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Ablation Of Raf-1 Kinase Inhibitory Protein (RKIP) Improves Photoreceptor Structure and Function in a Cep290-Mutant Mouse Model Of Severe Retinal Degeneration

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**Purpose:** Mutations in the *CEP290* gene are a frequent cause of childhood blindness disorder, Leber congenital amaurosis (LCA). Not much is known about the mode of action of *CEP290* in the retina. We previously showed that *CEP290* interacts with RKIP and that RKIP protein is abnormally accumulated in *rd16* (retinal degeneration 16) mouse, a model of *Cep290*- associated retinal degeneration. The purpose of this study is to evaluate the role of RKIP accumulation in mediating photoreceptor degeneration in the *rd16* mouse.

**Methods:** *rd16/rd16:Rkip ko/Rkip ko* double homozygous knock out mice were generated by breeding *rd16* and *Rkip ko* mice (both on C57BL6/J background). Photoreceptor structure and function were evaluated by Histology, Transmission electron microscopy (TEM), Immunofluorescence microscopy and Electroretinography (ERG).

**Results:** We detected improved photoreceptor structure in the double homozygous mutant mice compared to *rd16* at postnatal day 18 (P18). In addition, Rhodopsin and M-opsin staining in Rd16 Rkip<sup>-/-</sup> mouse showed increased outer segment localization in the double mutant mice. Finally, ERG analysis showed 40% scotopic response recovery in Rd16 Rkip<sup>-/-</sup> from Rd16 mouse.

**Conclusions:** We propose that accumulation of RKIP due to mutation in *CEP290*, although not the only pathway is a critical step in the pathogenesis of associated severe retinal degeneration. Altering RKIP levels may potentially be used in combination with other modalities as an approach for treating such disorders.