

GENETIC LANDSCAPE OF PRIMARY CONGENITAL GLAUCOMA: FROM LOCUS HETEROGENEITY TO OLIGOGENIC MODELS

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ABSTRACT

Primary congenital glaucoma (PCG) is the leading inherited cause of childhood blindness and has long served as a paradigm for monogenic eye disease. Biallelic loss-of-function variants in CYP1B1 at the GLC3A locus remain the single most consistent cause; their contribution, however, ranges from under a quarter of cases in East Asian cohorts to nearly all cases in founder populations such as the Slovak Roma and Saudi Arabian consanguineous families. This review synthesises three decades of linkage, sequencing, and functional data to reassess PCG as a genetic landscape rather than a single Mendelian disease. We revisit the taxonomy of GLC3 loci, including the still largely gene-negative GLC3B and GLC3C intervals and the more recently resolved LTBP2 and TEK genes, and we identify concrete methodological reasons genotype-phenotype correlations diverge between cohorts. Null CYP1B1 alleles reproducibly predict earlier onset and worse surgical outcomes, but penetrance is incomplete and severity varies even within families sharing a genotype, implicating modifier loci such as MYOC, FOXC1, PITX2, and SVEP1. Between 20% and 40% of clinically typical patients remain genetically unsolved after comprehensive screening. We weigh two explanations for this gap – undetected oligogenic interaction versus sequencing-technology limitations – and argue both should be tested empirically before either is favoured. We discuss clinical translation, including tiered sequencing algorithms, interpretation of heterozygous findings, and genetic counselling for sibling risk, and close with concrete priorities: multicentre consortia, functional validation at GLC3B/GLC3C, and near-term as well as long-term strategies for a disease whose therapy must act on development, not degeneration.

KEYWORDS: primary congenital glaucoma; CYP1B1; genotype-phenotype correlation; oligogenic inheritance; TEK; next-generation sequencing

1. INTRODUCTION: the changing view of PCG

Primary congenital glaucoma occupies an uncomfortable position among inherited eye diseases: it is rare by any epidemiological measure, yet it accounts for a disproportionate share of irreversible childhood blindness worldwide [1,2]. The clinical picture is deceptively uniform – elevated intraocular pressure from birth or early infancy, corneal oedema and Haab striae, buphthalmos, and optic nerve cupping – which for much of the twentieth century encouraged the assumption that a single developmental defect of the anterior chamber angle was responsible. The identification of the GLC3A locus on chromosome 2p21 and its causal gene, CYP1B1, seemed to confirm this view: here, at last, was a single enzyme whose loss could explain trabeculodysgenesis [3,4,5]. PCG must also be distinguished from phenotypically similar glaucomas occurring as part of broader syndromes – Sturge-Weber syndrome, neurofibromatosis type 1, and Axenfeld-Rieger spectrum disorders – addressed only briefly here since their genetic basis and systemic implications differ from isolated PCG.

Three decades on, the single-gene picture has fractured instructively. CYP1B1 remains the most frequently implicated gene, but its contribution varies by an order of magnitude across populations, two further loci (GLC3B and GLC3C) have resisted gene identification for almost as long as they have been mapped, and genes originally associated with adult and juvenile glaucomas – LTBP2, TEK, MYOC, FOXC1 – turn out to cause, mimic, or modify the congenital phenotype [6,7,8]. What was once a textbook monogenic recessive disease is better understood as a genetically heterogeneous landscape in which a shared final pathway – failure of trabecular meshwork and Schlemm canal morphogenesis – is reached by several independent, sometimes interacting, genetic routes.

This review has four aims: to set out a current taxonomy of the GLC3 loci; to examine genotype-phenotype correlations and the methodological reasons they are inconsistent between cohorts, rather than simply cataloguing them; to weigh, as competing testable hypotheses rather than a settled conclusion, whether oligogenic interaction or sequencing-technology limitations better explain the persistent “missing heritability” of PCG; and to translate these findings into a testing and counselling framework that is explicit about its own current limitations.

2. Taxonomy of the genetic loci in PCG

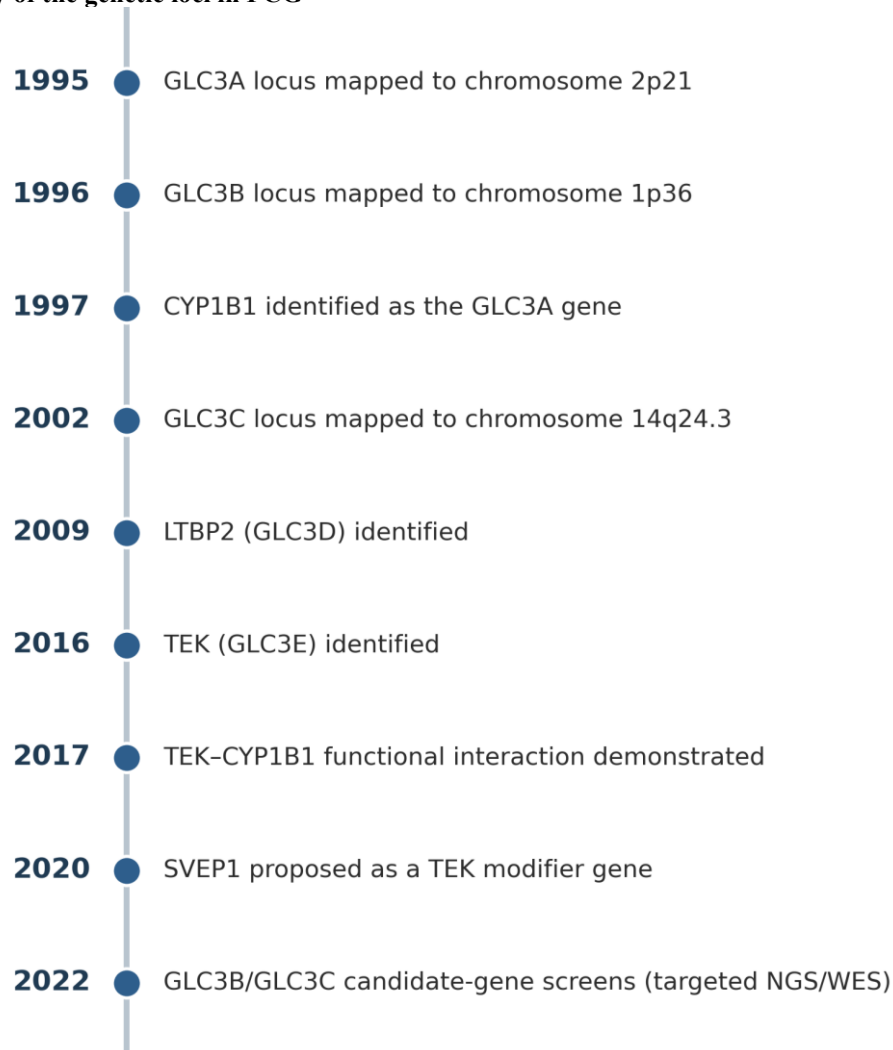


Figure 1. Milestones in the genetic dissection of primary congenital glaucoma, 1995-2022.

2.1 The principal locus: GLC3A and CYP1B1

GLC3A was mapped to chromosome 2p21 in 1995 through linkage analysis of consanguineous Turkish and Slovak Roma families with autosomal recessive PCG [3], and CYP1B1 was identified as the causal gene two years later [4]. CYP1B1 encodes a cytochrome P450 enzyme expressed in the trabecular meshwork, ciliary body, and iris that oxidises retinol to retinoic acid and also metabolises steroid hormones and arachidonic acid derivatives [9]. Retinoic acid signalling governs neural-crest-derived periocular mesenchyme differentiation, and disruption of this pathway is plausibly, though not definitively, linked to the trabeculodysgenesis seen histologically in PCG donor tissue, alongside a second, non-exclusive mechanism of CYP1B1-deficiency-driven oxidative stress within the outflow pathway [10,9]. More than 150 CYP1B1 variants – missense, nonsense, frameshift, and splice-site – have now been catalogued in PCG cohorts worldwide [11].

One speculative but useful framework for why CYP1B1 tolerates, and in some populations accumulates, such a large number of coding variants notes that the gene's principal ancestral role is detoxifying polycyclic aromatic hydrocarbons and other xenobiotics, a function distinct from its ocular role [9]. If selective pressure on CYP1B1 has been shaped mainly by xenobiotic and metabolic considerations rather than ocular development, hypomorphic ocular-relevant alleles could persist at appreciable frequency, particularly where consanguinity increases the chance that two such alleles meet in one individual. This is offered only as a hypothesis-generating framework, not an established explanation, and it does not by itself account for the population-specific mutation spectrum discussed next.

2.2 The orphan loci: GLC3B and GLC3C

GLC3B was mapped to chromosome 1p36.1-p36.2 in 1996 in families showing no linkage to GLC3A [6], and GLC3C was subsequently localised to 14q24.3 in a large consanguineous pedigree unlinked to either locus [12,13]. Almost thirty years later, neither locus has yielded a confirmed causal gene. Whole-exome sequencing of PCG families excluded from GLC3A, GLC3B, and GLC3D by linkage analysis has searched explicitly for the GLC3B/C genes, without a reproducible candidate emerging from the modest number of pedigrees studied [14]. A more targeted approach – next-generation sequencing restricted to the GLC3B and GLC3C intervals in a

Chinese cohort in whom fewer than one in five cases carry a CYP1B1 or LTBP2 variant – has begun nominating candidates, though functional validation is still awaited [15]. The same sequencing-driven logic has nominated genes entirely outside the classical GLC3 loci: a rare homozygous nonsense variant in GUCA1C was identified in two affected siblings, with a guca1c knockout zebrafish model showing retinal ganglion cell apoptosis and expression of the encoded protein, GCAP3, in ciliary epithelium and retina [16,17]. This persistence demonstrates that linkage mapping does not guarantee gene discovery when a locus harbours many genes, when causal variants lie in regulatory rather than coding sequence, or when available families are too few for exome-wide significance.

2.3 Rarer, more recently resolved loci: LTBP2, TEK, and ANGPT1

LTBP2, mapped near but distinct from the GLC3C interval on 14q24, encodes an extracellular matrix glycoprotein of the latent TGF- β binding protein family. Null LTBP2 mutations cause PCG in consanguineous Pakistani families and in Roma/Gypsy patients, in whom a single founder nonsense variant accounts for a substantial share of disease alleles [7,18]. LTBP2-related disease frequently co-occurs with ectopia lentis and microspherophakia, reflecting the protein's zonular role; homozygosity for the Roma founder allele produces a more severe phenotype and higher surgical burden than compound heterozygous or CYP1B1-driven disease in the same population [18]. LTBP2 variants have also been identified alongside CYP1B1 in Indian PCG families, so the gene, while a minor overall contributor, is not confined to founder populations [19].

A mechanistically distinct route emerged in 2016, when heterozygous loss-of-function TEK variants were identified in a multiethnic cohort of 189 PCG families already negative for CYP1B1, LTBP2, MYOC, and FOXC1 [8]. TEK signalling is required for Schlemm canal endothelial development, and Tek-hemizygous mice show a hypoplastic canal with elevated intraocular pressure, mirroring the human phenotype [8]. Unlike the recessive GLC3A/D pattern, TEK-related disease (GLC3E) is autosomal dominant with markedly incomplete penetrance – more than a third of confirmed carriers in the original cohort showed no early-onset phenotype [8]. Subsequent cohorts from China and Mexico confirmed both this variability and, in the Chinese series, a distinctive concentration of variants in the receptor's ectodomain, while the Mexican series again showed that penetrance and severity cannot be predicted from mutation status alone [20]. Rare variants in ANGPT1, a TEK ligand, have since been reported in patients lacking mutations in the other known PCG genes [1].

Table 1 summarises the recognised GLC3 loci, their genes where identified, inheritance pattern, and approximate contribution to case series.

Table 1. Genetic loci associated with primary congenital glaucoma (GLC3 series).

Locus	Chr.	Gene	Protein function	Inheritance	Status / approximate contribution	Ref.
GLC3A	2p21	CYP1B1	Cytochrome P450; retinoic acid/steroid metabolism	Autosomal recessive	Most frequent identified cause; ~5% (East Asia, South Africa) to >90% (Slovak Roma, Saudi Arabia)	[3,4]
GLC3B	1p36.1-p36.2	Not yet identified	–	Autosomal recessive (mapped)	Gene unresolved since 1996; candidate-gene screens ongoing	[6,15]
GLC3C	14q24.3	Not yet identified	–	Autosomal recessive (mapped)	Gene unresolved since 2002; distinct from adjacent GLC3D/LTBP2 interval	[13, 15]
GLC3D	14q24 (near GLC3C)	LTBP2	Extracellular matrix glycoprotein; zonular microfibril assembly	Autosomal recessive	Minor overall contributor; founder allele dominant in Roma/Gypsy population; ectopia lentis/microspherophakia	[7,18]
GLC3E	9p21	TEK (ANGPT1 as related ligand gene)	Angiopoietin receptor tyrosine kinase; Schlemm canal endothelial development	Autosomal dominant, incomplete penetrance	Identified in ~5% of previously gene-negative multiethnic PCG cohort; penetrance ~64%	[8]

3. Global mutation spectrum: an ethnogenomic perspective

Perhaps no single fact about PCG genetics is as clinically important, or as frequently under-appreciated, as the scale of population variation in CYP1B1 contribution. Systematic reviews report CYP1B1 variants explaining as little as 5% of PCG cases in some South African, Chinese, and Japanese cohorts, 30-55% in Indian, Turkish, Iberian, and Latin American series, and 64-87% in Pakistani, Iranian, and Saudi Arabian cohorts, rising to effectively all cases in the endogamous Slovak Roma population [1,21,22,23,24,25,26,27]. Table 2 and Figure 2 summarise this gradient with representative recurrent alleles.

Table 2. Population variation in CYP1B1 contribution to primary congenital glaucoma.

Population / cohort	Approx. proportion of PCG attributable to CYP1B1	Notable recurrent allele(s)	Ref.
Slovak Roma (founder population)	~90-100%	p.Glu387Lys and related founder haplotypes	[18]
Saudi Arabia	76-87%	p.Gly61Glu, p.Arg469Trp	[27]
Pakistan	64-85%	Multiple recurrent alleles, high consanguinity	[25,11]
Iran	47-86%	p.Gly61Glu common in some cohorts	[26]
India	~30-55%	p.Glu229Lys, p.Arg368His (also reported as polymorphic)	[24,28]
Spain / Portugal	~30-55%	Multiple null and hypomorphic alleles characterised functionally	[29]
Mexico	~20-45%	Population-specific founder contribution reported	[30]
Brazil	~30-55%	Poor-prognosis alleles linked to worse surgical outcome	[31,32]
United States	~20-30%	Heterogeneous; combined CYP1B1/MYOC/LTBP2 screening	[33]
China	~5-23%	Low overall contribution; GLC3B/C candidate work ongoing	[15,23]
Japan	~5-23%	Low overall contribution	[22]
South Africa	~5-23%	Low overall contribution on exome screening	[21]

This gradient tracks two forces. The first is consanguinity: a high rate of first-cousin marriage raises the probability that both alleles of a rare recessive variant are inherited identical-by-descent, which both increases PCG incidence and concentrates a small number of founder mutations – p.Gly61Glu in Saudi Arabia, p.Glu229Lys/p.Arg368His across the Middle East and South Asia [27,11,34]. The Slovak Roma illustrate the founder effect at its most extreme: a handful of ancestral CYP1B1 and LTBP2 haplotypes account for the great majority of disease alleles generations later [18]. Outside strongly consanguineous or founder populations, contribution is more heterogeneous: a US cohort with limited consanguinity found a causal variant in only a minority of probands on combined CYP1B1/MYOC/LTBP2 screening, a yield comparable to Australasian registry data [33,35].

The second, less intuitive force is what happens where CYP1B1 contribution is low. In Chinese and Japanese cohorts, only a minority carry pathogenic CYP1B1 or LTBP2 variants even after complete coding-sequence analysis [15,22,23]. This is compatible with other, still unidentified genes predominating in East Asian PCG, consistent with the GLC3B/GLC3C work above. It does not, however, exclude a second possibility. Environmental or epigenetic modifiers may interact with a common genetic background to determine whether a comparable variant burden crosses the threshold into overt disease. Distinguishing “different genes” from “same genes, different modifying context” as competing explanations for regional heterogeneity is one of the more tractable open questions in the field, requiring large, harmonised international cohorts rather than further isolated single-population studies.

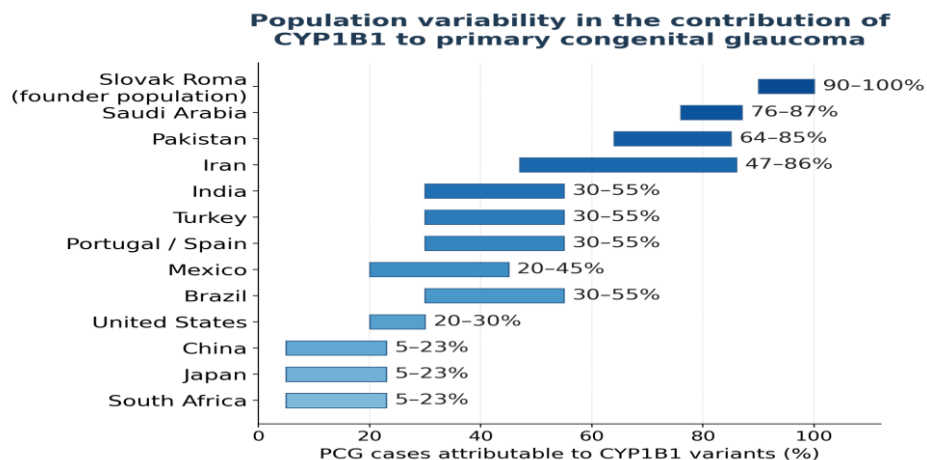


Figure 2. Population variability in the proportion of primary congenital glaucoma cases attributable to CYP1B1 variants, drawn from the cohort studies cited in the text. Ranges reflect heterogeneity across cohorts within the same region rather than a single point estimate.

4. Genotype-phenotype correlations: what holds and what does not

4.1 Reasonably consistent associations for CYP1B1

Across many cohorts, patients carrying two null (nonsense, frameshift, or canonical splice-site) CYP1B1 alleles present earlier, more severely, and with a poorer surgical prognosis than those carrying missense or hypomorphic

alleles. In a detailed Spanish series, patients homozygous for null alleles had onset at birth or within the first month of life, whereas hypomorphic missense alleles showed incomplete penetrance and later presentation [29]. Comparable severity gradients by mutation class are reported in Egyptian, Brazilian, and Indian cohorts, with the proportion of eyes classified as severe highest among frameshift carriers [31,32,24]. Structural correlates support this gradient: electron microscopy of trabeculectomy specimens shows that goniodysgenesis severity – underdeveloped collector channels, an abnormally inserted ciliary muscle, trabecular endothelial cell loss – tracks with residual CYP1B1 enzymatic activity predicted from genotype [10]. CYP1B1-positive disease is associated with a higher rate of repeat surgery in several series, though in others it correlates with better initial surgical success once corneal transparency is accounted for [36,32].

4.2 Where the correlation breaks down

The severity gradient above is a tendency, not a rule. Identical CYP1B1 genotypes, including the same homozygous missense variant, have produced markedly different ages of onset and severity within members of the same family – a discordance the primary variant alone cannot explain [1]. Roughly a fifth of PCG patients carrying a CYP1B1 variant are heterozygous, with no second pathogenic allele found despite thorough screening, a finding incompatible with simple recessive causation and an early clue to modifying factors [37].

What is established, from a small number of well-documented families, is that digenic interaction is biologically possible; what remains unresolved is how common or clinically weighty it is. A family with autosomal dominant glaucoma showed markedly earlier onset (mean age 27 versus 51 years) when a MYOC mutation was co-inherited with a CYP1B1 variant, compared with MYOC alone – a single-family observation that nonetheless prompted the proposal that CYP1B1 can modify MYOC-driven disease [38]. TEK and CYP1B1 interact directly: CYP1B1 protein attenuates TEK signalling, and heterozygous variants in both genes co-occur in some patients otherwise carrying an apparently incidental heterozygous CYP1B1 finding [39]. SVEP1 has similarly been proposed as a TEK modifier, based on eight families in which loss-of-function SVEP1 alleles reduced TEK expression in Schlemm canal endothelium and correlated with greater severity in one pedigree [40]. Screening of FOXC1 in CYP1B1/MYOC-negative families identified rare variants with both increased and decreased transactivation, including one carrier who also carried a hypomorphic PITX2 variant [37]. A larger, dedicated FOXC1 screen found the gene's independent contribution limited, and a further study extended the modifier framework to FOXC2/PITX2 variants of mild functional effect [41,42].

4.3 Phenotypic mimicry and its diagnostic consequences

A further complication, with direct clinical stakes, is that clinically indistinguishable PCG can arise from mechanistically unrelated genes. Recessive CYP1B1- or LTBP2-driven disease, dominant TEK-related disease with incomplete penetrance, and FOXC1/PITX2-associated anterior segment dysgenesis with glaucoma can all present with photophobia, epiphora, and corneal enlargement in the first months of life, yet carry different recurrence risks and surgical responses [8,43]. Figure 3 illustrates the two best-characterised convergent routes: CYP1B1 loss primarily disrupts neural-crest-derived periocular mesenchyme differentiation, whereas TEK/ANGPT1 loss primarily disrupts Schlemm canal endothelial specification, yet both converge on the same final defect – a hypoplastic drainage structure with elevated outflow resistance. This convergence means initial testing cannot rely on phenotype alone to select which gene or panel to test first, a point developed in Section 6 and in Table 3.

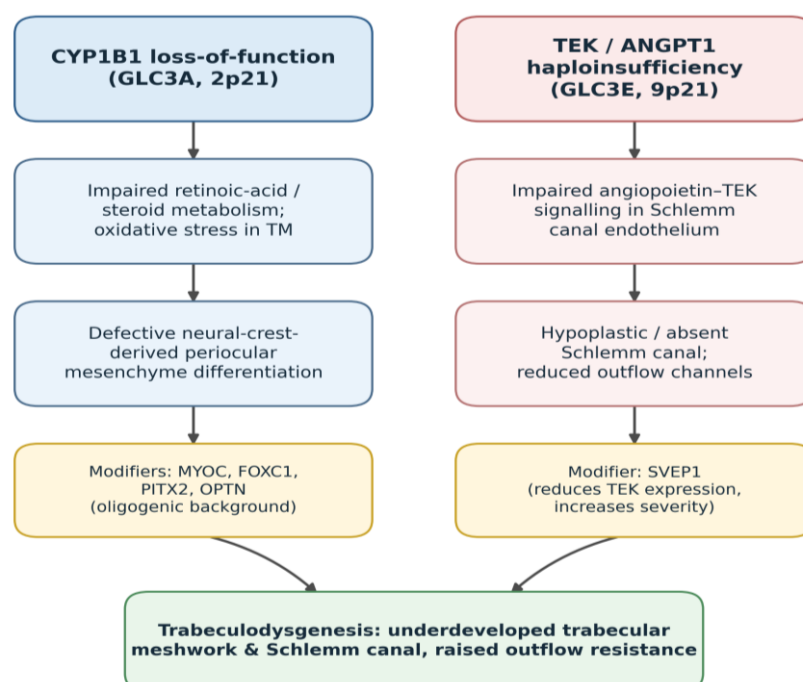


Figure 3. Two genetically distinct but convergent pathogenic routes to the primary congenital glaucoma phenotype, illustrated by the CYP1B1 (GLC3A) and TEK (GLC3E) pathways.

4.4 Methodological sources of inconsistency between cohorts

A critical reading of this literature must go beyond cataloguing discordant findings to ask why they are discordant, and the honest answer is that most apparent contradictions reflect study design rather than biology. Four sources of variability recur. First, inclusion criteria differ: some cohorts define PCG strictly by onset before three years with a fixed corneal-diameter threshold, others include broader age windows or secondary glaucomas, so a “CYP1B1 contribution of 55%” in one series and “20%” in another may reflect different denominators as much as different genetics. Second, completeness of second-allele identification varies: studies relying on Sanger sequencing of coding exons alone systematically under-ascertain deep intronic, promoter, and copy-number variants, inflating the apparent heterozygous-only fraction used as evidence for oligogenic inheritance. Third, follow-up duration and surgical outcome definitions are inconsistent, so pooled comparisons of “repeat surgery rate” between cohorts are not strictly comparable. Fourth, several digenic and oligogenic findings in Section 4.2 rest on single families or cohorts of fewer than ten pedigrees – sufficient to show an interaction is biologically possible, not to estimate its population frequency. Publication bias toward positive, novel-mutation findings compounds this, as negative modifier-gene screens are rarely reported with equal prominence [1].

These four sources are not equally fixable. Two – incomplete second-allele ascertainment and heterogeneous outcome definitions – are technical problems, correctable by standardising sequencing depth and coverage of non-coding regions and by publishing agreed criteria for surgical success. The other two – divergent inclusion criteria and small modifier cohorts – reflect the underlying reality of a rare disease and cannot be solved at the level of a single centre; they require multicentre consortia and harmonised phenotyping protocols, the theme we return to in Sections 5 and 8. Without this distinction, the discussion remains descriptive rather than prescriptive.

Table 3 illustrates a related point: distinguishing PCG genetically from other early-onset glaucomas with overlapping features is itself methodologically important, since pooling these entities in a single “childhood glaucoma” cohort – common practice in smaller series – further confounds genotype-phenotype comparison.

Table 3. Distinguishing primary congenital glaucoma from other early-onset glaucomas with overlapping clinical features.

Feature	Primary congenital glaucoma	Juvenile open-angle glaucoma	Axenveld-Rieger spectrum with glaucoma
Typical age of onset	Birth to 3 years	5-40 years	Variable; often childhood, can be later
Primary genes implicated	CYP1B1, LTBP2, TEK, ANGPT1	MYOC, less commonly CYP1B1 as modifier	FOXC1, PITX2
Recommended first-tier genetic test	CYP1B1 sequencing (+ CNV analysis); LTBP2 if ectopia lentis/microspherophakia	MYOC sequencing	FOXC1 and PITX2 sequencing
Inheritance pattern	Mostly autosomal recessive; TEK dominant with incomplete penetrance	Autosomal dominant (MYOC)	Autosomal dominant, variable expressivity
Characteristic non-ocular/ocular clues	Buphthalmos, Haab striae, corneal oedema	Usually no anterior segment structural anomaly	Iris/corneal dysgenesis, systemic (dental, umbilical, cardiac) features possible
Angle appearance	Trabeculodysgenesis	Grossly open, structurally unremarkable angle	Anterior segment dysgenesis with iridocorneal adhesions
Key systemic associations / prognosis note	None typical; surgical prognosis tracks CYP1B1 null vs. missense status	None; prognosis tied to age at diagnosis and IOP control	Dental hypoplasia, redundant periumbilical skin, cardiac defects; glaucoma risk ~50% and often later-onset, so lifelong surveillance is needed even after a normal childhood exam

5. Missing heritability: oligogenic biology or technical ceiling?

A substantial minority – commonly cited at 20-40%, higher in some East Asian cohorts – of clinically classical PCG patients remain without an identified causal variant after CYP1B1 and LTBP2 sequencing, and frequently after broader panel or exome sequencing as well [15,1]. Two explanations compete, and both deserve to be tested rather than assumed.

What is established, from Section 4.2, is a small number of well-documented families showing that oligogenic interaction is biologically possible (CYP1B1 with MYOC or TEK, FOXC1 with PITX2, TEK with SVEP1) [38,39,37,40]. What remains hypothesis is that this mechanism explains a meaningful share of the unsolved 20-40%, rather than being a rare curiosity; no study has yet performed a systematic rare-variant burden analysis across the anterior-segment gene set in a large, harmonised, unsolved PCG cohort against an ancestry-matched reference, nor applied formal statistical tests for epistasis. Such a design – several hundred to a thousand unrelated

probands, pooled across centres – is the concrete next step needed to move this model from plausible narrative to tested hypothesis.

It is equally important to weigh the null hypothesis: that missing heritability is not oligogenic at all but reflects technical limitations of current sequencing – deep intronic variants, promoter mutations, structural rearrangements, and mosaicism, none reliably detected by exome or short-read genome sequencing. This mechanism is not mutually exclusive with oligogenic inheritance, but the two are empirically distinguishable: systematic long-read whole-genome sequencing, paired with RNA-seq from accessible tissue where feasible, would clarify what fraction of “unsolved” cases reflect non-coding or structural variation before oligogenic biology is invoked to explain the remainder. Until both experiments are done, oligogenic interaction, technical ceiling, and additional undiscovered monogenic causes at loci such as GLC3B/C remain equally plausible and not mutually exclusive.

6. Clinical genetics: from diagnosis to prognosis

6.1 Diagnostic testing algorithms and their trade-offs

Genetic testing in PCG serves three purposes: confirming a molecular diagnosis, informing prognosis, and enabling accurate counselling. Testing strategy should be informed by consanguinity, ancestry, and family history rather than applied uniformly. A pragmatic tiered approach begins with CYP1B1 sequencing, including copy-number screening that Sanger sequencing alone can miss, extends to LTBP2 where ectopia lentis, microspherophakia, or relevant founder ancestry is present, and moves to a broader panel or exome covering TEK, MYOC, FOXC1, PITX2, and ANGPT1 when first-tier testing is negative or family history suggests dominant, incompletely penetrant inheritance [43,1]. In practical terms, this means: in populations with documented high CYP1B1 contribution (e.g. Middle Eastern, South Asian, or known founder ancestry), Sanger sequencing of CYP1B1 first is the more cost-effective default; in low-contribution or ethnically mixed populations, or wherever first-tier testing is negative, moving directly to exome-based testing is more efficient than sequential single-gene panels, since pooled data show whole-exome sequencing outperforming panel sequencing specifically for PCG (approximately 47% versus lower panel yields) [44]. Real-world panel yields in unselected childhood glaucoma populations are more modest, 13-39%, and comparable strategies across congenital eye malformations report similar cumulative yields with a staged approach [44,45].

A recurring practical problem is a heterozygous CYP1B1 finding with no second identified allele, occurring in roughly a fifth of CYP1B1-positive cases (Section 4.2). Such a result should be neither reported as diagnostic nor dismissed as incidental: reflex testing should include copy-number analysis and screening of TEK and other modifier candidates in the same sample, since a heterozygous CYP1B1 variant with a second-gene finding may together explain the phenotype even though neither alone meets conventional single-gene criteria.

6.2 Genotype as a prognostic tool, and prenatal testing considerations

Beyond diagnosis, genotype meaningfully informs expectations about disease course. Null CYP1B1 genotypes are consistently, if imperfectly, associated with earlier onset, greater baseline severity, and more surgical procedures than missense or CYP1B1-negative disease [29,32,36]. Surgical scarring has a partly modifiable biological basis: TGF- β 1 is a principal driver of post-trabeculectomy fibrosis, is upregulated by VEGF signalling in the surgical wound, and is targeted by anti-fibrotic strategies including anti-placental growth factor antibodies, which may eventually let surgical planning be informed by a patient's genetically and biochemically indicated fibrosis risk rather than clinical staging alone [46,47]. This connection between genotype and fibrotic risk remains inferential rather than directly demonstrated.

For families with a confirmed biallelic CYP1B1 or LTBP2 finding, sibling recurrence risk is the standard 25% for autosomal recessive inheritance. Prenatal or early postnatal testing of at-risk siblings is clinically useful because prompt surgery improves visual outcome, but it is only possible once the specific familial mutations are known from the affected proband – de novo prenatal screening without a prior molecular diagnosis in the family is not informative [43]. Because PCG is treatable and even null genotypes do not predict outcome with certainty, prenatal diagnosis functions mainly to enable planning for immediate postnatal assessment rather than reproductive decision-making, and families should be counselled accordingly. For TEK-related disease the problem is more acute: because penetrance is only around two-thirds and severity is modified by at least one identified gene (SVEP1) and probably others unknown, a prenatal or presymptomatic TEK finding cannot be translated into a specific risk of disease or its severity, and counselling should say so explicitly [8,40].

DISCUSSION

Three broader conclusions emerge. First, the GLC3A/CYP1B1 story is a genuine success of positional cloning and remains the backbone of clinical testing, but should not stand in for the whole disease: in much of the world CYP1B1 explains a minority of PCG, and the field's historical concentration on this one gene has likely slowed progress on GLC3B, GLC3C, and the broader modifier landscape. Second, genotype-phenotype studies that treat each gene in isolation will keep producing inconsistent, population-specific results until the fixable methodological sources identified in Section 4.4 are addressed and analyses jointly model variant burden across the anterior-segment gene set rather than gene-by-gene [38,37,39]. Third, clinical translation has so far been more successful in diagnosis and counselling than in altering management: genotype informs prognosis, but no gene-

directed therapy has reached clinical use, and current gene-editing and cell-based strategies for adult glaucomas remain preclinical [48,49,50].

A brief, speculative aside on epigenetics is worth flagging rather than developing at length, because no PCG-specific epigenetic study yet exists. DNA methylation regulates gene expression in the adult trabecular meshwork – pro-fibrotic genes are hypomethylated and anti-fibrotic regulators hypermethylated in glaucomatous relative to healthy adult tissue, a shift reproducible by hypoxic exposure in vitro [51]. Whether analogous prenatal methylation changes modulate PCG penetrance is an untested extrapolation from adult tissue biology, not a demonstrated mechanism.

These conclusions warrant caution on their own terms. Much of the literature derives from single-centre cohorts of modest size with heterogeneous phenotyping and variable completeness of second-allele identification; the ranges in Figure 2 illustrate population variability rather than precise epidemiological estimates. Publication bias toward positive associations likely inflates the apparent strength of some correlations [1]. As Section 5 makes explicit, oligogenic inheritance and sequencing-technology limitations are competing, empirically distinguishable, and currently untested explanations for missing heritability, and both remain live possibilities alongside additional undiscovered monogenic causes.

CONCLUSION

Primary congenital glaucoma is best understood not as a single monogenic disease but as a clinically convergent phenotype produced by a limited number of genetically distinct developmental pathways, modulated by an expanding set of interacting genes and, plausibly but unconfirmed, by epigenetic factors. This favours tiered, population-informed testing over single-gene screening and genotype-aware counselling, while requiring honesty about what genotype cannot yet predict, particularly for incompletely penetrant TEK-related disease.

Progress on GLC3B/GLC3C, and on adjudicating between the oligogenic and technical-ceiling explanations outlined in Section 5, will depend on international consortia assembling cohorts large enough for exome- or genome-wide significance – a scale individual centres cannot reach given disease rarity. Functional validation remains rate-limiting: candidate genes require confirmation in independent families and in models capable of recapitulating trabecular meshwork and Schlemm canal dysgenesis, for which CRISPR-engineered zebrafish knockouts, as already used for GUCA1C, and iPSC-derived outflow tissue offer increasingly realistic platforms [16,50].

Gene-directed therapy for PCG faces an obstacle adult glaucoma gene therapy does not: PCG is a disorder of development, so a durable fix would need to act on, or before, a developmental window typically already closed by diagnosis, restoring trabecular meshwork and Schlemm canal morphogenesis rather than modulating aqueous dynamics in an already-formed eye – a harder problem than the ciliary-body or trabecular-meshwork targets of current adult CRISPR approaches [48,49]. Three directions, all early-stage, are nonetheless worth pursuing. Family-history-based neonatal screening in known biallelic-carrier families could identify at-risk infants before symptom onset, preserving whatever developmental window remains for any future intervention. Ex vivo strategies – harvesting and gene-correcting a patient's own trabecular meshwork or iPSC-derived outflow cells before reimplantation, building on platforms already validated in animal models – sidestep some in vivo delivery constraints [50]. For hypomorphic missense genotypes retaining partial enzymatic activity, small-molecule pharmacological chaperones that stabilise misfolded CYP1B1 protein, analogous to chaperone strategies explored for other misfolding enzyme deficiencies, are a speculative but mechanistically plausible alternative to gene replacement. None of these is close to clinical testing in PCG specifically, but together they indicate that the obstacle described above is a research priority rather than a dead end.

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