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REVIEW

Primary open-angle glaucoma genes

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Abstract

A substantial fraction of glaucoma has a genetic basis. About 5% of primary open angle glaucoma (POAG) is currently attributed to single-gene or Mendelian forms of glaucoma (ie glaucoma caused by mutations in *myocilin* or *optineurin*). Mutations in these genes have a high likelihood of leading to glaucoma and are rarely seen in normal subjects. Other cases of POAG have a more complex genetic basis and are caused by the combined effects of many genetic and environmental risk factors, each of which do not act alone to cause glaucoma. These factors are more frequently detected in patients with POAG, but are also commonly observed in normal subjects. Additional genes that may be important in glaucoma pathogenesis have been investigated using quantitative traits approaches. Such studies have begun to identify genes that control the magnitude of important quantitative features of glaucoma that may also be important risk factors for POAG, such as central corneal thickness. Each of these different approaches to study glaucoma genetics is providing new insights into the pathogenesis of POAG.
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Genes are important in eye disease

Research breakthroughs have shown that genes have key roles in the pathogenesis of common eye diseases, including age-related macular degeneration,[1–4] Fuchs corneal endothelial dystrophy,[5] exfoliation syndrome,[6] and primary open-angle glaucoma (POAG).[7–9] The recent discovery of important risk factors for these common eye diseases underscores the utility of studying ophthalmic genetics.

The identification of disease-causing genes provides information about the pathogenesis of heritable eye diseases at the most basic level. For example, disease-causing genes may be part of important biological pathways that once identified may help clarify the mechanisms that lead to disease. The discovery of disease genes will also continue to provide insights into the normal function of the eye.

Discovery of the genes that cause eye disease may also provide useful information for patients and their physicians. Identifying these genes will enable the design of DNA-based tests that may help physicians assess their patient's risk for disease and may also differentiate between clinically similar disorders. Many such tests are already available on both a fee-for-service and research basis (http://www.genetests.org). Identification of the specific mutation or mutations that are responsible for a patient's disease not only solidifies the diagnosis, but may also help predict its likely clinical course. Several mutation-specific phenotypes of hereditary eye diseases have already been reported, including glaucoma,[10] retinitis pigmentosa,[11] and Von Hippel Lindau syndrome.[12] Genetic variations may also influence a patient's response to therapeutic interventions and will help guide selection of their clinical and surgical care.

Discovery of the genes that cause disease is a vital step in the development of new treatments for heritable eye conditions. The biological function of a disease-causing gene may in some cases suggest the application of currently available medical and surgical therapies. In other cases, new interventions may be developed to compensate a genetic defect after it is identified. Such gene-directed therapies might include currently available or newly designed medications, gene therapy (replacing a mutant gene with a normal copy), and/or other molecular genetic approaches such as blocking mutant gene expression.[13,14]

Many eye diseases, including glaucoma, are both genetically and mechanistically heterogeneous, meaning that it is unlikely that one therapy will be effective for all forms of a disease. Genetic studies of complex diseases may also provide crucial information for future animal and clinical treatment trials. The most

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relevant animal models of eye disease will be those that are designed to have the same genetic defects that are found in human disease. Such animal models would have great value for testing both the safety and efficacy of new therapies. Additionally, researchers may use genetic tests to identify relatively homogeneous populations of study patients for treatment trials or to study patients with the same molecular cause of disease.

Glaucoma is a heritable disease

The idea that heredity has an important role in glaucoma pathogenesis is not new. Some of the earliest evidence came from reports of large pedigrees in which glaucoma was passed down from generation to generation in a Mendelian pattern that demonstrated that at least some cases of glaucoma have a genetic basis. Twin studies and familial clustering studies have also indicated that some portion of glaucoma is caused by heredity.[15–20] Finally, several domesticated animal breeds, including the DBA/2J mouse (pigmentary glaucoma), cats, and dogs, have been documented to be afflicted by inherited glaucoma.[21–25] Together these data provide strong evidence that genes have an important role in the pathogenesis of glaucoma and provide support for efforts to find these genes.

In the last two decades significant progress has been made in unraveling the genetic basis of POAG. Mutations that lead to POAG can be divided into two groups with very distinct characteristics (Table 1). One class of mutations are capable of 'causing' POAG on their own with little influence from other genes or the environment. These single-gene forms of glaucoma are responsible for disease that is transmitted as a Mendelian trait, often with an autosomal dominant inheritance pattern. Individuals that carry these types of mutations almost always develop POAG and these mutations are rarely observed in subjects with normal eyes. Mutations in the *myocilin* (*MYOC*) and *optineurin* (*OPTN*) genes are examples of mutations that 'cause' POAG and are discussed in more detail below. The other class of mutations, 'risk alleles', may promote the development of POAG when combined with other glaucoma risk alleles and environmental factors but do not cause disease on their own (Table 1). These alleles or genetic risk factors are statistically more common in POAG patients, although they are very frequently detected in both patients and controls. In this report, the current state of our knowledge of the genetic basis for glaucoma is reviewed, including glaucoma causing genes, glaucoma genetic risk factors, and quantitative traits related to the development of glaucoma.

POAG-causing genes (Mendelian—single-gene disease)

Myocilin (MYOC, *OMIM #601652)*

Myocilin was the first gene to be associated with POAG, and mutations in this gene are the most common cause of glaucoma with a known molecularly defined basis. Glaucoma-causing mutations in myocilin were first detected in linkage-based studies of large pedigrees with juvenile open angle glaucoma (JOAG).[7,27] *Myocilin* mutations have since been found in 3–4% of POAG patients[7,26] and a range of glaucoma-associated *myocilin* mutations have now been cataloged in review articles[28,29] and online at http://www.myocilin.com. In most cases, *myocilin*-associated glaucoma appears to be transmitted as an autosomal dominant trait and is associated with markedly elevated IOP.

Myocilin and JOAG. Glaucoma-causing mutations have been identified in many JOAG pedigrees with glaucoma that is inherited as an autosomal dominant trait. Myocilin mutations are relatively common in patients with JOAG, and have been detected in 8–36% of patients in published case series.[30–32] The likelihood of detecting myocilin mutations in subjects with JOAG appears to be greater in patients with stronger family histories of glaucoma than in patients with apparently sporadic glaucoma.

Table 1 Two classes of POAG mutations

Features of mutations	*Glaucoma-'causing' mutations*		*Glaucoma risk alleles*	
	Generally	*Myocilin (GLN368Stop)*	*Generally*	*Chromosome 7q31 risk allele (rs4236601A)*
Frequency in POAG cohorts	Low	1.6%	Common	28.7%
Frequency in normal cohorts	Usually absent	0.13%	Common	22.8%
Likelihood of POAG in those with mutations	High	98.6%	Low	Odds ratio 1.36

This table highlights the differences between mutations that primarily 'cause disease' on their own (such as the GLN368STOP mutation) and those that contribute to the overall risk for developing disease (such as the chromosome 7q31 risk allele). The data for the myocilin mutation (GLN368STOP) are from http://www.myocilin.com and Fingert *et al*.[26] The data for the chromosome 7q31 risk allele are from Thorleifsson *et al*.[8]

Myocilin and POAG. Myocilin mutations are also co-inherited with POAG in an autosomal dominant pattern and have been detected in cohorts of POAG patients from around the world. However, due to the later onset of disease, the POAG pedigrees are smaller and the mode of inheritance is not as obvious as is observed with JOAG families.[26] Many mutations are only observed in specific geographic or ethnic populations, but one *myocilin* mutation (GLN368STOP) has been detected in nearly all of the examined POAG populations, including African-Americans and Caucasians from the United States, Canada, Australia, Europe, and South America.[28] This most common myocilin mutation has not, however, been observed in Asian glaucoma patients. Some studies have suggested that a founder effect may be responsible for the high relative frequency of the GLN368STOP mutation in some populations.[26]

Myocilin genotype–phenotype correlations. Individual *myocilin* mutations have been associated with specific clinical features of *myocilin*-related glaucoma such as age of diagnosis, maximum intraocular pressure (IOP), and response to medical therapy. The best correlations between genotype and phenotype come from the two classes of mutations that have been detected in most glaucoma patients: myocilin mutations that cause JOAG and the GLN368STOP mutation. In addition to having an earlier age of onset, the myocilin mutations that cause JOAG are also associated with higher IOP and greater resistance to medical therapies than mutations that cause POAG. Although a number of reports have shown that subjects with JOAG respond poorly to medical treatment and generally require surgical interventions,[33,34] a study by Graul *et al*[35] has shown that POAG patients with a GLN368STOP myocilin mutation have similar rates of laser trabeculoplasty and surgery as POAG patients with no myocilin mutations. However, another study by Craig *et al*[36] reported that glaucoma patients with GLN368STOP mutations had increased rates of filtration surgery compared with patients with no myocilin mutations.

Myocilin and glaucoma pathogenesis. Myocilin was first identified as a glaucoma gene in 1997, but we still know little about the normal function of the protein it encodes. In health, myocilin protein is produced by many cell types of the eye and is secreted into the aqueous humor for an unknown purpose. Studies of both cell culture and human tissue have shown that the abnormal protein that is produced by *myocilin* mutations is poorly secreted and is retained within trabecular meshwork cells.[37–40] Accumulation of abnormal myocilin protein may be toxic to trabecular meshwork cells and may lead to their dysfunction or death, which may ultimately produce decreased aqueous outflow, elevated IOP, and glaucoma.[41,42] Animal models harboring *myocilin* mutations have been developed and are beginning to reveal the specific molecular steps that lead from mutations in *myocilin* to the elevated IOP that is characteristic of *myocilin*-related glaucoma.[43–45]

Optineurin (OPTN, *OMIM #602432)*

Optineurin was identified as a glaucoma-causing gene through investigations of a large normal tension glaucoma (NTG) pedigree. The dominantly inherited glaucoma in this family was shown to be caused by a GLU50LYS mutation in the *optineurin* gene.[9,46] Subsequently, most studies of *optineurin* in large populations of glaucoma patients have suggested that mutations in this gene may be responsible for up to 1.5% of NTG cases.[47–49] The strongest data linking mutations in *optineurin* with glaucoma are focused on the GLU50LYS mutation. The links between other *optineurin* mutations and glaucoma are more complex, as these mutations are associated with glaucoma in some but not all populations. For example, the MET98LYS variant in *optineurin* is statistically more common in NTG patients than control subjects in some Caucasian and Asian populations,[47,50,51] but not in others.[47,52,53] Overall, mutations in *optineurin* do not appear to be associated with cases of POAG that have elevated IOP in most[47,48,52,54–57] but not all populations.[51,55] The significance of some *optineurin* variations appears to depend upon the population in which they are observed.

Optineurin and glaucoma pathogenesis. The mechanism by which *optineurin* causes glaucoma has been investigated using *in vitro* and *in vivo* studies. There is some evidence that *optineurin* may have neuro-protective effects that are reduced or eliminated by disease-causing mutations. Overexpression of wild-type optineurin appears to provide some protection from apoptosis induced by oxidative stress in a cell culture system. This protective effect is not observed with overexpression of mutant optineurin protein.[58] More recently, experiments with transgenic mice have demonstrated that the GLU50LYS mutation in *optineurin* leads to apoptosis of retinal ganglion cells. Further studies of these mice have suggested that *optineurin*-mediated glaucoma may result from a disruption of an interaction between optineurin and a GTP-binding protein, Rab8, and its effects on protein trafficking.[59]

TANK-binding kinase-1 (TBK1)

TBK1 encodes a kinase that regulates the expression of genes in the NF-κB signaling pathway. Copy number

variations (duplications) that encompass the *TBK1* gene were recently shown to be associated with glaucoma through family-based studies.[60] First, linkage analysis of a large African-American NTG pedigree mapped a new glaucoma gene to chromosome 12q14. Subsequent investigations of this part of the genome demonstrated that all family members with glaucoma possessed a duplication of the *TBK1* gene and some neighboring genes. This particular duplication was never seen in control subjects. When a cohort of additional NTG patients were similarly tested for copy number variations, 2 (1.3%) of 152 NTG patients were found to have unique but overlapping duplications of chromosome 12q14 that also spanned the *TBK1* gene.[60] These data suggest that an extra copy of *TBK1* leads to NTG and may be responsible for some fraction of sporadic-appearing NTG cases.

The role of *TBK1* in glaucoma pathogenesis is also supported by previous studies of *optineurin*, the only other known NTG gene. In 2008, Morton *et al*[61] showed that the protein encoded by *optineurin* interacts with TBK1 and that this interaction is influenced by an *optineurin* mutation (GLU50LYS) that was previously shown to be associated with glaucoma. This interaction with *optineurin*, a known NTG gene, further supports a role for *TBK1* in glaucoma pathogenesis.

Little is known about how copy number variations in *TBK1* might cause glaucoma. The interaction between *TBK1* and genes in the NF-κB signaling pathway may influence important processes that are involved in the pathogenesis of glaucoma, including apoptosis and modulation of the immune system. Initial studies have shown that *TBK1* is expressed in human retinal ganglion cells and that duplication of this gene significantly alters its expression in cultured fibroblasts.[60] Therefore, it is a plausible hypothesis that copy number variations of *TBK1* cause a dysregulation of NF-κB signaling that ultimately leads to apoptosis of retinal ganglion cells and the development of NTG.

WD-repeat domain 36 (WDR36, *OMIM 609669*)

Linkage analysis of two POAG pedigrees mapped a glaucoma gene to chromosome 5q22, and subsequent studies of genes in this locus suggested that mutations in *WDR36* might cause some cases of POAG.[62] However, many subsequent studies failed to confirm this link.[63–65] Furthermore, two additional POAG pedigrees have been identified with glaucoma that is linked to the same chromosome 5q22 locus, but these pedigrees were found to harbor no *WDR36* mutations. These results suggest the presence of a different glaucoma gene in the region.[66,67] Nonetheless, a few studies have identified rare *WDR36* variants that may be associated with POAG in some populations. As a result, there is continued controversy over the role of *WDR36* in glaucoma pathogenesis.

Although *WDR36* was initially identified in studies focused on genes that 'cause' Mendelian forms of POAG, some researchers have investigated the possibility that variants in this gene may either contribute to the risk for developing complex, polygenic forms of glaucoma[68,69] or influence the severity of disease.[63] The mechanism by which such common *WDR36* variants might contribute to the risk for POAG is unknown. However, some common variants of *WDR36* have been shown to alter cell viability in yeast[70] and axon growth in mouse retinal ganglion cells.[71]

Genetic risk factors for glaucoma (complex genetic disease)

Family-based studies have been successful in discovering a number of genes that are capable of causing POAG with minimal influence from other genes or the environment. However, the known glaucoma-causing genes are together responsible for $<5\%$ of POAG cases. Many of the remaining cases of POAG are likely due to the combined action of several genes and environmental factors. In the last several years, researchers have searched for genetic risk factors that contribute to the development of glaucoma by conducting genome-wide association studies (GWAS). These investigations compare the genomes of POAG patients and control subjects with normal eyes to find gene sequences that are statistically more common in patients with glaucoma. Association studies have been very effective in discovering important risk factors for other inherited eye conditions such as age-related macular degeneration,[1–4] Fuchs endothelial corneal dystrophy,[5] and exfoliation syndrome.[6]

More recently, association studies have begun reporting genetic risk factors for POAG. Some of these discoveries are discussed below.

S1 RNA binding domain 1 (SRBD1)

In a recent GWAS analyzing the genetic risk factors for NTG in a Japanese population, the strongest signal was on chromosome 2 and spanned the *SRBD1* gene.[72] The most tightly associated genetic marker (rs3213787) in this GWAS is located within intron 17 of *SBRD1* and produced a *P*-value of 2.5×10^{-9} and an odds ratio of 2.80 for NTG. The high-risk allele of this genetic marker influences the expression of *SRBD1* and may be the source of risk for NTG at this locus. Both the function of *SRBD1* and the mechanism by which variants in this gene might increase the risk for NTG are unknown. However, it has been hypothesized that *SRBD1*'s binding properties may promote the development of NTG

through their proposed influence on protein synthesis, growth, and apoptosis in retinal ganglion cells.[72] This association has not yet been confirmed by replication studies.

Elongation of long-chain fatty acids family member 5 (ELOVL5)

A second association with NTG in Japan was also reported between glaucoma and genetic markers on chromosome 6 spanning the *ELOVL5* gene.[72] The most significant association was identified with a genetic marker located within the 3′ untranslated region of *ELOVL5* (rs735860), which produced a *P*-value of 4.14×10^{-6} and an odds ratio for NTG of 1.69. The *ELOVL5* gene encodes a protein that is involved in the production of long-chain polyunsaturated fatty acids (LCPUFAs). The risk allele of rs735860 influences the expression of *ELOVL5*[72] and it has been suggested that this effect might lead to increased LCPUFAs and promote apoptosis in retinal ganglion cells that leads to NTG. Replication studies of this association have not yet been reported.

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

A large GWAS conducted by Thorleifsson *et al*[8] mapped a risk factor for POAG to a region of chromosome 7q31 that encompasses two genes, *caveolin 1* (*CAV1*) and *caveolin 2* (*CAV2*). The risk allele in this locus is presumed to lie within either *CAV1* or *CAV2*, but has not yet been identified. One genetic marker in this locus, rs4236601, produced a *P*-value of 5.0×10^{-10} and an odds ratio of 1.36 for POAG in a discovery cohort from Iceland.[8] The same study included additional large cohorts of POAG patients and controls from Sweden, United Kingdom, Australia, Australia, and China. Pooled analyses of these replication cohorts confirmed the association with statistically significant, but much less remarkable *P*-values (0.0015 in Caucasian and 0.003 in Chinese cohorts) than what was observed in the discovery cohort from Iceland. Moreover, no association was detected in some of the individual replication cohorts in this study, such as those from the United Kingdom.[8] More recently, a second study with a single POAG cohort from the United States also failed to detect an association between glaucoma and rs4236601.[73] These data suggest that the POAG risk factor in the caveolins locus may be more important in some patient populations than in others.

The mechanism by which caveolin genes might confer risk for glaucoma is presently unclear. These genes encode proteins expressed in ocular tissues that are critical in glaucoma pathogenesis, including the trabecular meshwork and Schlemm's canal.[73] The caveolins form invaginated structures of cell membranes (caveolae) that are believed to influence transport of macromolecules across membranes and modulate signal pathways.[74] It has been proposed that risk for glaucoma might be increased by caveolin variants that alter TGF-β or nitric oxide signaling.[8]

A number of additional risk alleles for POAG have been reported that are noteworthy but are awaiting confirmatory reports. These potential risk alleles have been cataloged elsewhere.[75]

Summary

Risk alleles of major effect have been detected for several important eye diseases. For example, the complement factor H risk allele has an odds ratio of 2.45 and a population attributable risk of 43% for macular degeneration.[3] The *LOXL1* risk allele produces an odds ratio of 20.10 for exfoliation syndrome with a population attributable risk of 99%.[6] Similarly, an odds ratio of 5.5 and population attributable risk of 61% for Fuch's corneal endothelial dystrophy are produced by a risk factor in the *TCF4* gene.[5] Moreover, these risk alleles have been detected in most patient populations that have been tested. In contrast, no risk alleles of major effect for POAG have been detected to date. Association studies of POAG have identified risk alleles of smaller effect with more modest odds ratios and population attributable risks. The results of these initial GWAS suggest that POAG may be caused by the combined small effects of a very large number of genetic factors.

Quantitative traits approaches to the genetics of POAG

Many important features of glaucoma are quantitative traits. For example, POAG is defined by the quantitative assessment of cup-to-disc ratio and visual field defects. IOP is another vital quantitative measure for establishing and assessing treatment goals. More recently, central corneal thickness (CCT) has been established as another important quantitative measure in the assessment of glaucoma.

The magnitudes of most quantitative traits are generally controlled by a number of genes as well as environmental influences. Large studies of twins, siblings, and small pedigrees have shown that CCT,[76,77] cup-to-disc ratio,[78–81] and IOP[80–84] are all highly heritable traits and are likely determined in part by the actions of genes. Investigations to identify these genes will likely provide important insights into the pathophysiology of glaucoma. The same genes that determine the magnitudes of individual features of glaucoma are likely to be contributors to the overall risk for developing glaucoma as well.

Three recent large-scale GWAS have identified genetic factors that influence the magnitude of CCT.[85–87] A segment of chromosome 16q near the gene *ZNF469* was identified as an important quantitative traits locus for CCT in all three studies. *ZNF469* is an excellent candidate for regulating CCT as mutations in this gene were previously linked with brittle cornea syndrome (BCS OMIM #229200).[88] The specific variant in *ZNF469* that influences corneal thickness has not been identified; however, it has been estimated that it may be responsible for 1.29% of CCT variance. Other genetic factors that influence CCT[85–87] have been discovered, including variants in collagen genes (*COL5A1* and *COL8A2*). Detection of the first genetic factors for CCT is a significant advance and has paved the way for more discoveries. Although previous heritability studies clearly demonstrated that genes have a major influence on CCT, the number of genes that are important determinants of CCT is unclear. However, initial studies have found factors that exert a relatively modest influence on CCT and suggest that many more factors remain to be discovered.

Summary

A range of different types of genetic discoveries have been reported for glaucoma, which may be categorized as POAG-causing mutations or POAG genetic risk factors. Some cases of POAG can be attributed to the action of a single POAG-causing gene, whereas others are likely due to the interaction of many POAG genetic (and environmental) risk factors. It is important to distinguish between these types of factors to best interpret their clinical significance for both individual patients and large populations.

Rare POAG-causing mutations in genes such as *myocilin*, *optineurin*, and *TBK1* lead to disease without significant influence from other factors and are responsible for ~5% of POAG cases. Discovery of these POAG-causing genes has facilitated both the advancement of patient care and future glaucoma research strategies. Genetic testing for myocilin and optineurin mutations may provide select patients and their ophthalmologists with clinically useful data because these mutations are very rarely observed in people without glaucoma. The discovery of POAG-causing genes has also provided researchers with tools to engineer relevant animal models of glaucoma. Several mouse models of myocilin and optineurin-related POAG have been generated and will facilitate further studies of the biological mechanisms of vision loss in glaucoma.[43,44,59,89]

In contrast, for complex genetic forms of disease, an individual genetic risk factor for POAG is not capable of causing glaucoma on its own, and most carriers of this type of risk factor will never develop glaucoma. In the future, when more of these risk factors have been identified, testing patients for the presence of several genetic factors may have more clinical utility for predicting which patients are at highest risk for developing disease and need closer surveillance. Similarly, physicians may someday be able to improve clinical outcomes by customizing treatment regimens with such genetic tests.

It is very likely that additional important genetic factors for glaucoma will be discovered in the not too distant future. More large families with POAG are currently being studied with linkage analysis and hold the potential of discovering additional disease-causing glaucoma genes. Similarly, the largest GWAS of POAG that are underway will provide greater potential than ever to identify new important genetic factors that contribute to the complex forms of glaucoma. There is great promise that these studies will continue to clarify the role of genes in POAG and begin to reshape the way in which we diagnose and treat glaucoma.

Conflict of interest

The author declares no conflict of interest.

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