Genetics and Molecular Research

Association of single nucleotide polymorphisms in the *CYP1B1* gene with the risk of primary open-angle glaucoma: a meta-analysis

Z. Wang[1], M. Li[2], L. Li[3], H. Sun[4] and X.Y. Lin[5]

[1]Department of Ophthalmology, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, China
[2]Department of Ophthalmology, Jiaozhou Central Hospital of Qingdao, Qingdao, Shandong, China
[3]Department of Orthopedics, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, China
[4]Department of Cardiology, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, China
[5]Department of Neurology, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, China

Corresponding author: X.Y. Lin
E-mail: linxiaoying333@163.com

Genet. Mol. Res. 14 (4): 17262-17272 (2015)
Received August 29, 2015
Accepted October 18, 2015
Published December 16, 2015
DOI http://dx.doi.org/10.4238/2015.December.16.26

ABSTRACT. Mutations in the *CYP1B1* gene were detected in primary open-angle glaucoma (POAG) patients. However, the association between these mutations and the incidence of POAG remains to be elucidated. Here, we have conducted a meta-analysis to analyze this correlation, using relevant studies obtained from an extensive search of various electronic databases, including EMBase, Web of Science, and PubMed. The extracted studies were selected for the meta-analysis based on the inclusion and exclusion criteria. The quality of each included study was assessed by the Newcastle-

Ottawa scale (NOS), and the I^2 value was calculated to evaluate the heterogeneity between studies. The combined effect size was presented as the odds ratio (OR), and confidence intervals (CI) were used to assess the association between POAG and *CYP1B1* mutations. Eight studies, each with a high NOS score, were included in the analysis. Compared to the mutant allele, the wild-type allele of the rs180040 polymorphism in POAG patients showed a 12% decrease in OR (OR = 0.88, 95%CI = 0.76-1.00); also, the wild-type allele of rs1056827 showed a 23% decrease in OR of the incidence of POAG (OR = 0.77, 95%CI = 0.60-0.99). However, the latter result was controversial. Polymorphisms at rs1056836, rs10012, and rs1056837 were not correlated with the incidence of POAG (using any evaluation model). In conclusion, three of the tested SNPs in the *CYP1B1* gene were correlated with POAG; however, the SNPs rs180040 and rs1056827 showed an association with risk of POAG. These results must be further validated with larger-scale evaluations.

Key words: Primary Open-angle glaucoma; CYP1B1; SNP; Meta-analysis

INTRODUCTION

Glaucoma causes irreversible visual impairment, and has been diagnosed in an estimated 60.5 million people worldwide in 2010 (Quigley and Broman, 2006). Primary open-angle glaucoma (POAG), which accounts for approximately 50% of the types of glaucoma, is an autosomal dominant or recessive inherited disease (Iancu and Corbu, 2014; Kothari et al., 2014; Weinreb et al., 2014). Previous studies have reported that the risk factors (or predictors) of POAG are the baseline age (Gordon et al., 2002), diabetes mellitus (Zhou et al., 2014), a greater number of visual field tests, and increased/wider range of peak intraocular pressure (Hung et al., 2015). Low intraocular pressure was shown to prevent further visual field loss in the eyes (Ermis et al., 2002; Heijl et al., 2002). Despite this, POAG exerts a high economic and social burden on both developed and developing countries (Dirani et al., 2011; Ting et al., 2014). The direct costs, such as the cost of its diagnosis and treatment, and the indirect costs involved exert a heavy burden on both the patients and their families (Ting et al., 2014). Therefore, prenatal genetic screening has emerged as a method to identify individuals who are genetically susceptible to POAG, to facilitate early treatment and/or prevention.

The *CYP1B1* gene was correlated with PCG in 1997 (Stoilov et al., 1997). *CYP1B1* codes for an oxidation protein that affects the structure and function of the eyes, using a compound that participates in ocular development (Choudhary et al., 2008, 2009). Recent studies have reported conflicting results regarding the relationship between the occurrence of POAG and mutations in the *CYP1B1* gene. Several studies have reported that POAG patients express only mutated *CYP1B1* (Melki et al., 2004; Lopez-Garrido et al., 2006; Chakrabarti et al., 2007; Kumar et al., 2007; Suri et al., 2008; Hilal et al., 2010; Lopez-Garrido et al., 2010; Milla et al., 2013; Zhou et al., 2013). Some studies have also observed an association between single nucleotide polymorphisms (SNPs) in the *CYP1B1* gene and POAG incidence (Melki et al., 2005; Acharya et al., 2006; Bhattacharjee et al., 2008; Burdon et al., 2010; Fan et al., 2010; Patel et al., 2012; Buentello-Volante et al., 2013; Gong et al., 2015; Micheal et al., 2015; Williams et al., 2015). On the other hand, a meta-

analysis conducted by Dong et al. (2012) showed the absence of any correlation between POAG and polymorphisms at the SNP sites rs1056836, rs10012, rs1056837, rs1056827, rs2567206, and rs180040. However, this meta-analysis did not analyze the association between SNPs and POAG, based on the allele frequency, dominant model, recessive model, and co-dominant model.

Thus, the possible correlation between POAG incidence and mutations in the *CYP1B1* gene remains to be substantiated. Therefore, this systematic review and meta-analysis was conducted to determine the possible association between particular SNPs in the *CYP1N1* gene and POAG.

MATERIAL AND METHODS

Literature search

The scientific literature published in the PubMed, Cochrane library, EMBase, and Web of Science databases was electronically searched to identify studies analyzing the association between *CYP1B1* and POAG. The following word combinations were utilized for this search: "*CYP1B1*" with "primary open-angle glaucoma" or "primary open angle glaucoma", and "POAG" with "polymorphism", "variant", "SNP", or "SNPs". Only studies conducted on human samples were selected; a language or age restriction was not applied. Additional studies were manually identified from the references provided in the selected articles, and from review articles focusing on this topic.

Criteria for inclusion and exclusion

The target trials were limited to case control or cohort studies analyzing the connection between the incidence of POAG (in POAG patients) and mutations in the *CYP1B1* gene. Mutations in the *CYP1B1* gene were tested by DNA sequencing or the enzymatic method; the POAG patients were selected based on the diagnostic code or the medical records. The final decision regarding inclusion or exclusion of the identified studies was taken by an ophthalmology and an epidemiology expert; in case of a differing opinion between these experts, the study was included or excluded based on the discretion of the author.

Data extraction and assessment of study quality

The following data was extracted from the included publications: author, date of publication, ethnicity, age, genotyping method, and POAG outcomes. The risk assessment conducted in all studies was strictly separated based on the 9-star Newcastle-Ottawa Scale (NOS) (Choudhary et al., 2008). The 9-stars NOS was used to evaluate the selection, comparability, and exposure of a case-control study, and the outcome of a cohort study. Studies with more than 6 stars were considered to be of high quality.

Determination of combined effect size, and heterogeneity and publication bias testing

The conformance of the control groups to the Hardy-Weinberg equilibrium (HWE) was analyzed by the χ^2 test; those studies with controls that were not in HWE were excluded from the analysis. Heterogeneity among the studies was determined using the I^2 index. I^2 values ≤25, ≥25, ≤50, and >50% indicated low, moderate, and high heterogeneity between studies, respectively.

Moreover, the random effects model was also used to combine effect size in case of high heterogeneity. The odds ratio (OR) and 95% confidence interval (95%CI) values were used to assess the association between POAG and *CYP1B1* mutations in the allele, dominant, recessive, homozygous, and heterozygous models. The P values presented in this study were estimated by bidirectional estimation, and 0.05 was set as the statistically significant cutoff. Publication bias was tested by Harbord Weight liner regression. P values < 0.05 indicated a publication bias.

RESULTS

Data search strategy and results

We identified 87 relevant studies after an extensive literature search spanning several databases. Fifty-three studies remained after the removal of duplicated studies. A schematic illustration of the literature search strategy has been provided in Figure 1. Papers describing case reports, reviews, and basic experiments, as well as those POAG studies that did not focus on *CYP1B1* mutations were excluded after a careful reading of the summary or abstract; this resulted in 15 relevant publications. These were read in detail, and the studies with incomplete data were removed; this subsequently resulted in 8 relevant studies, which were included in this meta-analysis (Table 1).

Characteristics of the included studies

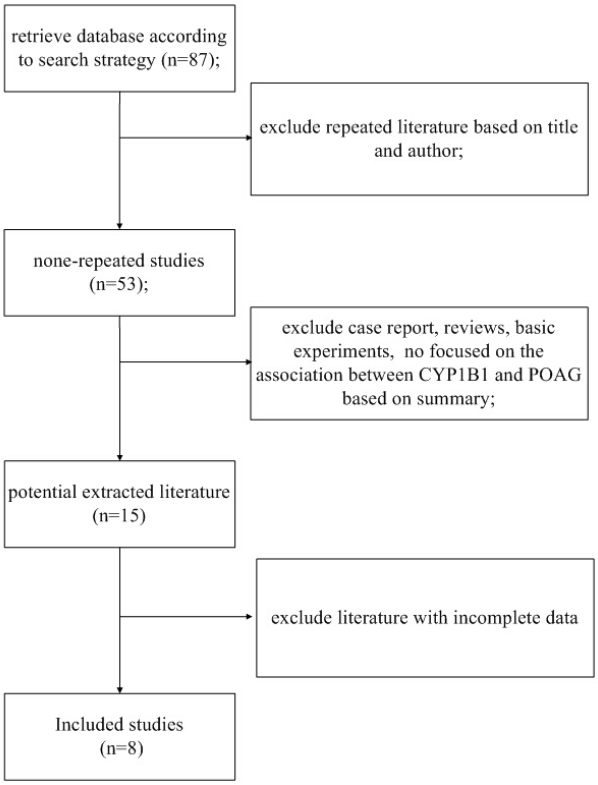

Figure 1. Search plot. A brief description of the literature search strategy employed in this study.

Table 1. Characteristics of included studies.

Study	Country	Ethnicity	rs180040 Genotypes (case/control) + HWE						rs1056837 Genotypes (case/control) + HWE				
			GG	AG	AA	G	A	P_{HWE}	TT	CT	CC	T	C	P_{HWE}
Beatriz et al. (2013)	Mexico	Caucasian	2/1	11/10	105/89	15/12	221/188	0.26	9/1	26/10	83/89	44/12	192/188	0.26
Fan et al. (2010)	China	Asian	0/0	2/0	395/201	2/0	792/402	1.00						
Micheal et al. (2015)	Pakistan	Asian	10/13	106/49	74/78	126/75	254/205	0.20	5/5	53/35	132/100	63/45	317/235	0.39
Gong et al. (2014)	China	Asian				8/19	824/1295					483/777	349/537	
Bhattacharjee et al. (2008)	India	Indian				67/20	461/170							
Burdon et al. (2010)	Australia	Caucasian	34/28	245/262	566/600	313/292	1377/1462	0.93						
Melki et al. (2005)	France	Caucasian				98/22	350/72					194/38	254/56	
Acharya et al. (2006)	India	Indian				33/14	167/86							

Continued on next page

Table 1. Continued.

Study	rs1056836 Genotypes (case/control) + HWE						rs10012 Genotypes (case/control) + HWE						rs1056827 Genotypes (case/control) + HWE						NOS
	GG	CG	CC	G	C	P_{HWE}	GG	CG	CC	G	C	P_{HWE}	TT	GT	GG	T	G	P_{HWE}	
Beatriz et al. (2013)	6/2	10/10	102/88	22/14	214/186	0.02	14/10	37/38	67/52	65/58	171/142	0.44	14/10	42/37	62/53	70/57	166/143	0.24	7
Fan et al. (2010)	3/1	61/135	333/65	67/137	727/265	0.00	17/9	130/72	250/120	164/90	630/312	0.66							6
Micheal et al. (2015)	9/6	44/33	137/101	62/45	318/235	0.14	32/16	104/49	54/75	168/81	212/199	0.08	32/16	104/49	54/75	168/81	212/199	0.08	8
Gong et al. (2014)			516/821	316/493					168/243	664/1071					159/232	673/1082			6
Bhattacharjee et al. (2008)			258/26	270/164					170/68	358/122									7
Burdon et al. (2010)	168/188	403/412	243/267	739/788	889/946	0.22													6
Melki et al. (2005)			202/39	246/55					112/21	336/73					122/21	326/73			7
Acharya et al. (2006)			98/41	102/59					87/39	113/61					87/39	113/61			8

HWE = Hardy-Weinberg equilibrium; NOS = Newcastle-Ottawa scale.

The included studies were published between 2005 and 2015. Five SNPs occurring in the *CYP1B1* gene (rs180040, rs1056837, rs1056836, rs10012, and rs1056827) were identified from these studies (Table 1). All of these SNPs, excluding rs1056836, complied with the HWE. Therefore, two studies analyzing the rs1056836 SNP were excluded from further analyses. The HWE score of the remaining studies was >6, indicating a high quality of research.

Pooled data, heterogeneity, and publication bias

Compared to the mutant allele, the wild-type allele of rs180040 showed a 12% decrease in the Odd's ratio (OR = 0.88, 95%CI = 0.76-1.00); this allele also showed no heterogeneity (I^2 = 0.00%) and publication bias (t = -1.35, P = 0.24; Table 1). The wild-type allele of rs180040 also showed a 15% decrease in the Odd's ratio of POAG incidence (OR = 0.85, 95%CI = 0.73-0.99) when the samples complied with the HWE. Evaluation using the dominant, recessive, homozygous, and heterozygous models indicated that the SNPs at the rs18004 site were not related to POAG.

Compared to the mutant allele, the wild-type allele of rs1056827 showed a 23% decrease in the OR of POAG incidence (OR = 0.77, 95%CI = 0.60-0.99). However, the samples complying with the HWE, and the subgroup of samples with unknown HWE, showed no association between the allele and POAG (OR = 0.69 and 0.88, 95%CI = 0.38-1.25 and 0.73-1.06, respectively). We observed a high heterogeneity among the participants (I^2 = 0.00%). Therefore, the random model was used. The meta-analysis of the SNP rs1056827 showed no publication bias. The SNP rs1056827 was not correlated with POAG when evaluated by any of the other models.

None of the SNPs excluding rs18004 and rs1056827 were associated with the incidence of POAG (rs1056836, rs10012, and rs1056837) (Table 2). The meta-analysis of rs10012 showed a significant publication bias (t = 49.05, P = 0.01).

DISCUSSION

Eight studies investigating the connection between *CYP1B1* and POAG were included in this meta-analysis. An evaluation of the NOS scale revealed that all studies were of high quality.

Tang et al. (1996) reported that the *CYP1B1* gene contained 3 exons and a putative ORF, lasting 1629 bp, starting from the second exon (Tang et al., 1996). This gene encodes a member of the cytochrome P450 super-family, which comprises monooxygenases that catalyze reactions related to the metabolism of the steroids, retinol, arachidonate, and melatonin (Vasiliou and Gonzalez, 2008). The protein product of *CYP1B1* is localized to the endoplasmic reticulum and metabolizes pro-carcinogens, such as polycyclic aromatic hydrocarbons and 17β-estradiol (Chang et al., 2014). A previous study has demonstrated an association between *CYP1B1* and renal carcinogenesis (Chang et al., 2014). Other studies have also reported a correlation between the *CYP1B1* gene and primary congenital glaucoma (Vasiliou and Gonzalez, 2008; Chang et al., 2014).

The results of this meta-analysis reveal that three SNPs of the *CYP1B1* gene, rs1056836, rs10012, and rs1056837, are not associated with an increased risk of POAG incidence. This observation partly supported the results obtained by Dong et al. (2012). However, the major limitation of this previous study was that the connection between POAG and *CYP1B1* mutation was not separately analyzed based on the allele, dominant, recessive, homozygous, and heterozygous models.

The results of this meta-analysis revealed a correlation between the mutant allele of

Table 2. Pooled effect size of five models.

	W allele vs M (Allele model)				WM+MM allele vs WW (Dominant model)				MM vs WW + WM (Recessive model)				MM vs WW (Homozygous model)				MM *vs* WM Publication bias (Heterozygous model)				t	P
	OR	95%CI	I^2 %	P_z#	OR	95%CI	I^2 %	P_z#	OR	95%CI	I^2 %	P_z#	OR	95%CI	I^2 %	P_z#	OR	95%CI	I^2 %	P_z#		
rs180040 c.1358A< G	0.88	0.76 1.00	0.00	0.05	1.28	0.78 2.08	72.00	0.32	0.97	0.51 1.86	34.90	0.93	1.16	0.75 1.80	0.00	0.502	0.82	0.29 2.34	68.00	0.71	-1.35	0.24
HWE	0.85	0.73 0.99	0.00	0.04																		
HWE unknown	0.98	0.72 1.32	0.00	0.88																		
rs10012 c.142C< G	0.90	0.68 1.19	69.20	0.45	1.28	0.58 2.83	89.70	0.55	1.28	0.83 1.99	0.00	0.27	1.45	0.70 3.00	59.20	0.31	1.08	0.68 1.72	0.00	0.74	49.05	0.01
HWE	0.85	0.51 1.41	85.10	0.52																		
HWE unknown	1.00	0.78 1.29	0.00	0.99																		
rs1056836 c.1294G < C	1.42	0.95 2.12	91.70	0.09	1.06	0.84 1.33	0.00	0.64	0.96	0.80 1.17	0.00	0.70	1.01	0.78 1.32	0.00	0.94	0.94	0.77	0.00	0.57	2.28	0.26
HWE	1.00	0.88 1.34	94.60	0.10																		
HWE unknown	1.74	0.79 3.83	0.00	0.17																		
rs1056827 c.355G < T	0.77	0.60 0.99	54.80	0.04	1.74	0.62 4.85	88.30	0.29	1.43	0.86 2.40	0.00	0.17	1.91	0.84 4.34	53.20	0.12	1.04	0.60 1.81	0.00	0.89	3.26	0.19
HWE	0.69	0.38 1.25	80.40	0.22																		
HWE unknown	0.88	0.73 1.06	0.00	0.17																		
rs1056837 c.1347T < C	1.30	0.85 1.99	78.80	0.23	0.47	0.04 5.37	75.30	0.54	0.54	0.18 1.63	84.30	0.27	0.42	0.03 5.50	77.60	0.51	0.59	0.25 1.40	71.30	0.23	3.12	0.20
HWE	1.88	0.55 6.35	89.50	0.31																		
HWE unknown	0.98	0.83 1.15	0.00	0.78																		

W = wild-type allele; M = mutant allele; WW = wild homozygote; WM = heterozygote; MM = mutant homozygote; SNP = single nucleotide polymorphism; P_z# = P value of the Z test; OR = odd's ratio; CI = confidence interval; HWE = Hardy-Weinberg equilibrium.

rs180040 and POAG. This SNP in exon 3 (located at position 1358) of the *CYP1B1* gene resulted in a mutation from A to G. This SNP was first reported in 2002, and was correlated with POAG in French patients; the proposed mechanism with which this SNP (rs180040) affected the incidence of POAG was by decreasing the cupping of the optic disk and by causing mild alterations in the visual field (Stoilov et al., 2002; Melki et al., 2005). Bandiera et al. (2005) also reported that the substitution of asparagine to serine at aa 453 in the CYP1B1 protein caused a 3-fold decrease in its half-life and a 2-fold decrease in its cellular expression, resulting in a higher incidence of proteasomal degradation of the protein (Bandiera et al., 2005).

The mutant allele of SNP rs1056827 was correlated with POAG; however, this association was controversial. We found no associations between the rs1056827 SNP and POAG in the sample populations that conformed to, as well as did not conform to, the HWE. Nevertheless, this correlation was observed in all participants. The factors that contributed to the conflicting results obtained in this meta-analysis remain to be determined. Multiplex genetic structures in populations from different regions might be responsible for these disparate results.

The level of this evidence is low because of some limitations. Firstly, we did not consider the effect of the environment and genetic interactions. The possible correlation between mutations in *CYP1B1* and incidence of POAG in subjects from different regions remains unknown, because of the low number of subjects included in each subgroup. Moreover, the high heterogeneity of these studies could not be avoided, as the baseline information (for age, etc.), which could contribute to the heterogeneity, was not provided in these studies.

In conclusion, among the five *CYP1B1* SNPs included in this analysis, rs180040 was found to be correlated with POAG; in addition, the SNP rs1056827 appeared to be controversially correlated with the incidence of POAG. Further well-designed and large sample studies concentrating on the effect of environment and gene interaction on this correlation must be performed in the future to test and verify this conclusion.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Research supported by grants provided by the National Natural and Science Foundation of China (Grant #30900608 and #81170087), the Provincial Natural and Science Foundation, Shandong, China (Grant #ZR2010HQ048), the Shandong Provincial Medicine and Health Science Technology Development Plan Program of China (Grant #2011BJZD05), and the Jinan Science & Technology International Cooperation Project (Grant #201401356).

REFERENCES

Acharya M, Mookherjee S, Bhattacharjee A, Bandyopadhyay AK, et al. (2006). Primary role of CYP1B1 in Indian juvenile-onset POAG patients. *Mol. Vis.* 12: 399-404.

Bandiera S, Weidlich S, Harth V, Broede P, et al. (2005). Proteasomal degradation of human CYP1B1: effect of the Asn453Ser polymorphism on the post-translational regulation of CYP1B1 expression. *Mol. Pharmacol.* 67: 435-443.

Bhattacharjee A, Banerjee D, Mookherjee S, Acharya M, et al. (2008). Leu432Val polymorphism in CYP1B1 as a susceptible factor towards predisposition to primary open-angle glaucoma. *Mol. Vis.* 14: 841-850.

Buentello-Volante B, Elizondo-Olascoaga C, Miranda-Duarte A, Guadarrama-Vallejo D, et al. (2013). Association study of

multiple gene polymorphisms with the risk of adult-onset primary open-angle glaucoma in a Mexican population. *Exp. Eye Res.* 107: 59-64.

Burdon KP, Hewitt AW, Mackey DA, Mitchell P, et al. (2010). Tag SNPs detect association of the CYP1B1 gene with primary open angle glaucoma. *Mol. Vis.* 16: 2286-2293.

Chakrabarti S, Devi KR, Komatireddy S, Kaur K, et al. (2007). Glaucoma-associated CYP1B1 mutations share similar haplotype backgrounds in POAG and PACG phenotypes. *Invest. Ophthalmol. Vis. Sci.* 48: 5439-5444.

Chang I, Fukuhara S, Wong DK, Gill A, et al. (2014). Cytochrome P450 1B1 polymorphisms and risk of renal cell carcinoma in men. *Tumour. Biol.* 35: 10223-10230.

Choudhary D, Jansson I, Sarfarazi M and Schenkman JB (2008). Characterization of the biochemical and structural phenotypes of four CYP1B1 mutations observed in individuals with primary congenital glaucoma. *Pharmacogenet. Genomics* 18: 665-676.

Choudhary D, Jansson I and Schenkman JB (2009). CYP1B1, a developmental gene with a potential role in glaucoma therapy. *Xenobiotica* 39: 606-615.

Dirani M, Crowston JG, Taylor PS, Moore PT, et al. (2011). Economic impact of primary open-angle glaucoma in Australia. *Clin. Experiment. Ophthalmol.* 39: 623-632.

Dong S, Yang J, Yu W, Kota P, et al. (2012). No association of genetic polymorphisms in CYP1B1 with primary open-angle glaucoma: a meta- and gene-based analysis. *Mol. Vis.* 18: 786-796.

Ermis SS, Ozturk F and Inan UU (2002). The short-term IOP-lowering effect of brimonidine 0.2% and dorzolomide 2% combination in primary open-angle glaucoma. *Acta Ophthalmol. Scand.* 80: 632-634.

Fan BJ, Liu K, Wang DY, Tham CC, et al. (2010). Association of polymorphisms of tumor necrosis factor and tumor protein p53 with primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.* 51: 4110-4116.

Gong B, Qu C, Li X, Shi Y, et al. (2015). Mutation spectrum of CYP1B1 in Chinese patients with primary open-angle glaucoma. *Br. J. Ophthalmol.* 99: 425-430.

Gordon MO, Beiser JA, Brandt JD, Heuer DK, et al. (2002). The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch. Ophthalmol.* 120: 714-720; 829-730.

Heijl A, Leske MC, Bengtsson B, Hyman L, et al. (2002). Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch. Ophthalmol.* 120: 1268-1279.

Hilal L, Boutayeb S, Serrou A, Refass-Buret L, et al. (2010). Screening of CYP1B1 and MYOC in Moroccan families with primary congenital glaucoma: three novel mutations in CYP1B1. *Mol. Vis.* 16: 1215-1226.

Hung KH, Cheng CY and Liu CJ (2015). Risk factors for predicting visual field progression in Chinese patients with primary open-angle glaucoma: A retrospective study. *J. Chin. Med. Assoc.* 78: 418-423.

Iancu R and Corbu C (2014). Intraocular pressure after phacoemulsification in patients with uncontrolled primary open angle glaucoma. *J. Med. Life* 7: 11-16.

Kothari R, Bokariya P, Singh R, Singh S, et al. (2014). Correlation of pattern reversal visual evoked potential parameters with the pattern standard deviation in primary open angle glaucoma. *Int. J. Ophthalmol.* 7: 326-329.

Kumar A, Basavaraj MG, Gupta SK, Qamar I, et al. (2007). Role of CYP1B1, MYOC, OPTN, and OPTC genes in adult-onset primary open-angle glaucoma: predominance of CYP1B1 mutations in Indian patients. *Mol. Vis.* 13: 667-676.

Lopez-Garrido MP, Sanchez-Sanchez F, Lopez-Martinez F, Aroca-Aguilar JD, et al. (2006). Heterozygous CYP1B1 gene mutations in Spanish patients with primary open-angle glaucoma. *Mol. Vis.* 12: 748-755.

Lopez-Garrido MP, Blanco-Marchite C, Sanchez-Sanchez F, Lopez-Sanchez E, et al. (2010). Functional analysis of CYP1B1 mutations and association of heterozygous hypomorphic alleles with primary open-angle glaucoma. *Clin. Genet.* 77: 70-78.

Melki R, Colomb E, Lefort N, Brezin AP, et al. (2004). CYP1B1 mutations in French patients with early-onset primary open-angle glaucoma. *J. Med. Genet.* 41: 647-651.

Melki R, Lefort N, Brezin AP and Garchon HJ (2005). Association of a common coding polymorphism (N453S) of the cytochrome P450 1B1 (CYP1B1) gene with optic disc cupping and visual field alteration in French patients with primary open-angle glaucoma. *Mol. Vis.* 11: 1012-1017.

Micheal S, Ayub H, Zafar SN, Bakker B, et al. (2015). Identification of novel CYP1B1 gene mutations in patients with primary congenital and primary open-angle glaucoma. *Clin. Experiment. Ophthalmol.* 43: 31-39.

Milla E, Mane B, Duch S, Hernan I, et al. (2013). Survey of familial glaucoma shows a high incidence of cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1) mutations in non-consanguineous congenital forms in a Spanish population. *Mol. Vis.* 19: 1707-1722.

Patel HY, Richards AJ, De Karolyi B, Best SJ, et al. (2012). Screening glaucoma genes in adult glaucoma suggests a multiallelic contribution of CYP1B1 to open-angle glaucoma phenotypes. *Clin. Experiment. Ophthalmol.* 40: e208-217.

Quigley HA and Broman AT (2006). The number of people with glaucoma worldwide in 2010 and 2020. *Br. J. Ophthalmol.* 90: 262-267.

Stoilov I, Akarsu AN and Sarfarazi M (1997). Identification of three different truncating mutations in cytochrome P4501B1

(CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. *Hum. Mol. Genet* 6: 641-647.

Stoilov IR, Costa VP, Vasconcellos JP, Melo MB, et al. (2002). Molecular genetics of primary congenital glaucoma in Brazil. *Invest. Ophthalmol. Vis. Sci.* 43: 1820-1827.

Suri F, Kalhor R, Zargar SJ, Nilforooshan N, et al. (2008). Screening of common CYP1B1 mutations in Iranian POAG patients using a microarray-based PrASE protocol. *Mol. Vis.* 14: 2349-2356.

Tang YM, Wo YY, Stewart J, Hawkins AL, et al. (1996). Isolation and characterization of the human cytochrome P450 CYP1B1 gene. *J. Biol*. *Chem.* 271: 28324-28330.

Ting NS, Li Yim JF and Ng JY (2014). Different strategies and cost-effectiveness in the treatment of primary open angle glaucoma. *Clinicoecon. Outcomes Res.* 6: 523-530.

Vasiliou V and Gonzalez FJ (2008). Role of CYP1B1 in glaucoma. *Annu. Rev. Pharmacol. Toxicol.* 48: 333-358.

Weinreb RN, Aung T and Medeiros FA (2014). The pathophysiology and treatment of glaucoma: a review. *JAMA* 311: 1901-1911.

Williams SE, Carmichael TR, Allingham RR, Hauser M, et al. (2015). The genetics of POAG in black South Africans: a candidate gene association study. *Sci. Rep.* 5: 8378.

Zhou M, Wang W, Huang W and Zhang X (2014). Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *PLoS One* 9: e102972.

Zhou XM, Yin Y, Fan N, Cheng HB, et al. (2013). Single nucleotide polymorphism of MYOC affected the severity of primary open angle glaucoma. *Int. J. Ophthalmol.* 6: 264-268.