Primary open angle glaucoma genetics: The common variants and their clinical associations (Review)

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Abstract. Glaucoma is a group of progressive optic neuropathies that have in common characteristic optic nerve head changes, loss of retinal ganglion cells and visual field defects. Among the large family of glaucomas, primary open-angle glaucoma (POAG) is the most common type, a complex and heterogeneous disorder with environmental and genetic factors contributing to its pathogenesis. Approximately 5% of POAG is currently attributed to single-gene or Mendelian forms of glaucoma. Genetic linkage analysis and genome-wide association studies have identified various genomic loci, paving the path to understanding the pathogenesis of this enigmatic, blinding disease. In this review we summarize the most common variants reported thus far and their possible clinical correlations.

Contents

1. Introduction

Glaucoma represents a group of chronic and progressive optic neuropathies with distinctive pattern of progressive visual field loss and optic disc damage, and is the leading cause of irreversible blindness worldwide. This enigmatic and heterogeneous disease has affected 3.5% of the world's population with approximately 5.7 million people visually impaired and 3.1 million blind, and an estimate to affect 111.8 million people by 2040 (1). Primary open-angle glaucoma (POAG), the most common representative, is characterized by a normal, open anterior chamber angle and elevated intraocular pressure (IOP) or even normal IOP, named normal tension glaucoma (NTG). Two hallmark theories attempt to explain the pathway of the disease; the mechanical and vascular theory. Although both present postulated mechanisms of progressive retinal ganglion cell (RGC) damage and eventual optic neuropathy, the exact etiology still remains unknown (2). The well recognised risk factors for POAG include higher age, high IOP, decreased central corneal thickness (CCT), African descent, high myopia and a positive family history (3,4). Amongst them, high IOP remains the only modifiable risk factor for the development and prognostic factor for the progression of POAG (3).

POAG has long shown a strong genetic component with 60% of patients with a positive family history and family based studies identifying a 10-fold increased risk of POAG for first degree relatives (5). Heritability of POAG can be divided into two major categories: direct association (increased POAG risk) and indirect (increased risk for a component of the disease). The first one deals with several genes linked to POAG through family-based genetic linkage analysis, with major examples being myocilin (MYOC), optineurin (OPTN), WD repeat domain 36 (WDR36), cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1) and neurotrophin 4 (NTF4) (6-10). With heritability ranging from 0 (no genetic component) to 1 (phenotype determined by genes), these genes attribute to POAG heritability at ~0.81 (11). The second factor refers to the endophenotype traits related to POAG pathogenesis, highly heritable and polymorphic. Notable examples are IOP (0.55), vertical cup-to-disc ratio (VCDR=0.48-0.66), CCT (0.72), cup area (CA=0.75) and disc area (DA=0.72) (12,13).

Genome-wide association studies (GWAS) have been used in the past decade in an attempt to uncover genetic variants of complex diseases. For POAG, over 70 single-nucleotide polymorphisms (SNPs) have been identified and linked to

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POAG or its endophenotypes, changing our understanding of the molecular pathways of the disease (14). Identification of the genes associated with the disease may also provide useful information for both patients and their physicians, by enabling the design of genetic screening tests that may help physicians assess the risk of patients for disease as well as to differentiate between clinically similar disorders. Valuable research available has provided details for many SNPs related to POAG. In this review the authors summarize the most common variants, present their possible clinical correlations and highlight their interactions.

2. Search strategy

A MEDLINE/PubMed search was performed for articles in English from January 2010 to January 2020. Keywords included glaucoma, primary open angle glaucoma, genetics, genetic association studies, GWAS and SNP. Further search was performed in the database upon relative findings in the articles.

3. Genomic loci

Genetic linkage analysis was the first genetic decoding of glaucoma. Classically used for Mendelian traits or mutations in a single gene, this method reveals chromosomal regions associated with a specific phenotype. Followed by GWAS in various populations, a number of variants and interactions unfolded, thus forming the complicated image of POAG. These genomic loci are marked GLC1A through GLC1P and show high heterogeneity (14,15) (Table I).

4. Common variants

Although a number of SNPs has been linked to POAG, those summarized in Table II, appear to be the most commonly studied in the literature.

MYOC/trabecular meshwork-induced glucocorticoid response protein (TIGR). Located on chromosome 1q24, *MYOC* encodes protein MYOC, which is believed to have a role in cytoskeletal function and represents the first gene to be associated with POAG (14). Mutations in *MYOC* (alternatively *TIGR*) are linked to the GLC1A locus (14,16). Over 100 POAG-associated mutations have been identified in the *MYOC* gene making it accountable for 3-5% of POAG cases (15). Primarily associated with juvenile-onset POAG, expresses an autosomal dominant and highly penetrant severe phenotype, with highly elevated IOP which often requires surgical management (10,17). A less severe form is observed in the adult onset form, the most prevalent one (10). Other associations include primary congenital glaucoma (18). The effect of *MYOC* mutations appears to be on the trabecular meshwork (TM) and aqueous humor outflow (19).

CYP1B1. Located on chromosome 2p22.2, CYP1B1 belongs to the cytochrome P450 superfamily of enzymes. Mutations in *CYP1B1*, although classically linked to anterior segment dysgenesis and congenital glaucoma, may also contribute to the GLC1A phenotype through a digenic inheritance, acting as a modifier for *MYOC* (20).

OPTN. Located on chromosome 10p13, *OPTN* encodes the coiled-coil containing protein OPTN that plays an important role in the maintenance of the Golgi complex, in membrane trafficking and exocytosis. Mutations in *OPTN* are linked to the GLC1E locus. Even though variable mutations have been recognised, E50K has been strongly linked to glaucoma (21). Primarily associated with NTG, it has also been reported in patients with amyotrophic lateral sclerosis (ALS) (22). A variety of interactions and cellular effects have been reported for *OPTN*, notably its role in autophagy and apoptosis (23,24). It has been reported that although *MYOC* overexpression has no effect on *OPTN* expression, *OPTN* overexpression upregulates endogenous *MYOC* in TM cells (25). Noteworthy, the most notable is the interaction of *OPTN* with TANK-binding kinase 1 (*TBK1*) as they may share a common pathway (23,26).

TBK1. Located on chromosome 12q14, mutations in TBK1 are linked to the GLC1P locus (10). Responsible for approximately 1% of NTG through a copy number variant (CNV) consisting of duplications in the *TBK1*, mutations have also been reported in patients with ALS and other central nervous system disorders (22,27,28). TBK1 is a kinase that regulates the expression of genes in the NF-κB signaling pathway, playing an essential role in regulating inflammatory responses to foreign agents and is also implicated in autophagy (29).

WDR36. Located on chromosome 5q22, *WDR36* encodes a member of the WD repeat protein family that is involved in T-cell activation. Mutations in *WDR36* are linked to the GLC1G locus (10). Linked to an increased risk for POAG, mutations in *WDR36* were initially reported to be responsible for 1.6 to 17% of POAG (8,30,31). *WDR36* appears to negatively affect TM cells via apoptotic cell death (32).

NTF4. Located on chromosome 19q13.33, *NTF4* encodes a neurotrophic factor that signals predominantly through the tyrosine kinase receptor B (TrkB) receptor tyrosine kinase. Mutations in *NTF4* are linked to the GLC1O locus. Negatively affecting the activation of TrkB, *NTF4* mutations have been found in 1.7% of POAG patients in a study of European patients (9).

Ankyrin repeat and SOCS box containing 10 (ASB10). Located on chromosome 7q36, *ASB10* encodes a protein that is a member of the ASB family of proteins. Mutations in *ASB10* are linked to the GLC1F locus (33). *ASB10* transcription appears to reduce aqueous humor outflow facility (34).

Atonal bHLH transcription factor 7 (ATOH7). Located on chromosome 10q21, *ATOH7* encodes a transcription factor that appears to play a role in the differentiation of the RGCs and determination of DA, possibly during embryogenesis. It is associated with DA, VCDR, CA and POAG risk (35,36).

Caveolin1/caveolin2 (CAV1/CAV2). Located on chromosome 7q31, CAVs are involved in a number of cellular processes such as transcellular transport, cell proliferation

Table I. Glaucoma genomic loci (GLC1A-P), candidate genes and locations and their associated glaucoma type.

Locus	Gene	Location	Glaucoma type
GLC1A	*MYOC*	1q24.3-q25.2	POAG/JOAG
GLC1B	-	2cen-q13	POAG, early onset
GLC1C	-	3q21-q24	POAG
GLC1D	-	8q23	POAG, early onset
GLC1E	*OPTN*	10p13	POAG/NTG
GLC1F	*ASB10*	7q36	POAG
GLC1G	*WDR36*	5q22	POAG
GLC1H	-	2p16-p15	POAG
GLC1I	-	15q11-q13	POAG
GLC1J	-	9q22	JOAG
GLC1K	-	20p12	JOAG
GLC1L	-	3p22-p21	POAG
GLC1M	-	5q22	JOAG
GLC1N	-	15q22-q24	JOAG
GLC1O	*NTF4*	19q13.3	POAG
GLC1P	Possibly *TBK1*	12q24	POAG

MYOC, myocilin; *OPTN*, optineurin; *ASB10*, ankyrin repeat and SOCS box containing 10; *WDR36*, WD repeat domain 36; *NTF4*, neurotrophin 4; *TBK1*, TANK-binding kinase 1.

Table II. Candidate genes and their possible association to glaucoma pathogenesis.

Gene	Location	Possible glaucoma mechanism/effect
MYOC/TIGR	1q24	TM, outflow[a]
CYP1B1	2p22.2	Anterior segment dysgenesis
OPTN	10p13	Autophagy, apoptosis
TBK1	12q14	Autophagy, inflammatory response
WDR36	5q22	TM via apoptosis
NTF4	19q13.33	Impaired neuronal survival
ASB10	7q36	Outflow
ATOH7	10q21	DA, VCDR, CA, POAG risk
CAV1/CAV2	7q31	IOP changes, outflow
CDKN2B-AS1	9p21	VCDR
SIX6	14q23	VCDR, myopia, reduced RNFL thickness
TMCO1	1q24.1	IOP changes, increased POAG risk
ABCA1	9q31	Inflammatory response, neurodegeneration
AFAP1	4p16.1	Unknown
ARHGEF12	11q23.3	IOP changes, outflow
TXNRD2	22q11	Oxidative stress
FOXC1	6p25.3	Anterior segment dysgenesis
ATXN2	12q24.12	Neurodegeneration
GAS7	17p13	CA, IOP changes
GALC	14q31.3	Increased POAG risk

[a]Outflow, aqueous humor outflow. TM, trabecular meshwork; DA, disc area; VCDR, vertical cup-to-disc ratio; CA, cup area; POAG, primary open angle glaucoma; RNFL, retinal nerve fiber layer.

and signal transduction (37). *CAV1* and *CAV2* are found to be expressed in ciliary muscle, TM, Schlemm's canal and retinal cells, and variants in the *CAV1/CAV2* region are associated with IOP changes, possibly through alterations of aqueous

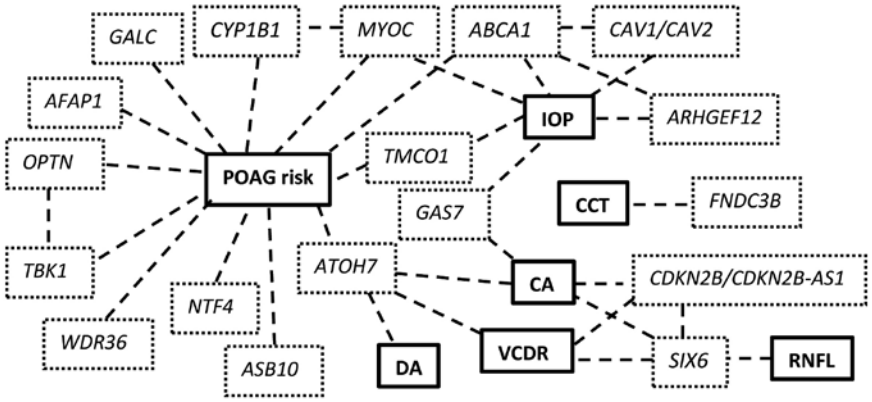

Figure 1. Common variants and their associations to POAG risk and/or endophenotypes and interactions. POAG, primary open-angle glaucoma; IOP, intraocular pressure; CCT, central corneal thickness; CA, cup area; DA, disc area; VCDR, vertical cup-to-disc ratio; RNFL, retinal nerve fiber layer.

outflow resistance (37-39). A possible direct, cell type specific interaction of *CAV1* with ATP-binding cassette, subfamily A, member 1 (*ABCA1*), also supports a possible role in POAG (40).

Cyclin-dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1). Located on chromosome 9p21, in the *CDKN2B-CDKN2A* gene cluster, *CDKN2B* protein is expressed in the inner nuclear layers of the retina and the ganglion cell layer. *CDKN2B-AS1* is detected in the retina, ciliary body and optic nerve and variants have been associated with VCDR changes and NTG especially in women, as well as various non-ocular disorders, namely myocardial infarction and intracranial aneurysms; an association of POAG risk and these conditions has not been made however (41-47).

Six homeobox 6 (SIX6). Located on chromosome 14q23, *SIX6* gene encodes homeobox proteins, critical for ocular development. The protein encoded by this gene is a homeobox protein that is similar to the *Drosophila* '*sine oculis*' gene product and is thought to be involved in eye development. Variants in this locus have been linked to POAG through VCDR, myopia and reduced retinal nerve fiber layer (RNFL) thickness. An interesting interaction of the POAG-risk His141 SIX6 variant with *CDKN2B-AS1* has been proposed as the former has been shown to elevate expression of the latter. A possibly protective Asn141 *SIX6* variant remains to be further observed (44,47,48-52).

Transmembrane and coiled-coil domains protein 1 (TMCO1). Located on chromosome 1q24.1, *TMCO1* encodes a transmembrane protein playing a key role in calcium homeostasis. It is expressed, among other ocular tissues, in the TM and retina. Sequence variants have been associated with IOP and increased POAG risk to a degree of 1.7-fold per risk allele, making it a significant quantitative trait (46,50,53-55).

ABCA1. Located on chromosome 9q31, *ABCA1* encodes a protein complex associated with extracellular and intracellular membrane transport. Although the locus is mainly associated with familial high-density lipoprotein deficiency and Tangier's disease, *ABCA1* is also expressed in numerous ocular tissues, namely TM, ciliary body and RGCs. Sequence variants have been linked to POAG and IOP, possibly through an inflammatory and neurodegenerative mechanism (56,57).

Actin filament-associated protein 1 (AFAP1). Located on chromosome 4p16.1, *AFAP1* encodes an adaptor protein that modulates changes in actin filament integrity in response to cellular signals. It is expressed, among others, in the retina and TM cells. Sequence variants have been associated with POAG through a still unknown mechanism (41,57).

RHO guanine nucleotide exchange factor 12 (ARHGEF12). Located on chromosome 11q23.3, *ARHGEF12* encodes a guanine nucleotide exchange factor (GEF) that may form a complex with G proteins and stimulate Rho-dependent signals. An intronic variant has been associated with POAG and IOP, possibly through activation of RhoA and subsequent ROCK activation, leading to decreased outflow and elevated IOP. An interesting interaction is that with *ABCA1* protein, with *ARHGEF12* preventing *ABCA1* degradation (58-60).

Thioredoxin reductase 2 (TXNRD2). Located on chromosome 22q11, *TXNRD2* gene encodes a mitochondrial protein important for scavenging reactive oxygen species in mitochondria. It belongs to the family of flavoenzymes that catalyze redox reactions, thus controlling the levels of reactive oxygen species. *TXNRD2* is found, among others, in the retina and optic nerve and sequence variants have been associated with POAG, possibly through a protective effect of *TXNRD2* against oxidative stress of the RGCs (41,61,62).

Forkhead box C1 (FOXC1). Located on chromosome 6p25.3, *FOXC1* is found next to GDP-mannose 4,6-dehydratase (*GMDS*) gene. It encodes a protein that has been shown to play a role in the regulation of embryonic and ocular development. Although mainly linked to anterior segment dysgenesis and Axenfeld-Rieger syndrome, sequence variants within the *GMDS* gene as well as variants located upstream of *FOXC1* have been associated with POAG (41,57).

Ataxin 2 (ATXN2). Located on chromosome 12q24.12, *ATXN2* is involved in regulating mRNA translation through its interactions with the poly (A)-binding protein. It is also involved in the formation of stress granules and P-bodies, which also play roles in RNA regulation (63). *ATXN2* is expressed, among others, in the ciliary body, retina, and optic nerve. Although mainly linked to spinocerebellar ataxia and ALS, variants in

ATXN2 have been associated with POAG possibly through neurodegeneration (41,64).

Growth arrest-specific 7 (GAS7). Located on chromosome 17p13, *GAS7* encodes a protein that plays a putative role in neuronal development as well as maturation and is primarily expressed *in vivo*, in terminally differentiated brain cells. *GAS7* has been associated with increased cup volume and IOP (47,54,55,65).

Galactosylceramidase (GALC). Located on chromosome 14q31.3, GALC encodes a lysosomal enzyme called galactosylceramidase, which is mainly linked to Krabbe disease, a rare disorder of the myelin sheath with progressive optic neuropathy. *GALC* has been associated with a 5-fold increased risk of POAG when heterozygous for a CNV deletion (66,67).

5. Additional genes associated with POAG

Single SNPs in the *MYOC*, *COL8A2*, *COL1A1* and *ZNF469* gene regions have shown marginal association with POAG in a study conducted in South Africa (68). Although the number of the subjects enrolled in the study was small, it was demonstrated that the main POAG-associated susceptibility alleles found in other populations, play a reduced role in populations of African ancestry. Moreover, a GWAS performed in India identified a novel candidate gene for POAG, called membrane palmitoylated protein 7 (*MPP7*), which is dysregulated under cyclic mechanical stress in the TM, thus causing dysfunction of cell to cell interaction (69), while another study in India led to an novel association of POAG with Opticin (*OPTC*) gene (70).

6. Endophenotypes and clinical association

Endophenotypes are stable, heritable quantitative traits, disease independent, that are usually helpful in analysing heterogeneous or variably phenotypic diseases. For POAG, these traits include IOP, CCT, VCDR, DA and RNFL thickness and as mentioned, contribute separately in the heritability of the disease (14). Studying the Endophenotypes helped dissect the disease and focus on separate components that are linked to clinical practice; nonetheless the variety of POAG endophenotypes highlights the complexity of the disease (Fig. 1).

IOP. Independent of the genetic component, IOP remains the only modifiable risk factor and IOP reduction the most commonly used treatment of POAG. Of the aforementioned genetic variants, *TMCO1*, *CAV1/CAV2*, *ARHGEF12*, *ABCA1* and *GAS7* have been linked to IOP through GWAS, among other susceptibility loci (43,54,55). Of great interest is that the combined heritability of these loci regarding IOP is less than 2%, meaning that the majority is still to be explained (55). This observation could mean that further investigating the IOP endophenotype could clarify its role in glaucoma both as a contributing factor and a therapeutic target.

CCT. Well recognized as an independent risk factor for POAG, over 26 loci have been identified for CCT (3,71). With a highly heritable trait, CCT shows association with ethnicity, with lower values in populations of African descent (11,72). Of the many sequence variants identified for CCT, of interest is fibronectin type III domain-containing protein 3B (*FNDC3B*) which appears to be involved also in IOP changes (71).

VCDR. Increased VCDR is one of the cardinal clinical signs of glaucomatous optic neuropathy. Of the above mentioned genetic variants, *ATOH7*, *CDKN2B-AS1* and *SIX6* have been linked to VCDR, among other susceptibility loci (73,74).

DA and CA. For DA 14 loci have been identified, 5 of which are also associated with VCDR. Of these, perhaps the most interesting is *ATOH7*, associated with DA, CA and VCDR, that appears to affect the differentiation of the RGCs (35,73,74). Approximately 27 variants have been associated with CA, notably *ATOH7*, *CDKN2B-AS1* and *SIX6* which, as mentioned previously, have also been linked to VCDR (49,75).

RNFL. Two susceptibility loci have been identified for RNFL thickness through linkage analysis. As previously discussed, a *SIX6* coding variant is one of them (51,76).

7. Conclusion

Since the turn of the century there has been an explosion of research using genetic and next generation, high-throughput DNA sequencing technologies and it is unquestionably expected that they will be extensively employed also for further investigation and diagnosis of glaucoma. We aimed to present the basic role of the most studied sequence variants regarding POAG and their complex interaction. Although many more have been identified and many remain to be further clarified, linkage analysis initially and, recently, GWAS, have opened the road to the admittedly enigmatic and heterogenic disease that is POAG. As regards the issue of genetic counselling, genetic testing for glaucoma may obviously be helpful in some specific situations, such as screening of family members with a known genetic mutation in autosomal dominant POAG of early onset, although at a population level this is not presently justified (77).

With various components and differential clinical expression, the identification of genetic factors either directly linked to the disease or endophenotype-related, brings us closer to understanding the molecular and cellular mechanisms and, eventually, to the development of efficient therapeutic approaches targeted at the root cause of the condition.

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Authors' contributions

AT, ETD, GNG, DAS and MIZ conceived and designed the study. AT, GNG and ETD researched the literature, performed critical analysis and review of the literature and drafted the manuscript. DAS and MIZ critically revised the article for important intellectual content. All authors read and approved the final manuscript.

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Patient consent for publication

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Competing interests

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