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GENETIC POLYMORPHISMS ASSOCIATED WITH PRIMARY OPEN-ANGLE GLAUCOMA: A SYSTEMATIC REVIEW

Batool Yahya Ali Asiri[1]*, Abdulrahman Mohammed A. Alamri[2]

[1] General Practitioner, College of Medicine, Taif University, Taif, Saudi Arabia
[2] Consultant Ophthalmologist, Department of Ophthalmology, King Khalid University, Abha, Saudi Arabia
*Corresponding Author: Batool Yahya Ali Asiri

ABSTRACT

Background: Primary Open-Angle Glaucoma (POAG) is the predominant type of glaucoma and causes irreversible blindness that is a major cause of blindness in the world. There is growing evidence that genetics is a crucial issue in the evolution and course of POAG. Consequently, it is necessary to synthesize the existing evidence to gain a better insight into the genetic architecture of POAG susceptibility.

Methodology: A systematic review was performed to find the studies that assessed genetic polymorphisms that were related to POAG. Eligible studies that examined genetic variants in patients with POAG were searched in electronic databases. These studies were case-control studies, mutation screening studies, and genome-wide association studies, which are all observational genetic association studies, whereas reviews and meta-analyses were excluded. Information obtained in the reviewed studies was in the form of study design, population of the study, sample size, genetic analysis procedures, genes under investigation, and results.

Findings: The review was comprised of 17 studies that were carried out in various regions. The majority of the studies involved case-control designs and involved the use of molecular methods including PCR-based genotyping, DNA sequencing or genome-wide SNP arrays to test genetic variants. The genes that were investigated included the established glaucoma-related genes, such as MYOC, OPTN, and WDR36, and the loci found in genome-wide research, such as CAV1/CAV2, CDKN2B-AS1, SIX1/SIX6, PLXDC2, and GAS7. A number of variants exhibited great relationships with POAG susceptibility specifically polymorphisms of MYOC, CDKN2B-AS1, CAV1/CAV2 and CAT genes.

Conclusion: The results of this systematic review show that POAG is affected by various genetic polymorphisms that influence a variety of biological pathways such as the structure of the optic nerve, vascular controls, and oxidative stress. Although some of the genes like MYOC and CDKN2B-AS1 seem to have important contributions in the susceptibility of the disease, the general genetic structure of POAG is not homogenous among populations.

INTRODUCTION

Glaucoma is a heterogeneous category of progressive optic neuropathies, which is accompanied by the degeneration of retinal ganglion cells and the related visual field defects [1,2]. Primary OpenAngle Glaucoma (POAG) is the most prevalent subtype of glaucoma in the world and a major cause of irreversible blindness [3]. The disease is normally marked by a wide anterior chamber angle, progressive atrophy of the optic nerve head and slow loss of visual fields that may be asymptomatic up to advanced stages [4]. Due to its insidious and chronic nature, it is important to identify the people at risk as early as possible to avoid permanent visual impairment [1]. The incidence of glaucoma is on the rise in the world as a result of the aging populations [5,6]. According to epidemiological estimates tens of millions of people are afflicted globally with a significant percentage of them having POAG [7,8]. Some of the risk factors that have been linked to the condition are high intraocular pressure, old age, African lineage, a history of glaucoma in the family, and some systemic diseases [9,10]. Nevertheless, these risk factors do not always result in the disease, which implies that genetic predisposition has a significant role in the pathogenesis of the disease [9].

In the last twenty years, the field of molecular genetics and genomic technologies have enhanced the knowledge on the genetic basis of POAG [11]. Various researchers have determined a number of susceptibility genes and loci linked to the disease [12]. Initial research efforts have identified mutations in genes like MYOC gene (myocilin), OPTN gene (optineurin) and WDR36 gene, which were first associated with familial type of glaucoma [13]. Later, extensive genomic studies have demonstrated other genetic variants linked to POAG vulnerability including polymorphisms in the CAV1 gene, CDKN2BplessAS1 gene, and SIX6 gene [14]. These findings indicate that POAG is a multidimensional disease with a complex nature which is affected by interplay of various genetic as well as environmental factors.

Due to the ever-growing body of genetic studies on POAG, it is imperative to synthesize the existing body of evidence to elucidate the most repeatable polymorphisms and their possible contribution to the pathogenesis of the disease. Systematic review of genetic polymorphisms linked to POAG can be used to bring together the results of different populations, determine gaps in the existing knowledge and to give a better insight into the molecular processes involved in glaucoma susceptibility. This kind of synthesis can also help to create better genetic screening methods and individual therapeutic interventions in the future.

METHODOLOGY

This systematic review was carried out to find and combine the published information on genetic polymorphisms related to Primary Open-Angle Glaucoma. The review was conducted in a systematic methodological fashion in accordance with the principles of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines to make the process of the study selection and reporting transparent and reproducible.

The extensive literature research was conducted in various electronic databases, such as PubMed, Scopus, Web of Science, Embase, and Cochrane Library. The databases were searched until the latest available records since the beginning of the databases. The search strategy was a combination of the relevant keywords and medical subject headings pertaining to genetic variations and glaucoma. Primary open-angle glaucoma, genetic polymorphism, genetic variants of genes, single nucleotide polymorphism, and genetic susceptibility were the key search terms. Manual screening of reference lists of the relevant articles and reviews was also carried out to detect other studies that could be overlooked in the electronic search.

The studies were selected to be included in the study on the basis of having conducted research on the relationship between genetic polymorphisms and the risk or susceptibility of primary open-angle glaucoma in human populations. They included observational studies like case control studies, cohort studies and genome wide association studies. The exclusion criteria were that the studies had to be a review article, editorial, conference abstracts without text, animal study, or the study had not reported genetic polymorphism data specifically concerning primary open-angle glaucoma. Articles that were not published in the English language or those that had inadequate methodological information were also omitted.

The process of the selection was conducted in a number of steps. To begin with, all articles that were retrieved were screened in terms of titles and abstracts in order to identify potentially useful studies. The entire text of the eligible articles was then analyzed to establish their appropriateness based on the established inclusion and exclusion criteria. Before the screening process, duplicate studies that were retrieved in other databases were identified and eliminated. Any difference in selection of study was sorted out by re-evaluation of the study eligibility criteria.

A structured data collection form was used to extract the data. Each included study was analyzed to extract relevant information which included the name of the first author, the year of publication, the country of study, the study design, the sample size, the population characteristics, the genes or polymorphisms under investigation, and the key reported results in the relationship between genetic variants and primary open-angle glaucoma. Reviewed data were checked thoroughly to make sure that the data were accurate and consistent across the studies included.

The quality of methodology of the studies included was determined by the Newcastle-Ottawa Scale of observational studies. This instrument was used to assess the quality of studies on three major areas: selection of study participants, comparability of study groups and exposure or outcome assessment. A score was allocated to each of the studies based on pre-established criteria, which made it possible to classify the studies as low, moderate, or high in terms of their methodological quality.

The synthesis of the findings was done in a descriptive manner after the selection of the studies and extraction of the data. Since the populations of the studies, genes that were investigated, and the outcomes were reported in a heterogeneous manner, the results were summarized in a narrative form and displayed in tables to make comparisons across studies. The synthesis was aimed at finding the generally reported genetic polymorphisms with primary open-angle glaucoma and the patterns or variations that can be seen in various populations.

RESULTS

The 17 studies (Figure 1, [15-31]) that were included that examined genetic polymorphisms relating to primary open-angle glaucoma were carried out in varied geographical locations, such as Asia, Middle East, Europe, North America, South America, and African ancestry populations. The majority of the studies followed a case-control design with the comparison of the patients with primary open-angle glaucoma to the healthy control groups, whereas fewer studies utilized mutation screening, genome-wide association studies (GWAS), or targeted genetic sequencing. The size of the samples was also significantly different, with small cohorts of under 30 patients sequenced being used in studies to larger genomic data sets of over 400,000 participants in population-based biobanks.

In the literature, age of the study participants generally mirrored the demographic profile of glaucoma with the majority of cohorts comprised of middle-aged or older adults, although some studies had wider age ranges or not given detailed demographic information. The percentage of males reported to have participated ranged between

about 40 and 78 percent indicating a fairly balanced sex composition in most cohorts [15,16,20,22,23]. Genetic analysis methods were also quite diverse in accordance with the design of the study and time. Previously, the most common methods of genotyping and screening of mutations were polymerase chain reaction (PCR)-based techniques, whereas the most recent studies used genome-wide SNP arrays, next-generation sequencing, and large-scale GWAS techniques [20,21,24,26].

The genes studied represented a wide range of biological processes that are involved in the pathogenesis of glaucoma. Some of the studies reported on well-established glaucoma susceptibility genes like MYOC, OPTN and WDR36, whereas others reported loci found in genome-wide studies, including CAV1/CAV2, CDKN2B-AS1, SIX1/SIX6, PLXDC2 and GAS7 [15-31]. Other studies investigated genes in vascular regulation, oxidative stress, and neuronal survival, such as MTHFR, CAT, and mitochondrial DNA variants, which is multifactorial in the development of glaucoma [18,27,28]. Massive genomic studies also increased the list of candidate loci, with several genes linked to ocular phenotypes and glaucoma susceptibility among various groups [24-26] (Table 1).

Table 1. General Characteristics of Included Studies and Patient Populations

Author	Year	Country / Population	Study Design	Sample Size	Age	Male	Genetic Analysis Method	Investigated Genes
Derakhshan et al. [15]	2019	Iran	Case–control	70 POAG / 70 controls	POAG: 56.7 ± 18.6; Control: 27.2 ± 6.9	POAG: 75.1%, Control: 50%	PCR-SSCP	MYOC
Li et al.[16]	2009	China	Case–control	176 POAG / 200 controls	POAG: 38.92±16.33; Control: 69.41±5.97	POAG: 78.4%: Control: 75%	SNP genotyping	MYOC, OPTN, WDR36, APOE
Kumar et al. [17]	2007	India	Mutation screening	251 POAG	45-65	NR	DNA sequencing	CYP1B1, MYOC, OPTN, OPTC
Abu-Amero et al.[18]	2006	Saudi Arabia	Genetic sequencing	27 POAG	57.9 ± 10.7	62.9%	mtDNA sequencing	MYOC, OPTN, mitochondrial genes
López-Martínez et al.[19]	2007	Spain	Case–control	110 POAG / 98 controls	POAG: 62.2±11.4 ; Control:61.1±12.6	POAG:51.8% ; Control:48.9%	PCR genotyping	MYOC, OPTN
Loomis et al. [20]	2014	USA	Case–control	976 POAG / 1140 controls	POAG: 63.6±9.8; Control: 65.5±9.2	POAG: 42%; Control: 40%	SNP genotyping	CAV1, CAV2
Burdon et al. [21]	2012	USA	Case–control	1432 POAG / 595 controls	POAG: 62.4±10	POAG: 46.8%	Genome-wide SNP arrays	CDKN2B-AS1
Nunes et al.[22]	2018	Brazil	Case–control	310 POAG / 247 controls	POAG: 67 ± 13; Control: 69 ± 8	POAG: 47.7%; Control: 69.4%	PCR genotyping	CAV1, CDKN2B-AS1
Eliseeva et al.[23]	2021	Russia	Case–control	208 POAG / 396 controls	POAG: 69.80±8.61 ; Control: 62.02±11.54	POAG: 43.8%; Control:44.4%	SNP analysis	CDKN2B-AS1

Hauser et al. [24]	2019	African ancestry populations	GWAS	2320 POAG / 2121 controls	African ancestry populations	NA	Genome-wide genotyping	Multiple loci
Chen L et al. [25]	2025	Hong Kong / China	Case–control genetic association with multi-center cohorts	POAG cases and controls from Hong Kong, Shantou, and Chengdu cohorts (exact numbers not specified)	Adults >30 years; children cohort included for phenotype analysis	Not reported	Targeted candidate gene sequencing and SNP genotyping	FOXC1, SPRED2/MIR4778, FNDC3B, AFAP1, LMX1B, CASC20, GAS7, TLCD5/ARHGEF12/TMEM136, ABCA1, MYOC, OPTN, WDR36, NTF4 and other GWAS-identified genes
Jin H et al. [26]	2025	UK Biobank (European population)	Genome-wide association study with Mendelian randomisation	459,195 participants (98,661 with ocular phenotypes)	Mean age: 56.76 years	45.7%	GWAS with gene-based analysis and Mendelian randomisation	CEP85L, GRIA4, GRIN2A, LRFN5, MAGI1, POU6F2, RBFOX1, RBMS1, RBMS3, RBPMS, TRHDE, TUBB3, ZFHX3, ZMAT4
Kaswal et al. [27]	2025	Jordan	Case–control	89 POAG / 94 controls	POAG: 58.73 ± 9.47; Control: 59.26 ± 10.39	POAG: 57.3%, Control: 58.5%	PCR-RFLP and ELISA for homocysteine	MTHFR (C677T)
Gong et al. [28]	2018	China	Case–control	416 POAG / 997 controls	Not reported	Not reported	SNaPshot SNP genotyping	CAT (rs769217, rs1001179, rs7943316)
Kondkar et al. [29]	2018	Saudi Arabia	Case–control	92 POAG / 94 controls	Not reported	Not reported	TaqMan SNP genotyping assay	SIX1/SIX6 locus (rs10483727)
Kondkar et al. [30]	2017	Saudi Arabia	Case–control	92 POAG / 95 controls	Not reported	Not reported	TaqMan SNP genotyping assay	GAS7 (rs11656696)
Mabuchi et al. [31]	2017	Japan	Case–control	417 POAG / 244 controls	POAG: 63.4 ± 14.3; Control: 67.7 ± 11.2	Not reported	SNP genotyping	ZP4 (rs547984), PLXDC2 (rs7081455), TMTC2 (rs7961953)

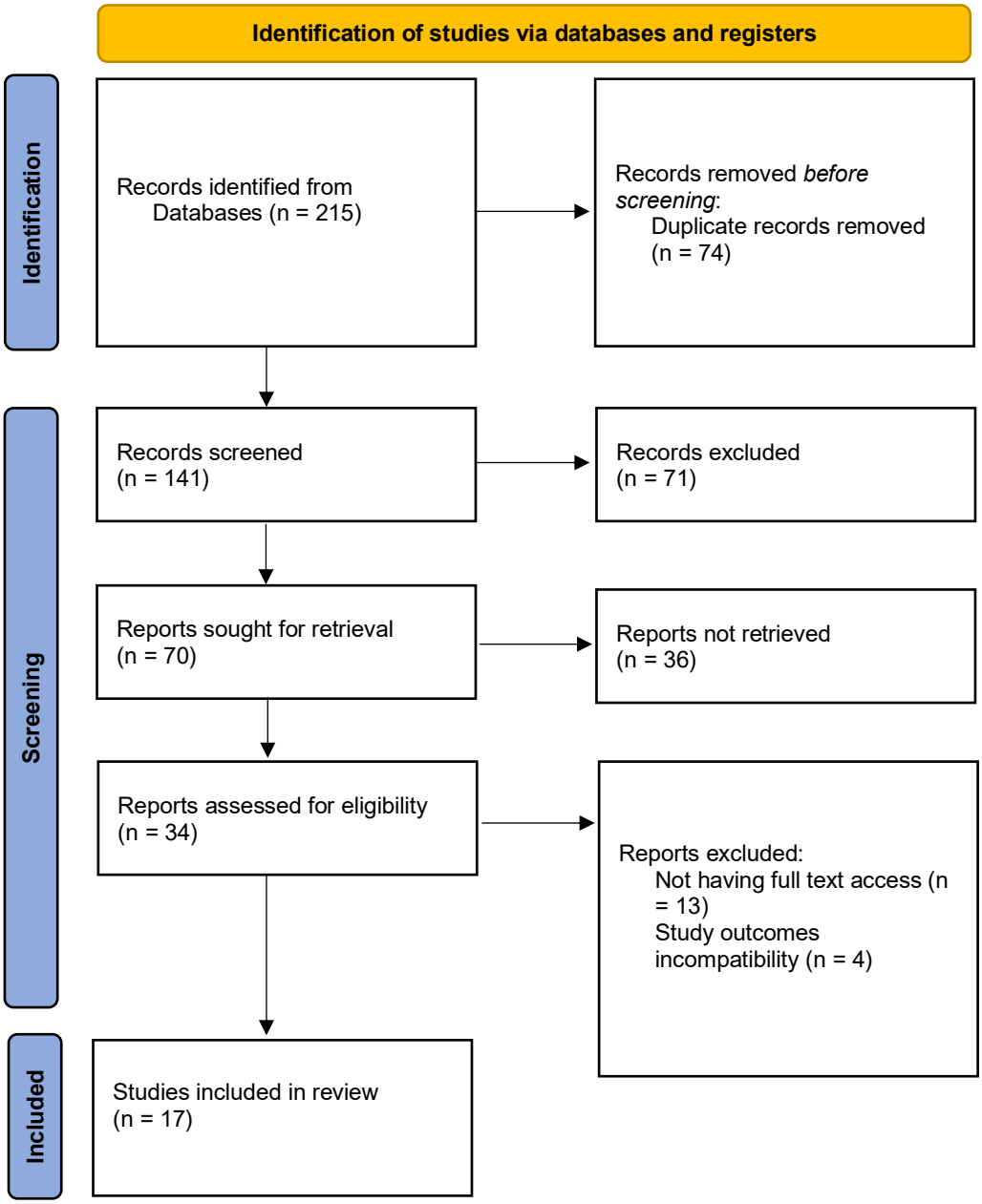

Figure 1: PRISMA flow for including studies

In general, the articles included showed a high level of heterogeneity in the genetic variants studied and their reported associations with primary open-angle glaucoma. Some of the genes were significantly associated with the disease susceptibility in many populations. Specifically, the mutations in MYOC were noted as prevalent contributors to glaucoma risk with one of the studies reporting mutant allele frequencies as significantly higher in the patients compared to the controls (40% vs. 11.5%; OR 5.1, 95% CI 2.1-12.4) [15]. Nevertheless, additional studies proposed that the prevalence of MYOC mutations in patients is relatively low, which means that they are a part of a larger genetic architecture of the disease [17,19].

Association studies of the genome-wide and candidate genes showed that there are other loci associated with the risk of glaucoma. Differences in CAV1/CAV2 were linked to high susceptibility, which contributes to the role of caveolin-mediated signaling pathways in glaucoma pathophysiology [20]. Equally, polymorphisms of CDKN2B-AS1, which is at chromosome 9p21, were associated with the risk and severity of the disease, especially when it comes to optic nerve damage [2123]. Massive genomic studies also characterized new loci linked with the ocular phenotypes and glaucoma susceptibility, such as genes that are related to neuronal signaling, vascular control, and optic nerve functionality [24,26].

Other papers examined the polymorphism of genes related to metabolic and oxidative stress pathways. The MTHFR C677T type was found to have a potential role in glaucoma susceptibility and was linked to high plasma homocysteine levels [27] and a polymorphism in the antioxidant gene CAT was found to be significantly associated with glaucoma risk, indicating that oxidative stress could have a role in the pathogenesis of glaucoma [28]. There were also genetic variations in developmental and neuronal genes, such as SIX1/SIX6 and PLXDC2, which were strongly related to the susceptibility to the disease or the level of intraocular pressure in some populations [29,31]. Conversely, other variants studied like GAS7 rs11656696 were not significantly associated with the risk of glaucoma [30]. All these results together contribute to the idea that primary open-angle glaucoma is a genetically complex disease that is conditioned by a variety of susceptibility sites and biological mechanisms (Table 2).

Table 2. Outcomes and Main Findings

Author	**Primary Outcome**	**Genetic Variant Investigated**	**Statistical Association**	**Main Findings**
Derakhshan et al.[15]	POAG susceptibility	MYOC exon variants	POAG: 40% vs Control: 11.5%; OR: 5.1 (95% CI: 2.1 to 12.4, P< 0.001)	Mutant MYOC alleles significantly increased glaucoma risk.
Li et al.[16]	Gene–gene interaction	MYOC, OPTN, WDR36, APOE SNPs	No significant difference was detected between POAG cases and controls in the genotypic or allelic frequencies	Combined gene interactions contributed to disease risk.
Kumar et al.[17]	Mutation prevalence	CYP1B1, MYOC, OPTN	Rare mutations detected	Only ~3.6% of POAG patients carried mutations.
Abu-Amero et al.[18]	Genetic mutations	mtDNA variants	Observational association	Mitochondrial mutations suggested role in optic nerve degeneration.
López-Martínez et al.[19]	POAG genetic risk	MYOC variants	No significant association	MYOC mutations detected in small proportion of cases.OPTIN is not involved in POAG.
Loomis et al.[20]	POAG susceptibility	CAV1/CAV 2 SNPs	Significant association; OR=1.26, 95% CI: 1.16-1.38	Caveolin gene variants linked with glaucoma risk.
Burdon et al. [21]	Disease severity	CDKN2B-AS1 SNPs	Glaucoma risk alleles at 9p21, particularly, rs7049105 and rs10120688, were associated with the presence of both NTG and advanced POAG.	Variants associated with optic nerve damage severity.
Nunes et al.[22]	Genetic susceptibility	CDKN2B-AS1	heterozygous genotype (G/A) of rs2157719 is more frequent in control group; OR: 0.52, CI 95%: 0.36–0.75	Polymorphism significantly increased POAG risk in Brazilians.
Eliseeva et al.[23]	Risk haplotypes	CDKN2B-AS1 haplotypes	studied SNPs were associated with POAG (OR = 3.99, pperm = 0.001)	Specific haplotypes increased POAG risk (AAAGG of loci rs1063192-rs7865618-rs2157719-rs944800-rs4977756).
Hauseret al. [24]	Genetic association	APBB2 locus	Minor C allele was observed to be associated with increased risk of POAG; OR = 1.32, 95% CI, 1.20-1.46, P<0.0001.	Risk allele increased POAG susceptibility in African ancestry populations.

Chen L et al. [25]	Genetic susceptibility and genotype–phenotype correlation in POAG	SNP rs2745572 (FOXC1), rs4414666 (SPRED2/MIR4778), rs62283813 (FNDC3B), rs938604 (AFAP1), rs3829849 (LMX1B), rs2326788 (CASC20)	FOXC1 rs2745572: OR=0.73, P<0.001; SPRED2/MIR4778 rs4414666: OR=1.18, P=0.023; FNDC3B rs62283813: OR=1.22, P=0.032	Multiple SNPs across GWAS-identified loci were associated with POAG risk and intraocular pressure. FOXC1 variant showed a protective effect and was associated with lower IOP.
Jin H et al. [26]	Genetic association between ocular perfusion pressure and POAG	Multiple loci including MAGI1, ZFHX3, TRHDE, ZMAT4, LRFN5, RBFOX1, GRIN2A, RBPMS	CH OR=0.998 (P<0.001); CRF OR=0.998 (P<0.001); MOPP OR=0.998 (P<0.001); IOP OR=1.002 (P=0.009)	Identified 14 genetic loci associated with ocular phenotypes and POAG. Mendelian randomisation analysis indicated that mean ocular perfusion pressure (MOPP) may have a causal role in POAG development, supporting the vascular theory of glaucoma pathogenesis.
Kaswal et al. [27]	Association of MTHFR polymorphism and homocysteine levels with POAG	MTHFR C677T (CC, CT, TT genotypes)	CT OR=1.38 (95% CI: 0.98–1.95); TT OR=1.21 (95% CI: 0.87–1.88); T allele OR=1.53 (95% CI: 0.97–2.49)	Elevated plasma homocysteine levels were significantly higher in POAG patients. MTHFR C677T polymorphism showed a potential contribution to POAG susceptibility in the Jordanian population.
Gong et al. [28]	Association between antioxidant gene polymorphisms and POAG	CAT rs769217	OR=1.27 (95% CI: 1.08–1.49; P=0.004)	CAT rs769217 variant was significantly associated with POAG risk, suggesting oxidative stress may contribute to disease pathogenesis.
Kondkar et al. [29]	Genetic association with POAG susceptibility	SIX1/SIX6 rs10483727	C allele OR=0.58 (95% CI: 0.38–0.89; P=0.013); T allele OR=1.7 (95% CI: 1.11–2.58; P=0.013)	The T allele increased susceptibility to POAG, while the C allele demonstrated a protective effect in the Saudi population.
Kondkar et al. [30]	Association of GAS7 polymorphism with POAG	GAS7 rs11656696	OR=0.76 (95% CI: 0.50–1.16; P=0.214)	No significant association was identified between GAS7 polymorphism and POAG risk or clinical indices such as IOP and cup-to-disc ratio.
Mabuchi et al. [31]	Association of previously reported POAG variants with disease phenotype	PLXDC2 rs7081455	OR=1.52 (95% CI: 1.14–2.01; P=0.0042)	The PLXDC2 rs7081455 G allele increased POAG risk and was associated with higher intraocular pressure in Japanese patients.

The quality of the methodology of the included studies was evaluated with the help of the Newcastle-Ottawa Scale. In general, the majority of studies proved to be of moderate to high methodological quality with total scores of 4 to 9. A number of large-scale genetic association studies received high-quality ratings and low risk of bias, especially those that used genome-wide association methods and large population-based cohorts, which received the highest possible score in the selection, comparability, and exposure domains [20,21,24–26,31]. Many case

control studies were of moderate quality because of the lack of control over potential confounding factors or the lack of reporting on exposure assessment, which created a moderate risk of bias [15,17,19,22,23,27-30]. It was only in one study that the methodological quality was relatively low and the risk of bias was higher, primarily because of small sample size and the lack of comparability between the study groups [18]. On the whole, the quality evaluation indicates that most of the studies had credible genetic association information, however, the inconsistency of the methodological rigor must be taken into account when the reported results are interpreted (Table 3).

Table 3. Quality Assessment and Risk of Bias of Included Studies (Newcastle–Ottawa Scale)

Author	Selection (4)	Comparability (2)	Exposure/Outcome (3)	Total Score	Quality Level	Risk of Bias
Derakhshan et al. [15]	3	1	2	6	Moderate	Moderate
Li et al. [16]	4	1	2	7	Good	Low
Kumar et al. [17]	3	0	2	5	Moderate	Moderate
Abu-Amero et al. [18]	2	0	2	4	Low	High
López-Martínez et al. [19]	3	1	2	6	Moderate	Moderate
Loomis et al. [20]	4	2	3	9	High	Low
Burdon et al. [21]	4	2	3	9	High	Low
Nunes et al. [22]	3	1	2	6	Moderate	Moderate
Eliseeva et al. [23]	3	1	2	6	Moderate	Moderate
Hauser et al. [24]	4	2	3	9	High	Low
Chen L et al. [25]	4	2	3	9	High	Low
Jin H et al. [26]	4	2	3	9	High	Low
Kaswal et al. [27]	3	1	2	6	Moderate	Moderate
Gong et al. [28]	3	1	2	6	Moderate	Moderate
Kondkar et al. [29]	3	1	2	6	Moderate	Moderate
Kondkar et al. [30]	3	1	2	6	Moderate	Moderate
Mabuchi et al. [31]	4	1	3	8	High	Low

DISCUSSION

This was a systematic review of the evidence provided by various genetic association studies on polymorphism associated with Primary Open-Angle Glaucoma (POAG) in different populations. The results all point to a complex and multifactorial genetic framework of POAG, which includes rare mutations, as well as common polymorphisms, which affect the susceptibility of the optic nerve, the regulation of intraocular pressure and neurodegenerative mechanisms. The findings of the studies included are generally in line with the findings of already published systematic reviews and meta-analyses, which underline that the susceptibility to glaucoma depends on a number of genetic loci in the interaction with environmental and vascular risk factors [11,32]

MYOC (myocilin) is one of the most common genes studied in the genetics of glaucoma [33]. Some of the studies incorporated in this review found that some patients with POAG had mutations in the MYOC but the frequency of these mutations was significantly different across populations. These findings are in line with the past systematic reviews that show that MYOC mutations do not explain a large percentage of POAG cases but still are one of the most established monogenic causes of the disease [34]. A meta-analysis of published reports on MYOC

mutations found that the overall penetrance of glaucoma of the MYOC type is about 60 percent with a higher penetrance with age and a wide range of penetrance depending on the type of mutation and ethnicity [35]. This fact can be used to justify the idea that MYOC mutations are significant yet relatively minor factors in the overall genetic environment of POAG.

In addition to MYOC, a number of the included studies have examined the polymorphisms in the OPTN, WDR36, and CYP1B1 that have been previously reported in relation to optic nerve degeneration and glaucoma susceptibility. Even though there were inconsistent associations between these genes and individual studies, past reviews indicate that the genes play a role in disease risk, but they do so by gene-gene interaction, instead of being causative variants on their own. Genetic research has demonstrated that the interplay between these loci could be involved in pathways that regulate retinal ganglion cell apoptosis and optic nerve head remodelling, and that polygenic mechanisms are important in the pathogenesis of glaucoma [36-38].

Genome-wide association has significantly advanced the knowledge on glaucoma genetics by revealing locus of susceptibility beyond the conventional candidate genes []39. In the current review, variants in CAV1/CAV2, CDKN2B-AS1 and others were often found to be linked to POAG susceptibility. These results are in agreement with other meta-analyses that have shown a strong association between CDKN2B-AS1 polymorphism and glaucoma susceptibility [40]. Indicatively, a large meta-analysis of over 21,000 individuals has reported specific variants to pose a high risk of POAG including, but not limited to, rs4977756 and rs10120688, but other polymorphisms had a protective effect in some ethnic groups [14]. These findings indicate the high role of the chromosome 9p21 region in the susceptibility to glaucoma in various populations.

Experimental studies also examined the biological processes through which CDKN2B-AS1 variants are related to glaucoma [41]. There is evidence that this locus affects cellular senescence and extracellular matrix remodeling of the trabecular meshwork that could also cause aqueous humor outflow impairment and elevated intraocular pressure [42]. Functional studies have shown that changes in the CDKN2B/CDKN2B-AS1 regulatory network can facilitate aging of the trabecular meshwork cells and damage to the optic nerve, which further proves the pathogenic importance of the variants [40].

Besides structural genes in the physiology of optic nerve, some of the studies in this review also investigated polymorphisms associated with vascular and metabolic pathways. Differences in genes like MTHFR and CAT were also related to the high susceptibility to glaucoma in some groups of people. These results confirm the hypothesis that oxidative stress and vascular dysregulation have a role in glaucomatous optic neuropathy. Past reviews have proposed that oxidative stress may cause retinal ganglion cells and the trabecular meshwork to be damaged, thus making optic nerve degeneration faster and causing intraocular pressure to rise [43]. Equally, high homocysteine concentrations related to MTHFR polymorphs could also disrupt microvascular perfusion of the optic nerve head, which could also lead to the development of the disease [44].

In spite of the useful information given by these studies, there are a number of limitations that can be taken into account. Numerous candidate gene studies were done in relatively small groups which could reduce statistical power and raise chances of false-positive or inconsistent results. Also, study design, genotyping and diagnostic criteria heterogeneity can be a factor in discrepancies in reported associations. Past systematic reviews have also identified the same methodological issues in glaucoma genetic research, and the importance of larger multicenter studies and cross-population replication.

CONCLUSION

In conclusion, the results of this review confirm the accumulating evidence that POAG is a genetic heterogeneous disease that is affected by a variety of susceptibility genes and biological pathways. Rare mutations in genes like MYOC and common polymorphisms discovered due to genome-wide research are all associated with the risk of the disease. Further studies that combine genomic, transcriptomic and functional studies will be necessary to explain the biological pathways between these genetic variants and optic nerve degeneration and may help to determine therapeutic agents that can be used to prevent and treat glaucoma.

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