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Glaucoma Genes and Mechanisms

Janey L. Wiggs[1]

Harvard Medical School, and Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

Abstract

Genetic studies have yielded important genes contributing to both early-onset and adult-onset forms of glaucoma. The proteins encoded by the current collection of glaucoma genes participate in a broad range of cellular processes and biological systems. Approximately half the glaucoma-related genes function in the extracellular matrix, however proteins involved in cytokine signaling, lipid metabolism, membrane biology, regulation of cell division, autophagy, and ocular development also contribute to the disease pathogenesis. While the function of these proteins in health and disease are not completely understood, recent studies are providing insight into underlying disease mechanisms, a critical step toward the development of gene-based therapies. In this review, genes known to cause early-onset glaucoma or contribute to adult-onset glaucoma are organized according to the cell processes or biological systems that are impacted by the function of the disease-related protein product.

1. INTRODUCTION

Glaucoma is a collection of disorders that result in degeneration of the optic nerve. Common forms of glaucoma (primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), exfoliation glaucoma (XFG), and angle-closure glaucoma) are leading causes of irreversible blindness worldwide. Angle-closure glaucoma, caused by anatomical narrowing of the iridocorneal angle with subsequent blockage of the trabecular outflow pathways, is particularly common in Asia.[1] XFG develops in patients with exfoliation syndrome (XFS) characterized by the deposition of a heterogeneous mix of aggregated macromolecules throughout the ocular anterior segment.[2] POAG is the most common subtype of glaucoma and is defined as glaucoma occurring in the absence of any secondary features such as exfoliation. Approximately one-third of patients with open-angle glaucoma have NTG with progressive optic nerve degeneration despite intraocular pressure (IOP) in the normal range. Early-onset glaucoma (developing before the age of 40) includes juvenile open-angle glaucoma, developmental glaucoma (related to abnormal development of the ocular anterior segment), and congenital glaucoma (developing at birth or with the first three years of life).

Glaucoma has significant heritability with early-onset forms inherited as Mendelian autosomal dominant or recessive traits and adult-onset (after age 40) diseases inherited as complex traits.[3] Mutations in genes causing earlyonset glaucoma are rare and have a large biological impact, while variants contributing to various forms of adult-onset glaucoma are

[1]Corresponding author: Janey_Wiggs@meei.harvard.edu.

common and individually have incremental effects on disease pathogenesis (Fig. 1). Genes responsible for early-onset glaucoma have been discovered using linkage analysis of large families while genes contributing to adult-onset disease have been identified using genome-wide association studies (GWAS) that typically require very large numbers of glaucoma cases and controls.

Current molecular techniques and approaches, especially GWAS and next-generation sequencing, are successfully identifying glaucoma-associated genes. While the function of these genes in health and disease are not completely understood, a number of cellular processes and systems with relevance to disease development are emerging. In this review, genes known to cause early-onset glaucoma or contribute to adult-onset glaucoma are organized according to the cell processes or biological systems that are impacted by the function of the disease-related protein product (Table 1). The types of glaucoma caused by (early-onset disease) or associated with (adult-onset disease) are listed in Table 2. The biological processes and systems implicated in glaucoma by genetic studies may be future targets of novel therapies that could prevent disease development.

2. ENDOPLASMIC RETICULUM STRESS RESPONSE

The endoplasmic reticulum (ER) stress response can be caused by overexpression of genes or gene mutations that lead to protein aggregation or other processes that prevent the nascent polypeptide from progressing through the ER.[92] Genetic abnormalities that disrupt the normal function of the ER can lead to the unfolded protein response which can trigger cell death.[93] ER-related cell death contributes to several diseases, including neurodegenerative disorders, renal disease, and ocular disease.[94–96] Missense mutations in MYOC, coding for myocilin, are likely to cause ER stress through the misfolded protein response[4,5,70].

2.1 *MYOC* (Myocilin)

MYOC mutations are a cause of early-onset POAG (juvenile-onset open-angle glaucoma). The majority of disease-causing mutations are dominantly inherited missense alleles. There is a range in disease onset with some mutations causing disease during the first decade of life (PRO370LEU, TYR357HIS) while others cause later-onset.[71] A nonsense mutation (GLN368X) is a common mutation in individuals with later-onset disease.[72] Interestingly, whole-gene deletions or a nonsense mutation near the N-terminal do not cause disease suggesting that the underlying disease mechanism is not loss of function but dominant negative or gain of function.[97–99] Using an *in vitro* system, *MYOC* mutations were shown to decrease protein solubility and mutant protein solubility was correlated with disease severity.[100] In a Tyr357His transgenic mouse (one of the most insoluble mutations), mutant myocilin accumulates in the ER causing the misfolded protein response[5] and elevation of IOP. Sodium 4-phenylbutyrate, a molecular chaperone known to relieve the misfolded protein response in urea cycle disorders,[101] also relieved ER stress and lowered IOP in this animal model.[4] Reagents that relieve the presumed misfolded protein response in humans could be developed as novel therapies for patients with glaucoma caused by *MYOC* mutations.

3. EXTRACELLULAR MATRIX, CELL JUNCTIONS, AND CELL ADHESION

Processes involving extracellular matrix, especially in the trabecular meshwork, can influence aqueous outflow and elevation of IOP.[102] A number of glaucoma-related genes code for proteins that function in the extracellular matrix. Additionally, two glaucoma-associated genes influence cell junctions and several extracellular collagens also contribute to glaucoma pathogenesis.

3.1 *LTBP2* (Latent TGF-Binding Protein 2)

LTBP2 loss of function mutations can cause a range of ocular phenotypes including autosomal recessive congenital glaucoma,[54,55] microsperophakia,[66,67] and Weill Marchesani syndrome.[68] Recent work suggests that impaired *LTBP2* function primarily causes abnormal development of the ciliary zonules resulting in lens dislocations and other abnormalities.[47,103] *LTBP2* codes for latent TGF-binding protein 2, an extracellular matrix protein that is associated with microfibrils.[6] LTBP2 also has cell-adhesive properties[7,8] and a functional role in elastic fiber assembly.[9] A possible role in TGF beta signaling is not well established despite the protein homology to LTBP1 which does bind TGF beta.[104]

3.2 *LOXL1* (Lysyl Oxidase Like 1)

Common variants in *LOXL1* are significantly associated with XFS, an ocular condition characterized by the distribution of aggregated macromolecules throughout the eye including the trabecular outflow pathways.[91] XFS is the leading cause of secondary open-angle glaucoma (XFG) worldwide.[105] Lysyl oxidase like 1 is necessary for proper elastin formation and maintenance, a critical component of the extracellular matrix.[10] Initially, *LOXL1* missense alleles were associated with disease in populations worldwide,[106] however subsequent studies showed that the missense alleles are not likely to impact the amine oxidase activity of the enzyme.[107] It is likely that dysregulation of *LOXL1* is associated with disease development[108] and *LOXL1* variants influencing gene expression could influence disease risk. A *LOXL1* null mouse has some, but not all, features of XFS.[109]

3.3 *FNDC3B* (Fibronectin Type III Domain Containing 3B)

Recent GWAS have identified common variants within and near *FNDC3B* associated with elevated IOP[81] and thin central corneal thickness,[82] both risk factors for POAG. *FNDC3B* codes for an extracellular matrix protein involved in several signaling pathways, including PI3-kinase/Akt, Rb1 and TGFβ signaling.[11] TGF beta is known to induce extracellular matrix remodeling and can alter the cytoskeleton though both the canonical Smad and noncanonical signaling pathways.[110] Experiments have shown that variation in TGF beta2 can cause elevation of IOP in an *ex vivo* perfusion organ culture model, and also elevation of IOP in rodent eyes.[111]

3.4 *AFAP1* (Actin Filament-Associated Protein 1)

The protein encoded by *AFAP1* binds to actin filaments and promotes crosslinking. Modulation of the actin cytoskeleton is known to contribute to the regulation of aqueous outflow and IOP.[112] While not technically in the extracellular matrix, actin formation and stability can have a significant effect on cell shape, cell adhesion, and responsiveness to

external stimuli presented by the extracellular matrix. A recent GWAS involving 4702 POGA cases and 9695 controls identified significant association of common *AFAP1* variants with POAG.[12] Immunohistochemistry showed that AFAP1 was present in both anterior segment and poster segment tissues, particularly trabecular meshwork and retinal astrocytes.

3.5 *PLEKHA7* (Pleckstrin Homology Domain-Containing Protein 7)

PLEKHA7 codes for a protein necessary for formation of adherens junctions that can control paracellular permeability.[13] This protein is expressed in ocular ciliary body and choroid and common variants in the gene have been associated with angle-closure glaucoma.[14] Hypothetically *PLEKHA7* may be related to angle closure though a mechanism involving compromise of the normal barrier to fluid leakage and/or aberrant fluid dynamics.

3.6 *COL11A1* (Collagen Type XI, Alpha1)

COL11A1 encodes one of the two α chains of type XI collagen. Common variants in *COL11A1* are associated with angle-closure glaucoma in Asian populations.[14] Rare *COL11A1* high-effect mutations cause Marshall syndrome, Stickler syndrome, type 2 or Stickler-like syndrome.[15] These syndromes include axial myopia, probably caused by abnormal fibrillary collagen matrix in the sclera. As angle-closure glaucoma patients generally are hyperopic, the associated *COL11A1* variants may influence (or are in linkage disequilibrium with variants that influence) *COL11A1* expression resulting in smaller hyperopic eyes predisposed to angle closure. Alternatively, as *COL11A1* is also expressed in the trabecular meshwork a direct effect on aqueous outflow is also possible.

3.7 *COL15A1* (Collagen Type XV, Alpha1) and *COL18A1* (Collagen XVIII, Alpha1)

COL15A1 and *COL18A1* code for multiplexin collagens type XV and XVIII. These two proteins are highly homologous and are localized to the extracellular matrix and basement membranes in multiple ocular tissues including the trabecular meshwork and Schlemm's canal.[16–18] Variants in both *COL15A1* and *COL18A1* appear to act as disease modifiers influencing the age of disease onset in families with early-onset glaucoma.[73] Interestingly, the *COL18A1* variant was only found in families who also carried the disease-causing *MYOC* mutation Gln368X, one of the *MYOC* mutations related to milder disease. This result suggests that there could be a specific interaction between *COL18A1* and *MYOC*, however further study is necessary to confirm this. The effect of the *COL15A1* and *COL18A1* variants could impair the stability of the trabecular outflow pathways including Schlemm's canal thereby reducing aqueous outflow and raising IOP which results in more severe disease at an earlier age compared to a family member with the primary mutation who does not also carry one of the collagen variants. More work will be necessary to confirm this hypothesis.

4. TGF BETA SIGNALING

4.1 *CDKN2BAS* (Cyclin-Dependent Kinase Inhibitor 2B Antisense)

TGF beta signaling is well known to contribute to processes involving the ocular anterior segment and IOP[113] as well as the glaucoma-related neurodegenerative processes involving the optic nerve.[114] Generally, TGF beta inhibits cell cycle progression resulting in terminal

differentiation or in some situations, apoptosis. In astrocytes, TGF beta signaling is SMAD dependent and increased TGF beta can lead to an increase in *CDKN2B* which is an inhibitor of *CDK4/6* (cyclin dependent kinase 4 and 6), which are necessary for cell cycle progression (Fig. 2). Excess *CDKN2B* inhibits cell cycle progression leading to apoptosis.[115] *CDKN2BAS* is an antisense RNA (also known as ANRIL) that regulates expression of CDKN2B among other molecules.[19–21] Common variants in the CDKN2BAS region are associated with POAG overall and in particular the NTG subgroup.[50,80,89,90] The minor allele of the *CDKN2BAS* variant with most robust association is protective. The role of CDKN2BAS in glaucoma is not yet defined. One hypothesis is that the associated CDKN2BAS allele (minor allele) could result in decreased expression of *CDKN2B* which would increase activity of *CDK4/6* promoting cell cycle progression (Fig. 2). Interestingly, the opposite allele of the variant associated with glaucoma is associated with glioma (lack of appropriate reduction in cell cycle progression) which provides some support for this hypothesis.[116] It is also possible that the associated SNPs are in linkage disequilibrium with other genomic variants within CDKN2BAS or other nearby genes that have a direct role in disease development.[117] Further experimentation is needed to clarify the role of this important molecule in glaucoma.

4.2 *TGFBR3* (TGFbeta Receptor 3)

Recently an association between a SNP near the gene coding for TGFbeta receptor 3 (TGFBR3) was identified for POAG in a mult-ethnic cohort, further supporting a role for TGFbeta signaling in this disease.[85]

5. TUMOR NECROSIS FACTOR-ALPHA SIGNALING

5.1 *OPTN* (Optineurin), *TBK1* (Tank-Binding Kinase 1)

Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine that may contribute to retinal ganglion cell death in glaucoma.[118,119] TNF-alpha binding to its receptor initiates a cascade of events that can activate NFkBeta. Under normal conditions *OPTN* (coding for optineurin) is a negative regulator of NFkBeta activation.[22,23] A rare *OPTN* missense mutation (E50K) causes familial NTG,[86–88] and some *OPTN* mutations are also known to cause familial amyotrophic lateral sclerosis.[120] Mutant forms of *OPTN* do not efficiently inhibit TNF-alpha stimulated NFkBeta transcription which may lead to increased transcription of proapoptotic genes and cell death.[121] Interestingly, a second protein responsible for familial NTG, TBK1 (Tank-binding kinase 1) interacts with OPTN and this interaction is enhanced in an optineurin mutant (E50K) suggesting that binding of TBK1 to mutant OPTN could prevent the protein from inhibiting NFkBeta activation.[24,25] CLYD (cylindromatosis turban tumor syndrome protein), another negative inhibitor of TNF-alpha induced NFkB activation has also been shown to interact with Optineurin and the interaction is also increased by OPTN mutations.[23] Together, these results suggest that TNF-alpha induced NFkB transcription is detrimental to ganglion cells in glaucoma and that loss of inhibitors normally present to modulate this process (OPTN, CLYD) can result in severe familial optic nerve disease.

6. REGULATION OF AUTOPHAGY

6.1 *OPTN* (Optineurin), *TBK1* (Tank-Binding Kinase 1)

In addition to roles in TNF-alpha signaling there is also evidence that *OPTN* and *TBK1* regulate autophagy, a process that eliminates accumulation or proteins, organelles and other cellular debris.[122] Autophagy has been observed in glaucoma animal models.[123,124] Both *TBK1* and *OPTN* are capable of regulating autophagy. When *OPTN* is upregulated or mutated, autophagy is activated in neuronal cells.[26] Phosphorylation of OPTN by TBK1 promotes the recruitment of microtubule-associated protein 1 light chain 3 beta (*MAP1LC3B*, *LC3B*) a critical step in the formation of autophagosomes and initiation of autophagy.[27] The OPTN E50K–TBK1 enhanced interaction also promotes protein instability that can lead to autophagy.[125] Using iPSCs derived from patients with TBK1 duplication increased expression of LC3-II a key marker of activation of autophagy was observed.[126] Data from *OPTN* and *TBK1* experiments suggests that autophagy may be an important pathway in the development of NTG.

7. LIPID METABOLISM

7.1 *ABCA1* (ATP-Binding Cassette, Subfamily A (*ABC1*) Member 1)

Recent GWAS have implicated *ABCA1* (coding for ATP-binding cassette, subfamily A (ABC1) member 1) in POAG.[12,74] Variants in this gene are also associated with IOP in normal populations.[81] The protein encoded by this gene is a major regulator of cellular cholesterol and phospholipid homeostasis.[28,29] ABCA1 is expressed in ocular tissues relevant to glaucoma including iris, ciliary body, retina, optic nerve head, optic nerve, and trabecular meshwork.[12] Previous studies using the DBA/2J mouse glaucoma model identified Abca1 in a cluster of transcripts with varied expression in response to ganglion cell death.[127] ABCA1 expression has also been reported to be higher in leukocytes from glaucoma patients.[128] A role for lipid metabolism in glaucoma is also supported by the protective effect of statins in patients with hyperlipidemia.[129]

8. ENDOTHELIAL NITRIC OXIDE SYNTHETASE SIGNALING AND CAVEOLAE

8.1 *CAV1/CAV2* (Caveolins 1 and 2)

Caveolae are invaginations of the plasma membrane formed primarily by the caveolin proteins.[30] These are especially common in vascular endothelial cells but can be present in many vertebrate cell types. Common variants near *CAV1*, coding for caveolin 1 have been associated with POAG in populations worldwide.[75–79] While dysregulation of *CAV1* has many downstream effects, one consequence of *CAV1* deficiency is activation of endothelial nitric oxide synthetase (eNOS) with subsequent increase in nitric oxide (NO).[31] NO can modulate the tone of luminal structures with adjacent smooth muscle including blood vessels and ocular structures such as Schlemm's canal and juxtacanalicular trabecular outflow pathways.[130,131] eNOS may play a role in the etiology of glaucoma; it is found in the human outflow pathway[132] and the vasculature supplying retinal ganglion cells,[133] which may affect the regulation of IOP and blood flow to the optic nerve, respectively.

NOS3 (nitric oxide synthetase 3, coding for eNOS) may interact with estrogen to contribute to POAG in women.[134] Recently, *CAV1* variants were shown to be preferentially associated with the POAG subgroup with initial paracentral visual field loss, a phenotypic feature more common in POAG patients with evidence of vascular dysregulation.[135] Another potential role for caveolae and *CAV1* in POAG is the formation of "giant vaculoles" noted in trabecular meshwork cells in the setting of elevated IOP.[136]

9. FRUCTOSE AND MANNOSE METABOLISM

Two genes (GMDS and PMM2) coding for enzymes in the fructose and mannose metabolism pathway have been associated with POAG. Interestingly, highly penetrant alleles in both of these genes cause congenital glycosylation disorders[32] and both genes code for enzymes involved in different steps of the overall fructose-mannose metabolism pathway (KEGG pathway hsa00051). One of the products of this pathway is N-glycans that have a role in a number of cellular processes including targeting of proteins to lysosomes for degradation.[33]

9.1 *GMDS* (GDP-mannose 4,6 dehydratase)

GMDS has been associated with POAG in a GWAS of Caucasians with European ancestry.[12]

9.2 *PMM2* (Phosphomannomutase)

PMM2 has been associated with POAG in a GWAS of Asians.[74]

10. REGULATION OF CELL DIVISION

Several genes coding for proteins that can regulate cell division contribute to adult-onset forms of glaucoma including POAG and NTG.

10.1 *GAS7* (Growth Arrest-Specific 7)

GAS7 is a member of the growth arrest-specific family of genes expressed in terminally differentiated tissues.[34] This member of the growth arrest-specific gene family is expressed primarily in terminally differentiated brain cells and mature cerebellar Purkinje neurons but also in terminally differentiated fibroblasts.[35] *GAS7* can induce neurite outgrowth in terminal neurons[36] and is also involved in some developmental processes such as osteoblast cell differentiation from mesenchymal cells.[37,38] Common variants near GAS7 were initially associated with elevated IOP in normal populations[78,83] and subsequently also associated with POAG.[12,50] RT-PCR shows that GAS7 is expressed in trabecular meshwork cells as well as retina and optic nerve.[38] Considering the expression of GAS7 primarily in neurons and its function in neurite outgrowth a role for the protein in IOP regulation is not clear. As part of the neurite outgrowth function GAS7 interacts with actin and microfilaments, and it is possible that this interaction also occurs in trabecular meshwork cells or other cells involved in aqueous humor dynamics.[137]

10.2 *TMCO1* (Transmembrane and Coiled-Coil Domains-1)

Common variants near *TMCO1* on chromosome 1q24 were initially associated with IOP in normal populations[38] and subsequently with POAG in Caucasians of European ancestry.[80] Loss of function mutations cause a recessive condition involving craniofacial dysmorphism, skeletal anomalies, and mental retardation that has been termed, "TMCO1 syndrome."[138,139] Coding sequence mutations do not appear to contribute to glaucoma, including the pedigrees affected by TMCO1 syndrome. The protein sequence is very highly conserved across mammalian species suggesting a critical biological function, and it is expressed in many human tissues including ocular tissues.[39] Using a GFP-TMCO1 fusion protein, the protein was localized to the ER[140] and mitochondria.[141] More recently, using immunohistochemistry *TMCO1* localized to nucleoli suggesting that the protein could have a role in aging through cell-cycle regulation.[39]

10.3 *CDKN2BAS* (Cyclin-Dependent Kinase Inhibitor 2B Antisense)

CDKN2BAS codes for a long noncoding antisense RNA that negatively regulates the expression of *CDKN2B*, coding for an inhibitor of cyclin-dependent kinases 4 and 6 necessary for cell cycle progression.[19–21] Common variants in the *CDKN2BAS* genomic region are strongly associated with POAG and NTG suggesting that cell-cycle regulation is an important feature of disease development.[50,80,89,90] Unlike *TMCO1* and *GAS7* which are asso ciated with IOP as well as POAG, *CDKN2BAS* was initially associated with the cup-to-disc ratio in normal populations[84] and is more robustly associated with NTG compared with POAG,[50,80,89,90] suggesting that the primary influence is on the optic nerve. The cells involved are not yet known.

11. REGULATION OF OCULAR DEVELOPMENT

A number of genes responsible for early-onset forms of glaucoma regulate ocular development. Mutations in these genes cause ocular dysgenesis, primarily of the anterior segment structures, resulting in elevated IOP and subsequent damage to the optic nerve. Currently one adult-onset gene, *SIX6* associated with POAG, codes for a protein involved in ocular development.

11.1 *FOXC1* (Forkhead Box C1)

FOXC1 codes for a member of the family of forkhead domain proteins involved in developmental processes in many human tissues.[142] In the human eye, *FOXC1* mutations cause a spectrum of phenotypic abnormalities that includes iris hypoplasia and other features of anterior segment dysgenesis.[56,57] In addition, some *FOXC1* mutations appear to cause hearing loss, and *FOXC1* may contribute to De Hauwere syndrome characterized by anterior segment dysgenesis, hypertelorism, retardation, hypotonia, hearing loss, femoral head anomalies, and hydrocephalus.[58,59] Disease-causing mutations in *FOXC1* include missense changes in the forkhead domain, nonsense and frameshift mutations, and whole-gene deletions and duplications.[57] Mutations resulting in disease cause a loss of protein function particularly of the transactivation domain[40,41] and are inherited as an autosomal dominant trait with variable penetrance. *FOXC1* interacts with *PITX2* (see later) and *PITX2* can negatively regulate *FOXC1* transactivity.[143,144] Moreover, patients who have mutations in

both genes have more severe disease.[145] In additional to hearing defects, patients with anterior segment dysgenesis caused by *FOXC1* mutations may also have heart defects.[146]

11.2 *PITX2* (Paired-Like Homeodomain 2)

PITX2 is a member of the bicoid class of homeodomain transcription factors that are necessary for embryonic development.[42,43] *PITX2* mutations were initially identified as a cause of classic Rieger syndrome defined by characteristic teeth and umbilical abnormalities as well as ocular anterior segment dysgenesis.[60–62] *PITX2* is also necessary for pituitary development[147] and *PITX2* variants have been associated with cardiac abnormalities, in particular atrial fibrillation.[148] *PITX2* mutations causing Rieger syndrome are loss of function and are inherited as an autosomal dominant trait with variable penetrance.[57] Deletion of an upstream regulatory region can also cause disease.[149] As noted above, *PITX2* interacts with *FOXC1* defining an important pathway for ocular development.[143,144] Induction of *PITX2* expression requires the Wnt/Dvl/beta-catenin pathway that leads to cell-type-specific proliferation.[150] Approximately 50% of patients with ocular dysgenesis caused by either *PITX2* or *FOXC1* mutations have glaucoma[57] characterized by high IOP. Glaucoma is likely caused by abnormal development of the trabecular outflow pathways, and in particular Schlemm's canal.[151]

11.3 *PAX6* (Paired Box 6)

PAX6 plays a critical role in ocular development.[44] *PAX6* loss of function mutations cause Aniridia, characterized by abnormal development of the iris,[63] as well as Peter's anomaly[64] and dominant forms of corneal keratitis.[65] Approximately 50% of patients with ocular developmental abnormalities due to *PAX6* mutations also are affected by early-onset glaucoma.[63] Interestingly, deletions of the downstream *PAX6* regulatory region are relatively common disease-causing mutations.[152] Large deletions that include *PAX6* can also involve the gene responsible for Wilm's tumor[153] and patients with ocular phenotypes suggestive of Aniridia or other conditions related to *PAX6* defects should have renal ultrasound screening.

11.4 *CYP1B1* (Cytochrome P450, Family 1, Subfamily B, Polypeptide 1)

CYP1B1 loss of function mutations are the most common cause of autosomal recessive congenital glaucoma worldwide.[51] Reported *CYP1B1* mutations include missense, frameshift, premature stop codons, small insertion/ deletions, and large deletions.[51–53] *CYP1B1* codes for cytochrome P-450 1B1, a member of the large cytochrome P450 family. P450 1B1 is known to metabolize complex molecules such as polycyclic aromatic hydrocarbons and 17-β-estradiol.[154–156] The role of the protein in congenital glaucoma is not clear; however, it has been hypothesized that the P-450 1B1 activity is responsible for metabolism of a compound involved in ocular development.[45,46] Recently, CYP1B1 mutations have also been shown to contribute to glaucoma in older children (juvenile-onset).[157–160] Mutations in juvenile-onset children (onset between the ages of 3 and 20) are primarily missense alleles which may confer some residual enzyme activity (hypomorph alleles).[161] A recent study has found that the carrier frequency of CYP1B1 mutations in two populations in the United States is higher than expected based on the disease incidence of congenital glaucoma only. In particular, the frequency of missense alleles was higher than

expected suggesting that missense mutations may contribute to disease other than congenital glaucoma and this could be juvenile-onset glaucoma and glaucoma related to ocular dysgenesis.[162]

11.5 *LTBP2* (Latent TGF-Binding Protein 2)

As noted earlier, *LTBP2* loss of function mutations can cause a variety of ocular conditions which result from abnormal development of the ciliary zonules.[47,54,55,66–68,103] *LTBP2* null mice develop lens abnormalities including lens dislocation, but not primary congenital glaucoma, suggesting that lens dislocation could underlie the development of glaucoma in humans with LTBP2 mutations.[47]

11.6 *SIX6* (SIX Homeobox 6)

SIX6 is one member of a human gene family originally identified by homology to the Drosophila sine oculis (so) gene required for eye development.[48] All six members of the human *SIX* family have a DNA-binding homeobox domain as well as a SIX domain which binds effector molecules. The human *SIX* genes also appear to regulate eye development through transcriptional activation of downstream genes.[49] *SIX6* expression is restricted to the eye and pituitary[163] and loss of function mutations in this gene are a cause of isolated microphthalmia with cataract type 2 (MCOPCT2).[69] Common *SIX6* variants, including a common missense mutation, are associated with POAG.[50,84] The missense change His141Asn, has also been associated with retinal nerve fiber layer thickness suggesting that the associated gene variants increase susceptibility to POAG by limiting the development of the retinal ganglion cells.[164] Using zebrafish and a morpholino knock-down complementation assay His141Asn and several other missense alleles were found to reduce the size of the optic nerve providing further support for the hypothesis that *SIX6* risk variants disrupt the development of the neural retina, leading to a reduced number of retinal ganglion cells which increases the risk of glaucoma-associated vision loss.[165,166]

12. CEREBROSPINAL FLUID PRESSURE

12.1 *8q22* Regulatory Region

A NTG GWAS identified significant association with common SNPs located in an evolutionarily conserved genomic region on chromosome 8q22.[50] This region contains regulatory sites annotated by ENCODE[167] as enhancers with highest activity in the choroid plexus (produces cerebrospinal fluid) and the ocular ciliary body (produces aqueous humor). Of interest, recent studies have suggested that low cerebral spinal fluid pressure may create a deleterious gradient across the lamina cribrosa in NTG mimicking a similar gradient induced by higher IOP in typical high-pressure POAG.[168] The genes influenced by the enhancers are not yet known although SNPs in this region may impact TGF beta signaling.[50]

13. SUMMARY

Genetic studies have yielded important genes contributing to both early-onset and adult-onset forms of glaucoma. The proteins encoded by the current collection of glaucoma genes participate in a broad range of cellular processes and biological systems. Extracellular

matrix proteins are especially prevalent among glaucoma genes; however, proteins involved in cytokine signaling, lipid metabolism, membrane biology, fructose and mannose metabolism, regulation of cell division, autophagy, and ocular development also contribute to disease pathogenesis. The genes currently known to contribute to glaucoma account for only a fraction of the overall disease heritability,[169] and GWAS with larger and better characterized patient cohorts and current next-generation sequencing approaches are needed for novel gene discovery. Delineating the complete genetic architecture of glaucoma will make it possible to develop sensitive and specific genebased tests that could identify individuals at risk for disease before irreversible damage to the optic nerve occurs. The discovery of disease-related genes will also provide new insights into the underlying molecular mechanisms responsible for glaucoma, an important step toward achieving novel gene-based preventative and protective therapies.

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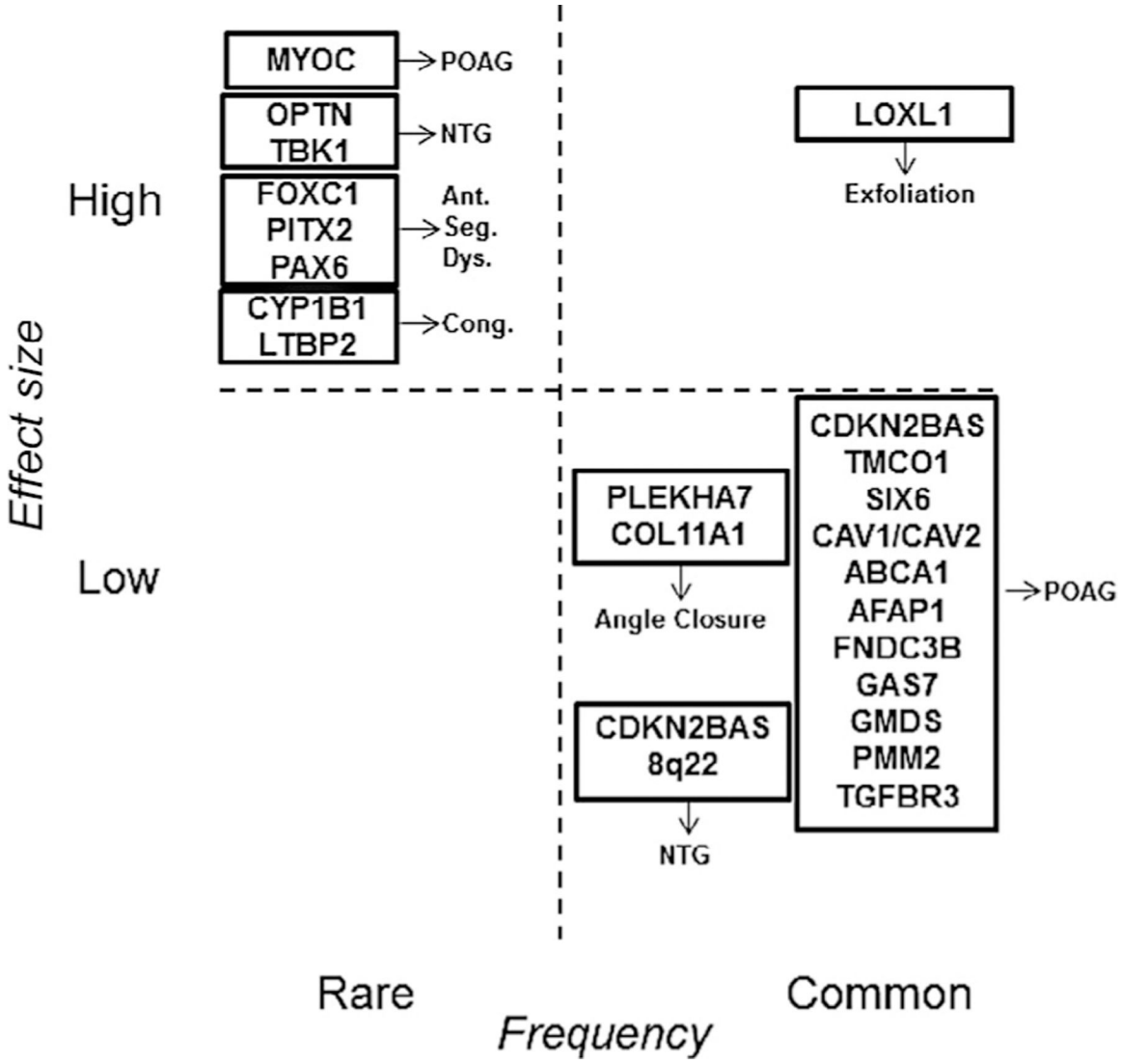

Figure 1.

Frequency and effect size of gene variants in glaucoma. Mutations in genes causing early-onset Mendelian forms of glaucoma are rare but have large biological effects (*MYOC, OPTN, TBK1, FOXC1, PITX2, PAX6, CYP1B1, LTBP1*). Variants in genes influencing the susceptibility to adult-onset forms of glaucoma with complex inheritance are generally relatively common and individually have small biological effects (*CDKN2BAS, TMCO1, SIX6, CAV1/CAV2, ABCA1, AFAP1, FNDC3B, GAS7, PLEKHA7, GMDS, PMM2, TGFBR3, COL11A1, 8q22*). *COL15A1* and *COL18A1*, modifiers of early-onset glaucoma, have intermediate frequency and effect size (not shown in this figure). Variants in *LOXL1* contributing to exfoliation syndrome are common but also have large biological effects.

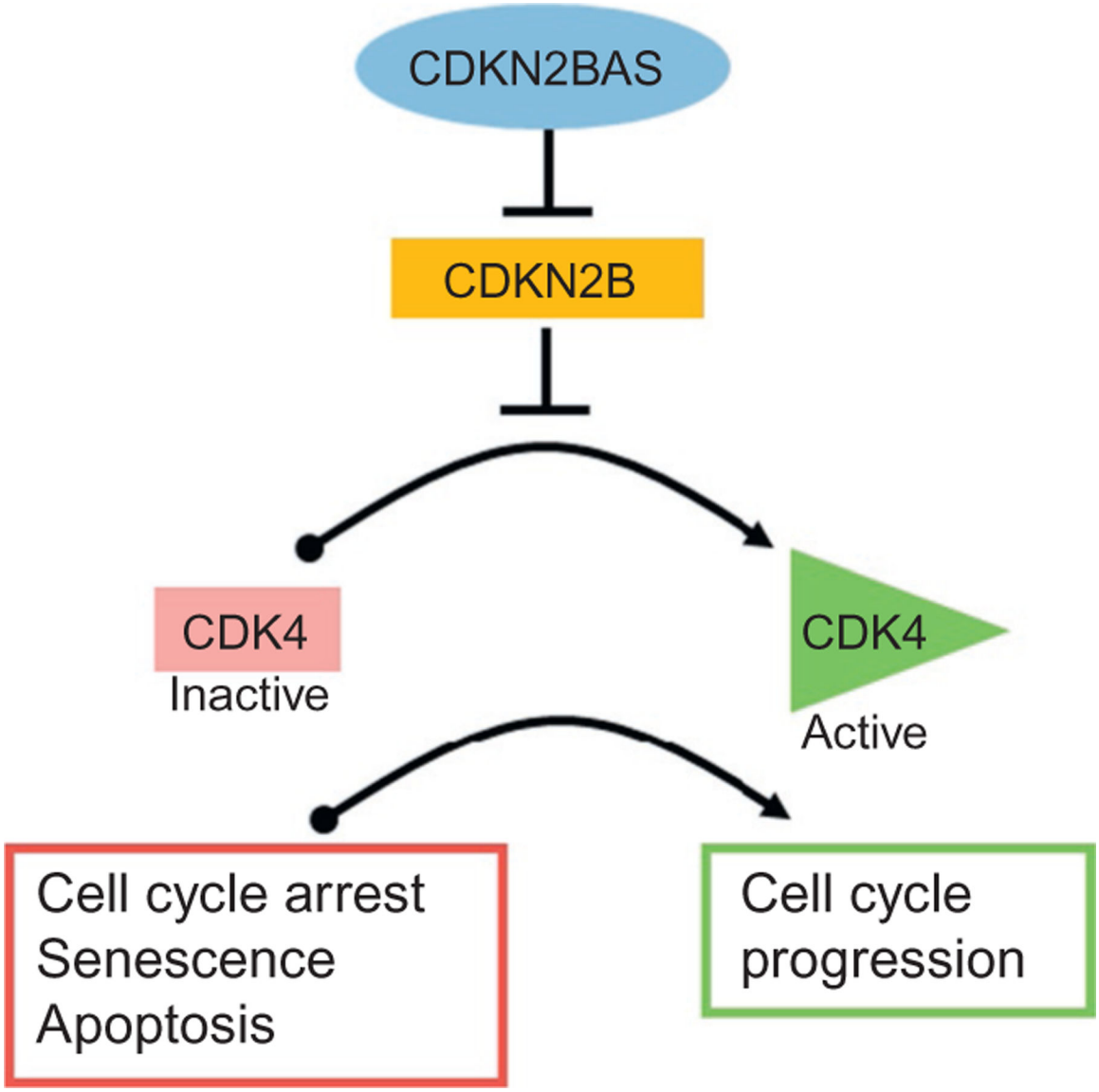

Figure 2.

CDKN2BAS and cell cycle progression. CDKN2BAS (*Cyclin dependent kinase inhibitor 2B antisense*) is a long noncoding antisense RNA that regulates expression of *CDKN2B* (*cyclin dependent kinase inhibitor 2B*), coding for an inhibitor of CDK4 (cyclin-dependent kinase 4) necessary for cell cycle progression.[19–21]

Table 1

Biological Systems and Processes Involved in Inherited Glaucoma

Biological Process or System	Gene	Protein	Key References
Endoplasmic reticulum stress, unfolded protein response	*MYOC*	Myocilin	4,5
Extracellular matrix, cell junctions, and cell adhesion	*LTBP2*	Latent TGF-binding protein 2	6–9
	LOXL1	Lysyl oxidase like 1	10
	FNDC3B	Fibronectin type III domain containing 3B	11
	AFAP1	Actin filament-associated protein 1	12
	PLEKHA7	Pleckstrin homology domain-containing protein 7	13
	COL11A1	Collagen type XI, alpha1	14,15
	COL15A1	Collagen type XV, alpha1	16–18
	COL18A1	Collagen XVIII, alpha1	16–18
TGF beta signaling	*CDKN2BAS*	Cyclin-dependent kinase inhibitor 2B antisense	19–21
	TGFBR3	TGFbeta receptor 3	
TNF-alpha signaling	*OPTN*	Optineurin	22,23
	TBK1	Tank-binding kinase 1	24,25
Regulation of autophagy	*OPTN*	Optineurin	26
	TBK1	Tank-binding kinase 1	27
Lipid metabolism	*ABCA1*	ATP-binding cassette, subfamily A (ABC1) member 1	28,29
eNOS signaling and Caveolae	*CAV1/CAV2*	Caveolins 1 and 2	30,31
Fructose and Mannose Metabolism	*GMDS*	GDP-mannose 4.6 dehydratase	32,33
	PMM2	Phosphomannomutase	
Regulation of cell division	*GAS7*	Growth arrest-specific 7	34–38
	TMCO1	Transmembrane and coiled-coil domains-1	39
	CDKN2BAS	Cyclin-dependent kinase inhibitor 2B antisense	19–21
Regulation of ocular development	*FOXC1*	Forkhead box C1	40,41
	PITX2	Paired-like homeodomain 2	42,43
	PAX6	Paired box 6	44
	CYP1B1	Cytochrome P450, family 1, subfamily B, polypeptide 1	45,46
	LTBP2	Latent TGF-binding protein 2	47
	SIX6	SIX homeobox 6	48,49
Cerebrospinal fluid pressure	*8q22*	NA	50

Table 2

Glaucoma Genes and Diseases

Disease	Gene	Protein	Key References
Congenital glaucoma	*CYP1B1*	Cytochrome P450, family 1, subfamily B, polypeptide 1	51–53
	LTBP2	Latent TGF-binding protein 2	54,55
Anterior segment dysgenesis, Rieger syndrome	*FOXC1*	Forkhead box C1	56–59
	PITX2	Paired-like homeodomain 2	60–62
Aniridia	*PAX6*	Paired box 6	63–65
Microsperophakia, Weill Marchasani	*LTBP2*	Latent TGF-binding protein 2	66–68
Microphthalmia and cataract	*SIX6*	SIX homeobox 6	69
Juvenile-onset primary open-angle glaucoma	*MYOC*	Myocilin	5,70–72
	COL15A1	Collagen type XV, alpha1	73
	COL18A1	Collagen XVIII, alpha1	73
Adult-onset primary open-angle glaucoma	*ABCA1*	ATP-binding cassette, subfamily A (ABC1) member 1	12,74
	AFAP1	Actin filament-associated protein 1	12
	CAV1/CAV2	Caveolins 1 and 2	75–79
	CDKN2BAS	Cyclin-dependent kinase inhibitor 2B antisense	80
	FNDC3B	Fibronectin type III domain containing 3B	81,82
	GAS7	Growth arrest-specific 7	78,83
	GMDS	GDP-mannose 4,6 dehydratase	12
	PMM2	Phosphomannomutase	74
	SIX6	SIX homeobox 6	50,84
	TGFBR3	TGFbeta receptor 3	85
	TMCO1	Transmembrane and coiled-coil domains-1	80
Familial normal-tension glaucoma	*OPTN*	Optineurin	86–88
	TBK1	Tank-binding kinase 1	25
Adult-onset normal-tension glaucoma	*8q22*	NA	50
	CDKN2BAS	Cyclin-dependent kinase inhibitor 2B antisense	50,89,90
Angle-closure glaucoma	*COL11A1*	Collagen type XI, alpha1	14
	PLEKHA7	Pleckstrin homology domain-containing protein 7	14
Exfoliation syndrome	*LOXL1*	Lysyl oxidase like 1	91