Genetics in Glaucoma Diagnosis and Management

Gene-based tests and therapies carry important implications for clinical practice.

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Glaucoma refers to a group of disorders characterized by the death of retinal ganglion cells, optic nerve cupping, and visual field loss. This highly complex and multifactorial disease has multiple genetic and environmental influences. In recent years, substantial progress has been made toward understanding the genetic basis of various forms of the disease.[1] The opportunity to translate into clinical practice the broadening knowledge of the genetic and biomolecular processes that cause glaucoma has become a reality. Gene-based screening tests are currently available for several early-onset forms of glaucoma (Table). For adult-onset forms, large-scale genome-wide association studies (GWAS) have identified multiple genes that increase the risk of developing primary open-angle glaucoma (POAG) and angle-closure glaucoma. Very recently, one common genetic variant was identified that functionally contributes to the pathogenesis of POAG.

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GENETIC TESTING RESOURCES

The field of glaucoma genetics is evolving at an accelerating pace. Many of the tests now available are covered by health insurance. Online databases such as GeneTests (www.genetests.org) and the National Institutes of Health Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr) identify the genetic tests that are currently available for various forms of glaucoma and the laboratories performing them. A referral to a geneticist or a genetic eye disease service can be useful when a provider is unfamiliar with genetic testing.

THE GENETICS OF GLAUCOMA

Primary Congenital Glaucoma

Mutations in the *CYP1B1* and *LTBP2* genes cause primary congenital glaucoma with autosomal recessive inheritance.[2,3] The *GLC3B* and *GLC3C* loci have also been linked to this form of glaucoma, although the causal genes at these loci are unknown.[4] The *CYP1B1* gene plays a role in oxidative and vascular homeostasis, whereas the *LTBP2* gene functions in cell adhesion.[4] Genetic testing for known disease-associated mutations is available for both *CYP1B1* and *LTBP2*.

Developmental Glaucomas

Axenfeld-Rieger syndrome and aniridia are both inherited in an autosomal dominant manner. Approximately 50% of individuals who carry genetic mutations will develop early-onset glaucoma. Mutations in the *PITX2* and *FOXC1* genes are associated with Axenfeld-Rieger syndrome, and *PAX6* mutations cause aniridia and Peters anomaly.[5-7] Each of these genes encodes transcription factors involved in the eye's development. Genetic testing is available for all three genes.

A novel therapy for aniridia is being investigated that is based on the molecular biology of *PAX6* genetic mutations.

TABLE. GENETIC TESTS CURRENTLY AVAILABLE FOR GLAUCOMA	
Type of Glaucoma	**Genetic Test**
Primary congenital glaucoma	*CYP1B1, LTBP2*
Axenfeld-Rieger syndrome	*PITX2, FOXC1*
Aniridia	*PAX6*
Juvenile-onset open-angle glaucoma	*MYOC*
Primary open-angle glaucoma	*MYOC, OPTN, WDR36*

Ataluran (formerly known as PTC124; Translurna [PTC Therapeutics]) is an investigational new drug that works by reducing ribosomal sensitivity to premature stop codons. Postnatal topical application of a drug formulation containing ataluren can reverse corneal, lenticular, and retinal defects in a mouse model of aniridia, which suggests that ataluren may be a viable therapeutic option for patients with *PAX6* genetic mutations.[8,9]

Juvenile-Onset Open-Angle Glaucoma

Juvenile-onset open-angle glaucoma (JOAG) is inherited as an autosomal dominant trait and usually presents before the age of 35. Mutations in the myocilin gene are found in up to one-third of patients with JOAG and can be identified with available genetic tests.[10] These tests are also valuable screening tools for first-degree relatives of JOAG patients, who have a 50% chance of inheriting the mutation.

Aggregation of mutant myocilin protein is thought to increase endoplasmic reticulum stress in the trabecular meshwork, which sensitizes cells to apoptosis.[11] Consistent with this hypothesis, the reduction of endoplasmic reticulum stress with chemical chaperones reduces cell death in human trabecular meshwork cells and in a glaucoma mouse model expressing mutant myocilin protein.[12,13] These findings suggest that chemical chaperones may be a viable therapeutic strategy for JOAG patients harboring myocilin mutations.

Primary Open-Angle Glaucoma

Genes that cause early-onset forms of glaucoma are responsible for less than 5% of all POAG cases.[1] Recent large-scale GWAS have identified a number of important POAG-associated genes and loci, including *CDKN2B-AS*, *SIX1/SIX6*, *TMCO1*, and *CAV1/CAV2*.[14-16] As investigations proceed, more genes will be discovered.

Very recently, a common genetic variant in the *SIX6* gene, rs33912345, was shown to reduce the size of the eye and optic nerve volume in an animal model.[17] Even more importantly, this variant was associated with decreased thickness of the retinal nerve fiber layer, as measured by spectral domain optical coherence tomography in POAG cases. The variant is found in approximately 40% of white populations, 70% to 80% of Asian populations, and nearly 100% of West Africans. This discovery carries enormous implications for testing and future therapeutic intervention for a very large number of people at risk of POAG.[17] How this variant reduces the thickness of the retinal nerve fiber layer and how soon this effect is observed are subjects of intense investigation.

Normal-tension glaucoma, a subtype of POAG, also has a strong genetic component. Recently, associations in the *CDN2B-AS* gene and in a proposed regulatory region on chromosome 8q22 were identified in a large cohort of patients with this form of glaucoma.[1,15]

In addition, new testing approaches for POAG-associated genetic variants are now being developed for use in patients. These tests, which examine multiple genetic variants, substantially improve the sensitivity and specificity of a discriminative POAG risk test, a finding that has important implications for future clinical practice.[18]

Weigh in on this topic now!

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1. How important do you think genetic testing is in glaucoma?
- ☐ Very
- ☐ Somewhat
- ☐ Not very

2. Do you believe its importance will grow in the future?
- ☐ Yes
- ☐ No

"Ultimately, the development of gene-directed therapies could lead to a cure, which has important implications for reducing the global burden of blindness."

Exfoliation Glaucoma

In contrast to POAG, where multiple genes contribute to disease risk, exfoliation glaucoma (XFG, also known as pseudoexfoliation glaucoma) is primarily associated with one gene (*LOXL1*). This discovery makes XFG a very attractive target for gene-based diagnostic and therapeutic approaches. Common DNA variants in *LOXL1* confer risk for XFG in all populations studied to date around the world.[1,19] The *LOXL1* gene encodes a protein involved in elastic fiber formation and stabilization.[20] None of the variants identified to date, however, is shared across all populations, suggesting that these variants are either markers for disease or play different roles depending on the specific population where they are found.

Multiple investigators are actively pursuing the mechanism for disease induced by variants in *LOXL1*. Their research will help lay the groundwork for improving the clinical management of this common disorder.

Primary Angle-Closure Glaucoma

A recent GWAS identified three susceptibility loci for primary angle-closure glaucoma (PACG): *PLEKHA7*, *COL11A1*, and an intergenic region between *PCMTD1* and *ST18*.[21] Another GWAS performed in an Asian population identified a variant in *ABCC5* that influences anterior chamber depth and risk for PACG.[22] The functional mechanisms whereby these genes confer risk for PACG are under active investigation.

FUTURE DIRECTIONS

Genetics will play a significant role in clinical glaucoma practice in the future. For early-onset forms of glaucoma, genetic testing already enables diagnosis and informative genetic counseling. Moreover, efforts are underway to develop treatments that target underlying molecular events involved in disease pathogenesis.

Personalized risk assessment and treatment are also on the horizon for adult-onset forms of glaucoma. There are several robust genetic associations for these disorders, and ongoing research efforts will likely identify additional ones. It will soon be possible to develop informative gene-based screening tests that identify individuals at high risk before irreversible damage has occurred. These genetic signatures may also guide treatment decisions and plans for disease surveillance. Ultimately, the development of gene-directed therapies could lead to a cure, which has important implications for reducing the global burden of blindness. ■

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