Glaucoma Phenotype in Pedigrees With the Myocilin Thr377Met Mutation

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Objective: To investigate the phenotype and age-related penetrance of primary open-angle glaucoma (POAG) in Australian families with the myocilin mutation Thr377Met.

Method and Design: Cross-sectional genetic study. Four unrelated pedigrees carrying the Thr377Met mutation were ascertained from more than 2000 consecutive cases of POAG in the Glaucoma Inheritance Study in Tasmania and from families with glaucoma referred to the study from throughout Australia. Index cases and available family members were examined for signs of glaucoma, and the presence of the GLC1A Thr377Met mutation was ascertained by single-strand conformation polymorphism analysis and subsequent direct sequencing.

Results: From the 4 pedigrees carrying the Thr377Met mutation, 23 individuals with either ocular hypertension (OHT) or POAG were found, with a mean ± SD age at diagnosis of 41.2 ± 11.5 years, and a mean peak intraocular pressure of 31.7 ± 9.9 mm Hg. A further 9 mutation carriers older than 18 years were studied who as yet showed no signs of OHT or POAG (6 of these 9 were younger than 30 years). A single individual with POAG was identified who did not carry the Thr377Met mutation. For Thr377Met carriers, age-related penetrance for OHT or POAG was 88% at age 30 years. A positive family history of POAG was present for 3 of the 4 index cases. Thirteen (57%) of the 23 Thr377Met carriers with OHT or POAG had undergone glaucoma drainage surgery. Although the glaucoma in these families appears to be pressure dependent, 2 individuals showed optic disc cupping before detected elevation in intraocular pressure. One family was of British origin, with a different background haplotype from the other 3 families from Greece or Macedonia, who shared a common haplotype.

Conclusions: The GLC1A Thr377Met mutation is associated with POAG that, in the pedigrees studied, had a younger age at onset and higher peak intraocular pressure than in pedigrees with the more common Gln368STOP mutation. In addition, patients with glaucoma with the Thr377Met mutation were more likely to have undergone glaucoma drainage surgery.

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Mutations in the myocilin gene at the GLC1A locus are responsible for a proportion of patients (4.6%) with primary open-angle glaucoma (POAG). The GLC1A locus on chromosome 1q21-31 was initially identified by linkage studies in families with severe juvenile open-angle glaucoma. Narrowing of this region led to the eventual identification of the gene encoding the trabecular meshwork–induced glucocorticoid response protein, or myocilin. More than 30 myocilin missense mutations have now been identified in juvenile and adult patients with POAG. The most frequently identified GLC1A mutation in the populations studied is a nonsense mutation Gln368STOP, being present in 1.6% of probands from 5 populations in the largest study to date. This mutation is associated with adult-onset POAG. Previous work from the Glaucoma Inheritance Study in Tasmania (GIST) showed that the average age at diagnosis of POAG, associated with this mutation, was 52 years. This later age of onset and the lower mean peak intraocular pressure (IOP) of 28 mm Hg suggest that the Gln368STOP mutation gives rise to a milder phenotype than mutations associated with juvenile open-angle glaucoma.

Many other mutations in myocilin have been described, and although some seem to have a local founder effect, several seem to be widely distributed and found by multiple research groups in different locations: Thr353Ile, Gly367Arg, Pro370Leu, Val426Phe, Tyr437His, Ile477Ser, and Ile499Phe. Alward et al described 2 families with the Thr377Met mutation (1 Australian and 1 American).
Wiggs et al described an additional family in which the proband was diagnosed at age 42 years with an IOP at diagnosis of 24 mm Hg. Shimizu et al described 3 siblings in a family with a mean age at diagnosis of 38 years and a mean maximum IOP of 44 mm Hg. We have now identified an additional 3 Australian families with this same mutation.

A large cohort of consecutive patients with POAG was recruited and subjected to molecular analysis of the myocilin gene to identify carriers of mutations. Affected individuals were thoroughly examined for glaucoma. Testing included stereo optic disc photographs and automated perimetry. Family history of POAG was sought and available family members were examined. We present a detailed analysis of 4 Australian pedigrees identified with the Thr377Met mutation.

**METHODS**

Pedigrees with the Thr377Met mutation were identified from 2000 cases of POAG in the GIST and from families with glaucoma referred to the study from throughout Australia. Index cases and available family members were examined for signs of glaucoma. Written informed consent was obtained from patients involved in the GIST, which was approved by the relevant ethics committees of The Royal Victorian Eye & Ear Hospital (Melbourne) and the Royal Hobart Hospital (Hobart). This study was conducted in accordance with the Declaration of Helsinki and subsequent revisions. The following clinical examination protocol was followed for all family members:

1. Applanation tonometry was performed by means of a recently calibrated Goldmann applanation tonometer (Haag Streit AG, Bern, Switzerland). The anterior segment was examined by slitlamp biomicroscopy including gonioscopy.

2. Automated perimetry (Humphrey 24-2; Humphrey Inc, San Leandro, Calif) was performed. Individual Humphrey 24-2 fields were classified as normal or glaucomatous by means of the GIST field score and the Glaucoma Hemifield Test results (Humphrey, Inc).

3. Optic disc appearance was classified by 2 clinicians at the time of examination according to the GIST scoring protocol; discs were classified as normal, suspicious, or frankly glaucomatous (cup-disc ratio ≥0.7 plus ≥1 qualitative sign; focal neuroretinal rim thinning or a notch extending to the margin, retinal nerve fiber layer defects, disc hemorrhages, and bared circumpapillary vessels). In addition, optic disc stereo photographs (Nidek Co Ltd, Gamagori, Japan) were reviewed according to the same criteria. Where there was disagreement, a consensus between the ophthalmologists was reached.

4. Patients were interviewed to determine the presence or absence of a known positive family history of POAG.

5. Venipuncture was performed to obtain blood for DNA extraction.

Subjects examined were classified as follows: normal (normal disc and results of Humphrey field analysis, and IOP of <22 mm Hg) or with ocular hypertension (OHT) (normal disc and results of Humphrey field analysis, and IOP of ≥22 mm Hg), POAG (glaucomatous disc and/or glaucomatous field defect), or normal-tension glaucoma (glaucomatous disc and/or glaucomatous field defect in which no IOP of ≥22 mm Hg has ever been documented). For further information on glaucoma phenotyping in the GIST study, the reader is referred to Coote et al.

**MUTATION AND HAPLOTYPE ANALYSIS**

Mutation analysis for the Thr377Met mutation was performed with the use of single-strand conformation polymorphism analysis. Of each patient's DNA, 12.5 ng was used as template in an 8.35-µL polymerase chain reaction using primer sequences and conditions previously described. Amplification products were denatured and electrophoresed in 6% polyacrylamide and 5% glycerol gels at 25 W for approximately 3 hours at room temperature. After electrophoresis, gels were stained with silver nitrate. Abnormal polymerase chain reaction products identified by single-strand conformation polymorphism analysis were sequenced by means of fluorescent deoxyxynucleotides on an automated sequencer (model 377; Applied Biosystems, Foster City, Calif). Mutations were identified by the approximately equal peak intensity of 2 fluorescent dyes at the mutant base. All sequencing was bidirectional. Individuals found to carry the Thr377Met mutation were included in the present study.

Haplotype analysis, using 4 short tandem repeat polymorphism markers closely flanking the myocilin gene, was performed for individuals found to carry the Thr377Met mutation. These markers include MY5, MY3, D1S2815, and D1S1619. With the use of 15 ng of each patient's DNA, the short tandem repeat polymorphisms flanking myocilin were polymerase chain reaction amplified, electrophoresed with DNA sequencers (model 377; Applied Biosystems), and genotyped (Genotyper 2.1; Applied Biosystems).

**LINKAGE ANALYSIS**

An analysis of only affected members of the pedigree GVic1 was run by means of the MLINK and LODSCORE programs of the LINKAGE program package as performed previously. A penetrance of 90% was used for linkage analysis. Allele frequencies for the Thr377Met and wild-type sequences were estimated at 0.001 and 0.999, respectively, for linkage calculations.

**STATISTICAL ANALYSIS**

SAS software version 6.10 (SAS Institute Inc, Cary, NC) was used in the data analyses. The χ² test and Fisher exact test were used for categorical data, and a t test was used for continuous data. P < .05 was considered to be statistically significant.

**RESULTS**

The family trees, disc photographs, and information regarding IOP and age at diagnosis are presented for the 4 pedigrees identified with the Thr377Met mutation (Figure 1 and Table 1). For individuals found to have the Thr377Met mutation, the diagnosis (of POAG or OHT) was verified. A family tree was constructed with the use of genealogic records, including any other individuals known to have POAG or OHT, who were then examined and who provided DNA for Thr377Met mutation analysis. All other available family members older than 18 years were also examined and DNA was obtained for analysis.

Four pedigrees were identified from index cases in this way, and the resultant family trees are shown in Figure 1A (pedigree GVic1, with 19 affected members examined), Figure 1B (pedigree GVic118, with 1 affected member examined), Figure 1C (pedigree GVic119, with 2 affected members examined), and Figure 1D (pedigree...
Figure 1. Pedigrees with the myocilin Thr377Met mutation. A, Pedigree GVic1. B, Pedigree GVic118. C, Pedigree GVic119. D, Pedigree GVic120. Phenotype information is included on the pedigrees: completely filled symbol indicates primary open-angle glaucoma (with elevated intraocular pressure); diagonal line, deceased; right half filled, ocular hypertension; left half filled, normal-tension glaucoma; N, examined individuals with no ocular hypertension or primary open-angle glaucoma; unfilled, no clinical data available. Carrier status for the Thr377Met mutation is shown with a plus sign. Individuals’ pedigree numbers and years of birth are displayed.
GVic120, with 1 affected member examined). Phenotype information differentiating individuals with glaucoma (with elevated IOP), OHT alone, and normal-tension glaucoma is displayed along with the mutation status (indicated by a plus sign in the pedigrees). Maximum known IOP, age at diagnosis, and surgical status are given in Table 1. Examples of optic disc photographs and Humphrey 24-2 visual fields are given for severe cases in Figure 2, intermediate cases in Figure 3, early optic disc cupping in Figure 4A, progression of disc cupping and development of elevated IOP and a field defect in Figure 4B, and as yet unaffected cases in Figure 5.

It is noteworthy that all of these families were identified in Victoria (population, 4 million) and that the population of Tasmania (475,000) was not large enough to have one pedigree with this mutation. One family was of British ancestry, with members of this family having been examined regularly during the last 7 years. The 3 smaller families were all from Greece or Macedonia. Genealogic records were unavailable for the latter 3 pedigrees, but they were not known to be related.

In total, 23 Thr377Met mutation carriers with POAG or OHT were studied in detail (Table 1). For the 23 Thr377Met mutation carriers with POAG or OHT, the maximum SD maximum IOP was 31.7 ± 9.9 mm Hg. In contrast, 1 non–mutation carrier with POAG from the GVic1 pedigree (subject II:7) had a maximum IOP of 26 mm Hg (Figure 6). For the 23 Thr377Met mutation carriers with POAG or OHT, the mean age at diagnosis was 41.2 ± 11.5 years. In contrast, for the 1 non–mutation carrier with POAG, the age at diagnosis was 60 years. Thirteen individuals (57%) of the affected 23 Thr377Met mutation carriers studied had undergone glaucoma filtration surgery.

In comparison with our extensive previous study of the Gln368STOP mutation, the maximum IOP for the Thr377Met mutation was higher (mean, 31.9 ± 10.1 mm Hg) than the mean peak IOP for the Gln368STOP mutation (28.4 ± 4.7 mm Hg), but the difference was not statistically significant (P = .11). The mean age at diagnosis for the Thr377Met mutation was significantly lower (40.4 ± 11.0 years) than the mean age at diagnosis for the Gln368STOP mutation (52.4 ± 12.9 years) (P < .001). Thirteen (57%) of the 23 Thr377Met mutation carriers required trabeculectomies; in contrast, only 8 (28%) of the 29 Gln368STOP mutation carriers with glaucoma required trabeculectomy (Fisher exact test, P = .048). A positive family history of POAG was found in 3 of the 4 pedigrees. A family history of POAG on both maternal and paternal sides was not seen for the families with the Thr377Met mutation, in contrast to this common observation in the families with the Gln368STOP mutation.

Variable expression was observed, with the oldest unaffected mutation carrier being 48 years of age. Two mutation carriers (subject III:1 in pedigree GVic1 [Figure 5A] and subject III:34 in pedigree GVic1 [Figure 5B]) older than 30 years who were studied showed no signs of OHT or POAG, while another individual (subject III:10 in pedigree GVic1 [Figure 4A]) with a maximum IOP of 21 mm Hg had discs that were suspicious for glaucoma but normal visual fields. This individual has been marked on the pedigree as having normal-tension glaucoma but is likely to develop elevated IOP. To gather further information regarding the penetrance of the Thr377Met mutation, additional families with this mutation should be identified and studied.

Table 1. Age at Diagnosis, Maximum Recorded IOP, and Surgical Status of Individuals With OHT or POAG Carrying the Thr377Met Mutation

<table>
<thead>
<tr>
<th>Figure</th>
<th>Pedigree</th>
<th>Subject No.</th>
<th>Year of Birth</th>
<th>Age at Diagnosis, y</th>
<th>Maximum IOP, mm Hg</th>
<th>Surgery</th>
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<td>1898</td>
<td>70</td>
<td>50</td>
<td>Trephines OU</td>
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<td>GVic1</td>
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<td>1926</td>
<td>56</td>
<td>39</td>
<td>Trab OU</td>
</tr>
<tr>
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<td>GVic1</td>
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<td>1933</td>
<td>38</td>
<td>23*</td>
<td>Iridencl OU</td>
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<tr>
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<td>1935</td>
<td>41</td>
<td>25</td>
<td>Trab OU</td>
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<tr>
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<td>36</td>
<td>30</td>
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<td>24</td>
<td>Trab OU</td>
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<td>1945</td>
<td>47</td>
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</table>

Abbreviations: ALT, argon laser trabeculoplasty; IOP, intraocular pressure; Iridencl, iridencleisis; OHT, ocular hypertension; POAG, primary open-angle glaucoma; Trab, trabeculectomy.
*During treatment. The maximum IOP is likely to be higher than this, but no records were available.
tation at different ages, we analyzed the proportion of individuals known to carry the mutation who were manifesting either OHT or POAG at (1) 30 years of age or older and (2) 40 years of age or older. Of mutation carriers 30 years of age or older, 22 (88%) of 25 had glaucoma or OHT. For carrier individuals aged 40 years or more, 19 (90%) of 21 had glaucoma or OHT.

Linkage analysis of the 19 Thr377Met mutation carriers with POAG or OHT and the 1 non–mutation carrier with POAG gave a logarithm of the odds score of 3.5.

Figure 2. Optic disc photographs and Humphrey 24-2 visual fields in severe cases: A, patient II:12 in pedigree GVic1; B, patient III:25 in pedigree GVic1; C, patient III:5 in pedigree GVic119.
The previous analysis of 15 affected subjects (including the phenocopy) yielded a maximum logarithm of the odds score of 1.3 ($\theta=0.2$). The haplotype data for the Thr377Met and the common Gln368STOP mutation are shown in Table 2.

**PHENOTYPE**

The phenotype of OHT and POAG associated with the Thr377Met mutation was thoroughly assessed in our data set. The mutation carriers with glaucoma seen in this study had a form of early adult-onset OHT or POAG associated with elevated IOP. In our study, POAG associated with the Thr377Met mutation typically had elevated IOP. However, progression of disc cupping and development of visual field defects was seen in 1 patient during a 5-year period, associated with a maximum recorded IOP of only 24 mm Hg noted at the time of the second fields shown herein (Figure 4B). Another individual with a maximum recorded IOP of 21 mm Hg had early disc cupping (Figure 4A). These individuals demonstrate that, although in this family the glaucoma is associated with high IOP, this elevated IOP may not be detected by means of standard random testing, before disc cupping is noted. Whether this indicates transient episodes of elevated IOP that are not sampled or whether there is an underlying concurrent disc abnormality secondary to the myocilin mutation requires further study. The age at diagnosis of OHT or POAG in mutation carriers ranged from 26 to 70 years (mean±SD, 41.2±11.5 years). In the family Gvic1, whose members were well aware of the family history, the age at diagnosis in the matriarch, subject I:1 (Figure 1), was 70 years (although her glaucoma was very advanced at diagnosis); in the next generation, the mean age at diagnosis in 6 mutation carriers was 44.5 years (range, 36-56 years), while in generation III the mean age at diagnosis in 11 cases was 34.4 years (range, 30-44 years). This “anticipation” is most likely explained by earlier screening, involved in the study, through which 8 of the new cases were diagnosed. The peak IOP recorded, for affected mutation carriers, ranged from 20 to 60 mm Hg (mean±SD, 31.7±9.9 mm Hg). The pressure of 20 mm Hg reflects the treated maximum IOP of a patient for whom the previous records were not available.) This compared with the mean IOP of the as yet unaffected mutation carriers of 16.9 mm Hg (range, 13-21 mm Hg). Optic disc appearance usually showed concentric cupping of the disc, which could be mild but was often advanced and in some cases end stage glaucomatous optic neuropathy was present (examples in Figure 2A). Humphrey 24-2 full threshold visual fields ranged from normal in patients with OHT to mild field loss typical of POAG such as a nasal step (Figure 4B) or a superior arcuate pattern deviation.
Figure 4. Optic disc photographs and Humphrey 24-2 visual fields in cases with disc cupping despite normal or minimally elevated intraocular pressure: A, patient III:10 in pedigree GVic1; B, patient III:22 in pedigree GVic1 on August 1996; C and D, same patient as in panel B. Note progression of cupping and field defect in the right eye. C, photograph taken February 1999; D, November 2000.
scotoma (Figure 3A) to severe bilateral field loss in some of the oldest subjects (Figure 2A).

Thirteen of the 23 Thr377Met mutation carriers with elevated IOP have required glaucoma drainage surgery to date. Most have good pressure control and arrested progression of field loss and cupping. However, 1 older family member (subject II:14 in pedigree GVic1) developed bilateral endophthalmitis from his filtering blebs with current visual acuities of hand motions in the left eye and no light perception in the right eye. One younger patient developed postoperative hypotony, and visual acuity dropped from 20/17 to 20/40 in one eye. The IOPs of the remaining subjects were controlled with medical therapy or required a combination of medical therapy plus argon laser trabeculoplasty. In several patients IOP was well controlled with latanoprost; however, 2 Thr377Met carriers with glaucoma involved in another drug trial had dramatic elevation in IOP during their latanoprost washout. The phenotype associated with the Thr377Met mutation in this study reflects an early adult-onset POAG associated with elevated IOP and concentric cupping of the optic discs. The currently available data from the 4 families in this report indicate that, at the age of 30 years, 22 of 25 individuals with the Thr377Met mutation have either OHT or POAG.

**LINKAGE ANALYSIS**

This article provides further supportive evidence of the pathogenicity of the Thr377Met mutation by providing a logarithm of the odds score of 3.5 (θ = 0.05) for the mutation. Zhou and Vollrath developed a Triton X-100 detergent solubility cellular assay for myocilin mutations that has provided direct evidence of a functional effect of the Thr377Met mutation on the myocilin protein.

**INDEPENDENT ORIGINS OF Thr377Met MUTATION**

The origin of 3 families from Greece or Macedonia, when the Australian Greek and Macedonian population is less than 2%, suggests that this mutation may be common in those countries with a possible founder effect. The haplotype data (Table 2) suggest that the Greek or Macedonian GLC1A Thr377Met mutation carriers share a common ancestor but are unrelated to the family of British origin. It is interesting to note the similarity of the haplotype of the British Thr377Met haplotype with the
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This study was presented in part at the meeting of the Association for Research in Vision and Ophthalmology, May 2, 2001; Ft Lauderdale, Fla.

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REFERENCES


Figure 6. Optic disc photographs and Humphrey 24-2 visual fields in an affected patient who does not carry the mutation (patient II:7 in pedigree GVic1).

Table 2. Marker Size for the Linked Haplotype in Families

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<th>Marker Size</th>
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Gln368STOP haplotype and postulate whether both mutations arose in an ancestral population with a selective advantage for the myocilin mutations.

With the relatively high penetrance, severe phenotype, and response to surgical treatment associated with the GLC1A Thr377Met mutation, it appears that predictive DNA testing of family members would be of value in these families. Like the common Gln368STOP mutation, which can be detected with a TaqI restriction digest, the Thr377Met mutation can be detected by the creation of a restriction enzyme digest site for NlaIII.15 We are currently investigating the impact of predictive DNA testing in these families.

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