Inherited, Familial and Sporadic Primary Open-Angle Glaucoma

Gordon Gong, MD, MS; Sade Kosoko-Lasaki, MD; Gleb Haynatzki, PhD; Henry T. Lynch, MD; Jane A. Lynch, BSN; and M. Roy Wilson, MD, MS

The U.S. surgeon general has recently launched a campaign to promote the awareness of the medical value of family history. Further attention should be paid to familial aggregation. Accordingly, we suggest that primary open-angle glaucoma (POAG) be classified into inherited, familial and sporadic categories. The three classes of POAG differ not only in inheritance pattern and familial aggregation but also in methodology and outcome of gene mapping. Inherited POAG follows Mendelian inheritance and has been linked to seven chromosomal loci to date by linkage analysis. Familial POAG does not show a clear pattern of Mendelian inheritance and is typically studied by sib-pair analysis and family-based association analysis, although the results often require replication in multiple samples. Interestingly, many sporadic POAG cases carry known POAG-causing mutations, suggesting genetic predisposition as well. Based on published data, we estimated that inherited and familial POAG cases may account for approximately 72% of all POAG cases. We further formulated a mathematic model to estimate disease prevalence and mutation frequency taking both ethnic background and familial aggregation into consideration.

Conclusion: POAG appears to be mainly caused by genetic predisposition in interaction with other risk factors such as age. The suggested classification of POAG may serve as a useful guide in clinical practice and genetic studies where ethnic background and familial aggregation must be taken into consideration.

Key words: glaucoma ■ familial aggregation ■ race/ethnicity ■ genetics

 From West Texas EXPORT Center, F. Marie Hall Institute for Rural and Community Health, Texas Tech University Health Science Center, Lubbock, TX (Gong, genetics); Departments of Surgery (Ophthalmology) (Kosoko-Lasaki), and Preventive Medicine and Public Health, (Kosoko-Lasaki, minority health, ophthalmology; Lynch, cancer genetics), and Osteoporosis Research Center, Creighton University, Omaha, NE (Haynatzki, biostatistics); and Chancellor's Office, University of Colorado at Denver and Health Science Center, Denver, CO (Wilson, minority health, ophthalmology). Send correspondence and reprint requests for *J Natl Med Assoc.* 2007;99:559–563 to: Dr. Gordon Gong, West Texas EXPORT Center, F. Marie Hall Institute for Rural and Community Health, Texas Tech University Health Science Center, Box 45013 Stop 5013, Lubbock, TX 79409; phone: (806)743-5602; fax: (806)743-1021; e-mail: gordon.gong@ttuhsc.edu

INTRODUCTION

Open-angle glaucoma is classified as primary open-angle glaucoma (POAG) when the etiology is unknown.[1,2] However, recent progress in molecular genetics has demonstrated that POAG can be caused by numerous gene mutations in various chromosomal loci.[3] Thus the current definition of POAG is outdated, and the disease should be redefined and reclassified.

Previous studies have shown that 34% of POAG patients or suspects had a positive family history.[4] The actual percentage of POAG patients with affected relative(s) could be higher because 50% of individuals with POAG are unaware of their clinical status.[5,6] Consistent with the above notion, a much higher percentage (56%) of probands with POAG have affected relatives whose disease status is determined by clinical examination rather than by family history alone.[7] These facts suggest that POAG has a strong genetic component. Family history is important clinically because the risk for POAG among first-degree relatives of a POAG patient is 7–10 times higher than that of the general population,[8,9] and surveillance targeting these individuals is indicated for early detection and treatment of POAG. Genetically, the presence or absence of a family history may represent distinct underlying causes, which is a very important piece of information for study design in the search for POAG-causing mutations. However, health professionals as well as patients tend to underestimate the value of family history.[10] For this reason, the U.S. surgeon general has suggested that Thanksgiving Day be National Family History Day as part of a campaign to promote the awareness of the medical value of family history, to facilitate data collection and to increase "genetic literacy."[10] We wonder whether the community of glaucoma researchers and clinicians has fully explored information from family history and has adequately taken the degree of familial aggregation of POAG into consideration in data collection, management and analysis. As the first step in response to these questions, we propose to classify POAG into three categories according to the degree of familial aggregation. The potential impact of the suggested classification on methodology and out-

come of genetic studies is examined.

Ethnic background is also an important piece of information in clinical practice and genetic research. In the estimation of disease prevalence and mutation frequency, ethnicity and familial aggregation are often ignored, resulting in incorrect conclusions. For example, previous studies showed that the frequency of mutations in the myocilin gene (*MYOC*) in *probands* with POAG was similar among Caucasians, African Americans and Asians.[11] It was thus concluded that the higher prevalence of POAG in African Americans was not due to a higher frequency of *MYOC* mutations in their general population.[11] In a recent study,[3] we showed that the similar frequency of *MYOC* mutations between African-American and Caucasian *probands* suggests higher frequency of *MYOC* mutations in the African-American general population because their prevalence of POAG is higher than that of Caucasians.[3] In this article, we formulate a mathematical model for estimating the disease prevalence and mutation frequency taking into account both ethnic background and familial aggregation.

Classification of POAG

Although the terms "familial",[7,12,13] "hereditary"[7] or "inherited"[14] POAG have been used in the literature, there has been no clear definition. According to the schemes for classification of other diseases such as cancer,[15-17] we suggest that POAG be classified into inherited, familial and sporadic categories. Inherited POAG is defined when ≥3 relatives inclusive of the proband (index case) are documented with POAG in ≥2 consecutive generations, one of which must be a first-degree relative of the other two. Familial POAG involves ≥2 first- and/or second-degree relatives and does not meet the criteria for inherited POAG. Sporadic POAG involves a single patient without affected first- or second-degree relatives. The three classes of POAG appear to be distinct not only in inheritance pattern and the degree of familial aggregation but also in methodology and outcome in mapping POAG genes as discussed below.

Inherited POAG

Inherited POAG exhibits strong evidence of Mendelian inheritance. To date, POAG has been linked to seven chromosomal loci (Table 1)[18-25] through studies on families with inherited POAG only. Six of the loci have been mapped in studies on single large pedigrees (8–22 affected members each), and one on multiple kindreds (3–7 affected members in each of the six kindreds involving ≥2 consecutive generations).[18-25] Notably, the disease in all the kindreds met the definition of inherited POAG in all these studies. One important lesson is that identifying kindreds with a large number of members with inherited POAG may pave the road to success.

Familial POAG

There are several reasons for differentiating familial from inherited POAG, although both are characterized by a positive family history. Firstly, evidence for Mendelian inheritance in familial POAG is not as strong as in inherited POAG.[26] For example, a conclusion of Mendelian inheritance would be doubtful based on two affected sibs without an affected parent. Secondly, study designs often differ (e.g., sib-pair analysis and family-based association studies as opposed to parametric linkage analysis). Duggal et al.[26] recently mapped intraocular pressure to a chromosomal region through sib-pair analysis of familial POAG. However, results from such studies often require confirmation in multiple samples.[27] Thirdly, the smaller number of affected members in familial POAG may represent reduced penetrance, which may suggest a genetic basis (mutations and genes involved) different from that of inherited POAG.[3]

It should be noted that in addition to potentially reduced penetrance, the smaller number of affected members in familial as opposed to inherited POAG may be due to: 1) smaller family size, 2) unawareness of affected relatives or 3) age below the typical age of onset in many members of a kindred. Longitudinal studies are warranted to determine the influence of these factors on the classification of POAG, and whether a considerable proportion of familial POAG cases in fact have inherited POAG.[7] Such longitudinal studies might be facilitated as more family records are expected to be available in the future in response to the U.S. surgeon general's initiative.[10] The discoveries of the seven loci linked to POAG have been the results of persistent collection and expansion of familial data over a long period of time.

Table 1. The number of affected members with which linkage is established

Linked Loci	Number of Affected Members with POAG	Maximal LOD Score	Number of Pedigrees	References
GLC1A	22	6.50	1	18. Sheffield et al.
GLC1B	24	6.48	6	19. Stoilova et al.
GLC1C	10	3.88	1	20. Wirtz et al.
GLC1D	8	3.61	1	21. Trifan et al.
GLC1E	15	10.00	1	22. Sarfarazi et al.
GLC1F	10	4.06	1	23. Wirtz et al.
GLC1G	7	N/A	1	24. Monemi et al.

Thus, a diagnosis of familial (even sporadic) POAG may be transitory. As familial data (pedigrees) are expanded and the degree of familial aggregation in a given kindred becomes clearer over time, the initial diagnosis may be adjusted.

Sporadic POAG

If sporadic cases are mainly due to low penetrance rather than smaller family size, unawareness of affected relatives, younger age of family members or undefined environmental exposure, then the putative mutations fall into the susceptibility (or modifier) gene category. Although genetic effects of susceptibility genes are typically weak, their impacts might be large affecting a large proportion of POAG cases. As a result, research on susceptibility genes has been a very active area, and genetic association (linkage disequilibrium) studies are more powerful in mapping such genes.[28,29] Interestingly, many sporadic POAG cases carry known POAG-causing mutations,[30-33] suggesting genetic predisposition as well. Many POAG cases that were initially considered as sporadic were subsequently proven to be familial or inherited.[7,11,34] This underlines the significance of the U.S. surgeon general's initiative.[10] Further investigation is needed to determine the proportion of sporadic POAG cases that are really sporadic by clinical examination of first- and second-degree relatives for potential POAG.[7]

It appears that *POAG is a class of open-angle glaucoma mainly caused by genetic predisposition in interaction with risk factors such as age in the absence of other known causes.*

Pooling of Inherited POAG Families in Linkage Analysis

Linkage analysis of a single pedigree with a large number of affected members is most powerful and has proven to be highly successful in gene mapping.[18-25] However, a single pedigree is often too small to achieve sufficient power. Thus, one tends to include a large number of unrelated individuals and/or families with sporadic, familial and inherited POAG for gene mapping.[35,36] However, such studies often do not yield reproducible results.[27,35,36] Interestingly, linkage analysis appears to be successful when pooling only inherited POAG families that have shown linkage to the same locus.[14,19] Caution should be taken with this approach since alleles across the genome may show "cosegregation" with the disease by chance alone in different families with inherited POAG. Those loci mapped through multiple unrelated kindreds will eventually be verified through single expanded pedigrees.

Familial Aggregation and Ethnic Background in the Estimation of Disease Prevalence and Mutation Frequency

In a previous publication,[3] we proposed to estimate the frequency (f) of POAG-causing mutations of a certain gene in the general population based on the mutation frequency among probands with glaucoma (f_G), the prevalence of POAG (p), the average penetrance $\bar{k}$ and a correction factor c. Here, we define c as the effect of familial aggregation and reformulate the previous equation:[3]

$$f=cpf_G/\bar{k}. \quad (1)$$

In equation 1, $\bar{k}$ is uncertain and so is f. The purpose of estimating f is to assess the contribution of gene mutations to the disease prevalence. Thus the *expressed frequency* (f_E) would be more informative, which is the frequency of mutations in a gene of interest that have actually caused POAG in the general population where

$$f_E=f\bar{k}. \quad (2)$$

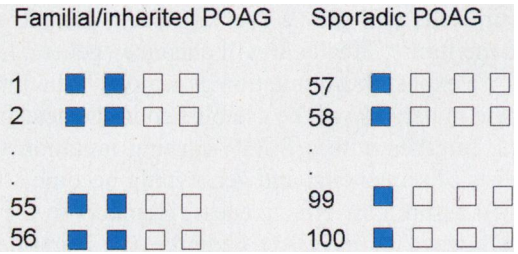
Since $f=cpf_G/\bar{k}$ in equation (1), we obtain

$$f_E=cpf_G. \quad (3)$$

The two variables (f and $\bar{k}$) with uncertain values are eliminated, while both p and f_G are known from published data.[3] f_E can be calculated if c can be determined, which is related to the clustering nature (familial aggregation) of POAG. Suppose that n families with POAG are ascertained by random cluster sampling, where n_1

Figure 1. Illustration of the effect of familial aggregation on the estimation of the percentage of inherited/familial versus sporadic POAG cases

In a population-based study, 100 POAG probands are ascertained with POAG, of whom 56% have familial/inherited POAG, and each family of 4 has two members with POAG (grey boxes). Familial/inherited POAG cases are 56 x 2 = 112, while sporadic are 44. Based on equation 4, familial/inherited POAG cases account for ≥112/156 = 72% of all POAG cases under survey. If each family had three affected members then the percentage would be 79%.



families carry POAG-causing mutations in the gene of interest, while n_2 families do not carry any such mutations. Let a_1 and a_2 be the average number of affected individuals per family with and without the mutations, respectively. Then, the frequency of the mutations among POAG *probands* is $f_G=n_1/n$, while the frequency of the mutations among all POAG *patients* (f_d) is

$$f_d = \frac{a_1 n_1}{a_1 n_1 + a_2 n_2} \quad (4)$$

Substituting f_d for cf_G in equation (3) we get

$$f_E = pf_d. \quad (5)$$

Note that p varies depending on ethnic background of the population studied.

Equation 4 can also be adopted to estimate the percentage of inherited/familial POAG cases with changes in denotations, where a_1 and a_2 are the average numbers of members per nuclear family with and without inherited/familial POAG, respectively, while f_d is the percentage of inherited/familial POAG among all patients in a population survey. Based on data of Williams-Lyn et al.[7] (56% of the *probands* have familial or inherited POAG), we estimate that approximately 72% of all POAG *cases* are predicted to have familial or inherited POAG (Figure 1) in the population studied.[7] The 95% confidence interval of the percentage can be calculated with real data.[7] Thus, POAG has a strong genetic component with a large proportion of inherited and familial cases.

Other Potential Benefits from the Classification of POAG

We may benefit from the classification of POAG in several aspects in addition to its usefulness in guiding genetic studies. First, it would promote the awareness and the importance of family history among clinicians and patients, because clinicians with the classification in mind will be more likely to ask for family history and to suggest clinical examination of first-degree relatives of a POAG patient, and the relatives would be more aware of their higher risks. In addition, it will facilitate data collection and analysis since the classification would be readily available in patients' medical records. This could be potentially important as the database becomes larger. Clinicians will play a crucial role in genetic studies in the future. Finally, it will enhance "genetic literacy."[10] We expect that "mutation genealogy" (the lineage with the mutation) will be established in the near future among families with a POAG-causing mutation when the costs of sequencing and genotyping become affordable. To assure cost-effectiveness, members in the mutation lineage of a POAG pedigree (i.e., first-degree relatives of mutation carriers) would be candidates for mutation testing and undergo more frequent and earlier surveillance while those in the nonmutation lineage would follow the guidelines for the general population.

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