Identification of MYOC gene mutation and polymorphism in a large Malay family with juvenile-onset open angle glaucoma

Z Mimiwati,1 K Nurliza,1 M Marini,3 AT Liza-Sharmini2

1Department of Ophthalmology, University Malaya, Lembah Pantai, Kuala Lumpur Malaysia; 2Department of Ophthalmology, School of Medical Sciences, University Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia; 3Human Genome Centre, School of Medical Sciences, University Sains Malaysia, Health Campus, Kota Bharu, Kelantan, Malaysia

Purpose: To screen for mutations in the coding region of the myocilin (MYOC) gene in a large Malay family with juvenile-onset open angle glaucoma (JOAG).

Methods: A total of 122 family members were thoroughly examined and screened for JOAG. Venipuncture was conducted. Genomic DNA was extracted from peripheral blood leukocytes. The presence of a mutation and a polymorphism was ascertained with PCR amplification followed by the direct sequencing technique.

Results: Thirty-two of the 122 screened family members were identified to have JOAG (11 new cases and 21 known cases). An autosomal dominant inheritance pattern with incomplete penetrance was observed. A C→A substitution at position 1440 in exon 3 that changes asparagine (AAC) to lysine (AAA) was identified in affected family members except two probands (III:5 and IV:6). Six probands were identified as having the Asn480Lys mutation but have not developed the disease yet. An intronic polymorphism IVS2 730+35G>A was also identified. There was a significant association between Asn480Lys (p<0.001) and IVS2 730+35G>A (p<0.001) in the affected and unaffected probands in this family.

Conclusions: The Asn480Lys mutation and the IVS2 730+35 G>A polymorphism increased susceptibility to JOAG in this large Malay pedigree. Identifying the MYOC mutations and polymorphisms is important for providing presymptomatic molecular diagnosis.

Glaucoma, characterized by progressive optic neuropathy with specific visual field defects, is one of the main causes of irreversible blindness in the world. Epidemiological studies have determined that a family history of glaucoma increases the risk of developing glaucoma from 13% to 60% [1,2]. Genetic predisposition of glaucoma is further supported by the strong association between glaucoma and endophenotypes of glaucoma in monozygotic twins compared to their spouses [3].

Juvenile-onset of open angle glaucoma (JOAG) is a variant of primary open angle glaucoma (POAG). JOAG is diagnosed earlier before the age of 40 and commonly described as a product of autosomal dominant inheritance [4]. The mode of inheritance in POAG is inconclusive [5]. POAG has been described as oligogenic, polygenic, even multifactorial and is regarded as a complex disease.

The discovery of the myocilin (MYOC; OMIM 601652) gene as the candidate gene for open angle glaucoma more than a decade ago has provided a new understanding of the genetic basis of glaucoma [6]. MYOC consists of three exons separated by two introns and a 5-kb promoter region, which encodes for a 55 to 57 kDa myocilin protein with 504 amino acids and an isoelectric point of approximately 5.21. It is located at the GLCIA (OMIM 601652) locus, chromosome 1q23-q25 [7]. MYOC mutations are associated with 2% to 4% of POAG [8]. MYOC gene mutations are reported to be higher in JOAG (8% to 30%) [9]. The majority of mutations occur in the third exon of the MYOC gene, which encodes the olfactomedin-like domain [10].

To date, more than 80 mutations have been identified in MYOC [10]. Several MYOC mutations have been shown to segregate with glaucoma in a statistically significant manner. These include Tyr437His, Ile477Asn, Gln368Stop, Thr377Met, 396INS397, and Gly364Val. The Gln368Stop mutation was found exclusively among Caucasians, responsible for the disease-causing mutation (DCM), while Arg46Stop was found as the DCM among Asians [10]. There are various reports on MYOC mutations in other Asian populations such as Chinese, Filipino, and Indian populations [11-13]. No common DCM has been found. In fact, no mutation was found among a Filipino population [12]. However, there is no report on Malays. Identifying MYOC mutations is important for presymptomatic diagnosis in young Malay patients with JOAG. Furthermore, this will enrich the myocilin database. The current study reports the first MYOC screening in four generations of a large Malay family.
family with JOAG. Phenotype and genotype association are also described.

METHODS

Identification of family members: This study was conducted in accordance with the Declaration of Helsinki for research on humans. Ethical approval was obtained from the Ethics Board of Universiti Malaya Medical Centre. The index case was a 34-year-old Malay man who presented to the eye clinic at Universiti Malaya Medical Centre in 2003 for intermittent eye pain and mild headache. Intraocular pressure (IOP) was 28 mmHg on the right eye and 20 mmHg on the left eye. He provided us with an interesting pedigree chart of four generations of affected family members.

The majority of his family members reside on the east coast of Malaysia particularly in the states of Kelantan, Terengganu, and Pahang. A total of 122 out of 152 family members who were still alive were examined. The majority of the family members were screened in hospitals, including Hospital Universiti Sains Malaysia, Kelantan, Hospital Raja Perempuan Zainab II, Kelantan, Hospital Sultanah Nur Zahirah, Terengganu, and Hospital Kuala Lipis, Pahang. A small number of family members were screened at their homes using portable slit lamps and binocular indirect ophthalmoscope, and intraocular pressure was obtained using Tonopen (Medtronic Solan, Jacksonville, FL). If there were any suspicious findings such as vertical cup disc ratio (VCDR) of more than 0.7 or elevated (IOP >21 mmHg), the subject was then reexamined at the nearest tertiary hospital for further confirmation.

Ocular examination in the tertiary hospitals including visual acuity assessment, slit-lamp examination to evaluate the anterior segment, dilated fundus examination to document the structural changes of glaucoma, and gonioscopic examination to evaluate the angle structure was conducted. The central corneal thickness (CCT) was also measured but not for all probands. The Humphrey visual field analysis 24–2 program was also conducted to identify the functional defect of glaucoma. Heidelberg retinal tomography (HRT) II of the optic nerve head was also obtained to further document structural changes in the optic nerve head. Newly diagnosed JOAG is defined as the presence of optic neuropathy with VCDR of >0.7, neuroretinal rim thinning and thinning of the retinal nerve fiber layer thickness on HRT II, glaucomatous visual field defect, grade 3 or 4 of modified Shaeffer classification on gonioscopic examination, and IOP >21 mmHg in at least one eye in any family member aged between 3 and 40 years old.

Clinical record review was also conducted on family members who had been diagnosed with JOAG and received treatment at other tertiary centers. Age at the initial diagnosis, clinical presentation, and subsequent treatment were documented. Ocular examination was also conducted on these family members to obtain their latest clinical findings. The severity of the disease was then categorized according to the mean deviation of the Humphrey visual field analysis of the right eye: mild (<4), moderate (4–7), and severe (>12).

DNA extraction and screening of MYOC: A total of 6 ml of venous blood was obtained during venipuncture. Genomic DNA was extracted from the blood samples using the commercial kit, QIAamp DNA Mini kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. PCR amplification of MYOC was done using six pairs of primer for three exons of the MYOC gene (Table 1 and Figure 1). The reactions contained 1X PCR buffer, 1.5 mM MgCl2, 0.5 mM dNTPs (Promega, Madison, WI), 0.1 μM of each primer (Sigma-Aldrich, St.Louis, MO), 1 U Taq DNA polymerase (Promega), 50 ng genomic DNA, and double-distilled water in a total volume of 20 μl. The following conditions were used to perform the amplifications: 94 °C for 7 min; followed by 34 cycles of 94 °C for 1 min (denaturation), 1 min for annealing (for temperature, refer Table 1) and 72 °C for 1min (elongation); followed by 72 °C for 7 min (final elongation). The PCR products were evaluated on 2% agarose gel (Promega) and stained with SYBR Green 1 (CambrexBioScience, Walkersville, MD) to confirm the band size.

Amplicons were then purified using a Novagen kit (Merck KGaA, Darmstadt, Germany) according to the manufacturer’s instructions. Sequencing was then conducted for the backward and forward primers using ABI Prism. Sequencing analysis was done using Biodeit Sequence Alignment Editor (Ibis Biosciences, Carlsbad, CA).

RESULTS

Clinical findings: The mean age during screening was 26.3±14.4 years, ranging from 6 to 71 years old. Based on the pedigree chart (Figure 1), the inheritance pattern was autosomal dominant in this large family. The first generation consists of the grandmother of our index patient. She died at the age of 60 with a history of bilateral blindness long before her death. She was married twice. She had three children by her first husband and five children from her second marriage. Four out of her eight children were affected by JOAG (II:3, II:7, II:9, II:14). On average, her children had 9.3 children each except the eldest son, who died a bachelor. She had 81 grandchildren. Her granddaughter (III:15) from her first marriage married her affected grandson (II:21) from
her second marriage. They have ten children, but none are affected yet. The majority of the immediate family members of our index patient are affected except III:22 and III:26. The youngest in his family (III:29) is not affected yet but carries the DCM.

We identified a total of 11 newly diagnosed JOAG (9 male; 2 female) probands newly diagnosed with JOAG during our screening (Figure 1 and Table 2). A total of 21 family members had already been diagnosed and treated at various hospitals. The mean age at diagnosis was 25.8±8.0 years (ranging from 16 to 37). Mean IOP before treatment of the right eye was 38.0±13.6 mmHg and 35.8±13.7 mmHg of the left eye. This is based on the 32 patients diagnosed with JOAG (11 newly diagnosed and 21 known cases). We were unable to obtain the IOP at the initial diagnosis of ten other known cases. The total prevalence of JOAG in this family was 26.2% of the total family members screened.

Genotyping: We identified C→A at position 1440 in exon 3, which results in a substitution of asparagine (AAC) to lysine (AAA; Figure 2). Asn480Lys was found in all affected individuals except III:5 and IV:6 (Figure 1). Six probands (III:17, III:48, III:58, IV:14, IV:57, IV:58) were not affected by JOAG but carried the DCM, Asn480Lys (Figure 1). However, probands III:5 and IV:6 developed severe disease but without the DCM. The logarithm of the odds (LOD) score was 6.23 calculated using Haplovew 4.2. We also found a synonymous polymorphism, G to A substitution, IVS2 730 +35 (Figure 2B,C). IVS2 730 +35G>A was also identified as rs2032555 in the NCBI database. There was a significant association between Lys480Lys and JOAG in this family (Table 3).

Similarly, IVS2 730 +35G>A increased the susceptibility to JOAG significantly (Table 3). The linkage disequilibrium between DCM Asn480Lys and IVS2 730 +35G>A was 0.619. Genotype and phenotype association: The analysis was conducted on 32 family members diagnosed with JOAG. Mean age at diagnosis was 29.3±9.2 years old. There was no significant association of the clinical parameters with Asn480Lys and IVS2 730 +35G>A (Table 4). However, the JOAG probands with Lys480Lys were diagnosed at a younger age (mid-20s) but with lower mean IOP at diagnosis. The JOAG probands with IVS2 730 +35AA were diagnosed in their late 20s and higher mean IOP at diagnosis.

DISCUSSION

Despite the popularity of MYOC as a candidate gene for glaucoma especially JOAG, no studies have examined the potential role of MYOC in Malay families. MYOC mutations are ethnic or population specific, and certain mutations are geographically specific, suggesting the possibility of the founder effect [8,10,14,15]. To the best of our knowledge, this is the first report on MYOC screening in a large Malay family with JOAG. Autosomal dominance with variable penetrance was observed in this family. Incomplete penetrance has been reported in most studies that involved families of JOAG [9,11,13]. Penetrance is age dependent and mutation specific [10]. The mean age of the fourth generation of this family is 17.4±7.1 years old. This may explain the incomplete penetrance in this pedigree.

The DCM has been identified mainly at the third exon of MYOC [10]. We identified a mutation in the third exon,
Asn480Lys, in this family. The Asn480Lys mutation is situated near the casein kinase II site that causes changes in polar amino acid (asparagine) to positively charged amino acid (lysine) and a gain of α-helix in the structural conformation of the MYOC protein [16]. The Asn480Lys mutation has been reported in families with open angle glaucoma in France [17]. The recurrent mutation was then reported in familial open angle glaucoma and case control studies of POAG in Europe, suggesting a possible founder effect [14,15]. Heterozygous C>A of Asn480Lys was reported in patients with POAG in southern India [18]. A variant of this missense mutation at nucleotide 1440 of C>G was reported in Andean families [19]. Heterozygous C>A of Asn480Lys was also seen in the majority of our JOAG probands, but Lys480Lys was observed.
| ID   | Sex | Visual acuity | Age | IOP | VCDR | CCT | HRT (RNFL thickness) | Visual field | Treatment |
|------|-----|---------------|-----|-----|------|-----|----------------------|--------------|-----------|
| II:3 | F   | NPL | NPL | 38  | 35   | 10  | Nil                  | Nil          | Severe    |
| II:7 | F   | NPL | 6/12 | 25  | Nil  | 12  | 0.9                  | 0.9          | Severe    |
| II:11| F   | 6/15 | 16  | 20  | 0.9  | 0.5 | 551                  | 527          | Abnormal  |
| II:14| M   | NPL | 6/7.5 | 40  | 58   | 58  | Nil                  | Abnormal     | Severe    |
| III:2| F   | NPL | NPL | 42  | 42   | 42  | Nil                  | Nil          | Severe    |
| III:3| F   | 6/6  | 56  | 56  | 0.9  | 0.9 | 468                  | 469          | Borderline|
| III:5*| M  | 6/7.5 | 24  | 16  | 0.8  | 0.2 | 515                  | Borderline   | Severe    |
| III:6| F   | 6/6  | 40  | 20  | 0.5  | 0.4 | Nil                  | Nil          | Mild      |
| III:7| M   | NPL | NPL | 36  | 46   | 45  | 1                   | 0.9          | Severe    |
| III:8| F   | HM  | 6/6  | 31  | 11   | 17  | 0.9                  | 0.9          | Normal    |
| III:19| F  | NPL | 6/6  | 36  | 40   | 40  | 0.9                  | 0.9          | Severe    |
| III:20| F  | 6/6  | 34  | 16  | 16   | 0.9 | Nil                  | Nil          | Severe    |
| III:21| M  | 6/7.5 | 29  | 32  | 32   | 0.7 | 466                  | 439          | Normal    |
| III:23| M  | 6/6  | 32  | 20  | 23   | 0.5 | 510                  | 512          | Normal    |
| III:24*| F  | 6/6  | 37  | 49  | 33   | 0.7 | 517                  | 509          | Normal    |
| III:25*| M  | 6/6  | 34  | 49  | 49   | 0.8 | 517                  | 506          | Normal    |
| III:27| F  | PL  | 6/9  | 17  | 30   | 22  | 0.9                  | 0.9          | Normal    |
| III:28*| M  | 6/7.5 | 23  | 28  | 35   | 0.4 | 501                  | 506          | Abnormal  |
| III:36| M  | 6/18 | 32  | 50  | 50   | 0.9 | 504                  | 499          | Normal    |
| III:39| F  | 6/6  | 24  | 16  | 14   | 0.5 | 510                  | 513          | Normal    |
| III:40| F  | 6/9  | 25  | 20  | 19   | 0.5 | 487                  | 488          | Normal    |
| III:41*| M  | 6/6  | 30  | 50  | 54   | 0.3 | 563                  | 560          | Normal    |
| III:42*| M  | 6/6  | 25  | 29  | 37   | 0.6 | 557                  | 556          | Normal    |
| III:43| F  | 6/5  | 16  | 24  | 22   | 0.3 | 519                  | 529          | Normal    |
| III:59*| M  | 6/7.5 | 22  | 27  | 25   | 0.4 | 557                  | 565          | Abnormal  |
| III:62*| M  | 6/6  | 36  | 36  | 0.8  | 0.7 | 537                  | 554          | Abnormal  |
| III:63*| M  | 6/7.5 | 38  | 40  | 0.6  | 0.9 | 527                  | 532          | Abnormal  |
| IV:1 | M   | NPL | NPL | 16  | 44   | 5   | 0.9                  | 0.9          | Abnormal  |
| IV:6 | M   | 6/9  | 6/7.5 | 33  | 33   | 54  | 0.9                  | 0.9          | Normal    |
| IV:11*| F  | 6/6  | 31  | 34  | 25   | 0.4 | 454                  | 455          | Normal    |
| IV:15*| M  | 6/7.5 | 18  | 26  | 26   | 0.6 | 465                  | 466          | Normal    |
| IV:48| F   | 6/12 | 6/9  | 13  | 33   | 33  | 0.4                  | 0.4          | Normal    |
Newly diagnosed juvenile-onset open angle glaucoma (11 cases); AGE*: Age at diagnosis; IOP: Intraocular pressure; VCDR: Vertical cup disc ratio; CCT: Central corneal thickness; HRT: Heidelberg retinal tomography II; RNFL: Retinal nerve fiber layer; NPL: no perception to light; HM: hand movement.
in five of our probands. Lys480Lys was found in our index patient’s mother and his family. However, his father refused to participate in the study. We postulated that his father may also have either Lys480Lys or Asn480Lys (heterozygous). The spouse or parent of the majority of the probands may have Asn480Asn resulting in a higher number of heterozygous C>A of Asn480Lys in this pedigree. Unfortunately, the majority of the spouses of the affected probands refused to participate in this study.

Unlike Pro380Leu, Thr377Met, and Gln368Stop that affect the clinical presentation and mode of management of JOAG [8,10], there was no significant association with Asn480Lys with severity of glaucoma in this Malay family. Probands with Lys480Lys may have been detected earlier and treated appropriately compared to Asn480Lys (heterozygous), resulting in less severe glaucoma at the recruitment period of this study. The Asn480Lys mutation has been reported to associate with middle-aged glaucoma and mean IOP at presentation of 39.0±10.6 mmHg [10]. We found that our probands with Lys480Lys were diagnosed at a much earlier age but with lower mean IOP. This is perhaps due to the relatively small number of probands with Lys480Lys (five probands) that may be responsible for the skewness of age, severity, and IOP distribution. However, the lower IOP at the initial diagnosis of these five probands may be due to inaccurate data obtained from the medical records from various hospitals. In addition, there was also some missing data.

Higher baseline IOP was observed in our probands with Asn480Lys (heterozygous). In this study, the IOP was analyzed without adjustment for CCT. This is because CCT
### Table 3. Genotype and allele frequency for Asn480 Lys and IVS2 730+35G>A (rs2032555) between affected and non-affected probands.

| MYOC variation | JOAG n=32 | Not affected n=90 | p-value* |
|----------------|-----------|-------------------|----------|
| **Asn480Lys**  |           |                   |          |
| Genotype       | N (%)     | N (%)             |          |
| Asn480Asn      | 2 (6.3)   | 84 (93.3)         |          |
| Asn480Lys      | 25 (78.1) | 6 (6.7)           | <0.001   |
| Lys480Lys      | 5 (15.6)  | 0 (0.0)           |          |
| **Allele frequency** | |                   |          |
| C              | 0.45      | 0.97              | <0.001   |
| A              | 0.55      | 0.03              |          |
| **IVS2 730+35G>A** | |                   |          |
| Genotype       | N (%)     | N (%)             |          |
| GG             | 5 (15.6)  | 4 (4.4)           |          |
| GA             | 22 (68.8) | 23 (25.6)         | <0.001   |
| AA             | 5 (15.6)  | 63 (70.0)         |          |
| **Allele frequency** | |                   |          |
| G              | 0.50      | 0.17              | <0.001   |
| A              | 0.50      | 0.83              |          |

### Table 4. Association between clinical parameters in JOAG probands and genotype frequency of Asn480 Lys and IVS2 730+35G>A (rs2032555).

| Genotype | Asn 480 Lys | IVS 2 730+35G>A |
|----------|-------------|-----------------|
| CC n=2   | CA n=25     | AA n=5          |
| Mean age (SD; year) n=32 | 40.0 (9.9) | 29.5 (9.1) | 24.4 (8.8) | 0.457* |
| Mean IOP (SD) (mmHg) n=22 | 34.5 (16.2) | 40.4 (12.8) | 27.0 (6.6) | 0.284* |
| Mean VCDR | 0.56 (0.25) | 0.70 (0.24) | 0.58 (0.22) | 0.280* |
| Mean MD (SD) n=23 | −23.64 (2.07) | −10.21 (12.11) | −5.28 (6.33) | 0.184* |
| Mean CCT (SD; µm) n=25 | 523 (11) | 518 (34) | 511 (41) | 0.890* |
| Severity |            |                 |             | 0.834* |

|          | Early | Mild | Moderate | Severe |
|----------|-------|------|----------|--------|
| CC n=2   | 0     | 0    | 0        | 2      |
| CA n=25  | 9     | 2    | 1        | 13     |
| AA n=5   | 3     | 0    | 0        | 2      |

p<0.05 is considered significant based on One way ANOVA* and Fisher exact test#; IOP: intraocular pressure; VCDR: vertical cup disc ratio; MD: mean deviation of Humphrey field analysis; CCT: central corneal thickness.
The present study provides the first molecular analysis of MYOC in a Malay family with JOAG. Identifying the genetic risk factor is important for early detection of JOAG. Early detection and prompt treatment may prevent blindness especially in young patients with JOAG.

ACKNOWLEDGMENTS

We thank the family members of this pedigree for participating in this study. This study was financially supported by the special short-term grant under research university grant of Universiti Malaya FS364/2008 and research university grant Universiti Malaya RG217/10HTM 2009/2011.

REFERENCES

1. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol 1994; 112:69-73. [PMID: 8285897]
2. Green CM, Kearns LS, Wu J, Barbour JM, Wilkinson RM, Ring MA, Craig JE, Wong TL, Hewitt AW, Mackey DA. How significant is a family history of glaucoma? Experience from the Glaucoma Inheritance Study in Tasmania (GIST). Clin Experiment Ophthalmol 2007; 35:793-9. [PMID: 18173405]
3. Sun C, Ponsonby AL, Brown SA, Kearns LS, MacKinnon JR, Barbour JM, Ruddle JB, Hewitt AW, Wright MJ, Martin NG, Dwyer T, Mackey DA. Association of birth weight with ocular biometry, refraction, and glaucomatous endophenotypes: the Australian Twins Eye Study. Am J Ophthalmol 2010; 150:909-16. [PMID: 20970773]
4. Alward WL, Fingert JH, Cote MA, Johnson AT, Lerner SF, Junqua D, Durcan FJ, McCartney PJ, Mackey DA, Sheffield VC, Stone EM. Clinical features associated with mutations in GLC1A. N Engl J Med 1998; 338:1022-7. [PMID: 9535666]
5. Nemesure B, He Q, Mendell N, Wu SY, Hejtmancik JF, Hennis A. Leske CM for Barbados Family Study Group. Inheritance of open-angle glaucoma in the Barbados Family Study. Am J Med Genet 2001; 103:36-43. [PMID: 11562932]
6. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, Nishimura D, Clark AF, Nystruen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC. Identification of a gene that causes primary open angle glaucoma. Science 1997; 275:668-70. [PMID: 9005853]
7. Richards JE, Lichter PR, Boehnke M, Uro JLA, Torrez D, Wong D, Johnson AT. Mapping of a gene for autosomal dominant juvenile-onset open-angle glaucoma to chromosome 1q. Am J Hum Genet 1994; 54:62-70. [PMID: 8279471]
8. Fingert JH, Heon E, Liebman JM, Yamamoto T, Craig JE, Rait J, Kawase K, Hoh ST, Buys YM, Dickinson J, Hockey RR, Williams-Lyn D, Trope G, Kitazawa Y, Ritch R, Mackey DA, Alward WL, Sheffield VC, Stone EM. Analysis of Myocilin mutations in 1703 glaucoma patients from five different...
populations. Hum Mol Genet 1999; 8:899-905. [PMID: 10196380].

9. Fingert JH, Stone EM, Sheffield VC, Alward WL. Myocilin glaucoma. Surv Ophthalmol 2002; 47:547-61. [PMID: 12504739].

10. Hewitt AW, Mackey DA, Craig JE. Myocilin allele-specific glaucoma phenotype database. Hum Mutat 2008; 29:207-11. [PMID: 17966125].

11. Wei YT, Li YQ, Bai YJ, Wang M, Chen JH, Ge J, Zhuo YH. Pro370Leu myocilin mutation in a Chinese pedigree with juvenile-onset open angle glaucoma. Mol Vis 2011; 17:1449-56. [PMID: 21677793].

12. Wang DY, Fan BJ, Canlas O, Tam POS, Ritch R, Lam DSC, Fan DSP, Pang CP. Absence of myocilin and optineurin mutations in a large Philipine family with juvenile onset primary open angle glaucoma. Mol Vis 2004; 10:851-6. [PMID: 15547491].

13. Zhao X, Yang C, Tong Y, Zhang X, Xu L, Li Y. Identification of a novel MYOC gene mutation in a Chinese family with juvenile-onset open angle glaucoma. Mol Vis 2010; 16:1728-35. [PMID: 20806035].

14. Adam MF, Belmouden A, Binisti P, Brézin AP, Valtort F, Béchetoille A, Dascotte JC, Copin B, Gomez L, Chaventré A, Bach JF, Garchon HJ. Recurrent mutations in a single exon encoding the evolutionarily conserved olfactomedin-homology domain of TIGR in familial open-angle glaucoma. Hum Mol Genet 1997; 6:2091-7. [PMID: 9328473].

15. Hulsman CAA, de Jong PTVM, Lettink M, van Duijn CM, Hofman A, Bergen AAB. Myocilin mutations in a population-based sample of cases with open-angle glaucoma: the Rotterdam study. Graefes Arch Clin Exp Ophthalmol 2002; 240:468-74. [PMID: 12107514].

16. Rozsa FW, Shimizu S, Lichter PR, Johnson AT, Othman MI, Scott K, Downs CA, Nguyen TD, Polansky J, Richards JE. GLC1A mutations point to regions of potential functional importance on the TIGR/MYOC protein. Mol Vis 1998; 4:20. [PMID: 9772276].

17. Brézin AP, Adam MF, Belmouden A, Lureau MA, Chaventre A, Copin B, Gomez L, De Dinechin SD, Berkani M, Valtort F, Rouland JF, Dascotte JC, Bach JF, Garchon HJ. Founder effect in GLC1A-linked familial open-angle glaucoma in Northern France. Am J Med Genet 1998; 76:438-45. [PMID: 9556305].

18. Rose R, Balakrishnan A, Muthusamy K, Arumugam P, Shanmugam S, Gopalswamy. Myocilin mutations among POAG patients from two populations of Tamil Nadu, South India, a comparative analysis. Mol Vis 2011; 17:3243-53. [PMID: 22194650].

19. Guevara-Fujita ML, Perez-Grossmann RA, Estrada-Cuzcano, Pawar H, Vargas E, Richards JE, Fujita R. Recurrent Myocilin Asn480Lys glaucoma causative mutation arises de novo in a family of Andean descent. J Glaucoma 2008; 17:67-72. [PMID: 18303389].

20. Brandt JD, Gordon MO, Gao F, Beiser JA, Miller JP, Kass MA for the Ocular Hypertension Treatment Study Group. Adjusting intraocular pressure for central corneal thickness does not improve prediction models for primary open-angle glaucoma. Ophthalmology 2012; 119:437-42. [PMID: 21705084].

21. Pang CP, Leung YF, Fan B, Baum L, Tong WC, Lee WS, Chua JKH, Fan DSP, Liu Y, Lam DSC. TIGR/MYOC gene sequence alterations in individuals with and without primary open-angle glaucoma. Invest Ophthalmol Vis Sci 2002; 43:3231-5. [PMID: 12356829].

22. Sripriya S, Uthra S, Sangeetha R, George RJ, Hemamalini A, Paul PG, Amali J, Vijaya L, Kumaramanickavel G. Low frequency of Myocilin mutations in Indian primary open-angle glaucoma patients. Clin Genet 2004; 65:333-7. [PMID: 15025728].

Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 27 May 2014. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.