Clinical Aspects of Ophthalmic Genetics

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European Reference Network for rare or low prevalence complex diseases

Network Eye Diseases (ERN-EYE)

Outline

Introduction

Albinism

Ocular developmental disorders

Generalised retinal dystrophies

Stationary retinopathies

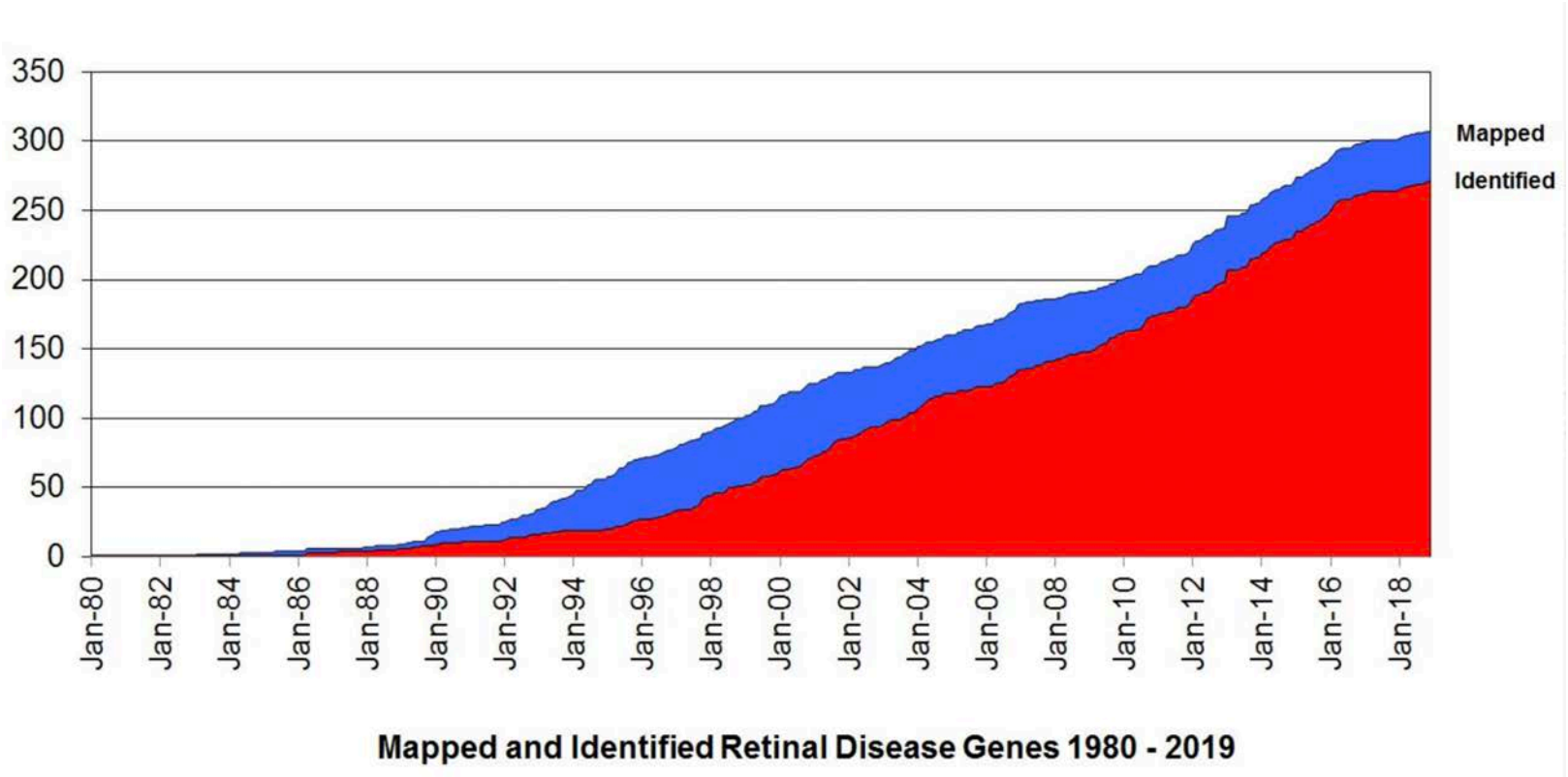
Dystrophies w/ predominant macular involvement

1/ Introduction

Introduction
Basic Genetics

- Humans: 20.338 genes x 2 (= 3.200.000.000 bp (x2))
  - Non-coding genes 22.521
  - Pseudogenes 14.638
  - Gene transcripts 200.310
- Inherited retinal & ON diseases: 329 genes (358 genes & remaining unidentified loci)
  (https://sph.uth.edu/retnet)

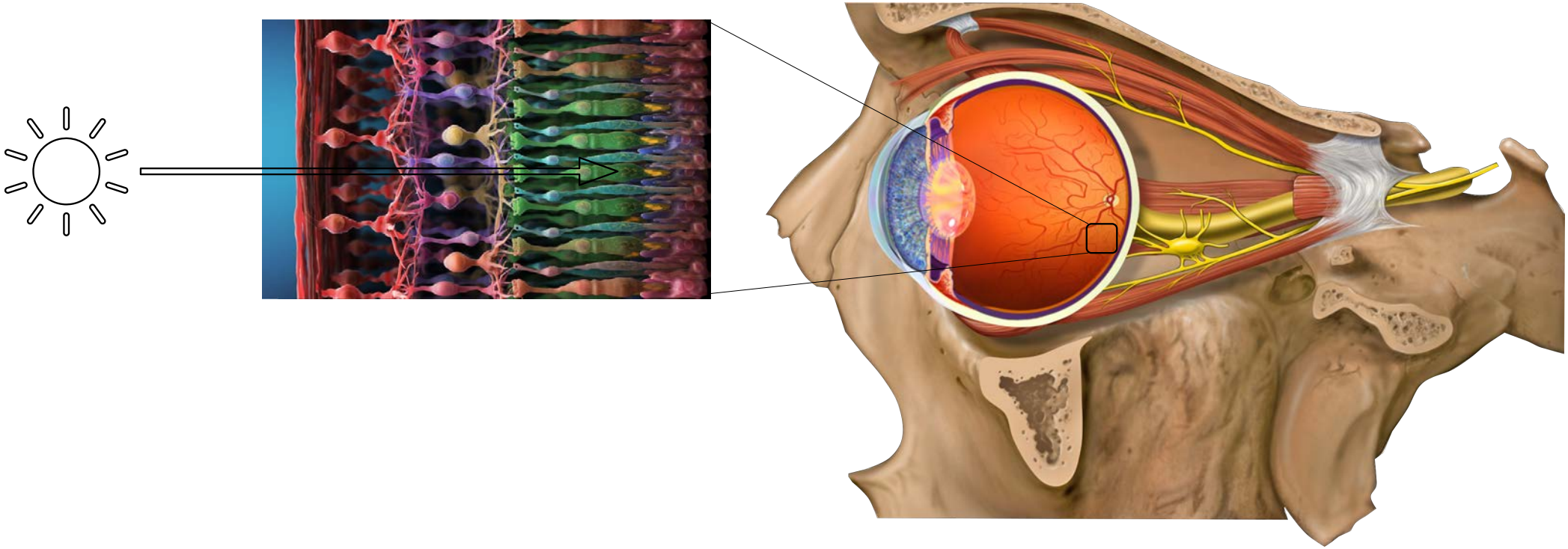
Introduction
History of Ocular Genetics



Mapped and Identified Retinal Disease Genes 1980 - 2019

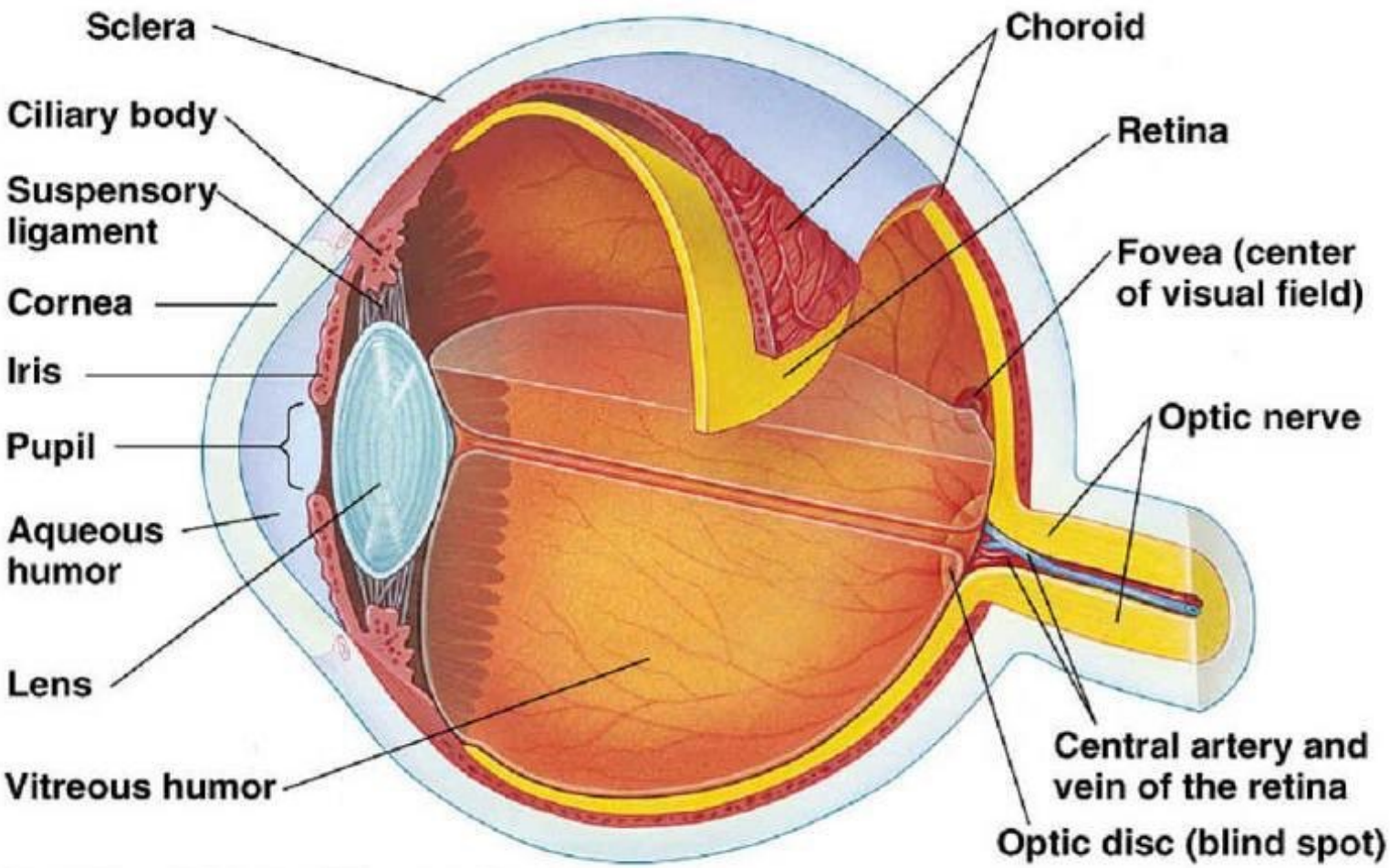
RetNet on https://sph.uth.edu/retnet/

Human Retina



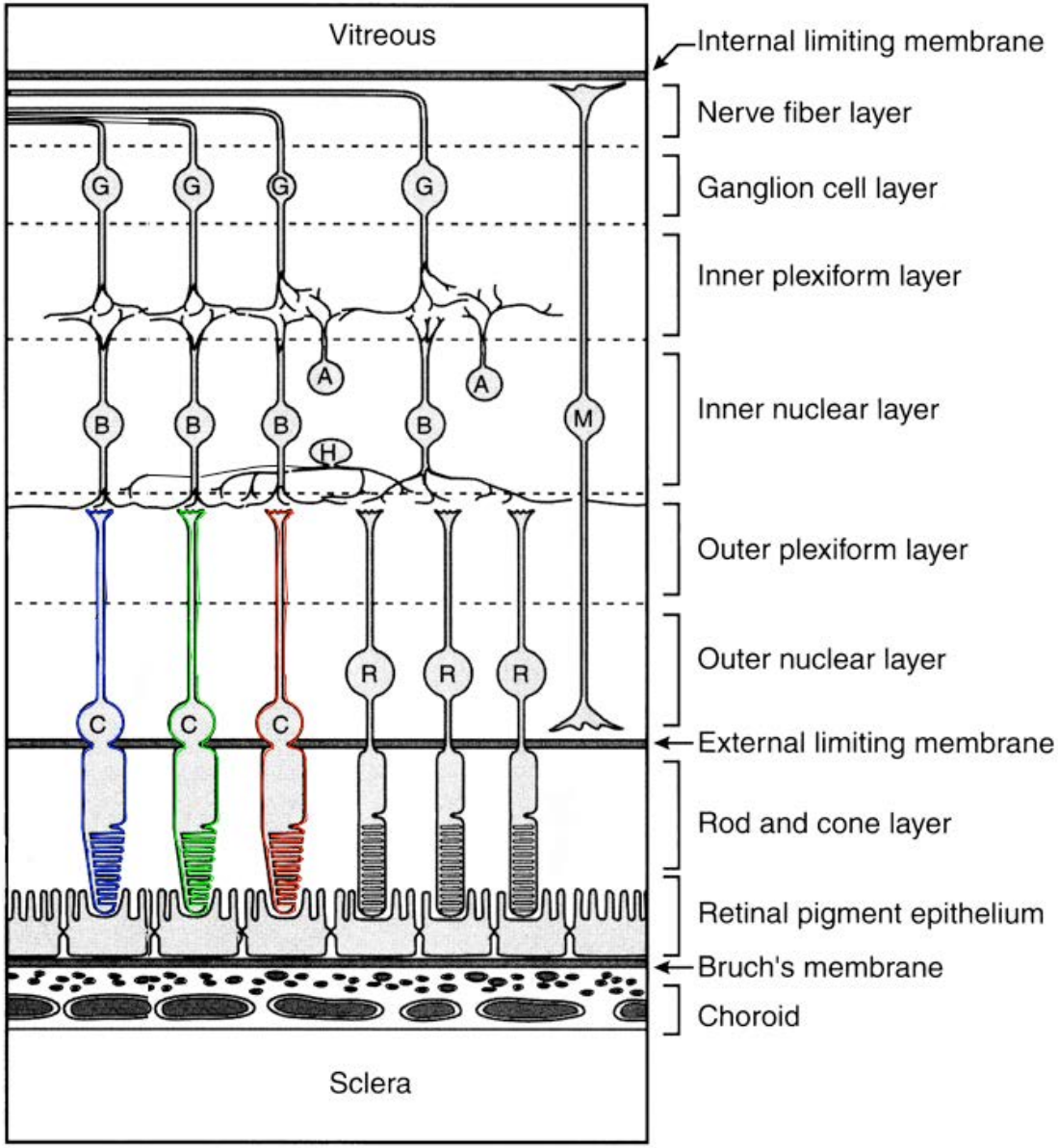
Eye translates light into electricity

Cross-section of Human Eye

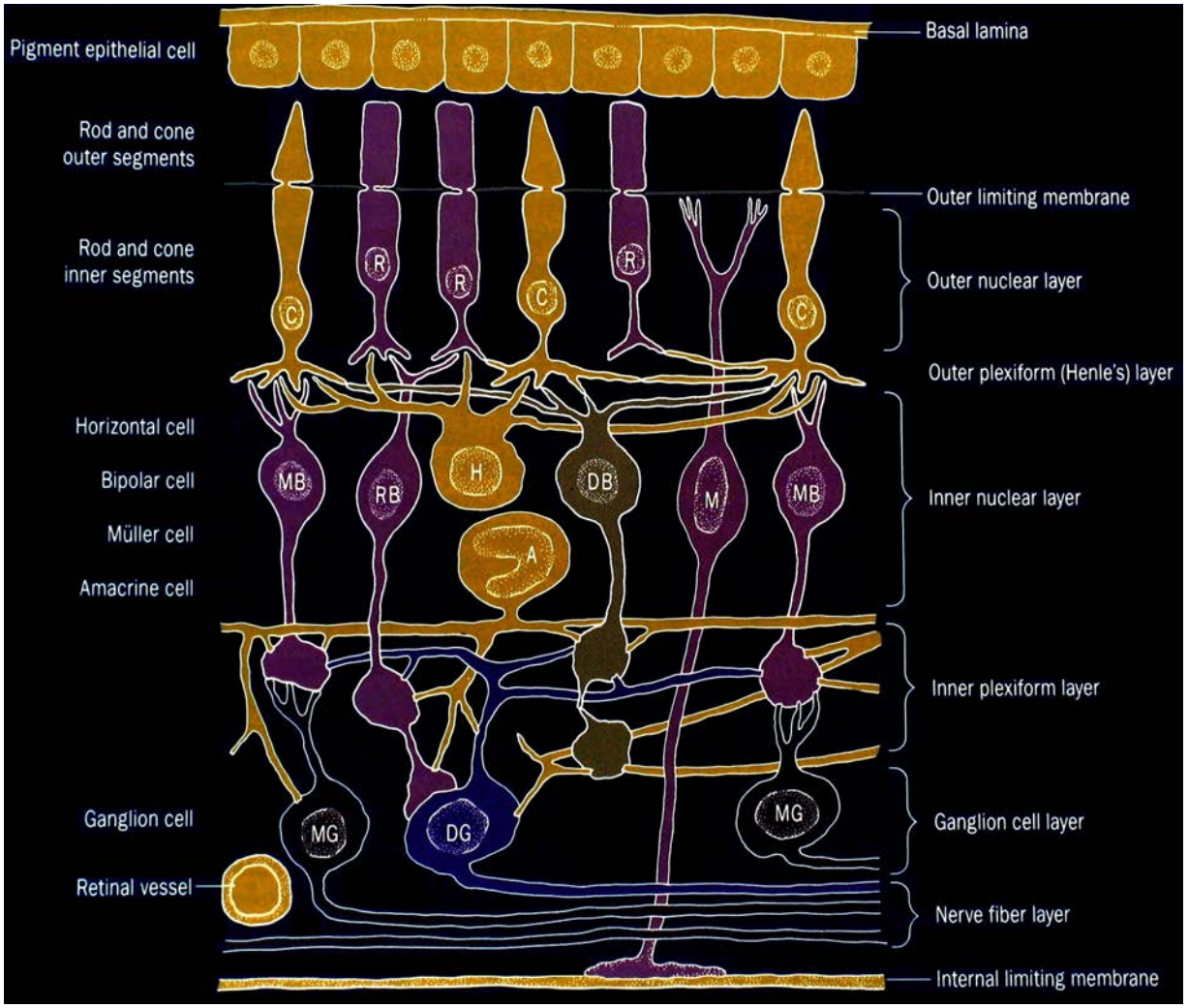


Introduction
Retinal Circuitry

Adapted from ***The Neurology of Vision*** by
JD Trobe



Retinal Cells & Layers



ERG a-wave
from PRs

Outer Retina

Blood Supply
from
Choroid

ERG b-wave
from Bipolar &
Müller Cells

Inner Retina

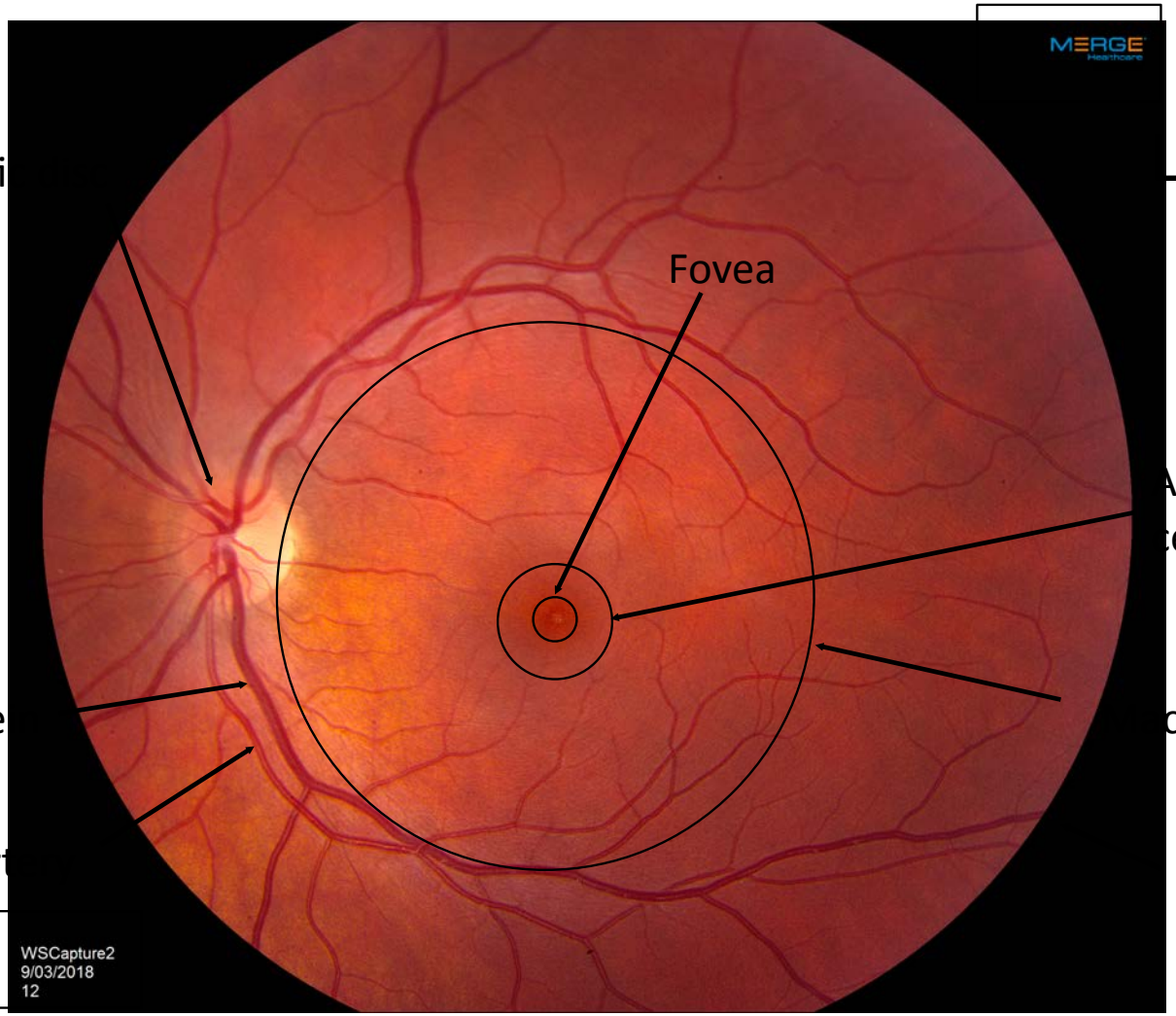
Blood Supply
from
Retinal Circulation

Retina

Retinal Periphery vs Macula

Visual Field vs Visual Acuity

Ocular Fundus



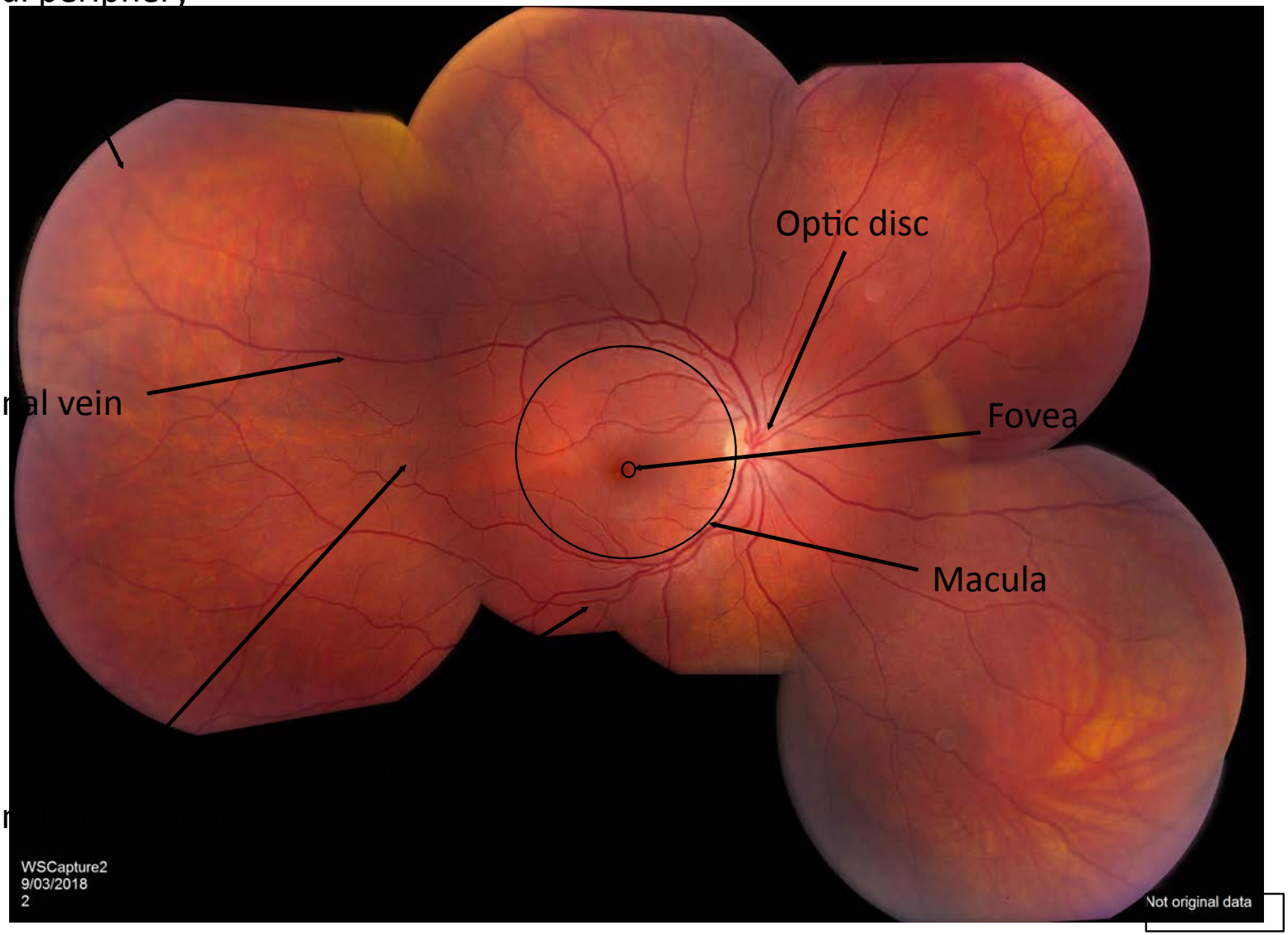
Opti LE

Area
entralis

Retinal ve cula

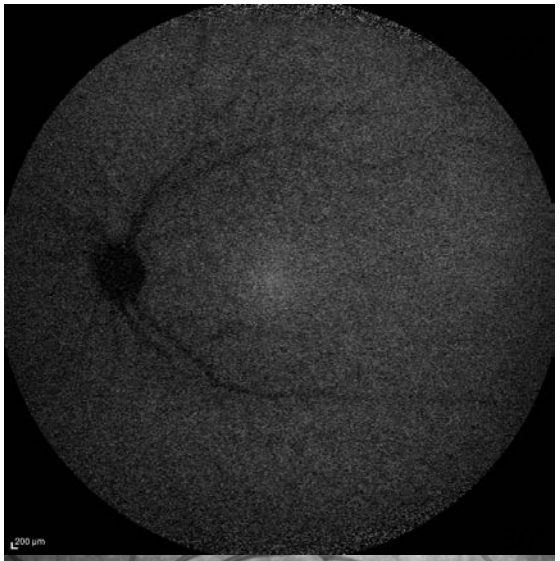
Retinal art Posterior
Pole

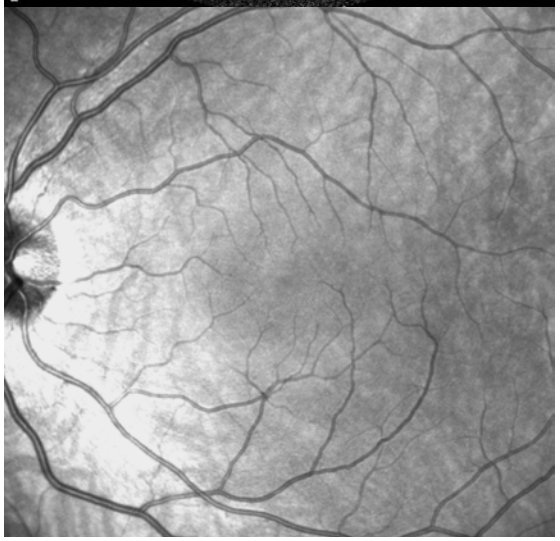
Ocular Fundus



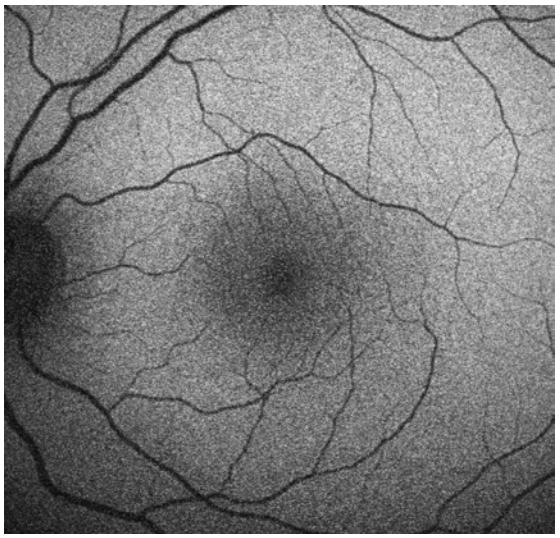
Fundus Imaging w/ Monochromatic Light

Posterior Pole of Normal LE

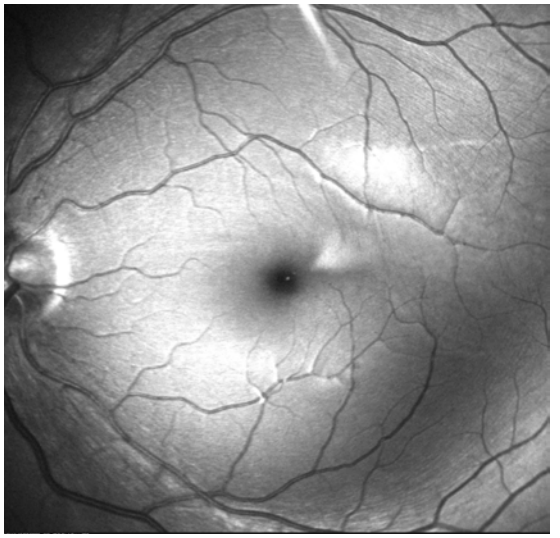




30°



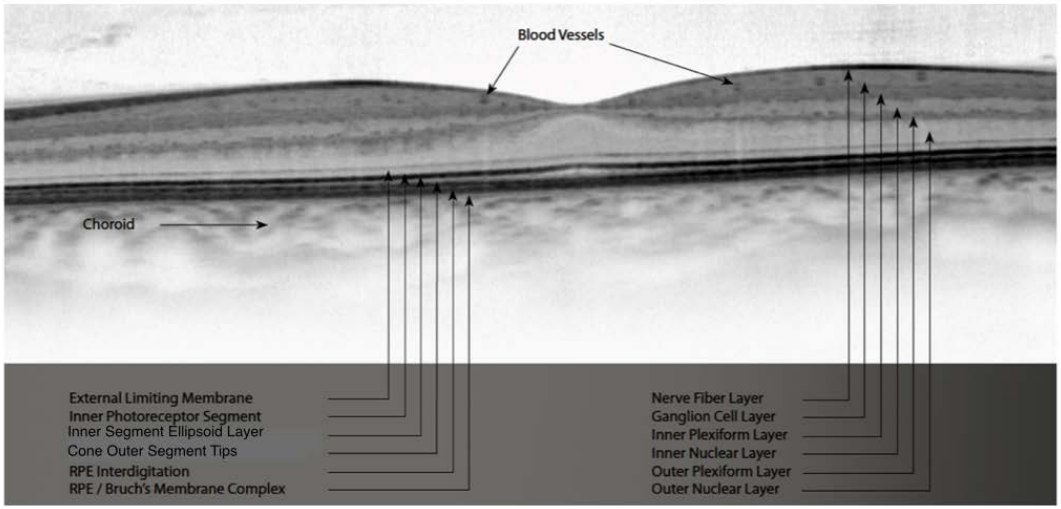
30°



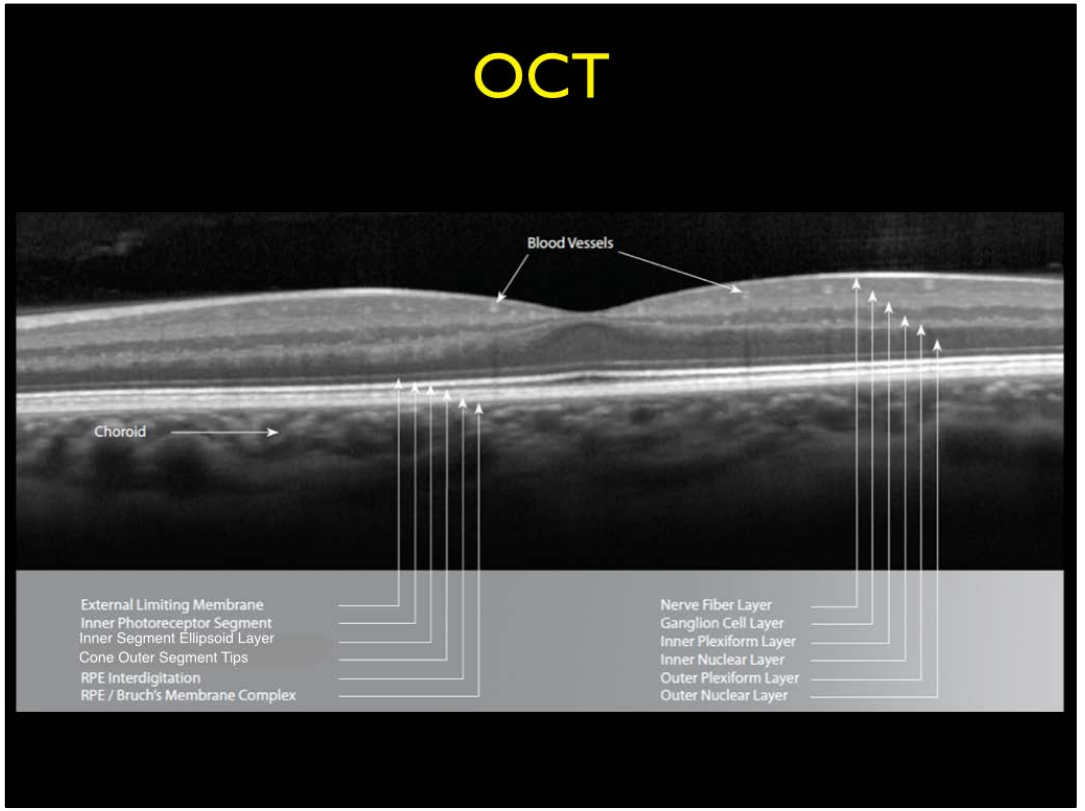
Type	Infrared autofluorescence (top) & reflectance (bottom)	Blue light autofluorescence	Blue light reflectance
Chromophore	Pigment	Lipofuscin	Inner retinal structures, blood

Retinal Anatomy

Optical Coherence Tomography (OCT)



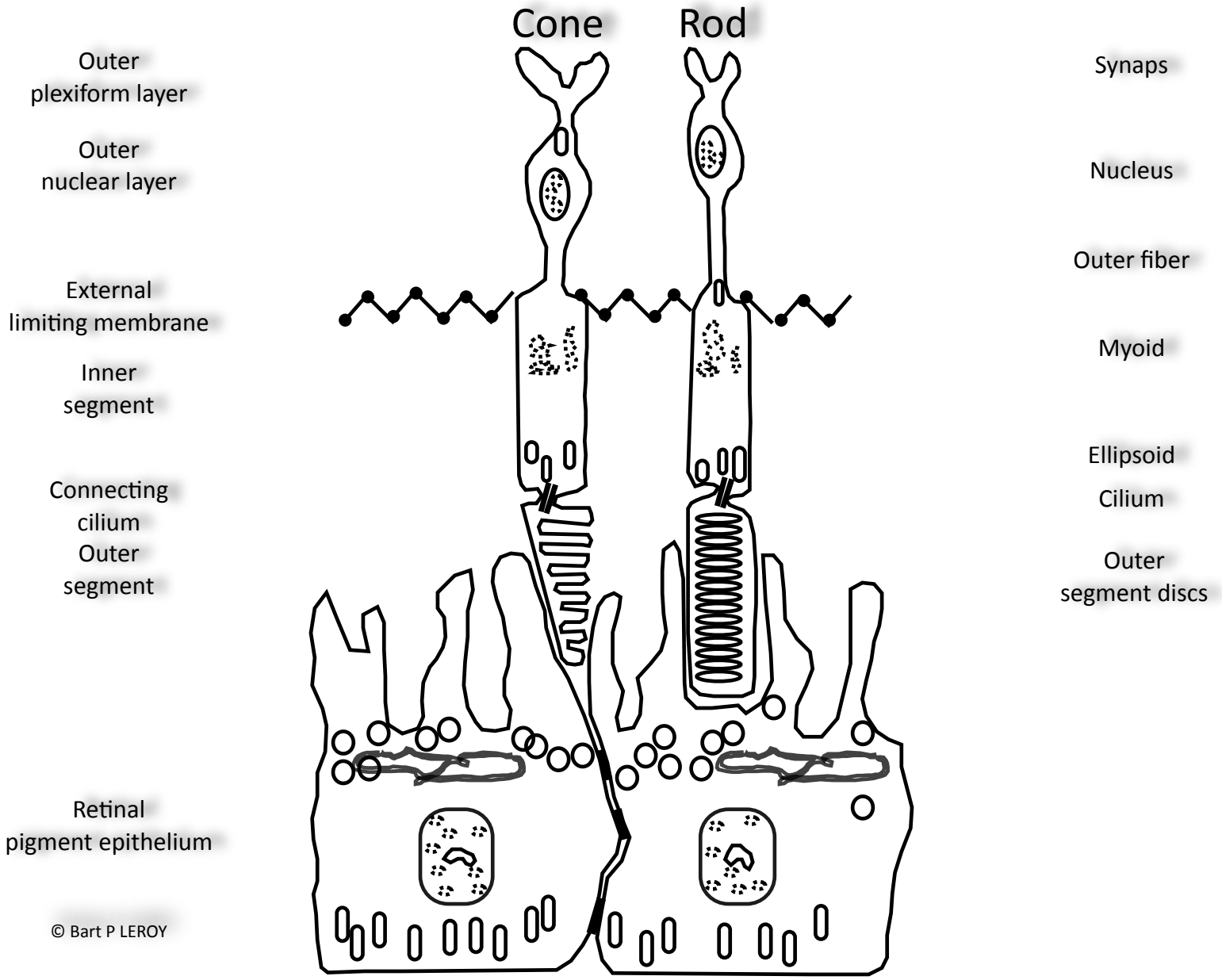
Black on white



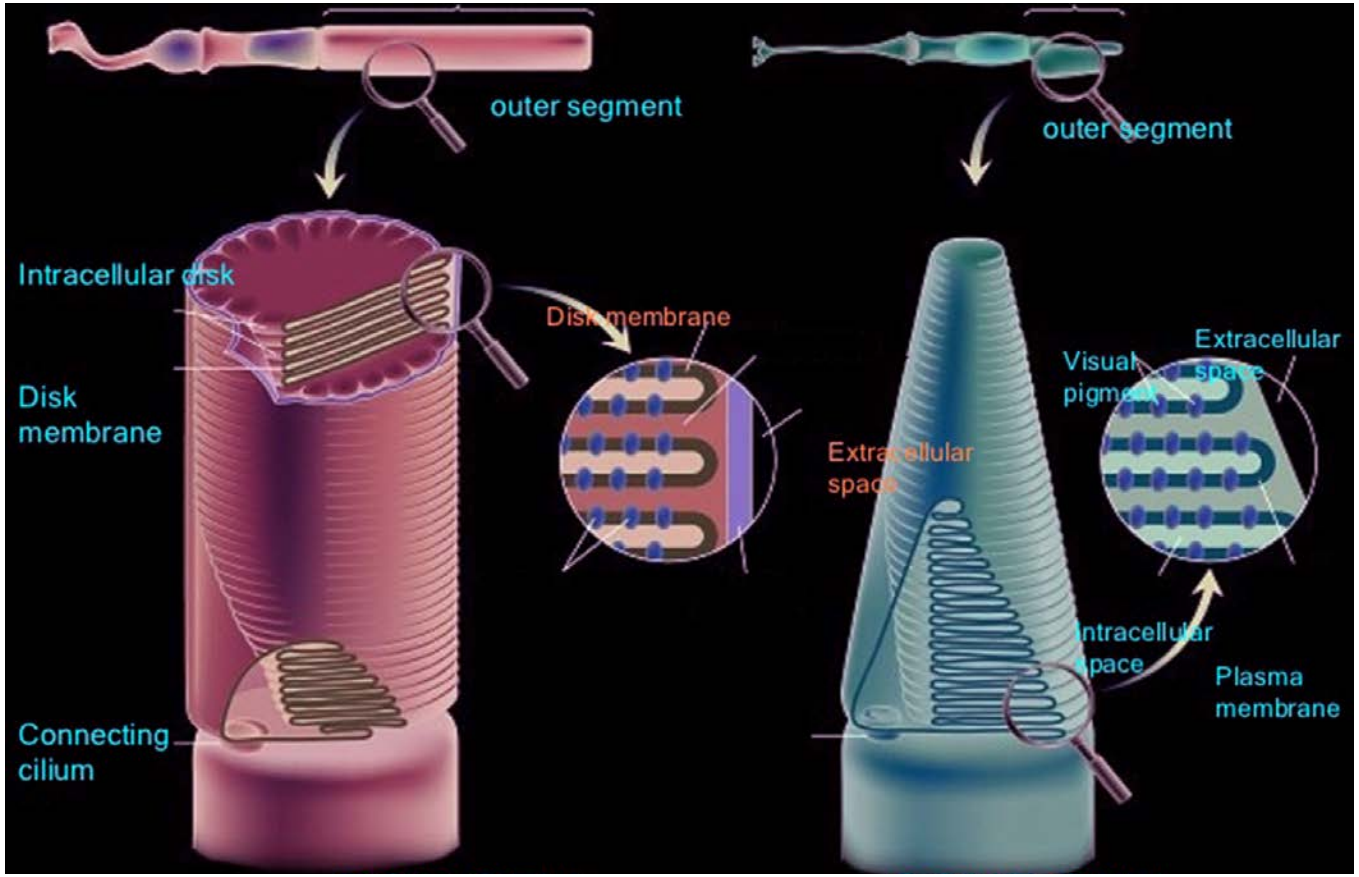
Retinal Pseudo-Anatomy

Rods & Cones

- Rods
  - 120.000.000 to 130.000.000 per retina
  - Navigational vision at night
  - Do not function in daylight
- Cones
  - 5.000.000 to 7.000.000 per retina
  - Visual acuity in daylight
  - Colour vision in daylight
  - Navigational vision in daylight
  - Colour vision at night

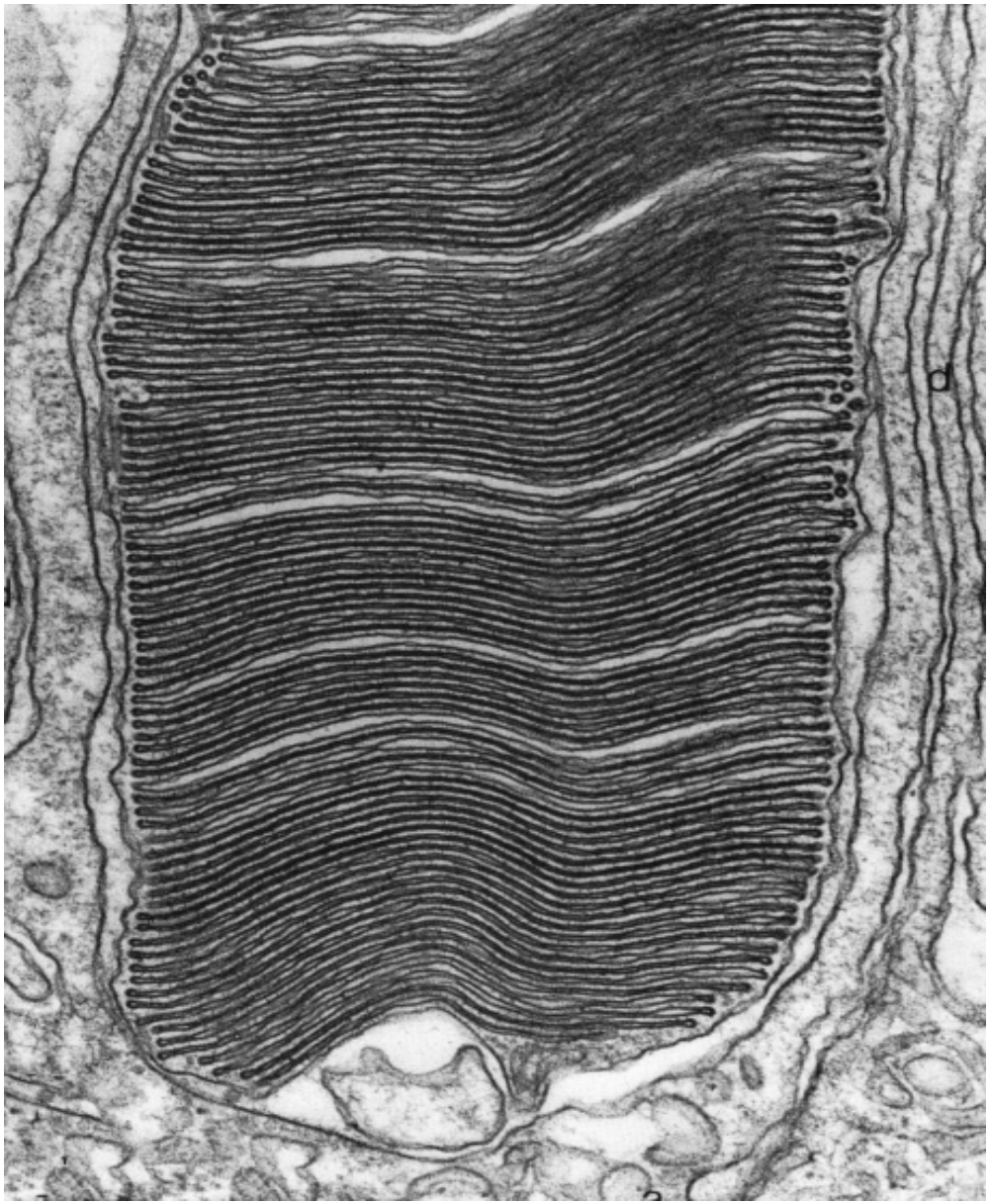

Cone
Rod
Outer plexiform layer
Outer nuclear layer
External limiting membrane
Inner segment
Connecting cilium
Outer segment
Retinal pigment epithelium
Synaps
Nucleus
Outer fiber
Myoid
Ellipsoid
Cilium
Outer segment discs

Rod & Cone Outer Segments



ROD OUTER SEGMENT

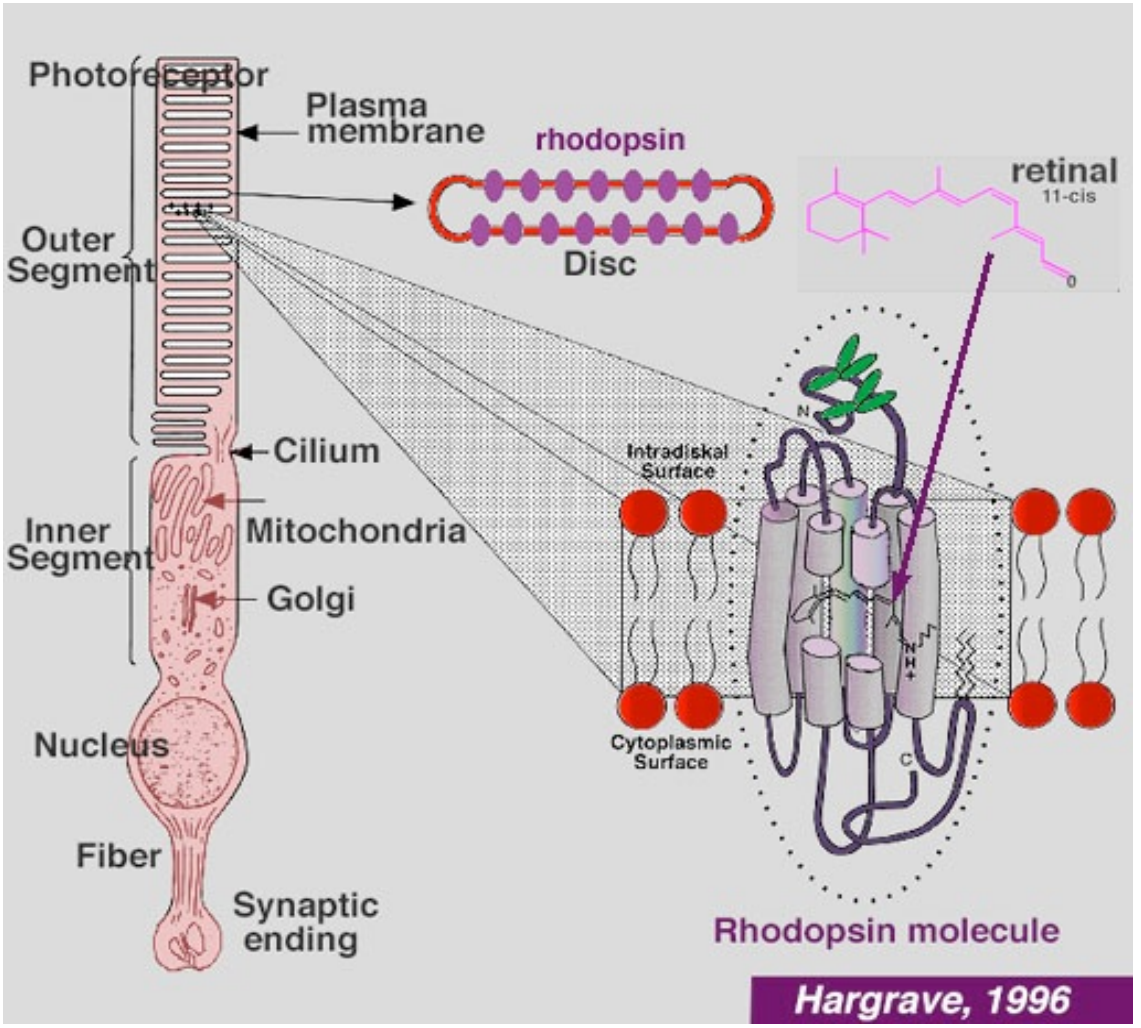
CONE OUTER SEGMENT



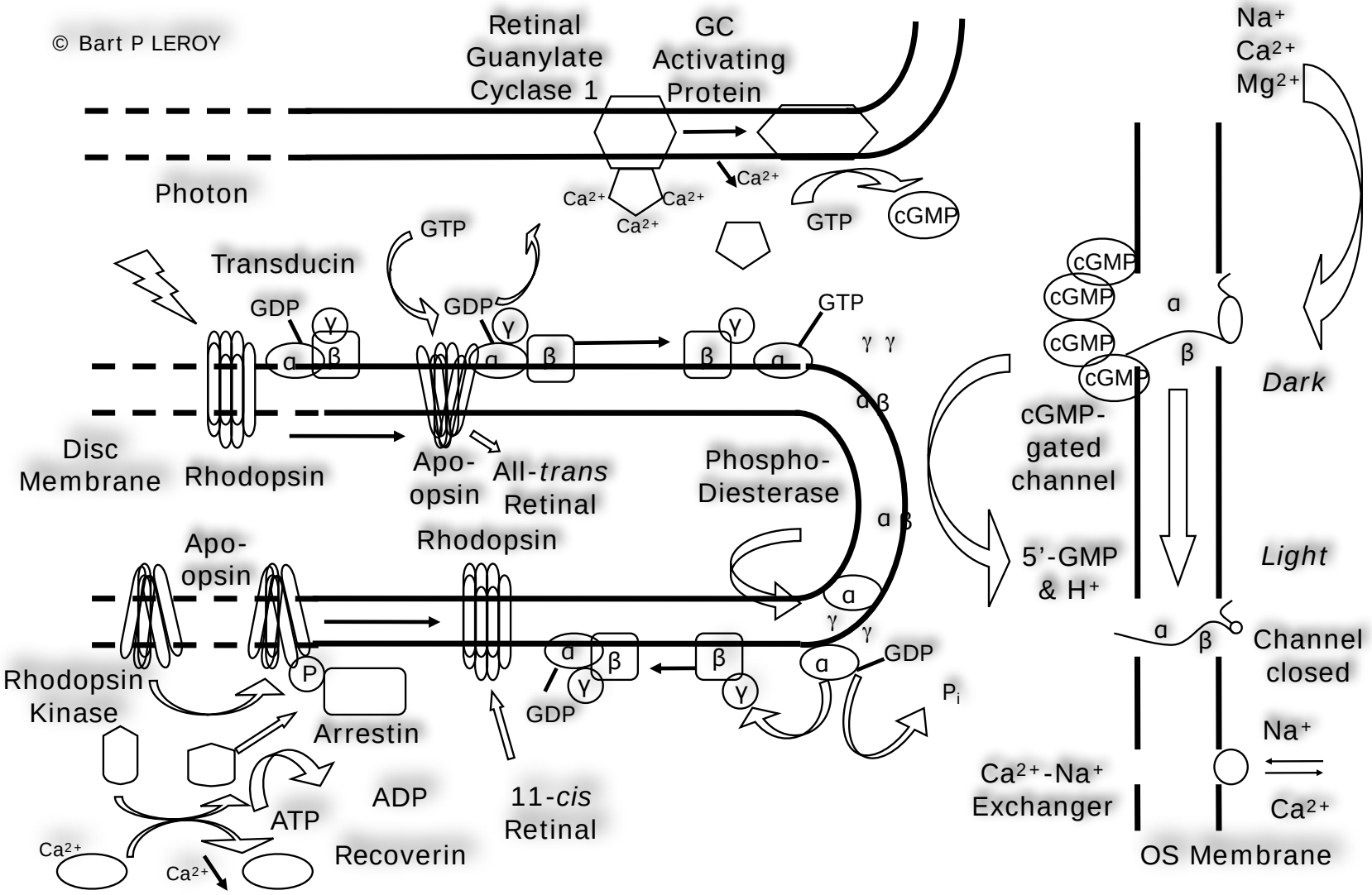
Rod Outer Segment

Pizza Calzone

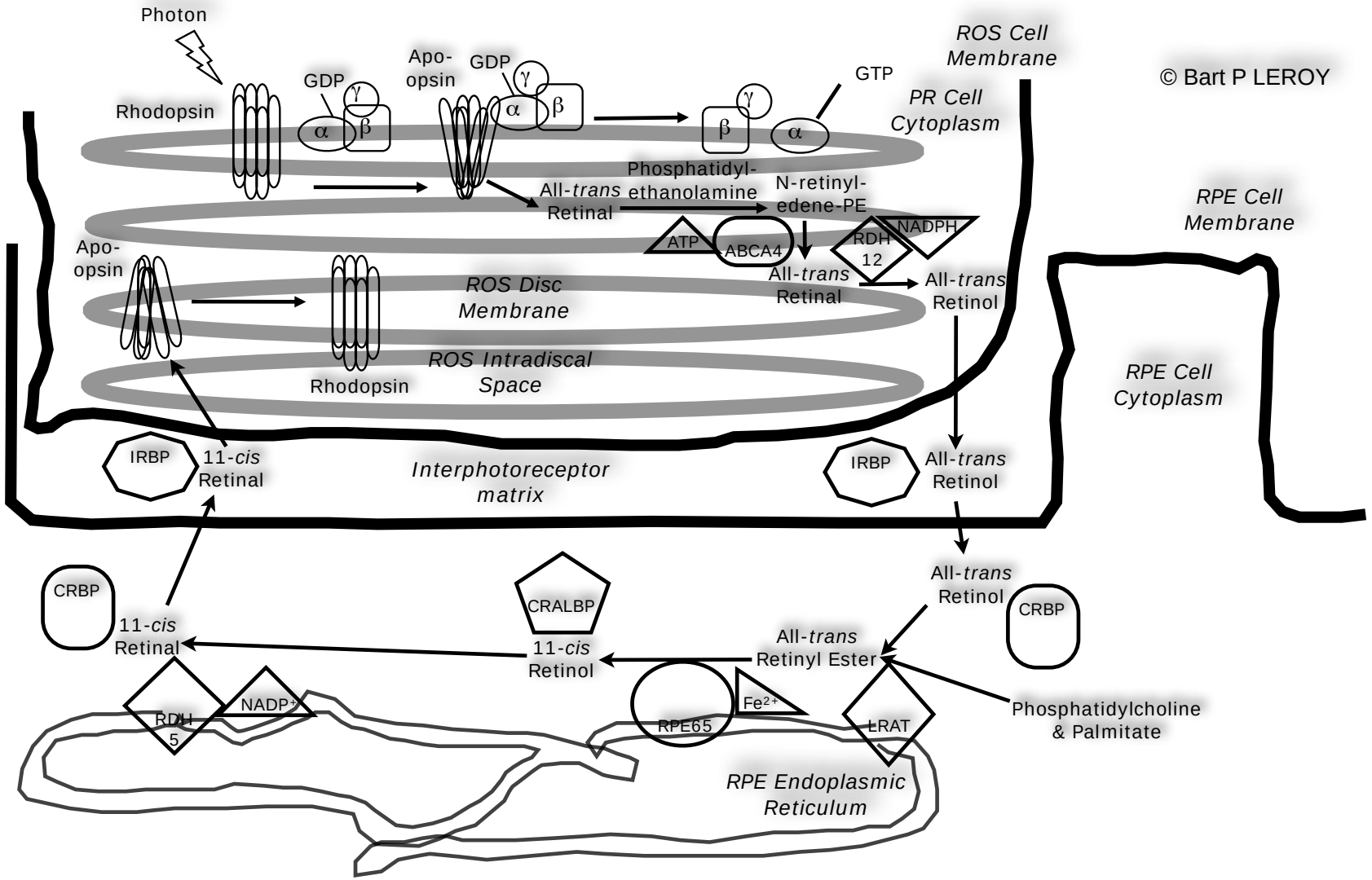
Rhodopsin & ROS



The Phototransduction Cascade



The Retinoid Cycle



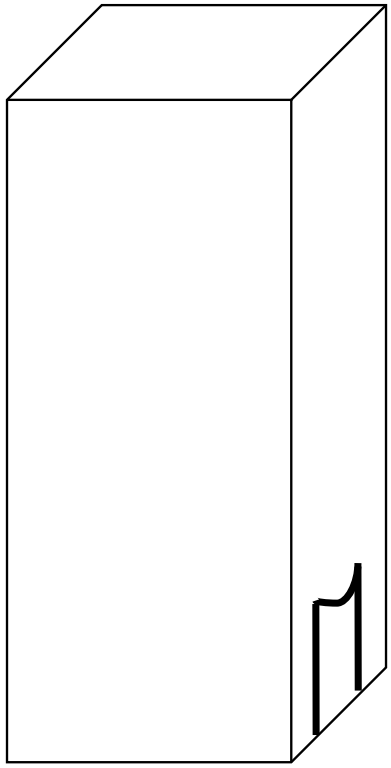
Diagnostic Test: Full-Field Flash Electroretinography Definition

= record of a diffuse electrical response generated by neural and nonneural retinal cells upon stimulation of the eye with a flash of light

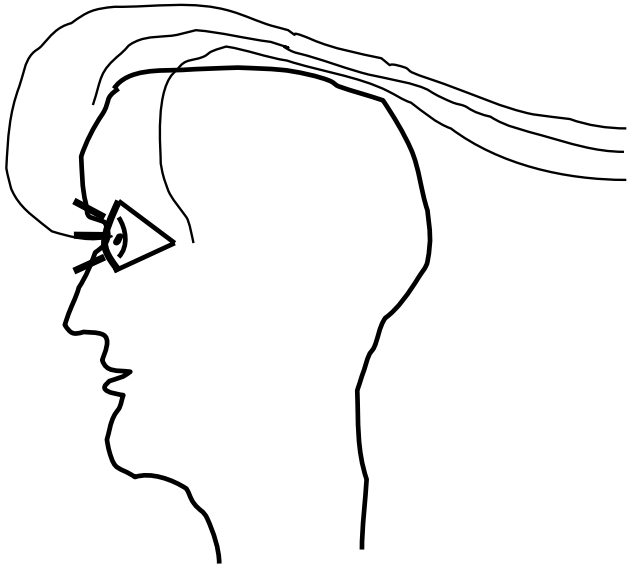
(dark- then light-adapted - dilated pupils)

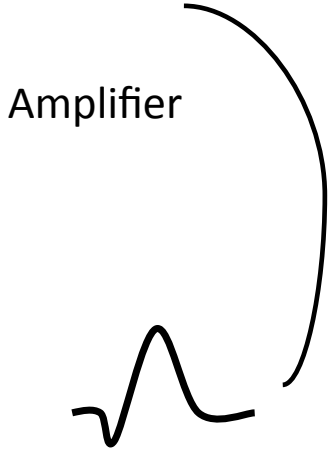
Full-Field Flash ERG

Settings



Ganzfeld

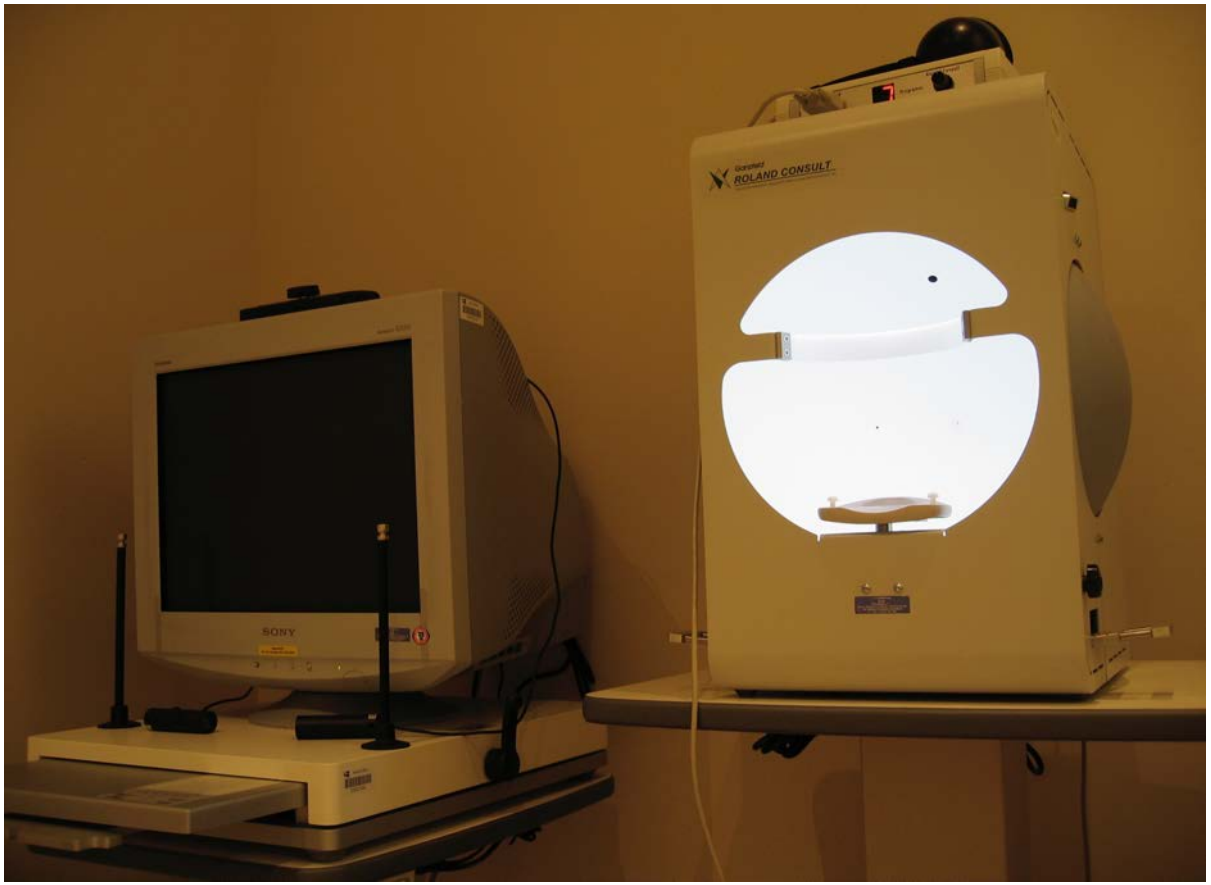




Amplifier

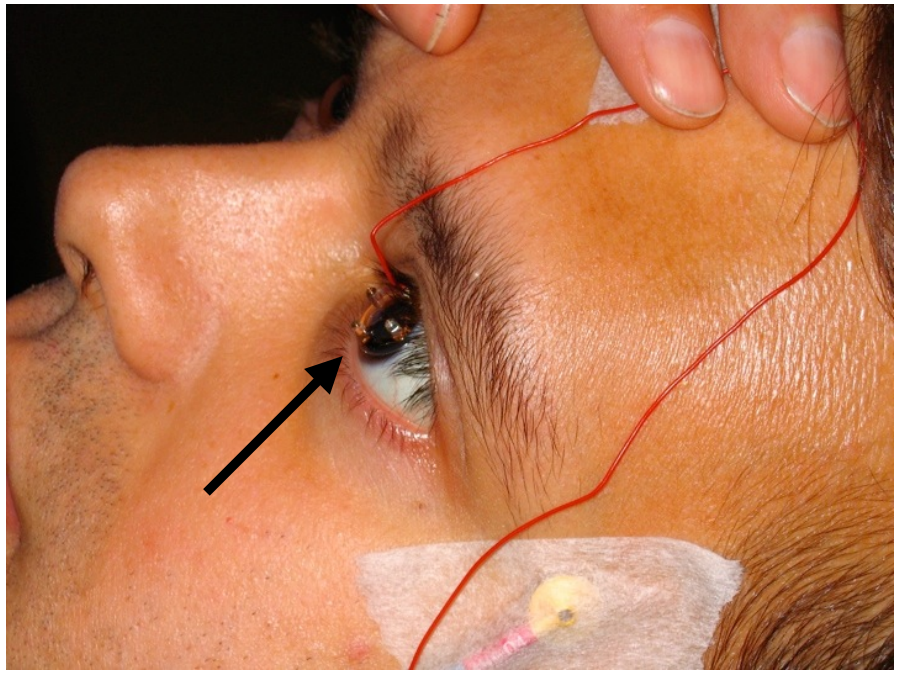
Display

Full-Field Flash ERG
Ganzfeld Stimulator

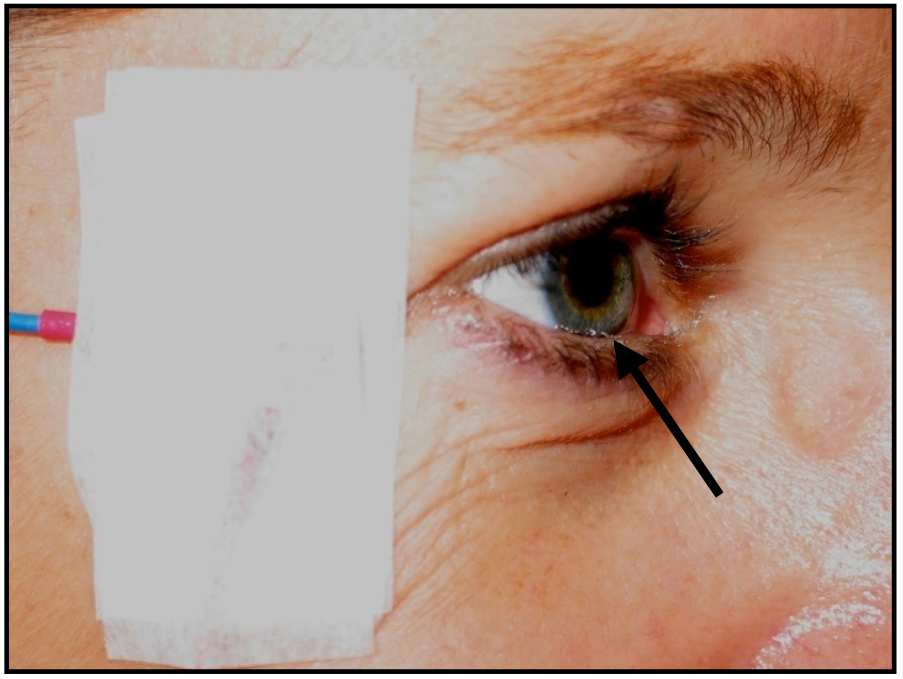


Full-Field Flash ERG
Electrodes

Contact lens

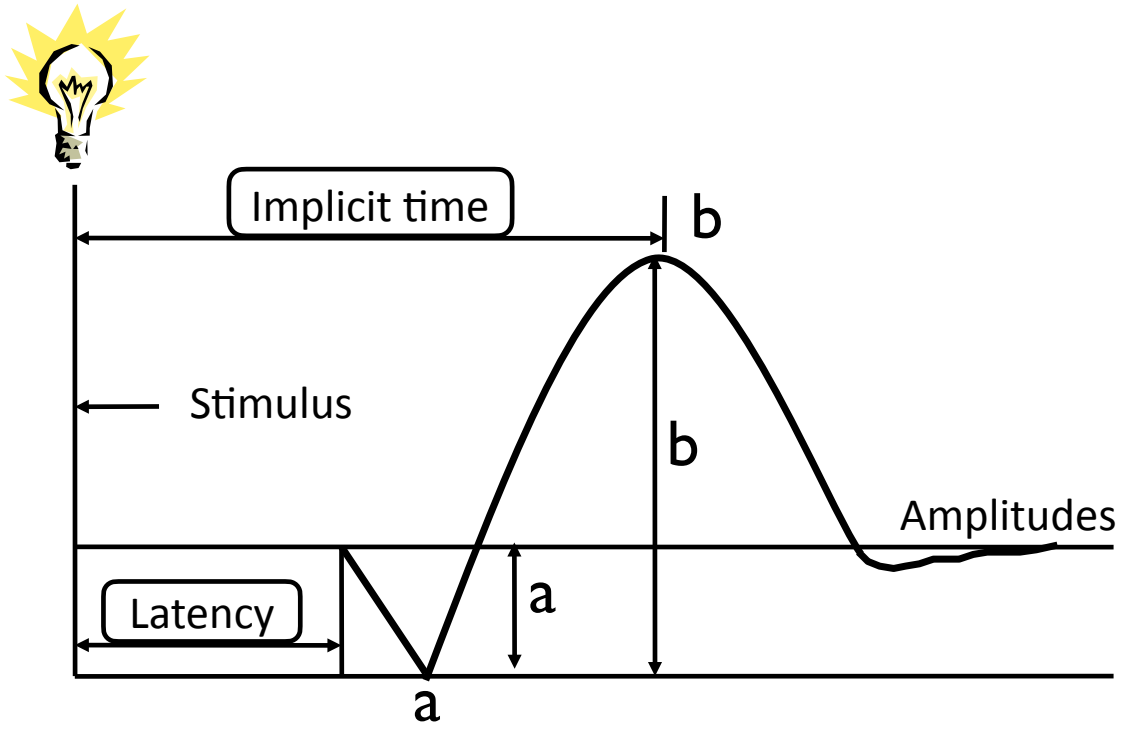


DTL



Alternatives: gold foil or HK loop

Full-Field Flash ERG
Basic Components



Currently shift towards usage of more universal “Peak Time”

Clinical Flash ERG
Basic Components

- a-wave (negative)
  - *amplitude: baseline to trough*
  - *latency: from stimulus to beginning of a-wave*
- b-wave (positive)
  - *amplitude: trough of a-wave to peak of b-wave*
  - *implicit time: from stimulus onset to peak of b-wave*

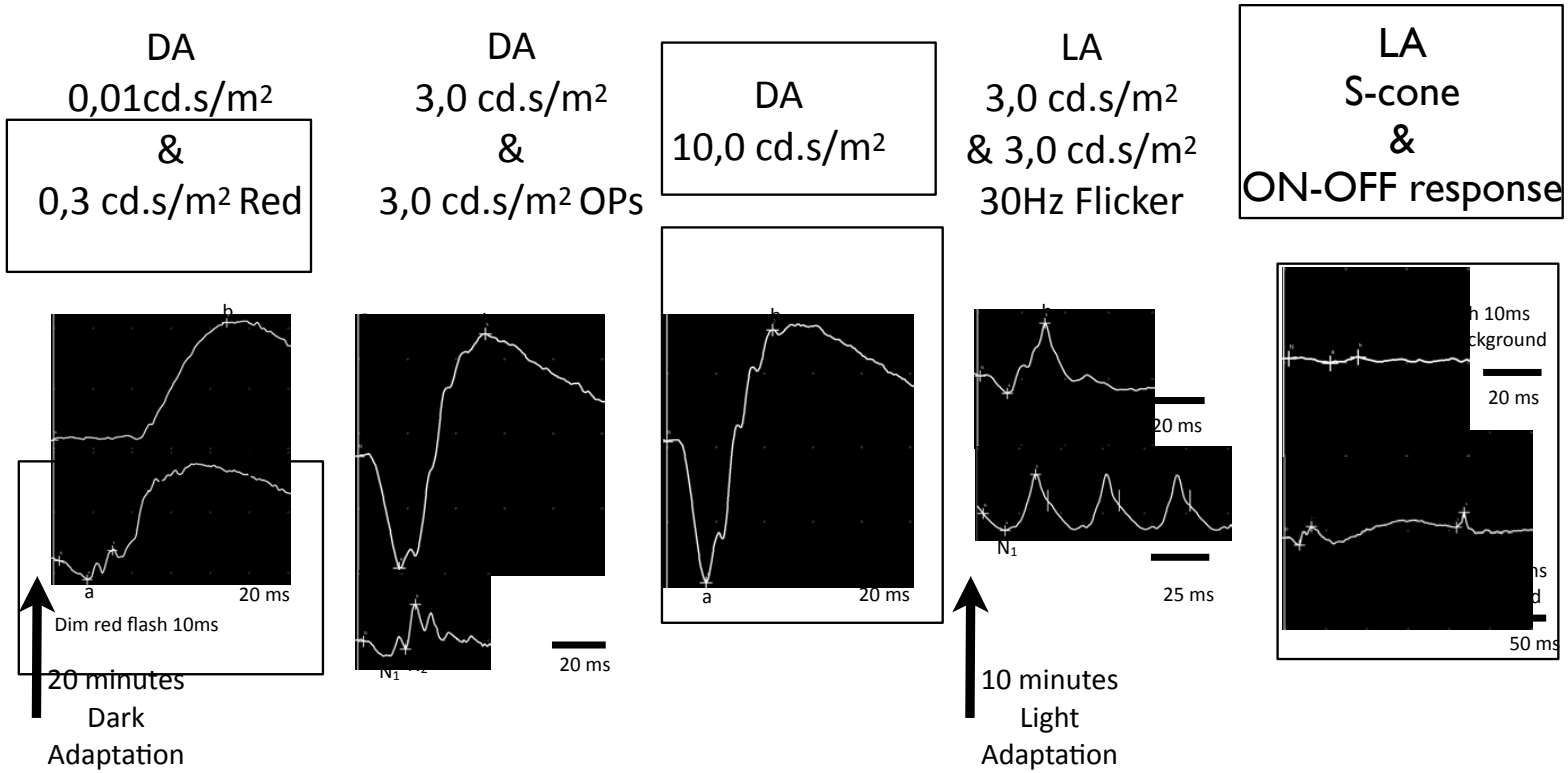
– Better: peak time

Full-Field Flash ERG
Origin of ERG components

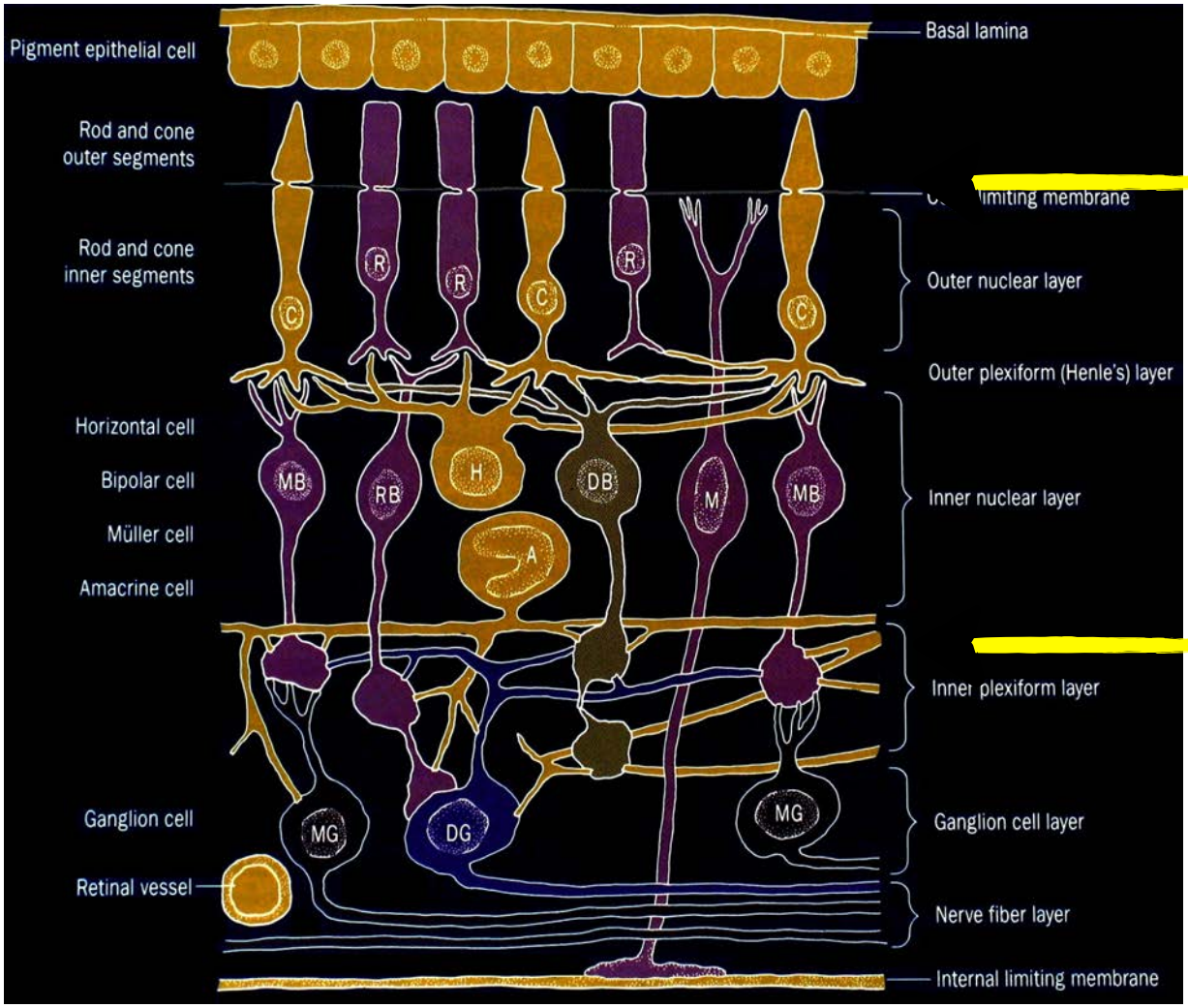
- a-wave: photoreceptors
- b-wave: bipolar & Müller cells

Full-Field Flash ERG

ISCEV Standard & Beyond



Retinal Cells & Layers



ERG a-wave from PRs

Outer Retina

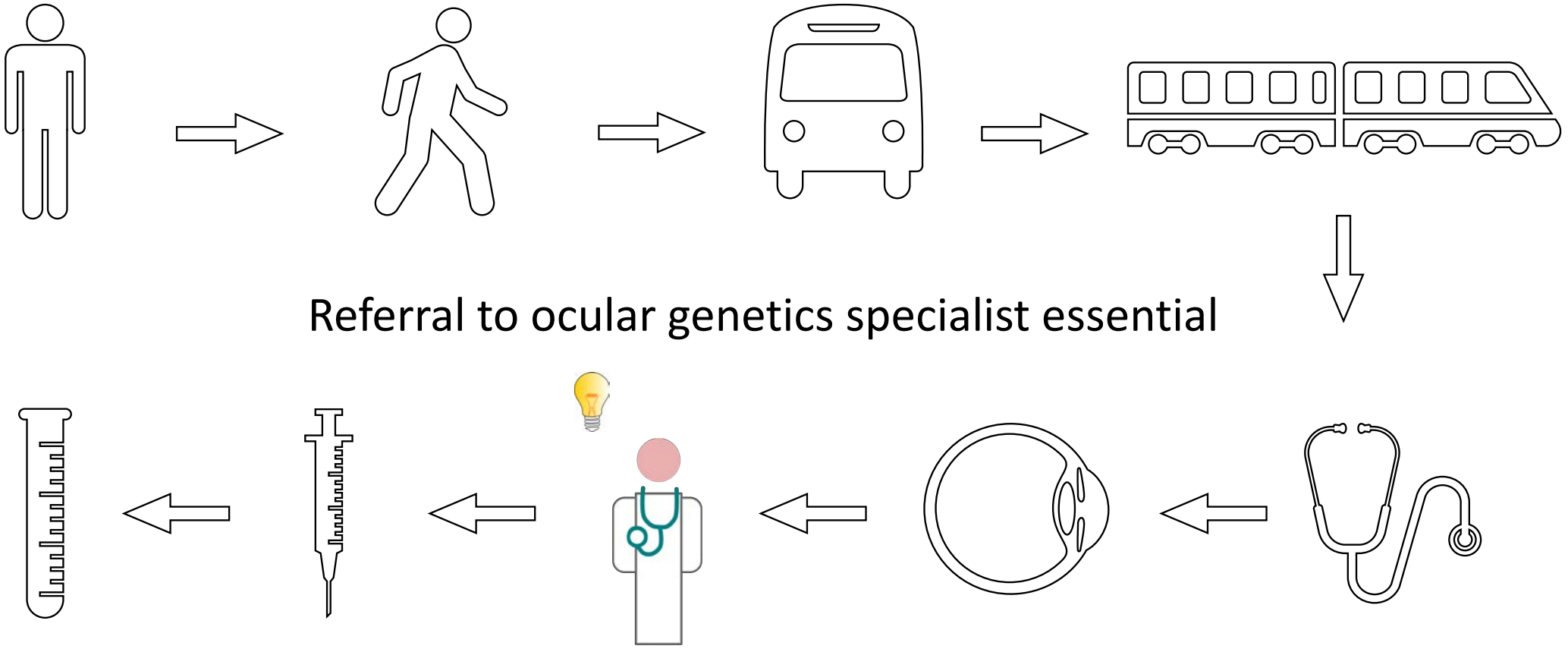
Blood Supply from Choroid

ERG b-wave from Bipolar & Müller Cells

Inner Retina

Blood Supply from Retinal Circulation

Patient Referral Pathway



Referral to ocular genetics specialist essential

2/ Albinism

Albinism

What?

Group of conditions

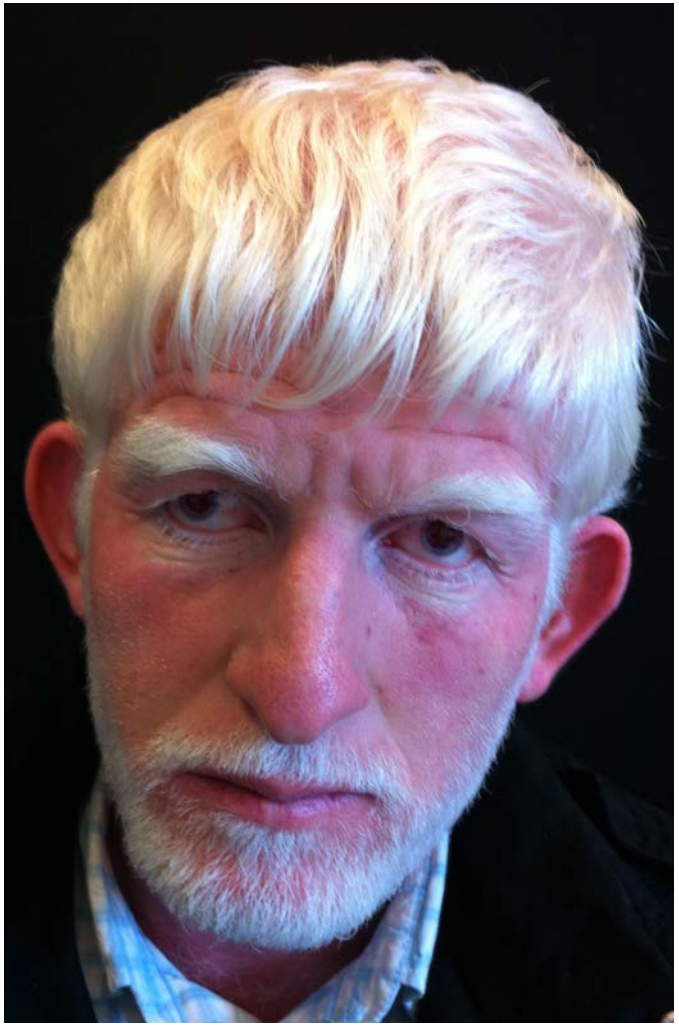
Caused by pathological decrease in melanin production

Genetically heterogeneous

Effects of mutations on genes not fully understood

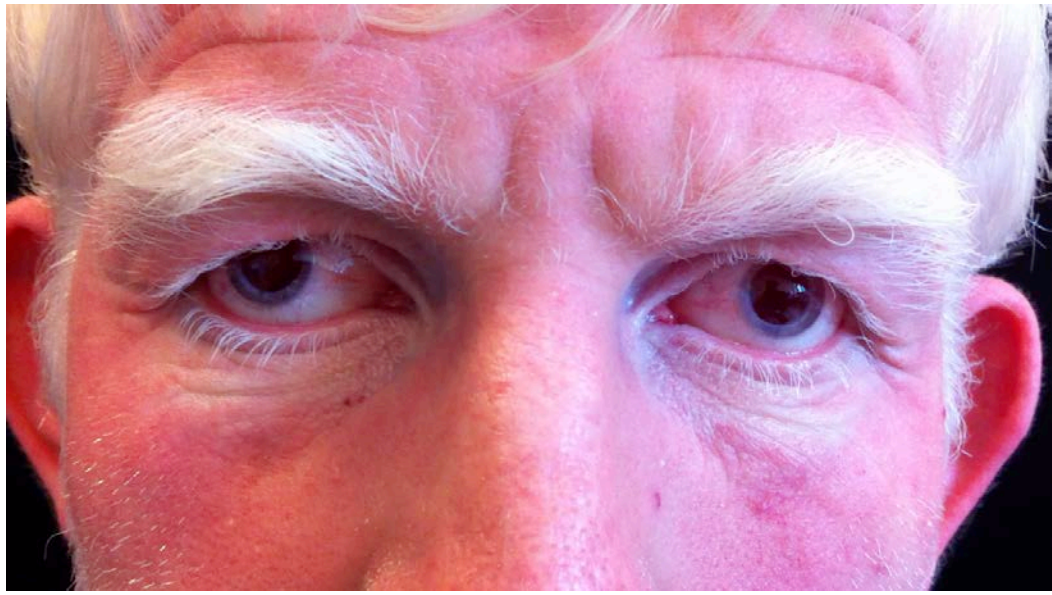
Common to all

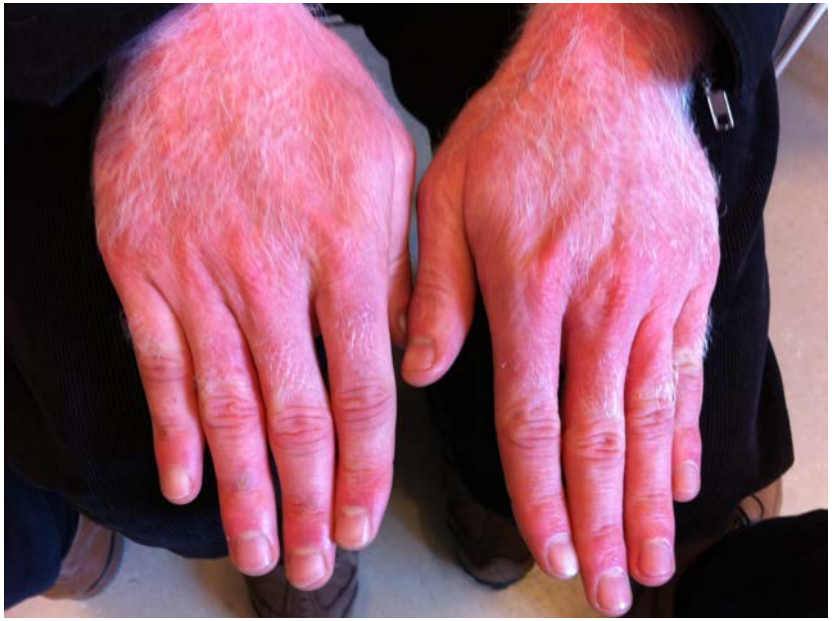
- Ocular involvement
- Some degree of hypopigmentation



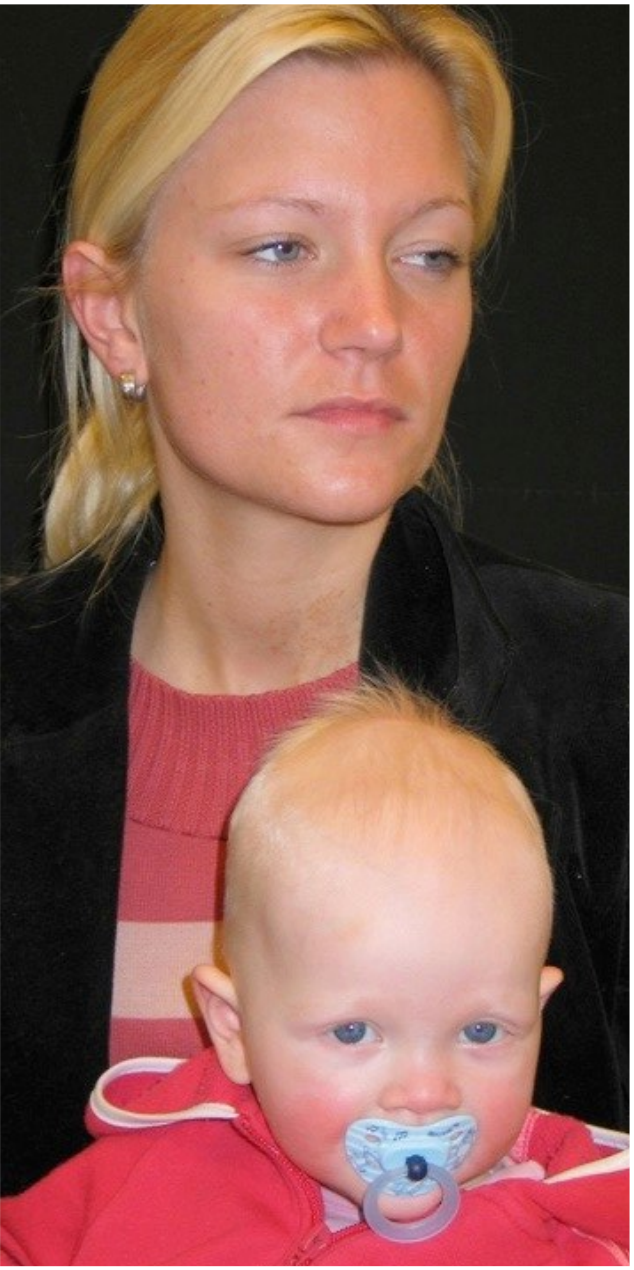
Case

M, 26 yr
Pakistani ethnicity
BCVA RE 1/10
LE 1.5/10
nystagmus





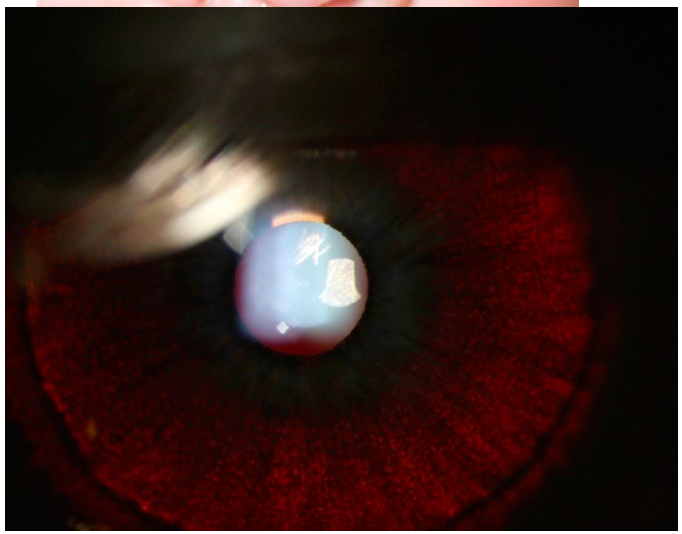
Oculocutaneous Albinism type 1
TYR HoZ c.1037G>A (p.Gly346Glu)



Case

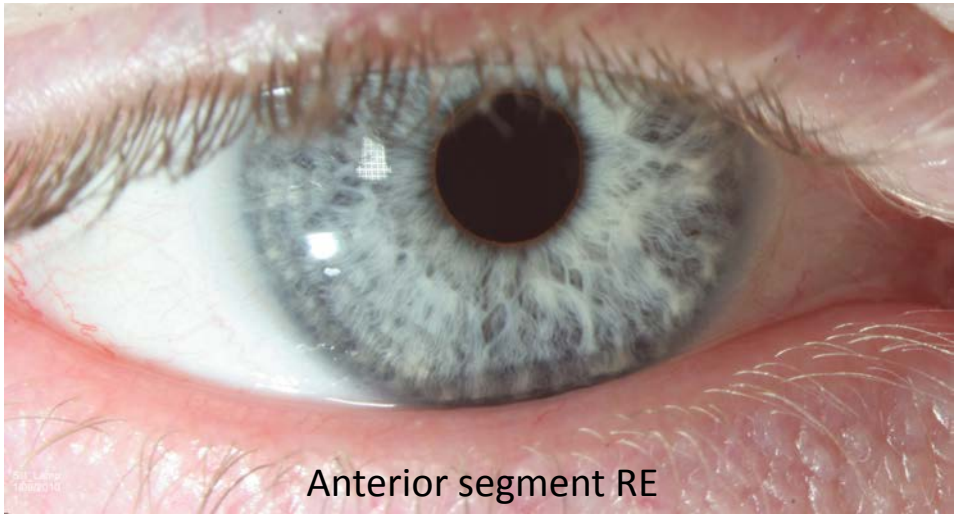
F, 7 mths

No fixing & following
until 4 mths
BCVA at age 9
5/10 & 3/10
Still nystagmus



Oculocutaneous Albinism type 2

P-gene mutations c.1327G>A (p.Val443Ile) in exon 13 & c.1465A>G (p.Asn489Asp)



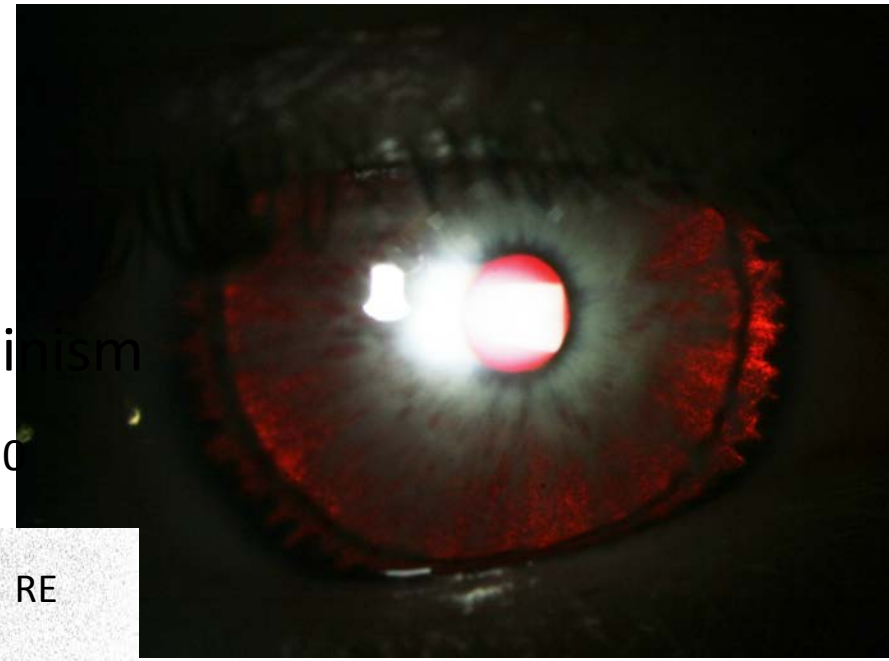
Anterior segment RE

Case

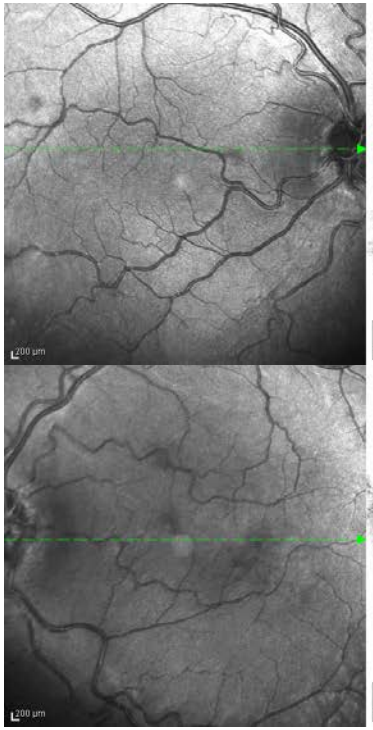
M, 33 yrs

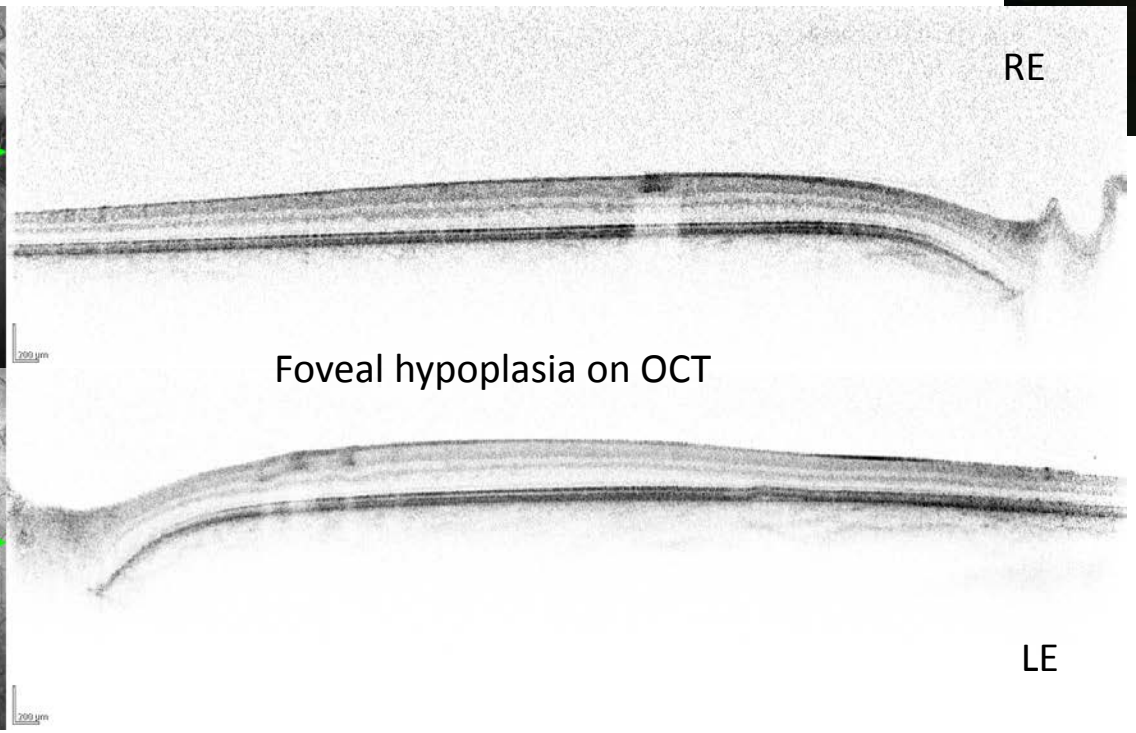
XL Ocular Albinism

BCVA BE 2/10



Iris transillumination RE





RE

Foveal hypoplasia on OCT

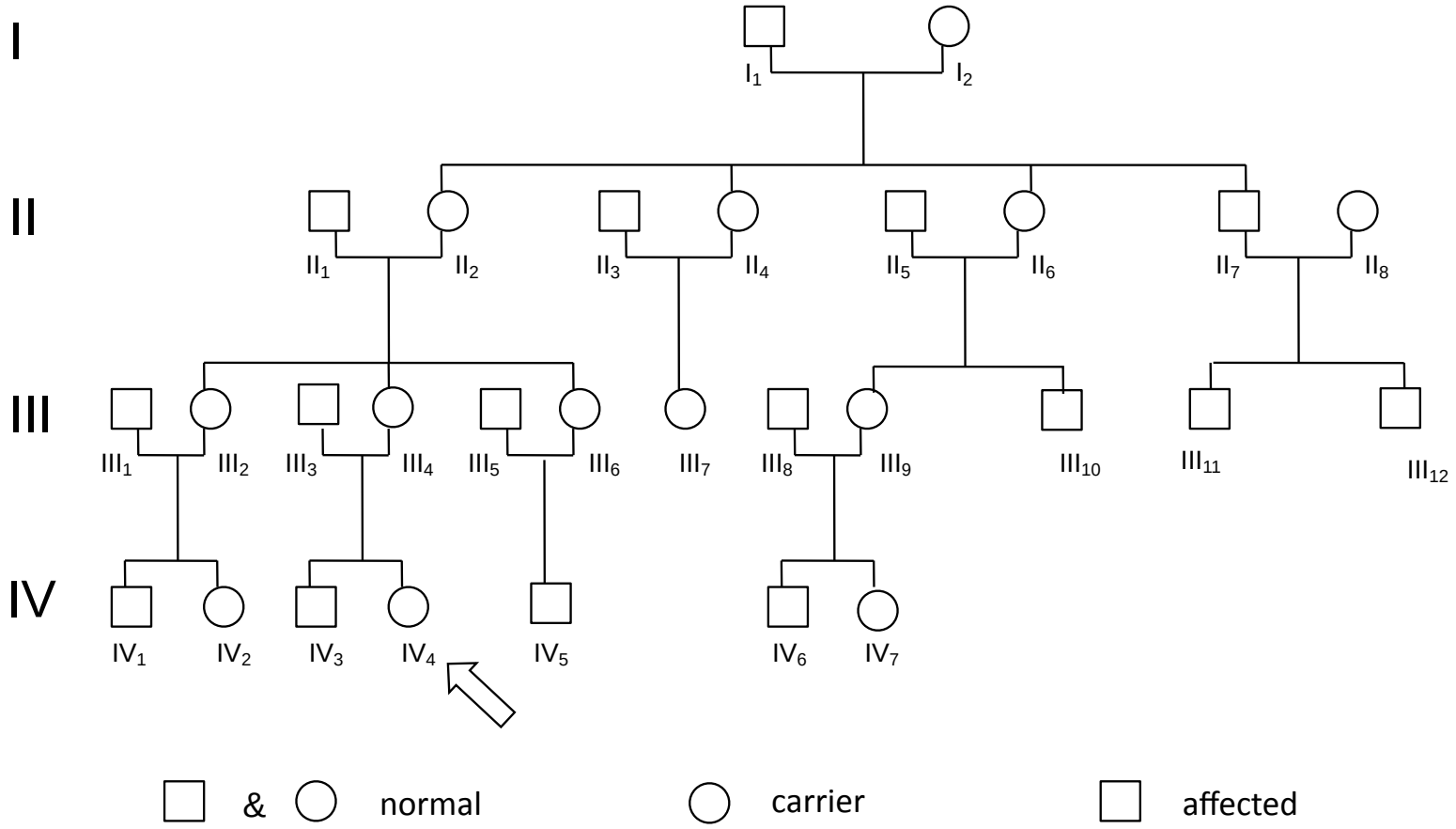
LE

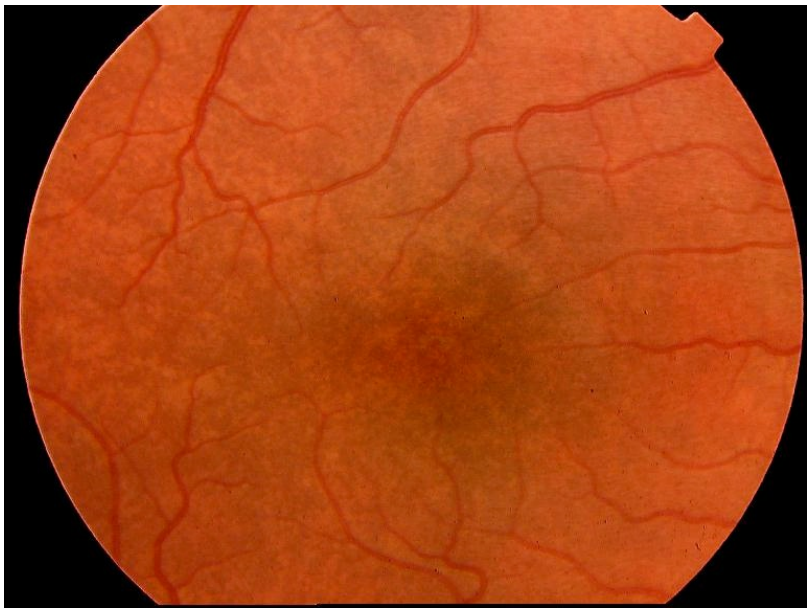
OA1

c.876G>C (p.Trp292Cys)

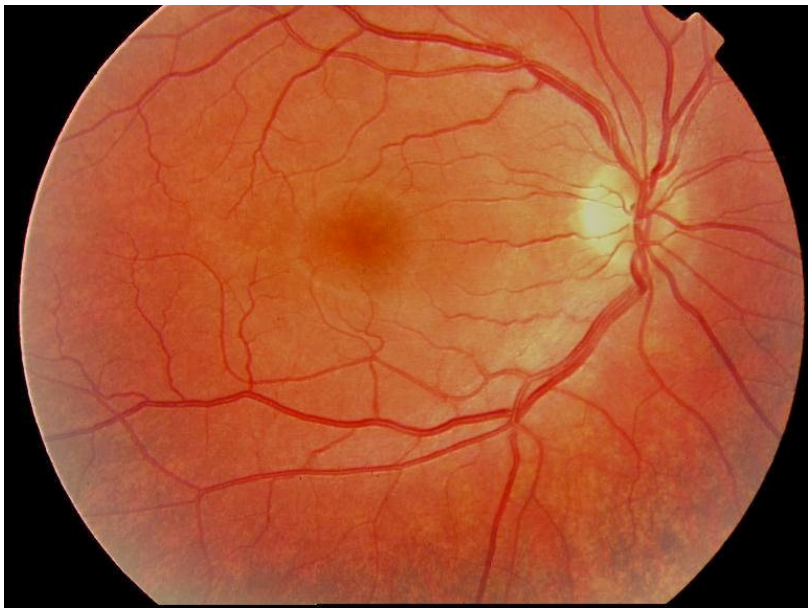
Ocular Albinism

Female Heterozygotes





PP RE

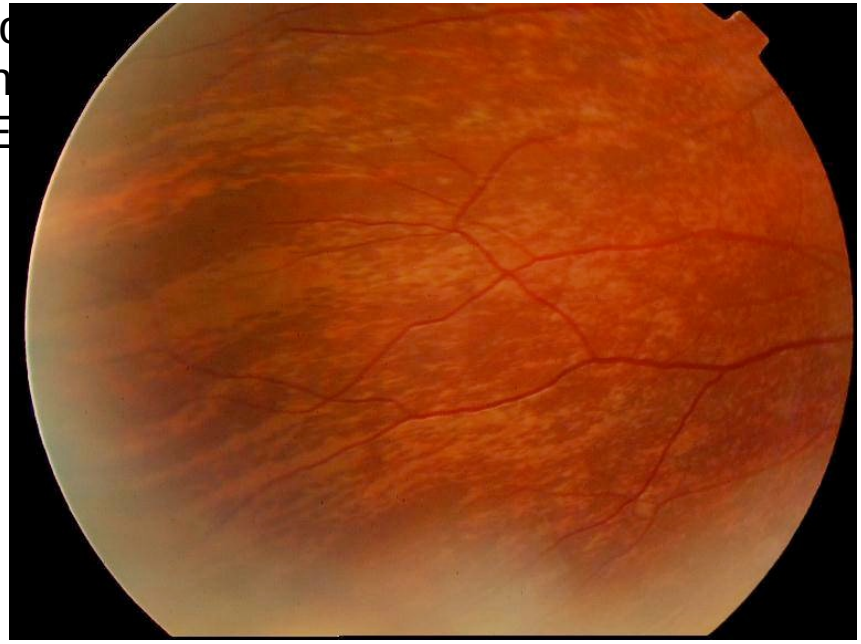


Case

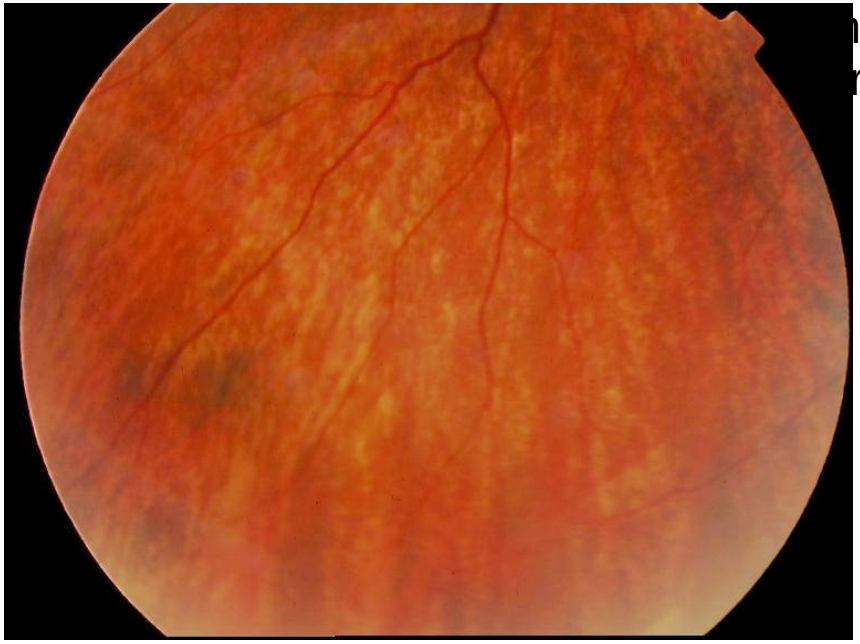
F, 25 yrs

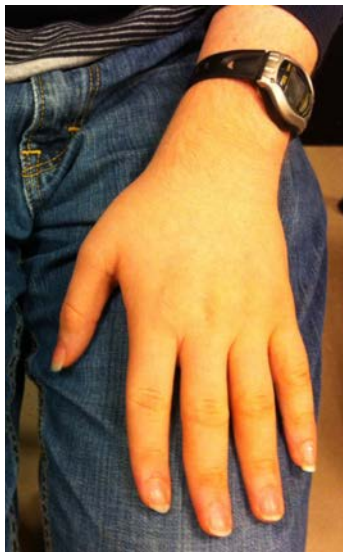
Carrier OA1
IVS3+1 G>C
mutation

Tempo
periph
RE



nferior
riphery
RE



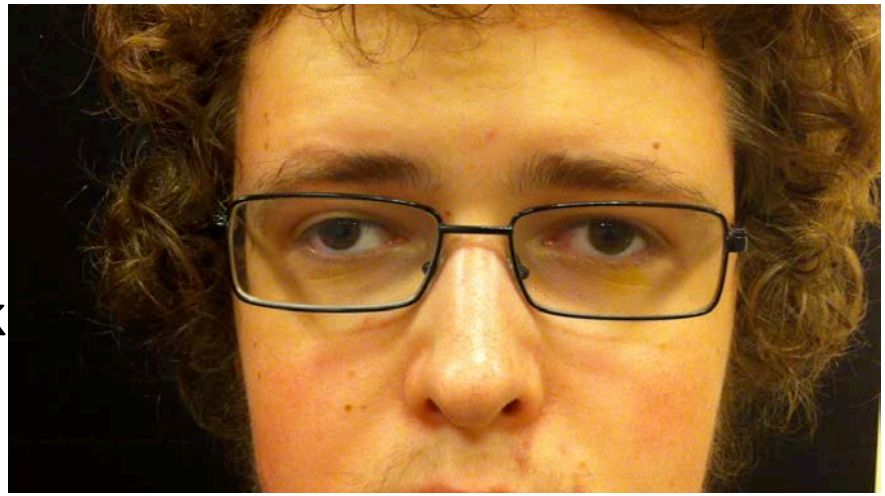


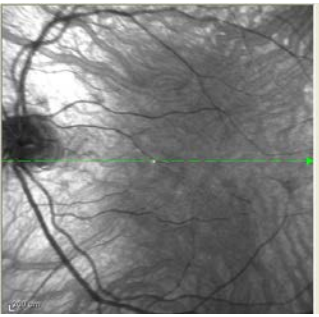
Case

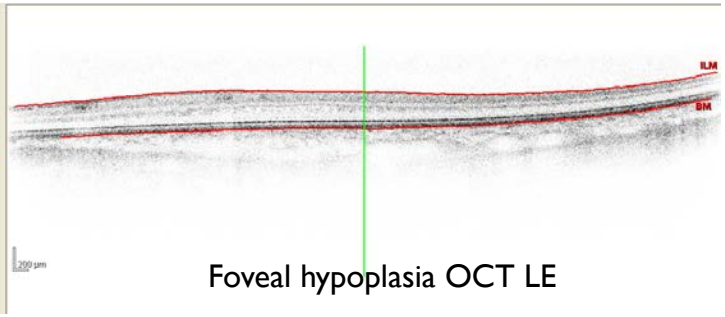
M, 22 yrs

Hermansky-Pudlak Syndrome

BCVA RE 1.5/10 LE 2/10





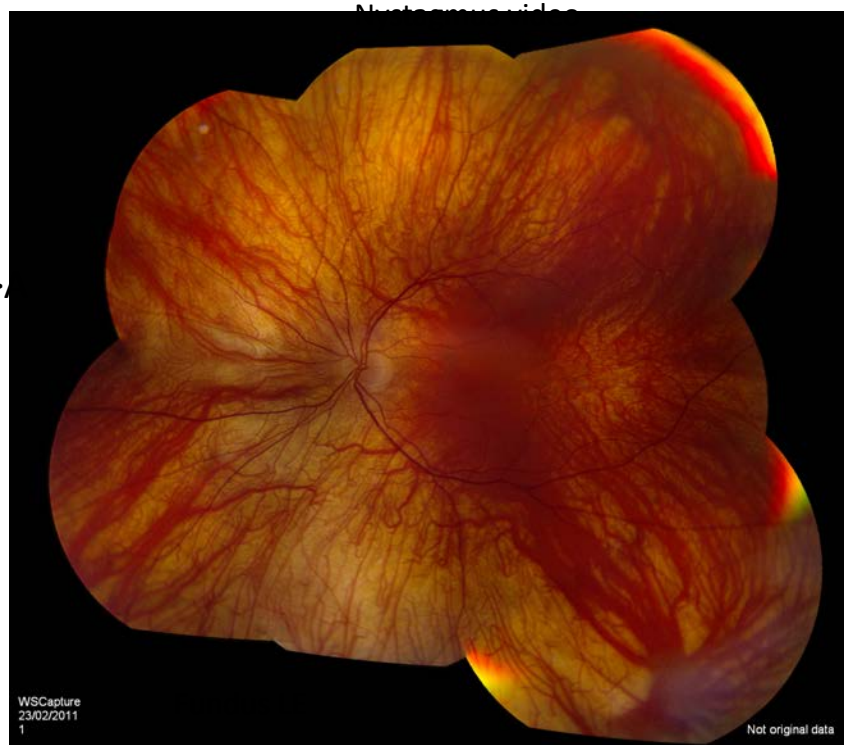


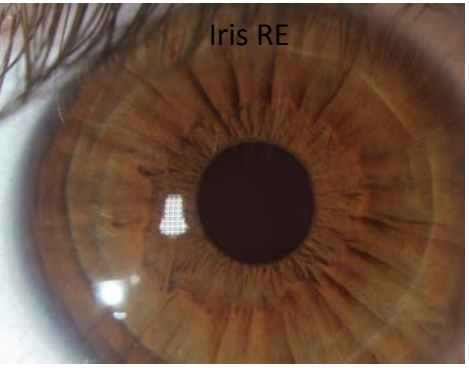
Foveal hypoplasia OCT LE

HoZ

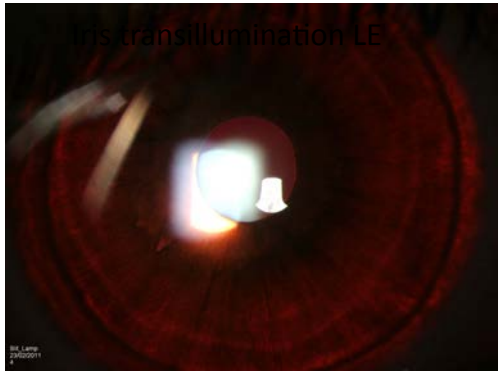
c.2888-1612G>A

in *HPS3*





Iris RE



Iris transillumination LE

3/ Ocular Developmental Disorders

Microphthalmia, Anophthalmia & Coloboma (MAC) Spectrum

Background

Microphthalmia = small eye (<21 mm adult AXL)

Nanophthalmos = simple microphthalmia

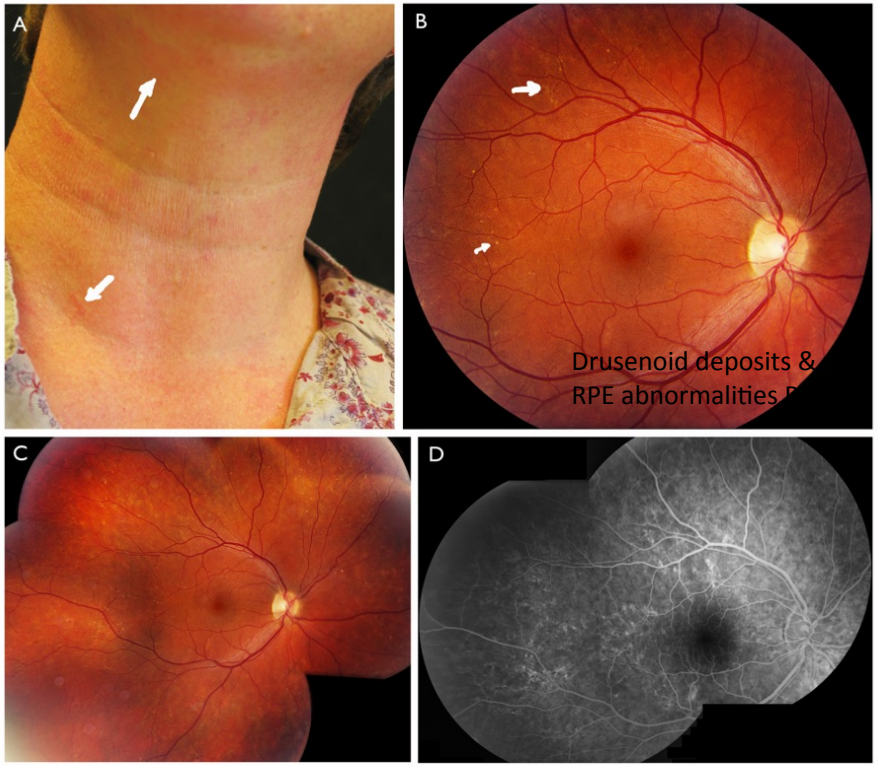
Anophthalmia = absence of eye

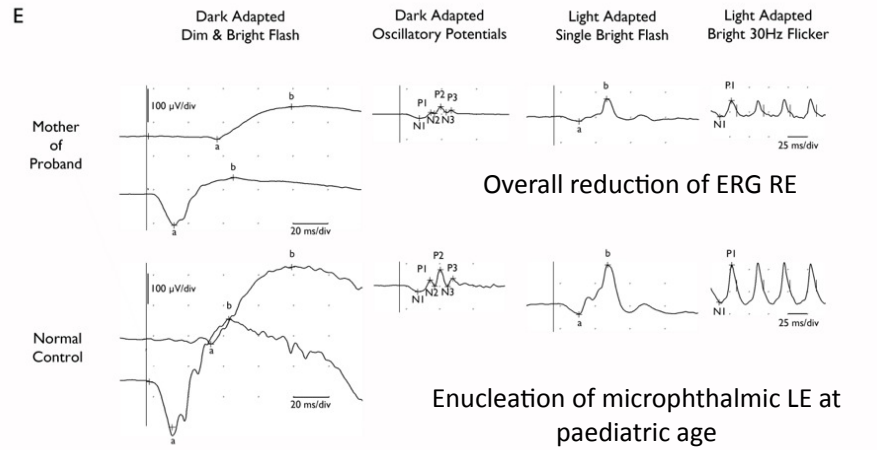
Coloboma = closure defect at level of optic fissure during embryonal development

Multiple genes & mechanisms

AR, AD & XL inheritance patterns

Isolated or syndromic





Overall reduction of ERG RE

Enucleation of microphthalmic LE at paediatric age

Mother Daughter

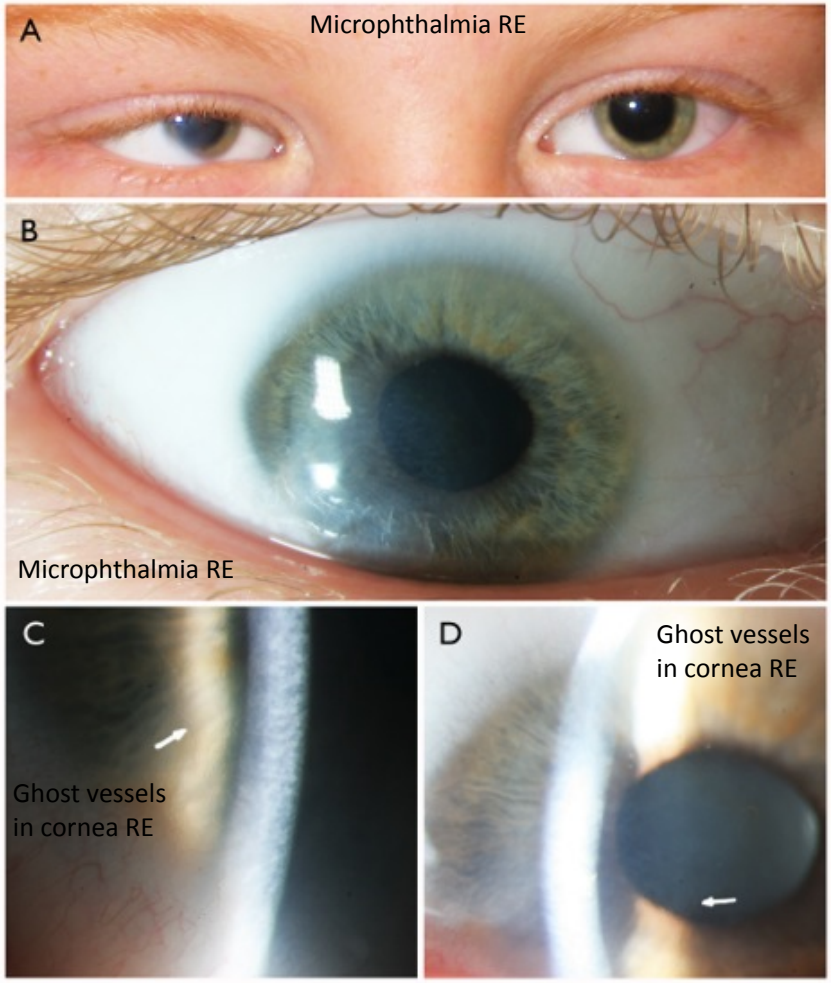
Cases

Mother, 42 yrs & daughter, 9 yrs

Microphthalmia w/ Linear Skin Defects (MLS or MIDAS)

Rare, severe, X-linked dominant condition

S Vergult, BP Leroy, I Claerhout, B Menten, Mol Vis, 19, 311-318, 2013



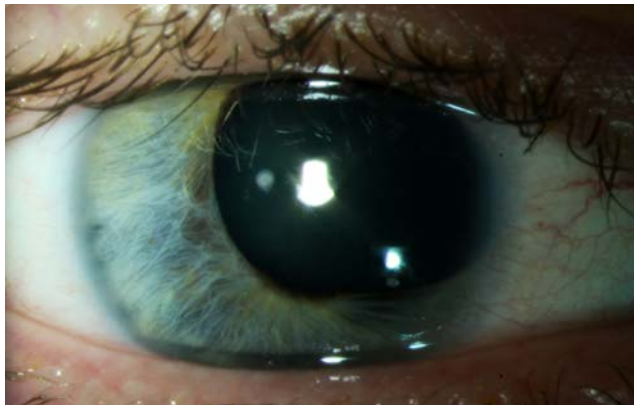
Array CGH revealed submicroscopic deletion of 185-200kb on Xp22.2 spanning entire *HCCS* & partially spans *ARHGAP6*; *HCCS* encodes mt enzyme holocytochrome c & c1

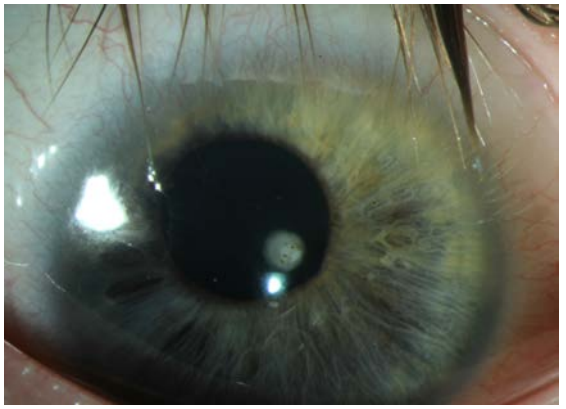
Aniridia
Background & Signs

Known eye abnormalities due to heterozygous *PAX6* mutations:

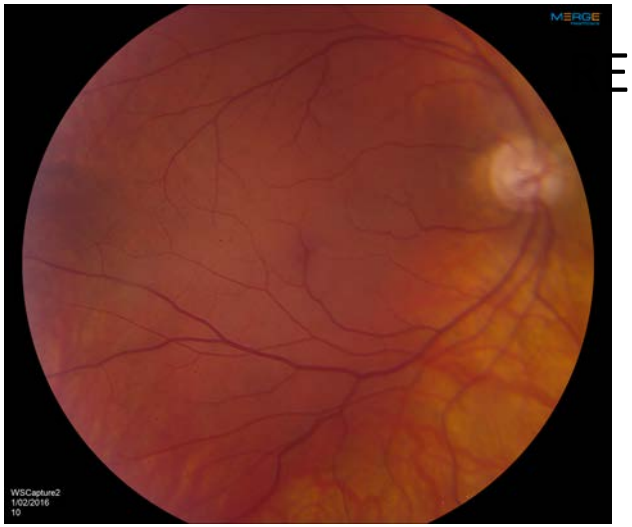
- Complete or partial absence of iris w/ photophobia
- Foveal hypoplasia leading to nystagmus
- Optic nerve hypoplasia
- Corneal stem cell failure w/ keratopathy (78-90%)
- Abnormal AS angle structures w/ glaucoma (50-70%)
- Cataract (frequently anterior polar)
- Microphthalmia & chorioretinal colobomata
- Peters anomaly (corneal clouding & iridolenticulocorneal adhesions)

Aniridia





E



Case

M, 33 yrs, aniridia

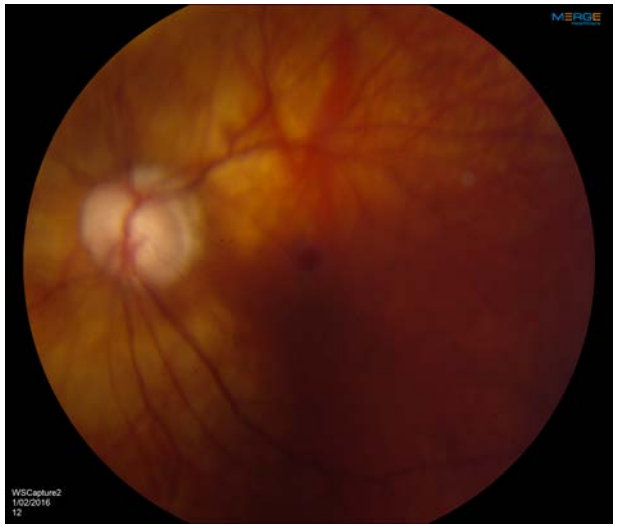
PAX6 c.10+1G>T p.Arg254X

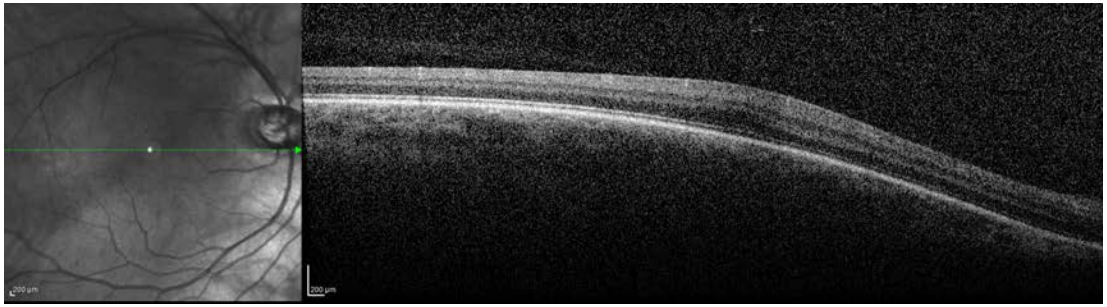
BCVA

BE 6/60

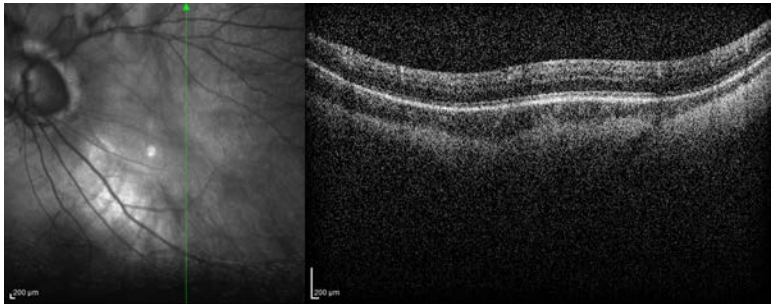
Nystagmus

LE





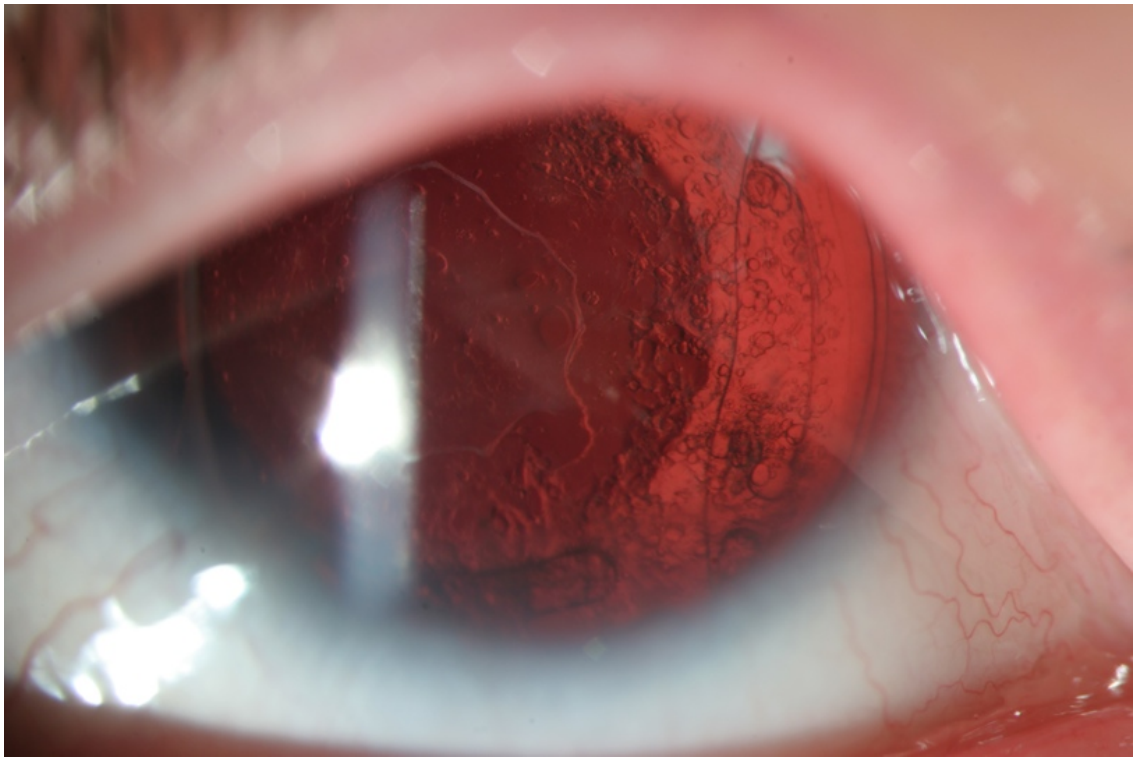
Foveal hypoplasia on OCT



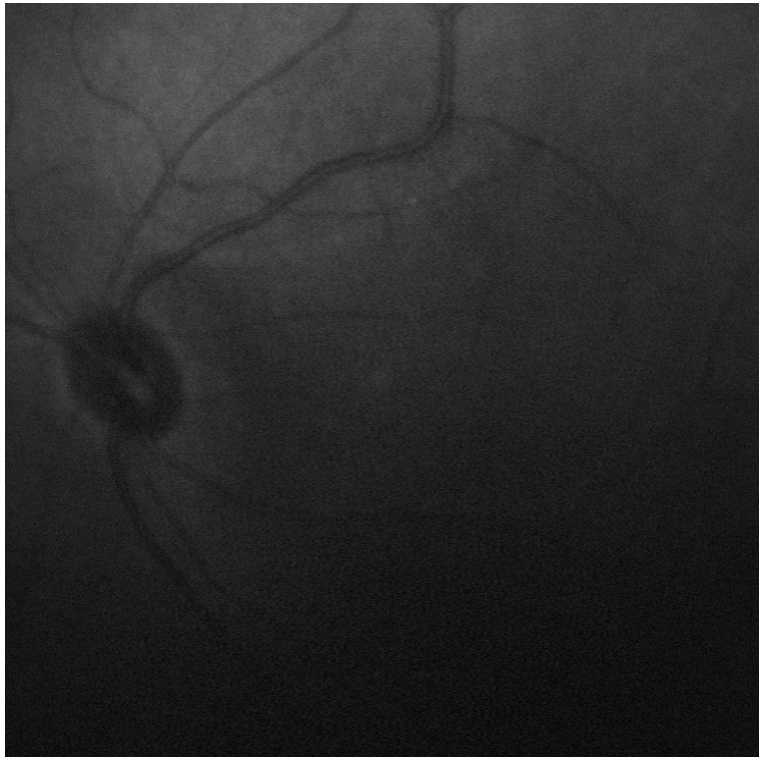
Aniridia
Case

M, 19 yrs, aniridia
PAX6 c.760C>T p.Arg254X

Complete aniridia & PC pseudophakia RE



NIR Nystagmus Video LE



4/ Generalised Retinal Dystrophies

Retinitis Pigmentosa
Background

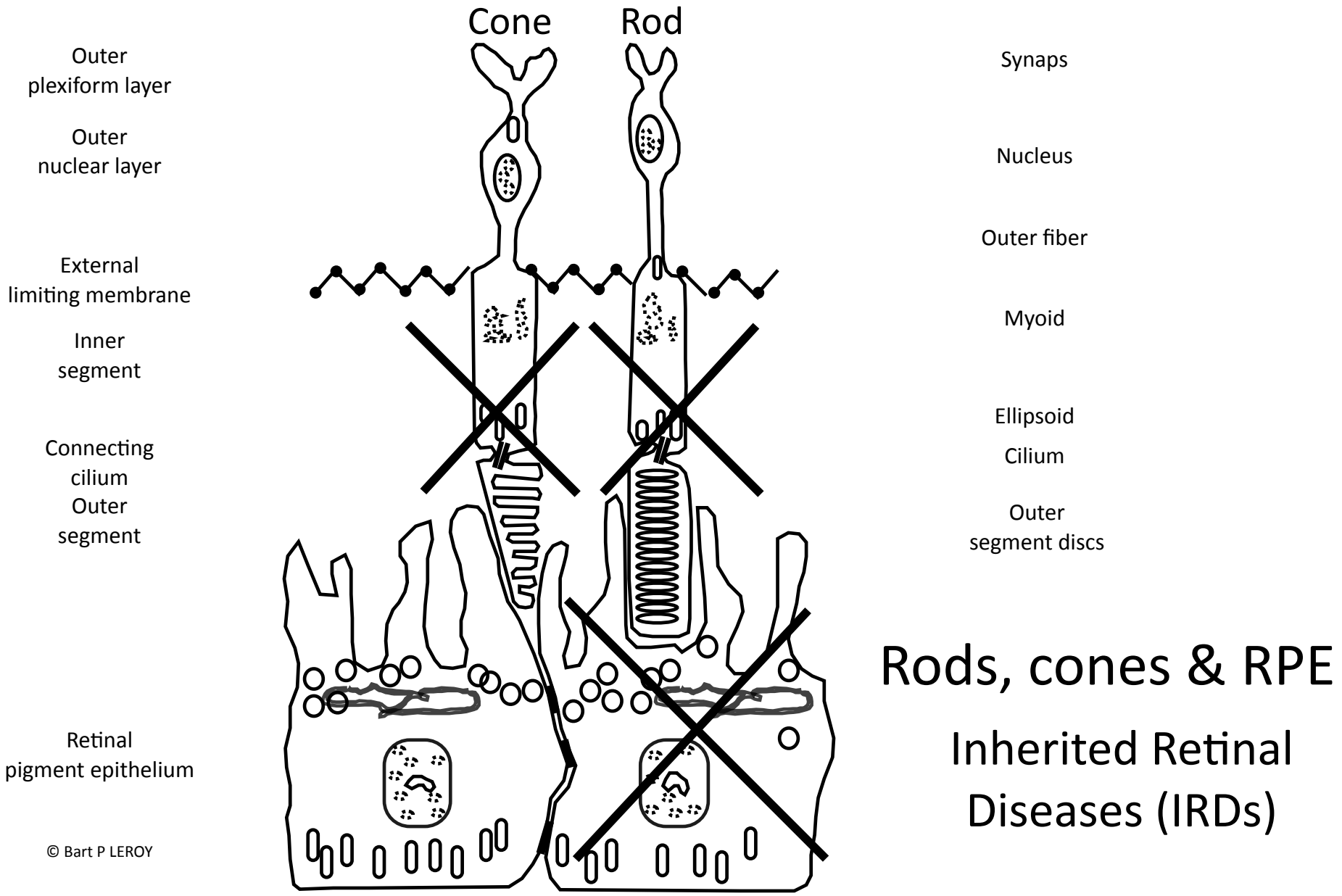
What? Outer retinal dystrophy with PR death by apoptosis

Signs:

- Progressive outer retinal atrophy
- Intraretinal pigment migration
- OD pallor & vessel attenuation

Symptoms:

- Night-blindness
- Peripheral VF constriction
- Eventually loss of central vision



Rods, cones & RPE

Inherited Retinal Diseases (IRDs)

Retinitis Pigmentosa
Background

Electrodiagnostically: rod-cone dystrophy

Genetically:

- Autosomal dominant
- Autosomal recessive
- X-linked
- Most: simplex cases

AD Retinitis Pigmentosa
General

15-20% of all RP cases

Best prognosis

Later onset

Variable expressivity

AD Retinitis Pigmentosa

Genes

RHO (25 to 40%)

PRPH2

RP1

NRL

RP9

HPRP3

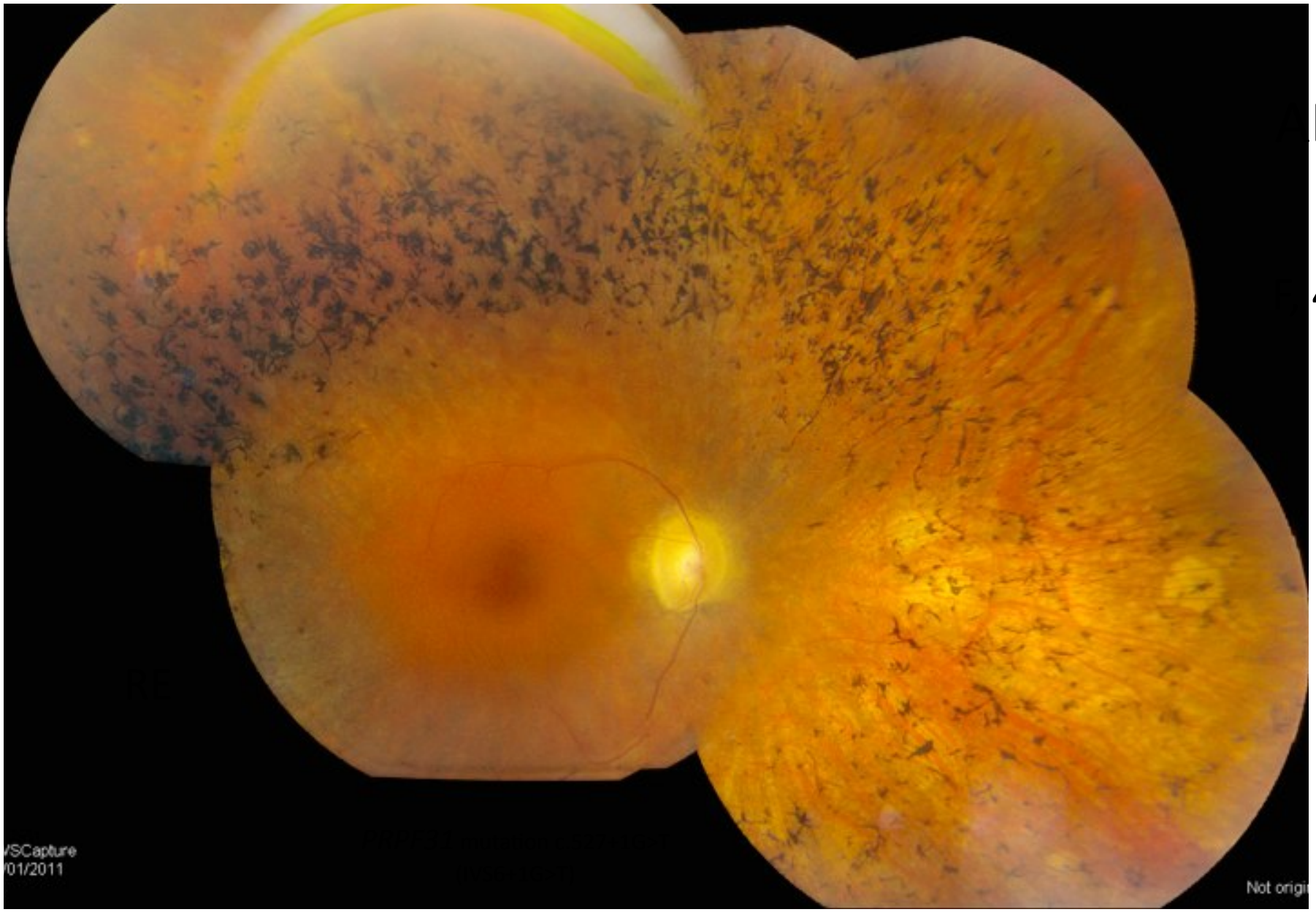
PRPC8

FSCN2

PRPF31

IMPDH1

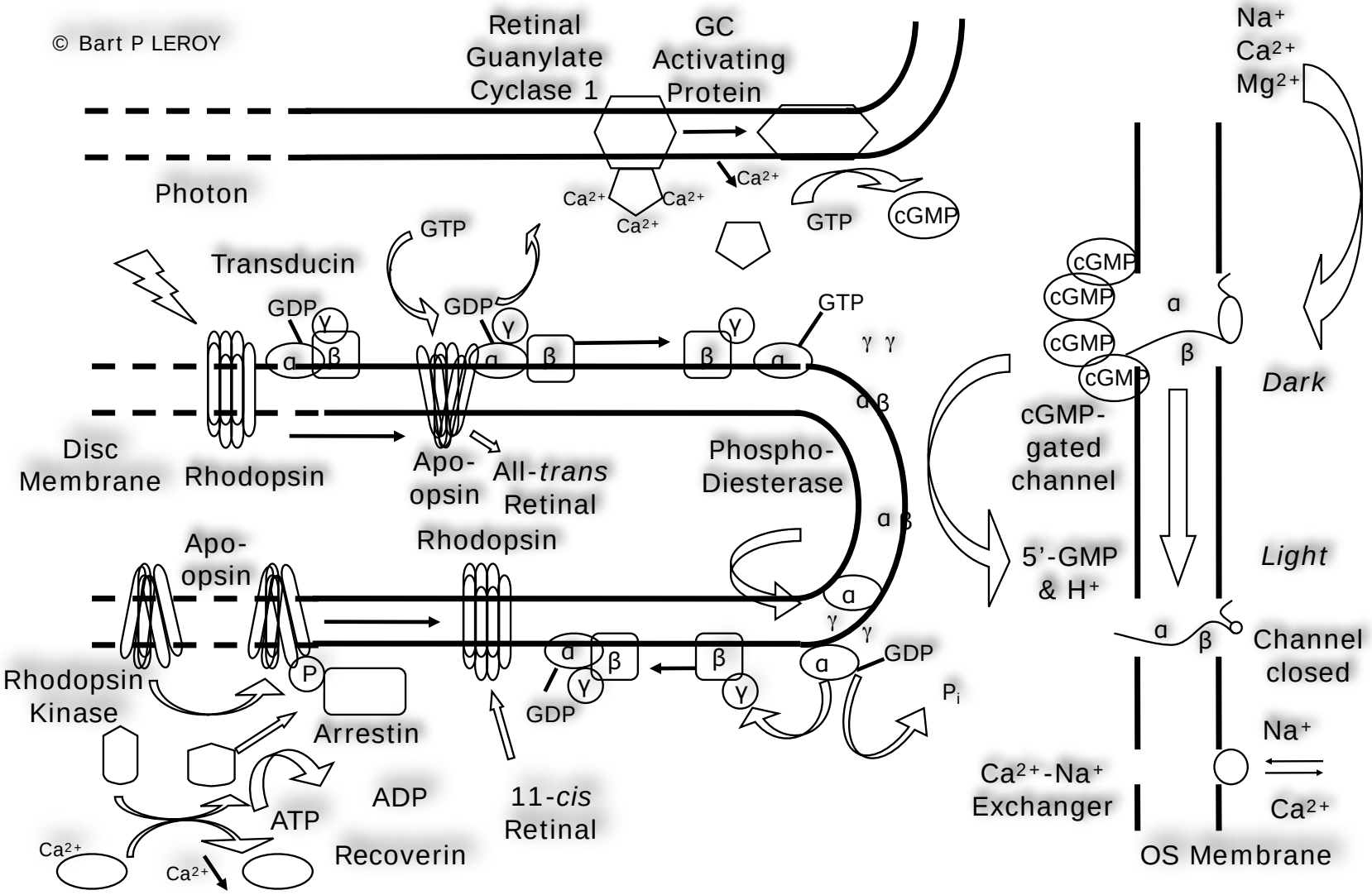
+ additional genes (total: 24; 23 cloned)



DRP

41yrs

The Phototransduction Cascade

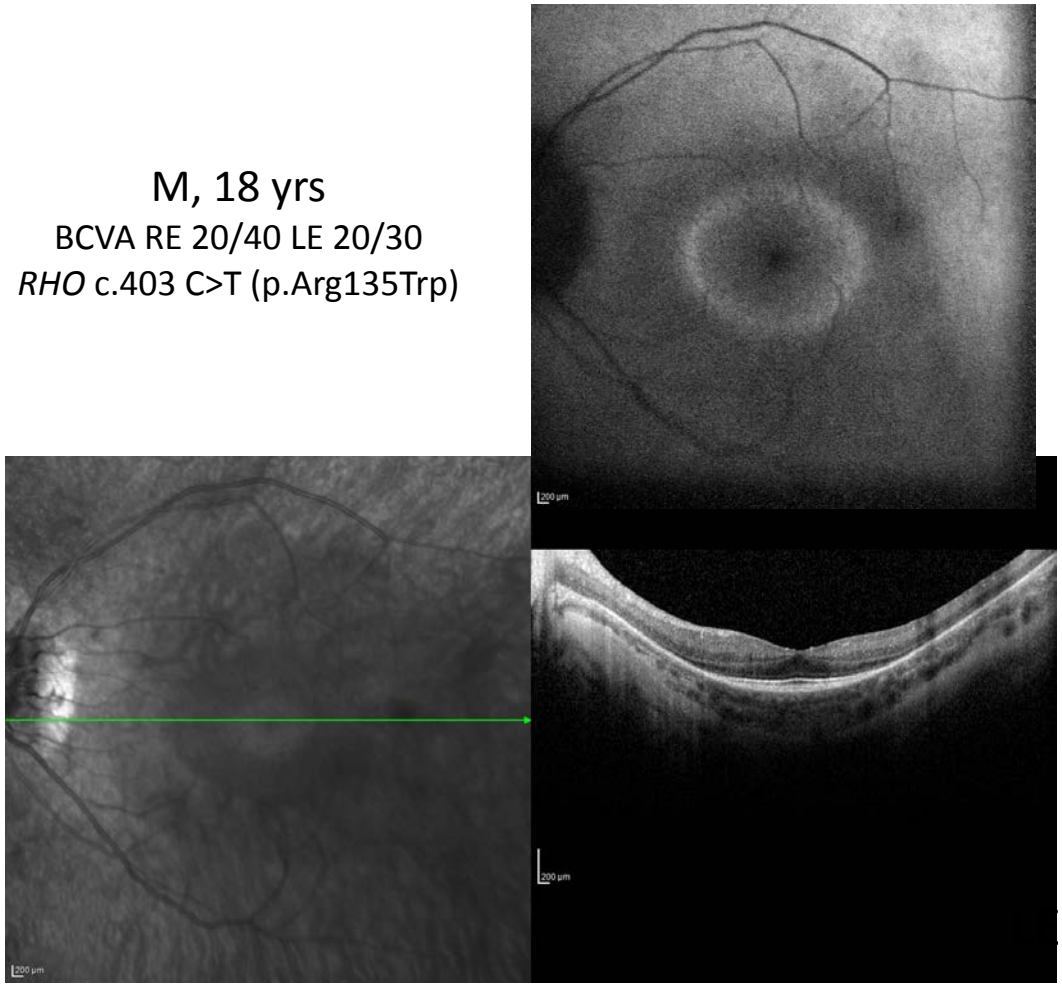


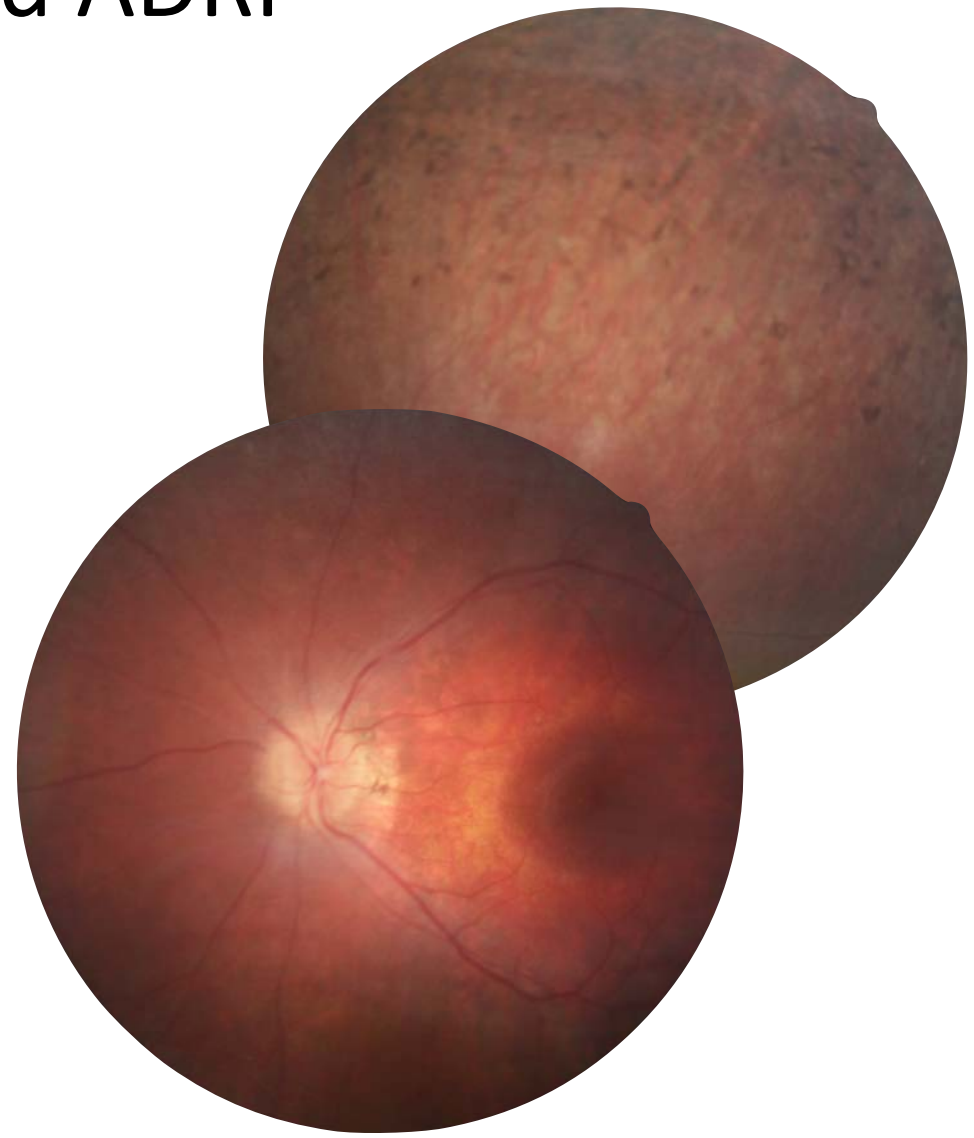
RHO-Related ADRP Case

M, 18 yrs

BCVA RE 20/40 LE 20/30

RHO c.403 C>T (p.Arg135Trp)





XL Retinitis Pigmentosa
General

10-15% of all RP cases

Most patients blind by age 35

Female heterozygotes:

- Many w/ mild & sometimes asymmetrical disease
- Abnormal “tapetal” reflex
- Abnormal b-wave implicit time

→ “normal fundus-abnormal function”

XL Retinitis Pigmentosa

Genes

OFD1

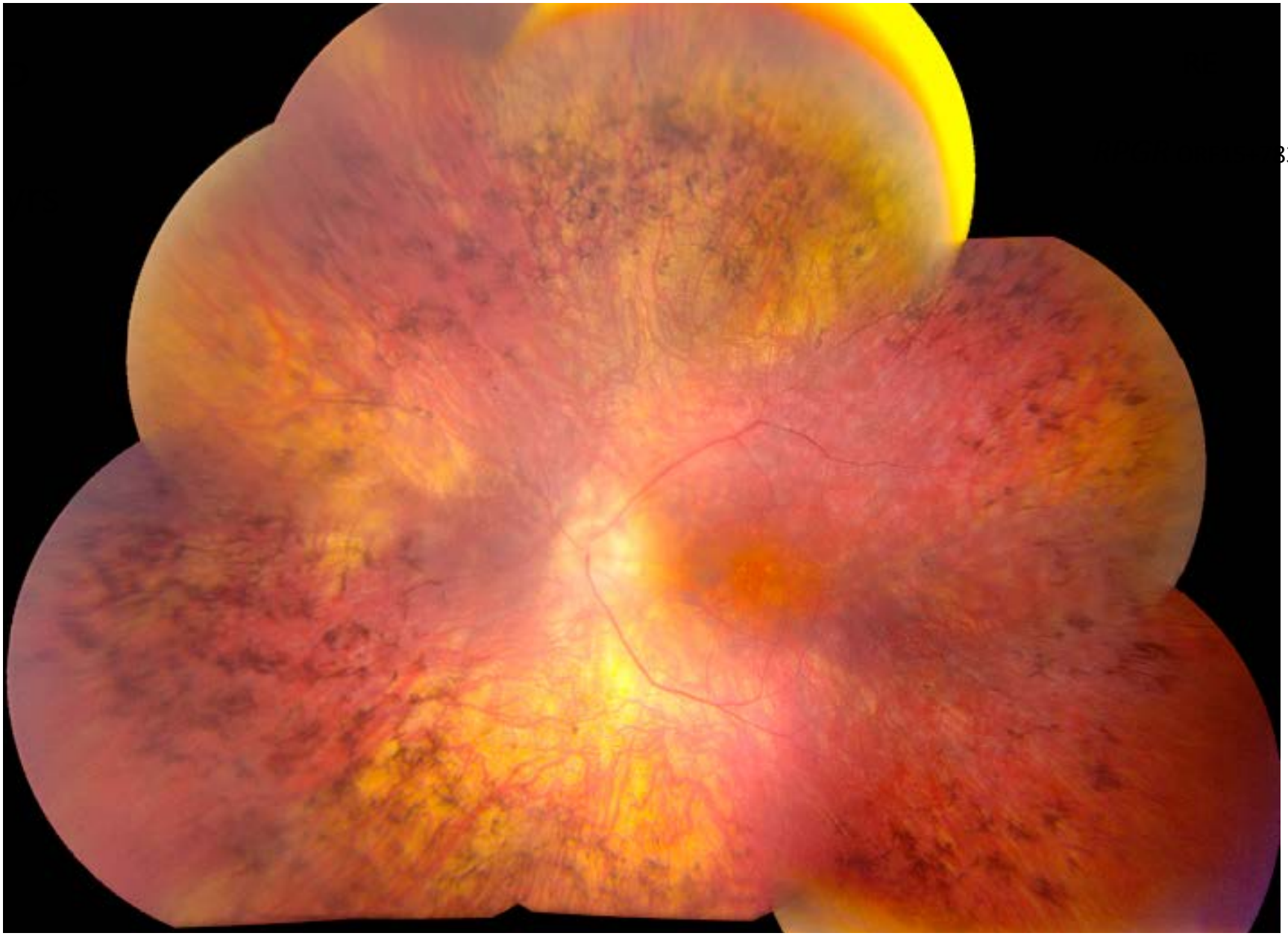
RPGR

RP2

3 extra loci

XLR

M, 36



3G>T

LE

AR Retinitis Pigmentosa
General

Variable prognosis

Most frequent (>25%)

AR Retinitis Pigmentosa

Genes

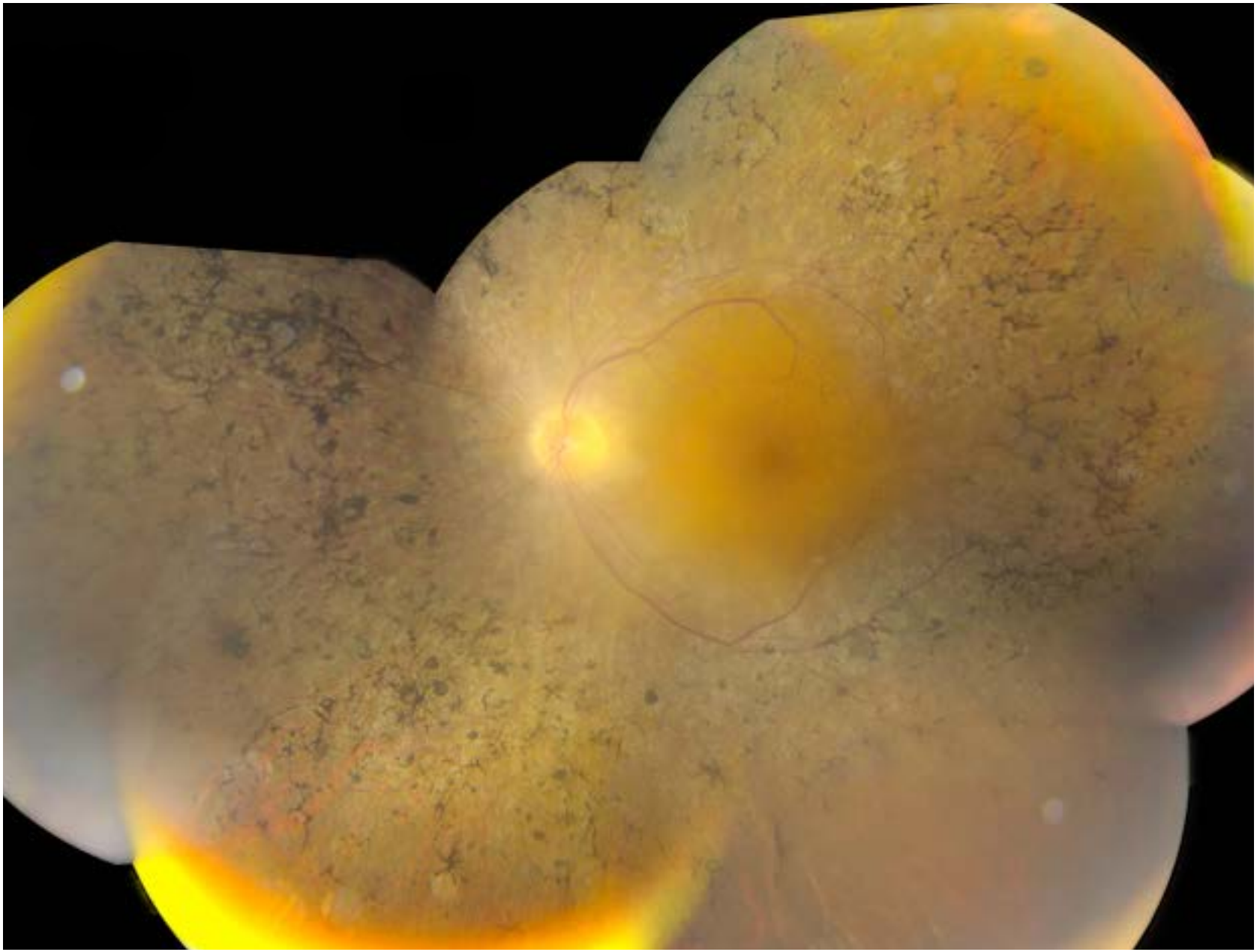
53 genes

51 cloned

2 loci

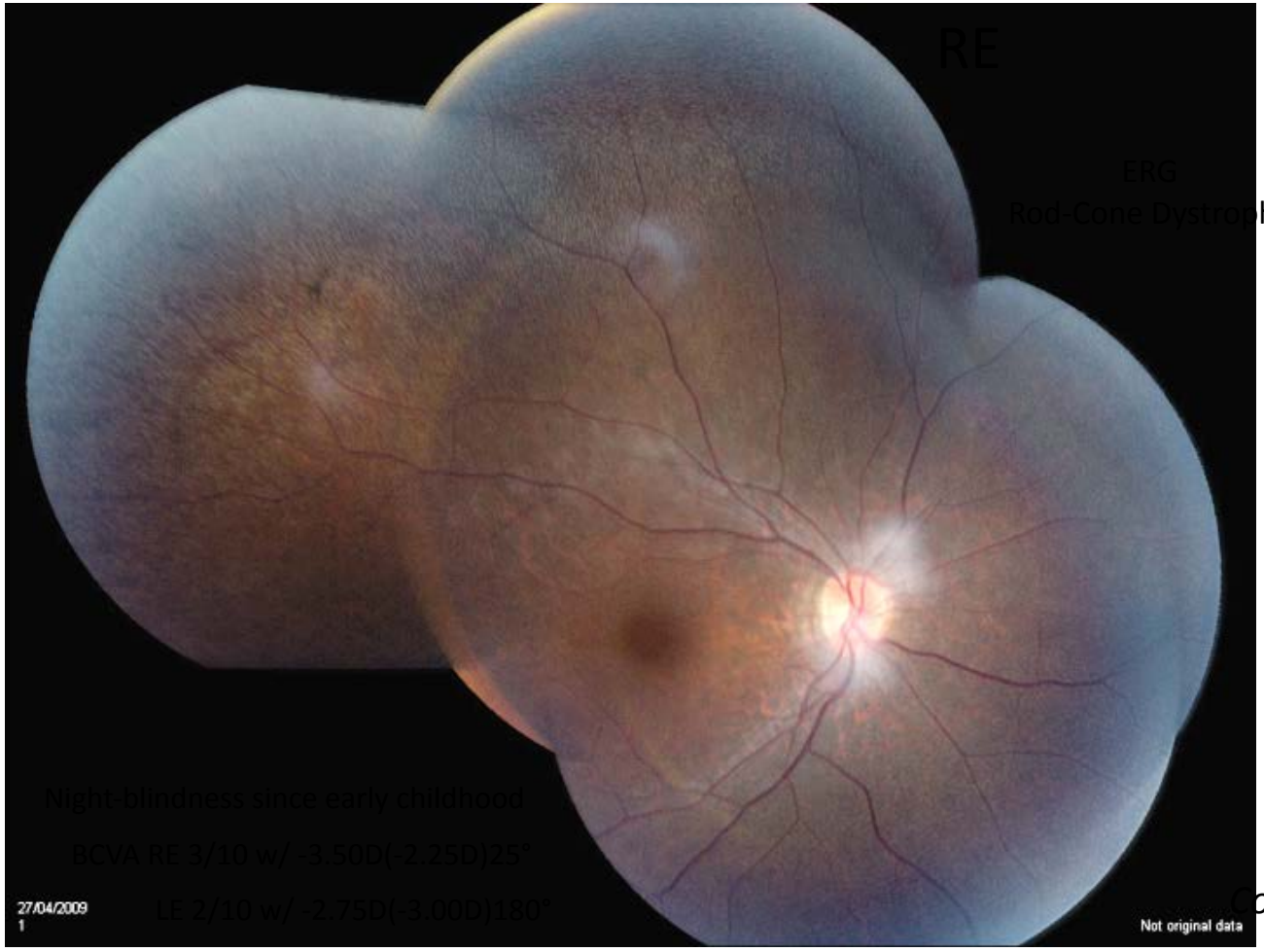
Genes currently known: see RetNet

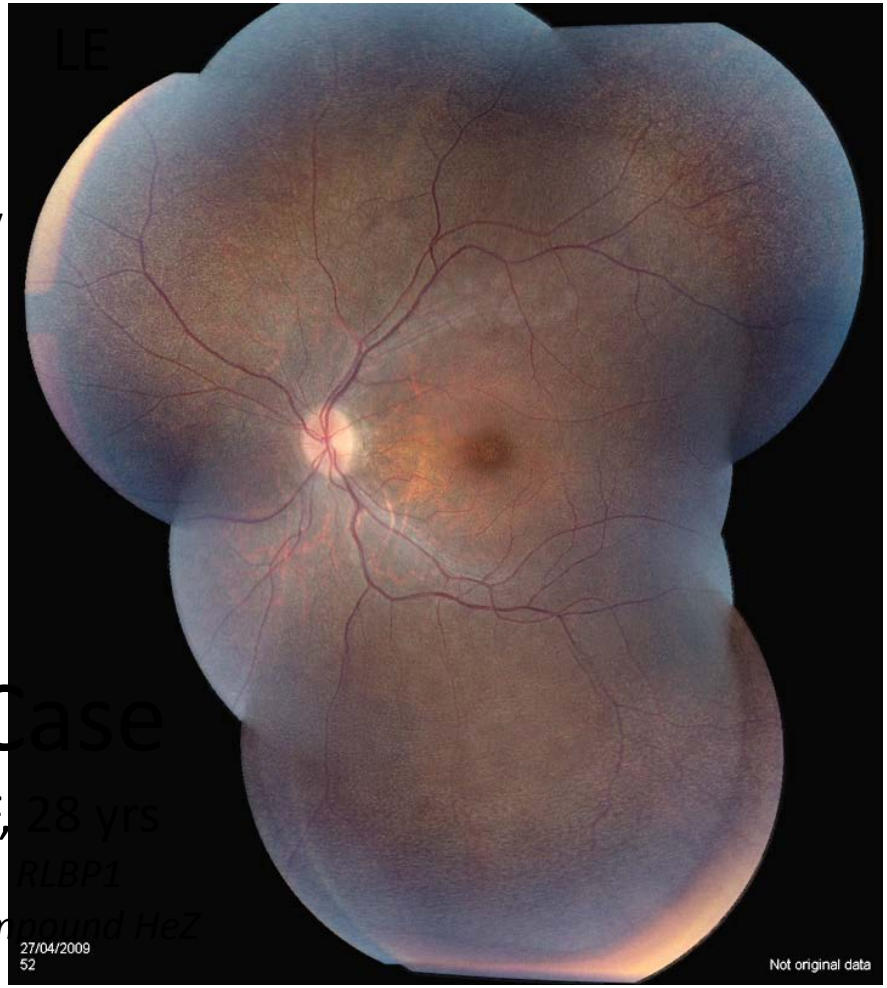
ABCA4, ADGRA3, AGBL5, AHR, ARHGEF18, ARL6, ARL2BP, BBS1, BBS2, BEST1, C2orf37, CC2D2A, CERKL, CLCC1, CLRN1, CNGA1, CNGB1, COQ2, COQ5, CRB1, CWC27, CYP4V2, DHDDS, DHX38, EMC1, ENSA, EYS, FAM161A, HSGNAT, IDH3B, IFT140, IFT172, IMPG2, KIAA1549, KIZ, LRAT, MAK, MERTK, MVK, NEK2, NEUROD1, NR2E3, NRL, PCARE, PDE6A, PDE6B, PDE6G, PDSS1, POMGNT1, PRCD, PROM1, PROS1, RAX2, RBP3, REEP6, RGR, RHO, RLBP1, RP1, RP1L1, RPE65, SAG, SAMD11, SLC37A3, SLC39A12, SLC66A1, SLC7A14, SPATA7, TRNT1, TTC8, TULP1, USH2A, ZNF408, ZNF513, …



Retinitis Pigmentosa

Differential Diagnoses: Retinitis Punctata Albescens





ERG

Rod-Cone Dystrophy

Case

F, 28 yrs

Night-blindness since early childhood

BCVA RE 3/10 w/ -3.50D(-2.25D)25°

LE 2/10 w/ -2.75D(-3.00D)180°

RLBP1

Compound HeZ

Retinitis Pigmentosa

DD: Choroideraemia

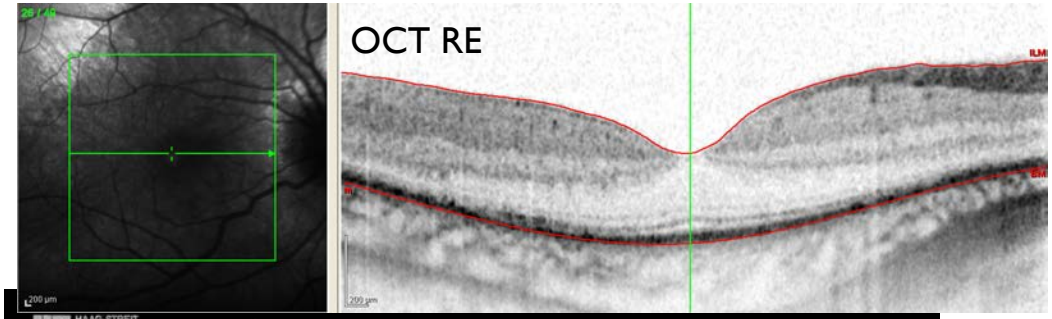
Mid-Stage

Choroideraemia

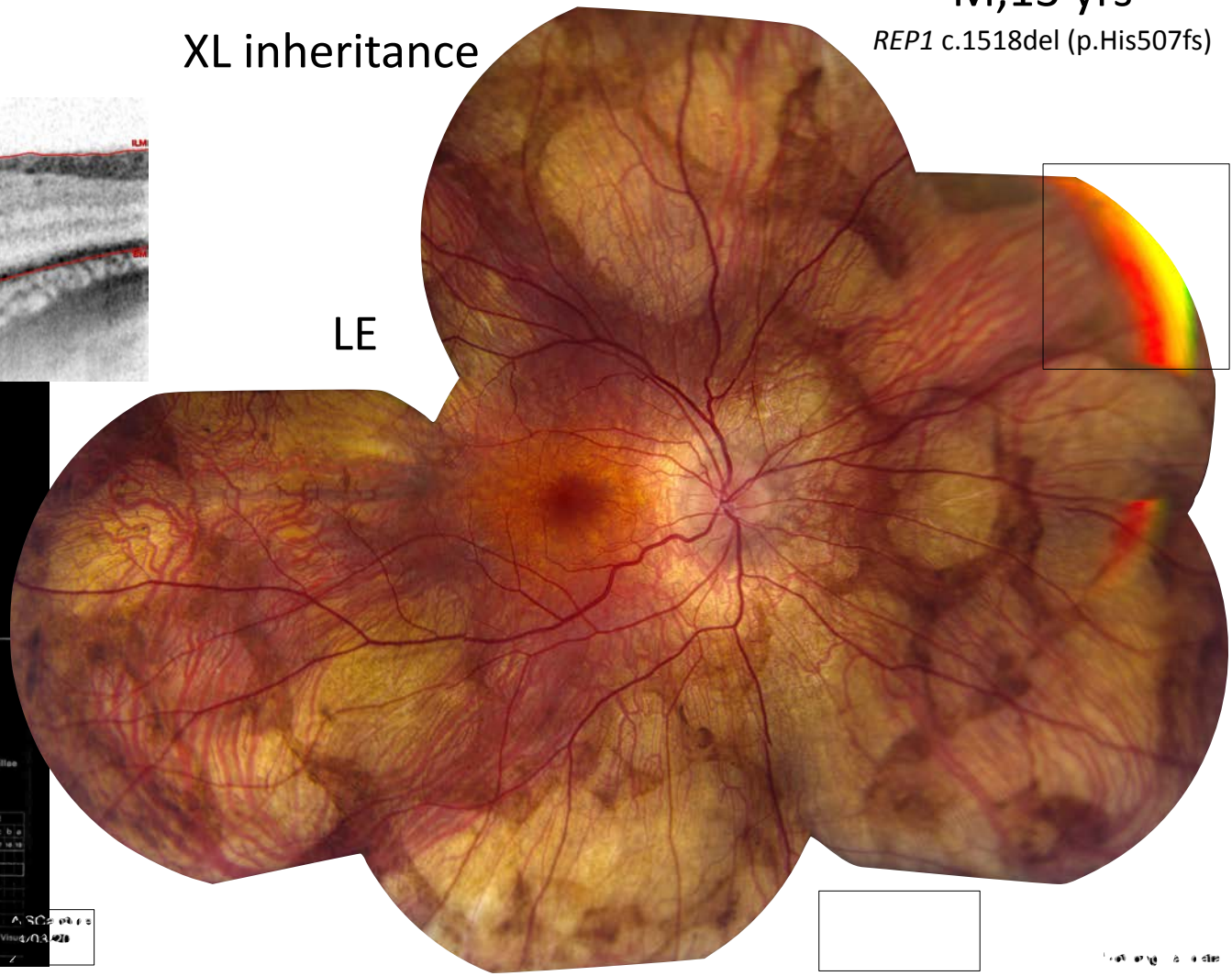
XL inheritance

M,13 yrs

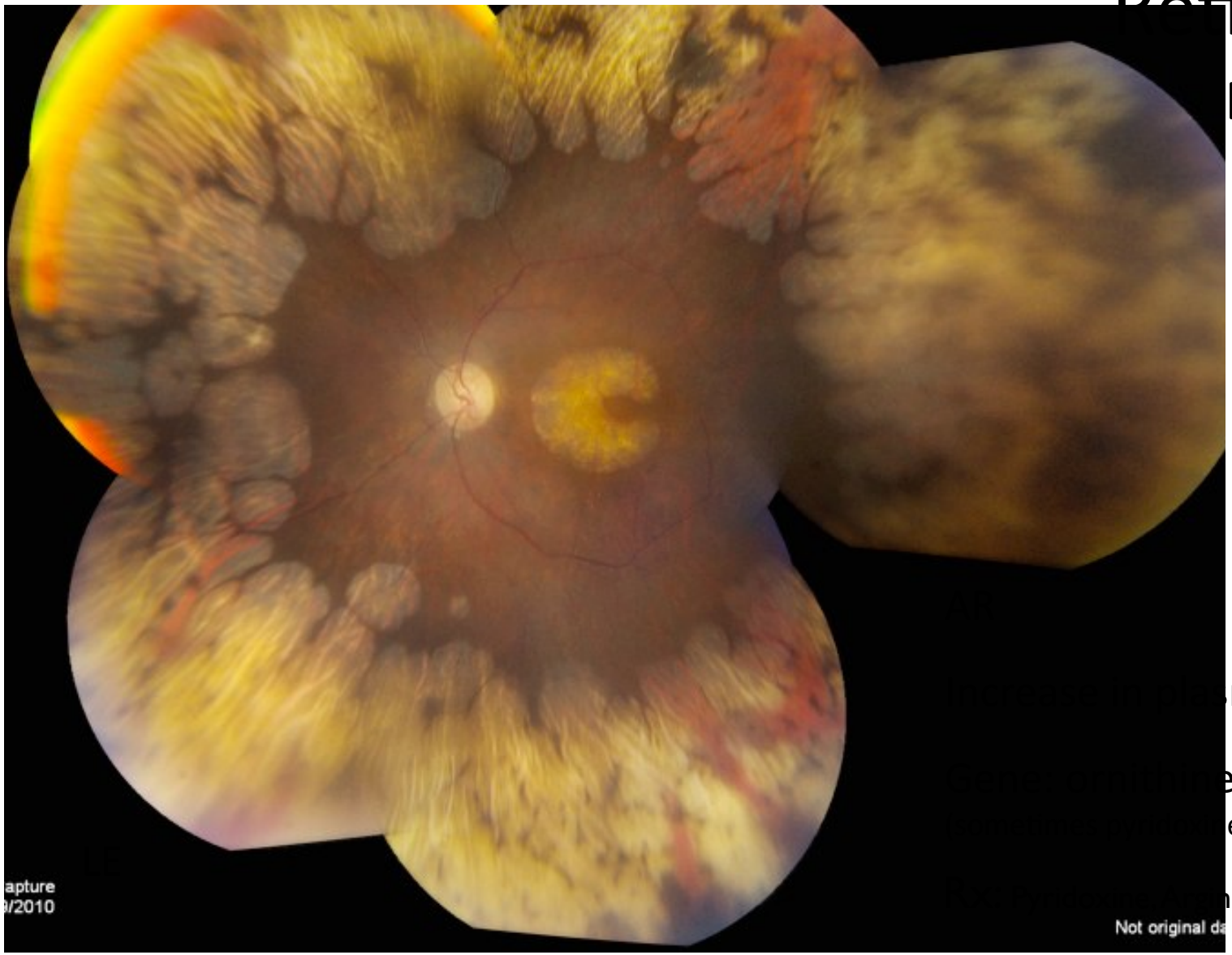
REP1 c.1518del (p.His507fs)



LE



Retinitis Pigmentosa



DD: Gyrate Atrophy

M, 46 yrs

ma ornithine

e-aminotransferase (OAT)

e responsive)

ine restriction & Proline supplementation

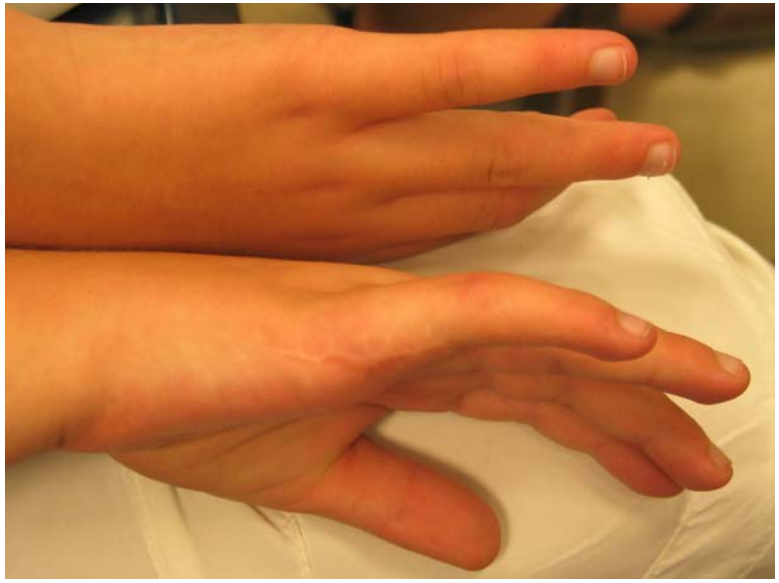
Syndromic Retinitis Pigmentosa Conditions

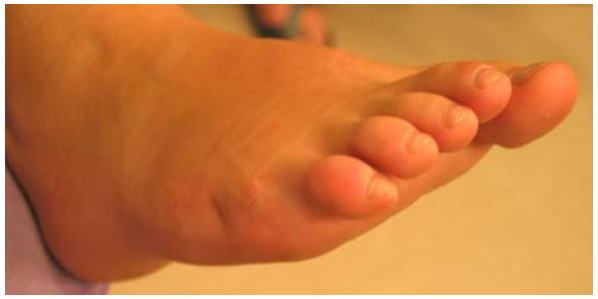
- Ciliopathies
  - Bardet-Biedl syndromes
  - Joubert syndrome & JSRD
  - Senior-Loken syndrome
  - Alström syndrome
- Mitochondrial disorders
  - Kearns-Sayre syndrome
- Usher syndromes
- Peroxisomal disorders
  - Zellweger syndrome
  - Adult Refsum disease
- Spinocerebellar ataxia 7
- Neuronal ceroid lipofuscinosis
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)

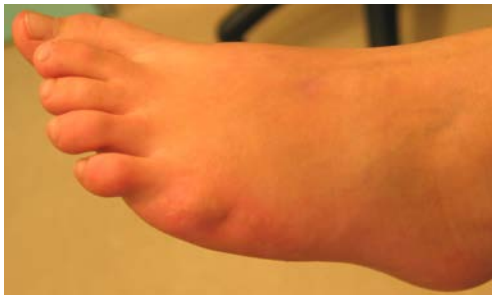
Retinitis Pigmentosa

DD: Bardet-Biedl Syndrome 1 (BBS1)

F, 10 yrs



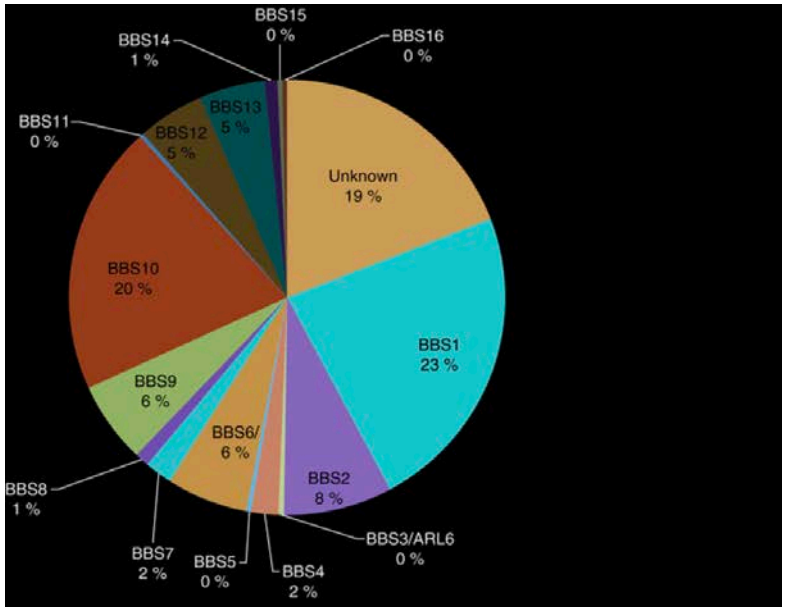




Biallelic mutations in *BBS1*

Bardet-Biedl Syndromes

16 Genes



Gene symbol	Chromosomal locus	Protein name
UNKNOWN		
BBS1	11q13	Bardet-Biedl syndrome 1 protein.
BBS2	16q21	Bardet-Biedl syndrome 2 protein.
BBS3/ARL6	3p12–q13	ADP-ribosylation factor-like protein.
BBS4	15q22.3–q23	Bardet-Biedl syndrome 4 protein.
BBS5	2q31	Bardet-Biedl syndrome 5 protein.
BBS6/MKKS	20p32	McKusick-Kaufman Bardet Biedl syndromePutative chaperonin
BBS7	4q27	Bardet-Biedl syndrome 7 protein.
BBS8/TTC8	14q32.1	Tetratricopeptide repeat protein 8.
BBS9/B1	7q21.2	Protein PTHB1.
BBS10	12q21.2	Bardet-Biedl syndrome 10 protein.
BBS11/TRIM32	9q31–q34.1	Tripartite modif-containing protein32.
BBS12	4q27	Bardet-Biedl syndrome 12 protein.
BBS13/MKS1	17q23	Meckel syndrome type 1 protein.
BBS14/CEP290	12q21.3	Centrosomal protein of 290 kDa.
BBS15/WDPC	2q15	WD repeat-containing and planar cell polarity effector protein.
BBS16/SDCCAG8	1q43	Serologically defined colon cancer antigen 8 homolog.

Retinitis Pigmentosa

DD: Bardet-Biedl Syndrome 1 (BBS1)

Syndromic Retinitis Pigmentosa Conditions

- Ciliopathies
  - Bardet-Biedl syndromes
  - Joubert syndrome & JSRD
  - Senior-Loken syndrome
  - Alström syndrome
- Mitochondrial disorders
  - Kearns-Sayre syndrome
- Usher syndromes
- Peroxisomal disorders
  - Zellweger syndrome
  - Adult Refsum disease
- Spinocerebellar ataxia 7
- Neuronal ceroid lipofuscinosis
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)

Retinitis Pigmentosa
Differential Diagnoses: Syndromic IRDs

Usher syndromes (AR) (RP + SNHL)

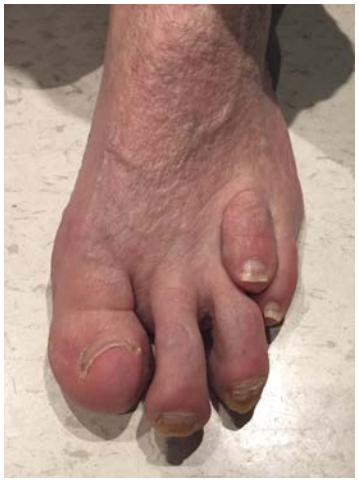
Bardet-Biedl syndromes (AR)

(RP + obesity, polydactyly, hypogonadism)

Adult Refsum disease (AR)

(RP + peripheral neuropathy + SNHL + loss of smell & taste)

Digital abnormalities
left foot
Adult Refsum
Disease



Leber Congenital Amaurosis

Symptoms & Signs

No or little sensitivity for visual stimuli from birth

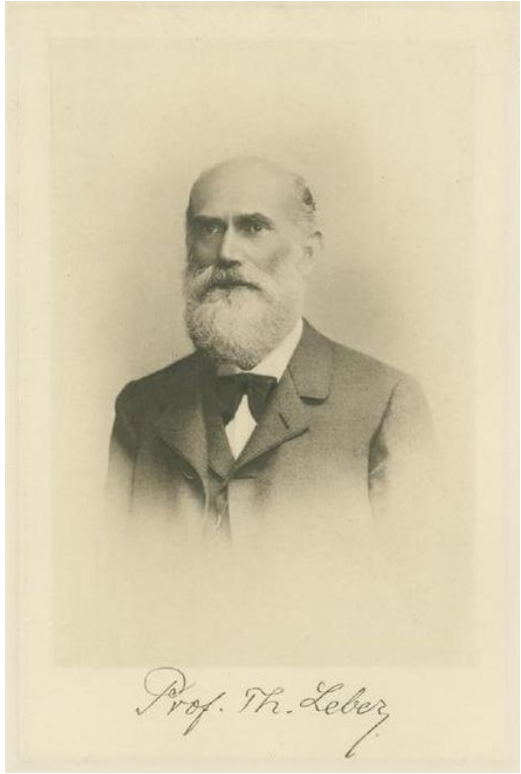
Variable aspect of retina

ERG abolished or profoundly abnormal

Autosomal recessive inheritance

Leber T: Uber retinitis pigmentosa und angeborene amaurose
Graefes Arch Klin Exp Ophthalmol, **15**, 13-20, 1869

LCA is responsible for 18% of legal blindness in children worldwide



Theodor Karl Gustav von Leber
19 Feb 1840 - 17 Apr 1917

Leber Congenital Amaurosis

Symptoms & Signs

No or little sensitivity for visual stimuli from birth

Variable aspect of retina

ERG abolished or profoundly abnormal

Autosomal recessive inheritance

Hyperopia

Sluggish pupillary responses

Oculodigital sign

Keratoconus

Occasional photophobia

LCA & EORD Genotypes

24 LCA genes:

GUCY2D on 17p13.1
RPE65 on 1p31
CRX on 19q13.3
AIPL1 on 17p13.1
CRB1 on 1q31-q32.1
RPGRIP1 on 14q11.2
MERTK on 2q14.1
RDH12 on 14q24.1
IMPDH1 on 7q31.3-32
TULP1 on 6p21
CEP290 on 12q21-q22
LCA5 on 6q11-q16
SPATA7 on 14q24
OTX2 on 14q21-22
IQCB1 on 3q21.1
PDE6G on 17q25
KCNJ13 on 2q37.1
RD3 on 1q32
NMNAT1 on 1p36
DTHD1 on 4p14
CAPB4 on Xp11.4
GDF6 on 8q22.1
IFT140 on 16p13.3
PRPH2 on 6p21.1

6 early-onset RP genes:

RDH12 on 14q23.3
LRAT on 4q31.2
MERTK on 2q14.1
TULP1 on 6p21.3
SPATA7 on 14q24
ADAMTS18 on 16q23.1

70% of patients

LCA

Differential Diagnoses

Achromatopsia (AR)

Blue cone monochromatism (XL)

CSNB (AR, AD or XL)

Albinism (AR or XL)

Neuronal ceroid lipofuscinosis (infantile) (AR)

LCA

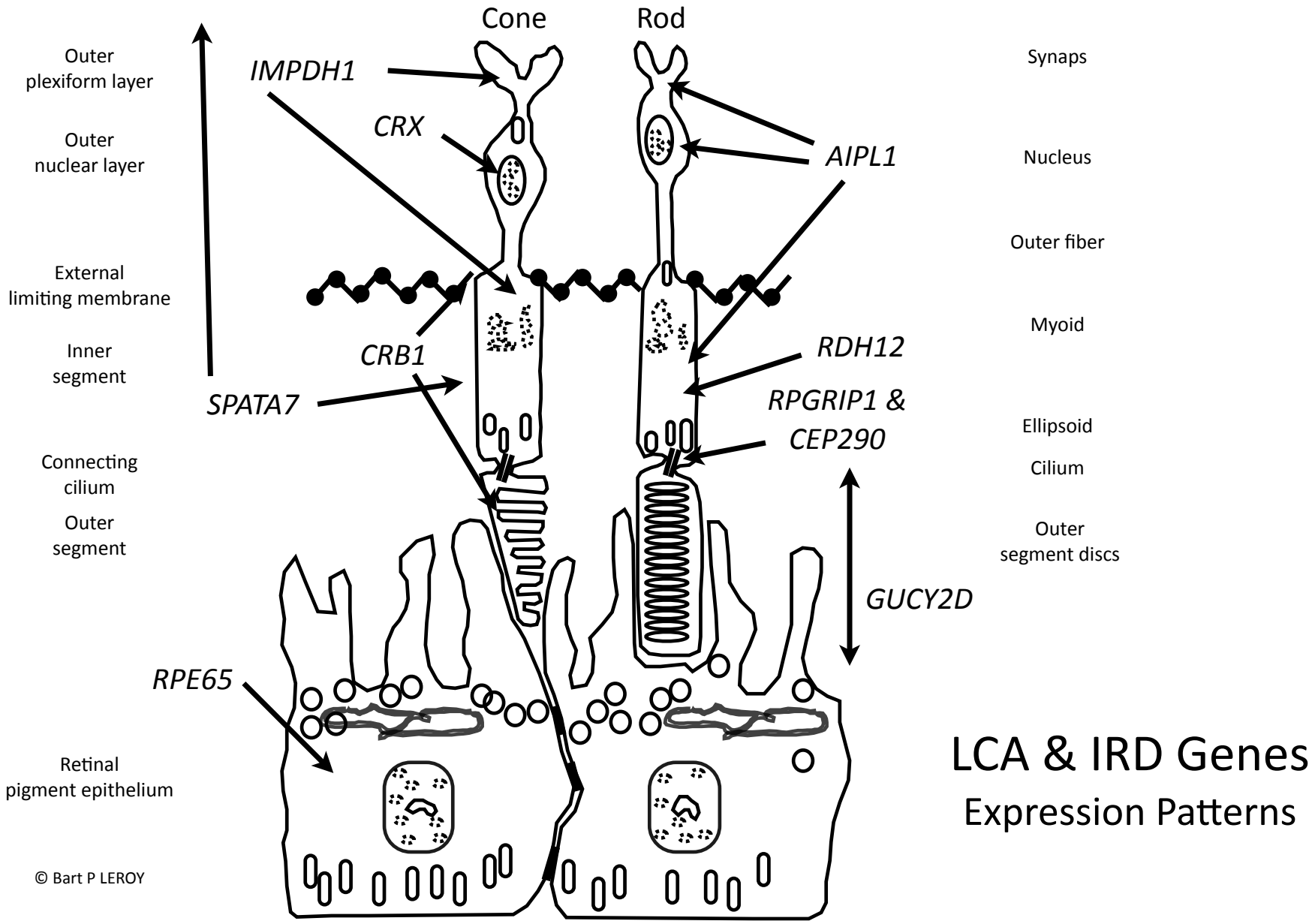
Differential Diagnoses: Syndromic IRDs

Early-onset retinal dystrophy + nephronophthysis (Senior-Loken syndrome) (AR)

Early-onset retinal dystrophy + nephronophthysis, cone-shaped epiphyses of hand & cerebellar ataxia (Saldino-Mainzer syndrome)

Early-onset retinal dystrophy + cerebellar vermis hypoplasia, oculomotor anomalies and neonatal respiratory problems (Joubert syndrome) (AR)

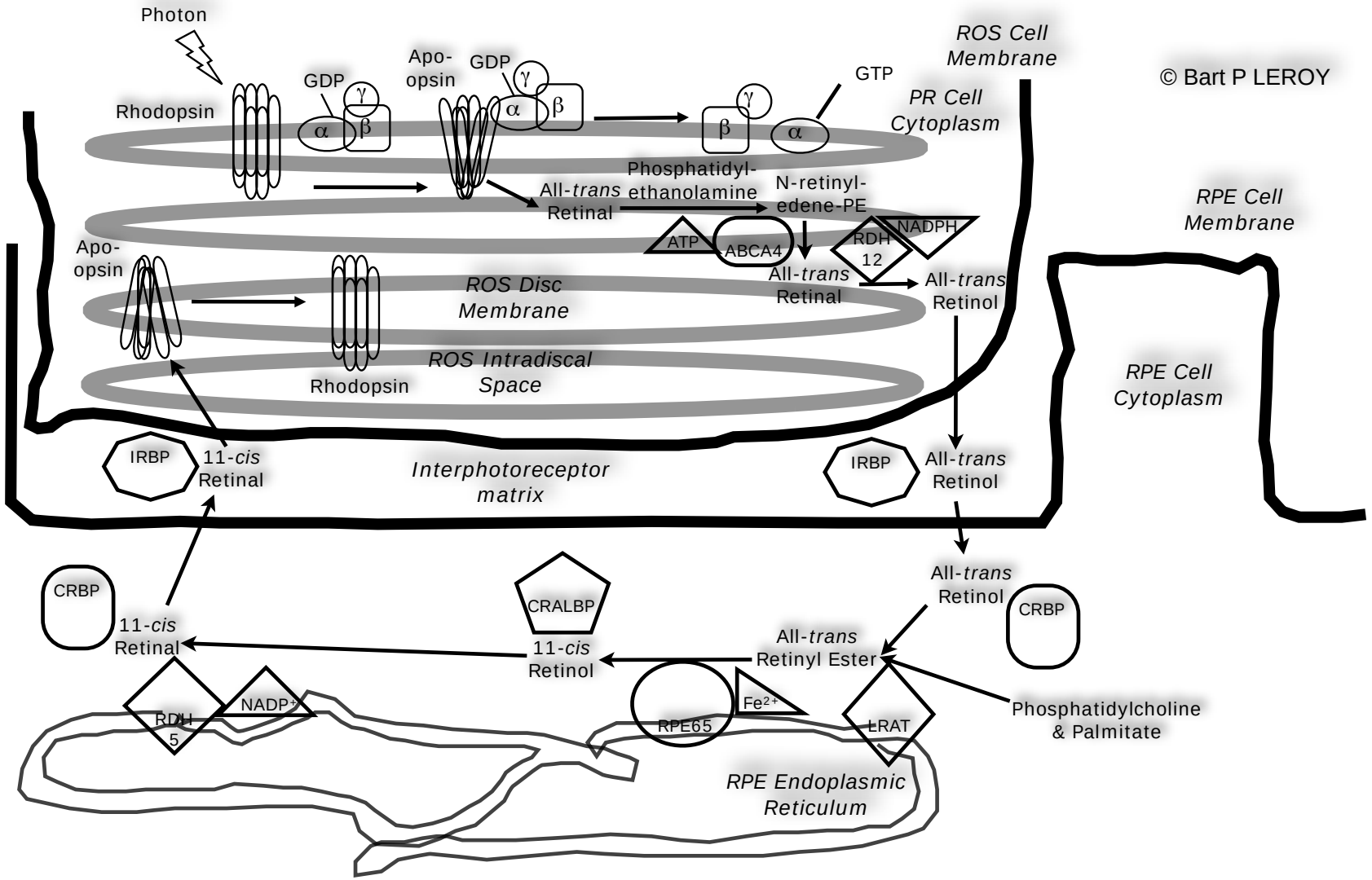
Early-onset retinal dystrophy + diabetes mellitus, cardiomyopathy, severe sensorineural deafness, obesity (Alström syndrome) (AR)



LCA & IRD Genes

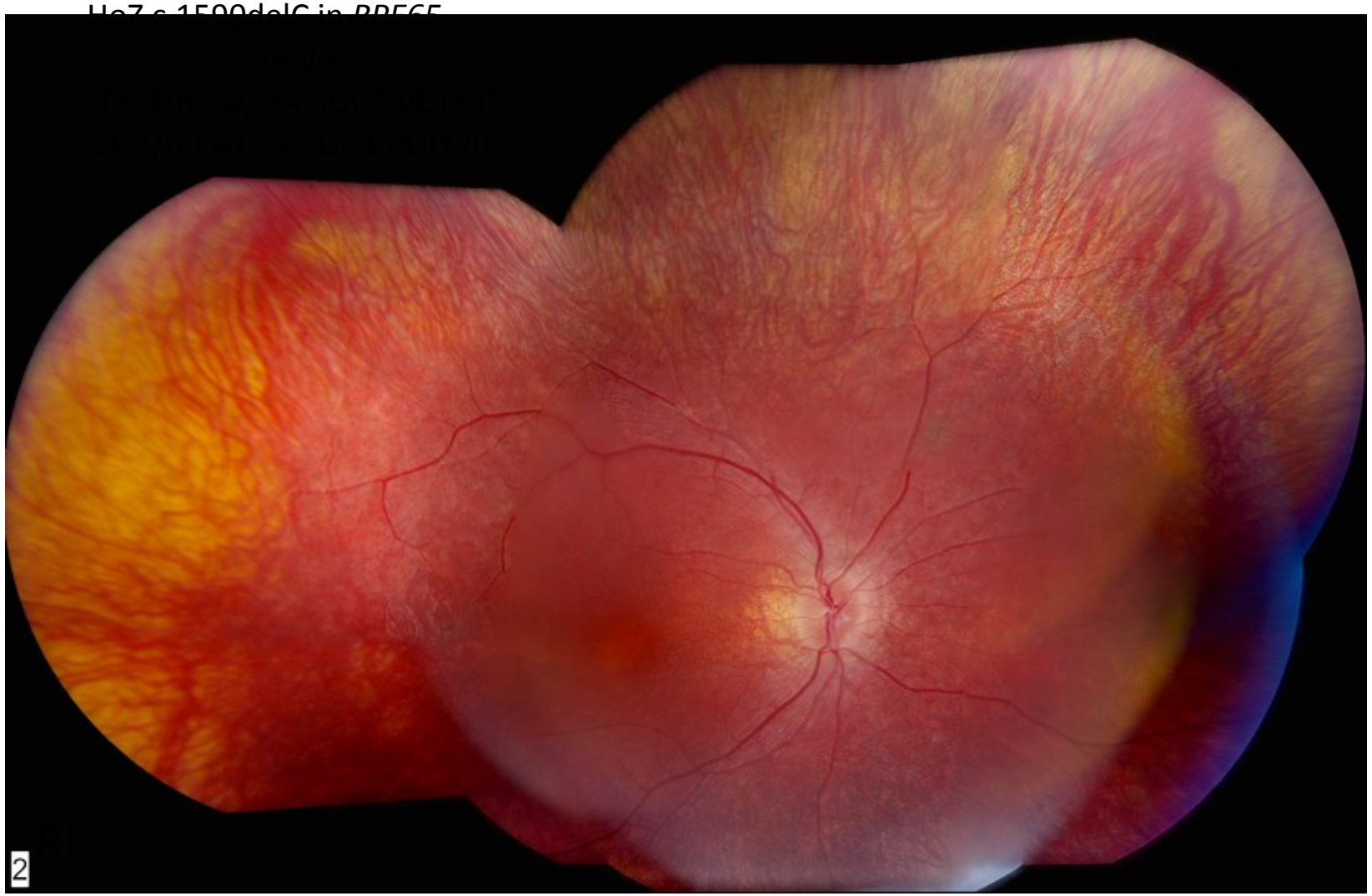
Expression Patterns

The Retinoid Cycle



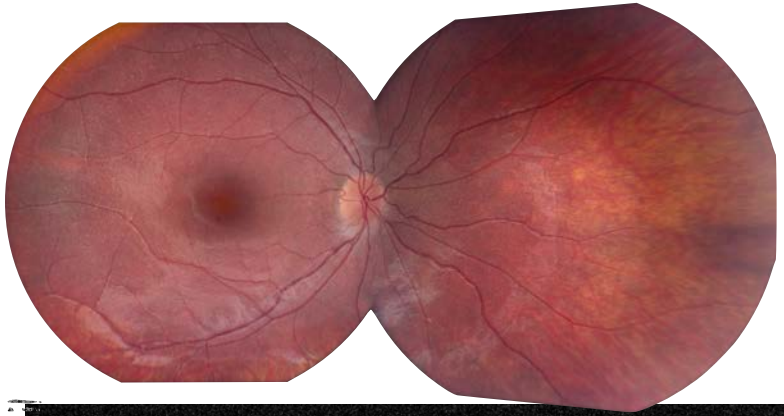
Case

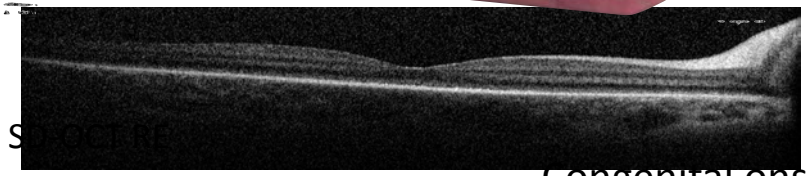
M, 9 yrs, LCA



RPE65-related Retinal Dystrophy Phenotype

F, 4 4/12 yrs
EORD





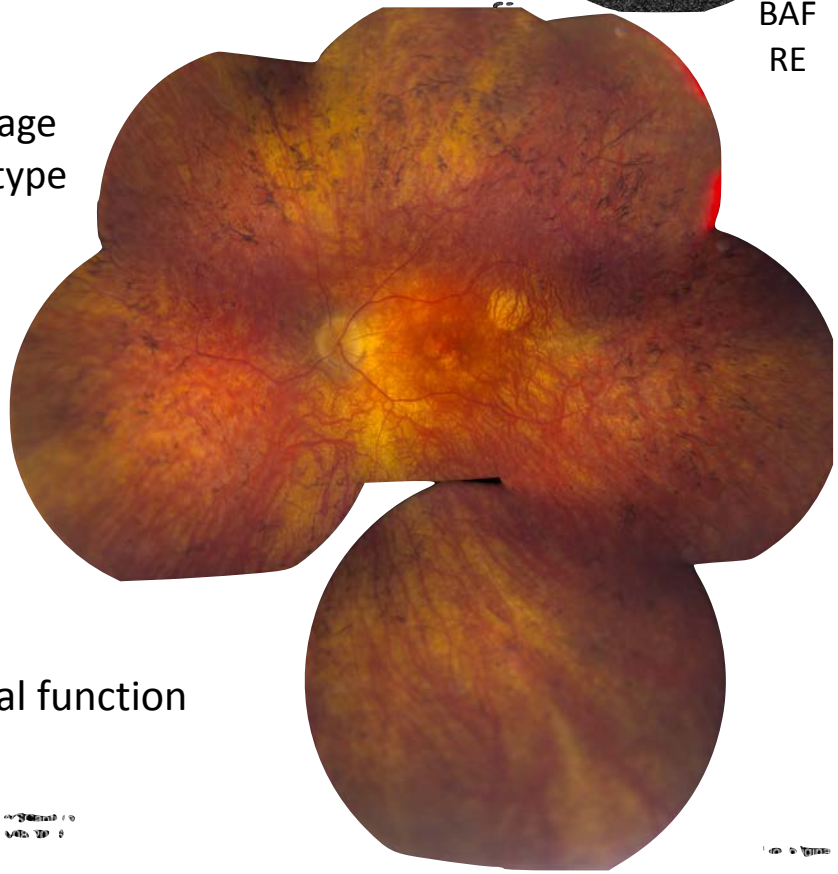
BAF RE

Early Stage Phenotype

Late Stage Phenotype

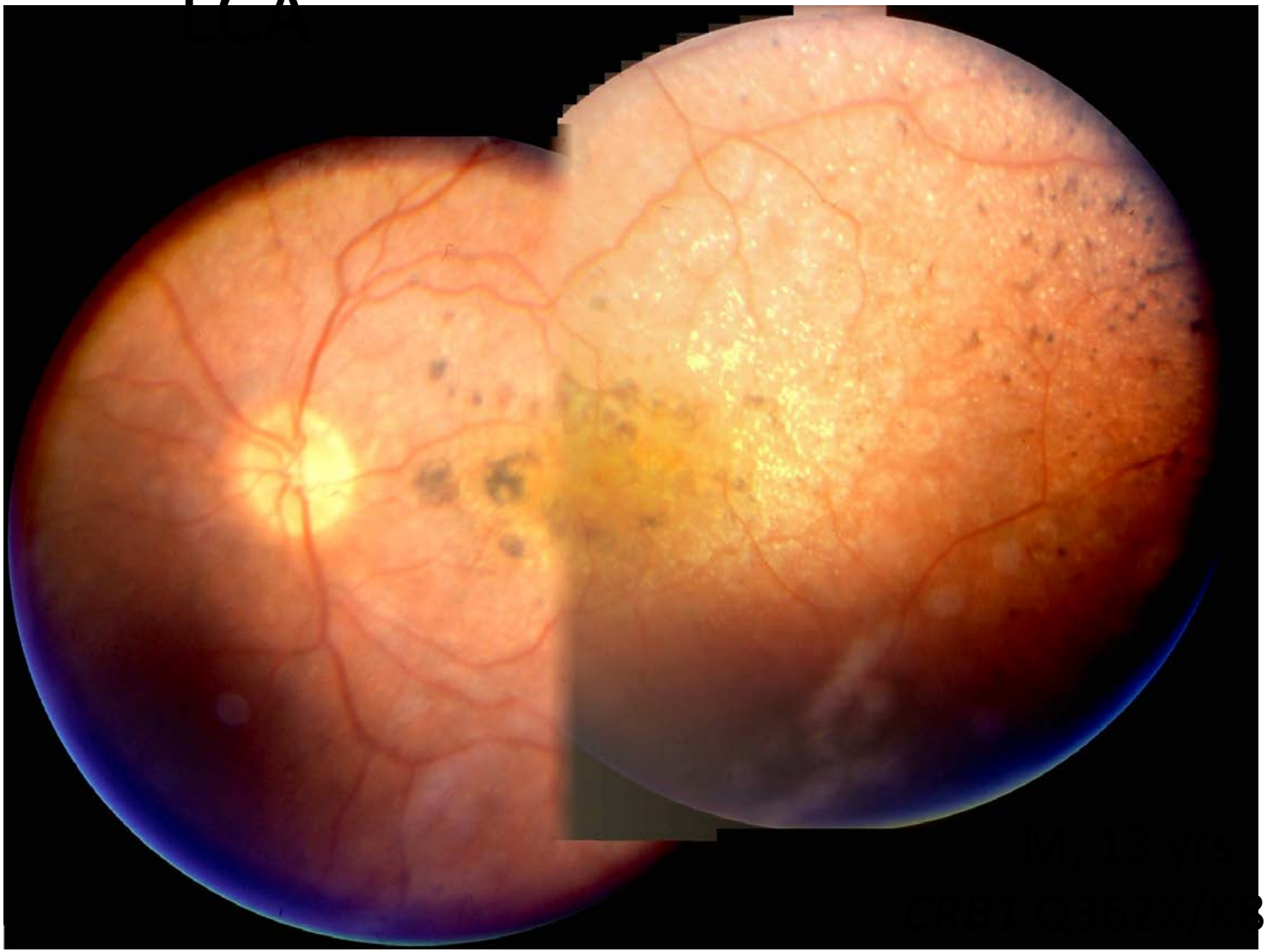
F, 29 yrs
EORD

BAF RE



- Congenital onset of night blindness
- Nystagmus often
- Initially retina looks fairly normal
- Many different initial diagnoses
- Later phenotype identical to that of classic RP
- Vascular attenuation suggests early loss of retinal function
- Absence of blue light autofluorescence typical
- Sometimes picked up late w/ Dx of RP
- Progression towards complete blindness; early treatment paramount

LCA



301X

NMNAT1-related LCA

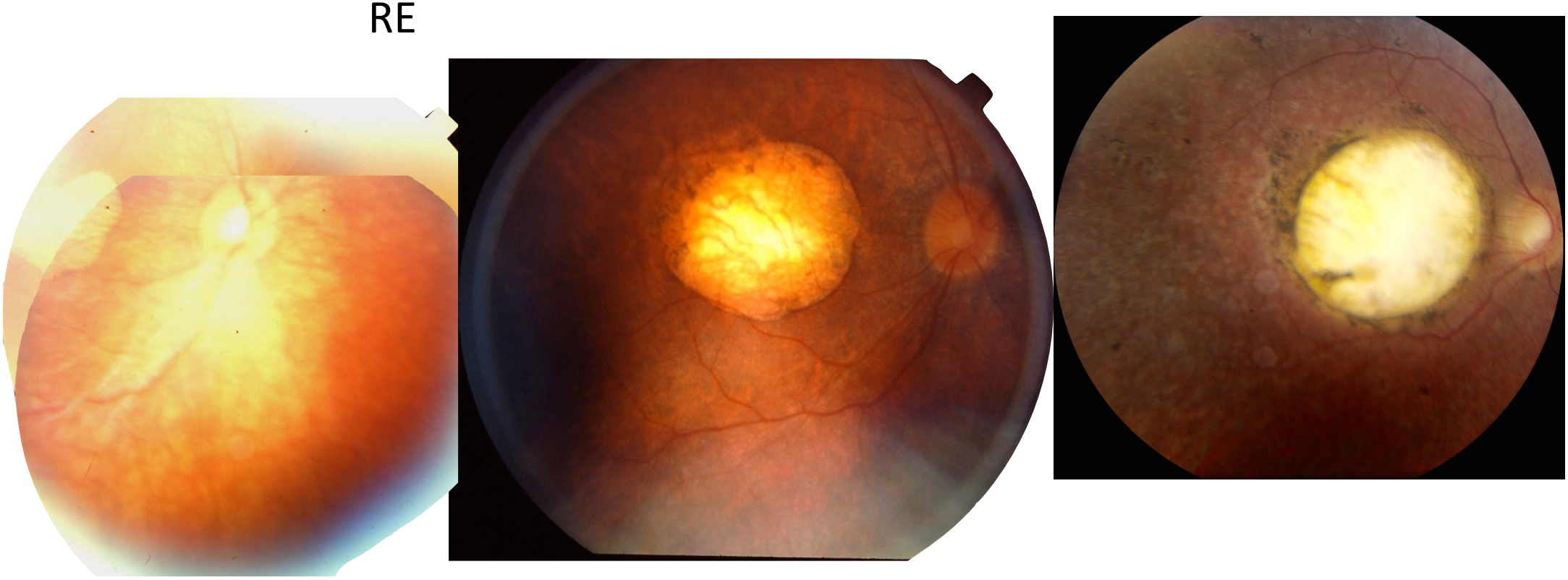
M,

HoZ for *NMNAT1* c.-69C>T

BCVA BE LP w/o localisation

Evolution of Macular Atrophy

RE



9 mths

3 8/12 yrs

21 yrs

Cone Dysfunction
General

Symptoms & signs:

- Reduced VA
- Abnormal colour vision
- Abnormal VF: central, paracentral, midperipheral & peripheral scotomas
- Photophobia

Cone-Rod Dystrophies
Genetics

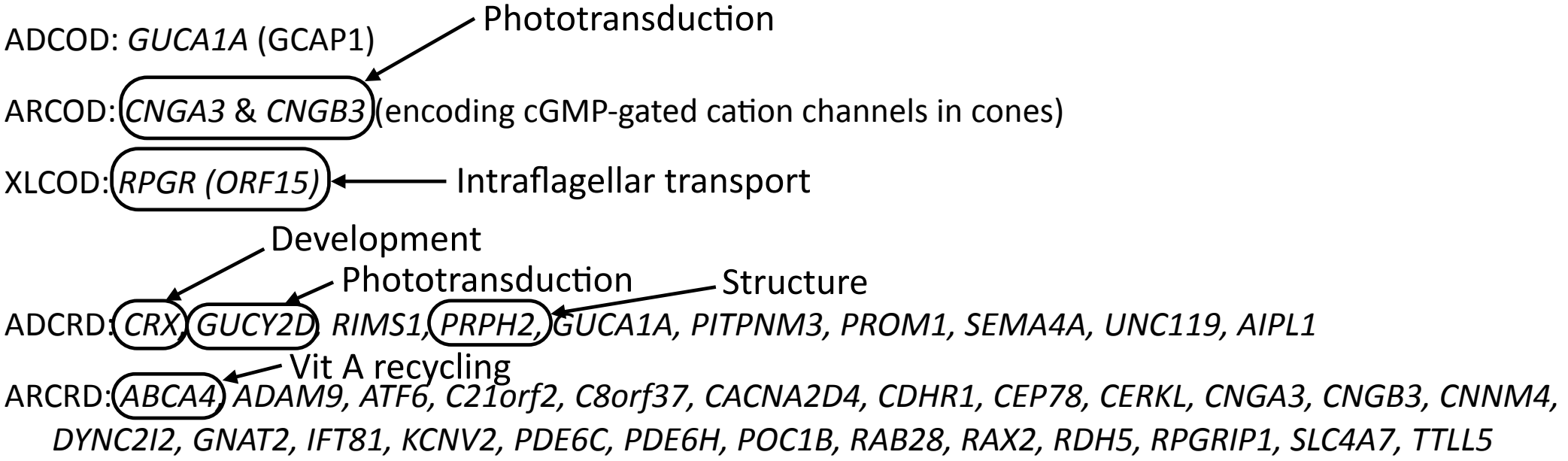
Heterogeneous

AD COD & CRD: 13 genes (10 cloned)

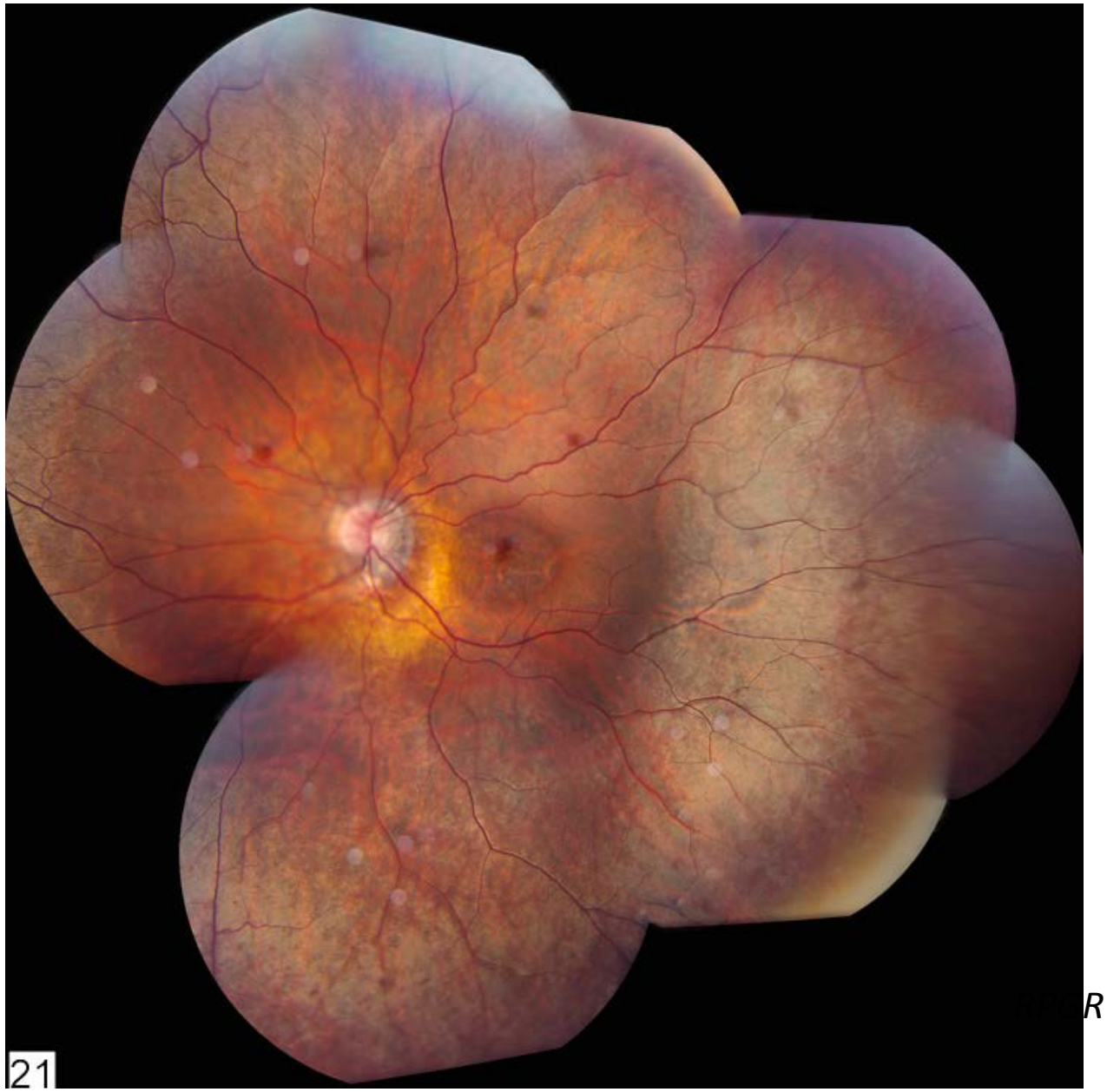
AR COD & CRD: 26 genes (25 cloned)

XL COD & CRD: 3 genes (2 cloned)

Cone & Cone-Rod Dystrophies
Genes



LE



M, 27 yrs
XLCRD
BCVA
RE 2/10
LE 3/10
w/ high myopic corr

R g.ORF15+652_653delAG

5/ Stationary Retinopathies

Achromatopsia
General

= Rod monochromatism

Signs & symptoms:

Photophobia

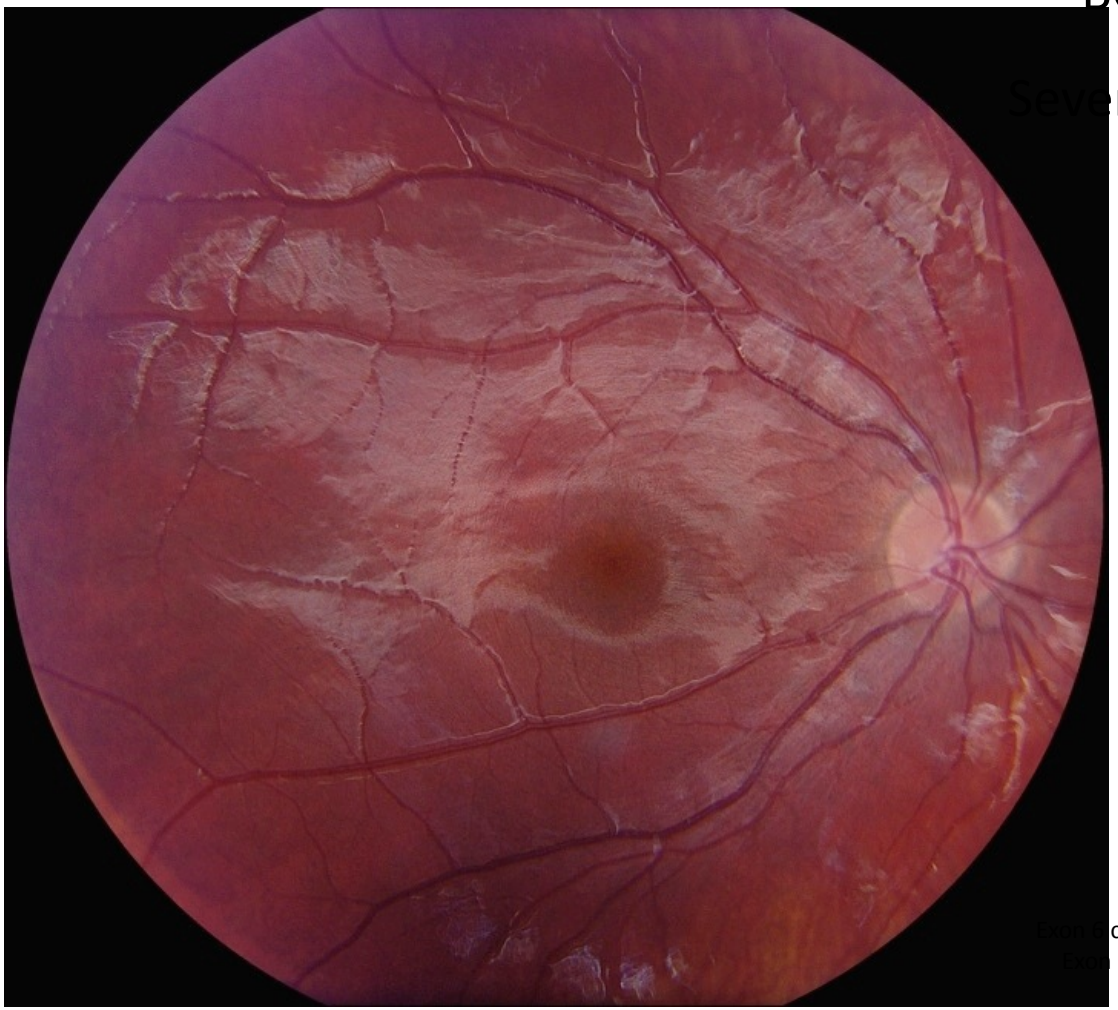
Nystagmus

Poor visual acuity

Absent colour vision

Case

M, 6 yrs Achromatopsia



BCVA 1/10 BE

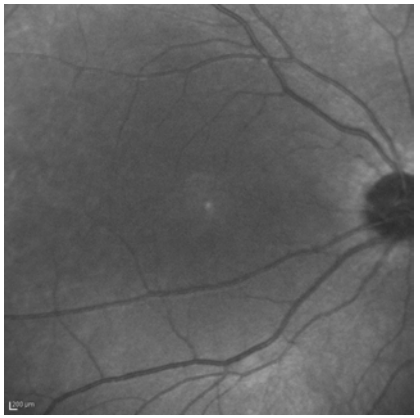
Severe photophobia

RE

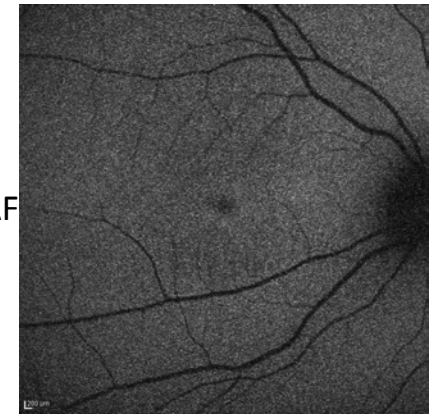
CNGB3

Exon 7 c.819_826del (p.Arg274fs) &
Exon 10 c.1148del (p.Thr383fs)

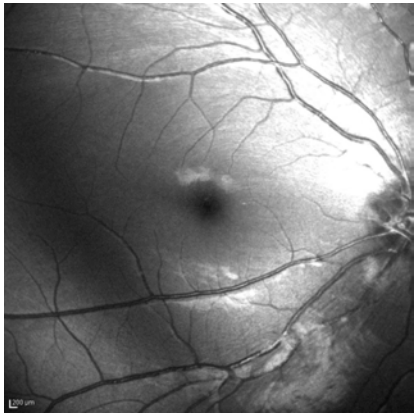
IR



BAF



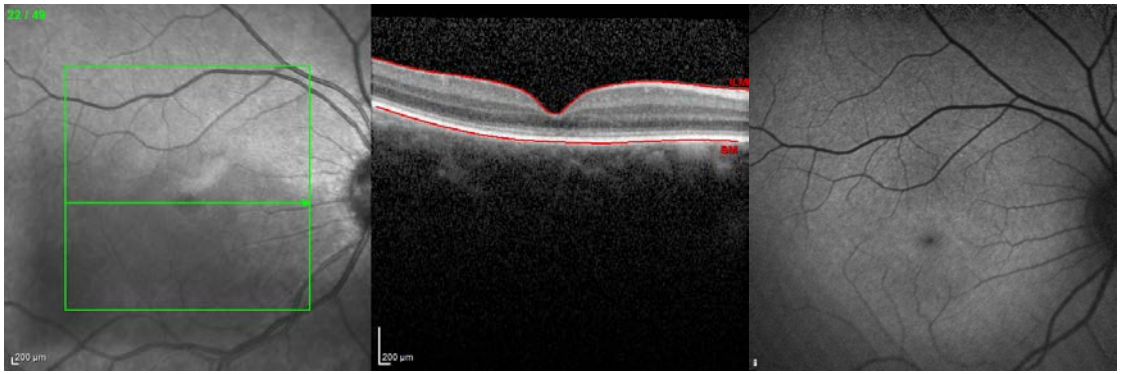
RF



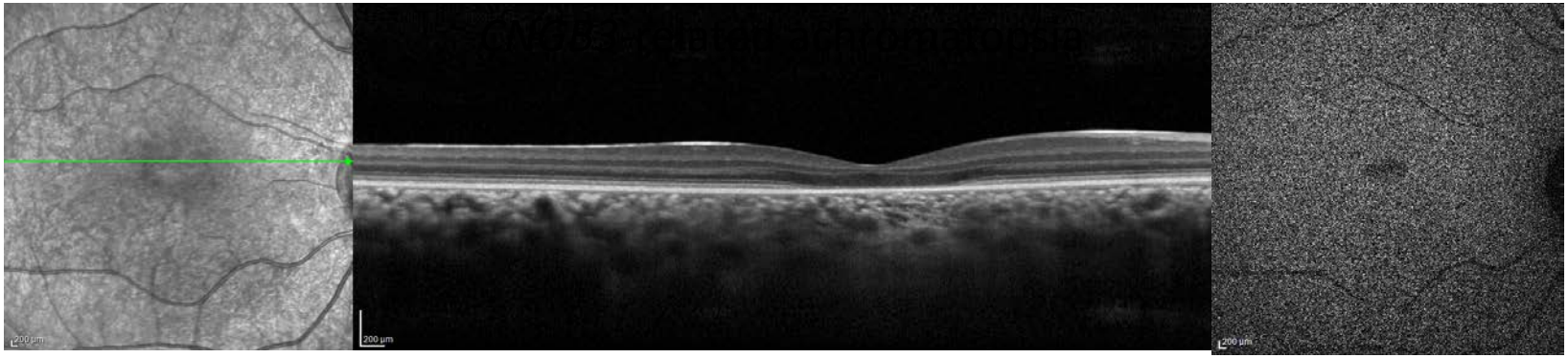
Cases

IRR, BAF & OCT in Achromatopsia

NIRAF BAF



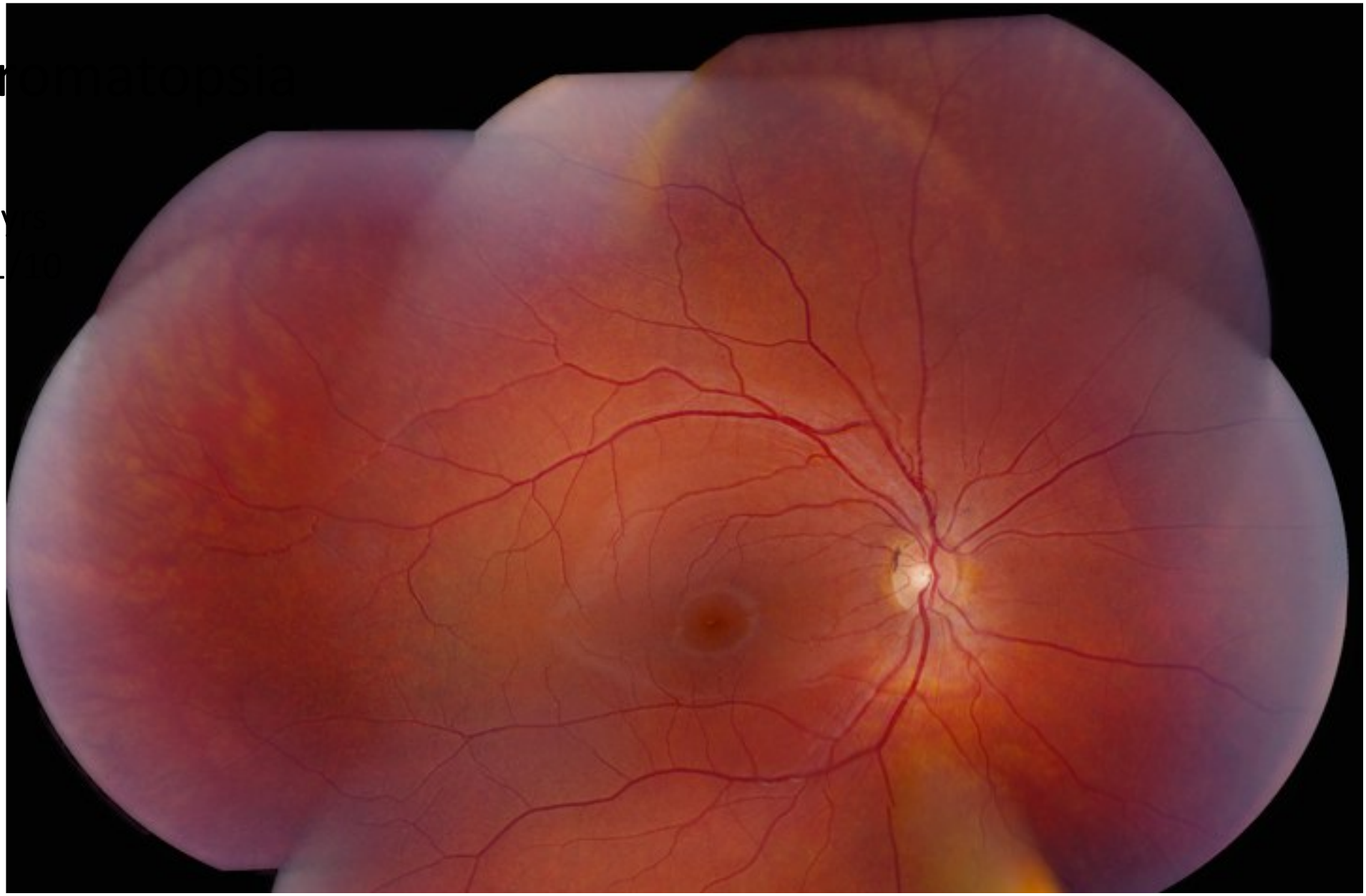
NIRAF F, 9 yrs, BAF



M, 11 yrs, *CNGA3*-related achromatopsia

Achromatopsia

M, 16 y
VA BE 1



RE

Achromatopsia Genetics

CNGB3 on 8q21-q22 (40-50% of cases)

encodes cone cGMP-gated cation channel, beta 3 subunit

CNGA3 on 2q11 (20-30% of cases)

encodes cone cGMP-gated cation channel, alpha subunit

GNAT2 on 1p13.3 (limited number of cases)

encodes cone-specific transducin, alpha subunit

PDE6C on 10q23.33 (limited number of cases)

encodes alpha subunit of cone-specific cGMP phosphodiesterase

PDE6H on 12p12.3 (limited number of cases)

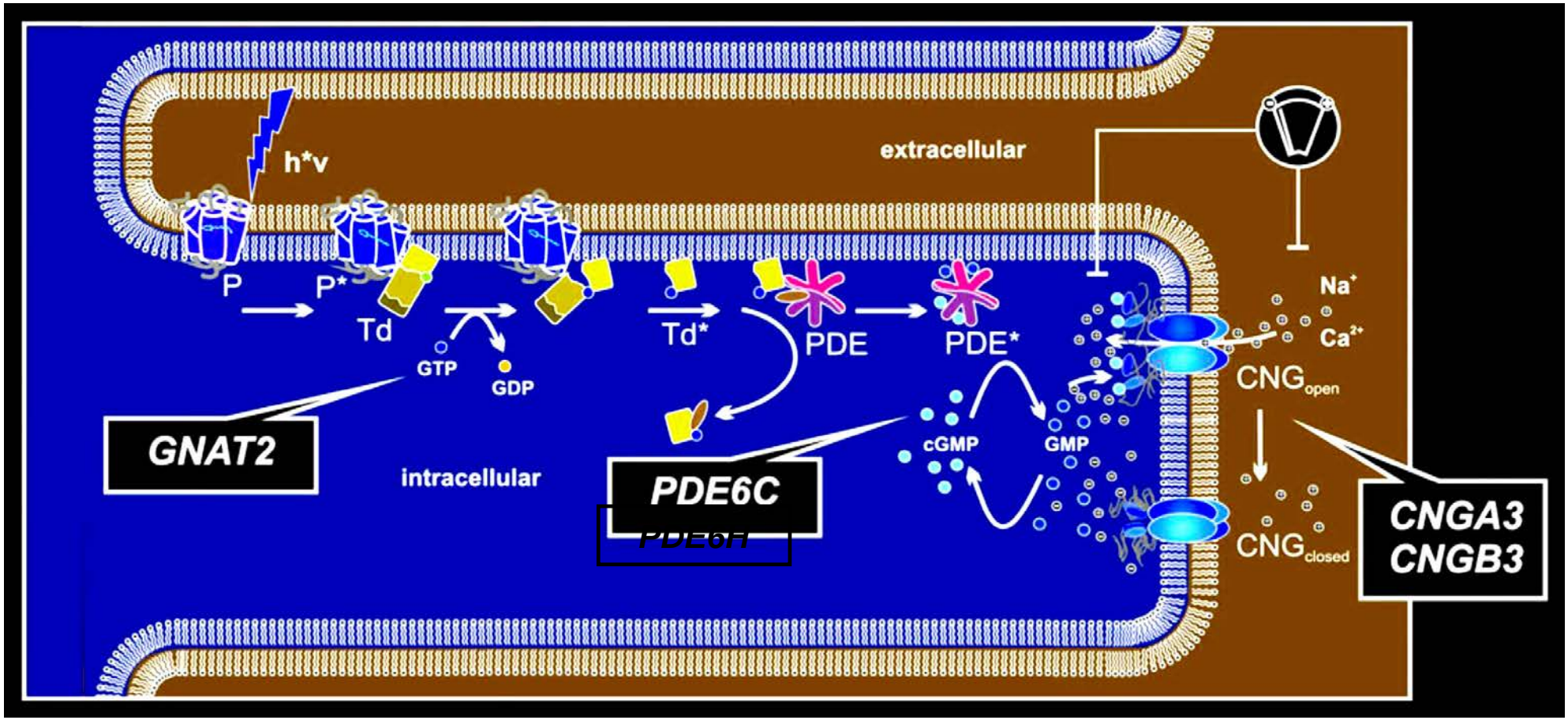
encodes gamma subunit of cone-specific cGMP phosphodiesterase

ATF6 on 1q23.3 (limited number of cases)

encodes transmembrane transcription factor, involved in unfolded protein response, localised throughout neural retina & RPE

Always
AR trait

Cone Phototransduction Cascade



Adapted from original courtesy of
Prof Bernd WISSINGER

Achromatopsia
Differential Diagnoses

Blue Cone Monochromacy (BCM) (XL)

Incomplete Achromatopsia (AR)

Congenital Stationary Night Blindness (CSNB) General

Stationary

Signs & symptoms:

Night blindness from birth

Myopia in AR and XL cases

Subnormal VA in XL & AR cases

Nystagmus in XL & AR cases

Normal fundus

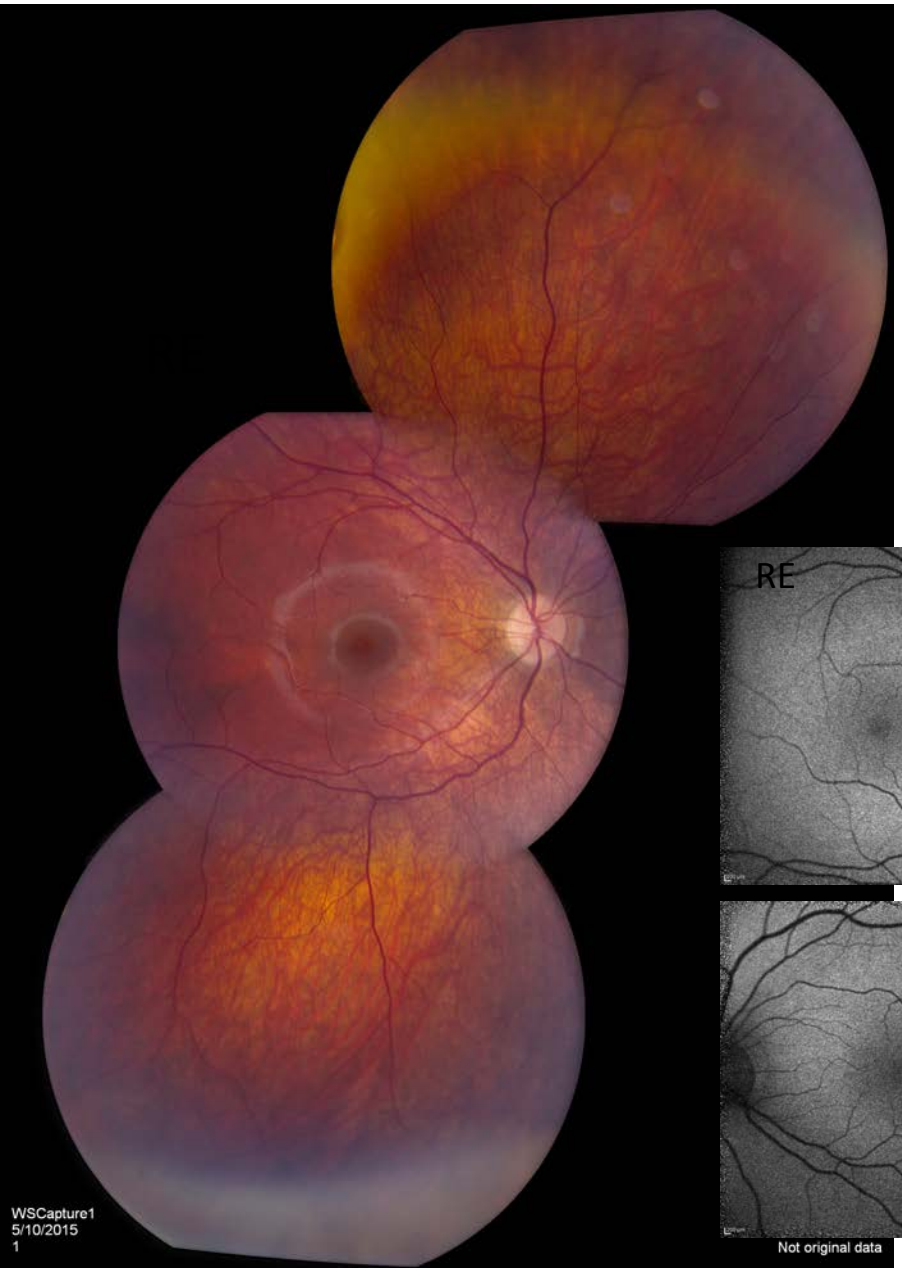
Congenital Stationary Night Blindness (CSNB) General

Stationary

Rod system does not work

Signs & symptoms:

- Night blindness from birth
- Myopia in AR and XL cases
- Subnormal VA in XL & AR cases
- Nystagmus in XL & AR cases
- Normal fundus



Case

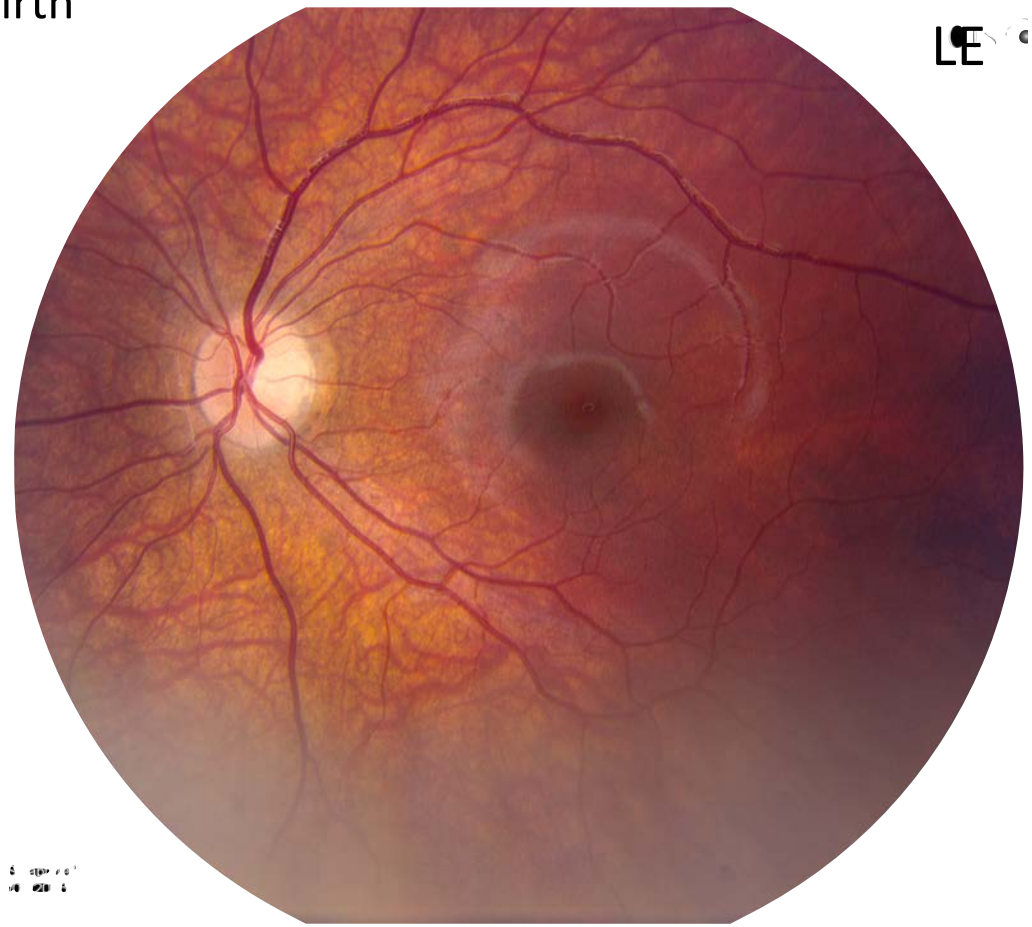
M, 5 yrs

Night blindness since birth

HeZ for *NYX*

c.619_627del in-frame deletion p.Arg207_Arg209del

XL cCSNB



CSNB
Mechanisms & Genetics

Mechanisms:

Infrequently due to HeZ mutations in genes encoding phototransduction proteins (PRs)

Most often due to mutations in genes encoding for PR-BPC synaptic proteins

Genetics: in order of relative frequency:

X-linked (XL) (large majority)

Autosomal recessive (AR)

Autosomal dominant (AD)

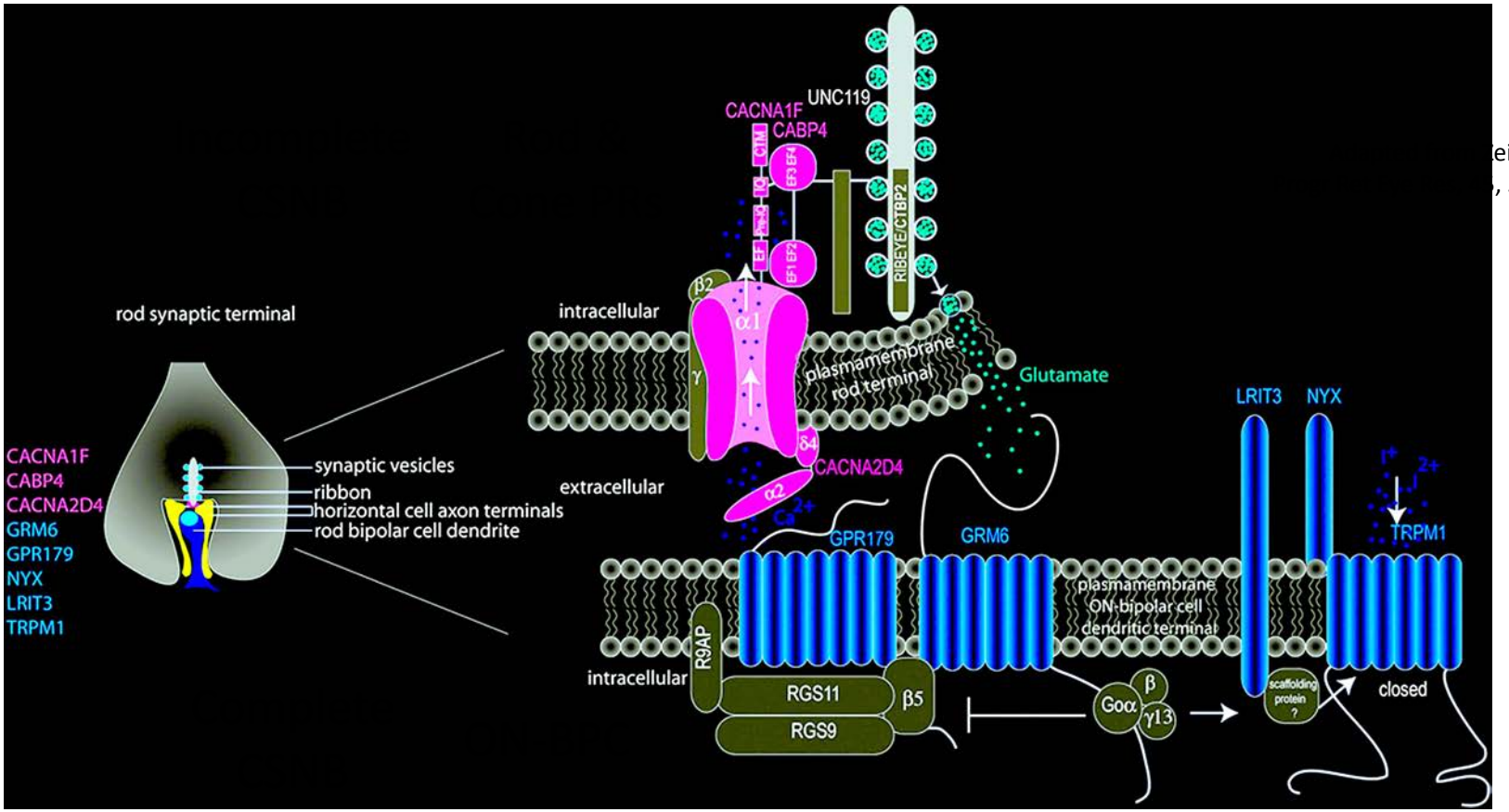
CSNB
General

Different ERG patterns described:

- Schubert-Bornschein: synaptic problem between PRs & BPCs
  - Miyake complete: problem in ON-BPC (postsynaptic)
  - Miyake incomplete: problem in PRs (presynaptic)
- Riggs: problem in phototransduction

CSNB Proteins

CSNB genes either encode proteins important in transmitting signals from PRs to BPCs (Schubert-Bornschein type ERG) or proteins of phototransduction cascade (Riggs type ERG)



eitz *et al*,
, 58-110, 2015

6/ Dystrophies w/ Predominant Macular Involvement

Stargardt Disease
Symptoms

Early visual loss

Stargardt Disease
Signs

Beaten metal appearance fovea

Yellow-white deep intraretinal flecks

Chorioretinal atrophy

Initially rather aspecific fundus picture

Stargardt Disease
Genetics

Complete penetrance

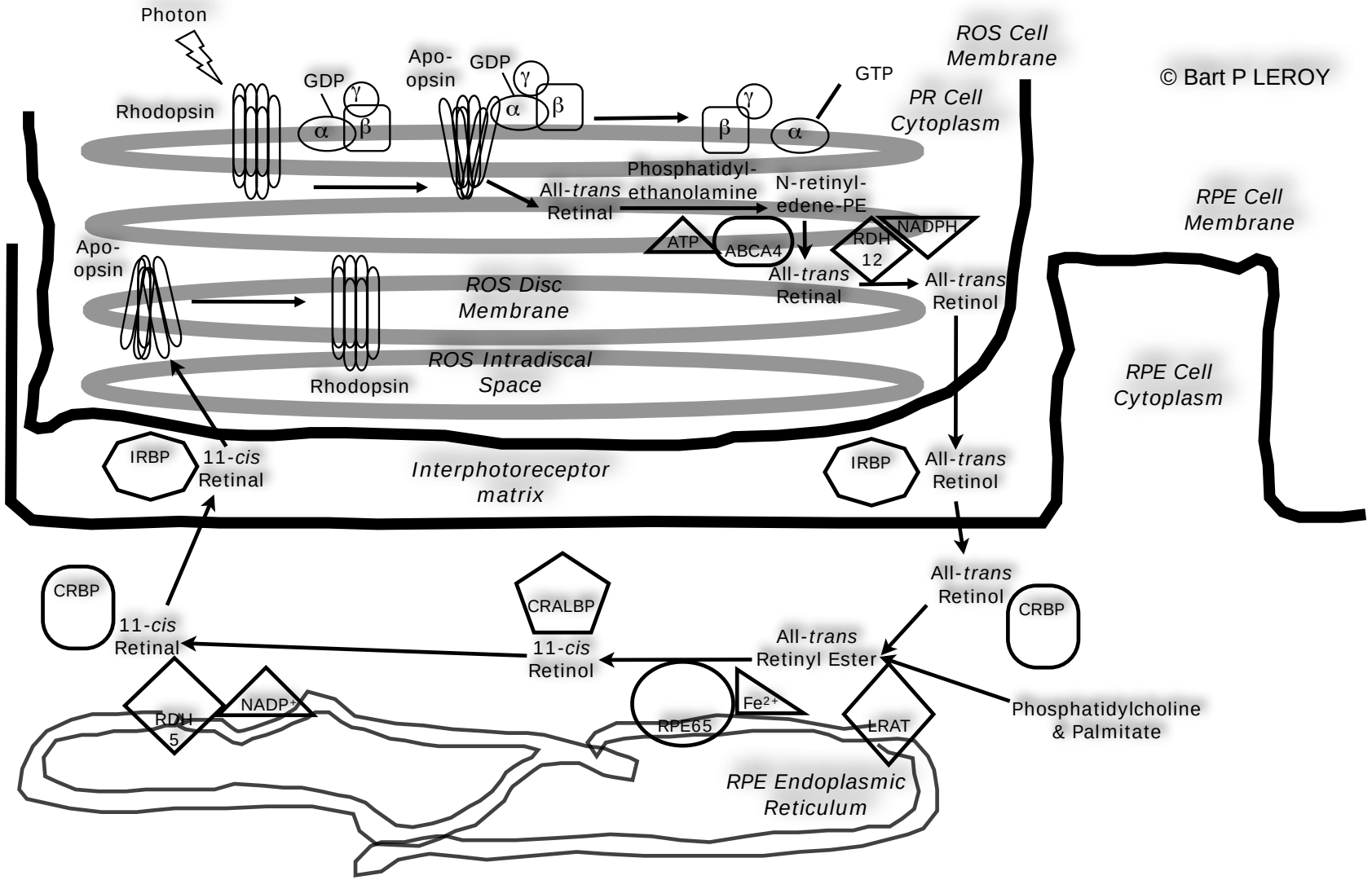
Variable expression

AR; *ABCA4* gene on 1p21-p22.1

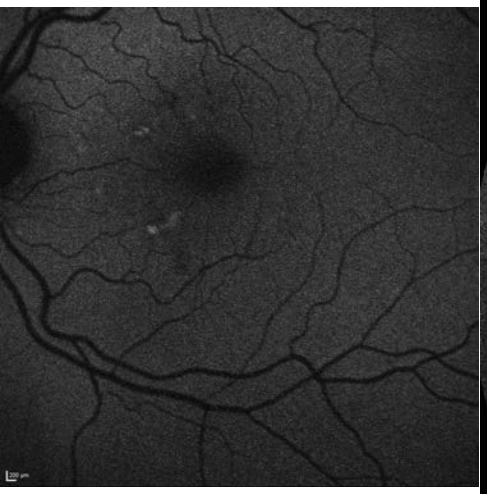
Expressed in rods & cones

ABCA4: moves retinal out of and into OS

The Retinoid Cycle



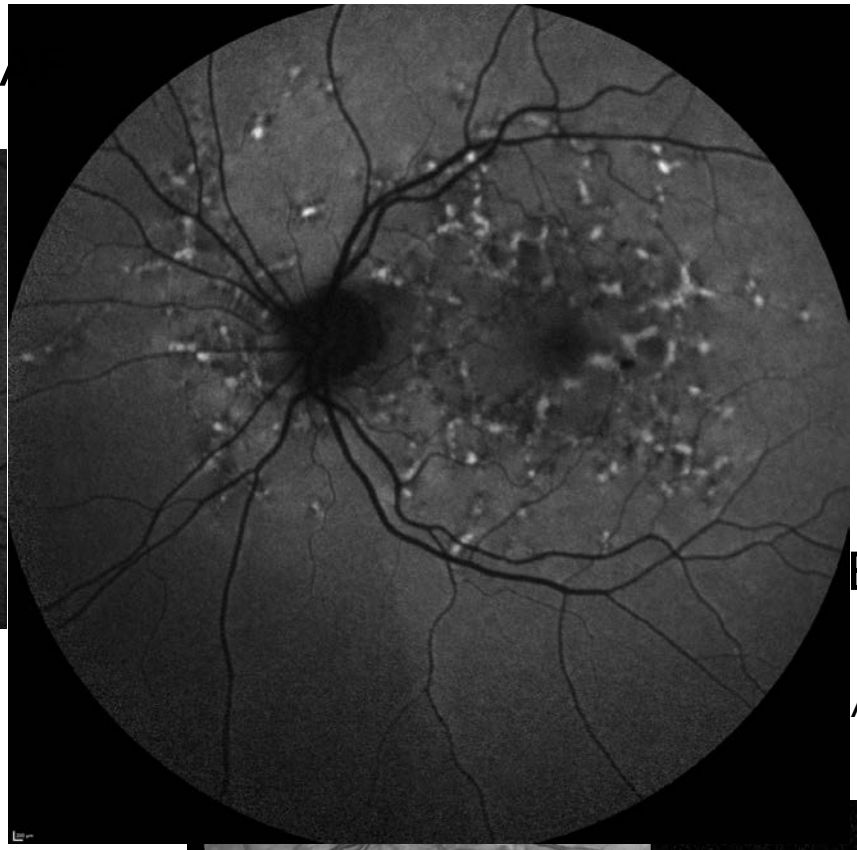
LE



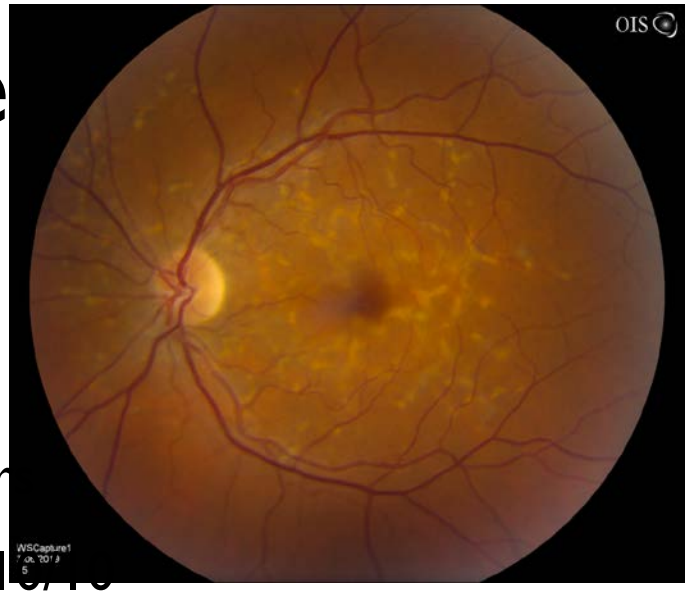
@42 yrs

BCVA BE 10/10

B



Case F



@56 yr

BCVA BE

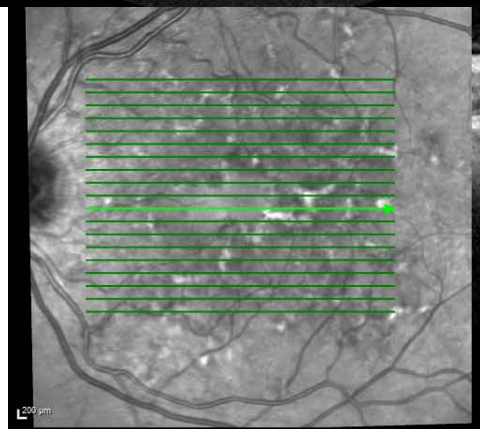
ABCA4 compound HeZ for

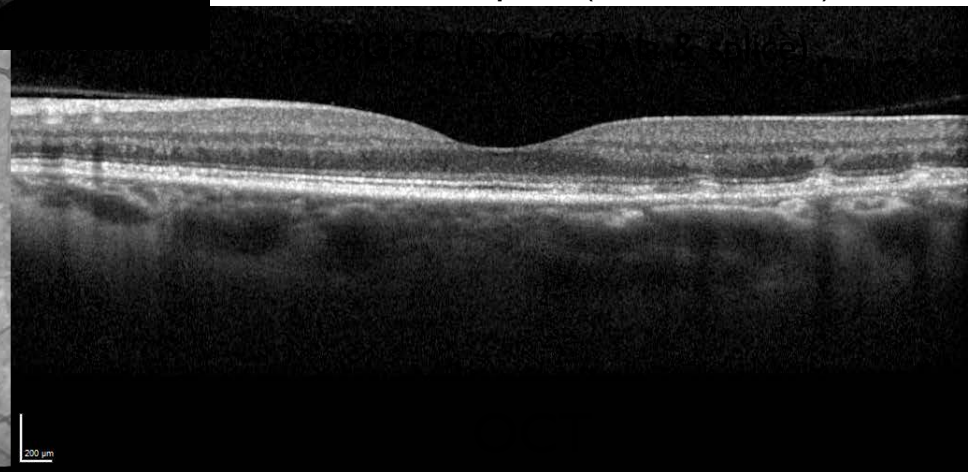
IVS40+5G>A splice (c.5714+5G>A)

LE

Classic Phenotype Stargardt Disease

NIRR





Stargardt Disease

Phenotypical Spectrum

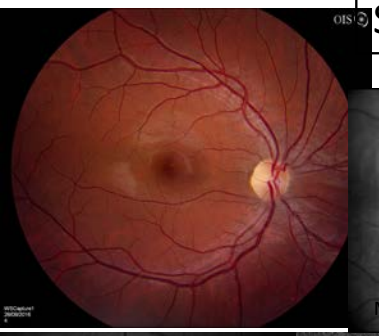
F, 25 yrs

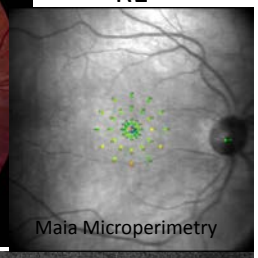
BCVA 20/20 BE

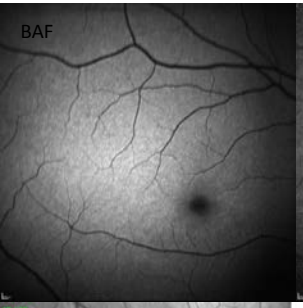
Sees flecks; normal GVF & ERG

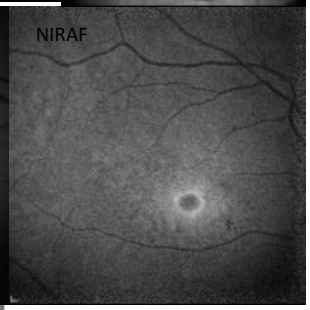
Supermild

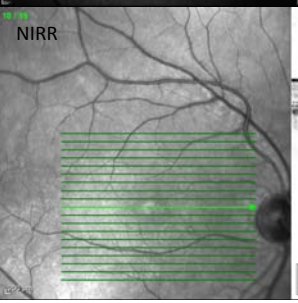
RE

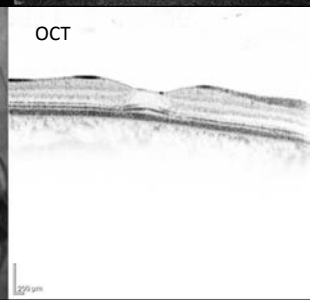












ABCA4

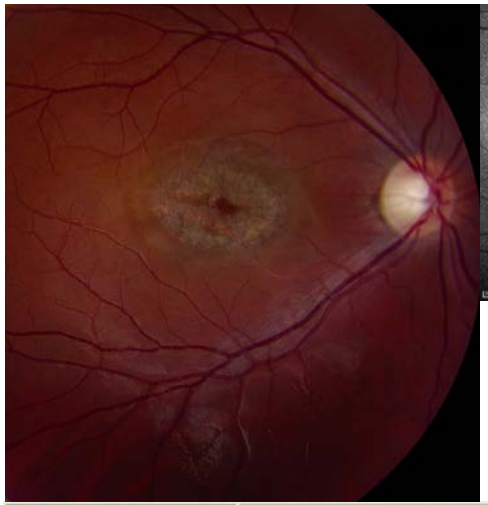
c.3886G>T (p.Arg1129Leu) &

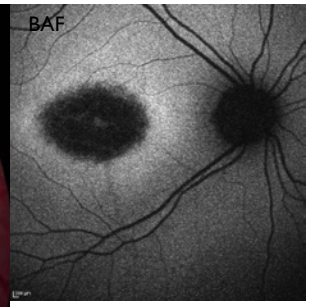
c.688T>A (p.Cys230Ser)

F, 22 yrs

BCVA 20/200 BE; normal ERG

Early Stage Classic



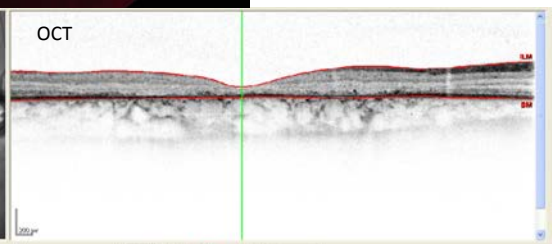


ABCA4

c. 5714+5G>A &

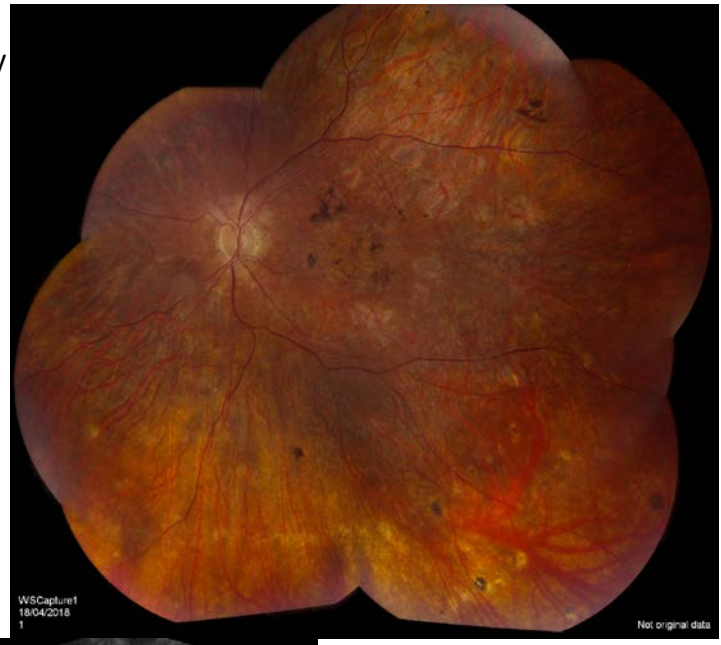
c.5413A>G

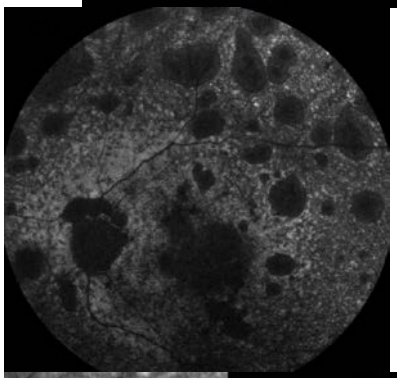
(p. Asn1805Asp)



F, 40 yrs

nearly





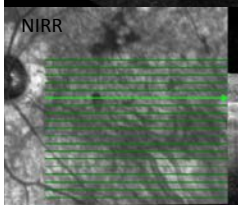
Severe

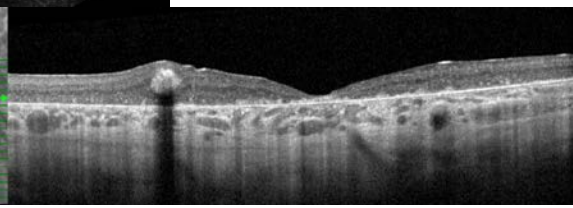
ABCA4

c. 768 G>T (splice) &

c. 5113 C>T

(p. Arg1705Trp)





Stargardt Disease
Electrophysiology

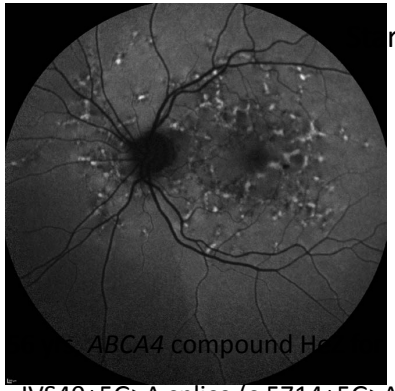
FF flash ERG:

normal in majority of cases

allows better phenotype description

Pattern ERG: abnormal

Stargardt Disease
Differential Diagnoses

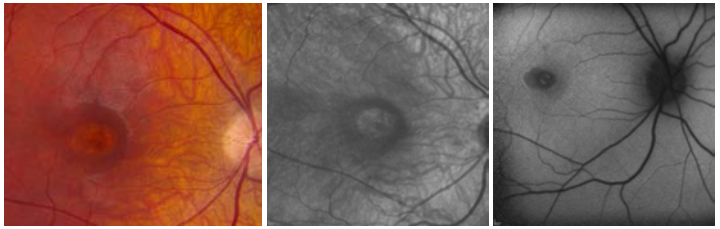


rgardt Disease

F, [illegible] *ABCA4* compound He[illegible]

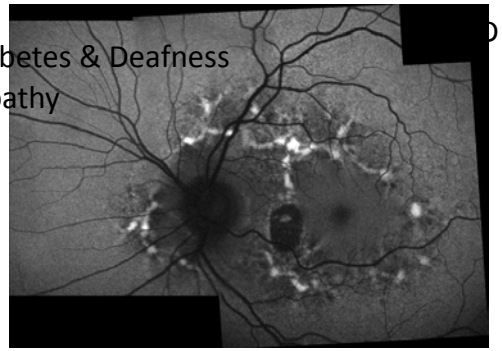
IVS40+5G>A splice (c.5714+5G>A)

c.2588G>C (p.Gly863Ala & splice)

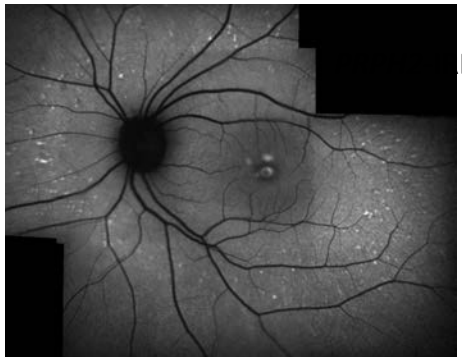


F, 8 yrs, *MFSD8* (NCL7 gene)
c.590del (p.Gly197Valfs*2) & c.439+3 A>C (donor splice site)

Maternally Inherited Diabetes & Deafness
w/ maculopathy



F, 47 yrs, *MTTL1* m.3243A>G



F, 35 yrs, *PRPH2* c.281G>A, p.(Trp94Ter)

Cone dystrophies

Cone-rod dystrophies

Maternally Inherited Diabetes & Deafness w/ maculopathy (MIDD)

m.3243A>G in *MTTL1* (85%); m.14692A>G in *MTTE;* m. 8296A-G in *MTTK*

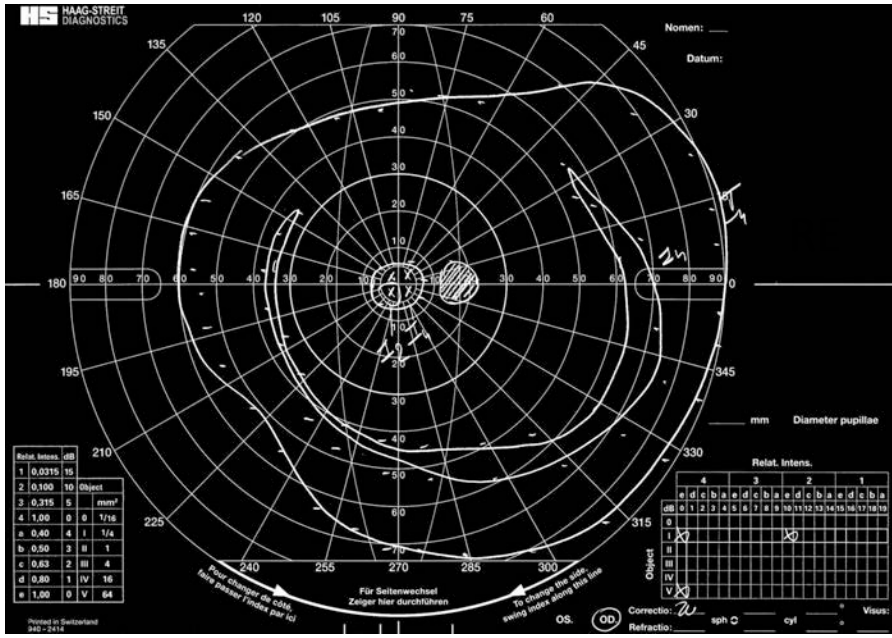
PRPH2-IRD, maculopathy type

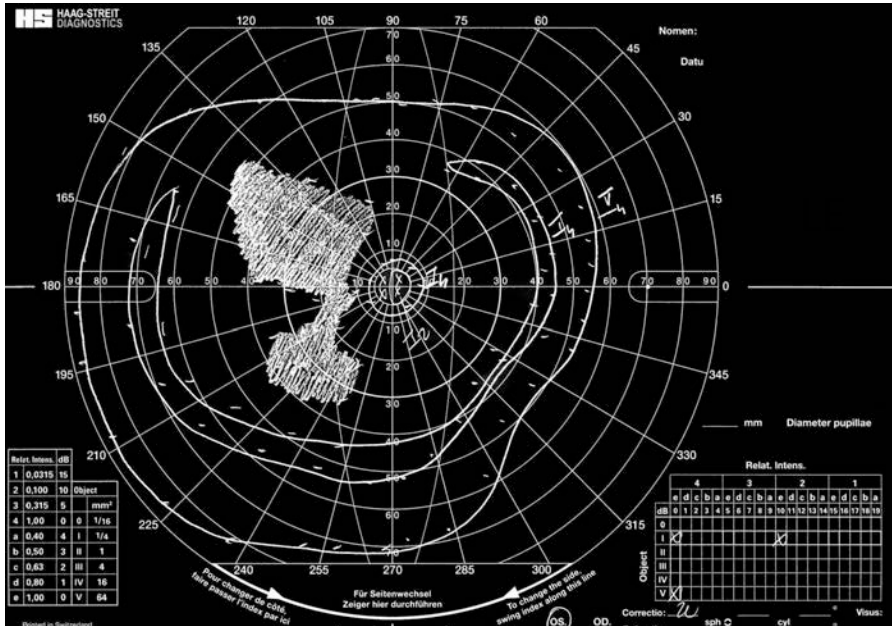
Neuronal Ceroid Lipofuscinoses (*CLN3*, *MFSD8*, …)

…

Case

GVF



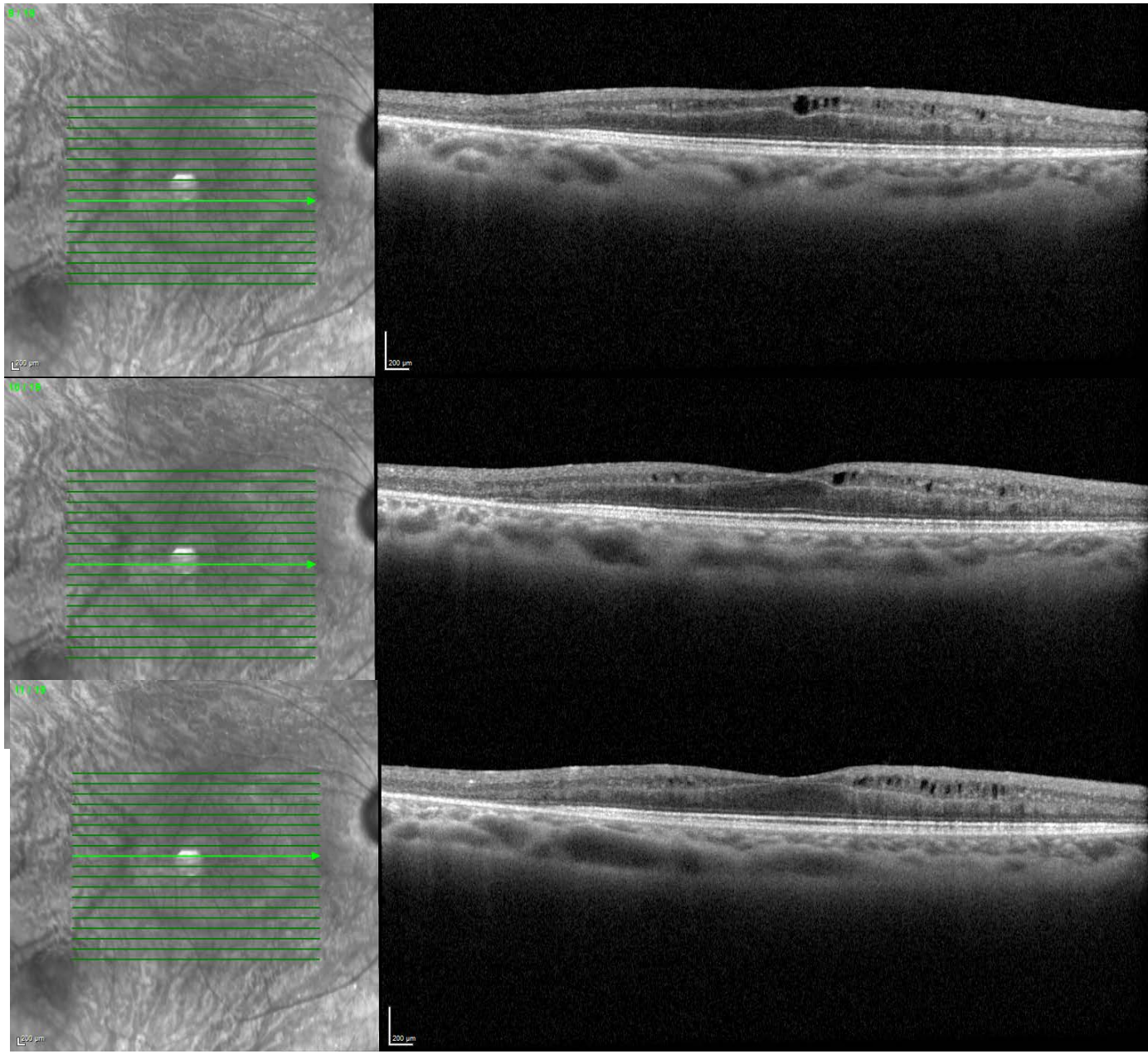


- F, 35 yrs
- Italian, works for EU parliament
- Has always had low BCVA BE
- Eye doctor in Italy retired
- Other Univ Hosp Dx her w/ Retinal Dystrophy due to *ABCA4*
- HeZ for c.5882G>A p.(Gly1961Glu) in *ABCA4* Exon 42
- BCVA RE 0,16 w/ corr & LE 0,1 (2-) w/ corr
- SLE BE unremarkable

OCT RE

Case

- F, 35 yrs
- Other Univ Hosp Dx her w/ Retinal Dystrophy due to ABCA4
- Deep intronic mutations in *ABCA4* excluded

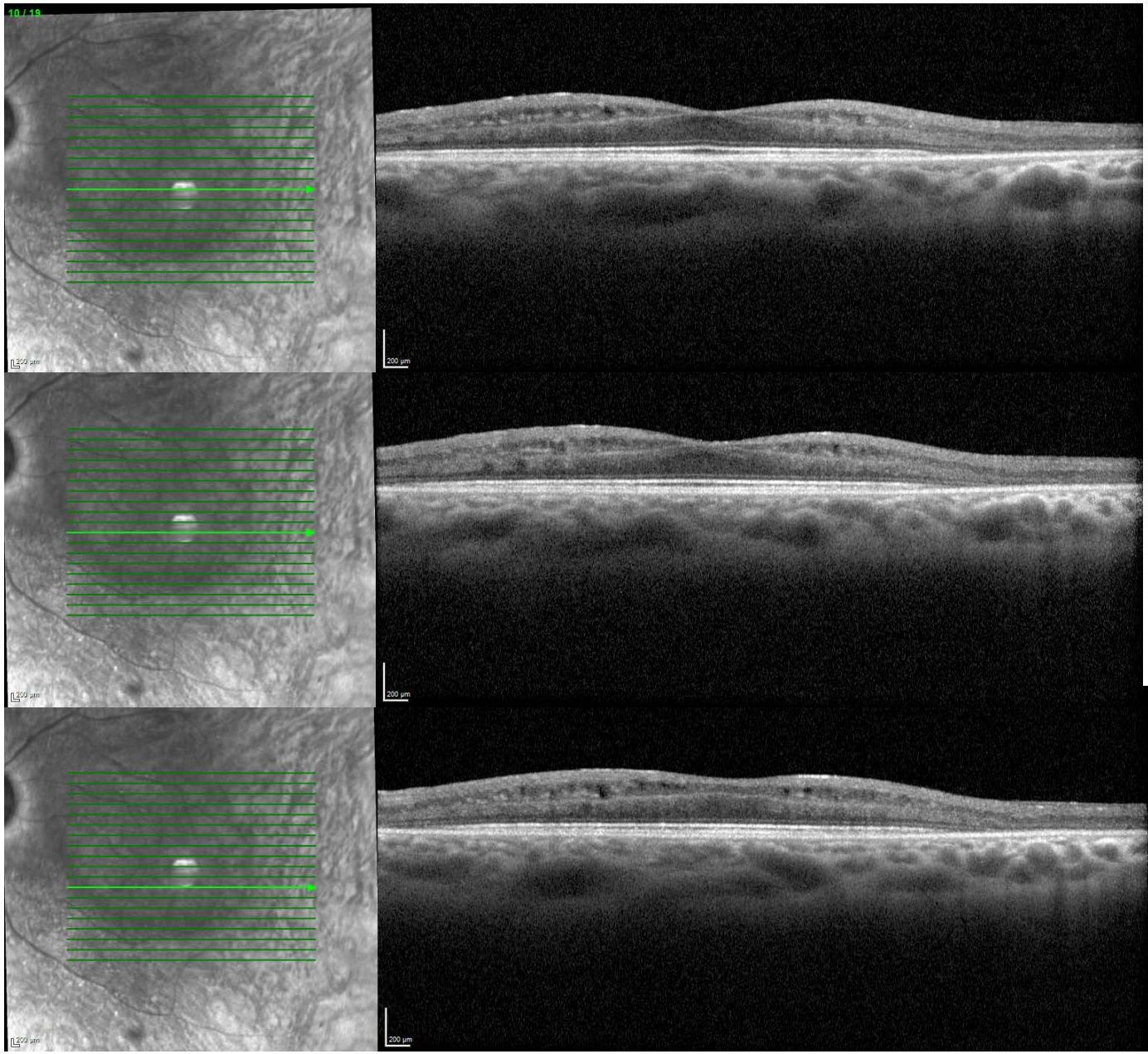


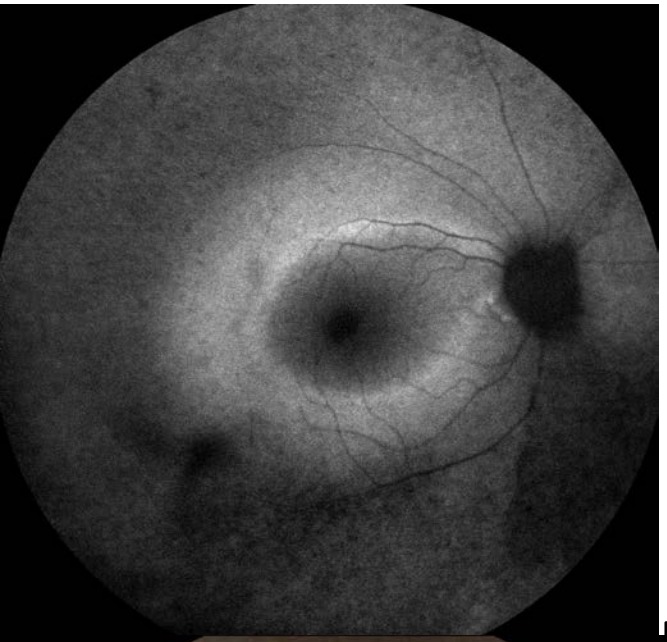
OCT LE

Case

- F, 35 yrs
- Other Univ Hosp Dx her w/ Retinal Dystrophy due to ABCA4
- Deep intronic mutations in *ABCA4* excluded

Phenotype NOT compatible w/ Stargardt disease

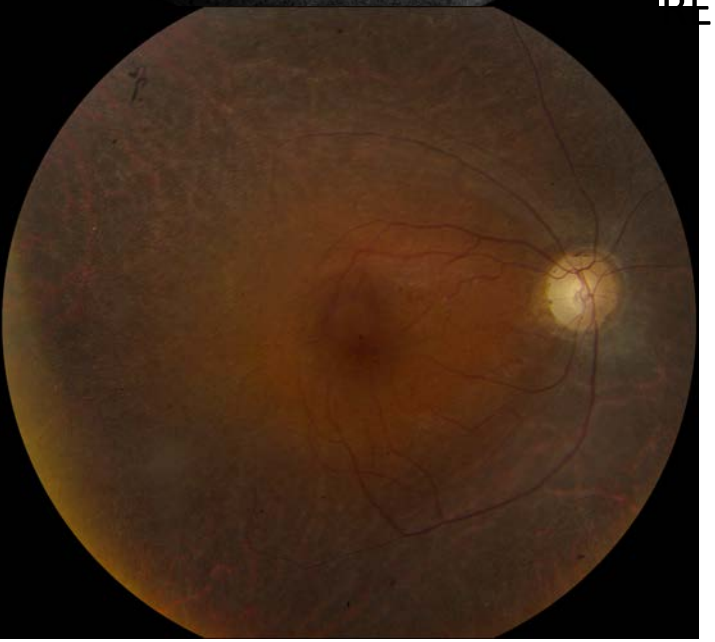




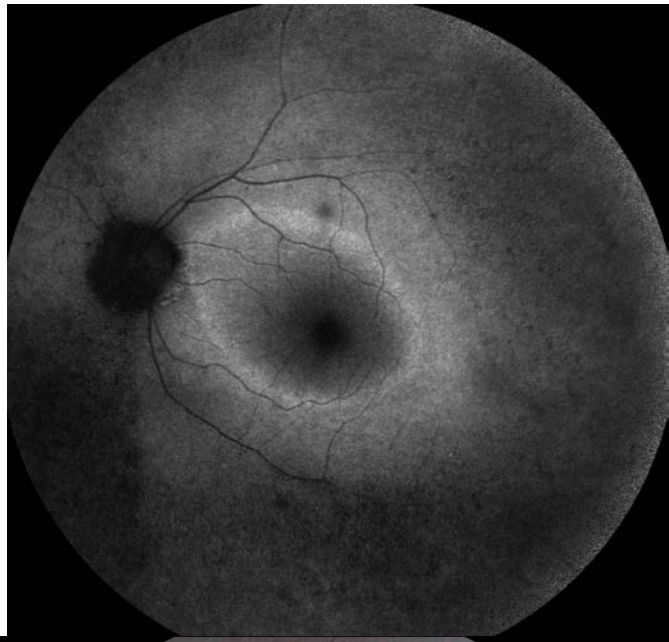
BAF

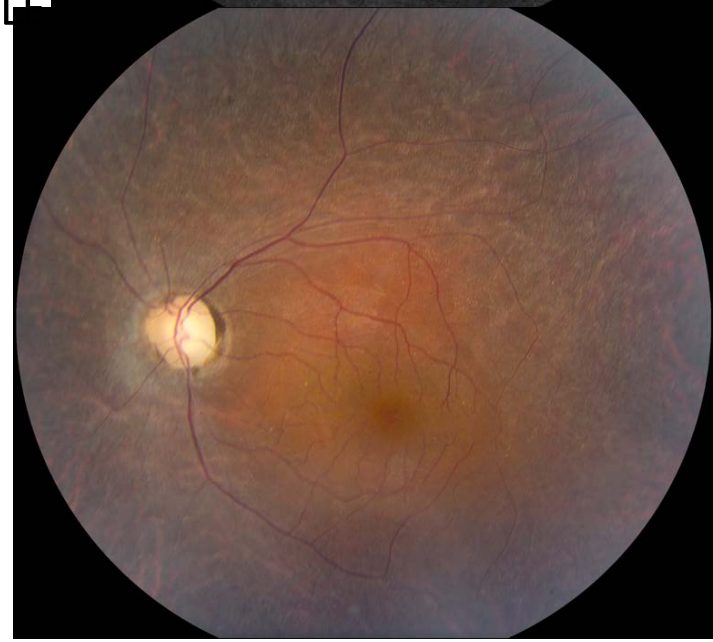
Case

F, 35 yrs



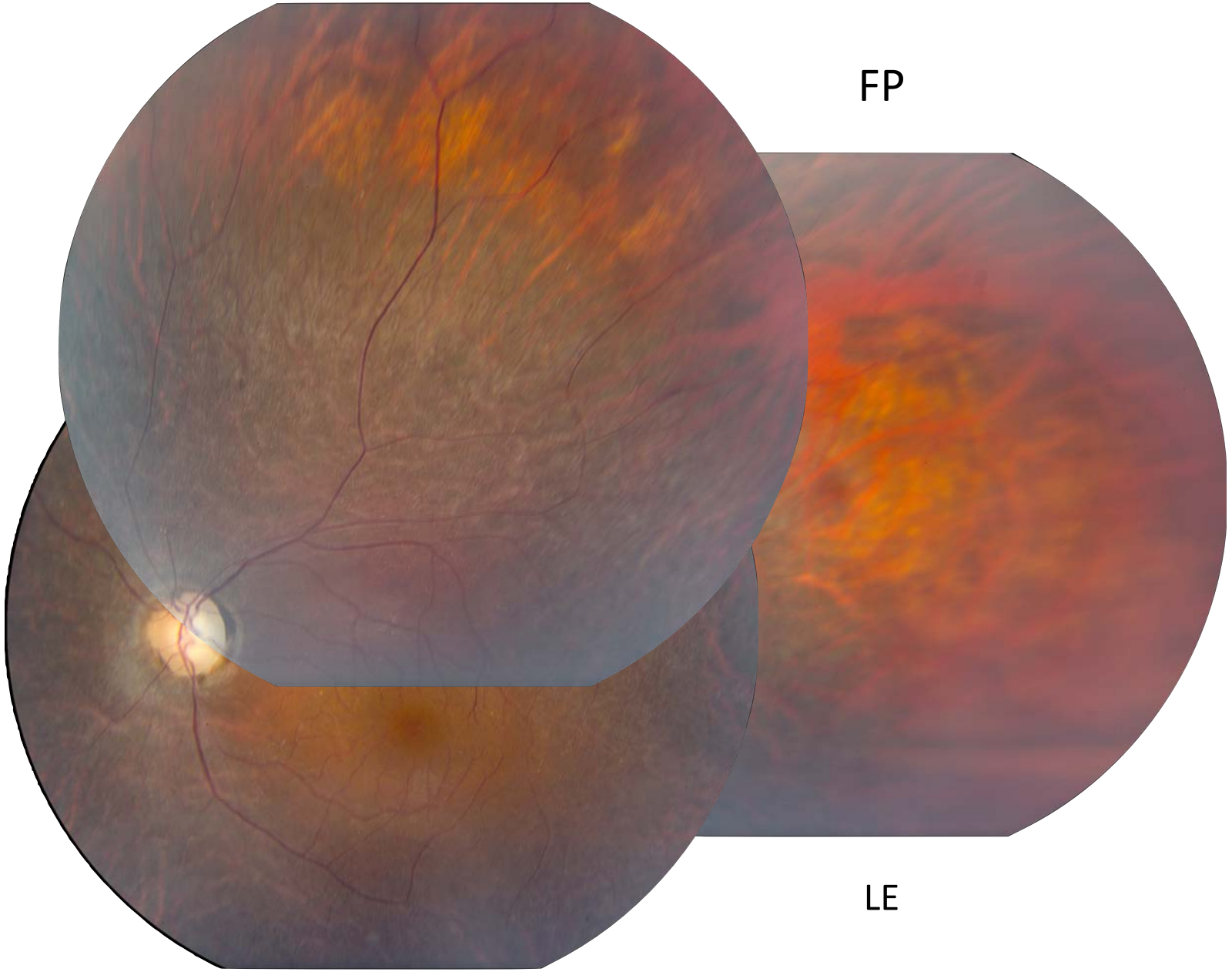
FP





Case

F, 35 yrs



Full-Field Flash ERG

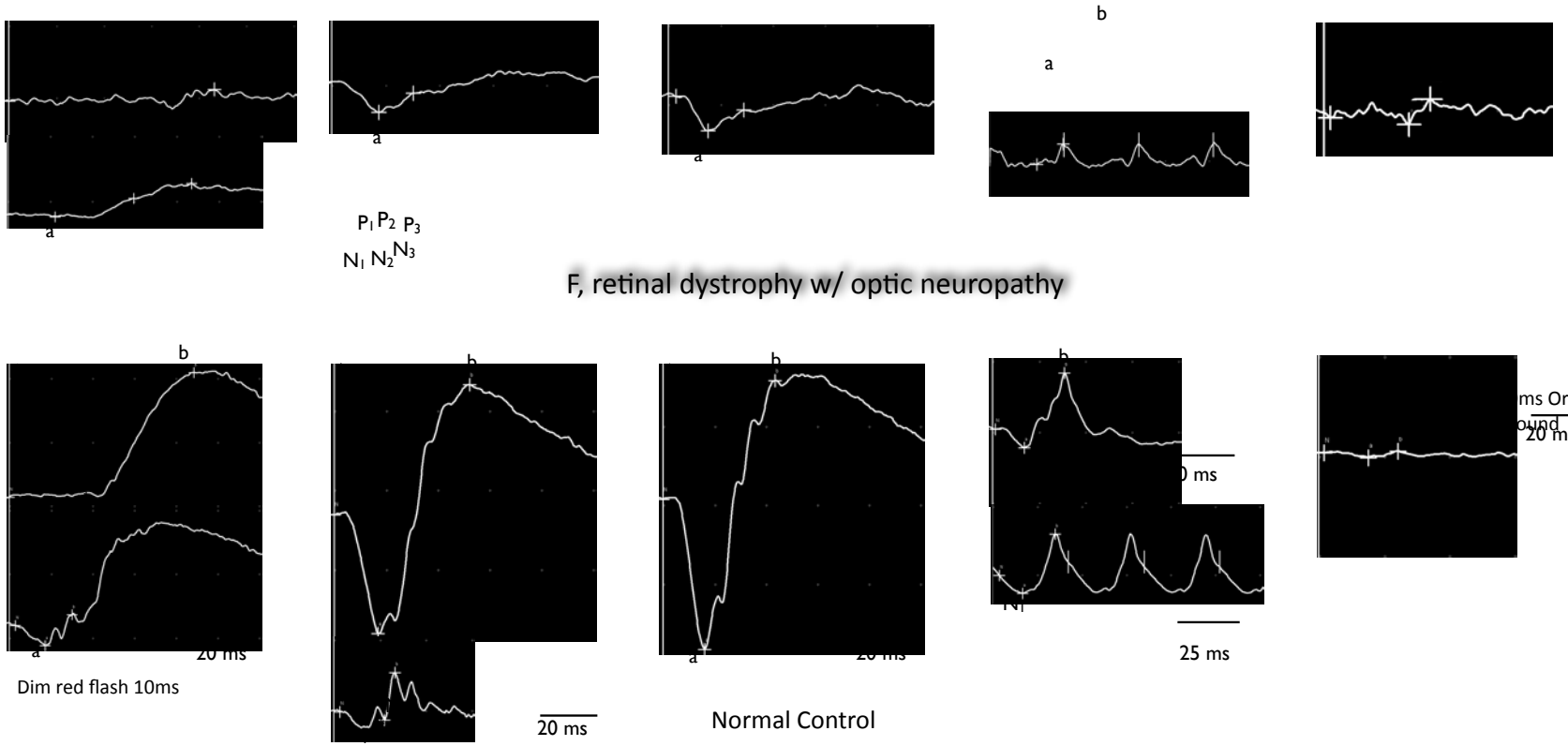
DA
0,01cd.s/m^2
&
0,3 cd.s/m^2 Red

DA
3,0 cd.s/m^2
&
3,0 cd.s/m^2 OPs

DA
10,0 cd.s/m^2

LA
3,0 cd.s/m^2
& 3,0 cd.s/m^2
30Hz Flicker

LA
S-cone

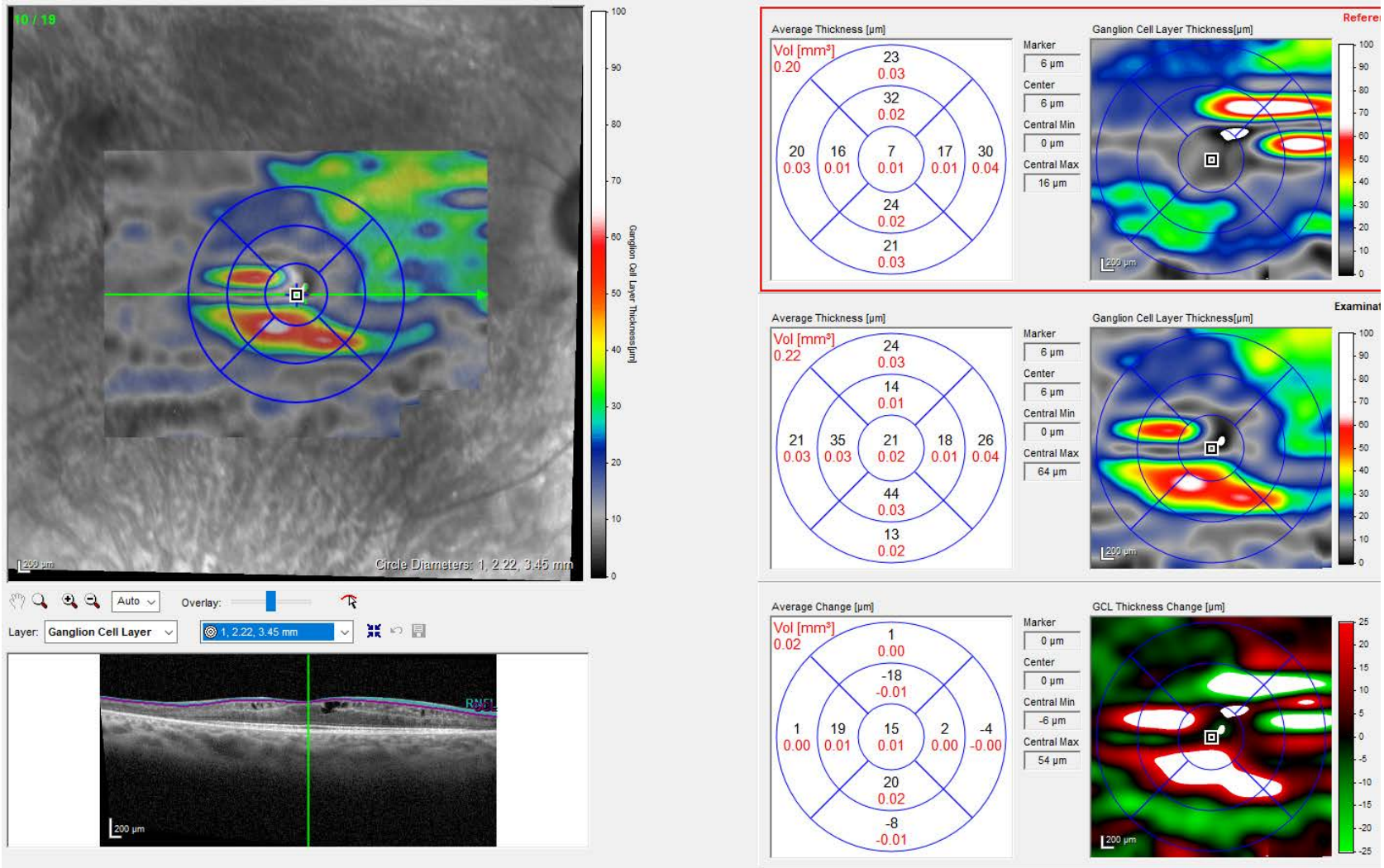


Case

OCT Ganglion Cell Layer

RE

F, 35 yrs

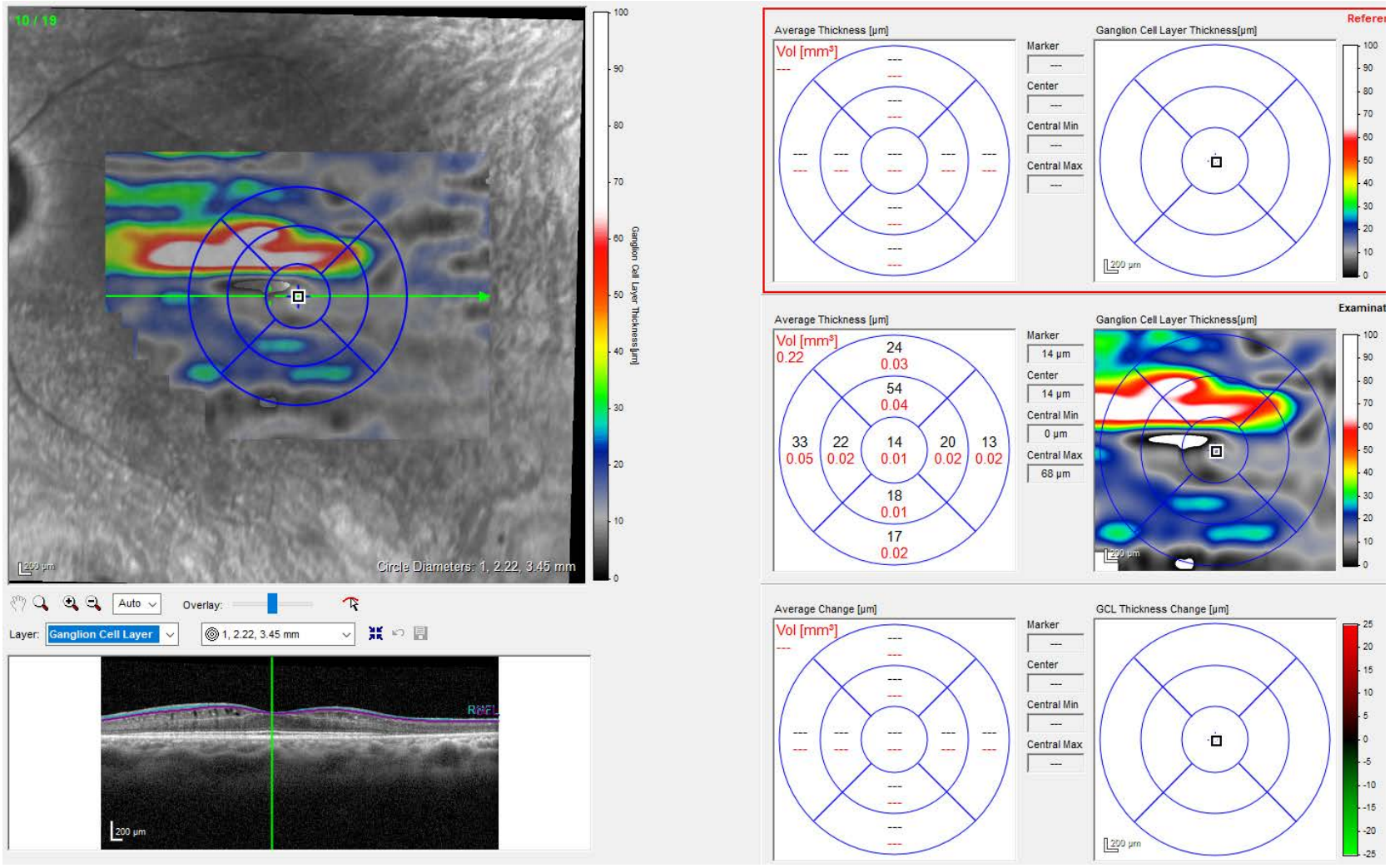


Case

OCT Ganglion Cell Layer

LE

F, 35 yrs



Case

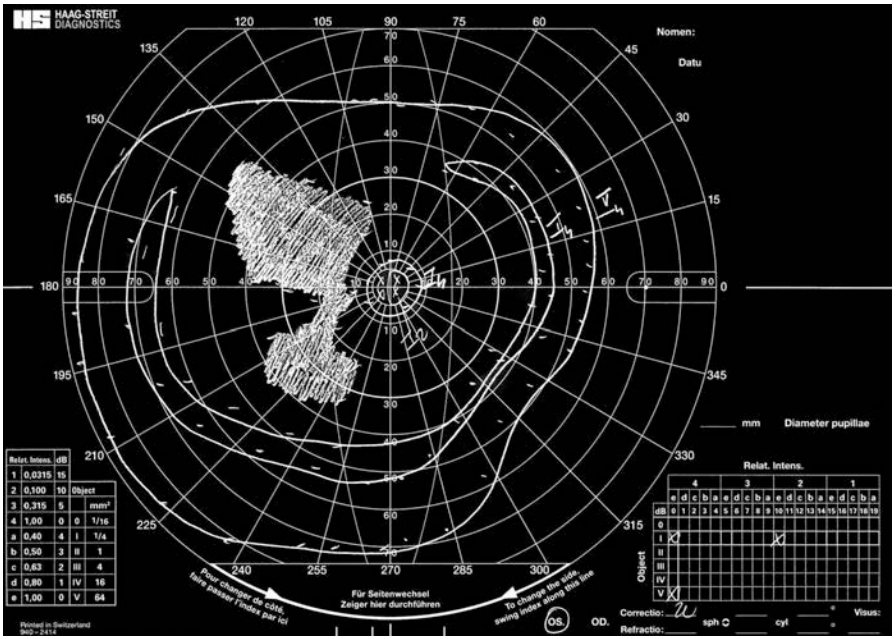
At presentation

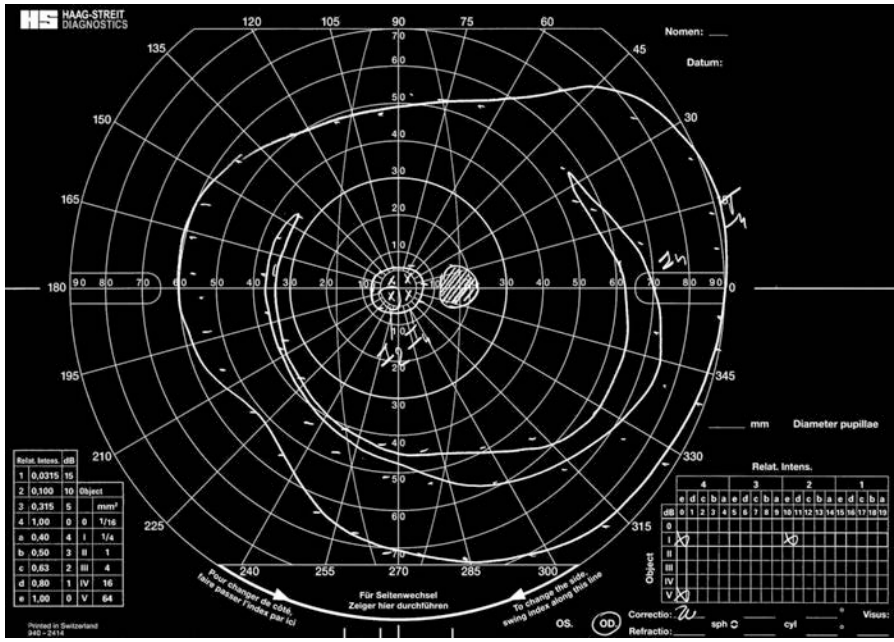
F, 39 yrs

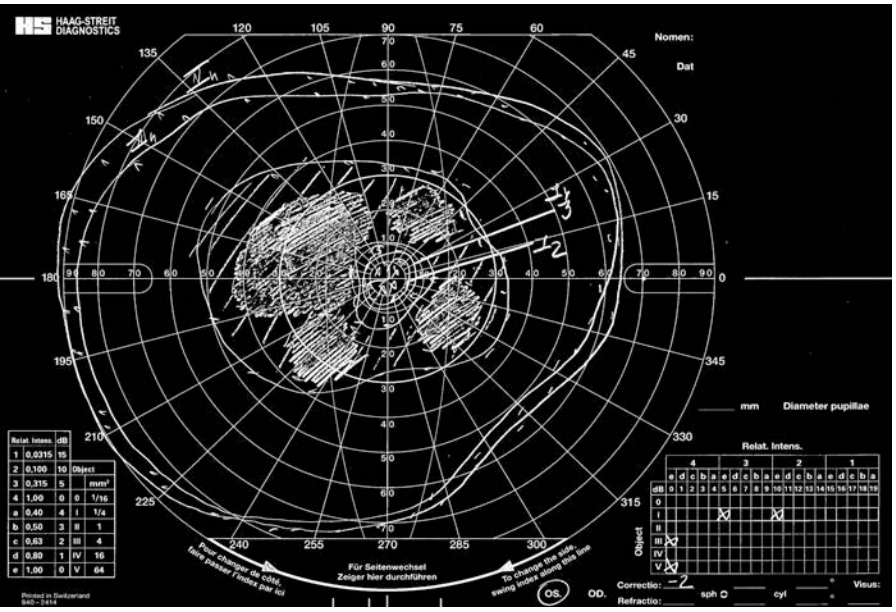
LE RE

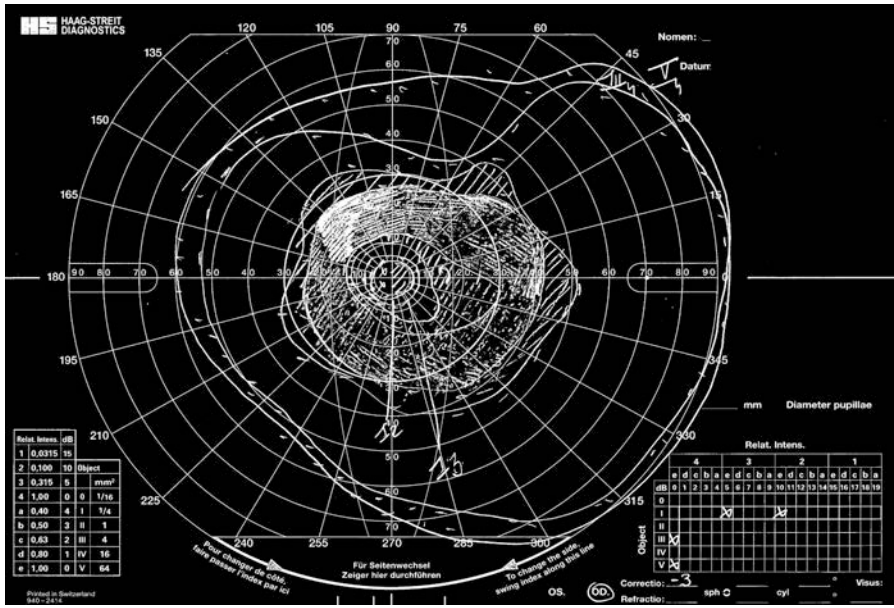
GVF

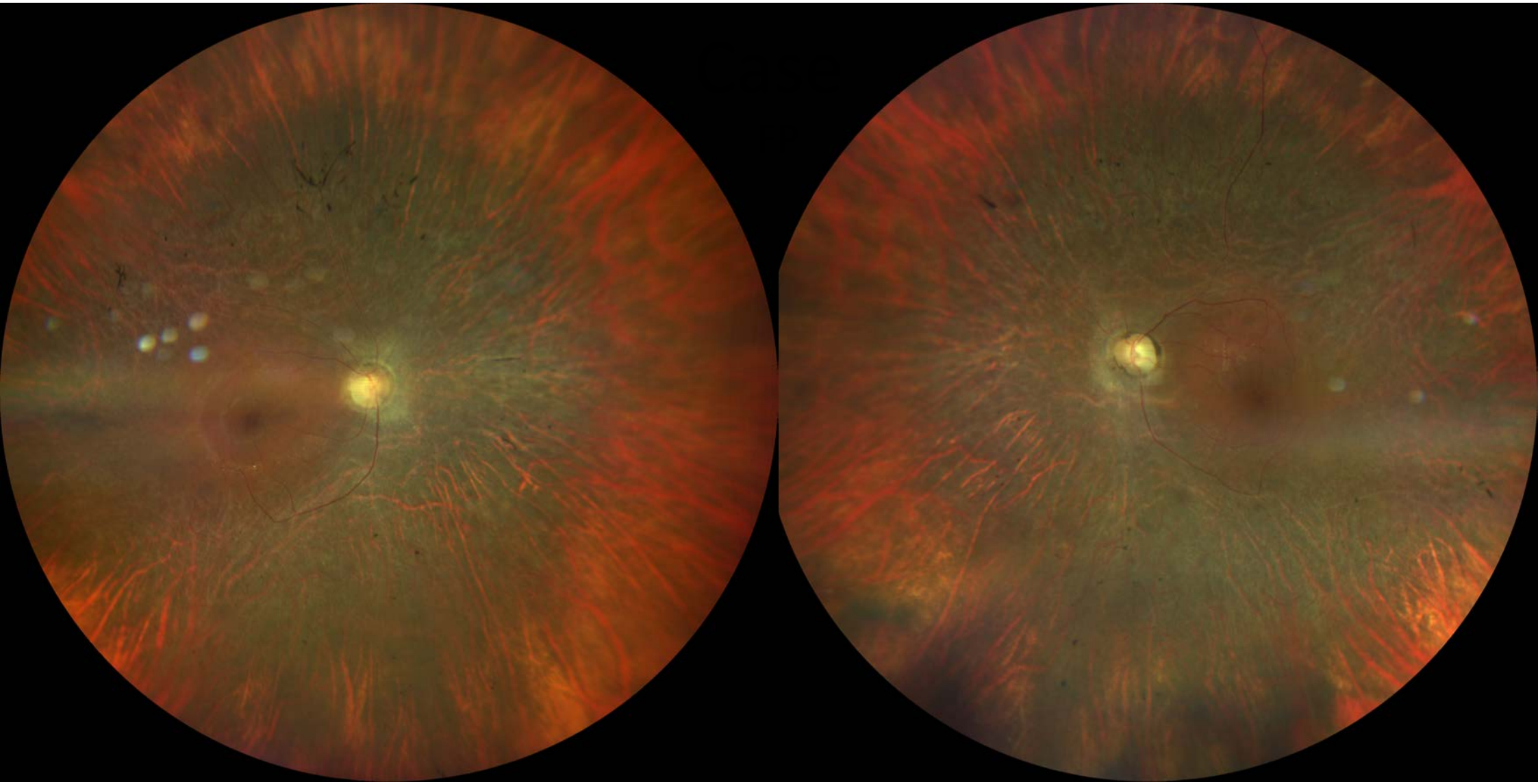
4 years later









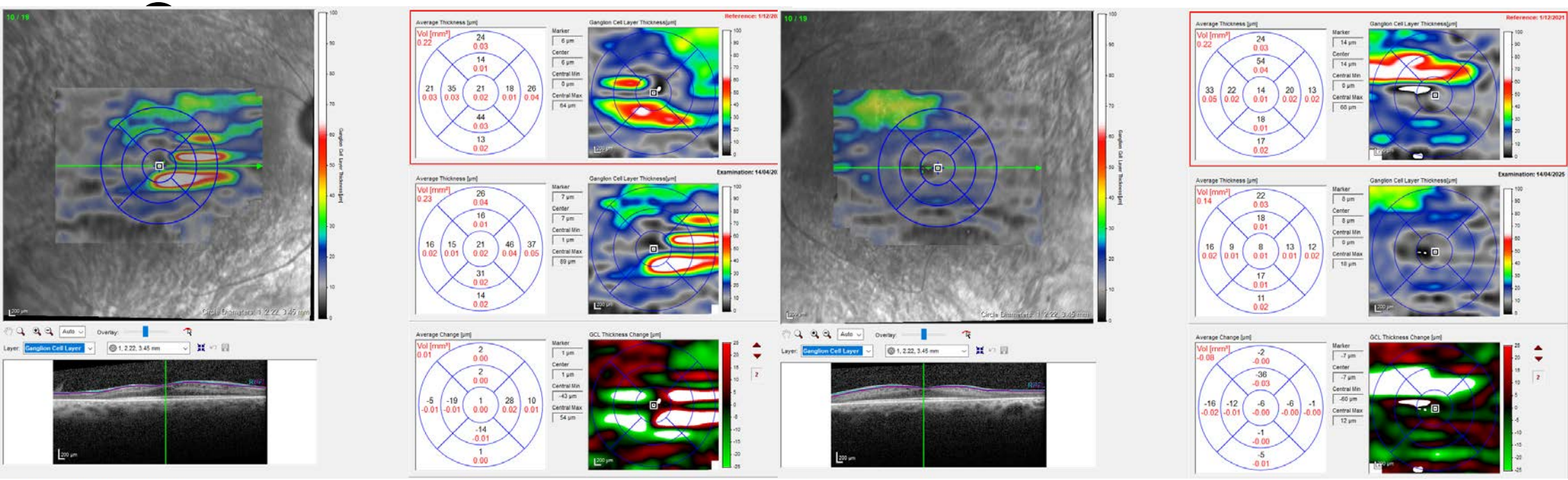


4 years later

RE

LE

Case



4 years later

RE

LE

Case
Conclusions

- F, 35 yrs
- Combination of pericentral rod-cone dystrophy & optic atrophy
- WGS: *RTN4IP1*: compound HeZ for
  - c.621-1G>A, intron 4, heterozygous, class 5
  - c.890A>G, p.(Tyr297Cys), exon 7, heterozygous, class 3
- Parental & familial segregation confirmed
- Biallelic variants in *RTN4IP1* are associated with autosomal recessive isolated & syndromic optic atrophy as well as an early form of rod-cone dystrophy (Meunier et al. 2021, Angebault et al. 2015)
- In syndromic cases optic neuropathy & rod-cone dystrophy is associated w/ epilepsy, intellectual disability, growth retardation, and elevated lactate levels

A Novel Dominant *RPE65*-related Retinopathy due to Ultrarare Founder Variant c.1555G>A p.(Asp519Leu)

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RPE65

Discovery in 1997 as cause of LCA[1] & EORD[2]

Encodes isomerase w/ crucial role in visual cycle[3]

AR-*RPE65*-IRD:

- More than 200 recessive disease variants
- Wide range of disease severity
- Voretigene neparvovec-rzyl (Luxturna®) is gene Rx for AR-*RPE65*-IRD

AD-*RPE65*-IRD: Single dominant variant c.1430A>C, p.(Asp477Gly)[4]

- Irish heritage
- Wide range of disease severity
- Non-penetrance

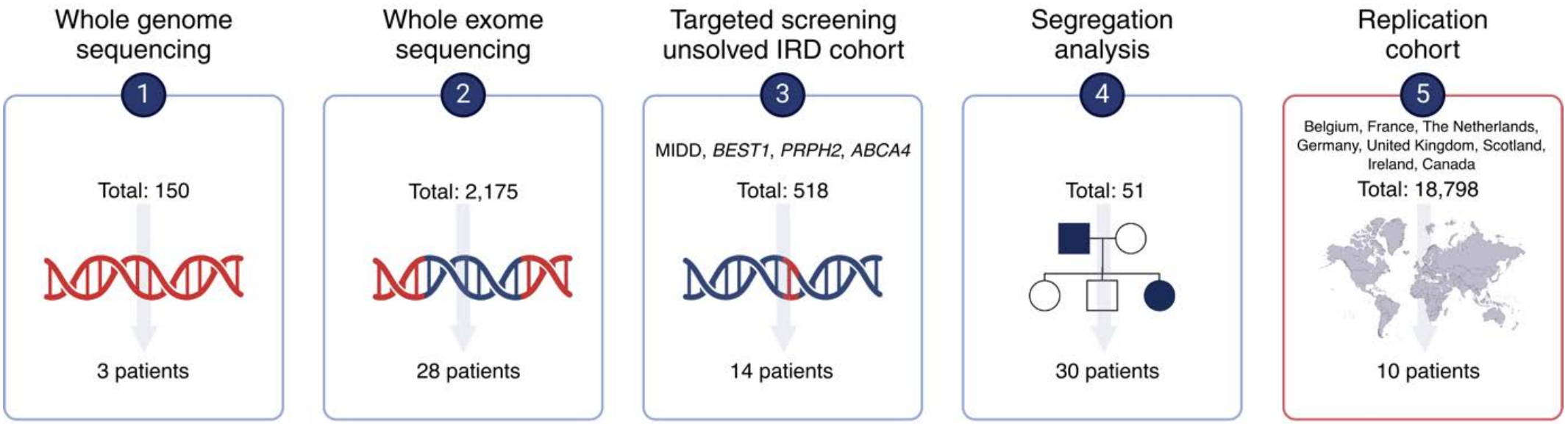
[1] Marlhens et al. 1997

[2] Gu et al. 1997

[3] Redmond et al. 1998

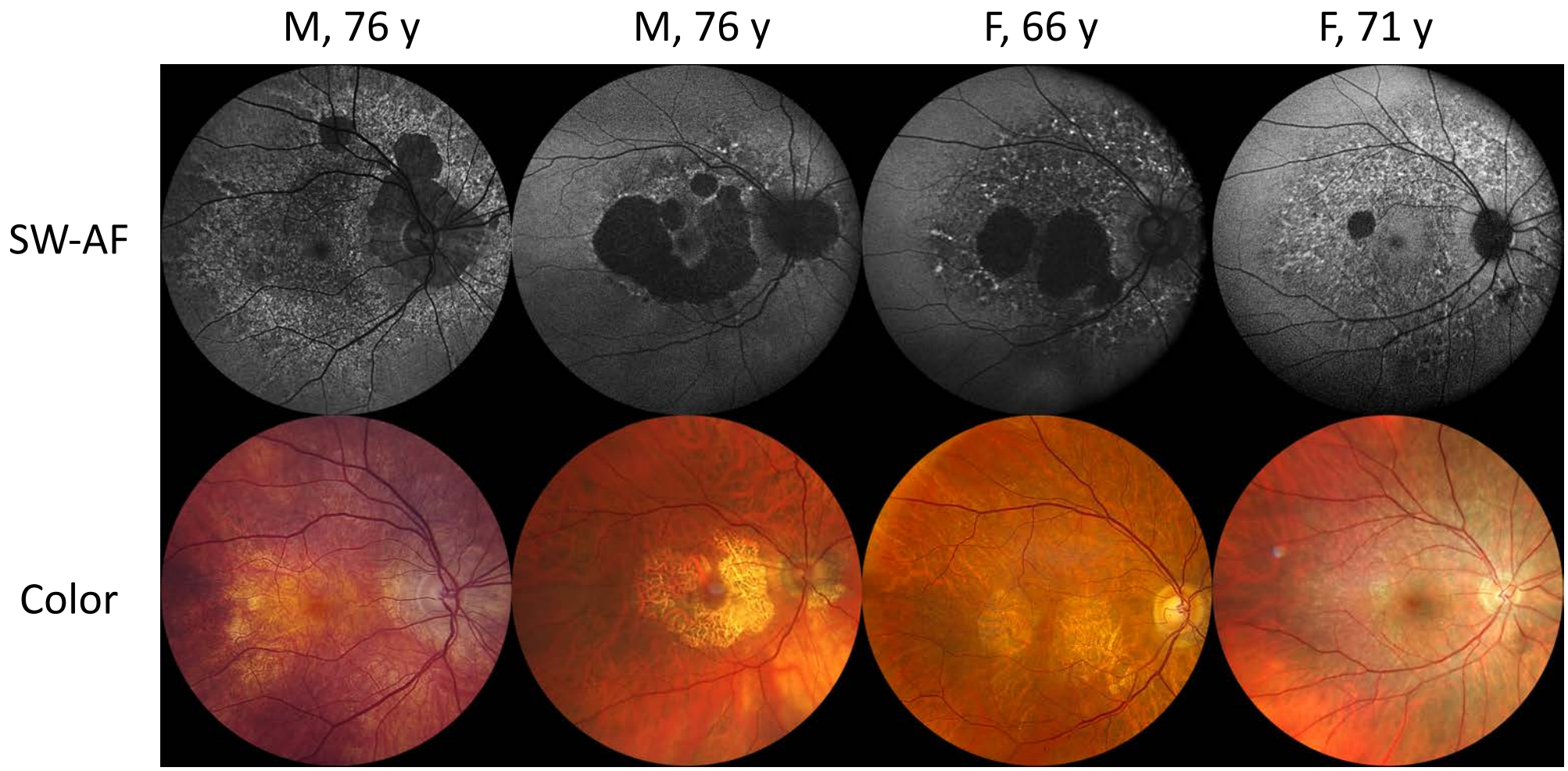
[4] Bowne et al. 2011

Discovery of HeZ *RPE65* c.1555G>A p.(Asp519Leu)



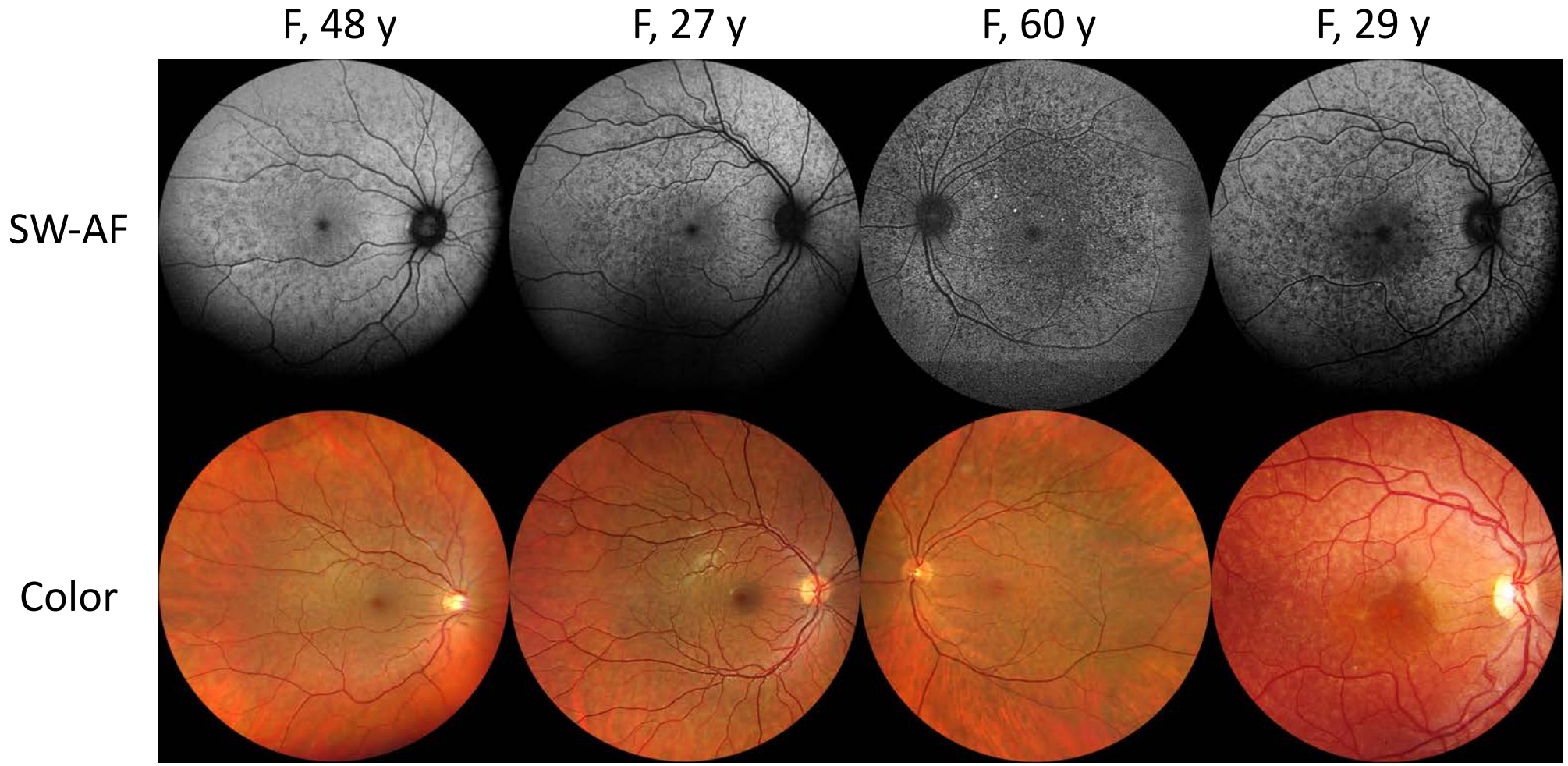
AD Maculopathy due to HeZ *RPE65* variant c.1555G>A p.(Asp519Leu)

Phenotype (1)



AD Maculopathy due to HeZ *RPE65* variant c.1555G>A p.(Asp519Leu)

Phenotype (2)



AD Maculopathy due to HeZ *RPE65* variant c.1555G>A p.(Asp519Leu)

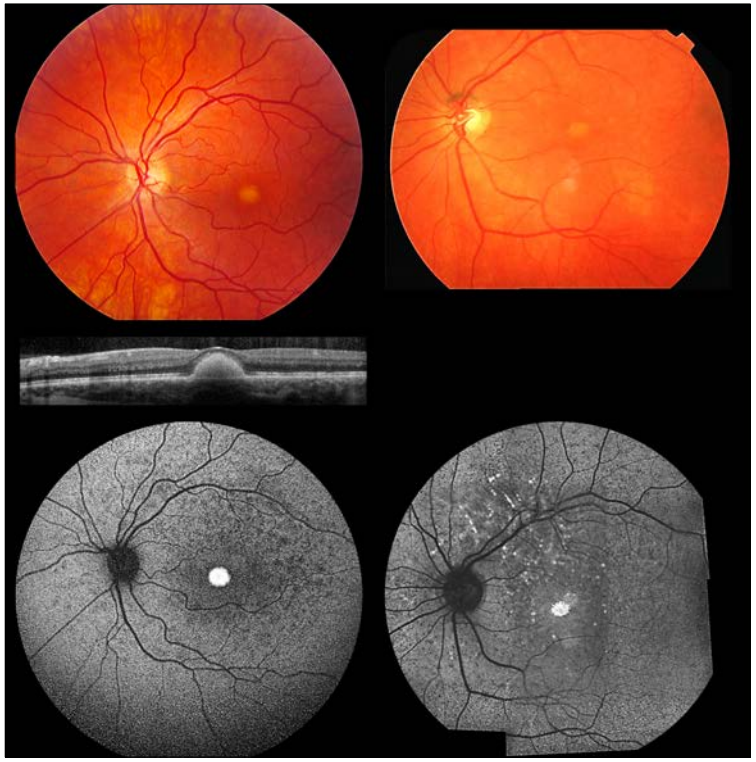
Phenotype (3)

F, 34 y F, 59 y

Color

OCT

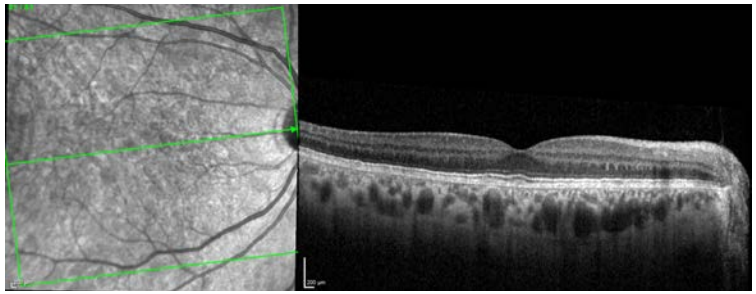
SW-AF



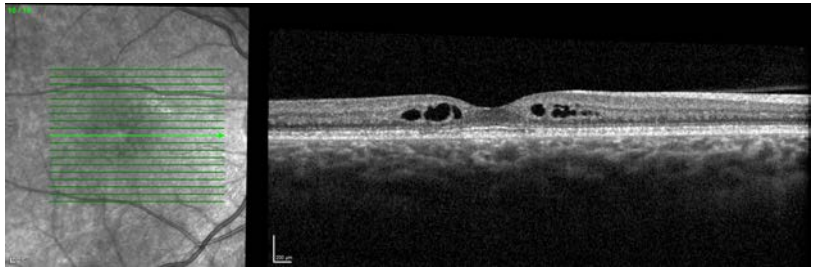
EOG Peak-to-trough ratio: 1.7 to > 3

OCT

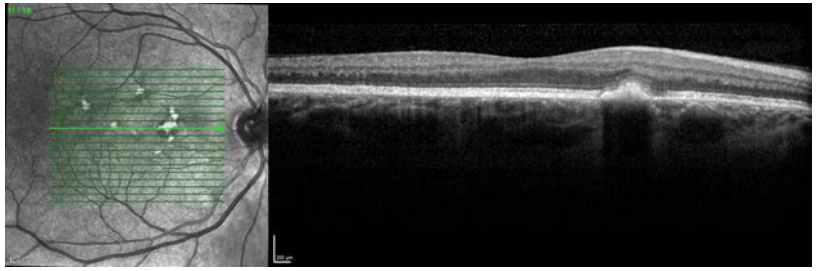
F, 60 y



F, 38 y

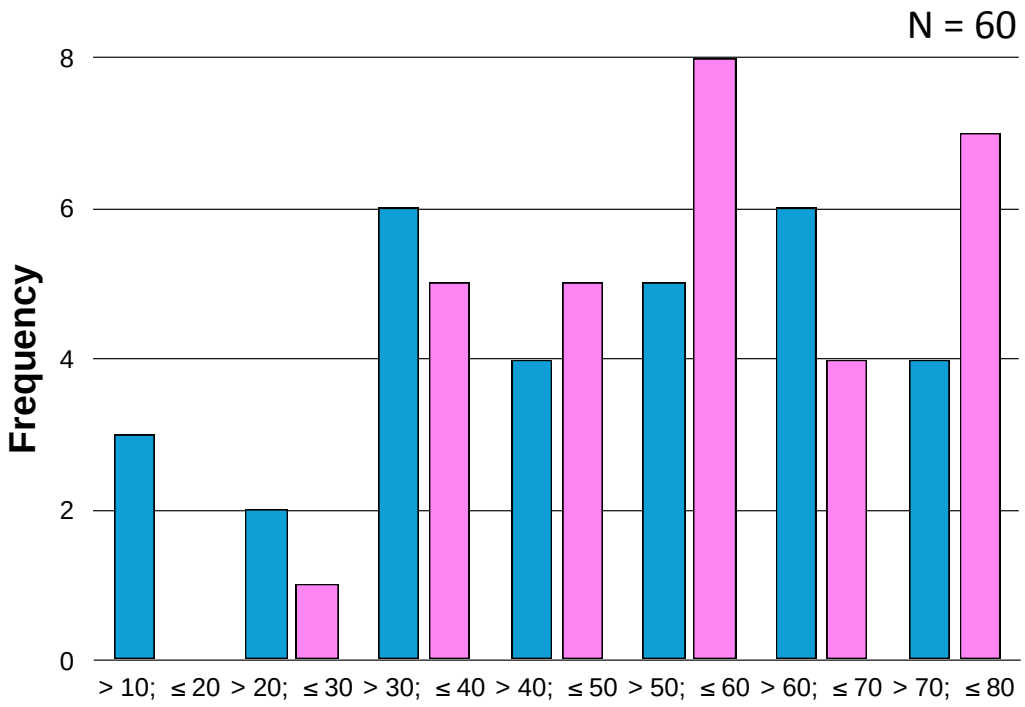


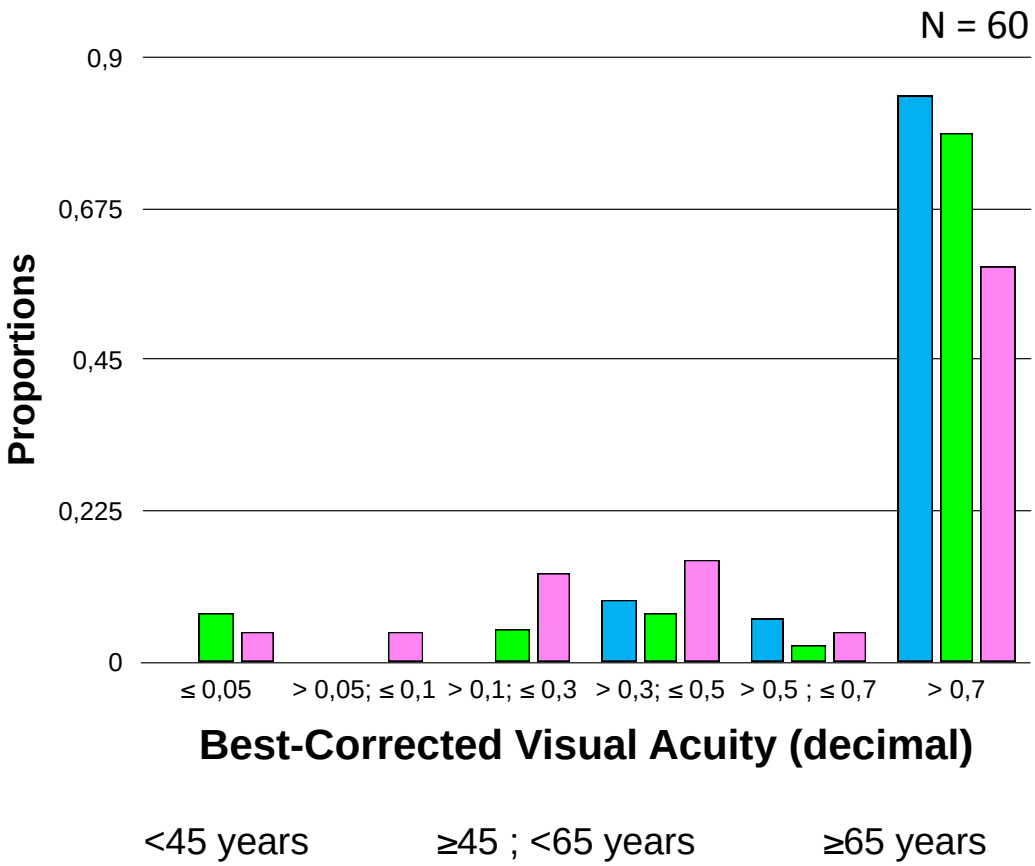
F, 47 y



AD Maculopathy due to HeZ *RPE65* variant c.1555G>A p.(Asp519Leu)

Phenotype (4)





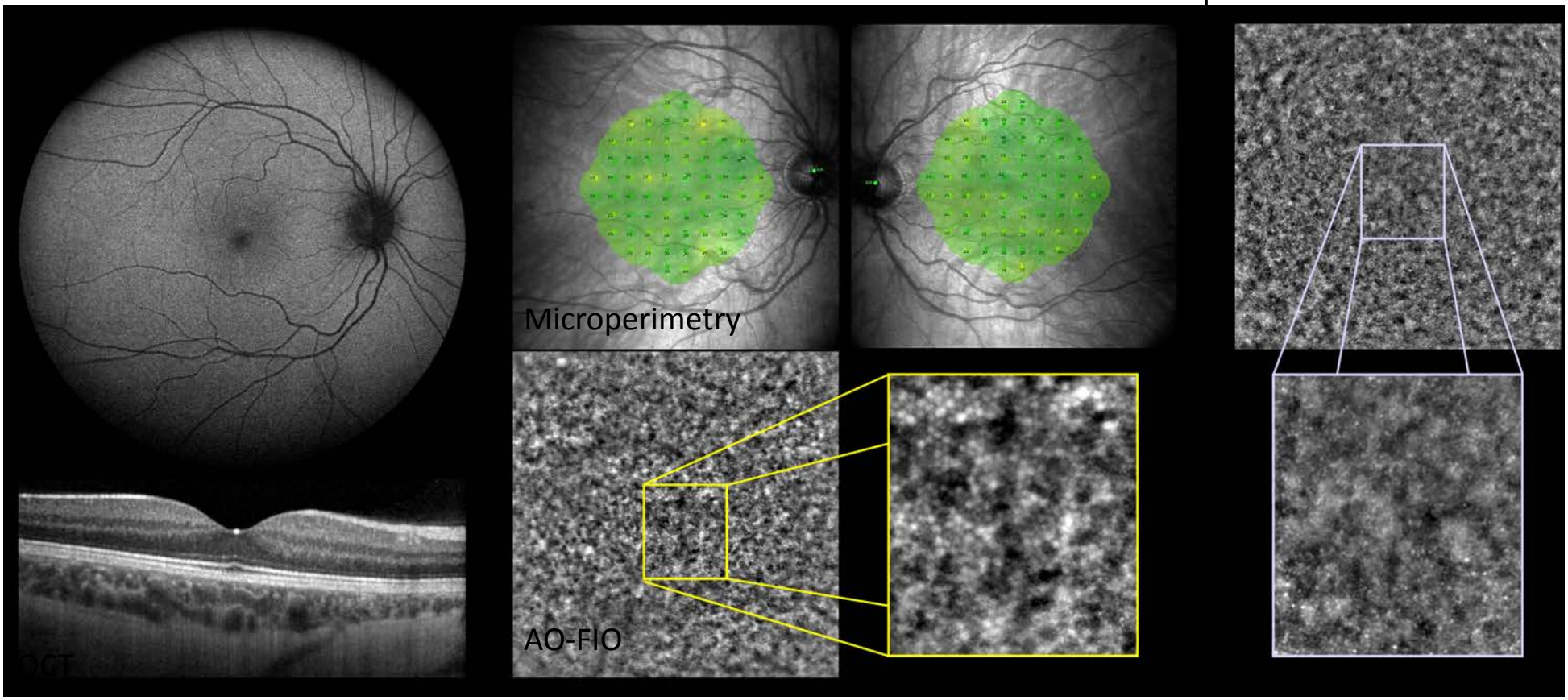
ffERG: normal in half of patients; rod involvement, rarely cone involvement in other half

A Adaptive Optics Imaging (AO-FIO) da

F, 35 y

Normal

Control



A Conclusions da

Two very rare *RPE65* alleles cause autosomal dominant IRD

The novel, Belgian, heterozygous *RPE65* c.1555G>A p.(Glu519Leu) variant causes an AD macula predominant retinal dystrophy

- Distinct from IRD due to biallelic variants and due to the Irish dominant variant
- Specific hypo-autofluorescent mottling
- Pattern dystrophy (DDx MIDD, *PRPH2*, *ABCA4*)
- Macular chorioretinal atrophy (DDx geographic atrophy)
- Vitelliform lesions are rare but impact vision early on
- Cystoid macular edema

Conclusions
Identifying Novel Conditions

RPE65 is involved in pathogenesis of 3 distinct conditions:

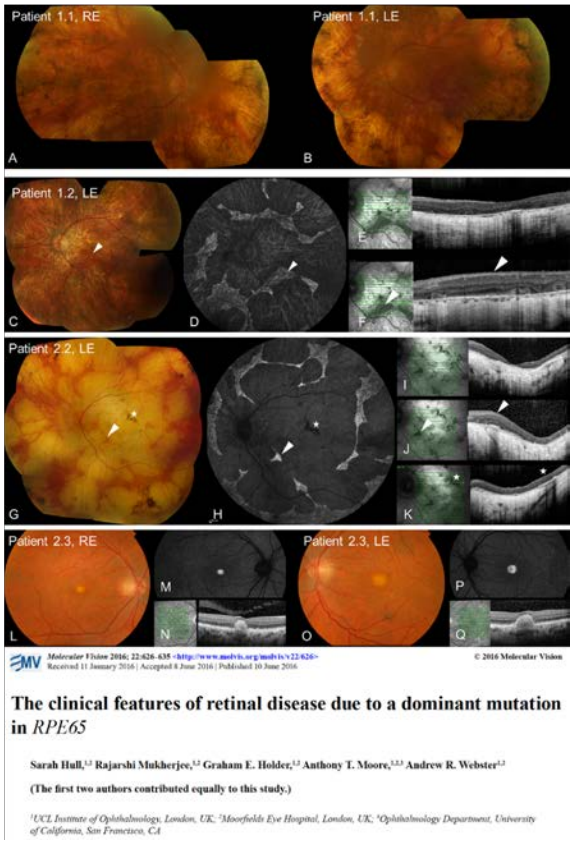
AR *RPE65*-IRD: spectrum of LCA to RP

AD *RPE65*-Chorioretinal Atrophy due to Irish mutation p.(Asp477Gly)

AD *RPE65*-Maculopathy due to Belgian mutation

p.(Glu519Lys)

RPE65 is expressed in RPE



Molecular Vision 2016; 22:626-635 <http://www.molvis.org/molvis/v22/626>
Received 11 January 2016 | Accepted 8 June 2016 | Published 10 June 2016

The clinical features of retinal disease due to a dominant mutation in *RPE65*

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(The first two authors contributed equally to this study.)

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Bestrophinopathies
Different Phenotypes due to *BEST1* Mutations

Juvenile Vitelliform Macular Dystrophy or Best Disease

AD or AR macular dystrophy

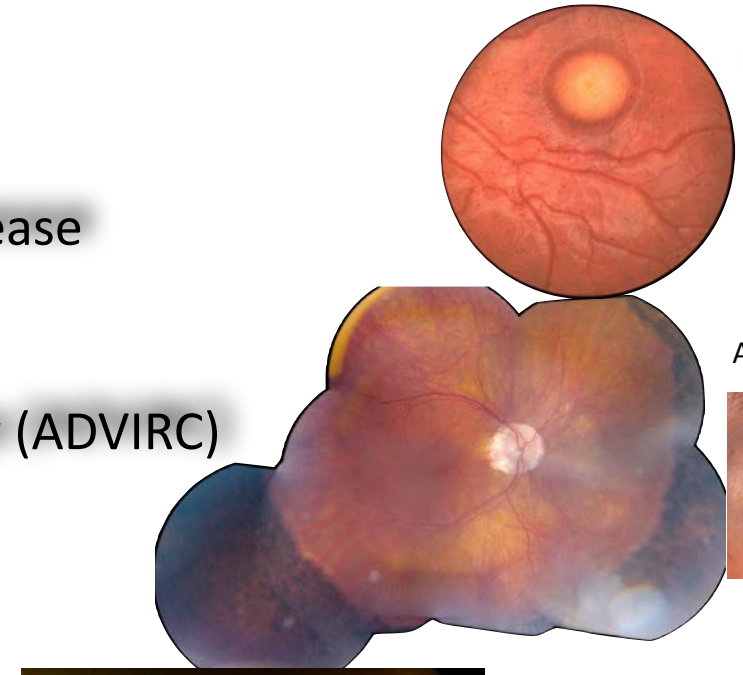
Autosomal Dominant VItreo-Retino-Choroidopathy (ADVIRC)

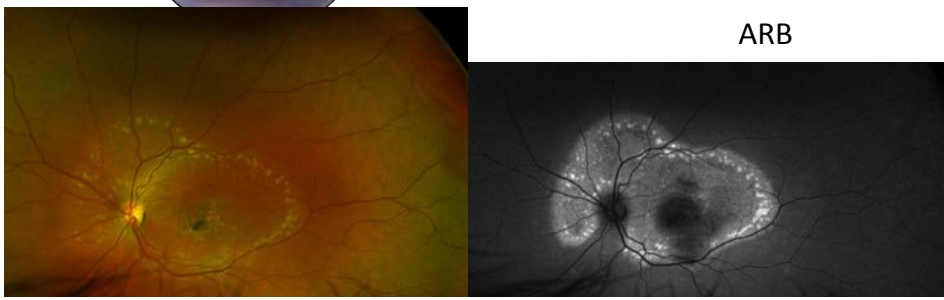
AD generalised rod-cone dystrophy w/ AS involvement

Autosomal Recessive Bestrophinopathy (ARB)

AR generalised rod-cone dystrophy w/ AS involvement

BEST1 is also expressed in RPE





7/ Conclusions

Conclusions
Genotyping All Patients: Why?

Gives closure to patients

Recurrence risk for next generations

Options for pre-implantation genetic Dx & prenatal Dx

Clinical specificity is not 100%: IRD phenotypes often look alike & one phenotype can be caused by mutations in multiple genes

Most gene therapies are gene specific, antisense oligonucleotide Rx is even mutation specific; no margin for error in gene Rx

Current Clinical Practice in Ophthalmic Genetics
Conclusions

Classic practice in ophthalmic genetics: making clinical Dx & stop

New clinical practice in ophthalmic genetics:

- Making clinical Dx
- Referring to ophthalmic genetics & IRD expert
- Pedigree analysis
- Genetic testing
- Genetic counseling regarding RR
- Genetic counseling regarding prenatal Dx & pre-implantation genetic Dx
- Counseling regarding visual prognosis
- Counseling regarding current, emerging & future therapies
- Rx

Clinical Aspects of Ophthalmic Genetics
Conclusions

Ophthalmic genetics is complex

Clinical issues to consider

- Age of onset
- Progression or stability
- Additional signs & symptoms
- Phenotype (also beyond eyes)

Genetic analysis

- Pedigree
- Molecular analysis

Gene therapies available

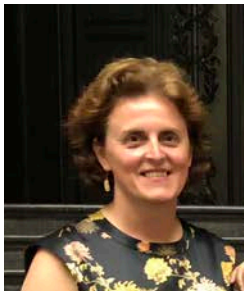
- Deep phenotyping essential
- Need for genotyping

Ghent Ocular Genetics Team

Ophthalmic Genetics & Visual Function Team

Julie DE ZAEYTIJD | Bart LEROY | Joke RUYS | Sophie WALRAEDT

Molecular Genetics



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