Common and Rare Genetic Risk Factors for Glaucoma

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The characterization of genes responsible for glaucoma is the critical first step toward the development of gene-based diagnostic and screening tests, which could identify individuals at risk for disease before irreversible optic nerve damage occurs. Early-onset forms of glaucoma affecting children and young adults are typically inherited as Mendelian autosomal dominant or recessive traits whereas glaucoma affecting older adults has complex inheritance. In this report, we present a comprehensive overview of the genes and genomic regions contributing to inherited glaucoma.

RATIONALE FOR DISCOVERY OF GENES CONTRIBUTING TO GLAUCOMA

The characterization of genes responsible for glaucoma is the critical first step toward the development of gene-based diagnostic and screening tests, which could identify individuals at risk for disease before irreversible optic nerve damage occurs. Current glaucoma therapies are limited to reducing elevated intraocular pressure (IOP), a major risk factor for the disease. The discovery of disease-related genes could provide new insights into the underlying molecular mechanisms responsible for glaucoma that could form the basis of novel gene-based therapies, including strategies for neuroprotection. Understanding the role of the protein product in health and disease will also provide new insights into the underlying molecular mechanisms responsible for disease.

Glaucoma can affect individuals of all ages. Early-onset forms of glaucoma affecting children and young adults are typically inherited as Mendelian autosomal dominant or recessive traits whereas glaucoma affecting older adults has complex inheritance. Early-onset forms of glaucoma are rare whereas adult-onset forms are more common.

RARE VARIANTS CAUSING EARLY-ONSET GLAUCOMA WITH AUTOSOMAL DOMINANT OR AUTOSOMAL RECESSIVE INHERITANCE

Compared with adult-onset glaucoma, early-onset forms of glaucoma are rare with incidence ranging from 1/2500 to 1/20,000, depending on the condition and the population (Stoilov et al. 1997; Bejjani et al. 2000; Chakrabarti et al. 2010). Genetic variants causing early-onset

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glaucoma are highly penetrant, although variable expressivity may be observed. The genes currently known to cause early-onset glaucoma are listed in Table 1. All of these genes were initially identified using genetic linkage analyses of large, multigenerational families. These genes are responsible for congenital glaucoma (*CYP1B1* and *LTBP2*), developmental glaucoma (*PITX2*, *FOXC1*, *PAX6*, and *LMX1B*), juvenile-onset primary open angle glaucoma (*MYOC*), and familial normal-tension glaucoma (*OPTN* and *TBK1*).

Congenital Glaucoma

Congenital glaucoma (or infantile glaucoma) typically develops before three years of age (Aponte et al. 2010). The condition is primarily inherited as an autosomal recessive trait, although autosomal dominant families have been described (Sarfarazi et al. 2000). Genetic linkage studies have identified three loci likely to contain genes contributing to congenital glaucoma: GLC3A (2p21), GLC3B (1p36), and GLC3C (14q22) (Sarfarazi et al. 1995; Akarsu et al. 1996; Stoilov and Sarfarazi 2002). Two genes have been discovered: *CYP1B1*, encoding cytochrome P450 1B1 (GLC3A), and *LTBP2* (latent transforming growth factor binding protein 2) (Ali et al. 2009; Beijani et al. 2000). Mutations in both *CYP1B1* and *LTBP2* cause autosomal recessive disease.

CYP1B1 mutations are the most common cause of congenital glaucoma worldwide (Stoi-

lov et al. 1997). Disease-causing mutations include missense mutations, nonsense mutations, frameshifts, and large-gene deletions (Stoilov et al. 1997; Sarfarazi 2000; Michels-Rautenstrauss et al. 2001). Although these mutations are highly penetrant, variable expressivity is a well-known feature of *CYP1B1*-related disease. Genotype–phenotype studies have suggested that mutations causing premature truncation of the protein (frameshifts, deletions, insertions, and nonsense mutations) cause more severe disease with earlier onset than disease caused by missense mutations. The gene product, cytochrome P450 1B1, metabolizes complex molecules such as polycyclic aromatic hydrocarbons and 17 β -estradiol (Tokizane et al. 2005; Tsuchiya et al. 2005; Sowers et al. 2006). The role of the protein in congenital glaucoma is not clear; however, it has been hypothesized that cytochrome P450 1B1 activity is responsible for metabolism of compounds involved in ocular development (Choudhary et al. 2008; Choudhary et al. 2009).

LTBP2 (Latent transforming growth factor, TGF, β -binding protein 2) was initially identified as the causative gene in patients with early-onset glaucoma from Pakistan and in patients of Gypsy ethnicity (Ali et al. 2009; Narooie-Nejad et al. 2009). The gene is located 1.3 Mb from the GLC3C locus on 14q22; however, *LTBP2* mutations have not been identified in the family initially used to define the GLC3C locus, suggesting that a second congenital glaucoma gene is located in this region (Sharafieh et al. 2013).

Table 1. Genes responsible for early-onset glaucoma

Disease	Juvenile open-angle glaucoma	Anterior segment dysgenesis	Congenital glaucoma	Familial normal-tension glaucoma
Genes	<i>MYOC</i>	<i>PITX2</i> , <i>FOXC1</i> , <i>PAX6</i>	<i>CYP1B1</i> , <i>LTBP2</i>	<i>OPTN</i> , <i>TBK1</i>
Protein function	Extracellular matrix	Developmental regulation of gene expression	Cytochrome P450 1B1 (<i>CYP1B1</i>); extracellular matrix (<i>LTBP2</i>)	TNF- α signaling, autophagy
Mutation	Endoplasmic reticulum stress	Abnormal ocular development	Abnormal ocular development	Increased rate retinal ganglion cell apoptosis
Reference(s)	Stone et al. 1997	Gould et al. 1997; Mears et al. 1998; Riise et al. 2001	Stoilov et al. 1997; Ali et al. 2009	Rezaie et al. 2002; Morton et al. 2008

The *LTBP2* protein is located in the extracellular matrix, where it associates with microfibrils containing fibrillin-1 (Jelodari-Mamaghani et al. 2013). Interestingly, *LTBP2* mutations have been associated with Weill-Marchesani and Weill-Marchesani-like syndrome, a condition characterized by microspherophakia and abnormal ocular anterior segment development (Haji-Seyed-Javadi et al. 2012). *LTBP2* appears to be a rare cause of congenital glaucoma in ethnically diverse populations, such as in the United States (Lim et al. 2012).

Developmental Glaucoma

Abnormal development of the anterior segment can lead to dysgenesis of critical anterior segment structures involved in glaucoma, including the trabecular outflow pathways and Schlemm's canal. Developmental glaucoma may be syndromic (Axenfeld-Rieger syndrome and aniridia) or limited to only ocular involvement. Some patients with anterior segment dysgenesis never develop glaucoma, whereas others have very severe disease evident at birth (Gould and John 2002). Four genes coding for proteins involved in regulation of gene expression can contribute to developmental glaucoma (*PITX2*, *FOXC1*, *PAX6*, and *LMX1B*). Mutations in these genes cause autosomal dominant disease with high penetrance but variable expressivity both within and among affected families. The phenotypic features of disease caused by these genes, as well as those caused by *CYP1B1* and *LTBP2*, are similar, making it impossible to establish the genetic diagnosis through clinical examination alone (Fig. 1). Genetic testing can establish a molecular diagnosis as well as clarify the inheritance information necessary for accurate genetic counseling.

PITX2 and *LMX1B* cause syndromic forms of developmental glaucoma (Rieger syndrome and Nail-Patella syndrome, respectively). Approximately 50% of patients with *PITX2* mutations develop glaucoma (Reis et al. 2012). Recently, mutations involving a genomic region distal to *PITX2* have been identified as disease causing (Volkman et al. 2011). Patients with *LMX1B* mutations are affected by Nail-Patella

Figure 1. Anterior segment phenotypes in patients with developmental glaucoma. Anterior segment photographs taken with a camera attached to a slit-lamp are shown for four patients with mutations in genes associated with early-onset glaucoma. Notable features are peripheral corneal opacification (*CYP1B1*), irido-corneal adhesions (*PITX2*) and iris atrophy (*FOXC1*). In the patients with *FOXC1* mutations the atrophic iris makes it possible to see the pupillary sphincter muscle, which is normally not visible because of overlying iris stroma.

syndrome, which can involve the eye, causing a variety of glaucoma-related features (Chen et al. 1998; Dreyer et al. 1998; Mimiwati et al. 2006). Mutations in *PAX6* cause abnormal development of stem cells in the iris and corneal limbus, resulting in a broad range of clinical features, from agenesis of the iris to corneal opacification caused by a deficiency of limbal stem cells (Hingorani et al. 2009). *FOXC1* was initially identified as a gene responsible for iris hypoplasia (Mears et al. 1998). Subsequent studies have identified cardiac abnormalities and possibly other systemic features in patients with mutations in these genes (Gould et al. 1997; Swiderski et al. 1999; Winnier et al. 1999).

Juvenile-Onset Primary Open-Angle Glaucoma

Patients affected by open-angle glaucoma have disease despite normal anatomic structures.

Adult-onset primary open-angle glaucoma (POAG) develops after 50 years of age, whereas juvenile-onset (or early-onset) open-angle glau-

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coma affects children and young adults, with onset typically between the ages of 3 and 20. Juvenile open-angle glaucoma is inherited as an autosomal dominant trait (Wiggs et al. 1998) and is characterized by very high IOP (Wiggs et al. 1995; Johnson et al. 1996). Linkage studies using large families have identified a number of juvenile open-angle glaucoma loci: GLC1A (1q24.3-q25.2) (Sheffield et al. 1993), GLC1J (9q22) (Wiggs et al. 2004), GLC1K (20p12) (Wiggs et al. 2004), GLC1M (5q22.1-q32) (Wang et al. 2004; Pang et al. 2006; Fan et al. 2007), and GLC1N (15q22-q24) (Wang et al. 2006). Among these loci only one gene, *MYOC*, coding for myocilin, has been identified (Kubota et al. 1997; Stone et al. 1997). Missense changes in the protein account for 10% of the cases of juvenile open-angle glaucoma and also 3%–5% of the cases of adult-onset POAG (Wiggs et al. 1998; Fingert et al. 1999). Disease-causing mutations are primarily located in the protein's olfactomedin domain (Fig. 2) (Adam et al. 1997; Stone et al. 1997; Fingert et al. 1999). Myocilin is an extracellular protein of unknown

function, and loss of the protein function does not result in glaucoma (Wiggs and Vollrath 2001; Kim et al. 2001), suggesting that the underlying genetic mechanism is likely to be a gain-of-function or dominant-negative effect. Additionally, a common nonsense variant located in exon 1 (Fig. 2) is a benign polymorphism and does not cause glaucoma or any other phenotype (Lam et al. 2000). Disease-causing mutations reduce the solubility of the protein, leading to protein misfolding and subsequent protein aggregation in the endoplasmic reticulum (Aroca-Aguilar et al. 2010). The misfolded protein response may lead to a loss of trabecular meshwork cells, resulting in high IOP (Joe et al. 2003). Interestingly, limiting protein aggregation using the small molecule phenyl butyrate (PBA) causes reduction in IOP both in vitro and in vivo, possibly pointing to novel gene-based therapy for patients with myocilin mutations (Yam et al. 2007; Zode et al. 2011, 2012). Recently, common variants in genes coding for multiplexin collagens XV and XVIII have been shown to modify the severity of myocilin-related glau-

Figure 2. *MYOC* mutations causing glaucoma. The gene location of selected *MYOC* mutations known to cause glaucoma are shown. Exon 1 extends from codon 1–201, exon 2 from codon 202–243, and exon 3 from codon 244–504. Exon 1 contains a leucine zipper (LZ) and exon 3 contains the Olfactomedin domain (Olf). Mutations causing early-onset glaucoma are shown in blue, adult-onset glaucoma in red, and a nonsense mutation known to be a benign polymorphism in green.

coma, suggesting that myocilin may interact with these protein in the extracellular matrix and/or in maintaining the integrity of the trabecular outflow pathways (Liton et al. 2005; Wiggs et al. 2013b).

Familial Normal-Tension Glaucoma

Normal-tension glaucoma (NTG) is a type of open-angle glaucoma characterized by optic nerve degeneration despite normal IOP. Most NTG patients have adult-onset disease; however, rarely, the disease can have early onset with autosomal dominant inheritance. Two genes have been associated with familial NTG: *OPTN* and *TBK1* (Rezaie et al. 2002; Morton et al. 2008; Fingert et al. 2011).

Rare missense mutations in *OPTN*, which encodes optineurin and particularly the E50K mutation, cause a severe early-onset familial form of NTG. (Aung et al. 2005; Morton et al. 2008). Optineurin is involved in basic cellular functions including protein trafficking, maintenance of the Golgi apparatus, as well as the NF- κ B pathway, antiviral responses, and antibacterial signaling (Ying 2012). Of interest, optineurin interacts with Tank1 (*TBK1*), which has also been implicated in familial NTG (Morton et al. 2008). The optineurin E50K mutation causes the protein to become inactive and/or insoluble (Minegishi et al. 2013). This mutation also enhances the interaction of optineurin with Tank1 (Fingert et al. 2011).

COMMON VARIANTS CONTRIBUTING TO ADULT-ONSET GLAUCOMA WITH COMPLEX INHERITANCE

POAG, adult-onset NTG, pseudoexfoliation glaucoma, and primary angle-closure glaucoma are common traits with complex inheritance. Genetic variants contributing to these conditions have been identified using genome-wide association approaches (Thorleifsson et al. 2007, 2010; Burdon et al. 2011; Vithana et al. 2012; Wiggs et al. 2012, 2013a). Generally, variants contributing to common complex traits such as adult-onset glaucoma have small individual effects on disease development. Aggregated effects from multiple risk factors, including environmental risk factors, can have a larger impact. Robust genetic associations have been observed for POAG (*CDKN2BAS* [Burdon et al. 2011; Wiggs et al. 2012], *SIX1/SIX6* [Wiggs et al. 2012], *CAV1/CAV2* [Thorleifsson et al. 2010; Wiggs et al. 2011], *TMCO1* [Burdon et al. 2011]), NTG (*CDKN2BAS* [Wiggs et al. 2012] and a regulatory region on 8q22 [Wiggs et al. 2012]), pseudoexfoliation (*LOXL1* [Thorleifsson et al. 2007]), and primary angle-closure glaucoma (*PLEKHA7* and *COL11A1* [Vithana et al. 2012]) (Table 2). Additionally, genetic variants associated with quantitative ocular traits that are risk factors for common forms of glaucoma have also been identified. These include IOP (van Koolwijk et al. 2012), central corneal thickness (CCT) (Vithana et al. 2011; Lu et al. 2013), and optic nerve parameters including

Table 2. Genes/loci contributing to adult-onset glaucoma

Gene	Disease	Function	Reference(s)
<i>CDKN2BAS</i>	POAG, NTG	Cell cycle regulation, TGF- β signaling	Burdon et al. 2011; Wiggs et al. 2012
<i>TMCO1</i>	POAG	Unknown	Burdon et al. 2011
<i>SIX1/SIX6</i>	POAG	Optic nerve development	Fan et al. 2011; Ramdas et al. 2011
8q22 enhancer	NTG	Regulation of fluid production in ciliary body and choroid plexus	Wiggs et al. 2012
<i>CAV1/CAV2</i>	POAG	Endothelial membranes	Thorleifsson et al. 2010
<i>LOXL1</i>	Pseudoexfoliation	Elastinogenesis and maintenance	Thorleifsson et al. 2007
<i>PLEKHA7</i>	Angle-closure glaucoma	Adherens junction protein	Vithana et al. 2012
<i>COL11A1</i>	Angle-closure glaucoma	Sclera development	Vithana et al. 2012

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cup-to-disc ratio and optic nerve area (Ramdas et al. 2010; Macgregor et al. 2010; Axenovich et al. 2011) (Table 3).

The clinical features of POAG generally include both elevated IOP and optic nerve degeneration. Patients with optic nerve disease without elevation of IOP are referred to as the NTG subgroup. Large genome-wide association studies (GWAS) have been completed for POAG in the Icelandic population (Thorleifsson et al. 2010), Australian population (Burdon et al. 2011), and in the United States (Wiggs et al. 2012). The Icelandic study identified a significant association between genetic variants located in the *CAV1/CAV2* genomic region and POAG. This finding has been replicated in a case-control sample from the US (Wiggs et al. 2011) and recently, *CAV1/CAV2* variants have been shown to be preferentially associated with patients who have loss of the central visual field early in the disease (Loomis et al. 2014). Both the Australian and the US studies identified significant associations with *CDKN2BAS*, a long noncoding antisense RNA that inhibits the expression of *CDKN2B*, an inhibitor of *CDK4*, a protein involved in promoting cell division (Burdon et al. 2011; Wiggs et al. 2012). The Australian study showed significant association with variants in the *TMCO1* genomic region, a gene that also appears to be associated with elevated IOP (see below). The US study identified significant association with variants in the *SIX1/SIX6* genomic region; these are also associated with the cup-to disc ratio, a quantitative optic nerve parameter (Ramdas et al. 2010; Wiggs et al. 2012).

NTG

Optic nerve degeneration without IOP elevation (<21 mmHg) is the defining clinical feature of NTG. Identifying the genetic factors that contribute to this condition could provide important insights into neuroprotective therapies for glaucoma. An analysis of the NTG subgroup in a large genome-wide association study of POAG using a United States case-control sample identified common variants in the *CDKN2BAS* region and a novel regulatory region on chromosome 8q22 as significant risk factors (Wiggs et al. 2012). The 8q22 region is a DNaseI hypersensitivity site that has high activity in the choroid plexus, which is responsible for the production of cerebrospinal fluid, and the ciliary body, which is responsible for the production of aqueous humor. Interestingly, recent hypotheses suggest that the translaminal pressure across the lamina cribrosa may be a risk factor for optic nerve damage, and this pressure gradient is defined by the difference between the IOP and cerebrospinal fluid pressure (Jonas and Wang 2013).

Pseudoexfoliation Syndrome

Pseudoexfoliation syndrome is a generalized disorder of extracellular matrix that results in a chronic deposition of fibrillar aggregates throughout the ocular anterior segment. Accumulation of the fibrillar material in the trabecular meshwork is thought to contribute to the development of glaucoma associated with this condition (Schlötzer-Schrehardt et al. 1995;

Table 3. Selected genes/loci contributing to quantitative ocular traits related to glaucoma

Gene	Trait	Function	Reference(s)
<i>CDKN2BAS</i>	Cup-to-disc-ratio	Cell cycle regulation, TGF- β signaling	Fan et al. 2011; Ramdas et al. 2011
<i>SIX1/SIX6</i>	Cup-to-disc-ratio	Developmental protein	Fan et al. 2011
<i>ATOH7</i>	Optic nerve area	Developmental protein	Macgregor et al. 2010
<i>TMCO1</i>	IOP	Unknown function	van Koolwijk et al. 2012
<i>GAS7</i>	IOP	Unknown function	van Koolwijk et al. 2012
<i>ZNF469</i>	CCT	Regulates expression of extracellular matrix components	Abu et al. 2008
<i>COL5A1</i>	CCT	Extracellular matrix	Lu et al. 2013
<i>COL8A2</i>	CCT	Extracellular matrix	Vithana et al. 2011

Naumann et al. 1998). A genome-wide association study conducted in the Icelandic population first identified common variants in the *LOXL1* gene as significant risk factors (Thorleifsson et al. 2007). Subsequently, association between *LOXL1* gene variants and pseudoexfoliation has been replicated in populations worldwide (Fan et al. 2011). *LOXL1* (lysyl-oxidase like 1) is necessary for formation and maintenance of elastin. It is not yet known how *LOXL1* variants influence development of pseudoexfoliation; however, recent evidence suggests that the variants associated with disease cause a decrease in gene expression, possibly resulting in reduced enzyme activity (Schlotzer-Schrehardt 2009). The *LOXL1* risk alleles are very common in pseudoexfoliation cases (95%–99%) but are also common in the normal population (60%–80%) suggesting that the gene variants are necessary but not sufficient for disease development (Fan et al. 2011). Recently, residence in northern latitudes has been identified as an environmental risk factor for this condition (Stein et al. 2011; Kang et al. 2012).

Primary Angle-Closure Glaucoma

Primary angle-closure glaucoma is common in Asian countries. A recent genome-wide association study using five independent Asian case-control samples identified three genomic regions statistically associated with POAG: rs3753841 (*COL11A1*), rs1015213 (located between *PCMTD1* and *ST18*), and rs11024102 (*PLEKHA7*) (Vithana et al. 2012). All of these single-nucleotide polymorphisms were also replicated in a combined Australian-Nepalese case-control sample (Awadalla et al. 2013). *COL11A1* is expressed in the sclera, and mutations in *COL11A1* are known to cause Stickler's syndrome, a condition that includes myopia, among other ocular features (Richards et al. 1996). As primary angle-closure glaucoma can be related to hyperopia, the genome-wide association study results may point to a role for *COL11A1* in development of refractive errors, possibly because of abnormal scleral development.

Quantitative Ocular Traits that Are Risk Factors for Glaucoma

For traits with complex inheritance, it can be useful to identify genetic factors influencing the underlying individual traits, such as IOP, optic nerve parameters, and CCT, that contribute to the overall disease (Charlesworth et al. 2010). These traits are quantitative, highly heritable, and show substantial variation in human populations. IOP is the only modifiable risk factor for glaucoma. Recent genome-wide analyses using normal populations have identified two genes significantly associated with IOP, *GAS7* and *TMCO1* (van Koolwijk et al. 2012). Similar analyses for optic nerve parameters associated with glaucoma risk have identified *CDKN2BAS* and *SIX1SIX6* as genetic risk factors contributing to cup-to-disc-ratio (Ramdas et al. 2010; Fan et al. 2011) and *ATOH7* as an important determinant of optic nerve size (Macgregor et al. 2010). Populations from around the world have been used to identify genetic factors contributing to CCT, one of the most heritable of the quantitative ocular traits (Toh et al. 2005). A recent study from the International Glaucoma Genetics Consortium (IGGC) identified 16 loci significantly associated with CCT (Fig. 3) (Lu et al. 2013). Pathway analyses suggested that collagen and extracellular matrix pathways are important regulators of CCT (Lu et al. 2013).

COMPLEX INTERACTIONS: GENE–ENVIRONMENT, GENE–GENE INTERACTIONS, AND EPIGENETIC EFFECTS

Complex genetic and gene–environment interactions are expected to contribute to the genetic architecture of common adult-onset disorders. Nutritional factors, such as dietary fat, antioxidant intake, and other lifestyle factors including smoking and postmenopausal hormone use may influence the development of POAG (Pasquale and Kang 2009). A gene–environment interaction involving hormone replacement therapy and *NOS3* (the gene coding for nitric oxide synthase 3) has been identified as a risk

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Figure 3. Gene and genomic regions with common variants that contribute to glaucoma and glaucoma-related ocular quantitative traits. Variants contributing to both primary open-angle glaucoma and normal tension glaucoma as well as selected ocular quantitative traits (CCT, IOP, and optic nerve parameters) are shown. Gene names are presented in dark font. Genes contributing to POAG are contained in the orange ellipse, NTG in the purple ellipse, CCT in the blue ellipse, IOP in the red ellipse, and optic nerve parameters in the green ellipse. Genes that contribute to more than one trait are indicated by their placement in the overlapping regions. For example, *CDKN2BAS* contributes to NTG, POAG, and to optic nerve parameters.

factor for POAG (Kang et al. 2010). The estrogen metabolism pathway is also associated with POAG in women (Pasquale et al. 2013). Gene–gene interactions contributing to POAG have been suggested for *WDR36* and *p53* (both influencing apoptosis) (Blanco-Marchite et al. 2011) and for genetic variants in *ATOH7* and *SIX1/SIX6* (Fan et al. 2011).

BIOLOGICAL PATHWAYS AND PROCESSES SUGGESTED BY GENETIC VARIANTS CONTRIBUTING TO GLAUCOMA

Genome-wide association studies have identified multiple genes potentially involved in glaucoma pathogenesis; however, the stringent correction for multiple testing and type I error identifies only variants with the largest main effects as statistically significant (Manolio et al.

2008). Many biologically meaningful associations of smaller effect size may go undetected; including variants with smaller effect size in systematic groups could reveal novel biological pathways or systems underlying disease susceptibility. Pathway-based analysis groups gene variants into biologically meaningful entities to distinguish the actual from the false-positive associations. In short, this type of analysis can be used to uncover additional genotype–phenotype associations that the single-allele genome-wide association analysis may have missed. Hypothesis-independent pathway analyses suggest that the underlying molecular pathogenesis of POAG involves a broad range of biological processes, including cell adhesion, immune responsiveness, energy metabolism, and neurotransmission (Cooke Bailey et al. 2013). Identification of genes contributing to both early-on-

set and adult-onset forms of glaucoma are also highlighting biological pathways and processes of importance to glaucoma pathogenesis. Several of these are discussed below.

Extracellular Matrix Metabolism

Maintenance of extracellular matrix is emerging as an important theme in glaucoma pathogenesis (Acott et al. 2008; Crawford Downs et al. 2011). Several of the genes contributing to early-onset glaucoma (*MYOC*, *LTBP2*, *COL18A1*) and adult-onset glaucoma (*LOXL1*) have important roles in extracellular matrix (Ueda et al. 2002; Ali et al. 2009; Sethi et al. 2011; Wiggs et al. 2013b), and three important genes related to CCT impact extracellular matrix (Lu et al. 2013). Further investigation of genes shown to contribute to extracellular processes in ocular tissues relevant to glaucoma could be of interest.

Transforming Growth Factor β (TGF- β) Signaling

TGF- β I and TGF- β II appear to have important roles in optic nerve degeneration (Zode et al. 2009; Fuchshofer 2011) as well as trabecular meshwork function (Sethi et al. 2011; Fuchshofer 2012). *LTBP2* (associated with congenital glaucoma and anterior segment dysgenesis) and *CDKN2BAS* (associated with POAG, NTG) are part of the overall TGF- β signaling pathway. Additionally, NTG pathway analysis showed significant association with the TGF- β signaling pathway overall (Wiggs et al. 2012).

Tumor Necrosis Factor α (TNF- α) Signaling

Both genes contributing to familial NTG (*OPTN*, *TBK1*) can impact TNF- α signaling (Fingert et al. 2011). Blocking of the TNF- α receptor in an animal model of glaucoma appears to be neuroprotective (Roh et al. 2012). These results suggest that TNF- α signaling can have an important role in ganglion cell apoptosis in glaucoma. Higher levels of soluble TNF- α have been identified in women before the development of NTG (Kang et al. 2013), a finding consistent with this hypothesis.

Estrogen Metabolism

The hormone 17 β -estradiol can regulate expression of both *CAV1* and *NOS3* (both associated with POAG), and loss of caveolin-1 function can cause increased expression of *NOS3* (Zhou et al. 2009; Sud et al. 2010), suggesting an interaction between these proteins. Additionally, P450 1B1 (*CYP1B1*, associated with congenital glaucoma) is an important factor in estrogen metabolism (Hanna et al. 2000). Gender effects in glaucoma have also been suggested by studies showing that estrogen receptors are expressed on the retinal ganglion cells of the optic nerve (Munaut et al. 2001), and that estrogen may have a neuroprotective effect in animal models of glaucoma (Zhou et al. 2007; Russo et al. 2008). Further studies examining gender effects in POAG, and gender interactions with genes contributing to this disorder will be of interest.

CONCLUDING REMARKS

Genes responsible for both early-onset and adult-onset glaucoma have been identified using genetic and genomic technologies and approaches. Family-based genetic linkage analyses have yielded disease-causing genes for early-onset glaucoma, whereas genome-wide association studies have identified genes and genomic regions contributing to adult-onset forms of the disease. Biological pathways contributing to glaucoma and other complex interactions (gene–gene and gene–environment) are emerging. Future directions for new gene discovery include whole exome sequencing and other next generation sequencing technologies, genome-wide association studies using larger numbers of cases and controls and including rare variant analyses, and further evaluation of the contributions of biological pathways, gene–gene and gene–environment interactions.

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