New hope for blinding eye disease gene therapies

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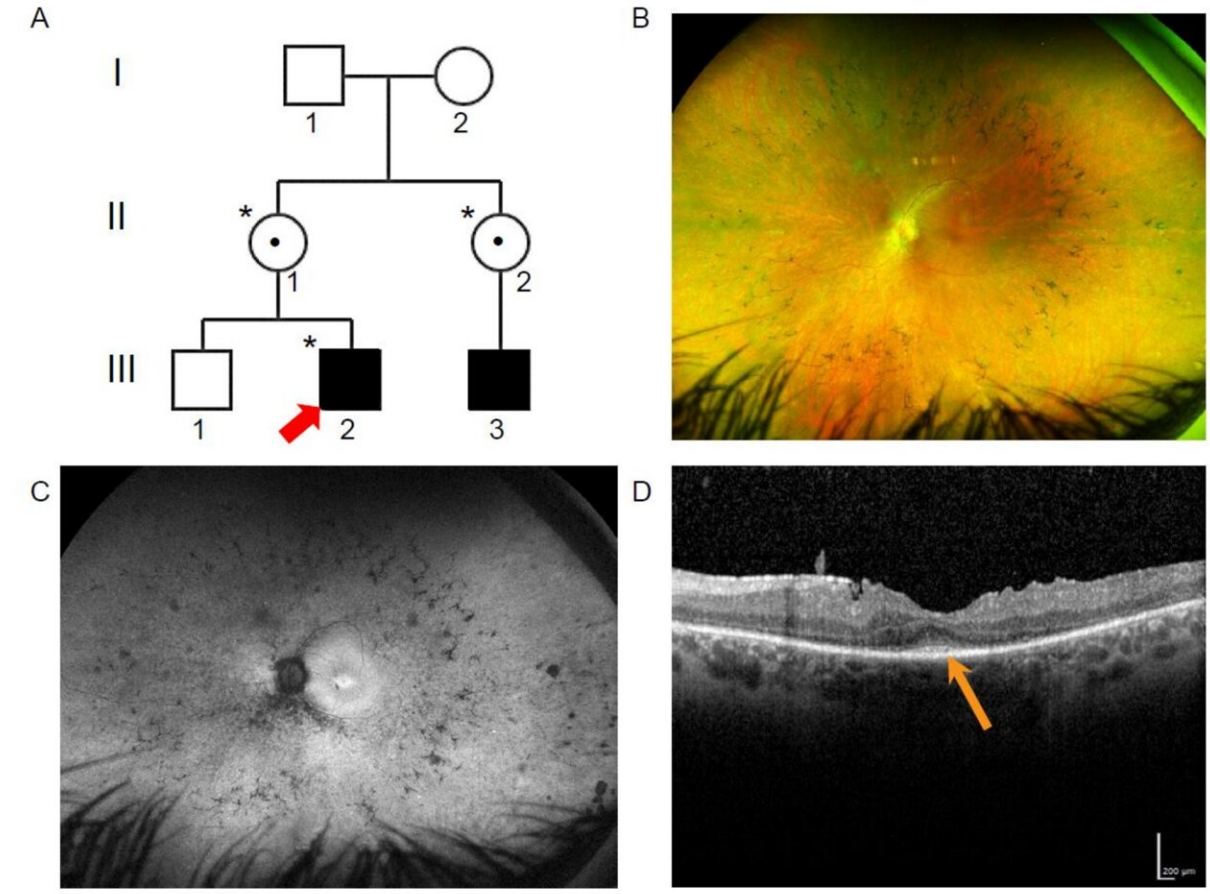

	SSF [0–100]	MaxEnt [0–16]	NNSPLICE [0–1]	GeneSplicer [0–15]	HSF [0–100]
Threshold	*≥ 70*	*≥ 0*	*≥ 0.4*	*≥ 0*	*≥ 65*
Intron 11 – c.1415-8	— ⇒ 83.12	— ⇒ 8.73	— ⇒ 0.91	— ⇒ 4.83	— ⇒ 81.91
Exon 12 – c.1415 N	81.92 ⇒ —	8.01 ⇒ 2.03 *(-74.6%)*	0.75 ⇒ 0.78 *(+4.4%)*	5.82 ⇒ —	85.77 ⇒ 85.89 *(+0.1%)*

Figure 1. Ophthalmic investigations and RPGR novel variant. (A) The proband (Patient III-2; red arrow) was affected with RCD, as was his maternal cousin (III-3). The proband was hemizygous for the intronic variant in RPGR (*), and his mother and maternal aunt were heterozygous for the same variant (*), while his unaffected brother did not have the variant. Known female carriers are

denoted (•). (B) Patient III-2 fundal images demonstrating mild pigmentary disturbance in the mid periphery. (C) Ultra-widefield fundus autofluorescence demonstrating a narrow ring of hyperautofluorescence around the fovea and patchy hypoautofluorescence scattered throughout the fundus. (D) The Spectral Domain Optical Coherence Tomography demonstrated a residual blurred ellipsoid zone at the fovea (orange arrow). (E) Patient III-2, RPGR, c.1415 – 9A>G highlighted in red in intron 11 of RPGR (NM_000328.2). (F) In silico prediction across five programs using Alamut Visual scored above the threshold for the novel variant c.1415 – 9G>A behaving as an acceptor site. Scores were below threshold for the canonical acceptor site, indicating a potential loss of function in the presence of the novel variant. Credit: *Journal of Personalized Medicine* (2022). DOI: 10.3390/jpm12030502

New opportunities towards gene therapy and diagnosis for the blinding eye disease, retinal dystrophy, may now become available following work done by the Eye Genetics Research Unit at Children's Medical Research Institute.

This work was published in the *Journal of Personalized Medicine* today.

The team looked at the RPGR gene which is involved in maintaining healthy photoreceptor cells. Variants in this gene are the main contributor to eye disease such as rod cone dystrophy and gene therapy for this condition is now in clinical trials.

Rod cone dystrophy affects rod and cone photoreceptor cells and manifests in decreased night and peripheral vision and progressive vision loss. There are more than 60 identified contributing disease genes.

CMRI's Eye Genetics team investigated a novel genetic variant in the RPGR gene in a patient who has rod cone dystrophy and, working alongside CMRI's Stem Cell Medicine team, used induced pluripotent

stem cells to produce retinal organoids. This work found that the novel variant impacted the function of the gene.

Head of CMRI's Eye Genetics Research Unit, Professor Robyn Jamieson said the first and second authors Fidelle Karam and To Ha Loi had put in tremendous work to show that this genetic variant was disease-causing, and they had now identified biomarkers to further investigate novel therapies directed at variants in the RPGR gene.

"There is potential for clinical trials in the future for genetic therapies related to disease caused by variants in RPGR, so this work provides a genetic diagnosis, as well as avenues for investigation and biomarkers for investigation of new therapies for people with variants in this gene—which is one of the most common causes of retinal dystrophy."

More information: Fidelle Chahine Karam et al, Human iPSC-Derived Retinal Organoids and Retinal Pigment Epithelium for Novel Intronic RPGR Variant Assessment for Therapy Suitability, *Journal of Personalized Medicine* (2022). DOI: 10.3390/jpm12030502

Provided by Children's Medical Research Institute (CMRI)