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Systematic Review Article *Open Access*

THE PREVALENCE AND SPECTRUM OF CYP1B1 AND LTBP2 VARIANTS IN PRIMARY CONGENITAL GLAUCOMA PATIENTS OF PAKISTANI POPULATION, A SYSTEMATIC REVIEW

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Abstract *Glaucoma is a leading cause of permanent vision loss in the world and impacts millions of people. Primary congenital glaucoma (PCG) is a form of congenital glaucoma that is more severe and is a result of defects in the anterior chamber angle and trabecular meshwork. The disease is a common occurrence in groups of people where there is a high incidence of consanguineous marriage, like in Pakistan. The purpose of this study is to investigate the mutational spectrum of the CYP1B1 and LTBP2 genes in patients of primary congenital glaucoma (PCG) from Pakistan. For assessing contribution to PCG, clinical and genetic data were analyzed to obtain the disease-associated variants. The results showed that mutations in the gene of CYP1B1 were the most frequent genetic defect associated with the disease. These included missense p.Arg390His (p.R390H), which was the most frequent variant. The gene was also shown to have other pathogenic mutations and polymorphisms. Pathogenic variants in the gene for LTBP2 were also detected. While this was not as prevalent as CYP1B1 mutations, these mutations included functionally significant frameshift, missense, and nonsense mutations, including p.Thr404Serfs*30, p.Asp1010Asn, and p.Arg299X. Both these genes are mutated, and this is part of the genetic heterogeneity of primary congenital glaucoma in Pakistan. In conclusion, the importance of CYP1B1 and LTBP2 in the pathogenesis of PCG and the potential for genetic screening for early diagnosis, genetic counselling, and better disease management in affected families is highlighted.*

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Keywords: *Primary Congenital Glaucoma (PCG); CYP1B1; LTBP2; Consanguinity; Genetic Heterogeneity; trabecular meshwork; anterior chamber angle*

Introduction

Glaucoma is a collective term for a group of neurodegenerative eye diseases that may cause a gradual and permanent decrease in vision (Guo et al., 2005). The disease is classified according to its cause, age of onset, and structure of the iridocorneal angle (Kaur, Mandal, & Chakrabarti, 2011). In primary congenital glaucoma (PCG), rare developmental abnormalities of the anterior chamber angle and the trabecular meshwork are present (M. A. Faiq, Dada, Qadri, & Dada, 2015). These defects cause poor drainage of the aqueous humour, which causes a rise in intraocular pressure and damage to the optic nerve (Kaushik et al., 2023). PCG is rare but the most common glaucoma in infants. Symptoms typically develop in the first year of life and are a leading cause of childhood blindness (Ho & Walton, 2004). The following findings are common: photophobia, excessive tearing, enlargement of the eyeball, corneal edema, and defects in Descemet's membrane (M. A. Faiq et al., 2015). Diagnosis is performed by clinical examination and measuring the intraocular pressure, corneal diameter, and eye axial length (Afzal et al., 2019). The primary treatments are surgical, such as goniotomy and trabeculotomy (Gagrani, Garg, & Ghate, 2020). Prompt diagnosis and treatment are critical to maintain vision and avoid problems like amblyopia, optic nerve damage, and scarring of the cornea. PCG children should have a long-term management plan and recurrent visits to the GPs. Multiple genetic sites are associated with the disease, such as GLC3A, GLC3B, GLC3C, and GLC3D (Sarfarazi, Stoilov, & Schenkman, 2003). Mutations in genes like CYP1B1, LTBP2, MYOC, FOXC1, and TEK have been linked to the onset of PCG (Kabra et al., 2017).

CYP1B1 is highly expressed in various ocular tissues such as cornea, iris, ciliary body, and retina (Quigley & Broman, 2006). Three exons, two of which result

in a protein of 543 amino acids (Ou et al., 2018). Many mutations of this gene have been discovered, including missense mutations, deletions, insertions, and variants in the regulatory regions of the gene. Mutations in CYP1B1 are a significant genetic risk factor in PCG, especially in populations that have a high frequency of consanguineous marriages (Firasat, Riazuddin, Khan, & Riazuddin, 2008). PCG is more prevalent in areas where there is high consanguinity. Familial and sporadic cases of PCG have been reported in Pakistan, and mutations in the CYP1B1 gene make up a significant share of patients with PCG (Hussain & Bittles, 2004). Hence, CYP1B1 is still one of the most important genes related to the genetic basis of PCG. Another important gene in relation to PCG is the LTBP2 gene. It encodes a protein that is required for the development and maintenance of the structures of the extracellular matrix in ocular tissues. Pathogenic variants in LTBP2 are less frequent than those in CYP1B1 but have significant functional impacts (Micheal et al., 2016). Several LTBP2 variants were found, including a frameshift mutation (p.Thr404Serfs*30) (Abu-Amero et al., 2011), a missense mutation (p.Asp1010Asn), and a nonsense mutation (p.Arg299X) (Ali et al., 2009). The findings further support that PCG is genetically heterogeneous in the population, suggesting that several genes are involved in the development of PCG (M. Faiq et al., 2013). It is a systematic review with the aim of providing a detailed independent analysis of the genetic variants in both CYP1B1 and LTBP2, which are associated with PCG among the Pakistani population.

Methodology

We performed a systematic review by compiling a detailed clinical data set with the information obtained from the recent literature on the Pakistani population. Specific variant frequencies, regional demographics, and phenotypic correlations were obtained from the data extracted. The data were then divided into two separate data streams to study CYP1B1 and LTBP2 independently.

Results

Demographic data showed that a significant number of the affected were from the Punjab and Sindh provinces of Pakistan. We analysed the variants individually for each gene.

Spectrum of CYP1B1 Variants

In our cohort, the main cause for PCG is CYP1B1. There were a variety of mutations, primarily missense and nonsense mutations. The most prevalent missense mutation was p.Arg390His, found in 17 cases, implying it to be a significant contributor to the disease in this population.

Table 1: Represents the Identified variants of CYP1B1 in Pakistani Families

Exon	Nucleotide Change	Protein Change	Count	Type
3	c.1169G>A	p.Arg390His	17	Missense
3	c.1103G>A	p.Arg368His	4	Missense
3	c.1294C>G	p.Leu432Val	3	Missense
3	c.1063C>T	p.Arg355X	2	Nonsense
3	c.1405C>T	p.Arg469Trp	2	Missense
3	c.1460T>C	p.Leu487Pro	2	Missense
2	c.685G>A	p.Glu229Lys	2	Missense
2	c.142C>G	p.Arg48Gly	2	Missense
2	c.736_737insT	p.Trp246Leufs*80,	1	Frameshift
3	c.1358A>G	p.Asn453Ser	1	Missense
3	c.1122C>G	p.Asp374Glu	1	Missense
3	c.1300T>C	p.Trp434Arg	1	Missense
3	c.1243_1256del	p.Glu415Argfs*596	1	Frameshift
3	c.1325delC	p.P442Qfs15*	1	Frameshift
3	c.1331G>A	p.Arg444Gln	1	Missense
3	c.1200_1209dup	p.Thr404Serfs*30	1	Frameshift
3	c.1103G>A	p.Arg390His	1	Missense
2	c.530T>G	p.Leu177Arg	1	Missense

Spectrum of LTBP2 Variants

The pathogenic variants of LTBP2 were surprisingly scarce but severely functional. These included frameshift, missense, and nonsense mutations like p.Thr404Serfs*30, p.Asp1010Asn, and p.Arg299X. These mutations were identified, thus supporting the genetic heterogeneity of the Pakistani PCG population.

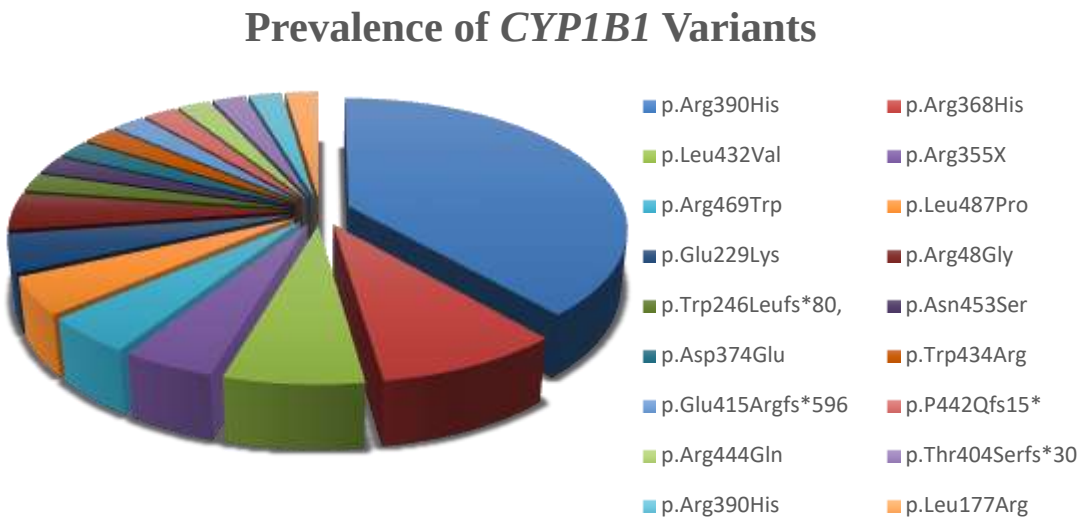

Figure 1: Pie chart showing the prevalence of CYP1B1 variants

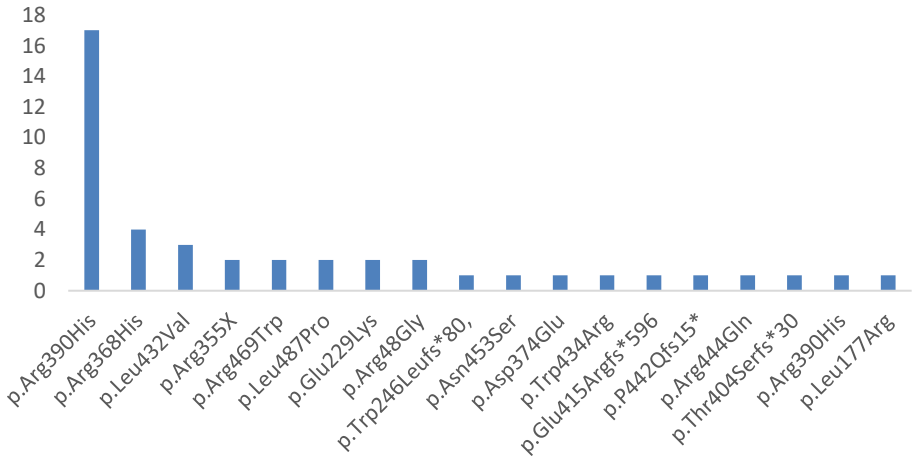

Figure 2: Bar graph showing the frequencies of CYP1B1 variants

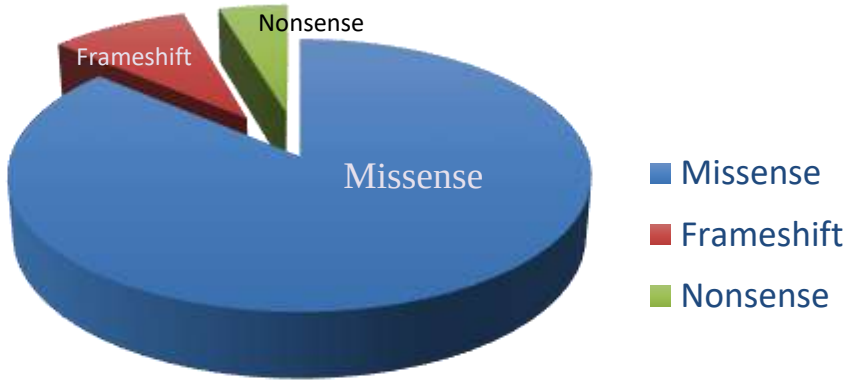

Figure 3: Showing the Types of Mutations in CYP1B1 Gene

Table 2: Represents the identified variants of LTBP2 in Pakistani Families

Exon	Nucleotide Change	Protein Change	Count	Type
1	c.331C>T	p.Gln111X	1	Nonsense
4	c.895C>T	p.Arg299X	1	Nonsense
6	c.1200_1209dup	p.Thr404Serfs*30	1	Frameshift

19	c.3028G>A	p.Asp1010Asn	1	Missense
23	c.3427delC	p.Cys1143Argfs*35	1	Frameshift
35	c.5270G>A	p.Cys1757Tyr	1	Missense

Discussion

Glaucoma is a progressive eye disease that can result in permanent vision loss. The consanguineous marriage is an important factor in the occurrence of primary congenital glaucoma (PCG) among the Pakistanis (Zenteno et al., 2008). Usually transmitted in an autosomal recessive manner, but autosomal dominant forms have been reported. The prevalence of familial and sporadic glaucoma is quite common in the Pakistani population. PCG has different prevalence rates in various parts of the country. There may also be incomplete penetrance, meaning that the number of affected family members may vary (Arshad, Alyas, Arshad, & Arshad, 2024). CYP1B1 is located at the GLC3A locus on chromosome 2. It is a key factor in the normal function of the trabecular meshwork of the eye and oxidative balance (Song et al., 2022). Mutations in this gene are a common cause of PCG in many ethnic groups (Afzal et al., 2019). The mutation p.Arg390His (p.R390H) was the most important (Achary et al., 2006). This mutation has been reported in several countries, such as Saudi Arabia, China, Japan, and South Korea (Chouiter & Nadifi, 2017). It was first seen in Pakistan and later in patients with PCG, with the diagnosis made in India and Iran (Reddy et al., 2004). The p.R390H mutation is one of the most prevalent mutations in Asia in CYP1B1 (Suri et al., 2008). There are differences in the mutation of the CYP1B1 gene between populations. Variations in different countries. The p.Ser476Pro mutation is more common in India, while mutations like p.Arg469Trp, p.Arg368His, p.Arg390His, p.Gly61Glu, and p.Glu173Arg are more prevalent in Iran. The p.Gly61Glu, p.Arg390His, and p.Glu229Lys mutations are very common in Saudi Arabia (Afzal et al., 2019). The mutations p.Arg330Phe and p.Arg390His have been reported more frequently in China (Shah, Bouhenni, & Benmerzouga, 2022). In addition to CYP1B1, LTBP2 has also been linked to PCG in Pakistan, but with a small percentage (Ali et al., 2009). Pathogenic variants in LTBP2 are less frequent than those in CYP1B1 but have significant functional impacts (Micheal et al., 2016). Several LTBP2 variants were found, including a frameshift mutation (p.Thr404Serfs*30) (Abu-Amero et al., 2011), a missense mutation (p.Asp1010Asn), and a nonsense mutation (p.Arg299X) (Ali et al., 2009). These variants point to the genetic heterogeneity of primary congenital glaucoma in the Pakistani population and indicate that other genes, except CYP1B1,, play a role in the pathogenesis of primary congenital glaucoma (M. Faiq et al., 2013).

Conclusion

This study revealed that consanguinity is one of the predisposing factors for primary congenital glaucoma (PCG) that is prevalent in Pakistan. The disease is primarily transmitted through autosomal recessive gene transmission, and occurs more frequently in a high-consanguinity marriage community. The mutations in the CYP1B1 gene were found to be the primary cause of the studied families with PCG. The most prevalent missense mutation that was identified was p.Arg390His (p.R390H). Other pathogenic variants and polymorphisms were also found, which provide further evidence of the importance of CYP1B1 in the progression of disease-Pathogenic variants in the LTBP2 gene were also found. Less frequently found were the variants, which also included frameshift, missense, and functionally important nonsense mutations. In the presence of a mutation in both the genes (CYP1B1 and LTBP2), it means that there is genetic heterogeneity of PCG in the Pakistani population, and multiple genes are responsible for the pathogenesis of PCG. The results highlight the need for molecular screening and genetic diagnosis of the families. There is also a need to educate the public and to provide genetic counselling to educate the public about the disease, its mode of inheritance, and associated risks. Moreover, the screening of newly diagnosed families and expansion of studies in various parts of Pakistan will facilitate the detection of other disease-causing variants and guide effective management, early diagnosis, and prevention of primary congenital glaucoma.

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Statements and Declarations

Data Availability statement

All relevant data are within the manuscript file.

Author's Contribution Statement

IA, AI, SS, IR, and MK collected data and wrote manuscript equally. MK, SS, and MAN make final editing. MAN supervised the whole research work. All authors have read the final manuscript and approve its submission.

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