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Predictive genetic testing in minors for Myocilin juvenile onset open angle glaucoma

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Key words: Genetic counseling, Glaucoma, Minor, Myocilin, Predictive genetic testing

Abstract

Myocilin glaucoma is an autosomal dominant disorder leading to irreversible blindness, but early intervention can minimize vision loss and delay disease progression. The purpose of this study was to discuss the benefits of predictive genetic testing in minors for *Myocilin* mutations associated with childhood onset glaucoma. Three families with *Myocilin* mutations associated with an age of onset before 18 years and six unaffected at-risk children were identified. Predictive genetic testing was discussed with the parents and offered for at risk minors. Parents opted for genetic testing in half of the cases. None carried the familial mutation. The age of disease onset in the family, the severity of the condition, and the age of the child are all factors that appear to influence the decision of the parent to test their children. Predictive genetic testing for early onset *Myocilin* glaucoma can facilitate early detection of disease or discharge from routine ophthalmic examinations.

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness worldwide, affecting 3% of the population over the age of 50 (1). The most common type is Primary Open Angle Glaucoma (POAG, MIM 137760) characterized by optic nerve damage with open drainage angles (2). Juvenile Open Angle Glaucoma (JOAG) is defined arbitrarily as diagnosis prior to age forty and is usually associated with a more severe phenotype (3). The early stages are asymptomatic and irreversible blindness may occur if left untreated. Therapeutic and/or surgical interventions aim at controlling intraocular pressure (IOP), and are usually effective in minimizing loss of visual function and delaying progression of the disease (4, 5).

Pathogenic variants in the *Myocilin* gene (MIM 601652) are the commonest cause of inherited POAG. We have previously reported a prevalence of 4% in POAG and 17% in JOAG in the Australian population (6). *Myocilin* glaucoma is inherited in an autosomal dominant manner and is usually associated with high IOP and earlier age of onset than other unselected glaucoma cases (6). Genotype-phenotype correlations exist with some mutations associated with a very young age of onset, as early as the teens or childhood (6-8).

Considering that effective treatments which minimize vision loss are available, it becomes important to identify at-risk individuals before any irreversible damage occurs. Adequate identification of families with onset of glaucoma in childhood is essential as children can benefit from early genetic testing. In this study, we report on 3 families with known pathogenic *Myocilin* variants associated with very early age of onset for which predictive genetic testing for unaffected minors was discussed.

MATERIALS AND METHODS

This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee and was conducted in accordance with the National Health and Medical Research Council statement of ethical conduct in research involving humans.

Patients were recruited through the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) via referral from their treating specialist as previously reported (9). *Myocilin* sequencing was performed through an accredited laboratory as described previously (6). When a pathogenic variant was identified, genetic counselling was offered and *Myocilin* genetic testing was made available to family members. Contact was made only through the proband referring relatives to the ANZRAG in order to promote a voluntary decision. In cases with an age at diagnosis of less than 18 years reported in the family or in the literature for the sequence variant in question, predictive genetic testing of unaffected minors was discussed with the children's parents and their treating specialist. Genetic counselling was provided, written informed consent was obtained from the parents and where possible children gave assent, and a blood sample was provided for the purpose of predictive genetic testing.

RESULTS

In the ANZRAG, *Myocilin* mutations are present in 4% of our POAG cases (50/1248). Among these, three families with *Myocilin* mutations associated with an age of onset before 18 years and six first-degree at-risk minors were identified (Figure 1). Predictive genetic testing was discussed with the parents, and three children from two families were tested. The clinical details of the three families are presented in Table 1.

The proband from Family A (III-1) was diagnosed at 11 years old. At the age of 17, she required trabeculectomy to control her glaucoma. She had a very strong family history of

severe JOAG with her daughter, father, sister, as well as a grandmother, aunt and cousin on the paternal side affected. All affected relatives were diagnosed in their childhood or teens, and all required glaucoma surgery.

Myocilin sequencing in the proband identified the previously reported mutation p.T438I (c.1313C>T). The mutation segregated with the condition in four affected family members. The proband's son (IV-1), aged 17 had normal IOP. Her nephew (IV-3), aged 3 is reported to be unaffected but has not been clinically examined. *Myocilin* predictive genetic testing of both children was requested by their respective parents. Neither child carried the familial mutation.

In Family B, the proband (III-2) was noted to have increased IOP and optic nerve changes consistent with JOAG at age 13. He presented at age 17 with a left ischemic central retinal vein occlusion which left the eye blind from retinal ischemia and uncontrolled glaucoma. Despite regular ophthalmic follow-up and topical therapy, there were periods of non-compliance, and at age 34 with uncontrolled IOP and worsening visual fields, he underwent a right trabeculectomy. His most recent visual field test is displayed in Figure 2. The patient had a significant family history of glaucoma with his father and paternal grandfather diagnosed with glaucoma in their teens.

Myocilin sequencing identified the previously reported mutation p.G367R (c.1099G>A) in the proband and his father (II-3). The proband's 10 year old son (IV-3) had normal IOP and optic nerves. Testing was requested by his father and results were negative for the familial mutation.

The proband from Family C (III-1) was diagnosed at 20 years old with significantly elevated IOP. She had laser trabeculoplasty and was on maximal medical therapy to control her IOP. Visual fields were largely intact but there was possibly an early defect on the right side

(Figure 2). There is a positive family history with a sister, father and paternal grandfather diagnosed with JOAG and requiring glaucoma filtration surgery to control their IOP.

The p.G367R (c.1099G>A) *Myocilin* mutation was identified in the proband and her sister. The proband's daughter (IV-1) aged 3, and her sister's sons (IV-3, IV-4), aged 1 and 3 have not been examined but were said to be unaffected. Predictive genetic testing of the three children was discussed with the parents but they decided to defer testing until the children were older.

DISCUSSION

While predictive genetic testing for adult or late onset conditions is accepted in adults, the international consensus is that such testing in minors should be deferred until they are old enough to make an informed decision (10). However, genetic testing for diseases that have childhood onset, where established early surveillance or treatment may alter the course of the disease, is generally supported (10, 11). This approach is mainly endorsed by the immediate and direct medical benefits for the child. *Myocilin* POAG is typically an adult-onset condition, however some mutations are known to be associated with a juvenile-onset (6-8). In these situations, predictive genetic testing of minors should be considered, particularly as POAG is difficult to clinically diagnose in its early stages, and earlier detection and intervention lead to better visual outcomes.

Based on these considerations, through the ANZRAG we identified three families with *Myocilin* mutations associated with very early age of onset POAG that could benefit from predictive genetic testing of at-risk minors. These families displayed two previously reported *Myocilin* mutations: p.T438I and p.G367R. Both variants have previously been reported in individuals displaying an age at diagnosis in childhood or early adulthood, significantly elevated IOP, and glaucoma surgery required for most individuals (7, 8, 12-15). Family A

carrying p.T438I, exhibited a similar phenotype. In Family B, the two affected individuals carrying p.G367R were diagnosed in their mid-teen years, and progressed to severe visual impairment by their mid-20s. In contrast, the two affected individuals from Family C carrying the same mutation presented in their early twenties and their glaucoma was not as advanced.

Among all three families, six unaffected children were identified as being at risk of carrying the familial *Myocilin* mutation. The parents of three of the children from two families (A & B) decided to opt for genetic testing and these three children did not carry the familial mutations. The third family (C) decided to defer testing. We previously showed that individuals who have a higher perceived severity of glaucoma and/or a higher perceived risk of developing glaucoma are more likely to act upon it (16). The two families who decided on testing their children had strong family histories of glaucoma developing during childhood or early teens, with some individuals having severe glaucoma and two of the children tested were getting near the age of onset of the familial mutations. Family C had so far experienced less severe glaucoma and vision loss than the affected members of Family B carrying the same mutation (Figure 2), had a later onset and the at-risk children were of younger age, which could account for their decision of deferring testing.

When counselling parents on deciding whether to test or not, the benefits and potential harms need to be reviewed and the best interests of the child should always be central to any decision. Medical benefits include close monitoring and surveillance to detect glaucoma signs at the earliest possible time point, and early intervention and/or treatment to prevent or minimize damage to the optic nerve and associated vision loss in the case of a positive genetic result. If results are negative, the advantages are reduced number of visits and eye exams required, including potential examination under anesthesia in the cases of very young children. Psychosocial benefits include the removal of uncertainty and the opportunity for

adjusting life plans. Potential harms for the child are mainly psychosocial in nature, including the alteration of self-image and self-esteem, increased anxiety, negatively altered life choices and potential for discrimination and stigmatization (10, 17). Distortion of parental perception and education of the child, parental anxiety and a potentially negative impact on the extended family dynamics are other potential harms to be considered.

The timing of testing for childhood onset conditions that have therapeutic options is an important question (11). A reasonable approach for *Myocilin* JOAG would be to offer testing near the age considered adequate for starting medical surveillance and/or interventions. This age could vary depending on the familial variant but should be based on the age at diagnosis within the family, and the reported age of onset for that variant in the literature.

The acceptability and the psychosocial experience of adults undergoing predictive genetic testing for glaucoma have been previously documented (16, 18). However, there are few studies on the psychosocial impact of genetic testing on children in general. A recent review of the literature did not suggest that a child's emotional state, self-perception or social wellbeing were significantly affected by predictive genetic testing (17). Future research will be needed to understand the potential impacts of predictive genetic testing for glaucoma in minors to better counsel the families.

In conclusion, we identified three families with *Myocilin* JOAG who could benefit from predictive genetic testing of at-risk minors in view of the potential immediate medical benefits for the children. Three children were found not to carry the familial mutation, removing the need for unnecessary regular ophthalmic examinations. The decision for testing seemed to be influenced by the personal experience of the family in question with glaucoma. Knowing how to better counsel parents during the decision making process, the best age to undergo testing, and the potential impact of the testing are key areas of future focus which will lead to better outcomes in families affected with early age of onset *Myocilin* glaucoma.

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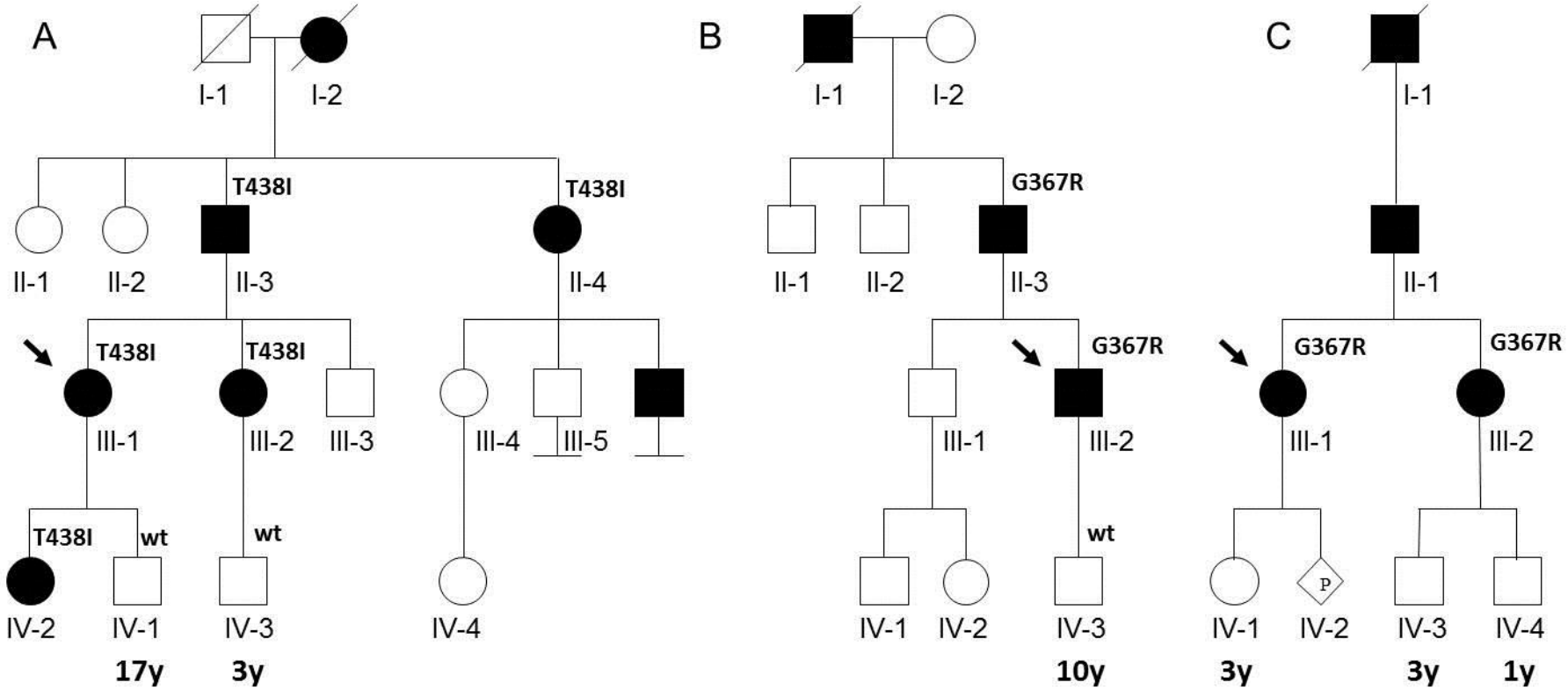
Figure 1

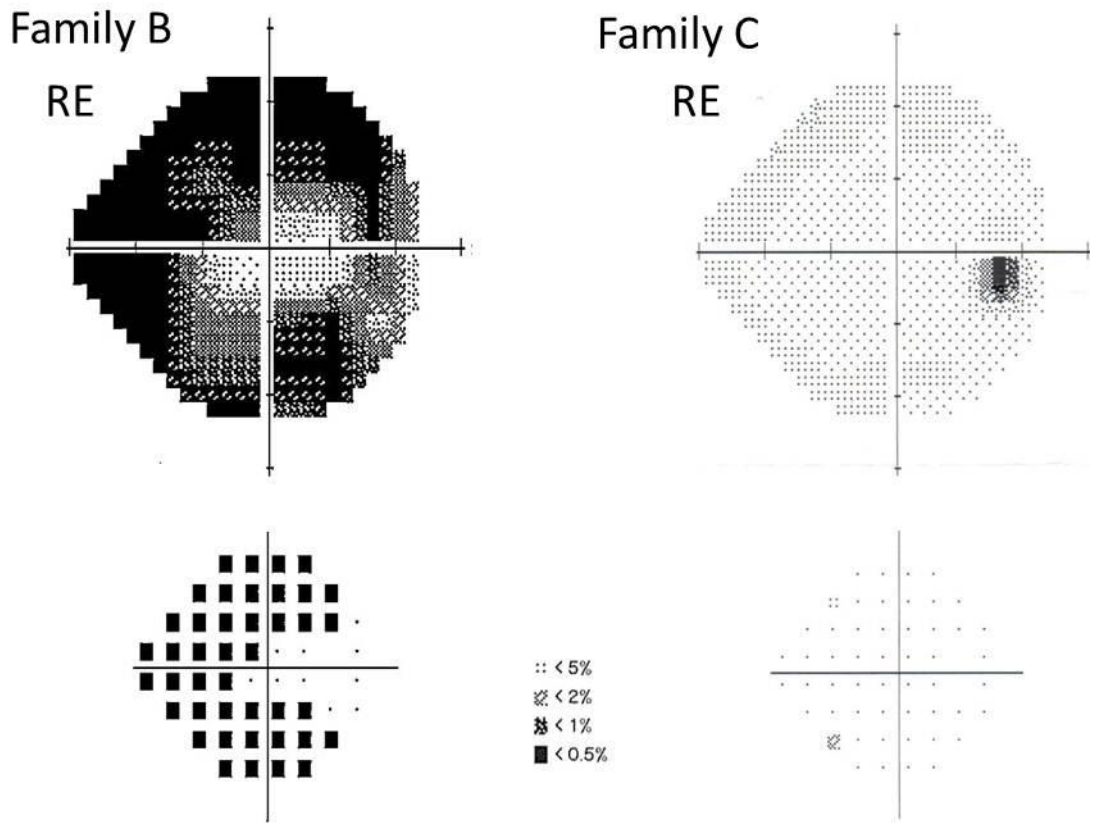
Pedigree of the families



Round symbols indicate females; square symbols, males; fully filled symbols, primary open-angle glaucoma; unfilled symbols, unaffected; diagonal line, deceased; arrow, proband; P, pregnancy; wt: wild-type allele. The age of the at-risk children is displayed at the bottom.

Figure 2

Visual Fields of the proband from Family B (III-2) and Family C (III-1) with the p.G367R *Myocilin* mutation. Note: As Individual III-2 from Family B is blind in his left eye, visual fields of both individuals are only displayed for the right eye.



RE: Right eye

Table 1

Clinical details and genetic results of the recruited individuals

Patient	Age at examination (years)	Phenotype	Myocilin mutation	Age at diagnosis (years)	Maximum IOP (mmHg, RE/LE)	BCVA (RE:LE)	CDR (RE/LE)	Glaucoma surgery
Family A								
II-3	70	JOAG	T438I	14	na	20/40:20/30	na	Yes
II-4	75	JOAG	T438I	11	25/20	20/20:20/20	0.8/0.6	Yes
III-1*	43	JOAG	T438I	11	16/31	20/25:20/25	0.4/1.0	Yes
III-2	42	JOAG	T438I	7	na	na	na	Yes
IV-1	18	JOAG	T438I	17	44/46	na	0.7/0.7	No
IV-2	17	Unaffected	wt		16/17	na	na	No
IV-3	3	Unaffected	wt		na	na	na	No
Family B								
II-3	62	JOAG	G367R	14	na	20/16:20/30	0.6/0.99	Yes
III-2*	34	JOAG	G367R	13	40/40	20/40:NLP	0.9/1.0	Yes
IV-3	10	Unaffected	wt		13/13	20/25:20/25	0.3/0.3	No
Family C								
III-1*	31	JOAG	G367R	20	35/35	20/16:20/16	0.3/0.4	No
III-2	33	JOAG	G367R	23	32/33	20/20:20/20	0.7/0.6	Yes

IOP: Intraocular pressure, BCVA: Best corrected visual acuity, CDR: Cup to disc ratio, RE: right eye, LE: left eye, na: not available, JOAG: Juvenile Open-Angle Glaucoma, *: proband, wt: wild-type allele