Analysis of *CYP1B1* Gene Mutations in Patients with Primary Congenital Glaucoma

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Abstract

Primary congenital glaucoma (PCG) is the most common type of infantile glaucoma, yet it remains a relatively rare disease, because the disease is often transmitted in an autosomal recessive pattern. However, PCG occurs up to 10 times more frequently in certain ethnic and geographical groups where consanguineous relationships are common. The aim of this study was to investigate the distribution of mutations in the cytochrome P450 1B1 gene (*CYP1B1*) in patients with PCG among different populations around the world from 2011 until May 2016. We referred to the electronic databases, such as Medline, Clinicalkey, Scopus, and ScienceDirect, to search for articles that were published in this area. Nineteen records were included in this qualitative synthesis. *CYP1B1* mutations were assessed in 1,220 patients with PCG and identified in 41.6% of them. According to these studies, 99 mutations including 60 novel mutations were found. Nonsignificant difference in the sex ratio has been reported. This current review shows that consanguinity plays an important role in the PCG pathogenesis and transmission; however, sporadic mutations have been found in some cases. A difference in penetrance was highlighted by some mutations. The *CYP1B1* mutations were mostly found in the Middle East and the Maghreb with a rate of 64.8 and 54.4%, respectively, followed by Europe (34.7%), Asia (21.3%), and finally the United States (14.9%). Founder mutations in different geographical areas have been discovered. For instance, the p.Gly61Glu, p.Arg390His, p.Gly61Glu, c.4,339delG, p.E387Lys, and p.Val320Leu were considered founder mutations for Iran/Saudi Arabia, Pakistan, Lebanon, Morocco, Europe, and Vietnam/South Korea, respectively. Many common mutations in different countries were found, such as in Morocco, where its mutations were similar to seven other countries. These findings suggest that the ethnic differences and the geographical distribution of PCG give us a large *CYP1B1* mutation pattern. Genetic tests looking for founder and common mutations should be the first step in genetic screening for patients with PCG.

Keywords
- primary congenital glaucoma
- *CYP1B1*
- cytochrome P450
- GLC3A

Introduction

Primary congenital glaucoma (PCG) is a rare form of glaucoma and is usually transmitted as an autosomal recessive disease with an incomplete penetrance.[1] PCG is characterized by elevated intraocular pressure (IOP), buphthalmos, edema, and opacification of the cornea with rupture of Descemet's membrane, thinning of the anterior sclera and

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iris atrophy, anomalously deep anterior chamber, and structurally normal posterior segment except for progressive glaucomatous optic atrophy. Symptoms include photophobia, blepharospasm, and hyperlacrimation. Typically, the diagnosis is made in the first year of life. In untreated cases, blindness invariably occurs. The diagnosis of PCG is based on clinical findings, but the genetic tests may confirm the diagnosis. Some attempts in understanding the molecular basis through genome-wide association studies and whole genome resequencing approaches are under way and may provide valuable insight regarding the underlying mechanisms.

Different PCG loci have been mapped, in contrast, cytochrome P450, family 1, subfamily B, polypeptide 1 (*CYP1B1*) remains the only gene identified to date. More than 150 mutations including missense, nonsense, regulatory, and insertions and/or deletions in *CYP1B1* have been associated to PCG,[2] and are the main known cause of PCG. The *CYP1B1* gene contains three exons, and the coding region starts within the second exon. The 543-amino acids long CYP1B1 protein belongs to the cytochrome P450 family, a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in a nicotinamide adenine dinucleotide phosphate (NADP)-oxidase–dependent electron transport pathway. The enzyme oxidizes various structurally unrelated compounds, including steroids, fatty acids, and xenobiotics. *CYP1B1* participates in the metabolism of an unknown biologically active molecule that contributes to eye development.[3]

Although the exact function of CYP1B1 protein in the eye is still unclear, but as it is a mono-oxygenase, some scenarios may be expected for its role in the development of the eye. Mutations in *CYP1B1* might result in the absence of its responsible morphogen for the trabecular meshwork (TM) development and the outflow system, which in turn alters the expression of genes.[4] They may also result in the accumulation of some active morphogen that should be eliminated, producing toxic effects, which in turn may lead to developmental arrest.[4] In addition, abnormalities in the TM structure could result in the disease phenotype, based on a study, that has compared trabeculectomy specimens of congenital glaucoma patients with normal human eyes at a histologic and ultrastructural level.[5]

A *CYP1B1* mutation is the predominant cause of inherited PCG. To date, several mutations have been identified in patients and families with PCG from numerous countries and ethnic groups.

In this current review, we describe 99 distinct *CYP1B1* mutations that we have retrieved from various studies. In addition, we analyze the spectrum of *CYP1B1* mutations in different populations.

The benefit of this qualitative synthesis is to highlight the involvement and the impact of *CYP1B1* mutations in different ethnical and geographical areas in the world. These informations can identify populations at a particular risk, provide a more reliable genetic test/counseling, and also guide the clinician in managing the harm of PCG by suggesting predictive testing and better prognosis.

Methods

Search Strategy

An extensive search was conducted in MEDLINE (2011 to May 2016), ScienceDirect (2011 to May 2016), Scopus (2011 to May 2016), and Clinicalkey (2012 to May 2016) for articles that have been published until May 2016, by using a combination of keywords (*CYP1B1*, cytochrome P450, GLC3A, PCG). Based on the first screening of the titles and abstracts, the studies were selected. A full screen was conducted to exclude studies that did not meet inclusion criteria.

Inclusion Criteria

This review includes all studies that met the following inclusion criteria:

1. Selecting only PCG patients with *CYP1B1* mutations either in comparative studies with other types of glaucoma or gene
2. Performing a mutational analysis of *CYP1B1* gene
3. Reporting the exact DNA sequence alteration
4. Disqualifying patients known to carry a systemic syndrome or other ocular pathology associated with glaucoma
5. Retaining a mutation only once if several members of the same family had the same mutation

Results

Total 68 records were identified, from which 2 duplicate records were removed. Titles and abstracts of 66 records were screened and 49 records were excluded because they did not meet the defined inclusion criteria. The full texts of the remaining 19 reports were examined.

Based on these reviewed studies, *CYP1B1* mutations have been searched in 1,220 PCG patients and identified in 508 patients with a rate of 41.6%. ►**Table 1** shows the number of PCG patients and *CYP1B1* mutation carriers.

CYP1B1 Mutations in Different Populations

The percentage of *CYP1B1* mutations varies among different ethnic groups and geographical areas, where the Middle East is predominant with a percentage of 64.8%, followed by the Maghreb (54.4%), Europe (34.7%), Asia (21.3%, except India), and then the United States with 14.9%.

According to the provided data, the sex ratio of patients with PCG and those with *CYP1B1* mutations was almost similar (1.11 and 1.09, respectively).

Discovered Mutations

By removing the repeated mutations, 99 mutations were found in 508 patients, with 39 already identified in the study of Li et al (2011).[6]

In this current review, 60 novel unlisted mutations have been reported from 2011 until May 2016 (►**Table 2**).

Founder Mutations

After analyzing the different included studies, some mutations were more frequent and widespread than others. These mutations can be considered as founder mutations to each

Table 1 Number of PCG patients and *CYP1B1* mutations carriers

Studies	Ethnicity	Total no. of PCG patients	M	F	No. of patients with CYP1B1 mutations	M	F
Do et al, (2016)[35]	Vietnamese	30	17	13	5	2	3
Al-Haddad et al, (2016)[9]	Lebanese	18	9	9	6	3	3
Abu-Amero et al, (2016)[8]	Saudi	1	0	1	0	0	1
Yazdani et al, (2016)[36]	Iranian	17	6	1	10	4	6
Morales-Fernandez et al, (2015)[37]	Spanish	3	2	1	3	2	1
Chen et al, (2015)[32]	Chinese	2	2	0	3	3	0
Cardoso et al, (2015)[38]	Portuguese	21	14	7	6	NM	NM
Berraho et al, (2015)[39]	Moroccan	94	53	41	51	27	24
de Melo et al, (2015)[40]	Indian/Brazilian	India: 301 Brazil: 150	NM	NM	India: 132 Brazil: 66	NM	NM
Vogt et al, (August 2014)[41]	Roma (Hungary)	1	1	0	1	1	0
Bouyacoub et al, (2014)[16]	Tunisian	18	5	13	10	5	5
Chen et al, (2014)[42]	Chinese	122	NM	NM	21	NM	NM
Sheikh et al, (2014)[43]	Pakistani	36	21	15	36	21	15
Badeeb M et al, (2014)[7]	Saudi	34 Saudi: 23 Non-Saudi: 11 (Yemen: 4 Sudan: 3 Afghanistan: 2 Burma: 1 Syria: 1)	21 14 7	13 9 4	27 Saudi: 21 Non-Saudi: 6	NM	NM
López-Garrido et al, (2013)[10]	European	161	88	73	56	NM	NM
Lim et al, (2013)[34]	United States	47	26	21	12	6	6
Khan et al, (2012)[44]	Saudi	5	3	2	0	0	0
Suh and Kee, (2012)[45]	Korean	85	46	49	22	10	12
Abu-Amero et al, (2011)[46]	Saudi	74	38	36	41	21	20

Abbreviations: F, female; M, male; NM, not mentioned.

geographic area. ►**Table 3** lists some examples of these founder mutations.

Middle East

In the Iranian population, the most common mutation was p.Gly61Glu. It was found in two homozygous patients and in one heterozygous patient, followed by p.Arg390His identified in two homozygous patients.

In Saudi Arabia, the p.Gly61Glu mutation is considered as the major mutation, found 17 times in the homozygous state and once in the heterozygous state.[7] Findings from Saudi Arabia suggest that novel PCG genes are more likely to arise in their population. However, in other case reports, not any *CYP1B1* mutations were found, where the glaucoma was probably related to novel CNVs (copy number variations).[8] Another example of Saudi Arabian children, affected by unilateral PCG, where no *CYP1B1* mutation was detected, suggests that the pathogenesis of unilateral glaucoma differs from the bilateral form.

In Pakistan, the p.Arg390His mutation was the most common, identified in five families (50%, 5/10), whereas the c.868_869insC, p.Glu229Lys, and Ala115Pro have each been found only once in three families.

In Lebanon, the most common mutation was p.Gly61Glu. *CYP1B1* mutations in Lebanese patients are rarer compared with the Middle East and other Arab populations. This is probably because the Lebanese originated from a mix of European and Asian populations, providing a wider genetic heterogeneity in Lebanese families, whereas homozygosity is more common in the Arab population.[9]

Maghreb

In Morocco, among the mutation carriers, 62.7% (32/51) had frameshift truncating mutations (g.4339delG, g.4330–4331delTG, and g.79016–7913del13bp) in both alleles, and 37.3% (19/51) had at least one missense mutation (nine patients were homozygous for p.Arg390Ser, p.Arg469Trp, p.Cys470Tyr, or p.Gly61Glu; eight patients were compound heterozygous, including (5) p.Glu173Lys, (2) p.Gly61Glu, (1) p.V364M ,and two heterozygous for p.Arg163Cys and p.Arg368His, respectively).

In Tunisia, the *CYP1B1* mutations were present in 55% of the patient's alleles. Two mutations p.Gly61Glu and

Table 2 List of new unlisted *CYP1B1* mutations

Population	Location	genomic DNA	Amino acid change scheduled change	Type of mutation	N	Homozygote	Heterozygote
Vietnamese	Exon 2	c.836A > T	p.His279Leu	NM	1	+	
Vietnamese	Exon 2	c.847C > T	p.Leu283Phe	NM	1	+	
Lebanese	NM	1793delC	p.Ser464	Frameshift	1	+	
Iranian	NM	NM	p.Tyr81	NM	1	+	
Iranian	NM	NM	p.Arg390His	NM	2	+	
Iranian-Saudi	Exon 2	c.685G > A	p.Glu229Lys	Missense	1 1	+	+
Iranian	NM	NM	p.Pro289*fs*	NM	1	+	
Iranian	NM	NM	p.Gly329Val	NM	1	+	
Iranian	NM	NM	p.Arg368Cys	NM	1	+	
Spanish	NM	NM	p.Thr404*fs*X38	NM	NM	NM	
Moroccan	NM	g.4339delG	NM	Frameshift		+	
Moroccan	NM	g.4330–4331delTG	NM	Frameshift	NM	+	
Moroccan	NM	g.79016–7913del13bp	NM	Frameshift	NM	+	
Indian-Brazilian	NM	8263T > C	p.Ser476Pro	NM	1 1	NM	
Indian-Brazilian	NM	8214_8215delAG	p.Val460*fs*	NM	2 3	NM	
Indian	NM	g.3925delG	p.Arg41*fs*	NM	NM	NM	
Indian	NM	g.3972C > T	p.Ala56Val	NM	NM	NM	
Indian	NM	g.4055 G > T	p.Val84Phe	NM	NM	NM	
Indian	NM	g.4095T > C	p.Leu97Pro	NM	NM	NM	
Indian	NM	g.4197C > G	p.Ser131Arg	NM	NM	NM	
Indian	NM	g.4347T > C	p.Leu181Pro	NM	NM	NM	
Indian	NM	g.4421_4423del	p.205delS	NM	NM	NM	
Indian	NM	g.4641A > C	p.His279Pro	NM	NM	NM	
Indian	NM	g.4793G > A	p.Ala330Thr	NM	NM	NM	
Indian	NM	g.7917G > A	p.Leu360L	NM	NM	NM	
Indian	NM	g.7949G > T	p.Cys371Phe	NM	NM	NM	
Indian	NM	g.8148del5bp	p.Pro437*fs*	NM	NM	NM	
Indian	NM	g.8162C > T	p.Pro442Leu	NM	NM	NM	
Indian	NM	g.8227T > C	p.Ser464Pro	NM	NM	NM	
Indian	NM	g.8393A > G	p.Asn519Ser	NM	NM	NM	
Brazilian	NM	g.4523delC	p.Leu240*fs*	NM	NM	NM	
Portuguese-United States	Exon 2	c.317C > A	p.Ala106Asp	Missense	NM		+ ch
Portuguese	Exon 3	c.1390dupT	p.Ser464*fs*	Frameshift	NM		+
Pakistani	NM	NM	p.Gly36Asp	Missense	4	+	
Pakistani	NM	NM	p.Gly67-Ala70del	Frameshift	2	+	
Chinese	NM	g.T3836C	p.Trp11Arg	Missense	NM		+ ch
Chinese	NM	g.4022delTC	p.73, stop at p.221	Frameshift	NM		ch
Chinese	NM	g.G4151T	p.Asp116Tyr	Missense	NM		+ ch
Chinese	NM	g.T4338A	p.Val178Glu	Missense	NM		+ ch
Chinese	NM	g.G4493A	p.Glu230Lys	Missense	NM		+ ch
Chinese	NM	g.T4509C	p.Val235Ala	Missense	NM	+	
Chinese	NM	g.T8137C	p.Trp434Arg	Missense	NM	+	
Chinese	NM	g.C8167T	p.Arg444	Nonsense	NM		+ ch

Table 2 (*Continued*)

Population	Location	genomic DNA	Amino acid change scheduled change	Type of mutation	N	Homozygote	Heterozygote
Chinese	NM	g.G4322A	p.Glu173Lys	Missense	NM		+ ch
Tunisian	NM	691T > A	p.Phe231Ile	NM	1	+	
Tunisian	NM	c.1309C > G	p.Pro437Ala	NM	1	+	
European	Exon 1	c.337G > T	NM	NM	NM	NM	
European	Exon 2	NM	p.Phe123Leu	NM	NM		+
European	Exon 2	I399_P400del	NM	NM	NM		ch
European	NM	NM	p.Ala237Glu	NM	NM	NM	
United States	NM	c.1063C > T	p.Arg355*	Nonsense	NM	1+	
United States	NM	c.171G > A	p.Trp57*	Nonsense	NM		+
United States	NM	c.1209_1210insTCATGCCACC	10-bp insertion	Frameshift	NM	NM	
United States	NM	c.1064_1076delGAGTGCAGGCAGA	13-bp deletion	Frameshift frame	NM	NM	
Korean	NM	c.970_971dupAT	p.Thr325Ser*fs*X104	NM	NM	+	
Korean	NM	c.985G > A	p.Gly329Ser	NM	NM	+	
Korean	NM	c. 1256_1257delTG	p.Val419Gly*fs*X11	NM	NM		ch
Saudi	NM	g.4160G > T	p.Ala119Ser	Missense	NM	NM	
Saudi	NM	g.8159A > G	p.Asp441Gly	Missense	NM	NM	
Saudi	NM	g.8233G > A	p.Gly466Ser	Missense	NM	NM	

Abbreviations: (+), present; ch, compound heterozygous; N, number; NM, not mentioned.

c.535delG were identified in a homozygous state in seven patients and two probands, respectively.

Asia

In Vietnam, only 5/30 of PCG patients have been associated with *CYP1B*1 alterations. *CYP1B1* is not considered as the major gene involved in the Vietnamese population compared with the Arab and Gypsy patients.

In a Chinese case report, the mutation c.517G > A/p.Glu173Lys was detected in a homozygous state in two affected individuals but also in a nonaffected individual, which could refer to an incomplete penetrance.

Europe

In the European study, 31 different mutations have been discovered, of which 56% were compound heterozygous and 25% homozygous.

United States

Five novel combinations of compound heterozygous mutations were identified, of which two were found with whole exome sequencing.

India and Brazil

In a comparative study between India and Brazil, the patients had a large spectrum of common mutations: p.Arg368His; p.Pro437Leu; p.Ala443Gly; p.Ser476Pro; p.Thr404*fs*X30; p.Val460*fs*.

Common Mutations among Different Populations

Almost 20 similar mutations have been discovered in different countries and continents. ►**Table 4** links each mutation to the countries where it was identified.

From these mutations (p.Gly61Glu, p.Val320Leu, p.Arg469Trp, p.Gly61Glu, p.Glu173Lys, p.Val364Met,

Table 3 Specific founder mutations from each geographic area

Geographical area	Location	Genomic DNA	Change amino acid/scheduled change
Morocco	Exon 2	g.4339delG	Frameshift
Saudi Arabia	Exon 2	c.182G > A	p.Gly61Glu
Iran	Exon 2	c.182G > A	p.Gly61Glu
Lebanon	Exon 2	3987G > A	p.Gly61Glu
Pakistan	Exon 3	8006G > A	p.Arg390His
Europe	Exon 3	7996G > A	p.Glu387Lys
Vietnam South Korea	Exon 2	958G > T	p.Val320Leu

Table 4 Common mutations in different countries

Location	Genomic DNA	Amino acid change/scheduled change	Type mutations	Country	Consanguinity
Exon 2	3987G > A	p.Gly61Glu	Missense	Lebanon Morocco Tunisia Saudi Arabia	+ + + +
Exon 2	958G > T	p.Val320Leu	Missense	Vietnam South Korea	− −
Exon 3	8242C > T	p.Arg469Trp	Missense	Lebanon Morocco Saudi Arabia	+ + +
Exon 2	182G > A	p.Gly61Glu	Missense	Iran Portugal Saudi Arabia	+ NM +
Exon 2	4322G > A	p.Glu173Lys	Missense	China Morocco	NM +
Exon 3	7927G > A	p.Val364Met	Missense	South Korea Morocco	− +
Exon 3	7940G > A	p.Arg368His	Missense	Brazil India Morocco South Korea	+ + + −
Exon 3	8147C > T	p.Pro437Leu	Missense	India Brazil Saudi Arabia	+ + +
Exon 3	8165C > G	p.Ala443Gly	Missense	India Brazil Saudi Arabia	+ + +
NM	8263 T > C	p.Ser476Pro	NM	India Brazil	+ +
NM	8037_8046dup10	p.Thr404*fs*X30	NM	India Brazil	+ +
NM	8214_8215delAG	p.Val460*fs*	NM	India Brazil	+ +
Exon 2	317C > A	p.Ala106Asp	Missense	Portugal United States	NM NM
Exon 3	1159G > A	p.Glu387Lys	Missense	Portugal United States	NM NM
Exon 3	8006G > A	p.Arg390His	Missense	Pakistan Saudi Arabia Korea	+ + −
Exon 2	4490G > A	p.Glu229Lys	Missense	Lebanon Pakistan	+ +
Exon 2	685 g > A	p.Glu229Lys	Missense	Saudi Arabia Iran	+ +
Exon 3	8168G > A	p.Arg444Gln	Missense	Korea Lebanon	− +
Exon 2	535delG	p.Ala179*fs*	Frameshift	Portugal Tunisia	NM +
Exon 3	7996G > A	p.Glu387Lys	Missense	Europe Hungary	+ NM

Abbreviations: (+), positive; (−), negative; NM, not mentioned.

p.Arg368His, p.Pro437Leu, p.Ala443Gly, p.Ala106Asp, p. Glu387Lys, p.Arg390His, p.Glu229Lys, p.Glu229Lys, p. Arg444Gln, p.Ala179*fs*, p.Glu387Lys), 47.1% locate in exon 2 and 52.9% in exon 3, respectively.

All the common mutations had almost the same mutation type in missense except for the frameshift mutation p. Ala179*fs*.

Morocco had similar mutations to other countries such as Lebanon, Tunisia, Saudi Arabia, China, South Korea, Brazil, and India.

Asian patients such as South Korean have no consanguinity status, yet they showed the same mutations as countries where the consanguinity is quite high as: 7927G > A/p. Val364Met, 7940G > A/p.Afg368His, 8006G > A/Arg390His, and 8168G > A/p.Arg444Gln.

Nevertheless, the 958G > T/p.Val320Leu remains the mutation observed only in Asia (Vietnam and South Korea).

Discussion

Advances in genetics studies of glaucoma have shown that some PCG cases are the outcome of an autosomal recessive inheritance pattern, despite the fact that it has traditionally been considered as sporadic. The PCG disease is genetically heterogeneous and may be caused by modifications in at least three different genes. To date, mutations in the *CYP1B1* gene remain the main known genetic cause of PCG.[10–12] The main characteristic feature of PCG is an abnormal iridocorneal angle. More specifically, the TM impedes the normal outflow of aqueous humor with the consequence of elevating IOP. The CYP1B1 protei belongs to the cytochrome P450 superfamily of enzymes and has been implicated in the development of ocular structures, involved in aqueous humor drainage through its action as a monooxygenase enzyme.[13] *CYP1B1* mutations in the presence of tyrosinase (TYR) deficiency develop a more severe phenotype, immediately suggesting *TYR* as a modifier gene.[14] TYR deficiency is also found in patients with anterior segment dysgenesis (ASD) and albinism.[15] Gene-gene interaction studies might lead to proper understanding of the disease pathogenesis and consequently revealing probable mechanisms for therapy required.

Extensive analysis of the *CYP1B1* gene in PCG patients in various populations around the world has revealed a great diversity, reflecting at the same time a similar mutation spectrum of the *CYP1B1* gene in the pathogenesis of the disease.

In this meta-analysis, the *CYP1B1* mutations were identified in 41.6% of the patients, which underlines its importance in PCG pathogenesis. However, other possibilities causing PCG (unknown regulatory loci, genes phenocopying PCG, mutations in modifier genes) should be suggested for the 58.2% remaining patients.

In addition, 99 mutations were found and 60 of them were novel compared with the study of Li et al.[6]

The prevalence of *CYP1B1* mutations shows a vast geographic variability where the Middle East and the Maghreb were predominant correlated to high rate of consanguinity, followed by Europe, Asia, and United States.

This review also revealed a nonsignificant difference in the sex ratio between different ethnic groups and *CYP1B1* mutation carriers.

In the Middle-East

According to Li et al,[6] the 3987G > A (p.Gly61Glu) seemed to be the most common mutation in Middle Easterners, accounting for 45.52% (183 out of 402) of *CYP1B1* mutations. The other common mutations were 8006G > A (p.Arg390His) (8.71%), 8242C > T (p.Arg469Trp) (8.21%), and 4339delG (5.72%).

In comparison with this current review, the p.Gly61Glu mutation was also prominent. It was discovered in four different countries with a high rate of consanguinity, such as Morocco, Tunisia, Lebanon, and Saudi Arabia. According to the literature, this mutation was also found in other countries such as Ecuador, Spain, India, Iran, Oman, Kuwait, Turkey, and especially in Saudi Arabia, where it was demonstrated as the founder mutation. This mutation has been introduced into North Africa and Southern Europe during the Arab invasion in the seventh century.[16] The Saudi study also confirms that *CYP1B1* mutations are the most common cause of PGC in their population, with the p.Gly61Glu as the main mutation.[7] This mutation has also been discovered in Iran and Portugal.

According to the literature, the p.Arg390His mutation was detected for the first time in a Pakistani patient.[17] It was the most common mutation in the Pakistani population with 50% of *CYP1B1* alleles (5/10) and 25% of PCG families (5/20). It was not only found in Pakistan but also in Saudi Arabia and South Korea, known to have a high and low rate of consanguinity, respectively. It could therefore be a sporadic or familial mutation. According to the literature, this mutation has been described as the second most frequent mutation among Indian and Iranian patients suffering from congenital glaucoma, representing 16 and 19.2%, respectively.[18,19]

The p.Arg469Trp mutation was found in the following countries: Lebanon, Saudi Arabia, and Morocco. It has also been found in different populations, including the Middle East, Arab, European, and Asian.[20–22]

The p.Glu229Lys and p.Arg444Gln mutations were identified in a Lebanese family. Although the mutation p. Glu229Lys was described in several ethnic groups,[20,23,24] the p.Arg444Gln has never been reported before in the Arab population. However, it has been reported in Japanese, French,[25,26] and Korean patients.

Maghreb

In the Tunisian study, there is a great probability that the p. Gly61Glu, 535delG, and two novel mutations p.Phe231Ile and p.Pro437Ala come from a common ancestor. Screening for the presence of these mutations should improve the genetic diagnosis and reduce the blindness due to late PCG diagnosis.

In Morocco, the first analysis of *CYP1B1* mutations in the Moroccan population was performed in isolated cases, more than 14 years ago. Two mutations were identified: g.4339delG and p.Gly61Glu. The novel frameshift mutation

g.4339delG was never described before and was considered the most frequent (25.8% of alleles). Nevertheless, it had been found in Algerian descendants (E. Colomb and HJ Garchon, unpublished data). Therefore, this should be closely related to the presence of the Berber people, representing a major part of the Algerian and Moroccan population. The other mutation, p.Gly61Glu, had already been identified in Turkish and Saudi patients.[27]

Since the myocilin (*MYOC*) gene has also been found to be involved in the etiology of the PCG, another Moroccan study was conducted to assess the mutation spectrum of both, the *CYP1B1* and *MYOC* gene. The *CYP1B1* gene was the major cause of GCP with a frequency of 48%, while *MYOC* played only a modest role in Moroccan patients. The g.4339delG mutation was the most frequent followed by p.Gly61Glu. These two mutations were present in 37.21% (30.55% and 6.66%, respectively) of the Moroccan alleles. The g.4339delG was also the most common mutation in Brazil[23] with a lower rate compared with Morocco (21%). Three mutations were novel (p.Arg163Cys, p.Cys470Tyr, and g.4330–4331delTG) and five were identified for the first time in the African population (p.Arg368His, p.Val364Met, p.Arg390Ser, p. Arg469Trp, and g.7901–7913del13bp).[28] Other mutations (p.Gly61Glu, p.Glu173Lys, and g.4339delG) have already been reported in different populations.[29]

All these mutations have been described in the Moroccan study included in our meta-analysis; 62.7% (32/51) of patients had mutations (4339delG, g.4330–4331delTG and g.79016–7913del13bp) in both alleles.

The 4339delG mutation was found widely in different Moroccan studies. It may therefore be a founder mutation for the Moroccan population.

Asia

According to the study conducted by Li et al, the three most common mutations in Asian patients were p.Val364Met, p. Arg390His, and p.Leu385Phe.[9]

In this meta-analysis, both p.Val364Met and p.Arg390His mutations were identified in South Korea, but also in Morocco and in some Middle East countries (Saudi Arabia, and Pakistan).

On the other hand, the p.Leu385Phe was not found either in Asian population or in other ethnic groups. It could be a mutation that had stopped being transmitted through generations or not found in our sample of patients.

The p.Val320Leu mutation appeared only in Asian countries including Vietnam and South Korea, where the consanguinity rate is low. This mutation has also been reported previously in the Chinese and Japanese population[30,31] suggesting that she could be a specific mutation for the Asian population.

The mutation p.Glu173Lys was detected in two Chinese patients and also in a nonaffected patient, which could be explained by an incomplete penetrance. It suggested the presence of a dominant modifier locus that is not genetically linked to *CYP1B1*. Further studies of a possible regulation of other factors or other genes (e.g., *LTBP2*) should be performed to explore the pathogenesis of PCG.[32] This mutation was first identified in an Egyptian family and later reported among Iranian patients.[18,33] It has also been found in Morocco.

Europe

The p.Glu387Lys is considered the most common mutation. This mutation was also found in a Hungarian patient in the homozygous state where both parents were heterozygous. It was also demonstrated that this mutation was the most frequent in Gypsy population.[9]

United States

In the United States study, two novel combinations of compound heterozygous mutations have been found with whole exome sequencing. Whole exome sequencing, coupled with Sanger sequencing, may identify novel genes for PCG patients who do not harbor mutations in known PCG genes.

However, *CYP1B1* mutations are less common in the United States (14.9%) than in other Arab or Gypsies countries. This highlights the fact that other genes may account for PCG in the U.S. population, reinforcing the idea that it is an ocular disease of genetic heterogeneity.[34]

India and Brazil

These countries have significant allelic heterogeneity with the R368H and 4340delG mutations because they prevail in India and Brazil, respectively. Interestingly, the most common mutation in Brazil 4340delG was not observed in the Indian population, and R368H was observed only in three Brazilian patients in the homozygous or compound heterozygous state.

Conclusion

In this meta-analysis, 99 *CYP1B1* gene mutations causing PCG from 2011 until May 2016 were identified. Moreover, 60 new mutations, not listed in the reference study of Li et al,[6] were reported.

CYP1B1 mutations were identified in 41.6% of the patients, which underlines the importance of CYP1B1 mutational analysis. Therefore, other possibilities may cause the PCG for the remaining 58.2% patients.

Nonsignificant difference in the sex prevalence between different ethnic groups has been reported.

Consanguinity plays an important role in the pathogenesis and the transmission of PCG; however, some sporadic mutations were also found. A difference in the penetrance for the same mutation was also highlighted in affected and nonaffected Chinese individuals in this review.

The mutations distribution and frequency vary considerably between different ethnic and geographic locations.

The G61E was the most frequent mutation and was discovered in four different countries where the consanguinity rate is high.

Some mutations may be considered as founder mutations for different populations. For example, the Gly61Glu, R390H, G61E, 4339delG, E387K, and V320L were estimated as founder mutations for these countries: Iran/Saudi Arabia,

Pakistan, Lebanon, Morocco, Europe, and Vietnam/South Korea, respectively.

In addition, many common mutations in different countries were found, such as Morocco where its mutations were similar to seven other countries.

This overview provides a *CYP1B1* mutations spectrum, causing GCP in different populations.

Genetic tests looking for common and specially founder mutations should be the first step in genetic screening for PCG patients.

Despite the fact that *CYP1B1* alone cannot explain the overall genetic contributions to PCG, it is still a promising development. Its role in classic cases of PCG and those devoid of mutations in *CYP1B1* would be interesting. In fact, more scientific studies should be done in the future to approach the exact PCG cause, because of the complexity and the genetic heterogeneity.

This overview can be helpful in developing reliable genetic tests for PCG patients and their families.

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Conflict of Interest
None.

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