

## Genetics of Glaucoma

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**Abstract :** Glaucoma belongs to a group of diseases that share a common clinical phenotype characterized primarily by progressive degeneration of the optic nerve. It is the second major cause of irreversible blindness in the world that affects 67 million people worldwide. There are three major types of glaucoma; Primary Open Angle Glaucoma (POAG), Primary Congenital Glaucoma (PCG) and Primary Acute Closed Angle Glaucoma (PACG); and ten loci have been identified for their inherited forms. Mutations in four genes – Myocilin, Optineurin, WDR36 and CYP1B1 have been implicated in the pathogenesis of glaucoma. However, the specific phenotype of glaucoma in an individual is determined by other associated genes as well as certain risk factors. Precise clinical documentation and classification of this disease is essential for its proper diagnosis, management and for understanding its etiology at the molecular level.

**Keywords :** Glaucoma, MYOC, CYP1B1, OPTN

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### Introduction :

Glaucoma represents a heterogeneous group of optic neuropathies with complex genetic basis. It is a disease of optic nerve in which nerve fibers are usually affected, but not always, by abnormally high intraocular pressure (IOP). The elevated IOP associated with glaucoma is on account of increased resistance to the outflow of aqueous humor from the eye. The loss of vision in all forms of glaucoma is due to gradual death of ganglion cells in neural retina (Shields *et al.* 1996). According to Quigley (1996), 67 million people are affected worldwide. In India, about 1.5 million people are believed to be blind due to it (Balasubramanian 2002). It is estimated that 2-4% of the individuals over the age of 40 will develop glaucoma during their lifetime, and most of the people having glaucoma are unaware about it.

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The glaucomas can be broadly divided into two major categories, primary and secondary, on the basis of etiology. The primary glaucomas can be further classified into different categories based on anatomy of the anterior chamber (Open angle, Closed angle), or age of onset (congenital, juvenile onset, adult onset) (Sarfarazi 1997). The secondary glaucomas includes various syndromes and ocular conditions e.g., neovascular glaucoma, pseudoexfoliation glaucoma, iridocorneal endothelial syndrome, reiger syndrome, iridogoniodysgenesis, pigment dispersion syndrome, nail-patella syndrome, etc. Some of these ocular conditions arise from a generalized developmental anomaly of the anterior segment and are known as developmental glaucoma. However, more precise classification of glaucoma needs to be done taking into account various etiological and other contributing risk factors, including genetic.

At present, seven loci for primary open angle glaucoma (POAG) and three loci for primary congenital glaucoma (PCG) have been identified. These loci include three genes; Myocilin (MYOC), Optineurin (OPTN), and WDR36 for POAG and one gene, Cytochrome P4501B1 (CYP1B1), for PCG (Table 1). The human genome organization (HUGO) (<http://www.gene.ucl.ac.uk/hugo>) has designed “GLC” symbol for primary glaucoma genes. The numbers 1, 2 and 3 are placed after GLC to represent open angle, angle closure and congenital glaucoma, respectively. Each newly mapped gene is given a letter, which is assigned in alphabetic order e.g., GLC1A is the first locus and GLC1G is the seventh locus to be described for POAG.

### **Primary Open Angle Glaucoma (POAG)**

Primary open angle glaucoma (POAG) (OMIM 137760) is the most common type of glaucoma, affecting about 37 million people (Goldberg 2000). It affects 1-2% of all individuals over the age of 40 years and 8-10% in the above 65 age group (Leske *et al.* 1999). The prevalence of POAG in African descendents is three to four times higher than in Caucasian and Asians (Mason *et al.* 1989, Wilson & Martone 1996, Racette *et al.* 2003). The painless progression of this disease leads to late diagnosis, when irreversible and appreciable loss of field of vision has already occurred. POAG shows strong evidence of a complex trait. It usually shows polygenic

Table 1: Loci/genes reported for different types of glaucoma

Locus	Location	Gene (Gen-Bank accession no.)	Type	Inheritance	Age at onset (Yrs)	Intraocular pressure	Reference
GLC1A	1q23-25	MYOC/ TIGR (NM_000261)	JOAG/ COAG	AD*	5-45	high	Sheffield <i>et al.</i> 1993
GLC1B	2cen-q13		COAG	AD	>40	Low/moderate	Stoilova <i>et al.</i> 1996
GLC1C	3q21-24		COAG	AD	56	high	Wirtz <i>et al.</i> 1997
GLC1D	8q23		COAG	AD	>30	high	Trifan <i>et al.</i> 1998
GLC1E	10p14-15	OPTN (NM_021980)	COAG	AD	44	low	Sarfarazi <i>et al.</i> 1998
GLC1F	7q35-36		COAG	AD	>40	moderate	Wirtz <i>et al.</i> 1999
GLC1G	5q22.1	WDR36	COAG	AD	-	high/ low	Monemi <i>et al.</i> 2005
GLC3A	2p21	CYP11B1 (NM_000104)	PCG	AR	<3	high	Sarfarazi <i>et al.</i> 1995
GLC3B	1p36		PCG	AR^	<3	high	Akarsu <i>et al.</i> 1996
GLC3C	14q24.3		PCG	AR	<3	high	Stoilov and Sarfarazi 2002b

AD\* - autosomal dominant; AR^ - autosomal recessive

inheritance and is associated with variable severity of phenotype with IOP ranging from 10 to 70 mmHg and incomplete penetrance (Quigley 1993, Shields *et al.* 1996). POAG has been divided into two groups on the basis of age of onset: juvenile onset open angle glaucoma (JOAG) and adult onset chronic open angle glaucoma (COAG), but with overlapping clinical presentations and differences in severity and IOP values (Shields *et al.* 1996). The clinical diagnosis of both groups is based on visual field loss, glaucomatous change of optic nerve and optic nerve damage. JOAG has onset before the age of 35, with significantly higher IOPs (40-50 mmHg) that usually do not respond to any treatment and therefore need multiple surgical interventions (Ellis 1948, Goldwin *et al.* 1970, Johnson *et al.* 1993). Normal Tension Glaucoma (NTG) is another important subtype of POAG in which typical glaucomatous cupping of optic nerve head and visual field loss are present, but IOPs are consistently within the statistically normal population range (= 20mmHg). POAG has complex inheritance pattern as it does not follow classical Mendelian autosomal recessive or dominant inheritance in some cases. Sarfarazi (1997) has reported autosomal dominant inheritance with incomplete penetrance for POAG. Wiggs *et al.* (1998) suggested that adult onset POAG is inherited as non-Mendelian trait while juvenile onset POAG exhibits autosomal dominant inheritance. Yoon *et al.* (1999) has reported autosomal recessive mode of inheritance for JOAG.

Mutation in three genes; myocilin, optineurin, WDR36 have been identified for POAG. Mutations in myocilin have been reported to cause JOAG and also COAG in 2-5% of cases in various population based studies (Stone *et al.* 1997, Alward *et al.* 2002). Mutations in optineurin are responsible for mild to moderate form of late onset normal tension glaucoma (Rezaie *et al.* 2002). In a recent study by Monemi *et al.* (2005), mutations in WDR36 have been reported to be responsible for mild to moderate form of open angle glaucoma. WDR36 is a novel gene with 23 exons, which encodes for 951 amino acids and a protein with multiple G-beta WD40 repeats. It is expressed in lens, iris, sclera, ciliary muscles, ciliary body, trabecular meshwork, retina and optic nerve. However, its role in the pathogenesis of glaucoma has not been fully characterized.

## Primary Open Angle Glaucoma Genes

### MYOC-GLC1A

In 1993, the first locus for JOAG was mapped to chromosome 1q24.3 as GLC1A locus. The trabecular meshwork-inducible glucocorticoid response gene (TIGR), also known as Myocilin (OMIM 601652) was the first of the 'GLC 1' disease genes to be associated with glaucoma (Sheffield *et al.* 1993). This gene was characterized initially as a glucocorticosteroid induced gene (TIGR) in trabecular meshwork (TM) (Polansky *et al.* 1997, Nguyen *et al.* 1998) and later as a gene expressed in retinal photoreceptors i.e., Myocilin (MYOC) (Kubota *et al.* 1997). The MYOC gene located at 1q24.3 spans about 17 kb, contains three exons and encodes for 504 amino acid long polypeptide. Polansky *et al.* (1997) reported that myocilin expression is increased in trabecular meshwork in glaucoma patients, which might be responsible for outflow obstruction in glaucoma. The over-expression could be due to environmental stimuli or genetic susceptibility.

More than 60 myocilin mutations and few benign polymorphisms have been reported to be associated with 2-5% of all POAG cases in various populations (Table 3). The majority of these mutations are observed in the third exon of MYOC gene that encodes the olfactomedin-like domain of the protein (Torrado *et al.* 2002). MYOC mutations cause glaucoma through gain of functions in myocilin. The deleterious affect of MYOC mutations seems to result from synthesis of a normal and mutant MYOC, which allows demerization of normal and mutant subunits (Wiggs & Vollrath 2001).

Most of the mutations exist in specific racial groups and no single mutation is shared by all major human populations. Fingert *et al.* (1999) and Gong *et al.* (2004) reported that frequency of MYOC mutations is almost similar in the major populations i.e., 3.86% in Caucasian probands with POAG (including normal tension glaucoma), 3.30% in African descendants, and 4.44% in Asian probands. The most common mutation (1.65%), Gln368Stop, was present exclusively in European descendants with one exception in an African American individual (Fingert *et al.* 1999). The second most common mutation, Arg46Stop (0.99%), was present only in Asians. Many mutations have been reported only in specific regions e.g., Gln48His mutation in India (Mukhopadhyay *et al.* 2002) and Cys433Arg

mutation in Brazil (Vasconcellos *et al.* 2000). Few mutations in MYOC have been reported in varying frequencies among different populations e.g., Gly252Arg, Gly367Arg and Pro370Leu mutations among Asians and Caucasians; and Thr293Lys, Thr377Met and Glu352Lys amongst African and Caucasian populations (Table 3).

Various glaucoma phenotypes are associated not only with different loci of open angle glaucoma but also with different MYOC mutation e.g., Pro370Leu mutation is associated with a more aggressive and an earlier onset form of glaucoma while the relatively common mutation Gln368stop is associated with a milder, later onset form of POAG (Stone *et al.* 1997, Alward *et al.* 1998, Shimizu *et al.* 2000, Alward *et al.* 2002). Certain other mutations e.g., Tyr437His and Ile477Asn are associated with more aggressive forms of glaucoma that may be resistant to medical treatment and need surgical interventions (Alward *et al.* 2002).

The penetrance of MYOC mutations appears to be age dependent and many probands with these show incomplete penetrance at the age of 30, with highest penetrance 88% being for Thr377Met and lowest (0%), for Gln368 Stop mutation. The MYOC mutations associated with early onset JOAG are highly penetrant, with 90 % of the individuals showing evidence of disease by 40 years (Wiggs *et al.* 1998, Vasconcellos *et al.* 2003). Craig *et al.* (2001) has suggested the influence of other susceptibility gene and environmental factors in the pathogenesis of glaucoma. Yoon *et al.* (1999) reported Arg46Stop mutation in homozygous state in POAG patient, suggesting autosomal recessive inheritance. However, Pang *et al.* (2002) reported a case of 77 years old woman homozygous for the Arg46Stop mutation who had no POAG, while a heterozygote had POAG. These findings suggests that POAG is a complex trait and various factors such as age-related gene expression, accumulation of environmental exposure with age, gene by gene and gene by environmental interaction may be necessary for the expression of disease phenotype (Gong *et al.* 2004).

POAG has been associated with number of polymorphisms e.g., p53 polymorphism (Arg72Pro) (Lin *et al.* 2002), apolipoprotein E (allele E) (Copin *et al.* 2002), OPA1 (Aung *et al.* 2002), - 1000G?C (MYOC.mt.1) (Colomb *et al.* 2001), -153T?C (Suzuki *et al.* 2000). Two SNP's (-83G?A

**Table 2: Various ocular conditions associated with glaucoma**

<b>Locus</b>	<b>Location</b>	<b>Gene</b>	<b>Phenotype</b>	<b>Age at onset (Yrs)</b>	<b>Inheritance</b>	<b>Reference</b>
RIEG1	4q25	PITX2	Reiger syndrome	<3	AD*	Heon <i>et al.</i> 1995
RIEG2	13q14		Reiger syndrome		AD	Phillips <i>et al.</i> 1996*
IGDA	6p25	FKHL7	Iridogoniodysgenesis	<3	AD	Nishimura <i>et al.</i> 1998
IRID2	4q25-26	PITX2	Iridogoniodysgenesis		AD	Sarfarazi and Stoilov 2000
GDPS1	7q35-36		Pigment dispersion syndrome	<3	AD	Andersen <i>et al.</i> 1997
NPS	9q34.1	LMX1B	Nail-patella syndrome	<3	AR^	Dreyer <i>et al.</i> 1998

AD\* - autosomal dominant; AR^ - autosomal recessive

**Table 3 : Mutations reported in Myocilin gene**

Accession number	Sequence change	Predicted effect	Country/Ethnicity	Reference
<b><u>Exon 1</u></b>				
CM032611	CAG-CAT	Gln 19 His	USA	Alward <i>et al.</i> 1998
CM990907	TGC-TGA	Cys 25 Arg	Italy	Bruttini <i>et al.</i> 2003
	CGA-TGA	Arg 46 Term	China	Yoon <i>et al.</i> 1999
CM023962	CAG-CAT	Gln 48 His	Japan	Kubota <i>et al.</i> 2000
CM981341	CGC-TGC	Arg 82 Cys	India	Mukhopadhyay <i>et al.</i> 2002
CM004394	CGA-TGA	Arg 91 Term	USA	Alward <i>et al.</i> 1998
CM0021645	CGG-TGG	Arg 126 Trp	USA/ Australian	Fingert <i>et al.</i> 1999
CM002376	CGA-CAA	Arg 158 Gln	China	Lam <i>et al.</i> 2000, Pang <i>et al.</i> 2002
<b><u>Exon 2</u></b>				
CM004705	GAC-GAG	Asp 208 Glu	Canada	Faucher <i>et al.</i> 2002
			Japan	Kubota <i>et al.</i> 2000
<b><u>Exon 3</u></b>				
CM023428	GGA-GCA	Gly 244 Ala	Japan	Lam <i>et al.</i> 2000
CM971019	GGA-AGA	Gly 246 Arg	Germany	Michels-Rautenstrauss <i>et al.</i> 2002
			France	Adam <i>et al.</i> 1997

Table 3 Contd.

Accession number	Sequence change	Predicted effect	Country/ Ethnicity	Reference
CM983953	GGA-AGA	Gly 252 Arg	USA China	Shimizu <i>et al.</i> 2000 Vincent <i>et al.</i> 2002
CM004564	GAA-AAA CGA-GGA ATG-ACG	Glu 261 Lys Arg 272 Gly Thr 285 Met	Spain USA Sweden	Vazquez <i>et al.</i> 2000 Shimizu <i>et al.</i> 2000 Jansson <i>et al.</i> 2003
CM981342	TGG-CGG ACG-AAG	Trp 286 Arg Thr 293 Lys	USA/ Australian USA USA/ Australian, Africa Canada Dutch	Fingert <i>et al.</i> 1999 Alward <i>et al.</i> 1998 Fingert <i>et al.</i> 1999 Faucher <i>et al.</i> 2002 Vincent <i>et al.</i> 2002
CM994292	GAG-AAG	Glu 300 Lys	China	Pang <i>et al.</i> 2002
CM971020	GAA-AAA CAG-CGG	Glu 323 Lys Gln 337 Arg	Barbados USA	Nemesure <i>et al.</i> 2003 Stioloa <i>et al.</i> 1997
CM004565	CAG-GAG	Gln 337 Glu	Spain	Vazquez <i>et al.</i> 2000
CM023963	AGA-AGG	Arg 342 Lys	Ghana	Challa <i>et al.</i> 2002
CM023429	ATA-ATG	Ile 345 Met	Germany	Michels-Rautenstrauss <i>et al.</i> 2002

Table 3 Contd.

Accession number	Sequence change	Predicted effect	Country/Ethnicity	Reference
CM990908	GAG-AAG	Glu 352 Lys	USA/ African USA/ Canadian Canada/ African	Allingham <i>et al.</i> 1998 Fingert <i>et al.</i> 1999 Faucher <i>et al.</i> 2002
CM990909	ACA-ATA	Thr 353 Ile	Japan Korea China	Fingert <i>et al.</i> 1999 Yoon <i>et al.</i> 1999 Pang <i>et al.</i> 2002
CM002377	ATC-AAC	Ile 360 Asn	Japan	Kubota <i>et al.</i> 2000
CM981343	CCT-TCT	Pro 361 Ser	USA USA/ Australian	Alward <i>et al.</i> 1998 Fingert <i>et al.</i> 1999
CM002378	GCT-ACT	Ala 363 Thr	Japan	Kubota <i>et al.</i> , 2000
CM971021	GGC-GTC	Gly 364 Val	USA/ Australian	Fingert <i>et al.</i> 1999
CM971022	GGA-AGA	Gly 367 Arg	Japan Germany Canada	Suzuki <i>et al.</i> 1997 Michels-Rautenstrauss <i>et al.</i> 2002 Faucher <i>et al.</i> 2002
CM971023	CAG-TAG	Gln 368 Term	N.America USA/ Australian Spain Switzerland	Wiggs <i>et al.</i> 1998 Fingert <i>et al.</i> 1999 Vazquez <i>et al.</i> 2000 Matafisi <i>et al.</i> 2001

Table 3 Contd.

Accession number	Sequence change	Predicted effect	Country/ Ethnicity	Reference
CM971024	CCG-CTG	Pro 370 Leu	Canada USA England Sweden USA / African-American	Faucher <i>et al.</i> 2002 Alward <i>et al.</i> 2002 Vincent <i>et al.</i> 2002 Jansson <i>et al.</i> 2003 Fingert <i>et al.</i> 1999
11			France Japan Brazil India Germany Sweden	Adam <i>et al.</i> 1997 Suzuki <i>et al.</i> 1997 Vasconcellos <i>et al.</i> 2000 Mukhopadhyay <i>et al.</i> 2002 Michels-Rautenstrauss <i>et al.</i> 2002 Jansson <i>et al.</i> 2003
CM020159	ACG-AAG	Thr 377 Lys	Ireland, Scotland	Vincent <i>et al.</i> 2002
CM981344	ACG-ATG	Thr 377 Met	N.America USA/Australian USA Morocco	Wiggs <i>et al.</i> 1998 Fingert <i>et al.</i> 1999 Allingham <i>et al.</i> 1998 Melki <i>et al.</i> 2003
CM981345	GAC-GCC	Asp 380 Ala	Ireland	Kennan <i>et al.</i> 1998
CM981346	GAC-GGC	Asp 380 Gly	USA	Alward <i>et al.</i> 1998
CM023964	GAC-AAC	Asp 380 Asn	Ghana	Challa <i>et al.</i> 2002

Table 3 Contd.

Accession number	Sequence change	Predicted effect	Country/ Ethnicity	Reference
CM023430	AGC-AAC	Ser 393 Asn	Germany	Michels-Rautenstrauss <i>et al.</i> 2002
CM004363	AAA-AGA	Lys 398 Arg	USA	Shimizu <i>et al.</i> 2000
CM020160	GGT-GTT	Gly 399 Val	Canada/ Guyanese	Vincent <i>et al.</i> 2002
CM981347	CGT-CAT	Arg 422 His	USA	Alward <i>et al.</i> 1998
CM981348	AAG-GAG	Lys 423 Glu	Canada	Faucher <i>et al.</i> 2002
HMO30009	TCA-TGA	Ser 425Term	India	Chakrabarti <i>et al.</i> 2003
CM981349	GTC-TTC	Val 426 Phe	USA	Mansergh <i>et al.</i> 1998
CM021646	GCC-ACC	Ala 427 Thr	Canada	Faucher <i>et al.</i> 2002
CM001250	TGT-CGT	Cys 433 Arg	Brazil	Vasconcellos <i>et al.</i> 2000
CM023431	GGC-AGC	Gly 434 Ser	Germany	Michels-Rautenstrauss <i>et al.</i> 2002
CM971025	TAC-CAC	Tyr 437 His	N.America	Wiggs <i>et al.</i> 1998
			USA/ Australian	Fingert <i>et al.</i> 1999
			USA	Alward <i>et al.</i> 2002
			Morocco	Melki <i>et al.</i> 2003
CM032011	ACC-ATC	Thr 438 Ile	USA	Alward <i>et al.</i> 1998
CM981350	GCA-GTA	Ala 445 Val	USA/ Australian	Fingert <i>et al.</i> 1999
			France/ Canadian	Vincent <i>et al.</i> 2002
			Canada	Faucher <i>et al.</i> 2002

Table 3 Contd.

Accession number	Sequence change	Predicted effect	Country/Ethnicity	Reference
CM994391	ACC-CCC	Thr 448 Pro	Japan	Yokoyama <i>et al.</i> 1999
CM990910	AAT-GAT	Asn450Asp	Germany	Michels-Rautenstrauss <i>et al.</i> 2002
CM981351	ATC-ATG	Ile 465 Met	USA/ Australian	Fingert <i>et al.</i> 1999
CM024217	CGC-TGC	Arg 470 Cys	USA	Alward <i>et al.</i> 1998
CM981352	TAT-TGT	Tyr 471 Cys	USA/ Australian	Fingert <i>et al.</i> 1999
CM971026	ATT-AAT	Ile 477 Asn	China	Pang <i>et al.</i> 2002
CM971027	ATT-AGT	Ile 477 Ser	USA	Alward <i>et al.</i> 1998
CM990911	AAC-AAA	Asn 480 Lys	France	Adam <i>et al.</i> 1997
CM990912	CCC-CTC	Pro 481 Leu	France	Brezin <i>et al.</i> 1998
CM990913	CCC-ACC	Pro 481 Thr	France	Hulsman <i>et al.</i> 2002
CM971028	CCC-CGC	Pro 481 Arg	Netherland	Fingert <i>et al.</i> 1999
CM004364	GAG-TAG	Glu 483 Term	USA/ Australian	Faucher <i>et al.</i> 2002
CM981353	ATC-TTC	Ile 499 Phe	Canada	Fingert <i>et al.</i> 1999
	ATC-AGC	Ile 499 Ser	USA/ Australian	Jansson <i>et al.</i> 2003
	TCC-CCC	Ser 502 Pro	Sweden	Fingert <i>et al.</i> 1999
			USA/ Australian	Adam <i>et al.</i> 1997
			America	Shimizu <i>et al.</i> 2000
			USA	Stoilova <i>et al.</i> 1998

and Arg76Lys) have been reported to be in linkage disequilibrium in the Asian populations (Lam *et al.* 2000, Mabuchi *et al.* 2001, Mukhopadhyay *et al.* 2002). These SNP's were not in linkage disequilibrium in non-Asian populations e.g., Caucasians, African-American, Australian, Canadian (Alward *et al.* 1998; Fingert *et al.* 1999). Some studies have shown association of increased IOP levels and progression of optic neuropathy in POAG patients with MYOC.mt.1 SNP in the promoter region of the MYOC (Colomb *et al.* 2001, Polansky *et al.* 2003). However, Alward *et al.* (2002) did not observe any association of MYOC.mt.1 with POAG patients.

### **OPTN -GLC1E**

The GLC1E was identified by linkage analysis in large family with adult onset normal tension glaucoma (NTG) on chromosome 10p14 (Sarfarazi *et al.* 1998). Rezaie *et al.* (2002) observed that optineurin (OPTN) (OMIM 602432) was the second gene implicated in the pathogenesis of glaucoma. This gene spans ~ 37 kb region and contains 3 non coding exons and 13 coding exons which codes for a conserved 574 amino acid protein. Optineurin is expressed in ocular tissues like trabecular meshwork, non-pigmented ciliary epithelium and retina (Rezaie *et al.* 2002) as well as in non-ocular tissues such as brain, heart, skeletal muscles, placenta and liver (Li *et al.* 1998). OPTN is also identified as tumor necrosis factor-alpha (TNF- $\alpha$ ) inducible protein (FIP-2) (Li *et al.* 1998) and NEMO-related protein (NRP) (Schwamborn *et al.* 2000). Sarfarazi & Rezaie (2003) observed that optineurin plays a neuroprotective role and the mutant form of optineurin in glaucoma patients may provide inadequate neuroprotection that may lead to late onset presentation of optic neuropathy.

Mutations in optineurin gene are responsible for 16.7% of hereditary forms of normal-tension glaucoma in Caucasians (Rezaie *et al.* 2002). The most common OPTN mutation, Gln50Lys was identified in 13.5% of families, mostly with normal tension glaucoma. Another mutation, Met98Lys was identified in 13.6% of familial and sporadic cases of POAG as compared to 2.1% of controls, making it a considerable risk associated genetic factor for glaucoma (Rezaie *et al.* 2002). Such prevalence rates could potentially make the Gln50Lys and Met98Lys variants more frequent than the most common Gln368Stop MYOC mutation found in 1.6% of unrelated POAG patients. However, subsequent studies reported that Met98Lys

mutation was not associated with POAG in patients of North American origin (Wiggs *et al.* 2003) and normal tension patients of Germany (Weisschuh *et al.* 2005). Such prevalence differences may be due to recruitment strategies, presence/absence of disease history, ethnicity differences, small sample size or could be population-specific (Alward *et al.* 2003, Aung *et al.* 2003, Tang *et al.* 2003, Wiggs *et al.* 2003, Baird *et al.* 2004). Leung *et al.* (2003) observed new putative mutations and polymorphisms in the OPTN gene in China and suggested a different mutation pattern of OPTN in Asians individuals than Caucasians. However, Tang *et al.* (2003) found no mutations but some polymorphisms in OPTN in the Japanese population in POAG patients.

It is not known how mutations functions to produce clinical representation of glaucoma in the patients. Iwata *et al.* (2003) have reported that Glu50Lys mutation abolishes normal interaction of OPTN with RAB8 protein, which is involved in protein endocytosis and exocytosis. They further observed that another mutation in exon 6 (691-692 ins AG) shifted the open reading frame and truncated the normal protein by 76%. The truncated protein affected the normal interaction of optineurin with RAB8, TFIIIA, and HYPL protein. Another mutation Arg545Gln mutation in exon 16 that is located close to the C<sub>2</sub>H<sub>2</sub> zinc finger motif in OPTN molecule molecule has been reported to interfere with the normal function of optineurin (Rezaie *et al.* 2002).

### **Other POAG Loci**

The second POAG locus, GLC1B, was mapped, on chromosome 2cen-q13 (Stoilova *et al.* 1996). Most individuals with the GLC1B gene have late onset and low to moderate tension glaucoma. Mutations in the GLC1B gene may render the optic nerve abnormally sensitive to IOP or facilitate optic nerve damage independent of IOP. Wirtz *et al.* (1997) and Kitsos *et al.* (2001) observed that GLC1C, located on chromosome 3q21-24 was characterized by high pressure and late onset glaucoma with moderate response to medication. The glaucoma associated with GLC1D, mapped to 8p23 also resembled high-pressure adult onset POAG (Trifan *et al.* 1998). GLC1F, the sixth locus for POAG, mapped to 7q35-36, was associated with moderate glaucoma with IOP ranging from 22 to 38 mm Hg (Wirtz *et al.*

1999). Monemi *et al.* (2005) has identified a new adult-onset primary open-angle glaucoma locus (GLC1G) on 5q22.1. In addition to these loci various studies have identified potential regions containing glaucoma susceptibility genes on chromosome 1, 2, 6, 9, 11, 14, 17 and 19 (Wiggs *et al.* 2000, Nemesure *et al.* 2003). Wiggs *et al.* (2004) have also reported 2 novel loci for early-onset open angle glaucoma, one on chromosome 9q22 (JOAG2) and the other on chromosome 20p12 (JOAG3).

### **Developmental Glaucoma**

The developmental glaucomas also result from complex genetic interactions with the environment. A number of ocular conditions e.g., Reiger syndrome, iridogoniodysgenesis, pigment dispersion syndrome, nail-patella syndrome, etc. arise from a generalized developmental anomaly of the anterior segment, which leads to glaucoma (Table 2). During the third trimester of gestation, a developmental arrest of tissues derived from the neural crest cells leads to the ocular abnormalities in this group of disorders (Shields *et al.* 1985). These conditions show variable expression with high degree of penetrance (Sarfarazi 1997). Each of the involved genes can give rise to multiple phenotypes, depending on the individual in which they are expressed, e.g., mutations in one gene, such as PITX2 can give rise to Axenfeld anomaly, Rieger syndrome or Peter's anomaly within the same family (Honkanen *et al.* 2003).

### **Primary Congenital Glaucoma (PCG)**

Primary congenital glaucoma has onset in neonatal or infantile period, and is manifested by symptoms of increased intraocular pressure and corneal edema. These conditions can lead to excessive tearing, photophobia and an enlargement of the globe, clinically known as bupthalmos. The incidence of PCG varies across ethnic communities and geographical boundaries e.g., 1:10,000 in western countries (Francois 1980), 1:2500 in Middle East (Jaffar 1988) and 1:1250 in Romany population of Slovakia (Gencik *et al.* 1982). In India, the prevalence is 1:3300 in the State of Andhra Pradesh and accounts for 4.2% of all childhood blindness (Dandona *et al.* 2001). In familial cases, PCG is inherited in autosomal recessive manner. However, Gencik *et al.* (1980; 1982) and Bejjani *et al.* (2000) question

autosomal recessive mode of inheritance due to observation of factors like incomplete penetrance, sex bias, etc. Stoilov *et al.* (1997) has documented autosomal dominant inheritance in some families.

Genetic linkage studies have revealed that PCG is a genetically heterogeneous disease and three loci have been identified. GLC3A (OMIM 231300) located at 2p21 (Sarfarazi *et al.* 1995), GLC3B on 1p36 (OMIM 600975) (Akarsu *et al.* 1996) and GLC3C on chromosome 14q24.3 (Stoilov & Sarfarazi 2002b) (Table 1). Stoilov *et al.* (1998) identified the first gene, CYP1B1 (Cytochrome P4501B1), located at 2p21 that was directly implicated in the pathogenesis of PCG. CYP1B1 (OMIM 601771) is a dioxin inducible member of cytochrome P4501 gene family of drug-metabolizing enzymes. It participates in the metabolism of regulatory molecules such as xenobiotics as well as endogenous substrates and compounds that are important for the proper development and functioning of the anterior chamber of the eye (Nebert 1991). The CYP1B1 genomic region spans >12 kb and has 3 exons. Exon 1 represents untranslated regions while exon 2 and 3 encode for a protein of 543 amino acids.

More than 65 mutations and few polymorphisms have been reported to be associated with 80% of the PCG cases in populations of different ethnic backgrounds (Table 4). These include single-base nucleotide substitutions (transitions and transversions), insertions, duplications, and deletions. Few mutations that have been observed in the normal population are currently considered to be DNA polymorphisms. Many of the missense mutations affect elements of the conserved core structures that are shared by all P450 enzymes (Stoilov *et al.* 1998, Lewis *et al.* 2003). Therefore, these mutations are expected to interfere with the basic cytochrome properties such as folding, substrate recognition, heme-binding, and interaction with its redox-partner (Sarfarazi *et al.* 2003). CYP1B1 mutations have been observed more frequently in cases with positive familial history, or parental consanguinity. In familial cases, the frequency of CYP1B1 mutations has been reported to vary from 100% in Slovakian Gypsies (Plasilova *et al.* 1999) to 50% in Brazil (Stoilov *et al.* 2002a). Among sporadic cases, the frequency of CYP1B1 mutations varied from 40% in Brazil (Stoilov *et al.* 2002a) to 20% in Japan (Mashima *et al.* 2001). CYP1B1 mutations have been observed in only 12.5% of the individuals with unilateral disease (Stoilov *et al.* 2002a).

**Table 4 : Mutations reported in CYP1B1 gene**

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
<u>Intron 2</u>					
<u>Exon 2</u> CM011310	g.3807 T>C	Deletion of Partial IVS2 and Exon 3 ATG-ACG	Met 1 Thr	Turkey Canada/ French-Canadian	Stoilov <i>et al.</i> 1997 Vincent <i>et al.</i> 2001
CI023301	g.3834-3835 ins A	CCC TTG - CCC ATT G		India	Panicker <i>et al.</i> 2002
CM023062	g.3860 C>T	CAG-TAG	Gln 19 Term	Brazil	Stoilov <i>et al.</i> 2002a
	g.3905-3927 del 23 bp	GTG CAT GTG GGC CAG CGG CTG CTG AGG GCA - GTG _____ GCA _____ GCA		India	Reddy <i>et al.</i> 2004
CD014460	g.3964 del C	GGC CCG T - GGC _CG T		Japan	Mashima <i>et al.</i> 2001
CM980496	g.3976 G>C	TGG-TGC	Trp 57 Cys	Canada/ Hispanic	Stoilov <i>et al.</i> 1998
CM011311	g.3975 G>A	TGG-TAG	Trp 57 Term	Canada/ French-Canadian	Vincent <i>et al.</i> 2001
CDO33534	g.3979 del A	TGG CCA CTG - TGG CC_ CTG		France	Colomb <i>et al.</i> 2003

Table 4 Contd.

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
CM980497	g.3987 G>A	GGA-GAA	Gly 61 Glu	Saudi Arabia	Bejjani <i>et al.</i> 1998
CM000136	g.4035 T>C	CTG-CCG	Leu 77 Pro	Turkey India	Stoilov <i>et al.</i> 1998 Reddy <i>et al.</i> 2004
CDO32457	g.4081 del C	TGC CCC ATA - TGC C_C ATA		Saudi Arabia India Japan	Bejjani <i>et al.</i> 2000 Reddy <i>et al.</i> 2004 Soley <i>et al.</i> 2003
CM003809	g.4160 G>T g.4200 T>G	GCC-TCC ATG-AAG	Ala 119 Ser Met 132 Arg	Japan India	Watanabe <i>et al.</i> 2000 Reddy <i>et al.</i> 2004
CD000251	g.4238-4247 del 10bp	CAG CGG CGC GCA GC -CAG_____C		Saudi Arabia	Bejjani <i>et al.</i> 2000
HM030008	g.4236 A>G	CAG-CGG	Gln 144 Arg	India	Chakrabati <i>et al.</i> 2003
CI983070	g.4305-4306 ins T	GAG GGC - GAT GGG C		Turkey	Stoilov <i>et al.</i> 1998
CD022282	g.4339 del G	GTG GCG - GT_ GCG		Morocco Brazil	Belmouden <i>et al.</i> 2002 Stoilov <i>et al.</i> 2002a
CM014340	g.4380 A>T	GAC-GTC	Asp 192 Val	Japan	Mashima <i>et al.</i> 2001
CM023063	g.4382C>T	CCC-CCT	Pro 193 leu	India	Panicker <i>et al.</i> 2002
CM014341	g.4397G>A	GTC-ATC	Val 198 Ile	Japan	Mashima <i>et al.</i> 2001
CM030031	g.4449 G>T	AGC-ATC	Ser 215 Ile	Indonesia	Sitorus <i>et al.</i> 2003

Table 4 Contd.

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
CM014173	g.4457 G>A	GAA-AAA	Glu 229 Lys	Lebanon	Michels – Rautenstrauss <i>et al.</i> 2001
CM033363	g.4499G>C g.4520 A>C	GGG-CGG AGT-CGT	Gly 232 Arg Ser 239 Arg	India France	Panicker <i>et al.</i> 2002 Colomb <i>et al.</i> 2003
CM033364	g.4547 C>T	CAG-TAG	Gly 248 Term	France	Colomb <i>et al.</i> 2003 Reddy <i>et al.</i> 2004
CD000252	g.4611-4619 del 9bp	AGC AAC TTC ATC - A _ _ _ _ _ TC		Saudi Arabia	Colomb <i>et al.</i> 2003 Bejjani <i>et al.</i> 2000
CM014342	g.4645 C>A	TGC-TGA	Cys 280 Term	Japan	Mashima <i>et al.</i> 2001
CM980498	g.4646 G>T	GAA-TAA	Glu 281 Term	Turkey Indonesia	Stoilov <i>et al.</i> 1998 Sitorus <i>et al.</i> 2003
CI004542	g.4776 ins AT	ATC TTC - ATA TCT TC		Japan	Ohtake <i>et al.</i> 2000
CM014343	g.4763G>T	GTA-TTA	Val 320 Leu	Japan	Mashima <i>et al.</i> 2001
CI972587	g.4673-4674 ins C	GCC CCC CGC - GCC CCC CCG C		Turkey	Stoilov <i>et al.</i> 1997
CM020105	g.4793-4794 (GC>TT) g.4838 C>T	GCC-TCC; GCC-GTC CTC-TTC	Ala 330 Phe Leu 345 Phe	Japan Canada/ African- American	Mashima <i>et al.</i> 2001 Vincent <i>et al.</i> 2002

Table 4 Contd.

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
<b>Exon 3</b> CD030135	g.7899-7910 del 12bp g.7900-7901 del CG	ACT CGA GTG CAG GCA - AC_-----A GAC TCG AGT - GAC T_ AGT		Indonesia India	Sitorus <i>et al.</i> 2003 Reddy <i>et al.</i> 2004
CD972161	g.7901-7913 del 13bp	CGA GTG CAG GCA GAA - C_-----A		Turkey	Sitorus <i>et al.</i> 2003
CM014174 N <sub>1</sub>	g.7900 C>T	CGA-TGA	Arg 355 Term	Germany	Michels-Rautenstrauss <i>et al.</i> 2001
CM004520	g.7927G>A	GTG-ATG	Val 364 Met	Japan	Ohtake <i>et al.</i> 2000
CM980499	g.7930 G>T	GGG-TGG	Gly 365 Trp	USA	Stoilov <i>et al.</i> 1998
CM000137	g.7940 G>A	CGT-CAT	Arg 368 His	Saudi Arabia India Brazil USA	Bejjani <i>et al.</i> 2000 Panicker <i>et al.</i> 2002 Stoilov <i>et al.</i> 2002a Sena <i>et al.</i> 2004
CM980500	g.7957 G>A	GAC-AAC	Asp 374 Asn	Saudi Arabia	Bejjani <i>et al.</i> 1998
CM980501	g.7973 C>T	CCC-CTC	Pro 379 Leu	Turkey	Stoilov <i>et al.</i> 1998
CM980502	g.7996 G>A	GAA-AAA	Glu 387 Lys	Canada/ Hispanic, French- Canadian	Stoilov <i>et al.</i> 1998

Table 4 Contd.

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
CM980503	g.8006 G>A	CGC-CAC	Arg 390 His	Pakistan	Stoilov <i>et al.</i> 1998
CM000138	g.8005 C>A	CGC-AGC	Arg 390 Ser	India	Reddy <i>et al.</i> 2004
CM033365	g.8033T>G	ATT-AGT	Ile 399 Ser	Saudi Arabia	Bejjani <i>et al.</i> 2000
CI983071	g.8037-8046 ins 10 bp	ACC ACT - ACC TCA TGC CAC CAC T		India	Reddy <i>et al.</i> 2004
CM033366	g.8104 A>T	AAC-TAC	Asn 423 Tyr	France	Colomb <i>et al.</i> 2003
CI99460	g.8112>8113 ins G			UK, Turkey	Stoilov <i>et al.</i> 1998
CM980504	g.8147 C>T	CCG-CTG	Pro 437 Leu	India	Panicker <i>et al.</i> 2002
CM004465	g.8163 C>G	CCA-CGA	Pro 442 Arg	Brazil	Stoilov <i>et al.</i> 2002a
CM014175	g.8165 C>G	GCT-GGT	Ala 443 Gly	France	Colomb <i>et al.</i> 2003
CM014344	g.8168 G>A	CGA-CAA	Arg 444 Gln	France	Colomb <i>et al.</i> 2003
				Japan	Kakiuchi -matsumoto <i>et al.</i> 2001
				Turkey	Stoilov <i>et al.</i> 1998
				Indonesia	Sitorus <i>et al.</i> 2003
				Germany	Michels-Rautenstrauss <i>et al.</i> 2001
				Japan	Mashima <i>et al.</i> 2001

Table 4 Contd.

Accession No	Nucleotide change	Sequence change	Predicted effect	Country/ethnicity	Reference
CM033367	g.8167 C>T	CGA-TGA	Arg 444 Term	France	Colomb <i>et al.</i> 2003
HM030007	g.8172 T>G	TTC-TGC	Phe 445 Cys	India	Chakrabarti <i>et al.</i> 2003
CD982583	g.8182 del G	AAG GAT - AAG _AT		Canada /Hispanic	Stoilov <i>et al.</i> 1998
CD0232255	g.8214-8215 del AG	AGA GTG - AG _TG		Brazil	Stoilov <i>et al.</i> 2002a
3	g.8234G>A	GGC-GAC	Gly 466 Asp	India	Reddy <i>et al.</i> 2004
CM980505	g.8282 C>T	CGG-TGG	Arg 469 Trp	UK, Turkey	Stoilov <i>et al.</i> 1998
CM014345	g.8333 A>G	GAG-GGG	Glu 499 Gly	Japan	Mashima <i>et al.</i> 2001

Reddy *et al.* (2004) reported the frequency of CYP1B1 mutations in Indian population as 37.5%, which is lower than that reported for Saudi Arabian (95%) (Bejjani *et al.* 1998), or Slovakian Gypsy (100%) populations (Plasilova *et al.* 1999). This could be due to high consanguinity and allelic homogeneity in Saudi Arabian and Slovakian Gypsy populations respectively (Bejjani *et al.* 1998, Plasilova *et al.* 1999) and the genetic heterogeneity and ethnic diversity of Indian populations (Reddy *et al.* 2004). Mutation in CYP1B1 has also been reported to be associated with Peter's anomaly (Vincent *et al.* 2001). Vincent *et al.* (2002) have reported digenic inheritance of CYP1B1 and MYOC mutations, which resulted in more severe glaucoma phenotype e.g., Gly299Val mutation in MYOC gene in combination with a CYP1B1 mutation (Arg368His) resulted in early onset glaucoma (23-38 years). Chakrabarti *et al.* (2005) have reported Gln48His (MYOC) mutation in combination with Pro437Leu (CYP1B1) and Arg368His (CYP1B1) mutation resulting in POAG and PCG phenotypes respectively. They opined that juvenile and congenital glaucoma are allelic variants and proposed that CYP1B1 may act as a modifier for expression of the Myocilin gene and that these two genes might act through a common biochemical pathway.

### **Primary Acute Closed Angle Glaucoma (PACG)**

In PACG, the iris is pushed against the lens, closing off the drainage angle resulting in immediate rise in the pressure. Population studies indicate that it is common among Chinese (Congdon *et al.* 1992) and Greenland Eskimos (Alsbrink, 1982) and is frequent in middle aged females than males. Nanophthalmos, an uncommon developmental ocular disorder characterized by short axial length and high hyperopia, is associated with angle closure glaucoma. Othman *et al.* (1998) localized the first nanophthalmos locus (NNO1) on chromosome 11 in a large autosomal dominant family with 12 members affected with angle closure glaucoma. In a recent study in China by Aung *et al.* (2005), mutations in MYOC gene were observed in PACG cases. They reported few changes in MYOC gene, which included Arg46Stop and Thr353Ile mutations that have already reported in individuals with POAG. However, all the sequence alterations identified were also found in normal Chinese subjects, ruling out the role of MYOC mutations in the pathogenesis of chronic PACG patients.

## Conclusions

Glaucoma is genetically heterogeneous and is among the leading causes of blindness. Different types and subtypes of it are recognised by ophthalmologists but there is great discrepancy when its existing phenotypic classification is compared with the actual molecular defects. Mutations in some genes result in wide clinical spectrum of disease ranging from congenital glaucoma to juvenile glaucoma with severe early-onset to typical late-onset glaucoma with slow manifestation. There is need to localize, identify, and characterize more glaucoma causing genes. It would have considerable importance for the proper classification of glaucoma particularly for its subdivision into subtypes. Furthermore, the establishment of genotype–phenotype correlation would lead to clearer understanding of the mechanisms involved in the causation of glaucoma and ultimately to better treatment regimens. This would also enable its widespread screening, especially in the affected families and detection of the non-symptomatic carriers of the disease. Early intervention in these ‘at risk’ cases would help in the prevention of damage to the eye.

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