

# Research progress on human genes involved in the pathogenesis of glaucoma (Review)

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**Abstract.** Glaucoma is the leading cause of irreversible blindness globally. It is known that the incidence of glaucoma is closely associated with inheritance. A large number of studies have suggested that genetic factors are involved in the occurrence and development of glaucoma, and even affect the drug sensitivity and prognosis of glaucoma. In the present review, 22 loci of glaucoma are presented, including the relevant genes (myocilin, interleukin 20 receptor subunit B, optineurin, ankyrin repeat- and SOCS box-containing protein 10, WD repeat-containing protein 36, EGF-containing fibulin-like extracellular matrix protein 1, neurotrophin 4, TANK-binding kinase 1, cytochrome P450 subfamily I polypeptide 1, latent transforming growth factor  $\beta$  binding protein 2 and TEK tyrosine kinase endothelial) and 74 other genes (including toll-like receptor 4, sine oculis homeobox *Drosophila* homolog of 1, doublecortin-like kinase 1, RE repeats-encoding gene, retinitis pigmentosa GTPase regulator-interacting protein, lysyl oxidase-like protein 1, heat-shock 70-kDa protein 1A, baculoviral IAP repeat-containing protein 6, 5,10-methylenetetrahydrofolate reductase and nitric oxide synthase 3 and nanophthalmos 1) that are more closely associated with glaucoma. The pathogenesis of these glaucoma-associated genes, glaucomatous genetics and genetic approaches, as well as glaucomatous risk factors, including increasing age, glaucoma family history, high myopia, diabetes, ocular trauma, smoking, intraocular pressure increase and/or fluctuation were also discussed.

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## 1. Introduction

Glaucoma, a neurodegenerative eye disease, may lead to damage to the optic nerve and consequent vision loss, and is the leading cause of irreversible blindness globally (1). Vision loss results from damage to the optic nerve, which is caused by increased intraocular pressure (IOP) in glaucoma. If untreated, once vision loss from glaucoma has occurred, it is life long. There are an estimated 57.5 million people worldwide with glaucoma (2); for every 1,000 people, approximately eight are affected with glaucoma. It has been reported recently that there will be ~79.6 million people with glaucoma by 2020 (3) and an expected 111.8 million glaucoma cases by 2040 (4). Glaucoma has numerous subtypes; however, the different types have a number of common clinical manifestations, including nausea, mid-dilated pupils, serious eye pain, redness and blurred vision (5). Glaucoma has a number of classifications, according to anatomy, etiology, onset age and pathogenesis, and the clinical classifications (6) are presented in Fig. 1.

Besides genetics, there are numerous other risk factors for glaucoma, including increasing age (7-9), estrogen (10), frailty (11), myopia (12), diabetes (13-17), high myopia (18), hyperopia (19), hypertension (20), vasospasm (13), low ocular perfusion pressure (21), family history of glaucoma (7), sex (22), race (23), migraine (24), pigmentary dispersion syndrome (25), pseudoexfoliation syndrome (PEX) (7,9), oral microbiome (26),

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butanoate metabolism (27), unstable oxygen supply (28), infection (29,30), hematopoietic cell lineage (27), the p38-mitogen activated protein kinase pathway (31), retinitis pigmentosa (32), mitochondrial dysfunction (33), obstructive sleep apnea syndrome (34), basal transcription factors (27), calcium channel medication,  $\alpha$ -blocker medication (7), treatment for systemic hypertension or Raynaud's disease (35), adrenergic agents (36),  $\gamma$ -aminobutyric acid and acetyl-coenzyme A metabolism (27), sulfa-based drug (36), corticosteroids (37), smoking (17), lysine degradation (27), IOP fluctuation (38), IOP increase (39) and caffeine (40). Of those risk factors for glaucoma mentioned, increased IOP is the strongest risk factor in the majority of subtypes of glaucoma (41); however, its pathogenesis remains unclear. Increased IOP may subsequently lead to posterior displacement and thinning of the lamina cribrosa (LC), which causes axonal damage and disrupted axonal transport to and from the lateral geniculate nucleus (LGN). Disruption of axonal transport interrupts retrograde delivery of nutrients from relay neurons of the LGN to retinal ganglion cells (RGCs) (42), possibly leading to the death of RGCs.

In addition to the afore-mentioned pathogenic factors for glaucoma, heredity additionally serves an important role in the pathogenesis of glaucoma. A previous study suggested that glaucoma maybe inherited from one generation to the next (43), indicating that specific types of glaucoma may have a genetic basis. Furthermore, familial clustering and twin studies demonstrate that specific types of glaucoma arise from heredity (44,45). The present review focuses on the current understanding and newest breakthroughs in pathogenic genes for glaucoma with the purpose of providing a comprehensive analysis of how reported gene mutations involved in glaucoma lead to the clinical phenotypes expressed in glaucoma. An overview of glaucoma-associated genes is presented.

## 2. Genetics of glaucoma

It is well known that there is a genetic basis for glaucoma in specific populations due to sex, ethnicity and positive family history predisposition to glaucoma. There has been strong evidence suggesting that glaucoma is markedly affected by genetic factors and is a complex, multi-factorial disease (46). Glaucoma has numerous types, of which the two most common are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) (47). POAG is associated with high heritability and complex genetic factors. POAG is responsible for 74% of all glaucoma cases, of which 47% of POAG cases are of Asian descent and ~24% are European (1). In contrast to Asian and European descent, the prevalence of severe and rapid POAG progression is increased in Hispanic and African-Caribbean populations (48,49). A previous study additionally suggested that American Caucasians have a lower prevalence of severe and rapid POAG compared with African Americans, who have the highest severe and rapid POAG prevalence (5.2% at 60 years and 12.2% at 80 years) (50). The increase in POAG prevalence per decade of age is highest among Hispanic and Caucasian populations, with the lowest in East and South Asian populations (50). There has been strong evidence that the POAG incidence in populations of African descent is two to five times higher compared with those of European descent (50,51). All the data suggests that POAG

is affected via ancestral factors associated with genetics. Furthermore, certain articles indicate that men are more susceptible to POAG compared with women in Australia (52) and the Netherlands (53). Abu-Amero *et al* (50) demonstrated that a positive family history is a risk factor for POAG. A previous study demonstrated that the prevalence among individuals with a positive family history of POAG is five to 10 times greater compared with individuals without a positive family history (54).

For PACG, a positive family history is one of the principal risk factors. There is a lot of evidence to support the hypothesis. From previous studies it is known that there is high prevalence among siblings of patients affected with PACG (55), and that the risk of having PACG is increased by 3.7 times in Greenland Eskimos (56,57), 3.5 times in Eskimos (58), and six times in the Chinese (59) for siblings with a positive family history. Furthermore, high IOP (60,61) and the depth of the anterior chamber (56,57) are associated with genetic factors involved in the pathogenesis of PACG. The association between the depth of the anterior chamber and PACG reveals that a predisposition of morphological features to PACG is additionally heritable. It is recognized that high IOP and the size of the anterior chamber are markedly affected in PACG. Besides genetic risk factors, PACG is additionally associated with sex. There is evidence that the sex ratio of PACG prevalence is ~3.25 female to 1 male (62).

## 3. Genetic approaches for glaucoma study

Research on glaucoma inheritance has benefited from the development of genetic approaches to identify loci that are involved in a specific glaucomatous phenotype or mutations that account for glaucoma. Traditional linkage analysis based on one or more families with multiple members affected with glaucoma have been widely used to establish the linkage of different phenotypes of glaucoma to particular loci [GLC1A to GLC1N (63), GLC1P (63), GLC3A Online Mendelian Inheritance in Man (OMIM) no. 231300], GLC3B (OMIM no. 600975) and has been less frequently applied to glaucomatous gene mutations, except myocilin (MYOC) (64,65), optineurin (OPTN) (65,66), glutathione S-transferase mu-1 (65), WD repeat-containing protein 36 (WDR36) (65,67-69), cytochrome P450 subfamily I polypeptide 1 (CYP1B1) (65), neurotrophin 4 (NTF4) (70), ankyrin repeat- and SOCS box-containing protein 10 (ASB10) (71) and TANK-binding kinase 1 (TBK1) (63). The aforementioned studies demonstrated that this approach is useful to identify glaucomatous loci. However, linkage analysis is largely limited by its reliance on prior knowledge of disease pathophysiology. This traditional candidate gene approach appears to have been powerless to examine an unclear pathophysiology of complex diseases, such as glaucoma (72,73).

Glaucoma is a complex disease, which may be a polygenic disease rather than a monogenic disease. Glaucoma-causing genes have small variations, including single nucleotide polymorphisms (SNPs), and larger variations, including copy number variations (CNVs). Furthermore, the pathogenic levels of these variations differ, from highly to medium to weakly pathogenic, possibly pathogenic, or even protective. Therefore, traditional linkage analysis has not been applicable to study

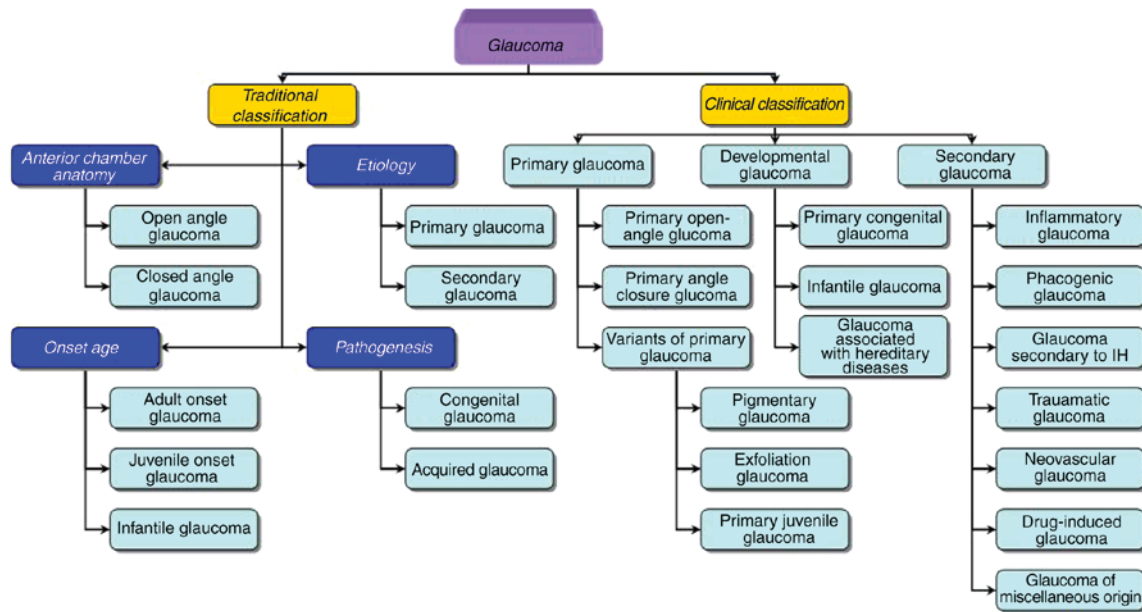


Figure 1. General classifications of glaucoma. IH, intraocular hemorrhage.

these variations in glaucoma, which is more complex and with unknown pathophysiology (72). A suggested alternative to linkage analysis, genome-wide association studies (GWAS), based on SNPs arrays (73), was proposed. GWAS, additionally known as whole genome association studies, is a genome-wide approach that compares the genetic profile of SNPs throughout the genome, among affected cases and unaffected controls to see if any genomic regions are associated with a certain trait or disease (73). In the examination of the glaucomatous pathology, the most common approach of GWAS to glaucoma is the case-control setup; one control group and the other case group affected with glaucoma. GWAS primarily focuses on the associations between SNPs and traits of glaucoma. There is strong evidence that GWAS is more powerful than linkage analysis in identifying causal variations in genes of weak effect, which may account for the development of glaucoma (73,74).

It was thought that SNPs were the most prevalent genetic variations. However, recently, certain studies revealed CNVs area principal source of variations (73) that may be pathogenic in POAG (75). CNVs manifest primarily as submicroscopic deletions and duplications. Numerous CNVs in POAG have been reported. It is worth mentioning that CNVs contain more nucleotide content compared with SNPs per genome, and that suggests the importance of CNVs in the evolution and diversity of genes (76).

#### 4. Pathogenic genes associated with glaucoma

*Pathogenic genes located in the GLC1A-GLC1Q and GLC3A-GLC3E loci.* To date, 22 loci of glaucoma (Table I) have been identified and designated as GLC1A-Q and GLC3A-E. POAG is linked to 17 loci; GLC1A, 1C, 1E-H, 1O-P, for which the responsible genes are MYOC, interleukin 20 receptor subunit  $\beta$  (IL20RB), OPTN, ASB10, WDR36, EGF containing fibulin-like extracellular matrix protein 1 (EFEMP1), NTF4 and TBK1, respectively; and

GLC1B, 1D, 1I-N, and 1Q, for which the responsible genes remain unidentified. There are five loci linking to primary congenital glaucoma (PCG), GLC3A and 3D-E, for which the responsible genes are CYP1B1, latent transforming growth factor- $\beta$ -binding-protein 2 (LTBP2) and TEK tyrosine kinase endothelial (TEK), respectively; the responsible genes of GLC3B-C remain unidentified. GLC1A-Q, except GLC1A, 1J, 1K, 1M and 1N, which contribute only to juvenile open angle glaucoma (JOAG), contribute to adult-onset POAG. All of GLC3A-E have been implicated in PCG. Glaucoma-causing mutations may be classified into two groups. One is autosomal dominant, including POAG-causing genes (MYOC, IL20RB, OPTN, EFEMP1 and TBK1) and a PCG-causing gene (TEK). The other is autosomal recessive, including a PCG-causing gene (CYP1B1). Of the 22 loci, GLC1A (MYOC) and GLC3A (CYP1B1) are the most important for glaucoma; they have correspondingly been the most investigated in research.

Only four pathogenic genes, MYOC (64,65), NTF4 (65,70), OPTN (65,77) and WDR36 (65,78), have been definitively linked to POAG. Furthermore, it was reported that mutations in OPTN, MYOC or WDR36 account for ~4% of all glaucoma (79). The link between ASB10, IL20RB and EFEMP1, and POAG, is less certain. TBK1 is controversial, since GLC1P covers three other genes, n-acetylglucosamine-6-sulfatase, ras association domain family protein 3 and exportin-t (80); however, TBK1 has been suggested to be the most possible glaucoma-causing gene for GLC1P (80).

Only one pathogenic gene for PCG, CYP1B1 (6), has been clearly identified in the locus GLC3A. Numerous genes have been observed in 1p36 that contain GLC3B, however, none have been demonstrated to be associated with PCG (6). To date, it remains to be investigated whether LTBP2 is associated with the GLC3C or GLC3D loci. LTBP2 is ~1.3 Mb proximal to GLC3C (82), thus there is a hypothesis that LTBP2 may be the GLC3C gene; however, the possibility that it may be an adjacent gene associated with PCG may not be ruled out. Another study suggested that GLC3D is distal to GLC3C

Table I. Candidate genes and 22 loci associated with glaucoma.

Authors, year	Locus name	Candidate gene	Location	Glaucoma subtype	Association with glaucoma	(Refs.)/OMIM no.
Faiq <i>et al</i> , 2013	GLC3A	CYP1B1 (P4501B1)	8q24.3	PCG, POAG	The most common pathogenesis of PCG; digenic pathogenic mechanism of CYP1B1 with MYOC and TEK, respectively; conferring increased susceptibility to PCG	(6)
Stone <i>et al</i> , 1997; Kumar <i>et al</i> , 2016	GLC1A (JOAG1)	MYOC (TIGR)	1q24.3	POAG, NTG, HTG, JOAG1	Decreasing AH outflow; increasing IOP; obstructing neurite outgrowth; accumulation of abnormal MYOC protein that is harmful to TM cells	(64,65)
-	GLC1B	-	2cen-q13	APOAG	Finding the disorder to GLC1B in adult-onset POAG	OMIM no.606689
-	GLC1C	IL20RB	3q21-q24	POAG	Expressed in human TM, possibly pathogenic	OMIM no.605621
-	GLC1D	-	8q23	POAG	Increased IOP preceded by optic neuropathy and visual field loss	OMIM no.602429
Kumar <i>et al</i> , 2016; Pasutto <i>et al</i> , 2009	GLC1O	NTF4	19q13.33	POAG	Significantly involved in POAG; possibly deriving from multiple ancestors	(65,70)
Kumar <i>et al</i> , 2016; Rezaie <i>et al</i> , 2002	GLC1E	OPTN	10p13	POAG, NTG	Impairing autophagy and trafficking leading to death of retinal cells	(65,77)
-	GLC1F	ASB10	7q36.1	POAG	Influencing AH outflow; in TM cells, involved in the ubiquitin-mediated degradation pathways	OMIM no.615054
Kumar <i>et al</i> , 2016; Monemi <i>et al</i> , 2005; Rangachari <i>et al</i> , 2011	GLC1G	WDR36	5q22.1	POAG, HTG	Widely expressed in many ocular tissues; a risk factor for POAG	(65,78,79)
-	GLC1H	EFEMP1	2p16-p15	POAG	Involved in decreasing the optic disc area	OMIM no.601548
-	GLC1I	-	15q11-q13	POAG	Requires investigation	OMIM no.609745
-	GLC1J (JOAG2)	-	9q22	JPOAG	Requires investigation	OMIM no.608695
-	GLC1K (JOAG3)	-	20p12	JPOAG	Requires investigation	OMIM no.608696
-	GLC1L	-	3p22-p21	Adult-onset	Requires investigation	OMIM no.137760
-	GLC1M	-	5q22.1-q32	JOAG	Location between NRG2 and D5S2051; excluding NRG2 as the causative gene for GLC1M	OMIM no.610535
-	GLC1N	-	15q22-q24	JOAG	Requires investigation	OMIM no.611274
Fingert <i>et al</i> , 2011	GLC1P	TBK1	12q14	POAG	Requires investigation as a causative gene for GLC1P	(80)
Porter <i>et al</i> , 2011	GLC1Q	-	4q35.1-q35.2	POAG	Requires investigation	(81)
-	GLC3B	-	1p36.2-p36.1	PCG	Requires investigation	OMIM no.600975
-	GLC3C	-	14q24.3	PCG	Requires investigation	OMIM no.613085
Ali <i>et al</i> , 2009	GLC3D	LTPB2	14q24	PCG, SG	Maintaining ciliary muscle tone; development of the anterior chamber of human eye	(82)



Table I. Continued.

Authors, year	Locus name	Candidate gene	Location	Glaucoma subtype	Association with glaucoma	(Refs.)/OMIM no.
-	GLC3E	TEK	9p21.2	PCG	Obstructing AH outflow and causing increased IOP	OMIM no.600221

EFEMP1 is unclear as a GLC1H gene. TIGR, trabecular meshwork-induced glucocorticoid response protein; POAG, primary open-angle glaucoma; NTG, normal tension glaucoma; HTG, high-tension glaucoma; JOAG, juvenile open angle glaucoma; AH, aqueous humor; IOP, intraocular pressure; TM, trabecular meshwork; JPOAG, juvenile POAG; PCG, primary congenital glaucoma; MYOC, myocilin; IL-20RB, interleukin 20 receptor  $\beta$ ; OPTN, optineurin; ASB10, ankyrin repeat- and SOCS box-containing protein 10; WDR36, WD repeat-containing protein 36; EFEMP1, EGF-containing fibulin-like extracellular matrix protein 1; NTF4, neurotrophin 4; TBK1, TANK-binding kinase 1; CYP1B1, cytochrome P450 subfamily I polypeptide 1; LTBP2, latent transforming growth factor- $\beta$ -binding protein 2; TEK, TEK tyrosine kinase endothelial; SG, secondary glaucoma.

without overlapping (83). Furthermore, there is evidence that LTBP2 is a candidate for GLC3D (82); therefore, in the present review LTBP2 is presented as the GLC3D gene. There is strong evidence (OMIM) that mutations of TEK may result in GLC3E, and the locus of TEK is GLC3E.

**Other genes associated with glaucoma.** To the best of the authors' knowledge, besides the 22 loci of glaucoma mentioned, there are 74 genes that are more closely associated with glaucoma presented in Table II. Of those 74, 48 (64%) are associated with POAG, followed by PACG (16%), PCG (4%) and pseudoexfoliation glaucoma (PEXG; 4%). Toll-like receptor 4, sine oculis homeobox *Drosophila* homolog of 1, doublecortin-like kinase 1, RE repeats-encoding gene, retinitis pigmentosa GTPase regulator-interacting protein, lysyl oxidase-like protein 1 (LOXL1), heat-shock 70-kD protein 1A (HSP70-1), baculoviral IAP repeat-containing protein 6, 5,10-methylenetetrahydrofolate reductase (MTHFR) and nitric oxide synthase 3 (ENOS) are human genes involved in more than one phenotype of glaucoma. Nanophthalmos 1 is identified to be the only human gene known to cause PACG (140). For other genes (ATP-binding cassette subfamily C member 5, SPARC-related modular calcium-binding protein 2, matrix metalloproteinase 9, membrane-type frizzled-related protein, hepatocyte growth factor, HSP70-1, pleckstrin homology domain-containing protein family A member 7, collagen type XI  $\alpha$ -1, MTHFR and ENOS) identified to be associated with PACG in Table II, it remains unclear whether they are pathogenic genes for PACG; however, they may be a risk factor for the development of PACG. Among genes associated with PEXG and PEX, the majority of research has been conducted on LOXL1 to determine whether it is pathogenic and how it contributes to the two diseases. PEX, characterized by the accumulation of protein fibers in the eyes, may have a genetic basis. The accumulation of protein obstructs aqueous humor (AH) outflow, and that results in PEXG. Previously, two studies (111,141) have confirmed that LOXL1 is significantly associated with PEXG and PEX. A decrease in LOXL1 expression may cause degenerative tissue alterations in LC, and consequently results in patients with PEX being more vulnerable to optic nerve damage caused by pressure (141), a risk factor for PEXG development.

## 5. MYOC in the GLC1A locus

To date, the majority of research efforts have been on MYOC among all the glaucoma-causing genes. There is a consensus that 2-4% of POAG cases harbor MYOC mutations (142) and MYOC mutations have been reported to be the most frequent in POAG. In the present review, the research findings on MYOC are detailed and summarized. In 1993, Sheffield *et al* (143) discovered the first genetic locus, GLC1A, for POAG, and in 1997, a glaucoma-causing gene, MYOC, was identified by Stone *et al* (64). MYOC is a gene associated with POAG, JOAG, normal tension glaucoma (NTG), high-tension glaucoma (HTG) and steroid-induced glaucoma (144). In 1997, the location of MYOC was linked to chromosome 1q23-q24 by Kubota *et al* (145), and there was a report on fine mapping to chromosome 1q24.3-q25.2 (146). In 1998, cells treated with steroids secreted the same MYOC protein, which was termed

Table II. Possible pathogenic or risk genes associated with glaucoma.

Authors, year	Gene symbol (name)	Location/locus	Glaucoma subtype	Association with glaucoma	(Refs.)
Fuchshofer <i>et al</i> , 2012	TGF- $\beta$ 1 (Transforming growth factor, $\beta$ -1)	19q13.2	POAG	Accelerating degeneration of the optic nerve axons	(84)
Millá <i>et al</i> , 2007	LMX1B (LIM homeobox transcription factor 1, $\beta$ )	9q33.3	OAG	Possibly pathogenic	(85)
Vishal <i>et al</i> , 2016	MPP7 (Membrane protein, palmitoylated 7)	10p12.1	POAG	Affecting AH dynamics, highly expressed in human TM	(86)
Al-Dabbagh <i>et al</i> , 2017	SMOC2 (SPARC-related modular calcium-binding protein 2)	6q27	PACG	Regulation of ECM and MMPs	(87)
Chakrabarti <i>et al</i> , 2009	FOXC1/FKHL7 (Forkhead box C1)	6p25.3	PCG	Limited role in glaucoma pathogenesis; regulation of MYOC secretion;	(88)
Moazzeni <i>et al</i> , 2016	PITX2 (Paired-like homeodomain transcription factor 2)	4q25	PCG	Affecting IOP	(89)
Othman <i>et al</i> , 1998	NNO1 (Nanophthalmos1)	11p	PACG	Possibly pathogenic	(90)
Nongpiur <i>et al</i> , 2014	ABCC5 (ATP-binding cassette, subfamily C, member 5)	3q27.1	PACG	Affecting anterior chamber depth	(91)
Simpson <i>et al</i> , 2017	TP63 (Tumor protein p63)	3q28	OAG	Possibly pathogenic	(92)
Wu <i>et al</i> , 2017	MMP-9 (Matrix metalloproteinase 9)	20q13.12	PACG	Possibly protective and susceptibility to acute PACG	(93)
Micheal <i>et al</i> , 2018	TP53BP2 (Tumor protein p53-binding protein 2)	1q41	POAG	Regulating RGC apoptosis, possibly pathogenic	(94)
Liao <i>et al</i> , 2016	B4GALT3 (UDP-Gal: $\beta$ GlcNAc $\beta$ -1,4-galactosyltransferase polypeptide 3)	1q23.3	POAG	Possibly pathogenic	(95)
Vithana <i>et al</i> , 2011	COL5A1 (Collagen, type V, $\alpha$ -1)	9q34.3	-	Affecting central corneal thickness, possible pathogenic	(96)
Vithana <i>et al</i> , 2011; Janssen <i>et al</i> , 2013	COL8A2 (Collagen, type VIII, $\alpha$ -2)	1p34.3	POAG	Affecting central corneal thickness, pathogenic	(96,97)
Janssen <i>et al</i> , 2013	EDNRA (Endothelin receptor, type A)	4q31.22-q31.23	POAG	Possibly pathogenic, highly expressed in the aorta	(97)
	FBN1 (Fibrillin 1)	15q21.1	POAG	Possibly pathogenic, highly expressed in CBE	(97)
	TLR4 (Toll-like receptor 4)	9q33.1	POAG, NTG PEXG	Possibly pathogenic, highly expressed in CBE	(97)
Tezel <i>et al</i> , 2008	TNF- $\alpha$ (Tumour necrosis factor $\alpha$ )	6p21.33	POAG	Apoptotic death of RGC, possible pathogenic	(98)
Fujikawa <i>et al</i> , 2010	VAV2 (Vav2 oncogene)	9q34.2	POAG	Elevated IOP caused by VAV2 deficiency	(99)
	VAV3 (Vav 3 oncogene)	1p13.3	POAG	Additive effect with VAV2 on glaucomatous phenotype	

Table II. Continued.

Authors, year	Gene symbol (name)	Location/locus	Glaucoma subtype	Association with glaucoma	(Refs.)
Cao <i>et al</i> , 2009	CALCRL (Calcitonin receptor-like gene)	2q32.1	Acute PACG	Possibly pathogenic in acute; however, not chronic PACG	(100)
Awadalla <i>et al</i> , 2012	MFRP (Membrane-type frizzled-related protein)	11q23.3	PACG	Tendency to be pathogenic	(101)
Mabuchi <i>et al</i> , 2012	CDKN2B (Cyclin-dependent kinase inhibitor 2B)	9p21.3	NTG	Possibly affecting VCDR, related to glaucoma	(102)
	SIX1 (Sine oculis homeobox, <i>Drosophila</i> , homolog of, 1)	14q23.1	POAG, NTG HTG	Optic nerve degeneration in glaucoma	
	CHEK2 (Checkpoint kinase 2, <i>S. pombe</i> , homolog of)	22q12.1	HTG	A genetic risk factor for glaucoma	
	ATOH7 (Atonal, <i>Drosophila</i> , homolog of, 7)	10q21.3	NTG	Possibly relevant, higher frequency in glaucoma	
	DCLK1 (Doublecortin-like kinase 1)	13q13.3	POAG, NTG HTG	Possibly pathogenic; however, not up to development of glaucoma	
	RERE (RE repeats-encoding gene)	1p36.23	POAG, NTG HTG	Possibly pathogenic; however, not up to development of glaucoma	
Junglas <i>et al</i> , 2012	TGF- $\beta$ 2/TGFB2 (Transforming growth factor, $\beta$ -2)	1q41	POAG	Higher amounts in AH of glaucoma	(103)
	CTGF (Connective tissue growth factor)	6q23.2	POAG	Modification of TM actin cytoskeleton, increasing IOP	
Wang <i>et al</i> , 2012	TNF- $\alpha$ /TNFA/TNF (Tumor necrosis factor $\alpha$ )	6p21.33	POAG	Possibly protective factor in the development of glaucoma	(104)
Dursun <i>et al</i> , 2012	MBL-2 (Lectin, mannose-binding, soluble, 2)	10q21.1	POAG	Higher MBL-2 serum levels in glaucoma	(105)
Kang <i>et al</i> , 2011	NOS3 (Nitric oxide synthase 3)	7q36.1	POAG	Interactions of reproductive factors with glaucomatous pathogenesis	(106)
Awadalla <i>et al</i> , 2011	HGF (Hepatocyte growth factor)	7q21.11	PACG	Significantly associated with glaucoma	(107)
Wittström <i>et al</i> , 2011	BEST1 (Bestrophin 1)	11q12.3	ACG	Anterior segment abnormality, shallow anterior chambers and reduced axial lengths	(108)
Fernández-Martínez <i>et al</i> , 2011	RPGRIP1 (Retinitis pigmentosa GTPase regulator-interacting protein)	14q11.2	POAG, NTG JOAG	Increasing the susceptibility to various types of glaucoma and possible pathogenic	(109)
Mookherjee <i>et al</i> , 2010	IL-1 $\beta$ (Interleukin 1- $\beta$ )	2q14.1	HTG	A risk to glaucoma	(110)
	IL-1 $\alpha$ (Interleukin 1- $\alpha$ )	2q14.1	HTG	Little association with glaucoma	
Zhou <i>et al</i> , 2016	CARD10 (Caspase recruitment domain-containing protein 10)	22q13.1	POAG	Possibly pathogenic	(111)
Álvarez <i>et al</i> , 2015	LOXL1 (Lysyl oxidase-like 1)	15q24.1	PEXG, PCG	Possibly pathogenic	(112)
Khawaja <i>et al</i> , 2016	Mitochondrial gene mutations	-	POAG, NTG, HTG, PACG	Pathogenic	(113)
Bailey <i>et al</i> , 2016	TXNRD2 (Thioredoxin reductase 2)	22q11.21	POAG	Causing RGC apoptosis and mitochondrial dysfunction	(114)

Table II. Continued.

Authors, year	Gene symbol (name)	Location/locus	Glaucoma subtype	Association with glaucoma	(Refs.)
Lascaratos <i>et al</i> , 2012	ATXN2 (Ataxin 2)	12q24.12	POAG	Neurodegeneration, pathogenic	(114)
	MFN1 (Mitofusin 1)	-	POAG	Susceptibility to glaucoma	(115)
	MFN2 (Mitofusin 2)	1p36.22	POAG	Susceptibility to glaucoma	
	PARL (Presenilin-associated rhomboid-like protein)	3q27.1	POAG	Susceptibility to glaucoma	
Liu <i>et al</i> , 2016	GST/SLCO6A1 (Gonad-specific transporter)	5q21.1	POAG	Susceptibility to glaucoma	
	SOD2 (Superoxide dismutase 2)	6q25.3	POAG	Development of glaucoma	
Chandra <i>et al</i> , 2016	MIR182 (MicroRNA 182)	7q32.2	POAG (HTG)	Possibly pathogenic	(116)
	CYP46A1 (Cytochrome P450, family 46, subfamily A, polypeptide 1)	14q32.2	POAG	Risk prediction	(117)
Shah <i>et al</i> , 2017;	SIX6 (Sine oculis homeobox, <i>Drosophila</i> , homolog of, 6)	14q23.1	POAG	Susceptibility to glaucoma; increasing VCDR; enhanced risk by p16INK4a to glaucoma	(118,119)
Skowronska-Krawczyk <i>et al</i> , 2015	CDKN2A/p16(INK4a) (Cyclin-dependent kinase inhibitor 2A)	9p21.3	POAG	Possibly pathogenic; leading to RGC senescence	(119)
Shin <i>et al</i> , 2016	GALC (Galactosylceramidase)	14q31.3	POAG	Possibly pathogenic	(120)
Nowak <i>et al</i> , 2015	BDNF (Brain-derived neurotrophic factor)	11p14.1	POAG	Possibly pathogenic	(121)
Janssen <i>et al</i> , 2013;	APOE (Apolipoprotein E)	19q13.32	POAG, NTG	Possibly pathogenic; decreasing NTG risk	(97,121)
Nowak <i>et al</i> , 2015					
Chen <i>et al</i> , 2014	ABCA1 (ATP-binding cassette, subfamily A, member 1)	9q31.1	POAG	Development of glaucoma	(122)
Ayub <i>et al</i> , 2010	ENOS (Nitric oxide synthase 3)	7q36.1	PACG, POAG	Significantly associated with glaucoma	(123)
Nowak <i>et al</i> , 2015;	HSP70-1 (Heat-shock 70-kD protein 1A)	6p21.33	POAG, PACG	Possibly pathogenic	(121,123)
Ayub <i>et al</i> , 2010			NTG		
Carbone <i>et al</i> , 2011	PDIA5 (Protein disulfide isomerase, family A, member 5)	3q21.1	POAG	Possibly pathogenic	(124)
Carbone <i>et al</i> , 2011;	BIRC6 (Baculoviral IAP repeat-containing protein 6)	2p22.3	POAG, PEXG	Possibly protective	(124,125)
Ayub <i>et al</i> , 2014					
Chen <i>et al</i> , 2014	PLEKHA7 (Pleckstrin homology domain-containing protein, family A, member 7)	11p15.2-p15.1	PACG	Conferring significant risk for acute glaucoma	(126)
Cuchra <i>et al</i> , 2013	COL11A1 (Collagen, type XI, $\alpha$ -1)	1p21.1	PACG	Conferring significant risk for acute glaucoma	(126)
	APE1/APEX1 (Apex nuclease 1)	14q11.2	POAG	Expressed in RGC, TM; possibly decreasing the risk of POAG progression	(127)



Table II. Continued.

Authors, year	Gene symbol (name)	Location/locus	Glaucoma subtype	Association with glaucoma	(Refs.)
Janssen <i>et al</i> , 2013; Surgucheva <i>et al</i> , 2011	CAV1 (Caveolin 1)	7q31.2	POAG	Glaucomatous alterations in TM	(97,128)
Surgucheva <i>et al</i> , 2011; Thorleifsson <i>et al</i> , 2010	CAV2 (Caveolin 2)	7q31.2	POAG	Expressed in TM and RGC	(128,129)
Lascaratos <i>et al</i> , 2012; Yu-Wai-Man <i>et al</i> , 2010	OPA1 (Optic atrophy 1)	3q29	NTG	A strong risk for glaucoma and causing optic atrophy	(115,130)
Mossböck <i>et al</i> , 2008	PAI-1 [Serpine peptidase inhibitor, clade E (NEXIN plasminogen activator inhibitor type 1, member 1)]	7q22.1	POAG	Decreasing proteolysis of ECM in TM and possibly increasing IOP	(131)
Wang <i>et al</i> , 2008	SAA2 (Serum amyloid A2)	11p15.1	-	Increasing IOP and possibly causing pathogenic alterations to TM in glaucoma.	(132)
Micheal <i>et al</i> , 2017	PRPF8 (Precursor mRNA-processing factor 8, <i>S. cerevisiae</i> , homolog of)	17p13.3	POAG	Pathogenic	(133)
Woo <i>et al</i> , 2009; Clement <i>et al</i> , 2009	MTHFR (5,10-methylenetetrahydrofolate reductase)	1p36.22	NTG, POAG	A genetic risk to glaucoma	(134,135)
Bhattacharya <i>et al</i> , 2005	COCH (Cochlin)	14q12	POAG	Increasing IOP, causing TM cell aggregation, impeding AH outflow	(136)
Bhattacharya <i>et al</i> , 2006	PADI2 (peptidyl arginine deiminase, type II)	1p36.13	POAG	Increasing in glaucomatous optic nerve	(137)
Vishal <i>et al</i> , 2016	MMP-7 (membrane protein palmitoylated 7)	11q22.2	POAG	Influencing the aqueous humor dynamics; highly expressed in the human TM cells	(138)
Lu <i>et al</i> , 2013	FNDC3B (Fibronectin type III domain-containing protein 3B)	3q26.31	POAG	Significantly associated with POAG risk	(139)

<sup>a</sup>International Radiation Hybrid Mapping Consortium. POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; PCG, primary congenital glaucoma; AH, aqueous humor; TM, trabecular meshwork; ECM, extracellular matrix; MMP, matrix metalloproteinase; IOP, intraocular pressure; RGC, retinal ganglion cell; NTG, normal tension glaucoma; PEXG, pseudoexfoliation glaucoma; HTG, high-tension glaucoma; VCDR, vertical cup/disc ratio; JOAG, juvenile open angle glaucoma.

TIGR (trabecular meshwork-induced glucocorticoid response protein) (147). Under stress, eyes may produce the MYOC protein in increased amounts, suggesting that MYOC may serve a protective role similar to a molecular chaperone (148). The MYOC protein is produced by numerous ocular tissues (43,73,149), including the ciliary body, trabecular meshwork (TM), optic nerve, LC, cornea, iris, sclera, retina and lens, and is usually visualized in muscles, including the ciliary muscle, iris and smooth muscle. MYOC is additionally secreted into the vitreous humor for undetermined reasons. Stone *et al* (64) suggested that there is a possible association of the muscle-associated ciliary body with increased IOP. MYOC expression does not exhibit a significant difference in the blood of patients with POAG compared with blood from individuals without POAG; however, there is a significant difference in the TM (150). Therefore MYOC expression may account for a genetic susceptibility to POAG in specific tissues, including the ciliary body and TM.

**Pathogenesis of MYOC.** The pathogenesis of MYOC mutations is unclear; however, the three most possible causes for glaucoma are as follows. In the unhealthy state, there is poor normal MYOC protein secretion. MYOC mutations may lead to accumulation of mutated MYOC proteins within the TM (151-154). Retention of abnormal MYOC protein may be harmful to TM cells and result in their dysfunction or death, which may obstruct AH outflow, and consequently increase IOP (43,64,147,155,156). In addition, accumulation of mutated MYOC proteins in the endoplasmic reticulum activates the unfolded protein response (UPR) in TM cells (157), subsequently leading to apoptosis that may cause high IOP. Over activated UPR may lead to certain neurodegenerative diseases, and inhibiting UPR is a possible therapy for these diseases (158). Thus, this method may additionally be applicable to glaucoma. Normal MYOC is involved in exosome shedding into the aqueous humor, and exosomes are associated with paracrine and autocrine signaling (74), that therefore may serve as vehicles of MYOC protein trafficking. Notably, normal MYOC protein is absent in the aqueous humor of glaucomatous patients with pathogenic MYOC mutations (151). Thus, another prevalent hypothesis on the pathogenesis of MYOC mutations is that they interfere with MYOC protein trafficking and lead to the intracellular aggregation of the misfolded MYOC protein (74). Accumulation of misfolded MYOC proteins decreases AH out flow, and that influences IOP regulation; however, its mechanism is unclear (74). The third hypothesis is regarding specific interactions between MYOC mutations and mitochondria in the TM (159,160). A subsequent study indicated that MYOC mutations lead to dysregulation of calcium channels resulting in mitochondrial depolarization in the TM, consequently resulting in TM contraction, which decreases AH outflow and further causes increased IOP (161).

**Digenic and polygenic mechanism of MYOC.** There is strong evidence that only ~5% of POAG (65) is caused by a single gene, and other cases of POAG are caused by digenic or polygenic cooperation mechanisms, none of which may alone cause glaucoma. Usually, cooperation of MYOC mutations with one or more genes contributes to glaucoma. Mutations in MYOC, OPTN and CYP1B1 are identified to coexist

in ~3.59% of POAG cases (162). This demonstrates that mutations in the three genes together may be involved in the pathogenesis of POAG. There are other studies investigating the association between MYOC and OPTN. OPTN and MYOC are observed in POAG (69,162-166), exfoliative glaucoma (164) and exfoliation syndrome (164). Overexpression of OPTN may upregulate MYOC in TM and stabilize MYOC mRNA (167). There is a possible polygenic interaction among MYOC, OPTN and apolipoprotein E (APOE). Disease-causing mutations in MYOC and OPTN contribute to only a small number of Chinese POAG cases (163). However, common polymorphisms in MYOC, OPTN (69,163,166), APOE (69,163) and WDR36 (69) may together account for POAG. Common polymorphisms of these genes are not associated with POAG alone; however, they may cooperatively contribute to the disease, which indicates a polygenic pathogenesis. A study reported that the mean onset age of carriers with only MYOC mutations is 51 years; however, the mean onset age of carriers with MYOC and CYP1B1 mutations is 27 years (168). This indicates that mutations in the two genes may interact to advance the onset age of glaucoma. Notably, in a study (169) Gln48His, a MYOC mutation, was observed in POAG and PCG; however, one patient with PCG had a CYP1B1 mutation (Arg368His), and the other patient with PCG had none of the CYP1B1 mutations. These results demonstrate that there is a possible digenic interaction between MYOC and CYP1B1, without excluding the possibility that there has been an unidentified gene associated with glaucoma. However, another study reported that none of the CYP1B1 mutations was observed in all five POAG cases with MYOC mutations (170). Forkhead box C1 (FOXC1) may regulate MYOC secretion through modulation of RAB3 GTPase-activating protein catalytic subunit 1 RAB, synaptosomal-associated protein 25-kD and RAB3 GTPase-activating protein noncatalytic subunit (144). A different study (171) suggested that MYOC and FOXC1 mutations are not associated with the pathogenesis of PCG. The mutations Leu486Phe in MYOC and Val108Ile in UDP-Gal:  $\beta$ -GlcNAc  $\beta$ -1,4-galactosyltransferase polypeptide 3 may cooperatively contribute to the pathogenesis of POAG (94).

## 6. Pathogenic genes in the GLC1B-GLC1Q loci

**OPTN.** OPTN, widely expressed in retinal ganglion cells (172), the nonpigmented ciliary epithelium, human TM and the retina (77), is an autophagy receptor. Autophagy may remove damaged organelles and proteins via lysosomal degradation (172). Autophagy and membrane vesicle trafficking serve an important role in the regulation of OPTN functions (172). Furthermore, the level of autophagy mediated through OPTN is very important for the survival of retinal cells (172). Mutations in OPTN are involved in POAG (172). Another conclusion contradicted this result, reporting that OPTN is not associated with POAG in Spain (173). Of these disease-causing mutations, two are noteworthy, Glu50Lys and Met98Lys.

The frequency of Glu50Lys in POAG is 13.5% (77). Notably, 81.6% of POAG cases with recurrent Glu50Lys have normal IOP; whereas only 18.4% of those have increased IOP (77). However, another study suggested that OPTN mutations are involved in POAG rather than glaucoma with normal IOP in Japanese patients (174). Glu50Lys impairs autophagy (172) and trafficking (172,175), resulting in the

death of retinal cells through apoptosis (172) and disrupting the endocytic recycling that is very important for maintaining homeostasis (175).

Rezaie *et al* (77) first reported that Met98Lys is a risk-causing mutation for POAG, and the frequency of Met98Lys in POAG (13.6%) is significantly higher compared with controls (2.1%). In another study by Sripriya *et al* (176), Met98Lys was not identified in controls; however, it was identified in POAG (4.1%) and NTG (6%) (162). Mukhopadhyay *et al* (177) did not detect Met98Lys in NTG, and the frequency of Met98Lys was 11% in POAG and 5.5% in controls. An alternative study (162) presented the contrary conclusion that Met98Lys may not be a risk-causing factor for POAG on account of a very similar frequency in POAG (7.97%) and controls (7.29%). Met98Lys is usually known as a disease-causing mutation and the majority of POAG cases with Met98Lys additionally have normal IOP, similar to Glu50Lys (77). The possible pathogenesis of Met98Lys is that it may impair autophagy, which consequently leads to the death of retinal cells through apoptosis and transferrin receptor degradation (172). However, the pathogenic mechanism of glaucoma-causing Met98Lys requires further research and examination.

**WDR36.** WDR36, located within the POAG linkage locus GLC1G and first identified by Monemi *et al* (78), is widely expressed in numerous ocular tissues, including the optic nerve, ciliary body, retina, TM, ciliary muscles, iris, lens and sclera. Monemi *et al* (78) formerly suggested that the frequency of WDR36 mutations in POAG is 1.6-17%. There is a possible association of WDR36 with the pathogenic mechanism of HTG (67,68). WDR36 mutations may alter the cell phenotype supporting the theory that WDR36 is associated with the polygenic pathogenesis of glaucoma (178). To date, WDR36 importance remains unclear; furthermore, its pathogenicity is controversial. As subsequent studies did not demonstrate WDR36 mutations to be POAG-causing mutations, it was demonstrated that WDR36 mutations may only be a risk factor for POAG (67-69). In addition, Fingert *et al* (179) were not able to confirm the association of WDR36 with pathogenesis of POAG.

**NTF4, ASB10, EFEMP1 and IL20RB.** NTF4, located within the POAG linkage locus GLC1O, is localized to RGCs (70). Pasutto *et al* (70) suggested that the frequency of NTF4 mutations in POAG is 1.7% and there is strong genetic evidence that NTF4 mutations are involved in POAG of European origin. Liu *et al* (180) additionally identified coding alterations in five POAG cases and 12 controls of European origin from Southeastern USA, of which two mutations were previously detected by Pasutto *et al* (70). Therefore, Liu *et al* concluded that these NTF4 coding alterations are not significantly associated with the pathogenesis of POAG. In addition, another study by Chen *et al* (181) suggested that NTF4 does not mainly contribute to the molecular genetics of POAG. From the above, the association of NTF4 mutations with POAG pathogenesis remains to be investigated. In addition, besides the European origin, NTF4 mutations have been identified in Chinese populations (182). This indicates that NTF4 mutations may derive from multiple ancestors.

ASB10, located within the POAG linkage locus GLC1F (183), influences AH outflow (71). ASB10 is most highly expressed in the iris, followed by human TM, RGCs, the ciliary body, choroid, optic nerve, retina, lamina and a little in the lens (71). Among patients with POAG and controls, the frequency of ASB10 mutations is 6 and 2.8%, respectively (71). To test whether ASB10 influences AH drainage, Pasutto *et al* (71) applied RNA interference silencing for knockdown of ASB10 mRNA expression in perfused human anterior segment cultures. The results revealed that the decrease in AH outflow facility was ~50%. In addition, ASB10 may be involved in the ubiquitin-mediated degradation pathways through interactions of ASB10 with the  $\alpha 4$  subunit of the 20s proteasome and with HSP70 in TM (184).

EFEMP1, located within the POAG linkage locus GLC1H, is a plausible candidate for POAG (185). Although there have been a few efforts to confirm the linkage to GLC1H, it remains uncertain. Mutations in EFEMP1 are involved in decreasing the optic disc area (186). Another mutation, c.418C>T in EFEMP1 may be predictive for POAG (185). Expression of EFEMP1 may be influenced by transforming growth factor (TGF)- $\beta 2$ . A study by Junglas *et al* (187) reported that TGF- $\beta 2$  is more highly expressed in AH of POAG and maybe associated with the increase in AH outflow resistance in POAG. Higher amounts of TGF- $\beta 2$  inhibit the expression of EFEMP1 (188).

IL20RB, located within the POAG linkage locus GLC1C, has a role in POAG pathogenesis (189). An IL20RB mutation, Thr104 Met, lying in an active binding site of IL20RB (190), has been observed in a large POAG family (189); therefore, this additionally demonstrates that IL20RB may be implicated in the pathogenesis of POAG. According to OMIM (no. 605621), IL20RB is highly expressed in human skin and testes, and less expressed in the muscle, placenta, heart, ovary and lung. Recently, IL20RB was detected to be additionally expressed in human TM (191). To the best of the authors' knowledge, thus far, little research effort has been made to investigate IL20RB as a POAG-causing gene.

## 7. Pathogenic genes in the GLC3A-GLC3E loci

**CYP1B1.** In humans, the CYP1B1 gene encodes cytochrome P450 1B1, and is regulated via the aryl hydrocarbon receptor. CYP1B1 was the first gene identified in PCG-associated loci (GLC3A-3E) (192), and its role has been clearly understood (65). CYP1B1 is widely expressed in the eyes, including the retina, iris, ciliary body and TM (193). However, certain previous studies suggested that CYP1B1 is not expressed in TM at any stage of eye development (194). CYP1B1 has been thought to be significantly associated with human fetal eye development (194). To date, at least 147 CYP1B1 mutations have been identified globally in 542 patients with PCG in various countries, including Brazil, China, India, Iran, Morocco, Russia, Saudi Arabia, Slovak Gypsy populations, Turkey, USA, Spain, Pakistan, Oman, the Netherlands, Mexico, Kuwait, Japan, Israel, Indonesia, Germany, Ecuador, Canada, Britain and Algeria (6,195). Among CYP1B1 mutations, Glu387Lys has been traced to a common genetic origin for PCG (196). CYP1B1 mutations, which have been reportedly associated with a wider range of glaucomatous phenotypes, including PCG (6,169,195-197), POAG (198-200), JOAG (201)



and PEXG (199), appear in patients with glaucoma at a higher frequency compared with other glaucoma-associated genes (199). CYP1B1 mutations may confer increased susceptibility to PCG and are the most common pathogenic factors of PCG (6). However, the frequency of PCG-causing mutations in CYP1B1 varies significantly in different populations, including Mexican (<10%) (202), Vietnamese (16.7%) (197), Chinese, Japanese and Indonesian (all 20%) (202), Indian (40%) (169). Furthermore, PCG-causing mutations in CYP1B1 occur with extremely high incidence in Slovak Gypsy and Saudi Arabian populations (202), which supports an additional study reporting that consanguinity is a fundamental mechanism for high PCG incidence in Slovak Gypsy and Saudi Arabian populations (203). Available data demonstrate that CYP1B1 may not be the primary disease-causing gene for glaucoma in East Asians and South East Asians, unlike in Gypsy and Saudi Arabian populations. Furthermore, PCG in Mexicans may not be caused by CYP1B1 mutations. In addition, only ~10% of cases of POAG in Mexico harbor CYP1B1 mutations (198), demonstrating that CYP1B1 mutations may not be the cause of the pathogenesis of POAG; however, dysfunction of CYP1B1 may increase the risk of POAG. A low percentage of JOAG cases (~5%) harbor CYP1B1 mutations (168), and CYP1B1 possibly contributes to JOAG in a monogenic model (201).

An increasing amount of research attention is focusing on the interactions of CYP1B1 with other genes. There is growing evidence that interactions of CYP1B1 with MYOC occur in patients with PCG (169,204). In the process of interactions, MYOC is a potential modifier gene (205). In addition, TEK mutations co-occur with CYP1B1 mutations in patients with PCG; notably, the parents of these patients with PCG harbor either heterozygous CYP1B1 or TEK alleles and are asymptomatic (206). Furthermore, there is strong evidence suggesting that the interaction between CYP1B1 and TEK accounts for the pathogenesis of PCG (206); however, the mode of interaction remains unclear regarding whether an overlapping or independent mode is involved in the pathogenic mechanism of PCG. The interaction of CYP1B1 with MYOC and TEK, respectively, in the pathogenesis of PCG further lends support to the digenic inheritance of PCG.

Although CYP1B1 mutations are the most common cause of PCG, these mutations only contribute to a very small proportion of the total amount of PCG (6). Besides CYP1B1, there are a number of genes demonstrated to be associated with PCG, including LTBP2, FOXC1 and MYOC. Therefore, it is reasonable to speculate that other genes may participate in the pathogenesis of PCG; however, there still remain a large number of unknown genes requiring identification.

**LTBP2.** LTBP2, located within the PCG linkage locus GLC3D, is the largest member of the latent TGF- $\beta$  family whose signaling failure in the anterior and posterior eye may cause pathogenic alterations in POAG (84). LTBP2 is most highly expressed in the lens capsule (192), secondly in the TM and ciliary processes (82,192) that are thought to be associated with PCG pathogenesis, with a very small amount in the sclera, corneal stroma and iris (192). LTBP2 mutations are identified in different populations, including Pakistani (82), Indian (207), Gypsy (82), Iranian, Moroccan, and Saudi Arabian populations (OMIM). From the aforementioned data, LTBP2 mutations

appear to derive from West Asia and South Asia. Although Morocco is located in Africa, 75% of Moroccans are of Arabic descent; furthermore, the origin of the Gypsy ethnicity is thought to be in Ancient India. To the best of our knowledge, LTBP2 mutations have been not observed in other populations. Therefore, it is reasonable to hypothesize that LTBP2 mutations may have the same ancestor.

LTBP2 is a disease-causing gene for PCG (192) and is very important in the development of the anterior chamber of the human eye, where LTBP2 possibly serves a role in maintaining ciliary muscle tone (82). Besides PCG, LTBP2 mutations maybe associated with PACG and POAG (208). Therefore, there may be an overlap in the pathogenic mechanism among various types of glaucoma. It is this overlap that may account for the common characteristics among these various types of glaucoma, including optic nerve impairment and decreased vision, and for the common clinical presentation at onset, including eye pain, red-eye, blurred vision, nausea and mid-dilated pupils. However, another study (207) had contrary conclusions that LTBP2 mutations are not implicated in the pathogenesis of PCG. In addition, LTBP2 is not thought to be a disease-causing gene for PCG in the Han Chinese population (209).

**TEK.** TEK, located within the PCG linkage locus GLC3E, is an angiopoietin receptor, additionally termed cluster of differentiation 202B and tyrosine kinase with immunoglobulin-like and EGF-like domains 2, and may regulate vascular homeostasis (210). Although TEK and other vascular growth factors are important for AH outflow and Schlemm's canal development, their association with glaucoma remains unclear (211). A 50% decrease in TEK adequately demonstrated defective Schlemm's canal development and impaired AH outflow (210), and this demonstrates that TEK concentration is important for the AH drainage pathways. Variable expression of TEK is possibly produced by oligogenic or digenic inheritance, in line with other ocular disorders of developmental origin produced by mutations in optic atrophy 1, FOXC1, paired box gene 6 and MYOC (210). In addition, another recent study demonstrated that TEK mutations co-occur with CYP1B1 mutations in PCG (206), and demonstrated that interactions between TEK and CYP1B1 account for digenic inheritance in PCG pathogenesis.

## 8. Potential pathogenic mechanism and recent advances in treatments

**Potential pathological mechanism.** Among the 96 genes, mutations of MYOC (GLC1A) and CYP1B1 (GLC3A) have the closest associations with potential pathological mechanisms in glaucoma. Besides the aforementioned glaucomatous pathogenesis, a novel pathogenic mechanism for MYOC-associated glaucoma is proposed. Extracellular matrix (ECM) proteins of TM are synthesized in the endoplasmic reticulum (ER) and finally secreted into the ECM. Malfunction of the ER during ER stress caused by mutant myocilin accumulation in the ER may affect ECM protein processing and secretion, which results in aberrant intracellular accumulation of ECM proteins in TM (212). The

accumulation of ECM proteins may deteriorate ER stress, leading to TM cell dysfunction and obstructing AH outflow, thereby increasing IOP (212).

CYP1B1 defects cause angle abnormalities involving TM and Schlemm's canal (213). CYP1B1 mutations lower activity or stability of the enzyme in the mitochondria (214,215) and reduce expression levels of ECM proteins in TM (215). These may impact the development or filtering function of TM. In addition, abnormal mitochondria caused by CYP1B1 mutations [the same case as with MYOC mutations (161)] may cause dysregulation of calcium channels resulting in mitochondrial depolarization in TM, consequent TM contraction, reduction of AH outflow and an increase in IOP.

**Recent advances in treatment.** Based on previous studies on the potential pathogenic mechanism of MYOC mutation, at present, there have been three novel approaches to treatment for MYOC-associated POAG: i) Using chemical chaperones (based on molecular mechanisms) to decrease misfolding or unfolding of proteins and increase MYOC secretion (216); ii) given the gain-of-function nature of MYOC mutations, another novel approach is targeting MYOC mRNA or the myocilin protein (216); and iii) targeting MYOC by gene editing with clustered regularly interspaced short palindromic repeats-Cas9 technology to reduce ER stress and lower IOP (216).

According to previous studies on potential pathogenic mechanisms of CYP1B1 mutation, researchers developed two novel therapies: One is the approach based on the gene, directly attempting to correct or replace abnormal CYP1B1 (217); the more novel approach differentiates into a specific lineage and transfers stem cells containing wild-type CYP1B1 to stimulate the normal development of TM cells (217).

## 9. Conclusion and prospects

As mentioned, the pathogenic mechanism of MYOC- or CYP1B1-associated glaucoma is associated with aberrant ECM proteins in TM. The accumulation of deposits of ECM proteins may lead to ER stress as described, resulting in the misfolding or unfolding of MYOC proteins. If ER stress is too severe or if UPR (an adaptive response to ER stress) fails to compensate for the ER stress, dysfunction and apoptosis occurs (218-221), which may cause increased IOP. At present, the novel protein-remodeling factors as potential therapeutics are highly promising to correct the misfolding or unfolding of proteins in neurodegenerative diseases or disorders (221). Therefore, as glaucoma is a neurodegenerative disease, the highly promising protein-remodeling factors (including engineered Hsp104 mutations) may be useful in the development of novel glaucoma therapies, and to better understand the glaucomatous mechanism.

Additionally, combined with the prospect for glaucoma healthcare, certain important problems require addressing in future studies. More *in vivo* animal models (monkey, pig and cow, whose eyes are similar to human), with stem cell-based studies on glaucoma-associated genes, including MYOC and CYP1B1, are required. In addition, using autologous stem cells, including bone marrow derived stem cells (217), that have been genetically modified to serve an important role in

the pathogenic mechanism of glaucoma may be a promising future therapy for MYOC- or CYP1B1-associated glaucoma.

In conclusion, strong evidence indicates that genes are significantly associated with the pathogenesis of glaucoma, and additionally provides a stimulus for the identification of these pathogenic genes. Further efforts to research clinical trials on potential feasible therapeutic targets are necessary, which may construct future therapeutic paradigms for glaucoma. Presently, although a number of genes have been identified to be associated with glaucoma, their pathogenic mechanisms remain unclear, with the exception of MYOC and CYP1B1. Furthermore, certain studies are controversial, even contradictory. Therefore, further research is required to better comprehend the association between pathogenic genes and glaucoma.

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## Availability of data and materials

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## Authors' contributions

H-WW produced the manuscript. H-WW, PS and FG conceived and designed framework of this article. YC, L-PJ, WZ and H-PW collected and analyzed the literature.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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