Comparison of Retinal Degeneration in *GUCY2D*- and *CRX*-related Autosomal Dominant Cone-Rod Dystrophy

Gurbani Kaur[1,2], Jessica Wong[2], Stephanie Duret[2], Austin Roorda[3], Jacque L. Duncan[2]

[1]School of Medicine, University of California San Francisco, San Francisco, CA, United States

[2]Department of Ophthalmology, University of California, San Francisco, CA, United States

[3]Herbert Wertheim School of Optometry & Vision Science, University of California, Berkeley, Berkeley, CA, United States

Introduction

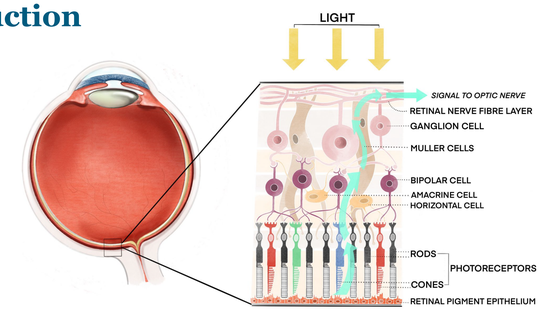


Figure 1: Schematic of Retinal Cell Layers (Adapted from Retina-Gene Vision)

• *GUCY2D* and *CRX* mutations are the most common causes of autosomal-dominant cone-rod dystrophy (AD-CRD).[1,2]

• *GUCY2D* encodes a protein that modulates restoration of photoreceptors to the dark state after light exposure through regulation of calcium metabolism.[3]

• *CRX* encodes the cone-rod homeobox transcription factor that supports maturation and maintenance of photoreceptor cell fate necessary for vision preservation.[4]

• We compared cone structure and function in patients with *GUCY2D*- and *CRX*-related AD-CRD using multimodal high-resolutioon retinal imaging.

Methods

Study Design

• Comparative, Single-Center, Cross-Sectional Study

Subjects

• AD-CRD (16 eyes of 8 patients): *GUCY2D* (8 eyes of 4 patients); *CRX* (8 eyes of 4 patients)

Outcome Measures

• Age, sex, genetic mutation, visual acuity, refractive error and clinical signs and symptoms of CRD.

• Color and short-wavelength autofluorescence fundus photos and spectral domain optical coherence tomography (SD-OCT) were analyzed.

• Cone images were acquired using confocal and split-detector adaptive optics scanning laser ophthalmoscopy (AOSLO) from one patient with each form of CRD.

Statistical Analysis

• Cone spacing was derived using a density recovery profile histogram method and analyzed as Z-scores, or standardd deviations from the normal mean at the eccentricity of measured cones; <2 was within normal limits.

• Differences between groups were assessed by Student's t-test (GraphPad PRISM-9).

Results

Patient	Age	Sex	Mutation	Effect on Protein	Pathogenicity	BCVA (OD, OS)	Refractive Error (sphere, cylinder, axis) [OD, OS]
*GUCY2D*_1	67	F	GUCY2D c.2707G>T	p.Asp903Tyr	Likely Pathogenic	20/200, 20/250	-10.00,+1.00,x070; -9.50,+0.75,x060
*GUCY2D*_2	55	F	GUCY2D c.2513G>A	p.Arg838His	Pathogenic	20/200, 20/160-	-1.00, -2.25, 170; +1.25, -2.75, 175
*GUCY2D*_3	30	F	GUCY2D c.218C>T	p.Pro73Leu	Likely Pathogenic	20/80-1, 20/100+1	-10.75,+3.25,x110; -9.00,+3.00,x067
*GUCY2D*_4	32	M	GUCY2D c.2512C>T	p.Arg838Cys	Pathogenic	20/100slow-1, 20/80slow-3	-5.50,+1.00, 090; -5.50, +1.50, 080
*CRX*_1	46	F	CRX c.118C>T	p.Arg40Trp	Pathogenic	20/30-2, 20/40-2	Former myope, s/p LASIK OU
*CRX*_2	42	F	CRX c.128G>A	p.Arg43His	Likely Pathogenic	20/30-1,20/300	-4.00+1.75x 112; -4.00+1.25x066
*CRX*_3	38	F	CRX c.262-275del	p.Lys88*	Pathogenic	20/25-3, 20/20-2	-1.50 DS; -1.75DS
*CRX*_4	38	F	CRX c.206G>A	p.Arg69His	Likely Pathogenic	20/100, 20/80	-4.00+0.75x080; -3.50+0.75x085

Table: Genetic and Clinical Characteristics of Study Participants

Patient: *GUCY2D*_1 **Patient: *CRX*_3**

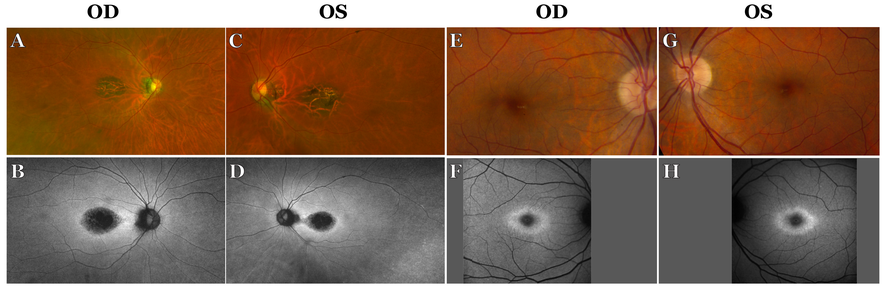


Figure 2: Color Fundus Photos (top row) and Short-Wave Autofluorescence Photos (bottom row) of Eyes of a Patient with *GUCY2D*- (A-D) and *CRX*-related (E-H) AD-CRD.

Patient: *GUCY2D*_4 **Patient: *CRX*_4**

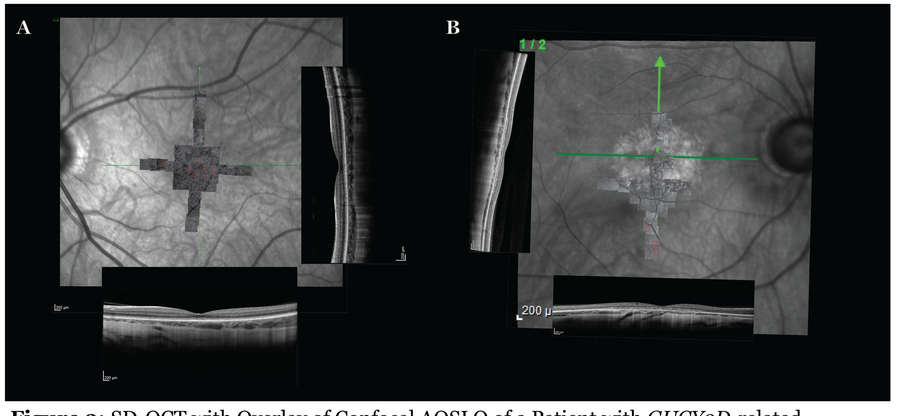
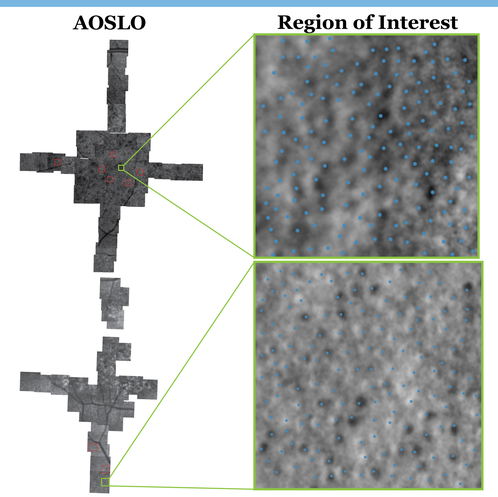


Figure 3: SD-OCT with Overlay of Confocal AOSLO of a Patient with *GUCY2D*-related AD-CRD (Panel A, OS) and *CRX*-related AD-CRD (Panel B, OD).

Patient: *GUCY2D*_4 OS

Patient: *CRX*_4 OD



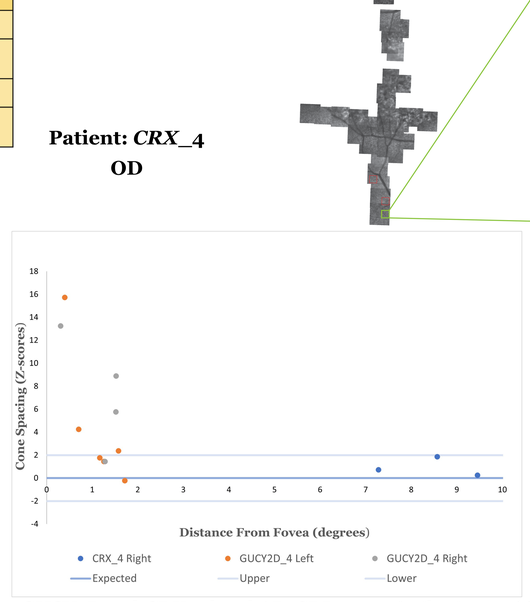


Figure 4: AOSLO montages (left column), AOSLO Split Detector magnified images at Selected Region of Interest (right column), and Graph of Cone Spacing (Z-scores) vs. Distance from Fovea (degrees) (bottom panel).

• *GUCY2D* and *CRX*-related AD-CRD were similar in age (*GUCY2D* mean ± std dev 51.3 ± 17.8 years; *CRX* 41.0 ± 3.8, $P = 0.3$).

• Visual acuity ($P = 0.013$), myopic refractive error ($P = 0.0075$), and cone spacing (5.2 +/- 5.3; n =10 regions) were significantly more abnormal in patients with *GUCY2D* compared to *CRX*-related AD-CRD

Conclusions

• Patients with *GUCY2D*-mutations had significantly worse visual acuity, greater myopic refractive error, and more abnormal cone spacing relative to similarly aged patients with *CRX* mutations.

• High resolution retinal imaging showed cone loss in all patients with AD-CRD (AOSLO) may serve as a powerful tool in monitoring patients with *GUCY2D*- and *CRX*-related AD-CRD.

References

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