Invited Commentary

Penetrance of Myocilin Mutations—Who Gets Glaucoma?

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Mutations in the myocilin (*MYOC*) gene were discovered as a cause of primary open-angle glaucoma (POAG) in 1997.[1] Twenty-one years later, mutations in *MYOC* remain the most common molecularly defined cause of glaucoma and are responsible for 3% to 4% of adult-onset POAG cases.[2] Glaucoma associated with *MYOC* is transmitted with autosomal dominant inheritance[3]; offspring from parents with glaucoma caused by a *MYOC* mutation have a 50% chance of inheriting the mutation and increased risk for glaucoma. The most common glaucoma-associated *MYOC* mutation is a nonsense mutation, Gln368Stop, that produces truncated MYOC protein that is missing its last quarter.[2] This mutation has been detected in 1.6% of patients with POAG in large case-control studies and is responsible for more glaucoma than any other known mutation.[2] In their article in *JAMA Ophthalmology*, Han et al[4] evaluated very large study populations to investigate just how high the risk for glaucoma is for those with this *MYOC* mutation.

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Not all of those with a Gln368Stop mutation have glaucoma. Some do not have glaucoma at the time of an initial examination but may develop disease later in life, while others will never develop glaucoma despite having the mutation. The proportion of people with a mutation (eg, Gln368Stop) that have an associated disease (eg, POAG and/or ocular hypertension) is referred to as the *penetrance* of that mutation. Determining the penetrance of a disease-associated mutation is of paramount importance for accurate diagnostic and prognostic counseling. Moreover, new potential drug therapies[5] and genome-editing therapies[6] are being developed for *MYOC*-associated glaucoma and their ultimate usefulness may be influenced by estimates of the penetrance of *MYOC* mutations.

Prior studies have estimated the penetrance of the Gln368Stop mutation. Penetrance was first calculated with studies[7,8] of large pedigrees of patients with glaucoma caused by the Gln368Stop mutation. These pedigree-based studies[7,8] have suggested that the Gln368Stop mutation has a high penetrance that is age dependent. Among these families, the proportion of mutation carriers with glaucoma was found to increase to 73% to 100% by the seventh decade of life.

While pedigree studies suggested that most Gln368Stop mutation carriers ultimately develop disease, population-based studies have indicated that this mutation may have a lower penetrance in other patient cohorts. In 2016, Nag et al[9] detected the Gln368Stop mutation in 39 of 17 281 participants in the TwinsUK registry and the Rotterdam Study who were enrolled without regard to the presence or absence of ocular disease. A lower penetrance was observed in this population study than in the previous pedigree-based analyses. Overall penetrance of the Gln368Stop mutation in these cohorts ranged from 9.7% to 12.5% and was also age dependent.[9] The proportion of mutation carriers with POAG in this population-based study increased to between 20% and 33% in participants older than 70 years.[9] Some of the Gln368Stop mutation carriers had ocular hypertension and remain at risk for developing glaucoma or may have undiagnosed disease. Consequently, participants in the TwinsUK registry and Rotterdam Study with either ocular hypertension or glaucoma were included in additional calculations of Gln368Stop penetrance. These looser definitions produced an overall penetrance of 12.5% to 19.4% that increased to 33% in the subset of patients older than 70 years.[9]

Each of the previous studies that estimated the penetrance of the Gln368Stop mutation with either pedigree-based approaches or with population-based approaches had limitations that may explain the somewhat discordant results. Prior pedigree-based analyses may have overestimated the penetrance of the Gln368Stop mutation because of biases of ascertainment, such as enhanced surveillance of family members, which leads to earlier and more frequent glaucoma diagnoses. Family members also share other genetic and environmental factors that may have promoted development of glaucoma and increased penetrance estimates. Conversely, prior population-based analyses may have underestimated penetrance because of undiagnosed disease or incomplete clinical data from participants. Another challenge for population-based studies of rare variants (such as the Gln368Stop mutation) is sampling bias associated with the relatively small numbers of identified mutation carriers. With fewer mutation carriers to study, analyses are more prone to sampling errors. The current study by Han et al[4] overcame some of these limitations by investigating the Gln368Stop mutation in cohorts of immense size.

Several important insights about the pathogenicity of the Gln368Stop mutation were provided in this study.[4] First, including 411 337 participants from the United Kingdom Biobank (UKBB) allowed an accurate assessment of the prevalence of the Gln368Stop mutation. A major strength is the large number of Gln368Stop mutation carriers that were detected (n = 1046, of whom 214 had intraocular pressure measurements).[4] These data indicate that the Gln368Stop mutation occurs in 0.13% of the participants in the UKBB, which is in close agreement with public database reports for European populations (http://gnomad.broadinstitute.org). As many as 1 in 786 people may carry a Gln368Stop mutation and have increased risk for glaucoma.

But how much risk? Prior pedigree studies suggested mutation carriers are at very high risk for glaucoma and most eventually develop glaucoma, while prior population studies indicated that as few as 1 in 3 would ultimately have ocular hypertension or glaucoma.

The study by Han et al[4] of penetrance for the Gln368Stop mutation in the UKBB produced intermediate results between those of prior pedigree studies and prior population studies. Clinical data were available from 214 of the 1046

Gln368Stop mutation carriers in the UKBB. The glaucoma risk for these Gln368Stop mutation carriers was estimated by assessing how many had developed either ocular hypertension or glaucoma. The penetrance of the Gln368Stop mutation in the UKBB cohort was 30.8% overall and increased to 48.0% in participants older than 65 years. A larger fraction of Gln368Stop mutation carriers in this population-based study had either ocular hypertension or glaucoma than in previous articles. These data also suggest that the context in which these Gln368Stop mutations are discovered must be considered when interpreting the results. Mutation carriers identified with glaucoma pedigree-based studies may have a higher likelihood of developing disease than those identified in population studies.

Han et al[4] also assessed the risk for developing glaucoma using a second cohort, which included 3071 patients with glaucoma from the Australian New Zealand Registry of Advanced Glaucoma and the Glaucoma Inheritance Study in Tasmania, as well as 6750 historic controls. Of particular interest is the analysis that estimated the cumulative glaucoma risk for Gln368Stop mutation carriers at various ages. The cumulative risk for glaucoma at 50 years of age was 56%, and this increased to 87% by 65 years of age.[4] Risk for ocular hypertension was even higher. These data provide further evidence that Gln368Stop carriers are at high risk for ocular hypertension and glaucoma.

As the risk for glaucoma associated with a Gln368Stop mutation is more precisely defined, better information will be available to patients and their physicians to make clinical prognoses and to assist with counseling offspring about risk. Genetic testing has been provided to family members of patients with known *MYOC* mutations with encouraging results for early detection of those at highest risk for glaucoma.[10] The higher penetrance reported by Han et al[4] may bolster the feasibility and cost-effectiveness of testing whole communities for the Gln368Stop mutation to identify undiagnosed glaucoma as a public health initiative.

ARTICLE INFORMATION

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