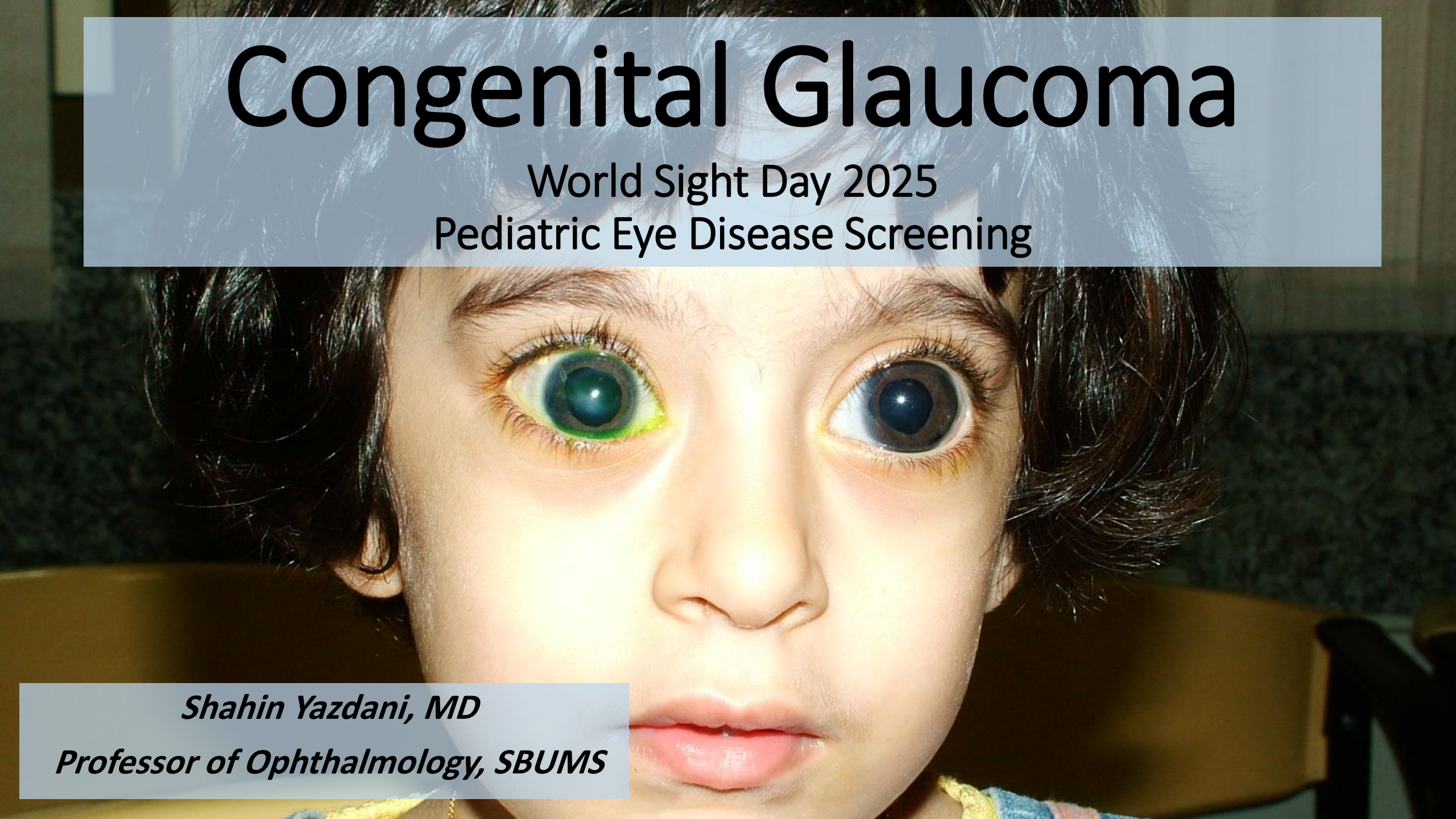
Congenital Glaucoma

World Sight Day 2025
Pediatric Eye Disease Screening

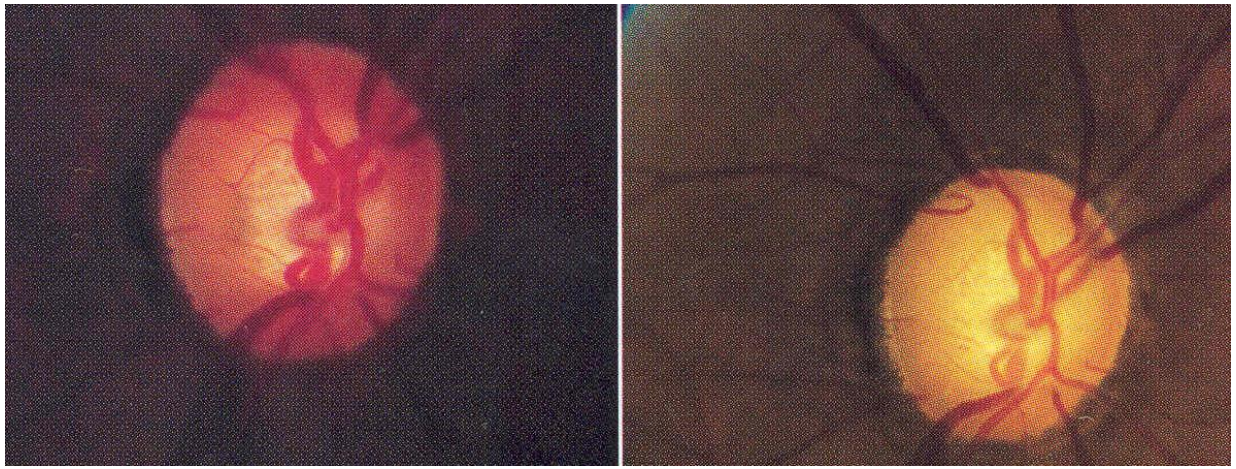


Shahin Yazdani, MD

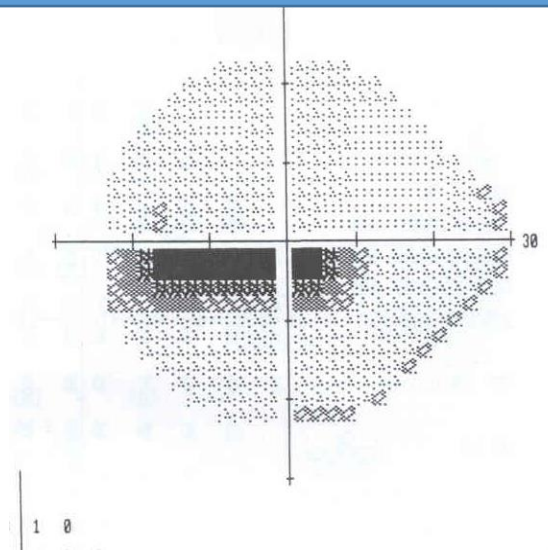
Professor of Ophthalmology, SBUMS

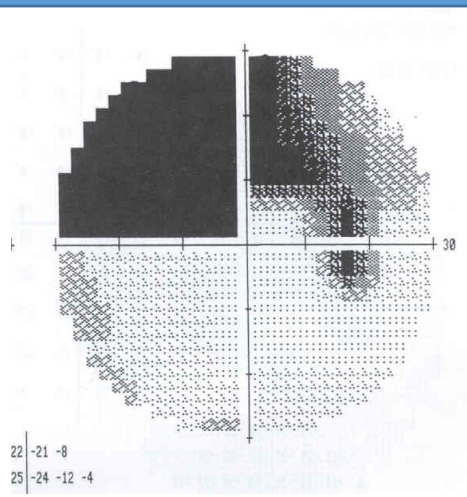
Glaucoma

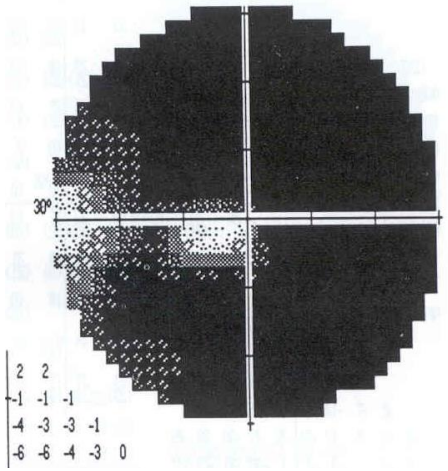
- The leading cause of **irreversible blindness** worldwide
- Glaucoma blindness is **preventable**
- A **lifelong but manageable** disease
- Most prevalent in adults over 40 years of age
- Age dependent increase in prevalence



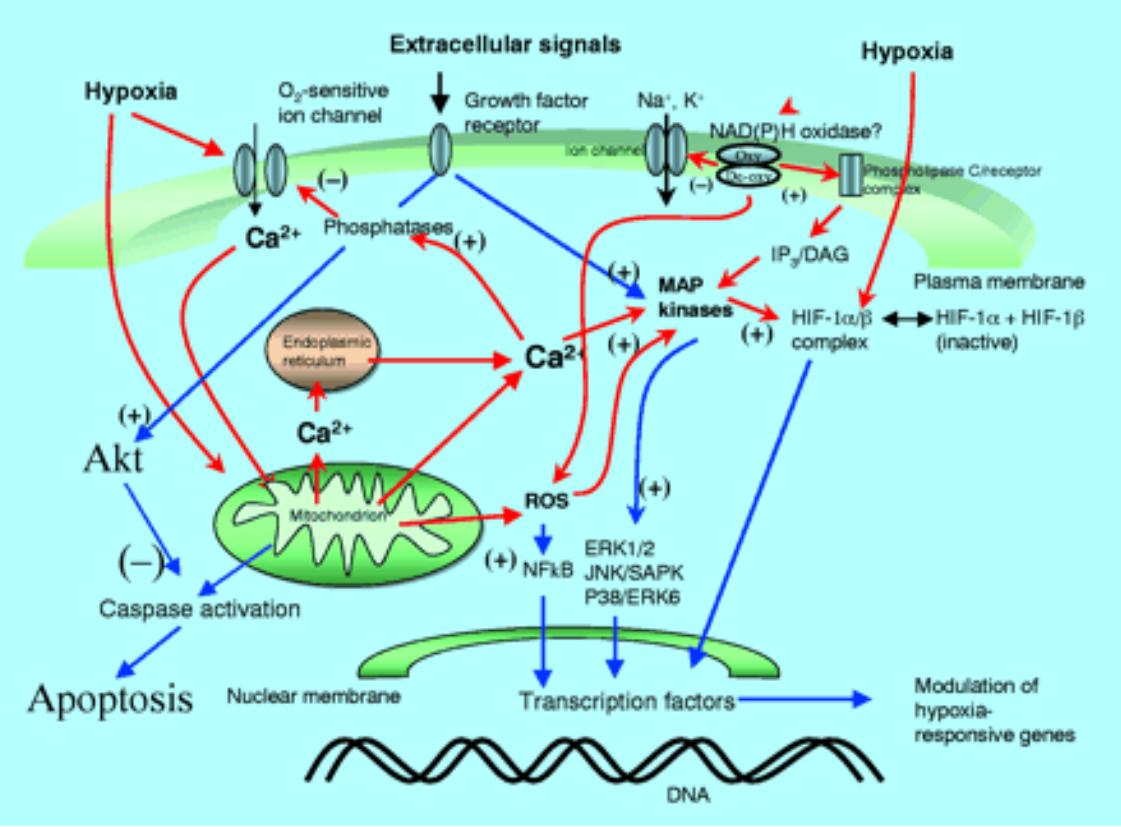
A chronic optic neuropathy with a characteristic pattern of damage leading to loss of visual function.

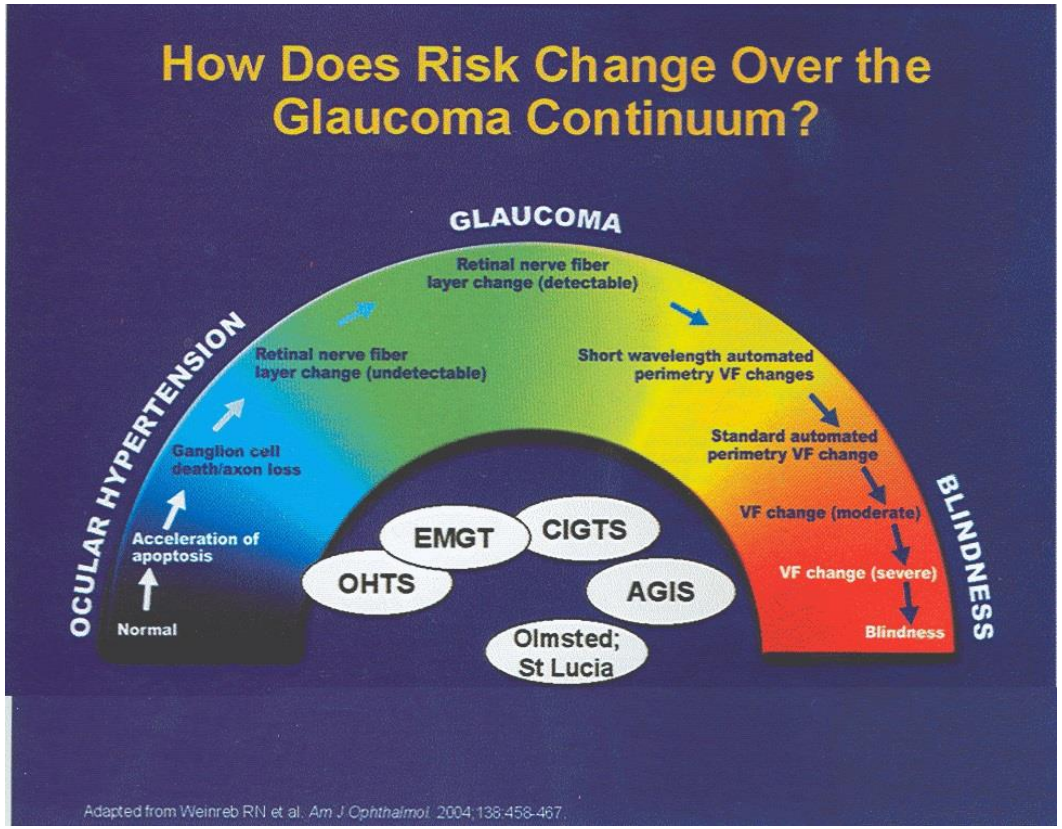




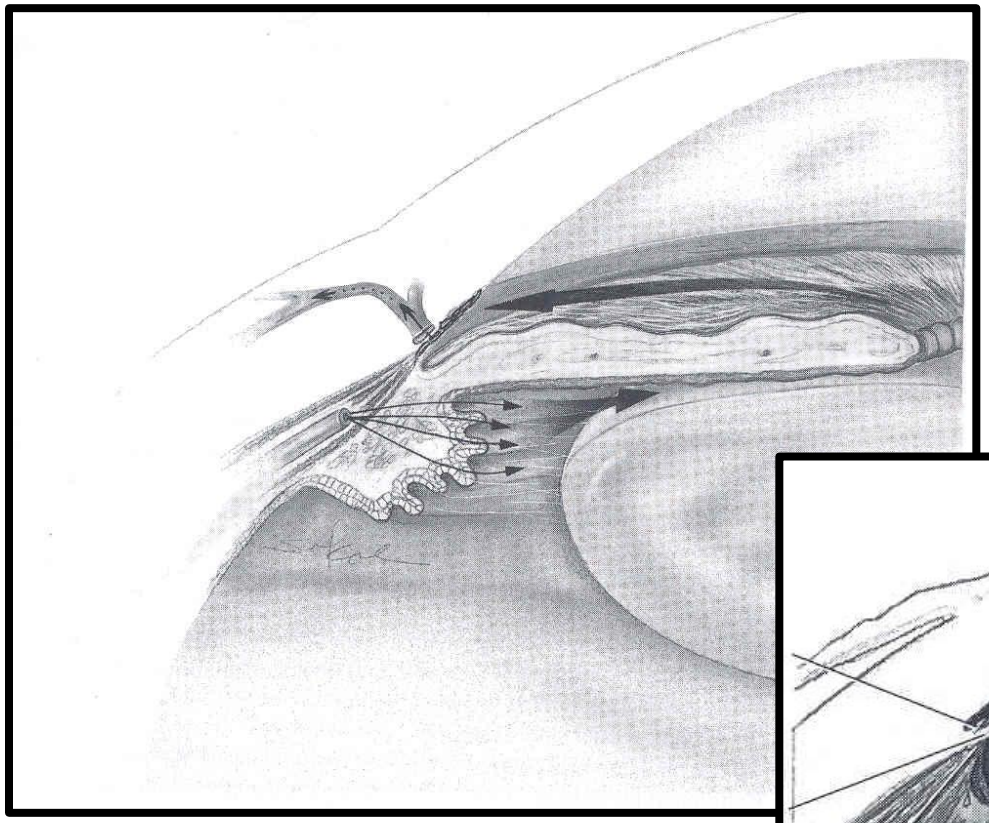


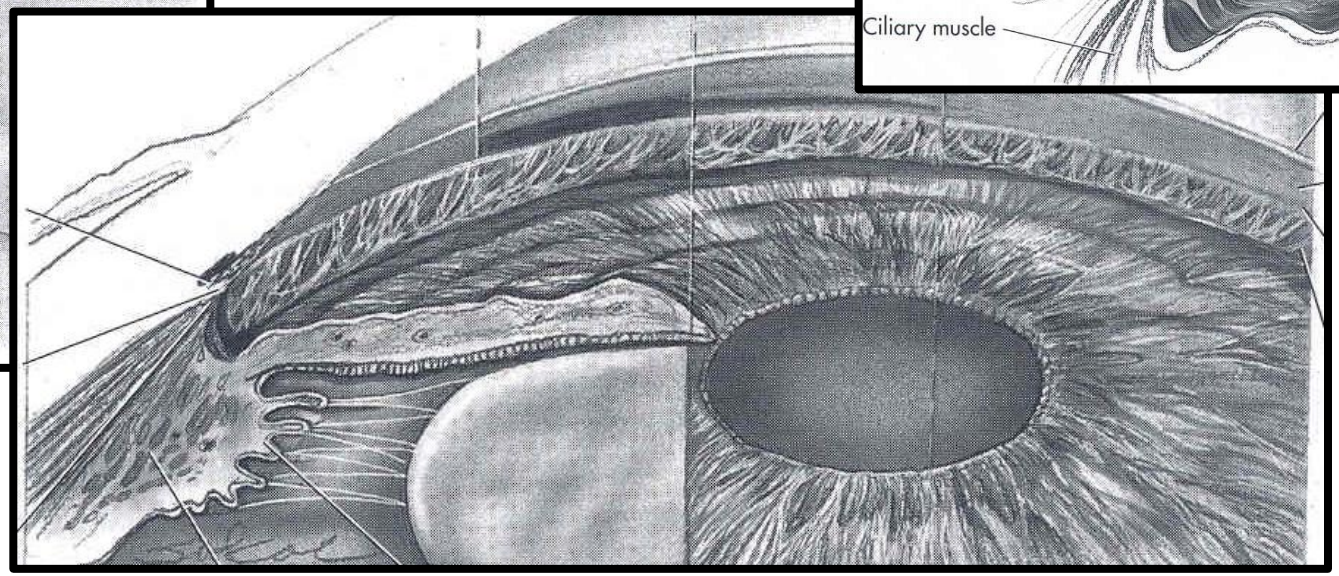
A multifactorial disease BUT the most well known and preventable risk factor is elevated IOP.

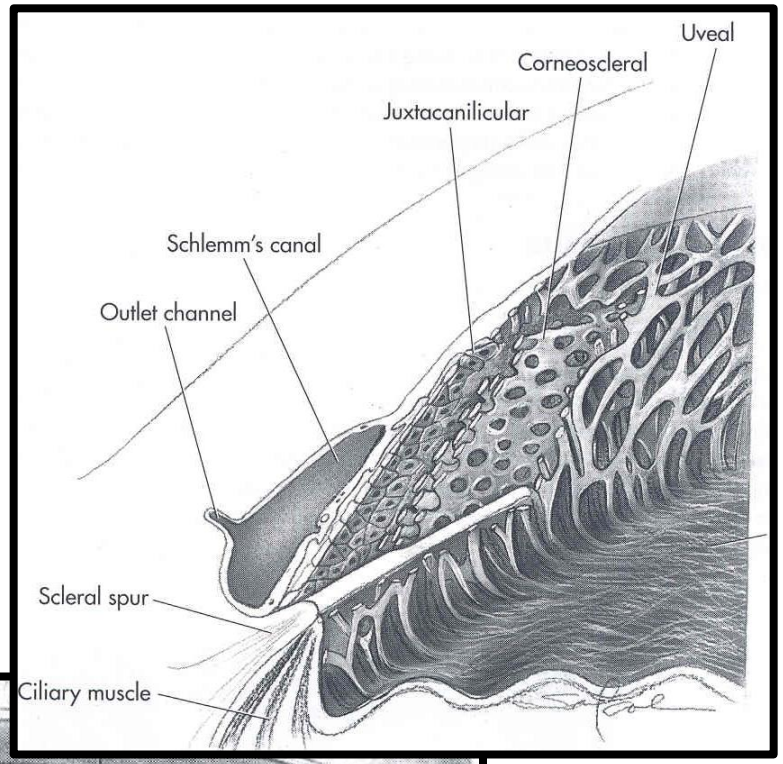




Normal aqueous production and outflow







Childhood glaucoma

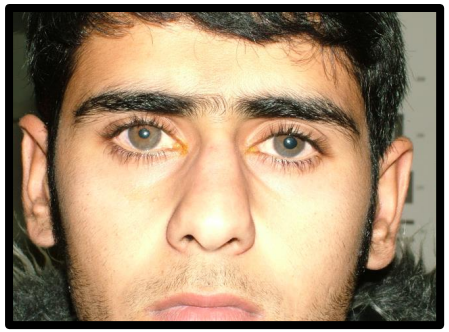
- A
- C
- D
- B

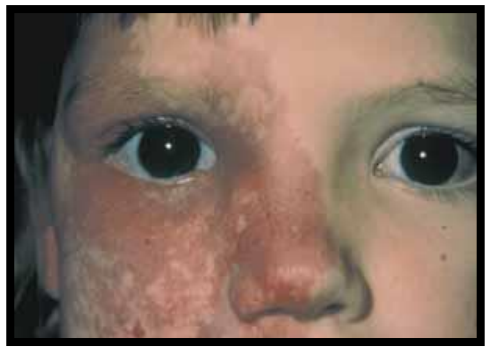
By nature, childhood glaucoma is more difficult to treat and entails a worse prognosis; reasons include:

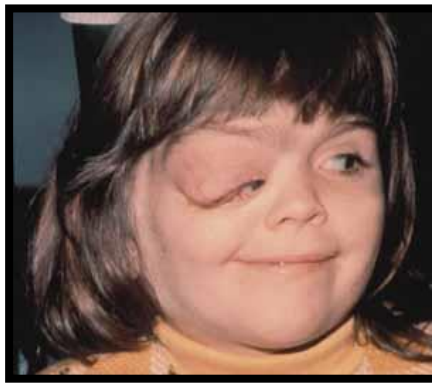
- **More severe structural abnormalities**
- **Concomitant ocular or systemic issues**
- **Induction of refractive errors and amblyopia**
- **Difficulty in diagnosis and challenges in F/U**
- **Less ideal response to medications and problems with side effects**
- **Less ideal response to surgery due to rapid healing response**

Childhood glaucoma (CGRN Criteria)

- **Primary**
  - Neonatal 25%
  - Late onset 10%
  - Infantile 65%
- **Secondary**
  - Ocular anomalies
  - Prior surgery
  - Systemic conditions







PCG in Iran

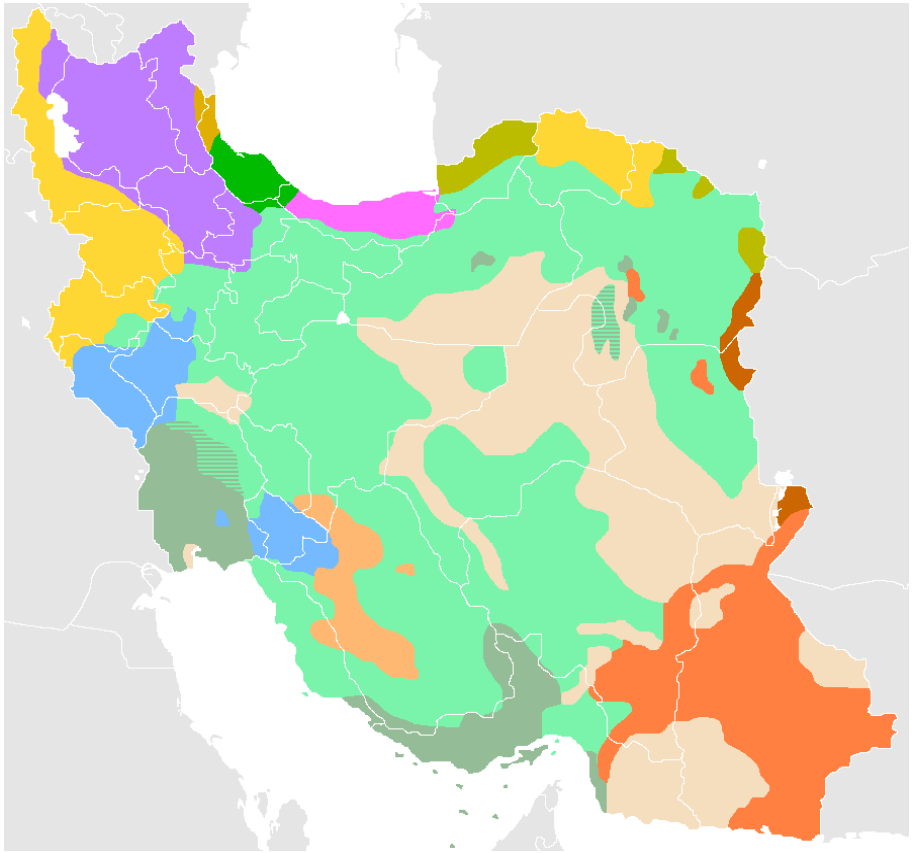
- Prevalence:
- Western countries1:10,000 : to 1;30,000
- Middle East: ↑) 1:2,500due
- Male predominance
- Mostly bilateral, although as
- Probably more severe and e countries

The incidence of PCG in Iran ???

- Burden:
- %15–7of blindness in Iranian blind schools

Ethnic constitution in Iran

Persian 51%, Azeri 24%, Gilaki and Mazandarani 8%, Kurd 7%
Arab 3%, Lur 2%, Baloch 2%, Turkmen 2%, other 1%



National Childhood Glaucoma Registry

Childhood Glaucoma Research Network (CGRN) member

- **Collaborating centers:**
- **SBMU (PI)**
- **IUMS**
- **AJUMS**
- **MUMS**

- - Demographics (age, gender, geography)
- - Clinical parameters (IOP, CDR, corneal clarity)
- - Surgical history, BCVA (LogMAR)
- Data validated by glaucoma specialists

Genetic Background

- PCG is mostly considered an autosomal recessive disorder
- CYP1B1 (and more recently LTBP2) mutations contribute to a variable proportion of the disease
- It occurs more commonly in consanguineous marriages

Rate of CYP1B1 mutations in PCG

- Range from 100 to 20%:
- 100% in Slovakia Roma
- 90% in Saudi Arabia
- 50% in Brazil and France
- 40% in India and Morocco
- 20% in Japan
- **70% in Iran**

CYP1B1 Mutation Profile of Iranian Primary Congenital Glaucoma Patients and Associa Haplotypes

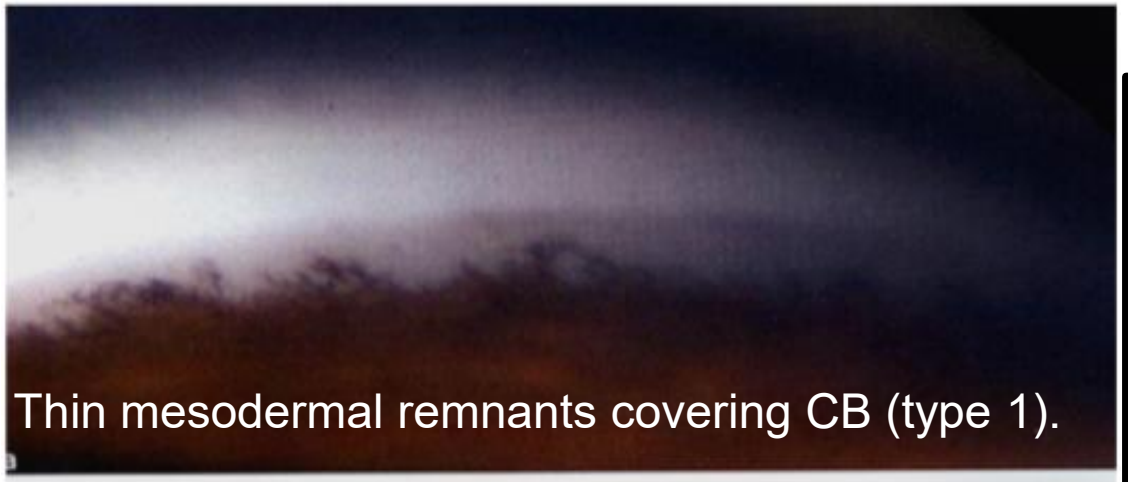
Fereshteh Chitsazian,*† Betsabeh Khoramian Tusi,*† Elahe Elahi,*‡ Hejdar Amini Saroei,§ Mohammad H. Sanati,* Shahin Yazdani,¶ Mohammad Pakravan,¶ Navid Nilforooshan,‖ Yadollah Eslami,§ Mohammad Ali Zare Mehrjerdi,§ Reza Zareei,§ Mahmood Jabbarvand,§ Ali Abdolahi,§ Ali R. Lasheyee,§ Arash Etemadi,§ Behnaz Bayat,* Mehdi Sadeghi,*‡ Mohammad M. Banoei,* Behnam Ghafarzadeh,** Mohammad R. Rohani,** Akram Rismanchian,†† Yvonne Thorstenson,‡‡ and Mansoor Sarfarazi§§

From the National Institute for Genetic Engineering and Biotechnology, Tehran, Iran; the Department of Biological Sciences† and the Bioinformatics Center,‡ Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran;*

with disease were identified. Ten mutations and three variations not associated with disease were novel. The 13 novel variations make a notable contribution to the ~70 known variations in the gene. *CYP1B1* mutations were identified in 70% of the patients. The four most common mutations were G61E, R368H, R390H, and R469W, which together constituted 76.2% of the *CYP1B1* mutated alleles found. Six unique core SNP haplotypes were identified, four of which were common to the patients with and without *CYP1B1* mutations and controls studied. Three SNP blocks determined the haplotypes. Comparison of haplotypes with those of other populations suggests a common origin for many of the mutations. *(J Mol Diagn 2007, 9:382–395; DOI: 10.2353/jmoldx.2007.060157)*

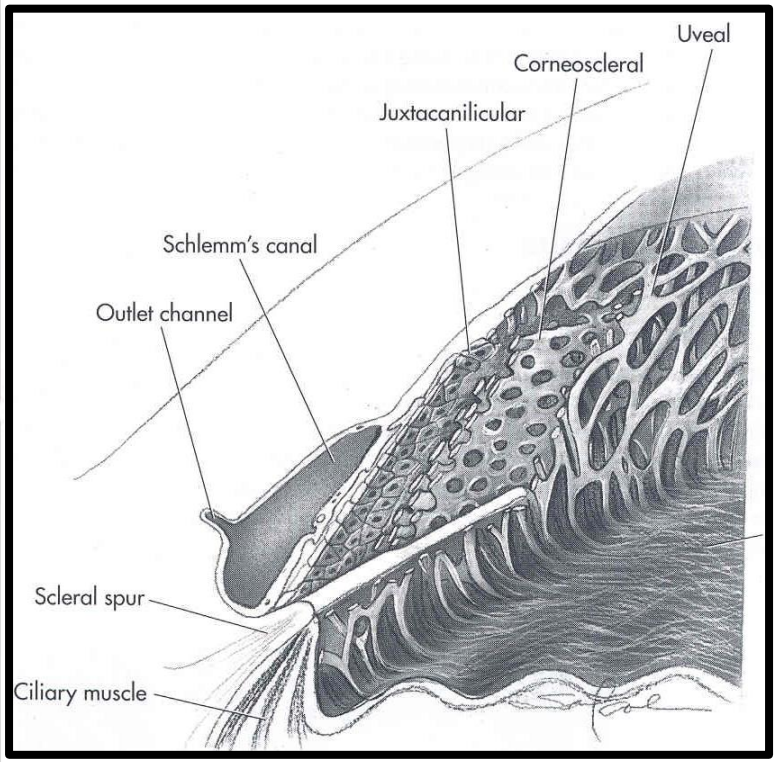
Spectrum of CYP1B1 among 104 Iranian PCG patients.

Angle dysgenesis in primary congenital glaucoma



Thin mesodermal remnants covering CB (type 1).

Apparent high iris insertion (type 2)



Is there a difference among PCG patients with or without *CYP1B1* mutations?

Genotype – Phenotype Correlation?

We assessed genotype-phenotype correlation in a subset of PCG patients with known CYP1B1 mutation profile

J Glaucoma. 2015 Jan 14. [Epub ahead of print]

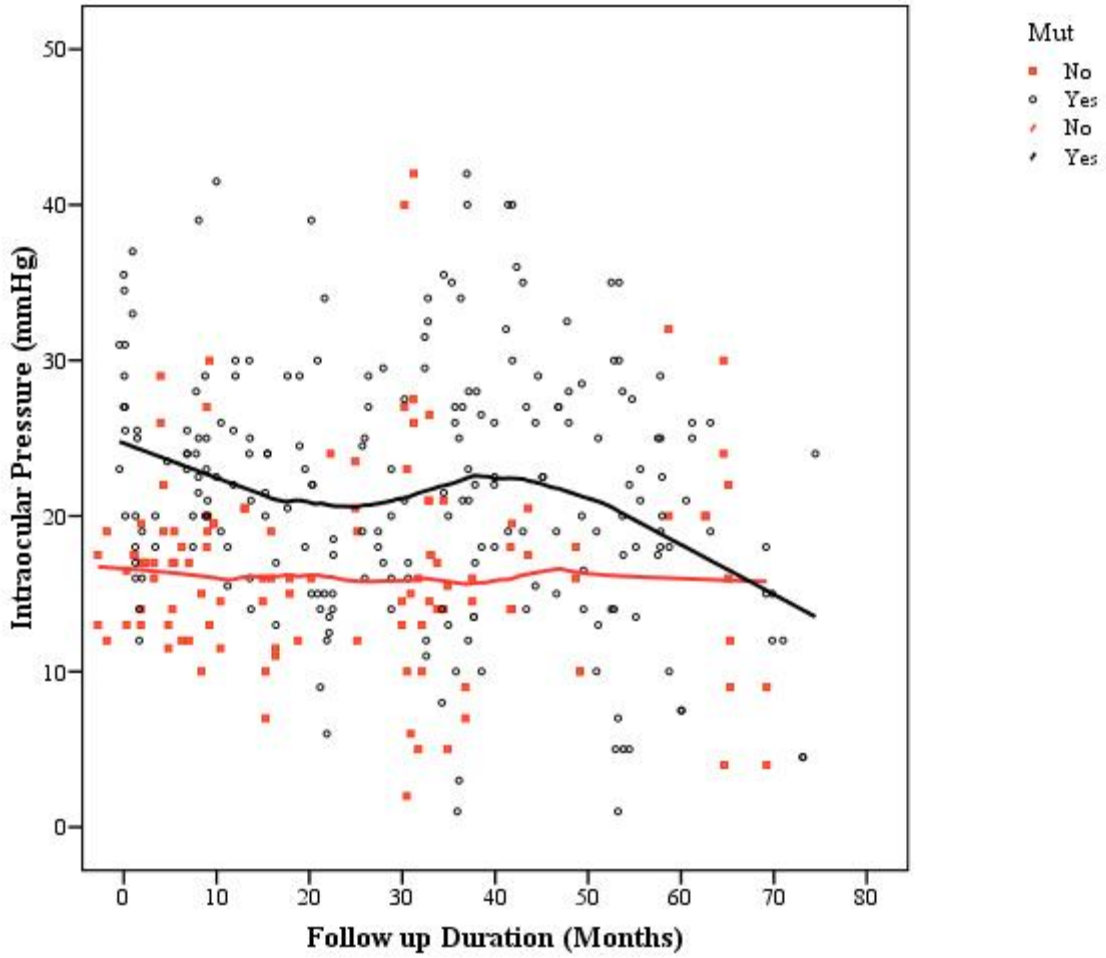
3. **Phenotype and Genotype Correlation in Iranian Primary Congenital Glaucoma Patients.**

Yazdani S[1], Miraftabi A, Pakravan M, Ghahari E, Tousi BK, Sediqh M, Yaseri M, Elahi E.

Author information

[1]*Ophthalmic Research Center, Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences †Eye Research Center, Iran University of Medical Sciences ‡School of Biology, University College of Science ||Department of Biotechnology ¶Center of Excellence in Biomathematics, School of Mathematics, Statistics and Computer Science §Department of Biostatistics and Epidemiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

IOP scatter plot throughout F/U



Is there something more to *CYP1B1* mutations apart from PCG?

Variable Expressivity and High Penetrance of *CYP1B1* Mutations Associated with Primary Congenital Glaucoma

Fatemeh Suri, MS,[1] Shahin Yazdani, MD,[2] Mehrnaz Narooie-Nejhad, MS,[3] Seyed Jalal Zargar, PhD,[1] Seyed Hassan Paylakhi, MS,[4] Sirous Zeinali, PhD,[5] Mohammad Pakravan, MD,[2] Elahe Elahi, PhD[1,6,7]

178 apparently unaffected family members of 40 unrelated probands

20 subjects carried two CYP1B1 mutations

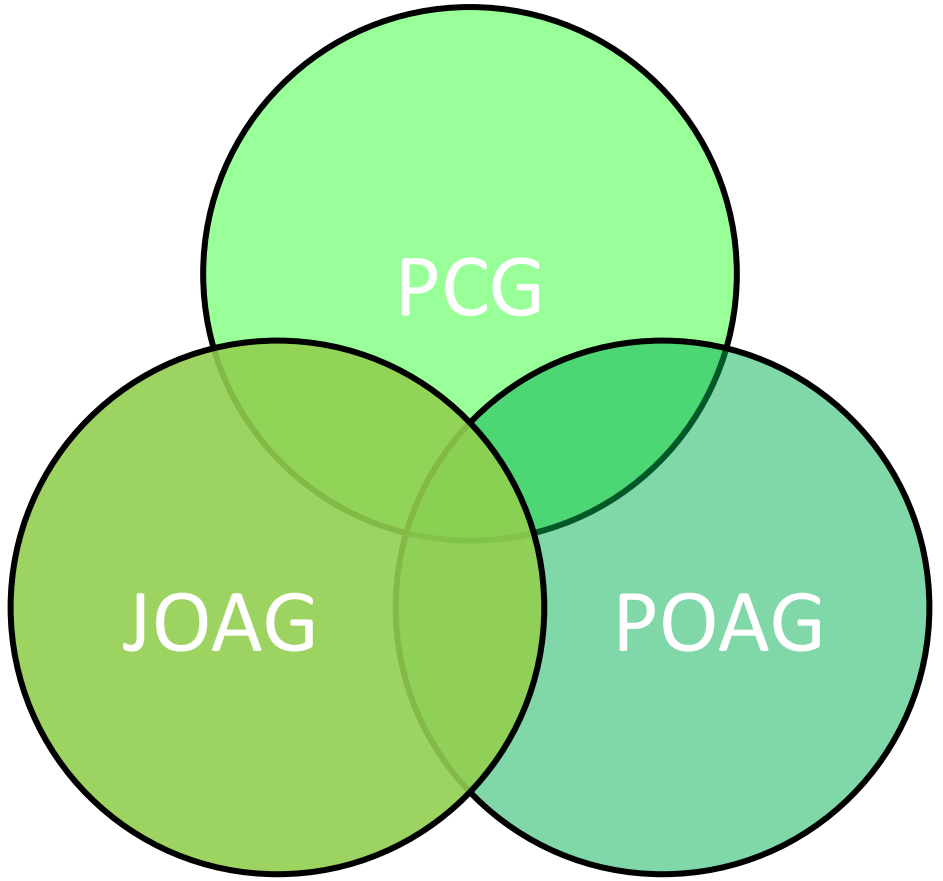
14 of 20 “normal” individuals examined

Clinical implication: seemingly unaffected relatives of patients with PCG, particularly those known to harbor *CYP1B1 mutations,* should undergo regular ophthalmologic examination to allow early diagnosis.

ng

Clinical Implications

- The genetic backgrounds of PCG, JOAG and POAG intermingle.
- CYP1B1 mutations are responsible for a wide range of glaucomas presenting from birth to the 6th decade of life, particularly JOAG.
- CYP1B1 mutations are associated with more severe disease in PCG.



The first documented case of prenatal diagnosis for PCG

Original research article

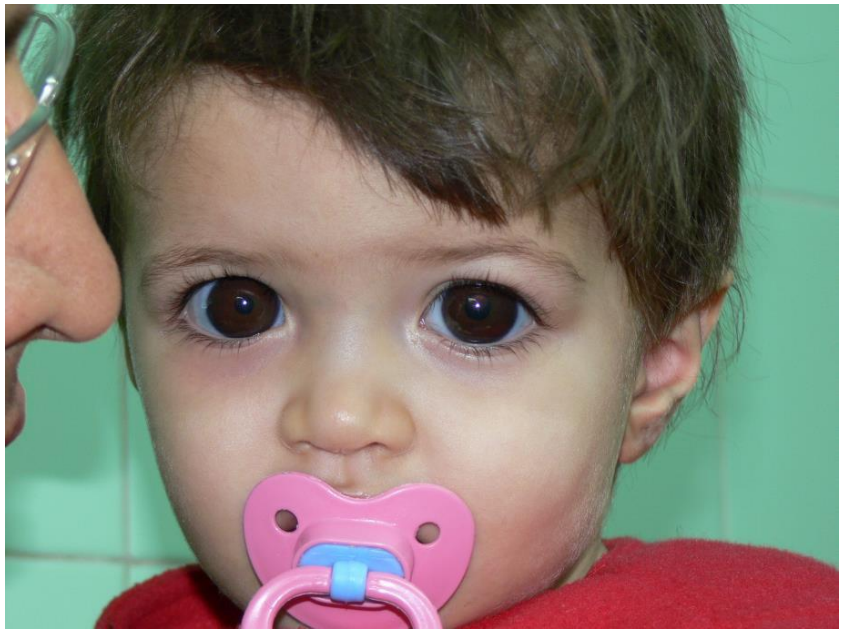
EJO European Journal of Ophthalmology

Prenatal diagnosis of primary congenital glaucoma and histopathological features in a fetal globe with *cytochrome p4501B1* mutations

Mozhgan Rezaei Kanavi[1,#], Shahin Yazdani[1,#], Elahe Elahi[2], Mehraban Mirrahimi[3], Maryam Hajizadeh[3,4], Sepideh Khodaverdi[5] and Fatemeh Suri[3]

European Journal of Ophthalmology
2022, Vol. 32(2) 933–941

DOI: 10.1177/1120672121051235
journals.sagepub.com/home/ejo
SAGE



- Non-related parents
- First child affected with CYP1B1 positive PCG
- Parents very anxious about the second pregnancy
- Strongly insisted on “taking no chances”

Proband

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(پلي كلينيك فوق تخصصي درماني تشخيصي)

Date of Answer	92/5/6	**Reason for Ref**	Glaucoma
Patient No		**Physician Name**	
Name	Erfan Siyahkolahi	**Physician Tel**	
Age and Sex	Male	**Physician Fax**	
Tel		**Physician e-mail**	

Template Type									
X	Blood		CVS		AF		Muscle		Other

Molecular Genetic Methods									
X	PCR		RFLP		ARMS		Southern		Sequencing

Results

DNA sample from the patient was investigated for the CYP1B1 gene(all the exons and exon - intron boundaries) by sequencing method. Two heterozygous mutation was found:

1) c.61 G>A (previously reported in literatures)
2) c.403 ins.tcatgccacc (previously reported in literatures)

So, the patient may be suffering from this type of glaucoma in compound heterozygote state further investigation is needed to prove it.

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تخلام پزشکی آ-۱۴۳۳
Dr. M. Houshmand

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Father

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مـركـز پـزشكي خـاص

(پلي كلينيك فوق تخصصي درماني تشخيصي)

Date of Answer	92/5/28	**Reason for Ref**	Glaucoma, CYP1B1-related
Patient No		**Physician Name**	
Name	Mahmoud Siahkolahi	**Physician Tel**	
Age and Sex	Male	**Physician Fax**	
Tel		**Physician e-mail**	

Template Type									
X	Blood		CVS		AF		Muscle		Other

Molecular Genetic Methods									
X	PCR		RFLP		ARMS		Southern		Sequencing

Results

DNA sample from the case was investigated for the CYP1B1 gene (for known familial mutation:c.61 G>A and c.403 ins tcatgccacc) by sequencing method. A heterozygous mutation as c.61 G>A was found. **So the case is likely to be carrier for CYP1B1-related Glaucoma.**

Massoud Houshmand (Ph.D)

دکتر مسعود هوشمند

تنظام پزشکی ۱۴۳۳

Dr. M. Houshmand

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Mother

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(پـلـي كـلـيـنـيـك فـوق تخصصي درمـانـي تـشخيصي)

Date of Answer	92/5/28	**Reason for Ref**	Glaucoma, CYP1B1-related
Patient No		**Physician Name**	
Name	Mahboubeh Naderi	**Physician Tel**	
Age and Sex	Female	**Physician Fax**	
Tel		**Physician e-mail**	

Template Type									
X	Blood		CVS		AF		Muscle		Other

Molecular Genetic Methods									
X	PCR		RFLP		ARMS		Southern		Sequencing

Results

DNA sample from the case was investigated for the CYP1B1 gene (for known familial mutation:c.61 G>A and c.403 ins tcatgccacc) by sequencing method. A heterozygous mutation as c.403 ins tcatgccacc was found.

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So the case is likely to be carrier for CYP1B1-related Glaucoma.

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CVS from fetus

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(پلی کلینیک فوق تخصصی درمانی و تشخیصی)

Date of Answer	92/12/7	**Reason for Ref**	Glaucoma, CYP1B1-related
Patient No		**Physician Name**	
Name	Mahboubeh Naderi(CVS)	**Physician Tel**	
Age and Sex		**Physician Fax**	
Tel		**Physician e-mail**	

Template Type									
	Blood	X	CVS		AF		Muscle		Other

Molecular Genetic Methods									
X	PCR		RFLP		ARMS		Southern		Sequencing

Results

DNA sample from the CVS was investigated for the CYP1B1 gene (for known familial mutation:c.61 A>G and c.403 ins tcatgccacc) by sequencing method.Two heterozygous mutations as c.403 ins tcatgccacc and c.61 A>G was found. **So the fetus is very likely to be suffering from CYP1B1-related Glaucoma in compound heterozygous state.**

DNA sample from the CVS was investigated for the CYP1B1 gene (for known familial mutation:c.61 A>G and c.403 ins tcatgccacc) by sequencing method.Two heterozygous mutations as c.403 ins tcatgccacc and c.61 A>G was found. **So the fetus is very likely to be suffering from CYP1B1-related Glaucoma in compound heterozygous state.**

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قوه قضاییه
سازمان پزشکی قانونی کشور

اداره کل پزشکی قانونی استان ....

برگ درخواست مشاوره پزشک

محل الصاق یا چاپ عکس

شماره پرونده :

تاریخ ۹۲/۱۲/۷
شماره ....
پیوست ....

ریاست محترم بیمارستان ....
جناب آقای / خانم دکتر چشم پزشک مطلع

نامبرده ذیل به حضور معرفی میگردد. خواهشمند است پس از احراز هویت و انجام موارد درخواستی نتیجه را در پاکت سربسته به این مرکز اعلام نمائید.

نام خانوادگی :	نام :	نام پدر :	تاریخ تولد :	جنس :
نادری	محبوبه			

گزارشات کلینیکی و موضوع مشاوره :

نامبرده حدوداً ۱۵ هفته باردار است جنین مبتلا به گلوکوم مادرزادی می‌باشد. لطفاً اعلام نظر فرمایید.

۱) آیا این بیماری درمان دارد؟
۲) آیا شروع اقدامات درمانی از بدو تولد می‌تواند از کاهش بینایی کودک جلوگیری کند؟
۳) نوع اقدامات درمانی لازم جهت این نوع بیماری چیست؟

نام و امضا پزشک مسئول معاینات بالینی :

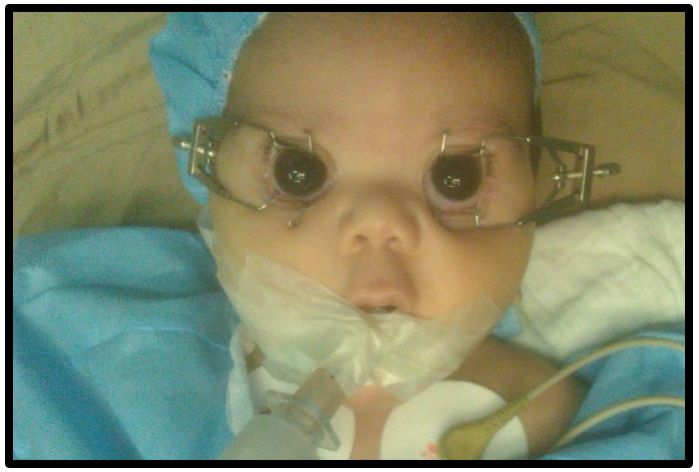
سازمان پزشکی قانونی کشور
معاینات
اداره معاینات منطقه مرکزی تهران

مشاهدات و نظریات پزشک مشاور :

مهر نظام پزشکی و امضا پزشک مشاور :

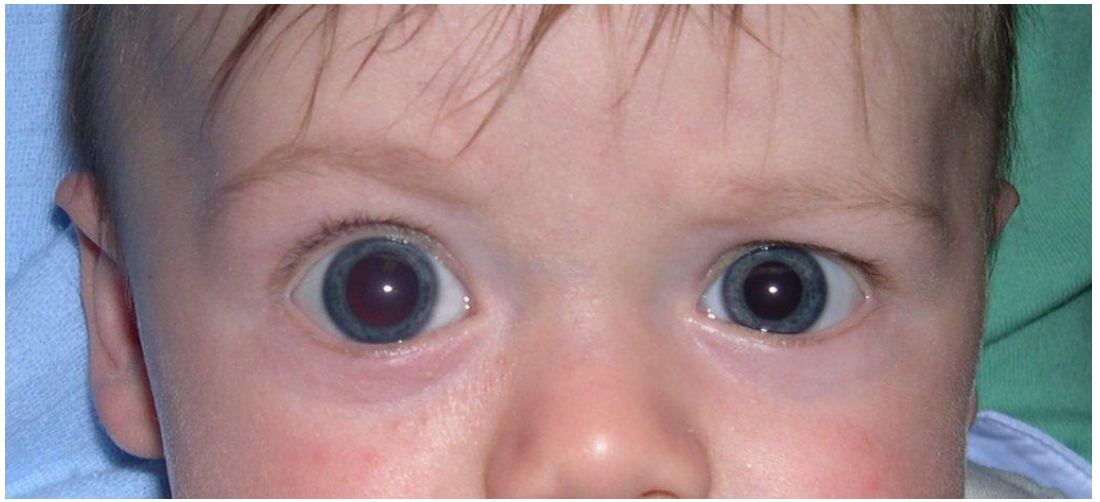
Signs & Symptoms of Glaucoma In Infancy & Childhood

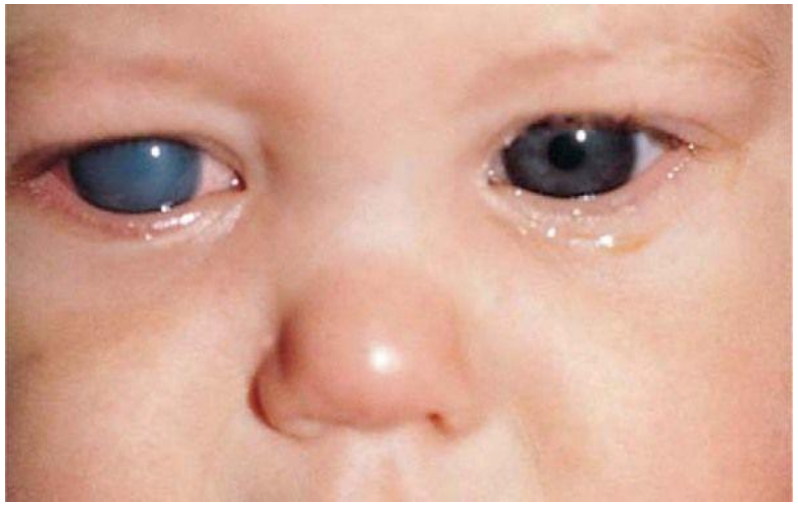
Symptoms	Signs
Photophobia	Buphthalmos
Epiphora	Corneal enlargement
Blepharospasm	Corneal edema
Red eye	Corneal size asymmetry
Irritability	Breaks in Descemet's membrane
Cloudy cornea	Iris and pupillary abnormalities
Enlarged cornea or eye	Elevated intraocular pressure
Poor vision	Visual impairment
Asymptomatic	Myopia or astigmatism
Irritability	Optic nerve cupping

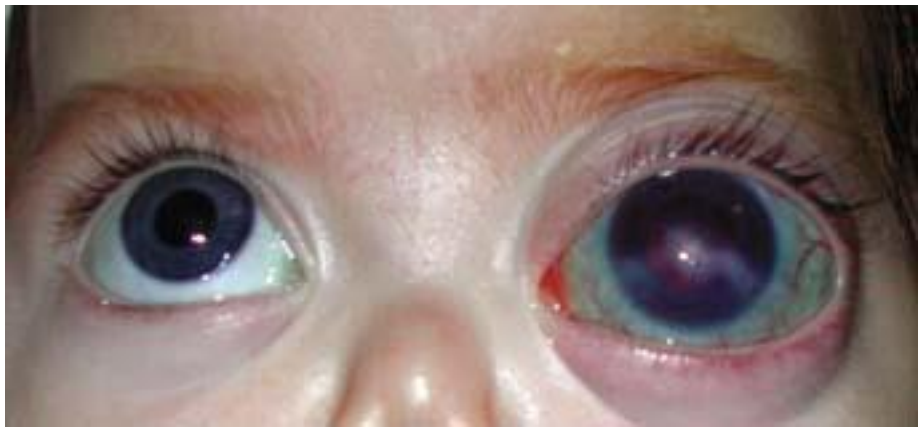


Examination Under Anesthesia

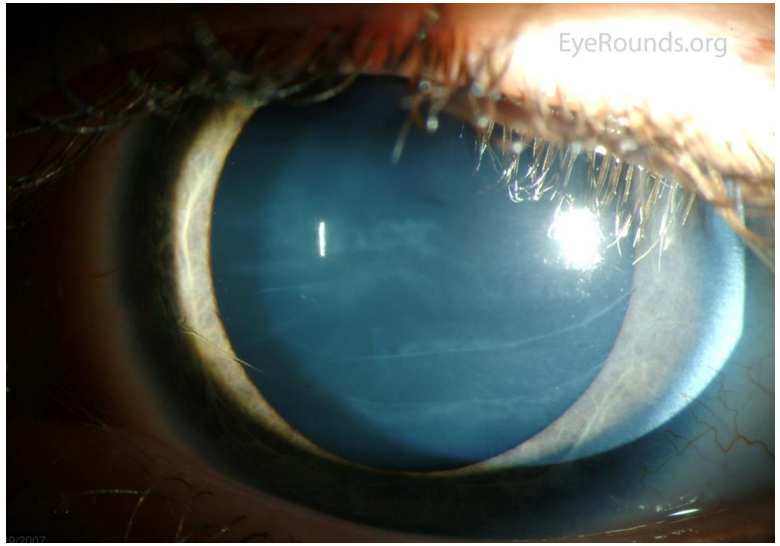
Megalocornea / Buphthalmos

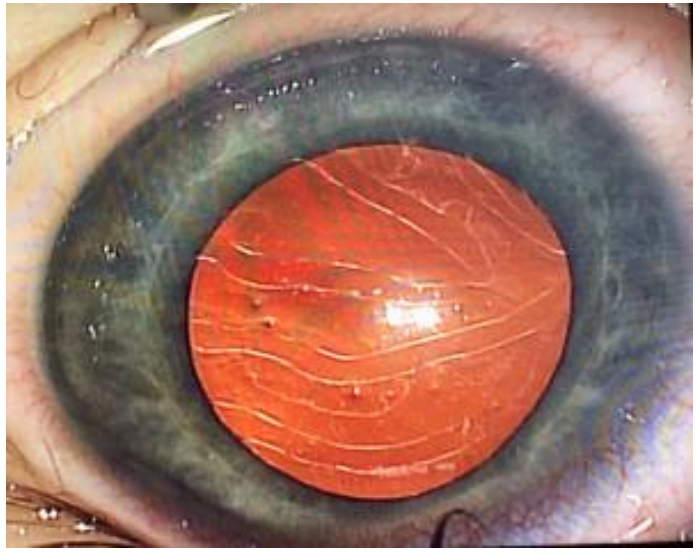


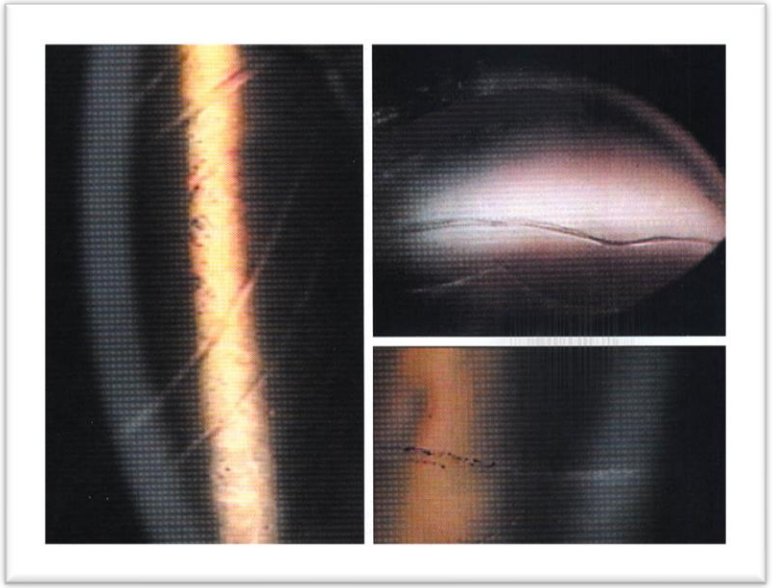




Ruptures in Descemet's membrane







Medical Treatment

- Only partially effective, but play an important role as adjunctive treatment but adverse effects should be considered.
- Systemic absorption of eye drops is an important issue, punctal occlusion should be explained.
- Beta blockers entail risks of bradycardia and respiratory depression.
- Metabolic acidosis and hypokalemia are side effects of CAIs.

Prostaglandin analogs

- Latanoprost, Immatures and Travaprost are systemically safe

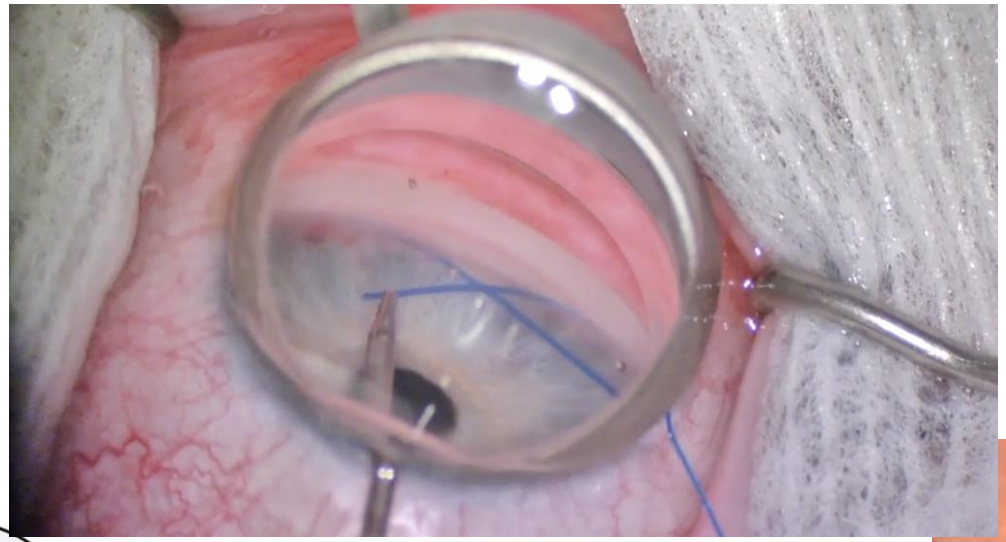
CONTRAINDICATED GLAUCOMA MEDICATIONS IN YOUNG CHILDREN

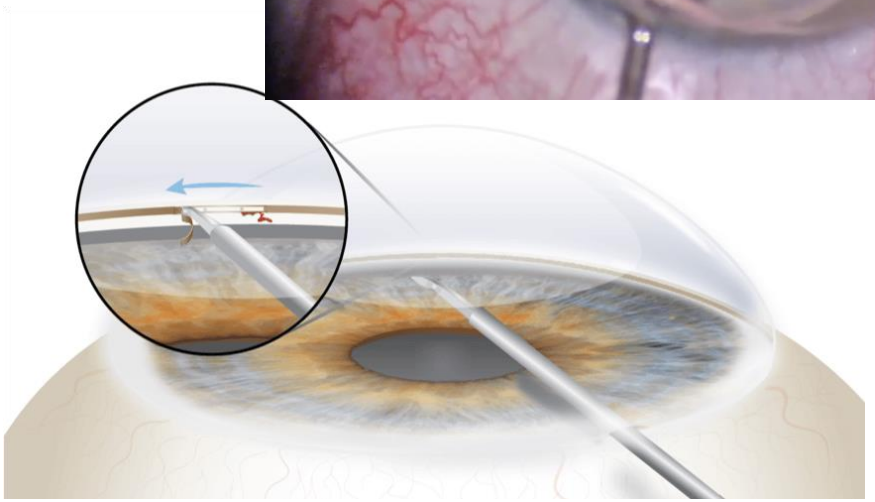
- **Alpha-2 agonists (e.g. Brimonidine) are <u>CONTRAINDICATED</u> under age 3Y**
- **And also relatively contraindicated under age 6Y**
- **Risk of CNS depression and apnea**

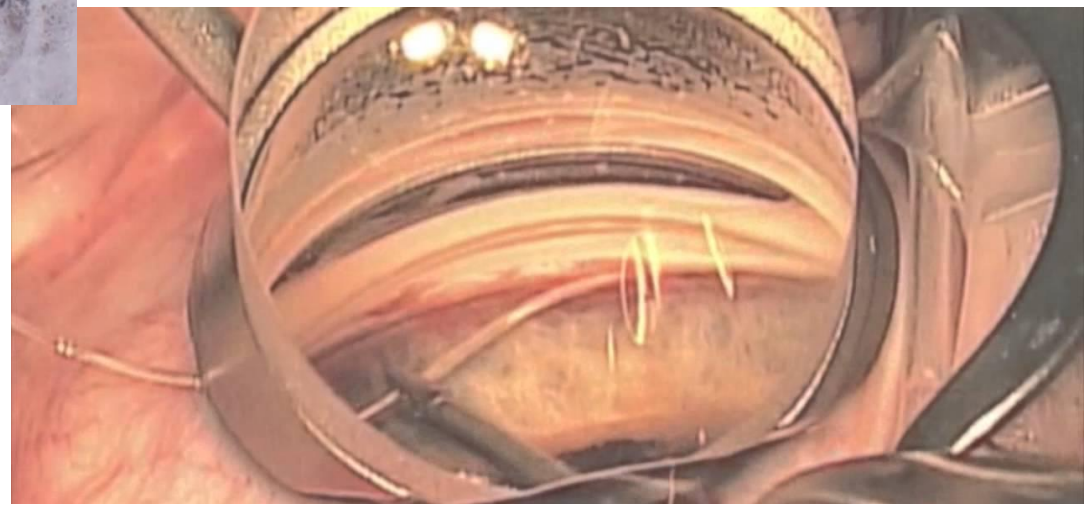
Surgical Treatment

- **Angle surgery**
  - Goniotomy
  - Trabeculotomy
- **Conventional glaucoma procedures.**
  - Trabeculectomy
  - Drainage implants
  - Cyclodestructive procedures

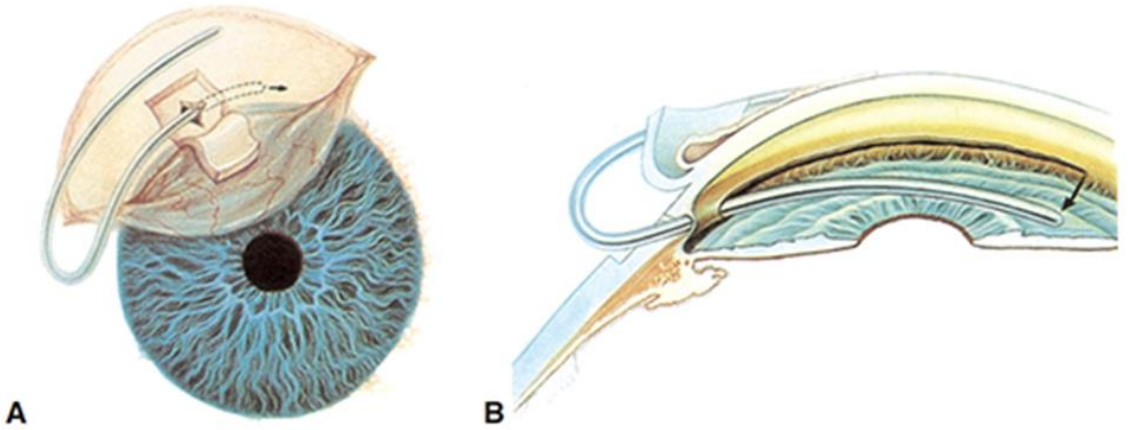
Goniotomy variations

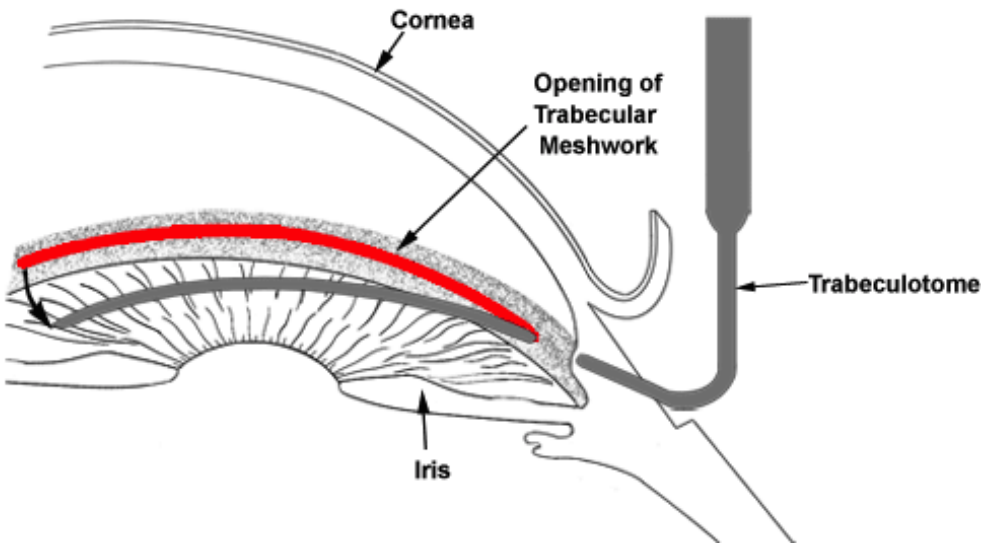






Trabeculotomy





Take Home Message

- **Be aware of and screen** for childhood glaucoma.
- The most common variant of the condition is **PCG**.
- Refer any patients with **systemic disorders associated with glaucoma**.
- Key features include **cloudy/large corneas**.
- **Consanguineous marriage and positive family history** of glaucoma are red flags.

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