

THE PROMISE OF GENETIC TESTING

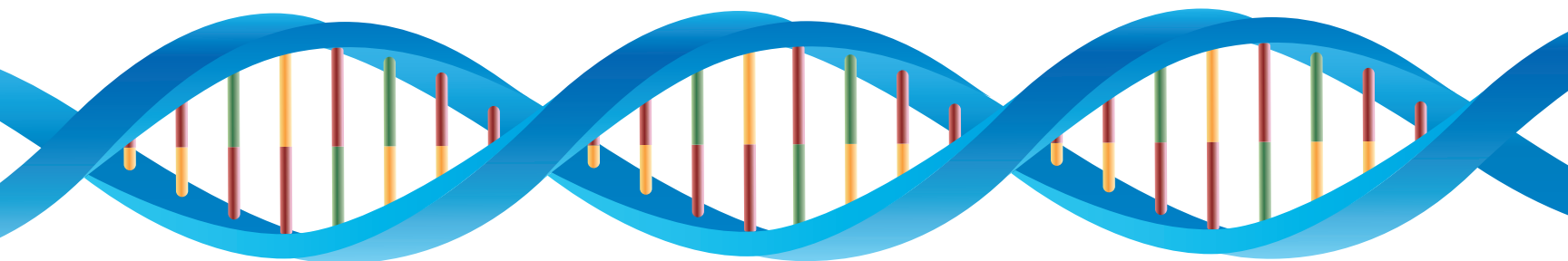
Research may improve the diagnosis and treatment of glaucoma.

BY JOHN FINGERT, MD, PhD



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.

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



JUVENILE OPEN-ANGLE GLAUCOMA

Mutations in the myocilin gene are responsible for 8% to 63% of juvenile open-angle glaucoma (JOAG) cases.¹⁻⁴ 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).⁵ 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.⁶

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

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.^{1,2} 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.^{7,8} 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.^{9,10} 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.^{8,11} Some cases of PCG have been attributed to mutations in latent transforming factor beta-binding protein 2 (*LTBP2*).¹² 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.



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.

“Genetic testing is ... available for a range of conditions that predispose people to the development of secondary glaucomas.”

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/1WFw2jI).¹³ ■

1. Stone EM, Fingert JH, Alward WL, et al. Identification of a gene that causes primary open angle glaucoma. *Science*. 1997;275(5300):68–670.
2. Fingert JH, Héon E, Liebmann JM, et al. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum Mol Genet*. 1999;8(5):899–905.
3. Wiggs JL, Allingham RR, Vollrath D, et al. Prevalence of mutations in TIGR/myocilin in patients with adult and juvenile primary open-angle glaucoma. *Am J Hum Genet*. 1998;63(5):1549–1552.
4. Adam MF, Belmouden A, Binistri P, et al. Recurrent mutations in a single exon encoding the evolutionarily conserved of factomedin-homology domain of TIGR in familial open-angle glaucoma. *Hum Mol Genet*. 1997;6(12):2091–2097.
5. Alward WL, Fingert JH, Coote MA, et al. Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). *N Engl J Med*. 1998;338(15):1022–1027.
6. Graul TA, Kwon YH, Zimmerman MB, et al. A case-control comparison of the clinical characteristics of glaucoma and ocular hypertensive patients with and without the myocilin Gln368Stop mutation. *Am J Ophthalmol*. 2002;134(6):884–890.
7. Fingert JH, Robin AL, Stone JL, et al. Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. *Hum Mol Genet*. 2011;20(12):2482–2494.
8. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science*. 2002;295(5557):1077–107.
9. Kumar S, Malik MA, Goswami S, et al. Candidate genes involved in the susceptibility of primary open angle glaucoma. *Gene*. 2016;577(2):119–131.
10. Kumar S, Malik MA, Goswami S, et al. Genes, pathways, and animal models in primary open-angle glaucoma. *Eye (Lond)*. 2015;29(10):1285–1298.
11. Moore DB, Tomkins O, Ben-Zion I. A review of primary congenital glaucoma in the developing world. *Surv Ophthalmol*. 2013;58(3):278–285.
12. Ali M, McKibbin M, Booth A, et al. Null mutations in LTBP2 cause primary congenital glaucoma. *Am J Hum Genet*. 2009;84(5):664–671.
13. Stone EM, Aldave AJ, Draack AV, et al. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. *Ophthalmology*. 2012;119(11):2408–2410.

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