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Predictive genetic testing experience for myocilin primary open-angle glaucoma using the Australian and New Zealand Registry of Advanced Glaucoma

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Purpose: Predictive genetic testing of relatives of known myocilin (*MYOC*) gene mutation carriers is an appropriate strategy to identify individuals at risk for glaucoma. It is likely to prevent irreversible blindness in this high-risk group because this treatable condition might otherwise be diagnosed late. The Australian and New Zealand Registry of Advanced Glaucoma has established genetic testing protocols for known glaucoma genes, including *MYOC*.

Methods: Through the Australian and New Zealand Registry of Advanced Glaucoma, we investigated the experience of 40 unaffected individuals who had undergone predictive genetic testing for *MYOC* mutations through questionnaires.

Results: The main motivations for being tested were (i) to make appropriate interventions and (ii) to reduce uncertainty. All our respondents perceived strong benefits, either medical or emotional, in being tested. However, different concerns were raised by the respondents that need to be addressed during counseling. Greater family awareness was reported by the majority of the respondents, and the ability to provide information to children was a strong motivation for being tested.

Conclusion: This study provides valuable information on the personal and familial impacts of having predictive genetic testing for glaucoma, which will help health professionals to better address the issues faced by patients and provide them adequate support.

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Key Words: genetic counseling; glaucoma; *MYOC*; predictive genetic testing; POAG

With the development of new technologies and a better understanding of the genetics of diseases, genetic testing is becoming increasingly available. Predictive genetic testing is now possible for treatable conditions such as glaucoma. Glaucoma is a progressive optic neuropathy that when untreated may cause irreversible blindness; it affects 60 million people worldwide.[1] There are strong medical benefits in favor of predictive genetic testing for primary open-angle glaucoma (POAG; OMIM no. 137760), the most common type of glaucoma. Half of all cases go undiagnosed[2,3] because the early stages of the condition are often asymptomatic, and appropriate therapeutic interventions can prevent or minimize glaucoma-induced blindness.[4–6] As a result, predictive genetic testing is an attractive goal to identify presymptomatic at-risk individuals, which allows them to be educated about their risks and options before the onset of the condition and to receive appropriate management to prevent or at least minimize the vision loss that would have otherwise occurred.

Mutations in the myocilin gene (*MYOC*, OMIM no. 601652), which are strongly associated with POAG, are transmitted in an autosomal dominant fashion and cause glaucoma at a younger age than is seen in the general population.[7,8] The most common mutation, Gln368X, has a mean age at diagnosis in the early 50s,[8,9] whereas other mutations, such as Pro370Leu, can be associated with an age at diagnosis as early as the teens.[10,11] Detecting a mutation in an unaffected individual does not predict the age of onset, the severity, or the progression of the condition but puts the person at a very high risk of developing glaucoma in his/her lifetime.

Because POAG is a treatable condition, predictive genetic testing is usually well accepted.[12] Although the medical benefits have been well studied, little is known about the internal motivations and the experience of individuals undergoing predictive testing for *MYOC* mutations. Decisions for undergoing genetic testing are usually driven by social and personal factors. These can range from personal experience with glaucoma in the family and knowledge of glaucoma and related treatment options to personality- and health-related locus of control. Knowledge about individuals' experiences of predictive genetic testing is essential to provide adequate counseling and support to people who have been tested or who are considering being tested. In this study, we examined the motivations, the perceived benefits, and the feelings and concerns of individuals who had undergone predictive genetic testing for *MYOC* mutations.

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MATERIALS AND METHODS

Recruitment

Participants were recruited through the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG).[13] Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee. In an antecedent study, potential participants with a definite diagnosis of glaucoma referred by their eye specialist were initially screened for *MYOC* mutations.[8] Genetic testing was then made available to all adult first-degree relatives of individuals confirmed as carrying a *MYOC* mutation. Because *MYOC* mutations display very high penetrance but some inter- and intrafamilial variability, we recommended that all at-risk adult relatives be offered genetic testing regardless of their age.[14] To promote autonomous and voluntary decisions, relatives interested in being genetically tested had to contact the ANZRAG registry of their own volition. At the initial contact, a trained genetic counselor (E.S.) reviewed the testing process and the implications with the individual. Written informed consent was obtained, and DNA was extracted from a blood sample. The test results were provided directly to the participants and, if nominated, an eye specialist. When the familial mutation was identified, a referral to a local ophthalmologist was facilitated.

Our cohort comprised family members of individuals carrying a *MYOC* mutation, aged 18 years and older, who had consented to genetic testing for glaucoma and had already obtained their test result. A questionnaire was posted to each of them, regardless of the outcome of the test. After 1 month, individuals who did not return their questionnaire were contacted as a reminder and were given the opportunity to complete it over the phone.

Questionnaire

The questionnaire collected data relating to sociodemographic variables, perceived risks and feelings before being tested, perceived benefits and disadvantages of being tested, personal impact of the result, and familial impact of the results. Sociodemographic questions included gender, age, marital status, number and age of children, and education level. For analysis, we chose to categorize respondents into age groups, comparing those aged 40 years and younger with those older than 40 years. The cutoff point of 40 years was selected based on the knowledge that those older than 40 years have a higher likelihood of developing glaucoma and therefore may have different motivations for undergoing genetic testing than younger respondents. The perceived lifetime risk of developing glaucoma and the perceived risk of carrying the familial mutation were measured using four alternative choices (highly unlikely, unlikely, likely, and highly likely). Responses of (i) highly unlikely and unlikely and (ii) likely and highly likely were then combined to create a dichotomous variable for analysis. The perceived severity of glaucoma was assessed on a scale of 1–5, with 1 being considered not severe and 5 being considered very severe. The motivations for engaging in genetic testing were explored through multiple-choice responses. In free-response questions, participants were asked about the perceived benefits and disadvantages of the test, their concerns and fears with regard to glaucoma before and after the test, their initial reaction after finding out their test result, their positive and negative feelings associated with the result, and their level of satisfaction with the testing. Finally, respondents were asked about the experience within their family, including communication and disclosure patterns to children and other relatives, and any wider impact that their testing had on the family as a whole.

Statistical analyses

Statistical analyses were conducted on all quantitative data using the Statistical Package for the Social Sciences, version 19 (SPSS, Chicago, IL). Significance was set at $P < 0.05$. Comparisons across demographic groups were made using χ^2 tests for independence. Analysis of qualitative responses was undertaken in Microsoft Excel, with similar responses categorized together in frequency tables.

RESULTS

Demographic data

We have previously shown that *MYOC* mutations account for 4.2% of advanced POAG patients.[8] In this study, we evaluated 18 *MYOC*-positive families, which comprised 82 at-risk relatives. The questionnaire was sent to the 52 (63%) participants who had requested to be tested and had received their *MYOC* test result; it was completed and returned by 43 respondents (83%) from 17 families. Three respondents were excluded from our analysis because they had already been diagnosed with glaucoma before being tested and thus their motivations and emotional reactions to their results were likely to differ from those who did not have a glaucoma diagnosis. The demographics of nonresponders and those excluded due to previous diagnosis did not differ significantly from those of the included participants on any demographic measures (all $P > 0.70$).

The demographic data of the 40 included respondents are shown in **Table 1**. The average age of the respondents was 46.6 ± 16.1 years (range: 18–87). Twenty-two respondents (55%) had tested positive for the *MYOC* gene. The *MYOC* mutations observed among the 18 families approached (Gln368X, Trp286Arg, Trp373X, and Thr377Met) were all of comparable severity. Three at-risk individuals younger than 40 years displayed a combination of two mutations (Gln368X and Thr377Met) associated with a more severe phenotype in one family.[15]

Risk perception and intentions regarding genetic testing

Before being tested, half (20/40) of the respondents perceived their risk of developing glaucoma as being likely, or highly likely, and almost three-quarters (28/40, 70%) perceived their risk of carrying the familial mutation as being likely or highly likely. Respondents believed glaucoma to be a moderately severe disorder, giving it an average severity score (on a scale of 1–5) of 3.6 ± 1.2. The perceived severity of glaucoma and the

perceived risk of developing glaucoma or of carrying the familial mutation were not influenced by gender, age, education, carrier status, or the tested *MYOC* mutation ($P > 0.20$ for all).

The motivations for individuals to undergo testing are summarized in Table 2. A significant interaction between respondent age group and motivations for having the genetic testing was found. Those older than 40 years of age reported that they had had testing in order to provide information to their children about their risk of developing glaucoma significantly more often than younger respondents ($\chi^2 = 4.263$, $P = 0.039$). However, this difference was no longer significant when data for just those respondents with children were analyzed ($P = 0.287$) because older respondents had children more often than younger ones. Neither gender nor education nor the tested *MYOC* mutation influenced respondents' motivations for being tested ($P > 0.10$ for all motivations).

Table 1 Descriptive characteristics of the respondents

	n (%)
Age (years)	
18–40	15 (37.5)
>40	25 (62.5)
Gender	
Male	19 (47.5)
Female	21 (52.5)
Marital status	
Single	8 (20.0)
Married/de facto	28 (70.0)
Divorced/separated	2 (5.0)
Widowed	2 (5.0)
Children	
No	9 (22.5)
Yes	31 (77.5)
<18 years old	17 (54.8)
≥18 years old	14 (45.2)
Education level	
Primary school	6 (15.0)
High school	10 (25.0)
Technical college	5 (12.5)
University	18 (45.0)
Not specified	1 (2.5)

Table 2 Individuals' motivations for being tested

	n (%)
Motivations for being tested	
Take appropriate interventions	32 (80.0)
Remove uncertainty	27 (67.5)
Family's recommendation	26 (65.0)
Provide information to children	23 (57.5)
Respondents with children	22 (71.0)
Provide information to relatives	14 (35.0)
Doctor's recommendation	2 (5.0)

Respondents could choose more than one answer from the listed suggested motivations.

Perceived benefits and disadvantages of genetic testing

All respondents considered predictive genetic testing for glaucoma useful. They described advantages of predictive testing for glaucoma, on the whole, more often than disadvantages. The main benefit reported by the respondents was the availability of monitoring for early detection and prevention of glaucoma-induced visual loss. The only disadvantage mentioned was that if identified as a carrier, they would have to live with the knowledge of being at increased risk of developing glaucoma.

Respondents' reactions and feelings

The main initial reaction of noncarriers was happiness and relief, whereas carriers experienced a range of different emotions (Table 3). Positive feelings expressed by carriers were the awareness and the accompanying ability to act and therefore help reduce the impact of glaucoma, in addition to the possibility of providing better information to their children. Negative feelings and concerns of carriers were various and are summarized in Table 4. Three carriers expressed feelings of guilt. One noncarrier expressed mixed feelings because a sibling was found to have the familial mutation when she did not. Regardless of their test results, all respondents were satisfied with their decision to be tested.

Impact on family

Almost all of the respondents had discussed having genetic testing with their families (36/40, 90%) and had discussed their genetic result with them (38/40, 95%). The majority of the respondents who had children had discussed their result with them (18/31, 58%). Respondents were significantly less likely to discuss positive results with their children if they were younger than 18 years old ($\chi^2 = 4.74$, $P = 0.029$). Almost all respondents with adult children (13/14, 93%) communicated their results to them, whereas a minority with minor children did so (5/17, 29%). However, 67% (8/12) of carriers who did not discuss their results with their minor children had selected the provision of information to children as a motivation for being tested. Finally, the majority of respondents (30/40, 75%) reported increased awareness in the family regarding glaucoma risks and genetic testing.

DISCUSSION

Genetic testing for POAG has been available since the discovery of the *MYOC* gene in 1997.[16] Even though *MYOC* mutations account only for 3-4% of all POAG cases,[7,8] relatives of *MYOC* carriers have had the opportunity to be screened and become educated about their glaucoma risk; moreover, they have been able to benefit from early prevention and management. However, there is a paucity of literature on the decision-making process and the impact of predictive genetic testing on individuals with treatable eye conditions such as glaucoma. In comparison, studies on inherited cancers have thoroughly evaluated patients' motivations, family communication, and experience with predictive testing.[17–20] Inherited cancers differ from glaucoma in that they are life-threatening and require invasive interventions.[17,21] However, both inherited cancers

and glaucoma can be of juvenile or adult onset, have treatment options, and have an incomplete but strong penetrance; moreover, associated genetic testing has proven to have clinical validity for both conditions. We therefore used the literature on inherited cancers to draw parallels with our results.

Several theoretical models have been created in attempting to predict health behaviors. The Health Belief Model[22] postulates that the higher the perceived susceptibility to and the perceived severity of the condition, and the higher the perceived effectiveness in taking actions, the more the person will engage in health behaviors.[21,23] Our findings show that the majority of individuals who chose to be tested had a high perceived risk of having the familial mutation before being tested and considered glaucoma to be a serious medical condition. Some previous studies on inherited cancers have shown that individuals are more likely to be tested if their perceived risk, not their actual risk, of cancer is high.[17,18,24]

A previous study on inherited cancers found that the perceived benefits component was the most powerful variable in explaining interest in predictive testing.[21] Another study identified two clusters of motives: one included perceived health benefits (early detection, prevention, and control), and the other included perceived emotional benefits (reassurance, reduction of uncertainty, and emotional preparation).[23] Similarly, in our study, taking appropriate medical interventions and the reduction of uncertainty were the two most-often-selected motivations for undertaking genetic testing, and the main reported benefit was monitoring for early detection.

A range of emotions were expressed by carriers of *MYOC* mutations after genetic results communication. These individuals were concerned about losing their vision, the potential impact on insurance, the transmission of the mutation to children, and the efficacy of interventions in treating glaucoma. Three carriers and one noncarrier also reported feelings of guilt. It is valuable to understand these concerns in order to better address them during counseling. Our findings show that people who undertake predictive genetic testing for *MYOC* mutations have no regrets with regard to being tested and are satisfied with their decision, regardless of their result. Healey *et al.* had previously reported the acceptability of genetic testing for *MYOC* glaucoma among the members of one very large affected Australian family.[12]

Greater family awareness following genetic testing was reported by the majority of the respondents. Recommendation by a family member was a major motivator for being tested. Almost all respondents disclosed their results to their family, regardless of their genetic result, and most of them even talked about the testing process before knowing their results, consistent with studies on hereditary cancers.[25,26] All respondents with adult children, except one, disclosed their genetic result. The individual who did not was a noncarrier, and we postulate that the person did not think it useful to discuss the result with her children because there was no increased risk of developing glaucoma. Respondents with minor children were less likely to communicate their genetic result to them. However, the majority of the respondents who tested positive but did not share their results with their children had indicated that providing their children with information was a motivation for them to be tested, and so it is likely they will pass on this information when the children are older. Previous studies on families with inherited breast and ovarian cancers showed that the majority of parents (70–80%) discussed their genetic result with children of adult age, regardless of their carrier status[27,28] and the age of the children was positively associated with communication. Most parents who did not disclose their result did so because they thought their children were too young or immature. Predictive testing is not offered to individuals younger than 18 years, unless the family age of onset is known to be less than 18 years and there is an immediate medical benefit to test.[29] However, without offering genetic testing, young children can still benefit from learning the family's carrier situation and therefore their potential risk. Genetic counselors can help parents in providing information to children while respecting their decisions and family dynamics.

There are some limitations to our study. Our sample is relatively small and our results might be skewed because our cohort reflects the motivations and concerns of individuals who decided to be tested. Further research in larger cohorts is required on the long-term perceived benefits and satisfaction of tested individuals, in addition to research on the at-risk relatives in our investigated families who did not request predictive *MYOC* testing. It also appears that people 40 years and younger who had received a negative result were less likely to respond to our invitation to participate and therefore our data were skewed to include an overrepresentation of

Table 3 Main reaction after testing according to genetic result

Emotional response	*n* (%)
Carriers	
Sad/disappointed	5 (22.7)
Anxious	3 (13.6)
Surprised	3 (13.6)
Not surprised	4 (18.2)
Upset	4 (18.2)
Proactive	3 (13.6)
Noncarriers	
Happy/relieved	18 (100.0)

This was a free-response question and similar responses were categorized together in frequency tables.

Table 4 Concerns relating to positive genetic test result

Concern	*n* (%)
Loss of vision	10 (45.5)
Impact on health insurance	5 (22.7)
Transmission to children	3 (13.6)
Efficacy of glaucoma treatments	2 (9.1)
Traveling distance to clinic when living in rural area	1 (4.5)

This was a free-response question and similar responses were categorized together in frequency tables.

individuals in this age group who had *MYOC* gene mutations. Although we do not make contact with the relatives' clinicians before the test, we cannot exclude the possibility that some relatives talked to their clinician before contacting us and that this might have influenced their decision to be tested or not. The fact that some individuals come from the same family could be another bias because it might create some familial clustering effects. The *MYOC* mutations identified among our respondents were of comparable severity and did not seem to have affected the responses. However, one family displayed two *MYOC* mutations and a more severe phenotype, and we acknowledge that this has the potential to have skewed the results with regard to motivations and psychological topics. Finally, this was a retrospective study asking participants to recall their feelings before genetic testing. Recall of events can be biased and may be influenced by the length of time elapsed between disclosure of results and administration of the questionnaire, as well as being affected by the test results. A two-part questionnaire gathering data both before and after respondents receive their results would control for this. However, our analysis showed no association between the carrier status and the perceived risks or the different motivations for being tested, suggesting that recall bias did not have a large impact on the results.

Despite these limitations, this study provides valuable preliminary findings on the motivators of asymptomatic individuals toward predictive genetic testing for POAG, and the personal and familial impacts of such testing. The acceptability of such an approach had been reported previously in an Australian family,[12] but, to our knowledge, this is the first study to address the motivations, feelings, and concerns of individuals as applied to a whole population rather than within a single large family. We demonstrate that the testing process increases awareness about glaucoma among relatives, especially children of adult age, of those tested. This is important because these individuals are at risk of having inherited the familial mutation and can greatly benefit from preventive measures. We show that, similar to individuals who chose to have predictive testing for inherited cancers,[20] individuals who chose to have predictive testing for glaucoma perceived strong benefits, either medical or emotional, in being tested and may represent a selected group of individuals more likely to be able to cope with genetic results. Our cohort expressed strong satisfaction with their choice, and few people reported concerns or fears associated with genetic testing. However, one should not conclude from these findings that these individuals do not need support. Pretest genetic counseling needs to address, among other things, participants' motivations for testing, perceived risks and benefits, potential concerns, and family dynamics. Posttest genetic counseling may need to focus more on associated feelings of guilt, regardless of the genetic result.

Our findings are valuable for health professionals involved in the genetic testing process and the management of carriers; these health professionals need to be sensitive to the differences in personal concerns and intentions toward predictive testing. Such results will help them in providing better support and in addressing the relevant medical, psychological, and familial issues with patients undergoing predictive genetic testing for POAG.

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DISCLOSURE

The authors declare no conflict of interest.

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