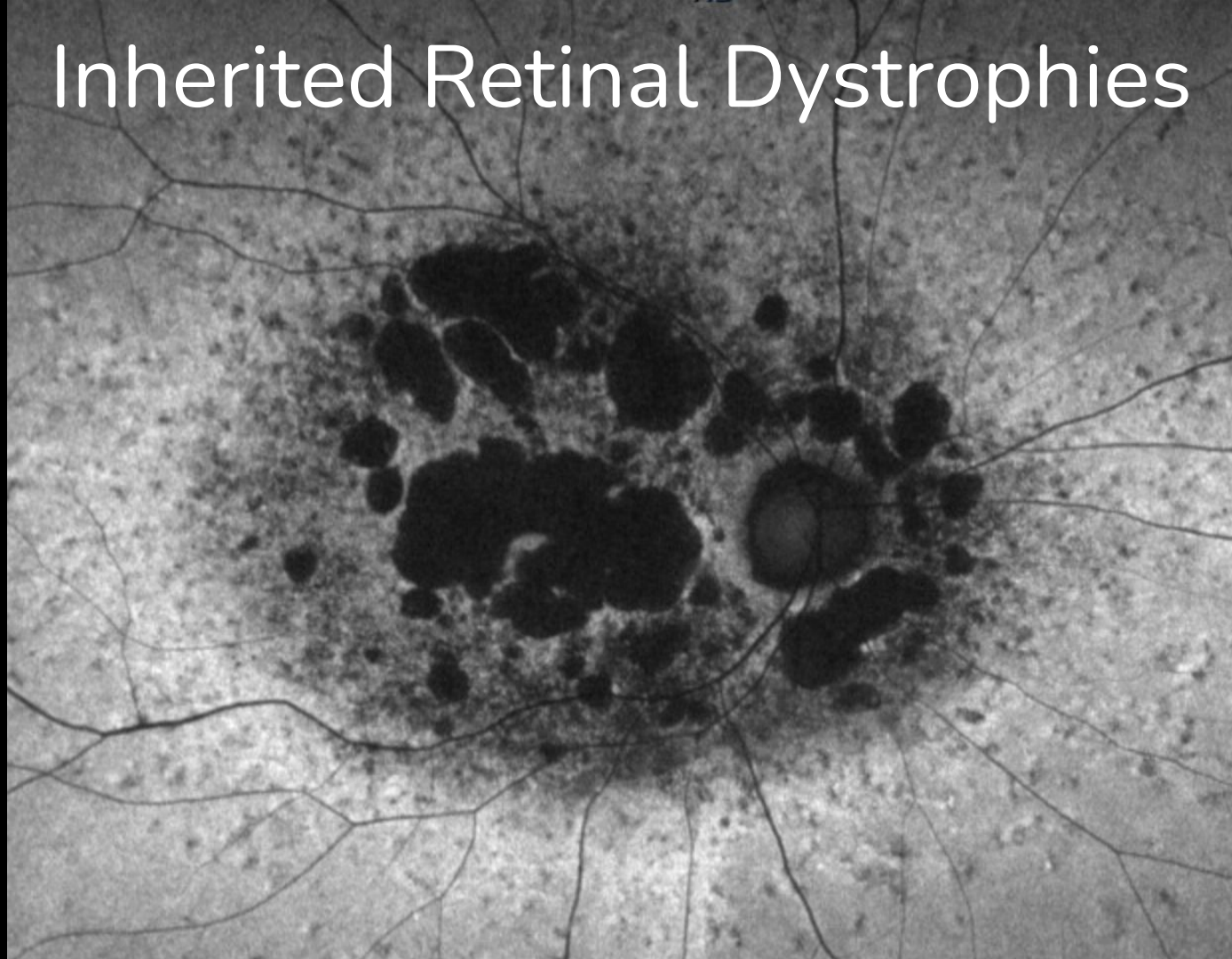
Inherited Retinal Dystrophies



Doron Hickey
DPhil FRANZCO

Medical Retina
Ocular Genetics
Cataract

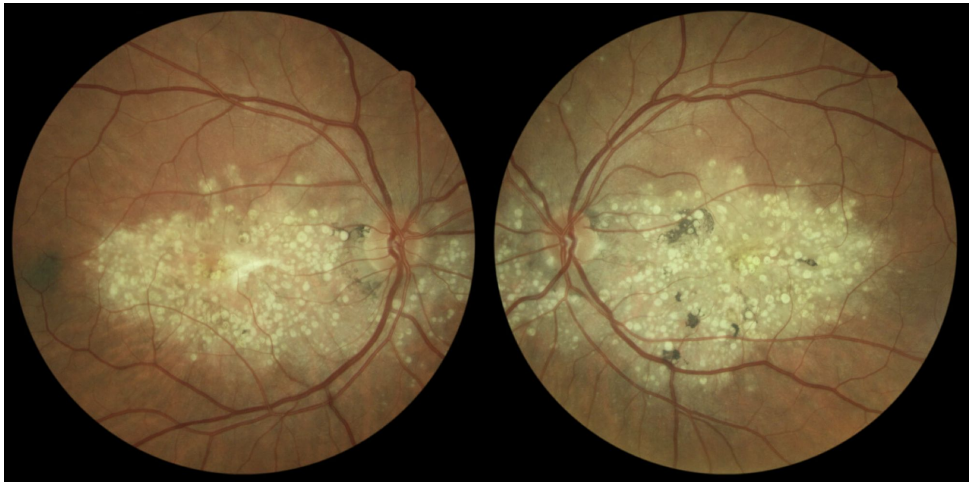
Victoria Parade Eye Consultants
The Royal Victorian Eye and Ear Hospital
The Centre for Eye Research Australia

Inherited retinal diseases/dystrophies

Retinal disease due to mutation(s) in a single gene

Includes:

- Rod-cone dystrophy (retinitis pigmentosa)
- Cone-rod dystrophy
- Macular dystrophy
- Congenital stationary night blindness
- Leber congenital amaurosis
- X-linked retinoschisis
- Exudative vitreoretinopathy
- ….



Greater interest in IRDs

- Historically a **neglected** population in ophthalmology
- Growing understanding of the genetic basis of IRDs
- **Earlier detection** due to greater awareness and improved imaging
- Availability of **genetic testing**
    - Ocular Genetics Clinic at RVEEH (in collaboration with RMH) opened 2018
    - Novartis sponsored testing program for Leber congenital amaurosis and rod-cone dystrophies. Available in public and private (including VPEC)
- Emerging **treatments**, many **trials** ongoing

“Some of my relatives have vision problems, and I would like to be checked before I have children”

EG 31F

POHx

Nil. Asymptomatic.

PMHx

Sinusitis

Dermatitis

Nil known renal or hearing issues

Examination		
6/6	s	6/6
17	i	14

SHx

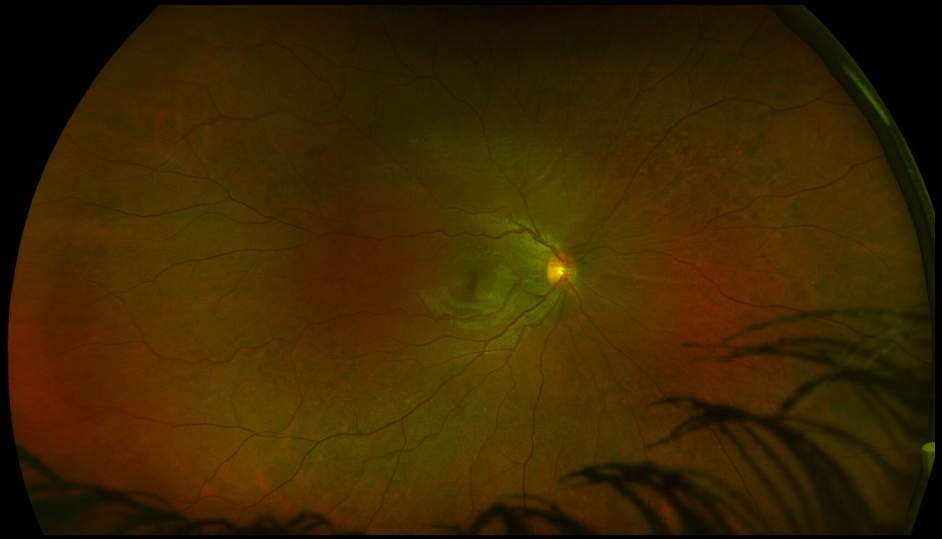
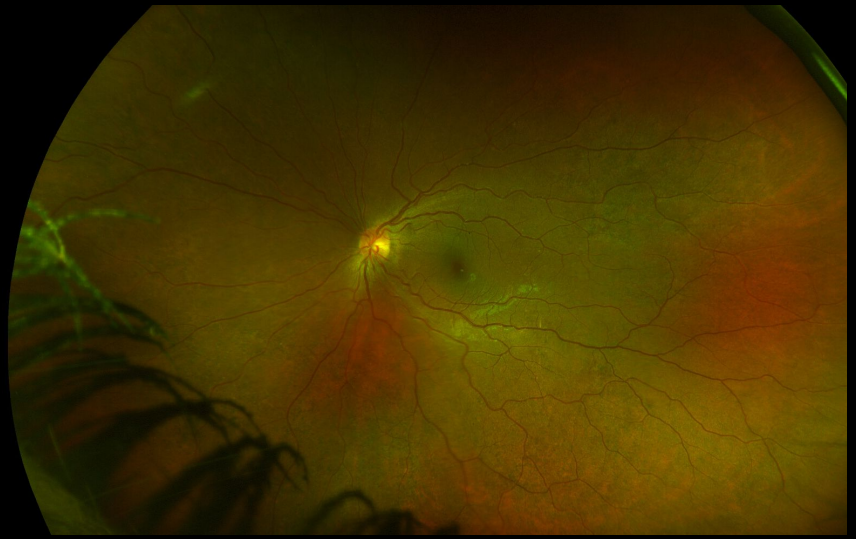
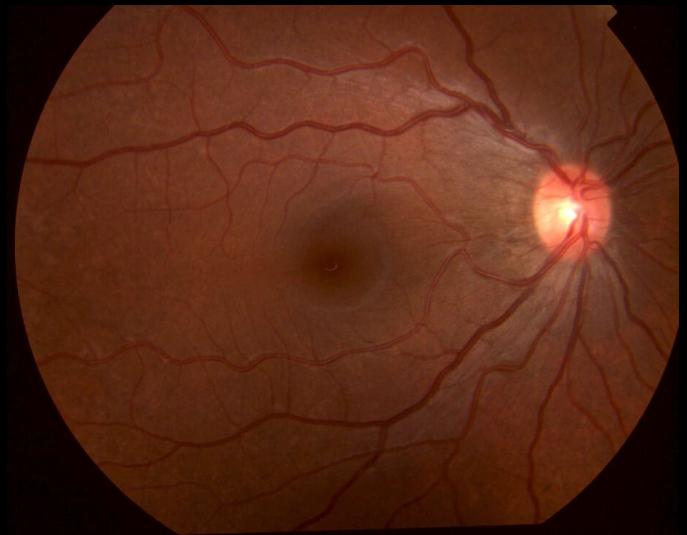
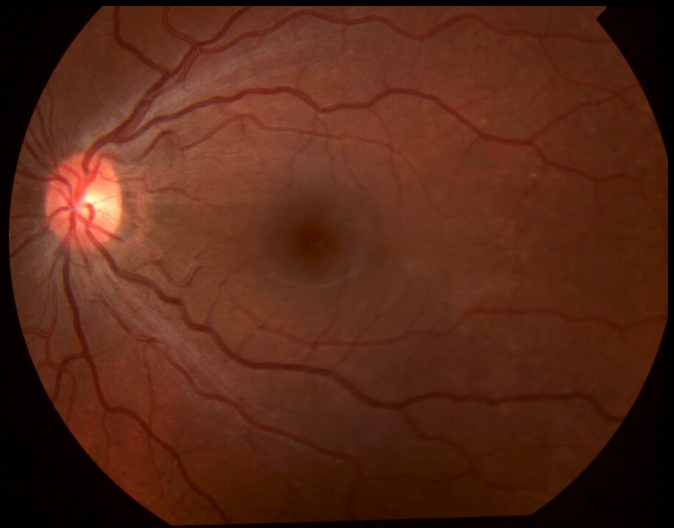
Primary school teacher

Getting married in 5 days!

FHx

Father and paternal uncle affected by retinal dystrophy

- ?Rod-cone dystrophy
- Awaiting genetic testing

“Can I start having a family and not worry about my children going blind?”

Our patient

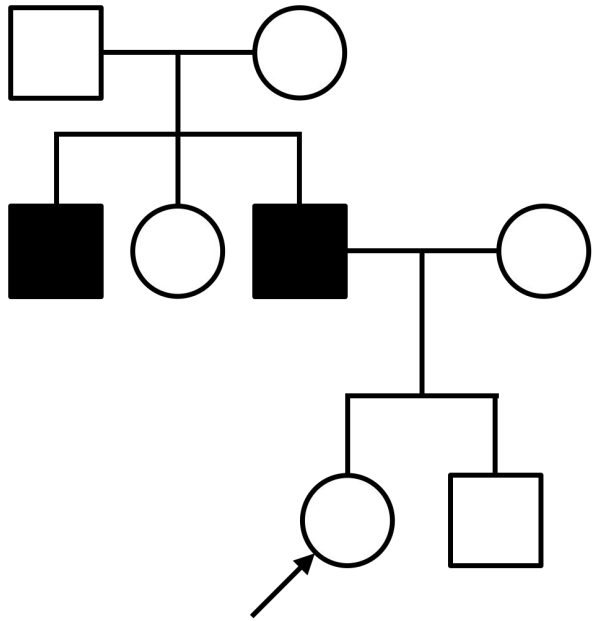
has **normal acuities**,

is **asymptomatic**,

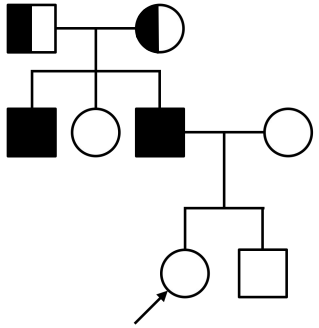
has a ***normal**** fundus examination and

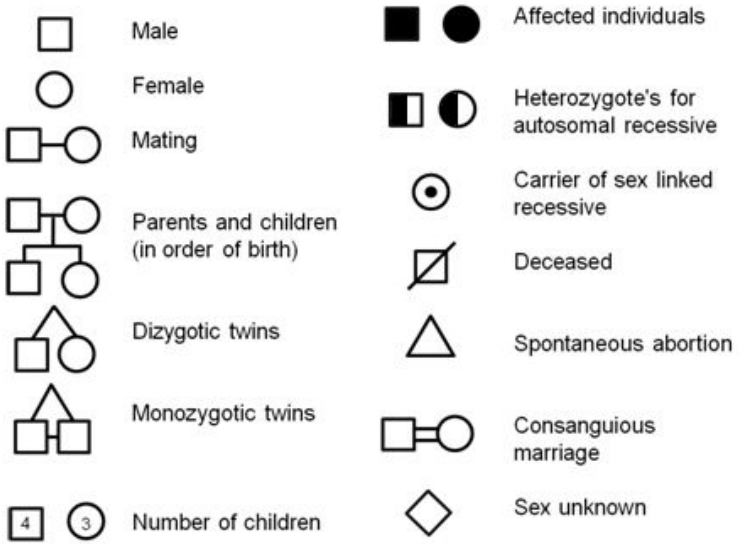
has a family history consistent with **autosomal recessive**, therefore she is likely to be a **carrier** and her children have a **very low risk of being affected**.

… Right?



Pedigree





As complete as possible

Focus on eye disease and associated conditions (e.g. SNHL, DM)

Possible patterns*

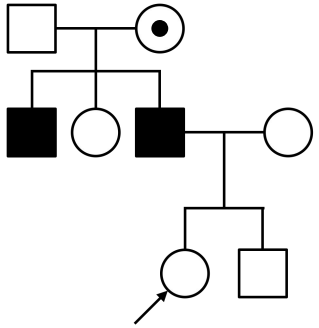
Autosomal dominant – affected individuals in each generation

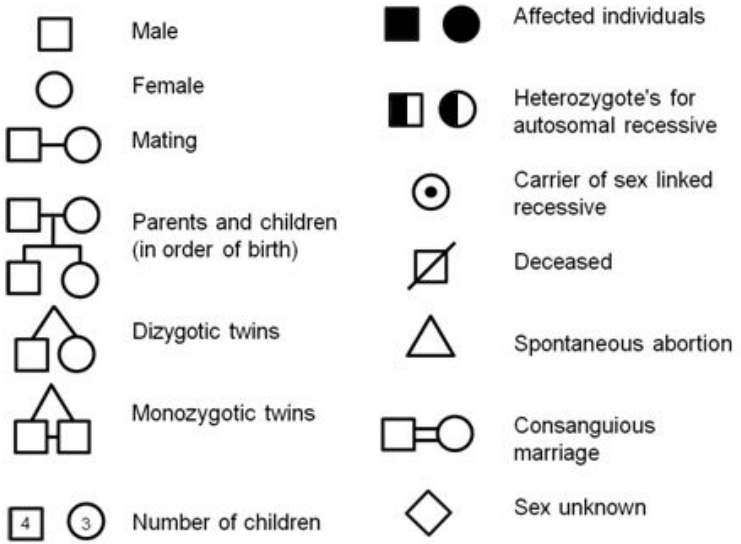
Autosomal recessive – unaffected parents and other relatives. Affected children (25% chance)

X-linked – males affected, females (generally) not affected. No male to male transmission

Mitochondrial – maternally inherited. No transmission from males

Pedigree





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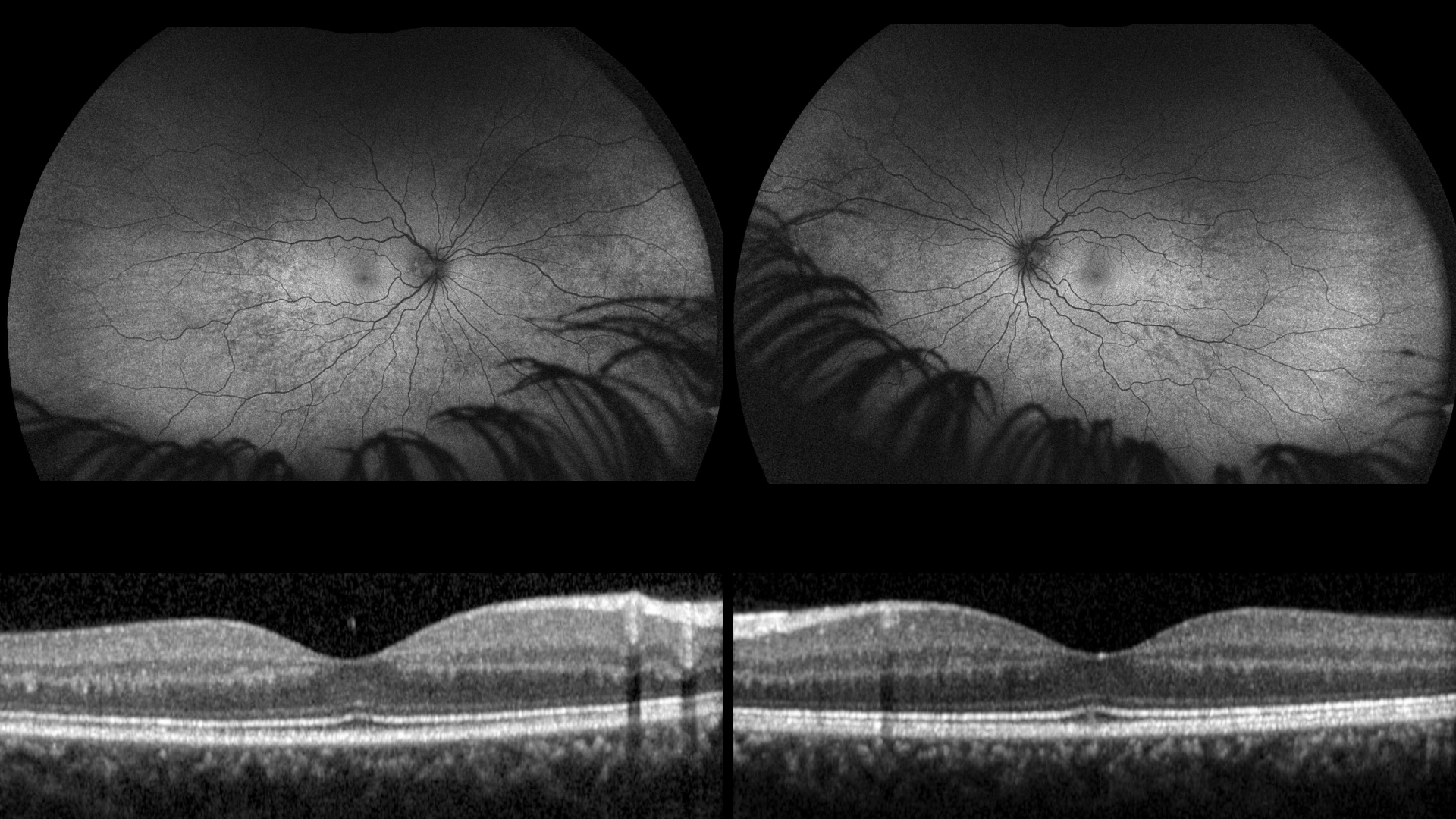
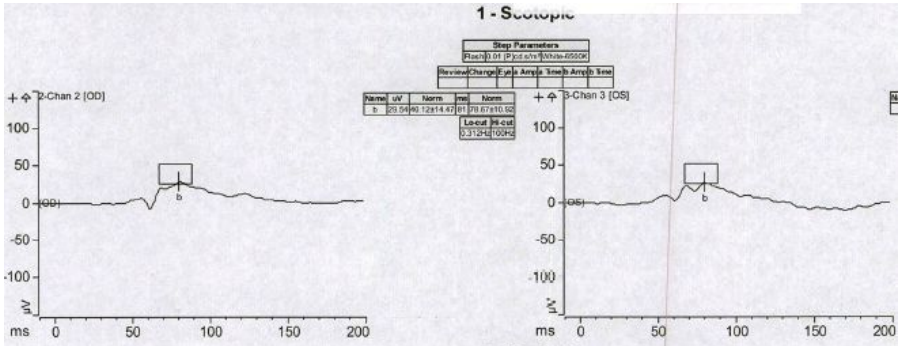
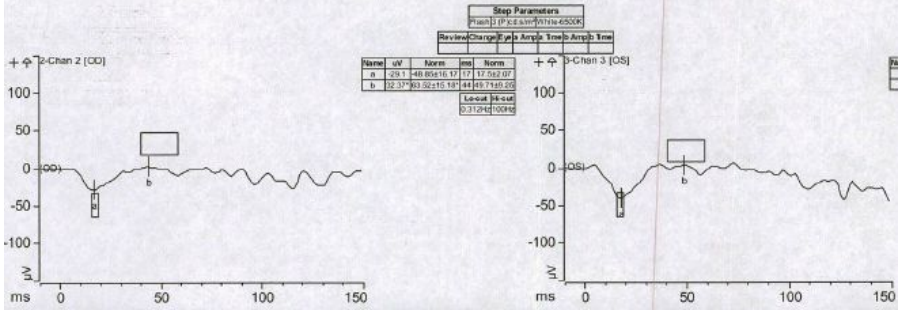


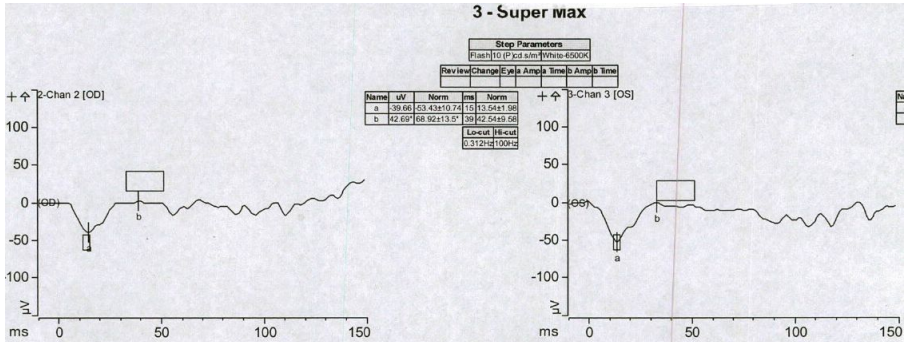
1 - Scotopic



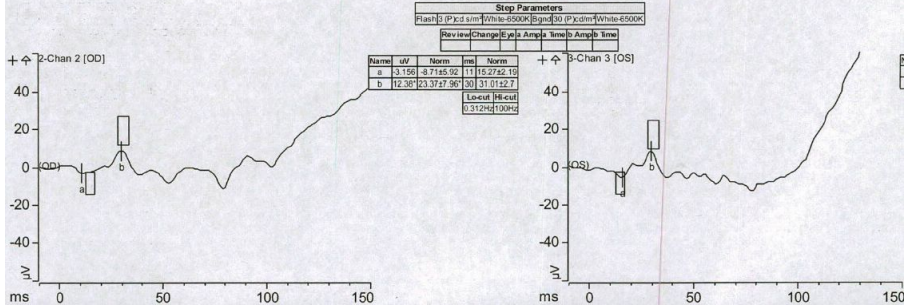
2 - Maximal



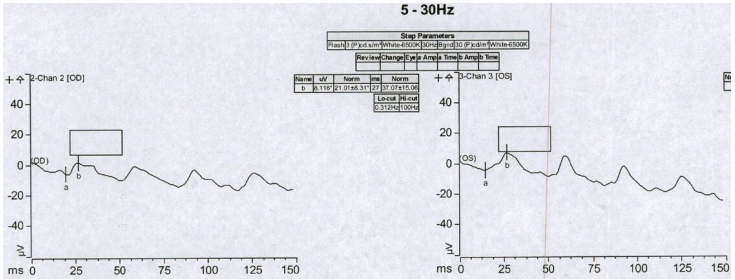
3 - Super Max



4 - Photopic



5 - 30Hz



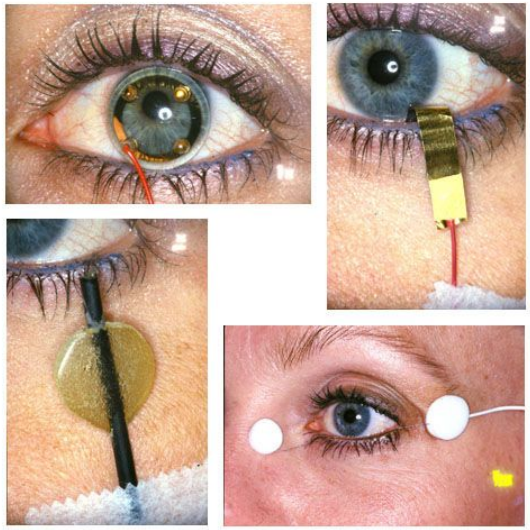
Full-field ERG

Placed in dark room for ~20 minutes to dark adapt

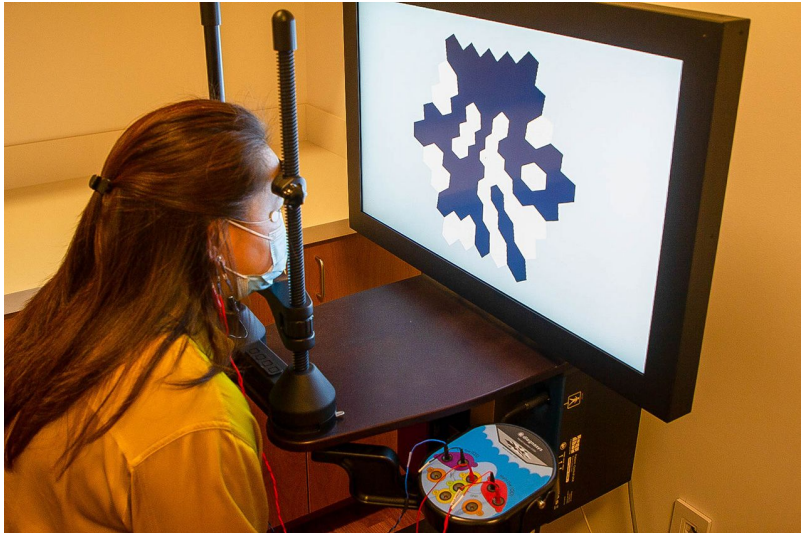
Brief, bright flashes with fine electrodes touching anaesthetised cornea

Mass electrical response of the retina to light simulation

Detect generalised rod, cone or both dysfunction



Multifocal ERG

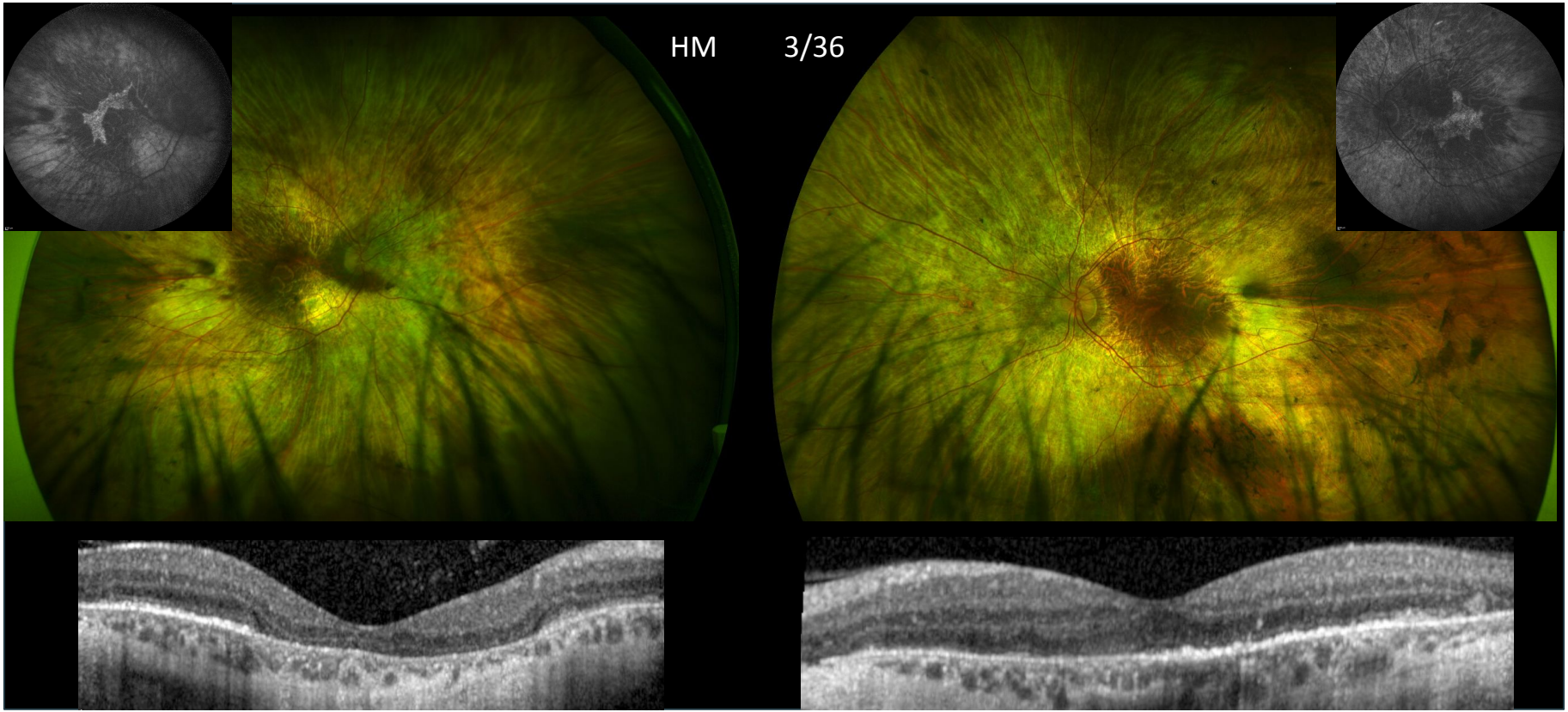


Changing pattern of black and white hexagons that rapidly flicker on and off

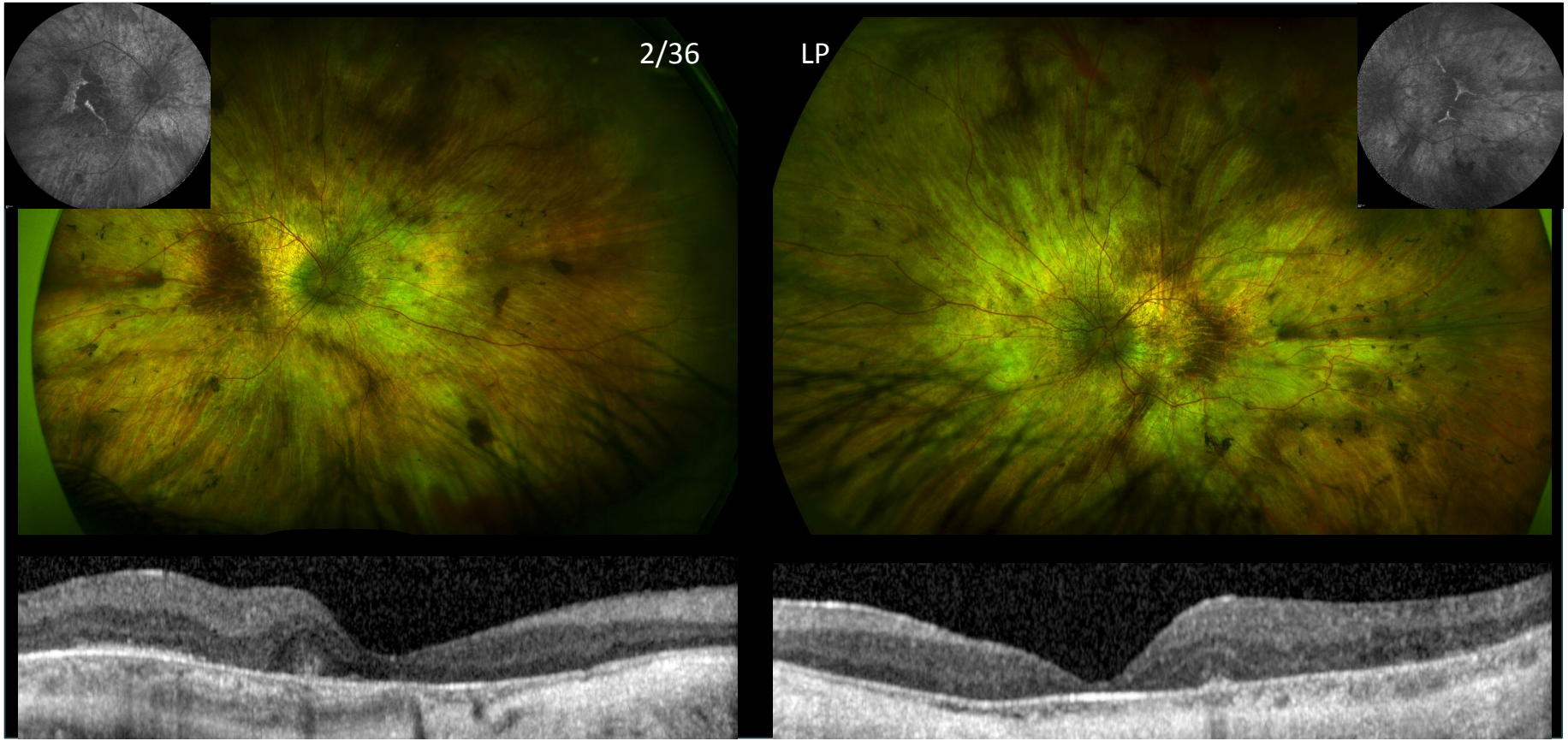
Macula-specific cone function

Isolated loss of cone function at the macula may not be detectable in full-field ERG

EG's father. 53M ?rod-cone dystrophy.



EG’s paternal uncle

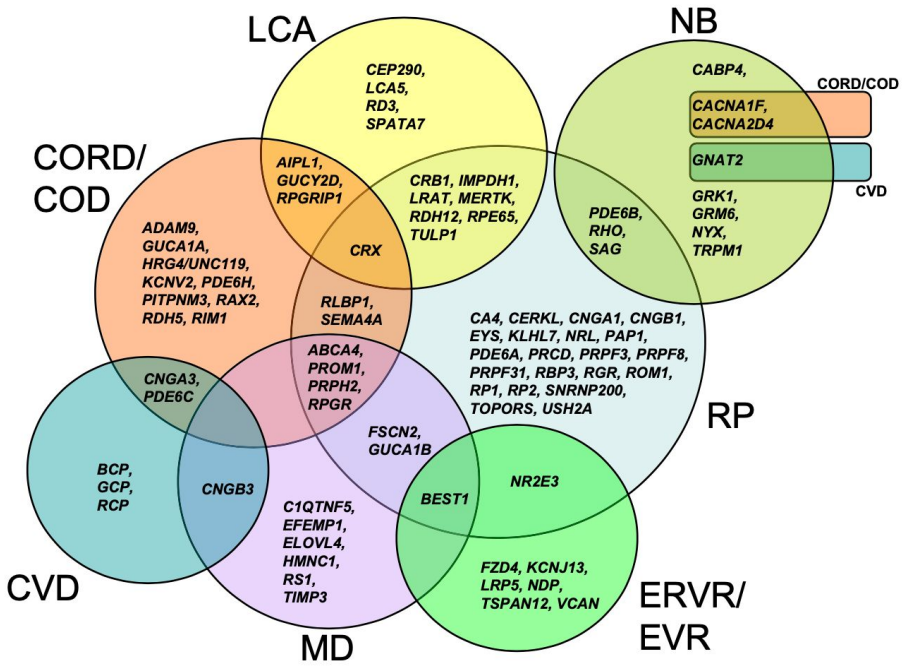


“What is the gene?”

Inherited eye diseases have become the **most common cause of blindness in the working age populations** of a number of industrialised countries.

Many different genes implicated in a given phenotype. One gene may cause a variety of phenotypes.

Knowing the causative gene and mutations **empowers** the patient to understand their condition and seek potential treatments.



Genetic testing

Why?

Confirm pathogenic cause

Family planning

Prognostication

Selection into natural history and therapeutics clinical trials

Patient interest

How?

Liaise with genetic counsellor and geneticist

Blood or saliva sample

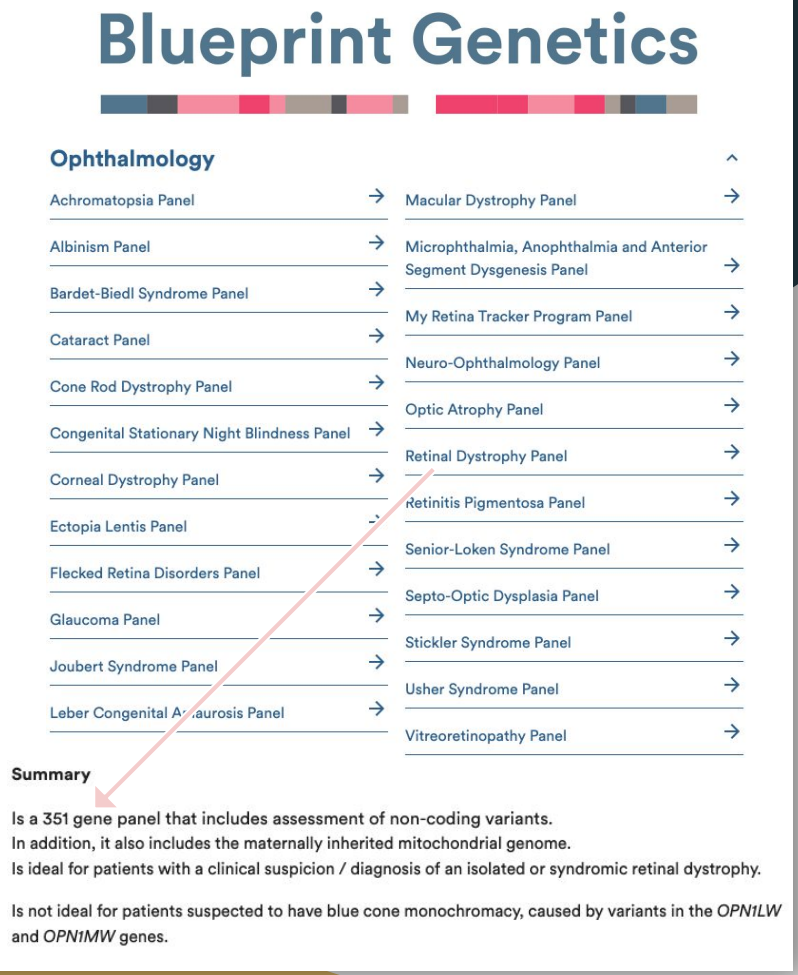
Targeted or non-targeted sequencing of DNA

Genetic testing

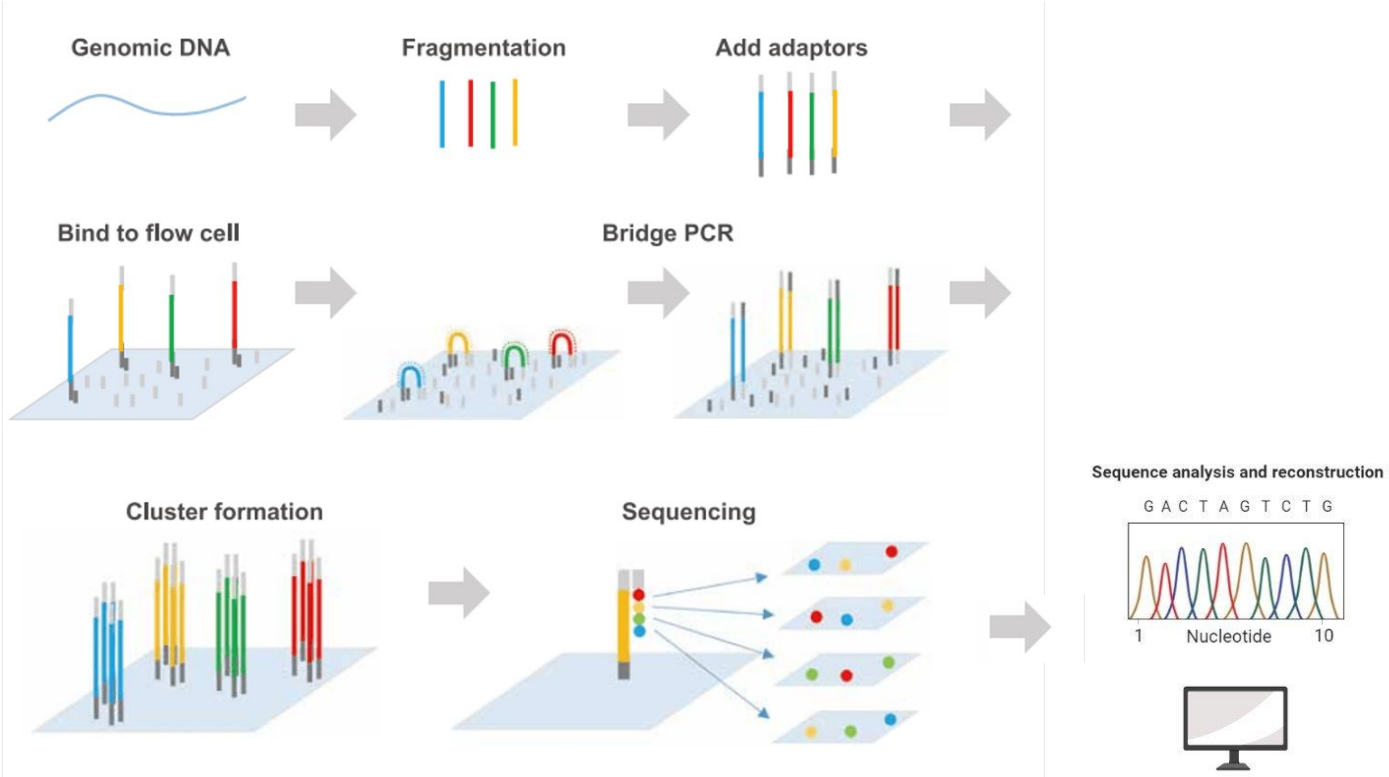
Next Generation Sequencing of **whole exome** and **exon/intron junctions** by Blueprint Genetics

Virtual panel – interpretation of genes related to IRDs (and complete mitochondrial genome)

Aim to complete within 28 days



Genetic sequencing

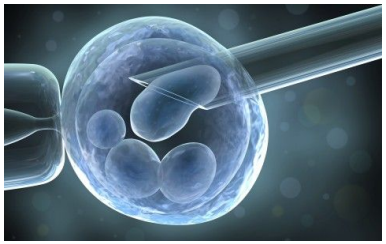


Genetic results

Father's research-grade testing shows *CHM* **nonsense mutation** of 799C>T causing an **arginine to STOP** codon

EG's Blueprint Genetics results confirm she is a **carrier of the *CHM* mutation**

⟹ Pursued IVF with pre-implantation genetic diagnosis



AUSTRALIAN INHERITED RETINAL DISEASE REGISTRY & DNA BANK

Sir Charles Gairdner Hospital

GENETIC ANALYSIS RESEARCH REPORT

DATE: 08/08/2019
NAME:
DOB:
GENDER:

REPORT ID: 1318
OPHTHALMOLOGIST: DR ALEX HEWITT
ISSUED TO: DR ALEX HEWITT
MS LISA KEARNS

PURPOSE OF TEST: Genetic confirmation that the participant harbours the familial *CHM* variant, c.799C>T (p.Arg267*), previously identified in an affected male family member, clinically diagnosed with choroideremia.

RESULT: Positive

Gene	c.DNA Reference Sequence	Nucleotide Change	Protein Change	ACMGG Classification	Zygosity	Parental Origin
CHM	NM_000390.2	c.799C>T	p.Arg267*	Pathogenic	Hemizygous	Maternal

RESULT DESCRIPTION:

A hemizygous *CHM* sequence variant, c.799C>T (p.Arg267*), was detected in the DNA of this participant. Maternal DNA was unavailable for confirmational targeted sequencing. However, the variant was also detected hemizygously in a matrilineal male family member.

The c.799C>T variant is a nonsense variant that has been reported as pathogenic for choroideremia in numerous unrelated families.[1-4] This classification is further supported by functional evidence.[5]

CONCLUSION:

This finding provides a molecular diagnosis of X-linked recessive choroideremia. Subsequent to our analysis, we were advised that, the familial clinical diagnosis had been changed from retinitis pigmentosa to choroideremia, which is in keeping with our results. Please advise if this is not the case.

Please see the following pages for Notes, References and Authorisation

[Slide courtesy of Josh Schultz]

GENETIC TESTING SUMMARY

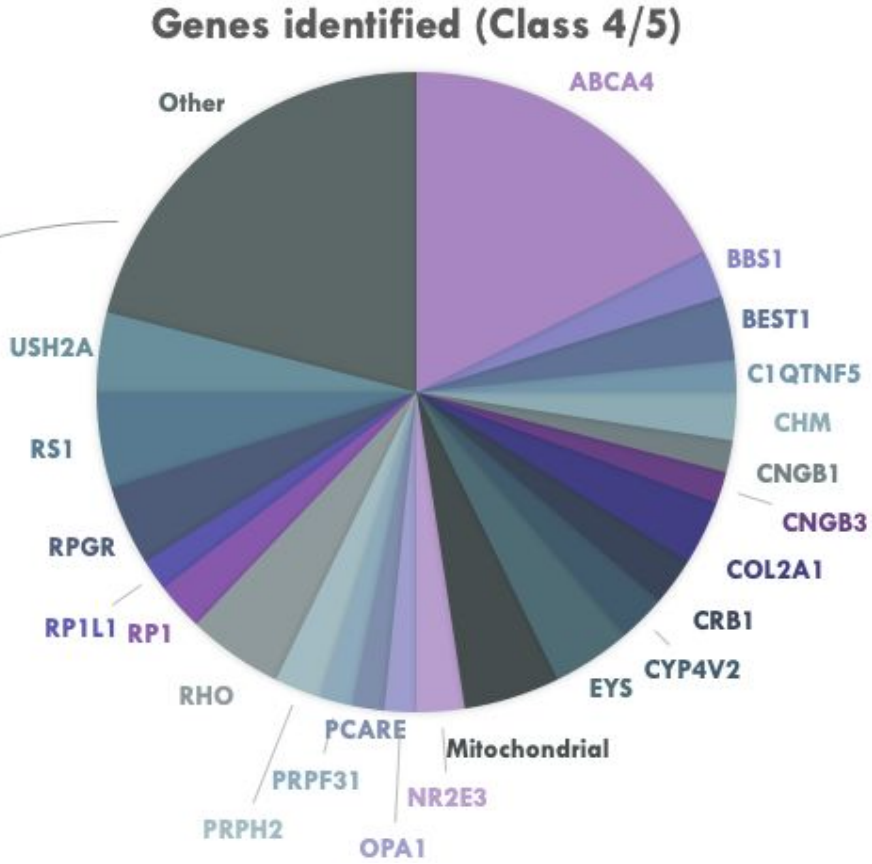
Clinical audit undertaken from Dec 2018 – May 2022

626 appointments seen across the Genetics streams

393 genetic tests requested (including diagnostic, predictive, confirmatory and segregation testing)

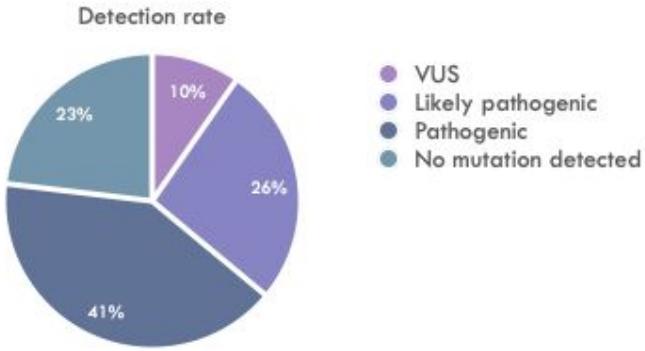
186 diagnostic test results received

Additional genes identified				
CERKL	FBN1	NRL	RP2	TREX1
CLN3	GRM6	NYX	RPE65	TULP1
CNGA1	GUCY2D	OPA3	RTN4IP1	TYRP1
CNGA3	INPP5E	PCDH15	SNRNP200	
COL11A1	KCNJ13	PRPF8	SPATA7	
CRX	KHL7	RDH12	TIMP3	



[Slide courtesy of Josh Schultz]

DETECTION RATE

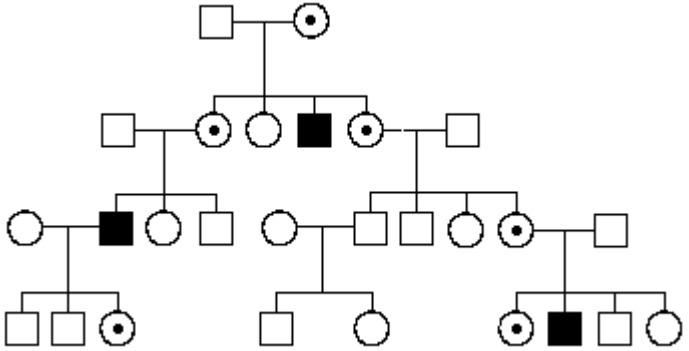


Overall detection rate: 67%

Change in diagnosis = 9.6% (12/126)

Clinical condition	(Likely) Pathogenic	VUS	Negative	Total	Detection rate:
Macular/Cone-rod dystrophy	32	7	5	44	73%
Rod-cone dystrophy	43	6	12	61	70%
LCA	3	1	1	5	60%
Optic atrophy	4	1	4	9	44%
Usher syndrome	4	1	1	6	67%
Retinoschisis	5	0	1	6	83%
Mitochondrial	5	0	2	7	71%
BCD	3	0	2	5	60%
CSNB	3	0	0	3	100%
Best disease	4	0	2	6	67%
Stickler syndrome	5	0	2	7	71%
Syndromic RP	5	2	6	13	38%
Other	9	0	5	14	64%
TOTAL	**125**	**18**	**43**	**186**	

Choroideremia



X-linked degeneration of retina, RPE and choroid

Almost exclusively **males**

Nyctalopia, peripheral field loss in second to third decade

Significant acuity loss in middle age

Gene encodes rab escort protein 1 – part of an enzyme involved in intracellular **protein trafficking**

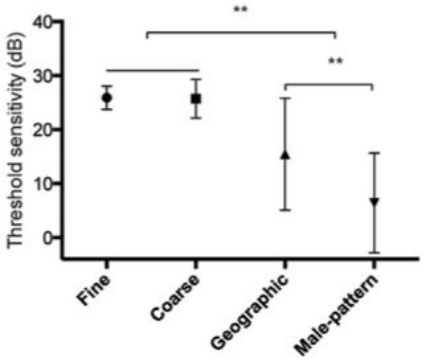
Choroideremia carriers

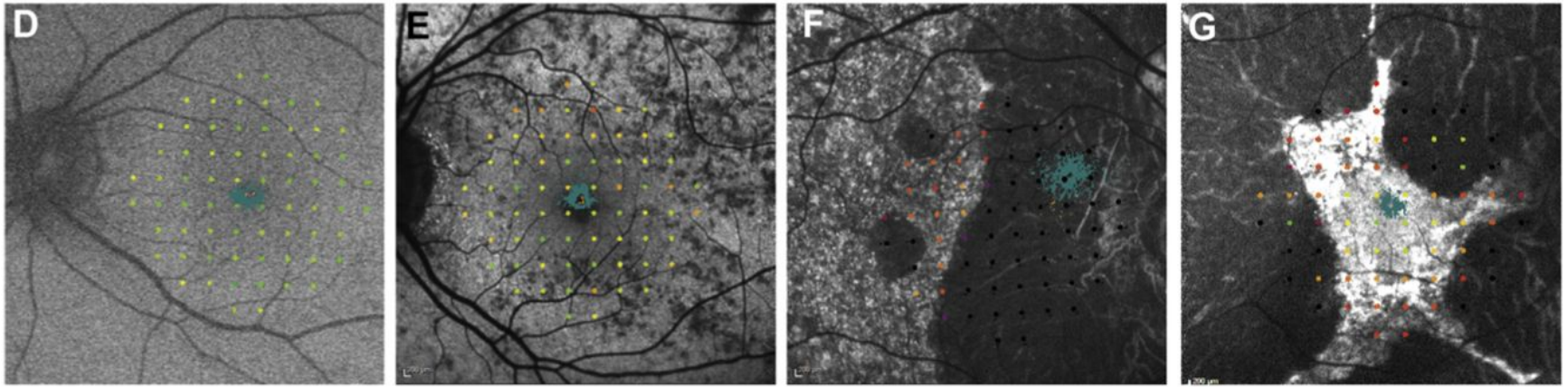
Mosaicism from X-chromosome inactivation

Mild to severe phenotype. Usually **asymptomatic**

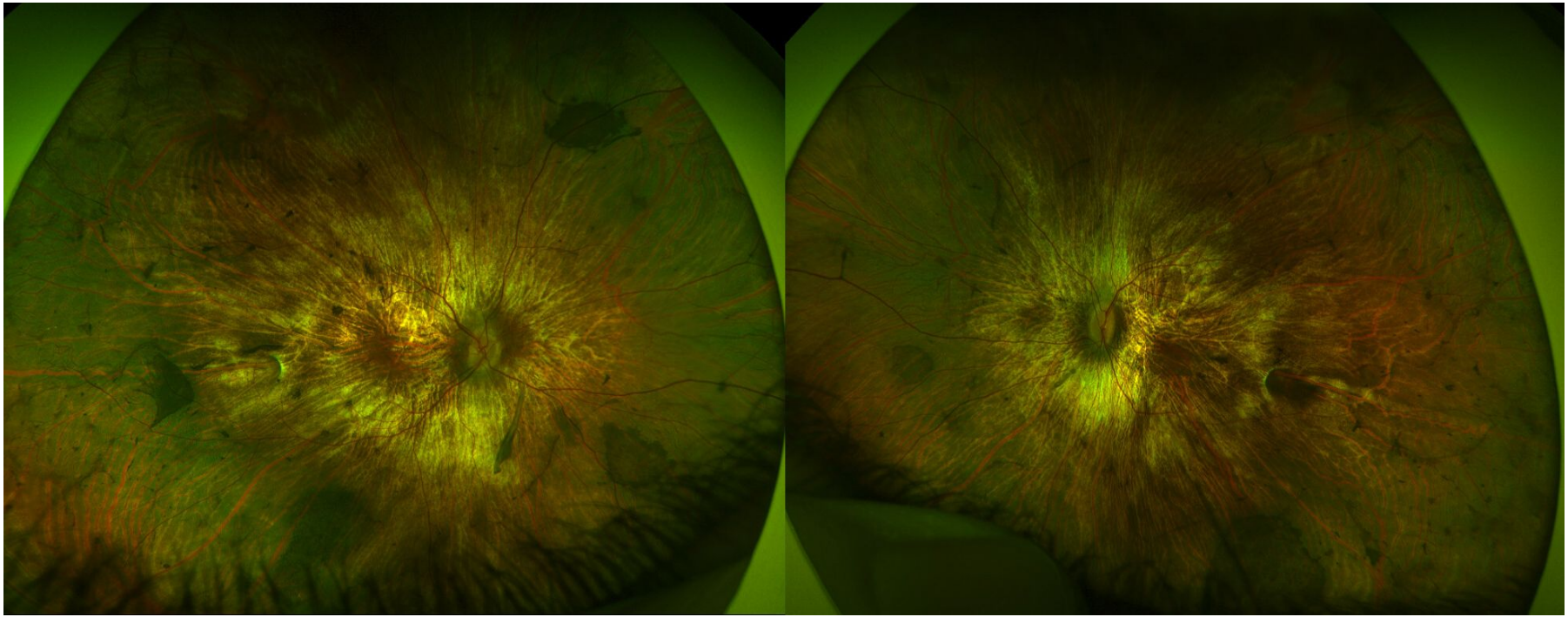
Phenotype can **progress**

Reduced mean retinal sensitivities, worse with advanced age

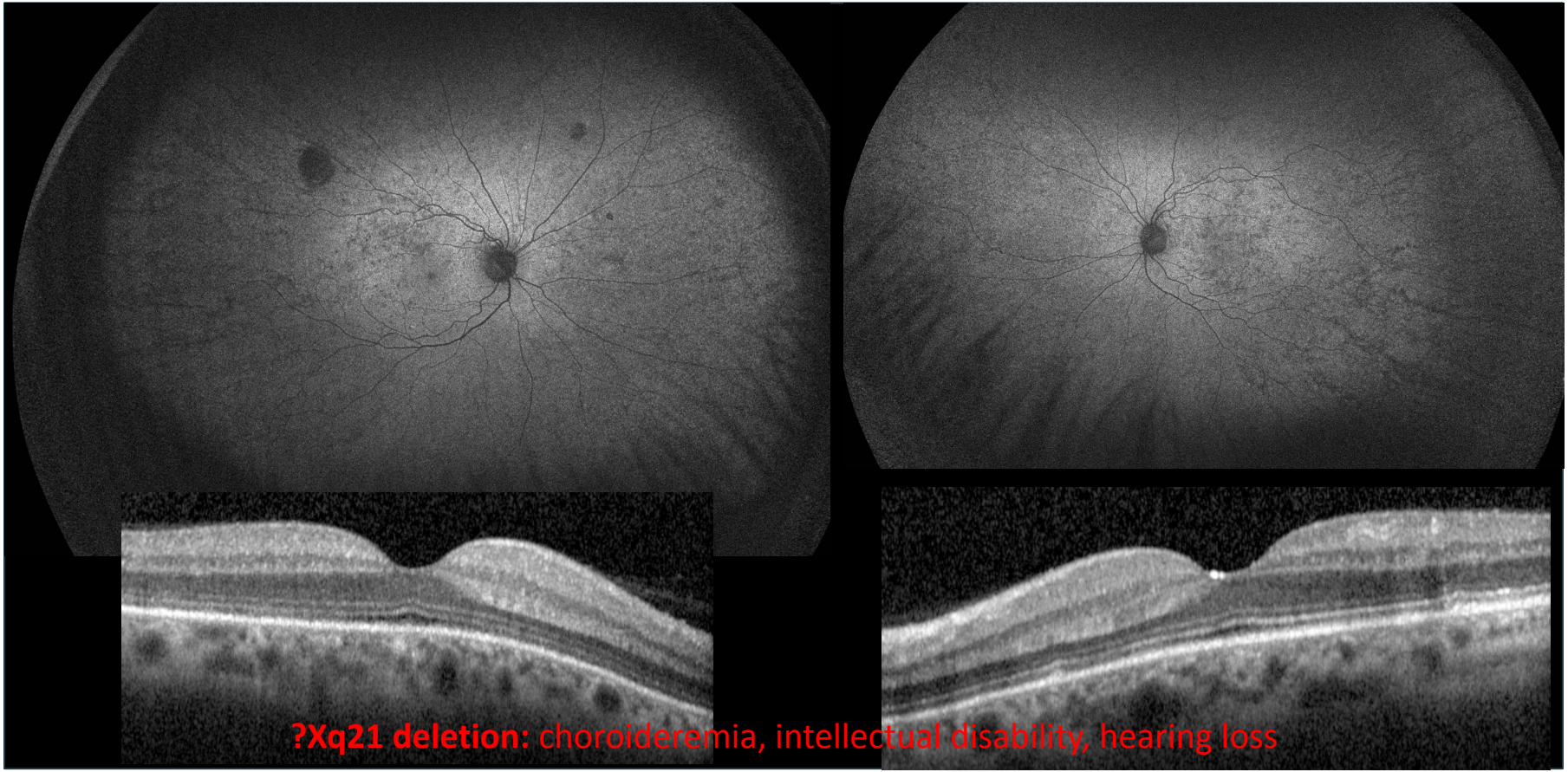




“There is nothing wrong with my vision”



Mother



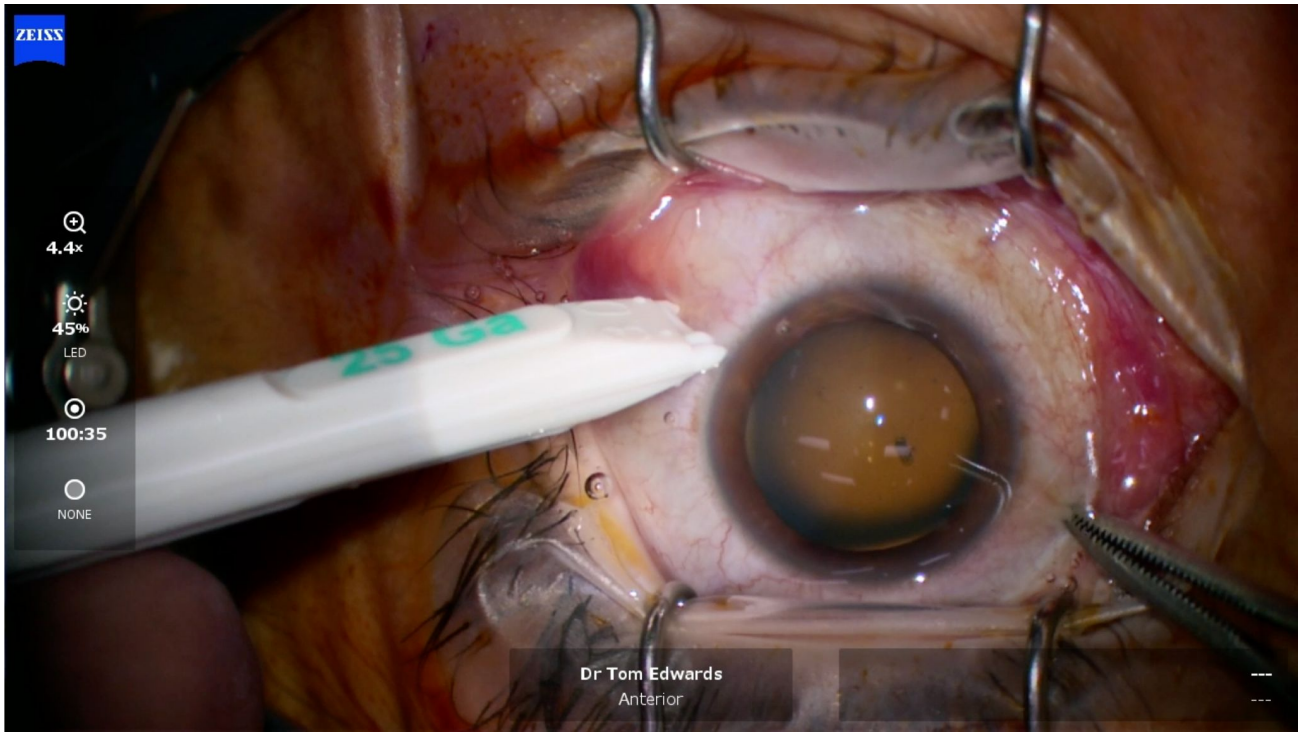
?Xq21 deletion: choroideremia, intellectual disability, hearing loss

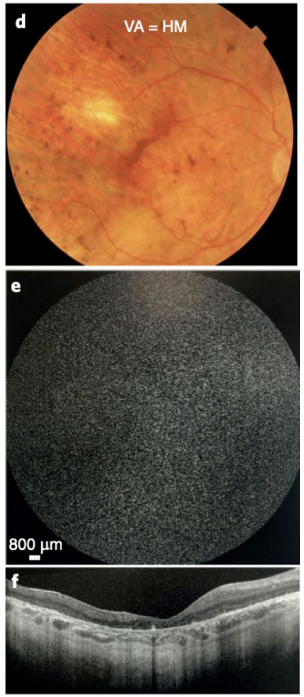
AAV choroideremia gene therapy

	nightstar THERAPEUTICS Biogen	Spark THERAPEUTICS Roche	4D molecular therapeutics
Clinical trial phase	3	1/2	1
n	169	15	15
Results	**Did not meet the primary endpoint** (>15 ETDRS letters at 12m)	?	No initial safety issues
Status	Programme **ended**	Study completion October 2022. Roche **ended** programme	Study completion ~May 2023

Gene therapy surgery

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

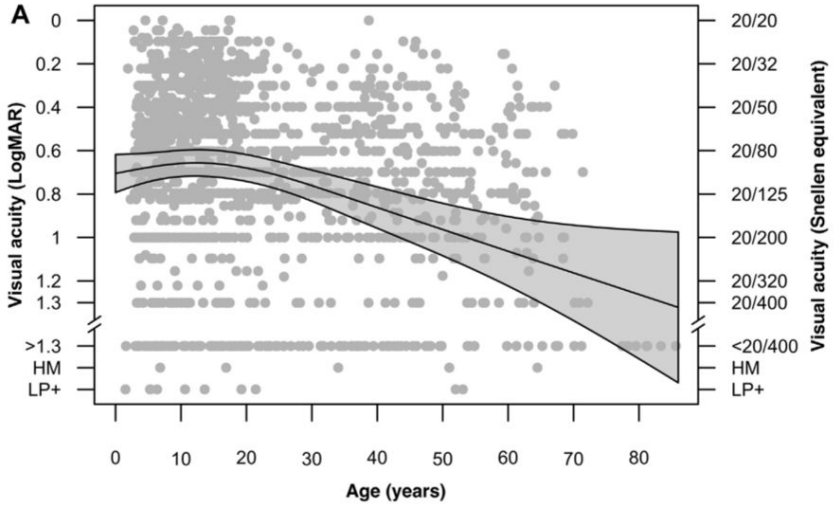




Genetic testing aids prognostication

X-linked retinoschisis natural history study

- 340 patients with X-linked retinoschisis
- Slight increase in VA in first 20 years
- Severe visual impairment and blindness >40 years old
- 25% blind by 60 years old
- No difference in VA between mild and severe variants



AMERICAN ACADEMY OF OPHTHALMOLOGY®

X-Linked Retinoschisis

Novel Clinical Observations and Genetic Spectrum in 340 Patients

Leo C. Hahn, MD,[1] Mary J. van Schooneveld, MD, PhD,[1,2] Nieneke L. Wesseling, MD,[1] Ralph J. Florijn, PhD,[3]

Genetic testing provides access to clinical trials

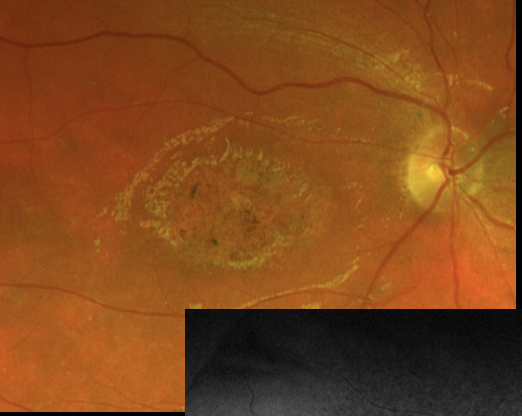
CENTRE FOR Eye Research Australia

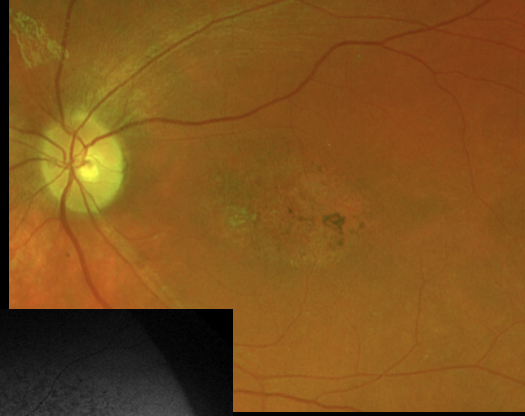
Belite BIO

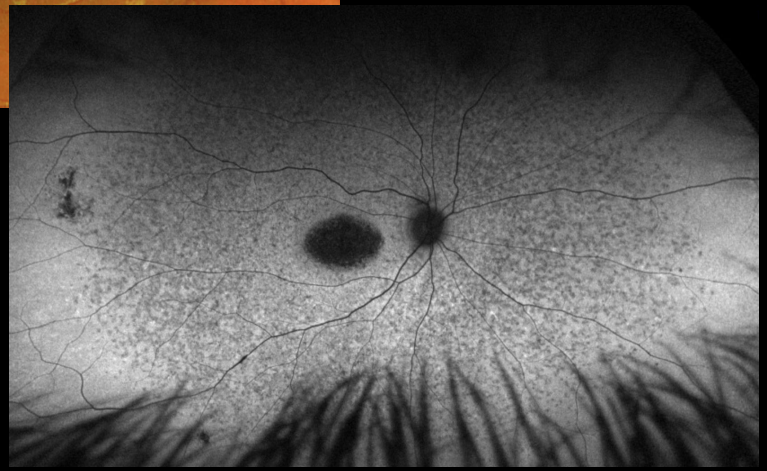
NACUITY PHARMACEUTICALS, INC

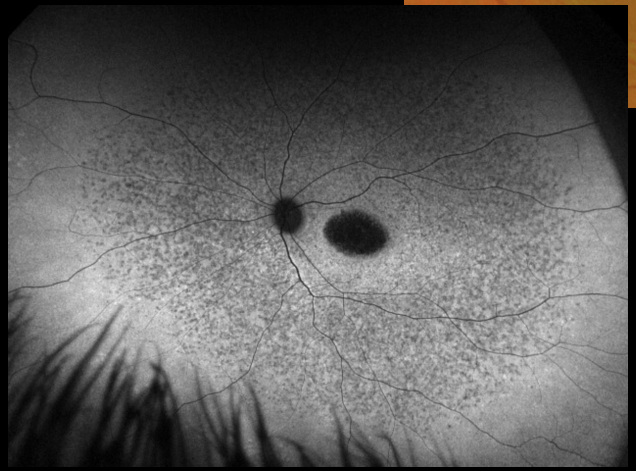
	DRAGON	SLO RP
Clinical trial phase	3	2
Patients	*ABCA4* mutations aged 12 - 20	Usher syndrome
Intervention	**Daily inhibitor of vitamin A transporter or placebo for 2 years**	**Daily antioxidant or placebo tablet for 2 years**
Status	Recruiting	Recruiting

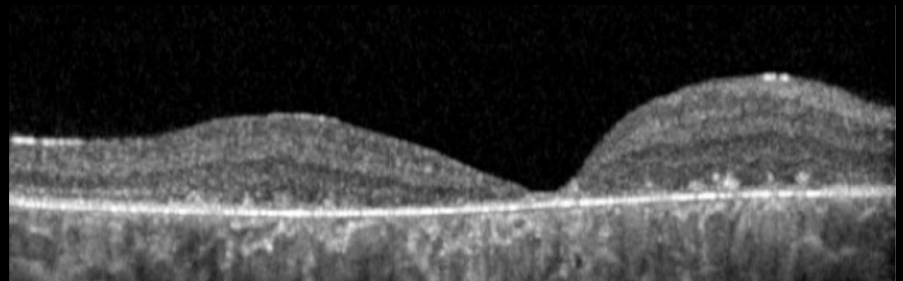
ABCA4 mutations
17 year old male

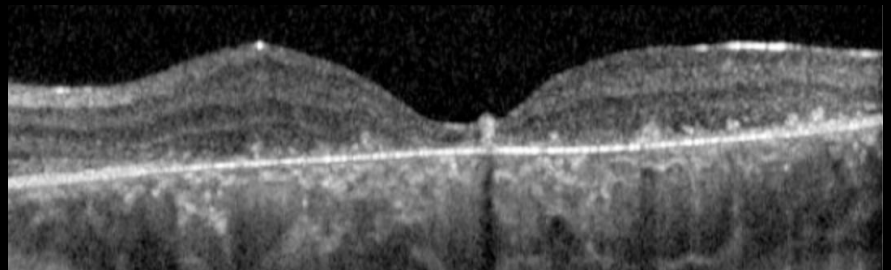












IRD clinical features

Symmetrical

Negative visual symptoms

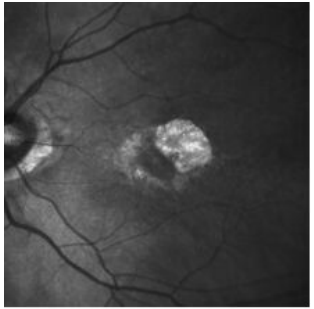
Rod dystrophy - night blind, peripheral vision loss

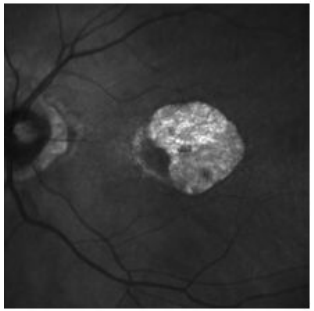
Cone dystrophy - reduced acuity, photophobia

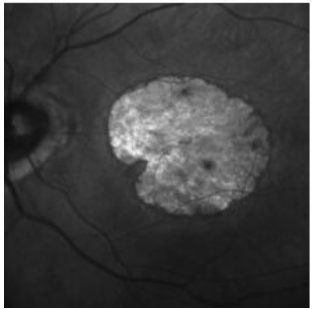
Gradual worsening

+/- Family history

+/- Systemic features: hearing loss, kidney disease, extra digits…







IRD referrals

New patient

- Concern for IRD
- Relative with IRD and requesting screening

Known IRD patient

- Change in nature of visual complaint (IRD patients still get non-IRD ophthalmic disease
- New cataract, cystoid macular edema
- Call for IRD patients for research project

Include in referral to assist triage:

- Symptoms, duration
- Family history
- Acuity
- Imaging
  - Widefield colour and FAF images
  - OCT (as wide as possible)
- Visual fields

Referral pathways

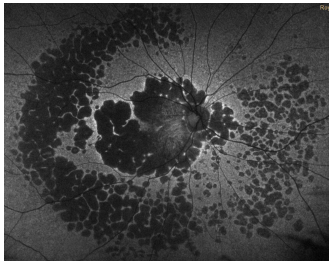
Public

- RVEEH/RMH Ocular Genetics Clinic
  - Multidisclipinary clinic with orthoptists, ophthalmologists, geneticists and genetic counsellors
  - Able to perform wide variety of genetic tests at **no cost** to patient
  - Can be long waiting list
  - First appointment with orthoptist for family history, imaging +/- electrodiagnostics
  - Second appointment: review with ophthalmologist to confirm diagnosis of likely IRD, offer genetic testing and collect sample
  - Third appointment in ~6 months to discuss results.
  - Complicated cases will also involve genetic counsellor or geneticist review.
  - If mutation found then testing may be requested/offered to family members.

Private

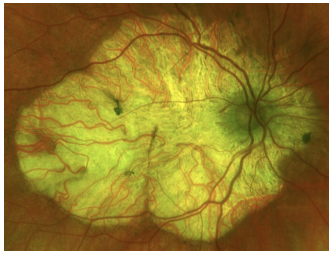
- Multiple ocular genetics subspecialist ophthalmologists who are able to order Novartis-sponsored genetic testing
  - **Free testing is limited to suspected rod-cone dystrophy and Leber congenital amaurosis patients**
  - Patients with other phenotypes (e.g. cone-rod dystrophy) would have to pay for test.
  - Imaging, family history and ophthalmologist review in initial appointment.
  - Sample for genetic testing on the day, or posted to patient to swab their own cheek.
  - Follow-up appointment in ~3 - 6 months to discuss results.

General IRD management



Exclude IRD mimics – drug toxicity, nutritional deficiencies, autoimmune, infectious etc.

Treat reversible non-IRD-related causes of vision loss – refractive error, cataract, cystoid macular edema



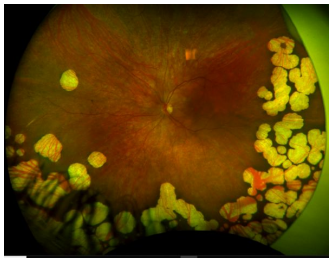
IRD specify management

OAT (gyrate atrophy) ⟶ high ornithine levels. Restrict dietary arginine. Give Vitamin B6

ABCA4 (Stargardt) ⟶ manage vitamin A intake

Leber Hereditary Optic Neuropathy ⟶ consider idebenone

RPE65 ⟶ Luxturna



Ensure appropriate **supports** – Vision Australia, Retina Australia, NDIS

Advocate for patient – they are often young, otherwise well patients with a poor visual prognosis – more should be done to facilitate accurate diagnoses and develop therapies

Moving from clinical diagnoses (“macular dystrophy”) to **molecular diagnoses** (“*ABCA4*-retinopathy”)

Case learning points

Not all carriers are the same – if X-linked the disease is much more likely to manifest in the next generation males. Don't dismiss someone with 'normal' exam and good VA – they may need genetic counselling.

Fundus autofluorescence invaluable in highlighting IRD pathology.

RVEEH Ocular Genetics Clinic and VPEC has access to powerful genetic testing capabilities with a **~67% positive detection rate.**

Choroideremia carriers have a variable phenotype

IRD clinical trials are ongoing, including two at CERA