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The *CYP1B1* gene mutation prevalence in primary congenital glaucoma: A review of Pakistani families

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Abstract
Glaucoma is the second leading cause of blindness worldwide. It is a neuropathic disease, mostly inherited in an autosomal recessive form. Primary congenital glaucoma (PGC) is characterized by increased intraocular pressure and optic nerve damage. It is a clinically and genetically heterogeneous eye disorder. To date, four genetic loci are reported to have been linked to PCG, including GLC3A, GLC3B, GLC3C, and GLC3D. The *CYP1B1* gene resides in the GLC3A locus on chromosome 2. Mutations in the *CYP1B1* gene are linked to PCG. It is most prevalent in countries like Pakistan, where consanguinity is common. Both familial and sporadic forms of PCG are common in Pakistan. This study was undertaken to analyze the mutations in the *CYP1B1* gene in the cause of PCG in consanguineous Pakistani families. The *CYP1B1* mutations linked to PCG in consanguineous Pakistani families were analyzed from a thorough analysis of the data available to date on Google Scholar, Medline, and PubMed, and were further demonstrated by a pie-chart diagram. The graphical representation of the percent prevalence of these mutations was accessed. A total of 98 missense, frameshift, and nonsense mutations were found. The missense mutation, p.Arg390His, was the most significant, particularly in Punjab, followed by the p.Glu229Lys mutation. In Pakistan, there is a higher prevalence of PCG in consanguineous families. Several mutations in the *CYP1B1* gene cause PCG in the Pakistani population, with p.Arg390His being the dominant one. Knowledge of prevalent PCG-causing mutations in a population is useful in establishing prenatal and pre-symptomatic diagnoses for better glaucoma management.

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Introduction

Glaucoma (the second leading cause of visual blindness) affects 65 million people, accounting for 15% of blindness nationwide (Pascolini and Mariotti, 2012; Arshad et al., 2024) According to the 2017 Global Burden of Disease (GBD) report, the third most common handicap was blindness and visual impairment, affecting 1·34 billion people worldwide (James et al., 2018). An estimated 1.12 million of Pakistan's 207.7 million citizens were blind, according to the GBD (2017) report. In Pakistan, glaucoma ranks as the fourth most frequent cause of reported blindness (Bashir et al., 2014).

Glaucoma is a group of neurodegenerative disorders with an autosomal recessive mode of inheritance (Vasiliou and Gonzalez, 2008; Vasconcelos et al., 2023). This disorder's categorization is

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based on etiology, onset, and iridocorneal angle (open/closed) (Sarfarazi et al., 2003; Wang et al., 2024). Primary congenital glaucoma (PCG) is a rare, congenital abnormality of the trabecular meshwork and anterior chamber angle. In this condition, fluid increases in the front part of the eye, causing increased pressure and damage to the optic nerve (Wiggs et al., 2004; Coviltir et al., 2025).

Although uncommon, PCG is the most prevalent type of glaucoma among infants, occurring in 1 in 10,000 births (Ho and Walton, 2004). It is a genetically heterogeneous eye disorder that often manifests during the first year of life and is one of the major causes of blindness in children across the world (Sarfarazi et al., 2003; Coviltir et al., 2025). Symptoms include photophobia, epiphora, signs of globe enlargement, edema, and breaks in the Descemet's membrane (Wiggs et al., 2004; Chan et al., 2015; Badawi et al., 2019).

Measurements of intraocular pressure (IOP), corneal diameter, axial length of the eyeball, and other parameters are used to corroborate the diagnosis, which is based on clinical signs such as ocular enlargement and corneal clouding (Cronemberger et al., 2025). The main therapeutic strategy is surgical management, such as goniotomy or trabeculotomy. Early diagnosis and treatments are essential for vision preservation and reducing consequences such as amblyopia, optic nerve injury, and corneal scarring (Ali et al., 2009; Lam and Suh, 2022).

Children with PCG require lifelong treatment and routine follow-ups to maximize their visual outcomes (Mandal and Chakrabarti, 2011; Yuksel Elgin and Elgin, 2025). GLC3A, GLC3B, GLC3C, and GLC3D, which are located at positions 2p21, 1p36, 14q24.3 (Narooie-Nejad et al., 2009a) and 14q24.2-q24.3 (Firasat et al., 2008), respectively, have all been associated with PCG. Mutations in the myocilin (MYOC), latent transforming growth factor-β-binding protein-2 (LTBP2) at GLC3D (Kaur et al., 2005; Ali et al., 2009; Narooie-Nejad et al., 2009b; Verma et al., 2025), cytochrome P4501B1 (CYP1B1) at GLC3A, forkhead Box C1 (FOXC1), and the angiopoietin receptor (TEK) have been documented to cause PCG (Kabra et al., 2017).

Human ocular tissues such as the cornea, ciliary body, iris, and retina highly express the wild-type CYP1B1 protein (Reddy et al., 2004; López-Garrido et al., 2010; Song et al., 2022). CYP1B1 has three exons, of which two encode a 543 amino acid protein. Until now, almost 270 mutations have been reported in the *CYP1B1* gene, including missense, small deletions, indels, gross deletions, and regulatory mutations (Tehreem et al., 2022). PCG is prevalent mostly in countries where consanguinity is common. About 34.6% cases of PCG (Glaucoma) result from a mutation in the *CYP1B1* gene in the Pakistani population (Bashir et al., 2014; Rauf et al., 2016). Almost 87% of familial and 27% of sporadic PCG cases worldwide are caused by *CYP1B1* (Coêlho et al., 2019). Both familial and sporadic glaucoma are prevalent in Pakistan. In the present study, this led to the selection of mutations in the CYP1B1 gene associated with PCG. There are many reports of PCG patients with autosomal recessive inheritance in Pakistan, where cousin marriage is preferred (Gupta et al., 2022; Tehreem et al., 2022).

The goal of the current investigation was to define the role of the *CYP1B1* gene in the pathogenesis of PCG. Thus, this study examined the role of the *CYP1B1* gene variants in the development of PCG in Pakistani consanguineous families.

Materials and Methods

As part of this study's approach, we searched several databases, including PubMed, MEDLINE, and Google Scholar, for relevant literature. We employed a carefully selected set of search phrases that included pertinent genetic terms. Studies were carefully selected for relevance to genetics, diagnosis, and ethnicity through an iterative method. For in-depth analysis, only the papers that satisfied our inclusion criteria were chosen. In Pakistan, mutations in the human cytochrome P450 gene, *CYP1B1,* are reported to cause PCG (Firasat et al., 2008; Rashid et al., 2019), including missense, frameshift, and nonsense mutations.

The primary focus of this study was to identify the reported mutations in *CYP1B1* and to analyze their prevalence in different families. The prevalence of PCG in Pakistani families of different regions was estimated. Different mutations are associated with the cytochrome p450 *CYP1B1* gene in causing PCG. In the current study, the mutations that appeared largely in different Pakistani families were assessed.

Results

Figure 1 depicts a patient with PCG. In this article, we particularly focused on the mutations presented in PCG patients in Pakistan. To our knowledge, no thorough analysis of all known mutations in the *CYP1B1* gene causing PCG in the Pakistani population has been published. To gather information about mutations in PCG patients, including the type of mutation, amino acid/protein change, and study protocol, all studies published until March 2024 were evaluated at www.ncbi.nlm.nih.gov/pubmed. We identified 74 types of PCG mutations that are presented in **Table 1**, whereas **Figure 2** shows the frequency of reported mutations in PCG patients across the Pakistani population.

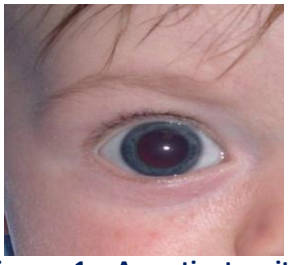

Figure 1: A patient with primary congenital glaucoma

Table 1: Spectrum of associated *CYP1B1* gene mutations in Pakistan

Mutation type	Nucleotide change	Protein change	Methodology	References
Missense	c.1405C>T	p.Arg469Trp	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1300T>C	p.Trp434Arg	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1405C>T	p.Arg469Trp	Sanger sequencing	(Rauf et al., 2016)
Frameshift	c.1200_1209dup	p.T404Sfs30*	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Frameshift	c.736_737insT	p.Trp246Leufs*81	Sanger sequencing	(Rauf et al., 2016)
Missense	c.685G>A	p.Glu229Lys	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1331G>A	p.Arg444Gln	Sanger sequencing	(Rauf et al., 2016)
Missense	c.241T>A	p.Tyr81Asn	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1103G>A	p.Arg368His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Frameshift	c.1325delC	p.Pro442Glnfs*15	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.109C>T	p.Gln37Ter	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1103G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1169G>A	p.Arg390His	Sanger sequencing	(Rauf et al., 2016)
Missense	c.1122C>G	p.Asp374Glu	Polymorphic microsatellite markers	(Firasat et al., 2008)
Missense	c.685G>A	p.Glu229Lys	Polymorphic microsatellite markers	(Firasat et al., 2008)
Missense	c.1460T>G	p.Leu487Pro	Polymorphic microsatellite markers	(Firasat et al., 2008)
Missense	c.530T>G	p.Leu177Arg	Polymorphic microsatellite markers	(Firasat et al., 2008)
Missense	-	p.Arg390His	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Glu229Lys	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Ala115Pro	Direct sequencing	(Sheikh et al., 2014)
Frameshift	c.868_869insC	p.Arg290fsTer37	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Gly36Asp	Direct sequencing	(Sheikh et al., 2014)
Frameshift	c.198–209del12	p.Gly67-Ala70del	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Arg390His	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Arg390His	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Arg390His	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Arg390His	Direct sequencing	(Sheikh et al., 2014)
Missense	-	p.Gly61Glu	Direct sequencing	(Sheikh et al., 2014)
Missense	c.457C>G	p.Arg153Gly	Direct sequencing	(Tehreem et al., 2022)
Missense	c.516C>A	p.Ser172Arg	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c. 629dup	p. Gly211Argfs*13	Direct sequencing	(Tehreem et al., 2022)
Missense	c.722T>A	p.Val241Glu	Direct sequencing	(Tehreem et al., 2022)
Missense	c.732G>A	p.Met244Ile	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c. 287dup	p. Leu97Alafs*127	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c.662dup	p. Arg222Profs*2	Direct sequencing	(Tehreem et al., 2022)

Frameshift	c.868dup	p. Arg290Profs*37	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c.247del	p. Asp83Thrfs*12	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c.758- 759insA	p. Val254Glyfs*73	Direct sequencing	(Tehreem et al., 2022)
Missense	c.1263T>A	p.Phe421Leu	Direct sequencing	(Tehreem et al., 2022)
Silent	c.1314G>A	p. (=)	Direct sequencing	(Tehreem et al., 2022)
Silent	c.1314G>A	p. (=)	Direct sequencing	(Tehreem et al., 2022)
Frameshift	c.789dup	p. Leu264Alafs*63	Direct sequencing	(Tehreem et al., 2022)
Missense	c.724G>C	p.Asp242His	Direct sequencing	(Tehreem et al., 2022)
Silent	c.771T>G	p. (=)	Direct sequencing	(Tehreem et al., 2022)
Missense	c.740T>A	p.Leu247Gln	Direct sequencing	(Tehreem et al., 2022)
Missense	c.685G>A	p.Glu229Lys	Termination sequencing (di-deoxy)	(Zahid et al., 2023)
Missense	c.355 G>T	p.Ala119Ser	Termination sequencing (di-deoxy)	(Zahid et al., 2023)
Somatic	c.693C>A	p.Phe231Leu	Termination sequencing (di-deoxy)	(Zahid et al., 2023)
Stop gained	c.840C>A	p.Cys280Ter	Termination sequencing (di-deoxy)	(Zahid et al., 2023)
Missense	c.1169G>A	p.Arg390His	Direct sequencing	(Waryah et al., 2019)
Missense	c.1169G>A	p.Arg390His	Direct sequencing	(Waryah et al., 2019)
Missense	c.1169G>A	p.Arg390His	Direct sequencing	(Waryah et al., 2019)
Missense	c.1169G>A	p.Arg390His	Direct sequencing	(Waryah et al., 2019)
Missense	c.685G>A	p.Glu229Lys	Direct sequencing	(Waryah et al., 2019)
Missense	c.1103G>A	p.Arg390His	Direct sequencing	(Waryah et al., 2019)
Missense	c.1405C>T	p.Arg469Trp	Direct sequencing	(Waryah et al., 2019)
Missense	c.1300T>C	p.Trp434Arg	Direct sequencing	(Waryah et al., 2019)
Missense	c.1331G>A	p.Arg444Gln	Direct sequencing	(Waryah et al., 2019)
Missense	c.241T>A	p.Arg444Gln	Direct sequencing	(Waryah et al., 2019)
Missense	c.107G>Aa	p.Gly36Asp	Direct sequencing	(Waryah et al., 2019)
Frameshift	c.198_209del 12a	p.Gly67_Val70delinsVal	Direct sequencing	(Waryah et al., 2019)
Frameshift	c.868-869 InCa	p.Arg290ProfsTer37	Direct sequencing	(Waryah et al., 2019)
Missense	c.746G>C	p.Ala115Pro	Direct sequencing	(Waryah et al., 2019)
Frameshift	c.1200_1209dup	p.Thr404SerfsTer30	Direct sequencing	(Waryah et al., 2019)
Frameshift	c.7+E88:F10036_737insTa	p.Trp246LeufsTer81	Direct sequencing	(Waryah et al., 2019)
Frameshift	c.1325delCa	p.Pro442GlnfsTer15	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.109C>T	p.Gln37Ter	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.1063C>T	p.Arg355Ter	Direct sequencing	(Waryah et al., 2019)
Missense	c.862G>Ca	p.Ala288Pro	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.725A>Ca	p.Asp242Ala	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.1460T>Ga	p.Leu487Pro	Direct sequencing	(Waryah et al., 2019)
Missense	c.530T>Ga	p.Leu177Arg	Direct sequencing	(Waryah et al., 2019)
Missense	c.1122C>Ga	p.Asp374Glu	Direct sequencing	(Waryah et al., 2019)
Missense	c.1311G>A	p.Pro437Leu	Direct sequencing	(Waryah et al., 2019)
Missense	c.1090G>A	p.Val364Me	Direct sequencing	(Waryah et al., 2019)
Missense	c.1048C>Aa	p.Pro350Thr	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.37C>T	p.Leu13Ter	Direct sequencing	(Waryah et al., 2019)
Nonsense	c.3028G>A	p. Asp1010Asn	Short tandem repeat (STR)	(Rauf et al., 2016)
Frameshift	c.3427delC	p.Gln1143Argfs*35	Short tandem repeat (STR)	(Rauf et al., 2016)
Missense	c.5270G>A	p.Cys1757Tyr	Short tandem repeat (STR)	(Rauf et al., 2016)
Frameshift	c.1044-1G>C	p.Tyr349Leufs*73	Sanger sequencing	(Afzal et al., 2018)
Missense	c.1405C>T	p.Gly61Glu	Sanger sequencing	(Afzal et al., 2018)

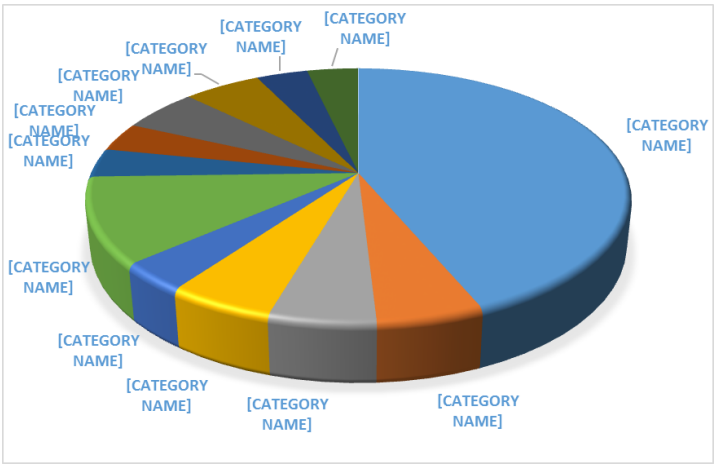

Figure 2: Graphical representation of the mutational spectrum of the *CYP1B1* gene in the Pakistani population

Mutations in the *CYPIBI* gene have been linked to PCG. The missense mutation p.Arg390His was predominant (with 24 cases of the total), followed by p.Glu229Lys (6 cases) (**Figure 2**). The pie chart excluded mutations found in only one case.

Since most of the recruited families were from Punjab (**Figure 3**), further studies are required to be conducted in different regions of the entire country, other than Punjab, to find out the prevalence of PCG in the whole country.

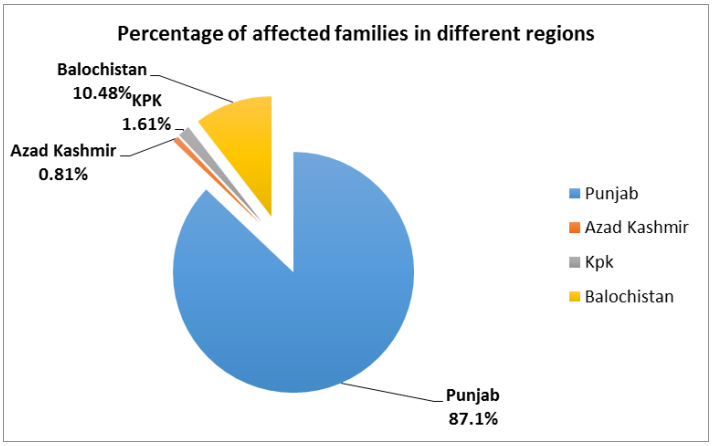

Figure 3: Percentage of affected families in different regions of Pakistan

Analysis of SNPs reported in different families showed that rs1056837 was reported the most with 38% cases, followed by rs1056836 in 11% and rs4646431 in 9% (**Figure 4**). The least reported SNP is g.35710_35711insT in only 2% of the cases. This result indicated that rs1056837 is largely linked to the cause of PCG in the Pakistani population. The variant g.35710_35711insT is novel and has not been previously reported in any study from Pakistan (Tehreem et al., 2022) (**Figure 4**)

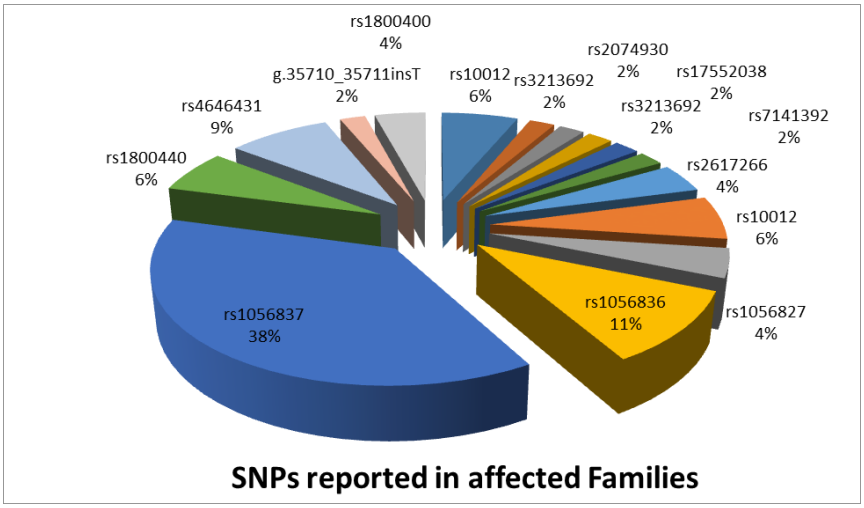

Figure 4: SNPs reported in affected families

Discussion

Glaucoma is a neuropathic disease that leads to irreversible vision loss. In Pakistan, the high frequency of consanguineous marriages is mainly attributed to the cause of PCG (Al-Hazmi et al., 2005; Zenteno et al., 2008). However, autosomal dominant forms do appear.

The familial and sporadic forms of glaucoma are attributed to a higher percentage of consanguinity in the Pakistani population (Arshad et al., 2024). The prevalence of PCG in different regions of Pakistan showed great variation. The number of individuals in a particular family affected with PCG also varies due to incomplete penetrance.

The *CYP1B1* gene resides in the GLC3A locus on chromosome 2. *CYP1B1* regulates oxidative homeostasis and functional performance of trabecular meshwork tissue in the eye (Zhao et al., 2013; Song et al., 2022). Mutations in *CYP1B1* are attributed to causing PCG in patients from various ethnic

backgrounds (Bagiyeva et al., 2007; Afzal et al., 2018). Previous studies showed that missense mutations in *CYP1B1* result in significant structural changes and reduced *CYP1B1* activity (Achary et al., 2006).

Different SNPs have also been associated with the *CYP1B1* gene mutation. The most prevalent polymorphism, rs1056837 (c.1347T>C), is present in a maximum of 38% in the current study. The high prevalence of this SNP rs1056837 (c.1347T>C) is also documented in other studies conducted on PCG cases from the Pakistani population (Shan et al., 2021). The SNP rs1056836 appeared in 11 of the cases. The least reported SNP, i.e., g.35710_35711insT, is present in the intronic region in the homozygous state.

The missense mutation, p.Arg390His, was the most significant (**Figure 2**). The p.Arg390His mutation is also continuously reported in the population of Saudi Arabia (Chouiter and Nadifi, 2017) and China, Japan, and South Korea (Jiao et al., 2017). Further studies are needed to ensure the prevalence of the p.Arg390His mutation in other regions of Pakistan. The missense mutation, p.R390H, was first noted in Pakistan; afterwards, it was reported in Indian and Iranian PCG patients (Reddy et al., 2004; Chitsazian et al., 2007). p.R390H(p.Arg390His) is one of the most common mutations in the Asian populations (Suri et al., 2009; Li et al., 2011; Shah et al., 2022).

The mutational spectrum of the *CYP1B1* gene varied among different populations. For instance, p.Ser476Pro is 44% prevalent in India, p.Arg469Trp, p.Arg368His, p.Arg390His, p.Gly61Glu, and p.Glu173Arg are 70% in Iran. The prevalence of p.Gly61Glu, p. Arg390His, and p.Glu229Lys in Saudi Arabia is 80–100% (Afzal et al., 2018; Tehreem et al., 2022). However, p.Arg330Phe and p.Arg390His have been predominantly reported from China (Shah et al., 2022). In addition to *CYP1B1* identified repeatedly in the Pakistani population for PCG, another gene linked to PCG in Pakistan is *LTBP2,* accounting for only a small percentage (Ali et al., 2009).

Since the present study included a large number of cases from Punjab, it would be more sensible to conduct more studies in other areas of Pakistan to find out the prevalence of PCG throughout the country.

Conclusion

Overall, it is evident that consanguinity plays a major role in the higher prevalence of PCG inherited in an autosomal recessive manner. Multiple mutations in the *CYP1B1* gene tend to cause PCG in Pakistan, with the missense mutation, p.Arg390His, being the most predominant one. Glaucoma awareness is required as the patients do not know about the disease's mode of inheritance and nature. Furthermore, to understand the higher occurrence of mutations in the *CYP1B1* gene in the population of Pakistan, all new families with previously reported cases must be prescreened. For better management of the disease, proper diagnosis of PCG-causing mutations would be helpful.

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Contribution of authors
Conceptualization planning of the study: AA, FL, SB, SA. Data collection, visualization, and interpretation: AA, SB, FL, MUA. Graphical presentation/visualization: AA, FL. Statistical analysis: AA, FL, SB, SA. Preparation of initial draft: AA, FL, SB, SA. Review of initial draft: AA, FL, SB, MUA. Proofreading and approval of the final version: AA, SB, FL, SA. Revisions and corrections: All authors.

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The authors declare no conflict of interest.

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Authors' consent
All authors have critically read this manuscript and agreed to publish in IJAaEB.

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