RPGR* promoter [13] and are now developing a mini promoter to drive *RPGR* expression in *RPGR* mutant animal models, which will provide preclinical data for progressing to a clinical trial. This will offer hope to RP patients with *RPGR* mutations.

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