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Genetics of primary congenital glaucoma

Muhammad Umer Khan[1*], Wajeeha Tabassum[1], Musbihul Qayyum Zia[1], Raima Rehman[1], Atif Amin Baig[2], Sajjad Ahmed Khan[3], Rizwan Ahmed Kiani[3]

[1]*University Institute of Medical lab technology, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan*

[2]*Faculty of Medicine, University Sultan Zainulabdin, Malaysia*

[3]*Department of Biochemistry, Pir Mehar Ali Shah University of Arid Agriculture Rawalpindi, Rawalpindi, Pakistan*

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Abstract

Primary Congenital Glaucoma (PCG) is a major risk factor for vision loss in children, which is manifested from birth to three years of age. In PCG the ocular developmental defects of the trabecular meshwork (TM) and front chamber position of eye lead to the blockage of aqueous loss and consequently an increased intraocular pressure (IOP). This results in photophobia, corneal clouding, optic nerve damage, and ultimately permanent loss of vision occurs. The incidence of PCG varies geographically. In Eastern culture, consanguineous marriages may play a role in a higher rate of PCG. Four loci of GLC3A, GLC3B, GLC3C, and 14q24.2-q24.3 to be linked to this ocular condition have been identified. Currently, mutations in two genes i.e.*CYP1B1* at GLC3A locus, which encodes cytochrome P4501B1, and *LTBP2* at GLC3D locus, which encodes LTBP2is known to cause PCG.*CYP1B1* comprises of 3 exons encoding a 543 amino acid protein. *CYPIBI* is a gene that belongs to the cytochrome P450 family of enzymes. The cytochrome P450 proteins are monooxygenases that catalyse many reactions involved in the synthesis of cholesterol, steroids, other lipids, and drug metabolism. A lot of mutations have been reported in *CYP1B1,* which results in the form of PCG.

* **Corresponding Author:** Muhammad Umer Khan ✉ umer.khan685@gmail.com

Introduction

Worldwide, glaucoma is the 2nd leading cause of blindness if it's left untreated (Hazin *et al.* 2009). Glaucoma is a collection of optic neuropathies(Quigley *et al.* 2006). The mark of glaucoma is the hourglass pattern of optic nerve atrophy combined with preferential loss of the more giant ganglion cells of the retina(Schlamp *et al.* 2006). Anomalies in the conformation or structure of iridocorneal angle may limit the outflow of aqueous humour and make a rise in IOP, which is a primary cause for developing glaucoma (Lewis *et al.* 2017).

It is currently considered that a variety of etiological factors, acting individually or in a multifactorial fashion, are capable of triggering pathogenetic cascades leading to these lesions. Almost in all types of glaucoma, the drainage system of the eyes becomes blocked, so the intraocular fluid can't drain. As fluids accumulate, it makes the pressure inside the eye. High pressure in the eye harms the sensitive part of the optic nerve and affects the vision loss.

The syndrome is classified based on analysis, the structure of the front chamber, and the age of onset. Classification of primary forms of glaucoma is done based onthe structure of front chamber as Primary angle-closure glaucoma(PACG), primary open-angle glaucoma(POAG) Primary congenital glaucoma (PCG), (Firasat 2008). POAG was positioned at GLC1A on chromosome 1. *MYOC* is present at GLC1A, which encodes myocilin protein. Disease linked changes of myocilin generally arise in the infantile or adult form of POAG by increasing level of Intraocular pressure (IOP). In people of adults with POAG, the existence of myocilin alters from 3%-5% (Kwon *et al.* 2009). In Western populations, Primary open-angle glaucoma is the most common and possibly other communities (Ali *et al.* 2009, Olawoye *et al.* 2013).

In PACG, several genes are involved, like myocilin (Rose *et al.* 2007) optineurin (Shastry 2013) and tryptophan-aspartic acid (W-D) repeat domain 36 (GLC1G)(Monemi *et al.* 2005)are linked with the autosomal dominant trait. Only 10% of glaucoma is caused by this type(Mandal *et al.* 2006).PACG is responsible for the most bilateral glaucoma-induced blindness in Singapore, China, and India (Cyrlin 2014, Suri *et al.* 2015).

Primary congenital glaucoma(PCG) occurs before 3 years of age without any structural defect of the eye(Abu-Amero *et al.* 2017). PCG is an autosomal recessive disorder with onset at newborn or early juvenile age.

It is affected by developing deficiencies in the trabecular meshwork, and the front cavity angle results in the blockage of aqueous drainage and leads to raised intraocular pressure (Kaur *et al.* 2011). A comparison of a normal eye and glaucoma eye has been shown in Fig.1(2019).

The covering of the juvenile eye is flexible; it stretches in response to the elevated intraocular pressure that results in an enlarged globe (Chan *et al.* 2015). Primary Congenital Glaucoma is bilateral in 70 % of patients (Mcculley 2015).

PCG is a blinding syndrome that starts with the onset of birth or between infancy.About 60% patients are diagnosed inthe first six months and the remaining 80% cases in first year of life. About 65% prevalence was found in males and involvement is usually bilateral(Mandal *et al.* 2011).

It occurs; when there is a developmental defect in trabecular meshwork often combined with other related signs. TM dysgenesis causes an apparent blockage to aqueous outflow that makes a rise in intraocular pressure leads to ocular hypertension mediated optic nerve cupping that results in loss of vision.

It is thought to be caused by a developmental defect of the anterior chamber of the eye (Guercio *et al.* 2007). Inheritance mode is autosomal recessive with adjustable penetrance, but some cases of pseudo-dominance are also observed in families with several consanguineous relations (Firasat *et al.* 2008).

Four loci of the chromosome have been associated with PCG, GLC3A, GLC3B, GLC3C, and 14q24.2-q24.3 discussed in Table 1 (Firasat *et al.* 2018).

No responsible gene has yet been identified at the *GLC3B* and *GLC3C* loci, although the mutations in *CYP1B1* are the leading known genetic cause of this type of glaucoma(Campos-Mollo *et al.* 2009). The syndrome starts in a newborn or juvenile period expressed by signs of increased intraocular pressure (lOP) and corneal oedema.

Table 1. Known Loci for PCG**.**

Candidate locus	Candidate gene	Chromosome mapping	Reference
GLC3A	CYP1B1	2p21 [MIM #231300]	(Sarfarazi *et al.* 1995, Stoilov *et al.* 1997)
GLC3B	N/A	1p36 [MIM #600975]	(Akarsu *et al.* 1996)
GLC3C	N/A	14q24.3-q31.1	(Stoilov *et al.* 2002)
GLC3D (OMIM613086)	LTBP2 (controversial)	14q24[MIM #602091] (outside GLC3C locus)	(Firasat *et al.* 2008)

N/A: Not available;
LTBP2: Latent transforming growth factor (TGF) beta binding protein 2;
OMIM: Online Mendelian inheritance in man;
MIM: Multiple-interval mapping.

PCG occurs in both familial and sporadic patterns (Chitsazian *et al.* 2007) and is inherited asan autosomal recessive pattern; prevalence mostly occurs in a region where consanguineous marriages are common(Verma *et al.* 2018). Parental consanguinity is frequently reported(Papadopoulos *et al.* 2007).The exact prevalence of primary congenital glaucoma (PCG) is not known in Pakistan, but it occurs in about 1 of 10,000 live births in the USA (Mahar *et al.* 2012).

Table 2. Effect and side effects of anti-glaucoma medication in Primary congenital glaucoma patient.

Medication class	Mode of action	Name of drug	Dosage interval	Adverse effects
α- adrenergic agonists	decrease aqueous humour production	Apraclonide(lopidine), brimonidine	2-3 times daily	Visual reaction, somnolence, unpleasant flavour,
β-blockers	decrease aqueous humour production	Brinzolamide (Betoptic), carteolol, levobunolol (Betagan), metipranolol (Optipranolol), timolol (Timoptic)	1-2 times daily Avoid night-time admin	Betaxolol is cardioselective and may have less breathing effects Bradycardia, bronchospasm, depression, tiredness, vision dryness
Carbonic anhydrase inhibitors	decrease aqueous humour production	dorzolamide (Trusopt)Brinzolamide (Azopt),	2dose everyday	bitter flavor
Cholinergics	Increase outflow through the trabecular meshwork	Pilocarpine	3-4dose everyday	Headache,eye pain, Blurry vision, poor night vision.
Prostaglandin analogues	Increase outflow through uveoscleral pathway	Bimatoprost, unoprostone latanoprost, travoprost, tafluprost Bimatoprost	1dose everyday normally at bedtime	Lengthening of eyelashes, change in iris colour or hyperemia, intraocular inflammation, periocular skin hyperpigmentation,

Primary Congenital Glaucoma (PCG)

Cytochrome P450

Cytochrome P450 is a family of membrane-bound oxidase enzymes that play a role in the breakdown, production of hormones and other metabolic development. *CYP1B1* belongs to Cytochrome p450 (Campos-Mollo *et al.* 2009).*CYP1B1* may be essential in the function and development of TM(Mookherjee

et al. 2012, Zhao *et al.* 2013).Cytochrome P450 B1 protein shows reduced enzymatic activity or protein stability (Pasutto *et al.* 2010). The data suggest *CYP1B1* mutation may change TM function, optic nervedamage and cause dysregulation of IOP and, ultimately, primary congenital glaucoma (Medina-Trillo *et al.* 2016).

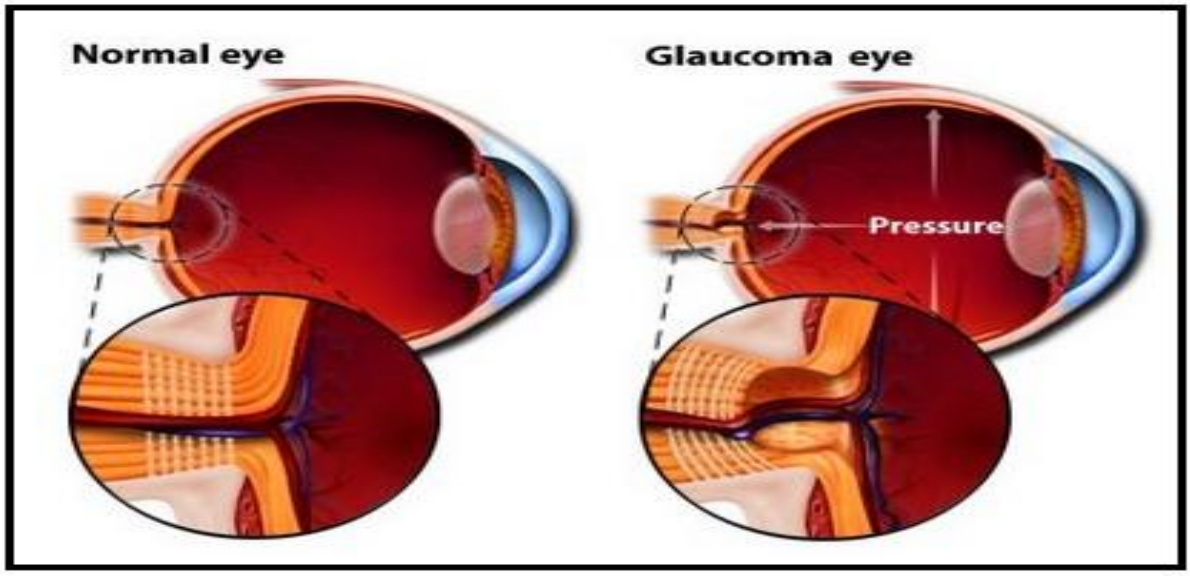

Fig. 1. The optic nerve in normal eye B. Glaucomatous optic neuropathy.

The *CYP1B1* gene is presenton the short (p) arm of chromosome 2 at position 22.2. More specifically, *CYP1B1* gene is positioned from bp 38,067,603-38,076,181 on chromosome 2 Fig.2 (2019). In worldwide, the Cytochrome P450 B1 gene harbors more than 70 mutations(Zanger *et al.* 2013) and 150 variants(Li *et al.* 2011) in PCG among various ethnic groups.Mutations in this gene are linked with autosomal recessive PCG.*CYP1B1* belongs to Cytochrome p450and consists of 2 coding exons (371bp, 1044bp and 3707 bp in length) and 1 non-coding exon (390 bpand 3032 bp in length) spanning 8.5 kb of genomic DNA(Campos-Mollo *et al.* 2009).

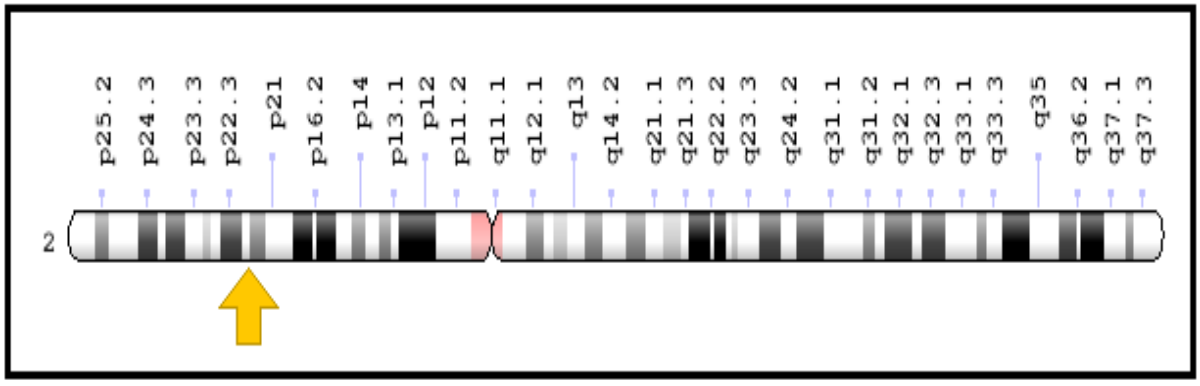

Fig. 2. Location of *CYP1B1*.

Its coding region begins at the 5'-end of the 2nd coding exon and ends with the last coding exon. Its position on the chromosome is 2p21 at locus GLC3A, and it encodes 543 amino acid, polypeptide 1, cytochrome P450 superfamily, subfamily B (Li *et al.* 2011). Firstly, *CYP1B1* was recognised as a causal gene for PCG(Yihong 2014).

Several in silico studieswere conducted worldwide to determinethe influence of any mutation of *CYP1B1* on

the underlying proteins. The purpose of these studies is to make a better understanding of the association of *CYP1B1* with the syndrome pathogenesis. One of the recent and significant contributions was made by ZhiyingOu *et al.* who explained the effect of different mutations on the molecular structure of *CYP1B1*. Following the 2 mutations L107 and R390 have been shown in Fig.3A and 3B. Heme binding region (HBR) lies in interhelical loop while the active site cavity (ASC) lies in the α-helices and location of both the mutations R307 and L107 are in the K- and B-helix, respectively. R390 and L107 are close to both the HBR and ASC in the tertiary structure as shown in Fig.3B, so that the mutations might affect both of the crucial functional regions.The secondary and tertiary structure of CYP1B1 well explained the role of both the mutations (Ou *et al.* 2018).

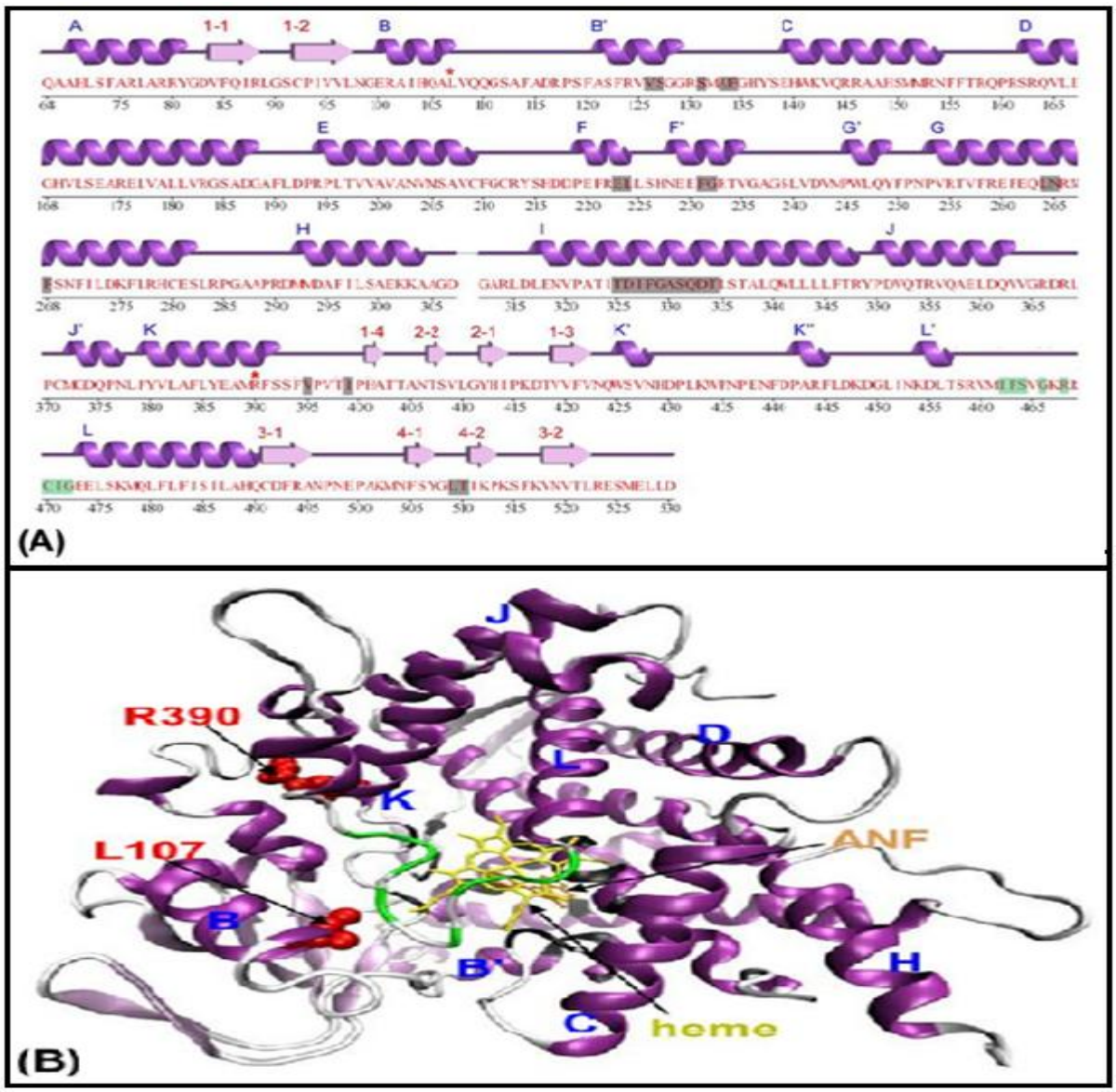

Fig. 3. Part (A) shows the secondary structure, and part (B) indicates the tertiary structures of human CYP1B1 protein (Ou *et al.* 2018).

(**A**) The secondary structure figure explains the secondary structure of the proteins (DSSP) algorithm that was achieved by the PDBsum website.Extended secondary structure and Helical are depicted in pink and purple form, correspondingly also label numerically and alphabetically beyond the sequence. The purple-coloured area is the ferrous haemoglobin-binding site.

The grey-coloured area is the active site amino acid residues. Red asterisks indicate the mutation sites. (B). The tertiary structure was highlighted according to the secondary structure. Van der Waals (VDW) spheres indicate mutation site while Licorices represents heme and inhibitor α-naphthoflavone (ANF). Investigation of the Molecular Model of L107V mutation further shows that mutation may alter the stability of B-helix. In WT CYP1B1 net of 3 intra-helical H-bond present among L107 and three more residues H104, S112, and I103. The existence of valine at 107 positions(L107V) can change the structure of protein backbone and also result in a major loss of 2 H-bonds with S112 and H104(Fig. 4A), which can disturb the B-helix conformation.

The finding of result from residue interaction net supports electrostatic potential investigation from APBS, which verify the modification from electro-negative to electro-positive(Fig. 4B) (Ou *et al.* 2018).

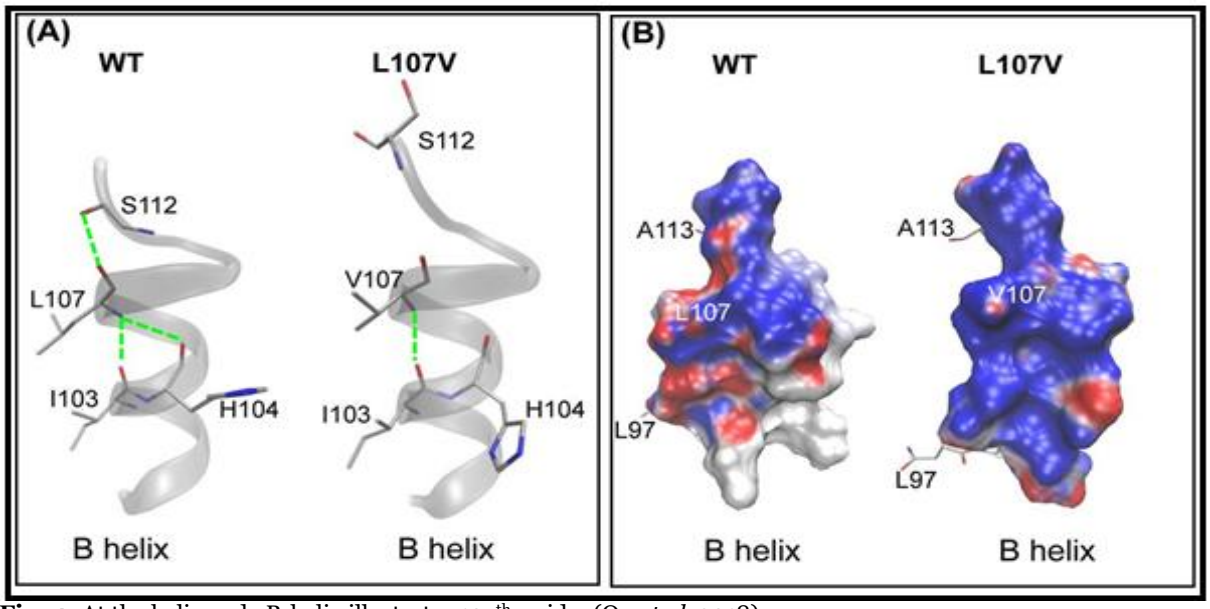

Fig. 4. At the helix end, B-helix illustrates 107th residue(Ou *et al.* 2018).

(A) The net of intrahelical H-bond interactions involves the 107th residue is shown in WT Cyp1b1. L107V mutation causes major loss of interactions that result in misfolding of the protein. (B) Illustrates the electrostatic potential of B-helix in L107V and WT. Potentials <-10kT/e are depicted in red and potentials >+10kT/e are colored in blue. +ve charge of B-helix in WT are considerably lower than those in L107V.

Occurrence

Further,as already discussed, the inheritance mode is autosomal recessive,mainly with variable penetrance, but some families with multiple consanguineous relations showed thepseudo-dominance (Verma *et al.* 2018).About 10%-40% of PCG cases are familial(Walton 2010).According to a report, 65% of cases of glaucoma, males were affected(Minckler *et al.* 2005). In Japan, the prevalence of Primary congenital glaucoma has not been determined, but most cases are sporadic (Li *et al.* 2011). A study reported females to have higher occurrence rate than males, while the occurrence rate of males and females is the same in Europe and the USA (Rudnicka *et al.* 2006). PCG occurrence is higher in individuals with high rates of consanguineous marriages, its occurrence in Western countries is estimated at 1:10,000 (El Akil *et al.* 2014), this rate in various inbred populations for which data is available such as India(Tanwar *et al.* 2009) and Saudi Arabia, ranges from 1:1,200–1:3,300 (Badeeb *et al.* 2014).According to British Infantile and Childhood Glaucoma (BIG), it shows that the rate of PCG was almost nine times more significant in Pakistanis than Caucasians (Papadopoulos *et al.* 2007). In middle eastern population occurence of *CYP1B1* is four times greater than western population (Sheikh 2019). Mutations

in *CYP1B1* account for approximately one in five PCG cases from Australia(Dimasi *et al.* 2007). In Africa less number of cases of glaucoma are reported as compared to other blinding disorders in global burden data(Kyari *et al.* 2015).

The connection between higher incidence of primary congenital glaucoma and consanguinity is more supported by statics that high prevalence of consanguinity is observed in the parents of primary congenital glaucoma as compared to the parents of secondary congenital glaucoma(Tamçelik *et al.* 2014). In some countries like Saudi Arabians and Slovakians Gypsies consanguinity is a major reason for having increased rate of primary congenital glaucoma(Faiq *et al.* 2015).

Diagnosis

In early glaucoma, symptoms can be unclear, and the analysis is often uncertain(Garway-Heath 2008). In glaucoma patients, heterogeneity of damage to visual function occurs. For the diagnosis of glaucoma, the sensory test is not enough to achieve high sensitivity. To diagnose, family history, elevated intraocular pressure, visual field damage and optic disc defects were observed(Pang *et al.* 2002). Photophobia, Tearing, buphthalmos and corneal opacification may present in patients of primary congenital glaucoma (Hollander *et al.* 2006). An increase in intraocular pressure lead to optic nerve defects.(Girgis *et al.* 2007).

Causal structural aberration of the anterior drainage angle, medically, there are fewer chances to control IOP in PCG, minimising IOP ultimately in <10 % of PCG patients (Chan *et al.* 2015). Table 2 showsa separate category of anti-glaucoma medicine and their effects in reducing IOP in PCG patients (Garway-Heath *et al.* 2015). Adverse competency, patients not responding and absence of safety treatment reduce the treatment of PCG.Many parents use eye drops in children suffering from PCG. The therapy is helpful with the objective of decreasing the corneal opacity before incision, interim treatment for incision and IOP decreased after the operation.

Conclusion

PCG is clinically and genetically a heterogeneous condition with only *CYP1B1* as the candidate gene known to date. The PCG associated mutations in *CYP1B1* have been reported worldwide. The exact role of this gene in the pathophysiology of the disease is not known. However, various in vitro and in-silico studies have shown the pathogenic nature of the identified mutations. Even though there are studies about the extensive screening of *CYP1B1* in PCG from various populations worldwide. Since PCG is a congenital disorder, early and consistent analysis is dynamic so that suitable and rapid therapeutic and surgical involvements can begin in time. It can stop unwanted visual loss. Based on genetics, primary congenital glaucoma may be reduced by avoiding consanguinity.

Conflict of interest

Authors have no conflict of interest in this publication.

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