

A Test for Primary Congenital Glaucoma (PCG)

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CMGS 2011



Great Ormond Street 
Hospital for Children
NHS Trust

ACKNOWLEDGEMENTS

Developmental Biology, UCL Institute for Child Health

- Dr Lily Islam
- Dr Dan Kelberman
- Dr Jane Sowden



Great Ormond Street Hospital & Moorfields Eye Hospital

- Mr Ken Nischal
- Professor Peng Khaw
- Miss Maria Papadopoulos

NE Thames Regional Molecular Genetics

- Lucy Jenkins, Head of Service
- Dr Nick Lench, Director

Primary Congenital Glaucoma (PCG)

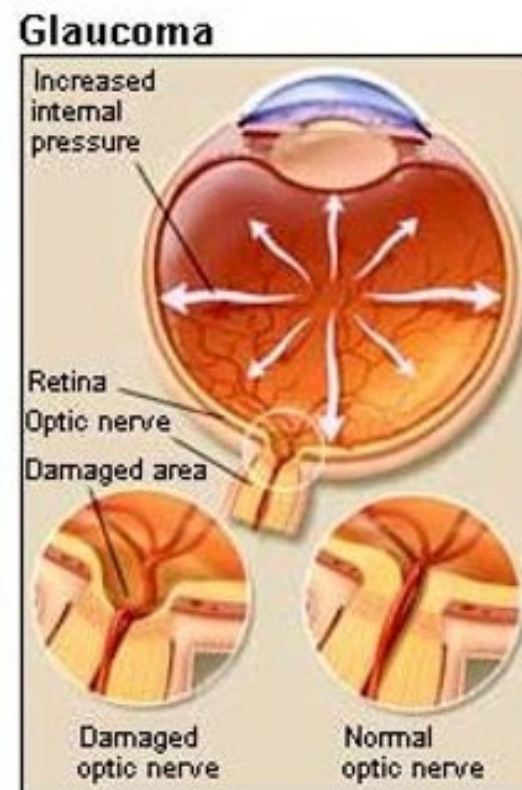
- OMIM 231300
- Also known as:
 - Glaucoma, congenital (GLC3)
 - Buphthalmos
 - Primary infantile glaucoma (PIG)
 - Infantile congenital glaucoma (ICG)



Mandal et al.(2007) *Eye* **20**: 135-143

Primary Congenital Glaucoma (PCG)

- Most common childhood glaucoma
- Usually presents in first 6 months of life
- Typically presents as:
 - raised intra-ocular pressure (IOP>21mmHg)
- If untreated raised IOP causes :
 - optic nerve damage
 - retinal ganglion cell death
 - corneal clouding
 - loss of sight
- IOP-lowering medications are often ineffective alone
 - primary mode of therapy: surgical



Primary Congenital Glaucoma (PCG)

- Incidence varies among different geographic locations & ethnic groups:



- Slovakian Roma: 1:1,250
- Middle East 1: 2,500
- Western nations (including UK) 1:10,000

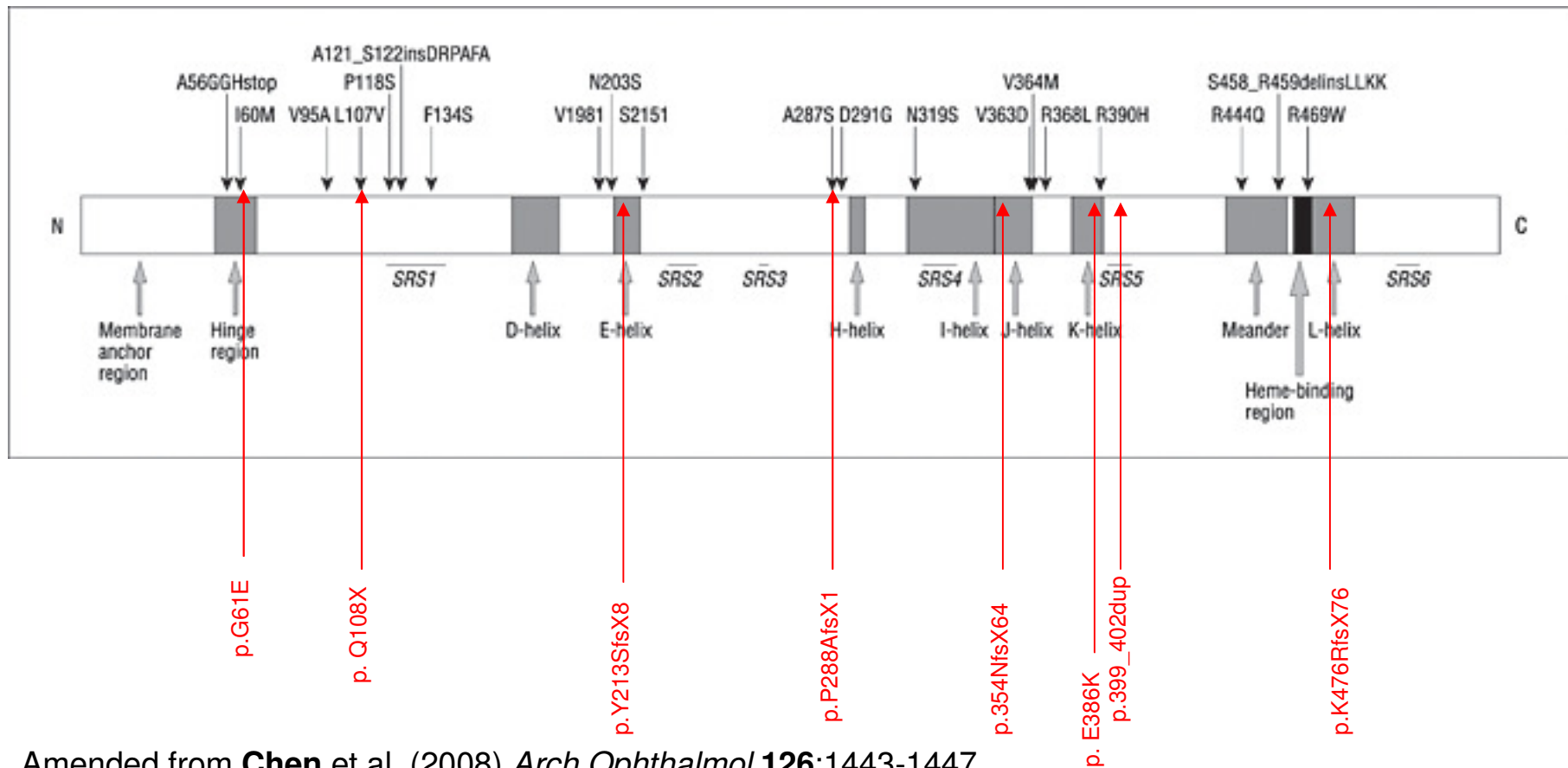
CYP1B1

(cytochrome P450, family 1, subfamily B, polypeptide)

- Mutations in *CYP1B1* been identified as responsible for PCG phenotype
 - **Stoliov** et al. (1997) *Hum. Mol. Gen.* **6**(4): 641-647
 - **Vasiliou and Gonzalez** (2008) *Ann. Rev. Pharm. Tox.* **48**: 333-358
- OMIM 601771
- Autosomal recessive mutations are principal cause of PCG
 - account for ~50% of cases

CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide)

- ~100 mutations have been reported throughout *CYP1B1* coding sequence in patients with PCG from various populations
 - include missense, nonsense, deletion and insertion/duplication mutations



Amended from **Chen** et al. (2008) *Arch Ophthalmol* **126**:1443-1447

CYP1B1

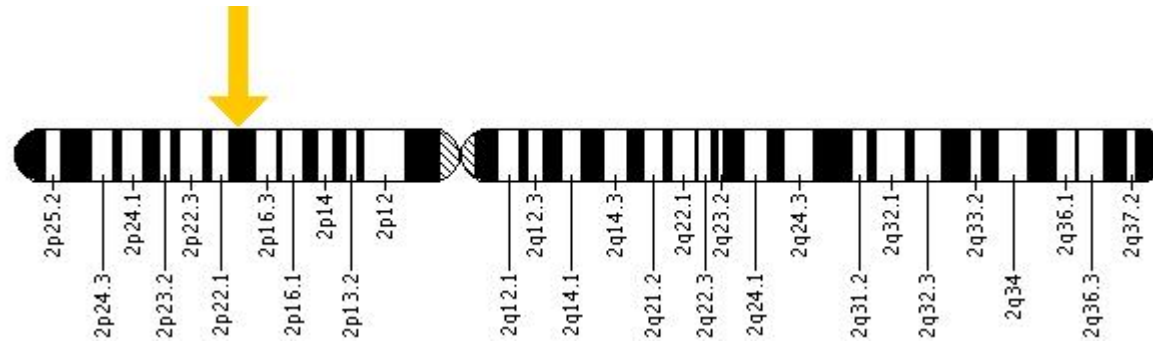
- Among patients with PCG, proportion due to *CYP1B1* mutations is variable among populations:



- Saudi Arabians & Slovakian Roma ~ 100%
 - Brazilians ~50%
 - Japanese ~20%
-
- In our ethnically diverse UK population we see mutations in ~50%
 - **Kelberman et al.** (in press) *Ophthalmology*

CYP1B1-testing

- Located at 2p22.2

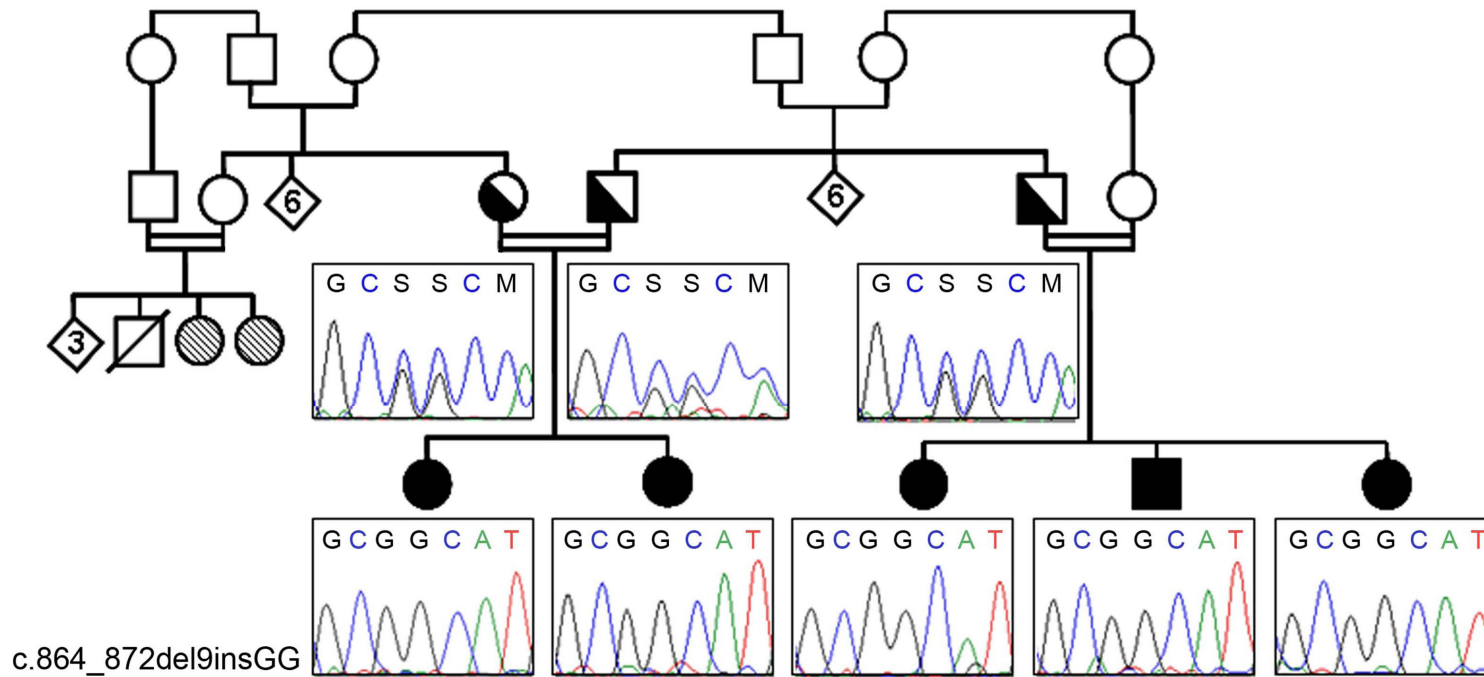


- 3 exons, 2 coding
- Longest transcript: 5347bp and 543 amino acids (NM_000104.3)
- Bidirectional sequencing of 2 coding exons
 - 6 overlapping fragments

CYP1B1-testing

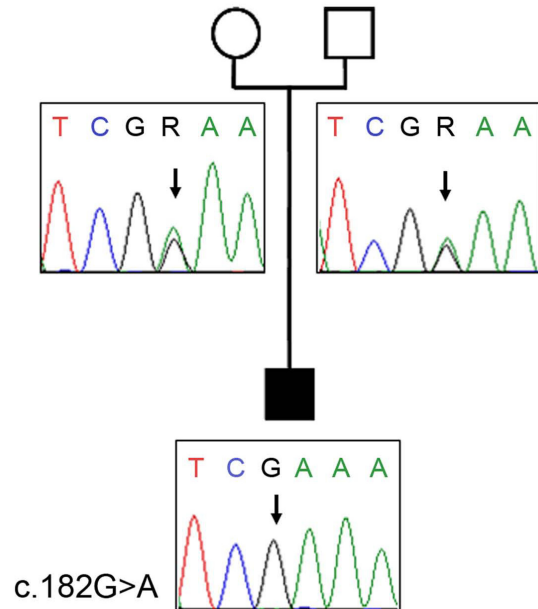
- Clinical sensitivity:
 - expect 50% of patients with clinical diagnosis of PCG to have *CYP1B1* mutations
- Clinical specificity: High
 - later onset disease caused by *CYP1B1* mutations rarely reported
- Positive predictive value: High
 - a patient with 2 mutations is expected to exhibit PCG symptoms
- Negative predictive value: High
 - no biallelic mutations detected in patients with other ocular phenotypes or in normal controls

CYP1B1- Example pedigrees

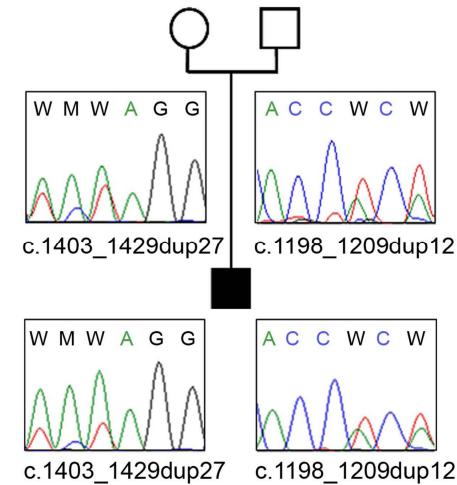


- Ethnicity: Asian-Pakistani
- Nucleotide change: c.864_870del9insGG
- Predicted effect on protein: p.P288AfsX1

CYP1B1- Example pedigrees

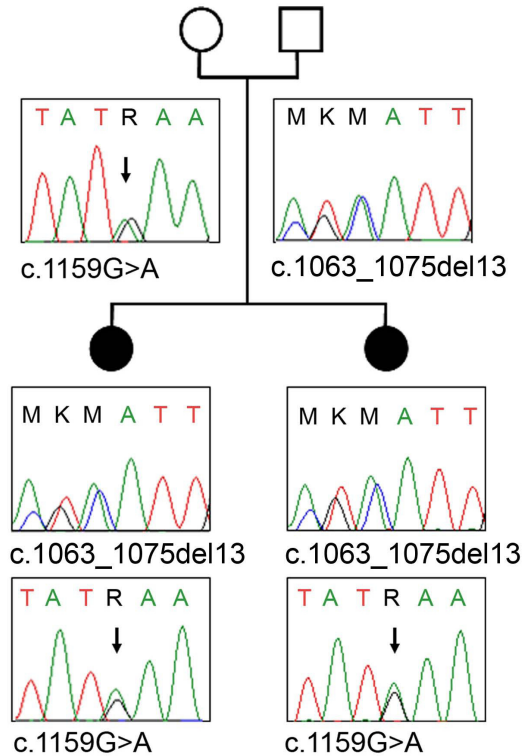


- **Ethnicity: Arab**
- **Nucleotide change: c.182G>A**
- **Predicted effect on protein: p.G61E**
- **Reported in multiple families/populations**
- **Affects highly conserved residue of cytochrome P450 family of proteins**

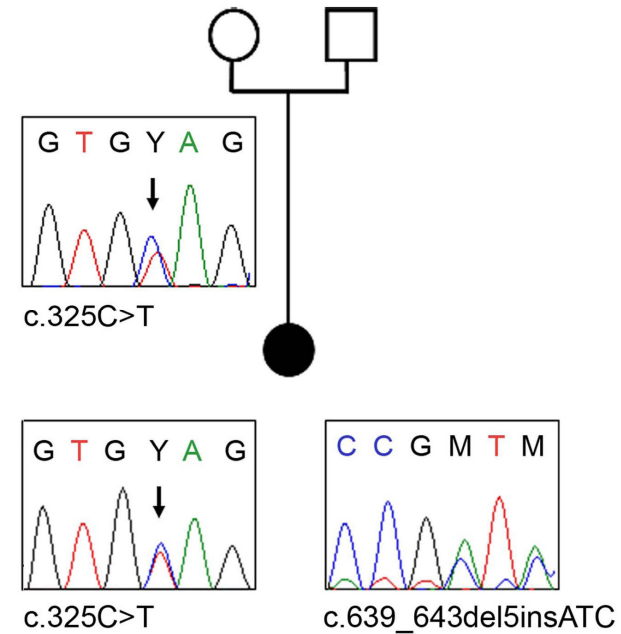


- **Ethnicity: White-European**
- **Nucleotide change: c. 1198_1209dup12 / c.1403_1429dup27**
- **Predicted effect on protein: p.399_402dup / p.K476RfsX76**

CYP1B1- Example pedigrees



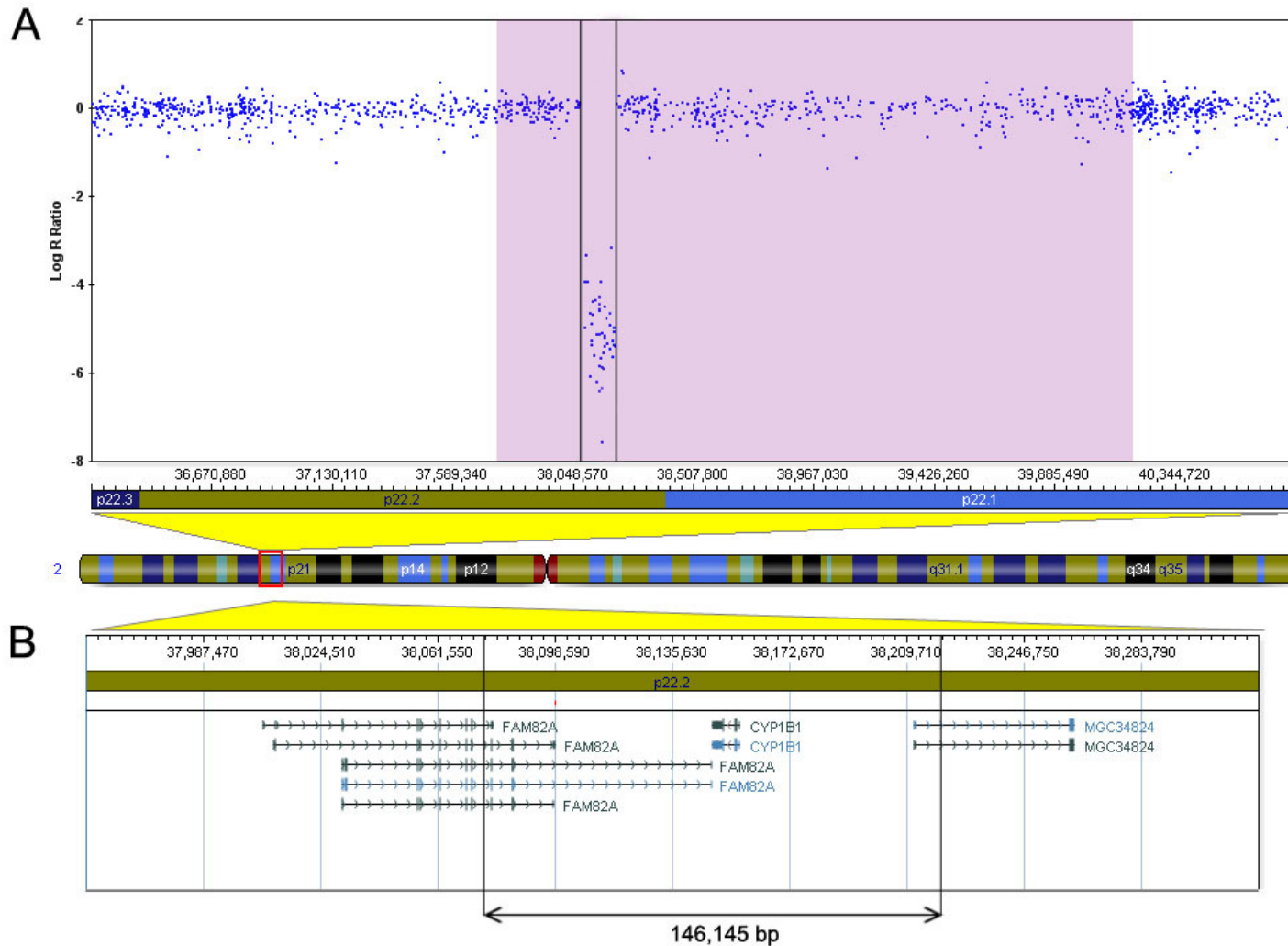
- **Ethnicity: White European**
- **Nucleotide change:**
c.1159G>A / c. 1063_1075del13
- **Predicted effect on protein:**
p.E386K/p.R354NfsX64



- **Ethnicity: African**
- **Nucleotide change:**
c.325C>T / c.639_643del5insATC
- **Predicted effect on protein:**
p.Q108X / p. Y213SfsX8

CYP1B1- Example pedigrees

- Ethnicity: Greek Cypriot – homozygous, 146Kb deletion encompassing *CYP1B1*
- Parental DNA unavailable; No known consanguinity within family



Clinical indications for *CYP1B1* testing

Primary congenital glaucoma, defined by:

- elevated IOP > 21 mmHg
- &/or signs consistent with elevated IOP, including:
 - disc cupping > 0.3 or disc asymmetry ≥ 0.2
 - progressive disc cupping
 - buphthalmos (prominent, enlarged eye)
 - enlarged corneal diameter (> 11 mm in newborn, > 12 mm in child < 1 yr, > 13 mm in child > 1 yr)
 - corneal edema
 - Descemet's membrane splits (Haab's striae)
 - visual field defects
 - progressive myopia

in a child < 2 yrs

Clinical utility of *CYP1B1* testing

- Early diagnosis and management of raised intraocular pressure crucial to prevent or minimise permanent visual deficit.
- Accurate genetic counselling to provide recurrence risk for parents of affected child.
- Add prognostic information:
 - some *CYP1B1* mutations associated with endotheliopathy; waiting for corneal clearing in these circumstances leads to stimulus deprivation amblyopia which could be treated by timely corneal transplant (**Kelberman et al.** (in press) *Ophthalmology*)
- Assist treatment decisions:
 - evidence suggesting a good surgical graft outcome in *CYP1B1* mutation positive patients with corneal opacity as compared with other corneal opacity patients

Impact on NHS of *CYP1B1* testing

- Family members can be tested and discharged from follow-up if no *CYP1B1* mutation found
- All children with *CYP1B1* mutations will need lifelong surveillance and management of their glaucoma.
- In infancy, accurate measurement of IOP can be difficult and may require examination under anaesthesia
 - risk
 - expense
 - this can be avoided if child does not have biallelic mutations
- By not doing the test:
 - clinicians have reduced information to assist in decision making
 - at-risk siblings subjected to continued follow-up

Summary

- PCG can lead to blindness
- *CYP1B1* mutations are associated with PCG
- *CYP1B1* testing can inform patient and family management
- NE Thames Regional Molecular Genetics offering sequencing of *CYP1B1* coding regions
 - UKGTN gene dossier has been submitted

Thank you!



Charity reg. nos 208701 and SC039284

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