An Unusual Pigmentary Retinopathy

Take Heart in the Diagnosis!

Retina Society Annual Conference
Interesting Cases
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I have no financial interests in the topic presented.

Summary Slide

11-year-old asymptomatic female presented with an unusual peripheral pigmentary retinopathy, symmetric and bilateral. Three years later, she underwent a cardiac transplant secondary to hypertrophic cardiomyopathy. Whole exome sequencing helped to link the retinal findings and the cardiac condition, confirming the diagnosis.

At presentation

HPI: 11 y.o. referred to the University of North Carolina (UNC) Ocular Genetics clinic from an outside ophthalmologist for further evaluation of peripheral retinal pigmentation and concern for retinitis pigmentosa (RP)

At presentation

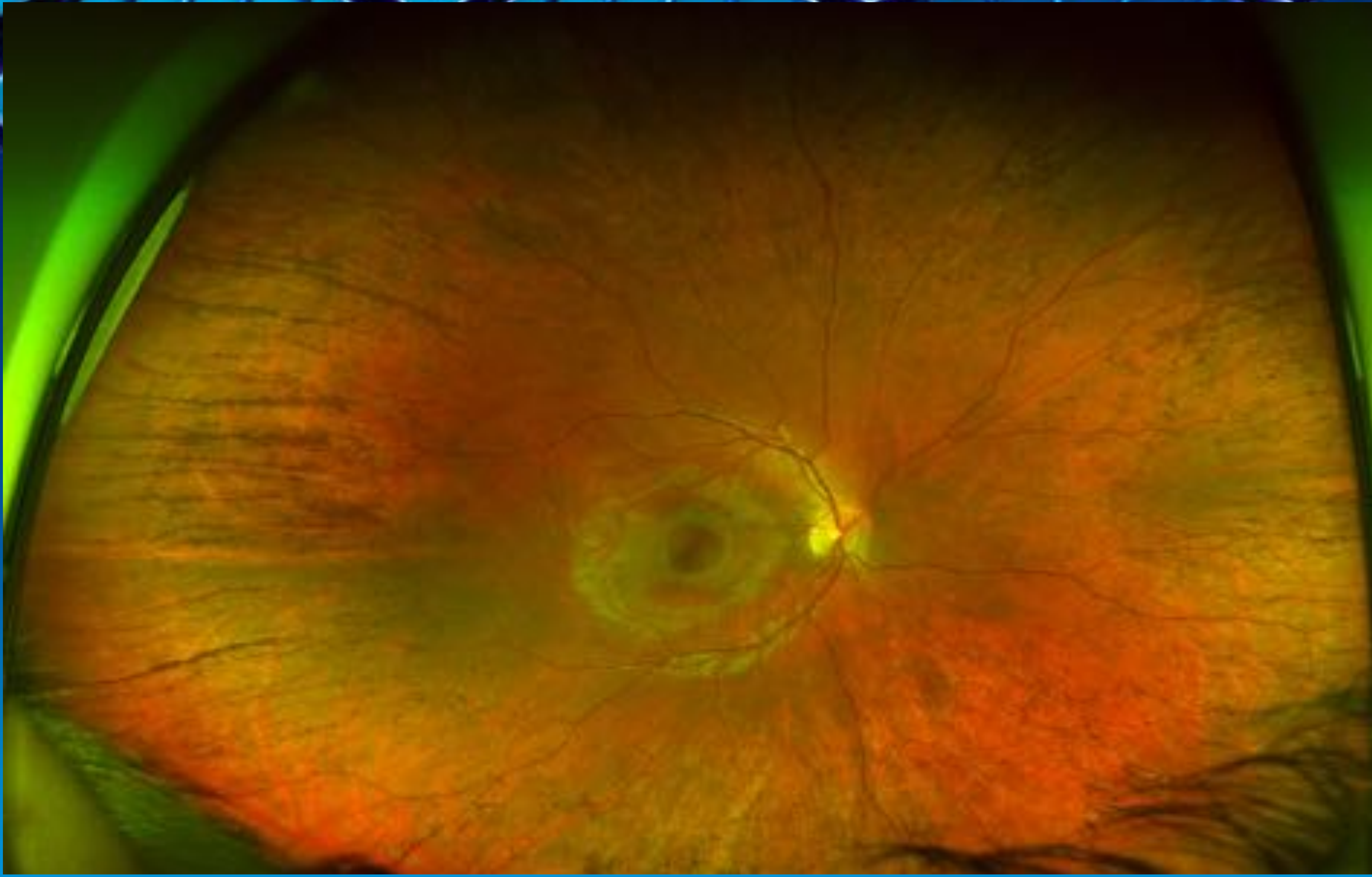
- No history of nyctalopia, decreased peripheral vision, difficulty differentiating colors, light hypersensitivity, or hearing loss
- POH: myopia (glasses since the age of 6)
- PMH: uncomplicated NSVD, no history of birth defects, met all developmental milestones. She has mild cognitive delay (confirmed on Differential Ability Scales - DAS II testing)

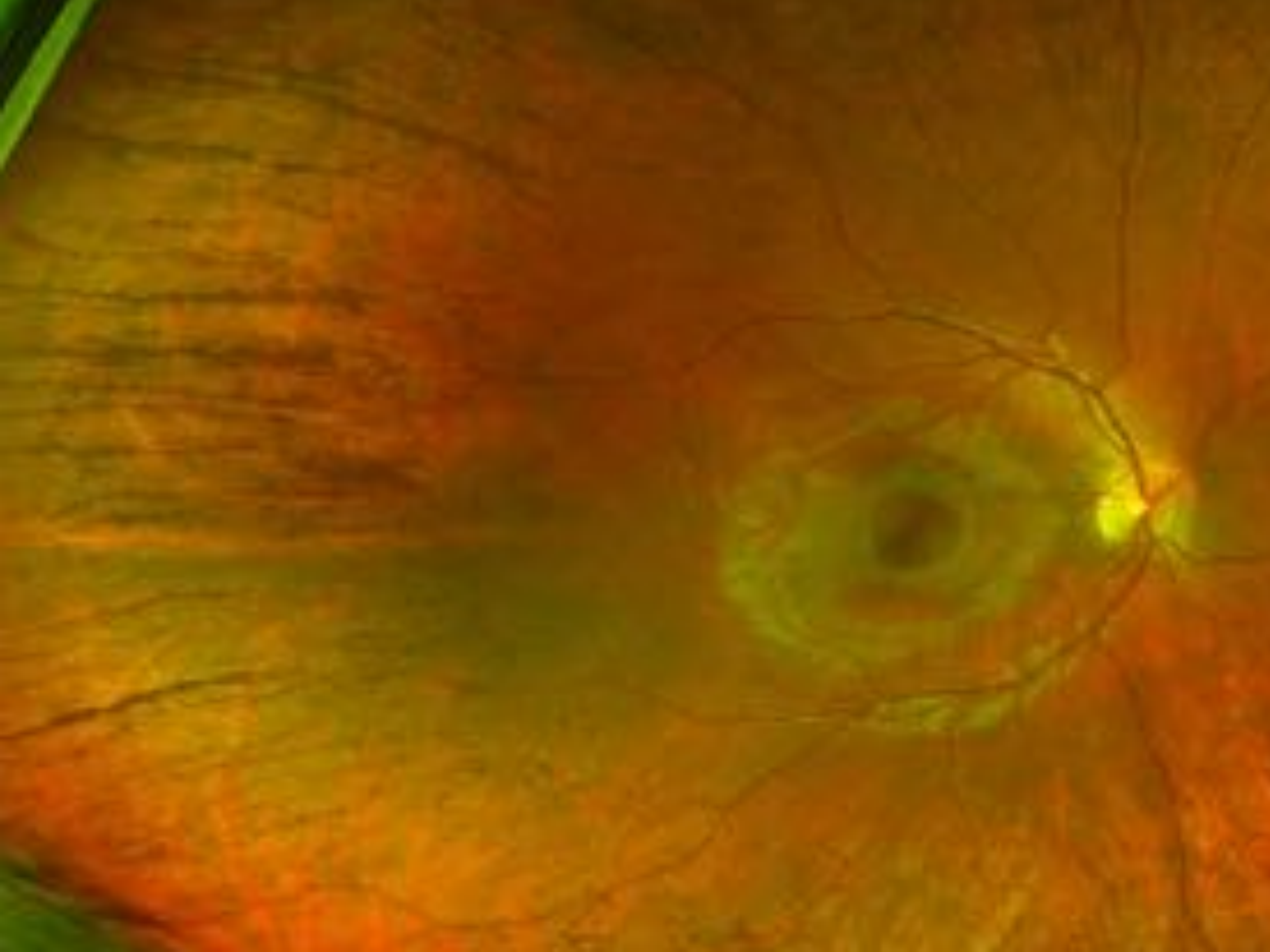
At presentation

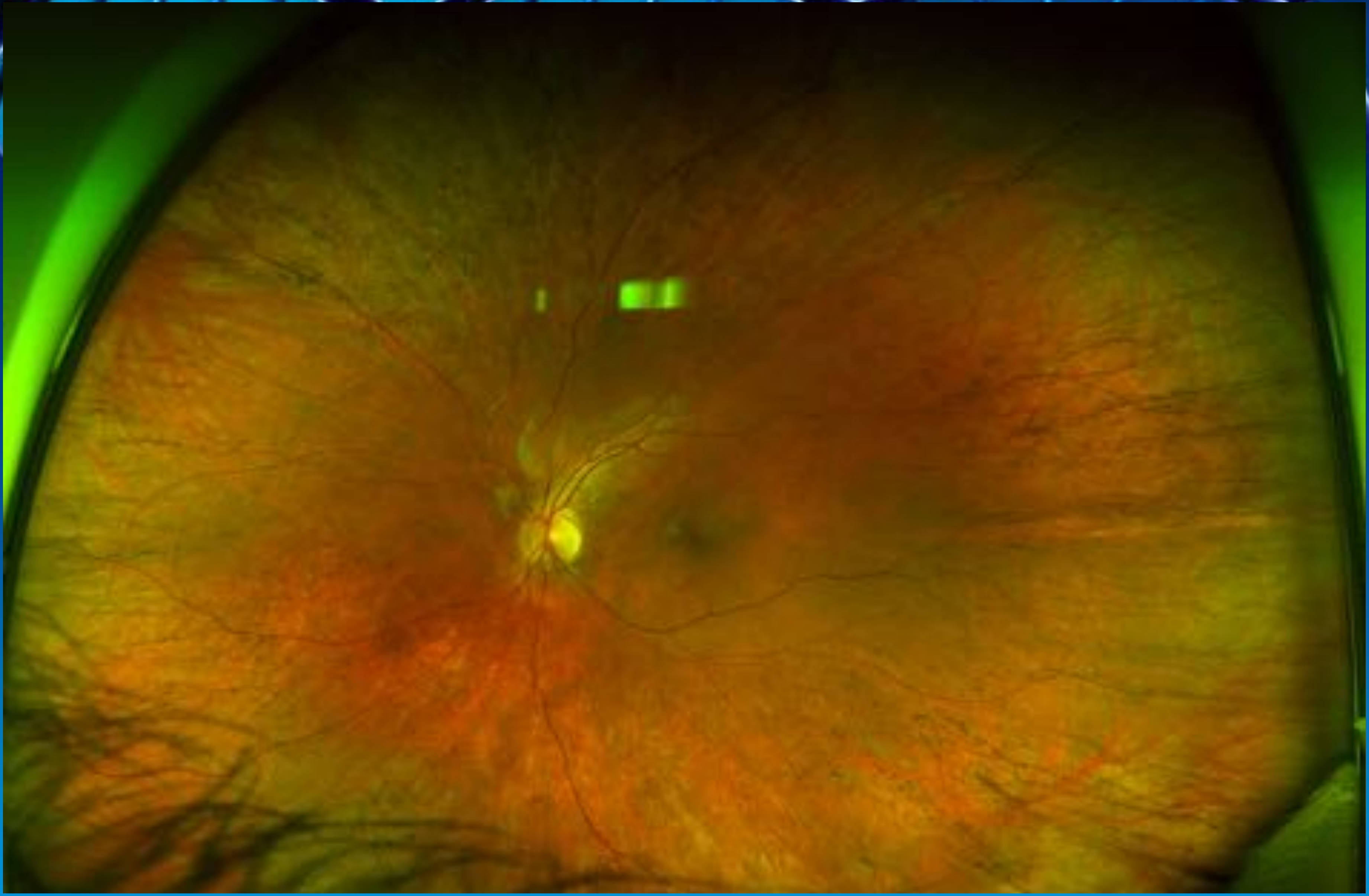
- Meds: none
- ROS: negative for cardiac or skeletal muscle complaints
- SOCIAL HISTORY: 5th grade. Lives with parents and older brother
- FAMILY HISTORY: Unknown, since patient was adopted in infancy.   Only birth records were available.

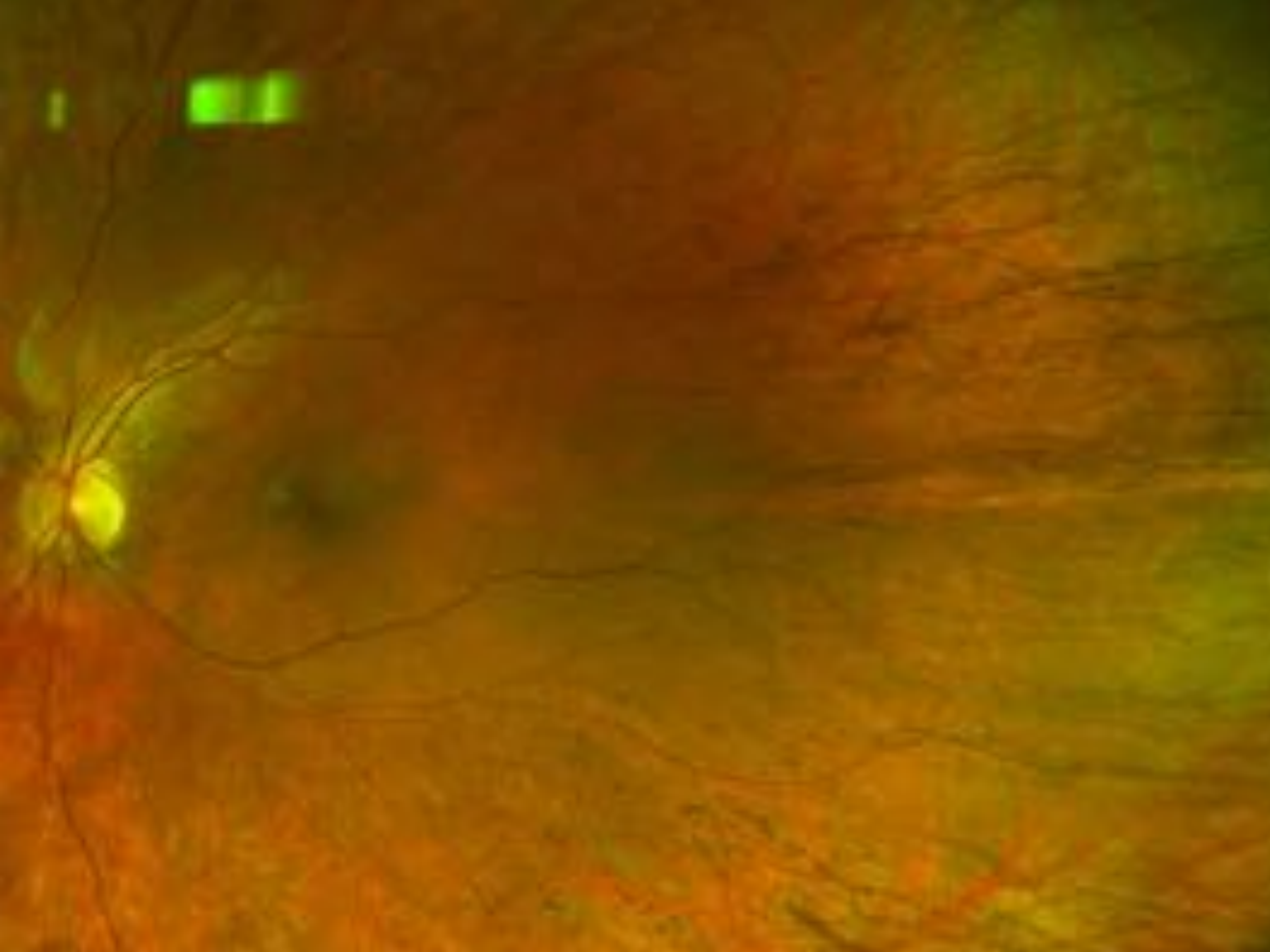
Ocular examination

- V_a (cc) $20/20^{-2}$ OD; $20/25^{-1}$ OS
- MRx:
  - OD -5.25 +2.5 @ 094
  - OS -5.25 +2.75 @ 080
- Pupils: No APD OU
- IOP (T_a): 18 OD, 15 OS
- Anterior segment WNL with no vitreous cell OU
- Fundus exam: linear peripheral pigmentation

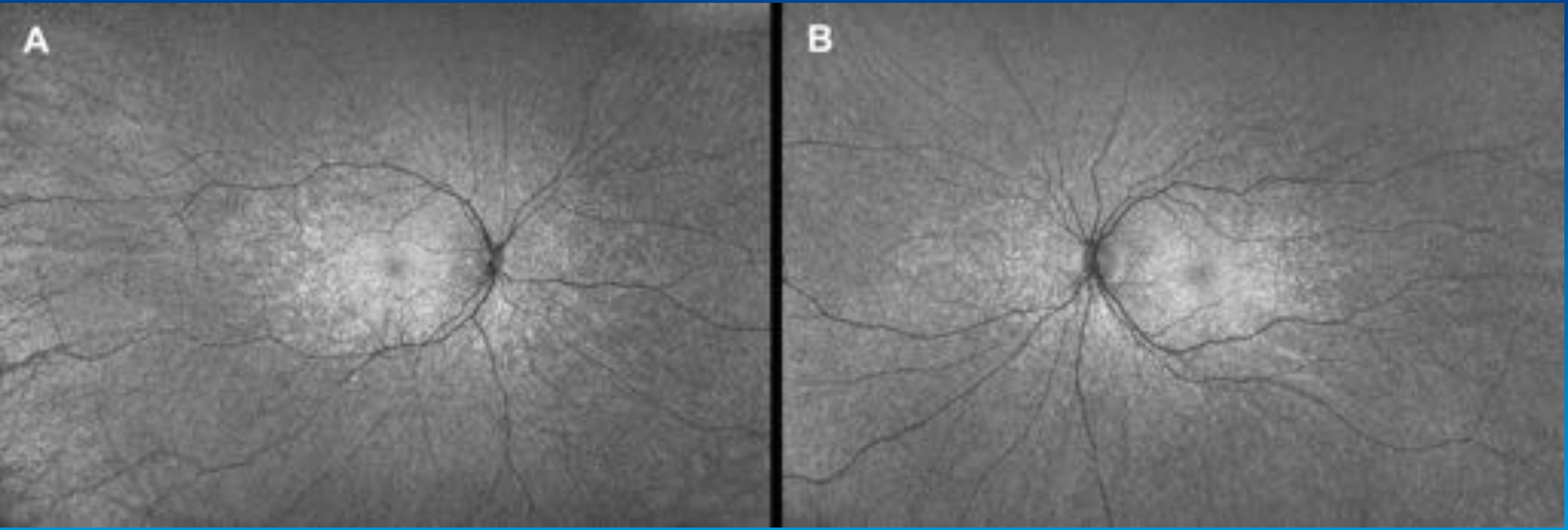




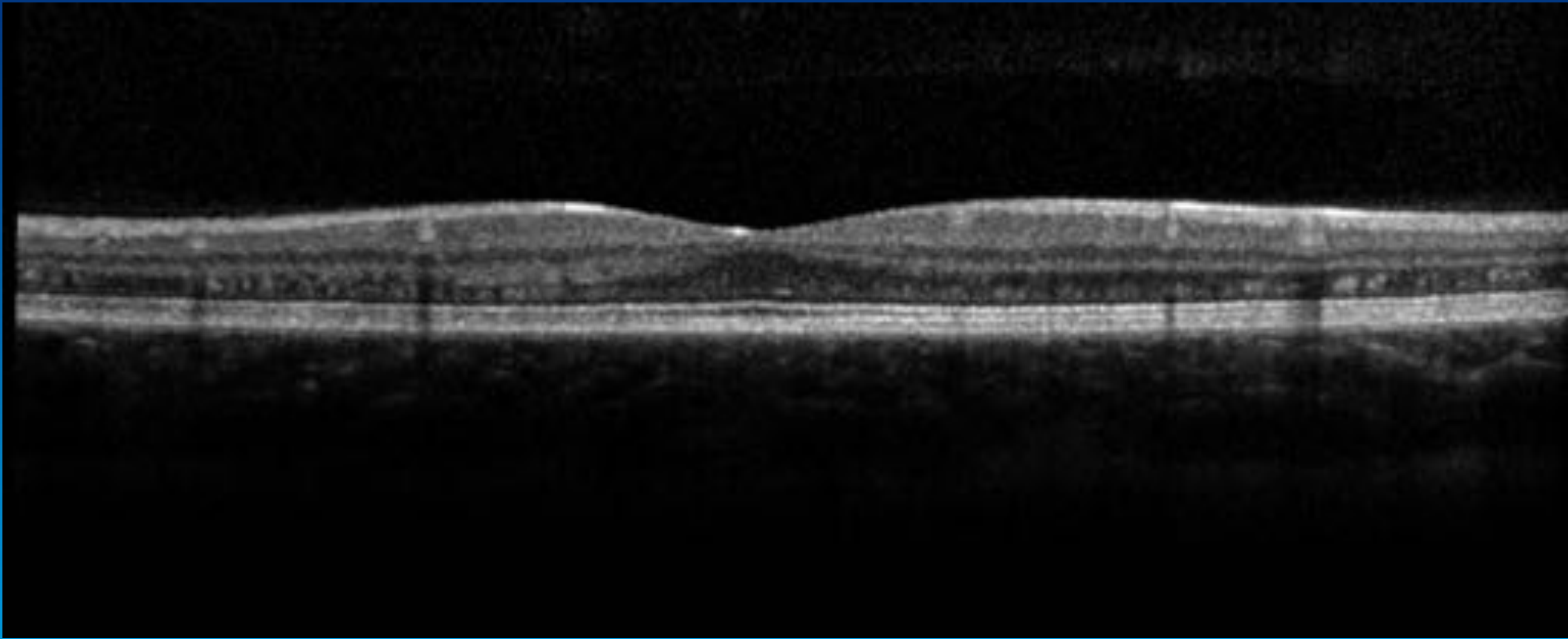


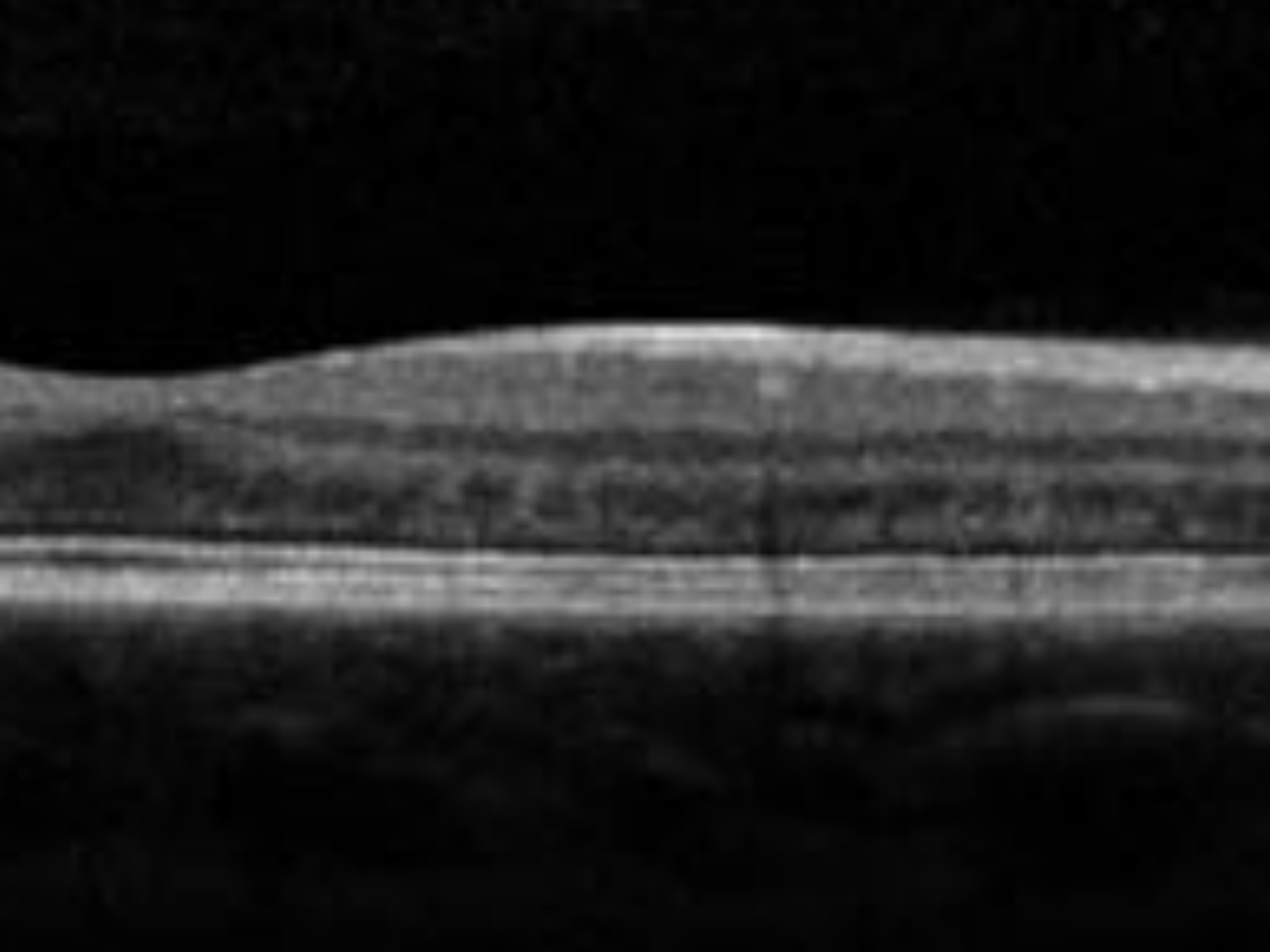


Fundus Autofluorescence

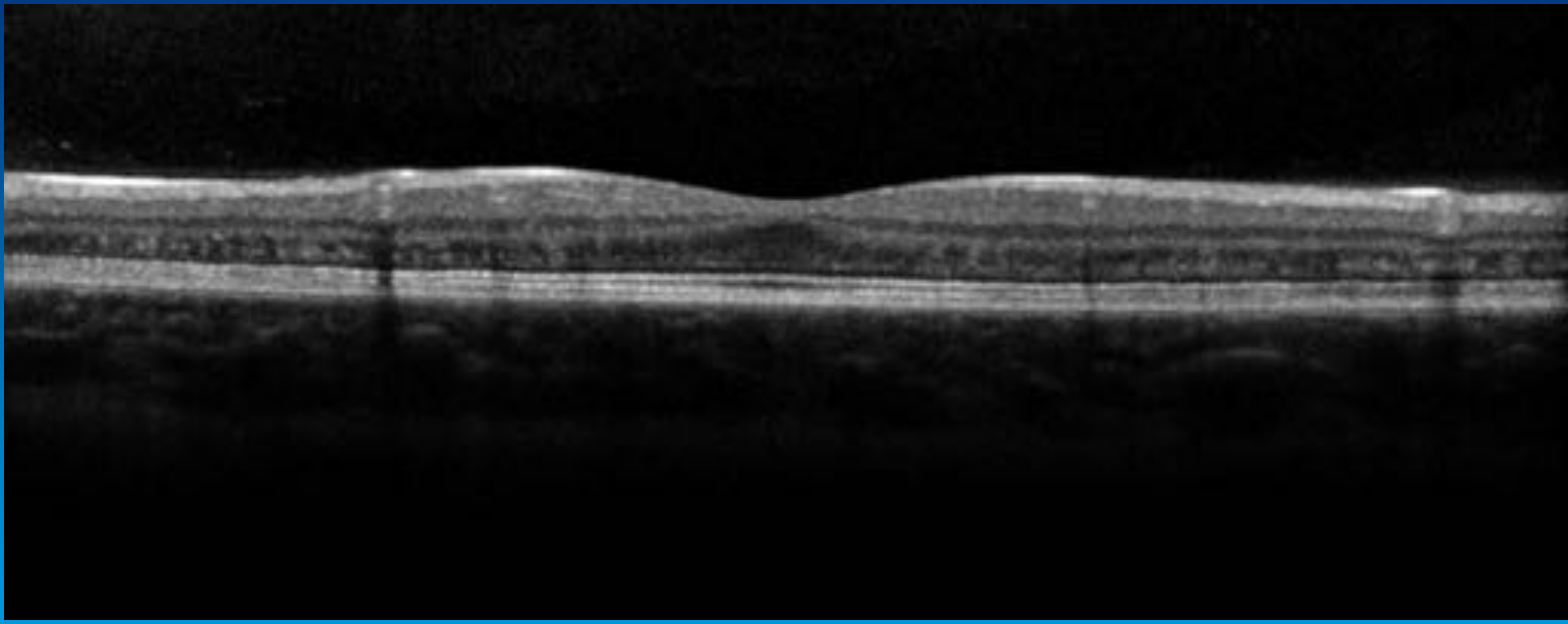


SD-OCT: OD

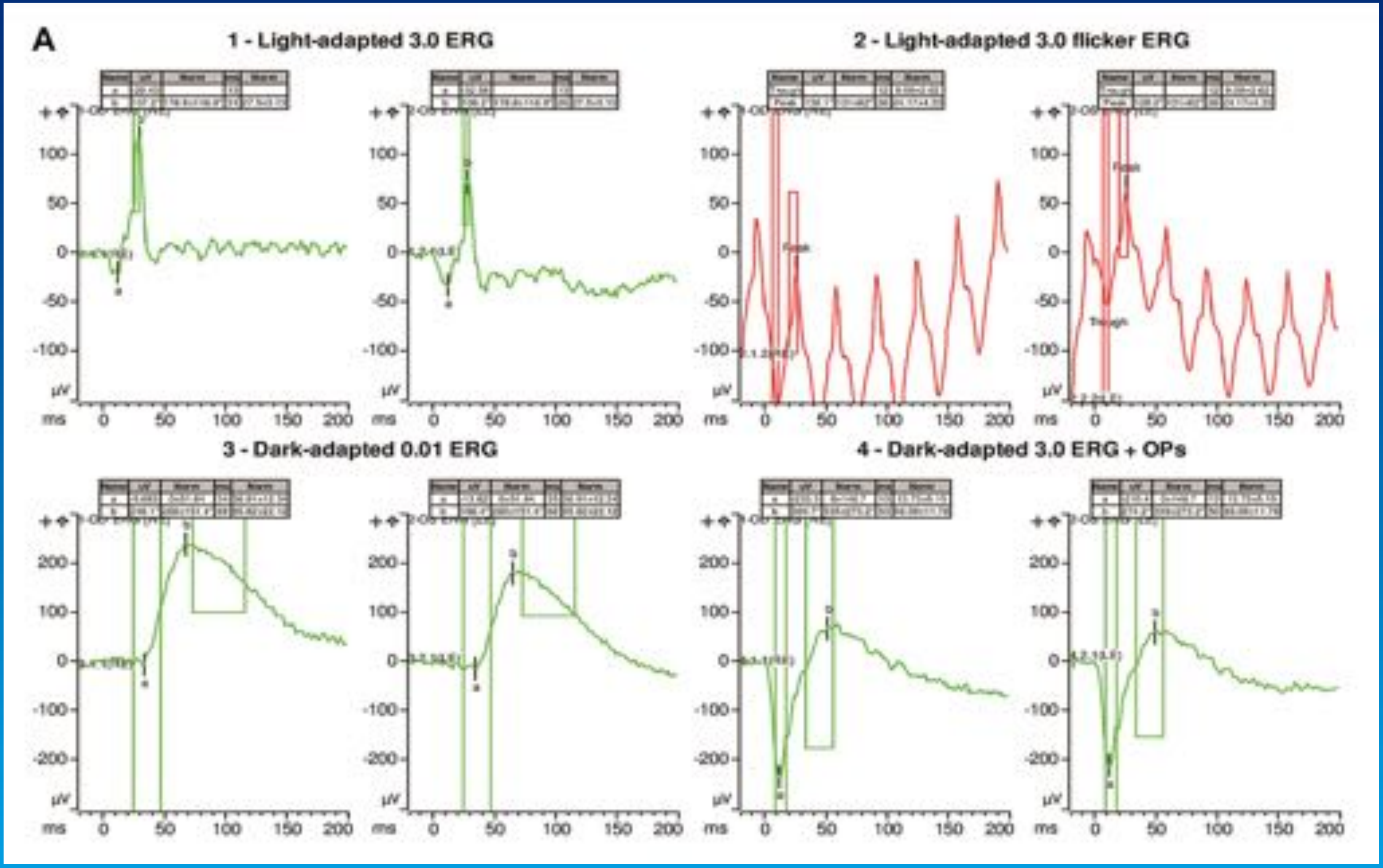




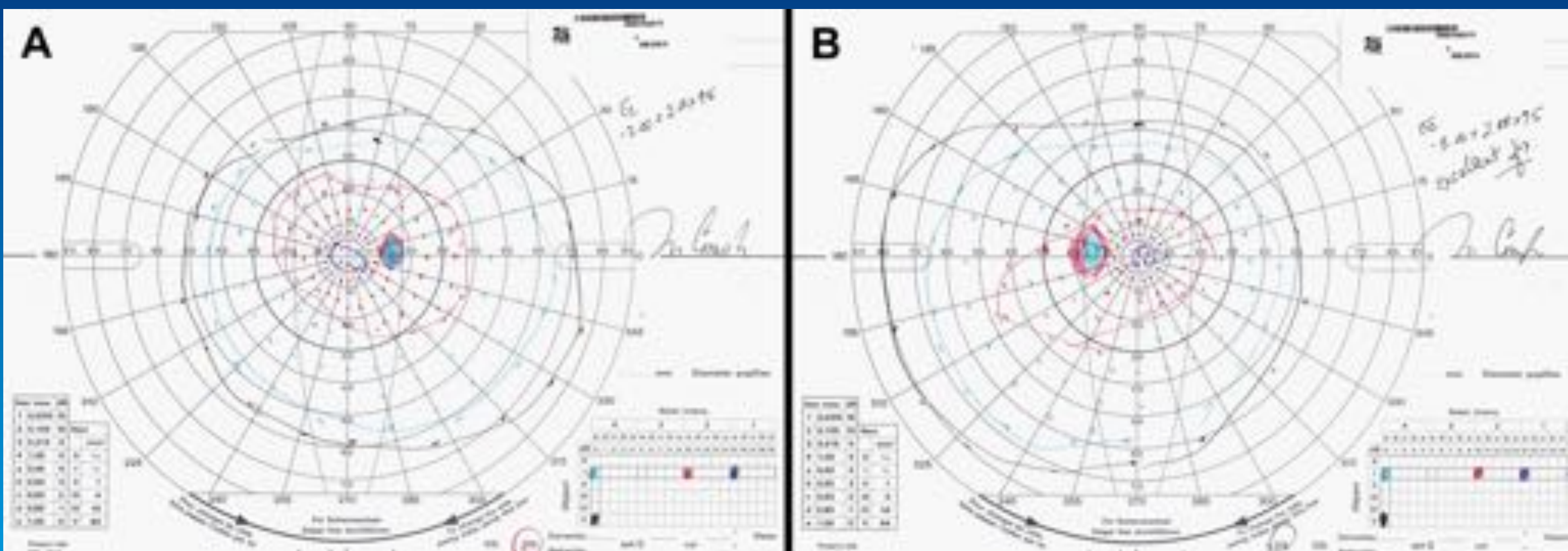
SD-OCT: OS



Full-field Electroretinogram



Goldman Visual Field



Genetic testing

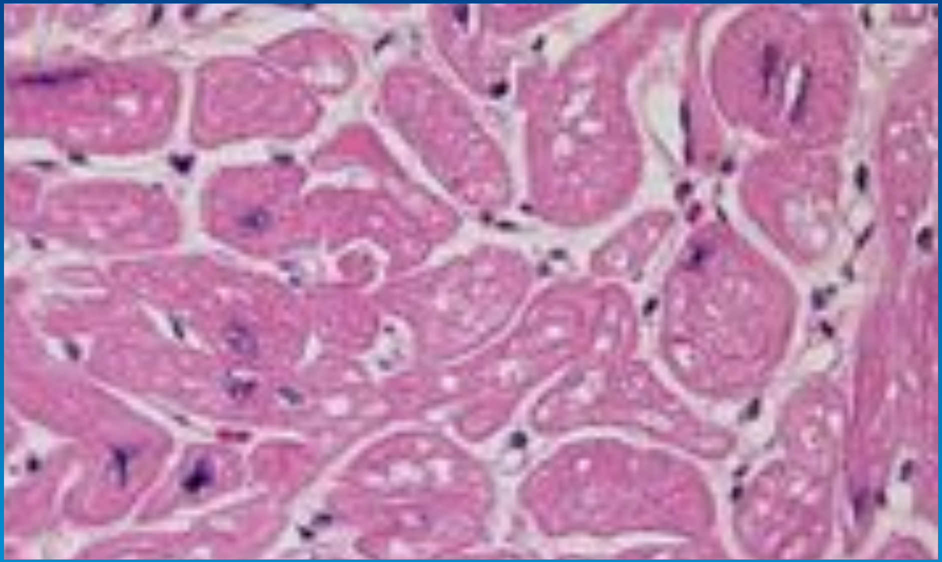
- Symptoms, exam, ancillary tests NOT consistent with RP
- With no known FH, dystrophy genetic panels had low diagnostic yield
- Since patient was asymptomatic, family declined genetic testing and opted for annual ophthalmic surveillance

Clinical course

- At age 12, patient developed nonspecific chest discomfort, initially diagnosed as gastroesophageal reflux disease (GERD)
- At age 14, she experienced acute congestive heart failure
- Within weeks, she underwent cardiac transplantation

Pathology Report

"Hypertrophic cardiomyopathy with extensive replacement fibrosis and myocyte vacuolization, mixture of glycogen, granular dark-staining material and degenerative lipid and lamellar debris"



Taylor, et al. Danon disease presenting with dilated cardiomyopathy and a complex phenotype. *J Hum Genet*.2007;52(10):830-835. doi:10.1007/s10038-007-0184-8

Genetics

- Cardiac genetics consultation at Carolinas Medical Center in Charlotte, NC
- Whole Exome analysis –> *LAMP2* mutation: c.815T>G; p.Leu272Arg
- Constellation of mild cognitive delay, peripheral retinal pigmentation, acute congestive heart failure, the cardiac pathology report and the LAMP2 mutation…

DANON DISEASE

Danon Disease

- caused by deficiency of lysosome-associated membrane protein 2 (*LAMP2*), important for degradation of autophagic material
- Classic triad of cardiomyopathy, skeletal myopathy and intellectual disability
- X-linked Dominant -- males develop symptoms earlier and are more severely affected

CLINICAL MANIFESTATIONS:	M (%)	F (%)
Cardiomyopathy Normally hypertrophic	100	61-100
Electrical cardiac abnormalities WPW most commonly (69% in M and 27% in F)	86-100	80-100
Myopathy From asymptomatic to wheelchair dependent Mild proximal weakness (shoulder, neck, and legs) most common	80-90	33-50
Intellectual disability (ID) Usually mild	70-100	6-47
Ocular disease (all forms)	69	64

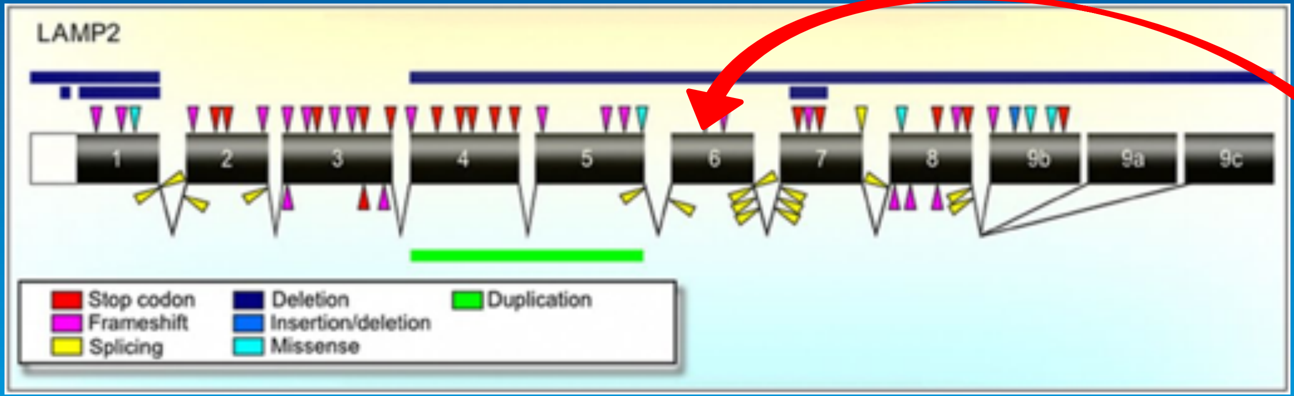
D'Souza R S, et al. Danon disease: clinical features, evaluation, and management. Circulation Heart failure 2014;7:843-9

Ocular manifestations

- Very few reports of ocular abnormalities in literature, first described in 2002
- LAMP2 mutation causes retinal pigment epithelial dysfunction leading to
  - peripheral pigmentary retinal dystrophy (PPRD)
  - “bull’s eye maculopathy”
  - cone-rod dystrophy

Genetics

- Point mutations, small deletions or insertions, and splicing mutations have all been identified on Xq24
- X- linked dominant with variable expressivity
  - Mosaicism is reported!
    - Likely contributes to the **SIGNIFICANT phenotypic variability** seen, even within families
  - Skewed X-inactivation (lyonization) in females



Our patient's mutation:

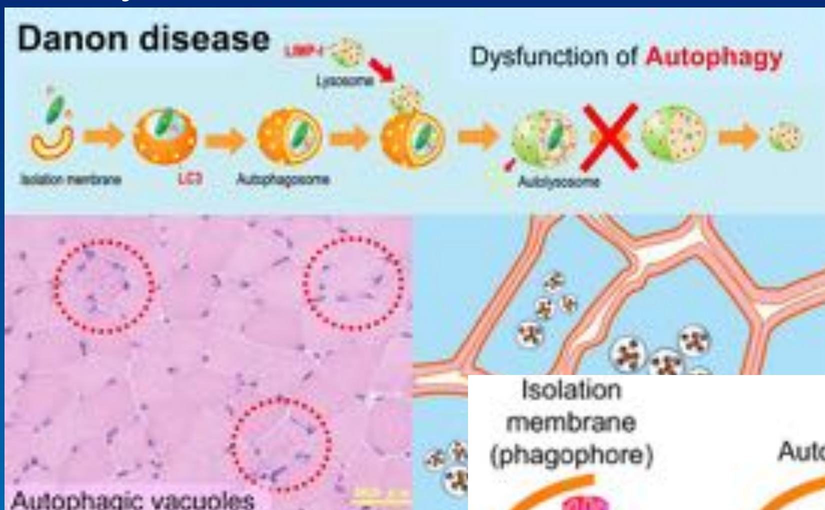
LAMP2 c.815T>G; p.Leu272Arg

A missense mutation on exon 6

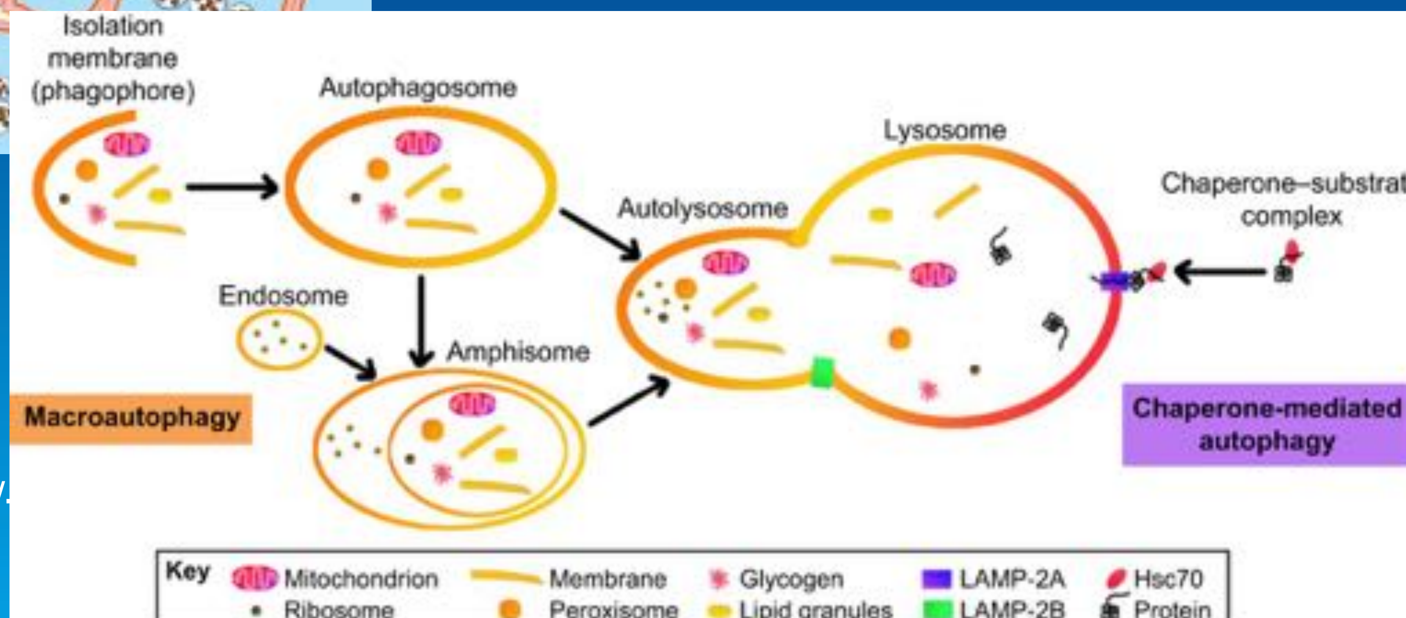
D'Souza R S, et al. Danon disease: clinical features, evaluation, and management. Circulation Heart failure 2014;7:843-9.

Pathogenesis simplified:

- LAMP2 = protein in membrane of lysosomes



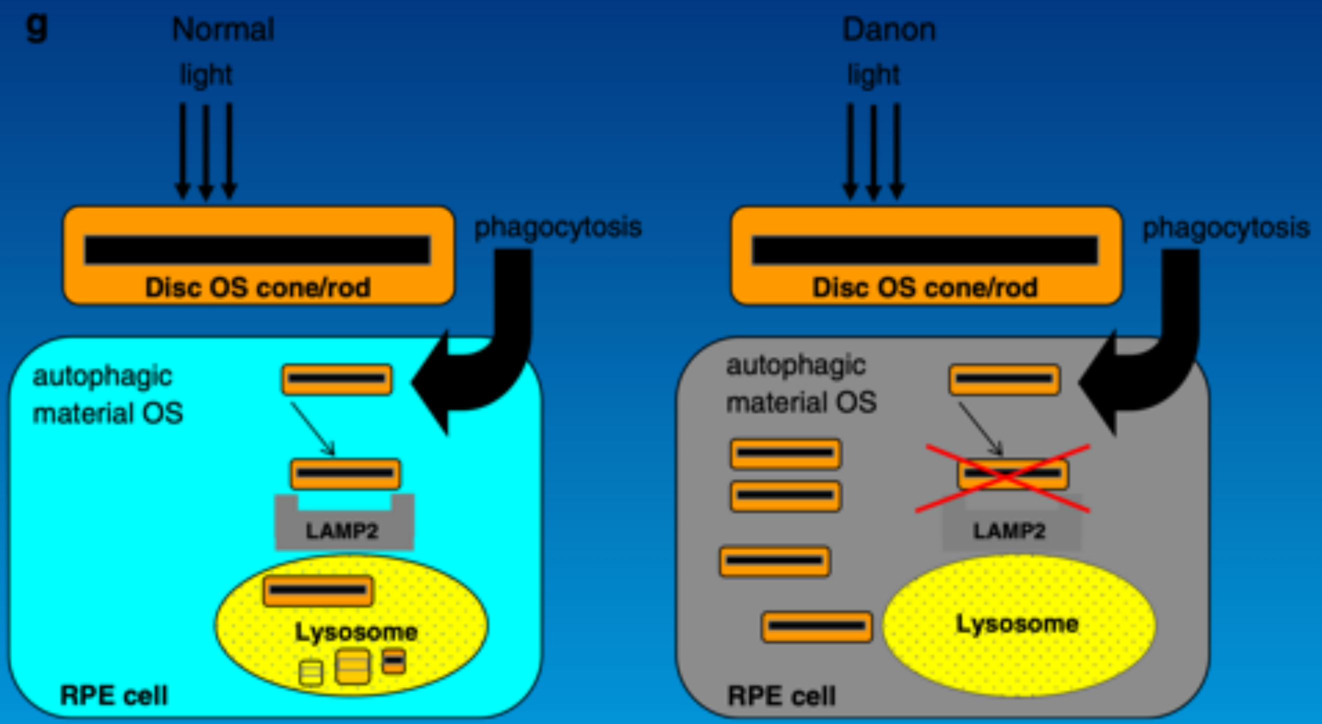
- Disruption of lysosome fusion processes
- Autolysosome formation and function is perturbed
- Accumulation of damaged mitochondria, proteins and glycogen
- Cell damage



Rowland TJ, et al. Danon disease - dysregulation of autophagy in a multisystem disorder with cardiomyopathy. Journal of cell science 2016;129:2135-43.

Pathogenesis in the eye

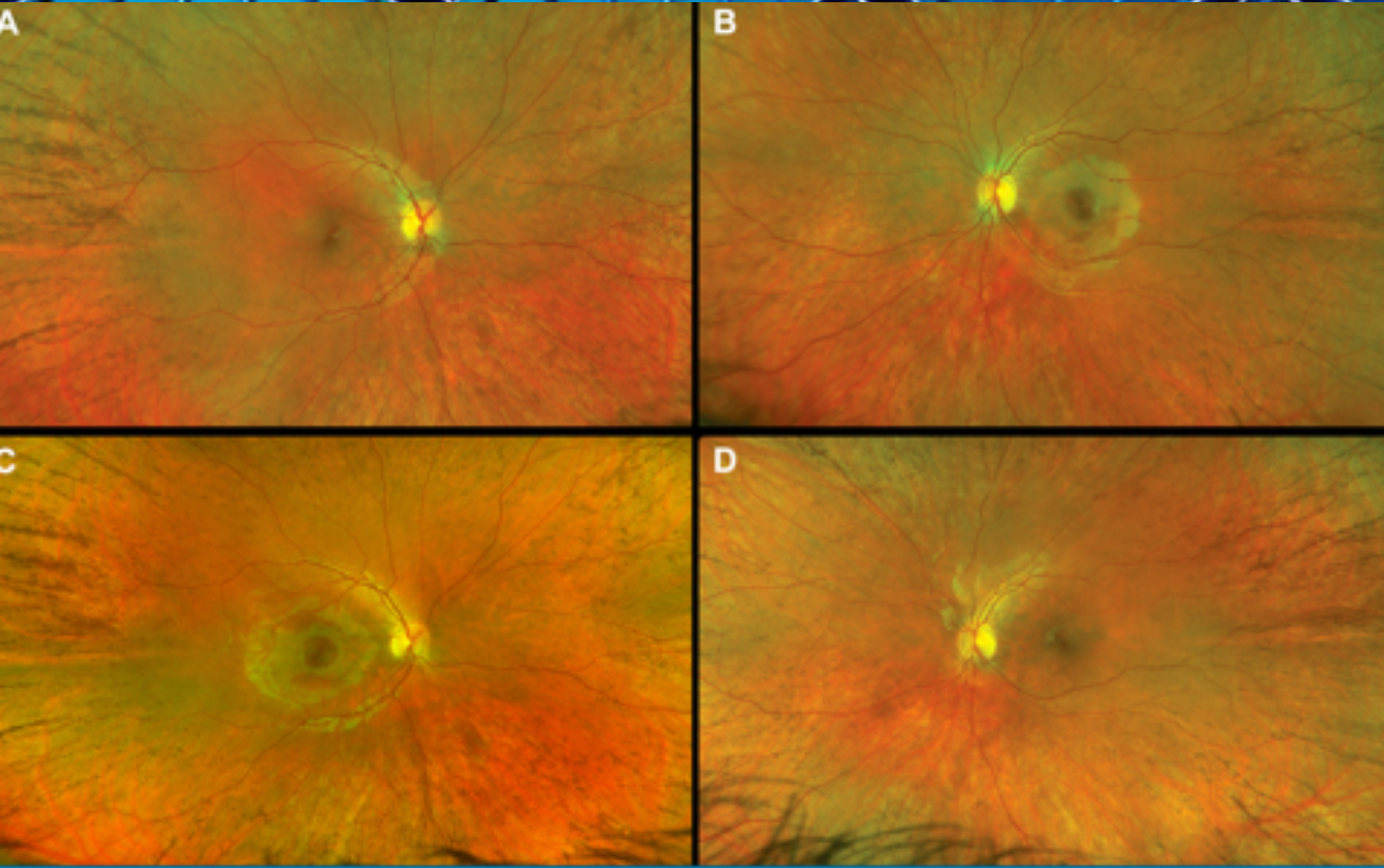
Mutation in LAMP-2 → RPE lysosome dysfunction → accumulation of deposits -> RPE damage → degeneration of cone and rod photoreceptor cells



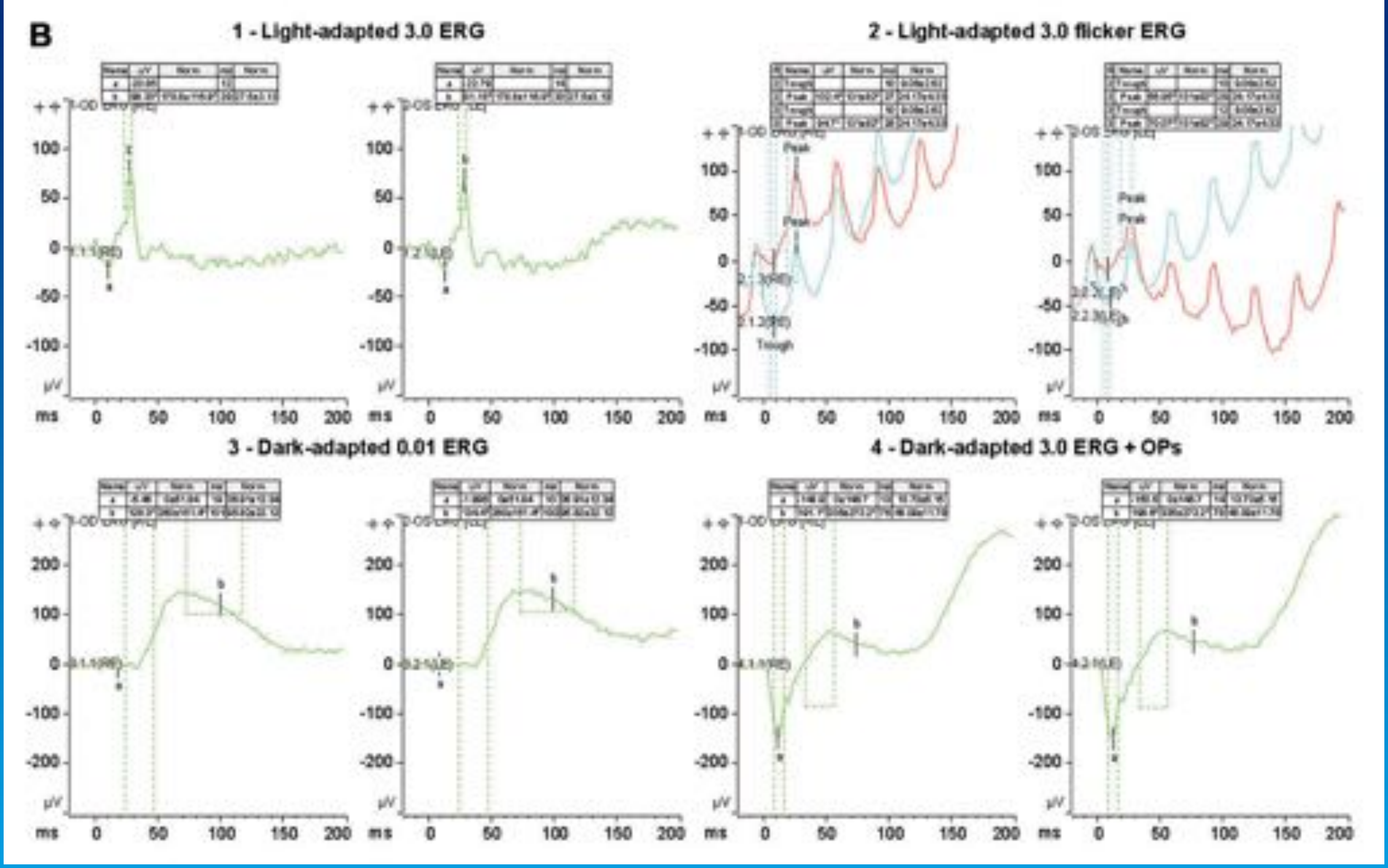
Thiadens AA, et al. Cone-rod dystrophy can be a manifestation of Danon disease. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2012;250:769-74.

F/U - Patient is now 15 y.o.

- Doing well, 1 year s/p cardiac transplant
- ROS still negative for skeletal muscle weakness
- BCVA still 20/25 OU
- OCT - stable thinning of the outer retinal layers, stable CMT OU
- Retina - increase in linear pigmentation


A
B
C
D

Full-field Electroretinogram



Conclusion

- Case demonstrates importance of considering Danon disease in differential diagnosis of atypical peripheral pigmentary retinopathy, even in females
- Since retinopathy often presents *before* signs of cardiomyopathy, early identification and confirmatory genetic testing by retina specialists could improve prognosis

References

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