John H. Fingert, MD, PhD

Dr. Fingert describes the thrill of genetic research in glaucoma and the joy of cycling.

What effect has your grandfather, a pediatrician, had on your professional life?

My grandfather has had a profound influence on my career as a physician. As a child, I was impressed by his tremendous work ethic and his dedication to caring for his patients—hospital rounds before dawn, clinic all day, and house calls each night. He was tireless in his work to help others. I admire his kind and personal attention to his patients and the satisfaction he got from helping them. I have always wanted to be like him.

How do you balance the clinical evaluation of patients who have glaucoma with your genetic research?

Limited time and opportunity cost are always challenges to physician-scientists. My approach to achieving a balance between clinical and research efforts has been to maximize the overlap between these activities. At its core, my research program investigates the genetic causes of glaucoma in the patients for whom I care in the clinic. I like to think that my research efforts complement my clinical work and vice versa.

FAST FACTS

- Associate professor in the Department of Ophthalmology and Visual Sciences (2010-present), in the Interdisciplinary Program in Genetics (2008-present), and in the Department of Anatomy and Cell Biology (2011-present), all at the University of Iowa in Iowa City, Iowa
- Dr. Fingert sees glaucoma patients at the University of Iowa's Department of Ophthalmology and Visual Sciences and directs the Glaucoma Genetics Lab (www.glaucoma-genetics-lab.org) at the Stephen A. Wynn Institute for Vision Research.
- Dr. Fingert and the Iowa research team discovered two of the known glaucoma genes, myocilin (*MYOC*) and TANK-binding kinase 1 (*TBK1*).

Will genetic testing become a part of physicians' treatment protocols for glaucoma?

Genetic testing is already available and useful for some forms of glaucoma, and the importance of its role in health care will almost certainly grow in the future. Heredity (genetic variation) makes important contributions to people's risk of developing primary open-angle glaucoma (POAG).

Some cases of glaucoma (approximately 5% of POAG) are caused primarily by mutations in one of the three currently known genes: myocilin (*MYOC*), optineurin (*OPTN*), or TANK-binding kinase 1 (*TBK1*). Mutations in these genes almost always lead to glaucoma and are rarely found in people with normal eyes, so testing for mutations in these genes is highly predictive of who will develop glaucoma.[1] Genetic testing for myocilin or optineurin mutations is widely available, and laboratories that perform the testing can be found via the website www.genetests.org. Testing for *TBK1* mutations, which are actually gene duplications, is not yet available.

Glaucoma caused by mutation of myocilin has specific features, including the early onset of disease, a strong family history of glaucoma, and often markedly elevated IOP. Approximately 3% to 4% of POAG cases are caused by myocilin mutations, which makes it the most common molecularly defined cause of glaucoma. Given the relatively low prevalence of myocilin mutations among POAG patients (3%-4%), testing unselected groups of glaucoma patients is not currently warranted. Genetic testing for myocilin is most effective when it is targeted to the subset of POAG patients who exhibit features of myocilin-associated glaucoma (ie, patients diagnosed with open-angle glaucoma at an early age who have a very high IOP and many affected family members).[2,3]

Conversely, glaucoma caused by mutation of the optineurin gene or by mutation of the *TBK1* gene is most often associated with normal-tension glaucoma (NTG) with an early onset of disease that runs in families.[4,5] Testing for optineurin mutations may be most useful in such familial cases of NTG.

Most cases of glaucoma, however, are not caused primarily by a single gene but rather by the collective action of multiple—maybe dozens—genetic and envi-

(Continued on page 48)

(Continued from page 50)
ronmental risk factors. The genes that are involved in this type of glaucoma do not cause disease on their own; instead, each confers a small amount of risk that, when combined, may lead to glaucoma. A number of such genetic risk factors for glaucoma have been identified (ie, *CAV1/2*, *CDKN2B-AS1*, *TMCO1*, *SIX1/6*, and others).[1] Many more remain to be discovered. At present, testing for the presence of these factors is not clinically useful. Testing for complex genetic forms of glaucoma may become helpful in the future, though, when enough of the genetic risk factors have been discovered for testing to be more predictive.

What area of glaucoma genetics do you currently find most exciting and why?

There has been a dramatic increase in the pace of discovery in glaucoma genetics that is thrilling. As more glaucoma genes are identified, patterns are beginning to emerge. For example, a number of genes that cause NTG participate in autophagy, a cellular process by which waste materials are delivered to the lysosomes for degradation. More and more is being learned about the role of autophagy in the pathophysiology of NTG through miraculous studies of transgenic mice and stem cell-based research. I am excited about the potential of these studies to reveal the basic biological mechanisms that cause glaucoma and to provide researchers with the tools to build the next generation of glaucoma therapies, especially treatments for glaucoma that occurs at low IOP.

What attracts you to cycling, and how do you indulge this passion?

I have been a fan of bicycling for years. There are lots of things that I like about it. Early on, I enjoyed pushing hard on the pedals and seeing how far and how fast I could go. For a while, I really got hooked on participating in endurance rides and other bike riding events (Triple-Bypass in Colorado, Death Ride in California, and the Paris-Brest-Paris in France). I am also a bit of a gear-head and love to tinker with my bikes, and I enjoy reading about the newest cycling gadgets. Now, I have to admit that I enjoy the short ride to work on my low-tech single-speed bike the most. ■

1. Fingert JH. Primary open-angle glaucoma genes. *Eye*. 2011;25(5):587-595.
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. 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.
4. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutation in optineurin. *Science*. 2002;295(5557):1077-1079.
5. 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.