Genetic research has provided doctors and patients with new diagnostic tools, insight into disease mechanisms, and even novel therapies. These advances have changed medicine and have the potential to change the way physicians care for patients with glaucoma. Numerous glaucoma-causing genes and genetic risk factors have been discovered over the past 20 years. The role of testing for these genes and factors is an important and ongoing discussion, because they may assist diagnosis and therapy for specific types of patients.

**JUVENILE OPEN-ANGLE GLAUCOMA**

Mutations in the myocilin gene are responsible for 8% to 63% of juvenile open-angle glaucoma (JOAG) cases. Different myocilin mutations are associated with different clinical courses, although high IOP is a common feature of glaucoma caused by this gene. For example, the Tyr437His myocilin mutation is associated with an early age at diagnosis (mean, 20 years old) and a high maximum IOP (mean, 44 mm Hg). Although many myocilin mutations are associated with therapy-resistant JOAG, patients with a different mutation, Gln368Stop, have glaucoma that responds to medical and surgical therapies in the same manner as patients with no known mutation.

Given the relatively high likelihood of positive results, genetic testing may be warranted in patients with JOAG. Many cases are familial and exhibit autosomal dominant inheritance. When a myocilin mutation is identified in a patient with JOAG, his or her family members have up to a 50% risk of inheriting the mutation. Further testing can identify family members who are at risk of developing glaucoma and ensure that they are closely observed to provide the best opportunity for an early diagnosis and initiation of therapy. Family members who test negative can be reassured that they are at the much lower general population risk of developing glaucoma. Testing can also provide families with more specific information by which to judge their risk of having additional children with JOAG. Genetic testing for myocilin mutations is widely available for diagnostic purposes from Clinical Laboratory Improvement Amendments-certified laboratories (see www.genetests.com).

**PRIMARY OPEN-ANGLE GLAUCOMA**

Whereas some mutations in myocilin cause JOAG, others are associated with 3% to 4% of adult-onset primary open-angle glaucoma (POAG) that typically occurs with high IOP. Conversely, mutations in two other genes, optineurin (OPTN) and TANK-binding kinase 1 (TBK1), are associated with 1% to 2% of POAG cases that typically occur at low IOP. Given the relatively low rate of positive results, testing for myocilin, OPTN, or TBK1 mutations in unselected POAG patients is not currently warranted, except as part of research studies. Testing might be considered in a limited set of patients who have an especially strong family history of glaucoma.
Other cases of POAG have a more complex genetic basis and are caused by the combined actions of many genetic and environmental risk factors. Nearly two dozen genetic risk factors have been identified. In the future, when more factors are known, it may be possible to accurately gauge a person’s risk of developing this complex genetic form of glaucoma with genetic tests. At this time, however, testing for these risk factors cannot predict who will develop disease and is therefore only useful for research studies.

**PRIMARY CONGENITAL GLAUCOMA**

Two genes have been identified that cause autosomal recessive primary congenital glaucoma (PCG). Mutations in the cytochrome P450 1B1 (CYP1B1) gene are responsible for a large proportion of PCG cases in Saudi Arabian and Roma populations and a smaller proportion in other populations worldwide. Some cases of PCG have been attributed to mutations in latent transforming factor beta-binding protein 2 (LTBP2). Genetic testing for both of these genes is widely available. When testing for recessive conditions, it is useful to have DNA samples available from parents as well as from affected children. Testing for these genes may help with genetic counseling about the risk of having additional children with PCG.

**SECONDARY GLAUCOMAS**

Genetic testing is also available for a range of conditions that predispose people to the development of secondary glaucomas such as Axenfeld-Rieger syndrome (PITX2 and FOXC1), aniridia (PAX6), and others.

**GENETIC COUNSELING**

When selected for the appropriate patients, genetic testing is a powerful and useful diagnostic tool. The results of testing can be complex, however, and may affect other family members by revealing their increased risk of developing glaucoma. Moreover, learning the results of genetic testing may be upsetting and stressful for some individuals. Genetic tests should therefore only be ordered by physicians and/or genetic counselors who are prepared to interpret the results and counsel the patients. The American Academy of Ophthalmology provides a set of recommendations to aid ophthalmologists in deciding when genetic testing is likely to be the most useful ([bit.ly/1WFwJt]).

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**AT A GLANCE**

- Numerous glaucoma-causing genes and genetic risk factors have been discovered over the past 20 years.
- Mutations in the myocilin gene are responsible for 8% to 63% of juvenile open-angle glaucoma cases and 3% to 4% of adult-onset primary open-angle glaucoma that typically occurs with high IOP.
- Mutations in optineurin and TANK-binding kinase 1 are associated with 1% to 2% of primary open-angle glaucoma cases that typically occur at low IOP.
- Two genes have been identified that cause autosomal recessive primary congenital glaucoma.
- When selected for the appropriate patients, genetic testing is a powerful and useful diagnostic tool.