**Genetics and Glaucoma**

Research is revealing much about the inheritance of disease. Genetic testing is useful for patients with early-onset glaucoma and for some families with multiple members affected by normal-tension and primary open-angle glaucoma.

**BY JANELY L. WIGGS, MD, PhD**

Genetic factors contribute to the development of most types of glaucoma. Early-onset disease (before age 35) exhibits autosomal dominant or autosomal recessive inheritance, whereas the inheritance of adult-onset glaucoma is complex due to the influence of multiple genetic and/or environmental risk factors. Current genetic and genomic methodologies have identified genes responsible for early-onset glaucoma as well as genetic risk factors contributing to adult-onset glaucoma.

**CONGENITAL GLAUCOMA**

Two genes are currently known to cause congenital glaucoma, CYP1B1 coding for cytochrome P450 1B1 and LTBP2 (latent transforming growth factor-β binding protein 2).\(^1\) Mutations in both genes cause autosomal-recessive congenital glaucoma. The role(s) of the mutant proteins in disease pathogenesis is not yet known.

**DEVELOPMENTAL GLAUCOMA**

Axenfeld-Rieger syndrome, aniridia, and glaucoma associated with anterior segment dysgenesis are caused by mutations in PITX2, PAX6, and FOXC1, respectively.\(^2,3\) All three of these genes code for transcription factors active in ocular development. Mutations in these genes cause dominantly inherited disease.

**JUVENILE OPEN-ANGLE GLAUCOMA**

Approximately 20% of patients with open-angle glaucoma before the age of 35 have mutations in MYOC coding for myocilin.\(^4\) The first-degree relatives of MYOC mutation carriers have a 50% chance of inheriting the mutation (dominant inheritance) and should undergo genetic testing and regular eye examinations. Patients with MYOC mutations may benefit from therapeutic approaches that relieve endoplasmic reticulum stress such as phenylbutyrate.\(^5\) Because several MYOC mutations cause adult-onset disease, genetic screening for MYOC mutations should also be considered for patients who develop the disease after age 35 and have a family history of glaucoma.\(^6\)

**FAMILIAL NORMAL-TENSION GLAUCOMA**

A duplication of the TBK1 gene causes a rare form of familial normal-tension glaucoma (NTG).\(^7\) TBK1 interacts with optineurin, a protein that is also a rare cause of NTG.\(^8\) Patients with NTG who have family members also affected by the disease could benefit from genetic screening for mutations in both TBK1 and OPTN. Because both genetic products are involved in tumor necrosis factor-α signaling, it is possible that mutation carriers could benefit from tumor necrosis factor-α inhibitors, although more studies are first necessary to confirm these findings.\(^9\)
ADULT-ONSET PRIMARY OPEN-ANGLE GLAUCOMA

Recent advances in genomic technologies have made it possible to study the genetic etiologies of common forms of adult-onset glaucoma. For example, several genome-wide association studies for primary open-angle glaucoma (POAG) have been completed. Research from Iceland identified DNA sequence variants in the CAV1/CAV2 gene region associated with POAG, and this finding was replicated in cases and controls involving white subjects from the United States. The advanced glaucoma found significant associations between POAG and the TMCO1 genes. The TMCO1 associations between POAG and the replicated in populations worldwide. The frequency useful to the disease. Additional research suggests that TMCO1 is associated with elevated IOP, whereas TMCO2 may primarily affect the optic nerve’s susceptibility to degeneration.

PRIMARY ANGLE-CLOSURE GLAUCOMA

A recent study using patients with primary angle closure and controls from five different Asian populations identified significant associations with the PLEKHA7 and COL11A1 genes and an intergenic region between PCMTD1 and ST18 on chromosome 8q. It is not yet known how these genes may contribute to primary angle-closure glaucoma, although potential mechanisms include the regulation of cellular permeability, scleral rigidity, and ocular growth.

EXFOLIATION SYNDROME AND GLAUCOMA

In the Icelandic population, a genome-wide association study identified LOXL1 as a major genetic risk factor for exfoliation syndrome, a finding that has been replicated in populations worldwide. The frequency of LOXL1 risk alleles is high in both affected and unaf-\footnotesize{ected} individuals, suggesting that other factors, which could be genetic or environmental, must also contribute to the disease.

GENETIC TESTING FOR GLAUCOMA

Genetic testing should be considered for patients with early-onset disease and for patients with adult-onset disease who have family members affected by glaucoma. The detection of mutations will make informed genetic counseling possible and could also affect surveillance planning and therapeutic decisions. Gene-based tests for adult-onset glaucomas (POAG, NTG, primary angle-closure glaucoma, and exfoliation syndrome) do not yet have the sensitivity and specificity expected for a clinically useful test. Ongoing research efforts are likely to yield additional genes associated with these conditions, however, making future genetic testing for adult-onset conditions possible.

Janey L. Wiggs, MD, PhD, is the Paul Austin Chandler associate professor of ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston. Dr. Wiggs may be reached at (617) 573-6440; janey_wiggs@meei.harvard.edu.