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REVIEW

Genetics of primary open angle glaucoma

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Abstract Glaucoma is a neurodegenerative disease and one of the leading causes of irreversible blindness, affecting over 60 million people worldwide. At the present time, glaucoma is clinically defined, but the exact etiology is unknown. Genetic studies are one approach to identify the molecules and pathways involved in disease pathogenesis. Familial aggregation of primary open-angle glaucoma (POAG) has long been recognized, and the analysis of POAG families with a Mendelian inheritance form of this disease has been employed to identify multiple loci linked to them. Some causative genes, such as myocilin, optineurin and WD repeat domain 36, have been identified. However, most cases of POAG are considered to be a prevalent, multifactorial disorder. Several association studies have been conducted for candidate genes, and genome-wide association studies recently identified new susceptibility loci for POAG, namely, S1 RNA binding domain 1 region on chromosome 2p21, the caveolin 1 and caveolin 2 regions on 7q31, transmembrane and coiled-coil domain 1 region on 1q24, cyclin-dependent kinase inhibitor 2B antisense RNA on 9p21, the SIX1 and SIX6 regions on 14q24 and, possibly, the regulatory region of 8q22. Further analysis of clinical manifestations caused by specific genes and functional analysis of these genes will contribute to the development of new strategies for the diagnosis and treatment of POAG.

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Introduction

Glaucoma is a neurodegenerative disease that leads to progressive loss of retinal ganglion cells [1, 2], causing irreversible visual field defects [3]. It is a leading cause of irreversible blindness, affecting over 60 million people worldwide [4]. At the present time, glaucoma is clinically defined by the existence of characteristic changes in the optic disc and corresponding visual field defects [5], but the exact etiology is unknown.

Primary open-angle glaucoma (POAG) is the most prevalent type of glaucoma, and typically characterized by adult onset and chronic intraocular pressure (IOP)-dependent progression. Familial aggregation studies have revealed that first-degree relatives of POAG patients have an increased likelihood of about tenfold for developing POAG [6], and twin studies have revealed significant heritability for POAG [7]. African-derived populations have a stronger heritability of POAG [8, 9]. Interestingly some population diversity is observed in the phenotypic manifestation of glaucoma. The prevalence of normal-tension glaucoma (NTG), that is, POAG associated with IOP consistently within a statistically normal range ($\leq$21 mmHg), differs substantially among populations. In Caucasians and African Americans, the prevalence ratios of NTG and POAG are both approximately 1.0 [8, 10–13], while in Koreans these are about 3 [14] and greater than those in Japanese (prevalence ratio 10) [15].

Multiple POAG families with a Mendelian inheritance form of the disease are well known, and linkage analysis

has identified multiple loci linked to them. Clinical manifestation of familial POAG can be divided into two phenotypes of juvenile-onset POAG (JOAG) accompanied by extremely high IOP and adult-onset POAG with mildly elevated IOP or normal IOP. Some genes on these loci have been proposed to be causative, but for most genes more evidence is needed to arrive at a definitive conclusion.

Familial POAG considered to be caused by a single gene forms a small part of POAG and, generally, POAG is considered to be a multifactorial disorder. Higher IOP, older age, systemic diseases, ethnicity, and family history are reported risk factors of POAG [6, 7, 16–20]. Association studies for candidate genes and genome-wide association studies (GWASs) provide useful information that facilitates the identification of genetic factors, each of which has a relatively small effect but contributes to a large number of cases. Significant association between several genetic loci and POAG have been reported.

Genetic studies of human genomes, such as linkage analysis and association studies, constitute one approach by which to identify the molecules and pathways involved in the pathogenesis of POAG.

Familial POAG and causative genes

Linkage studies on POAG families have revealed evidence of multiple loci linked to the disease, namely, GLC1A to P [21–26], with GLC1B, C, D, E, F, G, H, I, L, O, and P associated with adult-onset POAG and GLC1A, J, K, M and N associated with JOAG. To date, five genes have been reported to be a causative or presumably causative gene of POAG: myocilin (MYOC) for GLC1A [27], optineurin (OPTN) for GLC1E [28], WD repeat domain 36 (WDR 36) for GLC1G [29], neurotrophin 4 (NTF4) for GLC1O [30], and tank-binding kinase 1 (TBK1) for GLC1P [26].

GLC1A and MYOC

In 1993, linkage analysis of one large Caucasian family from the USA with autosomal dominantly inherited JOAG resulted in the identification of the first locus for POAG (GLC1A) on chromosome 1q21–q31 [31]. Linkage of this disease to this locus was confirmed in several JOAG patients and in adult-onset POAG families of multiple populations [32–39] and found to be confined to a 3-cM region at 1q23–q2 [27, 40]. In 1997, mutations in the MYOC gene located in the GLC1A locus were identified [27]. MYOC mutations are reported to be responsible for JOAG in 22–36 % of the cases in JOAG families [41, 42] and for POAG in about 2–4 % of POAG cases in different populations, including Caucasian, Asian and African American populations [27, 41, 43–47].

More than 180 variants in the MYOC gene have been documented, and these and their associate phenotypes are compiled in an online database [48]. Approximately 40 % of the identified variants have been characterized as disease causing, with the majority (85 %) of these being missense mutations [48], and strong genotype–phenotype correlations have been observed. The P370L variant causes extremely early-onset of the disease, with a mean age at diagnosis of 13.0 years old [49, 50]. Q368X causes late-onset POAG [42, 44, 51, 52]. In all cases studied, MYOC glaucoma seems to be associated with elevated IOP.

MYOC has three exons and is expressed as a 2.3-kb transcript, with a translated product of 504 amino acids [53]. MYOC is ubiquitously expressed throughout the body, including ocular tissues [e.g., sclera, ciliary body, iris, retina, optic nerve head, and trabecular meshwork (TM)] [54]. The majority of disease-associated MYOC mutations are located within exon 3, where the olfactomedin homology region is localized [48].

Wild-type MYOC is not considered to be involved in the normal regulation of IOP. Increasing or decreasing expression, or even the total loss of expression doesn't cause elevated IOP or signs of glaucoma [47, 55–58]. Although the exact pathophysiology of MYOC glaucoma is still unclear, MYOC mutations are suggested as a cause of glaucoma by gain-of-function. Mutant MYOC demonstrates features of mitochondrial dysfunction and may increase the vulnerability of TM cells [59]. Overexpression mutants cause an inhibition of neurite outgrowth and thus may contribute to the development of neurodegenerative glaucoma [60]. Failure to secrete MYOC [61], induction of endoplasmic reticulum (ER) stress, and mislocalization of mutant MYOC to peroxisomes [62–65] have been observed in mutant MYOC. Excessive ER stress can trigger apoptotic cell death in neurological disorders and may be responsible for TM cellular dysfunction contributing to elevated IOP [65, 66].

GLC1B

Linkage analysis of Caucasian families in the UK identified the GLC1B locus on 2cen-q13 as being linked to adult-onset POAG [67]. The clinical presentation of affected family members was low to moderate IOP, disease onset occurred when family members were in their 40s, and those affected responded well to medical treatment.

Because clinical manifestations were similar to those of NTG, the locus could be a candidate for association studies for NTG. An analysis of microsatellite markers around the GLC1B locus in sporadic Japanese NTG patients revealed two markers that were significantly associated with adult-onset POAG, of which the most significant one was near the gene NCK adaptor protein 2 (NCK2) [68]. Screening

single-nucleotide polymorphisms (SNPs) on GLC1B in another Japanese cohort demonstrated a significant association between SNP in the intron of hexokinase 2 (HK2) and both NTG and high-tension glaucoma (HTG) [69] and also provided data supporting previous reports of an association between NCK2 and NTG [69].

GLC1C

Linkage analysis of a large family in Oregon with adult-onset POAG inherited as an autosomal dominant trait has been mapped to 3q21–q24 [70]. Linkage of this GLC1C locus and POAG has also been reported in one large Greek family [71]. Further analysis identified a T377M nonsynonymous substitution in MYOC in family members of the Greek GLC1C family but not in those of the Oregon GLC1C family. Carriers of both the MYOC T377M and GLC1C haplotype were more severely affected at an earlier age than carriers with only one of these haplotypes, suggesting that these two genes interact or that both contribute to the POAG phenotype in a cumulative manner [72].

GLC1D

Linkage analysis for a family with adult-onset POAG identified chromosome 8q23 as the locus GLC1D [73]. The phenotype in this family appears to be variable, with onset of visual field loss in middle age, modest elevation of IOP, and progression of the disease in older individuals [73].

GLC1E and OPTN

Linkage analysis of one large British family with POAG identified an adult-onset POAG locus (GLCIE) on chromosome 10p14–p15 [74]. The eyes of most of the affected family members were afflicted with NTG. Subsequent analysis identified disease-causative sequence alterations in the OPTN gene in the GLCIE locus. OPTN was subsequently identified as being the causative genetic factor for POAG in nine (16.7 %) of the POAG families initially investigated. Of these nine families, the E50K mutation was observed in seven families and 691_692insAG and R545Q were observed in one family each. The M98K mutation in OPTN has been observed in 13.6 % of familial and sporadic cases [28].

Unlike the first report on the OPTN mutation [28], detection of E50K in POAG patients was rare (almost 1 %) in subsequent studies [75–84]; however, E50K remains the most evidenced causative alteration. It has been found in multiple populations of Caucasian, Asian, and Hispanic POAG cases [28, 75–77, 85] and has not been found in normal controls. In addition, the E50K mutation has been associated with a more severe form of NTG [86, 87]. A common variant, M98K, has been significantly associated with NTG [75, 76, 79, 83] or HTG [79, 83] in Japanese and British populations, but contradictory results have also been reported [77, 78, 80, 84, 88]. In some studies, R545Q was identified in only POAG patients and was absent in the control population [28, 79, 89], but there are some inconsistent reports suggesting that R545Q is a non-disease polymorphism [75, 83, 90]. A meta-analysis for the M98K, T34T, and R545Q polymorphisms demonstrated a modest association only between T34T and Asian POAG [91].

The human OPTN gene spans 37 kbp on chromosome 10 and encodes a cytosolic protein containing 577 amino acid residues. OPTN is ubiquitously expressed, and Rezaie et al. [28] demonstrated OPTN expression in human TM cells, non-pigmented ciliary epithelium, and the retina. OPTN interacts with proteins such as myosin VI, Rab8, huntingtin, transferrin receptor, and TBK1 and has a role in basic cellular functions, including protein trafficking, maintenance of the Golgi apparatus, and NF-κB pathway, antiviral, and antibacterial signaling [92].

Downregulation of OPTN has been found to significantly increase apoptosis in RGC-5 and PC12 cells [93]. In one study overexpression of OPTN protected cell survival under oxidative stress by relocating to the nucleus in an Rab8-dependent manner; however, this latter effect was not observed in the E50K mutant [94]. The E50K mutant was observed to induce cell death selectively in retinal ganglion cells and was inhibited by anti-oxidants [95]. The authors of another study suggest that the E50K mutant acquired the ability to induce cell death through the mitochondrial caspase-dependent cell death pathway [96]. A study involving transgenic mice demonstrated that the E50K leads to apoptosis of retinal ganglion cells and demonstrated disruption of the OPTN–Rab8 interaction by the E50K mutation and its effects on protein trafficking [85]. Overexpression of M98K–OPTN has also been reported to induce death of retinal ganglion cells (RGC-5 cell line) [97].

OPTN has also been reported to be a genetic factor for amyotrophic lateral sclerosis [98] and Paget's disease [99]. The tissue-specific function of OPTN may underlie the pathogenesis of each disease.

GLC1F

Linkage analysis of a large family with autosomal dominantly inherited adult-onset POAG identified a disease locus mapping to 7q35–q36 [100]. Most of the affected family members had untreated IOP of >22 mmHg, and their disease severity levels varied widely.

Subsequent analysis of the genes in the locus identified revealed unreported variants in ankyrin repeats and the suppressor of cytokine signalling (SOCS) box containing

protein 10 (ASB10), which was a synonymous variant, c.765C>T (T255T), at the center of a predicted exon splice enhancer site in exon 3 [101]. Further mutation screening of the ASB10 gene in two POAG cohorts from the USA and Germany identified a higher frequency of multiple non-synonymous variants in patients than in the controls [101]. However, analysis of another cohort in Iowa did not demonstrate a higher frequency of non-synonymous ASB10 coding sequence variations in POAG patients than in control subjects [102].

On one study, ASB10 mRNA and protein were found to be strongly expressed in trabecular meshwork, retinal ganglion cells, and the ciliary body. Silencing of ASB10 transcripts in perfused anterior segment organ culture reduced the outflow facility by approximately 50 % compared with control-infected anterior segments ($p = 0.02$) [101].

In their investigation for association between microsatellite markers of the GLC1F locus and NTG in Japanese patients, Murakami et al. found that one marker, D7S1277i, in ArfGAP with the GTPase domain, ankyrin repeat, and PH domain 3A (AGAP3), was significantly associated with NTG [103]. The AGAP3 gene is located about 50 kbp away from ASB10.

GLC1G and the WDR domain 36

An adult-onset POAG locus has been mapped on 5q22.1 (GLC1G). Mutation screening of candidate genes from the GLC1G critical region identified only one significant mutation (D658G) in the WDR36 (WD40-repeat 36) gene. Further screening of WDR36 in a total of 130 POAG families revealed 24 DNA variations. Overall, four non-synonymous substitutions (N355S, A449T, R529Q, D658G) were identified in 17 (5.02–6.92 %) unrelated POAG subjects, of whom 11 had high-pressure and six had low-pressure glaucoma [29]. The D658G mutation is reported to be very rare in familial POAG from the USA [104] and Italy [105], while investigations of POAG populations from Australia [67], Iowa [68], and Germany [106] suggest that the D658G mutation is a neutral variant, indicating that variants of this gene may act in certain populations as a causative or modifier gene for POAG. In their study of POAG patients in the USA, Hauser et al. identified other non-synonymous variants that occur more frequently in familial POAG than in controls, but without segregation for the occurrence of the disease. Rs10038177, located in the intron of WDR36, was reported to be significantly associated with sporadic HTG in small Taiwan cohort [107] and an East Indian cohort [108], but the risk alleles of each cohort were opposite. Multiple sequence variants have been reported in WDR36 in sporadic POAG cases in a German [106, 109] and Japanese [110] population and in a population from Iowa [111]; however, more evidence seems to be needed to conclude that these are associated with POAG.

WDR36 encodes a protein of unknown function. It is ubiquitously expressed, and its expression has been detected in ocular tissues, including lens, iris, sclera, ciliary muscles, ciliary body, trabecular meshwork, retina, and the optic nerve [29]. The loss of Wdr36 resulted in activation of the p53 stress-response pathway that disrupts nucleolar morphology and rRNA processing in the Wdr36-knockdown zebrafish [112]. When combined with disruption of STI1, which synthetically interacts with WDR36, four of the 11 tested POAG-associated variants, including D658G, had decreased cell viability [113]. A triple amino acid deletion of mouse Wdr36 at positions corresponding to positions 657–659 in humans resulted in progressive retinal degeneration at the peripheral retina with normal IOP [114].

GLC1H

GLC1H, mapped on chromosome 2p15–16.2, has been linked to adult-onset POAG in Caucasian families [115], with the IOP of the affected members being 24–60 mm Hg [115]. The overwrapped region of 2p14–16.3 has been reported to be linked to JOAG in Chinese families [116], and another region, 2p15–21, has been reported to be linked to adult-onset POAG in Afro-Caribbean families [117]. In this latter study, intergenic SNPs located on chromosome 2p16.3, just outside of GLC1H, were significantly associated to sporadic POAG in the Afro-Caribbean population [117]. However, only one (rs12994401) of the three SNPs could be replicated in an Afro-American population [118]. In the genetic linkage analysis of IOP in the Beaver Dam Eye Study, a peak in this region on chromosome 2 was identified, suggesting that this locus may affect IOP [119].

GLC1I

In their ordered subset analysis of multiplex families with POAG using age at diagnosis as a covariate, Allingham et al. identified chromosome 15q11–q13 as being linked to POAG [120], as originally identified by Wiggs et al. [25]. This result suggests that age at diagnosis and other phenotypic traits can be used as stratification variables to identify genes in complex disorders such as POAG.

GLC1J

An investigation of 25 pedigrees with typical JOAG inherited in an autosomal dominant fashion revealed MYOC mutations in 8 % of the propands. Linkage analysis

for the families without MYOC mutations identified the GLC1J locus on chromosome 9q22 [121].

GLC1K

Linkage analysis of JOAG families without the MYOC mutation identified the GLC1K locus on chromosome 20p12 [121]. Subsequent analysis reduced the GLC1K region to a maximum of 12.7 Mb and a minimum of 9 Mb. Four genes, BMP2, PLCB1, PLCB4, or BTBD3, are located within the refined region. Biologically significant DNA sequence variants were not identified in the genes in these families [122].

GLC1L

Primary open-angle glaucoma caused by alterations in the G368X sequence in MYOC is, as described above, typically a late-onset disorder. Craig et al. studied a large Tasmanian family affected by POAG in which some individual members were identified with MYOC G368X and some without MYOC. G368X carriers exhibited a younger onset and higher peak IOP than affected family members without G368X [123]. The form of the family was not a simple Mendelian inheritance. The second responsible locus for POAG in this family was identified on the short arm of chromosome 3; this turned out to be a novel glaucoma locus and was identified not by linkage analysis but by applying a Markov Chain Monte Carlo method to measure identity-by-descent sharing [22]. In subjects with the GLC1L disease haplotype (with or without G368X), the POAG phenotype was characterized by a mean age at diagnosis of 54.3 years and mean maximum IOP of 23.9 mmHg. The IOP in subjects with the disease haplotype was lower in those who were not G368X carriers than in G368X carriers. All four subjects with the GLC1L disease-associated haplotype without the G368X were NTG, and the GLC1L locus alone may be associated with NTG.

GLC1M

Linkage analysis and fine mapping of a large Philippine family with autosomal dominantly inherited JOAG [124] resulted in the identification of chromosome 5q22.1–q32 as a GLC1M locus [23]. Subsequent analysis refined the locus to a 28-Mb region between D5S2051 and NRG2 [125]. WDR36 lies centromeric to the region. The authors of these studies were unable to identify any disease causative alterations within the NRG2 and WDR36 genes [23, 125].

GLC1N

Linkage analysis of a large Chinese family with autosomal dominant JOAG resulted in the identification of chromosome 15q22–q24 as the GLC1N locus [24]. In affected members, no disease causative alterations were identified in the three candidate genes: nuclear receptor subfamily 2, group E, member 3 (NR2E3), SMAD family member 6 (SMAD6), and ceroid-lipofuscinosis, neuronal 6, late infantile, variant (CLN6) [24].

GLC1O and NTF4

Pasutto et al. [30] focused on the NTF4 gene, which codes for a member of the neurotrophin protein family, on chromosome 19q13 where one of the loci had been previously identified by linkage analysis of mainly Caucasian families from North America. These investigators identified seven different heterozygous non-synonymous variants in the NTF4 gene in 1.7 % of patients in high- and normal-tension POAG from Germany and The Netherlands. On the basis of molecular modeling, all NTF4 variants were predicted to affect either dimer stability of NTF4 or interaction between the NTF4 dimer and its receptor TrkB. In vitro experiments revealed that the most frequent variant, R206W, impaired both ligand-mediated TrkB signaling and neurite outgrowth [30].

However, another Caucasian and Indian cohort could not replicate the association between non-synonymous variants and POAG [126, 127]. Although extremely rare, variants in NTF4 have been reported [128, 129]. Therefore, more evidence is needed to prove the contribution of the NTF4 variant to POAG and whether NTF4 is truly responsible for GLC1O.

GLC1P and TBK1

A novel genetic locus (GLC1P) for NTG on chromosome 12q14 was identified through linkage studies of a large African–American family [26]. Based on an analysis of copy number variant (CNV) using microarray data of the family members, the authors of the study identified a large duplication within the linked interval. Overlapping duplications have also been detected in two (1.3 %) of 152 NTG subjects from Iowa [26]. In this study, two genes, TBK1 and XPOT, were located in the 300-kbp critical region of GLC1P, and duplication of GLC1P resulted in increased TBK1 and glucosamine (N-acetyl)-6-sulfatase (GNS) transcription. The authors considered GNS to be located outside the 300-kbp critical region and TBK1 to be responsible for GLC1P [26]. Furthermore, TBK1 has been found to be expressed in the ganglion cells, nerve fiber layers, and microvasculature of the human retina and to interact with OPTN [130].

In another study, of the 252 unrelated Japanese NTG subjects, only one (0.40 %) was found to carry a TBK1 duplication [131].

Association studies for common genetic variants

Most cases of POAG are believed to be caused by multiple genetic and environmental factors. In such cases, the contribution of a single genetic factor is considered to have a relatively small effect; consequently, association studies for cases and controls are widely applied. The genes reported to be significantly associated with POAG by the candidate gene approach are shown in Table 1. Although many genes seem to be identified, only a few studies have been sufficiently replicated, and most of the studies involved only a small sample size.

The candidate gene approach can be used to analyze known genetic variants such as SNPs, microsatellite markers, or CNVs located in or around the selected genes. However, using this approach it is difficult to select the target from the large number of genes, and the genetic regions of unknown functions are excluded from the beginning. In contrast to the candidate gene approach, a GWAS can be used to investigate genetic variants across the entire genome. In a GWAS, hundreds or thousands or more than a million SNPs are usually targeted using microarray analysis, and the association between each SNP and disease and/or sometimes a quantitative trait is subsequently analyzed. GWASs have been conducted for several common diseases, resulting in the identification of several new susceptibility genes and regions [132]. To identify novel genetic susceptibility loci, GWASs have been also conducted for POAG (Table 2).

Meguro et al. [133] conducted a GWAS for Japanese NTG and reported the presence of rs3213787 in S1 RNA binding domain 1 (SRBD1) as being associated with genome-wide significance [$p = 2.5 \times 10^{-9}$, odds ratio (OR) 2.80]. These results were replicated in two other studies involving a cohort of Japanese NTG and HTG [134] and a POAG cohort in the USA [135].

Table 1 Genes associated with primary open-angle glaucoma identified by candidate gene approach

Gene	Subtype/population
Glutathione *S*-transferase M1 (GSTM1)	HTG/Estonians [164][a], POAG/Brazilian [165]
Optic atrophy 1 (OPA1)	NTG/Caucasian from London [166][a], NTG/UK population [167], NTG/Japanese [168][a], NTG/population from England [169], meta-analysis [170]
Apolipoprotein E (APOE)	ε4 risk: NTG/Tasmanian [171], ε4 protective: POAG/Japanese[a] [172]
Tumor necrosis factor alpha (TNF-α)	POAG/Chinese [173], POAG/Shiraz [174], NTG/Chinese [175], POAG/Turkish [176], POAG/Chinese [177][a]
Cyclin-dependent kinase inhibitor 1A (CDKN1A)	POAG/Chinese [178]
E-cadherin (CDH1)	POAG/Chinese [179]
Interleukin 1, alpha (IL-1A)	POAG/Chinese [180][a]
Heat-shock protein70-1 (HSP70-1)	HTG, NTG/Japanese [181][a]
Cytochrome p450 1B1 (CYP1B1)	POAG/Indian [182]
Toll-like receptor 4 (TLR4)	NTG/Japanese [183][a], HTG, NTG/Japanese [184][a]
NCK adaptor protein 2 (NCK2)	NTG/Japanese [68], NTG/Japanese [69][a]
Hexokinase 2 (HK2)	HTG, NTG/Japanese [69][a]
Endothelial nitric oxide synthase (eNOS)	POAG/Pakistani [185][a], POAG/Chinese [186], POAG/Brazilian [187]
Tumor protein p53 (TP53)	POAG/Chinese [188], NTG POAG/Chinese [175]
X-ray cross-complementing group 1 (XRCC1)	Male POAG/Pakistani [189]
Xeroderma pigmentosum complementation group D (XPD)	Male POAG/Pakistani [189]
Matrix metallopeptidase 1 (MMP-1)	POAG/Caucasian [190][a]
Galactosylceramidase (GALC)	POAG/Caucasian [191][a]
Na(+)-dependent L-ascorbic acid transporter 2 (SLC23A2)	POAG/Mediterranean population [192][a], POAG/Mediterranean population [193][a]
Tocopherol-associated protein gene (SEC14L2/TAP)	POAG/Mediterranean population [193][a]
Methylenetetrahydrofolate reductase (MTHFR)	HTG/German [194], HTG/German [195]

POAG Primary open angle glaucoma, *NTG* normal-tension glaucoma, *HTG* high-tension glaucoma

[a] Reports that included >150 subjects in both the patient and controls group

Table 2 Genome-wide association studies for POAG

GWAS	Population	Phenotype	Chromosome	Gene symbol	SNP: p value, OR
Meguro et al. [133]	Japanese	NTG	2p21	SRBD1	rs3213787: $p = 2.5 \times 10^{-9}$, OR = 2.80
Thorleifsson et al. [136]	Caucasian (in Iceland)	POAG	7q31	CAV1/CAV2	rs4236601: $p = 5 \times 10^{-10}$, OR = 1.36
					rs1052990: $p = 1.1 \times 10^{-9}$, OR = 1.32
Burdon et al. [140]	Caucasian (in Australia)	POAG	1q24	TMCO1	rs4656461: p = 6.1×10^{-10}, OR = 1.68
			9p21	CDKN2BAS	rs4977756: $p = 4.7 \times 10^{-9}$, OR = 1.50
Osman et al. [144]	Japanese	POAG	9p21	CDKN2BAS	rs1063192: $p = 5.2 \times 10^{-11}$, OR = 1.33
			14q23	SIX1/SIX6	rs10483727: $p = 9.49 \times 10^{-8}$, OR = 0.79
Nakano et al. [143]	Japanese	POAG/NTG	9p21	CDKN2BAS	rs7865618: $p = 9.0 \times 10^{-11}$, OR = 1.78
Wiggs et al. [146]	Caucasian	POAG	9p21	CDKN2BAS	rs2157719: $p = 1.86 \times 10^{-18}$, OR = 1.45
			14q23	SIX1/SIX6	rs10483727: $p = 3.87 \times 10^{-11}$, OR = 1.32
		NTG	9p21	CDKN2BAS (gene desert)	rs2157719: $p = 1.17 \times 10^{-12}$, OR = 1.72
			8q22		rs284489: $p = 8.88 \times 10^{-10}$, OR = 0.62
Takamoto et al. [145]	Japanese	NTG	9p21	CDKN2BAS	rs523096: $p = 4.96 \times 10^{-11}$, OR = 2.13

GWAS Genome-wide association study, *SNP* single-nucleotide polymorphism, *OR* odds ratio

In their study of an Icelandic cohort, Thorleifsson et al. [136] observed that the presence of rs4236601 between the caveolin 1 (CAV1) and caveolin 2 (CAV2) genes on chromosome 7q31 was significantly associated with POAG. These authors replicated the results on this cohort in multiple cohorts of European descent and Chinese population. The association between POAG in a Caucasian U.S. population and these loci has been successfully replicated [137]. However, statistically significant results have not always been obtained [138, 139], and it is generally considered that this region has a relatively weak effect.

In 2011 Burdon et al. [140] reported the results of a GWAS for POAG in a Caucasian cohort in Australia and identified two susceptible genes: transmembrane and coiled-coil domains 1 (TMCO1) on 1q24 and cyclin-dependent kinase inhibitor 2B antisense RNA (CDKN2BAS) on 9p21. TMCO1 is highly expressed in the ciliary body and trabecular meshwork as well as in the retina. TMCO1 loci have also been reported to be associated with IOP in a GWAS for a Caucasian cohort [141], and carriers of risk alleles of a reported SNP (rs4656461) have been reported to be younger at diagnosis than subjects without the risk allele [142].

As described above, three genetic loci have been identified in Caucasian GWASs. Among these, rs4236601 in the CAV1/CAV2 region and rs4656461 and rs7518099 in the TMCO1 region are considered to have a minor allele frequency in Caucasian populations but to be extremely low in Asian ones (<0.01 in Asians compared with about 0.15-0.3 in Caucasians). Hence, any evaluation of association is difficult. GWASs for Japanese POAG did not demonstrate significant association with SNPs in these regions [143–145].

In contrast, the CDKN2BAS locus has been reported to be associated in subsequent GWASs with POAG in Caucasians and Japanese with genome-wide significance [143–146]. Association between the locus and POAG/NTG has also been demonstrated in several populations, including Caucasian [147], Asian [148], and Afro-Caribbean populations [149]. The results of relations of clinical manifestations and SNPs in CDKN2BAS loci are listed in Table 3. These loci are also known to affect vertical cup-to-disc-ratio (VCDR) in general populations not limited to glaucoma patients [150]. Risk alleles for glaucoma are associated with larger VCDR. A higher odds ratio was observed in NTG patients than in HTG patients, and in advanced POAG than in non-advanced POAG. POAG patients carrying risk alleles have larger VCDR and lower IOP. This evidence suggests the locus plays a crucial role as neuronal factor(s) in affecting optic disc vulnerability rather than elevating IOP and that a common genetic factor may be involved irrespective of baseline IOP.

The associated SNPs are located in a non-coding gene, CDKN2BAS, and near the tumor suppressor genes CDKN2A/B. The expression of CDKN2B was found to be dramatically induced by transforming growth factor beta (TGF-β) [151]. TGF-β is known to be involved in programmed cell death in the developing retina and optic nerve [152, 153] and suggested to play an important role in glaucoma [153–155]. CDKN2BAS is a large antisense non-coding gene that overlays the CDKN2B gene in an antisense strand. Although the function of CDKN2BAS is not well elucidated, recent GWASs of several common diseases (coronary artery disease [156], type 2 diabetes [156], aortic aneurysm [157], intra-cranial aneurysm [156], endometriosis [158], and glioma [159, 160]) revealed

associations with this long non-coding region. The locus is speculated as having a cross-disease, physiological and pathophysiological role.

Two GWASs for Japanese POAG and Caucasian POAG patients demonstrated an association with rs10483727, which is in the intergenic region between the SIX1 and SIX6 locus on chromosome 14q24 [144, 146]. Moreover, rs10483727 in the SIX1/SIX6 region is also replicated in another Caucasian POAG cohort [161]. The locus is also known to be associated with VCDR in normal eyes [150]. SIX6 is expressed in the developing retina, optic nerve, and other brain structures and involved in eye development [162, 163].

Table 3 Association between SNPs on the CDKN2BAS region and clinical manifestation

Study	Population	Association between SNPs and clinical manifestation
Ramdas et al. [150]	Caucasian	A glaucoma risk allele of rs1063192 is associated with larger VCDR in general population
Nakano et al. [143]	Japanese	rs523096: NTG (OR = 2.06, $p = 1 \times 10^{-8}$)/HTG (OR = 1.61, $p = 5.2 \times 10^{-4}$)
Burdon et al. [196]	Caucasian	rs7049105: NTG (OR = 1.61, $p = 4.47 \times 10^{-7}$)/HTG (OR = 1.32, $p = 0.0004$)
		POAG carrying risk alleles have larger VCDR and lower IOP
Dimasi et al. [161]	Caucasian	rs1063192: advanced POAG (OR = 1.6, $p = 2.2 \times 10^{-5}$)/non-advanced POAG (OR = 1.2, $p = 0.008$)
Wiggs et al. [146]	Caucasian	rs1063192: NTG (OR = 1.68, $p = 1.13 \times 10^{-11}$)/HTG (OR = 1.26, $p = 3.21 \times 10^{-5}$)
		rs2157719: exfoliation glaucoma (OR = 1.69, $p = 0.004$)/exfoliation only ($p = 0.54$)
Mabuchi et al. [148]	Japanese	rs1063192: NTG (OR = 1.8, $p = 0.0023$)/HTG (OR = 1.3, $p = 0.11$)
		POAG carrying glaucoma risk alleles at 9p21 have larger VCDR

VCDR Vertical cup-to-disc ratio

Table 4 Possible links between reported gene mutation and pathogenesis of POAG

Gene	Possible mechanism linked to pathogenesis of POAG
Myocilin (MYOC)	Mitochondrial dysfunction [59], failure to its secretion [61], excessive ER stress and mislocalization of mutant myocilin to peroxisomes [62–65], effect of mutations on TM cellular dysfunction and aqueous outflow which suggested by clinical manifestation [32–38]
Optineurin (OPTN)	Oxidative stress [95], the mitochondrial caspase-dependent cell death pathway [96], disruption of OPTN–Rab8 interaction and protein trafficking [85], Golgi body deformation and deteriorates intracellular traffic [197], secretory vesicle transport and decrease the release of the neurotrophic factor [197, 198] and prostaglandin E2 [197]
WD repeat domain 36 (WDR36)	Expression in ciliary body, trabecular meshwork, retina, and optic nerve [29], p53 stress-response pathway [112], decreased cell viability with disruption of STI1 [113], progressive retinal degeneration by mutant [114]
Tank-binding kinase 1 (TBK1)	Specific expression in human retinal ganglion cells [197], interaction with and phosphorylation to OPTN [130, 198], innate immune response and autophagy under conditions of infection [199]
Optic atrophy 1 (OPA1)	A causative gene for autosomal dominant optic atrophy [200–202] mitochondrial fusion and in cristae structural alteration during apoptosis [204, 205]
Toll-like receptor 4 (TLR4)	An increased expression in human glaucoma eyes [203], innate and adaptive immune responses [204], induction by up-regulated heat-shock proteins and oxidative stress [203]
S1 RNA binding domain 1 (SRBD1)	A part of RNA-associated proteins like polynucleotide phosphorylases which has a role in maintenance of mitochondrial homeostasis [205], inhibition of cell growth [206, 207], stimulation of proinflammatory cytokine production [208], and induction of apoptosis [209]
Cyclin-dependent kinase inhibitor 2B (CDKN2B)	Association the locus and VCDR in general population [150], involved in tumor suppression [210] and cell-cycle regulation cell cycle progression [211], up-regulation in response to elevated intraocular pressure [140], possible involvement in TGF-β pathway [151]
SIX homeobox 1 and SIX homeobox 6 (SIX1/SIX6)	Association with VCDR in normal eyes [150], expression in the developing retina and optic nerve, involvement in eye development [162, 163]
Caveolin 1 and caveolin 2 (CAV1/CAV2)	Expression in the trabecular meshwork and retinal ganglion cells [136] involvement in other neurodegenerative diseases [212, 213] possible interaction with synuclein family which is expressed in TM cells and participates in glaucomatous alterations [214–216]
Transmembrane and coiled-coil domains 1 (TMCO1)	Expression in the ciliary body, trabecular meshwork and retina [142], association with IOP [141]

TM Trabecular meshwork, *TGF* transforming growth factor, *IOP* intraocular pressure

In the GWAS reported by Wiggs et al. [146], the results demonstrate an association between Caucasian POAG and the CDKN2BAS and SIX1/SIX6 regions. The authors also report the presence of SNPs on chromosome 8q22 as novel susceptibility variants for NTG. The region is a gene desert, but may have regulatory functions for other genes.

Conclusions

Using genetic linkage or association studies, several genetic regions had been increasingly revealed. Some are involved in strong relations to specific phenotypes, such as early onset or elevated IOP. Some are associated with POAG irrespective of IOP and in normal phenotypic variation, such as VCDR, and not only with glaucomatous changes.

Genetic regions identified by linkage analysis are sometimes too large to enable a clear identification of the real causative genes, and susceptibility variants identified by association studies may only be markers on the genetic region. After identification of a genetic region, confirmation of reproducibility, identification of truly causative variants or genes, and evidence for functional involvement are needed. Possible links between these genes and glaucoma pathogenesis as reported here are summarized in Table 4; however, further investigation is required to clarify the precise contribution of these genes to the pathogenesis of glaucoma. The evidence provided by genetic studies is expected to improve current understanding of the etiology of glaucoma and facilitate the development of diagnostic and therapeutic strategies.

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