Genetic Etiologies of Glaucoma

Janey L. Wiggs, MD, PhD

Glaucoma can be inherited as a mendelian autosomal-dominant or autosomal-recessive trait, or as a complex multifactorial trait. Genetic approaches have helped define the underlying molecular events responsible for some mendelian forms of the disease and have identified the chromosome locations of genes that are likely to contribute to common complex forms. Future directions include the discovery of new glaucoma genes, determining the clinical phenotypes associated with specific genes and mutations, investigating environmental factors that may contribute to the disease, investigating gene-environment interactions and gene-gene interactions, and developing a mutation database that can be used for diagnostic and prognostic testing.

Glaucoma is the third most prevalent cause of visual impairment and blindness among white Americans and is the leading cause of blindness among black Americans. All forms of glaucoma have in common optic nerve degeneration characterized by typical visual field defects and are usually associated with elevated intraocular pressure (IOP). In most instances, the elevation of IOP results from impaired drainage of aqueous humor (produced by the ciliary body) through the trabecular meshwork outflow pathways. Glaucoma causes irreversible blindness that can only be prevented by therapeutic intervention at early stages of the disease.

A family history of the disease has long been recognized as a major risk factor for glaucoma, suggesting that specific gene defects contribute to the pathogenesis of the disorder. Glaucoma may be inherited as mendelian-dominant or mendelian-recessive traits (usually early-onset forms of the disease), or may exhibit a heritable susceptibility consistent with complex trait inheritance (typically adult-onset forms of the disease).

GENETIC APPROACHES

The identification of the molecular events responsible for glaucoma has been difficult because of a general lack of knowledge about the cellular and biochemical events that are necessary for the normal regulation of IOP and retinal ganglion cell function. Access to diseased human tissue is also difficult and animal models have only recently been developed and characterized. The advantage of a genetic approach is that the responsible protein can be identified without access to diseased tissue. The identification of genes (and their protein products) that can cause or contribute to glaucoma will help define the underlying pathophysiology, as well as lead to the development of new DNA-based diagnostic tests and novel therapeutic approaches.

The availability of predictive tests would provide a mechanism for early detection and treatment. Those individuals at risk who are identified early in the course of the disease and who begin therapy prior to significant damage to the optic nerve will have the best chance of maintaining useful sight.

Genes associated with forms of glaucoma that exhibit autosomal-dominant, autosomal-recessive, and other mendelian inheritance patterns can be located in the human genome using large affected pedigrees (typically at least 11 members) and standard linkage analysis. Once the chromosomal location of the gene is determined, the genes found within the linkage region can be evaluated for association with the disease. The simplicity of this overall approach has lead to substantial success and most of the genes currently known to be associated with various forms of glaucoma were identified using these methods (Table).

Common forms of adult-onset glaucoma, including primary open-angle glau-
of the identified genes do not appear ocular disease genes; however, most successful in the identification of some genes. This approach has been successes is another path to the desired rare mendelian forms of complex diseases (largely sibpairs) typically lead to the identification of a number of large genetic intervals containing many possible candidate genes. Using families affected with rare mendelian forms of complex diseases is another path to the desired genes. This approach has been successful in the identification of some ocular disease genes; however, most of the identified genes do not appear to have a major role in the complex phenotype. Recent efforts using whole genome–association methods and very large numbers of single nucleotide polymorphisms have successfully identified genetic factors conferring susceptibility to complex diseases, such as age-related macular degeneration, and it is expected that this will be a useful approach for adult-onset glaucoma.

GENES ASSOCIATED WITH FORMS OF GLAUCOMA WITH MENDELIAN INHERITANCE

Typically, early-onset forms of glaucoma are inherited as mendelian-dominant or mendelian-recessive traits, including early-onset open-angle glaucoma, congenital glaucoma, development glaucomas, including Rieger syndrome, glaucoma associated with nail-patella syndrome, and nanophthalmos, and glaucoma associated with pigment dispersion syndrome.

Congenital Glaucoma

In patients with congenital glaucoma, the development of the anterior segment of the eye and aqueous humor outflow pathways is abnormal, causing high IOP. Congenital glaucoma can be inherited as an autosomal-recessive trait and is prevalent in countries where consanguinity is common. Using consanguineous pedigrees from Saudi Arabia and Turkey, defects in the CYP1B1 gene coding for a protein that is a member of the cytochrome P450 family were found in individuals affected with congenital glaucoma. Subsequently, mutations in this gene have also been found in patients with congenital glaucoma from many countries including Slovakia (gypsies) and Japan, and from countries with more heterogeneous populations, such as the United States and Brazil. A loss of protein function is probably the underlying genetic mechanism, as most of the mutations are deletions, insertions, or missense mutations occurring in highly conserved protein regions that are necessary for its function. Recurrent mutations have been found in patients from varied ethnic backgrounds. Recent work indicates the recurrent mutations are on ancient chromosomes that have a common haplotype. The cytochrome P450 that is the product of the CYP1B1 gene participates in the metabolism of many compounds, including 17β-

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Table. Chromosomal Locations of Genes Associated With Glaucoma

<table>
<thead>
<tr>
<th>Chromosome Location</th>
<th>Condition</th>
<th>Locus (Gene)</th>
<th>Inheritance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q23</td>
<td>Early- and adult-onset POAG</td>
<td>GLC1A (MYOC)</td>
<td>Early-onset; AD</td>
</tr>
<tr>
<td>1p36</td>
<td>Congenital glaucoma</td>
<td>GLC3B</td>
<td>AR</td>
</tr>
<tr>
<td>2p21</td>
<td>Congenital glaucoma</td>
<td>GLC3A (CYP1B1)</td>
<td>AR</td>
</tr>
<tr>
<td>2cen-2q13</td>
<td>Adult-onset POAG</td>
<td>GLC1B</td>
<td>AD</td>
</tr>
<tr>
<td>3q21-24</td>
<td>Adult-onset POAG</td>
<td>GLC1C</td>
<td>AD</td>
</tr>
<tr>
<td>4q25</td>
<td>Rieger syndrome</td>
<td>RIEG1 (PTX2)</td>
<td>AD</td>
</tr>
<tr>
<td>5q22</td>
<td>Adult-onset POAG</td>
<td>GLC16 (VDRP36)</td>
<td>AD; complex</td>
</tr>
<tr>
<td>6p25</td>
<td>Iridodysgenesis</td>
<td>IRID1 (FOX1C1)</td>
<td>AD</td>
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<tr>
<td>7q35</td>
<td>Adult-onset POAG</td>
<td>GLC1F</td>
<td>AD</td>
</tr>
<tr>
<td>7q35-36</td>
<td>Pigment dispersion syndrome</td>
<td>GPDS1</td>
<td>AD</td>
</tr>
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<td>8q23</td>
<td>Adult-onset POAG</td>
<td>GLC1D</td>
<td>AD</td>
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<td>9q22</td>
<td>Early-onset POAG</td>
<td>GLC1J</td>
<td>AD</td>
</tr>
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<td>9q34</td>
<td>Glaucoma associated with nail-patella syndrome</td>
<td>(LMX1B)</td>
<td>AD</td>
</tr>
<tr>
<td>10p15-p14</td>
<td>Adult-onset POAG; low-tension glaucoma</td>
<td>GLC1E (OPTN)</td>
<td>AD</td>
</tr>
<tr>
<td>11p</td>
<td>Nanophthalmos</td>
<td>NNO1</td>
<td>AD</td>
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<td>11p13</td>
<td>Aniridia</td>
<td>AN2 (PAX6)</td>
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<td>11q23</td>
<td>Nanophthalmos</td>
<td>MFRP</td>
<td>AR</td>
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<td>Rieger syndrome</td>
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<td>AD</td>
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<td>14q11</td>
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<td>Locus pending</td>
<td>Complex</td>
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<td>GLC1I</td>
<td>Complex</td>
</tr>
<tr>
<td>20p12</td>
<td>Early-onset POAG</td>
<td>GLC1K</td>
<td>AD</td>
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</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; POAG, primary open-angle glaucoma.
estradiol. It has been hypothesized that alterations in the metabolism of estrogen may be the basis for the ocular abnormalities associated with defects in this gene.\(^{39,40}\)

Most patients with congenital glaucoma caused by mutations in \(\text{CYP1B1}\) have a severe case of the disease; however, there are some families with significant variation in phenotypic severity and even reduced penetrance, which is evident from the observation of apparently unaffected homozygote carriers.\(^{41}\) In mice, tyrosinase activity has been shown to modify the severity of the anterior segment defects caused by \(\text{CYP1B1}\) deficiency;\(^{42}\) however, this result has not been found in humans.\(^{43}\) Linkage studies have identified at least 1 other chromosomal region that is likely to harbor a gene for congenital glaucoma (1p36)\(^{44}\); numerous cytogenetic reports indicate other chromosome regions that may harbor congenital glaucoma genes.\(^{45}\) In addition, autosomal-dominant forms of congenital glaucoma have been identified.\(^{46}\)

Developmental Syndromes
(Axenfeld-Rieger, Nail-patella Syndrome, Aniridia, and Nanophthalmos)

In addition to congenital glaucoma, other forms of glaucoma are associated with abnormal development of the anterior segment of the eye. Axenfeld-Rieger syndrome, characterized by posterior embryotoxon, iris hypoplasia, and iridocorneal adhesions, can be caused by mutations in the \(\text{PITX2}\) gene.\(^{47}\) Defects in the \(\text{FOXC1}\) gene are found in patients with anterior segment dysgenesis.\(^{48,49}\) Patients with defects in both of these genes may also have associated systemic defects involving the teeth, facial bones, heart, and umbilicus. Abnormalities in the \(\text{PAX6}\) gene cause aniridia, as well as a spectrum of iris abnormalities related to glaucoma.\(^{50}\) Nail-patella syndrome is a systemic developmental disease associated with glaucoma caused by defects in \(\text{LMX1B}\).\(^{51}\) An autosomal-dominant form of nanophthalmos associated with vitreoretinocochroidopathy has been shown to be caused by abnormalities in the \(\text{VMD2}\) gene.\(^{52}\)

The genes responsible for these disorders participate in the regulation of gene expression during development,\(^{53-55}\) specifically in the development of the periocular mesenchyme, which includes neural crest– and cranial paraxial mesoderm–derived cells.\(^{56-59}\) These developmental disorders are all inherited as autosomal-dominant traits, and in general, the DNA defects lead to loss of function of the protein and haploinsufficiency.\(^{47,51}\)

Intrafamilial variability in disease severity is commonly encountered in pedigrees carrying defects in these genes. The variable phenotypic expressivity may be caused by dosage effects or by the coexistence of other genes that can modify the expression of the trait.

Early-Onset POAG

Defects in the \(\text{MYOC}\) gene coding for the myocilin protein were first associated with early-onset POAG. Up to 20% of patients with early-onset POAG and 3%-5% of patients with adult-onset POAG have defects in this gene.\(^{10,11}\) Some mutations are specifically associated with early-onset disease, while others are more common in adult-onset patients. One study has suggested that heterozygous defects of the \(\text{CYP1B1}\) gene can influence the severity of disease caused by mutations in \(\text{MYOC}\).\(^{58}\) This result may indicate that these 2 proteins affect the same biochemical pathway.

In patients with both early- and late-onset disease, the majority of the causative mutations are found in the olfactomedin domain of the protein, which is encoded by sequences found in the third exon of the gene.\(^{11}\) Myocilin is one member of a family of olfactomedin domain–containing proteins that are, in general, glycoproteins that function in the extracellular environment.\(^{59}\)

Although the clustering of glaucoma-associated mutations in the olfactomedin domain and the participation of olfactomedins in extracellular processes suggests that the myocilin protein functions in the extracellular matrix, the role of the normal protein in the outflow pathways is not well understood. Several studies suggest that myocilin is not needed for normal aqueous humor outflow.\(^{60-62}\) The normal protein has been detected in the extracellular matrix,\(^{63,65}\) suggesting it is secreted from the cell; studies have indicated that the mutant forms of the protein are not secreted.\(^{55-67}\)

It is likely that mutant forms of the myocilin protein have an abnormal function that may result in retention of the abnormal form of the protein in the cell.\(^{68,69}\) Mutant myocilin proteins form heterodimers and heteromultimers with wild-type myocilin and these heteromultimeric complexes remain sequestered intracellularly.\(^{70}\)

Disease-causing myocilin mutants appear to be misfolded and are highly aggregation prone, causing large-protein aggregates to accumulate in the endoplasmic reticulum. Secretion of mutant myocilin has been shown to be temperature sensitive, which supports the hypothesis that myocilin–induced glaucoma is a protein-conformational disease.\(^{71,72}\) Mutations associated with glaucoma also inhibit an intracellular endoproteolytic cleavage of myocilin that normally releases the olfactomedin domain.\(^{73}\) Mutant forms of the protein may be toxic to the trabecular cells or may prevent the processing and secretion of other proteins that are necessary for the normal function of the trabecular outflow pathways. Further studies will be required to determine the actual mechanism of myocilin–associated glaucoma.

NEW GENES ASSOCIATED WITH MENDELIAN FORMS OF GLAUCOMA SUPPORTED BY LINKAGE STUDIES

For a number of glaucoma-associated genes, the chromosomal location of the gene has been determined by linkage studies. The gene has yet to be identified.

Anterior Segment Dysgenesis Syndromes

Linkage studies and chromosome-deletion analyses suggest that genes responsible for anterior segment developmental abnormalities are located on chromosomes 13q14,\(^{28}\) 4p,\(^{74}\) 16q,\(^{73}\) and 20p.\(^{76}\) In mice, sev-
eral genes have been suggested as responsible for ocular developmental defects leading to glaucoma, including Bmp4, Foxe3, and Tgfβ2. 

**Pigment Dispersion Syndrome**

Of the individuals with clinical evidence of pigment dispersion syndrome, approximately 50% will develop glaucoma. In humans the disease can be sporadic or inherited, with most pedigrees demonstrating autosomal-dominant inheritance patterns. Specific genes responsible for the human condition have not yet been identified; however, linkage studies suggest that a gene is located on chromosome 11q13 has been located but not yet discovered. 

A third gene on chromosome 11 has been located but not yet discovered. 

**Nanophthalmos**

Nanophthalmos can be inherited as an autosomal-recessive or autosomal-dominant trait, and affected patients are at risk for angle-closure glaucoma. One gene, MFRP (membrane-type Frizzled-related protein), located on chromosome 11q23, has been shown to be associated with autosomal-recessive nanophthalmos. Mutations in a second gene, VMD2 (vitelliform macular dystrophy 2, also known as bestrophin), located on chromosome 11q13 have been found in patients with an autosomal-dominant form of nanophthalmos, also associated with vitreoretinochoroidopathy. Finally, a third gene on chromosome 11 has been located but not yet discovered. 

**Early-Onset POAG**

Although mutations in myocilin are currently the most identifiable cause of early-onset POAG, most cases (80%) are not caused by myocilin mutations. Three new chromosome locations of genes responsible for POAG have been identified on chromosomes 9q22 (GLC1F) and 20p12 (GLC1K), and on chromosome 5q. 

**GENES ASSOCIATED WITH FORMS OF GLAUCOMA WITH COMPLEX INHERITANCE**

Adult-onset forms of glaucoma, including POAG, low-tension glaucoma, and glaucoma associated with pseudoxfoliation, are inherited as complex traits. A positive family history is a major risk factor for these conditions, which suggests that specific gene defects are likely to contribute. However, a simple mode of inheritance is not evident, and a single underlying susceptibility gene is not likely. It is more likely that multiple genes contribute to these phenotypes and that environmental conditions may also participate. Because a genetic model cannot be defined, methods to identify genes responsible for these conditions are more complex than those used for mendelian disorders. Genome scans and model-free analyses have been performed using families demonstrating clustering of complex diseases (largely sibpairs), as well as families affected with rare forms showing apparent mendelian inheritance. 

**Low-tension Glaucoma**

In patients with low-tension glaucoma, degeneration of the optic nerve occurs even though the IOPs are not abnormally elevated. In patients with low-tension glaucoma, the clinical appearance of the optic nerve is similar to the appearance of the optic nerve in the Kjer form of autosomal-dominant optic atrophy. Loss of function mutations in the OPA1 gene are responsible for Kjer autosomal-dominant optic atrophy; polymorphisms in the OPA1 gene may be associated with low-tension glaucoma in some cases. 

Low-tension glaucoma has also been associated with mutations in a novel gene, OPTN. The protein optineurin is expressed in many ocular and nonocular tissues, including the trabecular meshwork, nonpigmented ciliary epithelium, retina, brain, heart, liver, skeletal muscle, kidney, and pancreas. Optineurin may participate in the tissue necrosis factor α signaling pathway, which has been proposed to be one pathway involved in retinal ganglion cell apoptosis in patients with low-tension glaucoma and in patients with POAG. 

Missense mutation in optineurin is an infrequent cause of low-tension glaucoma, with a possible increase in prevalence in the Japanese population. The E50K mutation, although exceedingly rare, has been associated with a severe form of low-tension glaucoma, characterized by significant loss of optic nerve function at relatively early ages. Surprisingly, researchers have not found optineurin mutations at an increased frequency in patients with typical high-pressure glaucoma, arguing that this gene does not contribute to adult-onset POAG. 

Studies of lymphocytes in patients with low-tension glaucoma have demonstrated altered expression of the p53 gene, a known regulator of apoptosis. Abnormal regulation of apoptosis may be one mechanism of low-tension glaucoma. Although not true for optineurin, the possibility remains that genes that predispose patients to low-tension glaucoma may also contribute to nerve degeneration in patients with POAG associated with increased IOP. 

**Adult-Onset POAG**

Primary open-angle glaucoma commonly occurs after age 50 years and is usually associated with elevated IOP. The relationship between pressure elevation and optic nerve disease is not linear, suggesting that variability in optic nerve susceptibility exists among glaucoma patients. Adult-onset glaucoma often occurs in multiple family members (familial aggregation) but does not
Defects in MYOC coding for myocilin are found in 3% to 5% of patients with adult-onset POAG.10,11 Certain MYOC mutations are more commonly found in older-onset patients than in early-onset patients.103 In particular, the nonsense mutation Q368X, which results in a truncated polypeptide, is more frequently found in patients with adult-onset POAG than in patients with early-onset POAG.102 Studies have shown that the Q368X mutation demonstrates a founder effect in white patients, which is possibly one explanation for its higher prevalence.103 In an in vitro assay that correlates the solubility of mutant forms of myocilin with clinical severity, the Q368X mutation is less likely to form a precipitate, supporting the suggestion that the Q368X mutation causes a milder form of the disease.68

Recently, DNA sequence changes have been identified in the WDR36 gene, located within the chromosomal region defined as GLC1G.104 Although the function of the protein product is unknown and the role of the protein in glaucoma remains to be confirmed,105 prior studies suggest that it may participate in immune responses106; other studies have also suggested that glaucoma may be influenced by immune reactivity.107 Interestingly, recent evidence suggests that mutations in the WDR36 gene are not an independent cause of glaucoma but may modify the severity of the disease in an affected person.108

NEW GENES ASSOCIATED WITH COMPLEX FORMS OF GLAUCOMA SUPPORTED BY LINKAGE STUDIES

Adult-Onset POAG

Using mendelian (model-dependent) linkage approaches and small numbers of large pedigrees affected by POAG, 7 genetic loci have been described for POAG (GLC1A-G).21,101,109-113 and glaucoma-predisposing genes have been identified in 3 of these loci: GLC1A, myocilin7; GLC1E, optineurin9; and GLC1G, WDR36.104 Each of these genes is only responsible for a small fraction of cases of POAG, reflecting the small percentage of POAG that is inherited as a mendelian trait rather than as a complex trait.

Genomic studies using model-free linkage analysis (complex disease gene approaches) have identified the chromosome locations of adult-onset POAG susceptibility genes. Using mainly white US sibling pairs affected by POAG, 7 genomic regions were identified,9 and recent follow-up information on this population demonstrates additional evidence for POAG-susceptibility loci on chromosomes 1q, 11 (locus pending) (J.L.W., unpublished data, 2006) and 15q (GLC1H).105,111 A study of sibling pairs from Barbados affected by POAG has identified 2 regions on chromosomes 2q and 10p as highly significant for POAG in this population,116 and a study of West Africans selected for elevated IOP have found loci on 5q and 14q.117 Because these studies were conducted using a large number of families affected by typical late-onset glaucoma, the genes located in these chromosome regions are likely to be significant risk factors for POAG. Single nucleotide polymorphism–based approaches are proving successful for complex diseases14-18 and the application of these technologies to adult-onset POAG is the focus of current studies.

Pseudoexfoliation

Although a linkage study has not yet been completed for pseudoexfoliation glaucoma, systemic abnormalities, including elevation of homocysteine, have been identified in affected patients.118-120 Evaluating the genetic factors that contribute to these systemic problems may lead to new insights about this common form of glaucoma.

GENES ASSOCIATED WITH PRIMARY OPTIC NEUROPATHIES

Inherited disorders of the optic nerve include degenerative processes (primarily glaucoma, as described previously), as well as primary disorders causing optic nerve atrophy.121 Mitochondrial function is a critical element in optic nerve disease: Leber hereditary optic neuropathy is caused by missense mutations in mitochondrial DNA,122 while Kjer autosomal-dominant optic atrophy is caused by mutations in the OPA1 gene. The protein product of OPA1, a dynamin-related GTPase, also has a role in mitochondrial function.123 OPA1 DNA sequence variants may be associated with low-tension glaucoma in some patients.92

FUTURE DIRECTIONS

Genotype-Phenotype Correlations and Clinical Outcomes Studies

The clinical features that define glaucoma phenotypes associated with specific mutations (genotypes) must be established before useful clinical information can be acquired from DNA-based diagnostic testing. For the genes that have been identified as responsible for glaucoma, or associated with glaucoma, clinical information about the onset of disease, course of disease, and response to therapy needs to be collected. As new genes responsible for different forms of inherited glaucoma are discovered, clinical disease features should be correlated with specific mutations. These genotype-phenotype studies will include the answers to the following questions: (1) What is the range of phenotypic variation of a given mutation, ie, can one predict the prognosis of the disease knowing the specific mutation responsible for the disease? (2) Are certain mutations associated with particular aspects of the disease phenotype? (3) Are certain mutations necessary but not sufficient to cause the disease? Such mutations would require other additional genetic defects or environmental factors to be fully manifest. The development of genotype-phenotype databases for glaucoma genes and mutations will be an important step toward clinically useful DNA-based diagnostic testing for glaucoma.
Identification of New Genes

Genetic factors are at least in part responsible for all forms of glaucoma, with the exception of glaucoma related to trauma and infection. Currently, the genetic origins of the majority of glaucoma cases are unknown, as the known genes account for only a small fraction of heritable cases. With the advent of single nucleotide polymorphism–based technologies, it is likely that a number of genes responsible for glaucoma will be identified in the next 5 years. Genes that contribute to glaucoma may influence elevation of IOP or susceptibility to optic nerve degeneration, or both. It is highly likely, as in any complex disease, that complex forms of glaucoma, such as adult-onset POAG, result not only from the independent actions of multiple genes but also from the interaction of multiple genes (epistasis).

Gene-Environment Interactions

For late-onset diseases it is likely that the genetically determined disease features are more sensitive to environmental influences because of disruption of normal physiologic homoeostatic mechanisms. Currently, little is known about environmental factors that may influence the onset or progression of adult-onset POAG. Recent studies suggest that factors related to glaucoma metabolism and type II diabetes mellitus may increase the risk of glaucoma.124 Another interesting gene-environment interaction that predisposes patients to glaucoma is steroid responsiveness, both from endogeneous steroids (ie, stress) and pharmacologic steroids.125 Evaluation of environmental factors that may be associated with POAG is ongoing, and investigations into specific gene-environment interactions in patients with adult-onset POAG is also under way.

Developing a Diagnostic Panel for Patients at Risk for Glaucoma

One of the goals of disease gene discovery is the development of predictive diagnostic tests. For a disease such as glaucoma, where early treatment can be beneficial, diagnostic tests designed to identify individuals at risk for the disease can be particularly valuable. Current testing for glaucoma genes is limited to genes that are known to be associated with glaucoma and is primarily diagnostic, rather than prognostic. Except for specific mutations in the MYOC and OPTN genes, details regarding the predicted clinical course associated with a glaucoma gene mutation cannot be provided. Genotype-phenotype studies as outlined earlier will help define the prognostic aspects of currently known glaucoma gene mutations. Ultimately the goal is to discover a complete panel of genes that contribute to glaucoma and develop diagnostic and prognostic correlates for the mutations found in each gene. Such a panel would provide a mechanism to identify individuals at risk for the disease and initiate timely treatment before irreversible optic nerve degeneration and blindness occurs.

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