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REVIEW ARTICLE

Genetic Risk Factors for Glaucoma and Exfoliation Syndrome Identified by Genome-wide Association Studies

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Abstract: ***Background*:** Glaucoma is a neurodegenerative disease characterized by the progressive loss of retinal ganglion cells and optic nerve axons. According to its anatomical features, glaucoma is mainly subdivided into primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). Exfoliation syndrome (XFS) and glaucoma (XFG) are characterized by the accumulation of extracellular materials in ocular tissues, particularly the lens surface and pupillary border. In addition to the two major forms of glaucoma, XFG is the most common cause of secondary open-angle glaucoma. Recent genome-wide association studies(GWASs) revealed genetic loci associated with each glaucoma subtype.

***Methods*:** Review of literatures regarding GWASs for POAG, PACG and XFS.

***Results*:** Several genetic loci were found to be independently associated with POAG, PACG, and XFS by large-scale GWASs.

***Conclusions*:** Genetic studies may not only provide a better understanding of the pathophysiological mechanisms underlying the diseases, but also facilitate the development of new drugs or treatments.

Keywords: Primary open-angle glaucoma, primary angle-closure glaucoma, exfoliation syndrome, exfoliation glaucoma, genome wide association study, genetic variants.

1. PRIMARY OPEN-ANGLE GLAUCOMA (POAG): (INTRODUCTION)

Glaucoma, the most prevalent optic neuropathy, is caused by genetic and environmental disorders and is one of the leading causes of irreversible blindness worldwide [1]. Glaucoma is characterized by progressive loss of ganglion cells and optic nerve fibers, leading to progressive visual field loss and vertical elongation of optic disc cupping. Depending on the anatomical features of the anterior segment, glaucoma is classified as primary open-angle glaucoma (POAG) or primary angle-closure glaucoma.

POAG is clinically subdivided into normal tension glaucoma (NTG) and high-tension glaucoma (HTG) according to intraocular pressure (IOP). NTG is POAG in which IOPs are consistently within the normal range. In contrast, HTG is POAG in which IOPs are elevated. The prevalence of POAG subtypes differs by ethnicity. The prevalence of NTG was reported to be higher in Asians than in Caucasians [2-5].

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Several causative loci were identified by familial linkage analysis including *Myocilin*, *Optineurin*, and *WD repeat domain 36*, as described previously [6].

In this chapter, we focus on genome-wide association studies (GWASs) of POAG and review the genetic risk factors for POAG.

2. GENOME-WIDE ASSOCIATION STUDY (GWAS) FOR POAG

In 2009, Nakano *et al*. [7] first reported a GWAS for POAG involving 1575 Japanese cohorts in the first discovery stage. They identified three genetic loci located on chromosomes 1, 10, and 12. A similar study was conducted to examine Korean subjects [8]. Thereafter, Meguro *et al*. [9] performed a GWAS for NTG of Japanese cohorts which included 305 patients and 355 controls and identified two loci associated with NTG, rs3213787 on *SRBD1* and rs735860 on *ELOVL5*. Subsequent studies of Japanese or Caucasian subjects reported a positive association of POAG with these genetic variants [10, 11].

Ramdas *et al*. [12] identified unique variants associated with POAG. First, they performed a GWAS of the optic disc area and vertical cup-to-disc ratio (VCDR) using data from

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Caucasian participants in the Rotterdam Study and identified an association between three loci and optic disc area: *CDC7/TGFBR3* region, *ATOH7*, *SALL1*; and six with VCDR: *CDKN2B*, *SIX1*, *SCYL1*, *CHEK2*, *ATOH7*, and *DCLK1*. Next, they investigated to what extent these loci are involved in glaucoma and found a positive association of variants in *CDKN2B, ATOH7*, and *SIX1* with POAG [13]. Subsequent GWAS studies confirmed the association of these genetic variants with POAG in different ethnicities [14-18]. It has been reported that *CDKN2B* and *ATOH7* are more strongly associated with NTG than with HTG [14, 19-21]. These variants may be associated with optic vulnerability rather than with elevated IOP. Recent studies reported that the variant showing the strongest association (rs1063192) of CDKN2B was significantly associated with females among all POAG patients [22].

Thorleifsson *et al*. performed a GWAS for POAG of Iceland cohorts and identified a common sequence variant (rs4236601) at 7q31 [23]. This variant is located close to *CAV1* and *CAV2*. *CAV1* and *CAV2* are expressed in the trabecular meshwork and retinal ganglion cells. A few reports have demonstrated that the association of this variant with POAG is particularly strong in women [24, 25]. Recently, this variant was also reported to be associated with elevated IOP [26, 27].

Because the allele frequency at CAV1/CAV2 locus is very low in Asians, no studies have demonstrated the association between POAG and the CAV1/CAV2 locus. A recent report from China demonstrated that rs4236601 in the CAV1 gene was associated with POAG according to tagging-single-nucleotide polymorphism (SNP) analysis [28].

In 2011, Burden *et al* [29]. conducted a GWAS for POAG in Australians and identified two variants: *TMCO1* on 1q24 and *CDKN2B-AS1* on 9p21. *TMCO1* is expressed in most tissues in the human eye, including the ciliary body, trabecular meshwork, and retina [29, 30]. It has been reported that patients with risk variants of *TMCO1* are younger at the time of diagnosis and have a higher prevalence of glaucoma family history [30]. Koolwijk *et al*. [31] performed a GWAS for IOP and reported that *TMCO1* (rs7555523) and *GAS7* (rs11656696) were significantly associated with higher IOP; these variants were also associated with POAG.*TMCO1* appears to be associated with elevated IOP. A minor allele frequency of this variant is extremely low in Asians; thus, GWASs of Asian POAG revealed no statistically significant association with this locus.

In 2013, a GWAS for IOP in Australian subjects revealed that a common variant (rs59072263) at 7p21 near *GLCCI1* and *ICA1* is a novel region associated with POAG and IOP [32].

In 2014, two independent groups reported related GWASs [33, 34]. Chen *et al*. performed a GWAS for HTG in southern Chinese subjects and identified a genome-wide significant association of variants near *ABCA1* (rs2487032) at 9q31.1 and *PMM2* (rs3785176) at 16p13.2. They also reported that both *ABCA1* and *PMM2* are expressed in ocular tissues, including the trabecular meshwork and optic nerve [34].

Gharahkhani *et al*. performed a GWAS for POAG in an Australian cohort. They found three loci associated with POAG. These loci were located upstream of *ABCA1* (rs2472493), within *AFAP1* (rs4619890), and within *GMDS* (rs11969985). These genes were found to be expressed in the human retina, optic nerve head, and trabecular meshwork based on RT-PCR and immunolabeling analyses; *ABCA1* and *AFAP* were also expressed in retinal ganglion cells [34].

In 2015, Springlekamp *et al*. performed a GWAS for IOP using Rotterdam study subjects and identified a new locus associated with IOP [35]. The most significantly associated SNP was rs58073046 in the ARHGEF12 gene. This SNP was also confirmed to be associated with POAG.

In 2016, Bailey *et al*. performed meta-analysis of GWAS results from eight independent studies from the United States involving 3853 cases and 33,480 controls [36]. A meta-analysis of the top SNPs associated with POAG revealed three new loci; rs2745572 on *FOXC1*, rs7137828 on *ATXN2*, and rs35934224 on *TXNRD2*. They confirmed TXNRD2 and ATXN2 expression in retinal ganglion cells and the optic nerve head.

Recently, Springelkamp *et al*. conducted a GWAS meta-analysis of IOP and optic disc characteristics including the vertical cup to disc ratio (VCDR), optic nerve cup, and disc area and identified 9 new loci for VCDR, 1 new locus (near gene:*ADAMTS8*) for IOP, 5 new loci for optic nerve cup area, and 6 for optic disc area [37]. In addition, they detected an association between POAG and a variant of *CDKN1A*. This variant has been reported to be associated with VCDR and cup area. Table **1** shows the POAG candidate genes identified by GWAS.

3. PRIMARY ANGLE-CLOSURE GLAUCOMA (PACG): (INTRODUCTION)

3.1. Prevalence and Classification

PACG affects an estimated 16 million people worldwide, with 4 million suffering from bilateral blindness. It is expected that the prevalence of PACG will increase to 5.3 million by the year 2020 [40, 41]. Population-based studies demonstrated that PACG is more prevalent in Asians than in Europeans and Africans [40, 42, 43].

According to the International Society of Geographic and Epidemiologic Ophthalmology, there are 3 categories of PACG: (1) primary angle closure suspect, (2) primary angle closure, and (3) PACG [44]. PACG can develop at any stage. A longitudinal study investigating the long-term outcome of eyes with acute primary angle closure reported that 17.8% of patients were blind and that half of the eyes with acute primary angle closure had glaucomatous optic neuropathy after several years [45]. Therefore, it is important to identify patients at risk for developing PACG and perform appropriate treatment such as peripheral laser iridotomy and lens extraction.

4. GENOME-WIDE ASSOCIATION STUDY (GWAS) FOR PACG

There have been three reports of GWASs for PACG. Vithana *et al*. examined 1854 cases and 9608 controls in Asians in the discovery stage and identified three loci

Table 1. Primary-open angle glaucoma candidate genes identified from genome-wide association studies.

Gene (Nearest Gene)	Chromosome	rs ID	Population	Refs.
ABCA1	9	rs2487032	Australia China	[33] [34]
ABO	9	rs8176743	Meta analysis	[27]
ADAMTS8	11	rs4936099	Meta analysis	[38]
AFAP1	4	rs4619890	Australia	[33]
ARHGEF12	11	rs58073046	Netherlands	[35]
ATOH7	10	rs1900005	Netherlands Singapore Meta analysis	[12] [18] [38]
ATXN2	12	rs7137828	Meta analysis	[36]
CAV1/CAV2	7	rs4236601 rs1052990	Iceland Meta analysis	[23] [16] [27]
CDC7/TGFBR3	1	rs4658101	Singapore Meta analysis	[18] [38]
CDKN1A	6	rs36592986	Netherlands	[37]
CDKN2B(-AS1)	9	rs4977756 rs1063192 rs7865618 rs523096	Netherlands Australia Japan UK Meta analysis Meta analysis	[12] [29] [17] [14] [15] [11] [16] [38]
ELOVL5	6	rs735860	Japan	[9]
FAM125	9	rs2286885	UK	[39]
FOXC1	6	rs2745572	Meta analysis	[36]
FNDC3B	3	rs6445055	Meta analysis	[27]
GAS7	17	rs11656696 rs9913911	Netherlands Meta analysis Meta analysis	[31] [16] [27]
GLCCI1/ICA1	7	rs59072263	Australia	[32]
GMDS	6	rs11969985	Australia	[33]
PLXDC2	10	rs7081455	Japan	[7]
PMM2	16	rs3785176	China	[34]
PTPRJ	11	rs747782 rs1681630 rs7946766	Meta analysis	[27]
RAPSN	11	rs12419342	Meta analysis	[27]
SIX1/SIX6	14	rs10483727 rs4901977	Netherlands Meta analysis	[12] [38]
SRBD1	2	rs3213787	Japan UK	[9] [11]
TMCO1	1	rs4656461	Australia Netherlands UK Meta analysis	[29] [31] [11] [27]
TMTC2	12	rs7961953	Japan	[7]
TXNRD2	22	rs35934224	Meta analysis	[36]
ZP4	1	rs547948 rs540782 rs693421 rs2499601	Japan	[7]

Table 2. Primary angle closure glaucoma candidate genes identified from genome-wide association studies.

Gene (Nearest Gene)	Chromosome	rs ID	Population	Refs.
ABCC5	22	rs140199	Chinese	[47]
CHAT	10	rs1258267	Meta analysis	[48]
COL11A1	1	rs3753841	Asian	[46]
DPM2-FAM102A	9	rs3739821	Meta analysis	[48]
EPDR1	7	rs3816415	Meta analysis	[48]
FERMT2	14	rs7494379	Meta analysis	[48]
GLIS3	9	rs736893	Meta analysis	[48]
PCMTD1-ST18	8	rs1015213	Asian	[46]
PLEKHA7	11	rs11024102	Asian	[46]

associated with PACG, which were replicated among 1917 cases and 8943 controls [46]. These loci were located on *PLEKHA7* (rs11024102), *COL11A1* (rs3753841), and between *PCMTD1* and *ST18* (rs1015213). However, these variants explained less than 2% of PACG risk. It is well-documented that a shallow anterior chamber is an important risk factor for PACG. Nongpiur *et al*. focused on anterior chamber depth (ACD) and performed a GWAS for ACD involving Chinese subjects, including Singaporean, Malays, and Chinese from Beijing [47]. They identified a sequence variant of the ABCC5 gene (rs140199) associated with ACD; this locus also increased the risk of PACG. A large-scale GWAS for PACG was recently performed on 6525 cases and 19,929 controls from 15 countries in Asia, Europe, and South America. SNPs at 10 distinct loci including 3 SNPs previously reported (*COL11A1*, *PCMTD1-ST18*, *PLEKHA7*) with p-values less than 10^{-6}. A replication study was performed of 3978 cases and 9678 controls from 14 countries [48]. Genome-wide significance was observed in 8 SNPs, including 3 previously reported SNPs. Table **2** shows the genetic variants susceptible to PACG revealed by GWAS.

5. EXFOLIATION GLAUCOMA (XFG): (INTRODUCTION)

Exfoliation syndrome (XFS) is an age-related ocular disorder characterized by extracellular febrillar deposition over several ocular tissues. The deposits are commonly observed in the anterior segment, particularly the lens surface and pupillary border. Components of exfloliative material are histologically found to be various basement membranes (*e.g.*, laminin, nidogen, and fibronectin), elastic fiber system (*e.g.*, fibrillin-1, elastin, and latent transforming growth factor binding proteins), and enzymatically active components (*e.g.*, metalloproteinases, the extracellular chaperone clusterin, and the cross-linking enzyme lysyl oxidase-like 1 [LOXL1]) [49].

It has been reported that nearly half of patients with XFS will develop XFG in their lifetimes [50]. XFG is the most common cause of secondary open-angle glaucoma worldwide. Compared with POAG, XFG is associated with higher intraocular pressure at diagnosis and faster progression of visual field loss [51]. XFS is also associated with zonule vulnerability and cataract progression, resulting in angle-closure glaucoma [51]. Therefore, the management of XFG is challenging.

6. GENOME-WIDE ASSOCIATION STUDY (GWAS) OF XFS

GWASs have also been performed for XFS/XFG. Compared with POAG or PACG, few variants have been found to be associated with XFS.

7. *LOXL1* GENE

LOXL1 is a member of the lysyl oxidase family of proteins that catalyzes oxidative deamination of lysine residues of tropoelastin, leading to their spontaneous cross-linking with consequent formation of elastin polymer fibers [49].

In 2007, Thorleifsson *et al*. demonstrated that two variants of the *LOXL1* gene (rs1048661 (R141L) and rs3825942 (G153D) located on exon 1) were strongly associated with XFG and possibly XFS in a Scandinavian cohort [52]. They reported that the high-risk haplotype of these coding variants was observed in 25% of the general population and that individuals with this high-risk haplotype have a greater than 700-fold higher risk of developing XFG compared with individuals homozygous for the low-risk haplotype. This association was observed in different ethnicities [53-56]. Thorleifsson *et al*. reported that the G allele of rs1048661 and rs3825942 was a risk allele for XFS and that the haplotype G-G was the highest risk haplotype. Similar to previous reports, subsequent studies of other Caucasians confirmed the risk allele, genotype, and haplotype frequency of the *LOXL1* gene. It has been reported that the T allele, but not the G allele, of rs1048661 is associated with XFS/XFG in Asians [53, 54]. It remains unclear why the risk variant of rs1048661 differs between Caucasians and Asians.

8. *CNTNAP2* GENE

In 2011, Krumbieg *et al*. conducted a GWAS for XFS in German cohorts using a DNA-pooling approach [57]. They performed a replication study of 17 SNPs showing significant allele frequency differences in DNA-pools and confirmed the association of 2 SNPs (rs2107856 and rs2141388) in *CNTNAP2* with XFS. CNTNAP2 was found to be ubiqui-

tously expressed in all human ocular tissues, particularly in the retina, and localized to the cell membranes of epithelial, endothelial, smooth muscle, glial, and neuronal cells.

9. *CACNA1A* GENE

CACNA1A encodes the pore-forming α1 subunit of human voltage-gated Cav2.1(P/Q-type) Ca^{2+} channels [58]. Mutations in the CACNA1A gene cause autosomal-dominant neurologic diseases such as several familial hemiplegic migraine type 1 and episodic ataxia type 2 [58]. It has been reported that eye movement disorder is an early manifestation of *CACNA1A* mutation [59]. CACNA1A mRNA expression was observed in the ciliary body, iris, anterior lens epithelium, retina, optic nerve glia, and vascular endothelial cells [60]. Electron microscopy studies of XFS eyes revealed high calcium concentrations in XFS fibrils [61]. Calcium was demonstrated to play a role in stabilizing fibrillin molecules and microfibrills. Calcium channel dysfunction may lead to changes in calcium concentration, causing the deposition of exfoliative material.

In 2015, Aung *et al*. performed a GWAS of XFS using 1484 cases and 1188 controls [60]. They found 66 single-nucleotide polymorphisms (SNPs) outside of the *LOXL1* gene with p-values less than 1.0×10^{-4} at the discovery stage. They designed validation assays for these 66 SNPs, together with *LOXL1* variants using 2628 cases and 8947 controls from 9 countries They demonstrated that a variant (rs4926244) of *CACNA1A* showing a p-value of 5.5×10^{-5} at the discovery stage was also significant in the validation stage ($p = 4.17 \times 10^{-5}$). In a meta-analysis of both the discovery and validation stages, only rs492644 of *CACNA1A* exhibited genome-wide significance ($p = 2.45 \times 10^{-8}$). They evaluated an additional 4273 cases and 11,780 controls and confirmed the association between XFS and rs492644 of *CACNA1A*.The association was maintained with a p-value of 1.14×10^{-4}. Together with discovery stage and two-replication stage (8385 XFS cases and 21,915 controls), rs492644 (G allele) is a significant risk variant for XFS ($p = 3.36 \times 10^{-11}$) and shows a similar trend among ethnicities (odds ratio [OR]: 1.14 Asians, OR: 1.19 Europeans, OR: 1.33 South Africans).

CONCLUSION

In this review, we presented genetic variants susceptible to POAG, PACG and XFS identified by GWASs. It has been revealed the expression and function of genes associated with glaucoma and exfoliation syndrome identified by GWASs, which might enable us to understand the precise mechanism of glaucoma development and facilitate development of new drugs and therapy. However, we don't make the best use of genetic variants associated with glaucoma in a clinical setting though we can speculate which type of glaucoma (NTG or HTG) develops through several genetic variants susceptible to glaucoma. It is because a lot of genetic variants (more than 25) are involved with development of POAG and the contribution of each genetic variants are considered to be very small. Therefore, it is important to combine the several genetic variants with clinical phenotype.

LIST OF ABBREVIATIONS

POAG	=	Primary open-angle glaucoma
NTG	=	Normal tension glaucoma
HTG	=	High tension glaucoma
GWAS	=	Genome-wide association study
VCDR	=	Vertical cup-to-disc ratio
IOP	=	Intraocular pressure
PACG	=	Primary angle-closure
ACD	=	Anterior chamber depth
XFG	=	Exfoliation glaucoma
XFS	=	Exfoliation syndrome

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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