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Primary Congenital Glaucoma

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Summary

Clinical characteristics

Primary congenital glaucoma (PCG) is characterized by elevated intraocular pressure (IOP), enlargement of the globe (buphthalmos), edema, and opacification of the cornea with rupture of Descemet's membrane (Haab's striae), thinning of the anterior sclera and iris atrophy, anomalously deep anterior chamber, and structurally normal posterior segment except for progressive glaucomatous optic atrophy. Symptoms include photophobia, blepharospasm, and excessive tearing. Typically, the diagnosis is made in the first year of life. Depending on when treatment is instituted, visual acuity may be reduced and/or visual fields may be restricted. In untreated individuals, blindness invariably occurs.

Diagnosis/testing

The diagnosis of PCG is based on clinical criteria including: elevated IOP in a child typically before age one year, enlargement of the globe, increased corneal diameter, cloudy corneas, breaks in Decsemet's membrane (Haab's striae) and anomalously deep anterior chamber. Identification of biallelic pathogenic variants in *CYP1B1* or *LTBP2* or identification of a heterozygous pathogenic variant in *TEK* confirms the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Surgery (goniotomy, trabeculotomy, trabeculectomy, or deep sclerectomy) as early as possible; use of drainage implants or cyclodestruction if surgery fails; medication preoperatively and postoperatively to help control IOP; routine treatment of refractive errors and amblyopia.

Prevention of secondary complications: Discontinuation of medications such as Phospholine Iodide® (echothiophate) before surgery to prevent prolonged apnea.

Surveillance: Lifelong monitoring to ensure control of IOP.

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Agents/circumstances to avoid: Alpha-2 agonists because of risk for apnea and bradycardia.

Evaluation of relatives at risk: If the pathogenic variant(s) have been identified in the family, molecular genetic testing of at-risk sibs as soon as possible after birth in order to avoid repeated examinations under anesthesia in young children who do not have the pathogenic variant(s).

Genetic counseling

PCG caused by biallelic pathogenic variants in *CYP1B1* or *LTBP2* is inherited in an autosomal recessive manner. PCG caused by a heterozygous pathogenic variant in *TEK* is inherited in an autosomal dominant manner.

- **Autosomal recessive inheritance.** At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic; carrier testing for at-risk family members is possible if the pathogenic variants in the family are known.
- **Autosomal dominant inheritance.** Each child of an individual with *TEK*-related PCG has a 50% chance of inheriting the pathogenic variant.

Prenatal testing for a pregnancy at increased risk is possible if the PCG-causing pathogenic variant(s) in the family are known.

Diagnosis

Suggestive Findings

Primary congenital glaucoma (PCG) **should be suspected** in infants or children with the following clinical features:

- Photophobia, blepharospasm, and excessive tearing
- Edema and opacification of the cornea with rupture of Descemet's membrane, known as Haab's striae
- Thinning of the anterior sclera and atrophy of the iris
- Structurally normal posterior segment except for progressive optic atrophy
- Absence of structural changes in the anterior chamber that are consistent with a diagnosis of anterior segment dysgenesis or associated systemic disease.

Establishing the Diagnosis

The diagnosis of PCG **is established** in a proband by the following clinical criteria:

- Elevated intraocular pressure (IOP) in an infant or child typically (but not always) before age one year. An IOP greater than 21 mm Hg (mercury) in one or both eyes as measured by applanation tonometry, I-care tonometry™, or pneumotonometry on at least two occasions is considered abnormally elevated. In general, normal intraocular pressure in children is 12.02 ± 3.74 mm Hg [Sihota et al 2006].
- Enlargement of the (infantile) globe (buphthalmos)
- Increased corneal diameter and cloudy corneas
- Breaks in Decsemet's membrane (Haab's striae)
- Anomalously deep anterior chamber
- Bilateral or unilateral findings

Identification of biallelic pathogenic (or likely pathogenic) variants in *CYP1B1* or *LTBP2* or a heterozygous *TEK* pathogenic (or likely pathogenic) variant on molecular genetic testing (see Table 1) confirms the diagnosis if clinical features are inconclusive.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Serial single-gene testing**. Perform sequence analysis of *CYP1B1,* followed by deletion/duplication analysis if only one or no pathogenic variant is found. If no *CYP1B1* pathogenic variants are identified, consider sequence analysis of *LTBP2*. Sequence analysis and gene-targeted deletion/duplication analysis of *TEK* can be considered next if one or no pathogenic has been identified.

  Targeted analysis for *CYP1B1* pathogenic variant p.Glu387Lys may be performed first in individuals of Rom Slovakian ancestry.

  CYP1B1 pathogenic variant p.Gly61Glu may be performed first in individuals of Saudi Arabian ancestry.

- **A multigene panel** that includes *CYP1B1, LTBP2, TEK*, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Primary Congenital Glaucoma

Gene [1]	Proportion of PGC Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
CYP1B1	20%-100% of familial cases [5] 10%-15% of simplex cases [6]	~ 90%-95%	~5%-10% [7]
LTBP2	≤40% [8]	~100%	Unknown [9]
TEK	10 families [10]	9/10 families	1 family

Table 1. continued from previous page.

Gene [1]	Proportion of PGC Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
Unknown [11, 12]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. The probability of identifying pathogenic variants in *CYP1B1* increases with the presence of: positive family history, parental consanguinity, and bilateral and severe disease. Differences in the number of individuals studied, the methods of ascertainment (familial vs simplex cases, unilateral vs bilateral disease), and the molecular genetic testing methods used make accurate estimates of variant detection frequency difficult.
6. Mashima et al [2001], Stoilov et al [2002], Curry et al [2004]
7. At least five *CYP1B1* alleles with gross deletions, sometimes including the entire *CYP1B1* along with adjacent genes, have been reported. Additionally, gross duplications and a complex mutational event are known. For details see Molecular Genetics, Table A, **Locus-Specific Databases** and **HGMD**.
8. Ali et al [2009], Narooie-Nejad et al [2009], Micheal et al [2016]
9. No data on detection rate of gene-targeted deletion/duplication analysis are available.
10. Heterozygous *TEK* pathogenic variants were identified in affected individuals from 10/189 unrelated families with PCG [Souma et al 2016].
11. Kaur et al [2005] presented evidence in a single individual that the combination of a heterozygous pathogenic variant in *MYOC* and a heterozygous pathogenic variant in *CYP1B1* was associated with PCG, suggesting digenic inheritance. A report of a Chinese family segregating both primary congenital open-angle glaucoma (POAG) and PCG suggested that homozygous *MYOC* variants may cause PCG [Zhuo et al 2006].
12. Two additional loci, GLC3B on 1p36 [Akarsu et al 1996] and GLC3C on 14q24.3 [Stoilov & Sarfarazi 2002], have been linked to PCG; however, the genes at these loci are not known. One additional locus linked to PCG, on 14q24.2-q24.3, does not appear to overlap the GLC3C critical region [Firasat et al 2008].

Clinical Characteristics

Clinical Description

Primary congenital glaucoma (PCG) is characterized by developmental defect(s) of the trabecular meshwork and anterior chamber angle that prevent adequate drainage of aqueous humor, resulting in elevated intraocular pressure (IOP) and stretching of the sclera that produces an enlarged globe (buphthalmos).

The following information comes from the detailed clinical papers on PCG of deLuise & Anderson [1983] and Ho & Walton [2004] unless otherwise noted.

By definition, congenital glaucoma is present at birth; it is typically diagnosed in the first year of life. PCG is more common in males (65%) and is bilateral in 70% of individuals.

The clinical signs and symptoms depend primarily on the age of onset and the severity of the disease. The classic symptoms include tearing, photophobia, and irritability. Occasionally, parents may notice cloudy and/or unusually large corneas in their child caused by corneal edema; the corneal enlargement generally occurs before age three years.

The most severe clinical features are typically seen in the newborn, who may present with corneal opacity, increased corneal diameter, increased IOP, and an enlarged globe [Walton 1998]. In 35 newborns with PCG, corneal edema was present in 100% of the eyes, either as diffuse (90%) or localized (10%) opacity [Walton 1998].

Early detection and appropriate treatment of congenital glaucoma can improve visual outcome. In contrast to the permanent optic nerve cupping and visual field loss seen in adults with adult-onset glaucoma, the pressure-induced optic nerve cupping in infants and young children with PCG is reversible, particularly in the early stages of the disease. This favorable outcome is believed to be a result of the highly elastic nature of the tissues of the optic nerves of infants and young children [Allingham et al 2005]. A delay in treatment can result in reduced visual acuity and/or restricted visual fields. In untreated individuals, blindness invariably occurs.

The ultimate visual outcome depends on the severity of the disease at diagnosis, the presence of other associated ocular abnormalities, response to surgical treatment, and success in controlling IOP on follow up. The earlier the onset of clinical manifestations of glaucoma, the worse the prognosis.

Despite early treatment and multiple surgical interventions, some individuals with severe disease evident at birth develop significant visual impairment from corneal opacification, advanced glaucomatous damage, or amblyopia, and may eventually become legally blind.

Individuals with milder forms of disease who present later in childhood often do well with a single surgical procedure and have an excellent visual prognosis later in life.

The IOP is a significant prognostic factor for postoperative visual function, with substantially better vision observed in individuals with IOP <19 mm Hg.

Phenotype Correlations by Gene

CYP1B1. Individuals with *CYP1B1* pathogenic variants needed significantly more surgical procedures to control intraocular pressure than individuals with congenital glaucoma of unknown cause, when both eyes of an individual were evaluated (P=0.003) or the worst eye was evaluated (P=0.011) [Della Paolera et al 2010]. The correlations with genotype have been inconsistent.

Individuals with *CYP1B1* pathogenic variants tend to have a higher operative success rate than individuals without identified *CYP1B1* pathogenic variants in terms of better intraocular pressure control effect. Together, the presence or absence of pathogenic variants in *CYP1B1* and the preoperative corneal opacity score can partially predict the outcome of PCG surgery [Chen et al 2014b].

Individuals with *CYP1B1* pathogenic variants had higher last postoperative visit indices in terms of postoperative haze and the need for anti-glaucoma medications than individuals without pathogenic variants in *CYP1B1* [Abu-Amero et al 2011].

LTBP2. Individuals with *LTBP2*-related PCG had clinical features not seen in individuals with pathogenic variants in *CYP1B1* or *TEK*; these features included ectopia lentis, high arched palate, and mild-to-moderate osteopenia [Ali et al 2009].

TEK. Individuals with *TEK*-related congenital glaucoma exhibit a clinical phenotype that is variable in severity and age of onset [Souma et al 2016].

Genotype-Phenotype Correlations

Walton and colleagues have shown that the phenotype can vary significantly in the same individual (one eye being more severely affected than the other) [Walton 1998].

CYP1B1. No consistent genotype-phenotype correlation has been observed for *CYP1B1* pathogenic variants. Intra- and interfamilial variability is reported among individuals with identical *CYP1B1* pathogenic variants [Berraho et al 2015, de Melo et al 2015]. No information is available on correlation between the *CYP1B1* pathogenic variants and the success of surgical therapy.

LTBP2. No genotype-phenotype correlation has been observed for *LTBP2* pathogenic variants.

TEK. No genotype-phenotype correlation has been observed for *TEK* pathogenic variants.

Prevalence

CYP1B1. The prevalence of *CYP1B1* pathogenic variants in individuals with PCG varies: 20% in Japanese [Plásilová et al 1999], 33.3% in Indonesians [Sitorus et al 2003], 44% among Indians [Chakrabarti et al 2010], 50% among Brazilians [Stoilov et al 2002], 70% in Iranians [Chitsazian et al 2007], and 80%-100% among Saudi Arabians [Bejjani et al 2000, Abu-Amero et al 2011] and the Rom Slovakian population [Plásilová et al 1999]. The relatively higher prevalence of these pathogenic variants in the latter two populations could be attributed to consanguinity.

Some pathogenic variants are more common in specific ethnic groups. For example:

- p.Glu387Lys accounts for all the pathogenic variants in the Rom Slovakian population.
- p.Gly61Glu accounts for 72% of the pathogenic variants in Saudi Arabians [Bejjani et al 1998].

Additional pathogenic variants have been associated (although with lesser frequencies) with other specific ethnic groups [Belmouden et al 2002, Panicker et al 2002, Chakrabarti et al 2006].

PCG occurs in all ethnic groups. The birth prevalence, however, varies worldwide:

- 1:5,000-22,000 in western countries
- 1:2,500 in the Middle East
- 1:1,250 in the Rom population of Slovakia [Plásilová et al 1998]
- 1:3,300 in the Indian state of Andhra Pradesh, where the disease accounts for approximately 4.2% of all childhood blindness [Dandona et al 2001]

In Saudi Arabia and in the Rom population of Slovakia, PCG is the most common cause of childhood blindness [Plásilová et al 1998, Bejjani et al 2000].

Genetically Related (Allelic) Disorders

CYP1B1

CYP1B1-related congenital glaucoma can be associated with an extreme form of anterior segment dysgenesis that includes recalcitrant glaucoma, corneal opacification, juvenile [Abu-Amero et al 2015] and adult open-angle glaucoma [Micheal et al 2015], and aniridia [Alzuhairy et al 2015].

Primary open-angle glaucoma (POAG). *CYP1B1* pathogenic variants have been reported in individuals of French ancestry with POAG, suggesting that *CYP1B1* pathogenic variants could pose a significant risk for early-onset POAG and could also modify the glaucoma phenotype in individuals who do not have an *MYOC* pathogenic variant [Melki et al 2004].

Congenital anterior staphylomas. *CYP1B1* pathogenic variants may be associated with congenital anterior staphylomas [Al Judaibi et al 2014].

Peters anomaly. Pathogenic variants in *CYP1B1* have been described in individuals with Peters anomaly (OMIM 604229), a uni- or bilateral developmental disorder of the anterior chamber that is distinct from PCG.

Clinical findings in Peters anomaly include central corneal opacity associated with corneal stromal thinning, absence of varying lengths of central Descemet's membrane, and iridocorneal and/or keratolenticular adhesions.

Juvenile open-angle glaucoma (JOAG). *CYP1B1* pathogenic variants have also been implicated in three individuals with JOAG (OMIM 137750) [Vincent et al 2002]. In that study, a family with autosomal dominant glaucoma showed cosegregation of a pathogenic variant in *MYOC* and a pathogenic variant in *CYP1B1* in an individual with more severe disease. Pathogenic variants in *MYOC* may, in conjunction with pathogenic variants in *CYP1B1,* increase the clinical severity of glaucoma in individuals with JOAG. Indeed, individuals who are heterozygous for a pathogenic variant in both *MYOC* and *CYP1B1* appear to have a more severe open-angle glaucoma phenotype than those who are heterozygous for a pathogenic variant in *MYOC* alone [Vincent et al 2002]. These results suggest that *CYP1B1* may act as a modifier of *MYOC* expression and that these two genes may interact through a common pathway [Vincent et al 2002].

Acharya et al [2006] suggested that on rare occasions homozygous *CYP1B1* pathogenic variants alone (i.e., without *MYOC* pathogenic variants) may cause JOAG.

In the study of Abu-Amero et al [2015]:

- 12 of 14 unrelated Saudi Arabians with JOAG had at least one *CYP1B1* variant.
- Eight were homozygous for the p.Gly61Glu pathogenic variant.
- Two were compound heterozygous for the p.Gly61Glu and p.Leu432Val variants.
- Two were heterozygous for the p.Gly61Glu variant with no other variant identified.

No genotype-phenotype correlation was demonstrated in those with biallelic *CYP1B1* pathogenic variants. None of the 14 had mutation of *MYOC* or *LTBP2*.

LTBP2

Kumar et al [2010] detected a homozygous *LTBP2* pathogenic variant in one family with microspherophakia. *LTBP2* pathogenic variants have also been associated with Weill-Marchesani syndrome. Homozygous *LTBP2* pathogenic variants were identified in eight individuals with congenital megalocornea from three families [Khan et al 2011].

TEK

Heterozygous *TEK* pathogenic variants have been identified in multiple individuals with hereditary and sporadic venous malformations.

Differential Diagnosis

A number of congenital ocular conditions can mimic PCG and must be considered by the clinician [Khan 2011]. For example, the nonspecific findings of tearing and redness of the eyes may mimic more common conditions such as conjunctivitis or congenital nasolacrimal duct obstruction; ocular irritation with photophobia and redness may mimic the more frequent problem of corneal abrasion.

Congenital glaucoma can be subcategorized by age of onset into the following three types:

- Primary "newborn"-type congenital glaucoma. The most severe type; clinically apparent between birth and age one month
- Primary "infantile" glaucoma (or infantile PCG) as described by Walton & Katsavounidou [2005]. Clinically recognized between age one month and two years
- "Juvenile" ("late-recognized") primary infantile glaucoma. Onset clinically apparent after age two years

The types do not correlate with a specific genetic cause, although primary "newborn"-type congenital glaucoma is more likely to be caused by mutation of *CYP1B1* than the other types of congenital glaucoma in some populations.

In the older child with juvenile onset, or in less severely affected individuals, the increase in intraocular pressure (IOP) is gradual; thus, corneal edema and opacity may be less obvious than in the newborn type. Progressive enlargement of the globe or "buphthalmos" usually does not occur after age three to four years [Ho & Walton 2004, Allingham et al 2005].

Conditions/syndromes associated with infantile glaucoma. A number of well-recognized conditions and syndromes may present with infantile glaucoma, along with other ocular and/or systemic findings. Some conditions may not be compatible with life (e.g., trisomy 13, trisomy 18, Walker-Warburg syndrome, and Zellweger Syndrome); others may be less severe or confined only to the eye.

It is important to establish the diagnosis of an associated syndrome because of the implications for genetic counseling and treatment (see Table 2).

Table 2. Conditions/Syndromes Associated with Infantile Glaucoma

Disorder	Gene(s)	MOI	Clinical Features	
			Eye Findings	Other
Aniridia	*PAX6* *WT1* [1]	AD	• Complete or partial iris hypoplasia w/assoc foveal hypoplasia, resulting in ↓ visual acuity & nystagmus • Presents in early infancy • Frequently assoc w/other ocular abnormalities, often of later onset, incl cataract, glaucoma, & corneal opacification& vascularization	May occur either as an isolated ocular abnormality w/o systemic involvement or as part of WAGR syndrome [1]
Anterior segment dysgenesis syndromes (e.g., Peters Plus syndrome)	See footnote 2.		Phenotypically & genotypically distinct from PCG in general, but severe or advanced PCG can be difficult to distinguish clinically from some of the anterior segment dysgenesis syndromes (e.g., Peters anomaly)	Peters Plus syndrome: developmental delay, mild to severe ID, cleft lip, cleft palate
Axenfeld-Rieger anomaly (anterior segment disorder)	*FOXC1* *PITX2*	AD	• Presents w/posterior embryotoxon & (variably) iris strands adherent to Schwalbe's line, iris hypoplasia, focal iris atrophy, & ectropion uveae. • Glaucoma develops in ~50% of persons but is more common in those w/central iris changes & marked anterior iris insertion • Always bilateral, but may be distinctly asymmetric	May occur in the setting of Axenfeld-Rieger syndrome (OMIM 180500): dysmorphic features, dental anomalies, sensorineural hearing loss, cardiac malformations, endocrine & orthopedic abnormalities
Microcornea	Unknown [3]		• Corneal diameter <10 mm • Can be assoc w/glaucoma & other ocular anomalies incl congenital cataracts, sclerocornea, & corneal plana	May be a feature of systemic syndromes

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Eye Findings	Other
Congenital hereditary endothelial dystrophy (CHED) (OMIM 217700)	*SLC4A11*	AR	• Bilateral corneal opacification • May be difficult to distinguish from microcornea, but corneal diameter & IOP are usually normal in CHED • The primary defect in the corneal endothelium leads to corneal edema & opacification. • CHED & CG are known to coexist; exact incidence unknown [4]	Sensorineural hearing loss
Lowe syndrome	*OCRL*	XL	• Dense congenital cataracts are found in all affected boys, infantile glaucoma in ~50% • All boys have impaired vision; corrected acuity rarely >20/100 • Almost all affected males have some ID	Congenital hypotonia, delayed development, proximal renal tubular dysfunction (renal Fanconi type), progressive chronic renal failure and ESKD after age 10-20 yrs
Neurofibromatosis type 1	*NF1*	AD	• Iris Lisch nodules • CG rarely observed	Multiple café au lait spots, axillary & inguinal freckling, cutaneous neurofibromas, learning disabilities in ≥50% of persons
Nance-Horan syndrome (OMIM 302350)	*NHS*	XL	Cataract and microcornea	Skeletal features
Sturge-Weber syndrome (OMIM 185300)	*GNAQ*	See footnote 5.	CG w/assoc angle anomalies in ≤60% of affected persons	Nevus flammeus of the face, angioma of the meninges

AD = autosomal dominant; AR = autosomal recessive; CG = congenital glaucoma; ESKD = end-stage kidney disease; ID = intellectual disability; MOI = mode of inheritance; WAGR = Wilms tumor-aniridia-genital anomalies-retardation; XL = X-linked

1. Pathogenic variants or deletions in *PAX6* or its control elements are associated with isolated aniridia. Contiguous gene deletions including *PAX6* and *WT1* are associated with aniridia and the risk of one or more additional manifestations of WAGR.

2. Anterior segment dysgenesis syndromes are a heterogeneous group of disorders that are usually inherited in an autosomal dominant manner with reduced penetrance.

3. Huang et al [2015]

4. Ramamurthy et al [2007]

5. Somatic mosaic pathogenic variants in *GNAQ* have been reported in individuals with Sturge-Weber syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary congenital glaucoma (PCG), examination under anesthesia or sedation is warranted to make a complete assessment of both eyes. The examination includes the following:

- Measurement of intraocular pressure (IOP) within the first few minutes of anesthesia
- Measurement of corneal diameter
- Examination of the anterior segment
- Direct gonioscopy to rule out secondary glaucoma
- Dilated fundus examination to evaluate for optic nerve damage

- If the cornea is opaque, ultrasound biomicroscopy or optical coherence tomography to aid in evaluating the anterior segment structures
- Measurement of axial length

If the child is examined under anesthesia, consent may be obtained to perform the appropriate surgical procedure after evaluation under anesthesia.

Consultation with a clinical geneticist and/or genetic counselor is recommended.

Treatment of Manifestations

The primary goal of treatment is to decrease IOP to prevent vision-threatening complications including corneal opacification and glaucomatous optic atrophy. Early treatment to control IOP will reverse some of these complications in children. A Cochcrane review analyzed the literature that addressed the surgical management of congenital glaucoma but could not draw any conclusions from the analysis [Ghate & Wang 2015].

Surgical treatment. The following approach is based on the work of deLuise & Anderson [1983], Ho & Walton [2004], Bowman et al [2011], Sharaawy & Bhartiya [2011], and Al-Obeidan et al [2014].

PCG is almost always managed surgically. The primary goal of surgery is to eliminate the resistance to aqueous outflow caused by the structural abnormalities in the anterior chamber angle. This goal may be accomplished through an internal approach (goniotomy) or an external approach (trabeculotomy or trabeculectomy).

In goniotomy, the surgeon visualizes the anterior chamber structures through a special lens (goniolens) to create openings in the trabecular meshwork. The goal of the procedure is to eliminate any resistance imposed by the abnormal trabecular meshwork. A clear cornea is necessary for direct visualization of the anterior chamber structures during this procedure.

In trabeculotomy, the trabecular meshwork is incised by cannulating Schlemm's canal with a metal probe or suture via an external opening in the sclera.

In trabeculectomy, a section of trabecular meshwork and Schlemm's canal is removed under a partial thickness sclera flap to create a wound fistula [Morales et al 2013, Chen et al 2014a].

In deep sclerectomy the dissection of a deep scleral flap, deroofing of Schlemm's canal, and preserving the structural integrity of the trabecular meshwork results in improved aqueous outflow outside the anterior chamber.

Note: In contrast to goniotomy, deep sclerectomy, trabeculotomy, and trabeculectomy can be performed in individuals with advanced glaucoma and cloudy corneas.

Glaucoma drainage implants or cyclodestruction may be used to control IOP when initial surgical procedures have failed.

More than one surgical intervention may be necessary to control IOP; thus, significant morbidity is associated with both PCG and the currently available surgical treatment options. Individuals with milder forms of disease who present later in childhood often do well with a single surgical procedure and have an excellent visual prognosis later in life.

Clarity of the cornea and other ocular media, control of the ocular dimensions (corneal diameters and axial lengths), and optic nerve damage are important indicators of the course of the disease following surgery. Reported success rates for each (initial) procedure are approximately 80%. Infants with elevated IOP and cloudy corneas at birth have the poorest prognosis. The most favorable outcome is seen in infants in whom surgery is performed between the second and eighth month of life. With increasing age, surgery is less effective in preserving vision.

Medications. Beta-blockers (e.g., timolol), parasympathomimetics (e.g., pilocarpine), sympathomimetics (e.g., adrenergic agonists and alpha-2 adrenergic receptor agonists), carbonic anhydrase inhibitors, and prostaglandin agonists have all been used. These medications, particularly the alpha-2 adrenergic receptor agonists, may have severe side effects and must be used with caution in infants and children [Maris et al 2005, Papadopoulos & Khaw 2007].

Surgery should not be delayed in an attempt to achieve medical control of IOP.

Medication may be used preoperatively to lower the IOP to prevent optic nerve damage, to reduce the risk of sudden decompression of the globe, and to clear the cornea for better visualization during examination and surgery.

Postoperatively, medication may help control IOP until the success of the surgical procedure is established.

Medical therapy is also used when surgery may be life threatening or has led to incomplete control of the glaucoma [deLuise & Anderson 1983].

Treatment of refractive errors. Amblyopia from uncorrected refractive errors often associated with PCG must be treated to obtain optimal visual function.

Prevention of Secondary Complications

Medications such as Phospholine Iodide® (echothiophate) need to be discontinued before surgery, especially if succinylcholine is used because of the danger of prolonged apnea.

Surveillance

Lifelong monitoring is necessary to ensure control of IOP to preserve remaining vision and to prevent further loss of vision; the intervals at which monitoring needs to be performed vary depending on the severity of disease and control of IOP.

Once IOP is controlled and the child is visually rehabilitated, follow up is typically every three months to keep IOP at the "target" level, which depends on the severity of the glaucomatous optic nerve damage and the age of the individual. Standard clinical follow-up tests include optic nerve photography and visual field testing. The complete ophthalmic evaluation often requires examination under anesthesia or sedation in infants and in young and uncooperative children. This process may be challenging to the individual, the family, and the treating physician [deLuise & Anderson 1983, Ho & Walton 2004].

Agents/Circumstances to Avoid

Alpha-2 agonists should be avoided in children in the treatment of elevated IOP because of the risk for apnea and bradycardia.

Evaluation of Relatives at Risk

Testing at-risk sibs in the neonatal period may be helpful in establishing the diagnosis of PCG early and in avoiding repeated examinations under anesthesia in at-risk young children.

- Molecular genetic testing alone is appropriate in sibs of affected individuals in whom the pathogenic variant(s) have been identified.
- If the PCG-related pathogenic variant(s) have not been identified in an affected family member (i.e., no definitive exclusion of the disease is possible by molecular genetic testing), screening including IOP measurements under anesthesia/sedation may be necessary.

Note: The literature is unclear as to timing of the onset of glaucoma, especially in families in whom pathogenic variants have been identified. In this high-risk group, it may be appropriate to perform yearly glaucoma screening into young adulthood.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary congenital glaucoma (PCG) caused by pathogenic variants in *CYP1B1* or *LTBP2* is inherited in an autosomal recessive manner.

PCG caused by a pathogenic variant in *TEK* is inherited in an apparent autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *CYP1B1* or *LTBP2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *CYP1B1* or *LTBP2*-related PCG are obligate heterozygotes (carriers) for a *CYP1B1* or *LTBP2* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier for a *CYP1B1* or *LTBP2* pathogenic variant.

Carrier detection. Carrier testing for at-risk family members requires prior identification of the *CYP1B1* or *LTBP2* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All probands with *TEK*-related PCG reported to date have the disorder as a result of a *de novo* pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo TEK* pathogenic variant include molecular genetic testing.

Sibs of a proband

- All affected individuals reported to date have had a *de novo TEK* pathogenic variant, suggesting a low risk to sibs.
- If the *TEK* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated at 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *TEK*-related PCG has a 50% chance of inheriting the pathogenic variant.

Other family members. Given that all individuals with *TEK*-related PCG reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CYP1B1*, *LTBP2*, or *TEK* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for PCG and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Children's Glaucoma Foundation**
  2 Longfellow Place
  Suite 201

Boston MA 02114
Phone: 617-227-3011
Email: info@childrensglaucomafoundation.org
www.childrensglaucoma.org

- **GL Foundation**
  5979 NW 151st Street
  Suite 221
  Miami Lakes FL 33014
  Email: info@gl-foundation.org
  www.gl-foundation.org
- **Glaucoma Research Foundation**
  251 Post Street
  Suite 600
  San Francisco CA 94108
  Phone: 800-826-6693 (toll-free); 415-986-3162
  Fax: 415-986-3763
  Email: question@glaucoma.org
  www.glaucoma.org
- **International Glaucoma Association (IGA)**
  Woodcote House
  15A Highpoint Business Village
  Ashford Kent TN24 8DH
  United Kingdom
  Phone: +44 1233 64 81 70; +44 1233 64 81 64
  Email: helpline@glaucoma.uk
  www.glaucoma.uk
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Facts About Glaucoma
- **National Library of Medicine Genetics Home Reference**
  Early-onset glaucoma
- **NCBI Genes and Disease**
  Glaucoma
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov

https://eyegene.nih.gov/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Congenital Glaucoma: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GLC3A	*CYP1B1*	2p22.2	Cytochrome P450 1B1	CYP1B1 database CYP1B1 @ PharmVar	CYP1B1	CYP1B1
GLC3B	Unknown	1p36.2-p36.1	Unknown			
GLC3C	Unknown	14q24.2	Unknown			
GLC3D	*LTBP2*	14q24.3	Latent-transforming growth factor beta-binding protein 2	LTBP2 database	LTBP2	LTBP2
GLC3E	*TEK*	9p21.2	Angiopoietin-1 receptor	TEK database	TEK	TEK

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Congenital Glaucoma (View All in OMIM)

231300	GLAUCOMA 3, PRIMARY CONGENITAL, A; GLC3A
600221	TEK TYROSINE KINASE, ENDOTHELIAL; TEK
600975	GLAUCOMA 3, PRIMARY INFANTILE, B; GLC3B
601771	CYTOCHROME P450, SUBFAMILY I, POLYPEPTIDE 1; CYP1B1
602091	LATENT TRANSFORMING GROWTH FACTOR-BETA-BINDING PROTEIN 2; LTBP2
613085	GLAUCOMA 3, PRIMARY CONGENITAL, C; GLC3C
613086	GLAUCOMA 3, PRIMARY CONGENITAL, D; GLC3D
617272	GLAUCOMA 3, PRIMARY CONGENITAL, E; GLC3E

CYP1B1

Gene structure. *CYP1B1* spans 12 kb, comprises three exons (exons 2 and 3 are coding exons), and produces a 1,631-base mRNA product. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 200 pathogenic variants are listed in the Human Gene Mutation Database (HGMD) (see Table A), including missense and nonsense variants, small deletions/insertions/duplications, and exon and whole-gene deletions.

Table 3. *CYP1B1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.182G>A [1]	p.Gly61Glu	NM_000104.3 NP_000095.2
c.1159G>A [1]	p.Glu387Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Prevalence.

Normal gene product. Cytochrome P450 1B1 is a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids. Cytochrome P450 1B1 localizes to the endoplasmic reticulum and metabolizes procarcinogens including polycyclic aromatic hydrocarbons and 17-β-estradiol [Murray et al 2001].

Abnormal gene product. In silico and in vitro studies have been carried out to determine the effect of *CYP1B1* pathogenic variants on the structure and function of the protein. In vitro studies to determine the effect of *CYP1B1* pathogenic variants on the stability and function of the protein were carried out by Jansson et al [2001]. The authors studied the effect of two missense variants (p.Gly61Glu and p.Arg469Trp) on the stability and enzymatic activity of *CYP1B1*. It was observed that mutated protein p.Gly61Glu had lost 60% of its stability, while p.Arg469Trp retained about 80% of the stability compared to the wild type. The effects of mutation on protein function were further determined by an enzymatic assay that further confirmed their decreased metabolic activity (50%-70%) for all the substrates when compared to the wild type protein.

LTBP2

Gene structure. *LTBP2* transcript NM_000428.2 comprises 36 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Ali et al [2009] first reported four *LTBP2* missense variants and small deletions that caused PCG in four consanguineous families from Pakistan and in persons of Rom ethnicity. Narooie-Nejad et al [2009] subsequently reported two *LTBP2* loss-of-function pathogenic variants in Iranian families with PCG.

Normal gene product. The encoded protein NP_000419.1, comprising 1821 amino acids, belongs to the family of latent transforming growth factor (TGF)-beta binding proteins (LTBP), which are extracellular matrix proteins with multidomain structure. This protein is the largest member of the LTBP family; it possesses unique regions and is the most similar to the fibrillins. It has thus been suggested that the protein may have multiple functions: as a member of the TGF-beta latent complex, as a structural component of microfibrils, and as a mediator of cell adhesion.

Abnormal gene product. Pathogenic variants are expected to extensively affect protein structure and function and to interfere with both fibrillin 1 and fibulin 5 binding [Narooie-Nejad et al 2009].

TEK

Gene structure. *TEK* has multiple transcript variants, the longest of which is NM_000459.4 which is 4.7 kb in length and comprises 23 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Ten pathogenic variants are listed in HGMD, including missense, nonsense, and splicing variants, small deletions & insertions resulting in frameshifts, and one gross deletion of exons 2-4 [Souma et al 2016].

Normal gene product. *TEK* encodes a tyrosine-protein kinase that acts as cell-surface receptor, the angiopoietin-1 receptor. It is expressed almost exclusively in endothelial cells.

Abnormal gene product. Souma et al [2016] proposed that gain-of-function pathogenic variants in *TEK* result in venous malformations in nonocular tissues, whereas loss-of-function variants affect anterior chamber vascular development and result in primary congenital glaucoma.

Chapter Notes

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Revision History

- 17 August 2017 (sw) Comprehensive update posted live
- 20 March 2014 (me) Comprehensive update posted live
- 25 August 2011 (cd) Revision: sequence analysis of *LTBP2* and deletion/duplication analysis of *CYP1B1* available clinically as listed in the GeneTests Laboratory Directory
- 21 July 2011 (me) Comprehensive update posted live
- 3 December 2007 (me) Comprehensive update posted live
- 30 September 2004 (me) Review posted live
- 3 June 2004 (bab) Original submission

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