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 JANEY 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.

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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.[10,11] A study using Australians with advanced glaucoma found significant associations between POAG and the *CDKN2BAS* and *TMCO1* genes.[12] The *CDKN2BAS* and *SIX1/SIX6* genes were associated with POAG, and the *CDKN2BAS* and a regulatory region on chromosome 8q22 were associated with NTG in a meta-analysis of the Glaucoma Gene Environment Initiative (GLAUGEN) and National Eye Institute Glaucoma Human Genetics Collaboration (NEIGHBOR).[13] Additional research suggests that *TMCO1* is associated with elevated IOP, whereas *CDKN2BAS* may primarily affect the optic nerve's susceptibility to degeneration.[14,15]

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.[16] 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,[17] a finding that has been replicated in populations worldwide. The frequency of *LOXL1* risk alleles is high in both affected and unaffected individuals, suggesting that other factors, which could be genetic or environmental, must also contribute to the disease.[18]

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 afflicted 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. ■

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