Restoration of Cone-Mediated Vision After Gene Augmentation in Children with LCA5

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Artur V. Cideciyan

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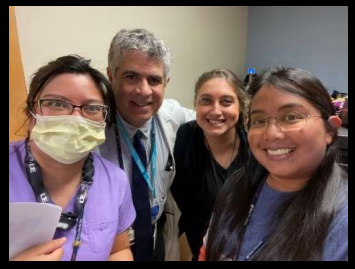

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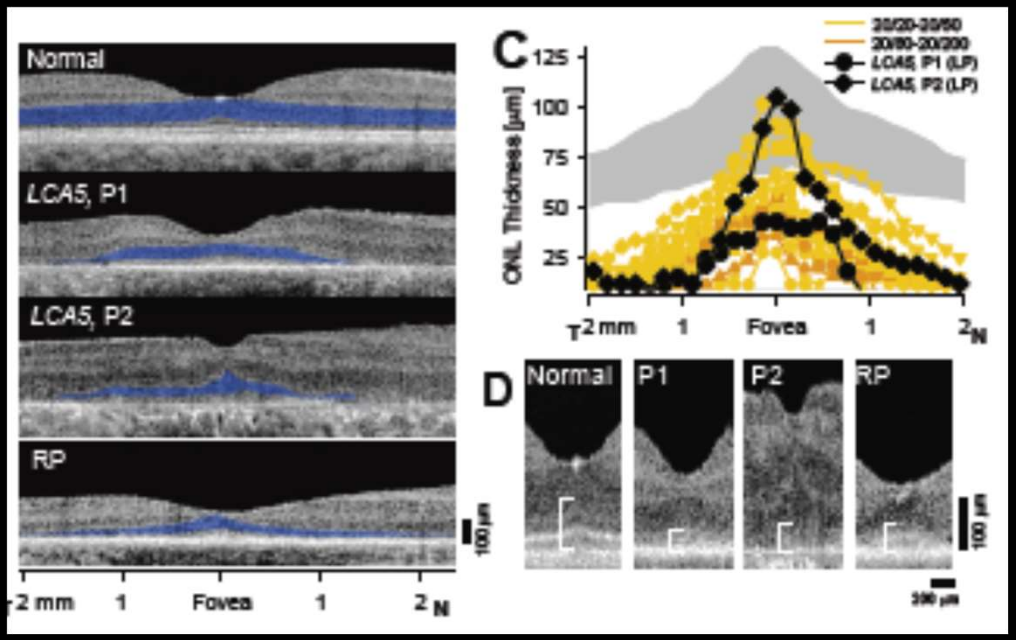
CHRD Center for Hereditary Retinal Degenerations

Perelman School of Medicine University of Pennsylvania

LCA5 just became a target for therapy



- ~2% of all LCA.
- Severe structural and functional phenotype.
- Relatively spared cone photoreceptors near the center.

Leber congenital amaurosis caused by *Lebercilin* (*LCA5*) mutation: Retained photoreceptors adjacent to retinal disorganization

Samuel G. Jacobson,[1] Tomas S. Aleman,[1] Artur V. Cideciyan,[1] Alexander Sumaroka,[1] Sharon B. Schwartz,[1] Elizabeth A.M. Windsor,[1] Malgorzata Swider,[1] Waldo Herrera,[1] Edwin M. Stone[2]

Molecular Vision 2009; 15:1098-1106

Treatment Potential for *LCA5*-Associated Leber Congenital Amaurosis

Katherine E. Uyhazi,[1,2] Puya Aravand,[1] Brent A. Bell,[1] Zhangyong Wei,[1] Lanfranco Leo,[1] Leona W. Serrano,[2] Denise J. Pearson,[1,2] Ivan Shpylchak,[1] Jennifer Pham,[1] Vidyullatha Vasireddy,[1] Jean Bennett,[1] and Tomas S. Aleman[1,2]

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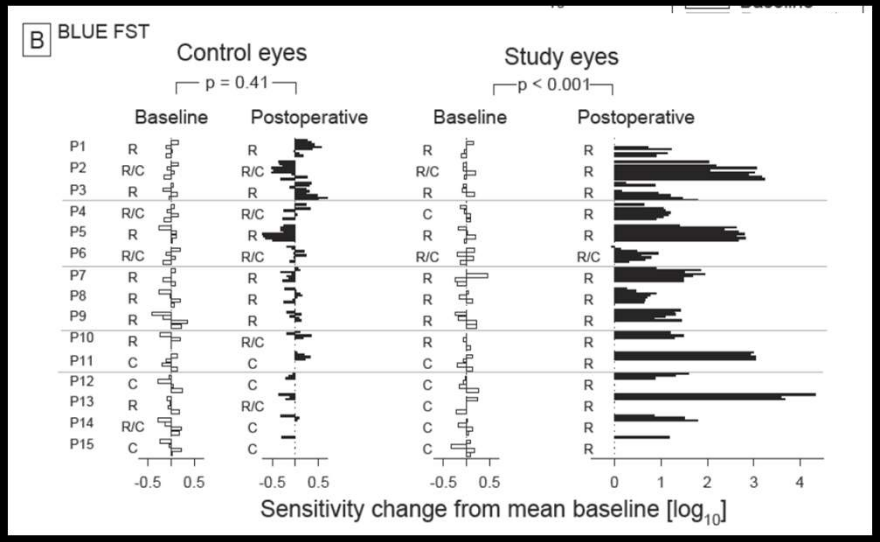
Improvements after retinal gene therapy have been dominated by rods

RPE65-LCA2



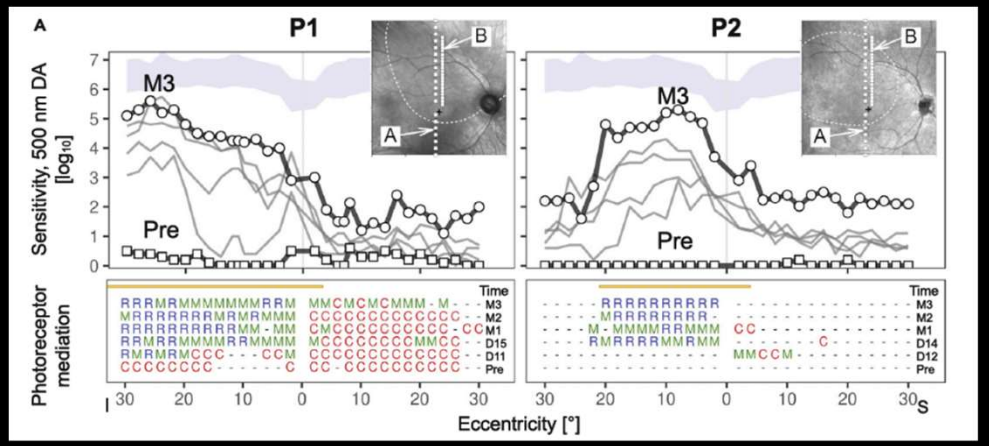
Gene Therapy for Leber Congenital Amaurosis Caused by *RPE65* Mutations

Safety and Efficacy in 15 Children and Adults Followed Up to 3 Years

Samuel G. Jacobson, MD, PhD; Artur V. Cideciyan, PhD; Ramakrishna Ratnakaram, MD; Elise Heon, MD; Sharon B. Schwartz, MS, CGC; Alejandro J. Roman, MS; Marc C. Peden, MD; Tomas S. Aleman, MD; Sanford L. Boye, MS; Alexander Sumaroka, PhD; Thomas J. Conlon, PhD; Roberto Calcedo, PhD; Ji-Jing Pang, MD, PhD; Kirsten E. Erger, BS; Melani B. Olivares, BA; Cristina L. Mullins, BA; Malgorzata Swider, PhD; Shalesh Kaushal, MD, PhD; William J. Feuer, MS; Alessandro Iannaccone, MD, MS; Gerald A. Fishman, MD; Edwin M. Stone, MD, PhD; Barry J. Byrne, MD, PhD; William W. Hauswirth, PhD

Arch Ophthalmol. 2012;130(1):9-24.

GUCY2D-LCA1



Samuel G. Jacobson, Artur V. Cideciyan, Allen C. Ho, ..., Igor V. Peshenko, Alexander M. Dizhoor, Shannon E. Boye

iScience

Night vision restored in days after decades of congenital blindness

CHRD Center for Hereditary Retinal Degenerations

Perelman School of Medicine University of Pennsylvania

What we recently learned from treating this condition

- Gene augmentation led to safe, robust and lasting efficacy in 3 adults.
- Efficacy corroborated through multiple mechanistically driven readouts.
- There were improvements in cone sensitivity in all patients.

What if we treat earlier in life?

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Molecular Therapy
Original Article

Recovery of cone-mediated vision in *Lebercilin* associated retinal ciliopathy after gene therapy: One-year results of a phase I/II trial

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OPGx-LCA5-1001 Study to Treat a Severe Photoreceptor Disease

Extension to pediatric patients

Protocol Design

- Phase 1b/2a, open-label of a uniocular subretinal injection of OPGx-LCA5.
- Nonrandomized, single dose (**1E10 vg/eye) from initial dose escalation**.
- Preliminary results to 6 months year in three patients.
- Support from FDA - OOPD [R01FD008174] and Opus Inc.

Protocol Design: OPGx-LCA5-1001 Study

Primary Objective	Primary Endpoints
Safety and tolerability	1. Number of dose limiting toxicity (DLT) events. 2. Number of procedure- or OPGx-hLCA5-related adverse events (AEs). 3. Change in vision and/or retinal structure.

Secondary Objective	Secondary Endpoints (for presentation)
Assess the efficacy	1. Dark-adapted full-field sensitivity testing (FST). 2. Dark-adapted transient pupillary light reflexes (TPLR). 3. Best Corrected Visual Acuity. 4. Microperimetry 5. Orientation and Mobility.

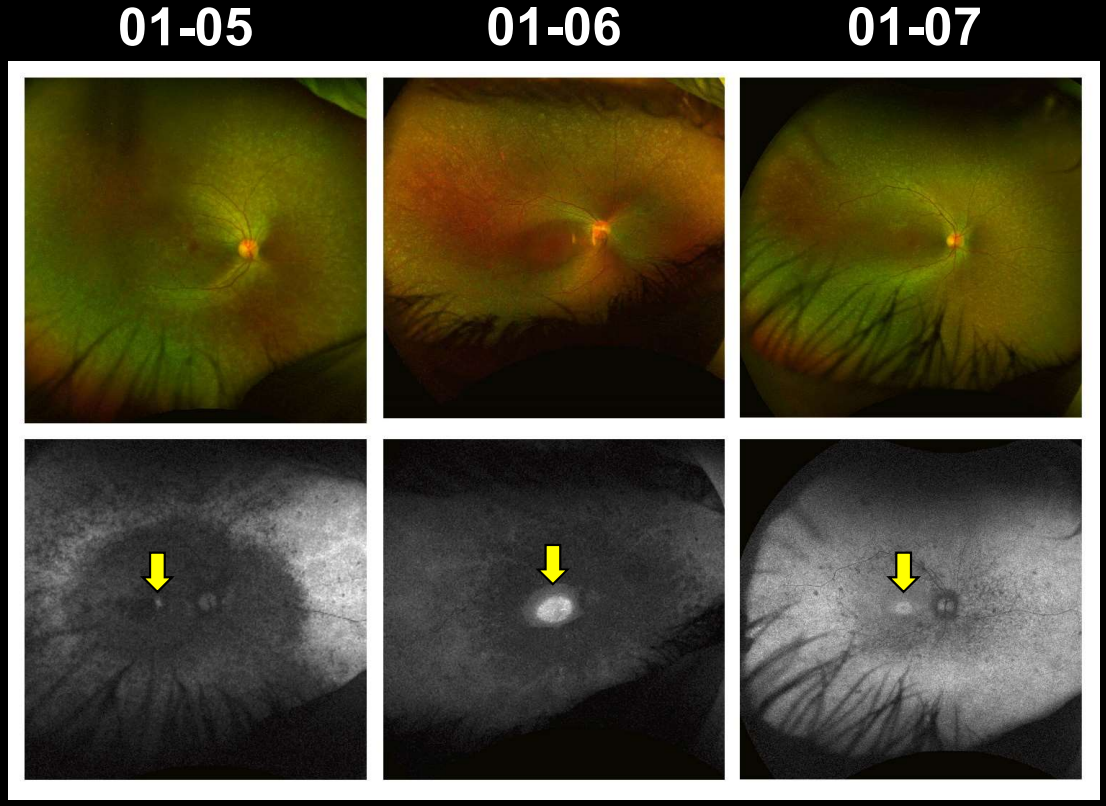
Characteristics of Patients + Pediatrics
(01-05, 01-06, 01-07)

Study ID	Age*/ Gender	Date IP Administration	Study Eye	LCA5 Variants† Allele 1/Allele 2	Visual Acuity‡		Refraction§	
					OD	OS	OD	OS
0103	26/M	07 Aug 2023	OS	Gln279*/Gln279*	3.20	2.90	+3.00	+3.00
0101	34/F	11 Sep 2023	OS	Arg255Gln/del. Exon 1	1.31	1.38	-1.50	-2.50
0104	19/F	13 Nov 2023	OD	Arg255*/Arg255*	0.96	0.91	+2.25	+2.00
0105	**17/F**	17 Feb 2025	OD	Gln421*/Gln421*	2.20	2.20	+1.00	+1.00
0106	**16/M**	31 Mar 2025	OD	Arg280*/Arg280*	0.96	0.88	+4.00	+4.00
0107	**17/F**	16 Jun 2025	OD	Tyr265Ter/Tyr265Ter	2.30	2.30	+3.00	+3.00

- Mutations led to non-functional proteins.
- Very poor VA.

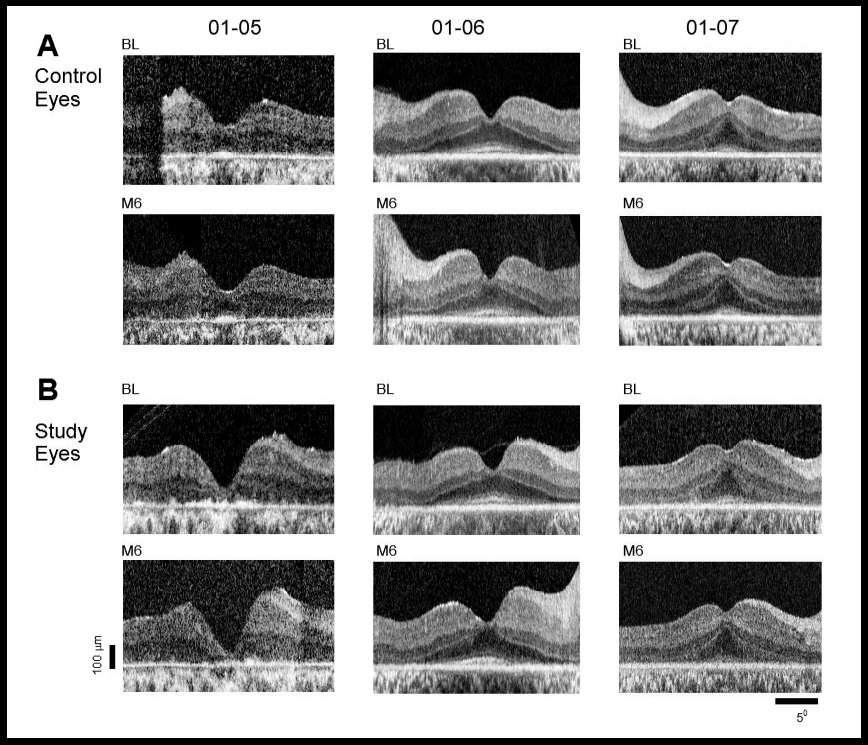
Similar phenotype, diverse severity

DETECTABLE CENTRAL PHOTORECEPTORS DESPITE SEVERE DISEASE



- Severe pericentral disease, ‘relative’ foveal and midperipheral sparing.
- Injections again targeted spared photoreceptors.

Safety: Central Retinal Structure



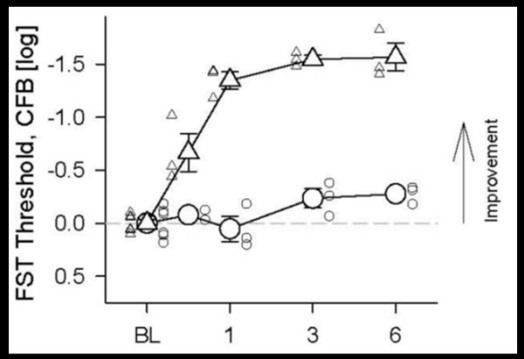
- Retina reattached.
- No major changes post-TX.

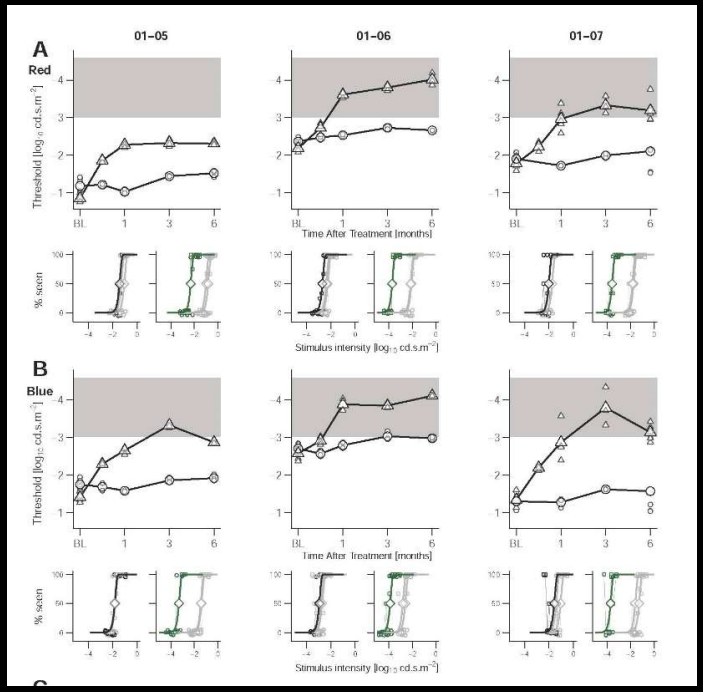
Safety and Tolerability

Pt ID	Sign or Symptoms	Eye*	Expected?*	Date of onset	Date of Resolution	IP Related?	Surgery-Related?	Oral steroid-related?/ Taper onset†	Action taken‡
01-05	Red Bumps – Skin Lesions		No	04Mar2025	21Mar2025	No	No	Yes	1
01-05	Sore Throat		Yes	12Mar2025	14Mar2025	No	No	No	2
01-05	Headache		Yes	13Mar2025	13Mar2025	No	No	No	2
01-05	Cataract	OD	Yes	20Mar2025	Ongoing	No	Yes	No	1
01-05	Hordeolum	OD	Yes	27Aug2025	04Sep2025	No	No	No	Compresses
01-05	Common Cold		Yes	18Dec2025	28Dec2025	No	No	No	2
01-05	Vitamin D deficiency		Yes	03Jan2026	Ongoing	No	No	No	2
01-05	Common Cold		Yes	16Jan2026	21Jan2026	No	No	No	2
01-06	Light Sensitivity	OU	Yes	07Apr2025	11Apr2025	No	No	No	1
01-07	Pain and Discomfort	OU	No	16Jun2025	16Jun2025	No	Yes	No	2
01-07	Post Op Anxiety		Yes	17Jun2025	17Jun2025	No	Yes	No	1

- No dose limiting toxicities.
- AE were mostly anticipated, mild and not related to OPGx-LCA5.
- All resolved.

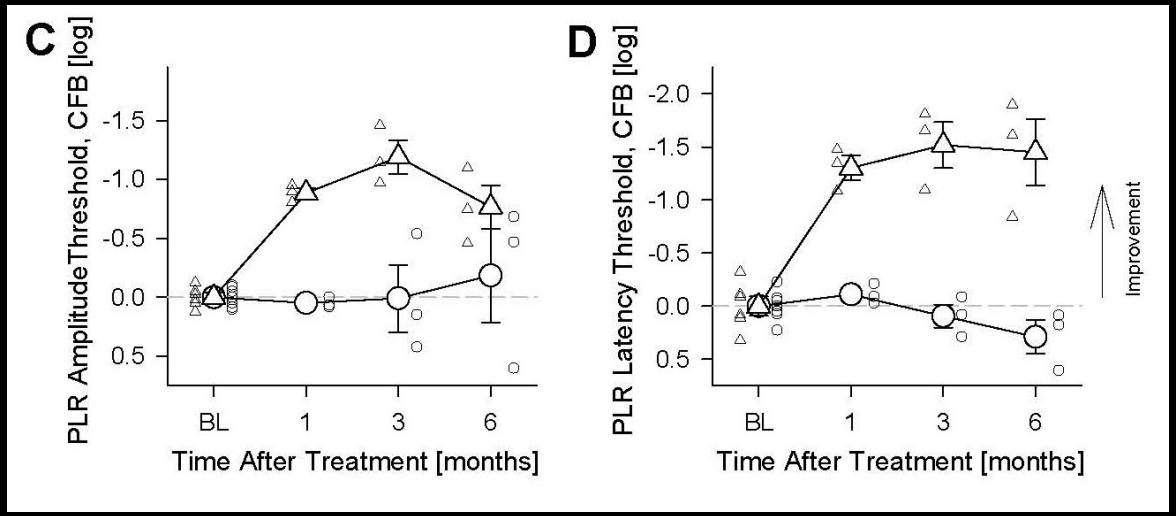
Gains in Cone Mediated Sensitivities





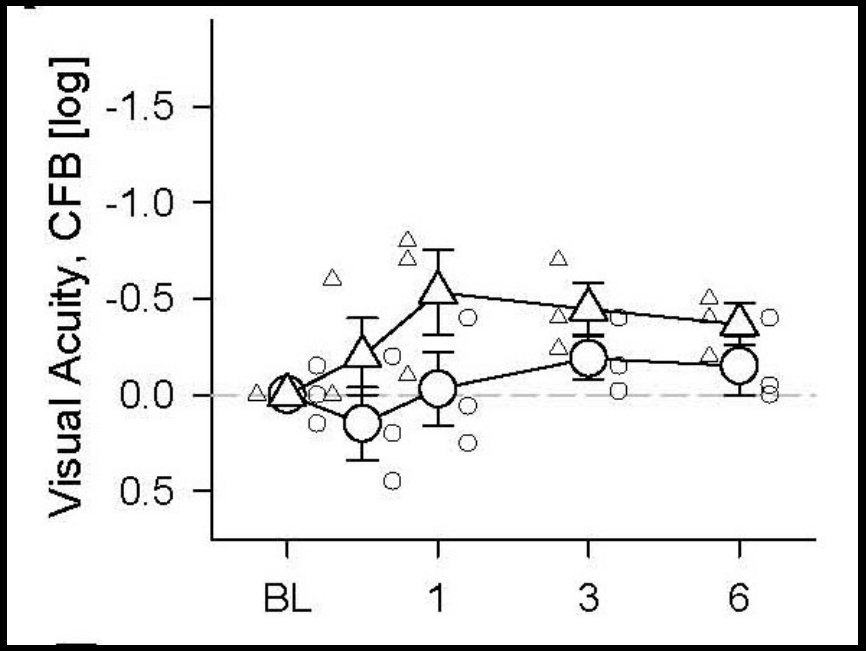
- Average 1.5 log unit gains in cone-mediated sensitivities in all three patients compared to baseline (BL) and contralateral control eye.
- Sensitivity gains reached normal limits (gray bands)

Pupillometry Objectively Confirms Efficacy



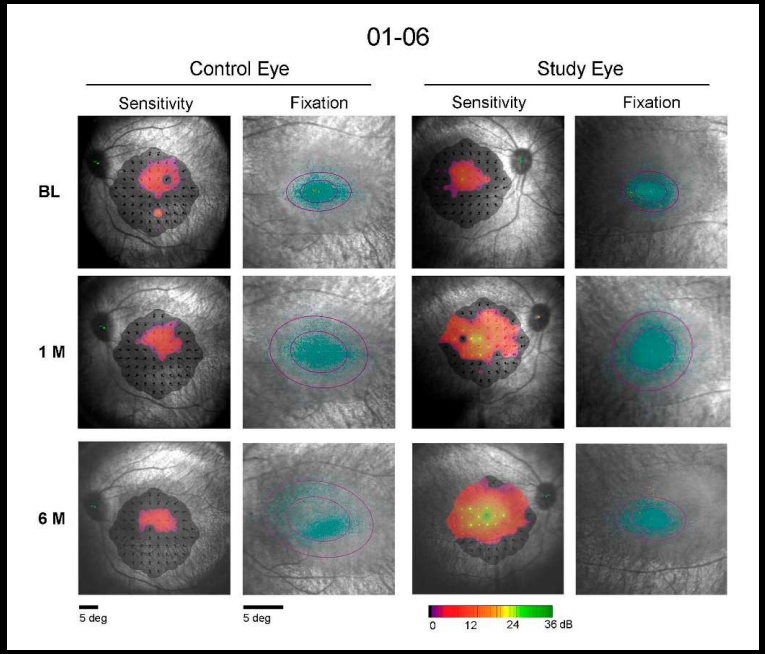
- Dark-adapted pupil responses show better Amplitude and Latency Thresholds.

Visual Acuity Gains



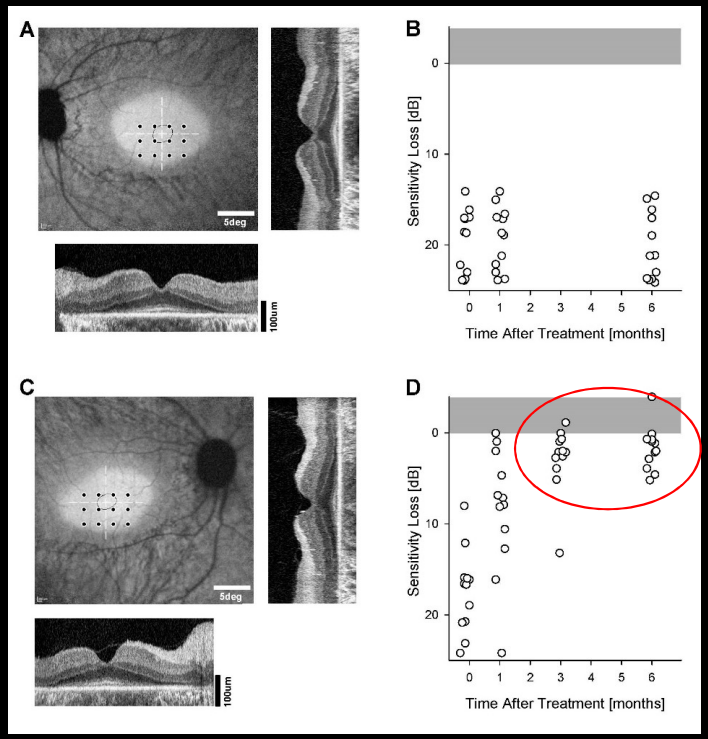
- On average better VAs in treated compared to baseline (BL) and untreated eye.

Restoration of the Fovea
Retina Tracking Perimetry [01-06]



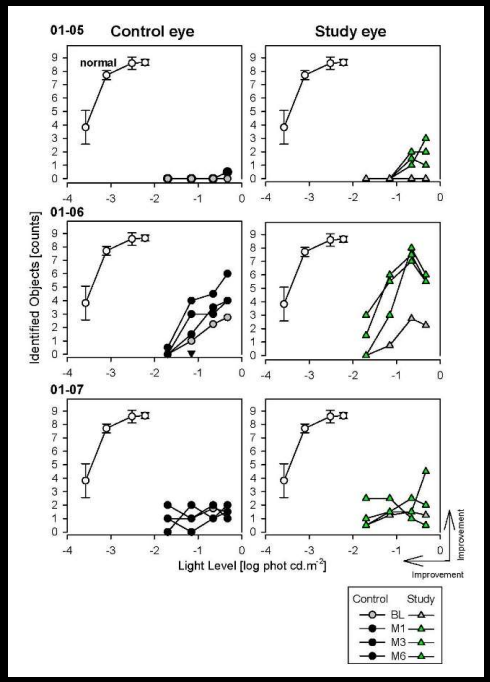
- Sensitivity gain post-treatment; no changes in control eye.
- Nearly double the area of detectable sensitivities post-treatment in study eye.

Restoration of the Fovea
Retina Tracking Perimetry [01-06]



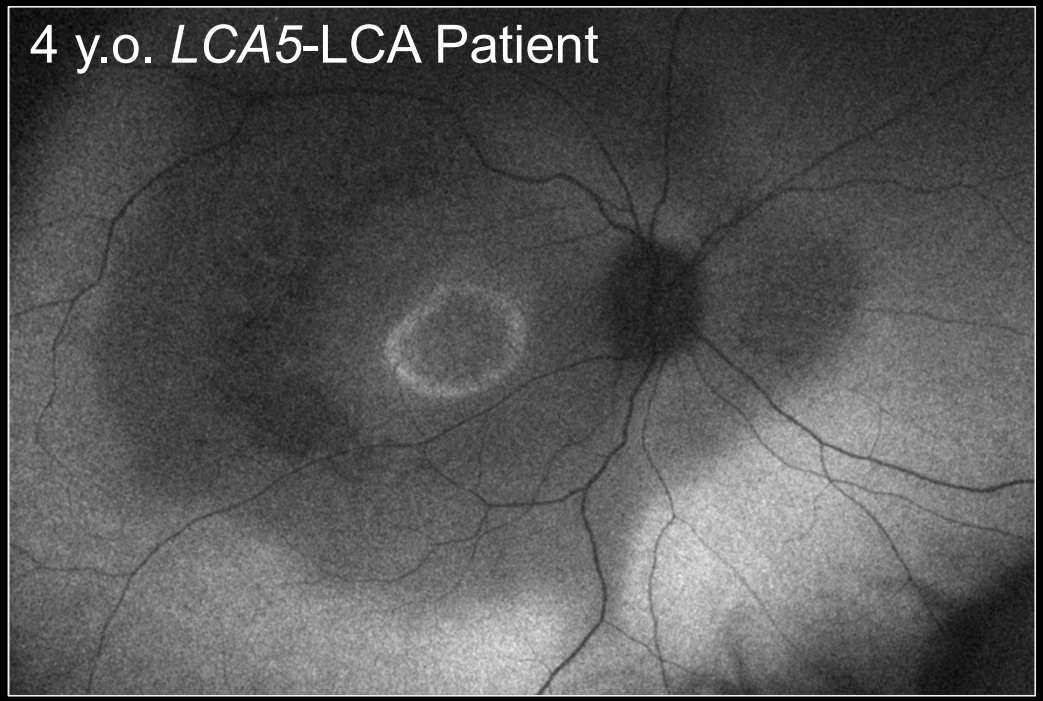
- Improvement post-treatment in study eye, no changes in control eye.
- Sensitivity gains reached normal limits (gray bands)

Functional Vision by D-MMLT



- Improved orientation and mobility (green up triangles) detected from earliest time in at least two of three patients.
- All patients reported improvements in their daily visual function.

Next steps: treat early vs just more patients?



Conclusions:

- Gene augmentation in LCA5 demonstrated complete and unprecedented recovery of the primary photon catching ability of cones.
- The finding provides the foundation for complete restoration of more complex attributes of vision.