Myocilin Polymorphisms and Primary Open-Angle Glaucoma: A Systematic Review and Meta-Analysis

Jin-Wei Cheng¹,², Shi-Wei Cheng²,², Xiao-Ye Ma¹, Ji-Ping Cai¹, You Li¹, Guo-Cai Lu³,³, Rui-Li Wei¹,²

¹Department of Ophthalmology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai, China, ²School of Life Sciences, Ludong University, Yantai, China, ³Center for New Drug Evaluation, Institute of Basic Medical Science, Second Military Medical University, Shanghai, China

Abstract

Background: Glaucoma is the leading cause of irreversible blindness in the world. Recent evidence indicates a role for genetic susceptibility to primary open-angle glaucoma (POAG). The relation between myocilin polymorphisms and POAG susceptibility has been studied in different populations.

Methods: A meta-analysis of 32 published genetic association case-control studies, which examined the relation between POAG and the R46X, R76K, T353I, and Q368X polymorphisms of the myocilin gene, was carried out.

Results: In meta-analysis, significant associations were observed between POAG risk and two myocilin polymorphisms with summarized odds ratio of 4.68 (95% CI 2.02–10.85) for Q368X and 2.17 (95% CI 1.32–3.57) for T353I. Both Q368X and T353I were significantly associated with high-tension glaucoma, with summarized odds ratio of 4.26 (1.69, 10.73) and 2.26 (1.37–3.72). In Westerners, significant association was observed for Q368X mutation (odds ratio, 5.17; 95% CI, 2.16–12.40). However, in Asians it was for T353I (odds ratio, 2.17; 95% CI, 1.32–3.57).

Conclusions: There is strong evidence that myocilin polymorphisms are associated with POAG susceptibility, and the prevalence of myocilin mutations might be ethnicity-dependent in Caucasians for Q368X and in Asians for T353I.

Introduction

Glaucoma, which causes optic nerve damage and visual field loss, is the leading causes of irreversible blindness worldwide [1]. A family history of the disease has long been recognized as a major risk factor for glaucoma, suggesting that specific gene defects contribute to the pathogenesis of the disorder [2]. The most common form of glaucoma is primary open-angle glaucoma (POAG), which is characterized with typical optic disc damage and visual field defects, in an eye which does not have evidence of angle closure on gonioscopy, accompanied with elevated or normal intraocular pressure (IOP). Several chromosomal loci have now been reported as linked to POAG, such as myocilin (MYOC; GLC1A, MIM 601652), optineurin (OPTN; GLC1E, MIM 602432), and WD repeat domain 36 (WDR36; GLC1G, MIM 609669) [3].

The MYOC gene, also known as trabecular meshwork-inducible glucocorticoid response (TIGR) gene, was the first discovered to be linked to POAG in 1997 [4]. Several large studies have suggested that MYOC mutations are associated with 2% to 4% of POAG in patient populations worldwide, with more than 30 disease-associated mutations identified [5,6]. The overall frequency of disease-causing mutations at MYOC is similar among African (4.44%), Caucasian (3.86%) and Asian (3.30%) probands with POAG [7]. Most disease-associated mutations at MYOC exist only in a specific racial group. The most frequent mutation Gln368Stop was present only in Caucasian descendants, and the second most frequent mutation Arg46Stop was shared only by Asian populations. However, the association of MYOC with POAG has been a source of controversy. After the initial discovery of POAG-causing mutations, the mutations were subsequently observed in controls, which were considered as non-disease-causing polymorphisms [8,9]. Otherwise, reports published previously showed apparent non-consistent results. In familial studies, over four fifths Gln368Stop-carriers did not have POAG [10]. Also, the most frequent mutation Arg46Stop in Asians was even more often found in normal controls than in POAG probands [11]. Because the currently published studies only refer to a modest sample size, each one might not achieve a reliable conclusion. Hence, to investigate the association of the MYOC genetic variation with POAG susceptibility, a newly meta-analysis of all of the available case-control studies was carried out.

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met criteria and were included in the present meta-analysis [8,9,11–40]. The flow of study selection is shown in Figure 1, and the detailed characteristics of the studies were shown in Table 1. 6,729 patients and 4,871 controls were included in this study. Among those 32 included studies, 18 were conducted in Asians, 12 in Caucasians, and 1 in mixed. There were 19 studies for high-tension glaucoma (HTG), 1 study for normal-tension glaucoma (NTG), and 11 studies for both HTG and NTG. For R46X, R76K, Y347Y, T353I, and Q368X, meta-analyses were conducted within 11, 26, 11, 12, and 9 studies, respectively.

The association between the MYOC Q368X mutation and POAG was investigated with a total of 3,820 cases and 2,144 controls. Meta-analysis suggested that Q368X mutation carriage might be a risk factor for POAG with a summarized OR of 4.68 (95% CI, 2.02–10.85) (Figure 2), and no heterogeneity between studies (P = 0.76; I² = 0.00%) was observed. There was no publication bias (P = 0.40 for Begg rank correlation analysis; P = 0.30 for Egger weighted regression analysis). In subgroup analysis by ethnicity, the association was significant in Caucasians, and 1 in mixed. There were 19 studies for high-tension glaucoma (HTG), 1 study for normal-tension glaucoma (NTG), and 11 studies for both HTG and NTG. For R46X, R76K, Y347Y, T353I, and Q368X, meta-analyses were conducted within 11, 26, 11, 12, and 9 studies, respectively.

It has been shown in Figure 3 that the T353I mutation was significantly associated with POAG (OR, 2.17; 95% CI, 1.32–3.57), with no evidence of heterogeneity among the overall 12 studies (P = 0.76; I² = 0.00%). No publication bias was observed (P = 0.58 for Begg rank correlation analysis; P = 0.97 for Egger weighted regression analysis). Significant relation was also observed in Asians (Table 2). The association was also significant for HTG.

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association. The strength of present meta-analysis investigating the relationship between the MOYC polymorphic variant and susceptibility to POAG is based on the large amount of published data giving greater information.

Although we tried to conduct a thorough review of the existing literature, this study has several potential limitations. First, the possibility of selection biases cannot be completely excluded because all of the included studies were observational, and the potential confounding effect of age and sex might make the interpretation of the results and stratified analyses difficult. Second, only five POAG mutations were included in this analysis. Other potential polymorphisms, such as those at G12R, T123T, D208E, T285T, I288I, T325T, K398R, and A488A, were not included. Third, only published studies were included. Although multiple databases and websites were searched, unfortunately, it is possible that we may have failed to include some papers, especially those published in other languages. We can’t find any evidence of publication bias by funnel plots, however, considerable between-study heterogeneity was found for R76K.

In conclusion, this systematic review summarized the strong evidence for an association between myocilin polymorphisms and POAG. Our results suggested Q368X and T353I variants of myocilin gene can be taken as reference loci for exploring POAG susceptibility, both in high-tension glaucoma. Furthermore, the prevalence of the two mutations of myocilin gene might be ethnicity-dependent, namely, in Caucasians for Q368X and in Asians for T353I.

### Table 1. Characteristics of publications included in meta-analysis of myocilin polymorphism and POAG.

| Reference        | Country          | Ethnicity | Patients          | Controls                      | No. (case/control) |
|------------------|------------------|-----------|-------------------|-------------------------------|--------------------|
| Alward 1998      | Iowa; Australia; US | Caucasian | POAG (HTG)       | General population and healthy participants | 716/596            |
| Yoon 1999        | Korea            | Asian     | POAG (HTG)       | Non-glaucma participants      | 45/106             |
| Fingert 1999     | Iowa; Australia; US; Canada; Japan | Caucasian; African; Asian | POAG (HTG) | General population and healthy participants | 1693/793           |
| Kubota 2000      | Japan            | Asian     | POAG (HTG and NTG) | Non-glaucma participants      | 140/100            |
| Lam 2000         | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 91/132             |
| Vázquez 2000     | Spain            | Caucasian | POAG (HTG)       | General population            | 79/90              |
| Mabuchi 2001     | Japan            | Asian     | POAG (HTG and NTG) | Non-glaucma participants      | 233/100            |
| Mataftsi 2001    | Switzerland      | Caucasian | POAG (HTG and NTG) | Non-glaucma participants      | 117/50             |
| Fan 2002         | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 82/150             |
| Faucher 2002     | Canada           | Caucasian | POAG (HTG)       | General population and healthy participants | 293/107            |
| Hulsman 2002     | Netherlands      | Caucasian | POAG (HTG and NTG) | Non-glaucma participants      | 50/100             |
| Mukhopadhysay 2002 | India           | Asian     | POAG (HTG)       | Non-glaucma participants      | 56/51              |
| Pang 2002        | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 201/388            |
| Izumi 2003       | Japan            | Asian     | POAG (NTG)       | Non-glaucma participants      | 80/100             |
| Jansson 2003     | Sweden           | Caucasian | POAG (HTG)       | Non-glaucma participants      | 200/200            |
| Meli 2003a       | France           | Caucasian | POAG (HTG and NTG) | Healthy participants         | 237/108            |
| Meli 2003b       | Morocco          | Caucasian | POAG (HTG)       | General population            | 57/60              |
| Fan 2004a        | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 157/155            |
| Fan 2004b        | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 32/96              |
| Ishikawa 2004    | Japan            | Asian     | POAG (HTG)       | Healthy participants          | 171/100            |
| Fan 2005         | China            | Asian     | POAG (HTG and NTG) | Non-glaucma participants      | 400/281            |
| Rahmannov 2005   | Russia           | Caucasian | POAG (HTG and NTG) | Non-glaucma participants      | 170/100            |
| Funayama 2006    | Japan            | Asian     | POAG (HTG and NTG) | Non-glaucma participants      | 532/240            |
| Yao 2006         | China            | Asian     | POAG (HTG and NTG) | Non-glaucma participants      | 142/77             |
| Bhattacharjee 2007 | India           | Asian     | POAG (HTG)       | General population and non-glaucma participants | 315/100            |
| Kumar 2007       | India            | Asian     | POAG (HTG and NTG) | Healthy participants          | 251/100            |
| Lopez-Martinez 2007 | Spain         | Caucasian | POAG (HTG)       | Healthy participants          | 110/98             |
| Yen 2007         | China            | Asian     | POAG (HTG)       | Healthy participants          | 48/100             |
| Bayat 2008       | Iran             | Caucasian | POAG (HTG)       | Healthy participants          | 23/100             |
| Jia 2009         | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 176/200            |
| Chen 2011        | China            | Asian     | POAG (HTG)       | Non-glaucma participants      | 118/150            |
| Whigham 2011     | US               | African   | POAG (HTG and NTG) | Non-glaucma participants      | 113/131            |

POAG: primary open angle glaucoma; HTG: high-tension glaucoma; NTG: normal-tension glaucoma.

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Figure 2. Meta-analysis of the association between primary open-angle glaucoma and myocilin Q368X mutation. doi:10.1371/journal.pone.0046632.g002

Table 2. Summary odds ratios from the meta-analysis of the association between primary open-angle glaucoma and myocilin polymorphisms.

| Polymorphism and subgroup | No. of studies | Event/Total (%) | Odds ratios (95% CI) | Test for heterogeneity | Test for overall effect |
|---------------------------|----------------|----------------|---------------------|------------------------|------------------------|
|                           |                | Case/Control   | Odds ratio         | X², P = 0.00         | Z, P = 0.00            |
| Q368X                     |                |                |                    |                        |                        |
| All                       | 9              | 69/3820 (1.8)  | 4/2144 (0.2)       | 4.68 (2.02, 10.85)    | X² = 4.974, P = 0.760, I² = 0.00% Z = 3.598, P = 0.000 |
| Africans                  | 1              | 1/312 (0.3)    | 0/90 (0.0)         | 0.87 (0.04, 21.58)    | X² = 0.000, P = 1.000, I² = 0.00% Z = -0.084, P = 0.913 |
| Asians                    | 1              | 2/315 (0.6)    | 0/100 (0.0)        | 1.60 (0.08, 33.67)    | X² = 0.000, P = 1.000, I² = 0.00% Z = 0.304, P = 0.761 |
| Caucasians                | 8              | 66/3086 (2.1)  | 4/1905 (0.2)       | 5.17 (2.16, 12.40)    | X² = 4.563, P = 0.713, I² = 0.00% Z = 3.680, P = 0.000 |
| HTG                       | 7              | 52/3446 (1.5)  | 4/1986 (0.2)       | 4.26 (1.69, 10.73)    | X² = 4.467, P = 0.614, I² = 0.00% Z = 3.076, P = 0.002 |
|                           |                |                |                    |                        |                        |
| T353I                     |                |                |                    |                        |                        |
| All                       | 12             | 44/3452 (1.3)  | 25/2609 (1.0)      | 2.17 (1.32, 3.57)     | X² = 6.308, P = 0.852, I² = 0.00% Z = 3.041, P = 0.002 |
| Asian                     | 12             | 44/3452 (1.3)  | 25/2609 (1.0)      | 2.17 (1.32, 3.57)     | X² = 6.310, P = 0.852, I² = 0.00% Z = 3.041, P = 0.002 |
| NTG                       | 2              | 3/154 (1.9)    | 5/358 (1.5)        | 1.58 (0.40, 6.22)     | X² = 0.000, P = 1.000, I² = 0.00% Z = 0.304, P = 0.761 |
| HTG                       | 12             | 42/3298 (1.3)  | 25/2609 (1.0)      | 2.26 (1.37, 3.72)     | X² = 5.989, P = 0.874, I² = 0.00% Z = 3.176, P = 0.001 |
|                           |                |                |                    |                        |                        |
| Y347Y                     |                |                |                    |                        |                        |
| All                       | 11             | 174/3715 (4.7) | 85/2164 (3.9)      | 1.20 (0.91, 1.57)     | X² = 3.719, P = 0.959, I² = 0.00% Z = 1.304, P = 0.192 |
| Africans                  | 2              | 8/425 (1.9)    | 2/221 (0.9)        | 1.37 (0.24, 7.88)     | X² = 0.000, P = 1.000, I² = 0.00% Z = 0.304, P = 0.728 |
| Asians                    | 2              | 9/457 (2.0)    | 0/177 (0.0)        | 3.24 (0.38, 27.46)    | X² = 0.000, P = 1.000, I² = 0.00% Z = 0.304, P = 0.728 |
| Caucasians                | 8              | 157/2736 (5.7) | 83/1717 (4.8)      | 1.19 (0.91, 1.57)     | X² = 2.057, P = 0.957, I² = 0.00% Z = 1.259, P = 0.208 |
| NTG                       | 2              | 3/68 (4.4)     | 7/177 (4.0)        | 1.89 (0.44, 8.23)     | X² = 0.000, P = 1.000, I² = 0.00% Z = 0.852, P = 0.394 |
| HTG                       | 12             | 157/3041 (5.2) | 77/1747 (4.4)      | 1.22 (0.92, 1.63)     | X² = 2.522, P = 0.773, I² = 0.00% Z = 1.393, P = 0.164 |
|                           |                |                |                    |                        |                        |
| R76K                       |                |                |                    |                        |                        |
| All                       | 23             | 769/5371 (14.3)| 608/3340 (18.2)    | 0.86 (0.69, 1.08)     | X² = 45.281, P = 0.002, I² = 51.42% Z = -1.319, P = 0.187 |
| Africans                  | 2              | 1/425 (0.2)    | 1/221 (0.5)        | 0.58 (0.06, 5.59)     | X² = 0.126, P = 0.721, I² = 0.00% Z = -0.473, P = 0.636 |
| Asians                    | 16             | 613/2999 (20.4)| 461/2301 (20.0)    | 0.89 (0.75, 1.06)     | X² = 15.748, P = 0.399, I² = 4.75% Z = -1.339, P = 0.180 |
| Caucasians                | 7              | 155/1947 (8.0) | 146/800 (18.3)     | 0.62 (0.48, 0.81)     | X² = 44.682, P = 0.000, I² = 86.57% Z = -3.586, P = 0.000 |
| NTG                       | 5              | 64/625 (10.2)  | 85/798 (10.7)      | 1.19 (0.83, 1.73)     | X² = 4.586, P = 0.332, I² = 12.78% Z = 0.939, P = 0.348 |
| HTG                       | 17             | 559/4092 (13.7)| 474/2701 (17.5)    | 0.84 (0.65, 1.08)     | X² = 37.401, P = 0.002, I² = 57.22% Z = -1.355, P = 0.175 |
|                           |                |                |                    |                        |                        |
| R46X                       |                |                |                    |                        |                        |
| All                       | 12             | 34/1826 (1.8)  | 35/1884 (1.9)      | 1.02 (0.61, 1.70)     | X² = 7.664, P = 0.743, I² = 0.00% Z = 0.073, P = 0.942 |
| Asians                    | 12             | 34/1826 (1.8)  | 35/1884 (1.9)      | 1.02 (0.61, 1.70)     | X² = 7.664, P = 0.743, I² = 0.00% Z = 0.073, P = 0.942 |
| NTG                       | 4              | 8/348 (2.3)    | 8/558 (1.4)        | 1.86 (0.60, 5.72)     | X² = 2.659, P = 0.447, I² = 0.00% Z = 1.080, P = 0.280 |
| HTG                       | 10             | 26/1359 (1.9)  | 35/1684 (2.1)      | 0.93 (0.55, 1.60)     | X² = 5.419, P = 0.796, I² = 0.00% Z = -0.250, P = 0.803 |
Methods

Search Strategy

Studies addressing the association between MYOC mutations and polymorphisms and POAG were identified by searching for articles in the PubMed, and EMBASE until 31 December 2011. A broad search strategy combined terms related to gene (including keyword search using *myocilin*, *MYOC*, *trabecular meshwork-induced glucocorticoid response protein*, *TIGR*, *GLC1A*) and terms related to disease (including MeSH search using exp "glaucoma, open angle" and keyword search using "open angle glaucoma" and its abbreviation). Additional studies were also identified by a hand search of all the references of retrieved articles.

We included only published manuscripts, without any language restriction. All the studies must meet the following inclusion criteria: (1) case-control study; (2) patients had to be POAG; and (3) Only the most widely mutations and polymorphisms were considered: R46X, R76K, Y347Y, T353I, Q368X. Exclusion criteria were: 1) studies with family-based designs; 2) studies on other polymorphisms other than the target polymorphisms.

Data extraction

Data extraction was performed by two reviewers independently and in duplicate. For each study, the following data were extracted: first authors and publication year, country of origin, study base, study participant ethnicity, numbers of cases and controls, diagnosis criteria, demographic data, and genotype distributions for each polymorphism among cases and controls.

Statistical Analysis

The association between MYOC polymorphism and POAG was calculated using co-dominant model. We used the odds ratio (OR) and corresponding 95% confidence intervals (CI) as the metric of choice. The statistical analysis was performed by Comprehensive Meta-Analysis (V2.0; Biostat, Englewood Cliffs, New Jersey, USA). The between-study heterogeneity was tested by the Q test and I² test. If no heterogeneity detected (P > 0.1), a fixed effects model was selected to pool the data. A random-effect model, otherwise, was employed after exploring the causes of heterogeneity. Stratified analyses were conducted with respect to ethnicity (Africans, Asians and Caucasians) and diagnosis criteria (NTG, HTG). Begg's rank correlation method and Egger's weighted regression method were used to statistically assess publication bias.

Author Contributions

Conceived and designed the experiments: JWC SWC GCL RLW. Performed the experiments: JWC SWC XYM JPC YL GCL RLW. Analyzed the data: JWC SWC. Contributed reagents/materials/analysis tools: GCL. Wrote the paper: JWC SWC XYM JPC YL GCL RLW.

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