National Institute for Health Research

UC

Inherited retinal disease

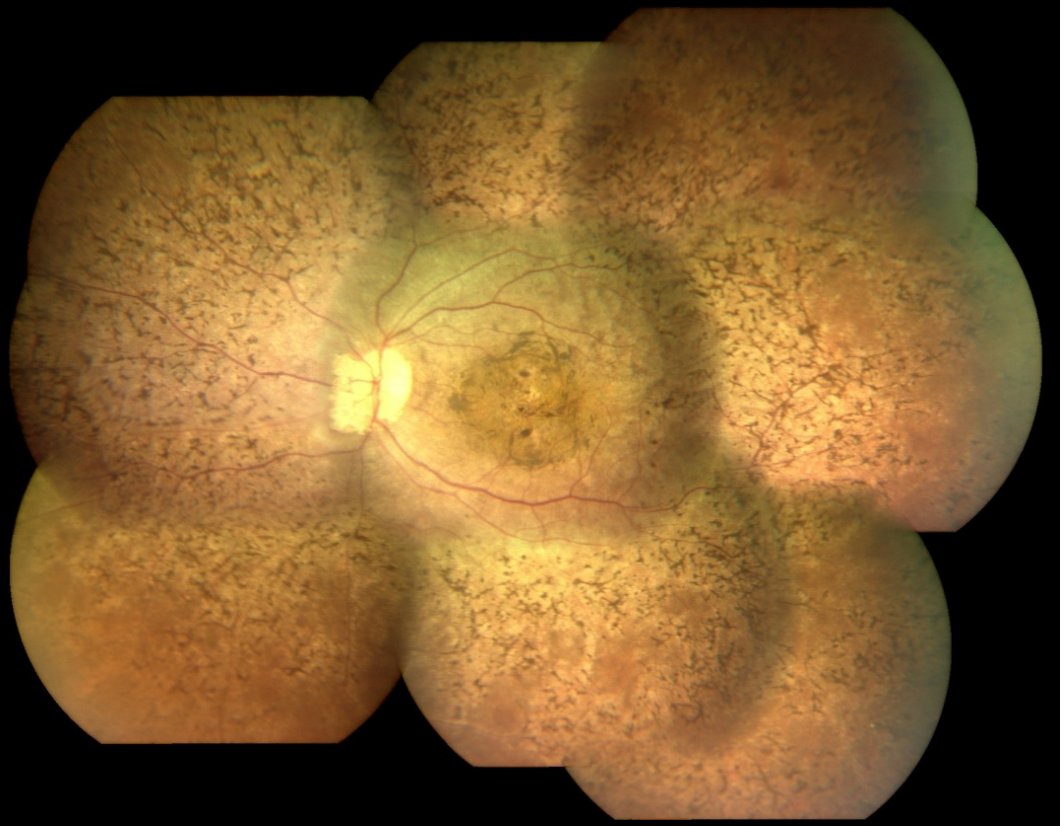
Anthony T Moore

UCL Institute of Ophthalmology

Moorfields Eye Hospital

Hospital for Children

Great Ormond St. London



Financial Disclosure

Chairman of DSMB Oxford Biomedica ocular gene therapy trial

Investigator for oral retinoid trial for rod-cone dystrophy sponsored by QLT

Inherited retinal disease

Common cause of blindness in children and adults of working age

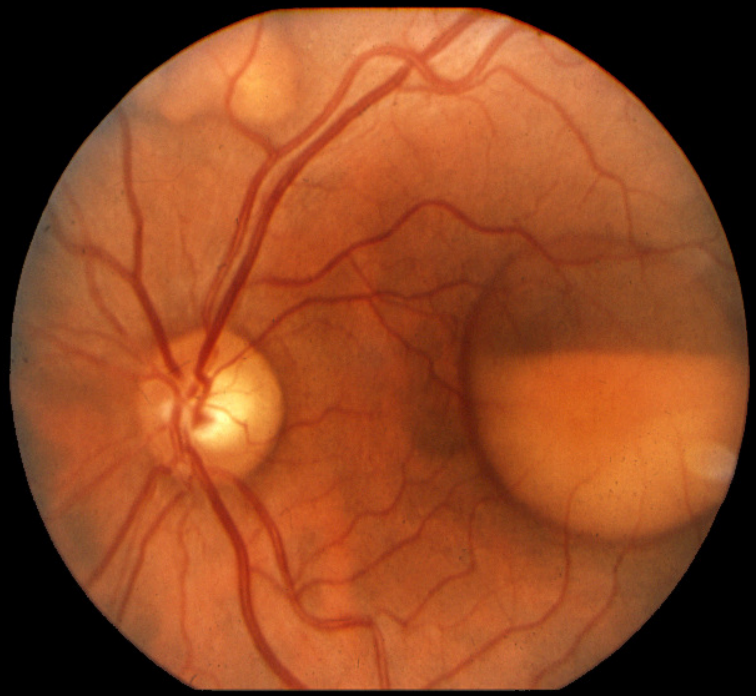
Affects about 1 in 4000 of population

50% of patients have no family history

No effective therapies

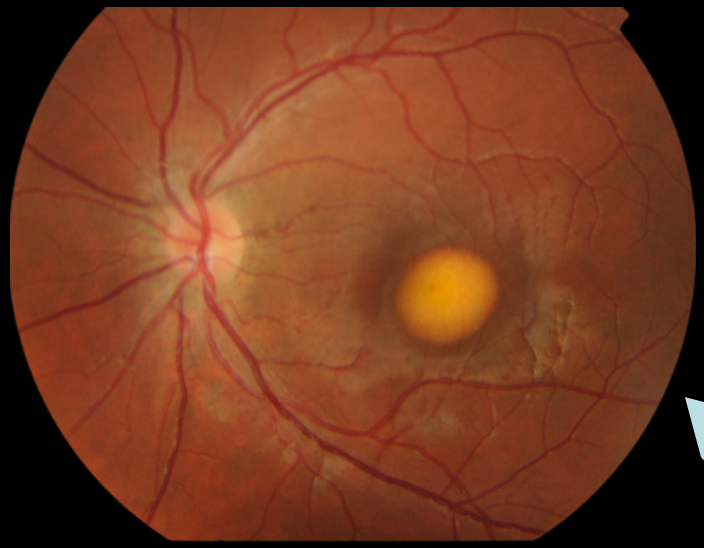
Inherited retinal disease
Clinical Classification

- Isolated or syndromic
- Stationary or progressive
- Mode of inheritance
- Site of dysfunction
- Retinal appearence
- Age of onset

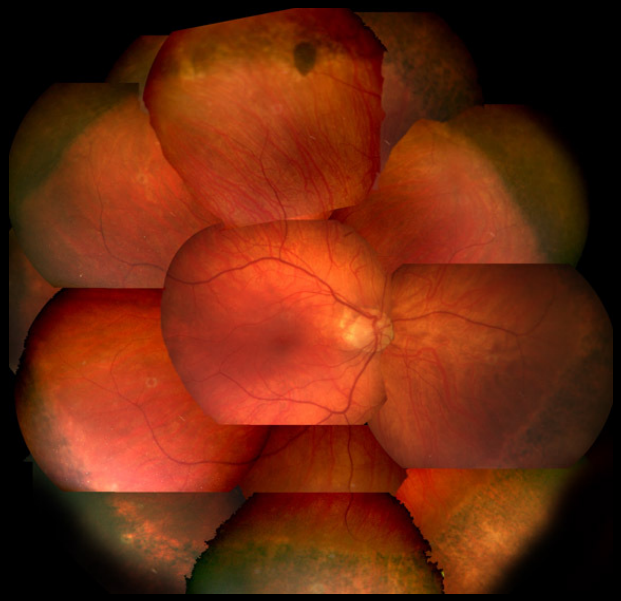


Increasingly being replaced by
classification based on molecular diagnosis

The bestrophinopathies

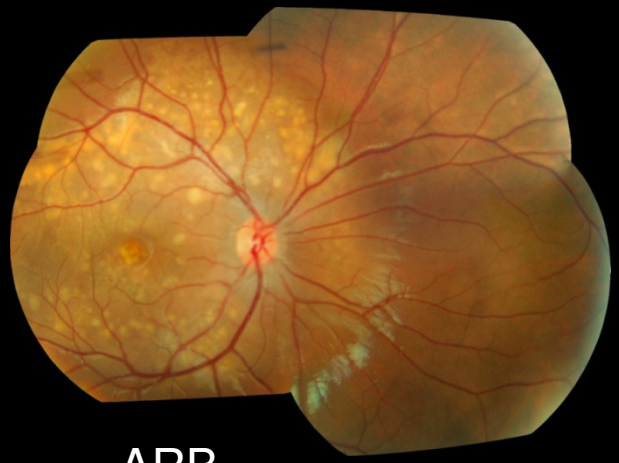


Best disease

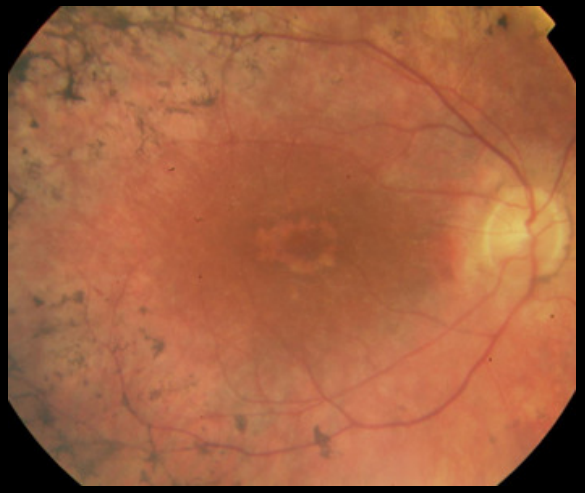


ADVIRC

Abnormal chloride channel function



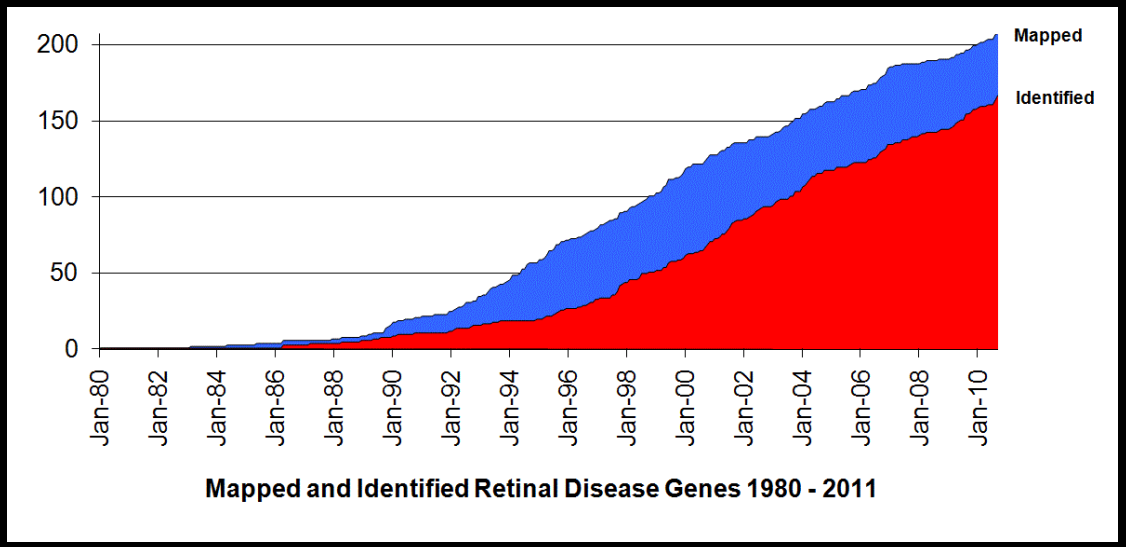
ARB



ADRP

Advances in molecular genetics

- Gene identification
- High throughput genotyping
- Statistical methodology
- Functional genomics
- Animal models
- Gene based therapies



Source: http://www.sph.uth.tmc.edu/Retnet

How does identification of genes help?

- Molecular diagnosis
- Better genetic counselling
- Improved understanding of disease mechanism
- Improved prospects for treatment
- Better evaluation of novel treatments

ADRP genes

- Rod Opsin - RP4 - 3q
- NRL - RP27 – 14q #
- PRPF8 - RP13 - 17p
- PRPF31 - RP11 - 19q
- PRPF3 - RP18 - 1q
- PRPF6 – RP60 – 20q
- PAP1 - RP9 - 7p
- SNRNP200 – RP33 – 2q
- IMPDH1 - RP10 - 7q
- KLHL7 – RP42 – 7p
- NR2E3 – 15q #
- RDH12 – 14q #
- TOPORS – RP31 – 9q
- RDS - RP7 - 6p
- ORP1 - RP1 – 8q
- (CRX - CORD2 - 19q)
- (RPE65 – RP20 – 1p)
- CA4 - RP17 - 17q
- FSCN2 - RP30 - 17q
- BEST1 – RP50 – 11q
- GUCA1B – RP48 – 6p
- ROM1 – 11q
- SEMA4A – RP35 – 1q

http://www.retnet.org

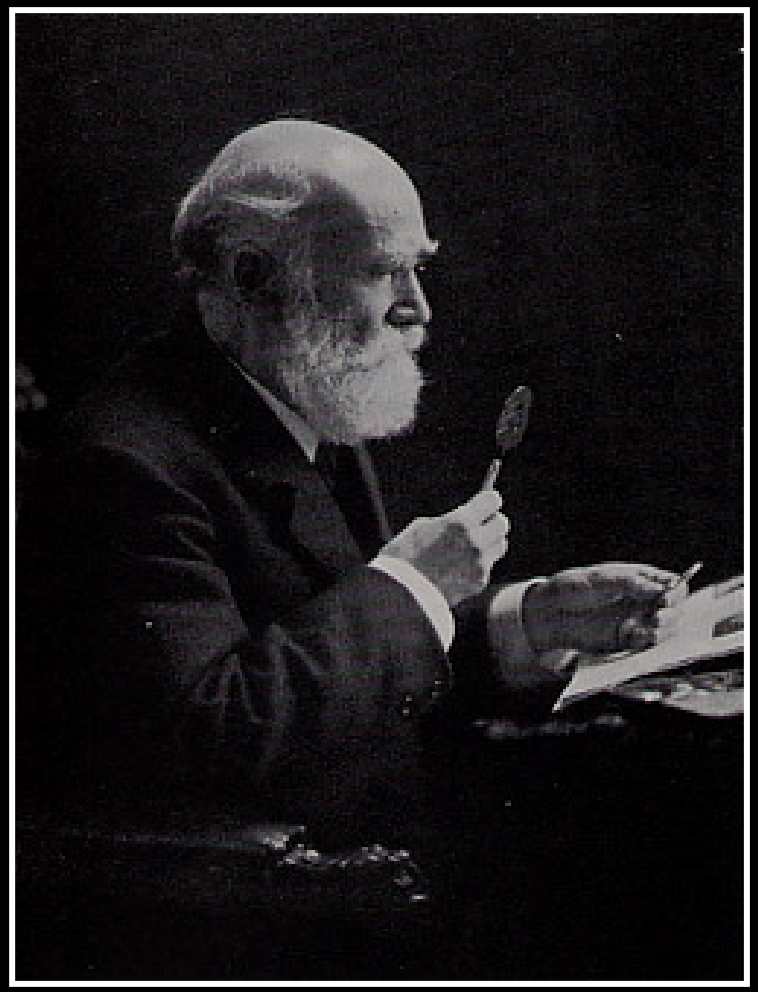
- other alleles cause recessive disease

Yellow rod specific expression
Green splicing factors

Lebers amaurosis

'tapetoretinale degeneration mit amblyopie'

- first described 1867
- infantile onset rod-cone dystrophy
- 2-3 per 100,000 live births
- 5% of congenital blindness
- AR inheritance
- poor vision from infancy
- nystagmus



Leber congenital amaurosis

LCA Genes

CRX

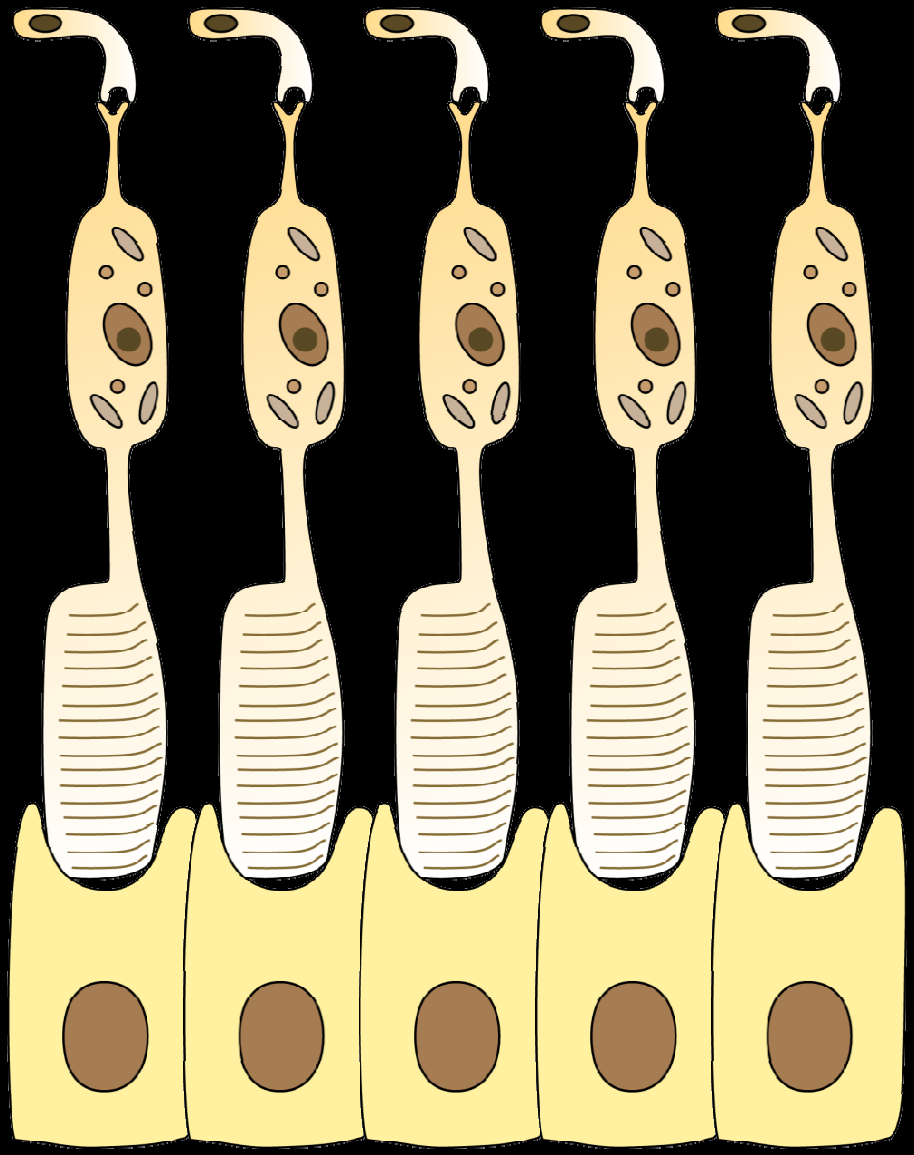
CRB1

CPE290
RPGRIP

RDH12

LRAT

RPE65



Photoreceptor

AIPL1

Lebercillin

SPATA7

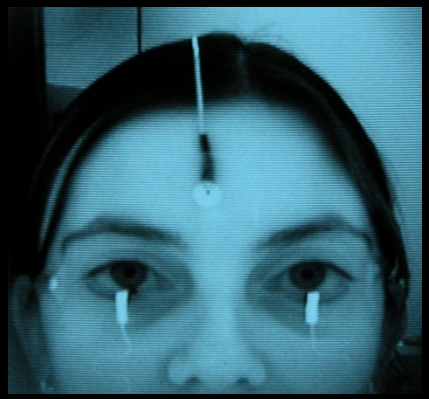
GUC2YD
KCNJ13

RPE

Characterising retinal disorder

- Mode of inheritance
- Electrophysiology
- Psychophysics
- Ocular imaging
- Molecular diagnosis

ISCEV Standard ERGs

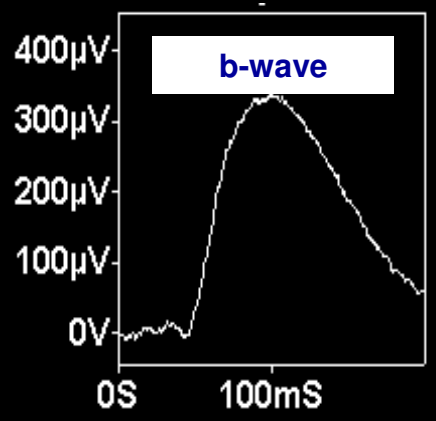


International Society for Clinical Electrophysiology of Vision

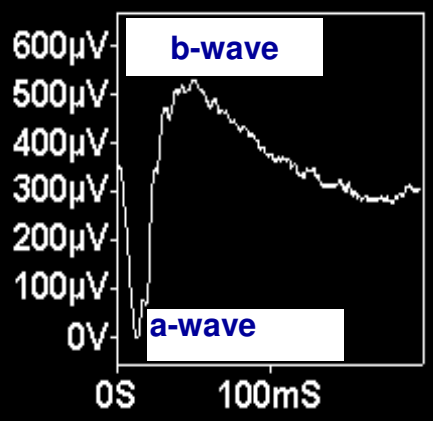
www.iscev.org

Dark adapted (>20 mins)

0.01 cd.s/m²

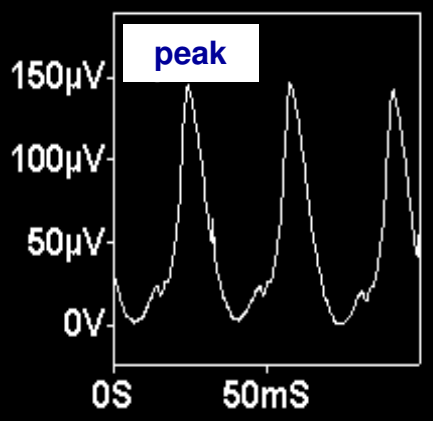


11.0 cd.s/m²

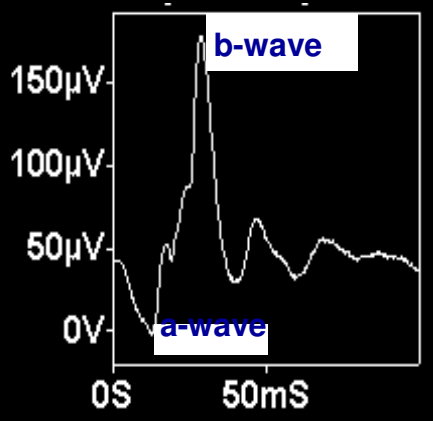


Light adapted (>10 mins)

3.0 30Hz flicker

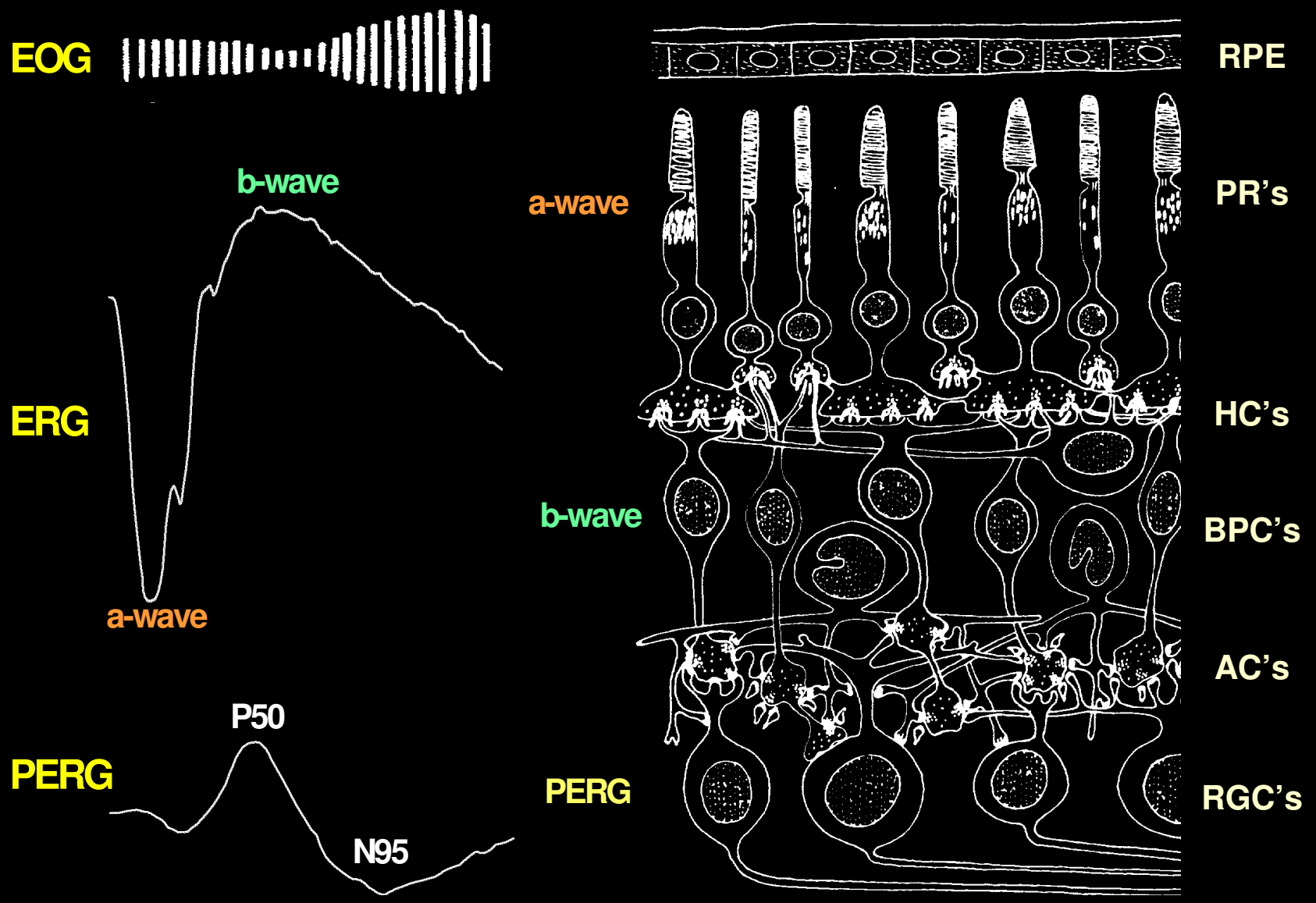


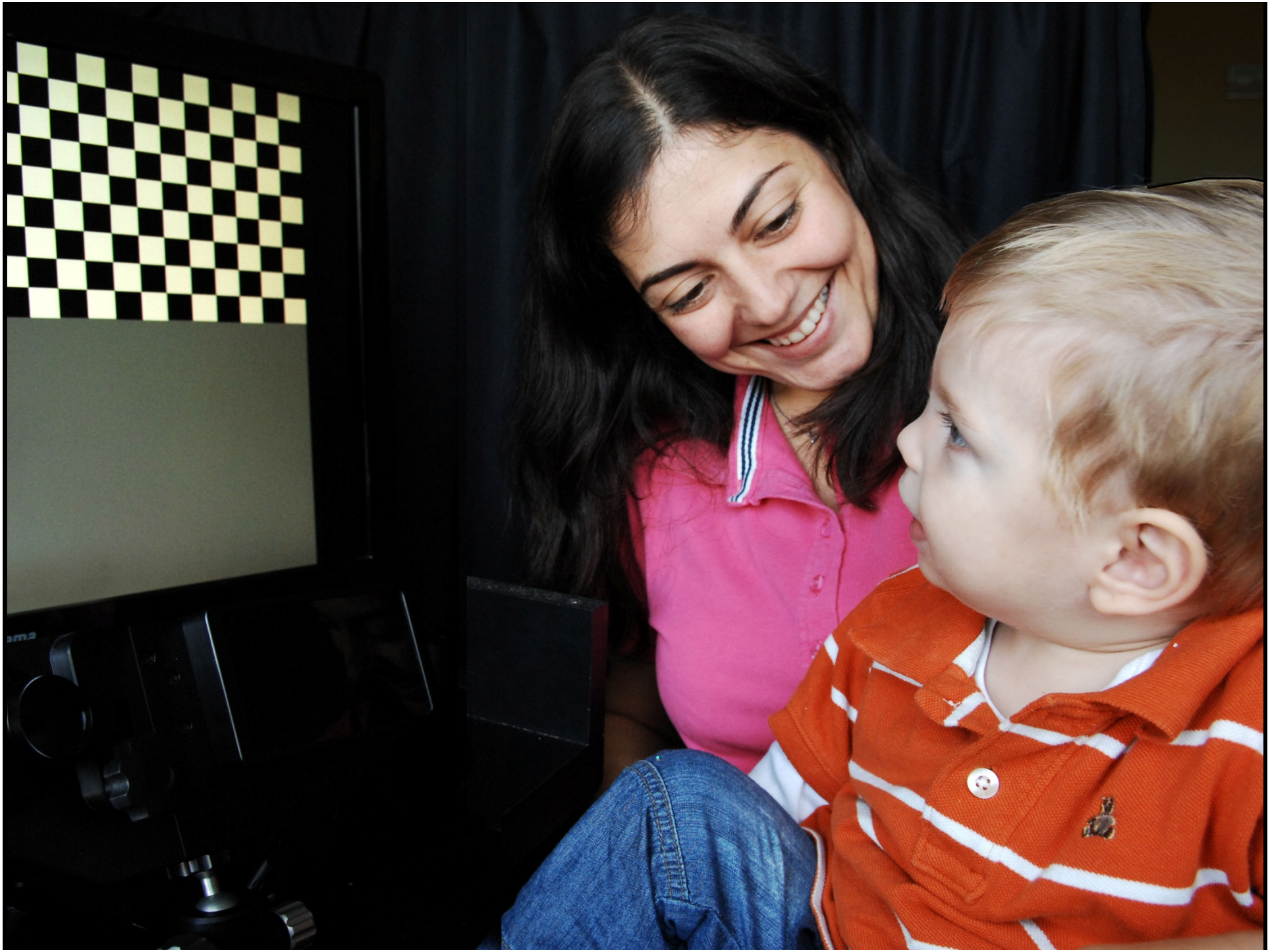
Photopic 3.0



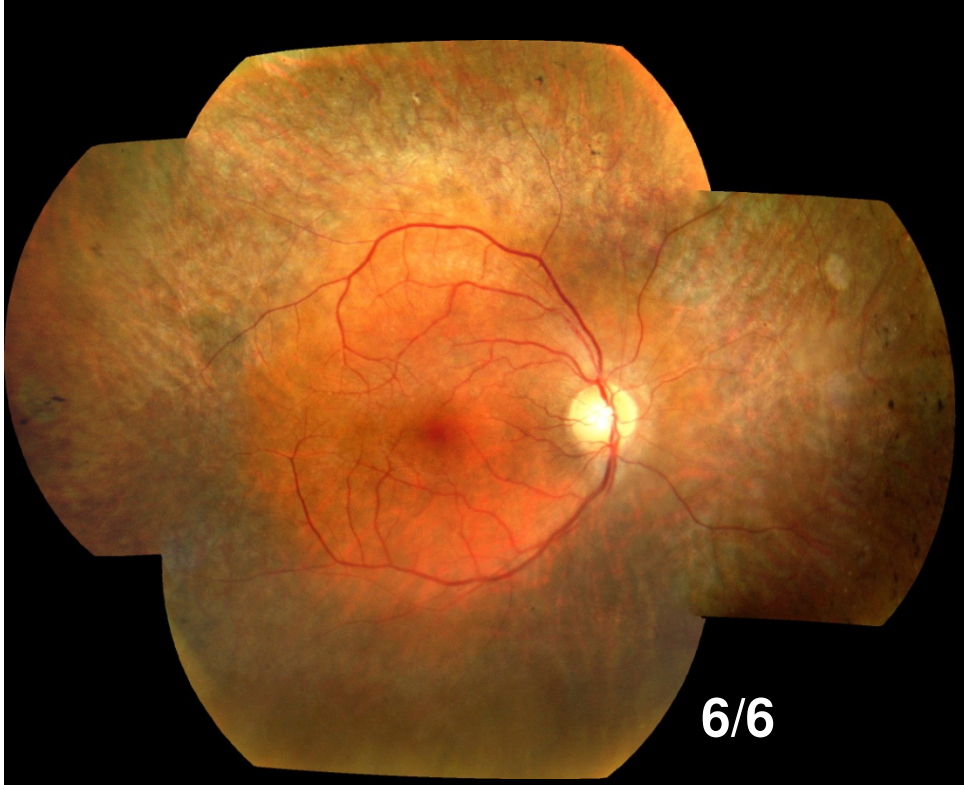
A minimum recommendation;
additional recordings may be needed for accurate diagnosis

Electrophysiology and retinal structure

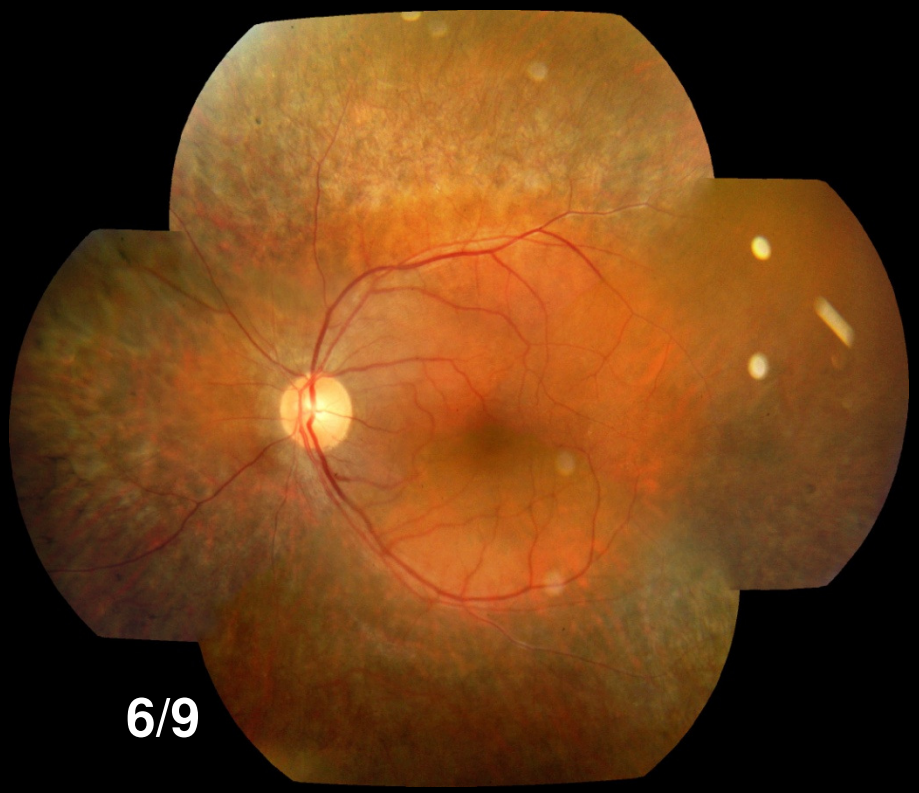




M, 56 yrs. Night blindness



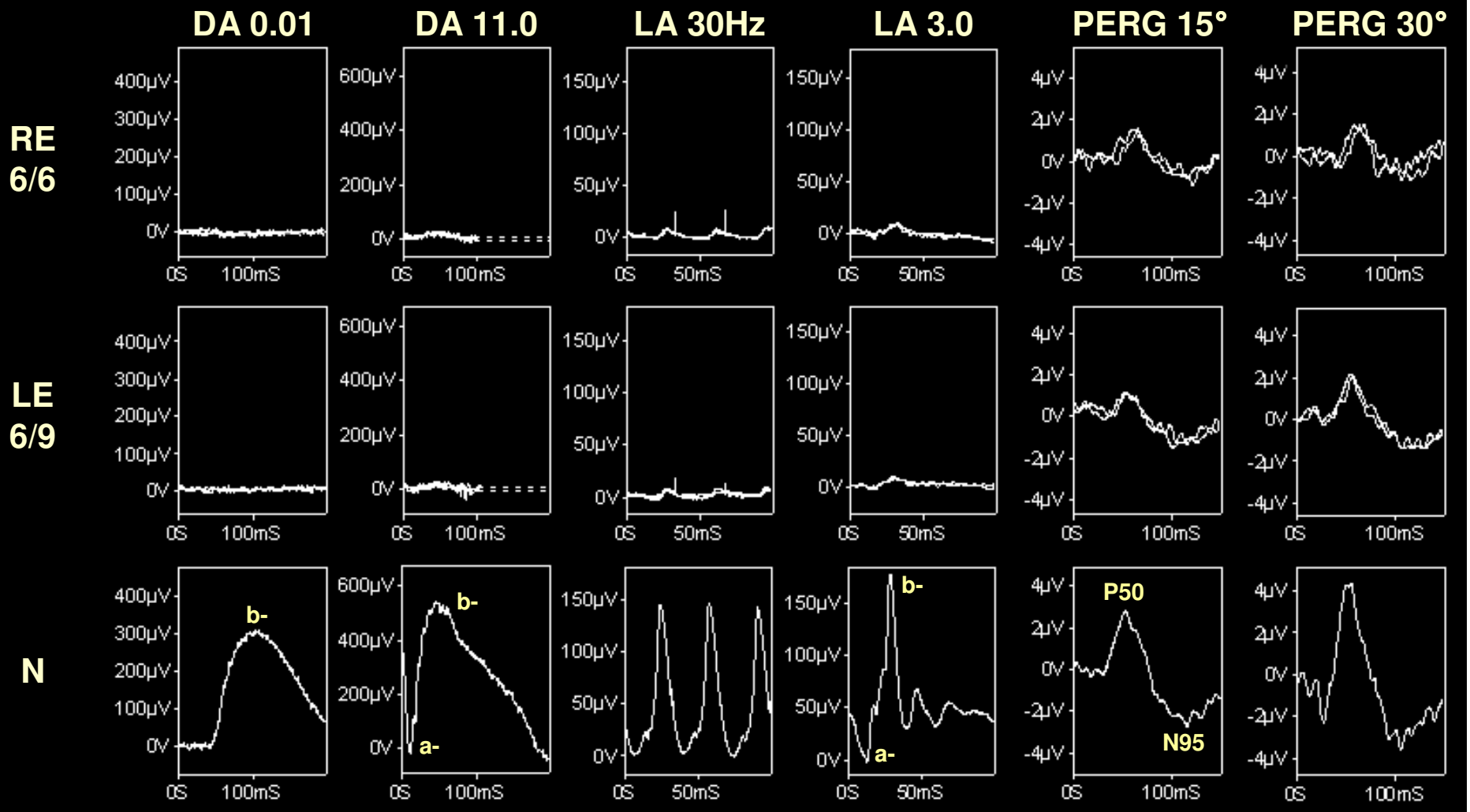
6/6



6/9

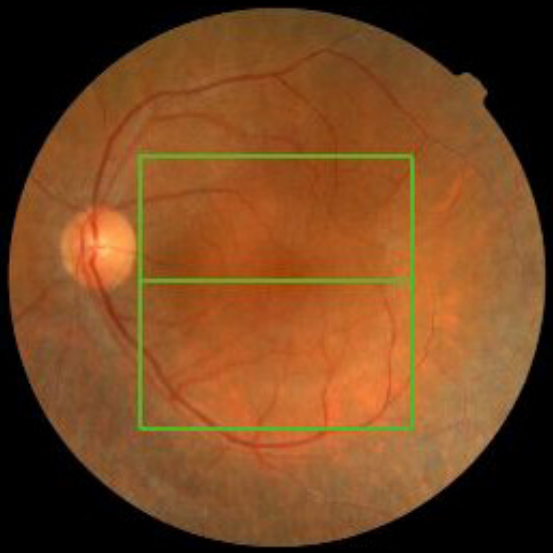
56567

M, 56 yrs.

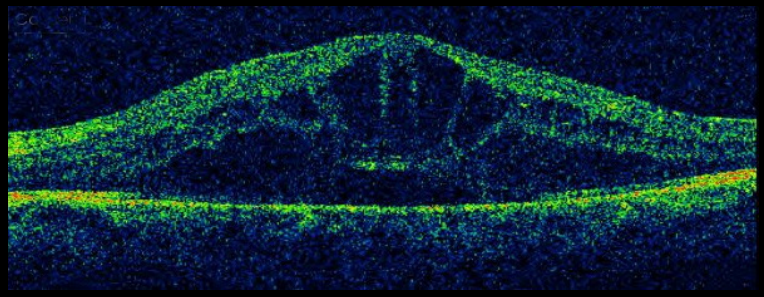


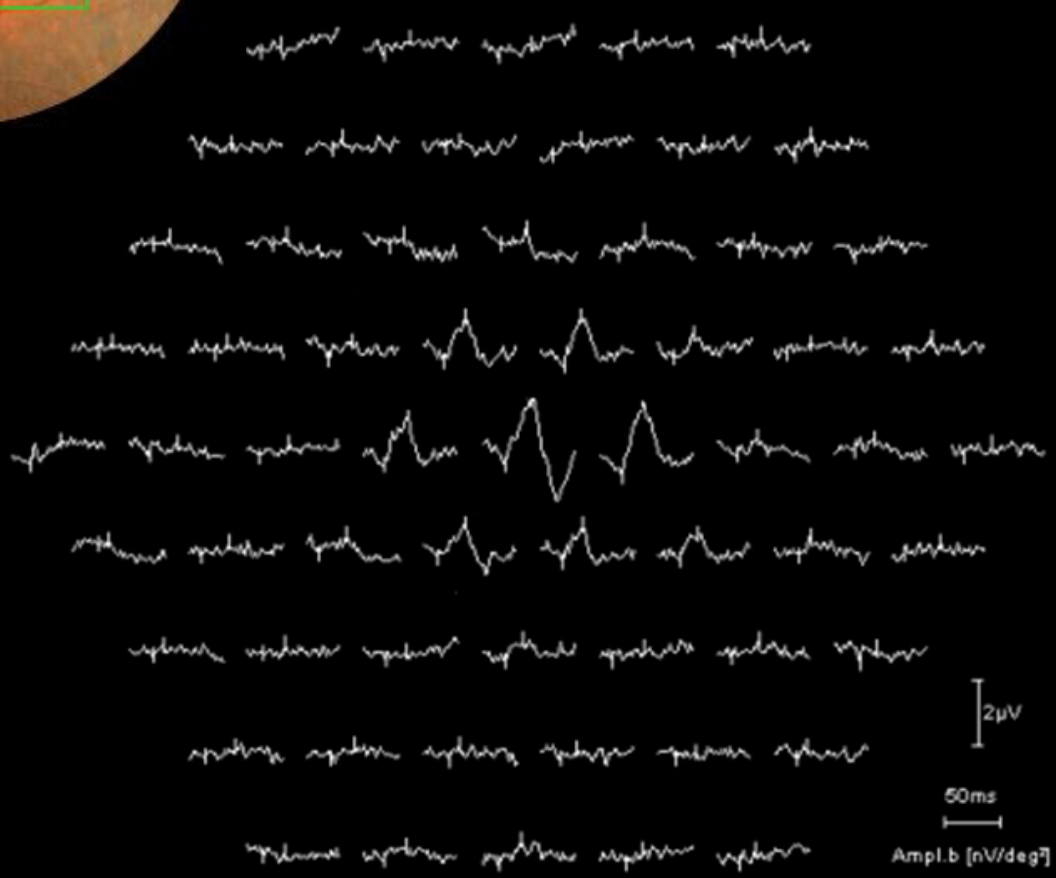
56567

M, 56 yrs.



6/9





56567

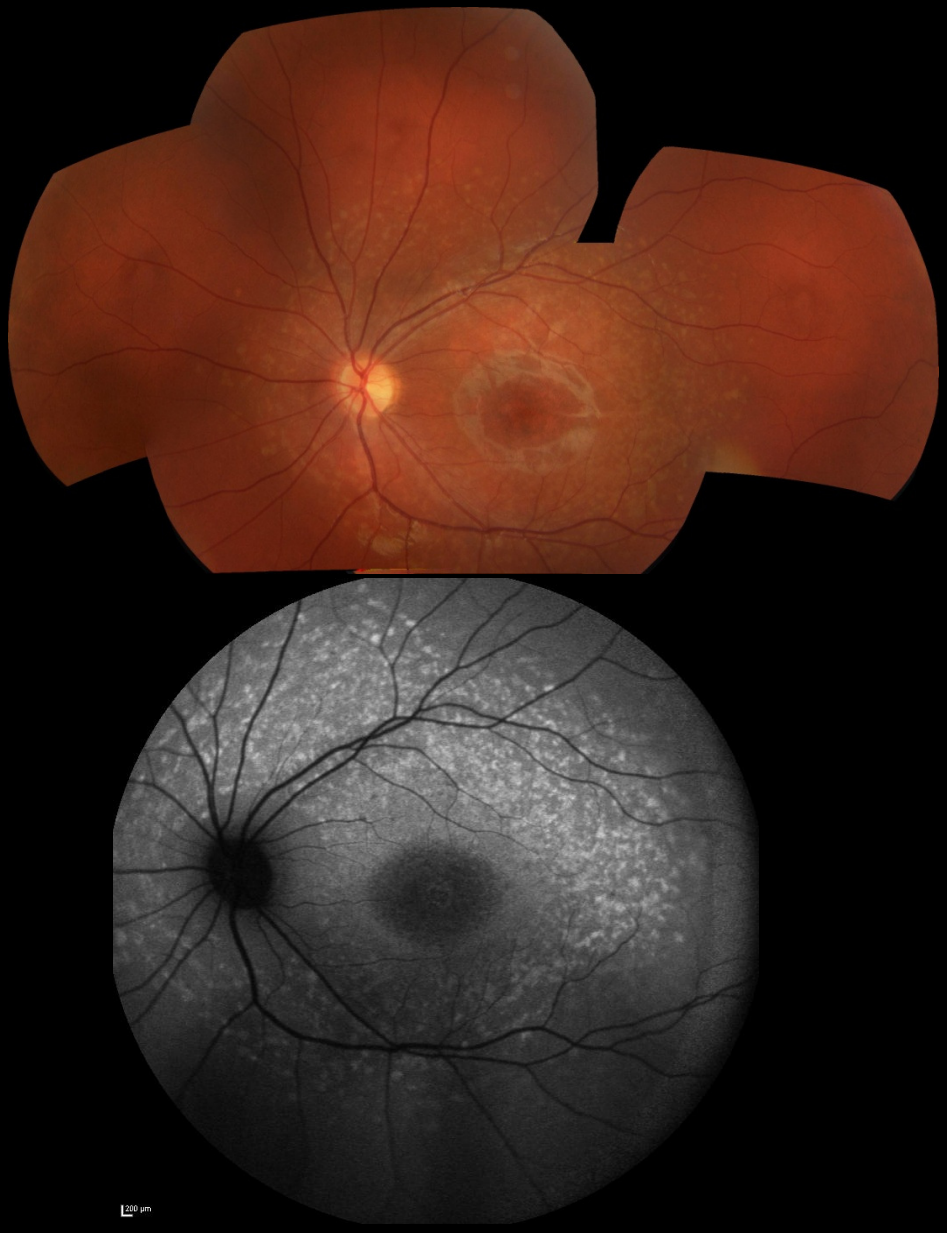
Retinal imaging

Colour photography

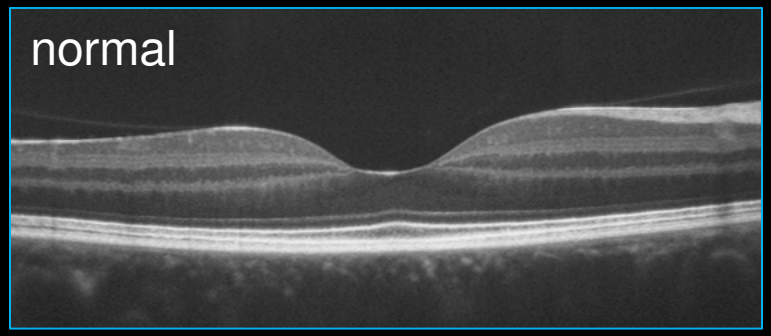
Autofluorescence Imaging

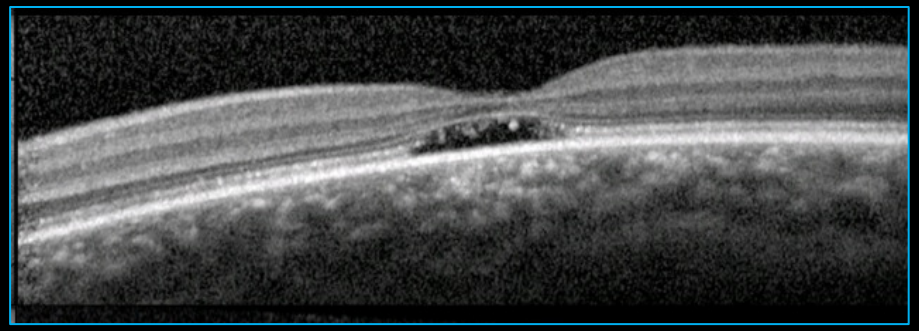
Optical coherence tomography

Adaptive optics

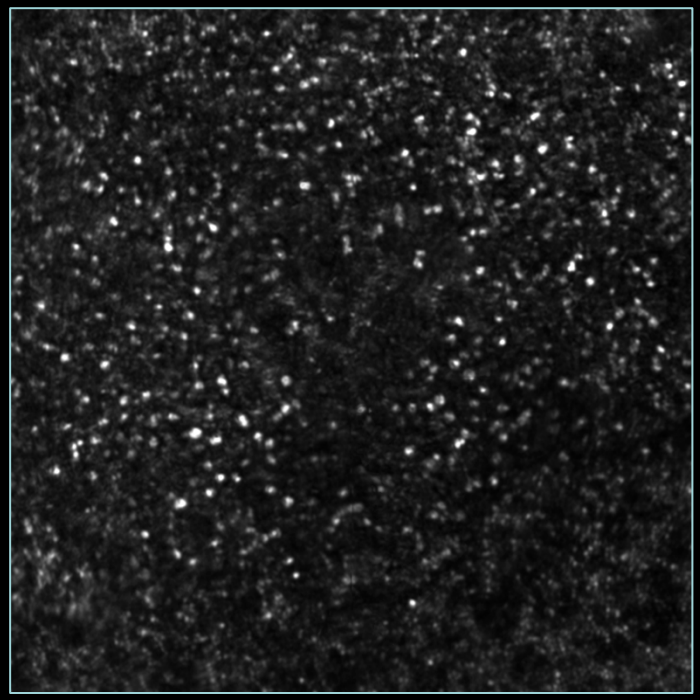


SDOCT



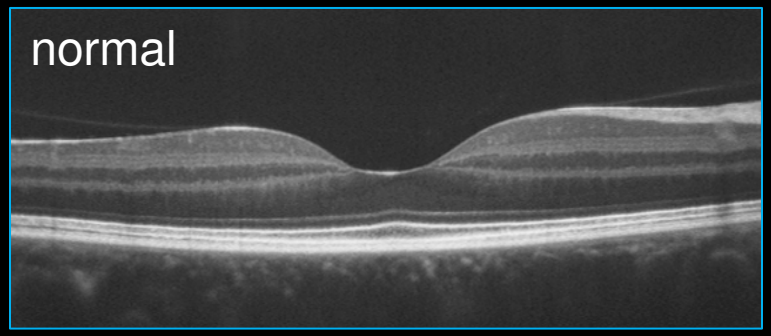


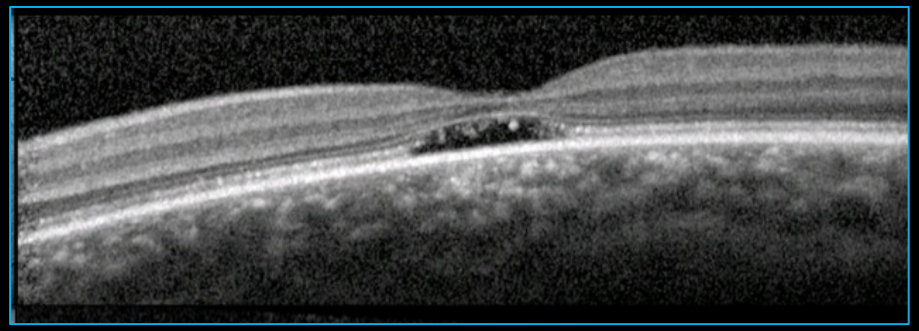
Adaptive Optics



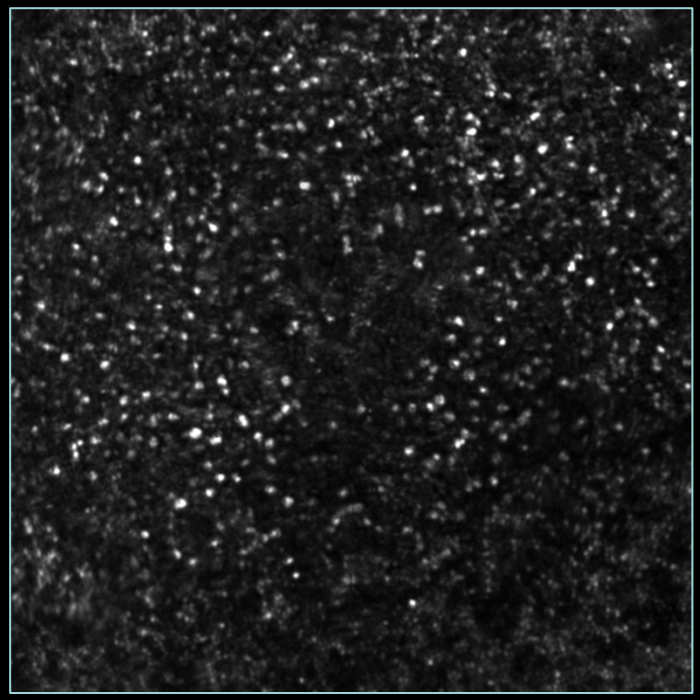
Courtesy
Joe Carroll

SDOCT



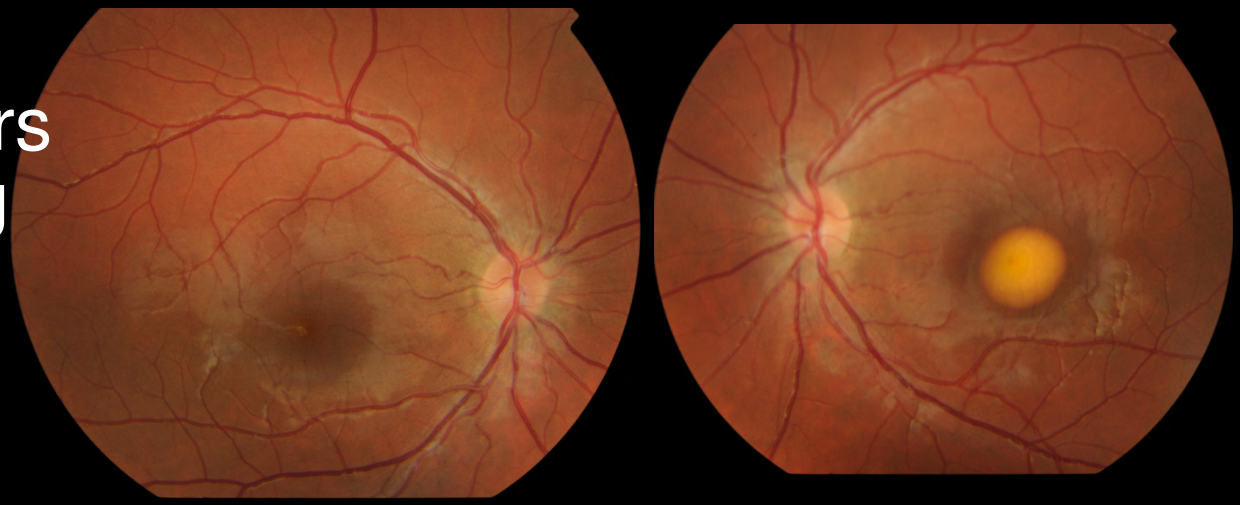


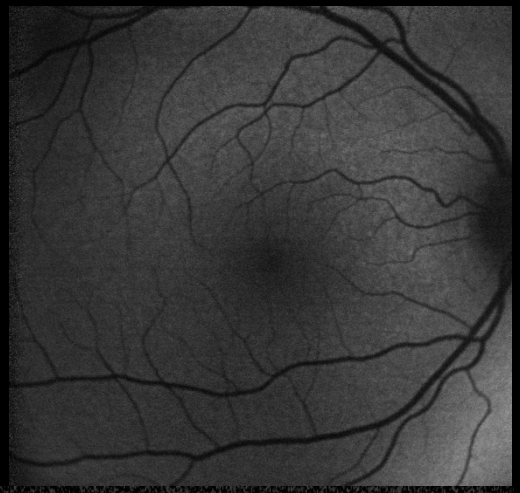
Adaptive Optics

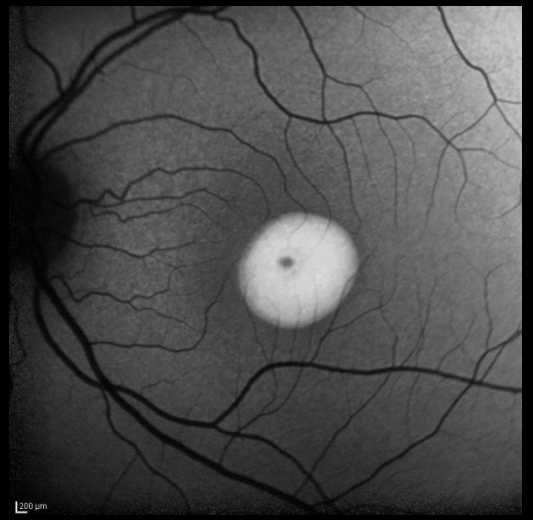


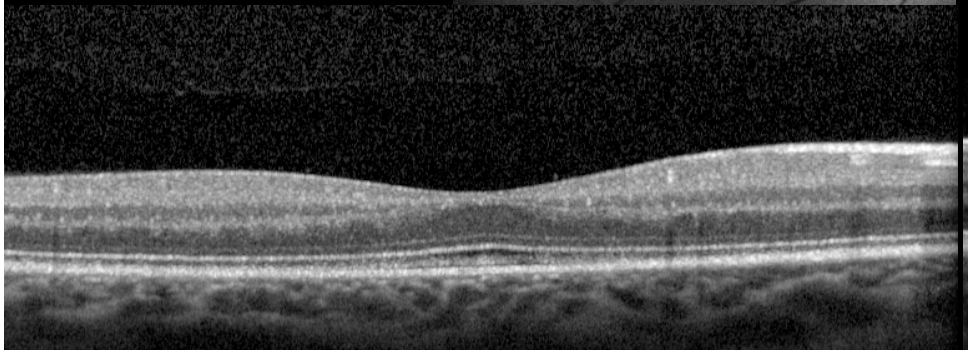
Courtesy
Joe Carroll

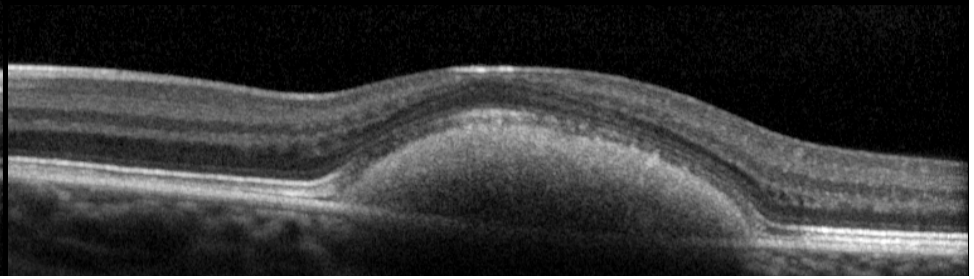
Male
Age 8 years
VA 6/6 OU









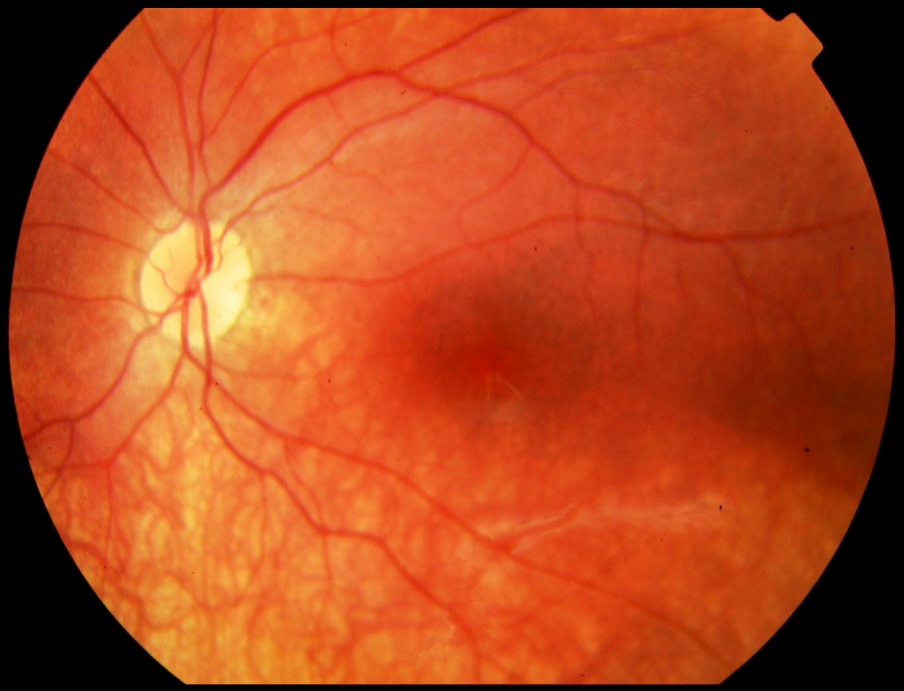


Inherited retinal disease

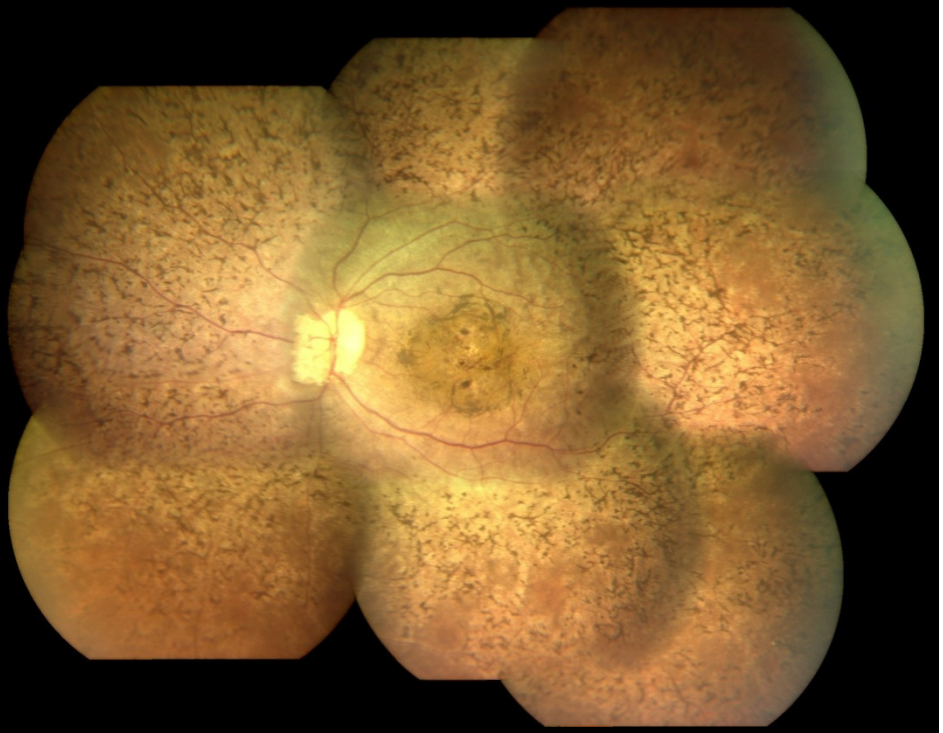
- Abnormal visual function is it due to photorecptor cell death or dysfunction?

- Are photoreceptors rescueable?

Leber amaurosis (infantile onset rod cone dystrophy)

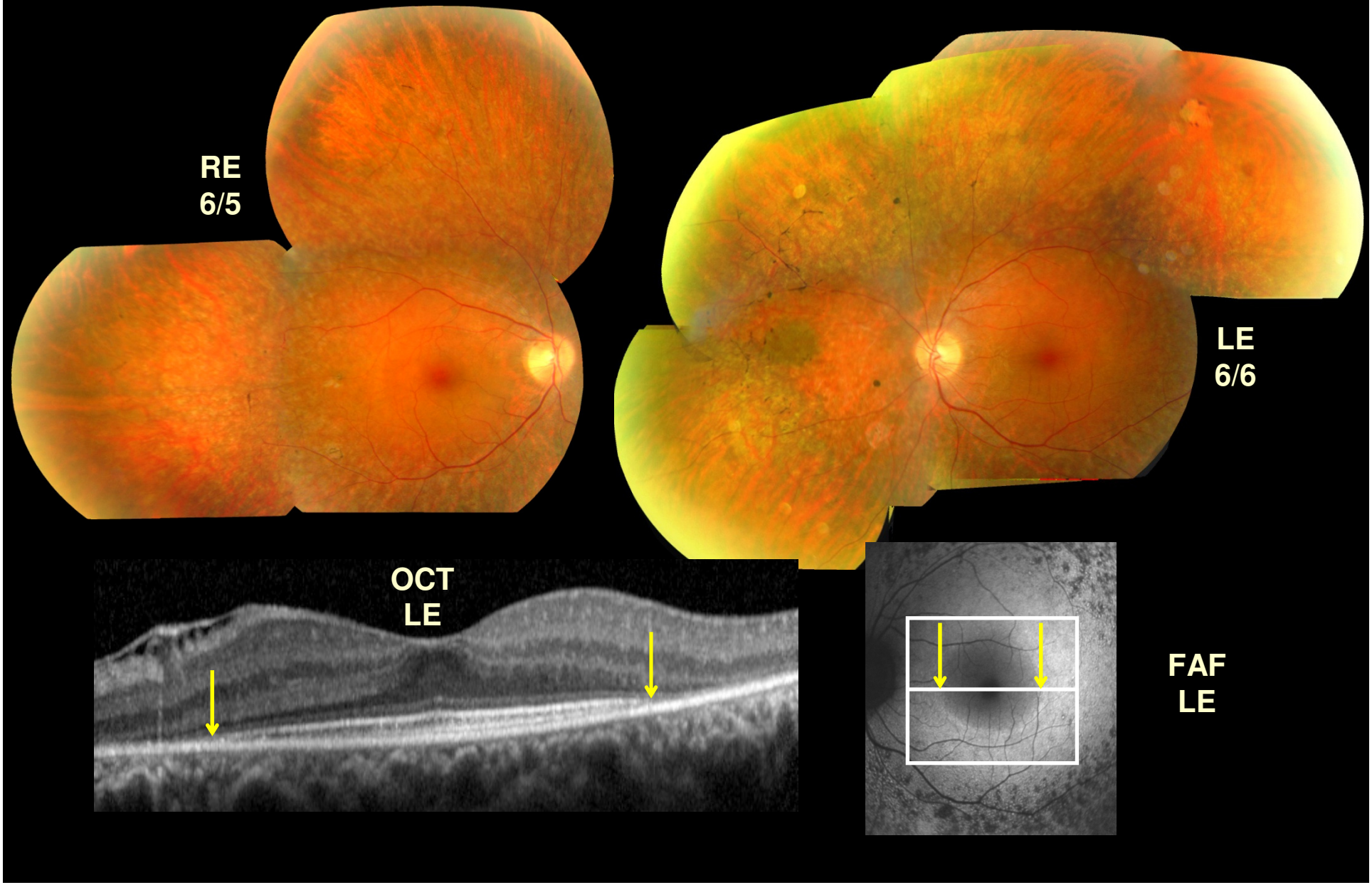


RPE65 deficiency

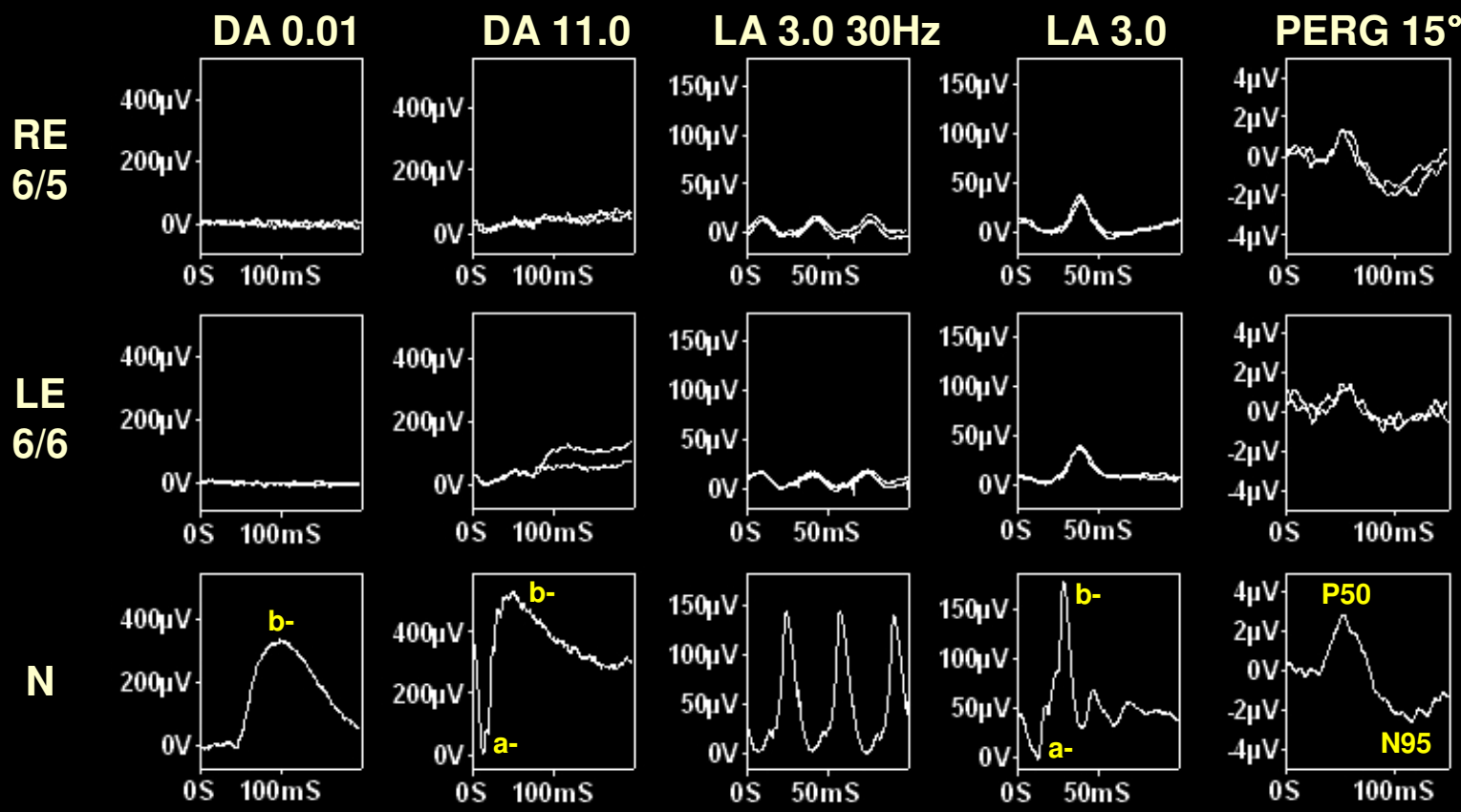


RDH12 deficiency

F, 42 yrs. Poor night vision. ?RP

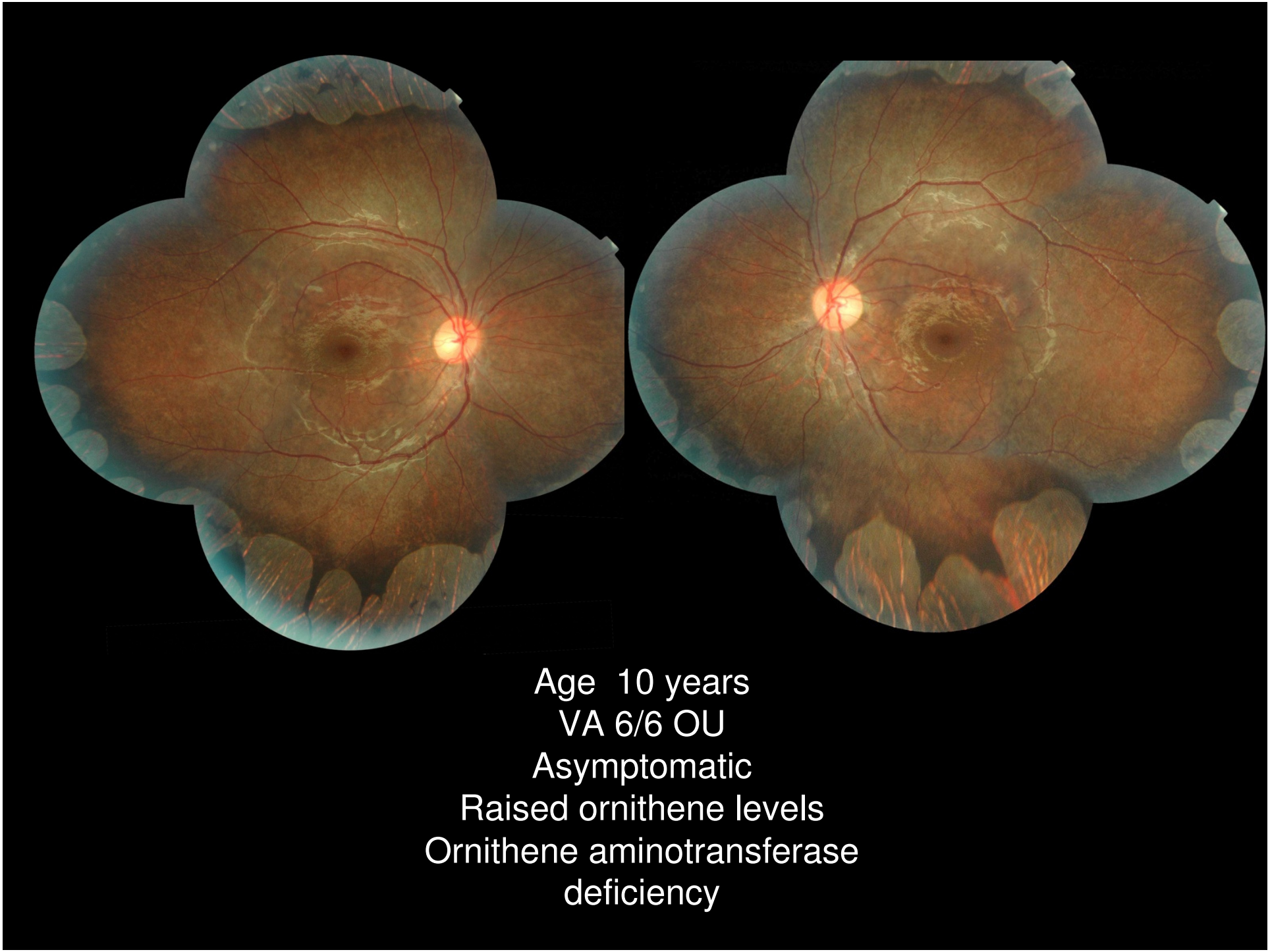


F, 42 yrs. Poor night vision. ?RP



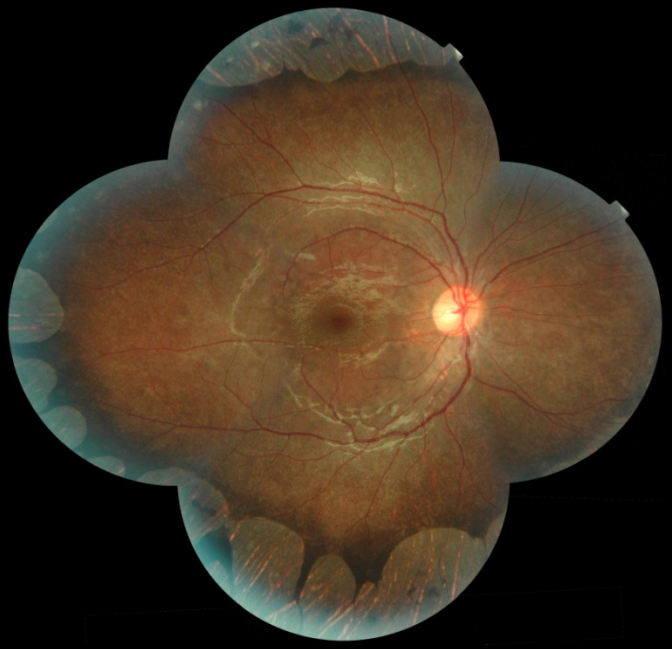
Current treatment for retinal dystrophies

- Dietary treatment available when biological pathway understood
  - Refsums disease
  - Abetaliproteinemia
  - Gyrate atrophy
- Treatment may slow disease progression



Age 10 years
VA 6/6 OU
Asymptomatic
Raised ornithene levels
Ornithene aminotransferase deficiency

How effective is treatment?

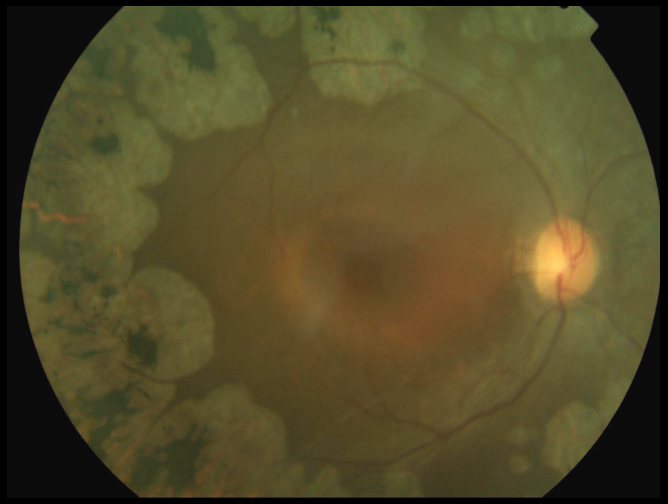


Age 12 years

Pyridoxine
Restricted protein diet

Annual Fields
Annual ERG

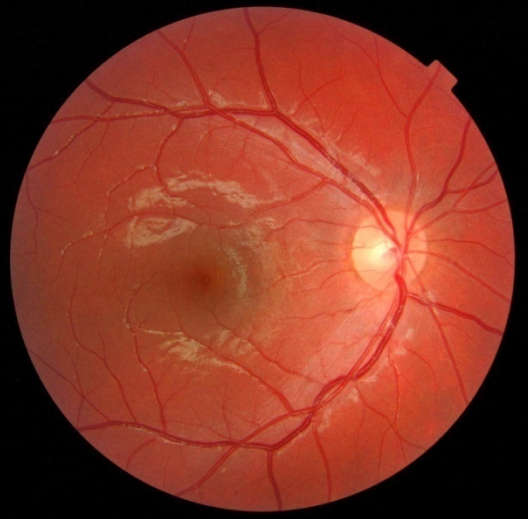
? Effect of treatment

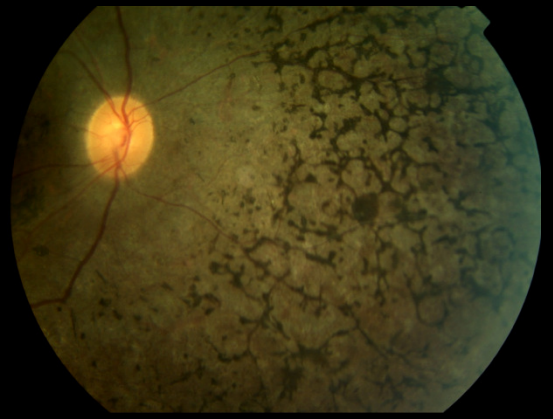


Age 34 years

Approaches to therapy

- Prevention of cell death
  - Gene therapy (replacement of normal copy the gene)
  - Other treatment strategies
- Tissue replacement
  - retinal transplantation
  - Stem cell therapy
- Artificial retina





Prospects for therapy in retinal dystrophies

- Photoreceptor rescue
  - growth factors
  - inhibition of apoptosis
  - pharmacological agents
  - gene therapy
- Tissue replacement
  - retinal/RPE transplantation
  - stem cell therapy
- Artificial vision
  - Retinal implants

Current trials

Pharmacological treatment

CTNF

Oral retinoid

Gene therapy

RPE65 deficiency

Choroideremia

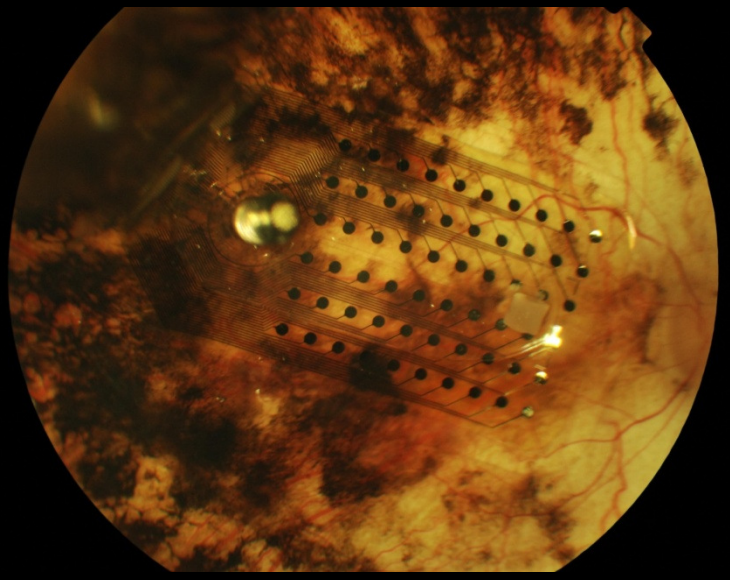
Stargardt disease

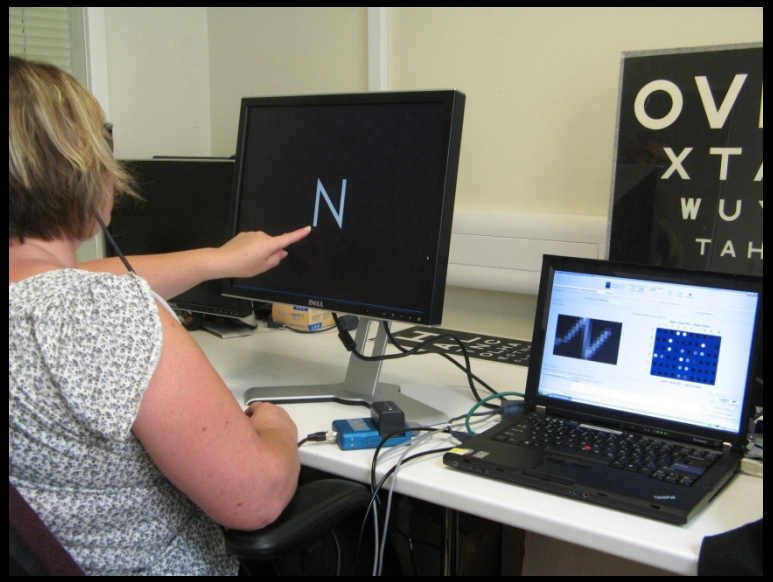
Usher syndrome

‘Stem cell therapy’

Stargardt disease

Retinal implants



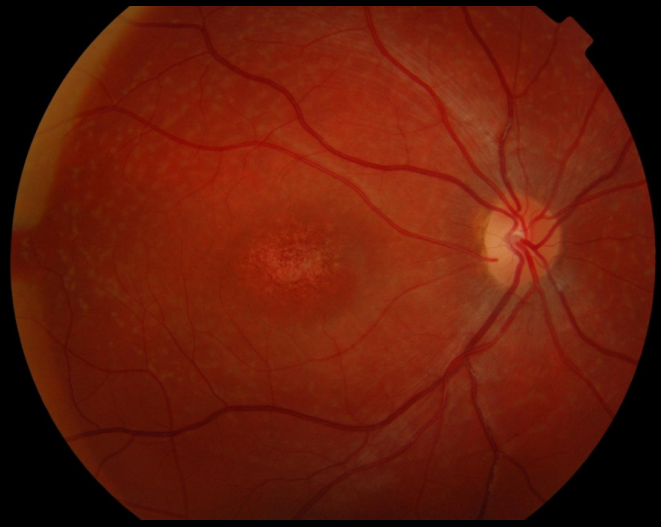


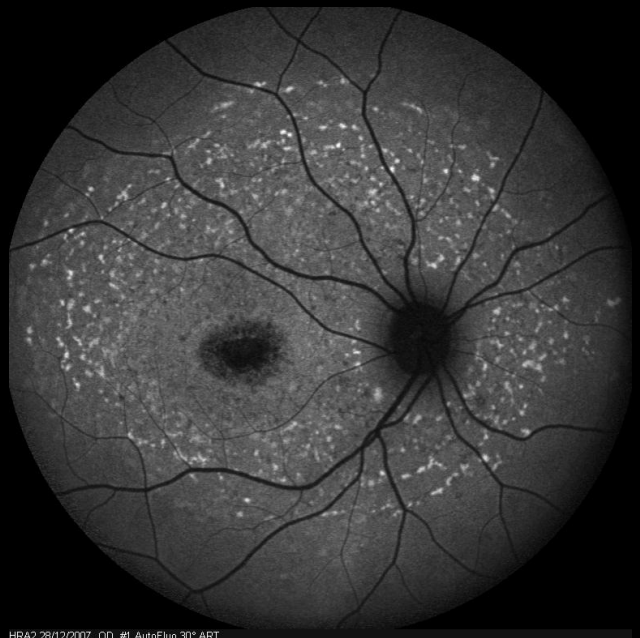
Courtesy Lyndon da Cruz

Stargardt disease

- AR retinal dystrophy
- macular atrophy
- white flecks at level of RPE
- abnormal autofluorescent material in RPE
- lipofuscin accumulation in RPE
- abnormal pattern ERG
- normal flash ERG in early stages

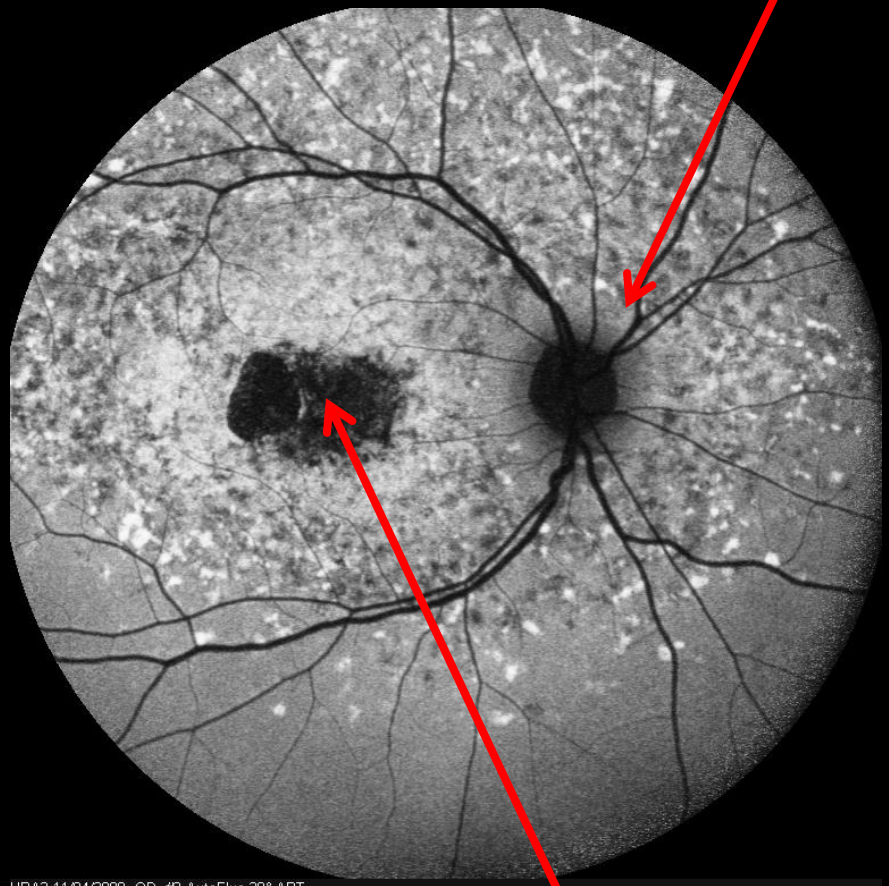
Age 14
VA 20/200



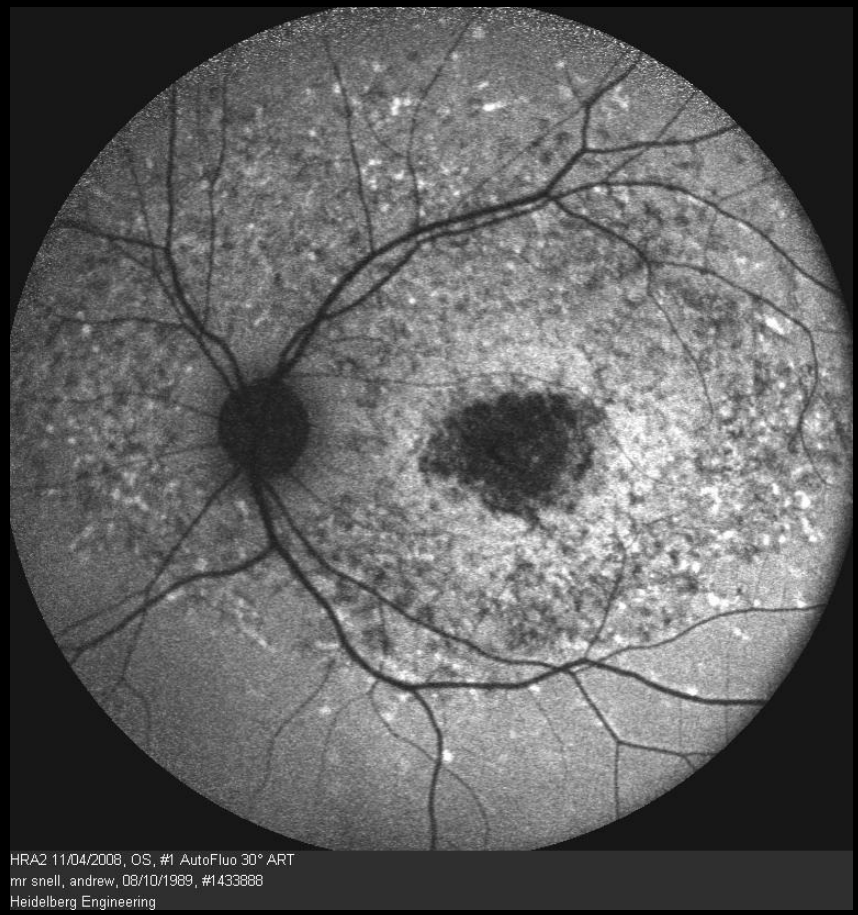


FAF imaging

peripapillary sparing

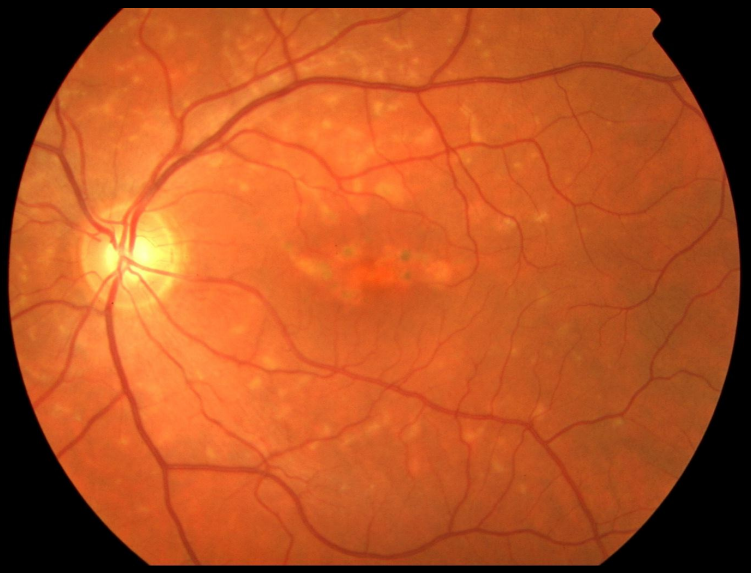


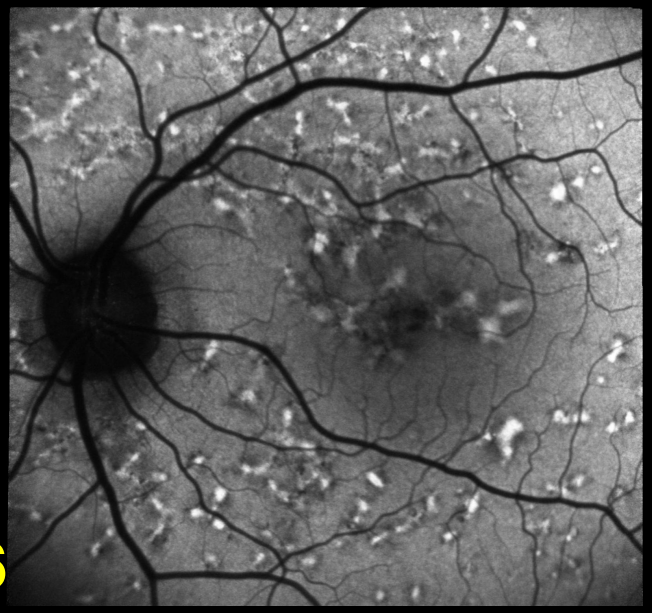
Cell death



ABCA4 gene

- Locus 1p21
- 50 exons
- highly polymorphic
- expressed in rod and cone photoreceptors
- encodes ABC transporter protein involved in removing all-trans retinal from OS discs

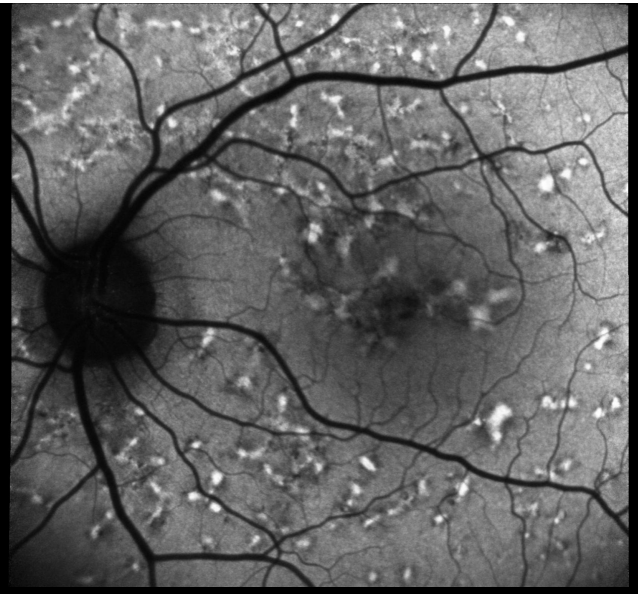


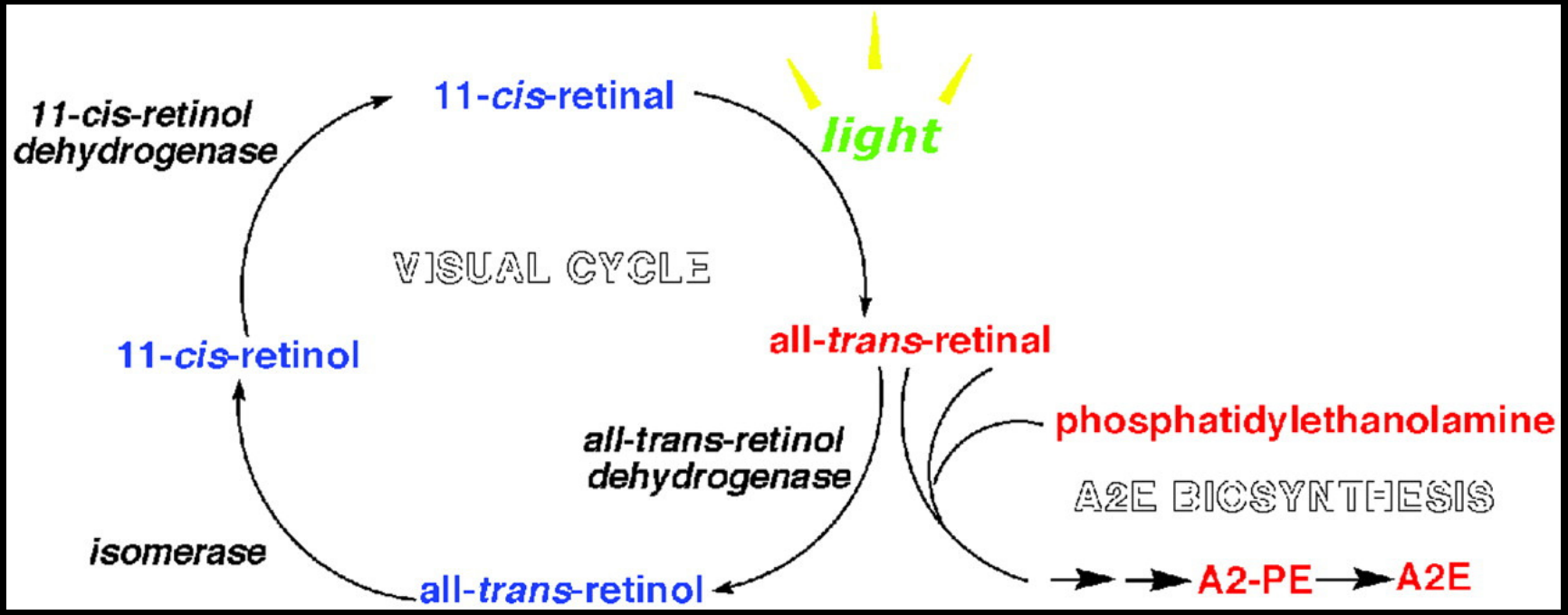


Allikmets et al Nat Genet 1997;17:826

A2E formation in RPE

A2E is major fluorophore of lipofuscin





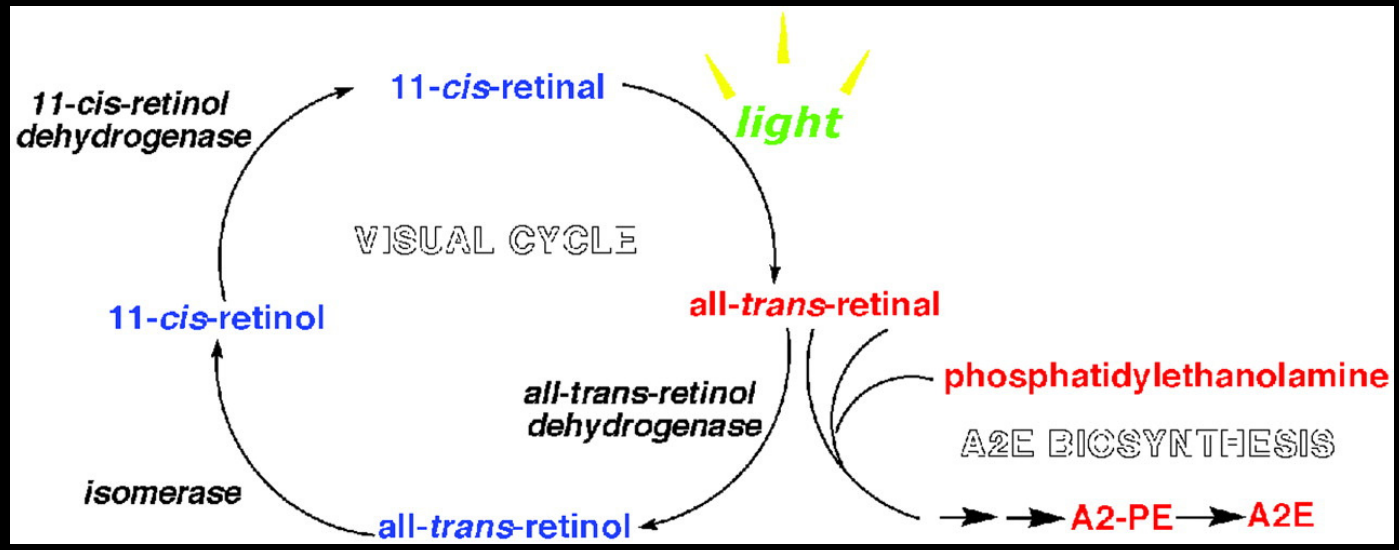
Sparrow, Janet R. (2003) Proc. Natl. Acad. Sci. USA 100, 4353-4354

Therapy in mouse model

Slow visual cycle

limit light exposure

isotretinoin (13-*cis* retinoic acid)



Sparrow, Janet R. (2003) Proc. Natl. Acad. Sci. USA 100, 4353-4354

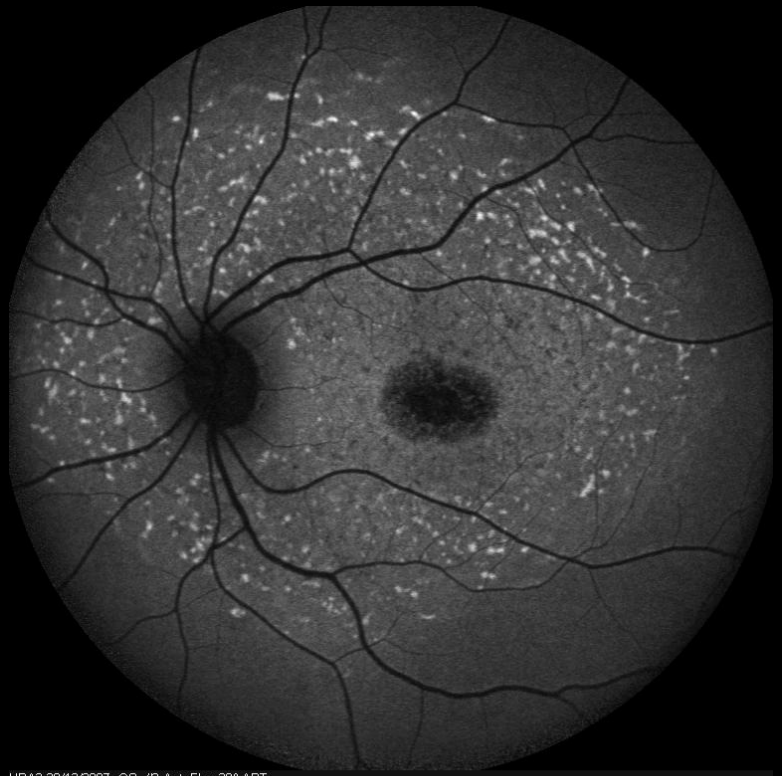
Approaches to treatment in Stargardt disease

Exclude light!

Inhibit visual cycle

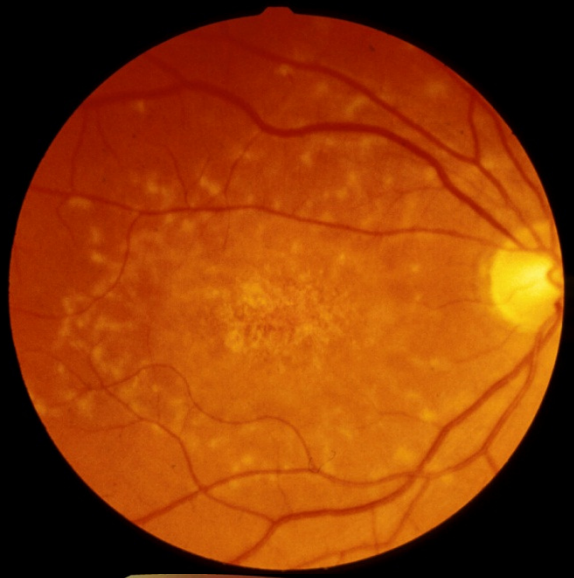
Inhibit A2E formation

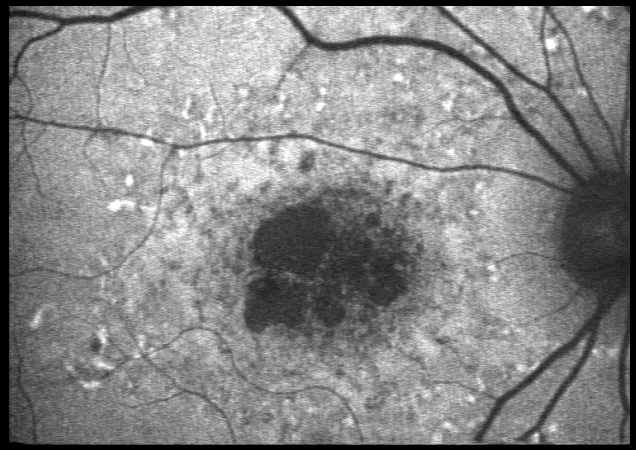
Replace tissue



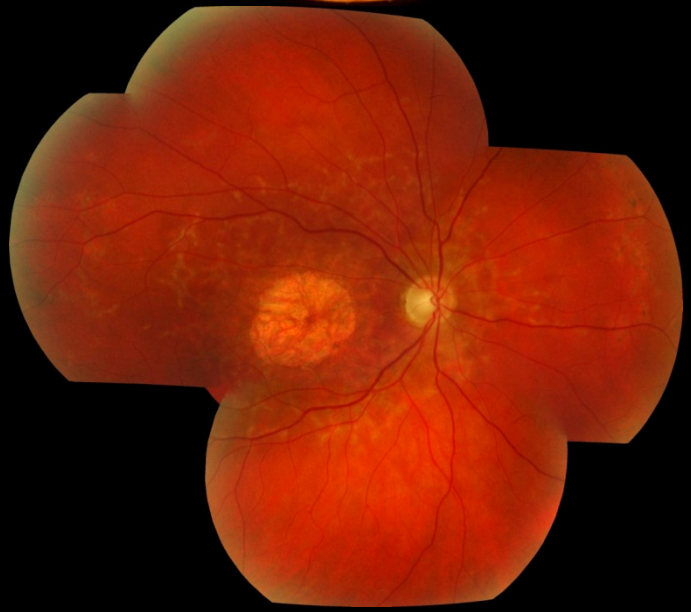
How do we identify treatment effect?

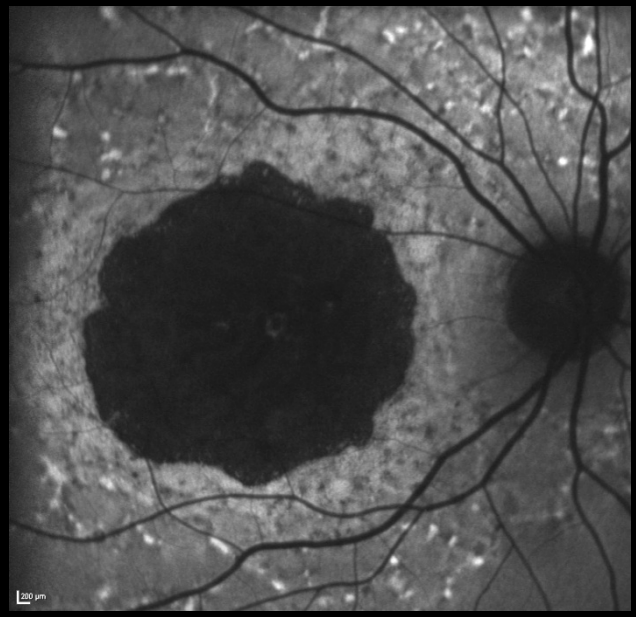
1998
VAR 6/60





2009
VAR 6/60

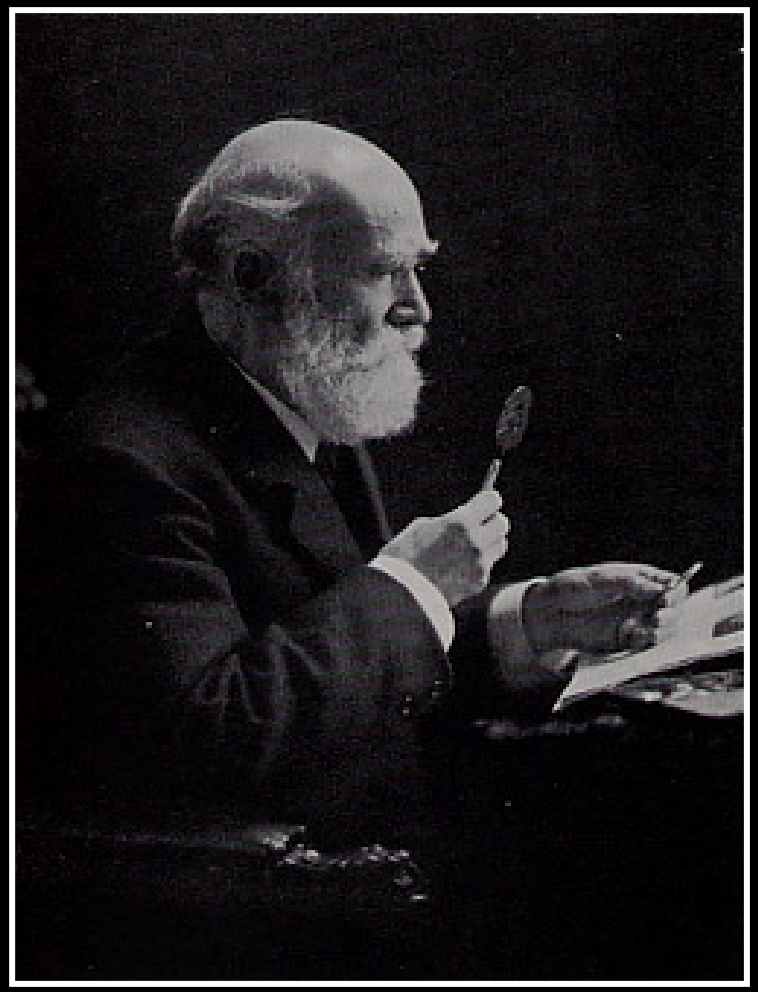




Lebers amaurosis

'tapetoretinale degeneration mit amblyopie'

- first described 1867
- infantile onset rod-cone dystrophy
- 2-3 per 100,000 live births
- 5% of congenital blindness
- AR inheritance
- genetically heterogenous
- poor vision from infancy
- nystagmus



Leber congenital amaurosis

LCA Genes

CRX

CRB1

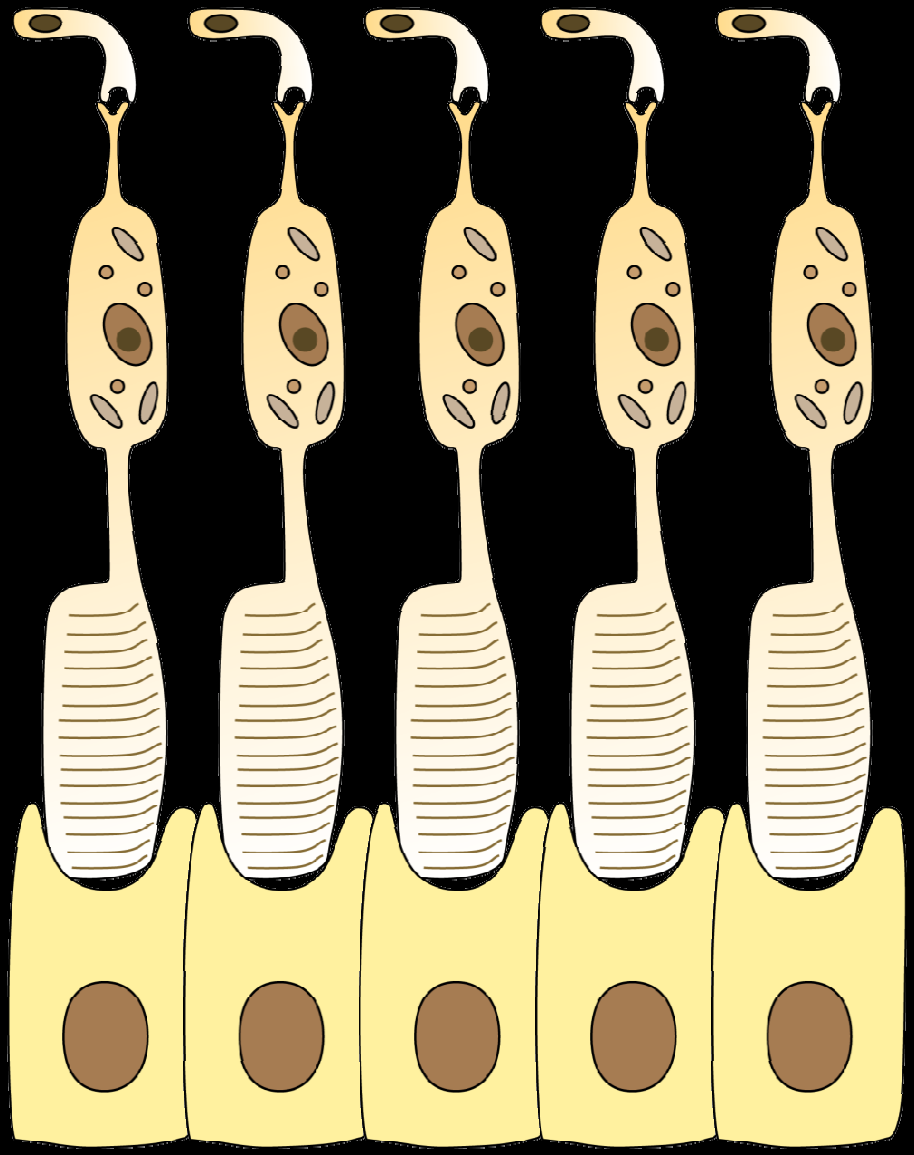
CPE290

RPGRIP

RDH12

LRAT

RPE65



Photoreceptor

AIPL1

Lebercillin

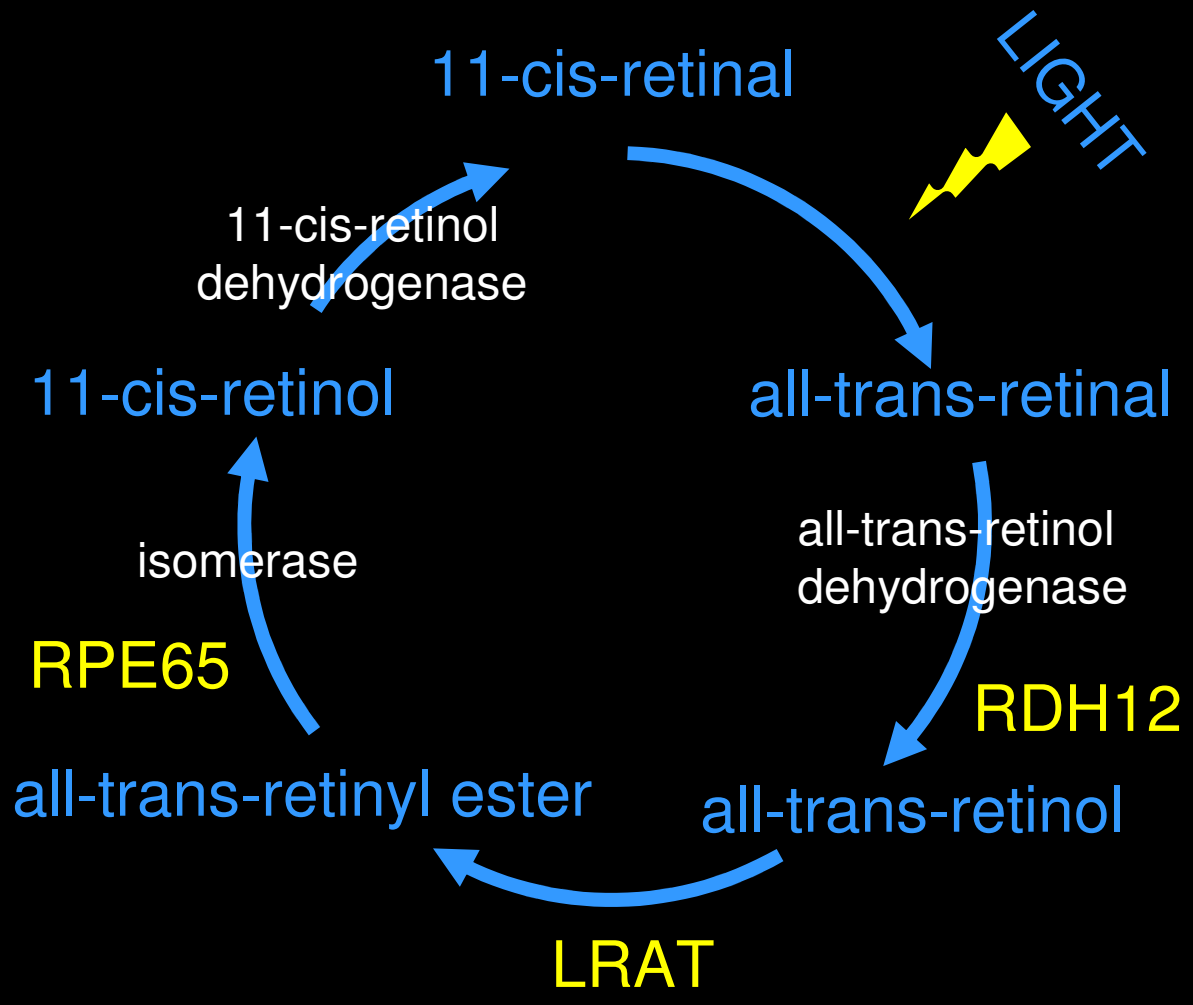
SPATA7

GUC2YD

RPE

EOSRD and visual cycle proteins

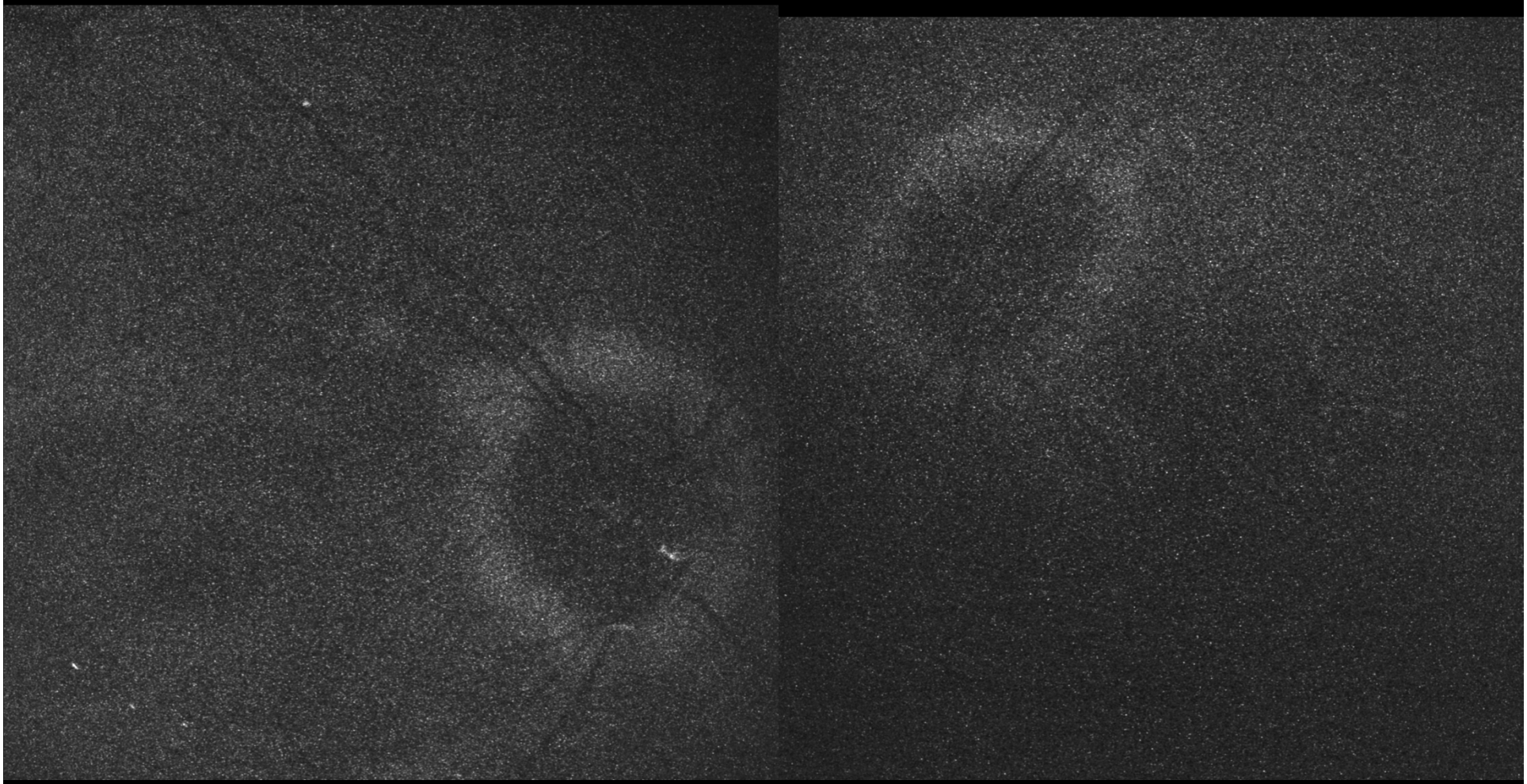
- RDH12
- LRAT
- RPE65



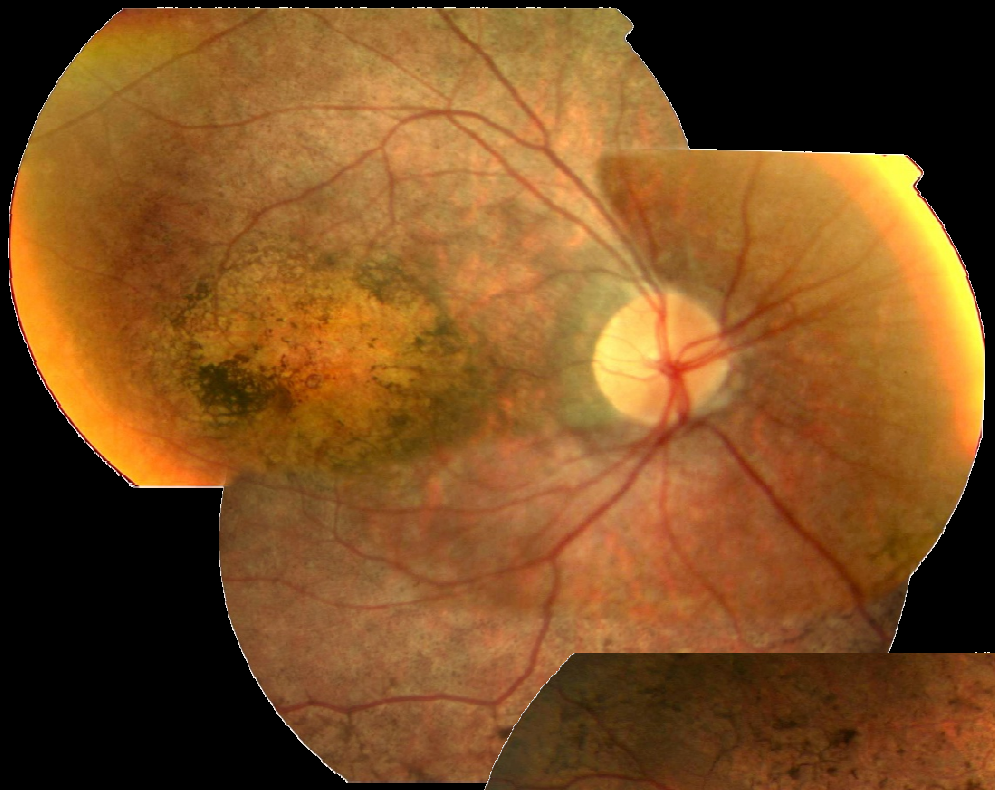
SH age 6
RDH12 mutation (V673L; 805DeI CCCTG)
Early onset rod cone dystrophy

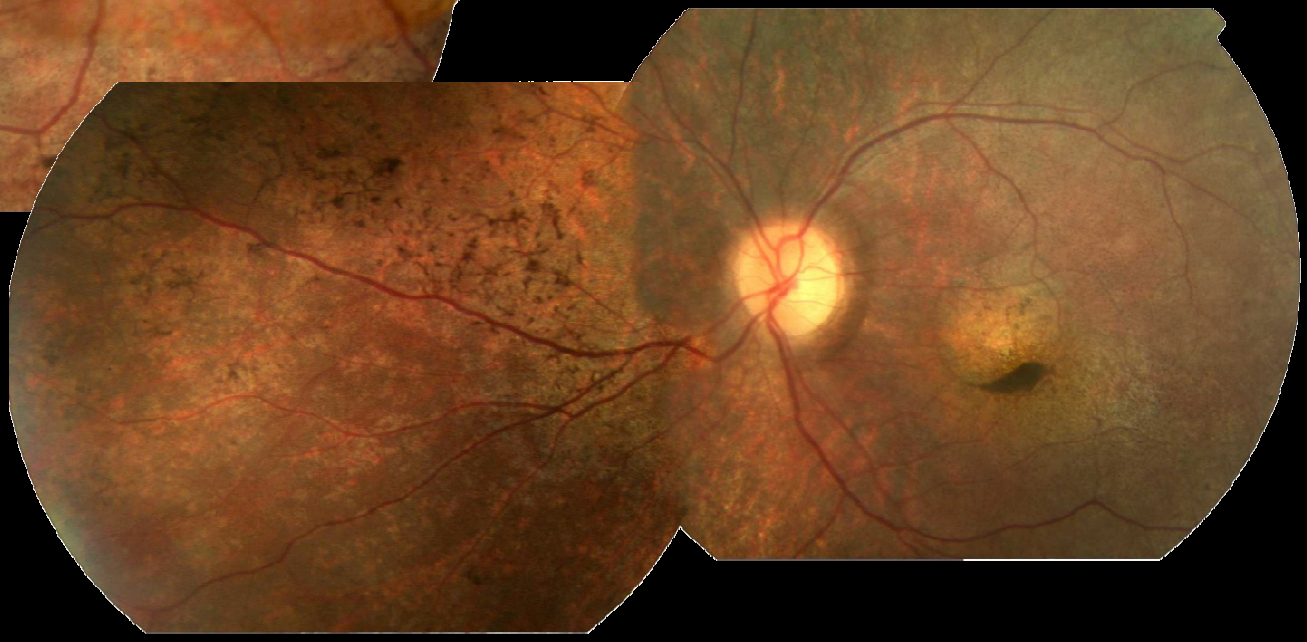
- Poor vision from 6/12
- Nyctalopia
- VA 6/36 R 6/60 L
- Hyperopic +4.50 DS
- Non-recordable ERG

SH age 6 years



RF aged 10 years
RDH 12 mutation (R239W ; 805delCCCTG)





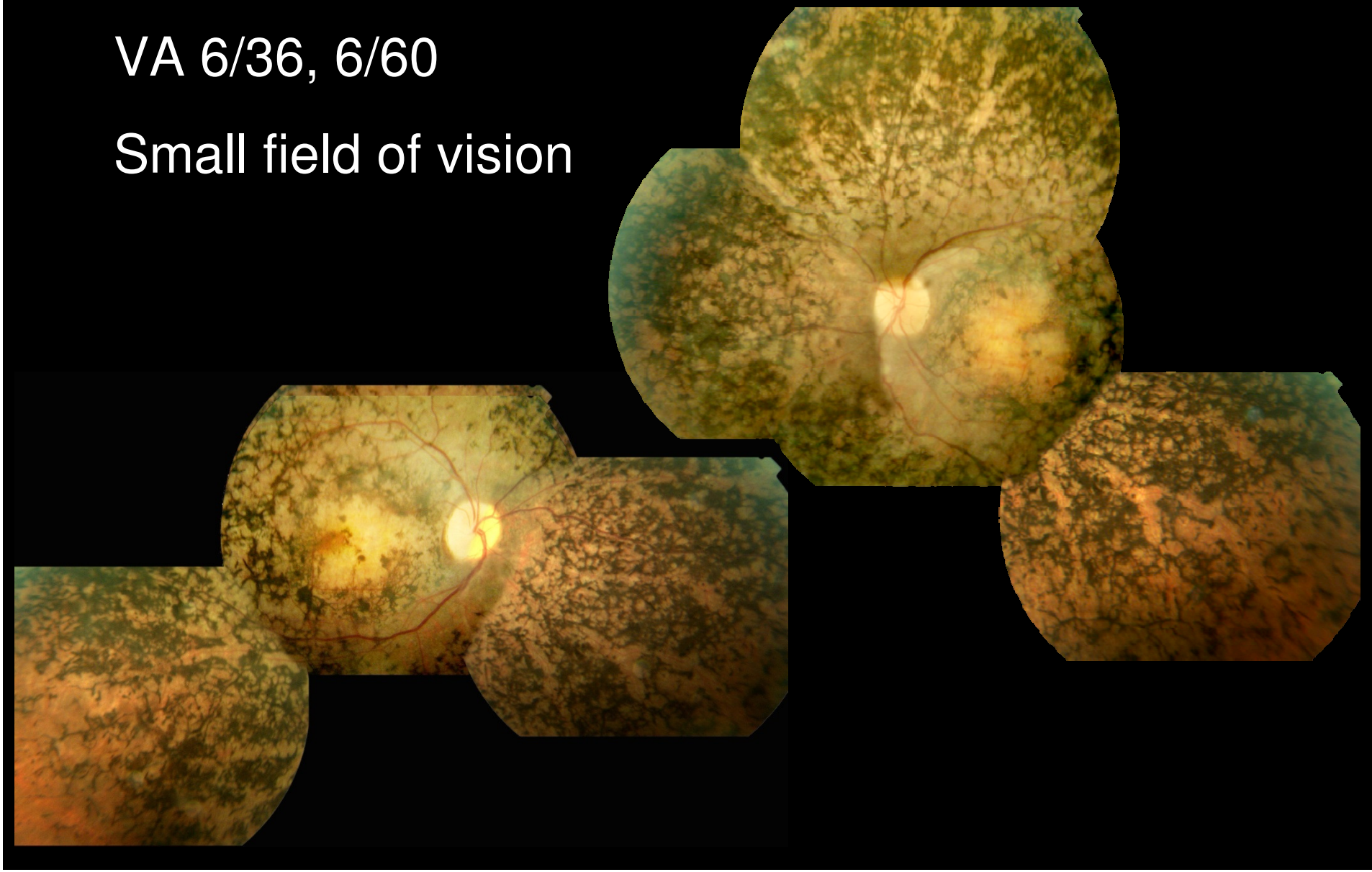
Poor vision and night blindness from infancy

VA 6/60 OU

LF age 23 (Sibling of RF)

VA 6/36, 6/60

Small field of vision



RDH 12 mutations and retinal disease

- Early onset of NB
- Useful vision in early childhood
- Progressive with macular atrophy
- Early cell death

Treatment window in very early childhood

RPE65 gene

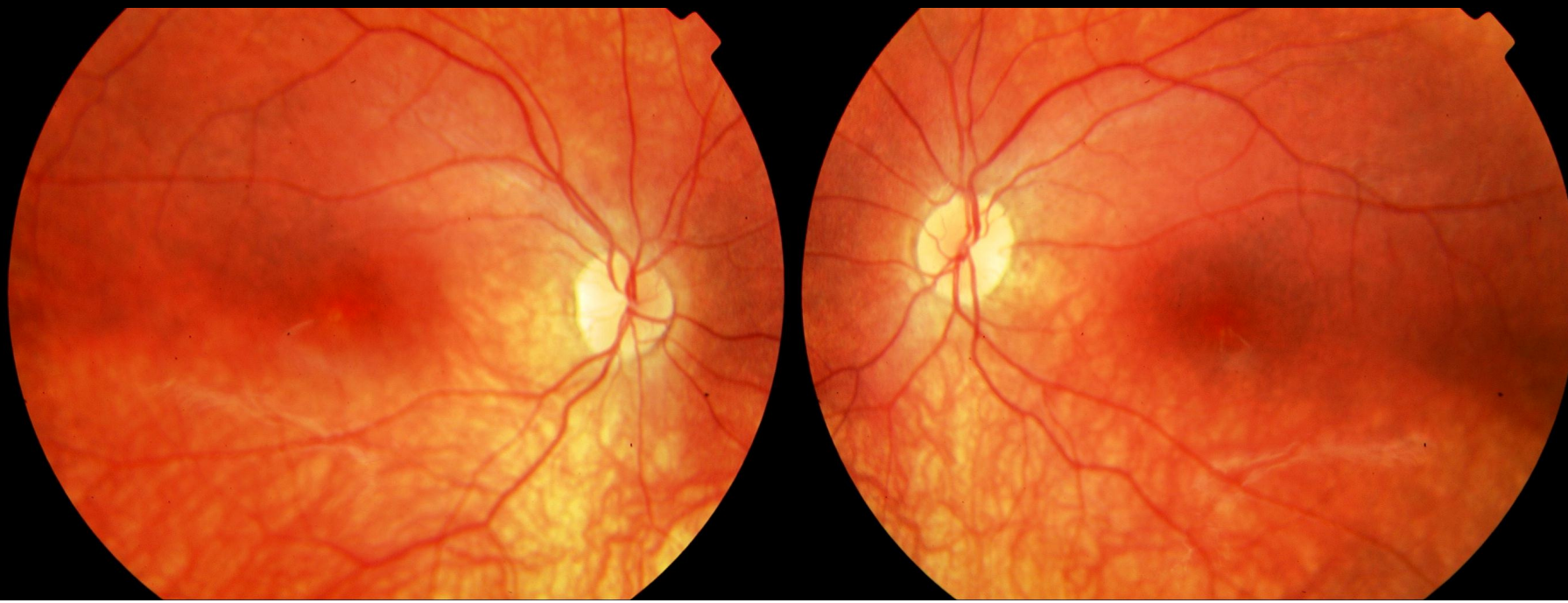
- Encodes a 65 KD protein within RPE
- Responsible for isomerisation of all-trans retinol to 11-cis retinol
- Mutations cause disease in man
- Mouse knockout
- Canine model
- Gene therapy rescue in mice and dogs

Subject OS

- Age 5
- Nyctalopia from birth
- Light staring from 2/52
- Poor vision noted from 10/12
- No nystagmus
- Non-recordable rod ERG
- Minimal cone ERG

Subject OS age 5 (compound heterozygous null)

- VAR 6/36) VAL 6/30 N5
- Poor colour vision
- Pupils reactive
- Minimal residual (cone) ERG



Subject RJ (Y368H; R91W)

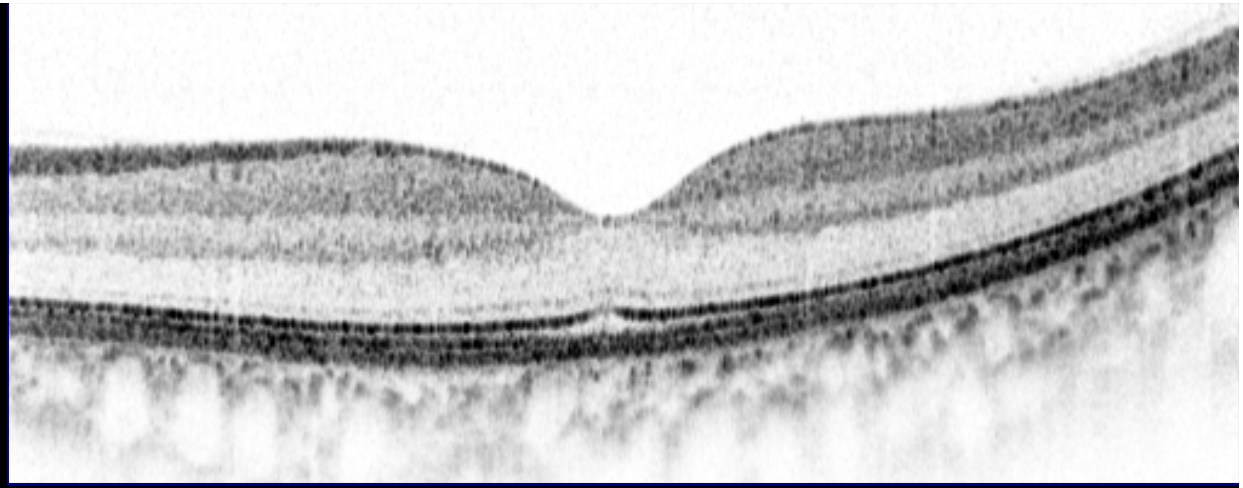
- Age 21
- Light staring prominent at 6/52
- Nyctalopia from infancy
- Poor vision noted 1 year
- Sighted education
- Minimal nystagmus
- No recordable ERG

Subject RJ age 20 years

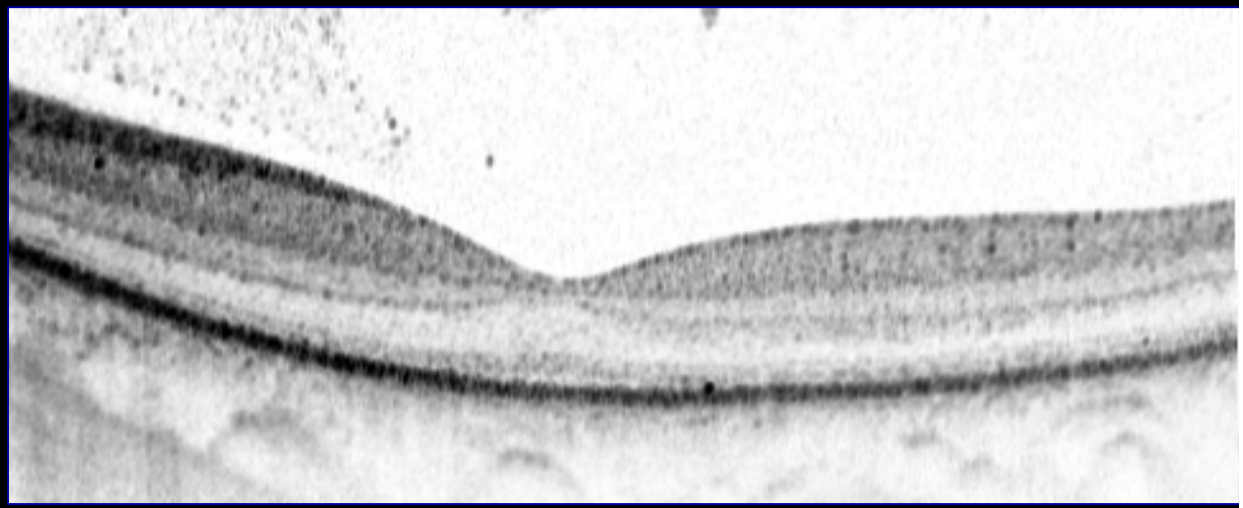
VA 2/60 each eye
15°field

SD OCT

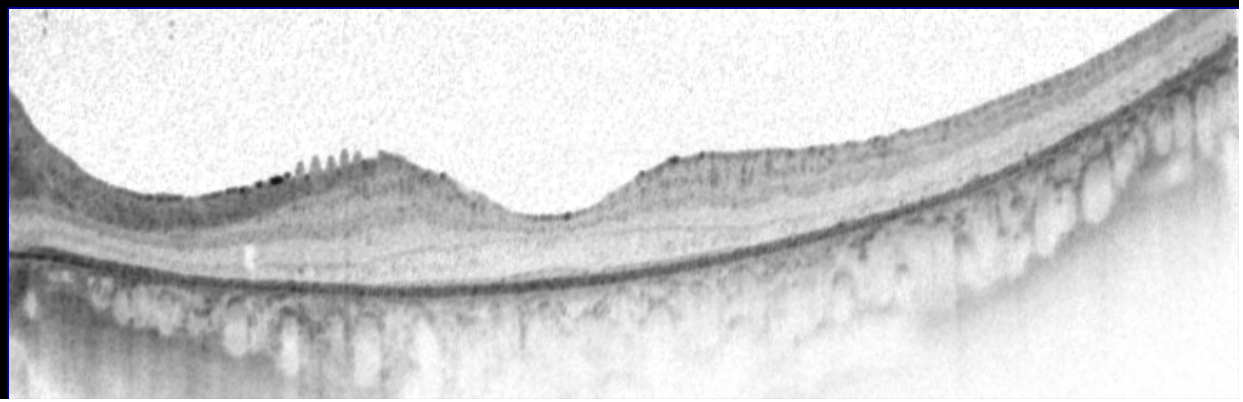
Normal



Patient age 6 years

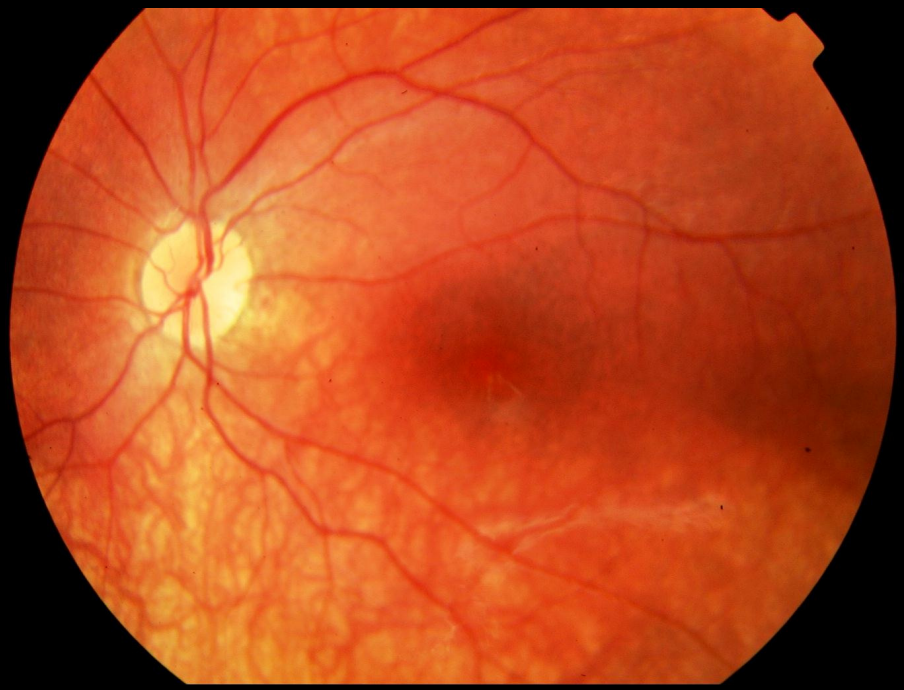


Patient age 23 years



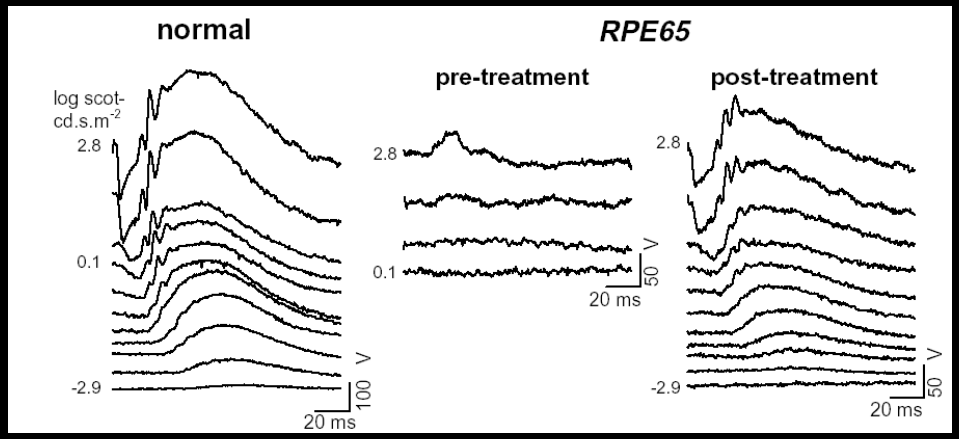
RPE65 deficiency

- Poor vision from infancy
- Profound night blindness
- Light staring
- Blindness by early 20s
- Late retinal cell death
- Window of opportunity for treatment in childhood



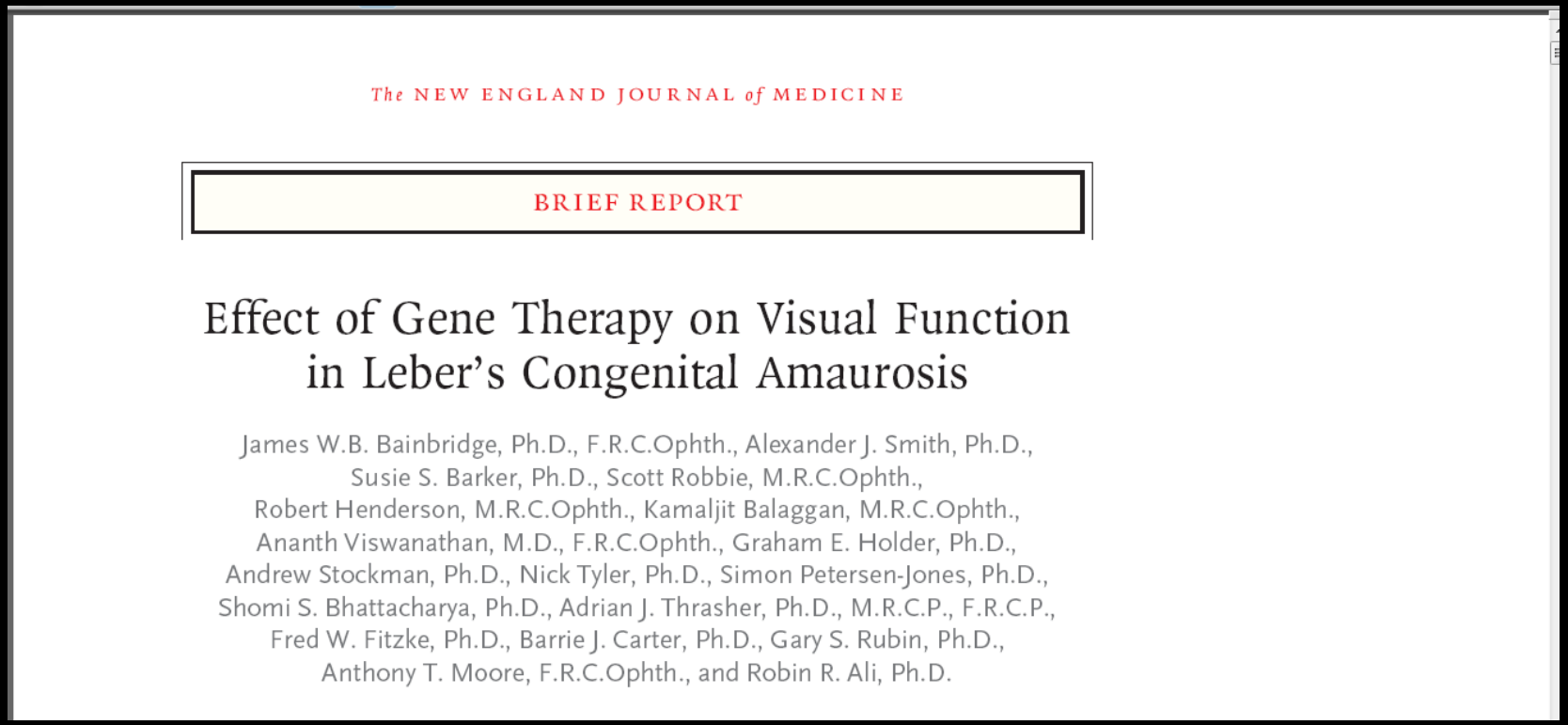
Good candidate for gene therapy

Lancelot: 2001



Acland G. M *et al.*, 2001. Gene therapy restores vision in a canine model of childhood blindness. *Nat Genet* **28,** 92-95.

Gene therapy for LCA due to RPE65 deficiency



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis

James W.B. Bainbridge, Ph.D., F.R.C.Ophth., Alexander J. Smith, Ph.D., Susie S. Barker, Ph.D., Scott Robbie, M.R.C.Ophth., Robert Henderson, M.R.C.Ophth., Kamaljit Balaggan, M.R.C.Ophth., Ananth Viswanathan, M.D., F.R.C.Ophth., Graham E. Holder, Ph.D., Andrew Stockman, Ph.D., Nick Tyler, Ph.D., Simon Petersen-Jones, Ph.D., Shomi S. Bhattacharya, Ph.D., Adrian J. Thrasher, Ph.D., M.R.C.P., F.R.C.P., Fred W. Fitzke, Ph.D., Barrie J. Carter, Ph.D., Gary S. Rubin, Ph.D., Anthony T. Moore, F.R.C.Ophth., and Robin R. Ali, Ph.D.

Bainbridge J et al N Eng J Med 2008 358(21):2231-9
Maguire AM et al N Eng J Med 2008 358(21):2240-8
Cideciyan A et al Proc Natl Acad Sci 2008;105:15112-7

Gene therapy for LCA

- Three groups have published preliminary results of treatment of RPE65 deficiency
- No safety issues
- Improved retinal function in some patients
- Limited if any improvement in visual acuity
- How do we improve results?

Bainbridge J et al N Eng J Med 2008 358(21):2231-9
Maguire AM et al N Eng J Med 2008 358(21):2240-8
Cideciyan A et al Proc Natl Acad Sci 2008;105:15112-7

Summary

- Advances in molecular genetics will lead to identification of most causative genes
- Much to be learnt about mechanism of photoreceptor cell death and how to prevent this
- Multiple treatment strategies needed
- Patient selection and determining treatment effects will be a major challenge

Humans are more complicated than animal models