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Review

Overview of Cytochrome P450 1B1 gene mutations in patients with primary congenital glaucoma

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ABSTRACT

The objective of this study was to investigate the distribution of mutations in the Cytochrome P450 1B1 gene (CYP1B1) in patients with primary congenital glaucoma (PCG) among different populations. All identifiable original studies on CYP1B1 gene mutations of patients with PCG were reviewed. Finally, DNA mutations within the CYP1B1 gene were identified in 542 patients with PCG according to 52 scientific articles and 147 distinct mutations were found. The 3987G>A (G61E) missense mutation is a founder mutation in Middle Eastern population, responsible for 45.52% of CYP1B1 mutations. In Gypsies, missense mutation 7996G>A (E387K) seems to be a founder mutation, accounting for 79.63% of CYP1B1 mutations. It seems that there is no founder mutation in Asian or Caucasian population, but also accumulates in some spots. Mutations 7927G>A (V364M), 7990C>T (L385F) and 8006G>A (R390H) are common in Asian population. In Caucasians, 7940G>A (R368H), 8037dup10, 8006G>A (R390H), 7901del13, 4340delG, 3987G>A (G61E), 7996G>A (E387K), 4490G>A (E229K) and 8005C>T/A (R390C/S) are common mutations. The findings suggest that ethnic differences and the geographical distribution of PCG may be associated with different CYP1B1 mutation patterns. Such information may be useful in developing strategies for reliable clinical genetic testing of patients with PCG and their families.

1. Introduction

Primary congenital glaucoma (PCG) is the most common childhood glaucoma characterized by a marked increase of intraocular pressure at birth or early childhood, buphthalmos, megalocornea, corneal edema, and optic nerve damage. PCG is restricted to a developmental abnormality that affects the trabecular meshwork without other ocular or systemic diseases. The association of cytochrome P450, family 1, subfamily B, polypeptide 1 (CYP1B1) gene mutation in PCG individuals has been known for about a decade (Choudhary et al., 2009; Sarfarazi and Stoilov, 2000; Sarfarazi et al., 2003; Vasiliou and Gonzalez, 2008). CYP1B1 gene is located on chromosome 2 at position p21 (GLC3A). The gene contains three exons and two introns. The coding region of CYP1B1 starts at the 5′ end of the second exon and ends within the third exon. The putative open reading frame is 1632 base pairs in length and codes for a 543 amino acid protein. This gene encodes a member of the cytochrome P450 superfamily of enzymes. The enzyme encoded by this gene localizes to the endoplasmic reticulum and metabolizes procarcinogens such as polycyclic aromatic hydrocarbons and 17beta-estradiol (Lai et al., 2001; Long et al., 2006; Paracchini et al., 2005; Sowers et al., 2006; Tokizane et al., 2005; Wang et al., 2002). Mutations in this gene have been associated with PCG; therefore it is thought that the enzyme also metabolizes a signaling molecule involved in eye development, possibly a steroid (Achary et al., 2006; Hollander et al., 2006; Michels-Rautenstrauss et al., 2001; Sitorus et al., 2003; Stoilov et al., 1997; Vincent et al., 2002).

Mutation in CYP1B1 is the predominant cause of autosomal recessive inherited PCG. To date, more and more mutations have been identified in patients and families with PCG from numerous countries and ethnic groups. In this overview we describe 147 distinct CYP1B1 mutations that we have retrieved from publications. In addition, we analyze the spectrum of CYP1B1 mutations in different populations. This information is important for the development of rapid procedures to detect mutations in patients and also to understand the molecular mechanisms leading to PCG.

2. Materials and methods

2.1. Search strategy

A comprehensive literature review was undertaken to identify original articles published in the English or Chinese language that

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reported mutations in the CYP1B1 gene in patients with PCG. The following electronic databases were searched: MEDLINE (1966 to August 2010), EMBASE (1966 to December 2010) and Chinese Bio-medicine Database (1979 to December 2010) for relevant articles published in English or Chinese. The search terms were *CYP1B1*, *cytochrome P450*, *GLC3A*, *and glaucoma*. Literature reference proceedings were hand-searched at the same time. The title and abstract of all potentially relevant articles were screened to determine their relevance. Then full articles were scrutinized if the title and abstract were ambiguous. Two reviewers (Ni Li, Yong Zhou) conducted searches independently, and the results were combined.

2.2. Inclusion and exclusion criteria

The following selection criteria were used to identify published studies for inclusion in this analysis: (1) mutational analysis was performed on CYP1B1 gene for patients with PCG; (2) data were derived from an original research study; (3) the exact DNA sequence alteration was reported. Exclusion criteria included patients with a known ocular or systemic syndrome associated with glaucoma. A patient was included only once if he or she was reported redundantly in more than one publication. A mutation was included only once when multiple members of the same family had the same mutation.

2.3. Data extraction

Two reviewers (Ni Li, Yong Zhou) performed the data extraction of studies that were included in the meta-analysis independently. Any differences were resolved by discussion to reach consensus among the investigators. Mutations were named based on CYP1B1 gene sequence listed in GenBank (accession number U56438). Each mutation was indicated on a full-length map of the CYP1B1 protein, and the predicted consequence of the mutation on translation of the CYP1B1 protein was determined. A nonsense mutation is a point mutation in a sequence of DNA that results in a premature stop codon. A frameshift mutation is a genetic mutation caused by insertions or deletions of a number of nucleotides that change the reading frame (the grouping of the codons) resulting in a completely different translation from the original. A missense mutation is a point mutation that causes a new amino acid to be substituted for the normal amino acid but does not cause termination of translation. In-frame deletion involves a loss of nucleotides in multiples of three, causing a loss of one or more amino acids but not termination of translation.

3. Results

There were 655 articles relevant to the searching words. Through the step of screening the title, 417 articles were excluded for not original research articles. Abstracts from 238 articles were reviewed and an additional 171 articles were excluded for not about CYP1B1 and PCG, leaving 67 studies for full publication review. Of these, 15 studies were excluded for duplication without usable information. Finally, DNA mutations within the CYP1B1 gene were identified in 542 patients with PCG reported in 52 scientific articles. Table 1 showed the studies included in the overview (Alfadhli et al., 2006; Bagiyeva et al., 2007; Bar-Yosef et al., 2010; Bejjani et al., 1998, 2000; Belmouden et al., 2002; Brinkmann et al., 2006a, b; Campos-Mollo et al., 2009; Chakrabarti et al., 2003; Chavarria-Soley et al., 2006; Chen et al., 2008; Chitsazian et al., 2007; Colomb et al., 2003; Curry et al., 2004; Della Paolera et al., 2010; Dimasi et al., 2007; El-Ashry et al., 2007; El-Gayar et al., 2009; Firasat et al., 2008; Fuse et al., 2010; Hilal et al., 2010; Hollander et al., 2006; Huang et al., 2009; Huang et al., 2007; Jiang et al., 2007; Kakiuchi-Matsumoto et al., 2001; Lopez-Garrido et al., 2009; Martin et al., 2000; Mashima et al., 2001; Messina-Baas et al., 2007; Michels-Rautenstrauss et al., 2001; Nirmaladevi et al., 2006a, b; Panicker et al., 2004; Plasilova et al., 1999; Ramprasad et al., 2007; Reddy et al., 2004, 2003; Sena et al., 2004; Sitorus et al., 2003; Sivadorai et al., 2008; Stoilov et al., 1998, 1997, 2002; Strom et al., 2006; Suri et al., 2009; Tanwar et al., 2009a, 2009b; Weisschuh et al., 2009; Yang et al., 2009; Zenteno et al., 2008).

Table 1
Studies included in the overview.

Study	Ethnic Origin	N
Stoilov et al., 1997	Turkish	5
Stoilov et al., 1998	Hispanic, USA, French Canadian, British, Turkish	17
Bejjani et al., 1998	Saudi Arabian	24
Plasilova et al., 1999	Slovak Gypsies	20
Martin et al., 2000	Canadian	2
Bejjani et al., 2000	Saudi Arabian	10
Michels-Rautenstrauss et al., 2001	Turkish, German, Lebanon	1
Mashima et al., 2001	Japanese	13
Kakiuchi-Matsumoto et al., 2001	Japanese	2
Belmouden et al., 2002	Moroccan	11
Stoilov et al., 2002	Brazilian	26
Reddy et al., 2003	Indian	37
Chakrabarti et al., 2003	Indian	2
Colomb et al., 2003	Algeria, French, Portugal	15
Sitorus et al., 2003	Indonesian-Sundanese, Turkish, Italian	6
Reddy et al., 2004	Indian	24
Curry et al., 2004	Ecuador	2
Panicker et al., 2004	Indian	1
Sena et al., 2004	Brazilian, USA	4
Messina-Baas et al., 2007	Mexican	4
Hollander et al., 2006	Asian, Hispanic, Middle Eastern, Caucasian	4
Strom et al., 2006	USA	1
Chavarria-Soley et al., 2006	CostaRica, Russia, Turkish, German, Switzerland, USA, Saudi Arabian	26
Alfadhli et al., 2006	Kuwaiti	12
Brinkmann et al., 2006a	Netherlands	1
Nirmaladevi et al., 2006a	Indian	1
Brinkmann et al., 2006b	Netherlands	1
Nirmaladevi et al., 2006b	Indian	1
Jiang et al., 2007	Chinese	7
El-Ashry et al., 2007	Saudi Arabian, Egyptian	5
Ramprasad et al., 2007	Indian	6
Chitsazian et al., 2007	Iranian	72
Dimasi et al., 2007	British, Italian, Indian	8
Bagiyeva et al., 2007	Turkish	15
Huang et al., 2007	Chinese	1
Chen et al., 2008	Chinese	20
Firasat et al., 2008	Pakistani	3
Zenteno et al., 2008	Mexican	2
Sivadorai et al., 2008	Gypsies	7
Campos-Mollo et al., 2009	Spanish	14
Yang et al., 2009	Chinese	6
Tanwar et al., 2009a	Indian	23
El-Gayar et al., 2009	Oman	8
López-Garrido et al., 2009	Spain	1
Tanwar et al., 2009b	Indian	9
Weisschuh et al., 2009	German	7
Della Paolera et al., 2010	Brazilian	9
Huang et al., 2009	Chinese	1
Suri et al., 2009	Iranian	13
Fuse et al., 2010	Japanese	4
Hilal et al., 2010	Moroccan	19
Bar-Yosef et al., 2010	Israeli Bedouin	9

N = number of patients.

3.1. Type of mutation

Altogether, 147 distinct mutations were observed in 542 patients. Table 2 lists the distribution of mutation types reported. CYP1B1