LVPEI
So that all may see

L V Prasad Eye Institute

How has genetics improved managing my glaucoma patients better?

Sirisha Senthil, MS, FRCS(Edin)
Head,VST Center for Glaucoma Care
L V Prasad Eye Institute
Hyderabad
India

No Financial disclosures to make

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Outline: How has genetics helped with….

Appropriate diagnosis of conditions with “similar” phenotypes

Tailor ocular and systemic management

Prenatal diagnosis and prevent disease in future generations

Ectopia Lentis

Congenital EL is the second leading cause of lens surgery in children after congenital cataract

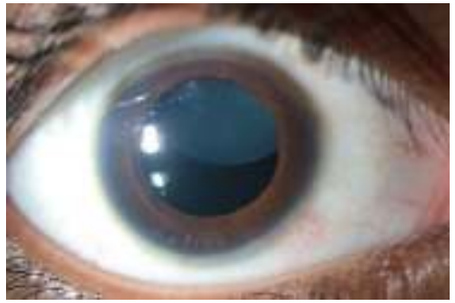
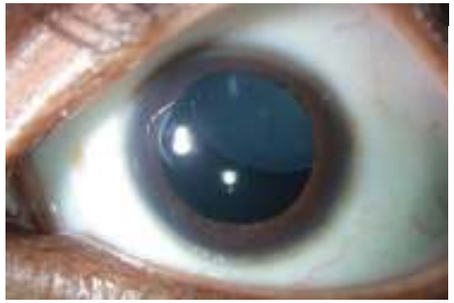
EL occurs in isolated and syndromic forms

Syndromic congenital EL can be a complex and potentially life-threatening

During early childhood it may be confused with isolated congenital EL as systemic syndrome symptoms often manifest at a later age

Early diagnosis and proper treatment are important to reduce complications and improve the prognosis

- 12-year-old
- High Myopia
- Ectopia lentis
- Elevated IOP: RE 23 LE 24 mmHg

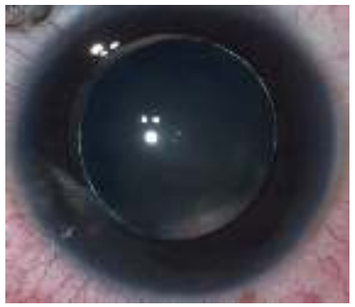
Marfan Syndrome

Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
FBN1 NM_000138.5	c.3874C>G p.Leu1292Val	Homozygous	Exon 32	Weill-Marchesani syndrome 2, dominant [OMIM ID: 608328] Marfan syndrome [OMIM ID: 154700]	Autosomal Dominant	Uncertain significance PM2, PM1 & PP2

Cardiovascular System

Dissecting aneurysm of ascending aorta

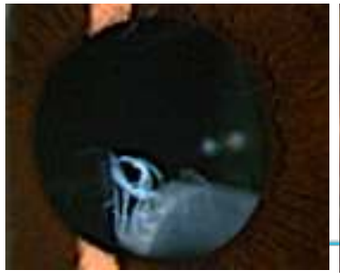
Mitral valve prolapse




WMS Syndrome

Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
FBN1 NM_000138.5	c.3874C>G p.Leu1292Val	Homozygous	Exon 32	Weill Marchesani syndrome 2, dominant [OMIM ID: 608328] Marfan syndrome [OMIM ID: 154700]	Autosomal Dominant	Uncertain significance PM2, PM1 & PP2

- *AR-- ADAMTS10/ 17*
- *AD -- FBN1 has* Cardiac problem




SERUM HOMOCYSTINE

Homocystine (Enzymatic recycling)	47.9	4-12 mmol/L

Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
CBS NM_000071.3	c.572C>T p.Thr191Met	Homozygous	Exon 7	Homocystinuria, B6-responsive and nonresponsive types / Thrombosis, hyperhomocysteinemic [OMIM ID: 236200]	Autosomal Recessive	Likely pathogenic PM2, PM5, PP2, PP3, PP5

Inherited metabolic condition, broken and curled zonules, intellectual disability, **risk of venous thrombosis**

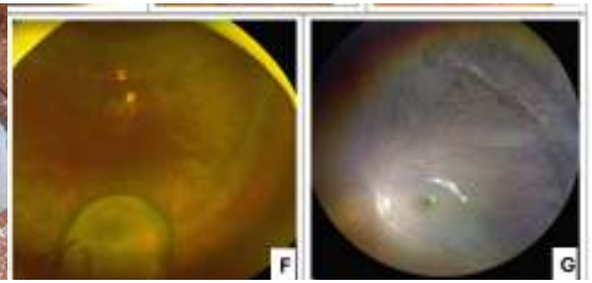
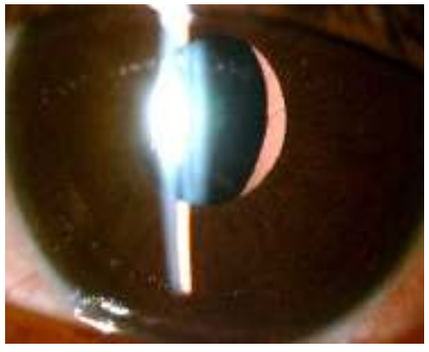


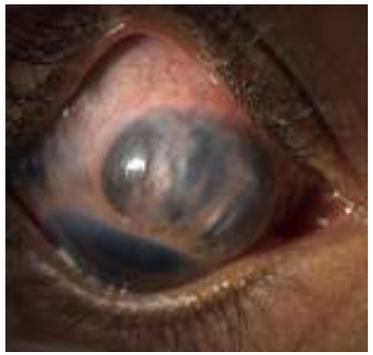
Table 1 : Likely Pathogenic Variant							
Gene	Genomic Position	Variant change	Zygosity/ Inheritance	Seq. Depth	Variant type	Exon	Associated Disorders
LTBP2	Chr14: 74975560	c.C3499T/ p.Gln1167Ter	Homozygous/ Autosomal Recessive	53x Ref:0 Alt:53	stopgain	23	Microspherophakia and/or megalocornea, with ectopia lentis and with or without secondary glaucoma

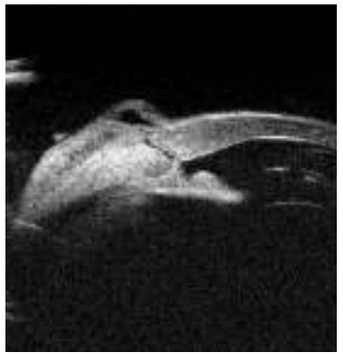
- No Glaucoma surgery
- Early lensectomy
- Risk of RD

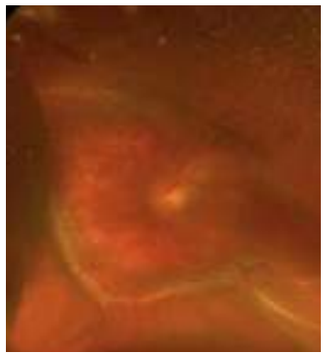


Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
ASPH NM_004318.4	c.2181_2183dupATG p.Val727_Trp728insTer	Homozygous	Exon 25	Traboulsi syndrome [OMIM ID: 601552]	Autosomal Recessive	Likely pathogenic PM2, PVS1_Strong & PP5

- Cardiac problem – dissecting aortic aneurysm can be life threatening







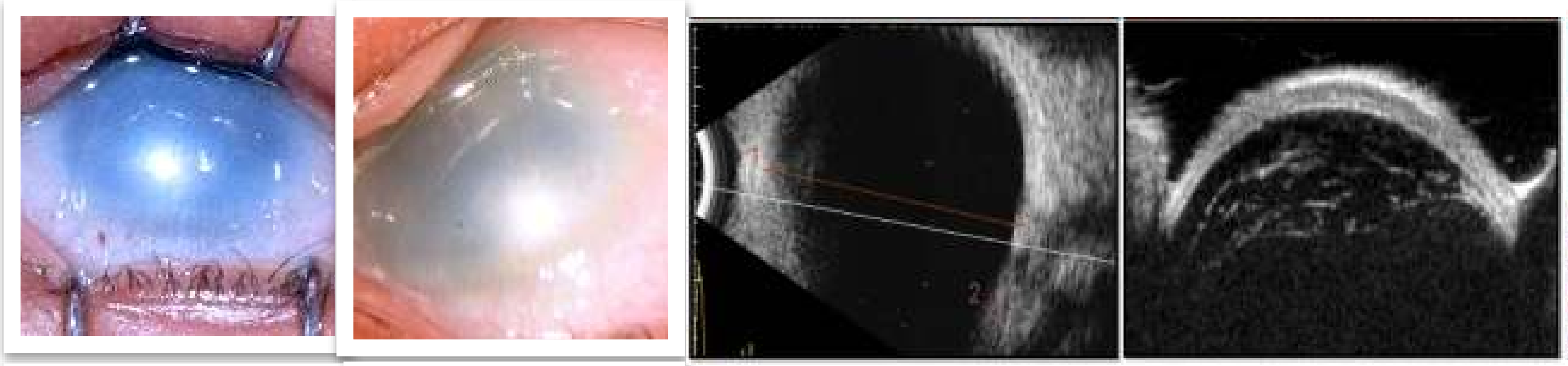
- Scleral defects with any intervention

While ECTOPIA LENTIS needs lensectomy……

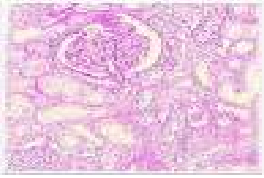
Understand the underlying genetic etiology is important

- ✓ Retinal detachment in Marfan
- ✓ Cardiac problem in FLAB, Marfan and WMS
- ✓ Homocystenemia—DVT and strokes
- ✓ Avoid scleral incisions in FLAB, SCLERAL REPAIR for Hypotony
- ✓ Avoid glaucoma surgery in *LTBP2*

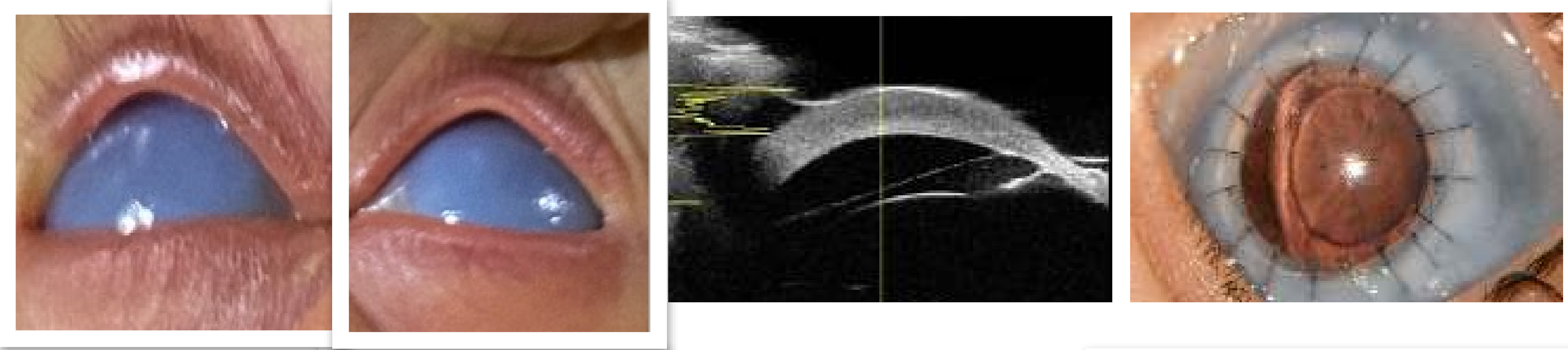
Appropriate diagnosis and prognostication!



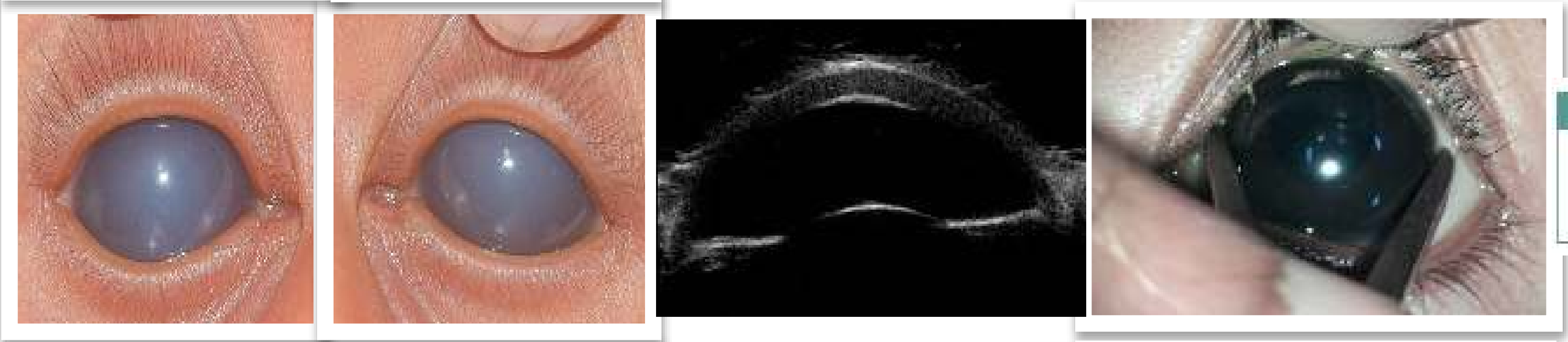
Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
PAX2 NM_000278.5	c.922C>T p.Arg308Cys	Heterozygous	Exon 8	Papillorenal syndrome [OMIM ID: 120330]	Autosomal Dominant	Uncertain significance PM2, PP2 & PP3



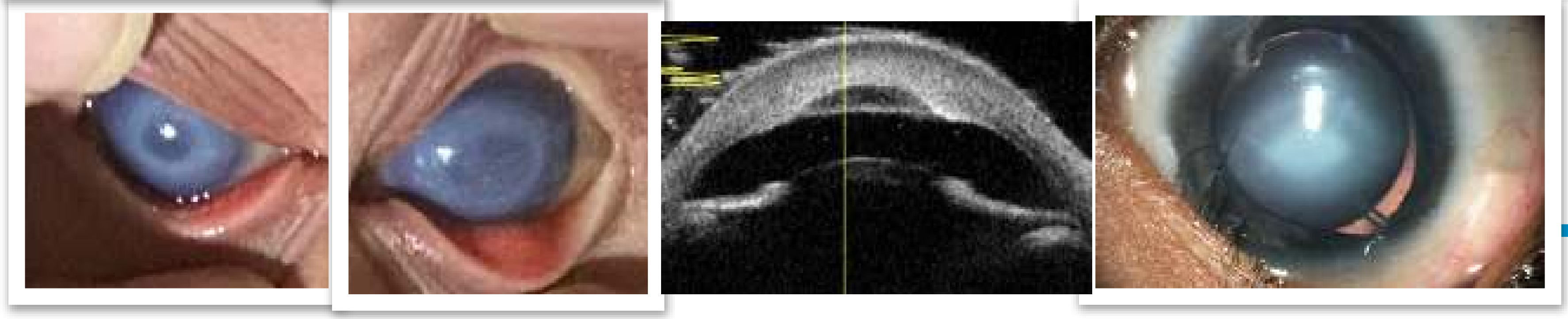
Focal segmental glomerulosclerosis (FSGS),



Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
PITX2 NM_000325.6	c.601_604dupTTCC p.Pro202fs*51	Exon 3	Heterozygous	NA	ANTERIOR SEGMENT DYSGENESIS 4; ASGD4:137600	Autosomal Dominant	Likely Pathogenic

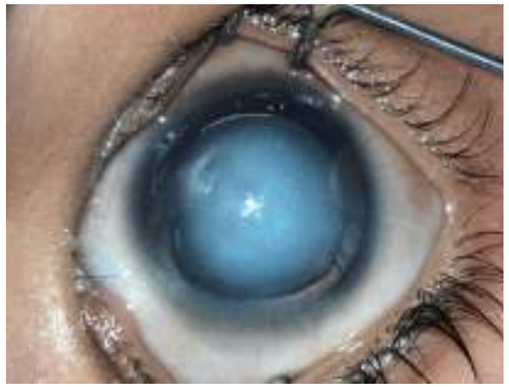


Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
CYP1B1 NM_000104.4	[illegible] p.Arg368His	Heterozygous	Exon 3	Glaucoma 3A, primary open angle, congenital, juvenile, or adult onset [OMIM ID: [illegible]]	Autosomal Recessive	Pathogenic PM1, PP5, PS3, PP3 & PM5
	[illegible]	Heterozygous	Exon 2			Likely pathogenic PM2 & PVS1



Gene	Genomic Position	Variant change	Zygosity/Inheritance	Seq. Depth	Variant type	Exon	Associated Disorder
CYP1B1	[illegible]	c.1168C>T / p.Arg390Cys	Homozygous / Autosomal Recessive	56x Ref=0 Alt=56	Missense	3	GLAUCOMA 3, PRIMARY CONGENITAL, A; GLC3A

Table1 : Known & Pathogenic variant(s)



Prenatal Diagnosis

Prenatal genetic testing

Family history or a previous child with a genetic condition

Parents who are known carriers of a specific genetic condition

Abu-Amero KK, Edward DP. Primary congenital glaucoma, Gene Review 2004

Chorionic villous sampling

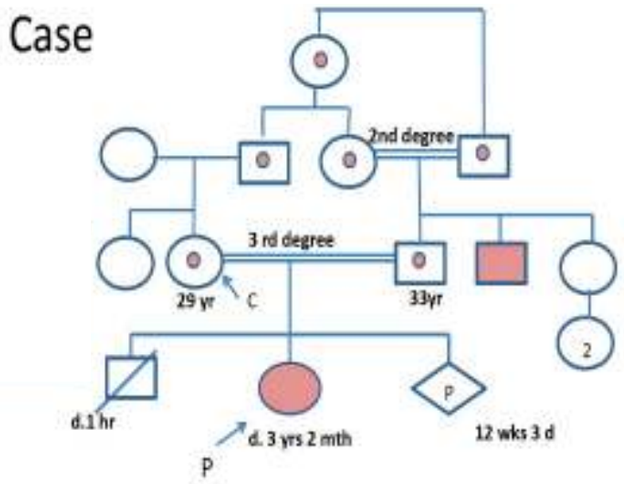
- Performed between 10.5 to 13.5 weeks of pregnancy
- Small tissue sample obtained from placenta
- Method used depends on the location of the baby and the placenta

Amniocentesis

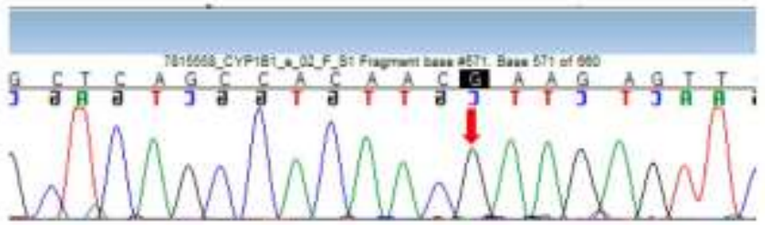
Performed from 15 weeks of pregnancy onward

Small amount of amniotic fluid is obtained

Understanding Genetics: July 8 2009



Mutations in the family and the proband needs to be known



Homozygous mutation in *CYP1B1*

- Target variant analysis in foetal DNA

RESULT SUMMARY

Analysis for the variant detected by Sequencing in the *CYP1B1* gene of the index patient, Baby Kokkera Manaswi

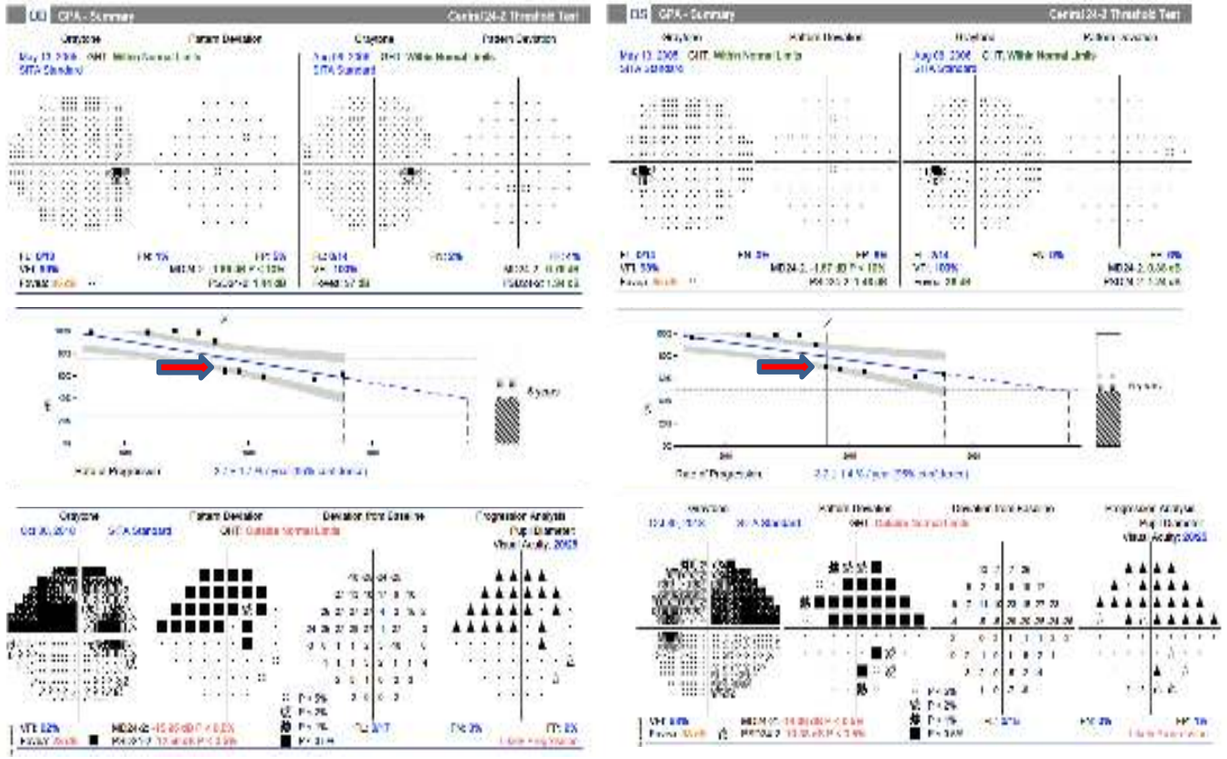
Sl. no.	Sample ID	Name, Gender, Age	Relationship to the index tested	Gene Name	Exon / Intron	Variant reported in the index patient	Variant identified in the fetus*
1.	7815558	[redacted]	To be sibling	*CYP1B1*	Exon 2	chr2:38301847 (GRCh37); c.685G>T (HOM); (p.Glu229Ter)	Absent

* The variant analysis in Sanger sequencing is based on the *CYP1B1* gene reference sequences NM_000104 [1]. The exon number and nucleotide numbers will differ based on the reference file chosen and the database used.

Reassurance
Targeted anomaly scan at 18-20 weeks
Newborn screening was done on day 3 of life

Targeted Screening

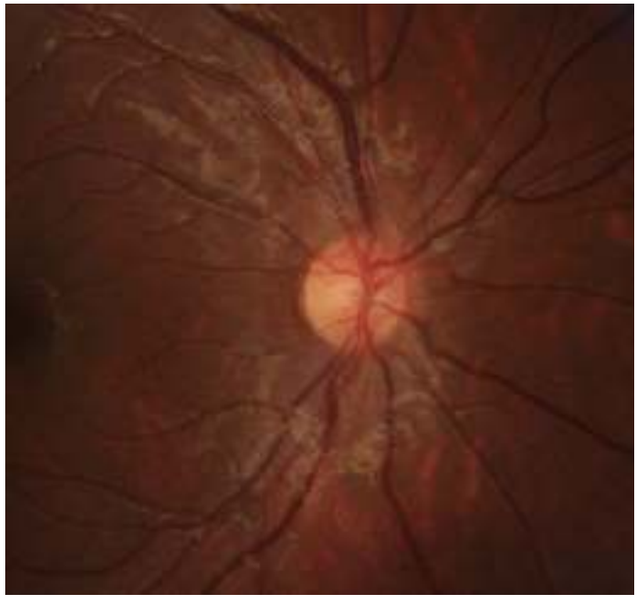
JOAG

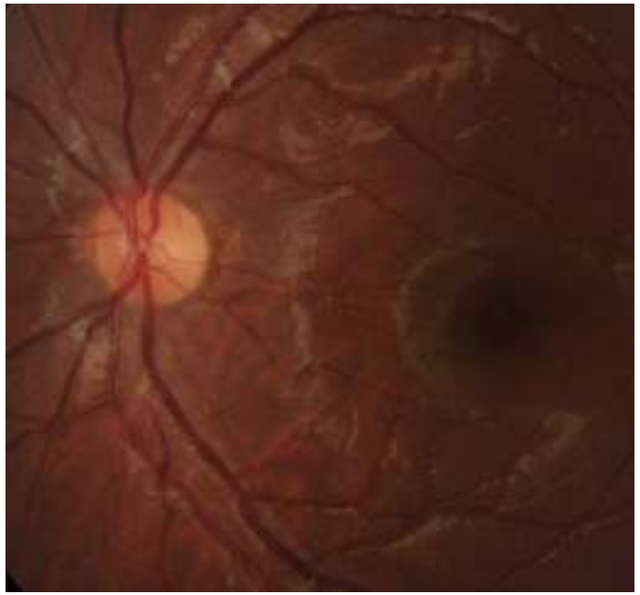


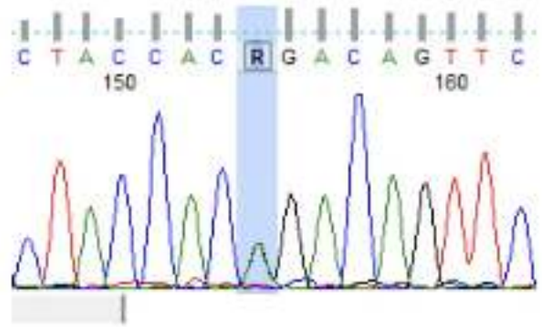
28-year-old, Progressing JOAG

Gene Name	Variant Reported in the Index Patient	Variant Status	Inheritance
MYOC	c.1099C>A (p.Gly367Arg)	Heterozygous	Autosomal Dominant

AD, *MYOC* mutation







: Sanger sequencing data (electropherogram) for the provided sample showing nucleotide change at c.1099G>A (p.Gly367Arg) in MYOC gene.

2 children screened at the age of 6 and 7 years, one tested positive

Recommendation:

Targeted periodic screening of the child with *MYOC* mutation for early diagnosis of JOAG

Device new treatment methods to prevent devastating complications!!

15-year-old boy

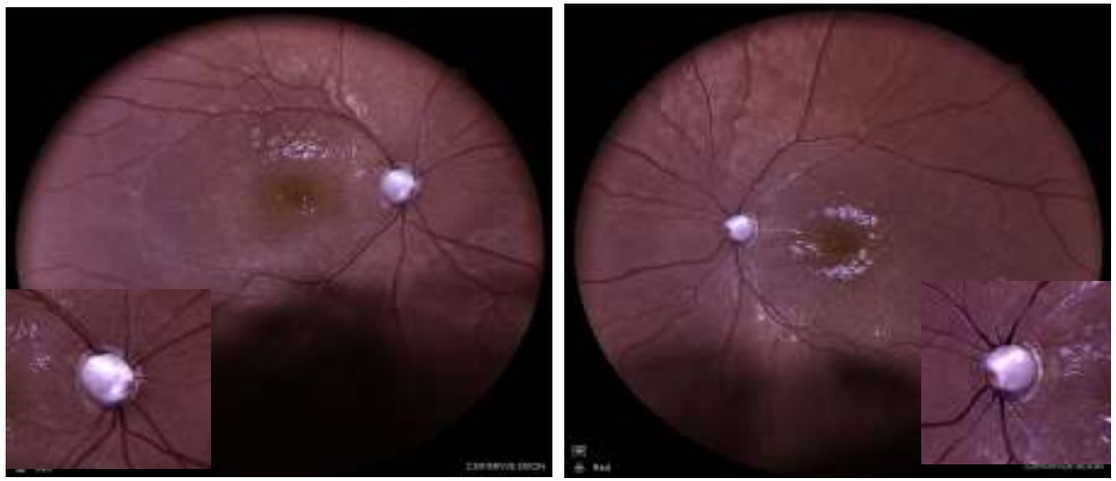
Decreased vision for 2 years

- Referred as JOAG for surgery

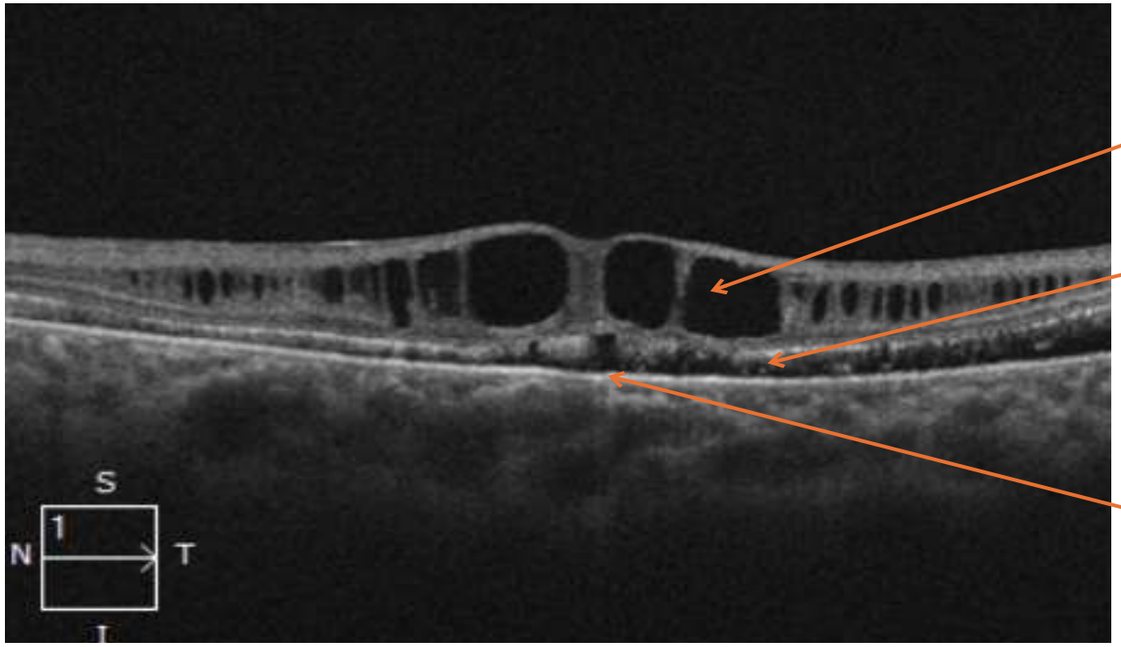
5 topical AGM and Oral Diamox TID

- PL PR inaccurate RE, 20/200 in LE

- High IOP despite MMT
- CLOSED angles
- Advanced disc damage, dull macula



Advanced Disc damage with deep cupping



Macular OCT revealed retinal layer schisis with cystoid fluid collections

thickened photoreceptors parafoveally, loss of photoreceptors sub-foveally

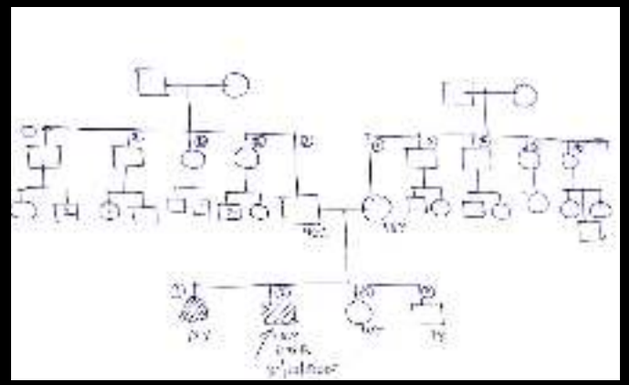
Serous subretinal fluid/ SRF like cavity

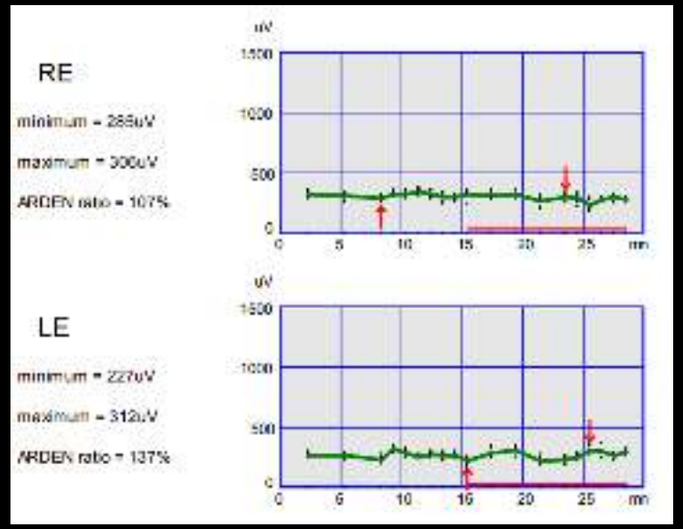
Secondary angle closure and ?
Bestrophinopathy

Stepped up AGM

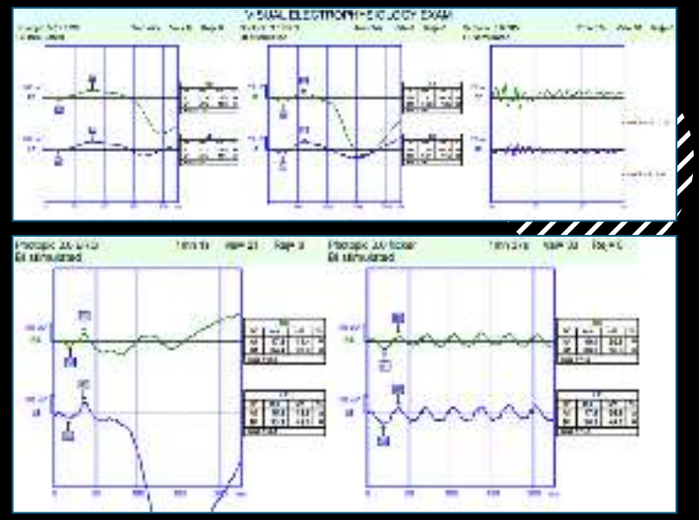
ERG and EOG

Genetic counseling and testing



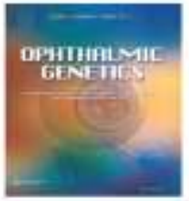


Severe reduction of light peak-to-dark trough ratio (Arden ratio) < 1.65 or 165 % Indicating severe generalized RPE dysfunction



Dark and light adapted responses area affected Indicating generalized rod and cone dysfunction

Gene & Transcript	Variant	Zygosity	Location	Disorder	Inheritance	ACMG Classification
BEST1 NM_004183.4	c.169G>T p.Glu57Ter	Heterozygous	Exon 3	Bestrophinopathy, autosomal recessive [OMIM ID: 611809]	Autosomal Recessive	Pathogenic PM2, PVS1 & PP5
	c.418C>G p.Leu140Val	Heterozygous	Exon 4			Likely pathogenic PM1, PM2, PM5, PP2, PP3 & PP5



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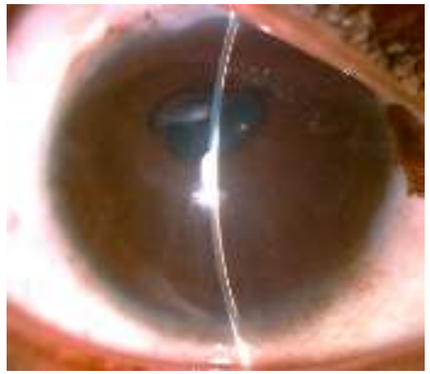

Taylor & Francis

RESEARCH ARTICLE

BEST1 associated bestrophinopathies with angle closure and post-surgical malignant glaucoma

Deepika C. Parameswarappa[a], Jeyapoorani Balasubramnian[b], Srikanta Kumar Padhy[c], Saurang Hemraj[d], Ramya Natarajan[b], Chitra Kannabiran[e], Chandrasekhar Garudadri[f], and Sirisha Senthil[g]

[a]Srimati Kanuri Santhamma Center for Vitreoretinal Diseases, Anant Bajaj Retina Institute, L V Prasad Eye Institute, Hyderabad, India; [b]Department of Ocular Genetic Counseling, L V Prasad Eye Institute, Hyderabad, India; [c]Vitreoretina and Uveitis Services, Anant Bajaj Retina Institute, L V Prasad Eye Institute, Bhubaneswar, India; [d]Department of Ophthalmic Biophysics, L V Prasad Eye Institute, Hyderabad, India; [e]Kallam Anji Reddy Molecular Genetics Laboratory, L V Prasad Eye Institute, Hyderabad, India; [f]VST Center for Glaucoma Care, L V Prasad Eye Institute, Hyderabad, India

Introduction: Mutations in *BEST1* gene have been linked to the development of refractory angle closure glaucoma (ACG). This study aims to delineate the clinical characteristics, genetic mutations, and disease progression in patients with autosomal recessive bestrophinopathy (ARB) and autosomal dominant Best vitelliform macular dystrophy (BVMD) who are presented with treatment-resistant ACG.

Methods: This retrospective analysis encompasses a comprehensive ophthalmic assessment, retinal imaging, and mutational profiling of six patients diagnosed with bestrophinopathy and concurrent ACG, with a particular emphasis on the risk of post-glaucoma filtration surgery malignant glaucoma (MG). Exome sequencing was conducted utilizing a next generation sequencing (NGS) based gene panel.

Results: The cohort included five patients with ARB and one with BVMD, with a mean (±SD) age at ACG diagnosis of 35.1 ± 6.8 years. NGS analysis revealed homozygous *BEST1* variants in four patients (ARB; cases 1–4) and a heterozygous *BEST1* variant in one patient (BVMD; case 5). One patient (ARB; case 6), despite a recessive pedigree, showed a single heterozygous variant, suggesting the presence of an undetected heterozygous variant indicative of compound heterozygous autosomal recessive inheritance. A novel non-frameshift deletion (c.841_843delTTC; p.Phe281del) was identified in case 2. Surgical intervention was required due to uncontrolled glaucoma in all cases except case 4. All five cases that underwent glaucoma filtration surgery developed MG, which was effectively managed with combined trifecon/ab-hyaloido-vitrectomy (ZIHV) and pars plana vitrectomy (PPV). Cases 5 and 6, harboring a heterozygous pathogenic variant (c.241 G>A; p.Val81Met), experienced refractory MG and corneal decompensation necessitating multiple interventions.

Conclusion: Genetic analysis plays a pivotal role in the management of bestrophinopathies with ACG. Characterization of mutational types facilitates prognostication and enables timely interventions. IZHV with PPV emerges as a promising standalone or adjunctive procedure for the management of glaucoma among patients with *BEST1* mutations and ACG.

ARTICLE HISTORY
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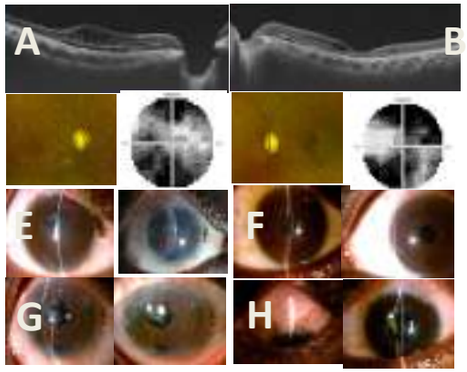
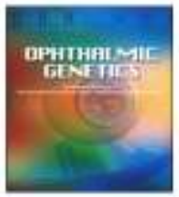
KEYWORDS
BEST1; angle closure glaucoma; bestrophinopathy; malignant glaucoma





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A paradigm shift in the treatment of refractory angle closure glaucoma in a patient with X-linked juvenile retinoschisis

Sirisha Senthil, Deepika C Parameswarappa & Jeyapoorani Balasubramannian

6 patients with *BEST1* ass bestrophinopathy and ACG

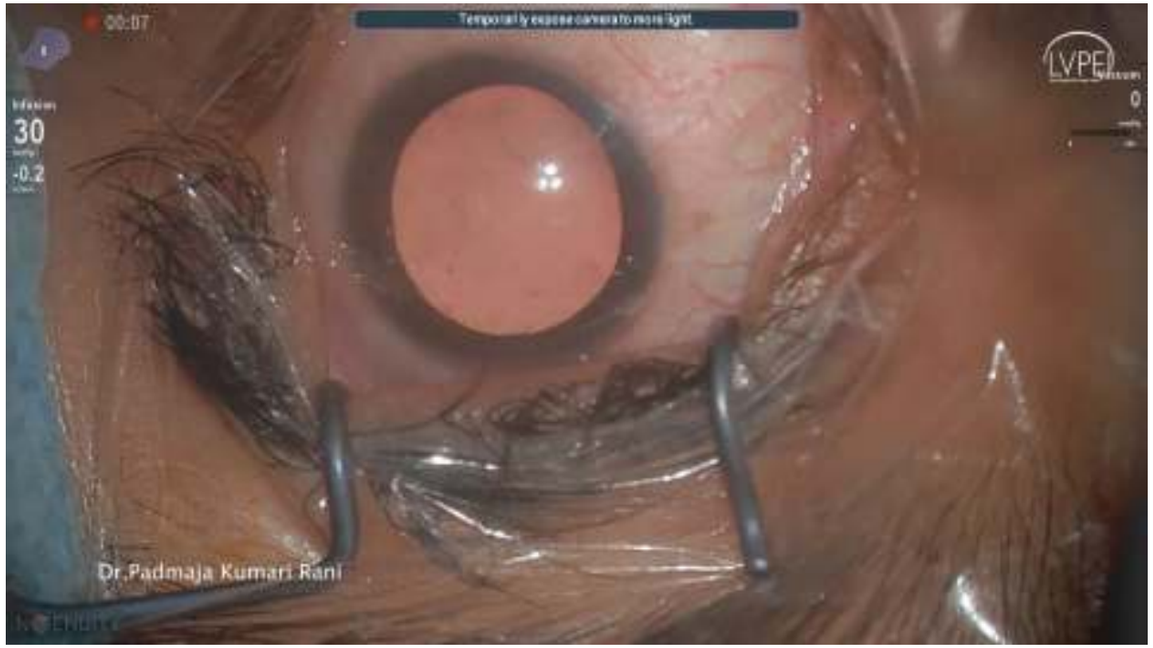
All 6 eyes had MG after GFS
Needed PPV and IZHV+/-LA

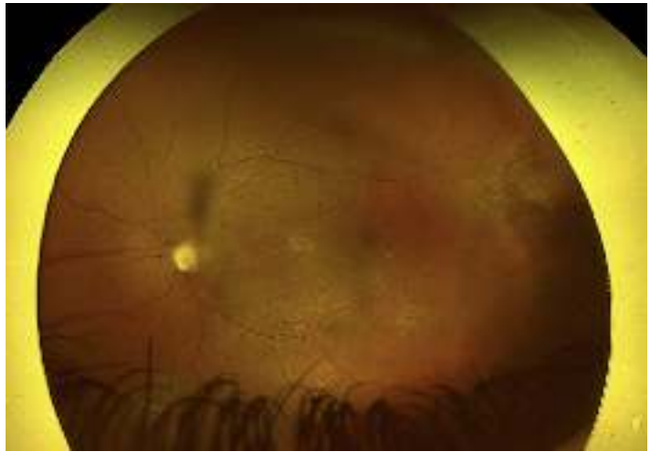
2 eyes with *BEST1* PPV and IZHV alone – NO MG and IOP controlled

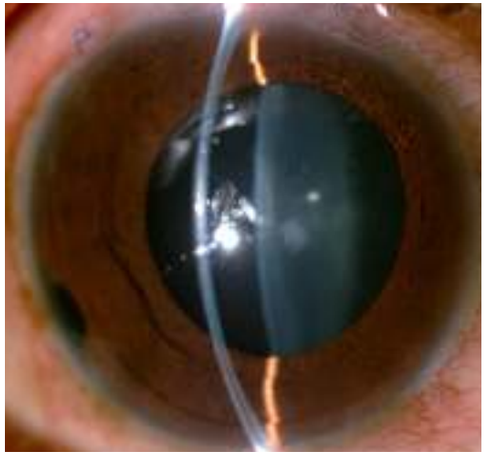
X linked retinoschisis– both eyes were treated with PPV, IZHV and CE,

no MG and IOP well controlled over 4 years now

LE PPV and IZHV

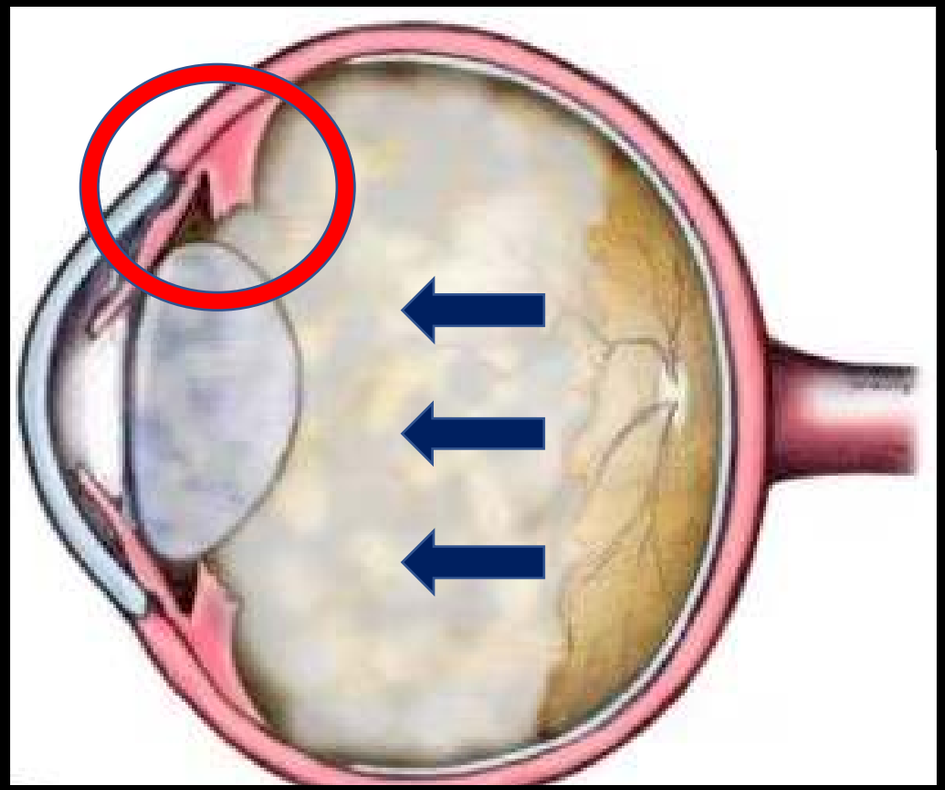






AC deep, vision stable, IOP controlled with 2 AGM

Patho-mechanism…



Progressive angle closure can be associated with inherited retinal dystrophies

Vitreoretinopathy—Thick anterior hyaloid

Forward push of iris lens diaphragm

Establish diagnosis

Clinical evaluation, retinal imaging, EOG, ERG

Genetic testing and Counseling are crucial

Malignant Glaucoma is 100%
PPV + IZHV +/ - GFS and/or adjunctive lens aspiration

Summary

Genetic testing helps..

- Appropriate Ocular diagnosis
- Risk of life-threatening systemic/ syndromic conditions
- Tailor or modify treatment
- Prenatal testing for prevention and targeted screening

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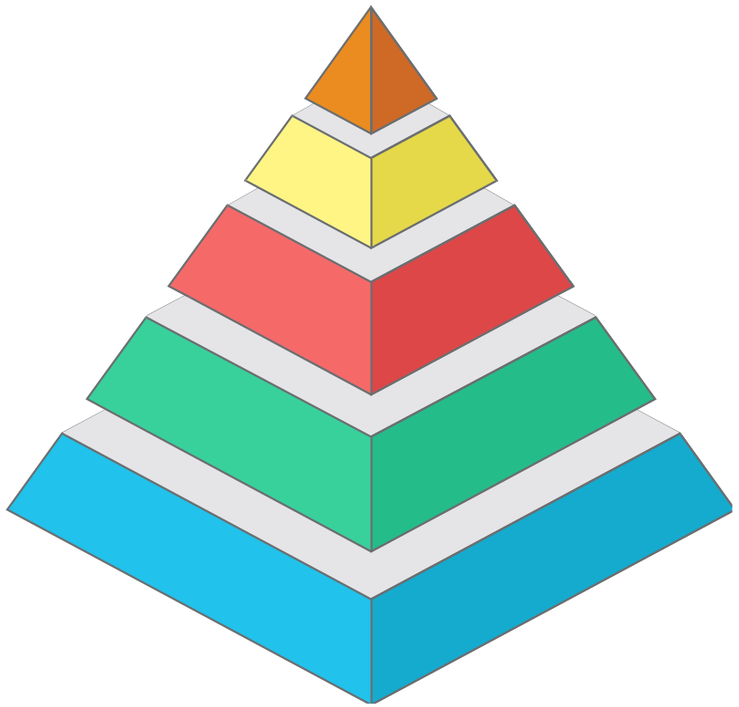
So that all may see

L V Prasad Eye Institute



Thank You