5 QUESTIONS

How did you become interested in the genetics of glaucoma?

I have always been interested in disease mechanisms and especially the molecular events that are responsible for disease. Because therapy usually involves a molecular interaction, understanding a condition on a molecular level makes it possible to think about actually curing a disease. Genetics is one way that the molecular events responsible for a disease can be identified. For glaucoma, a genetic approach makes it possible to define the molecular pathophysiology of the disease without directly accessing diseased tissue, which can be very difficult in glaucoma patients.

When will we be able to define glaucoma by genotypes, and how will that influence clinical care and therapy?

In some cases, we can already define glaucoma by genotypes, but currently those cases are rare and are limited to early-onset forms of the disease with mendelian inheritance. The identification of risk factors for the more common complex types of glaucoma (primary open-angle, exfoliation, and low-tension) is the anticipated result of the genome-wide association studies that my colleagues and I are currently conducting. Identifying these genetic risk factors will make it possible to screen patient populations for individuals who are at higher risk of developing glaucoma, thus allowing the initiation of treatment at earlier stages of the disease when it may be more effective. We also expect that the genetic risk factors discovered through our genome association studies will identify molecular abnormalities that contribute to the disease process. Finally, we anticipate that the modification of these abnormal molecular events could lead to novel therapeutic approaches that are directed toward the actual cause of the disease and that may be more effective than current pressure-lowering medications.

What are the challenges of conducting a genome-wide study, and what is the potential impact of your upcoming genome-wide association study for primary open-angle glaucoma, funded by the National Human Genome Research Institute and the National Eye Institute?

Genome-wide association studies have three main components: the patient sample collection (both DNA and

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phenotypic information); the molecular testing, in this case, whole genome genotyping of over 600,000 single-nucleotide polymorphisms for each sample; and analysis of all the data. Each step requires specialized expertise. For a complex disease such as glaucoma, the overall size of the study needs to be large enough that it has sufficient statistical power to identify multiple genetic factors of variable effect.

The NEIGHBOR (NEI Glaucoma Human Genetics Collaboration) Consortium has 22 investigators, involves eight institutions, and has enrolled more than 4,000 participants with DNA and phenotypic information. In addition, this study is being carried out in collaboration with the GENEVA (GLAUGEN; Louis Pasquale MD, primary investigator) Glaucoma Genome Wide Association Study funded by the National Human Genome Research Institute that includes another 2,400 participants. These two studies will produce billions of genotypes for analysis. Organizing and coordinating this project is challenging and has required grant writing, in-person meetings, conference calls, and many, many emails. Fortunately, we have a tremendous team of expert investigators involved in this work.

Your clinical practice includes patients with inherited ocular disorders. What teaching points for medical students, residents, and fellows do you draw from this patient population, and how are they similar to and/or different from those derived from your treatment of patients with glaucoma?

In my opinion, the most important part of clinical care is educating patients. In that regard, individuals with inherited ocular disorders do not differ from glaucoma patients. For patients with inherited eye disease, however, usually the whole family is in the examining room, and the discussion includes counseling about the risk of disease for all family members. For some of these cases, I can take a patient sample back to the laboratory to test for mutations in a specific gene. If a mutation is found, I can give definitive information to family members about their status as mutation carriers. One of the most gratifying patient/doctor discussions is when I get to tell someone that he or she does not have the mutation and that his or her children will not inherit the disease.

Aside from the academic environment, what do you enjoy about living in Boston?

Having spent the first 2 decades of my life on the West Coast, coming to Boston for medical school was an experiment that I expected to last only 4 years. I thought the winters alone would drive me back to Seattle or Berkeley, California, where I went to college. As it turns out, one of the things I like most about Boston is the weather. The change in seasons is refreshing, and unlike Seattle, it is never cloudy for more than a few days at a time, even in the winter. I am also a sports addict, and Boston is a great town for running, biking, skiing, and of course, watching the Red Sox at Fenway Park!