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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 pigmentosa (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 Electroretinography (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.