



## RESEARCH PAPER

## OPEN ACCESS

## Phenotype analysis, molecular genetics and therapeutics of glaucoma: Recent developments and future directions with respect to Pakistan

Muhammad Usman<sup>\*1,2</sup>, Muhammad Ali<sup>3</sup>, Qaisar Hanif<sup>4</sup>, Muhammad Qasim<sup>2</sup>, Muhammad Ibrahim Rajoka<sup>2</sup>, Muhammad Rashid<sup>2</sup>, Zulqarnain Manzoor<sup>5</sup>, Omer Draz<sup>3</sup>, Tehreem Anwar<sup>1</sup>, Mirza Jawad ul Hasnain<sup>1</sup>

<sup>1</sup>Department of Bioinformatics & Computational Biology, Virtual University of Pakistan, Lahore, Pakistan

<sup>2</sup>Department of Bioinformatics and Biotechnology, Government College University, Faisalabad, Pakistan

<sup>3</sup>Department of Zoology, Government College University, Faisalabad, Pakistan

<sup>4</sup>Department of Ophthalmology Allied Hospital, Medical University, Faisalabad, Pakistan

<sup>5</sup>Department of Biotechnology, International Islamic University, Islamabad, Pakistan

**Key words:** Blindness, Eye disease, Glaucoma, Genetic disease, Optical nerves

<http://dx.doi.org/10.12692/ijb/12.2.345-356>

Article published on February 28, 2018

### Abstract

Blindness is a major disability that severely compromises the life quality and makes the individuals unfit for every job. Genetic factors play key role in many types of eye disorders, involving those disorders that are the key reason of blindness amongst infants, children and adults. Glaucoma is a main source of sight loss not only sight and is categorized by enlightened deterioration of the optical nerve and is usually connected with higher intraocular pressure. Without adequate dealing, glaucoma can be developed to optical disability and ultimately sightlessness. Scientists had determined and mapped several genes for glaucoma. Pakistani population is relatively least investigating for genetic diseases as compare to European population. Because of the high degree of consanguinity Pakistani population offers a priceless genetic resource for identifying new genomic regions and to fill gaps in the existing knowledge. In this review, we provide detailed description of genetic and phenotypic heterogeneity of glaucoma disease with respect to Pakistan and also we shed some light on current therapeutic approaches and future directions. Furthermore, we identified 10 consanguineous glaucomatous families of Pakistan with multiple affected individuals and performed their clinical evaluation for better understanding of disease.

\*Corresponding Author: Muhammad Usman ✉ [dogarusman24@gmail.com](mailto:dogarusman24@gmail.com)

## Introduction

Inherited visual disorders leading to blindness is a serious problem all over the world, especially in developing countries. Congenital cataracts (CCs), glaucoma & Retinitis Pigmentosa (RP) are the leading causes of blindness which can be transmitted from parents to their offsprings in various patterns of inheritance.

The word “glaucoma” covers a number of miscellaneous eye disarrays, all of which comprehend injury to the optical nerve (Khan *et al.*, 2017). Glaucoma, a complicated heterogeneous set of disorders that is the second principal reason of blindness after cataract of visual disability and can cause permanent blindness if not treated (Rizzo *et al.*, 2017). Glaucoma is categorized by the deterioration of optic nerves related with increasing intraocular pressure and the destruction of retinal ganglion cells (RGC) (Faiq *et al.*, 2013). Molecular genetic techniques have been used to study the genetics of glaucoma in detail. Different types of glaucoma have been reported during the past few years. These studies indicate that Glaucoma is genetically and clinically heterogeneous in nature (Frick and Foster, 2003). The number of blind individuals would be increasing from 44 million in 2000 to 76 million in 2020 worldwide (Sarfarazi, 1997) out of which about 15% cases of blindness are because of glaucoma (Weisschuh and Schiefer, 2003).

It is an irreversible vision loss along with decreased contrast and color sensitivity (Casson *et al.*, 2012). Visual disorder in glaucoma is due to optic nerve damage because of high intra ocular pressure in most of the cases. It leads to blindness if left untreated (Wiggs *et al.*, 1998). Discharge of aqueous humour through trabecular meshwork is blocked that cause rise in intra ocular pressure. Molecular mechanism of normal as well as glaucomatous aqueous humour outflow is not yet known (Farkas and Grosskreutz, 2001). Retinal ganglionic cells die by apoptosis resulting in degeneration of optic nerve. Relationship of high intra ocular pressure and apoptotic death of ganglionic cell is not well understood. Early detection and continuous conventionally recommended treatment can reduce irreparable damage (Feldman, 2004).

Maintaining low intra ocular pressure by the use of ocular hypotensive agents is the major medical treatment for glaucoma (Sarfarazi and Stoilov, 2000). Expanding knowledge of Molecular Biology has made it possible us to describe the etiology of inherited disorders through identification of genes. It is very crucial to understand what differences exist among genes and their loci responsible for different hereditary disorders in Pakistan from the studies conducted elsewhere in the World. During the course of study, the affected individuals will be subjected to clinical examination and a series of ophthalmological tests for the correct diagnosis. Besides genetic dissection of these diseases, the study is also aimed at spreading awareness among affected individuals and their families as most genetic disorders in Pakistani population have a recessive mode of inheritance which is expressed where consanguinity is common.

### *Prevalence of Glaucoma*

It was forecasted that 161 million people globally had optical loss and 37 million people were suffered from blindness in 2002. Visual impairment had 12.3% of worldwide sightlessness, though cataract accounted for 47.8%. it is also estimated that glaucoma had effected adults more as compared to children and women are more effected as compared to men (Casson *et al.*, 2012; Faiq *et al.*, 2013). In 2010 study, it is founded out that 60.5 million individuals all over the world had open-angle glaucoma (OAG) and angle-closure glaucoma (ACG). It is roughly estimated that in 2020 this prevalence would be increased to 79.6 million. The collective (74%) people would have OAG. 70% will be women which would be effected by ACG and 87% will be Asians. Glaucoma is the loss of visual ability caused more in women and Asians (Buhrmann *et al.*, 2000). Visual loss is practically third time in African Americans as compared to white Americans, and POAG is the foremost source of sightlessness in African Americans (Rein *et al.*, 2006). There is a more risk to manage health care. 17.8% people who have disease of the visual impairment in USA contribute their self to take the medicine and bear the cost for that purpose. On behalf of a considerable percentage which is given that the yearly entire through medical costs for these illnesses was assessed to be \$16.2 billion and in coming years this cost will be increased unquestionably (Hussain and Bittles, 1998).

### *Phenotypic Heterogeneity in Glaucoma*

Glaucoma has been divided into different groups like congenital and non-congenital, primary and secondary, open and closed angle, infantile, juvenile and adult on the basis of etiology, anatomy of anterior chamber (Shastry, 2013). Primary defective molecules and all the risk factors should be taken into account while grouping glaucoma (Weisschuh and Schiefer, 2003). It is now believed that almost all forms of glaucoma have genetic basis. Inherited forms of glaucoma are heterogeneous, both autosomal dominant and recessive a very little literature is available about sex linked inheritance of glaucoma. There are three major classes of glaucoma (Khan *et al.*, 2017).

### *Primary Congenital Glaucoma*

Primary congenital glaucoma (PCG) is an infrequent form of glaucoma. It appears at birth or within first three years of life. It is due to progressive flaws in TM and anterior chamber resulting in high intra ocular pressure, optic disc destructions and raised corneal diameter (Weinreb *et al.*, 2014). It shows autosomal recessive Mendelian inheritance.

### *Open-Angle Glaucoma*

In open angle glaucoma (OAG) defect is in the outflow of aqueous humour due to decreased number of cells in filtration region and close to the interior wall of Schlemm's canal, extra cellular materials are accumulated. Primary open angle glaucoma (POAG) is the most common type of glaucoma, disturbing over 33 million persons wide-reaching (Khan *et al.*, 2017). Open-angle chronic glaucoma progress gradually, it is pain-free and most of the time shows no signs, until it has developed sufficiently. It is of adult onset and juvenile form. It has also been proposed that JOAG shows autosomal dominant inheritance while the adult onset POAG exhibits non-Mendelian inheritance (Weinreb *et al.*, 2014).

Increased level of IOP is the main discovery related to this disease. Additionally, on clinical trials, noticeable focal flaws in the retinal nerve fibre layer generally intercede optic disc modifications and visual field damage. Changes related to age in the trabecular region are the most probable reason of this condition.

Even though many cases of POAG are related with increased IOP, in some cases level of IOP is shown normal and it is stated as normal-tension glaucoma (NTG). This is possibly because of unnoticed change in levels of IOP but optic nerve is usually responsive to these changes (Fraunfelder *et al.*, 2004).

### *Angle Closure Glaucoma*

This is a set of disorders in which there is aqueous obstruction that results due to rescindable (appositional) or cohesional (synechial) closure of the anterior-chamber. There are two forms in which angle closure can occur and that is in acute and chronic form. In the acute form, there is sudden stoppage of the TM by the iris via pupillary block mechanism which results in elevation of IOP. The chronic form may grow after acute form where synechial closure of the angle remains, or it may grow over time as the angle closes from lengthened or recurring contact between the peripheral iris and the TM, which frequently contributes to functioning obstruction to the angle and peripheral anterior synechiae (PAS) (Kim and Jung, 1997). Primary angle closure glaucoma (PACG) occurs when access to the trabecular meshwork (TM) is physically obstructed, typically by the iris, and the drainage angle is closed.

Three main mechanisms hypothesized to be responsible for PACG are pupillary block, anterior iris rotation, and plateau iris. When the pressure of the posterior chamber overrun the pressure of the anterior chamber, pupillary block appears to be happen, and this blocks the TM by pushing peripheral and mid peripheral iris forward (Harasymowycz *et al.*, 2016).

Secondary angle-closure happens by some known genetics. Phacomorphic glaucoma is an example of secondary angle-closure, that happens because the angle is closed when lens pushes iris forward (Tello *et al.*, 2000). This might also happen in subluxation. Secondary pupil block may be caused by Uveitis, which is distinguished by posterior synechiae and iris bombe. Some other reasons comprise malignant glaucoma, neovascularisation, retinopathy of prematurity, Vogt-Koyanagi-Harada syndrome, posterior scleritis, acquired immunodeficiency syndrome, leukaemia, orbital or carotid cavernous fistula and neuropathia epidemica (Quigley and Broman, 2006).

In this review we assessed 269 patients of different families to check the type of glaucoma in different medical Hospitals with the help of an ophthalmologist

and recorded the phenotype of each patients and assigned a special family number to each family (Table 1) and also took images of each patient (Fig. 1).

**Table 1.** Phenotypic assessment of patients affected by glaucoma.

Family- ID	Phenotype	Age Range (Month-Year)	Average IOP range by Goldman tonometry	Trabeculectomy	Collected Samples	Affected Individuals (Collected)	Other Clinical features
GL-01	Open Angle Glaucoma	22y-60y	29±5.6 mmHg	Operated	25	17	Diabetes
GL-02	Open Angle Glaucoma	15y-70y	40±4.15 mmHg	Operated	34	26	Speech problem, Arthritis
GL-03	Primary Congenital Glaucoma	1M-12y	30±5.75 mmHg	Operated	24	13	Mental Retardation, Disable, Arthritis
GL-04	Open Angle Glaucoma	20y-50y	30±3.25 mmHg	Operated	28	15	Cataract
GL-05	Primary Open Angle Glaucoma	1y-50y	36±3.5 mmHg	Operated	16	11	Low Vision
GL-06	Primary Open Angle Glaucoma	25y-65y	31±6.4 mmHg	Operated	18	13	No
GL-07	Primary Angle Closure Glaucoma	15y-70y	44±4 mmHg	Operated	40	24	Visual problems
GL-08	Angle Closure Glaucoma	25y-75y	39±5 mmHg	Operated	22	17	No
GL-09	Angle Closure Glaucoma	15y-40y	42±9 mmHg	Operated	21	13	Very low vision
GL-10	Primary Congenital Glaucoma	3y-20y	27±4 mmHg	Operated	44	35	Mental Retardation, Speech Problem



**Fig. 1.** Phenotypic assessments of glaucoma patients.

#### Consanguinity in Pakistan

In West and South Asia consanguineous marriages are strenuously favoured. Cousin marriages or marriages within the same ethnic group are common in Pakistan, Percentage of consanguineous marriages was roughly 60%, in which percentage of marriages between first cousins were 80% (Iqbal *et al.*, 2011). Such unions were more usual among illiterate women

or had only basic education, migrants (first or secondary generation) from rural areas, lived in villages, in the PDHS and those whose parents had consanguineous marriage. The frequency of blindness in Pakistan is 2.7% according to National Health Survey conducted in 2003, on the inclusive side it affects 2% of world's population. Fourth utmost main cause stated for blindness in Pakistan is Glaucoma (Ferris *et al.*, 1982).

*Genetic Heterogeneity in Glaucoma**MYOC*

The location of gene *MYOC* (MIM601652) is at the *GLC1A* locus (MIM137750) on chromosome 1q25 (Fingert *et al.*, 2002). It was the first OAG gene to be defined and was associated with JOAG and POAG. *MYOC* has 3 exons and codes 57 kD Myocilin protein (Kubota *et al.*, 1997). This protein is cytoskeletal and usually expressed in the retinal photoreceptor cells and is present mainly in the basal body of photoreceptor linking cilium. Normally in eyes, *MYOC* mRNA is expressed in the iris, ciliary body, TM as well as in retinal photoreceptor cells and optic nerve head-specifically, the astrocytes (Ohlmann and Tamm, 2002). The contemporary purpose of Myocilin is still unidentified. By glucocorticoids, transmuting growth factor- $\beta$ , stretch, and elevated intraocular pressure (Filla *et al.*, 2002). Myocilin expression is expressed in trabecular meshwork cells. It is a discharged glycoprotein which is lightly coupled with the Trabecular meshwork out of the cell matrix. It exists in the aqueous humour and they are usually huge oligomers aggregated into themselves. The role of myocilin and its connections regarding pathophysiology of glaucoma. Enhanced Myocilin expression has been identified in the trabecular meshwork of glaucoma patients, including pseudo exfoliation glaucoma, POAG and pigmentary glaucoma (Bejjani *et al.*, 1998). An additional vital subtype of glaucoma is normal tension glaucoma (NTG), which is considered by glaucomatous damage to the ONH and progressive loss of vision in patients with normal IOP. The role of Myocilin in the physiopathology of NTG is still uncertain. It is most frequently mutated gene in familial glaucoma cases, accounting for 4% of adult onset POAG and 10% JOAG (Noda *et al.*, 2000).

*Cyp1B1*

Location of *CYP1B1* (MIM 601771) is at the *GLC3A* locus (MIM 231300) on chromosome 2p21 (Beckerman, 2002). *CYP1B1* contains 3 exons, in which protein coding exons are only two and three (Hayes *et al.*, 1996). *CYP1B1* displays the highest level of expression in endometrial tissue. It also has constitutive expression in extrahepatic tissues

involving mammary and lung tissue. Activation of both polycyclic aromatic hydrocarbons and aryl amines can be catalysed by *CYP1B1* (Christou *et al.*, 1994). Additionally, it also has constitutive expression in the human mammary carcinoma MCF-7 cell line and facilitates the hydroxylation of 17 $\beta$ -estradiol to form 4-catecholestrogen. *CYP1B1* level of expression is also seen in a many types of malignant tumours but is not noticeable in normal tissues, showing that this cytochrome P450 is a specific tumour causing form of cytochrome P450 (Sutter *et al.*, 1994). Although *CYP1B1* mRNA has been identified in a limited number of normal tissues, findings of an absence of detectable *CYP1B1* protein in normal tissues suggest that either *CYP1B1* protein is present at a very low level in normal tissues or the *CYP1B1* mRNA is not translated.

The *CYP1B1* expression and the development of 4-hydroxy estrogens have been related with estrogen-associated tumours in several tissues and species. Increased 4-hydroxy estrogen formation has been related with cancer formation of several cancers counting endometrial cancer (Jefcoate *et al.*, 2000). Juvenile glaucoma (JG) and congenital glaucoma (CG) are inherently heterogeneous, and categorization is only on small subset, with most frequent mutations found in *MYOC* and *CYP1B1*. These mutations are related with autosomal recessive CG. In Pakistani patients, in 10 out of 20 families (50%) homozygosity is expressed with *CYP1B1*- STR markers (Sheikh *et al.*, 2014).

*OPTN*

Optineurin (*OPTN*) gene is located on chromosome 10p14 at the *GLC1E* [55]. *OPTN* contains sixteen exons; in the 5' untranslated region, first 3 exons are non-protein coding and then they are followed by thirteen exons that codes a 577 amino acid (Faiq *et al.*, 2013). Its expression is usually in brain and ocular tissues such as the optic nerve, TM, non-pigmented ciliary epithelium and retina (Rezaie *et al.*, 2007). In broad sense it is expressed in both ocular and non-ocular tissues. This protein interacts with apoptosis related proteins and might show a role in protection of neurological system as it decreases susceptibility to apoptosis of retinal ganglion cells.

*OPTN* increased expression blocks cytochrome c discharge from the mitochondria and defends the cell from H<sub>2</sub>O<sub>2</sub>-induced cell death (Kumar *et al.*, 2007a).

The mechanical role of *OPTN* in the physiopathology of glaucoma still remains vague. *OPTN* genes is involved in the aetiology of adult-onset primary open-angle glaucoma (POAG) (Kumar *et al.*, 2007b). Most common variations of *OPTN* in Asia is *M98K* and *T34T*.

#### *WDR36*

*WDR36* (MIM 609669) gene is located at the *GLC1G* locus (Fingert *et al.*, 2011; Monemi *et al.*, 2005). *WDR36* is limited in centre between positions 111,037,156 bp and 147,210,429 bp at chromosome 5q22.1-q32 using the Human Genome Sequence. *WDR36* contains 23 exons and codes for a 951 amino acid protein with several *WD40* recursions. Its expression is seen in both human ocular and non-ocular tissues and also in adult mouse and embryonic tis The main function of this gene is the formation of coordinating multiprotein complicated assemblies, where the recurring units' aid as a stiff scaffold for protein interactions.

It has been anticipated that T-cell activation may be mediated by *WDR36* and currently, participation of T-cell facilitated responses is found in glaucoma-associated optic nerve degeneration (Bakalash *et al.*, 2005). In the Asian population, mutations in *WDR36* seem to play a negligible role in POAG pathogenesis but polymorphic variants have been found to be associated with primary open angle glaucoma, specifically in high tension glaucoma (Mookherjee *et al.*, 2011). More than 150 PCG-related mutations in *CYP1B1* have been defined. One missense variant, p. G36D, and a 12 bp in-frame deletion mutation, p. Gly67Ala70del, have recently been found in Pakistani Families.

#### *Other Molecular Players of Glaucoma*

A new locus (*GLC3D*) residing on the *LTBP2* gene has been categorized in developmental glaucoma but its role is still to be determined in standard cases of PCG (Bejjani *et al.*, 2000). One intronic SNP (rs3742793) was found in *LTBP2* gene within exon six and seven in 18 patients out of a cohort of 54 unconnected

Indian patients with PCG who were negative for *MYOC*, *CYP1B1* and *FOXC1* mutations. This SNP resulted in C to G mutation at position g. 75070493. There is no pathogenic variants were recognized in the *LTBP2* (Abu-Amero *et al.*, 2011). Tested patients of 54 dissimilar Saudi PCG families (74 patients), there is no mutation in these patients who were detected as having PCG via typical ophthalmological inspections and screened for mutations in *CYP1B1* and *LTBP2* by sequencing.

In exceedingly engrained populations like Slovakian Gypsies, Iranians and Saudi Arabians 80-100% occurrence of recessively inherited glaucoma is testified due to mutations in *CYP1B1*. 7 out of 9 PCG patients (78%) from 8 consanguineous families from Oman showed mutations in *CYP1B1* (Bashir *et al.*, 2014). *CYP1B1* mutations are the major (75.9%) cause of PCG in the Saudi Arabian population with G61E as the dominant disease-associated allele. British Infantile and Childhood Glaucoma, study shown that the frequency of PCG in the Pakistani children is about nine times higher than that in Caucasians. *GLC3A* contribute 17% of primary congenital glaucoma in sporadic cases besides 2 patients out of 3 families from Pakistan (Wiggs *et al.*, 2004).

Ethnic specific *OPTN* mutation patterns may exist. The wild type *OPTN* protein, functioning through the TNF- $\alpha$  pathway, is ventured to play a neuro-protective role in the eye and optic nerve. But when malfunctioning, it causes visual loss and optic neuropathy as typically seen in NTG and high-tension glaucoma (Alward *et al.*, 2003; Zhou *et al.*, 2013). Three genes at 14 chromosomal loci elucidate for less than 5% of all POAG cases signifying that 90% of contribution of genes in POAG cases is not known. D384N mutation has been stated as one of the major mutations in POAG, as reported by a Chinese family having POAG. Whereas T353I modification was thought as a high-risk factor for POAG. These two changes were first reported in one juvenile -onset POAG patient who presented with more acute clinical appearances, signifying that T353I polymorphism may be related with the acuteness of POAG.

The first indication for a mutation linked to familial PACG emanates from the analysis of a large family with nanophthalmos, hyperopia, and angle closure glaucoma (Dai *et al.*, 2008).

This study has directed towards the documentation of the gene nanophthalmos 1 (NNO1) which is present on chromosome 11. Presently the only human gene recognized which produce an angle closure glaucoma phenotype is NNO1. In distinction, several genetic loci have been recognized that may not be contributing, but increase an individual's risk to produce PACG. A positive connotation to CYP1B1, a gene concerned in the formation of congenital glaucoma, was highlighted in studies of PACG in patients of Chinese, Indian, and Canadian origin (Cheng *et al.*, 2013). A current meta-analysis of genome-wide associations for ocular axial length was shown in patients of European and Asian origin exhibiting refractive errors, which along with hyperopia and myopia is mainly defined by axial length. RSPO1, C3orf26, LAMA2, GJD2, ZNRF3, CD55, MIP, ALPPL2 and ZC3H11B were identified as nine genome-wide significant loci for axial length (McBrien *et al.*, 2001). Recently, genome-wide association study (GWAS) in an Asian population of PACG acknowledged three PACG vulnerability loci in PLEKHA7, COL11A1, and also in PCMTD1 and ST18. COL11A1 is a predominantly stimulating gene as it encodes one of the two alpha chains of type XI collagen, which is highly articulated in the scleral tissue. Several studies provide additional evidence for the potential role of collagen in glaucoma. Modifications in collagen deposition influence the biomechanical and remodelling competences of the sclera, thus result in glaucoma-predisposing axial length changes and associated refractive errors (Inamori *et al.*, 2007). In a Japanese and Chinese Han populations, single-nucleotide polymorphism (SNP) in the gene COL1A1 is related towards the increased risk of myopia and it is plausible that other genetic variants result in conformational variations to the anterior segment that incline toward the development of the disease (Norman *et al.*, 2011). Still, transformations in collagen composition of the sclera may be associated with suboptimal optic nerve head biomechanics, resulting in increased exposure to axonal damage in glaucomatous eyes (Consoli *et al.*, 2005).

#### *Glaucoma Treatment and concerns*

Glaucoma is a serious chronic disease. Its world widely occurrence is approximately 67 million. It is a visual disorder which causes blindness if no care is taken place and no proper treatment is taken place at specific time. It is not clearly understood that how it causes loss of visual sight and then lead to complete blindness. The speed of glaucoma causes can be reduced but not stopped or controlled and not specific measurement can be taken place to find out it earlier. It causes an attention disturbance situation analysis and by not full focusing on it and considering it well and due to no proper diagnostic measurements unproductive results are accompanied. The main reason of glaucoma increased percentage is post ponding of visual check-ups and no availability of proper machinery and techniques. If visual loss is taken place once then there is no adequate optical treatment is available to cover up it e.g. IOP is a major risk which lead to the loss of visual ability (Fechtner and Realini, 2004). Some other things also very important like cost, sustainability etc. Now these days its treatments are taken place including medication, laser and operation. With recently doing research and adequate medicinal treatment glaucoma can be stopped or well-orderedly controlled and sight loss can be recovered. In these days there is no remedy but glaucoma required more attention and treatment with care by doing this it can be recovered.

Glaucoma is treated with the help of specific medicine which take a good part to control the loss of quantity of liquid which is built by eyes. Some that kind of treatment causes safety of eye pressure for some years. Some medicines are used that control the attack of aqueous humour, enlightening the expenditure of aqueous humour, protecting the optical nerves. Prostaglandin F<sub>2α</sub> derivatives which causes enhancement of the uveoscleral discharges recently used at wide level. Bimatoprost is also widely used for glaucoma treatment as an anti-glaucoma (Khaw *et al.*, 2004). Acetylcholine receptor agonists is also used for IOP so that visual loss can be controlled. Timolol is utilized which is the major suggested drug and betaxolol is also used which has the slightest common harmful effects.

These both medicines are together used as a  $\beta_1$  receptor blockers. Laser treatment is used commonly for glaucoma by using ciliary and the pigmented trabecular meshwork cells. 20 to 30 percent patients are treated with laser technique and 70 percent patients are overwhelmed with it (Lau *et al.*, 2002). Some kinds of surgeries are also taken place like Minimally Invasive Glaucoma Surgery (MIGS) are taken place through which glaucoma is detected and then treated. Some kind of research is also taken place which would provide help us to overcome different kind of glaucoma and Gentler sorts of laser Cyclophotocoagulation is also taken place to recover the glaucoma.

The awareness of patients and their involvement in treatment of glaucoma is very necessary and play an important role to prevent and cure of such kind of disease just like Glaucoma. A huge amount of study is taken place on glaucoma that is caused in young persons. The patients who lose their eye visual power was studied and analysed and primary reason was find out but due to the less knowledge about blindness, more information was not obtained but increment of literature and educational system can enhance the betterment in treatment of visual loses (Gooch *et al.*, 2012).

Now these days' main focus is taken place on intraocular pressure. It is achieved by taking regular up-to-date eye drops but due to less awareness of patient and improper treatment glaucoma is increased. Many constant curing treatments are under research by some scientists. Conjunctively, punctal plugs intravitreal inserts and sub conjunctival, and drug sidings are recently in under clinical improvements (Garaci *et al.*, 2009a). Treatment of glaucoma is more expensive but there is a hope that dramatically improvement will come in this disease treatment in few coming years and improved IOP control system will be developed. Some researcher reviled that that glaucoma is a multifaceted neurologic disease that disturbs optic Nerves, optic radiations, and the adjacent geniculate nucleus also. Central nervous system (CNS) causes impairment accompanying with glaucoma that has

been perceived by modifications in optic nerves by using of magnetic significance imaging (Garaci *et al.*, 2009b). POAG affected person is treated with some early rehabilitations which show good effect during coming 10 years that results are obtained by utilizing the therapies which decrease the IOP.

In some cases, glaucoma patients are treated and cured during 5 years. Some filtration surgeries are taken place which controls the IOP that is the basic thing that is done with glaucoma patients and it reduces the effect of Glaucoma and enhances the curing chances (Ehrlich *et al.*, 2012). Recently some goals are in mind of scientists that glaucoma can be stopped by some basic treatments and its causing chances can be lowered by decreasing the IOP (intraocular pressure). By increase of the aqueous discharge glaucoma is caused and it reduces the better medication of glaucoma.

Treatment should not only decrease the glaucoma but it also should reduce the bad effects of that treatment. Full knowledge should be given to the patient and then according to their choice and betterment their treatment should be done (Kass *et al.*, 2002).

Nevertheless of the some chemical composites and or by using some technologies of accomplishment, the perfect ocular delivery system is that one which achieved and enhances the operational values of specific drug amount at the major position for anticipated time periods and it decrease the universal acquaintance and meet the expenses of patient which increased the volubility of life but there is a major task for scientist to find out technique which should be safe so that safe transport fences of eye can be done which should not contain the unwanted and unappealing bad effects and it should prove as a safe therapy.

### Conclusion

The biological origin of this disorder is not yet entirely tacit, and the aspects causative to its progression are not yet entirely characterised. The most imperative risk factor for glaucoma is raised by intraocular pressure. Because the optic-nerve damage in glaucoma is yet not acquiescent to direct treatment,



the provided treatment is only for the known risk factor that can be modified, increased intraocular pressure. We hope that further analysis of data from this study can be used to find some defining features of such population subsets, diagnostic risk factors, or perhaps clues to risk factors that may be docile to therapeutic changes.

#### Acknowledgment

The author is thankful to those families who were participated in this study voluntarily. The author is also thankful to Department of Ophthalmology Allied Hospital, Medical University Faisalabad, Pakistan for the phenotypic assessments of the patients.

#### Author's Contributions

MU Identified glaucomatous families, proceeded with clinical evaluation, wrote and corresponded the manuscript, QH performed clinical evaluation, MA, MQ and MIR helped in manuscript writing, MR, ZM, OD, TA, and MJH helped in families' identification.

#### References

- Abu-Amero KK, Osman EA, Mousa A, Wheeler J, Whigham B, Allingham RR, Hauser MA, Al-Obeidan SA.** 2011. Screening of CYP1B1 and LTBP2 genes in Saudi families with primary congenital glaucoma: genotype-phenotype correlation. *Molecular Vision* **17**, 2911.
- Alward WL, Kwon YH, Kawase K, Craig JE, Hayreh SS, Johnson AT, Khanna CL, Yamamoto T, Mackey DA, Roos BR.** 2003. Evaluation of optineurin sequence variations in 1,048 patients with open-angle glaucoma. *American Journal of Ophthalmology* **136**, 904-910.
- Bakalash S, Shlomo GB, Aloni E, Shaked I, Wheeler L, Ofri R, Schwart M.** 2005. T-cell-based vaccination for morphological and functional neuroprotection in a rat model of chronically elevated intraocular pressure. *Journal of Molecular Medicine* **83**, 904-916.
- Bashir R, Sanai M, Azeem A, Altaf I, Saleem F, Naz, S.** 2014. Contribution of GLC3A locus to Primary Congenital Glaucoma in Pakistani population. *Pakistan Journal of Medical Sciences* **30**, 1341.
- Beckerman M.** 2002. Modeling and Simulation of Microelectrode-Retina Interactions. Oak Ridge Y-12 Plant, TN (US).
- Bejjani BA, Lewis RA, Tomey KF, Anderson KL, Dueker DK, Jabak M, Astle WF, Otterud B, Leppert M, Lupski JR.** 1998. Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. *The American Journal of Human Genetics* **62**, 325-333.
- Bejjani BA, Stockton DW, Lewis RA, Tomey KF, Dueker DK, Jabak M, Astle WF, Lupski JR.** 2000. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. *Human Molecular Genetics* **9**, 367-374.
- Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB.** 2000. Prevalence of glaucoma in a rural East African population. *Investigative Ophthalmology & Visual Science* **41**, 40-48.
- Casson RJ, Chidlow G, Wood JP, Crowston JG, Goldberg I.** 2012. Definition of glaucoma: clinical and experimental concepts. *Clinical & Experimental Ophthalmology* **40**, 341-349.
- Cheng C-Y, Schache M, Ikram MK, Young TL, Guggenheim JA, Vitart V, MacGregor S, Verhoeven VJ, Barathi VA, Liao J.** 2013. Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. *The American Journal of Human Genetics* **93**, 264-277.
- Christou M, Savas Ü, Spink DC, Gierthy JF, Jefcoate CR.** 1994. Co-expression of human CYP1A1 and a human analog of cytochrome P450-EF in response to 2, 3, 7, 8-tetrachloro-dibenzo-pdioxin in the human mammary carcinoma-derived MCF-7 cells. *Carcinogenesis* **15**, 725-732.

- Consoli D, McMeekin A, Ramlogan R, Mina A, Tampubolon G, Metcalfe J.** 2005. Progress in medicine: The structure and evolution of know-how for the treatment of glaucoma. CRIC Discussion Paper.
- Dai X, Nie S, Ke T, Liu J, Wang Q, Liu M.** 2008. Two variants in MYOC and CYP1B1 genes in a Chinese family with primary angle-closure glaucoma. *Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese Journal of Medical Genetics* **25**, 493-496.
- Ehrlich JR, Radcliffe NM, Shimmyo M.** 2012. Goldmann applanation tonometry compared with corneal-compensated intraocular pressure in the evaluation of primary open-angle Glaucoma. *BMC Ophthalmology* **12**, 52.
- Faiq M, Sharma R, Dada R, Mohanty K, Saluja D, Dada T.** 2013. Genetic, biochemical and clinical insights into primary congenital glaucoma. *Journal of Current Glaucoma Practice* **7**, 66.
- Farkas RH, Grosskreutz CL.** 2001. Apoptosis, neuroprotection, and retinal ganglion cell death: an overview. *International ophthalmology clinics* **41**, 111-130.
- Fechtner RD, Realini T.** 2004. Fixed combinations of topical glaucoma medications. *Current Opinion in Ophthalmology* **15**, 132-135.
- Feldman RM.** 2004. An evaluation of the fixed-combination of latanoprost and timolol for use in open-angle glaucoma and ocular hypertension. *Expert Opinion on Pharmacotherapy* **5**, 909-921.
- Ferris FL, Kassoff A, Bresnick GH, Bailey I.** 1982. New visual acuity charts for clinical research. *American Journal of Ophthalmology* **94**, 91-96.
- Filla MS, Liu X, Nguyen TD, Polansky JR, Brandt CR, Kaufman PL, Peters DM.** 2002. In vitro localization of TIGR/MYOC in trabecular meshwork extracellular matrix and binding to fibronectin. *Investigative Ophthalmology & Visual Science* **43**, 151-161.
- Fingert JH, Robin AL, Stone JL, Roos BR, Davis LK, Scheetz TE, Bennett SR, Wassink TH, Kwon YH, Alward WL.** 2011. Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. *Human Molecular Genetics* **20**, 2482-2494.
- Fingert JH, Stone EM, Sheffield VC, Alward WL.** 2002. Myocilin glaucoma. *Survey of Ophthalmology* **47**, 547-561.
- Fraunfelder F, Keates EU.** 2004. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* **111**, 109-111.
- Frick KD, Foster A.** 2003. The magnitude and cost of global blindness: an increasing problem that can be alleviated. *American Journal of Ophthalmology* **135**, 471-476.
- Garaci FG, Bolacchi F, Cerulli A, Melis M, Spanò A, Cedrone C, Floris R, Simonetti G, Nucci C.** 2009a. Optic nerve and optic radiation neurodegeneration in patients with glaucoma: in vivo analysis with 3-T diffusion-tensor MR imaging. *Radiology* **252**, 496-501.
- Garaci FG, Bolacchi F, Cerulli A, Melis M, Spanò A, Cedrone C, Floris R, Simonetti G, Nucci C.** 2009b. Optic Nerve and Optic Radiation Neurodegeneration in Patients with Glaucoma: In Vivo Analysis with 3-T Diffusion-Tensor MR Imaging 1. *Radiology* **252**, 496-501.
- Gooch N, Molokhia SA, Condie R, Burr RM, Archer B, Ambati BK, Wirostko B.** 2012. Ocular drug delivery for glaucoma management. *Pharmaceutics* **4**, 197-211.
- Harasymowycz P, Birt C, Gooi P, Heckle L, Hutnik C, Jinapriya D, Shuba L, Yan D, Day R.** 2016. Medical management of glaucoma in the 21st Century from a Canadian perspective. *Journal of Ophthalmology* 2016.

- Hayes CL, Spink DC, Spink BC, Cao JQ, Walker NJ, Sutte TR.** 1996. 17 beta-estradiol hydroxylation catalyzed by human cytochrome P450 1B1. *Proceedings of the National Academy of Sciences* **93**, 9776-9781.
- Hussain R, Bittles A.** 1998. The prevalence and demographic characteristics of consanguineous marriages in Pakistan. *Journal of Biosocial Science* **30**, 261-275.
- Inamori Y, Ota M, Inoko H, Okada E, Nishizaki R, Shiota T, Mok J, Oka A, Ohno S, Mizuki N.** 2007. The COL1A1 gene and high myopia susceptibility in Japanese. *Human Genetics* **122**, 151-157.
- Iqbal S, Khan Z, Shah SA, Khan MY.** 2011. Types and presentation of glaucoma. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)* **22**.
- Jefcoate CR, Liehr JG, Santen RJ, Sutter TR, Yager JD, Yue W, Santner SJ, Tekmal R, Demers L, Pauley R.** 2000. Chapter 5: Tissue-specific synthesis and oxidative metabolism of estrogens. *JNCI Monographs* **2000**, 95-112.
- Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Gordon MO.** 2002. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Archives of Ophthalmology* **120**, 701-713.
- Khan L, Ali M, Qasim M, Jabeen F, Hussain B.** 2017. Molecular basis of glaucoma and its therapeutical analysis in Pakistan: an overview. *Biomedical Research and Therapy* **4**, 1210-1227.
- Khaw K-T, Wareham N, Bingham S, Luben R, Welch A, Day N.** 2004. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Annals of Internal Medicine* **141**, 413-420.
- Kim YY, Jung HR.** 1997. Clarifying the nomenclature for primary angle-closure glaucoma. *Survey of Ophthalmology* **42**, 125-136.
- Kubota R, Noda S, Wang Y, Minoshima S, Asakawa S, Kudoh J, Mashima Y, Oguchi Y, Shimizu N.** 1997. A novel myosin-like protein (myocilin) expressed in the connecting cilium of the photoreceptor: Molecular cloning, tissue expression, and chromosomal mapping. *Genomics* **41**, 360-369.
- Kumar A, Basavaraj MG, Gupta SK, Qamar I, Ali AM, Bajaj V, Ramesh T, Prakash DR, Shetty JS, Dorairaj SK.** 2007a. Role of CYP1B1, MYOC, OPTN and OPTC genes in adult-onset primary open-angle glaucoma: predominance of CYP1B1 mutations in Indian Patients. *Molecular Vision* **13**, 667.
- Kumar A, Basavaraj MG, Gupta SK, Qamar I, Ali AM, Bajaj V, Ramesh T, Prakash DR, Shetty JS, Dorairaj SK.** 2007b. Role of CYP1B1, MYOC, OPTN, and OPTC genes in adult-onset primary open-angle glaucoma: predominance of CYP1B1 mutations in Indian Patients. *Mol Vis* **13**, 667-676.
- Lau J, Lee V, Fan D, Lau M, Michon J.** 2002. Knowledge about cataract, glaucoma, and age related macular degeneration in the Hong Kong Chinese population. *British Journal of Ophthalmology* **86**, 1080-1084.
- Mc Brien NA, Cornell LM, Gentle A.** 2001. Structural and ultrastructural changes to the sclera in a mammalian model of high myopia. *Investigative Ophthalmology & Visual Science* **42**, 2179-2187.
- Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, Liebmann J, Ritch R, Héon E, Crick RP, Child A.** 2005. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. *Human Molecular Genetics* **14**, 725-733.
- Mookherjee S, Chakraborty S, Vishal M, Banerjee D, Sen A, Ray K.** 2011. WDR36 variants in East Indian primary open-angle glaucoma patients.
- Noda S, Mashima Y, Obazawa M, Kubota R, Oguchi Y, Kudoh J, Minoshima S, Shimizu N.** 2000. Myocilin expression in the astrocytes of the optic nerve head. *Biochemical and Biophysical Research Communications* **276**, 1129-1135.

- Norman RE, Flanagan JG, Sigal IA, Rausch SM, Tertinegg I, Ethier CR.** 2011. Finite element modeling of the human sclera: influence on optic nerve head biomechanics and connections with glaucoma. *Experimental Eye Research* **93**, 4-12.
- Ohlmann A, Tamm E.** 2002. Die Rolle von Myocilin bei der Pathogenese des primären Offenwinkelglaukoms. *Der Ophthalmologe* **99**, 672-677.
- Quigley HA, Broman AT.** 2006. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology* **90**, 262-267.
- Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ, McCall N, Klein R, Tielsch JM, Vijan S, Saaddine J.** 2006. The economic burden of major adult visual disorders in the United States. *Archives of Ophthalmology* **124**, 1754-1760.
- Rezaie T, Stoilov I, Sarfarazi M.** 2007. Embryonic expression of the optineurin (glaucoma) gene in different stages of mouse development. *Mol. Vis* **13**, 1446-1450.
- Rizzo MI, Greco A, De Virgilio A, Gallo A, Taverniti L, Fusconi M, Conte M, Pagliuca G, Turchetta R, de Vincentiis M.** 2017. Glaucoma: recent advances in the involvement of autoimmunity. *Immunologic Research* **65**, 207-217.
- Sarfarazi M.** 1997. Recent advances in molecular genetics of glaucomas. *Human Molecular Genetics* **6**, 1667-1677.
- Sarfarazi M, Stoilov I.** 2000. Molecular genetics of primary congenital glaucoma. *Eye* **14**, 422-428.
- Shastry BS.** 2013. Genetic susceptibility to primary angle closure glaucoma (PACG). *Discovery Medicine* **15**, 17-22.
- Sheikh SA, Waryah AM, Narsani AK, Shaikh H, Gilal IA, Shah K, Qasim M, Memon AI, Kewalramani P, Shaikh N.** 2014. Mutational spectrum of the CYP1B1 gene in Pakistani patients with primary congenital glaucoma: novel variants and genotype-phenotype correlations. *Molecular Vision* **20**, 991.
- Sutter TR, Tang YM, Hayes CL, Wo Y-Y, Jabs EW, Li X, Yin H, Cody CW, Greenlee WF.** 1994. Complete cDNA sequence of a human dioxin-inducible mRNA identifies a new gene subfamily of cytochrome P450 that maps to chromosome 2. *Journal of Biological Chemistry* **269**, 13092-13099.
- Tello C, Rothman R, Ishikawa H, Ritch R.** 2000. Differential diagnosis of the angle-closure glaucomas. *Ophthalmology Clinics* **13**, 443-453.
- Weinreb RN, Aung T, Medeiros FA.** 2014. The pathophysiology and treatment of glaucoma: a review. *Jama* **311**, 1901-1911.
- Weisschuh N, Schiefer U.** 2003. Progress in the genetics of glaucoma, *Genetics in Ophthalmology*. Karger Publishers pp. 83-93.
- Wiggs JL, Allingham RR, Vollrath D, Jones KH, De La Paz M, Kern J, Patterson K, Babb VL, Del Bono EA, Broome BW.** 1998. Prevalence of mutations in TIGR/Myocilin in patients with adult and juvenile primary open-angle glaucoma. *American Journal of Human Genetics* **63**, 1549.
- Wiggs JL, Lynch S, Ynagi G, Maselli M, Auguste J, Del Bono E, Olson L, Haines J.** 2004. A genomewide scan identifies novel early-onset primary open-angle glaucoma loci on 9q22 and 20p12. *The American Journal of Human Genetics* **74**, 1314-1320.
- Zhou X-M, Yin Y, Fan N, Cheng H-B, Li X-H, Wang Y, Yu W-H, Cai S-P, Liu X-Y.** 2013. Single nucleotide polymorphism of MYOC affected the severity of primary open angle glaucoma. *International Journal of Ophthalmology* **6**, 264.