# Modulation of severity of RPGR-associated retinal degeneration in mice due to mutations in RPGR-interacting proteins

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## Purpose:

In humans, over 80% of X- linked retinitis pigementosa (XLRP) is caused by mutations in *RPGR*. RPGR associated disease is clinically heterogeneous, indicating involvement of genes that can influence the associated phenotype. *RPGR* is known to interact with selected ciliary proteins including *CEP290*, *RPGRIP1*, *NPHP1, NPHP4* and *NPHP5*. The purpose of this study is to assess the contribution of these RPGR-interacting proteins on the severity of RPGR-associated retinal degeneration in $Rpgr^{ko}$ mice.

## Methods:

$Rpgr^{ko}$ female mice were bred with male $Cep290^{rd16/rd16}$, $Nphp1^{-/-}$, $Nphp4^{nmf192}$, $Nphp5^{-/-}$, $Rpgrip1^{-/-}$. Males from F1 generation with genotype $Rpgr^{KO}/Cep290^{+/rd16}$, $Rpgr^{ko}/Nphp1^{+/-}$, $Rpgr^{ko}/Nphp4^{nmf192/+}$, $Rpgr^{ko}/Nphp5^{+/-}$, $Rpgr^{ko}/Rpgrip1^{+/-}$ were selected for further analysis. Structural and function studies were performed using Histology, transmission electron microscopy (TEM), immunofluorescence staining, and Electroretinopgraphy (ERG).

## Results

The $Rpgr^{ko}$ mice exhibit degeneration of retina and relatively mild decrease in cone and rod function by 6 months of age. Our analysis of double mutant mice revealed that $Rpgr^{ko}/Cep290^{+/rd16}$ exhibit accelerated retinal degeneration as compared to $Rpgr^{ko}$ mice. TEM analysis of $Rpgr^{ko}/Cep290^{+/rd16}$ retina showed vesicle accumulation at the base of the outer segments of photoreceptors, which were not detected in the $Rpgr^{ko}$ mice. We also detected decreased cone-specific staining of M-opsin. No significant effect on the retina was observed in $Rpgr^{KO}/Nphp1^{+/-}$, $Rpgr^{KO}/Nphp4^{nmf192/+}$, $Rpgr^{ko}/Nphp5^{+/-}$, $Rpgr^{ko}/Rpgrip1^{+/-}$ (n=3) mice up to 6 months of age, as compared to $Rpgr^{ko}$.

## Conclusions

Our studies suggest that mutations in CEP290 can potentially influence the severity of retinal phenotype due to mutations in RPGR. Further studies are in progress to assess the influence of additional RPGR-interacting proteins on RPGR-disease.