The Gene Behind The Gaze

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Case Report

- A 27 year old female presented to the ophthalmology department with chief complaint of defective vision in both eyes for distance and near **noticed by parents at the age of 1 year**

- **History of present illness :**progressive painless loss of vision in both eyes for distance and near noticed by parents when was unable to follow objects and light
- Associated with **involuntary eye movements, photophobia and night blindness since childhood**

- **Past history :**

  History of usage of glasses for the past 24 years

  Patient had history of 2 episodes of seizures 17 years back

  No history of ocular trauma or ocular surgery

Birth history :

- Birth at 8 months of gestation
- Normal vaginal delivery
- No history of

❑incubation

❑phototherapy

❑blood transfusion

❑epilepsy

❑seizures immediately after birth

- No history of maternal infection

Family history :

- **Father and brother had seizures in childhood**
- **Paternal consanguinity present**

Treatment history :

- History of using anti epileptic medication since 17 years

Personal history :

- Mixed diet.
- Sleep and appetite normal.
- Bowel and bladder habits regular.

General Examination:

- Conscious and coherent
- Moderately built and nourished
- No pallor, no icterus, no cyanosis, no clubbing, no lymphadenopathy, no pedal edema.

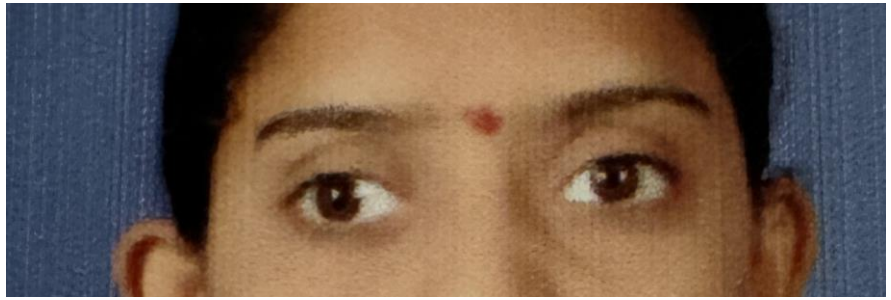
Vital data :

- Pulse rate: 86 beats/min, regular
- Blood pressure: 110/80 mm of Hg
- Respiratory rate: 16 breaths /min
- Temperature: afebrile

- **Ocular Examination :**

	Unaided	With pinhole	Near vision
Right eye	Counting fingers close to face(CFCF)	no improvement	Unable to read
Left eye	Counting fingers close to face(CFCF)	no improvement	Unable to read

Local examination:



Head and chin: midline in position

Face : bilaterally asymmetrical due to exotropia

Forehead wrinkles : present

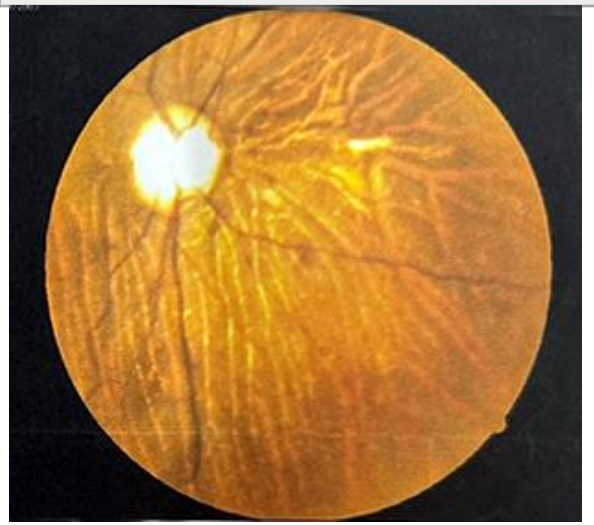
Eyes: **Alternating exotropia , horizontal jerky nystagmus in both eyes**

	Right Eye	Left Eye
Extra ocular movements	Full and free in all gazes	Full and free in all gazes
Anterior segment	Normal except direct pupillary reaction sluggish	Normal except direct pupillary reaction sluggish

- **Posterior Segment Findings :**

Fundus	Right Eye	Left Eye
Media	Clear	Clear
Optic disc	Optic disc pallor	Optic disc pallor
Blood vessels	Diffuse attenuation of arteries and veins AV ratio is altered	Diffuse attenuation of arteries and veins AV ratio is altered
Macula	Diffuse retinal pigment epithelium atrophy in macular area	Diffuse retinal pigment epithelium atrophy in macular area
Background	Tessellated background ,pigment clumping ,prominent large choroidal vessels seen	Tessellated background ,pigment clumping ,prominent large choroidal vessels seen

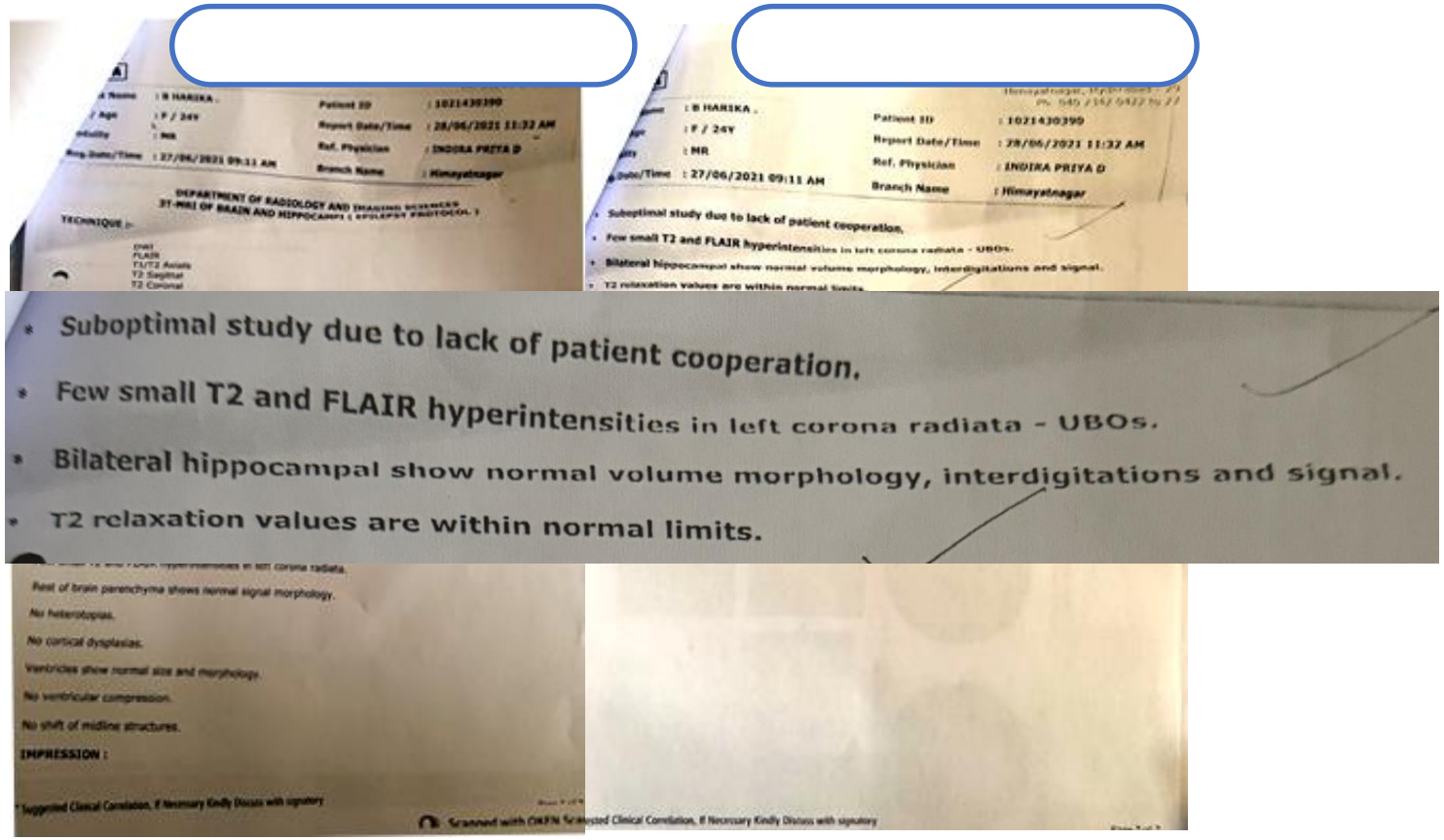
Right Eye



Left Eye

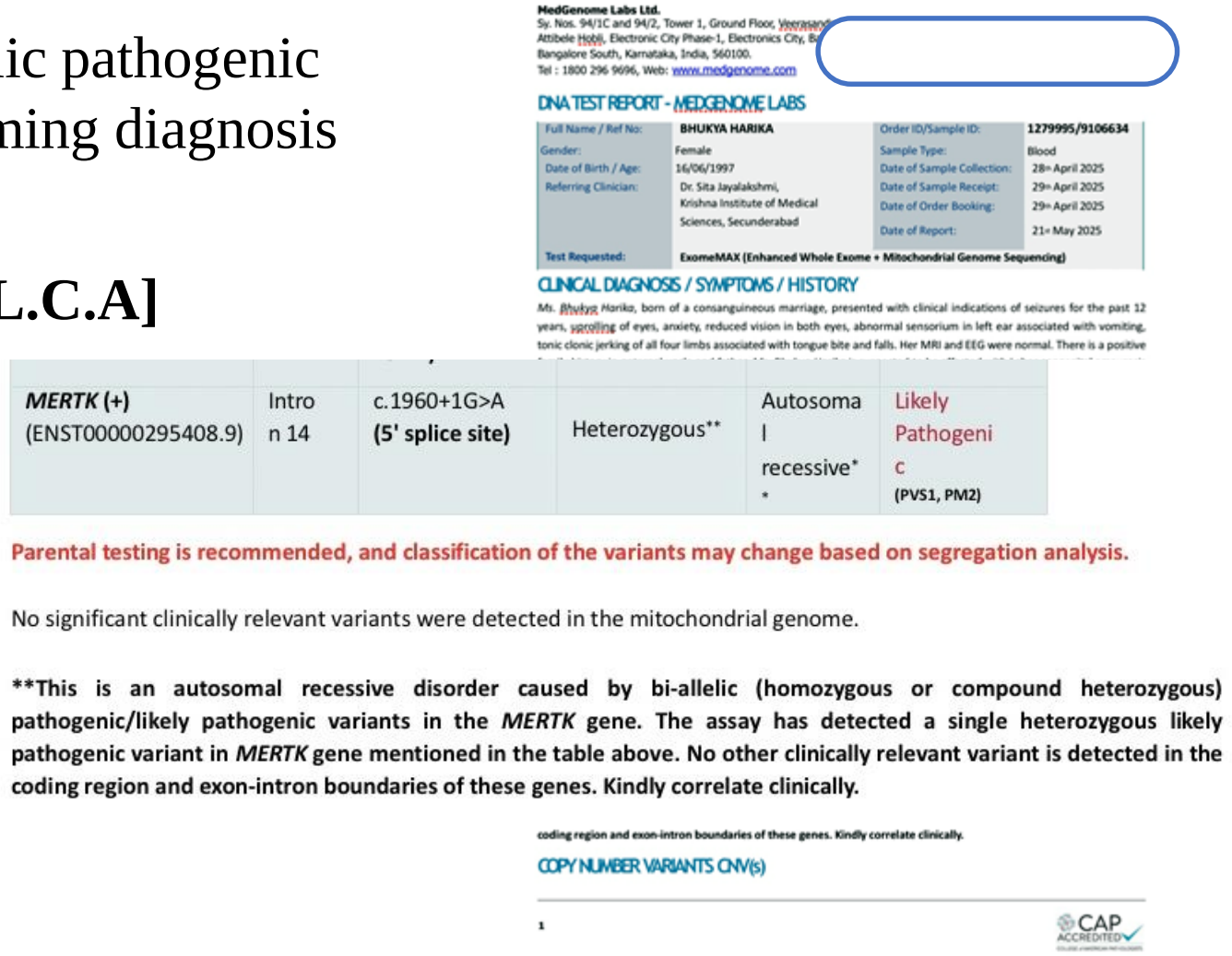
Investigations :

- MRI brain reveal few small T2 and FLAIR hyper intensities in left corona radiata



- Genetic testing identified a bi-allelic pathogenic mutation in **MERTK gene** confirming diagnosis of autosomal recessive

Lebers' Congenital Amaurosis [L.C.A]



MedGenome Labs Ltd.
Sy. Nos. 94/1C and 94/2, Tower 1, Ground Floor, Veerasandra,
Attibele Hobli, Electronic City Phase-1, Electronics City, B
Bangalore South, Karnataka, India, 560100.
Tel : 1800 296 9696, Web: www.medgenome.com

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	BHUKYA HARIKA	Order ID/Sample ID:	1279995/9106634
Gender:	Female	Sample Type:	Blood
Date of Birth / Age:	16/06/1997	Date of Sample Collection:	28th April 2025
Referring Clinician:	Dr. Sita Jayalakshmi, Krishna Institute of Medical Sciences, Secunderabad	Date of Sample Receipt:	29th April 2025
		Date of Order Booking:	29th April 2025
		Date of Report:	21st May 2025
Test Requested:	ExomeMAX (Enhanced Whole Exome + Mitochondrial Genome Sequencing)		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Ms. Bhukya Harika, born of a consanguineous marriage, presented with clinical indications of seizures for the past 12 years, sprolling of eyes, anxiety, reduced vision in both eyes, abnormal sensorium in left ear associated with vomiting, tonic clonic jerking of all four limbs associated with tongue bite and falls. Her MRI and EEG were normal. There is a positive

***MERTK* (+)** (ENST00000295408.9)	Intron 14	c.1960+1G>A **(5' splice site)**	Heterozygous**	Autosomal recessive* *	Likely Pathogenic **(PVS1, PM2)**

Parental testing is recommended, and classification of the variants may change based on segregation analysis.

No significant clinically relevant variants were detected in the mitochondrial genome.

****This is an autosomal recessive disorder caused by bi-allelic (homozygous or compound heterozygous) pathogenic/likely pathogenic variants in the *MERTK* gene. The assay has detected a single heterozygous likely pathogenic variant in *MERTK* gene mentioned in the table above. No other clinically relevant variant is detected in the coding region and exon-intron boundaries of these genes. Kindly correlate clinically.**

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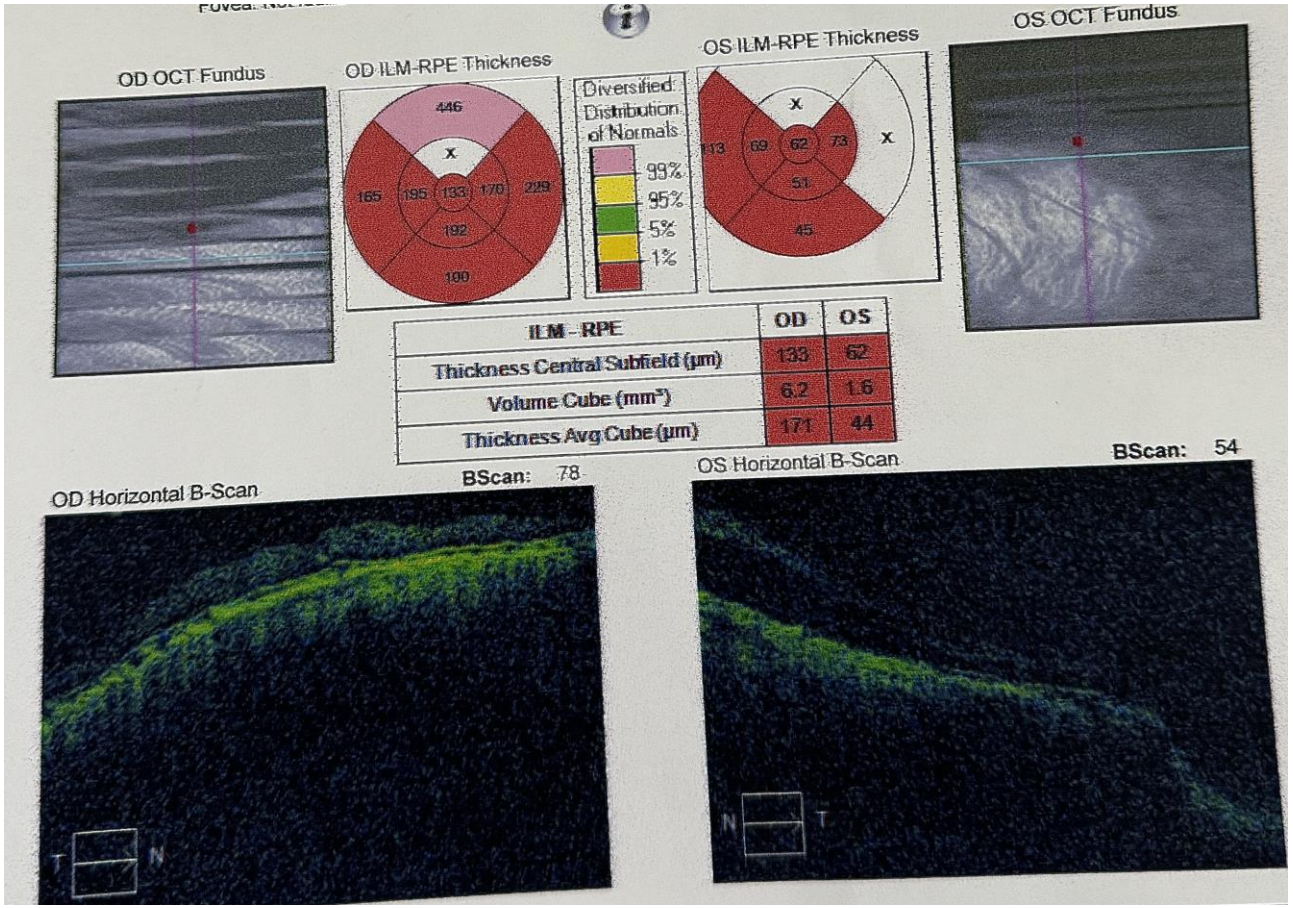
COPY NUMBER VARIANTS CNV(s)

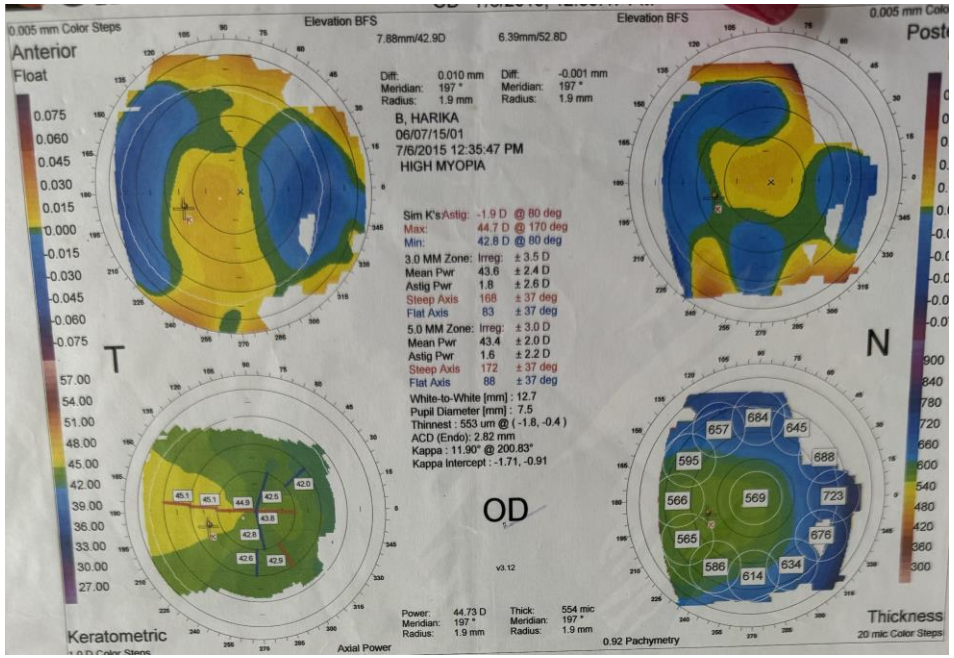
1

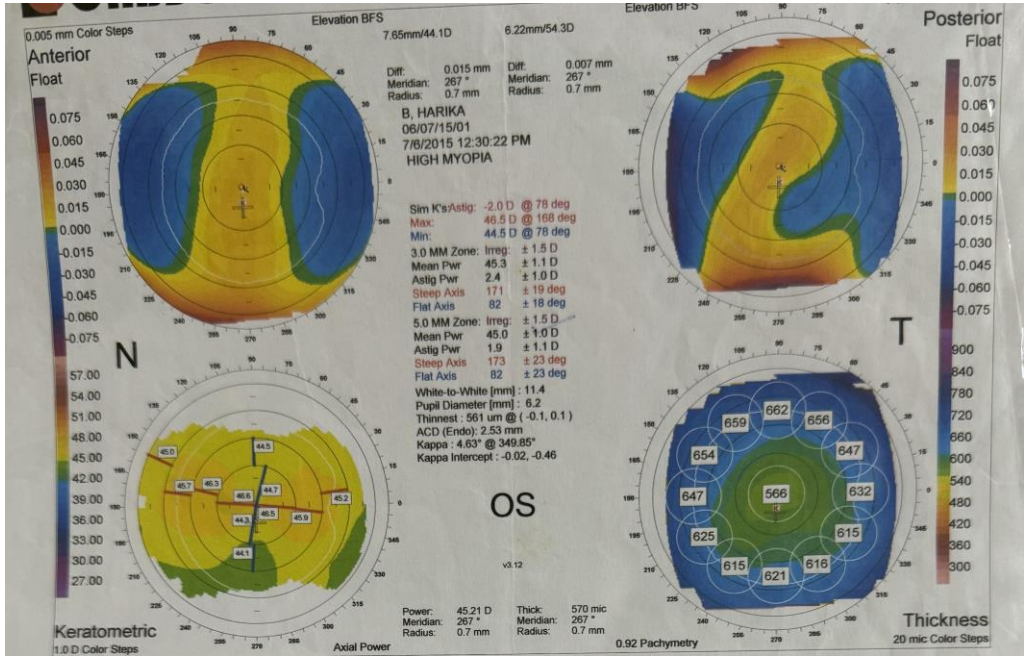
CAP ACCREDITED

- Optical Coherence Tomography shows BE foveal thinning.



- ORB SCAN - Normal



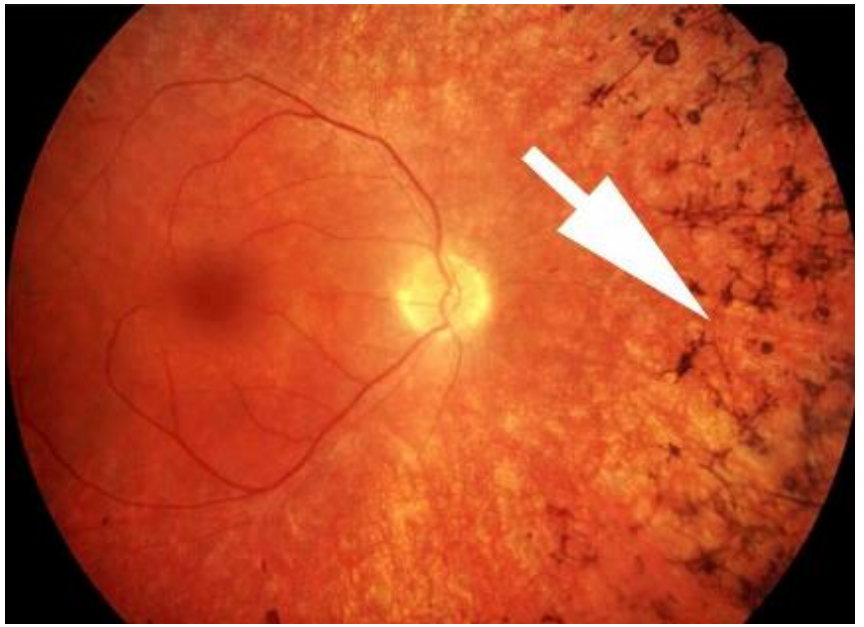


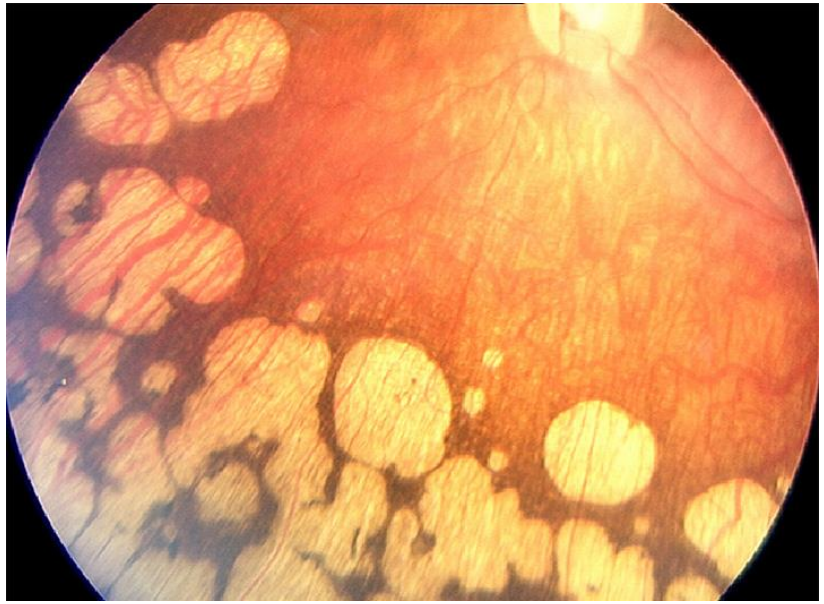
Diagnosis

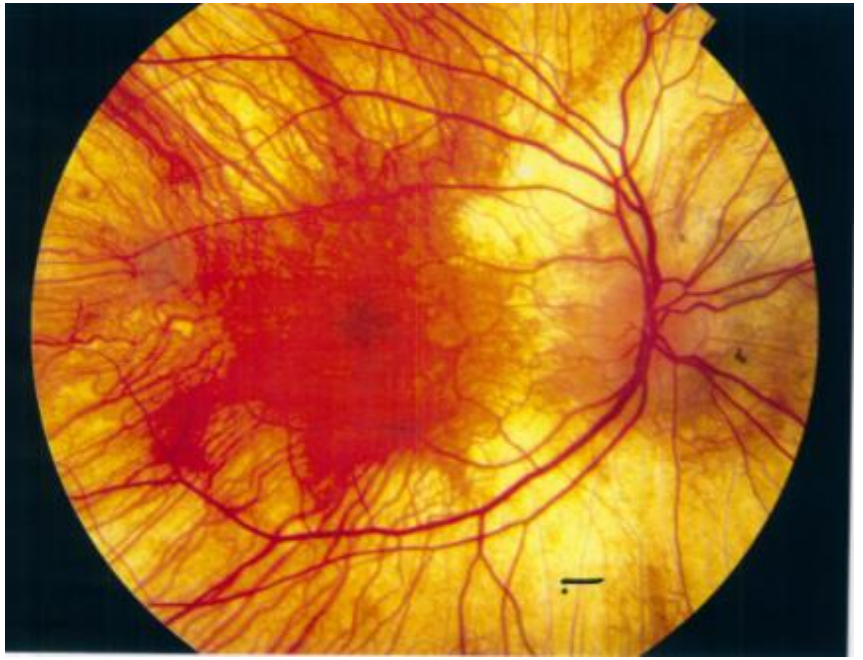
Both Eyes **: Lebers’ Congenital Amaurosis [L.C.A]**

Differential diagnosis

- Early onset retinitis Pigmentosa
- Choroideremia
- Gyrate Atrophy
- Phenothiazine Drug Toxicity







Discussion

- Lebers' Congenital Amaurosis (L.C.A) is a part of the spectrum of inherited retinal dystrophies.
- Rare autosomal recessive inheritance
- **Severe Early Childhood Onset Retinal Dystrophy(SECORD)**

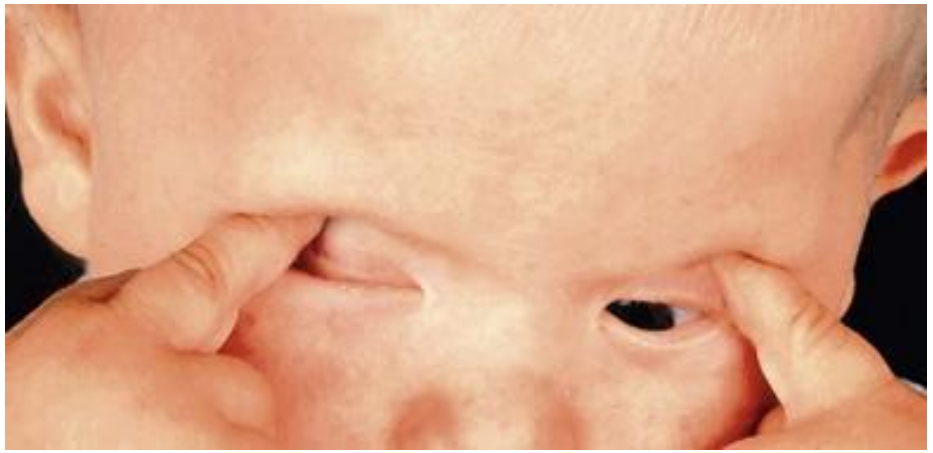
✓ reduced vision since birth

✓ nystagmus

✓ oculodigital sign

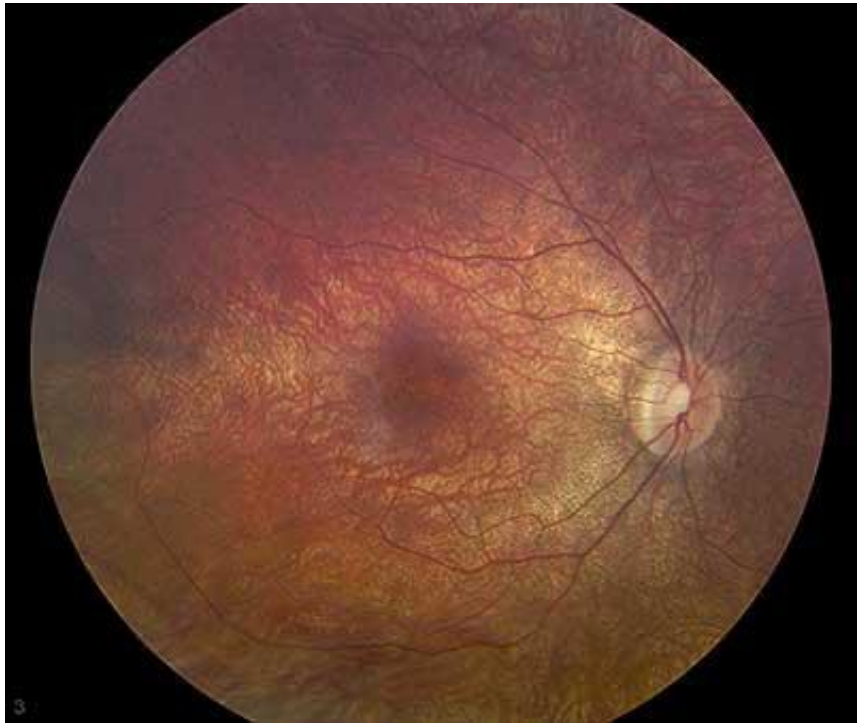
✓ poor pupillary responses.

- Prevalence 2-3/1,00,000 births



Oculodigital sign

- The fundus findings are the early stages have normal fundus or retinal pigment epithelial mottling and vessel narrowing.
- Later stages characterised by optic disc pallor and retinitis punctata albescens and nummular pigmentation



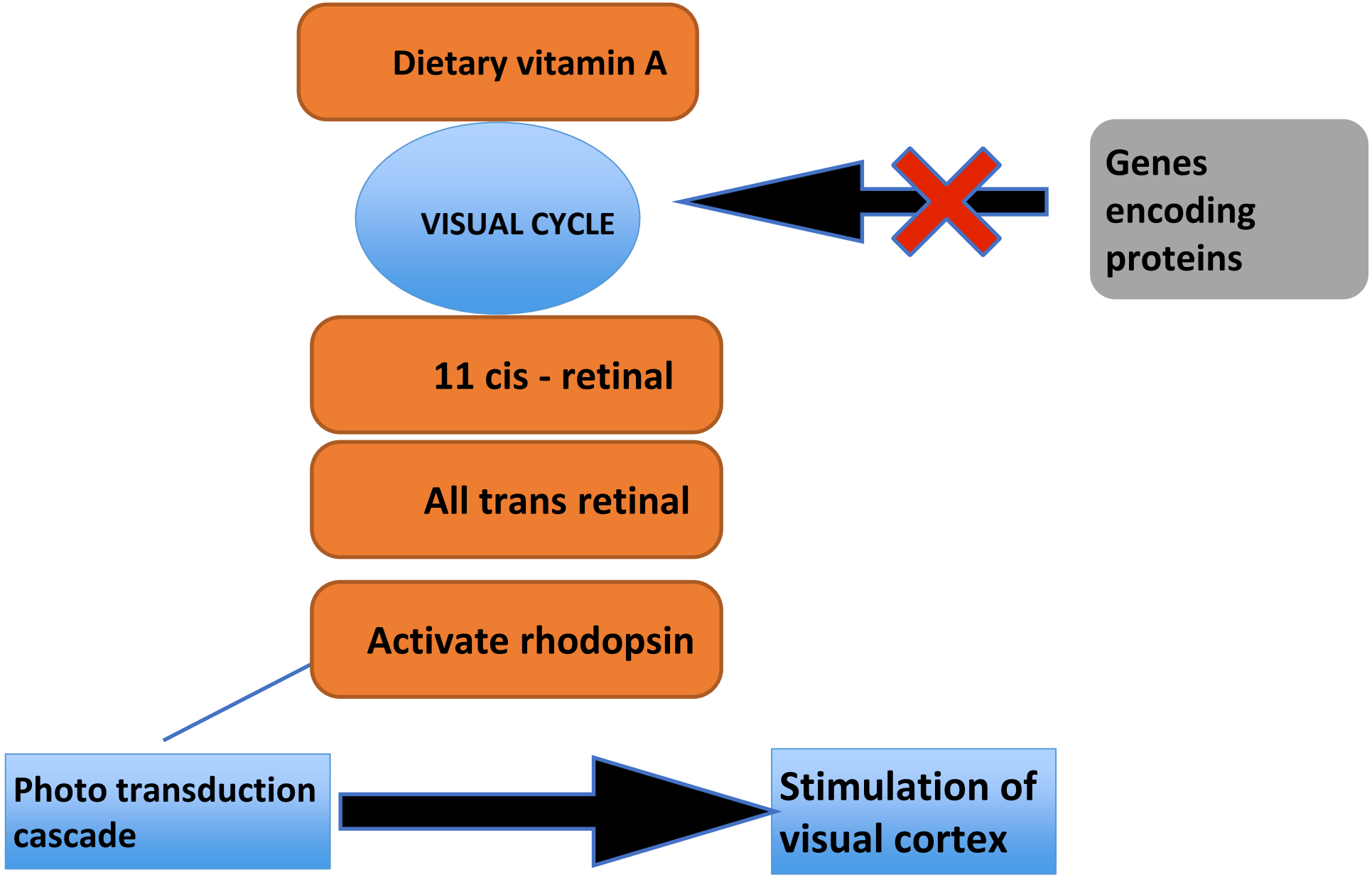
Risk factor

- The risk for 2 carrier parents to have an affected child is **25%** with each pregnancy
- The risk to have a child who is a carrier **50%** with each pregnancy
- The chance for a child to be genetically normal is **25%**

Pathophysiology

- It is related to the inability of the eye to undergo photo transduction due to disruption of the visual cycle

Pathophysiology



- Lebers’ Congenital Amaurosis caused by various gene mutations atleast 27 genes among them **CEP290, RPE65** are the most frequently mutated genes.
- LCA is often under diagnosed inherited retinal disease
- As a result patients are frequently told that no improvement possible leading to loss of hope and missed opportunities
- However, molecular genetic testing ,screening of family members ,as in this case **MERTK** gene mutation confirmation offers diagnostic clarity and open doors to future gene based therapies
- **RPE65 have FDA approved LUXTURNA gene therapy**

Take Home Message :

- This case highlights the importance of considering inherited retinal dystrophies like LCA in patients with unexplained lifelong vision loss
- Genetic confirmation of a **MERTK gene mutation** emphasizes the value of molecular testing
- Even in the absence of current treatment ,recognising the genetic cause offers clarity ,role of **Genetic counselling**,helps avoid misdiagnosis and eligibility for future gene based therapies
- This case reflects a shift from merely managing blindness to understanding its root cause and exploring interventions that may alter its course


Thank
you