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Novel nonsense-mutation in KCNJ13 cause Leber's congenital amaurosis

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This paper will present our recent discovery about a novel non-sense mutation that cause LCA-16 and determine the molecular mechanism of the disease pathobiology. Several mutations of the KCNJ13 gene that encode inwardly rectifying potassium channel (Kir7.1) were identified in patients with allelic anomalies and vision loss in Snowflake Vitreoretinal Degeneration (SVD) and Leber Congenital Amaurosis (LCA). LCA is a severe acquired blindness suffered by 20% of children attending schools for the blind. Kir7.1 controls the narrow sub retinal space microenvironment between retina photoreceptor and retinal pigment epithelium (RPE). RPE is a tight monolayer of postmitotic epithelial cells located posterior to the retina and forms key blood retina barrier. Although Kir7.1 is present in several other tissues, its physiology has been studied in the retina, uterus and brain. Kir7.1 is one of the seven members of the two transmembrane Kir protein families, and the reported mutations belong to extracellular selectivity loop and cytoplasmic regulatory domains. Heterologous expression of SVD mutant channel suggested a dominant negative loss of function, raising the questions of how loss of function of an RPE apical membrane Kir7.1 underlies vision phenotype. Here, we report the identification of a novel nonsense mutation in the second exon of the KCNJ13 gene leading to a premature stop codon in a young boy presented to the clinic with nyctalopia and decreased vision. We use heterologous expression, patient iPS-RPE and mouse to uncover the disease pathophysiology.

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