



Published in final edited form as:

Exp Eye Res. 2017 July ; 160: 62–84. doi:10.1016/j.exer.2017.05.002.

Major review: Molecular Genetics of Primary Open-Angle Glaucoma

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Abstract

Glaucoma is a leading cause of irreversible blindness worldwide. Primary open-angle glaucoma (POAG), the most common type, is a complex inherited disorder that is characterized by progressive retinal ganglion cell death, optic nerve head excavation, and visual field loss. The discovery of a large, and growing, number of genetic and chromosomal loci has been shown to contribute to POAG risk, which carry implications for disease pathogenesis. Differential gene expression analyses in glaucoma-affected tissues as well as animal models of POAG are enhancing our mechanistic understanding in this common, blinding disorder. In this review we summarize recent developments in POAG genetics and molecular genetics research.

Keywords

glaucoma; POAG; GWAS; linkage; association; differential expression; genetics; endophenotype

1. Introduction of Primary Open-Angle Glaucoma

Glaucoma is a heterogeneous group of optic neuropathies that are characterized by the progressive loss of retinal ganglion cells (RGC), optic atrophy, and visual field loss (Allingham et al., 2009; Allingham and Shields, 2011). Glaucoma is the most common cause of irreversible blindness that affects more than 70 million people worldwide (Quigley, 2011; Quigley and Broman, 2006; Tham et al., 2014). Primary open-angle glaucoma (POAG) is the most common type of glaucoma that is defined by characteristic glaucomatous retinal, optic nerve, and clinical findings without an identifiable secondary cause. Risk factors for POAG include increasing age, elevated intraocular pressure (IOP), and a positive family history. POAG has been identified in all populations studied to date. The prevalence of POAG varies between populations, but is notably more common in

persons of African and Hispanic descent (Budenz et al., 2012a; Budenz et al., 2012b; Chopra et al., 2008; Emanuelli et al., 2005; Memarzadeh et al., 2010; Quigley et al., 2001; Rodriguez et al., 2002; Tielsch et al., 1991). Elevated IOP is arguably the most important risk factor for developing POAG, and is often used to categorize patients into “high” or “normal” tension subtypes (HTG or NTG, respectively). While a cut-off between HTG and NTG may be useful for clinical or research purposes, the specific threshold (≥ 22 mmHg or ≥ 21 mmHg) is arbitrary. IOP is the only modifiable risk factor that is lowered with medications or surgeries to treat glaucoma patients in the clinic to delay the progression of vision loss due to glaucoma. While higher IOP confers greater risk for glaucoma, glaucoma can develop at a statistically normal or elevated IOP. POAG frequently remains undiagnosed or unrecognized by patients until visual field loss is clinically advanced.

POAG is a complex inherited trait. In this article, we will present an updated, comprehensive review of the genetic developments in POAG.

2. Genetic Approaches used in Glaucoma Research

Investigations into the inheritance of POAG have benefitted greatly from the development and integration of many genetic approaches to identify regions in the genome that are associated with a specific phenotype, or in some cases determine the specific genetic variants that are responsible. Family-based genetic linkage analysis was the first used to identify chromosomal locations for Mendelian forms of POAG. This approach has led to the identification of many POAG-associated loci and, less often, specific causative genes. Genetic mutations for POAG have been identified in three genes – myocilin (*MYOC*), optineurin (*OPTN*), and TANK-binding kinase 1 (*TBK1*) (Fingert et al., 2017; Fingert et al., 2011; Rezaie et al., 2002; Sarfarazi et al., 1998; Sheffield et al., 1993; Stone et al., 1997).

Next generation, high-throughput DNA sequencing technology is increasingly being used to sequence the complete coding sequence of the human genome (exome) or the human genome in its entirety (Zheng et al., 2015). These technologies offer a powerful approach to identify causal genetic variants for many rare and common genetic disorders, including POAG.

The genome-wide association studies (GWAS), based on high-throughput DNA genotyping, are currently the most powerful, broadly used approach to identify genomic regions associated with a specific disease or phenotype. GWAS utilize up to several million single nucleotide polymorphisms (SNPs) from an individual sample for analysis. The number of subjects in clinical datasets for GWAS may number from hundreds to hundreds of thousands. This approach has been used to identify the location of thousands of inherited disorders or phenotypes (Welter et al., 2014). In ophthalmology, the first successful GWAS identified the association of complement factor H (*CFH*) with age-related macular degeneration (AMD) (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005). Similarly, GWAS have been used to identify many genetic associations for POAG (Bailey et al., 2016; Burdon et al., 2011; Chen et al., 2014; Gharahkhani et al., 2014; Hysi et al., 2014; Lu et al., 2013; Springelkamp et al., 2014; Springelkamp et al., 2017; Springelkamp et al., 2015b; Thorleifsson et al., 2010; Wiggs et al., 2012).

In addition, the analysis of DNA copy number variants (e.g. genomic deletion and duplication) and differential expression analysis of mRNA and proteins have added to our understanding of human genetic disorders. Altogether, these technological innovations have advanced our understanding of POAG genetic etiology.

3. Genetic Linkage Analyses of POAG

Genetic linkage analysis is a family-based method used to localize chromosomal regions that are associated with a specific phenotype within related family groups. Genetic linkage is used for Mendelian traits, or traits with high heritability that are typically caused by mutations in a single gene. Genetic linkage analyses have been used to identify many genomic loci associated with POAG, designated GLC1A through GLC1P, and in some cases the gene within the locus (Table 1, Figure 1). Genes identified in these loci are discussed below.

3.1 *MYOC*

Mutations in the *MYOC* gene, located in chromosome 1q24, were first identified in families with autosomal dominant POAG linked to the GLC1A locus (Sheffield et al., 1993; Stone et al., 1997). Mutations in *MYOC* are primarily associated juvenile-onset POAG (Fingert, 2011; Fingert et al., 2002; Hewitt et al., 2008). The phenotype for glaucoma with *MYOC*-associated mutations is generally severe, typically IOP is highly elevated and surgical management is often required for treatment (Fingert et al., 1999). *MYOC*-associated glaucoma accounts for 3–5% of POAG cases worldwide (Liu and Allingham, 2011). The *MYOC* gene contains three exons and encodes a protein with 504 amino acids (OMIM 601652). Most mutations are located in the third exon, which codes for the olfactomedin-like domain. The crystal structure of the olfactomedin (OLF) domain shows that it is a member of a small protein family characterized by a high affinity calcium binding site with a five-bladed β -propeller structure (Donegan et al., 2015; Donegan et al., 2012). Several *MYOC* mutations are located within or near this binding site (Donegan et al., 2012). Although *MYOC* is widely expressed in ocular and non-ocular tissues, glaucoma is the only reported association with a clinical disease (Kwon et al., 2009).

Over 100 POAG-associated mutations have been identified in the *MYOC* gene (www.myocilin.com summary data by December 18, 2016). The most prevalent mutation produces a premature termination of the myocilin protein (Q368X). This mutation causes an older-adult age of onset form of glaucoma that is clinically less severe than that seen with other *MYOC* mutations (Allingham et al., 1998; Alward et al., 1998; Fingert, 2011; Kwon et al., 2009). Genetic screening and counseling should be considered for affected family members in families where *MYOC*-associated glaucoma has been found. Since mutations are autosomal dominant, highly penetrant, clinically severe, and usually present early in life, carriers can be identified in early stages of glaucoma or screening can be initiated in those without evidence of disease (Gharahkhani et al., 2015; Hewitt et al., 2008; Souzeau et al., 2013; Souzeau et al., 2014; Souzeau et al., 2015).

The primary effect of pathogenic mutations in *MYOC*, which is invariably associated with elevated IOP, appears to be on the trabecular meshwork (TM) and aqueous humor outflow

function. Reduced, complete loss (haploinsufficiency), or overexpression of MYOC protein does not cause glaucoma in animal models (Gould et al., 2004a; Kim et al., 2001; Kwon et al., 2009; Resch and Fautsch, 2009; Tamm, 2002; Zillig et al., 2005). The lack of a discernable ocular phenotype in these transgenic mice suggests that myocilin is not required for normal IOP or normal ocular morphology and therefore, haploinsufficiency is not the primary mechanism for POAG patients with *MYOC* mutations. Instead, pathology from these mutations in humans is likely caused by gain of function. Transgenic mice with the human or mouse Tyr437His develop features of glaucoma including elevated IOP, progressive RGC loss and axonal degeneration (Chou et al., 2014; Gould et al., 2006; Senatorov et al., 2006; Zhou et al., 2008; Zillig et al., 2005; Zode et al., 2012; Zode et al., 2011). Transgenic mice do not secrete myocilin into the aqueous humor; rather abnormal myocilin accumulates intracellularly. In addition to RGC loss, these mice demonstrate function loss measured by pattern electroretinogram (PERG) (Chou et al., 2014; Zhou et al., 2008).

Secretion of myocilin protein into the aqueous humor is significantly reduced in patients with POAG-associated mutations in *MYOC* (Jacobson et al., 2001; Resch and Fautsch, 2009; Resch et al., 2010). MYOC may enter the aqueous humor in MYOC-containing exosomes, which may help regulate aqueous outflow in the TM (Dismuke et al., 2015; Hardy et al., 2005; Hoffman et al., 2009; Liu et al., 2016; Perkumas et al., 2007; Stamer et al., 2011). It has been proposed that glaucoma-associated MYOC protein interferes with protein trafficking, receptor-mediated endocytosis, programmed cell death, myelination of the optic nerve, and stress to the endoplasmic reticulum (ER) (Koch et al., 2014; Kwon et al., 2013; Kwon et al., 2014; McKay et al., 2013; Zode et al., 2011).

Mutations of *MYOC* have been reported in juvenile open-angle glaucoma and primary congenital glaucoma (Chakrabarti et al., 2005; Kaur et al., 2011; Kaur et al., 2005; Mookherjee et al., 2012; Vincent et al., 2002). *MYOC* may interact with *CYP1B1* through a digenic mechanism with *CYP1B1* acting as a modifier for *MYOC* (Kaur et al., 2011). It has been reported that *CYP1B1* mutations with <10% enzymatic activity may increase the level of endogenous myocilin in human trabecular meshwork cells due to the lack of 17 β estradiol metabolizing activity with *CYP1B1* mutation (Mookherjee et al., 2012). However, the interaction between *MYOC* and *CYP1B1* with POAG pathogenesis remains poorly understood.

3.2 *OPTN* and *TBK1*

OPTN and *TBK1* are discussed together since they share cellular, molecular, and biological pathways. In addition, genetic variants in both of these genes cause NTG, and in some cases they are both associated with degenerative disorders of the central nervous system.

OPTN is located in the POAG-linked locus GLC1E on chromosome 10p13. Clinically, mutations in *OPTN* lead to NTG. This contrasts sharply with patients who have *MYOC*-associated POAG, which is consistently hypertensive (Ariani et al., 2006; Charlesworth et al., 2006; Hauser et al., 2006b; Rezaie et al., 2002). Among all *OPTN* mutations, E50K has been most clearly shown to cause glaucoma (Aung et al., 2005). POAG patients harboring

the E50K mutation have an earlier age of onset, more advanced optic nerve cupping, and more frequently require surgical intervention (Aung et al., 2005).

OPTN mutations have been reported in patients with amyotrophic lateral sclerosis (ALS), which has prompted broad interest in the functional role of *OPTN* in neural disorders (Cirulli et al., 2015; Maruyama et al., 2010). *OPTN* is involved in membrane trafficking, protein secretion, cell division, autophagy, and host defense against pathogens (Kachaner et al., 2012; Wild et al., 2011). *OPTN* interacts with many other proteins, such as TBK1, RAB8 (Rab protein 8), myosin VI, transferrin receptor, and autophagosomal protein LC3. *OPTN* inhibits TNF α -induced NF- κ B activation and affects apoptotic threshold (Kachaner et al., 2012; Morton et al., 2008; Sahlender et al., 2005; Tumbarello et al., 2012; Zhu et al., 2007). In addition, *OPTN* is an autophagy receptor that functions in removal of damaged mitochondria and proteins (Heo et al., 2015; Lazarou et al., 2015; Richter et al., 2016; Shen et al., 2015; Slowicka et al., 2016; Wong and Holzbaur, 2014).

Glaucoma-associated mechanisms caused by the E50K *OPTN* mutation are under intense study. Interaction of *OPTN* with TBK1 may be enhanced by overexpression of E50K (Minegishi et al., 2013; Morton et al., 2008). In addition, a wide variety of molecular and cellular effects have been reported (Chi et al., 2010a; Gao et al., 2014; Kryndushkin et al., 2012; Minegishi et al., 2013; Nagabhushana et al., 2010; Park et al., 2010; Shen et al., 2015; Shim et al., 2016; Vaibhava et al., 2012). However, it is unclear whether these effects result from overexpression of *OPTN* or from the mutation itself (Minegishi et al., 2016). An important step forward has been the development of an E50K transgenic mouse model that demonstrates an age-dependent decrease in RGCs and visual function in the absence of elevated IOP (Tseng et al., 2015).

TBK1 is located in the GLC1P POAG linkage locus on chromosome 12q14. *TBK1* encodes a serine/threonine kinase. It plays an essential role in the regulation of inflammatory responses to foreign agents (Fingert, 2011). A duplication of the *TBK1* gene has been identified in approximately 1% of normal tension POAG cases (Awadalla et al., 2015; Fingert et al., 2014; Fingert et al., 2011; Kawase et al., 2012; Liu et al., 2014b; Ritch et al., 2014; Seo et al., 2013). As discussed above, *OPTN* interacts with TBK1 and may share a common pathway in glaucoma pathogenesis (Heo et al., 2015; Morton et al., 2008). Like *OPTN*, mutations in *TBK1* have been identified in patients with CNS disorders including ALS and frontotemporal dementia (Bettencourt and Houlden, 2015; Cirulli et al., 2015; Freischmidt et al., 2015; Gijssels et al., 2015). RGC-like neurons derived from a patient with *TBK1*-associated NTG reportedly have increased levels of LC3-II protein and activation of LC3-II, which suggests that autophagy may be dysregulated in patients with *TBK1*-associated NTG (Tucker et al., 2014). This observation is consistent with reports that TBK1 and *OPTN* regulate autophagy of damaged mitochondria (Matsumoto et al., 2015; Moore and Holzbaur, 2016; Pilli et al., 2012; Richter et al., 2016). Transgenic mice that have a duplication of the human *TBK1* gene develop progressive RGC loss at 3 months of age and are normotensive (Fingert et al., 2017). However, it remains to be determined if or how abnormalities in autophagy contribute to NTG pathogenesis in patients with genetic variants in *TBK1* and *OPTN* (Pilli et al., 2012; Tucker et al., 2014).

3.3 WD repeat domain 36 (*WDR36*)

WD repeat domain 36 (encoded by *WDR36*) is a nucleolar protein involved in the maturation of 18s rRNA. It is located in the POAG linkage locus GLC1G on chromosome 5q22. The role of *WDR36* mutations in the pathogenesis of POAG is controversial. Mutations in *WDR36* were originally reported in 1.6% to 17% of POAG patients (Monemi et al., 2005). However, subsequent studies have failed to replicate these findings. More recent studies suggest that genetic variants of *WDR36* may alter POAG risk (Blanco-Marchite et al., 2011; Fan et al., 2009; Fingert et al., 2007; Frezzotti et al., 2011; Gallenberger et al., 2011; Hauser et al., 2006a; Hewitt et al., 2006; Janssen et al., 2013; Kramer et al., 2006; Miyazawa et al., 2007; Mookherjee et al., 2011; Pasutto et al., 2008; Ramdas et al., 2011a; Weisschuh et al., 2007). Knockdown of *Wdr36* in zebrafish reportedly reduces levels of 18S rRNA, activates the p53 stress-response pathway, and is associated with ocular abnormalities (Skarie and Link, 2008). *WDR36* mutations reportedly affect RGC axon growth that may lead to progressive peripheral retinal degeneration with normal IOP in transgenic mice (Chi et al., 2010b). *WDR36*-related variations in expression have been reported to delay the formation of 18S rRNA and up-regulate BAX, TP53, and CDKN1A, and lead to apoptotic cell death in human TM cells (Gallenberger et al., 2011). However, heterozygous *WDR36*-deficient mice do not demonstrate ocular structure abnormalities, changes in IOP, or reduced optic nerve axons (Gallenberger et al., 2014). Currently, evidence to support a major role for POAG-risk associated with the *WDR36* locus is limited.

3.4 Other Genetic Loci Identified by Linkage Analysis

Several other genes, listed in Table 1, have been identified as POAG candidate genes within loci found using genetic linkage approaches. These include *NTF4* (Neurotrophin 4), *ASB10* (Ankyrin Repeat and SOCS Box Containing 10), *EFEMP1* (EGF containing fibulin-like extracellular matrix protein 1), and *IL20RB* (Interleukin 20 receptor subunit beta).

NTF4 is located within the POAG linkage locus GLC1O on chromosome 19q13.33. Interestingly, *NTF4* was initially evaluated as a candidate gene for POAG without family-based studies or a linkage analysis (Pasutto et al., 2009). Using a case-control POAG dataset, seven heterozygous mutations in *NTF4* were found in 1.7% of POAG patients of European origin (Pasutto et al., 2009). Expression of the most prevalent *NTF4* variant reportedly decreases activation of tyrosine kinase receptor B (TrkB). This has been proposed as a possible mechanism for POAG risk in patients with *NTF4* variants (Pasutto et al., 2009). To date, follow-up studies in the US, India, and China have not replicated this observation (Chen et al., 2012; Huang et al., 2014; Liu et al., 2010; Rao et al., 2010).

ASB10 is located within the POAG linkage locus GLC1F on chromosome 7q36 (Murakami et al., 2010). A mutation affecting an exon splice enhancer (c.765C>T, p.Thr255Thr) has been identified in a large POAG family (Pasutto et al., 2012). Additional sequence analysis in 1172 cases and 461 controls has identified mutations in 6% POAG cases compared to 2.8% of controls. *ASB10* is highly expressed in TM, RGC, and ciliary body (Pasutto et al., 2012). Knock-down of *ASB10* transcription in perfused anterior segment organ culture reduced aqueous humor outflow facility by 50% (Pasutto et al., 2012). Functional studies in

primary human TM cells have suggested that ASB10 may play a role in ubiquitin-mediated degradation pathways through an interaction with HSP70 and the $\alpha 4$ subunit of the 20s proteasome (Keller et al., 2013). The up-regulation of ASB10 expression by TNF α and IL-1 α in TM cells provides further support for a role in glaucoma (Keller and Wirtz, 2017). Replication studies for the association of ASB10 variants with POAG have been mixed (Fingert et al., 2012; Micheal et al., 2015).

EFEMP1 is a juvenile-onset POAG candidate located in the GLC1H locus on chromosome 2p16. A missense mutation (p.Arg140Trp) was found in a 3-generation autosomal dominant African-American family with adult-onset, POAG (Mackay et al., 2015). *EFEMP1* is expressed highly in mouse ciliary body and cornea, at lower levels in the retina. The p.Arg140Trp mutation is located in the first of six calcium-binding EGF-like domains and may lead to abnormal accumulation of the mutant protein in the cell (Mackay et al., 2015). Mutations in *EFEMP1* have been associated other ocular disorders including Doyme honeycomb retinal dystrophy and Malattia Leventinese (Hulleman, 2016; Marmorstein, 2004; Stone et al., 1999; Takeuchi et al., 2010). Variants in *EFEMP1* are associated with reduced optic nerve disc area (Springelkamp et al., 2015b). *EFEMP1* expression in mouse retina is activated after optic nerve crush injury (Templeton et al., 2013). Expression of *EFEMP1* is inhibited by TGF- $\beta 2$, a cytokine that is elevated in POAG, in primary human TM cells, which suggests a potential role in glaucoma (Fuchshofer et al., 2009).

IL20RB is a POAG gene that is located in the GLC1C locus on chromosome 3q21. A specific *IL20RB* mutation T104M (rs367923973) has been identified in a large POAG family (Keller et al., 2014). Although the mutation was not present in all affected family members, there is supportive evidence that suggests its role in POAG pathogenesis. The T104M mutation lies within an active binding site of IL20RB with IL-20 subfamily cytokine members IL-19, IL-20, and IL-24 (Wirtz and Keller, 2016). *IL20RB* is expressed in human primary TM cells, which is upregulated in response to IL-20, IL-19, or IL-24. The expression of IL-24, but not IL-20 or *IL20RB*, is significantly upregulated in the retina of DBA/2J mice with moderate axon damage (Howell et al., 2011), which suggests a mechanism for IL-20 cytokines in glaucoma pathogenesis.

4. Association Studies in POAG

GWAS have advanced our understanding of the genetic architecture of numerous genetic disorders and traits. Since the first GWAS for POAG was performed in 2009 (Nakano et al., 2009), many genomic loci have been associated with POAG risk (Table 2). All reported genome-wide associations for POAG including their genomic locations are found in Figure 2. It is important to note that a large number of GWAS have been performed in populations of Asian and European derivation. However, at the time of this publication, no GWAS have been reported for POAG or other forms of glaucoma in populations of African ancestry or their diaspora, including African Americans. In addition to disease-associated studies for POAG, GWAS have been performed on quantitative traits that are associated with POAG and glaucoma. These traits include IOP, optic cup-disc ratio, optic disc area, central cornea thickness (CCT) and others. GWAS have been performed in many populations including the European, Chinese, and Japanese. POAG-associated genetic loci include *CDKN2B-AS1*,

TMCO1, CAV1/CAV2, SIX1/SIX6, LRP12/ZFPM2, ABCA1, AFAP1, GMDS, GAS7, PMM2, ARHGEF12, TGFBR3, TXNRD3, ATXN2, FOXC1, and C12ORF23. Importantly, the first common, *functional* POAG-associated variant in the gene *SIX6* (Asn141His) has been reported in European and Asian populations (Carnes et al., 2014; Cheng et al., 2015; Kuo et al., 2015; Skowronska-Krawczyk et al., 2015). As additional functional variants are found, a clearer picture of the underlying molecular and cellular interactions that cause POAG will emerge.

4.1 Caveolin 1 and 2 (*CAV1/CAV2*)

The *CAV1* and *CAV2* genes, encoding caveolins, are located on chromosome 7q31. Caveolins are involved in transcellular transport, endocytosis, mechanotransduction, cell proliferation, membrane lipid homeostasis, and signal transduction (Gu et al., 2017). The associated SNP (rs4236601), located in the intergenic region between *CAV1* and *CAV2*, was first reported in the Icelandic population and replicated in others (Kato et al., 2013; Kim et al., 2015; Loomis et al., 2014; Micheal et al., 2014; Rong et al., 2016; Thorleifsson et al., 2010; Wiggs et al., 2011). Two reports found a stronger association in women (Loomis et al., 2014; Wiggs et al., 2011). Variants in the *CAV1/CAV2* region are associated with IOP (Chen et al., 2015a; Hysi et al., 2014; Kim et al., 2015; Ozel et al., 2014; van Koolwijk et al., 2012). *CAV1* and *CAV2* are expressed in human and mouse retina, ciliary muscle, TM, and Schlemm canal (Gu et al., 2014; Kuehn et al., 2011; Li et al., 2012; Surgucheva and Surguchov, 2011).

CAV1 and *CAV2* are expressed in TM cells cultured from POAG and non-glaucoma donor eyes (Surgucheva and Surguchov, 2011). Expression of *CAV1* in these primary cells was induced by dexamethasone and inhibited by TGF- β 2 (Surgucheva and Surguchov, 2011). Expression levels of both *CAV1* and *CAV2* are up-regulated in Schlemm canal endothelial cells derived from POAG compared to non-glaucoma donor eyes (Cai et al., 2015; Liu et al., 2013a). *CAV1/CAV2* knock down has been shown to alter aqueous outflow resistance in anterior segment perfusion culture (Aga et al., 2014). *Cav1* knockout mice develop elevated IOP and reduced conventional outflow facility via increased eNOS activity (Elliott et al., 2016; Gu et al., 2017; Lei et al., 2016). These data suggest that *CAV1* and/or *CAV2* may influence risk of POAG through an effect on IOP.

4.2 *CDKN2B* antisense RNA 1 (*CDKN2B-AS1*)

CDKN2B-AS1 (cyclin-dependent kinase inhibitor 2B antisense RNA 1) is located within the *CDKN2B-CDKN2A* gene cluster on chromosome 9p21. Sequence variants in this locus are associated with vertical cup-disc ratio and POAG-risk in multiple non-African populations worldwide (Bailey et al., 2016; Burdon et al., 2012; Burdon et al., 2011; Cao et al., 2012; Chen et al., 2015b; Fan et al., 2011; Li et al., 2015; Liu et al., 2013b; Mabuchi et al., 2012; Osman et al., 2012; Ramdas et al., 2010; Ramdas et al., 2011b; Vishal et al., 2014; Wiggs et al., 2012). The association of *CDKN2B-AS1* appears to be strongest in POAG patients with normal tension, especially in females (Bailey et al., 2016; Burdon et al., 2012; Chen et al., 2015b; Ng et al., 2016; Pasquale et al., 2013a; Takamoto et al., 2012; Wiggs et al., 2012).

CDKN2B-AS1 is a long non-coding functional RNA that interacts with polycomb repressive complex -1 (PRC1) and -2 (PRC2). *CDKN2B-AS1* is expressed in multiple human eye tissues including ciliary body, retina, and optic nerve (Burdon et al., 2011). The *CDKN2B* protein (aka p15^{INK4B}) is localized to the inner retinal nuclear and ganglion cell layers and the corneal epithelium and TM in rat and human eyes (Chidlow et al., 2013). Transgenic mice that are heterozygous for a 70kb deletion of the *CDKN2B-AS1* genomic region have a significant reduction of CDKN2B, but have normal RGC representation in the retina (Gao and Jakobs, 2016; Visel et al., 2010). However, mice that are homozygous for this deletion are more susceptible to RGC loss in response to elevated IOP (Gao and Jakobs, 2016). In addition to POAG, variants in the *CDKN2B-AS1* locus are also associated with a variety of non-ocular disorders including myocardial infarction, intracranial aneurysm, diabetes, breast cancer, endometriosis, and gliomas (Kathiresan et al., 2009; Shete et al., 2009; Turnbull et al., 2010; Uno et al., 2010; Wrensch et al., 2009; Zeggini et al., 2007). It is not known if there is a relationship between POAG-risk and other disorders that are associated with the *CDKN2B-AS1* locus.

4.3 SIX homeobox 6 (*SIX6*)

Sequence variants located in the *SIX1-SIX6* locus (chromosome 14q23) have been associated with vertical cup-to-disc ratio (VCDR), myopia, and POAG (Burdon et al., 2015; Chen et al., 2015b; Fan et al., 2011; Osman et al., 2012; Philomenadin et al., 2015; Ramdas et al., 2010; Ramdas et al., 2011b; Sang et al., 2016; Verhoeven et al., 2013; Wiggs et al., 2012). *SIX6* protein in humans is homologous to the “sine oculis” protein in *Drosophila* (Carnes et al., 2014; Iglesias et al., 2014). Both *SIX6* genes in human and *Drosophila* encode homeobox proteins that play a critical role in ocular development. Mutations in *SIX6* can cause anophthalmia, an ocular phenotype observed in mice and humans (Gallardo et al., 1999; Li et al., 2002; Ruf et al., 2004). *SIX1* mutations lead to deafness and branchio-otorenal syndrome in humans (OMIM 113650). Currently, it is considered that genetic variants of *SIX6*, a highly conserved gene, are responsible for POAG risk within this locus.

SIX6 is expressed in the developing retina, optic nerve, cornea, and TM as well as the developing and adult mouse brain (Conte et al., 2005; Gallardo et al., 1999). Further sequencing and fine mapping have identified two missense variants rs33912345 (His141Asn) and rs146737847 (Glu129Lys) in *SIX6* that are highly associated with VCDR and POAG (Carnes et al., 2014; Iglesias et al., 2014).

Animal models and human studies provide support for a functional role of *SIX6* variants in POAG pathogenesis. POAG-associated *SIX6* coding variants affect eye size and optic nerve volume in the zebrafish model (Carnes et al., 2014; Iglesias et al., 2014) (Figure 3). In humans His141, the POAG-risk variant for *SIX6*, located in a highly conserved region, is associated with reduced retinal nerve fiber layer (RNFL) thickness measured by OCT. The effect on RNFL thickness is observed in European and Asian populations (Carnes et al., 2014; Cheng et al., 2015; Kuo et al., 2015). Similarly, this *SIX6* variant is associated with RNFL thickness in non-glaucomatous Singapore Chinese individuals (Cheng et al., 2015). Thinner RNFL is primarily observed in the superior and inferior RNFL sectors, a pattern that is similar to that observed in human glaucoma (Carnes et al., 2014; Cheng et al., 2015;

Kuo et al., 2015). A gene dosage effect has been observed in POAG and non-POAG subjects, meaning reduction in mean RNFL thickness for individuals homozygous (two copies) for the POAG-risk variant have significantly thinner RNFL thickness than persons who are heterozygous (one copy) (Cheng et al., 2015; Kuo et al., 2015). The gene dosage effect has been seen in populations of Asian and European ancestry (Cheng et al., 2015; Kuo et al., 2015).

Recent evidence supports interaction between the Asn141His *SIX6* variant with genes within another major POAG-risk locus, *CDKN2B-AS1*. Over-expression of the POAG-risk His141 *SIX6* variant in cell models elevates expression of CDKN2B (aka p16(INK4A)). Further in human fetal RGCs, the rate of cellular senescence is increased in cells with the POAG-risk *SIX6* variant compared to cells transfected with the protective Asn141 variant (Skowronska-Krawczyk et al., 2015). Increased expression of *SIX6* and CDKN2B associated with RGC senescence was also observed in a mouse glaucoma model with elevated IOP (Skowronska-Krawczyk et al., 2015). The *SIX6* His141 risk allele also leads to increased *CDKN2B-AS1* expression and subsequent RGC cellular senescence in a mouse model with elevated IOP and in human POAG eyes. These data, which remain to be corroborated, suggest that *SIX6* and elevated IOP play a role in RGC loss through a mechanism that includes increased expression of *CDKN2B-AS1*.

The protective *SIX6* variant, Asn141, is found only in humans (Blanchette et al., 2004). All mammals, including mice and most vertebrates, are monomorphic for the His141 *SIX6* genotype. Therefore, it is not possible to compare or analyze expression pattern and phenotype data that result from His141Asn, or any other *SIX6* variant, in currently available animal models (Blanchette et al., 2004; Skowronska-Krawczyk et al., 2015). Interestingly, the His141 risk variant is essentially monomorphic in the West and South African populations, or conversely, the protective Asn141 variant is essentially absent (Liu et al., 2013b; Williams et al., 2015). While the VCDR is greater and POAG prevalence is reportedly higher in populations of West African ancestry, for reasons just cited the effect of the His141Asn *SIX6* variant in these populations is challenging to test (Girkin, 2008; Girkin et al., 2010; Knight et al., 2012). Current preliminary evidence, based on population genetics, suggests that the protective Asn141 variant arose in East Africa prior to Man's migration out of the continent. This supports observed Asn141 population allele frequencies (Tishkoff and Allingham, *unpublished* data). It is currently unknown if the protective Asn141 variant has experienced positive selection pressure. Regardless, the presence of this common, functional variant provides a valuable new tool to explore molecular mechanisms responsible for POAG risk and protection.

4.4 Transmembrane and coiled-coil domains 1 (*TMCO1*)

TMCO1, an ER transmembrane protein, is evolutionally conserved and plays an active role in maintaining ER Ca²⁺ storage (Wang et al., 2016; Zhang et al., 2010). *TMCO1* undergoes reversible homotetramerization to form a Ca²⁺-selective ion channel in response to ER Ca²⁺ overloading or depletion (Wang et al., 2016).

Genetic sequence variants in *TMCO1* are associated with POAG risk and IOP, an important glaucoma-related quantitative trait (Bailey et al., 2016; Burdon et al., 2011; Burdon et al.,

2015; Chen et al., 2015b; Gibson et al., 2012; Hysi et al., 2014; Micheal et al., 2014; Ozel et al., 2014; Scheetz et al., 2016; van Koolwijk et al., 2012). It has been reported that POAG patients that are homozygous for the *TMCO1* POAG-risk allele (rs4656461, allele G) develop glaucoma 4–5 years earlier than those without the risk allele (Sharma et al., 2012). Recently, a genetic study of subjects enrolled in the Ocular Hypertension Treatment Study (OHTS) found that non-Hispanic white subjects with *TMCO1* risk alleles were at increased risk (12%) to develop POAG than subjects without these risk alleles after 13 years follow-up (Scheetz et al., 2016). In addition, the presence of glaucoma-risk associated *TMCO1* alleles increased relative risk of glaucoma by 1.7 fold per allele, which is comparable to other glaucoma risk factors (i.e., elevated IOP and aging) (Scheetz et al., 2016). *TMCO1* protein is expressed in most human ocular tissues, including TM and retina (Sharma et al., 2012). The mechanistic relationship between variants in the *TMCO1* locus and IOP remains to be determined.

4.5 Actin filament associated protein 1 (*AFAP1*)

The *AFAP1* gene is located on chromosome 4 and encodes actin filament associated protein 1. Variants within the *AFAP1* gene locus have been associated with POAG in populations of European ancestry (Bailey et al., 2016; Gharahkhani et al., 2014). *AFAP1* mRNA and protein are expressed in many human ocular tissues including retina, optic nerve, and cultured TM cells (Gharahkhani et al., 2014). POAG-associated SNPs within this region are correlated with the expression level of *AFAP1* and *AFAP1-AS1* in non-ocular human tissues including skin, fibroblast cells, brain, and whole blood (Consortium, 2015). The mechanistic role that *AFAP1* variants play in POAG risk remains to be determined.

4.6 ATP binding cassette subfamily A member 1 (*ABCA1*)

The *ABCA1* gene encodes a membrane-associated protein that is a member of the ATP-binding cassette (ABC) transporter family. This protein complex transports various molecules across extra- and intracellular membranes. *ABCA1* acts as a cholesterol efflux pump in the cellular lipid removal pathway. Mutations in *ABCA1* gene have been associated with Tangier's disease and familial high-density lipoprotein deficiency. Variants located upstream of the *ABCA1* gene are associated with POAG and IOP in multiple populations (Chen et al., 2014; Gharahkhani et al., 2014; Hysi et al., 2014; Luo et al., 2015). *ABCA1* mRNA and protein are expressed in human TM, iris, ciliary body, cornea, optic nerve, and retina; especially in the ganglion cell layer (Chen et al., 2014; Gharahkhani et al., 2014; Tserentsoodol et al., 2006). The expression of *ABCA1* protein is similar in glaucoma and non-glaucoma eyes (Gharahkhani et al., 2014). The IOP-related variant rs2472493 is associated with *ABCA1* transcript levels in lymphoblastoid cell lines (Gharahkhani et al., 2014; Hysi et al., 2014). *ABCA1* may regulate neuroinflammation and neurodegeneration in the mouse brain, which could potentially play a role in retinal and POAG pathogenesis.

4.7 Thioredoxin reductase 2 (*TXNRD2*)

The *TXNRD2* gene, located on chromosome 22, encodes a mitochondrial protein that is required for redox homeostasis (Chen et al., 2006). Sequence variants in the *TXNRD2* region have been associated with POAG (Bailey et al., 2016). *TXNRD2* mRNA and protein are found in retina and optic nerve tissue (Bailey et al., 2016). Oxidative stress is known to

cause RGC dysfunction in glaucoma models and clinical glaucoma samples (Chrysostomou et al., 2013). TXNRD2 regulates the cellular redox environment by scavenging reactive oxygen species in mitochondria. Overexpression of thioredoxin, produced by TXNRD2, is protective for RGCs after optic nerve axotomy, pharmacologically induced oxidative stress *in vitro*, and in an animal model (rat) of glaucoma (Caprioli et al., 2009). Further, computational analysis indicates that POAG-associated SNPs may locate within enhancers to regulate the expression of *TXNRD2* gene (Bailey et al., 2016). These data are consistent with the suspected role of oxidative damage in POAG pathogenesis and, more specifically, the contribution by pathways that include TXNRD2 that are related to mitochondrial biology.

4.8 FOXC1/GMDS

The gene Forkhead Box C1 (*FOXC1*) is physically located next to GDP-mannose 4,6-dehydratase (*GMDS*) on chromosome 6. Mutations in *FOXC1* have been associated with primary congenital glaucoma and developmental glaucoma including Axenfeld-Rieger's syndrome, Peter's anomaly, and iridogoniodysgenesis (Gould et al., 2004b; Liu and Allingham, 2012; Nishimura et al., 2001; Sowden, 2007). *GMDS* encodes an enzyme that converts GDP-mannose to GDP-4-keto-deoxymannose and is ubiquitously expressed in human eye tissues (Gharahkhani et al., 2014). Sequence variants within the *GMDS* gene have been associated with advanced POAG (Gharahkhani et al., 2014) while variants located upstream of *FOXC1* have also been associated with POAG (Bailey et al., 2016). Although these loci are near each other, a conditional analysis suggests that the associations are independent (Bailey et al., 2016). The most associated genetic variant, SNP rs2745572, near *FOXC1* is associated with the expression of a long noncoding RNA – *RP11-157J24.2* (*ELF2P2*, E74-like factor 2 pseudogene 2) (Consortium, 2015).

4.9 Ataxin 2 (*ATXN2*)

The gene Ataxin 2 (*ATXN2*), located on chromosome 12, encodes a membrane protein located in the ER and plasma membrane. This protein is involved in endocytosis and modulates mTOR signals that modify ribosomal translation and mitochondrial function. The association of genetic variants in the *ATXN2* locus with POAG has been reported in subjects of European ancestry (Bailey et al., 2016). *ATXN2* is expressed in normal human cornea, TM, ciliary body, retina, and optic nerve while the protein is expressed in mouse RGC and optic nerve (Bailey et al., 2016). Long expansions of CAG repeats within *ATXN2* are associated with spinocerebellar ataxia 2 with optic atrophy while intermediate length expansions of this repeat are a strong risk factor for ALS (Lattante et al., 2014). Mutations in *OPTN* and *TBK1*, as previously discussed, also contribute to POAG and ALS. The relationship between these POAG-risk associated genes lends further support for the presence of a biological relationship between POAG and disorders of the central nervous system.

4.10 Other POAG-associated Loci

There are many other reported associations between various genetic loci and POAG that are supported by recent GWAS and summarized in Table 2 and are briefly described here. *SRBD1* variants have been associated with POAG, especially NTG, in multiple studies

(Gibson et al., 2012; Kanemaki et al., 2013; Mabuchi et al., 2011, 2015; Meguro et al., 2010). *LRP12/ZFPM2* variants have been associated with NTG in multiple studies (Bailey et al., 2016; Wiggs et al., 2012). Variants in the *FNDC3B*, *GAS7*, and *ARHGEF12* are consistently associated with POAG and IOP, a quantitative trait (Luo et al., 2015; Micheal et al., 2014; Ozel et al., 2014; Sharma et al., 2012; van Koolwijk et al., 2012). Variants in *PMM2* and *CDC-TGFBR3* are associated with POAG while variants in *C12ORF23* have been associated with NTG (Bailey et al., 2016; Chen et al., 2014; Li et al., 2015). A variant in the *MIR182* gene has been associated with POAG, especially in those with elevated IOP (Drewry et al., 2016; Liu et al., 2016). Interestingly, elevated expression of miR-182 has been reported to contribute to stress-induced premature senescence in human TM cells (Li et al., 2009).

4.11 Populations, GWAS and POAG

To date GWAS for POAG have primarily been limited to European and Asian populations. Currently, there are a growing number of GWAS in populations of African ancestry. Two African American studies are in progress or have been reported (Charlson et al., 2015; Hoffmann et al., 2014). Surprisingly, a recent GWAS of POAG in a west continental African (Ghana and Nigeria) and African American dataset found no association with either variants in *CDKN2B-AS1* or *TMC01*, genetic loci highly associated with POAG in Asian and European populations (Hauser et al., 2017). To date, no genome-wide associations for POAG have been reported in populations of African descent. However, because of the unique ancestral relationship between populations of Sub Saharan Africa and all other global populations, this information is likely to be highly informative and of great scientific interest.

4.12 Copy number variants (CNV)

DNA copy number variants (CNVs), i.e. genomic duplications and deletions, have been increasingly associated with a variety of human genetic disorders, including ocular disorders like hereditary benign epithelial dyskeratosis (HBID) (Allingham et al., 2001; White and Nelson, 1975), AMD (Cantsilieris et al., 2012; Grassmann et al., 2016; Park et al., 2012; Sawitzke et al., 2011; Schmid-Kubista et al., 2009; Sivakumaran et al., 2011), uveitis (Hou et al., 2015) and non-ocular conditions like autism and schizophrenia (Alkan et al., 2011). CNVs are defined as changes in DNA copy number of a specific genomic region when compared to a reference genome.

A number of CNVs have been reported in POAG cases. Davis and colleagues performed a study of 400 cases/500 non-glaucoma controls that suggested rare CNVs may play a role in the development of POAG (Davis et al., 2011). A study of POAG in subjects of Indian and European ethnicity reported rare large genomic deletions that were highly enriched in POAG patients (Kaurani et al., 2014). Deletions on chromosome 5q21.2 that contained the gene *RAB9BPI*, a gene that has been associated with IOP, was associated with higher IOP but was not associated with high tension POAG (Nag et al., 2013). In another study individuals heterozygous for a deletion of the *GALC* gene (galactosylceramidase) had 5 fold increased risk of POAG (Liu et al., 2011a). Interestingly, Krabbe disease, a rare generally fatal disorder of the myelin sheath that includes progressive optic neuropathy and vision loss

occurs when both copies of *GALC* are nonfunctional (Wenger, 1993; Wenger et al., 1997; Wenger et al., 2000; Wenger et al., 1999). As discussed earlier, a CNV consisting of *duplications* in the *TBK1* are associated with NTG (Awadalla et al., 2015; Fingert et al., 2017; Fingert et al., 2016; Fingert et al., 2011; Kawase et al., 2012; Ritch et al., 2014). A study of DNA copy number variations in approximately 1,600 POAG cases and 1,500 controls identified the presence of rare genomic deletions/duplications in a large number of POAG-associated genes (Liu et al., 2014b). These data further support the role of CNVs as another contributor to POAG pathogenesis.

4.13 POAG-associated Molecular Pathways

POAG is a complex genetic disorder, which in most cases has contributions from multiple genetic factors that participate in a wide variety of cellular signaling pathways (Abu-Amro et al., 2015; Cooke Bailey et al., 2013; Fan and Wiggs, 2010; Janssen et al., 2013; Libby et al., 2005; Wang and Wiggs, 2014; Weinreb et al., 2014). *MYOC* mutations reportedly affect the ER stress response, which has been implicated in the pathogenesis of glaucoma (Chrysostomou et al., 2013; Zode et al., 2012; Zode et al., 2011). ER stress pathways also appear to play a role in the pathogenesis of POAG in the retina based on mouse models of optic nerve injury or transgenic mutated myocilin (Carbone et al., 2011; Hu et al., 2012; Yang et al., 2016a; Zode et al., 2012; Zode et al., 2011). Mitochondrial-related pathways have also been implicated in POAG pathogenesis. A genetic pathway analysis of mitochondrial genetic variations suggests a relationship between lipid and carbohydrate metabolism and POAG risk (Khawaja et al., 2016). Targeted pathway analyses have suggest the contribution of genes involved in pathways related to vascular tone and estrogen metabolism in women (Dewundara et al., 2016; Kang et al., 2014; Pasquale et al., 2013b).

A genome-wide hypothesis-independent pathway analysis implicated *gamma*-aminobutyric acid (GABA) and acetyl-CoA metabolism in glaucoma pathogenesis (Bailey et al., 2014). Multiple genetic and molecular studies indicate the important contribution of autophagy to the pathogenesis of POAG (Frost et al., 2014; Hirt and Liton, 2017; Liton, 2016; Minegishi et al., 2016; Porter et al., 2015; Porter et al., 2013; Porter et al., 2014; Slowicka et al., 2016; Tucker et al., 2014; Wong and Holzbaaur, 2014). As discussed earlier, a number of genetic factors are involved in or associated with the pathogenesis of POAG. Since a single genetic factor can play a role in multiple molecular pathways, several have been discussed here, any of which may play an important role in POAG pathogenesis (Janssen et al., 2013).

In addition to molecular pathways, interaction between glaucoma-associated genes may also contribute to pathogenesis of POAG. For example, interactions between *MYOC* and *CYP1B1*, *OPTN* and *TBK1*, and *SIX6* with *CDKN2B* have been reported (Kaur et al., 2005; Minegishi et al., 2013; Minegishi et al., 2016; Mookherjee et al., 2012; Morton et al., 2008; Richter et al., 2016; Seo et al., 2013; Shen et al., 2015; Skowronska-Krawczyk et al., 2015; Vincent et al., 2002). A gene-based SNP-SNP interaction analysis identified several gene-gene interactions with POAG. These include interactions between *ZNF385B* and *ELMO1*, *ALX4* and *RBFOX1*, *OPCML* and *RYR3*, *ROBO1* and *HTR2A*, and *CTNND2* with *NRG3* (Verma et al., 2016). Current and future genetic will help unravel POAG's complex inheritance.

5. Genetic Analyses of POAG-associated Traits (Endophenotypes)

Endophenotypes, a term coined by Bernard John and Kenneth Lewis in studies of grasshopper distribution, are defined as *heritable, stable traits that coexist in families and are not state dependent, so often exist whether illness is present or not* (John and Lewis, 1966). In other words, though endophenotypes may be related to a disease, they are *not* disease dependent. Endophenotypes are typically quantitative traits. Quantitative traits, by their very nature, are frequently more amenable to analysis. Association analysis of endophenotypes can be a useful approach to dissect an inherited disease, for example psychiatric disorders, where a disease phenotype may be vague or difficult to define. Well-known and studied endophenotypes for POAG include IOP, CCT, VCDR, and RNFL thickness. Heritability of ocular traits, the variation in a phenotypic trait that is attributable to genetic factors, can be high. For example, estimates for the heritability of IOP is 0.29–0.50, VCDR is 0.48–0.80, CCT is 0.71–0.95 and RNFL thickness is 0.48 (Chang et al., 2005; Charlesworth et al., 2010; Klein et al., 2004; Levene et al., 1970; Schwartz et al., 1975; Toh et al., 2005; van Koolwijk et al., 2007; Vitart et al., 2010a; Zheng et al., 2008). These traits, used to study and dissect a variety of ocular disorders, are individually addressed below.

5.1 IOP

IOP reduction is currently the only clinically validated treatment for glaucoma. Family-based genome-wide linkage analyses have identified several genomic loci (chr5q22, 14q22, and 10q22) that contribute to variation in IOP (Axenovich et al., 2011; Charlesworth et al., 2005; Duggal et al., 2005; Lee et al., 2010; Rotimi et al., 2006). GWAS have identified a large number of IOP-associated genetic variants near or within genetic loci. These loci include *TMCO1*, *GAS7*, *CAVI/CAV2*, *GLCCII/ICA1*, *MVB12B* (aka *FAM125B*), *ARHGEF12*, *FNDC3B*, *ABCA1*, *ABO*, *ADAMTS8*, and chr11p11.2 (Blue Mountains Eye and Wellcome Trust Case Control, 2013; Chen et al., 2015a; Hysi et al., 2014; Nag et al., 2014; Ozel et al., 2014; Springelkamp et al., 2015a; Springelkamp et al., 2017; van Koolwijk et al., 2012). Not surprisingly most IOP-associated variants are associated with POAG, the only exceptions in this list are *ABO* (blood group) and *ADAMTS8* loci. Most IOP-associated genes are expressed in adult human ocular tissues. Interestingly, when combined these loci accounts for less than 2% of the phenotypic variability observed in IOP, which leaves the vast majority of IOP heritability unexplained (Hysi et al., 2014). In addition to finding new IOP-associated loci, identifying rare variants that that lie in IOP-associated loci and contribute a large effect on IOP may account for some of the “missing” inheritance. IOP reduction is currently the only proven, effective therapy for glaucoma. Determining the mechanisms that underlie this quantitative trait will improve our understanding its contribution to glaucoma pathogenesis and will likely provide novel therapeutic targets.

5.2 CCT

CCT is a highly heritable trait that is estimated between 0.71–0.95 and is influenced by ethnicity (Aghaian et al., 2004; Charlesworth et al., 2010; Toh et al., 2005; Zheng et al., 2008). CCT is reportedly thinner in people of African ancestry (Chua et al., 2014; Sample et al., 2009). Although the mechanism is unclear, thinner CCT has been reported as a strong predictor of POAG risk (Deol et al., 2015; Gordon et al., 2002; Sng et al., 2017). Thicker

CCT is associated with ocular hypertension and glaucoma suspect status in adults and children (Gordon et al., 2002; Muir et al., 2004). GWAS have identified a large number of CCT-associated sequence variants near or within many genes. These include *ZNF469-BANP*, *FOXO1*, *COL5A1*, *RXRA-COL5A1*, *AVGR8*, *AKAP13*, *COL8A2*, *WNT7B*, *WNT10A-USP37*, *NR3C2*, *GPR15*, *TIPARP*, *LCN12-PTGDS*, *CWC27-ADAMTS6*, *GLT8D2*, *SMAD3*, *VKORC1L1*, *COL4A3*, *FAM46A-IBTK*, *LPAR1*, *ARID5B*, *TBL1XR1-KCNMB2*, *ARHGAP20-POU2AF1*, *C7ORF42*, *MPDZ-NF1B*, *FGF9-SGCG*, *TJPI*, *LRRK1*, *CHSY1*, *HS3ST3B1-PMP22*, and *FNDC3B* (Cuellar-Partida et al., 2015; Gao et al., 2013; Hoehn et al., 2012; Lu et al., 2010; Lu et al., 2013; Ulmer et al., 2012; Vitart et al., 2010b; Vithana et al., 2011). A pathway analysis of CCT in a population of European ancestry found that genes involved in collagen and extracellular matrix metabolism, collagen fibril organization, and myosin binding were enriched (Lu et al., 2013). However, similar to IOP, the combined genetic effect of these loci accounted for only a small portion (10%) of heritability (Charlesworth et al., 2010; Lu et al., 2013; Toh et al., 2005; Zheng et al., 2008). The relationship between CCT and POAG risk has been a subject of considerable discussion. Although CCT is considered a risk factor for POAG, the only genetic locus that is associated with CCT and POAG risk is *FNDC3B* (Lu et al., 2013). CCT has been inversely associated with oxygen levels in the human anterior chamber angle (Siegfried et al., 2015). This is consistent with the long-held belief that damage to components of the aqueous outflow pathways by reactive oxygen species (ROS) contributes to elevated IOP, a common feature observed in POAG (Siegfried et al., 2015). In other studies a correlation between CCT, optic nerve head topography, and visual field damage was found (Cankaya et al., 2008; Coman et al., 2014; Lester et al., 2012; Insull et al., 2010; Kaushik et al., 2006; Mokbel and Ghanem, 2010; Pakravan et al., 2007; Papadia et al., 2007; Saenz-Frances et al., 2015; Sullivan-Mee et al., 2005). The relationship between POAG risk and CCT is complex and poorly understood.

5.3 VCDR and RNFL

VCDR is a continuous variable that is used clinically as a measure of optic nerve head cupping to diagnose and follow disease status in glaucoma cases. It is a relatively simple and moderately robust method to approximate loss of neuroretinal rim in glaucoma patients (Foster et al., 2002). Optic nerve head and retinal parameters measured by high resolution imaging technologies like OCT, scanning laser polarimetry, and scanning laser topography are far more accurate and robust (Fallon et al., 2017). A number of genetic loci have been associated with optic nerve head and retinal parameters. These VCDR-associated variants are located near or within many genetic loci, including *CDKN2B-AS1*, *SIX6*, *ATOH7-PBLD*, *FRMD8-SCYL1*, *CDC7-TGFBR3*, *DCLK1*, *CHEK2*, *COL8A1*, *DUSP1*, *EXOC2*, *HSF2*, *PLCE1*, *SSSCA1*, *ADAMTS8*, *RPAP3*, *TMTC2*, *SALL1*, *BMP2*, *CHEK2*, *RERE*, *RPE65*, *F5*, *PDZD2*, *RREB1*, *DGKB*, *VCAN*, *PSCA*, *ENO4*, *RBM23*, and *CARD10* (Nannini et al., 2017; Ramdas et al., 2010; Springelkamp et al., 2014; Springelkamp et al., 2017). Variants in or near *CDC42BPA*, *CRISPLD1*, *FAM169B*, *CDKN1A*, *COL8A1*, *ATOH7*, *PLCE1*, *TMTC2*, *ASB7*, *CHEK2*, *SIX6*, *CDKN2B-AS1*, *SSSCA1*, *ADAMTS8*, *DCLK1*, *BMP2*, *FLNB*, *FAM101A*, *RERE*, *TRIB2*, *DUSP1*, *DDHD1*, *SALL1*, *BCAS3*, *EFEMP1/PNPT*, *TRIOBP*, and *HSF2* are associated with cup area (Springelkamp et al., 2014; Springelkamp et al., 2017; Springelkamp et al., 2015b). Variants in or near *ATOH7*,

TMTC2, *CHEK2*, *CDC7-TGFBR3*, *SALL1*, *ELP4-PAX6*, *CARD10*, *CDC42BPA*, *F5*, *DIRC3*, *RARB*, *ABI3BP*, *COL8A1*, *DCAF4L2*, *TMTC2*, *PRDM16*, *UGT8*, *CTNNA3*, *GADD45A*, *VGLL4*, *ASB7*, and *HORMAD2*, have been associated with optic disc area, which is the area of the oval scleral opening where the retinal ganglion cell axons exit the eye (Gasten et al., 2012; Ramdas et al., 2010; Springelkamp et al., 2015b). Variants in or near *CDKN2B-AS1*, *SIX6*, *ATOH7*, *CDC7-TGFBR3*, and *CDKN1A* are associated with POAG (Carnes et al., 2014; Iglesias et al., 2014; Li et al., 2015; Liu et al., 2013b; Ramdas et al., 2011b; Skowronska-Krawczyk et al., 2015; Springelkamp et al., 2017; Wiggs et al., 2012). It is interesting to note that there are two well-known long noncoding RNAs (lncRNAs), *NEAT1* (nuclear paraspeckle assembly transcript 1) and *MALAT1* (metastasis associated lung adenocarcinoma transcript 1), are located in the genomic region between *FRMD8* and *SCYL1* genes. lncRNA *MALAT1* has been associated with retinal neurodegeneration and diabetic retinopathy (Liu et al., 2014a; Yan et al., 2014; Yang et al., 2016b; Yao et al., 2016; Zhou et al., 2015). It is not known if these lncRNAs contribute to the development of POAG.

Family-based linkage analysis in a large Dutch pedigree identified two loci for RNFL thickness at chr3p22.2 (*DCLK3* locus) and 14q22–q23 (*SIX6* locus) (Axenovich et al., 2011). A quantitative analysis of rs33912345, a *SIX6* coding variant and a variant in strong linkage disequilibrium with this variant, rs10483727, have been associated with RNFL thickness (Cheng et al., 2015; Kuo et al., 2015). Both variants have been associated with POAG risk. As discussed earlier, there is strong evidence that the *SIX6* coding variant rs33912345 has a functional effect that influences RNFL thickness.

6. Differential Expression Tissue Studies in POAG

Microarray or next generation sequencing –based gene expression studies are used to identify disease-related genes and pathways (Jakobs, 2014). Expression profiling in normal and glaucoma-affected ocular tissues offers valuable new information that has advanced our genetic and molecular understanding of POAG. Due to the size of the field the focus of this review will be limited to studies that have used normal and/or glaucomatous human ocular tissues. There are excellent reviews of expression analyses in cell culture and animal models for glaucoma (Jakobs, 2014; Libby et al., 2005; Tezel, 2014; Yang and Zack, 2011). Expression profiling of normal human eye tissues has been performed for TM, ciliary body, iris, cornea, optic nerve head, RGC layer, and retina (Carnes et al., 2016; Diehn et al., 2005; Drewry et al., 2016; Farkas et al., 2013; Janssen et al., 2012; Karali et al., 2016; Kim et al., 2006; Liu et al., 2011b; Miao et al., 2008; O'Brien et al., 2014; Pinelli et al., 2016; Wagner et al., 2013; Whitmore et al., 2014). These studies have generated extensive, tissue specific information for baseline gene expression. These datasets and related databases are excellent tools for use by glaucoma researchers. These include The Ocular Tissue Database (genome.uiowa.edu/otdb), sSyTE (bioinformatics.udel.edu/research/isyte), NEIBank (neibank.nei.nih.gov), and EyeBrowse (<https://hpcwebapps.cit.nih.gov/eyebrowse>) (Lachke et al., 2012; Wagner et al., 2013; Wistow et al., 2008). Many of these datasets can be found and downloaded from NCBI Gene Expression Omnibus (GEO) repository (www.ncbi.nlm.nih.gov/gds).

TM tissues obtained from glaucoma cases, post-mortem or post-surgical, have been used for differential gene/protein expression studies to identify pathways that contribute to POAG. These pathways include those related to inflammation, cell adhesion, extracellular matrix, and exosome-related pathways in POAG (Borras, 2003; Diskin et al., 2006; Liton et al., 2006; Liu et al., 2013a; Micera et al., 2016; Wang et al., 2008). Expression analysis with glaucoma-affected human Schlemm canal endothelial cells suggests the contribution of cell adhesion, heparin binding, glycosaminoglycan binding, and extracellular matrix remodeling pathways in the pathogenesis of POAG (Cai et al., 2015; Overby et al., 2014). Microarray analyses in astrocytes obtained from optic nerve head tissue have demonstrated the involvement of a variety of biological processes in glaucoma, which include cell adhesion and proliferation, cell motility, extracellular matrix synthesis and degradation, neurosteroids, and signal transduction (Agapova et al., 2003; Hernandez et al., 2002; Lukas et al., 2008; Ricard et al., 1999). Expression analysis of primary lamina cribrosa cells has implicated involvement of TGF- β , extracellular matrix, and fibrosis in POAG (Kirwan et al., 2009). Proteomics analysis using human retina has identified the differential regulation of complement activation related to oxidative stress in glaucomatous retina (Tezel et al., 2010) as well as pathways related to cellular development, stress, and cell death (Funke et al., 2016).

Proteomic studies of tears from patients with POAG provide additional support for the role of inflammation in POAG (Pieragostino et al., 2013; Pieragostino et al., 2012). Elevated levels of zymosterol and glucopyranosyl cholesterol and decreased levels of galactosylceramide and glucosylceramide in glaucomatous aqueous humor suggest the potential contribution of glycosylceramide in glaucoma (Aljohani et al., 2013; Aribindi et al., 2013), which is consistent with involvement of *GALC* in glaucoma (Liu et al., 2011a). Proteomic studies of aqueous humor from POAG patients in comparison to non-glaucoma controls have found elevated concentrations of transthyretin, TGF- β 1, TGF- β 2, IL-6, IL-8, IL-10, IL-12, TNF- α , IFN- γ , and HGF (Balaiya et al., 2011; Chua et al., 2012; Cvenkel et al., 2010; Duan et al., 2010; Freedman and Iserovich, 2013; Grus et al., 2008; Hu and Ritch, 2001; Inatani et al., 2001; Janciauskiene et al., 2011; Kuchtey et al., 2010; Min et al., 2006; Ochiai and Ochiai, 2002; Ozcan et al., 2004; Picht et al., 2001; Sawada et al., 2010; Takai et al., 2012; Trivedi et al., 2011; Yamamoto et al., 2005). It is interesting that transthyretin, an abundant protein found in cerebrospinal fluid (CSF), has been shown to form amyloid deposits (Saraiva, 2001). The elevated level of transthyretin in glaucomatous aqueous humor may promote the formation of amyloid deposit in the eye while elevated levels of serum amyloid A has been identified in glaucomatous TM and aqueous humor (Takai et al., 2012; Wang et al., 2008). In summary, differential gene/protein expression analyses support evidence that processes involved in inflammation, extracellular matrix metabolism, cell adhesion, TGF- β , and cell motility in POAG pathology.

7. Conclusion

The rapid development in genome technology has accelerated the identification of POAG-related genetic factors using genome-wide association studies in glaucoma patients. Striking progress has been made toward our understanding of Mendelian and complex inherited forms of POAG. The identification of associations for disease- or endophenotype- related

genetic factors has generated new opportunities to investigate the cellular and molecular mechanisms that contribute to factors related to glaucoma. For example, the discovery of common and functional genetic variants for POAG (SIX6) will enable targeted investigations into POAG-associated pathways.

During the last few years, significant genomic resources including the ENCODE project (Encyclopedia of DNA Elements, www.encodeproject.org) (Kellis et al., 2014) and the GTEx project (Genotype-Tissue Expression project, www.gtexportal.org) (Consortium, 2015) have dramatically promoted “post-GWAS” research for a broad array of human disorders, such as cardiovascular disease, diabetes, cancer, and many neurodegenerative disorders. This has highlighted the need to expand the availability of human ocular tissues in health and disease that has slowed progress in the study of many human eye disorders including glaucoma. Specifically, it is of central importance to have access to surgical and postmortem human ocular samples with detailed clinical information for future research on functional genomics and epigenetics. The Duke-Miracles in Sight Program located in Durham, NC, and others have implemented mechanisms to obtain clinically documented ocular tissues that are necessary for high level ophthalmic research (Williams et al., 2016a; Williams et al., 2016b). Ultimately our advanced understanding of glaucoma development provided by these efforts will lead to more effective preventive, diagnostic and therapeutic options for patients with this common leading cause of irreversible blindness.

Acknowledgments

This work was supported by the Glaucoma Research Foundation (San Francisco, CA, USA) (YL), the Glaucoma Foundation (New York, NY, USA) (YL), BrightFocus Foundation (Formerly called American Health Assistance Foundation) (Clarksburg, MD, USA) (YL), Research to Prevent Blindness, Inc. (New York, NY, USA), National Eye Institute (NEI, Bethesda, MD, USA) Grant R01EY023242 (YL), R03EY014939 (RRA), R01EY015543 (RRA), and R01EY023646 (RRA)

Abbreviations

POAG	primary open-angle glaucoma
IOP	intraocular pressure
CCT	central cornea thickness
GWAS	genome-wide association studies
TM	trabecular meshwork
RGC	retinal ganglion cells
VCDR	vertical cup-to-disc ratio
RNFL	retinal nerve fiber layer
HTG	high tension glaucoma
NTG	normal tension glaucoma
CNV	copy number variants

ER	endoplasmic reticulum
SNP	single nucleotide polymorphism
ALS	amyotrophic lateral sclerosis
lncRNA	long non-coding RNA

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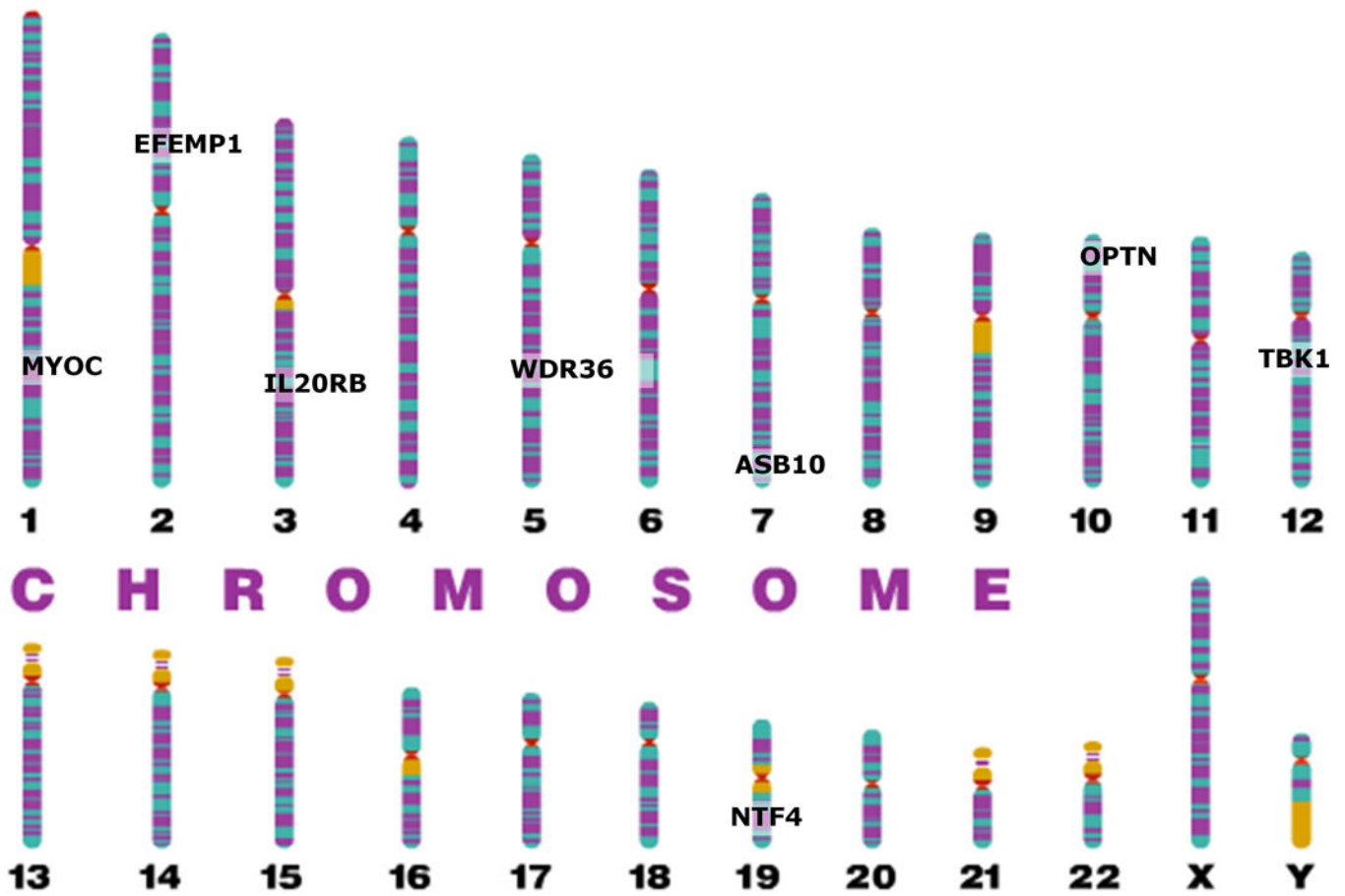


Figure 1.
Genome plot of Mendelian genes for POAG that have been identified through genetic linkage analysis.

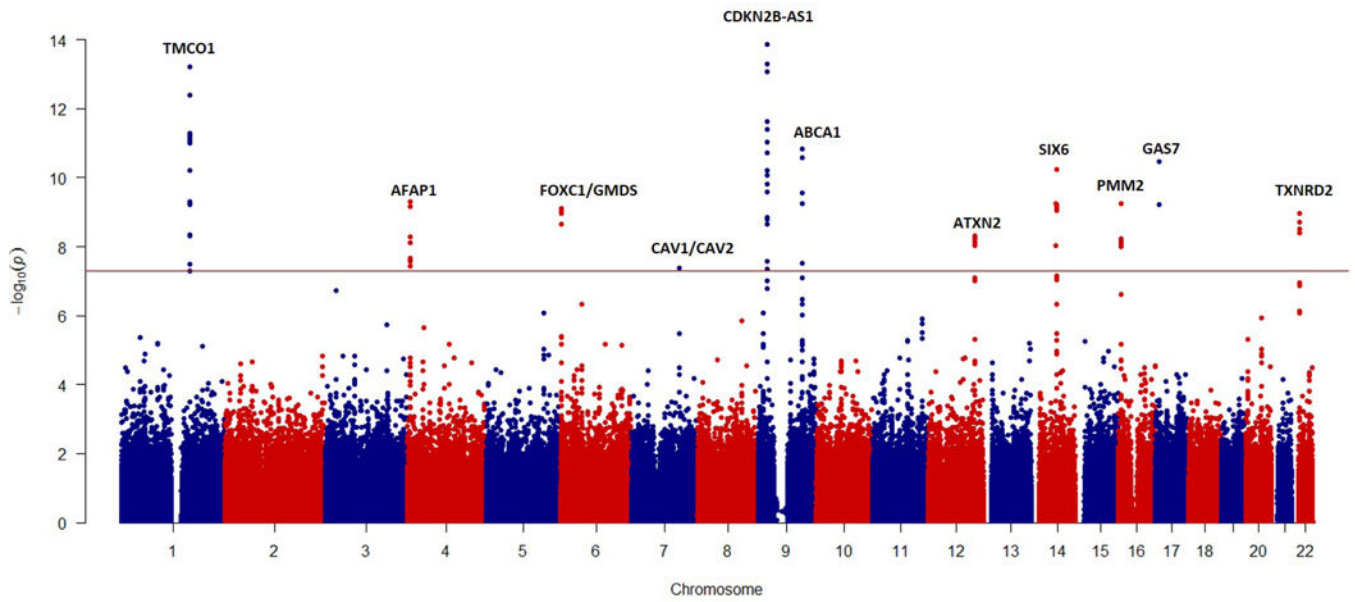


Figure 2. Manhattan plot of current genome-wide genetic associations for POAG (through January, 2017). The red line represents the cut-off for genome-wide significant association (5×10^{-8}). This figure is was generously provided by Chiea Chuen Khor, MD, PhD at the Genome Institute of Singapore.

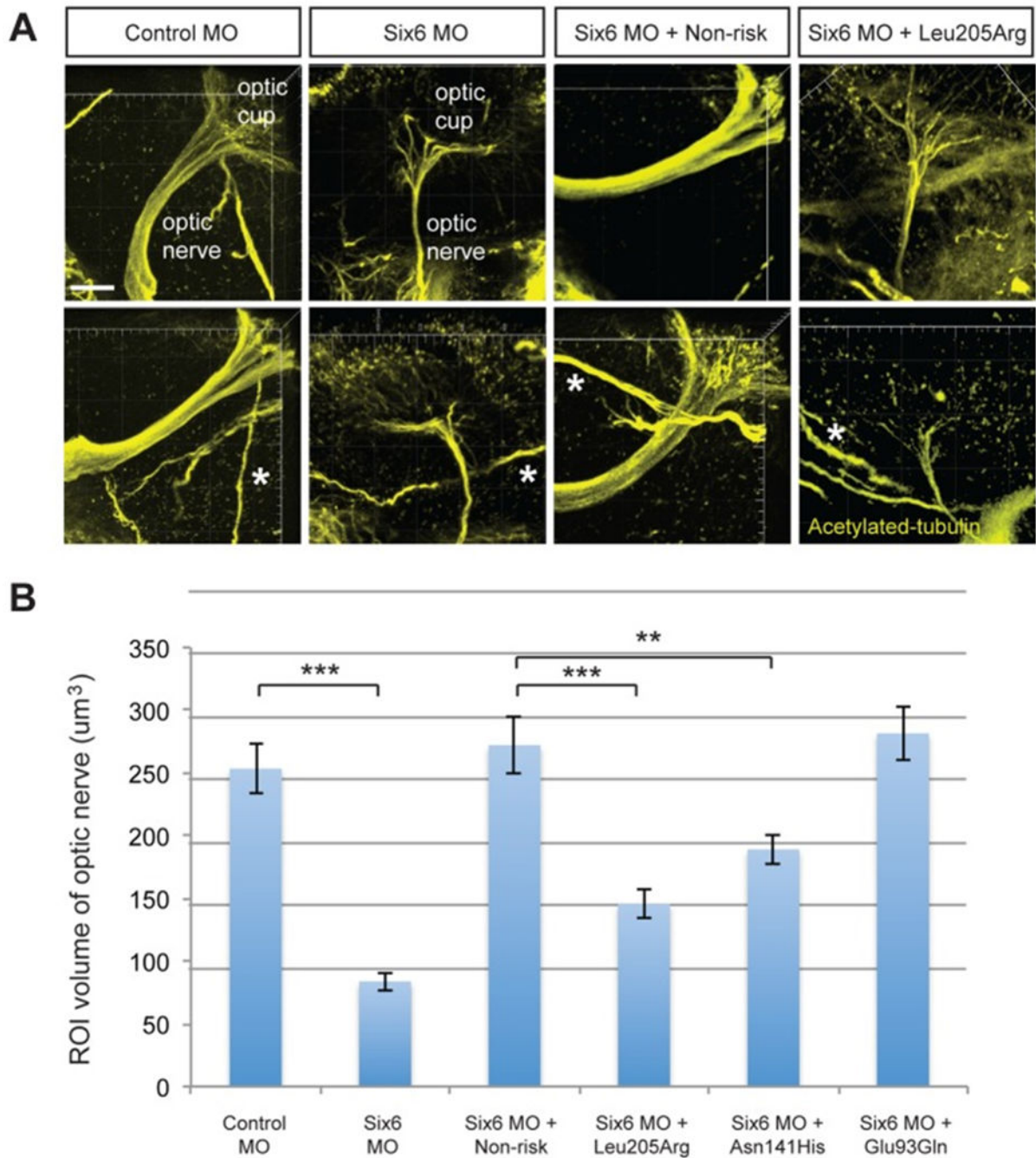


Figure 3.

Functional evaluation of *SIX6* variants on the volume of the optic nerve.

Representative whole mount images of acetylated-tubulin expression in the heads of zebrafish embryos injected with a control or six6a morpholino, rescued by co-injection with human non-risk *SIX6* transcript or a transcript containing the Leu205Arg hypomorphic variant (A). Acetylated-tubulin staining is restricted primarily to axon tracts and can be used to visualize the optic nerve. Relative to the control morphants, volumetric regions of interest (ROI) along the optic nerve in six6a morphants were reduced significantly. Co-injection of

human variants revealed a hypomorphic (Leu205Arg, Asn141His) or benign (Glu93Gln) role of the variants on the optic nerve (B). Sample size for all injection paradigms ranged from 7–9 and p-values are plotted for each comparison (***) $p < 0.001$; ** $p < 0.01$). No significant changes in the volume of other axonal tracts in the head (marked by an asterisk) were detected. Standard error of the mean is shown and white scale bars = 20 μm . (Figure adapted from (Carnes et al., 2014)).

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Table 1

POAG chromosomal Loci identified through linkage analysis

Locus Name	Chromosomal Location	POAG Phenotype	Candidate Gene	References
GLC1A	1q24.3	JOAG, Adult-onset	MYOC	(Sheffield et al., 1993; Stone et al., 1997)
GLC1B	2cen-q13	Adult-onset		(Akiyama et al., 2008; Charlesworth et al., 2006; Stoilova et al., 1996)
GLC1C	3q21-q24	Adult-onset	IL20RB	(Keller et al., 2014; Kitsos et al., 2001; Samples et al., 2004; Wirtz et al., 1997)
GLC1D	8q23	Adult-onset		(Trifan et al., 1998)
GLC1E	10p13	Adult-onset, NTG	OPTN	(Rezaie et al., 2002; Sarfarazi et al., 1998)
GLC1F	7q36.1	Adult-onset	ASB10	(Pasutto et al., 2012; Wirtz et al., 1999)
GLC1G	5q22.1	Adult-onset	WDR36	(Monemi et al., 2005)
GLC1H	2p16.3-p15	JOAG, Adult-onset	EFEMP1	(Lin et al., 2008; Mackay et al., 2015; Suriyapperuma et al., 2007)
GLC1I	15q11-q13	Adult-onset		(Allingham et al., 2005; Crooks et al., 2011; Wiggs et al., 2000; Woodroffe et al., 2006)
GLC1J	9q22	JOAG		(Wiggs et al., 2004)
GLC1K	20p12	JOAG		(Wiggs et al., 2004)
GLC1L	3p22-p21	Adult-onset		(Baird et al., 2005)
GLC1M	5q22.1-q32	JOAG		(Fan et al., 2007; Pang et al., 2006)
GLC1N	15q22-q24	JOAG		(Wang et al., 2006)
GLC1O	19q13.33	Adult-onset	NTF4*	(Liu et al., 2010; Pasutto et al., 2009; Vithana et al., 2010)
GLC1P	12q14	NTG, adult-onset	TBK1	(Bennett et al., 1989; Fingert et al., 2011; Ritch et al., 2014)

* *NTF4* gene in the GLC1O locus was evaluated as a candidate gene for POAG without family-based studies or linkage analysis.

Table 2

List of POAG-associated genomic regions identified with genome-wide association studies (GWAS). (*Asian and European ancestry)

Nearest Gene	Leading SNP	Sample Size (case/control)	Ethnicity	POAG	Odds Ratio	Significance	References
<i>ZPA</i>	rs693421	827/748	Japanese	POAG	1.35	4×10E-5	
<i>PLXDC2</i>	rs7081455	827/748	Japanese	POAG	1.49	1×10E-5	(Nakano et al., 2009)
<i>TMTC2</i>	rs7961953	827/748	Japanese	POAG	1.37	7×10E-5	
<i>SRBD1</i>	rs3213787	305/355	Japanese	NTG	2.80	3×10E-9	(Meguro et al., 2010)
<i>ELOVL5</i>	rs735860	305/355	Japanese	NTG	1.70	4×10E-6	
<i>CAVI/CAV2</i>	rs4236601	1263/34877	Icelandic	POAG	1.36	5×10E-10	(Thorleifsson et al., 2010)
<i>TMCO1</i>	rs4656461	892/4582	Australian	Advanced POAG/POAG	1.51	6×10E-14	(Burdon et al., 2011)
<i>CDKN2B-AS1</i>	rs4977756	892/4582	Australian	Advanced POAG/POAG	1.39	1×10E-14	
<i>CDKN2B-AS1</i>	rs2157719	3146/3487	European American	POAG	0.69	2×10E-18	
<i>SIX1/SIX6</i>	rs10483727	3146/3487	European American	POAG	1.32	4×10E-11	(Wiggs et al., 2012)
<i>CDKN2B-AS1</i>	rs2157719	720/3443	European American	NTG	0.58	1×10E-12	
<i>LRP12/ZFPM2</i>	Rs284489	720/3443	European American	NTG	0.62	9×10E-10	
<i>ABCA1</i>	rs2472493	4703/11488	European Ancestry	Advanced POAG/POAG	1.31	2×10E-19	
<i>AFAP1</i>	rs4619890	4703/11488	European Ancestry	Advanced POAG/POAG	1.20	7×10E-10	(Gharahkhani et al., 2014)
<i>GMDS</i>	rs11969985	4703/11488	European Ancestry	Advanced POAG/POAG	1.31	8×10E-10	
<i>ABCA1</i>	rs2472493	4284/95560	Multi-ancestry*	POAG	1.24	4×10E-9	
<i>TMCO1</i>	rs7555523	4284/95560	Multi-ancestry*	POAG	1.40	1×10E-16	
<i>CAVI</i>	rs10258482	4284/95560	Multi-ancestry*	POAG	1.20	6×10E-9	(Hysi et al., 2014)
<i>GA57</i>	rs9913911	4284/95560	Multi-ancestry*	POAG	0.80	3×10E-13	
<i>ABCA1</i>	rs2487032	2906/5974	Chinese	POAG	0.73	3×10E-19	
<i>ABCA1</i>	rs2487032	2147/3246	Chinese	HTG	0.71	2×10E-15	
<i>ABCA1</i>	rs2487032	759/2728	Chinese	NTG	0.77	1×10E-5	(Chen et al., 2014)
<i>PMM2</i>	rs3785176	2906/5974	Chinese	POAG	1.30	6×10E-10	
<i>PMM2</i>	rs3785176	2147/3246	Chinese	HTG	1.30	6×10E-7	
<i>PMM2</i>	rs3785176	759/2728	Chinese	NTG	1.28	2×10E-4	

Nearest Gene	Leading SNP	Sample Size (case/control)	Ethnicity	POAG	Odds Ratio	Significance	References
<i>ARHGFE12</i>	rs58073046	1225/4117	European Ancestry	POAG	1.53	2×10E-8	(Springelkamp et al., 2015a)
<i>ARHGFE12</i>	rs58073046	777/4117	European Ancestry	HTG	1.66	3×10E-9	
<i>CDKN2B-AS1</i>	rs2157719	9173/26780	Multi-ancestry	POAG	0.71	3×10E-33	(Li et al., 2015)
<i>CDC7-TGFBFR3</i>	rs1192415	9173/26780	Multi-ancestry	POAG	1.13	2×10E-8	
<i>TXNRD2</i>	rs35934224	3853/33480	European American	POAG	0.78	4×10E-11	
<i>ATXN2</i>	rs7137828	3853/33480	European American	POAG	1.17	9×10E-10	
<i>FOXC1</i>	rs2745572	3853/33480	European American	POAG	1.17	2×10E-10	
<i>LRP12/ZPPM2</i>	rs284491	725/11145	European American	NTG	0.66	2×10E-8	
<i>CDKN2B-AS1</i>	rs1333037	725/11145	European American	NTG	1.67	1×10E-12	(Bailey et al., 2016)
<i>C12ORF23</i>	rs2041895	725/11145	European American	NTG	1.48	2×10E-8	
<i>FOXC1</i>	rs2317961	1868/31497	European American	HTG	0.76	3×10E-8	
<i>TMCO1</i>	rs7555523	1868/31497	European American	HTG	N/A	1×10E-12	
<i>SIX1/SIX6</i>	rs33912345	1868/31497	European American	HTG	N/A	2×10E-9	